Identification de nouveaux partenaires d'interaction du récepteur à la prostaglandine D_2 DP1 et caractérisation de leurs effets sur son trafic et sa signalisation

Par

Louis Fréchette

Programme de pharmacologie

Thèse présentée à la Faculté de médecine et des sciences de la santé
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RÉSUMÉ

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L'étude des récepteurs couplés aux protéines G est un sujet d'importance en pharmacologie moléculaire car ces derniers constituent une cible pharmacologique de choix dans la pharmacopée actuelle. Ces derniers régulent de nombreux processus biologiques et sont également impliqués dans de nombreuses pathologies. Les processus régulant leur trafic ainsi que leur signalisation sont complexes et notre compréhension de ces phénomènes sont en constante évolution.

Parmi les protéines ayant un effet dans la régulation de ces récepteurs, les protéines ayant une action GTPasique et les protéines d'échafaudage sont particulièrement importante pour la régulation fine des mouvements et des phénomènes de signalisation induits par ces récepteurs. Les protéines telles que les Rabs sont essentielles aux déplacements et à l'adressage, tandis que les protéines d'échafaudages permettent de contrôler l'environnement immédiat du récepteur et de moduler les différents acteurs interagissant avec ce dernier.

Le but de cette présente étude était d'étudier les facteurs moléculaires permettant de réguler le trafic et la signalisation du récepteur DP1 et d'identifier de nouveaux partenaires d'interaction. Nous avons dans un premier temps démontré l'implication de la protéine adaptatrice GGA3 dans un mécanisme de recyclage rapide du récepteur vers la membrane plasmique. Dans un deuxième temps, nous avons identifié par spectrométrie de masse plusieurs partenaires d'interaction potentiels, classé ces derniers par sous-localisation cellulaire et avons sélectionné la protéine IQGAP1 afin de tester d'éventuels conséquences fonctionnels sur le récepteur DP1.

Mots clés : Récepteurs coupés aux protéines G, DP1, GGA3, Rab, IQGAP1, trafic, signalisation

SUMMARY

Identification of new interacting partners of the prostaglandin D_2 receptor DP1 and characterization of their effects on the receptor trafficking and signalling

By

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Pharmacology program

Thesis presented at the Faculty of Medicine and Health Sciences for the obtention of the *Philosophiae Doctor* (Ph.D) degree in pharmacology, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, Québec, Canada, J1H 5N4

Research on G-coupled protein receptors (GPCRs) is an important subject in molecular pharmacology because they are a choice target in the current pharmacopeia. GPCRs regulate different biological and pathophysiological processes. The biological mechanism controlling their trafficking and their signalling are complex and our comprehension of those phenomenon is in continuous improvement.

Among the proteins having an effect on GPCR regulation, the GTPase and scaffold proteins are particularly important for the fine tuning of the receptor trafficking and signalling. Rab proteins are essential for the routing of GPCRs whereas scaffold proteins are important to control the immediate environment and the various other proteins interacting with the GPCR.

The goals of this study were to elucidate the molecular factors regulating the traffic and signalling of the DP1 receptor and to identify new potential interacting partners. We have shown that the molecular adaptor GGA3 was implicated in a fast recycling mechanism for DP1 to return to the plasma membrane. We also characterized the interactome of the receptor by mass spectrometry and classified the potential interacting proteins by sub-cellular localization. The IQGAP1 scaffold protein was selected to validate our approach and to study its functionnal effects on the DP1 receptor trafficking and signalling.

Keywords : G-protein coupled receptor, DP1, GGA3, Rab, IQGAP1, traffic, signalisation

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Liste des abbréviations

AC	Adénylate cyclase
ADN	Acide désoxyribonucléique
AMPc	Adénosine monophosphate cyclique
ANKRD13C	*Ankyrin repeat domain-containing protein 13C*
ARNm	Acide ribonucléique messager
ASRT	*Actin-sorting nexin 27-retromer complex*
AT1R	Récepteur à l'angiotensine I
CB1	Récepteur aux cannabinoïdes type I
COPI	Coat protein I
COPII	Coat protein II
COX	Cyclooxygénase
CRTH2	*Chemoatractant receptor-homologous molecule expressed on Th2*
DAG	Diacylglycérol
DP1	Récepteur à la prostaglandine D2 (1)
DP2	Récepteur à la prostaglandine D2 (2)
DTT	Dithiothréitol
ECL	Boucle extracellulaire
ERAD	*Endoplasmic-reticulum associated degradation*
ERGIC	*Endoplasmic-reticulum-Golgi intermediate compartment*
ERK	*Mitogen-activated protein kinase*
FPR	*Formyl peptide receptor*
GDP	Guanosine diphosphate
GRK	*G protein-coupled receptor kinase*
GST	Glutathion s-transférase
GTP	Guanosine-5'-triphosphate
HGF	*Hepatocyte growth factor*
H-PGDS	Prostaglandine synthase de type hématopoïétique
Hrs	*Hepatocyte growth factor-regulated tyrosine kinase substrate*
Hsp	*Heat-shock protein*
ICL	Boucle intracellulaire
IP	Récepteur à la prostacycline
IP3	Inositol triphosphate
IQGAP	*Ras GTPase activating-like protein*
JNK	c-jun N-terminal kinase
L-PGDS	Prostaglandine D synthase de type lipocaline
MAPK	*Mitogen-activated protein kinase*
MEC	Matrice extracellulaire
MEK	*Mitogen-activated protein kinase kinase*
MMP	Métalloprotinase matricielle
NFκB	*Nuclear factor kappa-light-chain-enhancer of activated B cells*

NO	Monoxide d'azote
NSF	*N-ethymaleimide-sensitive factor*
PDZ	*Post-synaptic density 95/disc large/zonula occludens-1*
PGG2	Prostaglandine G2
PGH2	Prostaglandine H2
PI3K	*Phosphatidylinositol-4,5-bisphosphate 3 kinase*
PIP2	Phosphatidylinositol biphosphate
PKA	Protéine kinase A
PKC	Protéine kinase C
PLCB	Phospholipase CB
PPARγ	*Peroxisome proliferator-activated receptor gamma*
Raf	*mitogen-activated protein kinase kinase kinase*
RCPG	Récepteur couplé aux protéines G
SNX	*Sorting nexin*
Src	*Proto-oncogene tyrosine-protein kinase*
TGN	*trans-golgi network*
TM	Domaine transmembranaire
Vps	*Vacuolar protein sorting*
WASH	*Wiskott-Aldrich syndrome protein and SCAR homologue*

1.Introduction

La communication est un processus ayant été essentiel au développement ainsi qu'à la pérennité de l'espèce humaine. L'histoire regorge d'exemple de malentendus entre individus et nations ayant eu diverses conséquences saillantes. La gravité des conséquences est variable selon le manquement, pouvant aller de la panique d'une frange de la population, comme par exemple lors de la diffusion du radio-roman «La guerre des mondes» en 1938, en passant par l'erreur de communication concernant le trajet de Franz Ferdinand à Sarajevo en 1914 ayant ultimement mené à la première guerre mondiale et ses 20 millions de décès. Parallèlement à ce genre d'évènements facilement conceptualisable par l'Homme, il se déroule régulièrement une myriade d'évènements semblables de transmission d'informations au niveau de tous les systèmes, organes et cellules de notre corps. Ainsi, au même titre que la sémiotique et la sémantique analysent les différents concepts reliés à la communication entre les personnes et les systèmes à l'échelle macroscopique, la biologie cellulaire étudie la composition ainsi que les moyens de communications entre les cellules à l'échelle microscopique. Cette thèse portera donc sur l'un des nombreux acteurs permettant à la cellule de recevoir les signaux de son environnement, le récepteur à la prostaglandine D_2 DP1, ainsi que sur différents acteurs moléculaires ayant la capacité de moduler la signalisation induite par ce récepteur.

1.1 Récepteurs couplés aux protéines G (RCPG)

Le récepteur à la prostaglandine D2 DP1 fait partie intégrante de la superfamille des récepteurs couplés aux protéines G (RCPG), qui compte plus de 800 protéines distinctes. Les RCPG sont des protéines à 7 domaines transmembranaires et ses membres sont parmi les plus abondants dans la famille des protéines à domaine transmembranaire. Les RCPG sont retrouvés dans de multiples organismes vivants procaryotes et eucaryotes et ont comme fonction principale de relayer des messages de la membrane plasmique à l'intérieur de la cellule ou encore d'un compartiment cellulaire à un autre (Y. J. I. Jong, Harmon, and O'Malley 2018). Ils ont également un large éventail de ligands possibles, tel que des ions, des photons, des acides aminés, des acides nucléiques ou des lipides. Ils sont présents dans tous les tissus et cellules humaines et régulent de multiples processus physiologiques. Conséquemment, ces récepteurs sont

importants pour la pharmacopée moderne et ses différents membres comptent pour 30% à 40% des cibles des médicaments prescrits dans le monde (Hauser et al. 2017).

1.1.2 Structure des RCPG

Structurellement, les RCPG sont constitués d'une queue N-terminale, de 7 segments transmembranaires, 3 boucles intracellulaires, 3 boucles extracellulaires ainsi que d'une queue C-terminale (figure 1). Bien que cette structure soit commune à tous les RCPG, il est important de préciser que les séquences en acides aminés entre les différents récepteurs, mis à part certains motifs spécifiques, sont faiblement conservés entres elles. Les études phylogénétiques séparent généralement les RCPG en 5 grandes familles (voir tableau 1) selon le système de classification GRAFS (Schiöth and Fredriksson 2005), qui utilise des considérations hybrides de structure et de fonctions pour classifier les RCPG.

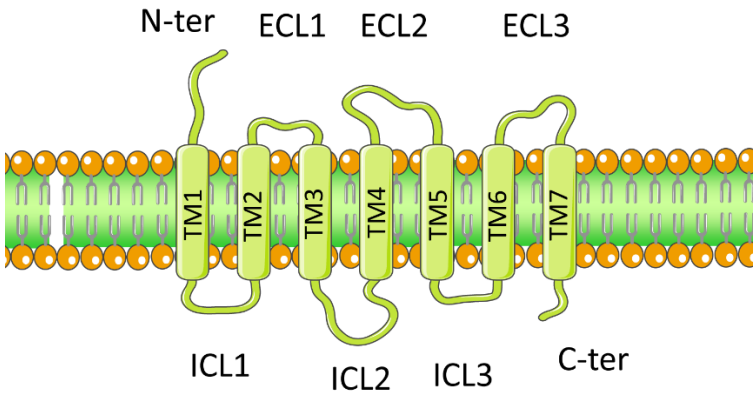


Figure 1 : représentation schématique d'un RCPG. N-ter :N-terminale, ECL :boucle extra-cellulaire, ICL : boucle intracellulaire, TM :domaine transmembranaire, et C-ter :domaine C-terminale.

G	Famille des récepteurs au Glutamate. Tous les récepteurs de cette classe ont un domaine de reconnaissance du ligand sur un long domaine N-terminale.
R	Famille des récepteurs à la Rhodopsine. La plus grande famille de RCPG. Ils ont systématiquement un motif NSxxNPxxY dans leur domaine transmembrane 7 et un motif DRY à la jonction des domaines transmembrane 3 ainsi que de la boucle intra-cellulaire 2.
A	Famille des récepteurs d'adhésion. Ces récepteurs ont un long domaine N-terminale riche en résidus sérine et thréonine pouvant servir de site de glycosylation.
F	Famille des récepteurs Frizzled/Taste2. Ils ont un long domaine N-terminale riche en cystéine conservés servant à la liaison du ligand Wnt.
S	Famille des récepteurs à la sécrétine. Le domaine N-terminale est riche en ponts disulfures importants pour la liaison de leurs ligands, qui sont généralement peptidiques.

Tableau 1 : Explication des différentes catégories de classification du système GRAFS

Il est important de noter que plusieurs systèmes de classification coexistent, tels que le système A-F, les systèmes de classifications basés sur l'intelligence artificielle, les systèmes de classification basés sur la similarité de séquence ainsi que les méthodes basés sur des approches protéochemométriques (Hu, Mai, and Chen 2017), mais le système GRAFS sera utilisé pour la suite de cette thèse car ce dernier permet de comparer distinctivement les différentes classes et répertorie les 5 classes de RCPG retrouvés chez l'humain (Tableau 1).

1.1.3 Synthèse, maturation et export des RCPG à la membrane plasmique

La synthèse des RCPG débute au réticulum endoplasmic (RE) lorsque le fragment d'ARNm codant pour la protéine passe à travers un processus appelé translocation co-traductionnelle.

Bien que ce processus peut sembler trivial à expliquer, il est important de noter que plusieurs études ont établi que le contrôle de la localisation de la translocation co-traductionnelle était un important facteur de contrôle de l'efficacité de la synthèse et du transport des RCPG à la membrane plasmique. En effet, l'augmentation de traduction des ARNm de RCPG par des polyribosomes périnucléaires mène à une production accrue de récepteurs, mais à une diminution du nombre de récepteurs actifs à la membrane plasmique (Tholanikunnel et al. 2010). Suite à la prise en charge du polypeptide naissant par la protéine SRP (Signal Recognition Peptide) et le complexe du translocon, de multiples protéines effectuent des modifications post-traductionnelles telles que la glycosylation du peptide naissant ou la création de ponts disulfures. Avant de passer au compartiment suivant, le RCPG en devenir doit passer une étape stricte de contrôle de la qualité effectué par des chaperonnes moléculaires telles que la calnexine, la calréticuline, les protéines de la famille des «heat shock protein» (HSP) ou des chaperonnes « Binding immunoglobulin protein» (BiP), qui détectent les surfaces hydrophobes exposées. Si la protéine naissante ne peut être formée correctement, cette dernière est rétro-transloquée dans le cytosol pour être ubiquitinée et dégradée par le protéasome (Chunmin Dong et al. 2007).

Si le RCPG naissant passe les étapes de contrôle du RE, il est pris en charge par les protéines du complexe COPII afin de continuer son transport *via* des vésicules de transport vers le compartiment intermédiaire du RE et Golgi (ERGIC). À ce stade, si le RCPG est mal replié ou dans une conformation anormale, les protéines du complexe COP I peuvent reconnaître des séquences di-lysines ou di-arginines des queues C-terminales des protéines et reformer des vésicules pour un transport rétrograde vers le RE (Wu 2012). Il est important d'ajouter que la formation de ces vésicules ne serait pas possible sans certaines GTPases essentielles au recrutement des protéines formant le manteau vésiculaire, telles que les protéines de la superfamille des petites protéines G sur laquelle nous reviendrons dans les sections suivantes. Parmi les protéines de cette superfamille importante pour le transport antérograde des RCPG, les protéines les mieux caractérisées pour le transport de l'ERGIC vers l'appareil de Golgi sont les GTPases Arf1, Arf6 ainsi que Rab1, toutes trois membres de la superfamille des petites protéines G (fig. 2).

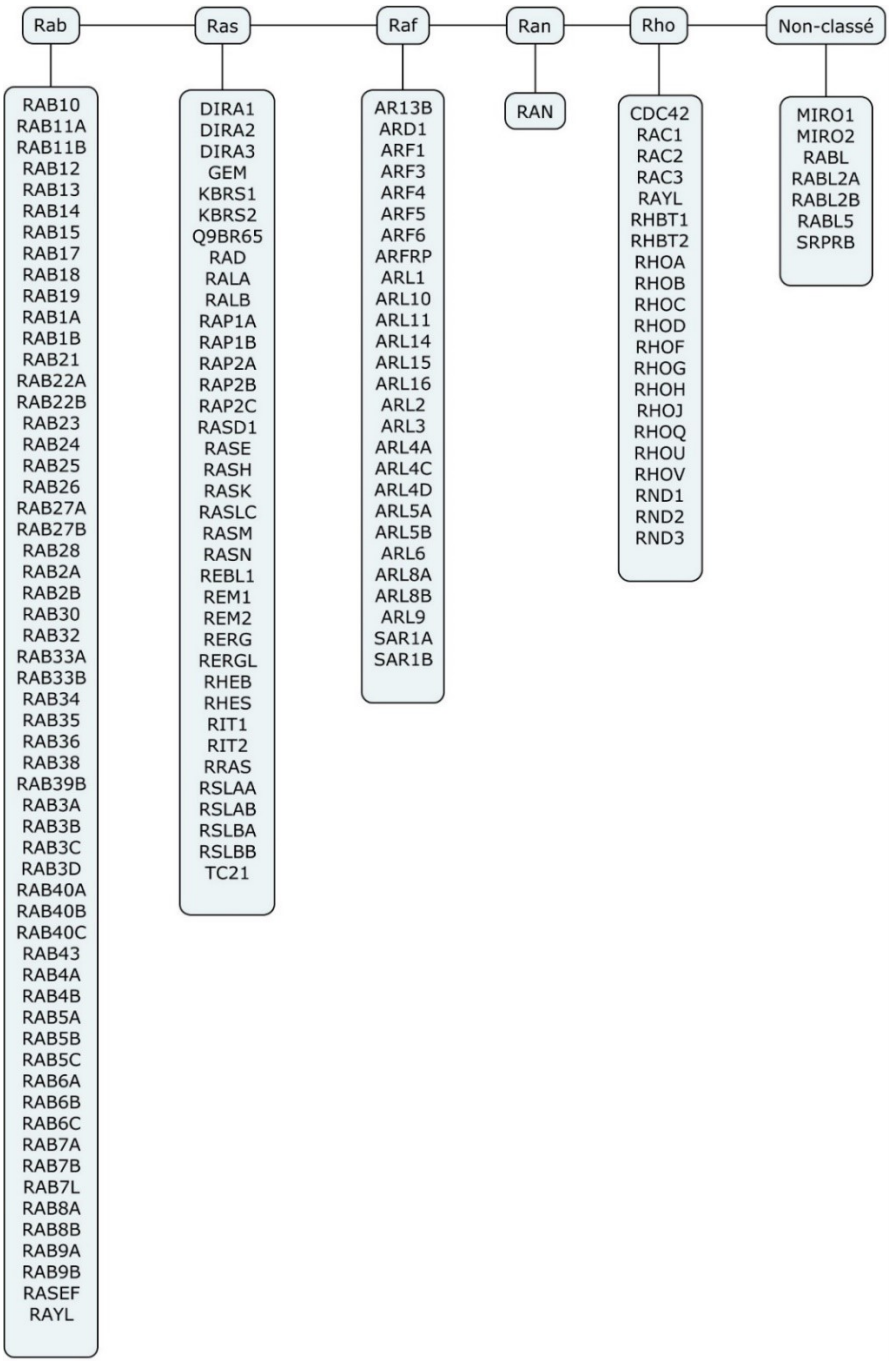


Figure 2. Représentation schématique de la superfamille des Ras et ses sous-familles

Au niveau de l'appareil de Golgi, les dernières modifications post-traductionnelles telles que la glycosylation ou la dimérisation/oligomérisation des récepteurs sont effectuées. Le TGN (Trans-Golgi Network) constitue par la suite l'ultime compartiment de triage pour le RCPG mature. Ce dernier pourra être acheminé à la membrane plasmique ou à la dégradation (Wu 2012). Une liste non-exhaustive des protéines connues pour le transport des RCPG du TGN vers la membrane plasmique est présenté à la figure 3.

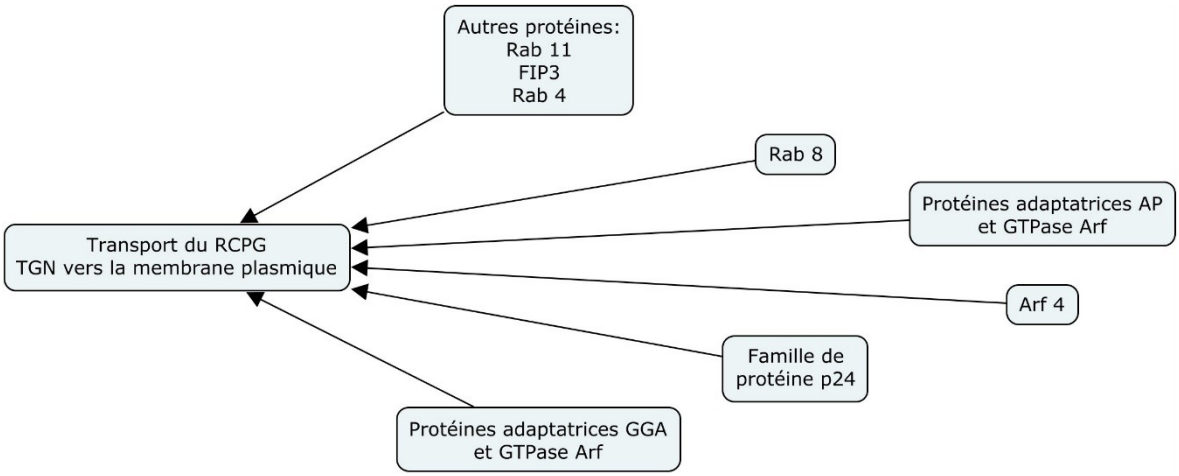


Figure 3 : Représentation des différents acteurs protéiques ayant un rôle dans le transport des RCPG vers la membrane

Il est important de mentionner ici que de multiples protéines régulent la maturation et le transport des RCPG. Plus d'une centaine d'acteurs protéiques ont été découverts à ce jour et cette brève explication ne se veut en aucun cas une description exhaustive de la voie sécrétoire du RCPG, qui serait au-delà des objectifs de ce projet de recherche.

1.1.4 Activation du RCPG à la membrane plasmique

Une fois arrivé à la membrane plasmique, le RCPG est généralement fonctionnel, c'est-à-dire dans une conformation favorisant la liaison d'une protéine G hétérotrimérique et permettant la liaison d'un ligand dans une pochette de liaison située du côté extra-cellulaire de la membrane. La liaison d'un ligand cause un changement conformationnel entraînant plusieurs conséquences fonctionnelles sur ses effecteurs, les protéines G hétérotrimériques (Hanlon and Andrew 2015).

1.1.5 Les protéines G hétérotrimériques

- Tel que spécifié dans leur nom, les RCPG sont généralement pairés d'une protéine G hétérotrimérique, constituée de trois sous-unités : une protéine G alpha (G_α), une protéine G beta (G_β) ainsi qu'une protéine G gamma (G_γ)

La liste des différents isoformes possibles de ces sous-unités de protéines G est présentée à la figure 4.

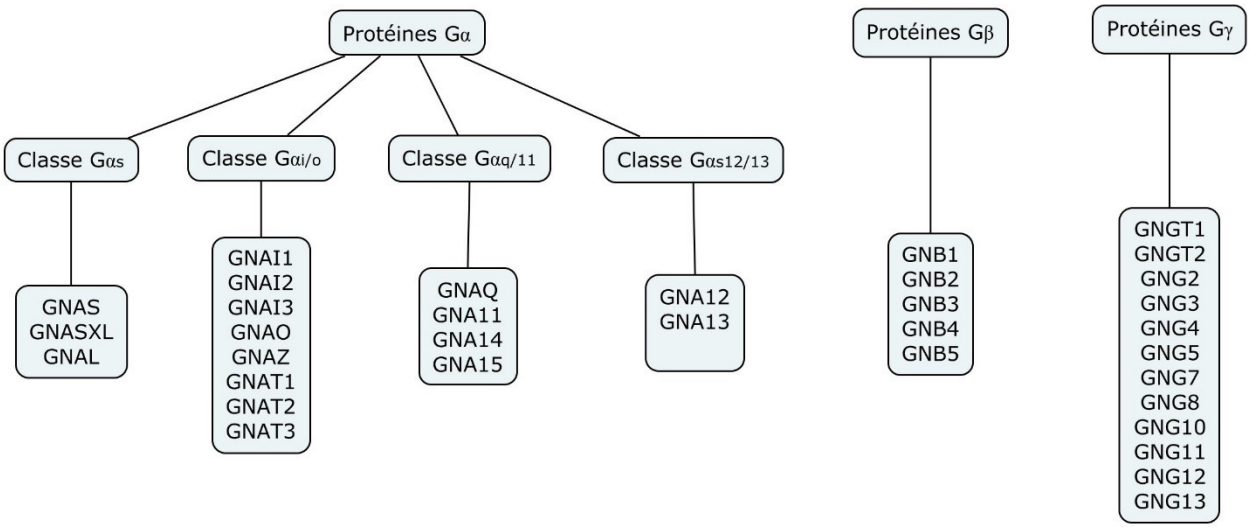


Figure 4 : Sous-unités des protéines G hétérotrimériques et isoformes de ces dernières

1.1.6 Protéine Gα : structure et voies de signalisation associées

De manière générale, les protéines G sont des protéines ayant comme caractéristique principale d'être lié au GDP (guanosine diphosphate) en condition basale. Lorsque la protéine G est dite «activée» lors d'un changement conformationnelle favorisant la liaison d'une molécule de GTP (Guanosine triphosphate) présente dans l'environnement, la nouvelle conformation de la protéine G liée au GTP lui permet alors d'activer des effecteurs de la cascade signalétique. La capacité d'hydrolyse intrinsèque du GTP de la protéine permet alors le retour à l'état basal en libérant un groupement phosphate. La transformation du GTP en GDP dans la pochette de liaison de la protéine Gα permet à ce moment un retour à la conformation tridimensionnelle originale de la protéine G (Roth et al. 2015). Les interacteurs protéiques des protéines Gα favorisant

l'échange du GDP pour le GTP sont appelés GEF (Guanine-nucleotide Exchange Factor). À l'opposé, les protéines shydrolysant le GTP en GDP sont nommées GAP (GTPase-Activating Protein). Lors de l'activation d'un RCPG, ce dernier agit donc comme une GEF de la protéine Ga (Oldham et al, 2008) . Une schématisation d'un cycle d'activation simplifié d'une protéine Ga est présenté à la figure 5.

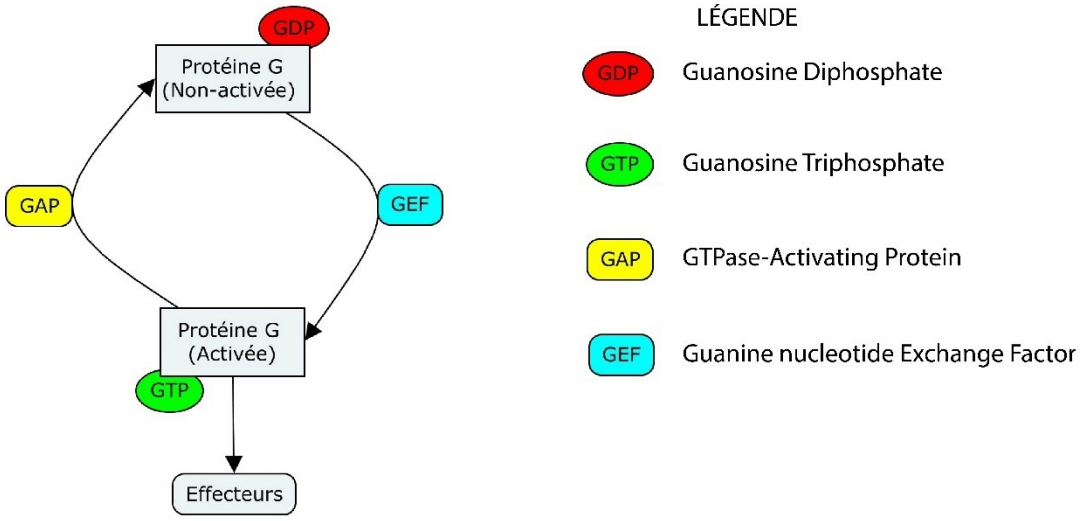


Figure 5 : Cycle d'activation d'une protéine G. Représentation graphique du cycle d'activation et d'inactivation d'une protéine G. Suite à l'intervention d'une GEF, la liaison d'une molécule de GTP est favorisée dans la pochette de liaison de la protéine G et la molécule de GDP est alors éjectée. La protéine G peut alors interagir avec ses effecteurs. Suite à l'intervention d'une GAP, la liaison de la molécule de GTP est défavorisée et la protéine G peut revenir à son état basal, c'est-à-dire liée au GDP.

La famille des protéines Ga comporte 4 membres, soit $G_{\alpha\ i/o}$, $G_{\alpha s}$, $G_{\alpha q/11}$ et $G_{\alpha 12/13}$, dont la moyenne de taille moléculaire moyenne varie entre 39kDa et 52kDa. Ils ont une séquence dont l'homologie en acides aminés oscille entre 35 et 95%. Ces dernières sont toutes attachées à une bicouche lipidique *via* une modification lipidique (palmitoylation ou myristoylation) à leur extrémité N-terminale. Toutes les protéines Ga ont deux domaines conservés, soit un domaine à action GTPasique et un domaine hélicoïdale (Kamato et al. 2015). Un résumé des fonctions associées à chacun de ces domaines est présenté dans le tableau 2.

DOMAINE À ACTION GTPASIQUE	A comme fonction d'hydrolyser le GTP et contient une interface permettant la liaison du dimère formé des protéines $G_{\beta\gamma}$. Contient cinq séquences hautement conservées pour la liaison du nucléotide (GDP/GTP) : - Séquence de liaison du diphosphate (P-loop) : GXGESGKS - Séquences de liaison du magnésium : RXXTXGI et DXXG - Les séquences guanine «ring-binding» : NKXD et TCAT Ce domaine contient également trois séquences dénommées «SWITCH I-II-III» dont la topologie est fortement influencée par la présence du GDP ou du GTP dans le site de liaison du nucléotide.
DOMAINE HÉLICOÏDALE	Composé de 6 hélices alpha formant un «chapeau» enfermant le nucléotide à l'intérieur de la pochette de liaison du nucléotide. Accroît l'affinité de la protéine G pour le nucléotide Augmente l'activité GTPasique de la protéine

Tableau 2 : Domaines structuraux des protéines Gα

Les quatre familles de protéines Ga sont également des activateurs de différentes voies de signalisation. Chaque isoforme de protéine Ga a ses caractéristiques particulières et peut activer une ou plusieurs voies de signalisation (Kamato et al. 2015), mais des voies signalétiques communes sont bien caractérisées dans la littérature pour chacune des quatre grandes familles et sont résumées dans la figure 6.

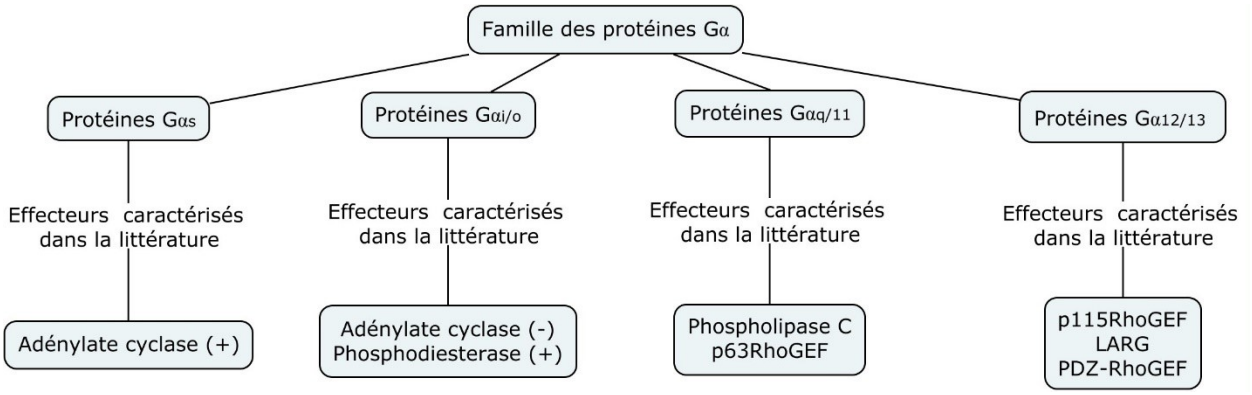


Figure 6 : Isoformes et fonctions des protéines Ga. Les différentes familles des protéines Ga ainsi que leurs effecteurs caractérisés dans la littérature.

1.1.7 Protéines Gβγ: structures et voies de signalisation associées

Les protéines Gbg, bien qu'étant deux polypeptides différents, forment une unité fonctionnelle et sont indissociables *in vivo.* Il existe 6 sous-unités b ($G_{\beta 1}$, $G_{\beta 2}$, $G_{\beta 3}$, $G_{\beta 4}$ ainsi que l'isoforme $G_{\beta 5}$ comportant deux variants) et ces isoformes ont un poids moléculaire moyen de 36 kDa. Structurellement, les protéines Gb comportent 7 hélices beta (b-propellers) composées chacune de 4 feuillets b anti-parallèles. L'extrémité N-terminale de la protéine est constituée d'une hélice alpha permettant l'interaction avec la sous-unité G_{γ} (Robillard et al. 2000).

Les sous-unités Gg sont de petits polypeptides ayant un poids moléculaire moyen de 7 kDa et ayant systématiquement une isoprénylation (farnésylation ou géranylgéranylation) au niveau de leur extrémité C-terminale. Cette modification post-traductionnelle permet l'ancrage aux membranes biologiques de la protéine $G_{\beta\gamma}$. Plusieurs effecteurs sont connus pour les différents dimères $G_{\beta\gamma}$: l'adénylyl cyclase, la PI-3 kinase, des canaux potassiques, des canaux calciques, des canaux sodiques, la protéine kinase D, la phospholipase C, la tubuline, plusieurs tyrosines kinases ainsi que plusieurs GEF (Robillard et al. 2000).

À l'état basal, le RCPG mature est intégré à la membrane et peut être lié aux divers interacteurs présents dans son environnement ainsi qu'à une protéine G hétérotrimérique et est en mesure d'activer diverses voies de signalisation (Ferguson et al. 2012). Il est donc possible de simplifier le système signalétique d'un RCPG de la manière suivante (Figure 7) :

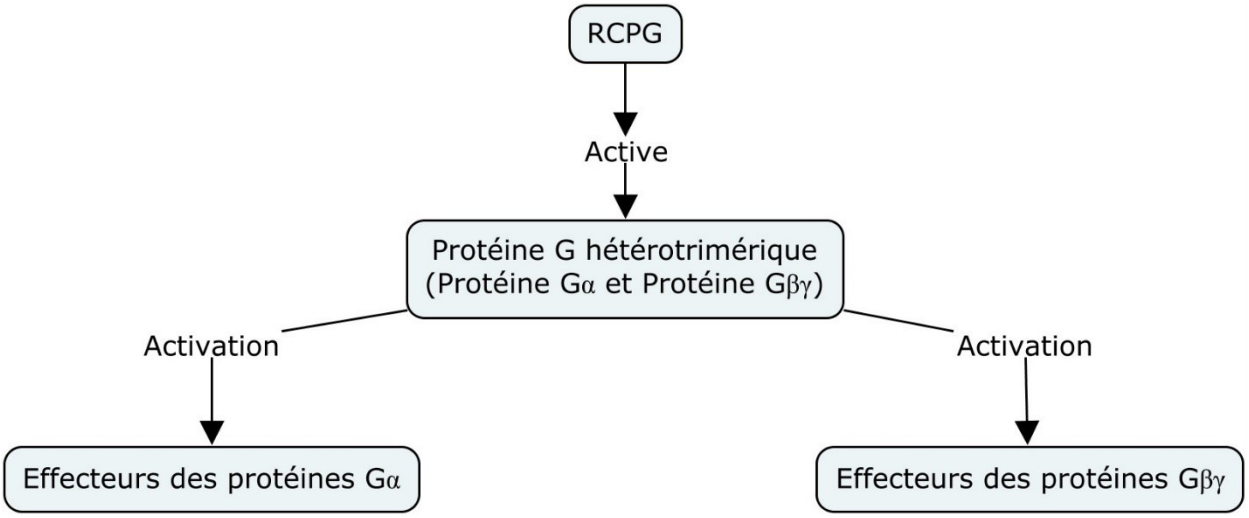


Figure 7 : Représentation simplifiée du système signalétique d'un RCPG. Le RCPG, lorsque qu'activé, engendre la dissociation de la protéine G hétérotrimérique et l'activation des effecteurs de ses sous-unités.

1.1.8 Mécanismes de désensibilisation

À la suite de son activation, un RCPG subit un phénomène de désensibilisation, ce qui permet une surstimulation des voies de signalisation induites par l'activation du récepteur. De nombreuses protéines sont responsables de la prise en charge du récepteur suivant son activation afin de terminer son action, de l'internaliser et de le diriger convenablement dans les vésicules destinées au recyclage ou à la dégradation. Il existe deux types de désensibilisation de récepteur pour les RCPG : La désensibilisation homologue et la désensibilisation hétérologue (Hanlon and Andrew 2015).

Dans la désensibilisation homologue, la première étape de l'inactivation du récepteur est la phosphorylation de résidus sérines et thréonines conservés dans la boucle intracellulaire 3 ainsi que le domaine C-terminale du RCPG. Cette action est effectuée par une famille de protéines kinases appelées GRK (G protein-coupled receptor kinase). Elles sont recrutées immédiatement après le changement conformationnel correspondant à l'activation du RCPG. La liaison des GRKs aide à dissocier le RCPG de la protéine G hétérotrimérique. De façon intéressante, d'autres kinases pouvant avoir été activées par le récepteur et peuvent contribuer également à cette inactivation en phosphorylant également les acides aminés identifiés précédemment (Kelly, Bailey, and Henderson 2008).

La deuxième étape nécessite le recrutement d'une protéine adaptatrice pouvant se lier au récepteur phosphorylé. Les protéines de la famille des arrestines sont les mieux caractérisées dans l'internalisation des RCPG et ont dans ce contexte deux fonctions principales :

- Ce sont des facteurs nécessaires pour l'endocytose du RCPG et peuvent faciliter le recrutement des différentes composantes du manteau protéique nécessaires à l'endocytose par des vésicules de clathrine.
- Elles empêchent l'interaction du RCPG avec sa protéine G hétérotrimérique

Un schéma représentant un cycle d'activation d'un RCPG typique est illustré à la figure 8.

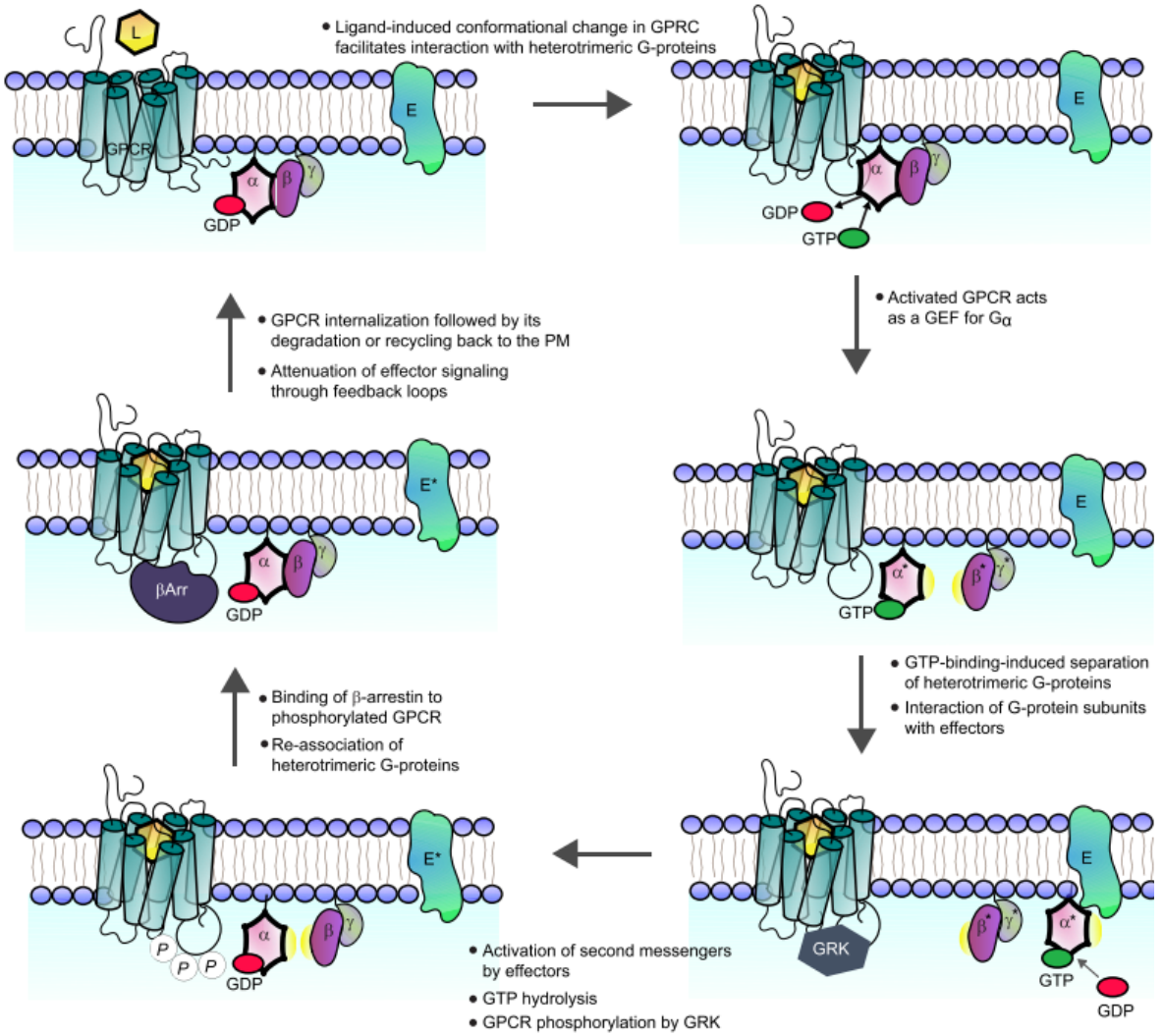


Fig 8 : Schéma du cycle d'activation et de désensibilisation d'un RCPG (Tiré de (Hanlon and Andrew 2015))

Dans la désensibilisation hétérologue, l'inactivation du récepteur n'est pas une conséquence de l'activation du récepteur lui-même mais vient plutôt d'une source externe, tel que l'activation d'un autre récepteur membranaire ou d'une cascade métabolique en cours. L'inactivation peut être causée par des kinases (PKA, PKC) activées par d'autre récepteurs (Magalhaes, Dunn, and Ferguson 2012).

1.1.9 Voies de signalisation n'étant pas directement reliées aux protéines G

Il a été vu précédemment que plusieurs voies de signalisation pouvaient être stimulées à la suite de l'activation des protéines G hétérotrimériques par les RCPG. Il existe des voies de signalisation dépendantes des arrestines. Les différentes arrestines peuvent ainsi faire office de protéine d'échafaudage pour plusieurs protéines reliées à différentes voies de signalisation, tel que présenté à la figure 9 (Gurevich and Gurevich 2019).

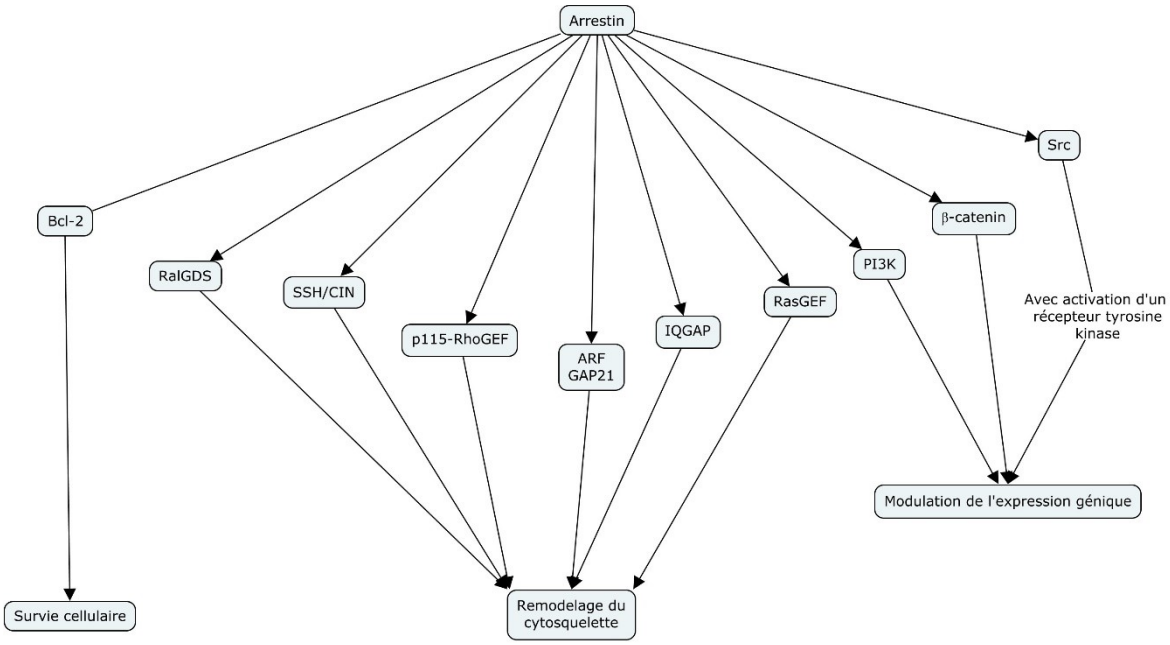


Figure 9 : Interacteurs majeurs et voies de signalisations activées par les arrestines. (Inspiré de (Bagnato and Rosanò 2019))

Les RCPG peuvent également lier différentes protéines ayant la capacité de moduler différentes voies de signalisation : les protéines d'échafaudage à domaine PDZ et les protéines d'échafaudage sans domaine PDZ.

Les protéines d'échafaudage à domaine PDZ : ces dernières peuvent lier des séquences PDZ-ligands généralement situées dans la queue C-terminale des RCPG. Elles peuvent aussi moduler l'activité de protéines kinases, de phospholipases et moduler l'ouverture de canaux ioniques. Une liste non-exhaustive de différentes protéines d'échafaudage à domaine PDZ ainsi que de leurs effets sur différents RCPG est présentée à la figure 10. Il est intéressant de noter qu'un même RCPG peut avoir plus d'une protéine échafaud et que les protéines échafauds peuvent avoir des effets opposés sur différents RCPG (Pavlos and Friedman 2017).

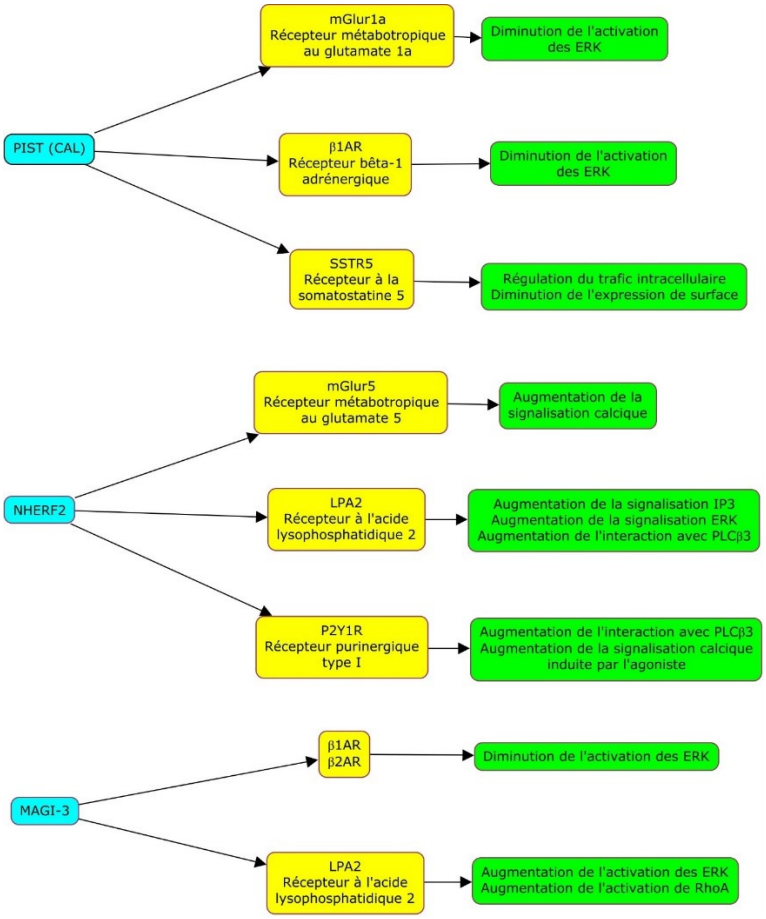


Figure 10 : Représentation schématique de plusieurs protéines échafauds à domaine PDZ influençant la signalisation des RCPG

Les protéines d'échafaudage sans domaine PDZ : lient la surface cytosolique des RCPG. Elles peuvent moduler l'activité de différentes kinases, phosphatases et d'autres récepteurs intracellulaires (Pavlos and Friedman 2017). Une liste non-exhaustive de ces différentes protéines d'échafaudage sans domaine PDZ ainsi que de leurs effets sur différents RCPG est présentée à la Figure 11.

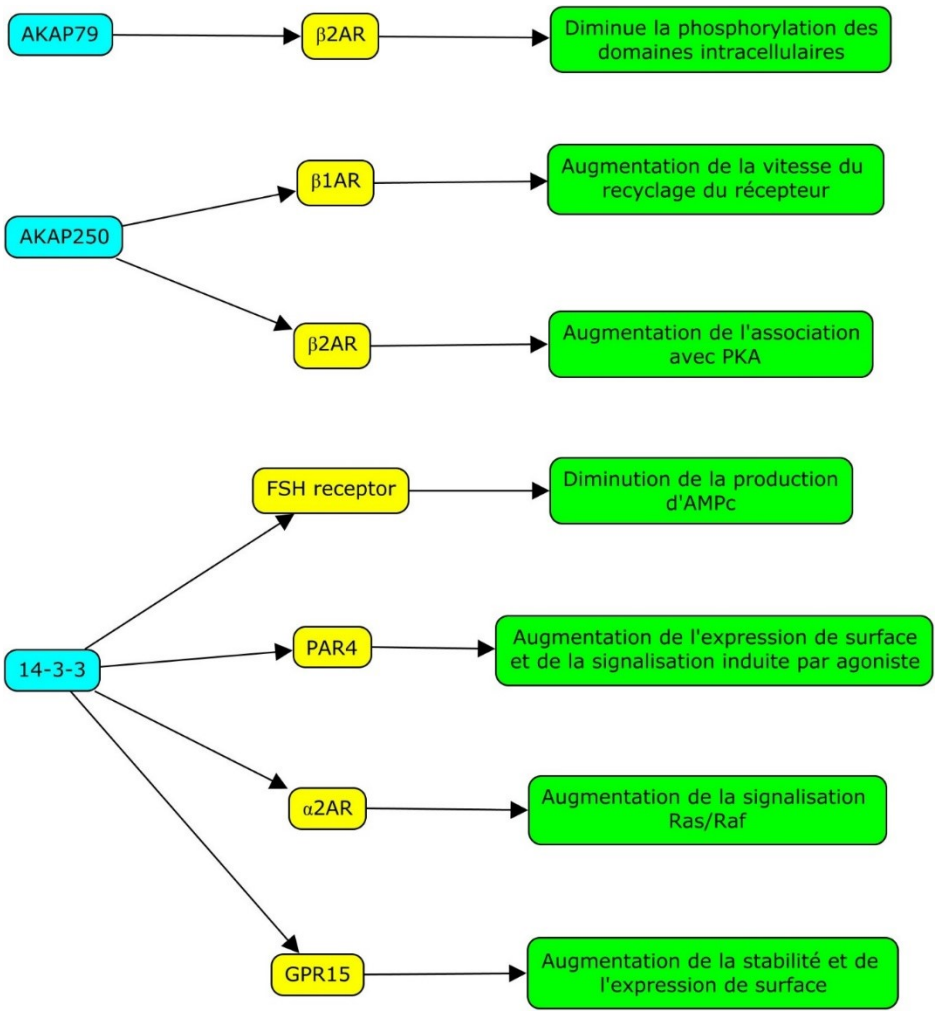


Figure 11 : Représentation schématique de plusieurs protéines échafauds sans domaine PDZ influençant la signalisation des RCPG

1.1.10 Signalisation biaisée

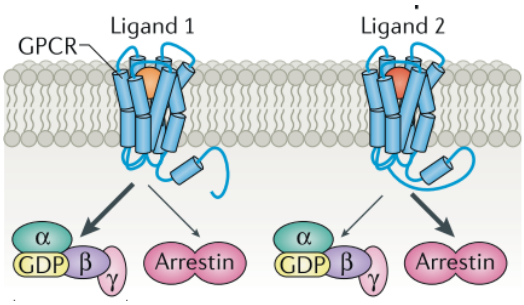
Comme nous venons de voir, les RCPG ont la capacité d'activer plusieurs voies de signalisation différentes selon le recrutement différentiel de différentes protéines d'échafaudages et d'autres partenaires. Or, l'activation de ces voies ne sont pas nécessairement modulées de manière

égales entre-elles et peuvent être activées avec différentes intensités (Wootten et al. 2018). Cette modulation différentielle des voies de signalisation peut dépendre de plusieurs facteurs :

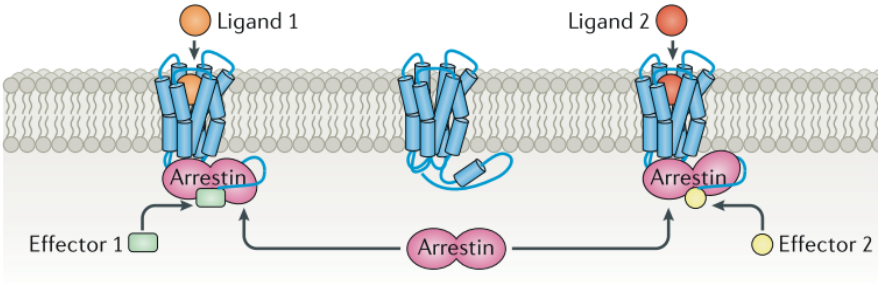
- La conformation du RCPG : Différents ligands peuvent entraîner des conformations tridimensionnelles distinctes du RCPG, pouvant ainsi favoriser ou défavoriser certaines voies de signalisation (Cahill et al. 2017).
- La conformation de la protéine d'échafaudage reliée au RCPG : Différentes localisations ou conjonctures cellulaires peuvent moduler de manière post-traductionnelle les protéines d'échafaudage responsables de l'assemblage de complexes de signalisation (Cahill et al. 2017). L'expression variable de ces partenaires protéiques selon le type cellulaire amène une source de variabilité de la signalisation pour un même ligand entre les différentes cellules de l'organisme.
- La conformation de la protéine G hétérotrimérique : Différents ligands peuvent entraîner différentes conformations tridimensionnelles de la protéine G hétérotrimérique, changeant ainsi l'efficacité de cette dernière à hydrolyser le GTP. La protéine G peut donc être active plus ou moins longtemps (Syrovatkina et al. 2016).

Un résumé des différents mécanismes pouvant entraîner une signalisation biaisée est illustrée à la figure 12.

A)



B)



C)

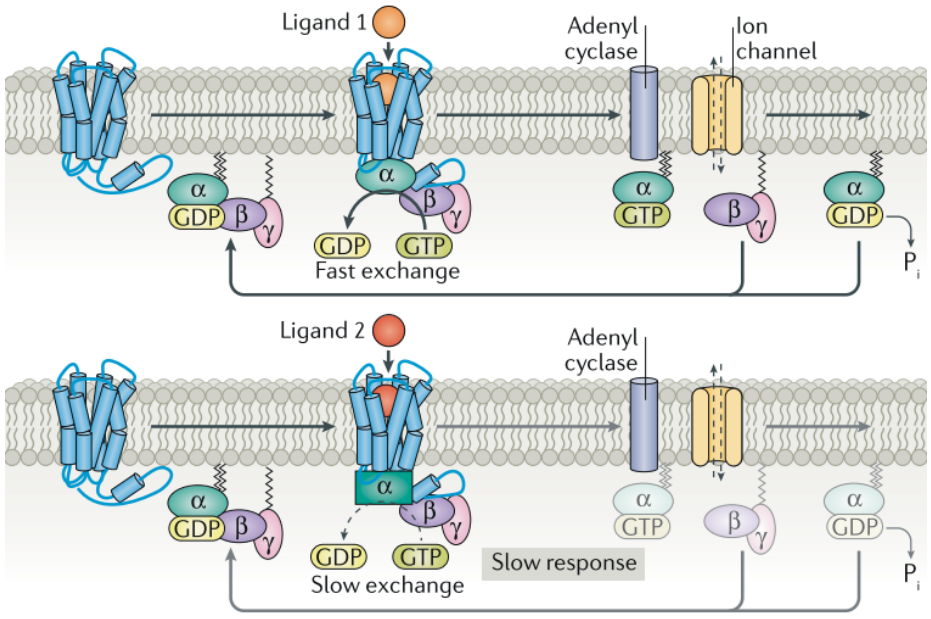


Figure 12 : Mécanismes de signalisation biaisé. A) Différents ligands peuvent entraîner un changement conformationnel différent chez le RCPG B) La conformation de la protéine

échafaud peut changer le signal en aval. C) Différents ligands peuvent entraîner un changement conformationnel différent chez la protéine G, favorisant ainsi une voie de signalisation en modulant son activité GTPasique.(Tiré et adapté de (Wootten et al. 2018))

1.1.11 Internalisation, recyclage ou dégradation des RCPG

Suite à leur désensibilisation, les RCPG phosphorylés sont internalisés grâce à un complexe de composantes moléculaires pouvant être composé de protéines d'échafaudage (*e.g.* arrestines), de protéines adaptatrices (*e.g.* Adaptor protein complex 2) ainsi que de leurs partenaires. Ces différents complexes peuvent alors promouvoir le bourgeonnement de vésicules d'internalisation de clathrine. Les vésicules ainsi formées sont par la suite dirigées vers un endosome précoce.

Une fois internalisés dans les endosomes précoces, les RCPG peuvent être envoyés à la dégradation lysosomale ou recyclés à la membrane plasmique. En ce qui concerne la dégradation, deux voies alternatives s'offrent aux RCPG : Une voie dépendante de l'ubiquitination et une voie indépendante de l'ubiquitination. Dans la voie dépendante, une protéine reconnaissant les molécules d'ubiquitine sur le récepteur grâce à un domaine UBD (Ubiquitine Binding Domain) va se lier au récepteur ubiquitiné et recruter les différentes protéines du complexe ESCRT. Ces dernières s'assembleront en corps multivésiculaires qui pourront ultimement fusionner aux lysosomes pour permettre la dégradation de son contenu (C. Dong et al. 2007).

Dans la voie indépendante de l'ubiquitine, ce sont les protéines du complexe GASP et la protéine SNX1 (Sorting Nexin 1) qui pourront directement transférer le RCPG aux corps multivésiculaires et à la dégradation lysosomale (Magalhaes et al. 2012).

Pour les récepteurs qui recycleront à la surface membranaire, plusieurs voies de recyclage sont possibles (Pavlos and Friedman 2017) et sont énumérées ci-dessous et résumés dans la figure 13.

- **Voie dépendante de ASRT (Actin-Sorting Nexin 27-Retromer Tubule) :** Les récepteurs ayant un domaine PDZ-ligand sont pris en charge par les protéines SNX27 (Sorting Nexin 27), le complexe du rétromère ainsi que le complexe WASH (Wiskott-Aldrich syndrome protein and SCAR homologue). SNX27 permet l'amarrage du RCPG au complexe, le rétromère permet la polymérisation de tubule aux endosomes précoces et

le complexe WASH favorise la polymérisation d'actine permettant le déplacement des vésicules d'endosome. La polymérisation d'actine est rendue possible grâce au recrutement de plusieurs protéines. La dynactine se lie au complexe WASH et permet de décoiffer le filament d'actine de ses protéines de protection terminales. L'actine décoiffée peut alors agir comme substrat du complexe protéique Arp2/3, qui allonge le filament d'actine et polymérise cette dernière. Le réseau d'actine ainsi créé favorise la fission de la vésicule endosomale et permet la création d'une force de traction, nécessaire pour le déplacement de l'endosome (Fokin and Gautreau 2021). Les vésicules empruntant cette voie sont Rab4 positives.

- **La voie indépendante de ASRT** est semblable à la voie précédente. Par contre, elle ne nécessite pas de liaison directe entre le RCPG et SNX27. La liaison entre le récepteur et le rétromère se fait via la création d'un complexe avec la protéine VPS26 (Vacuolar protein sorting-associated 26a). Cette voie de recyclage est moins bien caractérisée mais les vésicules l'empruntant sont également Rab4 positives.
- **La voie de recyclage lente** implique un transport rétrograde du RCPG par le rétromère jusqu'au TGN. Le RCPG est ensuite réacheminé à la membrane plasmique dans des vésicules Rab11 positives.

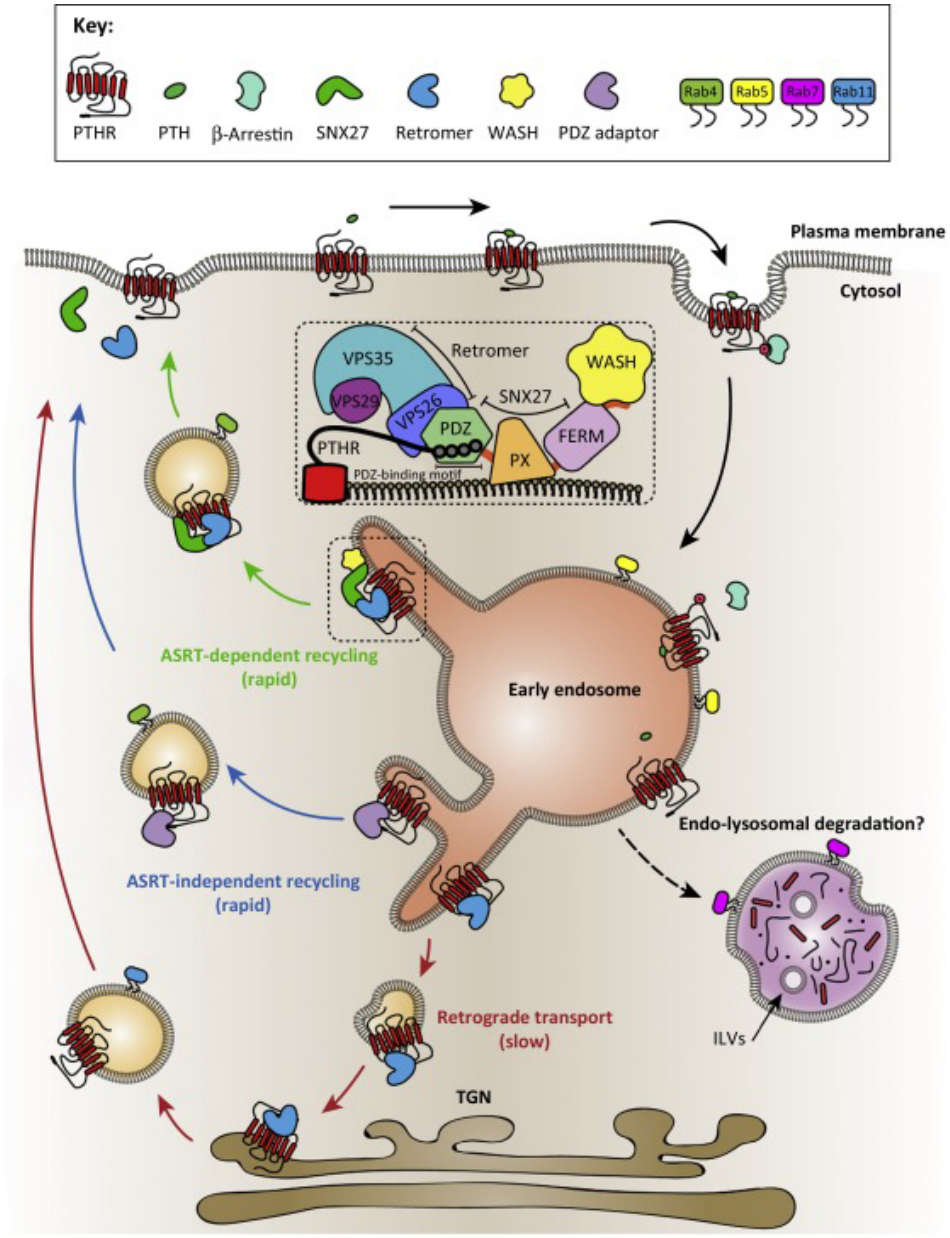


Figure 13 : Trafic des RCPG dans les compartiments endosomaux. (tiré de Pavlos et Friedman, 2016)

1.1.12 Les GTPases Rab

Tel que mentionné précédemment, la superfamille des petites protéines G comporte 5 familles de protéines, dont les GTPases Rab. Ces dernières, ainsi que les GTPases Raf, sont responsables du transport intracellulaire de plusieurs protéines. Elles jouent un rôle clé dans le transport de plusieurs types de vésicules, dont les vésicules d'endocytose, de dégradation ou de recyclage (Jean and Kiger 2012). Cette famille est composée d'environ 70 membres chez l'humain. Les

Rabs se différencient des autres familles par la présence de motifs conservés RAFS (Rab family motifs) qui sont importants pour la régulation de l'activité de ces protéines. Puisque les Rabs sont souvent exprimées de manière spécifique dans certains compartiments, elles sont souvent utilisées comme marqueurs pour différencier certains organites ou certaines vésicules (Pfeffer 2013). Les protéines Rab ont souvent des fonctions redondantes dans le cycle de vie des différents RCPG et il est ainsi possible de les classifier selon leurs effets sur ces derniers. Les Rab impliquées dans la voie biosynthétique des RCPG, pour le transport antérograde et rétrograde de ces derniers à travers les différents mécanismes de contrôle de qualité mentionnés plus haut sont principalement les protéines Rab1, Rab2, Rab6 et Rab8 (Wang, Wei, and Wu 2018). Au niveau des compartiments endosomaux, il est généralement possible de déterminer qu'un RCPG dans une vésicule Rab5-positive se trouve dans une vésicule d'endocytose (endosome précoce), qu'un RCPG dans une vésicule Rab7-positive est destinée aux endosomes tardifs et possiblement à un processus de dégradation. Finalement, un RCPG dans une vésicule Rab11 ou Rab4-positive se trouve dans une vésicule destinée au recyclage du récepteur à la surface membranaire (Pavlos and Friedman 2017). La figure 13 résume les différentes fonctions des Rab dans les compartiments endosomaux.

Comme la plupart des protéines de la superfamille des Ras, les Rab présentes au niveau des vésicules responsables du recyclage des RCPG ont des interacteurs permettant la modulation de l'activité GTPasique (GEF et GAP) et ces dernières permettent une régulation fine sur le trafic du récepteur. Bien que plusieurs de ces protéines régulatrices de GTPases aient été étudiées ces dernières années, plusieurs protéines Rab n'ont pas encore de partenaire ayant une activité GEF ou GAP connu. C'était notamment le cas de la protéine Rab4, qui juste qu'à tout récemment, n'avait pas de partenaire GEF connu. Une étude de notre laboratoire a cependant montré qu'une synthase de prostanoïde, la L-PGDS (Lipocalin-type prostaglandin D synthase), avait la capacité d'augmenter l'activité d'échange GDP-GTP de Rab4 et ainsi réguler le recyclage du récepteur DP1 (Binda et al. 2019). La caractérisation d'une protéine influençant l'activité GTPasique de la protéine Rab4 est particulièrement intéressante au point de vue physiologique, car cette petite GTPase est impliquée dans plusieurs phénomènes pathologiques tels que le potentiel invasif des cellules tumorales (Frittoli et al. 2014), la maladie d'Huntington (Gunawardena 2020) ainsi que la maladie d'Alzheimer (Zhang et al. 2018). La recherche de nouveaux mécanismes d'activation

et/ou d'inhibition de cette Rab GTPase est donc un sujet de recherche prometteur pour tenter de trouver de nouvelles cibles pharmacologiques dans ces diverses pathologies.

1.2 Récepteur à la prostaglandine D2 DP1

Les prostanoïdes sont des médiateurs lipidiques stimulants l'activation de multiples voies de signalisation cellulaires. Comme nous pouvons le voir à la figure 13, ces derniers sont dérivés de l'acide arachidonique et la production de cette dernière est l'étape limitante du processus de biosynthèse.

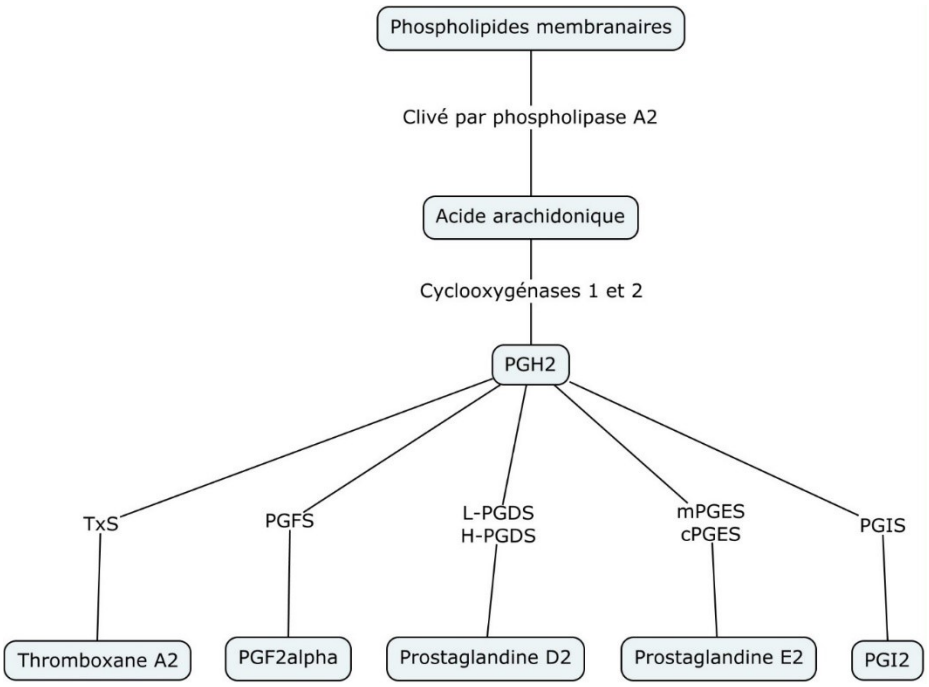


Figure 13 : Voies de synthèse des différents prostanoïdes

La première étape de la synthèse des prostanoïdes est le clivage de phospholipides membranaires par une phospholipase A2 en acide arachidonique. Par la suite, cette dernière peut être métabolisée par les cyclooxygénases 1 et 2 pour permettre la création de PGH2, qui est le précurseur commun des différents prostanoïdes (Korbecki et al. 2014). Par la suite, des isomérases spécifiques à chaque tissu et/ou type cellulaire pourront produire les différents produits finaux de cette voie de synthèse.

Le prostanoïde qui sera principalement discuté dans le cadre de cette thèse sera la prostaglandine D_2 (PGD_2). Ce dernier a deux récepteurs spécifiques, soit le récepteur DP1 (l'un des principaux sujets de cette thèse, voir figure 14) et le récepteur DP2, également appelé CRTH2 (Chemoattractant receptor-homologous molecule expressed on Th2 cells). Ce dernier est structurellement différent du récepteur DP1 et très peu d'acides aminés sont conservés entre les deux récepteurs.

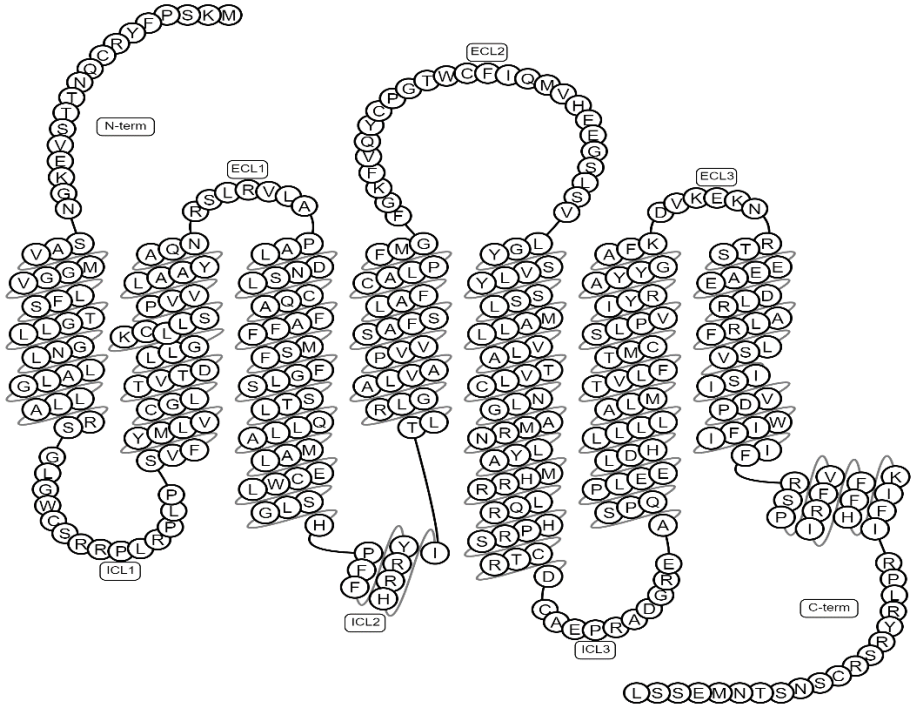


Figure 14 : Schéma de style serpent du récepteur DP1. Schéma tiré du site de GPCR database https://gpcrdb.org/ (Kooistra et al. 2021)

L'activation des récepteurs DP1 et DP2 n'ont pas les mêmes effets cellulaires. En effet, leurs cascades de signalisation cellulaires, leur localisation tissulaire ainsi que leurs effets physiologiques sont distincts (Gallant et al. 2007). Le récepteur DP2 comporte une homologie importante avec les récepteurs de la chimiotaxie tel que FPR (Formyl peptide receptor). Il est principalement exprimé dans les cellules du système immunitaire, telles que les basophiles, les monocytes, les éosinophiles ainsi que les lymphocytes T. Au niveau cellulaire, le récepteur DP2 est connu pour être couplé à une protéine $G_{\alpha i}$ lui permettant donc d'inhiber l'adénylate cyclase et de diminuer la production d'AMPc (Jandl and Heinemann 2017). Au niveau de la signalisation

des protéines $G_{\beta\gamma}$, le récepteur DP2 peut activer la phospholipase Cβ et ainsi augmenter localement la concentration de calcium intracellulaire. Cette augmentation de calcium est utile dans les cellules du système immunitaire afin de déclencher les phénomènes de dégranulation et de chimiotaxie (Sandig, Pease, and Sabroe 2007).

Le récepteur DP1 est moins caractérisé et est exprimé plus faiblement dans l'organisme que le récepteur DP2. Bien que son ligand naturel le plus puissant soit la PGD_2, il peut également être activé par d'autres prostanoïdes telles que la PGE_2 ou la PGF_{2a}, bien que ces derniers aient une affinité beaucoup plus faible que la PGD_2 (Boie et al. 1995). L'expression de DP1 dans l'organisme est limitée aux cellules immunitaires, à certaines cellules neuronales, à l'endothélium vasculaire, aux cellules osseuses ainsi qu'aux épithéliums respiratoires (bronchiques et nasaux principalement) et intestinaux (particulièrement au côlon) (Matsuoka and Narumiya 2007). DP1 est couplé à une protéine $G_{\alpha s}$ et est donc en mesure d'augmenter l'activité de l'adénylate cyclase ce qui permet l'activation de la protéine PKA permettant la phosphorylation de ses différents effecteurs (Maher et al. 2015). DP1 est également connu pour activer les voies de signalisation des MAPK (mitogen-activated protein kinases) et des ERK1/2 (Extracellular signal-related kinases).

Il est important de noter aussi que la PGD_2 est chimiquement instable dans des conditions physiologiques normales et est rapidement dégradée par des processus enzymatiques et non-enzymatiques. Des métabolites de la PGD_2, tel que la PGJ_2, la 13-14-dihydro-15-keto-PGD_2 ainsi que la 15-deoxy-$\Delta^{12\text{-}14}$-PGD_2 sont également connus pour activer certains récepteurs nucléaires, tels que les récepteurs de la famille des PPAR (Peroxisome Proliferator-Activated Receptors). L'activation des membres de cette famille de récepteur permet en général une réduction de la production de molécules pro-inflammatoires, telles que l'interleukine 1, le TNF_α (Tumor Necrosis Factor a) ainsi que l'IFN_γ (Interféron gamma) (Ricciotti and FitzGerald 2011).

1.2.1 Effets physiologiques et physiopathologiques de DP1

Au niveau physiologique, l'activation du récepteur DP1 a été caractérisée comme un acteur important dans les phénomènes de bronchoconstriction (Ricciotti and FitzGerald 2011), de régulation du cycle veille-sommeil (Qu et al. 2006), du rétablissement de la circulation sanguine

normale suite à un accident vasculaire cérébrale (Ahmad 2014), de la maturation des cellules de Sertolli (Moniot et al. 2009), d'inhibition de l'agrégation plaquettaire (Giles et al. 1989) ainsi que dans la résorption osseuse (Gallant et al. 2010).

Au niveau physiopathologique, l'activation du récepteur DP1 est impliquée dans plusieurs pathologies :

- **ASTHME :** Le récepteur DP1 contribue au maintien de l'inflammation en permettant la survie des cellules immunitaires impliquées (Peinhaupt et al. 2018). Deux polymorphismes dans la région promotrice du gène *PTGDR* (Gène codant pour la protéine DP1) ont été associés à une augmentation des probabilités de souffrir de symptômes asthmatiques (Isidoro-García et al. 2011).
- **ARTHRITE RHUMATOÏDE :** La PGD_2, via son action sur le récepteur DP1, est connu pour son action protectrice contre l'inflammation dans les articulations de modèles murins d'arthrite. L'effet de la signalisation de DP1 dans les ostéoblastes et les chondrocytes du tissu cartilagineux par l'augmentation de l'AMP cyclique vient contrecarrer la signalisation induite par la cytokine inflammatoire interleukine-1b, permettant ainsi l'inhibition de la formation des métalloprotéinases matricielles 1 et 13, connues pour leurs effets délétères sur la matrice extracellulaire entourant les os et les articulations (Zayed et al. 2008).
- **INFLAMMATION :** Une étude portant sur des tissus de patients humains étant/ayant été atteints de colite ulcéreuse (maladie inflammatoire du côlon/rectum) démontre que les patients en rémission, contrairement aux patients en phase aigue ou aux patients contrôles, ont une élévation marquée de prostaglandine D_2 dans leurs tissus intestinaux (Vong et al. 2010). Ce groupe a également une élévation de niveau d'expression du récepteur DP1 (mais non DP2), tout en ayant des niveaux normaux et égaux de COX-1, COX-2 et de H-PGDS. Ces études suggèrent donc un potentiel anti-inflammatoire de DP1 dans certaines conditions pathologiques.
- **CANCERS :** Une étude portant sur des souris KO pour le gène DP1 et transgènes pour APC min/+ (une mutation dans le gène APC favorisant l'apparition de cancers intestinaux) a démontré que ces souris avaient de 30% à 40% fois plus de tumeurs du système digestif que les souris WT (Tippin et al. 2014). La même étude a également démontré que les souris surexprimant le gène HPGDS (Hematapoietic prostaglandin D synthase,

une des deux enzymes produisant la PGD_2) diminue le nombre d'adénomes de 63%. Ces mêmes souris ayant le transgène HPGDS exprime également moins d'ARNm du proto-oncogène c-myc (Tippin et al. 2014). De plus, la suppression de DP1 augmente la progression tumorale et l'expansion vasculaire dans un modèle de xénogreffe chez la souris. Le traitement des souris par un agoniste sélectif à DP1(BW245C) diminue la croissance tumorale, mais est demeuré sans effet sur des souris DP1 -/- (Murata et al. 2008).

1.2.2 Trafic du récepteur DP1

Bien que le récepteur DP1 ne soit pas très bien caractérisé dans la littérature scientifique, certaines informations sur le trafic intracellulaire de ce dernier ont été découvertes au cours des dernières années. Cette section se veut un résumé des connaissances précédemment acquises sur ce sujet.

Au niveau de la voie biosynthétique, peu de choses sont connues pour le récepteur DP1, mis à part que la chaperonne Ankrd13c régule son export et sa biosynthèse au niveau du RE (Parent et al. 2010a) et que la chaperonne Hsp90, en concomitance avec la L-PGDS, sont impliquées dans l'export du récepteur à la membrane plasmique (Binda et al. 2014). Au niveau de la membrane plasmique, le récepteur DP1 subit une internalisation dépendante de la dynamine. D'ailleurs, à l'aide d'expériences impliquant un mutant dominant-négatif de la dynamine (K44A), notre laboratoire a démontré que le récepteur DP1, contrairement au récepteur DP2, ne subissait pas d'internalisation constitutive (Gallant et al. 2007). Concernant la désensibilisation du RCPG à la membrane, c'est principalement l'isoforme GRK2 qui phosphoryle les résidus sérines et thréonines des boucles intracellulaires et de la queue C-terminale du récepteur DP1 (Roy et al. 2010). Par la suite, l'internalisation du récepteur est dépendante de l'arrestine 2 et de l'arrestine 3 (Gallant et al. 2007). Le recyclage du récepteur s'effectue ensuite dans des vésicules Rab4 positives (Gallant et al. 2007). Il est pertinent de noter que la L-PGDS joue un rôle dans l'activation de cette dernière et module également le recyclage du récepteur (Binda et al. 2019).

1.3. La protéine GGA3

La famille des protéines GGA (Golgi-localized, Gamma adaptin ear-containing, Arf-Binding) comporte trois membres, soit GGA1, GGA2 et GGA3. Ce sont des protéines adaptatrices ubiquitaires dans l'organisme et ont comme fonction d'être des adapteurs monomériques entre les molécules de clathrine et certains cargos. Au niveau de sa localisation cellulaire, elle est présente au niveau du cytosol ainsi qu'à la surface de plusieurs endomembranes, tels que les endosomes de transport, les vésicules de recyclage ainsi qu'à l'appareil de Golgi et au réticulum endoplasmique. Elles sont donc des protéines essentielles à la création de vésicules de transport intracellulaire et elles font partie intégrante du manteau protéique de ces dernières (Bonnemaison, Eipper, and Mains 2013). La première fonction attribuée à ces protéines lorsqu'elles ont été découvertes a été d'effectuer le transport de diverses protéines du TGN jusqu'aux compartiments endosomaux et lysosomaux (Dell'Angelica et al. 2000). Bien que les trois GGA aient une bonne homologie de séquence, il a été découvert que les trois protéines, bien qu'ayant un rôle commun de transport, ont des différences notables dans leurs différents domaines de liaison à l'ubiquitine, leurs mécanismes d'auto-inhibition ainsi que leurs méthodes d'incorporation différentes dans les vésicules de clathrine (Nakayama and Wakatsuki 2003).

1.3.1 Structure

Les GGA ont une similarité de structure dans les différents domaines protéiques qui lui servent à accomplir leurs fonctions. Voici un bref aperçu de ces quatre domaines :

- **DOMAINE VHS (VPS27, Hrs, Stam domain) :** Reconnaît les séquences de type AC-LL (DXXLL) dans les domaines cytoplasmiques des protéines cargo (Kato et al. 2002).
- **DOMAINE GAT (GGA and TOM1 domain):** Interagit avec le phosphatidylinositol 4-phopshate (PI4P) et peut interagir avec une protéine Arf active (liée au GTP). C'est donc ce domaine qui permet à la protéine GGA d'être recrutée à une membrane. Pour GGA1 et GGA3, ce domaine permet également de reconnaître les molécules d'ubiquitine (Rosa Puertollano et al. 2001).
- **DOMAINE CHARNIÈRE:** Région désorganisé (sans structures secondaires ou tertiaires) permettant le recrutement des molécules de clathrine. C'est donc cette région qui permet l'assemblage du manteau de clathrine des vésicules (Dell'Angelica et al. 2000).

- **DOMAINE GAE (Gamma adaptin-Ear):** Permet l'ancrage de plusieurs molécules / protéines accessoires nécessaires au transport du cargo (Rosa Puertollano et al. 2001).

Une représentation visuelle générique des différents domaines des protéines GGA est présentée à la figure 15. Considérant que la protéine d'intérêt de la famille des GGA pour cette thèse est GGA3, nous nous attarderons sur cette dernière dans la prochaine section.

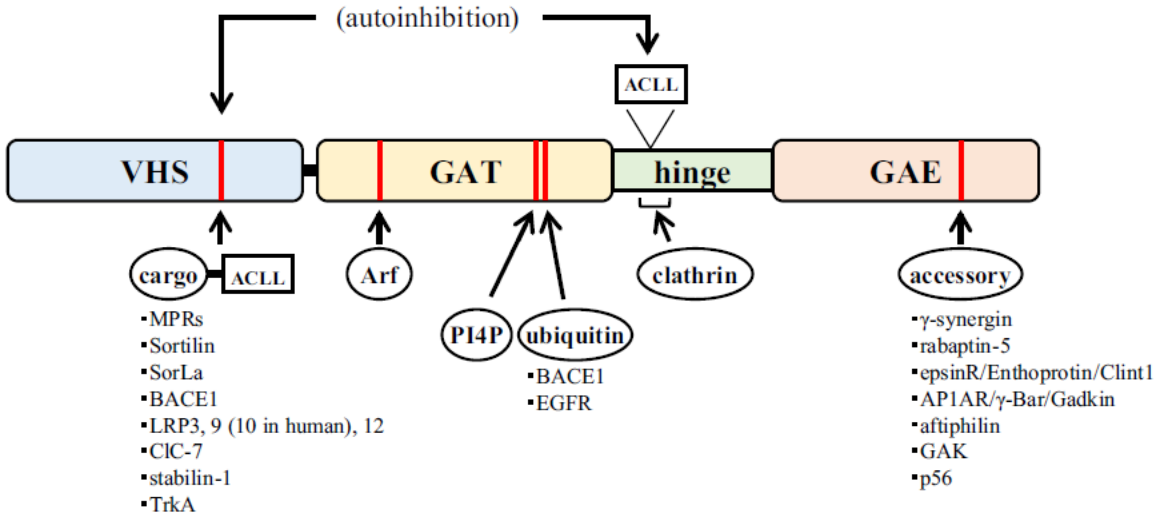


Figure 15 : Domaines caractérisées des protéines GGA. Les différents domaines connus des protéines GGA sont présentés. Plusieurs partenaires d'interaction connus ainsi que les domaines des protéines GGA permettant l'interaction sont également précisés. (tiré et adapté de (Uemura and Waguri 2020))

1.3.2 Fonctions connues de GGA3

Plusieurs interactions avec des protéines cargo différentes ont été caractérisées et ce, dans plusieurs voies de trafic intracellulaire, soulignant des rôles multiples de GGA3 dans le trafic de protéines. En effet, cette dernière a été caractérisée comme modulant le recyclage ainsi que la signalisation de trois récepteurs tyrosine kinase, soit RET51 (Crupi et al. 2019), TrkA (Xuezhi Li, Lavigne, and Lavoie 2015) et Met (Parachoniak et al. 2011). Dans le cas du récepteur Met, il est intéressant de constater que l'action de GGA3 sur le recyclage du récepteur est dépendante de la GTPase Arf6 et que le recyclage s'effectue via des vésicules Rab4 positives. GGA3 a également été démontré comme facteur important dans le recyclage de la β-intégrine, facteur cruciale dans la migration, la prolifération et la survie cellulaire (Ratcliffe et al. 2016). Kang et ses collègues ont également montré que GGA3 pouvait moduler différentiellement le trafic de la protéine BACE1, dans un premier temps en favorisant le trafic rétrograde des endosomes vers le TGN et

dans un deuxième temps en permettant le triage vers les lysosomes lorsque BACE1 est ubiquitinilé (Kang et al. 2010). Ces observations soulignent ainsi la capacité de GGA3 à reconnaître des modifications post-traductionnelles et à moduler le triage des protéines en conséquence (Kang et al. 2010). Dans un contexte de trafic antérograde, GGA3 peut promouvoir un transport du TGN vers la membrane plasmique du récepteur adrénergique-alpha2B (AR-a2b) (Maoxiang Zhang et al. 2016a).

1.4. Les protéines IQGAP

La famille des protéines d'échafaudage IQGAP (IQ motif containing GTPase Activating Protein) est composé de trois membres (IQGAP1, IQGAP2, IQGAP3) ayant une masse moléculaire moyenne d'environ 190 kDa. L'isoforme la mieux caractérisé est IQGAP1 et constitue la seule isoforme ubiquitaire de cette famille (Malarkannan et al. 2012). Ces protéines comportent de multiples domaines et ont de nombreux interacteurs protéiques caractérisés dans la littérature scientifique (Hedman, Smith, and Sacks 2015; Samson et al. 2017; Jessica M Smith, Hedman, and Sacks 2015). Ce sont des protéines dont la localisation intracellulaire est très diversifiée. Elles peuvent se retrouver au cytosol, dans le compartiment nucléaire, à la surface des endosomes ainsi qu'à la surface de plusieurs membranes biologiques (Jessica M. Smith, Hedman, and Sacks 2015) . Cette section se concentrera principalement sur IQGAP1 étant donné qu'elle est la mieux connue, mais les deux autres isoformes seront brièvement abordés.

1.4.1 Structure

Les trois isoformes contiennent plusieurs domaines permettant les nombreuses fonctions associées à cette famille de protéine. Les fonctions des six principaux domaines sont décrites ci-dessous et résumés à la figure 16 :

DOMAINE CHD (Calponin Homology Domain): Domaine permettant la liaison à la F-actine, à la calmoduline ainsi qu'aux ions Ca^{2+}(Trenton et al. 2020)

DOMAINE CC (Coiled-Coiled) : Répétition de résidus hydrophobes et de résidus chargés. Permet la liaison à l'ezrine, une protéine permettant la liaison entre la membrane plasmique et le cytosquelette (Abel et al. 2015).

DOMAINE IQ : Permet la liaison à divers interacteurs protéiques. Permet également la formation de dimères ou d'oligomères de IQGAP (Wu et Chen 2014).

DOMAINE WW : Domaine riche en tryptophanes liant normalement les régions riches en prolines, mais de manière intéressante, le domaine WW de IQGAP lie des régions n'ayant pas ou peu de prolines (Jessica M Smith et al. 2015).

DOMAINE GRD (GAP-related Domain): Malgré une grande similitude avec les domaines GAP, l'absence d'un résidu arginine dans la pochette catalytique permet la stabilisation des petites protéines G dans une conformation active (LeCour et al. 2016).

DOMAINE RGCT (Ras-GAP_C terminus) : Domaine unique aux IQGAP qui permet de lier plusieurs protéines partenaires (Jessica M Smith et al. 2015).

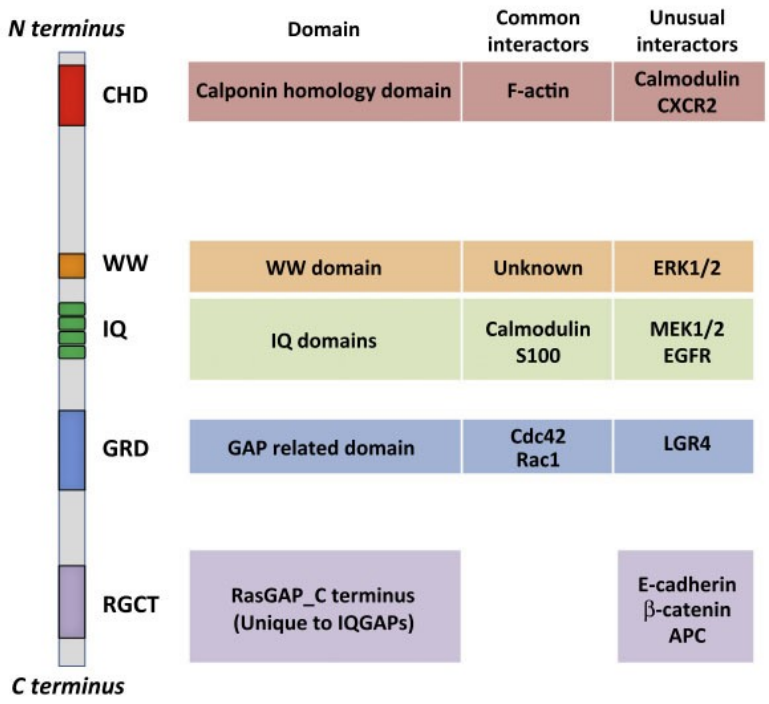


Figure 16 : Domaines caractérisées des protéines IQGAP .Tiré de (Jessica M Smith et al. 2015)

1.4.2 Fonctions de IQGAP1

La multiplicité des domaines d'interactions de IQGAP1 permet à cette dernière d'être impliquée dans de multiples processus cellulaires, tels que la régulation de la migration cellulaire, la régulation de l'actine et du cytosquelette, la régulation de l'endocytose, la régulation de la signalisation cellulaire, la régulation et la stabilité des ARN messagers ainsi que la création de signalosome (Hedman et al. 2015; Jessica M Smith et al. 2015). Concernant la migration cellulaire, IQGAP1 régule la création et le maintien des points focaux permettant aux intégrines de s'ancrer au cytosquelette lors de leur contact avec la matrice extracellulaire. Elle augmente la stabilité des cadhérines à la surface membranaire, permettant un meilleur ancrage cellule-cellule. Elle régule la dynamique du cytosquelette sous la membrane plasmique en régulant les filaments de filamin A et permettant la polymérisation de ces derniers. De manière semblable, elle permet la polymérisation de microtubule sous la membrane plasmique en régulant la protéine AKAP220, favorisant ainsi la migration cellulaire (Logue et al. 2011). Au niveau de la régulation du cytosquelette, son domaine CH lui confère la capacité de promouvoir la polymérisation d'actine et d'interagir avec diverses autres protéines régulatrices de la polymérisation (Cdc42, Rac1, APC) (Brandt and Grosse 2007). Un bon exemple du rôle de IQGAP1 dans le processus d'endocytose est observable dans les cellules sécrétrices bêta du pancréas. Dans ce type cellulaire, le recyclage de la membrane plasmique aux vésicules d'exocytose doit se faire rondement afin de permettre le rapatriement des composantes membranaires et ainsi favoriser une sécrétion efficace de l'insuline. Cette membrane sécrétrice d'insuline est internalisée grâce à un complexe IQGAP1-Rab27-Cdc42-Coronin-3 dans ces cellules (Yamaoka 2015). IQGAP1 est de plus nécessaire à l'endocytose des cadhérines dans plusieurs types cellulaires (Noritake et al. 2005). IQGAP1 est également en mesure de moduler, d'intégrer et d'amplifier plusieurs voies de signalisations dépendantes de récepteurs de surface. Elle peut amplifier la signalisation des récepteurs tyrosine kinase. Par exemple, IQGAP1 augmente la signalisation des MAPK et de AKT suite à l'activation de EGFR (Chen et al. 2019). IQGAP1 peut également moduler et amplifier la signalisation des RCPG en complexe avec les arrestines (C. D. White, Erdemir, and Sacks 2012). Elle augmente aussi la signalisation de Wnt en stabilisant la bêta-caténine et augmentant ainsi sa concentration cytoplasmique et nucléaire (Goto et al. 2013a). Au niveau de la membrane nucléaire, il a également été rapporté que IQGAP1 forme un complexe avec la protéine Dvl, l'importine bêta 5 ainsi que la bêta-caténine

afin de favoriser son transport vers le noyau et ainsi permettre son action sur des facteurs de transcription pro-oncogènes (Goto et al. 2013b). Au niveau des ARN messagers, IQGAP1 interagit avec les protéines de liaison à l'ARNm et diminue la dégradation de ces derniers (Jessica M Smith et al. 2015). Finalement, IQGAP1 permet la liaison de multiples substrats d'une cascade de signalisation et augmente l'efficacité de la transmission signalétique (Hedman et al. 2015). En effet, comme nous pouvons le voir à la figure 17, IQGAP1 sert d'échafaudage afin de permettre le rapprochement des divers effecteurs de la voie MAPK.

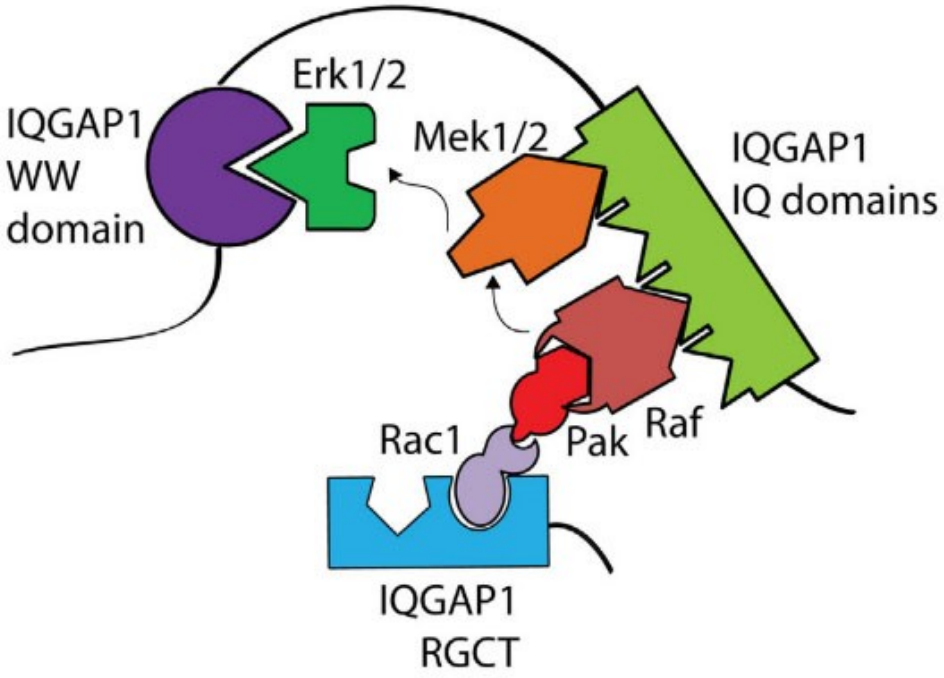


Figure 17 : IQGAP1 est une protéine échafaud pour la signalisation ERK (Tiré et adapté de (Abel et al. 2015))

L'implication de IQGAP1 dans les différentes voies de signalisation cellulaire en font une cible de choix pour les cellules tumorales en devenir. En effet, il existe une forte corrélation entre le niveau d'expression de IQGAP1 et le grade de plusieurs cancers (White, Brown, and Sacks 2009; Zoheir et al. 2016). La capacité de IQGAP1 à amplifier les voies de signalisation liées à la survie cellulaire, la prolifération ainsi que la migration cellulaire peut devenir délétère lorsque cette dernière est présente en trop grande quantité dans la cellule. En effet, les mêmes rôles exercés

par IQGAP1 en situation physiologique lorsqu'elle est exprimée normalement peuvent devenir néfastes lorsque cette dernière est surexprimée dans un contexte tumoral.

Au niveau de la signalisation des MAPK par exemple, la capacité de IQGAP1 d'amplifier la cascade de signalisation est problématique car une augmentation globale de la signalisation ERK est reliée à une progression tumorale dans plusieurs types de cancers. De plus, l'hypothèse a été émise que IQGAP1 active préférentiellement la voie MEK1, qui est une voie promouvant la prolifération plutôt que la différentiation cellulaire, qui serait plutôt entraînée par une activation préférentielle de MEK2 (Jameson et al. 2013).

Concernant l'implication de IQGAP1 dans la voie de signalisation Wnt, la surexpression de IQGAP1 entraîne une forte augmentation de la concentration cytosolique de bêta-caténine, permettant à cette dernière de transloquer de manière importante au compartiment nucléaire et de moduler de manière exagérée la transcription induite par le facteur TCF-LEF, entraînant la sur-transcription de facteurs proto-oncogènes (Goto et al. 2013b). Cette voie de signalisation est d'ailleurs mutée dans plus de 95% des cancers colorectaux (Zhan, Rindtorff, and Boutros 2017).

Au niveau des jonctions cellulaires, la capacité de IQGAP1 de lier les E-cadhérines devient délétère lorsque surexprimée car elle entraîne la formation d'aggrégats IQGAP1-cadhérine. Ces aggrégats nuisent à la fonction physiologique des cadhérines à la membrane plasmique, entraînant une diminution de l'adhésion cellule-cellule et permettant aux cellules tumorales d'envahir les tissus environnants (Hayashi et al. 2010).

Au niveau de l'exocytose, IQGAP1 interagit avec plusieurs des composantes de l'exocyste, la structure permettant l'exocytose, et a été démontrée nécessaire pour la formation d'invadopodes et le relâchement des métalloprotéinases nécessaires à dégradation de la matrice extracellulaire dans des cellules MDA-MB-231 (Sakurai-Yageta et al. 2008).

1.4.3 IQGAP2

IQGAP2 est exprimée principalement dans le foie, la prostate et l'estomac. Il a été constaté que dans certains cancers hépatiques, l'expression de IQGAP2 est considérablement diminuée alors que l'expression de IQGAP1 est augmentée (White et al. 2010). De manière intéressante, des

expériences sur des souris KO pour les gènes codants pour IQGAP1 ou IQGAP2 ont démontré que les souris KO pour IQGAP2 développait un carcinome hépatique, mais que les souris double KO pour IQGAP1 et IQGAP2 présentaient un phénotype normal, suggérant que IQGAP2 est un suppresseur de tumeur et qu'IQGAP1 est un proto-oncogène (Schmidt et al. 2008).

1.4.4 IQGAP3

IQGAP3 est le membre de la famille des IQGAP le moins étudié. Il a cependant été constaté qu'au même titre qu'IQGAP1, l'expression de IQGAP3 stimule la migration, l'invasion et la prolifération de certains types de cellules cancéreuses. Tout comme IQGAP1, IQGAP3 est également considéré comme un proto-oncogène (Nojima et al. 2008; Yang et al. 2014).

2. Problématique, hypothèses et objectifs

2.1 Problématique, hypothèse et objectifs généraux

Le récepteur à la prostaglandine D_2 DP1 est un RCPG ayant une localisation membranaire et intracellulaire. L'interactome de ce récepteur est très peu connu, tout comme les facteurs moléculaires déterminant sa localisation. Les processus dirigeant son routage suite à son activation sont tout aussi peu connus. Considérant l'important rôle de DP1 dans plusieurs phénomènes physiologiques et pathophysiologiques, il est pertinent de trouver de nouvelles informations sur ses partenaires d'interaction, son trafic et sa signalisation. Il a déjà été établi dans notre laboratoire que la synthase responsable de la synthèse de la PGD_2, la L-PGDS, contribuait de manière importante au trafic du récepteur à l'état basal et lors d'une stimulation par un agoniste (Binda et al. 2014, 2019). Il a également été déterminé que le recyclage du récepteur était dépendant de la protéine Rab4 (Gallant et al. 2007) et que cette dernière était nécessaire à l'effet de la L-PGDS sur le recyclage du récepteur DP1 (Binda et al. 2019).

Nous émettons donc l'hypothèse que certaines protéines adaptatrices ou d'échafaudage caractérisées dans la littérature comme influençant la localisation ou la fonctionnalité de récepteurs membranaires pourraient également être impliquées dans le transport et la signalisation du récepteur DP1.

L'objectif principal de cette étude sera d'une part d'identifier de nouveaux partenaires moléculaires du récepteur DP1 et d'autre part de déterminer si ces dernières ont un rôle dans le trafic ainsi que la signalisation de ce récepteur.

2.2 – Hypothèse et objectifs de l'article 1

Considérant que Rab4 a déjà été caractérisée comme pouvant réguler le recyclage d'un récepteur tyrosine kinase (récepteur Met) via un processus GGA3-dépendant (Parachoniak et al. 2011), nous avons émis l'hypothèse que le récepteur DP1 pouvait emprunter un processus semblable lors de la régulation de son trafic intracellulaire post-stimulation.

Les objectifs de cet article sont multiples :

- Vérifier s'il existe une interaction entre le récepteur DP1 et la protéine GGA3.
- Caractériser l'effet de cette protéine adaptatrice sur l'internalisation et le recyclage du récepteur.
- Déterminer si le processus requiert les autres facteurs moléculaires déjà connus pour influencer le recyclage de DP1, c'est-à-dire Rab4 et la L-PGDS
- Caractériser l'effet de GGA3 sur la signalisation de DP1

2.3 – Hypothèse et objectifs de l'article 2

L'interactome du récepteur DP1 étant très peu connu, nous avons émis l'hypothèse que ce dernier avait de multiples partenaires d'interaction inconnus répartis dans plus sous-localisation cellulaires puisque ce dernier a une forte présence intracellulaire. Plusieurs objectifs ont alors été proposés :

- Établir une liste de partenaire d'interactions potentiels dans les cellules HEK 293 à l'aide d'une technique de IP LC-MS/MS
- Déterminer la sous-localisation cellulaire de ces partenaires d'interaction ainsi que leurs fonctions générales
- Trouver un partenaire d'interaction d'intérêt et valider son importance dans le trafic et/ou la signalisation du récepteur DP1.

ARTICLE 1 : GGA3 interacts with L-type prostaglandin D synthase and regulates the recycling and signaling of the DP1 receptor for prostaglandin D_2 in a Rab4-dependent mechanism

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AVANT-PROPOS : Cet article a été écrit en totalité par Louis Fréchette sous la supervision du professeur Jean-Luc Parent (Directeur de recherche). La conception des expériences de même que la réalisation de celles-ci ont été faite en majorité par Louis Fréchette. Quelques expériences de microscopie ont été réalisé par Samuel Génier. Quelques expériences de GST-PULLDOWN, d'activation de ERK et d'immunoprécipitation ont été réalisés par Chantal Binda. Jade Degrandmaison a effectué une expérience de GST-PULLDOWN et Marilou Boisvert a réalisé des clonages.

RÉSUMÉ

Les mécanismes contrôlant le recyclage des récepteurs couplés aux protéines G (RCPG) restent encore largement à être élucidés. Nous rapportons que la protéine GGA3 (Golgi-associated, γ adaptin ear containing, ADP-ribosylation factor-binding protein 3) régule le recyclage et la signalisation du récepteur à la prostaglandine D2 DP1 avec un nouveau mécanisme. Une interaction entre DP1 et GGA3 a été détectée par co-immunoprécipitation dans des cellules HeLa. L'interaction et augmentée lorsque le récepteur est stimulé, un fait qui est supporté par l'augmentation de la colocalisation du récepteur avec GGA3 en microscopie confocale. Les expériences de pulldown ont démontré que GGA3 interagissait avec la boucle intracellulaire 2 et la queue C-terminale de DP1, tandis que le récepteur interagit avec le domaine VHS de GGA3. Le mutant incapable de lier les protéines Arfs GGA3 N194A a le même effet sur le trafic du récepteur que GGA3 sauvage, impliquant qu'un nouveau mécanisme d'action de GGA3 dans le recyclage a été identifié. La diminution par ARN interférent de Rab4 inhibe l'effet de GGA3 sur DP1, révélant ainsi un mécanisme Rab4-dépendant dans le recyclage. De manière intéressante, la L-PGDS (L-type prostaglandin synthase, l'enzyme produisant l'agoniste de DP1) diminue l'habileté de GGA3 à médier le recyclage de DP1, tandis que la diminution de GGA3 par ARN interférent empêche la L-PGDS de favoriser le recyclage de DP1, indiquant ainsi un mécanisme interdépendant des deux protéines. Une nouvelle interaction a été observée par co-immunoprécipitation dans les cellules HeLa entre L-PGDS et GGA3 ainsi qu'en protéines recombinantes purifiées *in vitro*. La redistribution de L-PGDS dans des vésicules GGA3 et Rab4-positives a été induite par la stimulation de DP1. La diminution de GGA3 par ARN interférent a inhibé la signalisation ERK induite par le récepteur. Nos données suggèrent donc une nouvelle fonction pour GGA3 ainsi qu'une nouvelle interaction avec la L-PGDS qui permet de réguler le recyclage et la signalisation d'un RCPG, DP1.

SUMMARY

Mechanisms controlling the recycling of G protein-coupled receptors (GPCRs) remain largely unclear. We report that GGA3 (Golgi-associated, γ adaptin ear containing, ADP-ribosylation factor-binding protein 3) regulates the recycling and signaling of the PGD_2 receptor DP1 through

a new mechanism. An endogenous interaction between DP1 and GGA3 was detected by co-immunoprecipitation in HeLa cells. The interaction was promoted by DP1 agonist stimulation, which was supported by increased DP1-GGA3 co-localization in confocal microscopy. Pulldown assays showed that GGA3 interacts with the intracellular loop 2 and C-terminus of DP1, whereas the receptor interacts with the VHS domain of GGA3. The Arf-binding deficient GGA3 N194A mutant had the same effect as wild-type GGA3 on DP1 trafficking, suggesting a new mechanism for GGA3 in recycling. Depletion of Rab4 inhibited the GGA3 effect on DP1 recycling, revealing a Rab4-dependent mechanism. Interestingly, depletion of L-PGDS (L-type prostaglandin synthase, the enzyme that produces the agonist for DP1) impaired the ability of GGA3 to mediate DP1 recycling, while GGA3 knockdown prevented L-PGDS from promoting DP1 recycling, indicating that both proteins function interdependently. A novel interaction was observed between co-immunoprecipitated endogenous L-PGDS and GGA3 proteins in HeLa cells, and *in vitro* using purified recombinant proteins. Redistribution of L-PGDS towards GGA3- and Rab4-positive vesicles was induced by DP1 activation. Silencing of GGA3 inhibited ERK1/2 activation following DP1 stimulation. Altogether, our data reveal a novel function for GGA3, in a newly described association with L-PGDS, in the recycling and signaling of a GPCR, namely DP1.

Keywords: DP1, GPCR, GGA3, L-PGDS, Rab4, recycling.

1. Introduction

Prostaglandin D_2 (PGD_2) is a bioactive lipid mediator(Ricciotti and FitzGerald 2011) implicated in a multitude of physiological processes such as sleep/wake regulation(Ahmad et al. 2019; Qu et al. 2006), sex differentiation in embryogenesis(Moniot et al. 2009), bone formation(Gallant et al. 2004, 2010), pain(Eguchi et al. 1999; Ito, Okuda-Ashitaka, and Minami 2001) and bronchoconstriction(Johnston et al. 1995; Murata et al. 2013). It is also involved in a number of pathological conditions, such as asthma(Hammad et al. 2007b; Oguma et al. 2004), atherosclerosis(Linton and Fazio 2008; Song et al. 2018), Parkinson's disease(Choi et al. 2019; Corwin et al. 2018) and major depressive disorders(Chu et al. 2017; Onaka et al. 2015). PGD_2, as all prostanoids, is initially generated from arachidonic acid from membrane phospholipids by phospholipase A_2. Arachidonic acid is then converted to PGG_2 and PGH_2 by

cyclooxygenases(Harizi, Corcuff, and Gualde 2008). The final isomerization of PGH_2 to PGD_2 is catalyzed by two tissue-specific prostaglandin D synthases (PGDS), namely the Hematopoietic PGDS (H-PGDS) and Lipocalin-type PGDS (L-PGDS) (Kanaoka and Urade 2003). Although sharing functional similarity, H-PGDS and L-PGDS differ vastly in their tertiary structure, cellular sub-localization, tissue distribution and non-enzymatic biological activity(Urade and Eguchi 2002). For instance, belonging to the lipocalin family, L-PGDS also partakes in the transport of lipophilic molecules such as bilirubin(Beuckmann et al. 1999), gangliosides(Mohri et al. 2006) and retinoic acid(Tanaka et al. 1997).

PGD_2 activates two different types of G protein-coupled receptors (GPCRs), the D prostanoid receptor (DP1) and the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2, also known as DP2). Belonging to the family of prostanoid receptors(Boie et al. 1995), DP1 is coupled to $G\alpha_s$ and its activation by PGD_2 leads to an increase in cAMP production. On the other hand, CRTH2 is a member of the chemoattractant receptor family coupled to $G\alpha_{i/o}$ proteins, displaying higher sequence homology to the fMLP and C5a receptors than to the prostanoid receptor family(Hirai et al. 2001).

GPCRs form the largest family of transmembrane proteins. They respond to a plethora of stimuli, including lipids, hormones, peptides, neurotransmitters, light, and odorants, to induce various physiological responses(Benleulmi-Chaachoua, Wojciech, and Jockers 2013). They are characterized by a common molecular topology composed of a hydrophobic core of seven transmembrane α-helices separated by alternating intracellular and extracellular loops, an extracellular N-terminus, and an intracellular C-terminus. Mechanisms governing intracellular trafficking of GPCRs are complex but general principles are well accepted(Lohse and Hofmann 2015; Pavlos and Friedman 2017). Synthesized at the endoplasmic reticulum (ER), they proceed through maturation steps at the ER-Golgi intermediate complex, Golgi apparatus and the trans-Golgi network (TGN) to undergo various post-translational modifications and reach a mature state(C. Dong et al. 2007). GPCRs are typically delivered to the plasma membrane in an agonist-responsive and signaling-competent form. Following agonist-mediated activation, the majority

of GPCRs internalize into endosomes from which they are recycled to the cell surface or targeted for lysosomal degradation(Weis and Kobilka 2018). The actors controlling the function and fate of GPCRs are diverse and the specific protein interactome of each receptor is distinct in composition(Sokolina et al. 2017).

In addition to being the only lipocalin family member to display enzyme activity, L-PGDS was shown to possess other intriguing properties. Indeed, our prior findings showed that L-PGDS interacts with DP1 and directs the anterograde transport of the receptor by acting as a co-factor of the Hsp90 molecular chaperone. L-PGDS was also observed to regulate DP1-mediated ERK1/2 signaling by forming a protein complex with DP1 and ERK1/2(Binda et al. 2014). We and others have shown that GPCRs interact with small Rab GTPases (Rabs) to control their trafficking(Dateyama et al. 2019; Esseltine, Dale, and Ferguson 2011; Hamelin et al. 2005; Lachance et al. 2014; Parent et al. 2009; Seachrist and Ferguson 2003). However, the molecular partners taking part in GPCR-Rab complexes assembly and in the activation of Rabs that are important for the correct routing of a given GPCR remain largely unknown. Interestingly, we recently demonstrated that L-PGDS interacts with Rab4 and regulates DP1 recycling by participating in Rab4 recruitment and activation by the receptor(Binda et al. 2019).

GGA3 (Golgi associated, γ adaptin ear containing, ADP-ribosylation factor-binding protein 3) is a multidomain clathrin adaptor participating in a wide range of trafficking events(McMahon and Mills 2004). It is known to facilitate clathrin assembly to modulate the cell surface transport of α_{2B}-adrenergic receptor from the TGN(Maoxiang Zhang et al. 2016a), to mediate trafficking of the mannose-6-phosphate receptor from the TGN to endo-lysosomal compartments(R Puertollano et al. 2001) and to regulate the recycling and signaling of tyrosine kinase receptors(Crupi et al. 2019; X. Li, Lavigne, and Lavoie 2015). Since both L-PGDS and GGA3 take part in Rab4-mediated recycling of membrane receptors, we were interested in investigating whether they could function concertedly. Here, we report that L-PGDS and GGA3 interact and functionally cooperate to regulate DP1 trafficking and signaling in a Rab4-dependent

mechanism, identifying a novel interaction partner and function for GGA3 in the routing of a GPCR.

2. Materials and methods

2.1 Reagents

The LS-C146656 polyclonal DP1 antibody was obtained from LifeSpan Bioscience Inc. The sc-25778 anti-GAPDH antibody, 4E11 anti-Rab4a mouse monoclonal antibody and Protein-G agarose beads were from Santa Cruz Biotechnology. The rabbit polyclonal anti-FLAG antibody, the mouse monoclonal FLAG M2 antibody, the poly-L-lysine, the alkaline phosphatase-conjugated goat anti-rabbit antibody and the alkaline phosphatase substrate kit were from Sigma-Aldrich. The 612310 monoclonal mouse anti-GGA3 antibody was from BD Transduction Laboratories. The anti-Myc-HRP polyclonal antibody was from Abcam. The 160003 polyclonal and 10004342 monoclonal anti-L-PGDS antibodies and PGD_2 were obtained from Cayman Chemical Co. The Alexa Fluor 546 donkey anti-rabbit, Alexa Fluor 633 goat anti-mouse antibodies, Lipofectamine 2000 and ProLong Gold antifade reagent were purchased from Invitrogen. Lipofectamine LTX was obtained from Thermo Fisher Scientific. The 9191 anti-Phospho-ERK 1/2 and 4695 ERK1/2 antibodies were purchased from Cell Signaling.

2.2 Plasmid constructs

The cDNA fragment coding for human Myc-GGA3 was amplified by PCR from a human HeLa MATCH-MAKER cDNA library (Clontech) using a high-fidelity DNA polymerase (Phusion, New England Biolabs) and the following primers: Myc-GGA3 Forward 5'-AAA GAA TTC ATG GAA CAG AAA CTC ATC TCT GAA GAG GAT CTG GCG GAG GCG GAA GGG GAA AGC CTG G -3' and GGA3 Reverse 5'- TCA CTC CAG TCA TAG GTT CCC CCA CTG TTC CAC AGG AGG GAA CTG GTC C -3'. The Myc GGA3 N194A mutant was obtained from the previously described Myc-GGA3 construct by PCR site-directed mutagenesis with the previously mentioned primers and the following primers: GGA3 N194A Forward 5'- CCC AGA TGA CCT GCA GGA GGC CGC CAA GCT CAT CAA

GTC CAT GG – 3'. GGA3 N194A Reverse 5'- CCA TGG ACT TGA TGA GCT TGG CGG CCT CCT GCA GGT CAT CTG GG - 3'. The full-length fragments and a pcDNA3 vector were digested with EcoRI and XhoI and subsequently ligated. The pcDNA3-L-PGDS-Myc, pGEX-4T1-L-PGDS and pRSETA-L-PGDS constructs were generated as described elsewhere(Mathurin et al. 2011). The pEGFP-C2-Rab4 and pcDNA3-Flag-DP1 constructs were produced as described in (Binda et al. 2019) and (Gallant et al. 2007), respectively. The pGEX-4T1-DP1-CT, pGEX-4T1-DP1-ICL1, pGEX-4T1-DP1-ICL2 and pGEX-4T1-DP1-ICL3 constructs were obtained as described in (Binda et al. 2014) (Parent et al. 2010a) . All the constructs corresponding to the different GGA3 domains fused to GST in a pGEX-4T1 vector were a kind gift from Christine Lavoie's lab (Université de Sherbrooke, Qc, Canada). The integrity of the coding sequences of all constructs was confirmed by sequencing at Génome Québec (McGill University, Qc, Canada).

2.3 Cell culture and transfections

Human embryonic kidney 293 (HEK293) and HeLa cells were maintained in DMEM (Invitrogen) supplemented with 10% fetal bovine serum at 37°C in a humidified atmosphere containing 5% CO_2. Transient transfection of HEK293 cells grown to 50–70% confluence was performed using the TransIT-LT1 reagent (Mirus Bio LLC) according to the manufacturer's instructions. Transient transfection of HeLa cells grown to 50-70% confluence was performed using Lipofectamine 2000 according to manufacturer's instructions, and the medium was changed 6 h after transfection to mitigate cellular toxicity. The total DNA amount was kept constant by adding pcDNA3 vector in each transfection condition.

2.4 siRNAs and DsiRNAs

The siRNA targeting L-PGDS (PTGDS) gene (siRNA ID s11446) and the negative control (silencer negative Control) were purchased from Ambion. The siRNA was transfected in a concentration of 70 nM in HeLa cells with Lipofectamine 2000 and the medium was changed 6 h later to mitigate cellular toxicity. Twenty-four hours later, cells were transfected with a combination of pcDNA3-Flag-DP1 and pcDNA3-Myc-GGA3 as described above. Endpoint experiments were carried out 48 h post DNA transfection. The Dicer-substrate short interfering RNAs (DsiRNAs)

targeting GGA3, Rab4 (HSC.RNAI.N004578.12.9) and the negative control (NC1) were obtained from Integrated DNA Technologies. DsiRNAs duplexes silencing GGA3 had the following sequences: GGA3 12.1: 5'-GAAGCCAAUUAUGUAUUCCCAGUCCUC-3' and 3'-CTUCGGUUAAUACAUAAGGGUCAGG-5'; GGA3 12.2: 5'-GGACUGGGAAUACAUAAUUGGCUTC-3' and 3'-CUCCUGACCCUUAUG UAUUAACCGAAG-5'. The DsiRNA duplexes targeting Rab4 and GGA3 were transfected at a concentration of 25 nM with Lipofectamine 2000 according to the manufacturer's instructions.

2.5 Recombinant Protein Production and Pulldown Analysis

The fusion proteins were produced in the Overexpress™ C41 (DE3) *Escherichia coli* strain (Avidis) following the manufacturer's instructions. The pGEX-4T1 vector was used to produce GST-tagged fusion protein. Gluthatione-Sepharose 4B (Amersham Biosciences) was used for protein purification. The purified recombinant proteins were analyzed by SDS-PAGE and stained with Coomassie Brilliant Blue R-250 to quantify proteins level. The pRSETA construct was used to produce His-tagged fusion proteins using the Overexpress™ C41 system as described above and the resulting proteins were purified using Ni-NTA-agarose resin (Qiagen) according to the manufacturer's instructions. Ten micrograms of gluthatione-Sepharose-bound GST-tagged fusion proteins were incubated overnight with 30 µg of the purified His-tagged proteins in binding buffer (10 mM Tris-HCl (pH 7.4), 150 mM NaCl, 1 mM EDTA, 10% glycerol, 0.5% IGEPAL, and 2 mM dithiothreitol) supplemented with protease inhibitors (10 µM chymostatin, 10 µM leupeptin, 10 µM antipain and 10 µM pepstatin). For GST-pulldown performed in cell lysates, 10 µg of GST-fused protein were incubated with 1200 µg of cell lysate proteins from cells transfected with the indicated constructs. The reactions were then washed five times with binding buffer. SDS sample buffer was added to each reaction before boiling the tubes for 5 minutes. All reactions were analyzed by Western blotting using the indicated specific antibodies.

2.6 Measurement of DP1 Internalization and Recycling

For quantification of receptor internalization, HEK293 or HeLa cells were respectively plated at 5 X 10^4 or 3 X 10^4 cells per well in 24-well plates pre-treated with 0.1mg/ml poly-L-lysine

(Sigma). Cells were transfected the following day with the indicated constructs and 48 h post-transfection, cells were stimulated with 1 μM PGD_2 for the indicated times. The cells were then fixed with 3.7 % formaldehyde/Tris-buffered saline (TBS) (20 mM Tris, pH 7.5, 150 mM NaCl) for 10 min and then washed twice with TBS. Cells were blocked with TBS containing 1 % BSA for 45 min to block non-specific binding. A FLAG polyclonal antibody was then added at a dilution of 1:1000 in 1% TBS-BSA for 60 min. Cells were then washed three times and blocked again with 1% TBS-BSA for 15 min. Cells were incubated with an alkaline phosphatase-conjugated goat anti-rabbit antibody at a 1:10,000 dilution in 1% TBS-BSA for 60 min. The cells were then washed three times before adding 250 μl of a colorimetric alkaline phosphatase substrate as described in the manufacturer's instructions. The plates were incubated at 37 °C for 15 min before adding 250 μl of 0.4 M NaOH to stop the reaction. One hundred microliters of the colorimetric reaction were collected, and the absorbance was measured at 405 nm using a spectrophotometer (Titertek Multiskan MCC/340; Labsystem). For quantification of receptor internalization using DsiRNAs, HEK293 cells were plated at 5 X 10^4 cells per well in 24-well plates and transfected the same day with the desired DsiRNAs. Cells were transfected the following day with the indicated constructs and 48 h after the DNA transfection, cells were stimulated with 1 μM PGD_2 for the indicated times. ELISAs were carried out as mentioned above. For quantification of receptor recycling, cells were plated and transfected as mentioned above and maintained for 48 h. Cells were then stimulated with 1 μM PGD_2 for 30 min at 37 °C to favor receptor internalization. Cells were washed once with PBS to remove the ligand before adding DMEM medium containing 0.5% BSA and 20 mM HEPES to allow receptor recycling. Recycling was then stopped at the desired times and cell surface receptor expression was assessed by ELISA as described above.

2.7 Immunoprecipitation

HEK293 cells were transiently transfected with the indicated constructs and were maintained as described above for 48 h. The cells were then washed with ice-cold PBS and harvested in 200 μl of lysis buffer (150 mM NaCl, 50 mM Tris (pH 8.0), 0.5% sodium deoxycholate, 0.1% SDS, 10 mM $Na_4O_7P_2$, 1% IGEPAL, and 5 mM EDTA supplemented with protease inhibitors (10 μM pepstatin, 10 μM antipain, 10 μM leupeptin, and 10 μM chymostatin). After a 60 min

incubation in lysis buffer at 4 °C, the lysates were then centrifuged for 20 min at 14 000 g at 4 °C. One microgram of specific antibodies was then added to the supernatants and incubated for 60 min at 4 °C with rotation. Forty µl of 50 % protein G-agarose beads were added to the supernatant, followed by an overnight incubation at 4 °C with rotation. Samples were then centrifuged for 1 min in a microcentrifuge and washed three times with 1 ml of lysis buffer. Immunoprecipitated proteins were eluted by addition of 40 µl of SDS sample buffer, followed by a 30 min incubation at 37°C. Initial lysates and immunoprecipitated proteins were analyzed by SDS-PAGE and immunoblotting with specific antibodies. Experiments were done at least 3 times. Endogenous immunoprecipitations were performed in HeLa cells. Cells were harvested and processed as described for HEK293 cells except proteins were immunoprecipitated overnight using 5 µg L-PGDS specific, 1 µg GGA3 specific or appropriate control antibodies and 40 µl of 50 % protein G-agarose beads.

2.8 Immunofluorescence staining and confocal microscopy

For the co-localization experiments, HeLa or HEK293 cells were seeded directly onto coverslips previously coated with 0.1 mg/mL of poly-L-lysine at a density of 7.5 X 10^4 or 5 X10^4 cells/well in 6-well plates, respectively. The cells were then transiently transfected with the indicated constructs using Lipofectamine LTX according to the manufacturer's instructions. After 48 h, the cells were fixed with 4% paraformaldehyde in phosphate-buffered saline (PBS), washed with PBS, permeabilized with 0.1% Triton X-100 in PBS and blocked with 0.1% Triton X-100 in PBS containing 2% BSA. They were then incubated with primary antibodies diluted in blocking solution for 60 min, washed twice with 0.1% Triton X-100 in PBS, blocked with 0.1% Triton X-100 in PBS containing 2% BSA, and incubated with the appropriate secondary antibodies diluted in blocking solution for 60 min. The cells were then washed twice with 0.1% Triton X-100 in PBS followed by three washes with PBS. The coverslips were mounted using ProLong® Gold antifade reagent. Confocal microscopy was performed using a scanning confocal system (TCS SP8; Leica) coupled to an inverted microscope with an 60x oil-immersion objective (DMI8; Leica) and the images were processed using LAS X software (Leica), Imaris (Oxford Instruments Group) and deconvolution was done with Huygens (Scientific Volume Imaging).

2.9 ERK1/2 phosphorylation

HEK293 cells were seeded in 6-well plates at 8 x 10^5 cells per well, immediately transfected with indicated DsiRNAs and then incubated for 24 h before being transfected with the indicated DNA constructs as described above. Forty-eight hours after DNA transfection, cells were starved for 180 min in DMEM supplied with 0.5% BSA and 20 mM HEPES pH 7.5, and then treated with 1 · M PGD_2 or DMSO for the indicated times. The reactions were stopped with 250 · l of 1x sample buffer (62.5 mM Tris pH 7.0, 2% w/v SDS, 10% glycerol, 50 mM DTT, 0.01% w/v bromophenol blue) and sonicated. The samples were then analyzed by Western blotting using phospho-p42/p44 and secondary horseradish peroxidase-conjugated anti-rabbit antibodies. Blots were then stripped and re-probed with p42/p44 antibodies. Experiments were done at least 3 times and densitometry analyses were carried out using NIH ImageJ software 1.8.0.

2.10 Statistical Analyses

Statistical analyses were performed using Prism v7.01 (GraphPad Software, San Diego, CA, USA) using the repeated measure one-way ANOVA, unless state otherwise. A Tukey's multiple comparisons test was made as a post-hoc test to establish statistical significance between conditions. Data were considered significant when *P* values were 0.05 (*), 0.01 (**), 0.001(***) or 0,0001 (****). Nonsignificant values are abbreviated as "ns".

3. RESULTS

3.1 GGA3 regulates the recycling of DP1

To investigate the involvement of GGA3 in the trafficking of DP1, we characterized the effect of overexpression of this adaptor protein on the agonist-induced internalization of DP1. Cell surface ELISA were performed on HEK293 cells that were transfected with pcDNA3-Flag-DP1 in combination with pcDNA3, pcDNA3-Myc-GGA3 or pcDNA3-Myc-GGA3 N194A (a mutant defective in Arf-binding), as described previously(Cartier et al. 2011; Labrecque, Sébastien J. Roy, et al. 2013; Lachance et al. 2011). As shown in Fig 1A, there was a significant reduction in measured internalization of Flag-DP1 when Myc-GGA3 or Myc-GGA3 N194A were co-expressed in time-course experiments of PGD_2 stimulation. The maximal effect of GGA3 was observed after 15 min of DP1 stimulation with a ~46% reduction in internalization, followed by a ~37% reduction after 30 min. Similar results were obtained with GGA3 N194A, with 57% and 38% reductions in internalization after 15 min and 30 min of receptor stimulation, respectively. These data suggest that GGA3 mediates its effect on DP1 trafficking through a mechanism that is independent of binding to Arf proteins. To further address the role of GGA3 in DP1 trafficking, time-course experiments of receptor internalization were also performed when endogenous GGA3 expression was depleted using two different DsiRNAs. Efficiency of the DsiRNAs to inhibit endogenous GGA3 expression was confirmed by western blot (Fig. 1B). Knockdown of endogenous GGA3 expression resulted in an increase in DP1 agonist-induced internalization (Fig. 1C), consistent with the reverse effects produced by GGA3 overexpression.

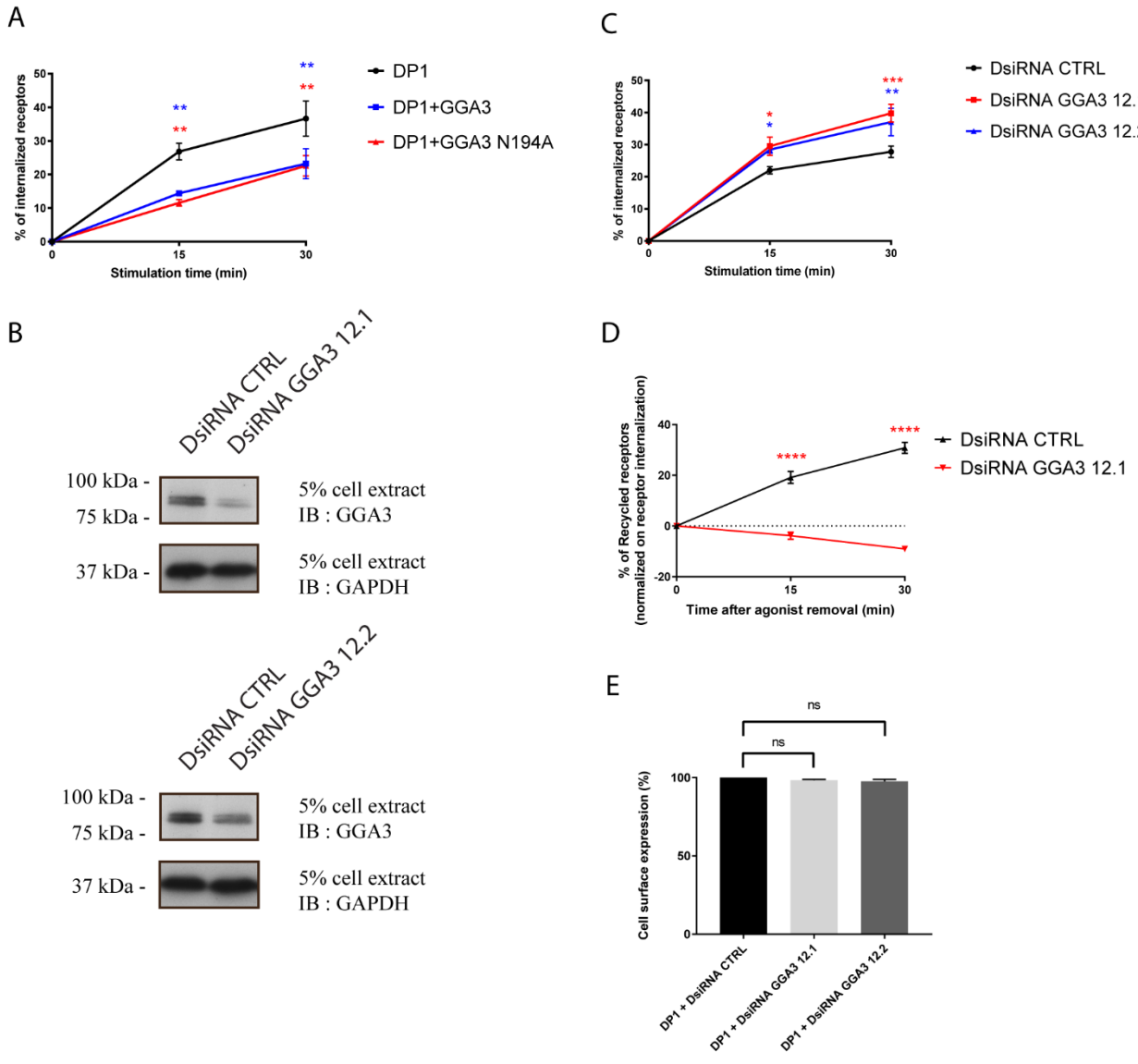

Fig. 1. GGA3 regulates DP1 trafficking. A) Cell surface expression of the receptor was measured by ELISA in HEK293T cells transiently transfected for 48 h with Flag- tagged DP1 in combination with pcDNA3, pcDNA3-Myc-GGA3 or pcDNA3–Myc-GGA3 N194A. 48 h post-transfection, cells were stimulated with 1 µM PGD2 for the indicated times, and the percentage of receptor internalization was calculated. B) HEK293T cells were transfected with negative control DsiRNAs or DsiRNAs targeting GGA3 for 72 h and immunoblotting (IB) was performed with a GGA3 specific monoclonal antibody. C) HEK293T cells were transfected with DsiRNAs targeting GGA3 or a negative control DsiRNA. 24 h after DsiRNAs transfection, cells were transiently transfected with pcDNA3-Flag-DP1. 48 h after the second transfection, cells were treated with 1 µM PGD2 for the indicated times. Receptor cell surface expression was measured by ELISA, and the percentage of receptor internalization was calculated. (D) HEK293T cells were transfected with DsiRNA GGA3 12.1 or a negative control DsiRNA. 24 h after DsiRNAs transfection, cells were transiently transfected with pcDNA3-Flag-DP1. 48 h

after the second transfection, cells were treated with 1 μM PGD2 for 30 min and then incubated in DMEM for the indicated time periods to allow receptor recycling. Cell surface expression of the receptor was detected by ELISA, and the percentage of receptor recycling was calculated. E) HEK293T cells were transfected with DsiRNA GGA3 12.1, DsiRNA GGA3 12.2 or a negative control DsiRNA. 24 h after DsiRNAs transfection, cells were transiently transfected with pcDNA3-Flag-DP1. 48 h after the second transfection, cell surface expression was measured by ELISA and statistical significance was assessed using a one-way ANOVA analysis in the GraphPad Prism software. Results are presented as mean ± S.E. (error bars) of three separate experiments. *, P≤0,05; **, P≤0,01; ***, P≤0,001; ****, P≤0,0001; ns, non-significant

GGA3 plays a role in the recycling of cell surface receptors(Crupi et al. 2019; Parachoniak et al. 2011; Ratcliffe et al. 2016). Given that an increase in receptor recycling can reduce the measured percentage of receptor internalization, we determined whether GGA3 affected DP1 recycling to the cell surface after agonist-induced internalization. Cells expressing Flag-DP1 transfected with control DsiRNA or the most efficient DsiRNA targeting GGA3 (GGA3 12.1) were stimulated with PGD_2 for 30 min to promote receptor internalization and were then incubated in agonist-free culture medium for various times to allow receptor recycling to the cell surface, which was measured by ELISA as we described before(Binda et al. 2019). As shown in Fig. 1D, DP1 recycling was abrogated when endogenous GGA3 was depleted. Cell surface expression assays at the basal state revealed that GGA3 does not regulate the anterograde transport of DP1 (Fig. 1E).

3.2 GGA3 interacts with DP1

Our next interest was to study whether there is an interaction between GGA3 and DP1. A time-course experiment of co-immunoprecipitation was designed to determine if: 1) GGA3 and DP1 interact *in cellulo* and 2) the interaction is modulated by the natural ligand of DP1, PGD_2. GGA3 was found to co-immunoprecipitate with DP1 in an agonist- and time-dependent manner (Fig. 2A), with an interaction peak of ~2,8 fold after 15 min of agonist treatment that gradually returned to basal level after 60 min of receptor activation, as determined by densitometry analyses (Fig. 2B). The DP1-GGA3 co-immunoprecipitation was confirmed at the endogenous level in HeLa cells (Fig. 2C), which endogenously express both proteins of interest and produce PGD_2(Binda et al. 2014, 2019).

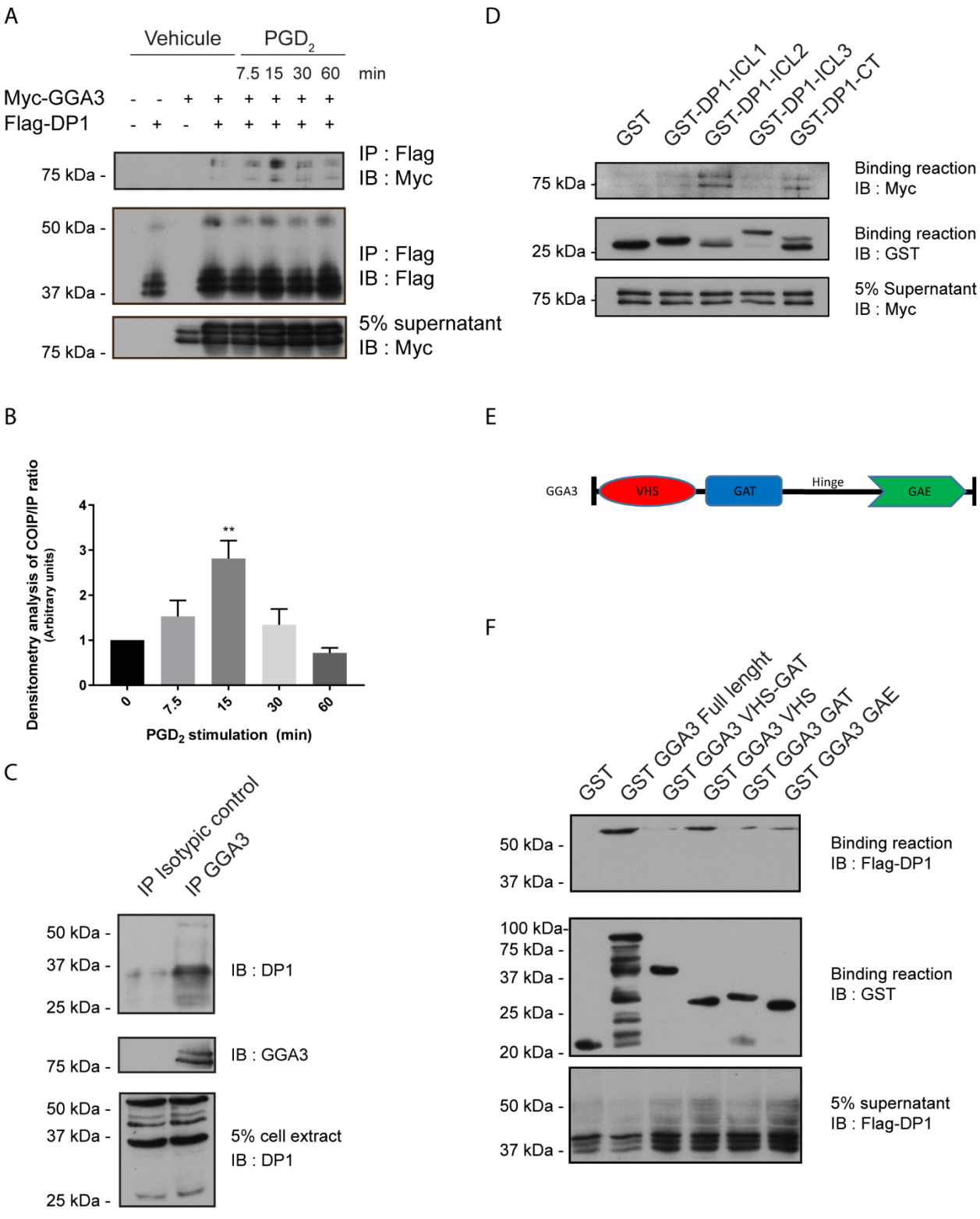

Fig. 2. DP1 interacts with GGA3. (A) HEK293T cells transiently transfected with pcDNA3-Flag-DP1, pcDNA3-Myc-GGA3, or a combination of constructs were stimulated for the indicated times with 1 μM PGD2. Immunoprecipitation (IP) of the receptor was performed using a Flag-specific mAb, and immunoblotting (IB) was performed with Flag-specific polyclonal or anti-Myc antibodies. (B) Densitometry analyses were performed on three

different experiments. Myc-GGA3 pixels were normalized on Flag-DP1 pixels, and results are presented as the ratio of these values (mean ± S.E.). (C) Immunoprecipitations were performed in HeLa cells using GGA3-specific monoclonal antibodies or isotypic control IgG antibodies, and immunoblotting was performed using DP1-specific polyclonal antibodies or GGA3- specific monoclonal antibodies. Blots shown are representative of three independent experiments. (D) Binding assays were performed using purified glutathione- Sepharose–bound GST-DP1-carboxyl terminal (CT) and intracellular loops (ICL) incubated with cellular lysates of HEK293T cells transfected with pcDNA3-Myc- GGA3. The binding of GGA3 to the receptor domains was detected by immunoblotting (IB) using an anti-Myc antibody, and the GST fusion proteins present in the binding reaction were detected using an anti-GST antibody. (E) Visual representation of GGA3 and its domains. (F) Binding assays were performed using purified glutathione-Sepharose–bound GST-GGA3 Full length, GST-GGA3 VHS-GAT domain, GST-GGA3 VHS domain, GST-GGA3 GAT domain and GST-GGA3 GAE domain incubated with cellular lysates of HEK293T cells transfected with pcDNA3-Flag-DP1. The binding of DP1 to the GGA3 domains was detected by immunoblotting (IB) using an anti-Flag antibody, and the GST fusion proteins present in the binding reaction were detected using an anti-GST antibody. Blots shown are representative of at least three independent experiments.

To identify the intracellular domain of DP1 that interacts with GGA3, we generated and purified each DP1 intracellular domain in fusion with GST and performed GST pull-down assays on lysates of HEK293T cells overexpressing Myc-tagged GGA3. Intracellular loop 2 (ICL2) and the C-terminal tail (C-tail) of DP1 were found to be the major DP1 binding domains for GGA3 (Fig. 2D). GGA3 is a multi-domain protein, each with different ascribed functions(Dell'Angelica et al. 2000) (Fig. 2E). In order to identify the GGA3 domains involved in the interaction with DP1, we purified various GST-GGA3 fusion constructs and performed GST pull-down assays on lysates of HEK293T cells transiently expressing Flag-DP1 (Fig. 2F). As expected, full-length GGA3 interacts with DP1. The VHS domain of GGA3 appears as the predominant interaction site with DP1 while the GAT, GAE, and VHS-GAT constructs interacted less with the receptor, and no interaction was observed with GST alone.

3.3 Activation of DP1 increases its colocalization with GGA3

Confocal microscopy was then performed to determine whether DP1 and GGA3 co-localize intracellularly in the basal state and after DP1 activation with PGD_2 for 15 min in HEK293 cells (Fig. 3). There was virtually no co-localization between Flag-DP1 and Myc-GGA3 in absence of agonist stimulation (Fig. 3 upper panel). On the other hand, co-localization of the two proteins was noticeably enhanced by PGD_2 stimulation (Fig. 3, lower panel) as shown by the increase in co-localizing pixels.

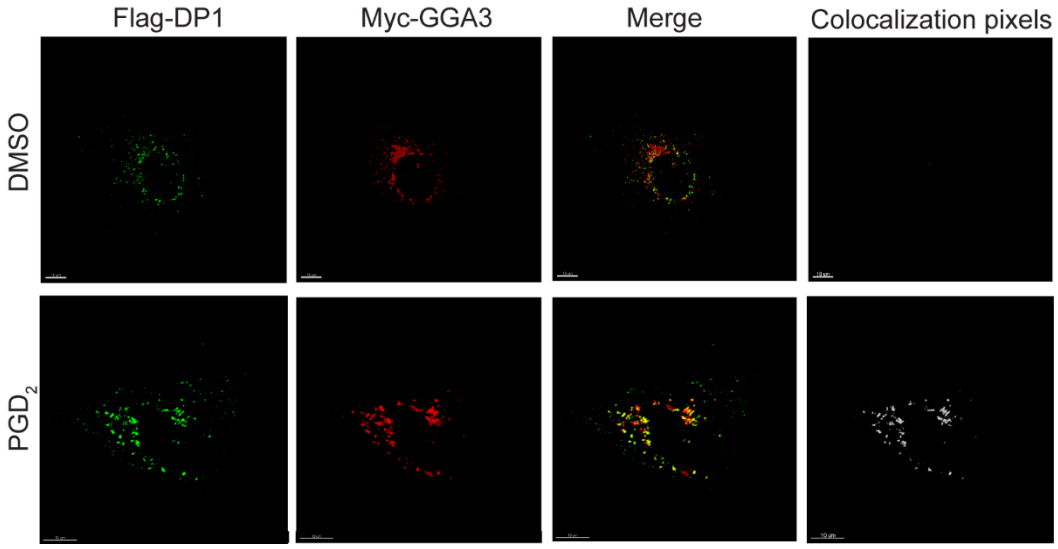

Fig. 3. GGA3 and DP1 colocalize intracellularly. HEK293 cells were transiently transfected with pcDNA3-Flag-DP1 and pcDNA3-Myc-GGA3 for 48 h. The cells were then incubated with vehicle (DMSO, upper panel) or with 1 μM PGD2 (lower panel) for 15 min. Flag-DP1 was visualized using a 633 nm emission laser line and an Alexa Fluor 633 detection filter. Myc-GGA3 was visualized using a 543 nm emission laser line and an Alexa Fluor 546 detection filter. The areas with high degree of colocalization appear in white (Colocalization pixels). The images shown are single confocal slices and are representative of approximately 100 observed cells over three independent experiments. Bars, 10 μm.

3.4 GGA3 regulates DP1 trafficking through a Rab4-dependent mechanism

GGA3 was shown to regulate Met receptor recycling through a Rab4-dependent pathway(Parachoniak et al. 2011). We recently demonstrated that DP1 recycling is controlled by Rab4(Binda et al. 2019). We thus wondered if the effect of GGA3 on DP1 trafficking was Rab4-dependent. Of different DsiRNAs targeting Rab4, Rab4 DsiRNA HSC.RNAI.N004578.12.9 was shown to be the most efficient to inhibit DP1 recycling in our previous work(Binda et al. 2019). HEK293T cells expressing Flag-DP1 alone or in combination with Myc-GGA3 were transfected with control DsiRNAs or Rab4 DsiRNA HSC.RNAI.N004578.12.9. Cell surface receptor internalization was monitored by ELISA following 30 min of PGD_2 stimulation. Rab4 expression knockdown significantly reduced the ability of GGA3 to affect DP1 trafficking. Indeed, GGA3 reduced DP1 internalization by ~22% in presence of control DsiRNAs (column 2 vs 1, Fig.4A) compared to ~4% for the condition with Rab4 DsiRNA HSC.RNAI.N004578.12.9 (column 4 vs 3, Fig.4A). These results support the idea that GGA3 regulates DP1 trafficking through a Rab4-dependent mechanism.

3.5 GGA3 and L-PGDS have interdependent roles in DP1 trafficking

We previously reported that L-PGDS interacts with Rab4, promotes the association of DP1 with Rab4 and modulates the activation of this small GTPase to regulate DP1 recycling(Binda et al. 2019). Given the fact that both GGA3 and L-PGDS regulate DP1 recycling through a Rab4-dependent mechanism, we were interested in investigating whether GGA3 and L-PGDS were mutually involved in the trafficking of DP1. First, we carried out DP1 recycling assays in HEK293T cells expressing Flag-DP1 alone or with Myc-GGA3 and L-PGDS individually or in combination. As shown in Fig. 4B, 30 min after agonist removal, recycling of DP1 was promoted by ~35% and ~44% when GGA3 and L-PGDS were co-expressed individually, respectively. The combined co-expression of GGA3 and L-PGDS increased DP1 recycling by ~71% compared to when the receptor was expressed alone.

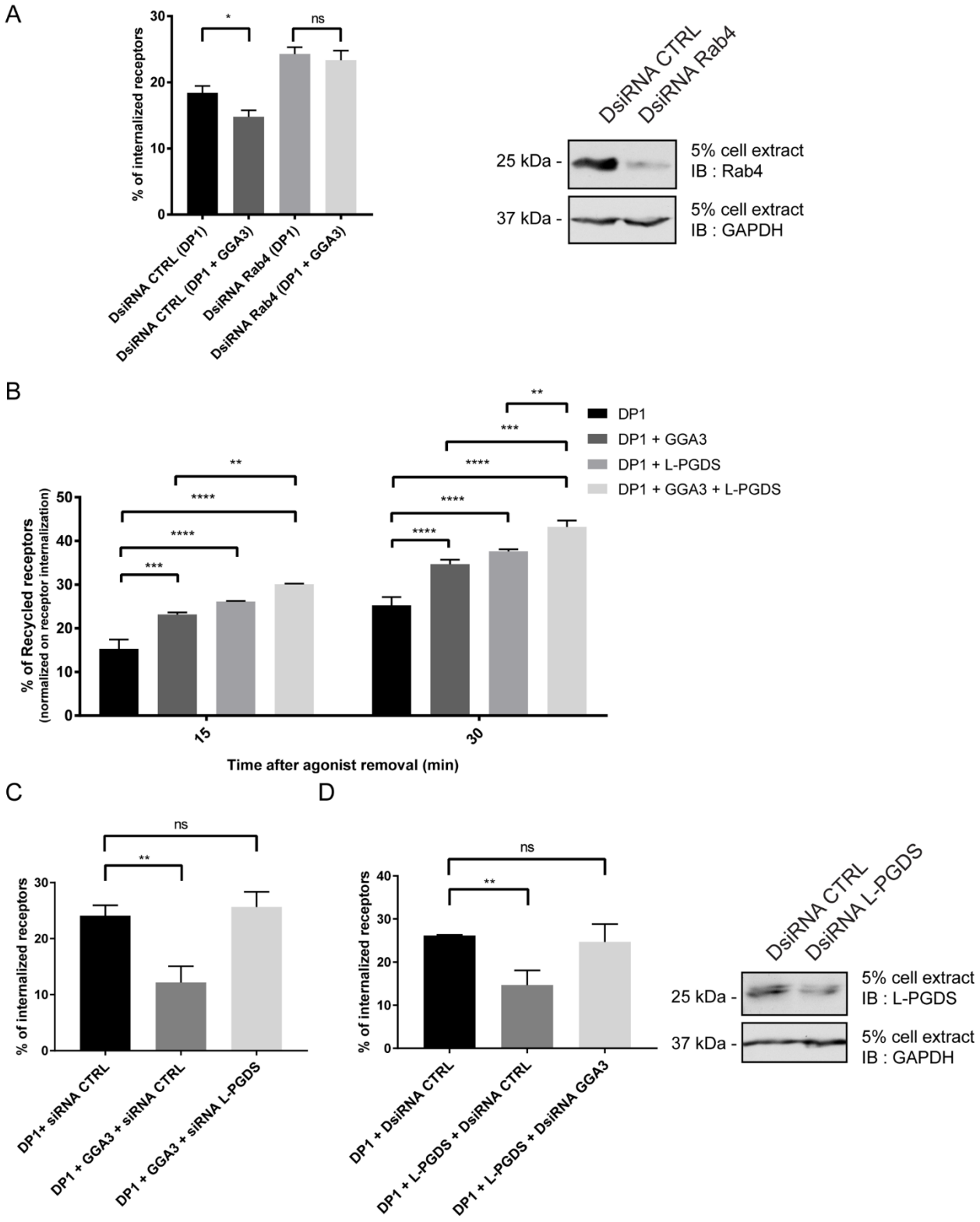

Fig. 4. GGA3 is dependent of Rab4 and L-PGDS to modulate DP1 trafficking (A) HEK293T were transfected with Rab4 DsiRNA HSC.RNAI.N004578.12.9 or a negative control DsiRNA. Cells were then transiently transfected 24 h later with pcDNA3-Flag-DP1 in combination with pcDNA3 or pcDNA3–Myc-GGA3. 72 h post-transfection of

DsiRNAs, cells were stimulated with 1 μM PGD2 for 30 min, and the percentage of internalized receptors was calculated. (B) HEK293T cells were co-transfected with pcDNA3-Flag-DP1, pcDNA3-L-PGDS or pcDNA3-Myc-GGA3. Cells were treated with 1 μM PGD2 for 30 min and then incubated in DMEM for the indicated time periods to allow receptor recycling. Cell surface expression of the receptor was detected by ELISA, and the percentage of receptor recycling was calculated. (C) and (D) HeLa cells were transfected with GGA3 DsiRNA 12.1 or control DsiRNA (C) or L-PGDS siRNA s11446 or control siRNA (D). 24 h later, cells were transiently transfected with pcDNA3-Flag-DP1 with or without (C) pcDNA3-Myc-L-PGDS and (D) pcDNA3-Myc-GGA3. 48 h after the second transfection, cells were treated with 1 μM PGD2 for 30 min. Receptor cell surface expression was measured by ELISA, and the percentage of receptor internalization was calculated. Protein levels of L- PGDS were assessed using L-PGDS specific antibody showing silencing of L-PGDS by the siRNA s11446 in HeLa cells compared to the negative control siRNA. Results are mean ± S.E. (error bars) of three separate experiments. *, P≤0,05; **, P≤0,01; ***, P≤0,001; ****, P≤0,0001.

To determine whether the involvement of GGA3 in DP1 recycling is L-PGDS-dependent, we transfected HeLa cells, which endogenously express L-PGDS(Binda et al. 2014, 2019), with control or L-PGDS-specific siRNAs. The L-PGDS siRNA ID s11446 (Ambion) was used as we have reported before that it is the most efficient siRNA among other L-PGDS siRNAs for inhibiting L-PGDS expression and DP1 recycling(Binda et al. 2014). The cells were also transfected with pcDNA3-Flag-DP1 alone or together with pcDNA3-Myc-GGA3 and stimulated with PGD_2 for 30 min prior to cell surface ELISAs. The ability of GGA3 to decrease DP1 internalization by ~50% (Fig. 4C, column 2 vs. 1) by enhancing receptor recycling in the presence of the control siRNA was abrogated by L-PGDS depletion (Fig. 4C, column 3 vs. 2). Conversely, we then verified if the effect of L-PGDS on DP1 recycling was dependent on GGA3. HeLa cells overexpressing Flag-DP1 alone or in combination with L-PGDS and transfected with control DsiRNA or GGA3 DsiRNA 12.1 were stimulated with PGD_2 prior to measurement of receptor internalization. The ability of L-PGDS to inhibit DP1 internalization by ~56%, by promoting its recycling(Binda et al. 2019), (Fig. 4D, column 2 vs 1) was abolished by depletion of GGA3 (Fig. 4D, column 3 vs 2). Altogether, these data suggest that GGA3 and L-PGDS have mutually dependent roles in the regulation of DP1 recycling.

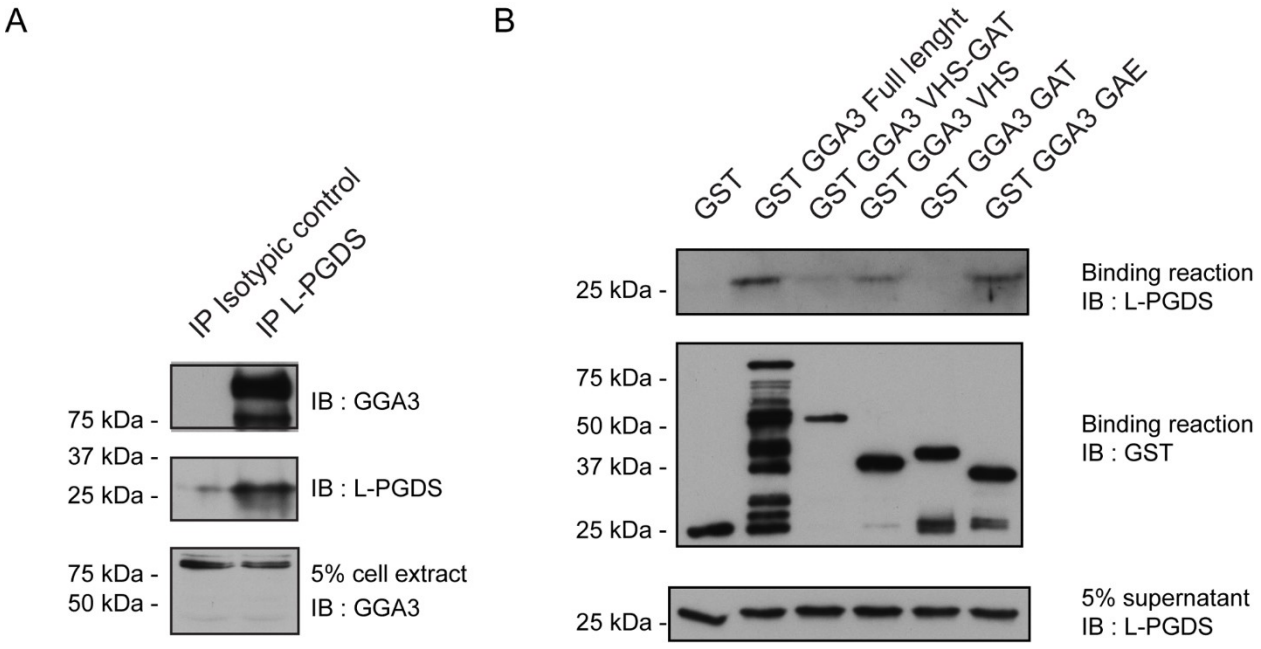

Fig. 5. L-PGDS interacts with GGA3 (A) Immunoprecipitations were performed in HeLa cells using L-PGDS-specific polyclonal antibodies or rat isotypic control IgG antibodies, and immunoblotting was done using GGA3-specific monoclonal antibodies or L-PGDS polyclonal antibodies. Blots shown are representative of three independent experiments. (B) Binding assays were performed using purified glutathione-Sepharose–bound GST-GGA3 Full length, GST-GGA3 VHS-GAT domain, GST- GGA3 VHS domain, GST-GGA3 GAT domain and GST-GGA3 GAE domain incubated with purified His-L-PGDS. The binding of L-PGDS to the GGA3 constructs was detected by immunoblotting (IB) using an anti-L-PGDS polyclonal antibody, and the GST fusion proteins present in the binding reactions were detected using an anti- GST antibody. Blots shown are representative of at least three independent experiments.

3.6 GGA3 and L-PGDS interact and colocalize

Considering the last results, whether there is a physical association between GGA3 and L-PGDS was investigated by co-immunoprecipitation experiments between the endogenous proteins. As seen in Fig. 5A, immunoprecipitation of endogenous L-PGDS, as we performed before(Binda et al. 2014, 2019), resulted in the co-immunoprecipitation of endogenous GGA3 in HeLa cells. To determine if the interaction could be direct, the various purified GST-GGA3 constructs described above were combined with purified recombinant His-L-PGDS to perform *in vitro* GST pull-down assays (Fig. 5B). Data obtained indicate that GGA3 and L-PGDS can interact directly, predominantly through the VHS and GAE domains of GGA3. Confocal microscopy revealed that there is colocalization between GGA3, Rab4 and L-PGDS at the basal state in HeLa cells, but that L-PGDS is mainly localized at the periphery of Rab4- and GGA3-containing vesicles (Fig. 6,

upper panel). Cell stimulation with PGD_2 triggered a redistribution of L-PGDS towards Rab4 and GGA3 positive vesicles (Fig. 6, lower panel).

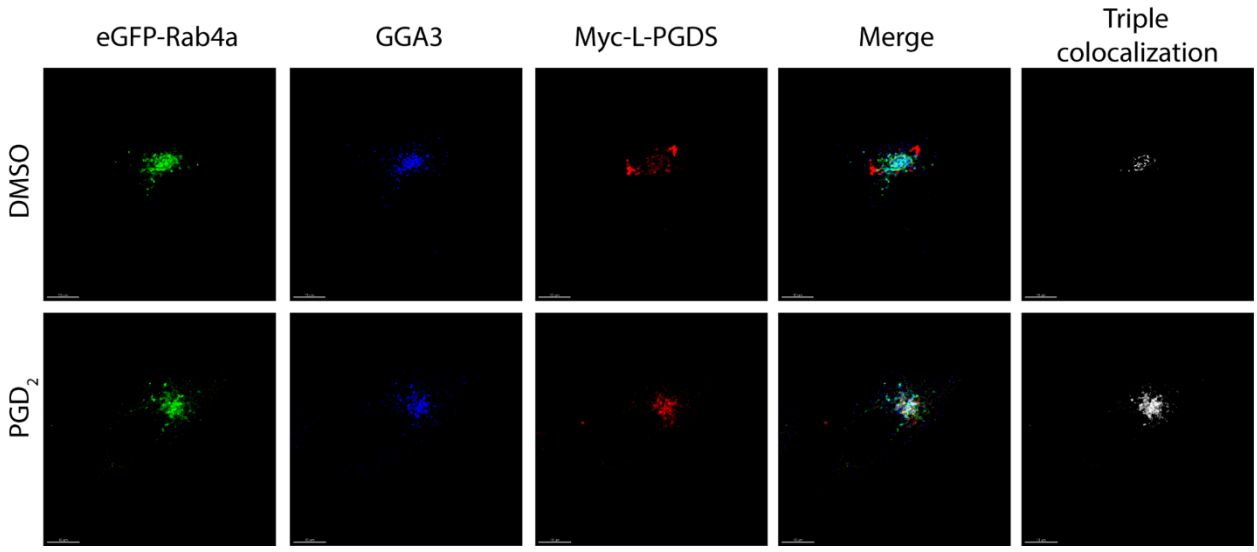

Fig. 6. L-PGDS colocalizes with GGA3. HeLa cells were transiently transfected with pcDNA3-L-PGDS-MYC and pEGFP-C2-Rab4a for 48 h. The cells were then incubated with vehicle (upper panel) or with 1 µM PGD2 (lower panel) for 15 min. The cells were then fixed and prepared for confocal microscopy as indicated in Materials and Methods. Endogenous GGA3 was labelled using a specific monoclonal antibody and an Alexa Fluor 546-conjugated anti-mouse IgG secondary antibody. GGA3 was visualized using a 543 nm emission laser line and an Alexa Fluor 546 detection filter. eGFP-Rab4a was visualized using a 488 nm emission laser line and an eGFP detection filter. L-PGDS was labelled using a Myc-specific polyclonal primary antibody and an Alexa Fluor 633-conjugated anti-rabbit IgG secondary antibody. L-PGDS was visualized using a 633 nm emission laser line and an Alexa Fluor 633 detection filter. Overlays of the staining patterns of the eGFP-Rab4a, GGA3 and L- PGDS are presented in the merge panels and the colocalizing pixels were extracted (white). All lasers intensity and acquisition parameters were conserved among the different conditions to allow comparison. The images shown are single confocal slices and are representative of approximately 200 observed cells over three independent experiments. Bars, 10 µM.

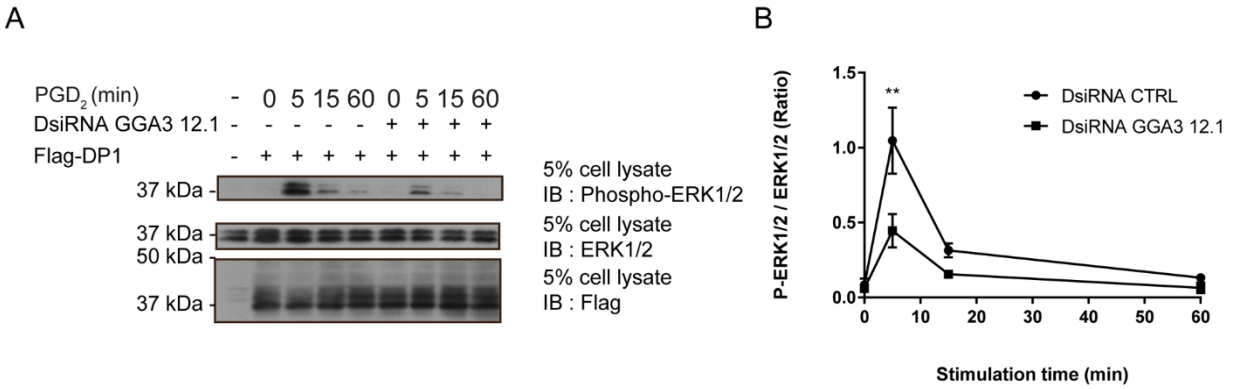

Fig. 7. Depletion of GGA3 attenuates DP1 signaling. (A) HEK293T cells were transfected with the GGA3 DsiRNA 12.1 or a negative control DsiRNA and transiently transfected with Flag-DP1 24 h later. 48 h later, cells were serum-starved for 3 h and stimulated with 1 µM PGD2 for the indicated times. Protein levels were assessed

by Western blot using Flag, p-ERK1/2 and ERK1/2 antibodies. (B) Densitometry analyses were performed on three different experiments. p-ERK1/2 pixels were normalized on ERK1/2 pixels, and results are presented as the ratio of these values (mean ± S.E.). **, P≤0,01.

3.7 GGA3 knockdown decreases DP1-mediated ERK1/2 activation

We previously showed that an outcome of DP1 stimulation is ERK1/2 activation(Binda et al. 2014; Labrecque, Sébastien J. Roy, et al. 2013). Since the alteration of the recycling dynamics of DP1 could impact its downstream signaling, the role of GGA3 in DP1 function was studied by time-course analyses of ERK1/2 activation following PGD_2 stimulation in HEK293 cells transfected with GGA3 DsiRNA 12.1 or a negative control DsiRNA (Fig. 7A). PGD_2-induced ERK1/2 activation peaked after 5 min of DP1 stimulation in both the negative control and GGA3 DsiRNAs-transfected cells. However, GGA3 knockdown resulted in a reduction in DP1-mediated ERK1/2 activation throughout the time-course that was statistically different at the peak activation time of 5 min of PGD_2 stimulation (Fig. 7B).

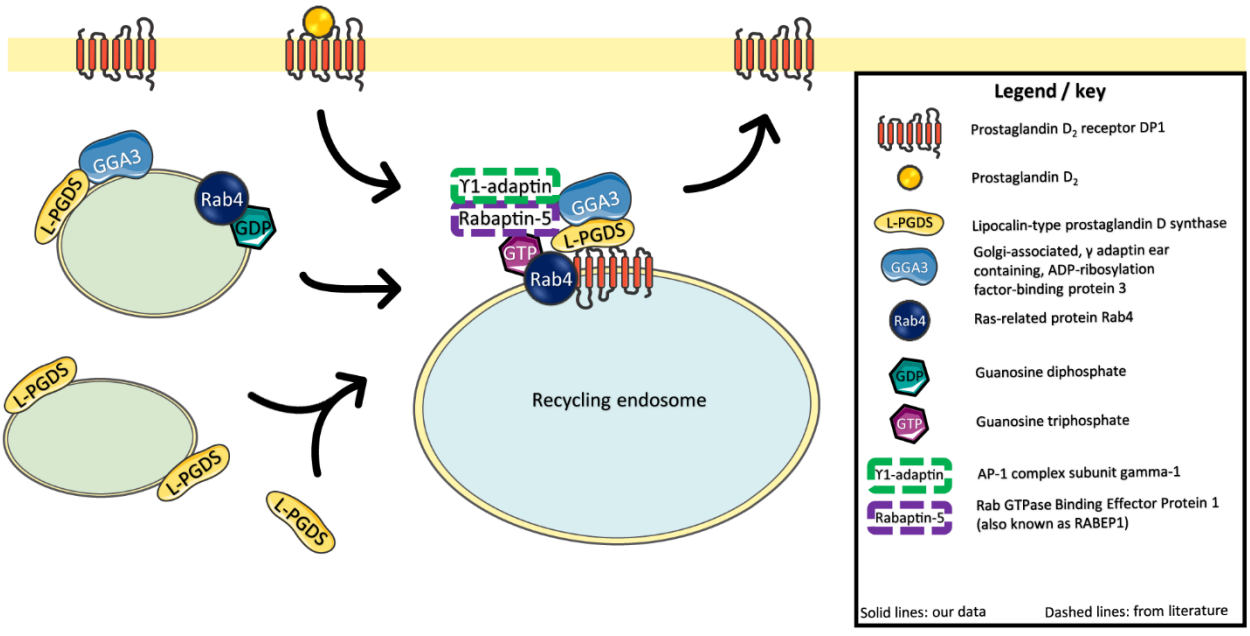

Fig. 8. Schematic representation of a potential mechanism by which L-PGDS, GGA3 and Rab4 regulate DP1 recycling. At the basal state, L-PGDS colocalizes with Rab4 and GGA3 but is predominantly distributed at the periphery of Rab4- and GGA3-containing vesicles. Stimulation of DP1 with PGD2 triggers internalization of the receptor, redistribution of L-PGDS to Rab4- and GGA3-containing endosomes, and formation of DP1/L-PGDS/Rab4 complexes in recycling endosomes. This in turn leads to Rab4 activation [40] and its interaction with its effector rabaptin-5. GGA3, via its interaction with the latter [61], could be recruited to the membrane and interact with L-

PGDS. Alternatively, L-PGDS could promote activation of Rab4, and then its interaction with GGA3 could bring rabaptin-5 in close vicinity with Rab4 to favor their interaction. Rabaptin-5 serves as a linker between Rab4 and γ1-adaptin [64]. By interacting with γ1-adaptin and their other partners, GGA3 and rabaptin-5 would continue the chain of events leading to the recycling of the receptor. Whether rabaptin-5 and γ1-adaptin are involved and the exact sequential order of the implication of the different proteins remain to be determined. The proteins involved in interactions that were shown by us are shown in solid lines, while those reported in the literature can be seen in dashed lines (rabaptin-5 and γ1-adaptin).

4. Discussion

Internalization and recycling are major events for regulation of spatial and temporal activation of GPCRs. It is generally well accepted that most internalized receptors are sent to degradation or recycled to the plasma membrane upon their activation. Although internalization of GPCRs has been studied for several years, the underlying molecular mechanisms governing GPCR recycling remain largely unclear. Our previous work demonstrated that DP1 recycles through the small GTPase Rab4(Binda et al. 2019; Gallant et al. 2007). We showed that L-PGDS plays a key role in DP1 recycling by promoting Rab4 activation and recruitment to DP1. This role of L-PGDS was specific to DP1 (Binda et al. 2019). In the present study, we revealed that GGA3 regulates the recycling of DP1 through a Rab4- and L-PGDS-dependent mechanism.

GGA3 was originally described as a coat protein binding clathrin and mediating vesicular transport in the trans-Golgi network(Dell'Angelica et al. 2000). It was also characterized as a sorting protein mediating transport between the early and late endosomes allowing degradation of the cation-independent mannose-6-phosphate receptor(Puertollano and Bonifacino 2004) . It was later observed that a subpopulation of GGA3 is enriched in Rab4 recycling endosomes(Parachoniak et al. 2011; Ratcliffe et al. 2016; Zaoui et al. 2019). Indeed, GGA3 was revealed to be involved in the fast recycling of the Met receptor through Rab4 recycling endosomes by a mechanism requiring Arf6 and the adaptor protein Crk (Parachoniak et al. 2011). Recycling of TrkA, RET51, and · 1 integrins was also shown to be regulated by GGA3 in an Arf6-dependent mechanism (X. Li et al. 2015) (Crupi et al. 2019) (Ratcliffe et al. 2016). Moreover, GGA3 was reported to regulate the cell surface export from the trans-Golgi network of the · $_{2B}$-adrenergic receptor, a GPCR(M Zhang et al. 2016). In our cell models, GGA3 had no effect on the cell surface expression of DP1 in the basal state, suggesting that it is not involved

in the anterograde transport of the receptor contrary to the ·$_{2B}$-adrenergic receptor. Therefore, we described here a new function for GGA3 in the recycling of a GPCR, namely DP1.

GGA3 interacts with cargo proteins to mediate their recycling (Crupi et al. 2019; Xuezhi Li et al. 2015; Mardones et al. 2007; Parachoniak et al. 2011). We observed a DP1-GGA3 interaction by co-immunoprecipitation at the endogenous level in HeLa cells. This interaction was promoted by agonist stimulation of the receptor in HEK293 cells, which was supported by increased DP1-GGA3 co-localization in confocal microscopy. GGA3 is known to bind to various motifs in its cargo proteins : the acidic-cluster di-leucine domain(R Puertollano et al. 2001), the tri-arginine motifs(Maoxiang Zhang et al. 2016b), the FGPLV motif(Mattera et al. 2003) and the WNSF motif(Nakayama and Wakatsuki 2003). A triple Arg motif in the third intracellular loop of the ·$_{2B}$-adrenergic receptor was shown to be responsible for the interaction with GGA3(Maoxiang Zhang et al. 2016a). The binding of GGA3 to the intracellular loop 2 and the C-terminus of DP1 is interesting, considering the lack of classical GGA3-binding motifs in these domains. Further experiments will be needed to delineate whether the DP1-GGA3 interaction is mediated through an intermediate adaptor protein or by a novel mode of direct interaction with GGA3. DP1 interacts predominantly with the VHS domain of GGA3, analogously to the ·$_{2B}$-adrenergic receptor(M Zhang et al. 2016). Intriguingly, the receptor does not interact with the GGA3 VHS-GAT construct. This may be explained by the ability of the GAT domain to inhibit binding of proteins to the VHS domain by conformational/structural hindrance when the hinge and GAE domains are deleted from GGA3(Hirsch et al. 2003).

GGA3 was reported to regulate recycling of receptors through an interaction with Arf6(Xuezhi Li et al. 2015; Parachoniak et al. 2011; Ratcliffe et al. 2016). In the latter studies, the GGA3 N194A mutant, deficient in Arf-binding, failed to regulate receptor recycling. In our system, however, the GGA3 N194A mutant had the same effect on DP1 trafficking as the wild-type protein, which is indicative of an Arf-independent mechanism. This prompted us to investigate other avenues to explain how GGA3 regulates DP1 recycling. Considering that Rab4 is involved in the recycling of DP1 (Binda et al. 2019) and that GGA3 was shown to control recycling through endosomal

structures enriched in Rab4(Parachoniak et al. 2011; Ratcliffe et al. 2016), we explored whether Rab4 was implicated in the GGA3-mediated effect on DP1 trafficking. Rab4 expression knockdown virtually abrogated the ability of GGA3 to affect DP1 trafficking. Since we recently demonstrated that L-PGDS regulates the recycling of DP1 through an interaction with Rab4, we decided to study if L-PGDS and GGA3 are mutually involved in the regulation of DP1 recycling. Silencing endogenous L-PGDS expression inhibited the GGA3-mediated effect on DP1 trafficking. Conversely, GGA3 expression knockdown prevented L-PGDS from modulating the trafficking of DP1. Taken together, these results establish a concerted role for GGA3 and L-PGDS in the recycling of DP1.

Given their interdependent roles in DP1 trafficking, we next considered whether there is an interaction between GGA3 and L-PGDS. Immunoprecipitation studies revealed an endogenous interaction in HeLa cells and the direct interaction between the two proteins was confirmed using *in vitro* binding assays with purified recombinant proteins. The fact that L-PGDS interacts principally with the VHS and GAE domains is interesting considering the roles of these domains in GGA3 function. The VHS domain is known to bind to specific cargo proteins while the GAE domain binds to multiple accessory proteins, including rabaptin-5(Mattera et al. 2003), a Rab4 effector. This may indicate a role for L-PGDS in affecting endosomal tethering or fusion events. Confocal microscopy in HeLa cells showed a basal colocalization between GGA3 and L-PGDS. However, L-PGDS was primarily distributed at the periphery of Rab4- and GGA3-containing vesicles. Interestingly, DP1 stimulation induced a redistribution of L-PGDS and its colocalization with GGA3 and Rab4. Our data reveal a new interaction between GGA3 and L-PGDS in a Rab4-positive compartment that is regulated by activation of their DP1 cargo protein.

Based on the literature and our own current and previous findings (33, 40), we propose one of the possible mechanisms by which L-PGDS and GGA3 might regulate DP1 recycling (Fig. 8). At the basal state, L-PGDS colocalizes with Rab4 and GGA3 but is predominantly distributed at the periphery of Rab4- and GGA3-containing vesicles. Stimulation of DP1 with PGD_2 triggers internalization of the receptor, redistribution of L-PGDS to Rab4- and GGA3-containing

endosomes, and formation of DP1/L-PGDS/Rab4 complexes in recycling endosomes. This in turn leads to Rab4 activation and its interaction with its effector rabaptin-5. GGA3, via its interaction with the latter (61), could be recruited to the membrane and interact with L-PGDS. This could explain how GGA3 is recruited to the membrane in an Arf-independent mechanism. Alternatively, L-PGDS could promote activation of Rab4, and then its interaction with GGA3 could bring rabaptin-5 in close vicinity with Rab4 to favor their interaction. Rabaptin-5 serves as a linker between Rab4 and g1-adaptin. By interacting with g1-adaptin and their other partners, GGA3 and rabaptin-5 would continue the chain of events leading to the recycling of the receptor. Whether rabaptin-5 and g1-adaptin are involved and the exact sequential order of the implication of the different proteins remain to be determined.

Receptor recycling is also involved in the regulation of GPCR signaling following agonist stimulation. Measurements of ERK1/2 activation following DP1 activation by PGD_2 showed that depletion of endogenous GGA3 significantly reduced DP1 signaling. This is in agreement with reports showing that through its role in receptor recycling, GGA3 plays a role in the signaling of the Met, TrkA, β1-integrin and Ret51 receptors(Crupi et al. 2019; Xuezhi Li et al. 2015; Parachoniak et al. 2011; Ratcliffe et al. 2016).

5. Conclusions

In summary, we discovered novel interactions between GGA3, L-PGDS and DP1, in which GGA3 and L-PGDS cooperate in a new mechanism to mediate the recycling of the receptor in an Arf-independent, Rab4-dependent process with a functional impact on receptor signaling.

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ARTICLE 2 : Identification of the interactome of the DP1 receptor for Prostaglandin D_2: regulation of DP1 receptor signaling and trafficking by IQGAP1

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AVANT-PROPOS : Cet article a été écrit en totalité par Louis Fréchette sous la supervision du professeur Jean-Luc Parent (Directeur de recherche). La conception des expériences de même que la réalisation de celles-ci ont été faite en majorité par Louis Fréchette. Jade Degrandmaison a aidé pour l'analyse, la réalisation et la conception des expériences de spectrométrie de masse. Quelques expériences de GST-PULLDOWN, d'activation de ERK et d'immunoprécipitation ont été réalisés par Chantal Binda. Marilou Boisvert et Laurie Côté ont aidé à la réalisation de certains panneaux de figures. Thomas Michaud et Marie-Pier Lalumière ont aidé pour les révisions de l'article et ont effectués des clonages.

RÉSUMÉ

Les mécanismes gouvernant la localisation, le trafic ainsi que la signalisation des récepteurs couplés aux protéines G sont essentiels dans le fonctionnement d'une cellule. Les interactions protéines-protéines sont des facteurs importants dans ces fonctions. Nous rapportons ici la première analyse de LC-MS/MS de l'interactome de DP1. En plus d'avoir identifié des protéines attendues tel que les sous-unités des protéines G, nous avons identifiés plusieurs protéines impliquées dans la signalisation, le trafic et le repliement dans différentes sous-localisations cellulaire. Afin de valider les données obtenues dans cet essai de LC-MS/MS, nous avons étudié l'implication d'une protéine échafaud, IQGAP1, dans le trafic et la signalisation de DP1. Une co-immunoprécipitation endogène a été observée dans des cellules d'adénocarcinome du côlon HT-29. L'interaction et augmentée par la stimulation de DP1 par son agoniste naturel dans les cellules HEK 293 et les essais de GST-pulldown ont démontré que IQGAP1 lie les boucles intracellulaires 2 et 3 de DP1. La colocalisation des deux protéines a été observée par microscopie confocale à la membrane plasmique ainsi que dans les vésicules intracellulaires à l'état basal. Un traitement à la PGD_2 a résulté en une redistribution de la colocalisation des deux protéines dans la région périnucléaire. L'internalisation de DP1 a été augmentée par la surexpression de IQGAP1 et diminuée lorsque des ARN interférents de IQGAP1 ont été utilisés. La diminution de IQGAP1 a également causé une diminution de l'activation des ERK1/2 due à la stimulation de DP1. De manière intéressante, la signalisation ERK1/2 a été augmentée lors de la diminution de IQGAP2 par ARN interférent, mais a été diminuée lors de l'utilisation d'ARN interférents de IQGAP3. Nous avons caractérisé un interactome potentiel à DP1, un récepteur important au point de vue physio-pathologique et validé l'interaction de IQGAP1 et ses effets fonctionnels sur DP1. Nos données révèlent également une signalisation différentielle de la signalisation par les différents isoformes de IQGAP.

ABSTRACT

Mechanisms governing localization, trafficking and signaling of G protein-coupled receptors (GPCRs) are critical in cell function. Protein-protein interactions are determinant in these processes. We report here the first LC-MS/MS analysis of the DP1 receptor interactome. In addition to expected interacting proteins such as heterotrimeric G protein subunits, we identified

proteins involved in signaling, trafficking, and folding localized in various cell compartments. To functionally validate our LC-MS/MS data, we studied the implications of the interaction with the IQGAP1 scaffold protein in the trafficking and signaling of DP1. Endogenous DP1-IQGAP1 co-immunoprecipitation was observed in colon cancer HT-29 cells. The interaction was augmented by DP1 agonist activation in HEK293 cells and GST-pulldown assays showed that IQGAP1 binds to intracellular loops 2 and 3 of DP1. Co-localization of the two proteins was observed by confocal microscopy at the plasma membrane and in intracellular vesicles in the basal state. PGD_2 treatment resulted in the redistribution of the DP1-IQGAP1 co-localization in the perinuclear vicinity. DP1 receptor internalization was promoted by overexpression of IQGAP1, while it was diminished by IQGAP1 knockdown with DsiRNAs. DP1-mediated ERK1/2 activation was augmented and sustained overtime by overexpression of IQGAP1 when compared to DP1 expressed alone. IQGAP1 knockdown decreased ERK1/2 activation by DP1 stimulation. Interestingly, ERK1/2 signaling by DP1 was increased when IQGAP2 was silenced, while it was impaired by IQGAP3 knockdown. Our findings define the putative DP1 interactome, a patho-physiologically important receptor, and validated the interaction with IQGAP1 in DP1 function. Our data also reveal that IQGAP proteins may differentially regulate GPCR signaling.

Keywords: DP1, GPCR, IQGAP1, interactome, signaling, trafficking.

1. **Introduction**

G protein-coupled receptors (GPCRs) form the largest class of transmembrane proteins and control a vast array of cellular functions(Hauser et al. 2017). They display 7 transmembrane domains and are coupled to heterotrimeric G proteins. GPCRs respond to a plethora of structurally and chemically distinct ligands such as peptides, proteins, hormones, lipids, tastants, odorants, photons, ions, nucleotides and a panoply of metabolic intermediates(Wacker, Stevens, and Roth 2017). The importance of GPCRs in physiology, pathogenesis and therapeutics is well established. Approximatively 35% of approved drugs target this class of receptors(Sriram and Insel 2018). Agonist-induced activation of GPCRs can result in the modulation of ion channels activity(Burke and Bender 2019), intracellular calcium mobilization(Predescu et al. 2019), phospholipids metabolism(Oude Weernink et al. 2007) and cyclic AMP levels(Hill, Williams, and May 2010). Spatial/intracellular distribution of the receptors may diversify the signaling output following receptor activation(Lohse and Hofmann 2015; Pavlos and Friedman 2017). Although GPCRs were classically thought to signal from the plasma membrane, increasing evidence indicates that the receptors can also signal from endosomal compartments and other intracellular organelles such as the nucleus and mitochondria(Y. J. I. Jong et al. 2018). Considerable research efforts were devoted to elucidating the canonical signaling and trafficking pathways of GPCRs in the last decades. Our awareness of the complexity of GPCR signaling and trafficking mechanisms has increased as new interaction partners and intracellular sites of activity were identified in recent years. Proteomics approaches proved to be pivotal in furthering our understanding of GPCR biology.

Prostaglandin D_2 (PGD_2) is a bioactive lipid implicated in many physiological processes, such as pain(Eguchi et al. 1999; Ito et al. 2001), bronchodilation(Johnston et al. 1995; Murata et al. 2013), bone formation(Gallant et al. 2005, 2010) and sleep/wake regulation(Ahmad et al. 2019; Qu et al. 2006). PGD_2 is known to be the ligand of two GPCRs, namely the prostanoid DP receptor (DP1) and the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2, also known as DP2)(Narumiya and Furuyashiki 2011). In contrast to DP1, which is a member of the prostanoid receptor family, CRTH2 displays higher homology with the N-formyl peptide receptor family(Hirai et al. 2001). DP1 signals through $G\alpha_s$ and activates the ERK1/2 mitogen-activated protein kinase (MAPK) pathway(Labrecque, Sébastien J. Roy, et al. 2013). There are

many reports on DP1 as being highly relevant in a number of pathological states, including major depressive disorder(Chu et al. 2017; Onaka et al. 2015), asthma(Hammad et al. 2007b; Oguma et al. 2004), Parkinson's disease(Choi et al. 2019; Corwin et al. 2018) and colon cancer(Murata et al. 2008). However, very little is known about the interacting partners of DP1 and the molecular mechanisms involved in PGD_2-mediated effects.

Scaffold proteins are generally described as proteins that may partake in at least 4 cellular functions: 1) defining the localization of proteins or components at a specific subcellular area; 2) protecting its substrate from enzymatic action; 3) modulating a signaling output; and 4) spatially assisting in scaffolding components of a signaling cascade(Shaw and Filbert 2009). IQ-motif containing GTPase activating proteins (IQGAPs) are a multidomain, multifunction family of scaffold proteins of high molecular weight implicated in a wide array of cellular functions that comprise three members, IQGAP1, IQGAP2 and IQGAP3(Hedman et al. 2015). The best characterized member of this family is IQGAP1, a 189 kDa protein involved in several major cellular pathways, such as cell migration, endocytosis, cellular signaling, nuclear transcription, mRNA processing and mitotic spindle orientation(Jessica M Smith et al. 2015). Altered expression and localization of IQGAP1 are highly correlated with cancer progression in several cancer types(Johnson, Sharma, and Henderson 2009).

In this study, we performed mass spectrometry experiments to determine the interactome of DP1 and cross-referenced the results with the Catalogue of Somatic Mutations in Cancer (COSMIC). A large proportion of the putative DP1 interactors, such as IQGAP1, are listed in the COSMIC database and expressed in the large intestine. Considering that DP1 and IQGAP1 were reported to be implicated in colon cancer, we analyzed the interaction between these proteins and monitored the functional impact of IQGAP1 on DP1. We report that IQGAP1 regulates DP1 trafficking and signaling.

2. **Materials and methods**

2.1 *Reagents*

TransIT-LT1 transfection reagent was acquired from Mirus Bio LLC. The 9191 anti-Phospho-ERK1/2 and 4695 ERK1/2 antibodies were purchased from Cell Signaling. The LS-C146656

polyclonal DP1 antibody was obtained from LifeSpan Biosciences, Inc. The sc-25778 anti-GAPDH antibody and Protein-G PLUS-agarose sc-2002 beads were from Santa Cruz Biotechnology. The rabbit polyclonal anti-FLAG antibody, the monoclonal anti-FLAG M2 antibody (uncoupled or immobilized on magnetic beads), the poly-L-lysine, the alkaline phosphatase-conjugated goat anti-mouse antibody, the X-tremeGENE™ HP transfection reagent (trademark of ROCHE) and the alkaline phosphatase substrate kit were from Sigma-Aldrich. The 610611 monoclonal mouse anti-IQGAP1 antibody was from BD Transduction Laboratories. The anti-GST-HRP antibody was from Bethyl Laboratories and the anti-Myc-HRP polyclonal antibody was from Abcam. PGD_2 was obtained from Cayman Chemical Co. The ProLong® Gold antifade reagent, Lipofectamine 2000, the Alexa Fluor 488 donkey anti-rabbit and Alexa Fluor 633 goat anti-mouse antibodies were purchased from Invitrogen.

2.2 *Mass spectrometry design and analysis*

Mass spectrometry experiments were carried out basically as we reported before(Degrandmaison et al. 2020; Roy et al. 2013). Three 100 mm Petri dishes of confluent HEK293 cells, transfected either with pcDNA3 or pcDNA3-FLAG-DP1 were grown for 48 h after transfection. All following steps were performed on ice using chilled solutions. Cells were washed twice on plates with PBS, harvested, pelleted by a 1000 g centrifugation for 5 min and then lysed in 10 mL lysis buffer (Tris 5 mM pH 7.4, EDTA 2 mM, 10 µM pepstatin, 10 µM antipain, 10 µM leupeptin, and 10 µM chymostatin). Cellular debris were cleared with a 1000 g spin for 20 min at 4ºC and the supernatants were collected and further centrifuged at 30 600 g for 20 min at 4ºC to pellet the crude membranes. The supernatant was removed, and membranes were resuspended in 500 µL of solubilization buffer (1% octylglucoside, 75 mM Tris-HCl pH 8.0, 2 mM EDTA, 5 mM $MgCl_2$, 10 µM pepstatin, 10 µM antipain, 10 µM leupeptin, and 10 µM chymostatin) for 40 min. Thirty µL were kept for Western blot analysis. To immunoprecipitate the receptor, the samples were then incubated overnight at 4ºC with 75 µL of FLAG-M2 conjugated magnetic beads prewashed four times with equilibration buffer (50 mM Tris HCl, 150 mM NaCl, pH 7.4). Beads were then washed with solubilization buffer (without protease inhibitors) and washed 5 more times with ammonium bicarbonate buffer (20 mM ammonium bicarbonate pH 8.0). The following steps were performed by the Proteomics Platform of the Faculty of Medicine and Health Sciences of the University of Sherbrooke. Supernatants were removed and beads were then

incubated at 37 ºC with 50 ng of chymotrypsin overnight and 1% formic acid was added to stop chymotrypsin digestion. The supernatant was transferred to a clean Eppendorf® Protein Lo-Bind tube. Beads were resuspended in 60% acetonitrile / 0.1% formic acid at room temperature for 5 min and the supernatants were pooled. The samples were dried in a speed vac and resuspended in 20 µL of sample buffer (0.1% trifluoroacetic acid). Resulting peptides were then desalted with Zip Tip pipette tips as per manufacturer's instructions and separated by HPLC (Ultimate 3000 Binary RSLCnano-Thermo Scientific). Samples were then analyzed on a Q exactive Hybrid Quadripole-Orbitrap ™ mass spectrometer (Thermo Scientific).

The MaxQuant software package version 1.5.1.2 was used to process, search, and quantify the data collected using the Uniprot human protein database containing 75776 proteins, to which 175 commonly observed contaminants and all the reversed sequences had been added. The initial mass tolerance was set to 7 p.p.m. and MS/MS mass tolerance was 0.5 Da. Enzyme was set to Chymotrypsin with 2 missed cleavages. Carbamidomethylation of cysteine was searched as a fixed modification, whereas *N*-acetyl protein and oxidation of methionine were searched as variable modifications. Identification was set to a false discovery rate of 1%. To achieve reliable identifications, all proteins were accepted based on the criteria that the number of forward hits in the database was at least 100-fold higher than the number of reverse database hits, thus resulting in a false discovery rate of less than 1%. A minimum of 3 peptides were quantified for each protein, and quantification performed only in the presence of 3 ratio counts(Babeu et al. 2019).

Proteins identified by LC-MS/MS analyses were considered as positive hits when the ratio of peptide intensity displayed at least a 1.5-fold increase over the negative control (pcDNA3) and when present in at least 2 out of 3 mass spectrometry experiments. All positive hits were analyzed using the Functional Enrichment Analysis Tool(Pathan et al. 2015) (FunRich) and compared with the Catalogue Of Somatic Mutation In Cancer(Tate et al. 2019) (COSMIC, cancer.sanger.ac.uk). Classification of the potential DP1-interacting proteins according to their cellular localization was performed using the PANTHER Classification System Online Tool(Thomas et al. 2003). Analysis of signaling pathways were carried out with the REACTOME pathway database(Jassal et al. 2020) (https://reactome.org).

2.3 *Plasmid constructs*

pcDNA3-Myc-IQGAP1 was a gift from David Sacks (Addgene plasmid #30118; http://n2t.net/addgene:30118 ; RRID:Addgene_30118)(Ho et al. 1999). The pcDNA3-FLAG-DP1, pGEX-4T1-DP1-CT, pGEX-4T1-DP1-ICL1, pGEX-4T1-DP1-ICL2 and pGEX-4T1-DP1-ICL3 constructs were generated as previously described(Binda et al. 2014; Gallant et al. 2005; Parent et al. 2010a) .

2.4 *Cell culture and transfections*

Human embryonic kidney (HEK293) and human colorectal adenocarcinoma (HT-29) cells were maintained in DMEM (Wisent) or McCoy's medium (Wisent), respectively, supplemented with 10% fetal bovine serum at 37°C in a humidified atmosphere containing 5% CO_2. Transient transfection of HEK293 cells or HT-29 cells grown to 50–70% confluence was performed using the TransIT-LT1 reagent or the X-tremeGENE HP™ reagent, respectively, and according to the manufacturer's instructions. The total DNA amount was kept constant by adding pcDNA3 vector in each transfection condition. Transfection of pcDNA3-Myc-IQGAP1 resulted in a two-fold increase in IQGAP1 expression compared to the endogenous expression level (not shown).

2.5 *DsiRNAs*

The DsiRNAs targeting IQGAP1 (hs.Ri.IQGAP1.13.1 and hs.Ri.IQGAP1.13.2), IQGAP2 (hs.Ri.IQGAP2.13.1 and hs.Ri.IQGAP2.13.2), IQGAP3 (hs.Ri.IQGAP3.13.1 and hs.Ri.IQGAP3.13.2) and negative control (DS NC1) were obtained from Integrated DNA Technologies. HEK293 or HT-29 cells were transfected with 10 nM DsiRNAs using Lipofectamine 2000. Cells were transfected 24 h later with pcDNA3-FLAG-DP1 as described above and endpoint experiments were performed 48 h post DNA transfection.

2.6 *Recombinant protein production and pulldown analysis*

The fusion proteins were produced in the Overexpress™ C41 (DE3) Escherichia coli strain (Avidis) by following the manufacturer's instructions. Gluthatione-Sepharose 4B beads (Amersham Biosciences) were used for protein purification. The purified recombinant proteins were analyzed by SDS-PAGE followed by a Coomassie Brilliant Blue R-250 to quantify proteins

levels. For GST-pulldown assays, equal quantities of GST-fusion proteins were incubated for 90 min at 4 ºC with 1200 µg of lysate proteins from cells transfected with the indicated constructs, as mentioned above. The reactions were then washed five times with lysis buffer (150 mM NaCl, 50 mM Tris (pH 8.0), 0.5% sodium deoxycholate, 0.1% SDS, 10 mM $Na_4P_2O_7$, 1% IGEPAL, and 5 mM EDTA). SDS sample buffer was added to each reaction before boiling the tubes for 5 min. All reactions were analyzed by Western blotting using the indicated specific antibodies.

2.7 *Measurement of DP1 cell surface expression and internalization*

Cell surface expression and internalization assays were performed by ELISA as we reported before(Binda et al. 2014; Fréchette et al. 2020). For quantification of receptor internalization, HEK293 cells were plated at a density of 5 X 10^4 in 24-well plates pre-treated with 0.1 mg/ml poly-L-lysine (Sigma). Cells were transfected the following day with the indicated constructs and were stimulated 48 h post-transfection with 1 µM PGD_2 in stimulation buffer (serum-free DMEM supplemented with 20 mM HEPES and 0.5% BSA) for the indicated times. The cells were then fixed in 3.7% formaldehyde/Tris-buffered saline (TBS) (20 mM Tris, pH 8.0, 150 mM NaCl) for 10 min and then washed twice with TBS. Cells were blocked with TBS containing 1% BSA for 45 min to avoid non-specific binding. A rabbit anti-FLAG polyclonal antibody was then added at a dilution of 1:1500 in 1% TBS-BSA for 60 min. Cells were then washed three times and blocked again with 1% TBS-BSA for 15 min. Cells were incubated with an alkaline phosphatase-conjugated goat anti-rabbit antibody at a 1:10,000 dilution in 1% TBS-BSA for 60 min. The cells were then washed three times before adding 250 µL of a colorimetric alkaline phosphatase substrate as described per the manufacturer's instructions. The plates were incubated at 37°C for 15 min before adding 250 µL of 0.4 M NaOH to stop the reaction. One hundred microliters of the colorimetric reaction were collected, and the absorbance was measured at 405 nm using a spectrophotometer (Titertek Multiskan MCC/340; Labsystem). Cells transfected with pcDNA3 alone were studied concurrently to determine background which was subtracted from the readings of the various experimental conditions.

For quantification of receptor internalization using DsiRNAs, HEK293 cells were plated at respectively 5 X 10^4 and 6 X 10^4 cells in 24-well plates and transfected the same day with the desired DsiRNAs. Cells were transfected the following day with the indicated constructs and 48

h after the DNA transfection, cells were stimulated with 1 µM PGD_2 for the indicated times. ELISAs were carried out as mentioned above.

2.8 *Immunoprecipitations*

HEK293 cells were transiently transfected with the indicated constructs and were maintained as described above for 48 h. The cells were then washed with ice-cold PBS and harvested in 200 µL of lysis buffer (150 mM NaCl, 50 mM Tris (pH 8.0), 0.5% sodium deoxycholate, 0.1% SDS, 10 mM $Na_4P_2O_7$, 1% IGEPAL, and 5 mM EDTA supplemented with protease inhibitors (10 µM pepstatin, 10 µM antipain, 10 µM leupeptin, and 10 µM chymostatin). After a 60 min incubation in lysis buffer at 4°C, the lysates were then centrifuged for 20 min at 17 000 g at 4°C. Following centrifugation, 40 µL of 50% protein G-agarose beads and one microgram of specific antibodies were added to the supernatant, followed by an overnight incubation at 4°C with rotation. Samples were then centrifuged for 1 min in a microcentrifuge and washed three times with 1 mL of lysis buffer. Immunoprecipitated proteins were eluted by the addition of 40 µL of SDS sample buffer, followed by a 30 min incubation at 37°C. Initial lysates and immunoprecipitated proteins were analyzed by SDS-PAGE and immunoblotting was carried out using the indicated specific antibodies. Experiments were done at least 3 times.

Endogenous immunoprecipitations were performed in HT-29 cells. Cells were harvested and processed as described for HEK293 cells except proteins were immunoprecipitated overnight using 5 µg of IQGAP1 specific antibodies, 1 µg of DP1 specific antibodies or appropriate control antibodies and 40 µL of 50% protein G-agarose beads.

2.9 *Immunofluorescence staining and confocal microscopy*

For co-localization experiments, HEK293 cells were seeded directly onto coverslips previously coated with 0.1 mg/mL of poly-L-lysine at a density of 4 X 10^4 cells/well in 6-well plates. The cells were then transiently transfected with the indicated constructs using TransIT-LT1 according to the manufacturer's instructions. After 48 h, the cells were fixed with 4% paraformaldehyde in PBS, washed with PBS, permeabilized with 0.1% Triton X-100 in PBS and blocked with 0.1% Triton X-100 in PBS containing 2% BSA. They were then incubated with primary antibodies diluted in blocking solution for 60 min, washed twice with 0.1% Triton X-100 in PBS, blocked

with 0.1% Triton X-100 in PBS containing 2% BSA, and incubated with the appropriate secondary antibodies diluted in blocking solution for 60 min. The cells were then washed twice with 0.1% Triton X-100 in PBS followed by three washes with PBS. The coverslips were mounted using ProLong® Gold antifade reagent. Confocal microscopy was performed using a scanning confocal system (TCS SP8; Leica) coupled to an inverted microscope with a 60x oil-immersion objective (DMI8; Leica) and the images were processed using LAS X software (Leica) and Imaris (Oxford Instruments).

2.10 *ERK1/2 activation*

HEK293 cells were seeded in 6-well plates at a density of 5 x 10^5 cells per well, immediately transfected with indicated DsiRNA and incubated for 24 h before being transfected with the indicated DNA constructs as described above. Forty-eight hours after DNA transfection, cells were starved for 180 min in serum-free DMEM supplemented with 0.5% BSA and 20 mM HEPES pH 7.5 and then treated with 1 µM PGD_2 or DMSO for the indicated times. The reactions were stopped by adding 250 µL of 1X sample buffer (62.5 mM Tris pH 7.0, 2% w/v SDS, 10% glycerol, 50 mM DTT, 0.01% w/v bromophenol blue) and sonicated. The samples were then analyzed by Western blotting using phospho-p42/p44 and secondary horseradish peroxidase-conjugated anti-rabbit antibodies. Blots were then stripped and re-probed with p42/p44 antibodies. Experiments were done at least 3 times and densitometry analyses were carried out using NIH ImageJ 1.8.0 software.

2.11 *Statistical Analyses*

Statistical analyses were performed using Prism v7.01 (GraphPad Software, San Diego, CA, USA) using the repeated measure one-way ANOVA. A Tukey's multiple comparisons test was made as a post-hoc test to establish statistical significance between conditions. Data were considered significant when P values were < 0.05 (*), <0.01 (**), <0.001(***) or <0,0001 (****).

3. Results

3.1 *Identification of putative DP1 interaction partners by LC-MS/MS*

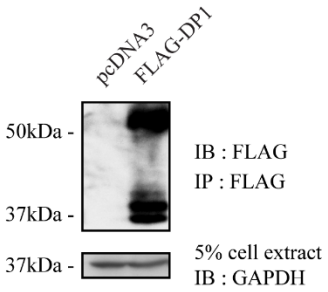
Given its significant relevance in various physiological and pathological conditions, we sought to characterize the interactome of DP1 in order to provide new leads for our understanding of the molecular and cellular mechanisms underlying its regulation and effects. To do so, we performed LC-MS/MS analyses of the potential interactors of DP1 in a cellular context. Due to the low expression levels of GPCRs and the lack of efficient antibodies for their immunoprecipitation, the study of their interactome at endogenous levels is challenging(Jo and Jung 2016; Michel, Wieland, and Tsujimoto 2009). Therefore, N-terminally FLAG-tagged DP1 was transiently expressed in HEK293 cells and immunoprecipitated from cell lysates using anti-FLAG M2 monoclonal antibodies coupled to magnetic beads (Fig. 1A), and the potential DP1 interactors were identified by LC-MS/MS as we recently reported(Degrandmaison et al. 2020; Roy et al. 2013). Controls consisted of lysates of cells transfected with empty pcDNA3 vector that were subjected to the same treatments. Note that multiple bands can be observed in the FLAG-DP1 Western blots reflecting the various levels of DP1 glycosylation and maturation(Parent et al. 2010a). The protocol was performed three times. Candidate interacting proteins were considered as positive hits when the ratio of peptide intensity FLAG-DP1/pcDNA3 displayed at least a 1.5-fold increase and when present in at least 2 out of 3 mass spectrometry experiments. A total of 704 potential DP1-interacting proteins were identified and are listed in Supplementary Table 1. Proteins that are commonly found in such proteomics analyses were not subtracted from our list. Indeed, proteins like chaperones and chaperonins are frequently identified as interaction partners but were shown to have important functions in GPCR biology(Binda et al. 2014; Génier et al. 2016). To help readers evaluate how common is a given identified interaction, we included a column in Supplementary Table 1 indicating the number of times each protein was identified in 716 mass spectrometry experiments catalogued in the CRAPome database (https://reprint-apms.org/). The list of candidate DP1-interacting proteins that were identified in only one of the experiments that were not included in our analyses can be found in Supplementary Table 2.

Table 1. Potential DP1-interacting proteins involved in ERK1/2 signaling. A protein was considered as a positive hit when the ratio of peptide intensity DP1/pcDNA3 displayed at least a 1.5 fold increase in 2 out of 3 experiments. Results from experiments are separated by a hyphen. ∞ indicates that peptides were detected only in the DP1 condition. The sequence coverage represent the percentage of amino acids of the proteins detected by the mass spectrometer. Number of protein partners shared between these DP1-interacting proteins and DP1 are indicated.

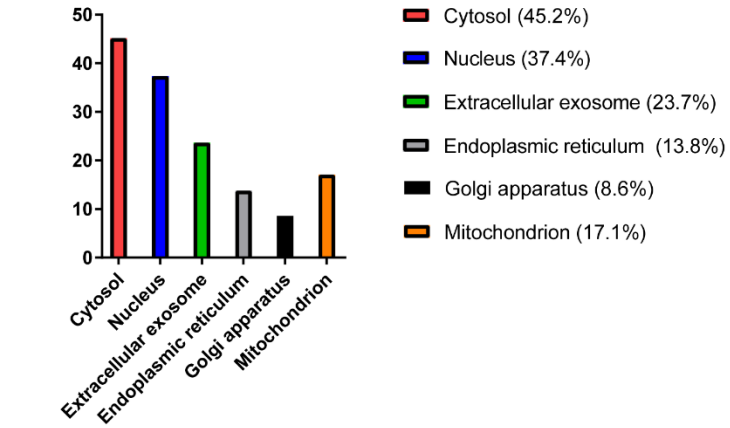
Gene symbol	Fold intensity DP1/pcDNA3	Sequence coverage (%)	Number of unique peptides	Number of partners shared with DP1
IQGAP1	8.1-∞	20.1-3.6	26-4	48
LAMTOR3	6.2-∞	30.6-6.0	2-1	10
KRAS	5.4-∞	38.8-7.4	6-1	177
JAK1	∞-2.4	7.1-1.0	6-1	9
RPS6KA2	∞-∞	5.0-5.4	2-1	16

A

BAIT Protein Prostaglandin D2 receptor (PTGDR)	MS1		MS2		MS3	
	CTRL	DP1	CTRL	DP1	CTRL	DP1
Number of unique peptides	0	5	0	3	0	7
Sequence coverage (%)	0	13.1	0	5	0	16.2
Fold intensity (DP1/CTRL)	∞		∞		∞	



B



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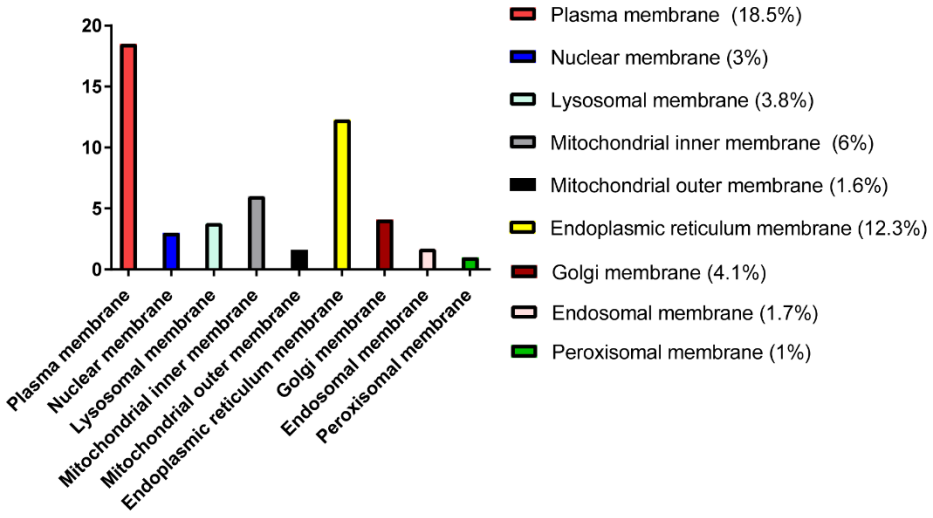

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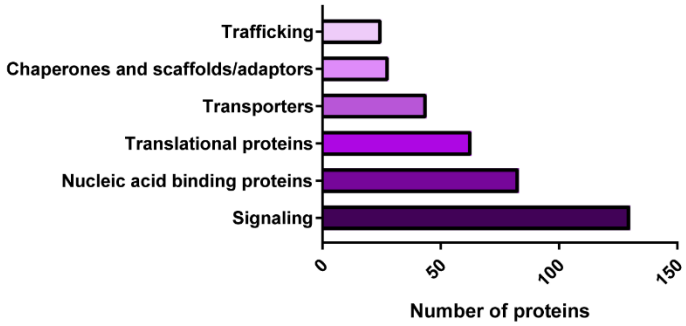
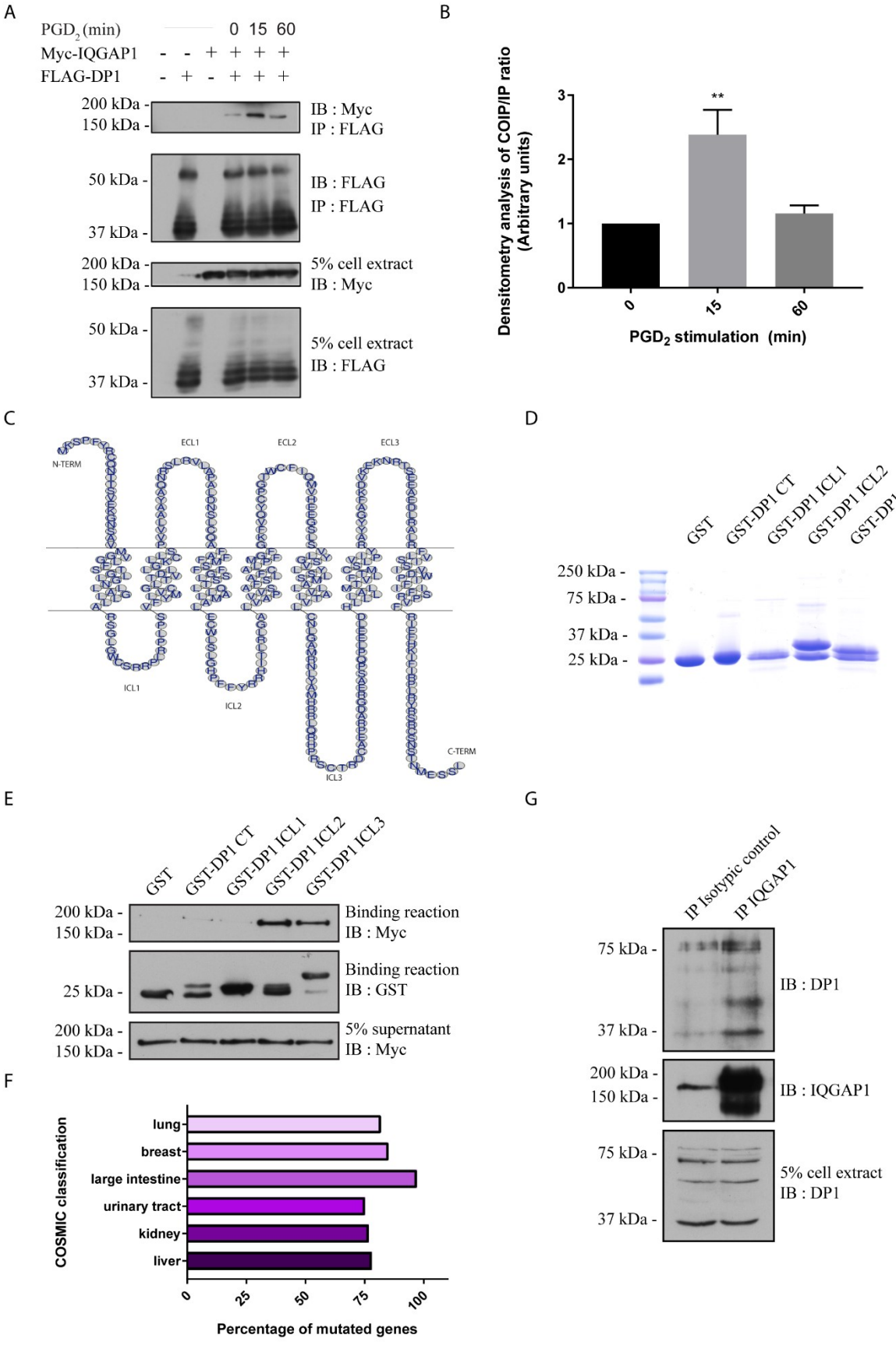


Fig. 1. Identification of putative DP1-interacting partners by LC-MS/MS. (A) Left, Summary of LCMS/MS data obtained for DP1 in the 3 experiments (MS1, MS2 and MS3). ∞ indicates that peptides were found only in the DP1 condition. Right, Control Western blot of the immunoprecipitation of transiently expressed FLAG-DP1 in HEK293 cells that was used in LC/MS-MS studies. IP: immunoprecipitation; IB: immunoblot. (B) Subcellular distribution of potential DP1-interacting partners according to the UNIPROT subcellular location. The sum of the percentages is superior to 100% since proteins may have multiple localizations. (C) Distribution of the candidate DP1-interacting proteins through various cellular membranes according to the UNIPROT subcellular location. (D) Classification of DP1-interacting proteins functions according to the PANTHER Classification system (PC). Trafficking (PC00150), Chaperones and scaffolds/adaptors (PC00072, PC00226), Transporters (PC00227), Translational proteins (PC00263), Nucleic acid binding (PC00171) and Signaling (PC00262, PC00207, PC00264, PC00197, PC00095, PC00077).

Using the PANTHER Classification System, the positive hits were clustered into 6 cellular components (Fig. 1B). Note that the sum of % distribution of all the components exceeds 100% because several proteins can be associated with multiple components. A large proportion (45.2%) of the identified interacting proteins are known to be localized in the cytosol (Supplementary Table 3). It is interesting to note that 37.4% of the interacting partners may display nuclear localization (Supplementary Table 4). Other potential DP1-interacting proteins can be found in exosomes (23.7%, Supplementary Table 5), mitochondrion (17.1%, Supplementary Table 6), endoplasmic reticulum (13.8%, Supplementary Table 7), and Golgi apparatus (8.6%, Supplementary Table 8). Although 37.2% of the candidates are proteins localized to biological membranes (Supplementary Table 9), only 18.5% are associated with the plasma membrane (Supplementary Table 10). The association of the potential DP1 interacting proteins with various cellular membranes is described in Fig. 1C. Candidates of interest were further classified according to their reported functions (Fig. 1D), covering protein folding and chaperones (25 proteins, Supplementary Table 11), proteins belonging to the transporters family (42 proteins, Supplementary Table 12), intracellular trafficking (25 proteins, Supplementary Table 13), translational proteins (61 proteins, Supplementary Table 14), nucleic acid binding (81 proteins, Supplementary Table 15) and signaling (129 proteins, Supplementary Table 16).


A
PGD2 (min) 0 15 60
Myc-IQGAP1 - - + + + +
FLAG-DP1 - + - + + +
200 kDa -
150 kDa -
IB : Myc
IP : FLAG
50 kDa -
37 kDa -
IB : FLAG
IP : FLAG
200 kDa -
150 kDa -
5% cell extract
IB : Myc
50 kDa -
37 kDa -
5% cell extract
IB : FLAG
B
Densitometry analysis of COIP/IP ratio (Arbitrary units)
**
PGD2 stimulation (min)
C
N-TERM
ECL1
ECL2
ECL3
ICL1
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D
GST
GST-DP1 CT
GST-DP1 ICL1
GST-DP1 ICL2
GST-DP1 ICL3
250 kDa -
75 kDa -
37 kDa -
25 kDa -
E
GST
GST-DP1 CT
GST-DP1 ICL1
GST-DP1 ICL2
GST-DP1 ICL3
200 kDa -
150 kDa -
Binding reaction
IB : Myc
25 kDa -
Binding reaction
IB : GST
200 kDa -
150 kDa -
5% supernatant
IB : Myc
F
COSMIC classification
lung
breast
large intestine
urinary tract
kidney
liver
Percentage of mutated genes
G
IP Isotypic control
IP IQGAP1
75 kDa -
37 kDa -
IB : DP1
200 kDa -
150 kDa -
IB : IQGAP1
75 kDa -
37 kDa -
5% cell extract
IB : DP1

Fig. 2. IQGAP1 interacts with DP1. (A) HEK293 cells transiently transfected with the specified combinations of pcDNA3-FLAG-DP1 and pcDNA3-Myc-IQGAP1 were stimulated for the indicated times with 1 μM PGD2. Immunoprecipitation (IP) of the receptor was performed using a FLAG-specific mAb, and immunoblotting (IB) was performed with polyclonal FLAG-specific or anti-MYC specific antibodies. (B) Quantification of Myc-IQGAP1 co-IP with FLAG-DP1 (mean ± S.E. (error bars)). (C) Schematic representation of the amino acid sequence of DP1. ECL: extracellular loop, ICL: intracellular loop. (D) Coomassie staining of an SDS-PAGE gel of the different purified GST-proteins using in the pulldown assays. (E) Binding assays were performed using purified glutathione Sepharose-bound GSTDP1-carboxyl terminal (CT) and intracellular loops (ICL) incubated with cellular lysates of HEK293 cells transfected with pcDNA3-Myc-IQGAP1. The binding of IQGAP1 to the receptor domains was detected by immunoblotting (IB) using an anti-Myc antibody, and the GST fusion proteins present in the binding reactions were detected using an anti-GST antibody. (F) Percentage of potential interacting partners of DP1 coding genes reported to be mutated in different cancer types by the COSMIC database. (G) Endogenous immunoprecipitations were performed in HT-29 cells using an IQGAP1-specific monoclonal antibody or isotypic control IgG antibody, and immunoblotting was performed using DP1- specific polyclonal or IQGAP1-specific monoclonal antibodies. Blots shown are representative of three independent experiments.

3.2 *IQGAP1 interacts with DP1*

We were next interested in studying the relevance of the candidate interacting proteins in DP1 trafficking and signaling. We have shown that DP1 activates MAPK/ERK1/2 signaling(Binda et al. 2014, 2019; Fréchette et al. 2020; Labrecque, Sébastien J. Roy, et al. 2013). To reveal the proteins that may participate in this signaling pathway, the Functional Enrichment Analysis Tool (FunRich) was used to compare the list of potential DP1 interacting partners with the MAPK-regulating constituents of the REACTOME pathway database(Jassal et al. 2020). Five proteins (IQGAP1, LAMTOR3, KRAS, JAK1, and RPS6KA2) involved in MAPK signaling and interacting with DP1 were identified. To determine whether these proteins shared interacting proteins with DP1, their reported interactomes were extracted from the Biological General Repository for Interaction Dataset (BioGRID)(Chatr-Aryamontri et al. 2017) and compared with the list of DP1 interacting partners. The number of interacting proteins shared between these five proteins involved in ERK1/2 signaling and DP1 is shown in Table 1.

Of these five proteins, IQGAP1 is the only one known to regulate both trafficking and ERK1/2 signaling, and it shares 48 interacting partners with DP1 (Table 1). IQGAP1 was thus an attractive potential DP1-interacting protein to further investigate and validate our LC-MS/MS data. The first step was to confirm the DP1-IQGAP1 interaction and whether it is modulated by receptor activation. Lysates of HEK293 cells expressing FLAG-DP1 and Myc-IQGAP1 that had been stimulated with PGD_2 or vehicle for the indicated times were immunoprecipitated with an anti-FLAG antibody and the samples were analyzed by Western blot (Fig. 2A). The DP1-IQGAP1

interaction was confirmed at basal state (t = 0 min) and was transiently increased after 15 min of PGD_2 stimulation of the receptor and returned to basal level after 60 min of receptor activation. To identify the intracellular domains of DP1 that interact with IQGAP1, GST fusion proteins of the four DP1 intracellular domains as well as the GST protein alone as a control were purified in bacterial cells and used in pulldown assays on lysates of HEK293 cells overexpressing Myc-IQGAP1. Intracellular loop 2 (ICL2) and intracellular loop 3 (ICL3) were identified as the predominant sites for the interaction with IQGAP1, with virtually no interaction detected in the GST control, GST-CT and GST-ICL1 lanes (Fig. 2B).

We then wanted to confirm the DP1-IQGAP1 interaction at the endogenous level in a relevant cell line. Since gathering evidence supports a role for DP1 in processes linked to cancer-related inflammation and inflammation-induced cancer (Gustafsson et al. 2007b; Hawcroft, Gardner, and Hull 2004; Yang, Tang, and Wei 2013), we were interested in studying whether the genes of candidate DP1 interacting partners were subject to mutations in a variety of cancer types. This was undertaken by using the FunRich tool (Pathan et al. 2015) to compare the list of potential DP1-interacting proteins with the Catalogue of Somatic Mutations in Cancer database (COSMIC)(Tate et al. 2019). A large percentage of the genes of putative DP1 interactors can be mutated in cancers of the urinary tract (75 %), kidney (77 %), liver (78 %), lung (82 %), breast (85 %), and large intestine (97 %) (Fig. 2C). Accordingly, we chose to study the endogenous DP1-IQGAP1 interaction in HT-29 cells, a colorectal adenocarcinoma cell line. HT-29 cell lysates were immunoprecipitated with an anti-IQGAP1 antibody or an isotypic control antibody, and the samples were analyzed by Western blotting with anti-DP1 and anti-IQGAP1 antibodies (Fig. 2D). Immunoprecipitation of endogenous IQGAP1 resulted in significantly higher quantities of DP1 co-immunoprecipitation compared to the control immunoprecipitation with the isotypic antibody. This confirmed that the endogenous DP1-IQGAP1 interaction can be detected in a relevant cell line.

3.3 *DP1 and IQGAP1 co-localization*

Confocal microscopy experiments were performed to determine the distribution of FLAG-DP1 and Myc-IQGAP1 in HEK293 cells. When expressed alone in the basal state, DP1 was detected

weakly at the plasma membrane and predominantly localized in intracellular vesicles in the perinuclear region of the cytoplasm, as we observed before in transfected and endogenous conditions(Binda et al. 2014; Fréchette et al. 2020; Parent et al. 2010a) (Fig. 3A, left panel). On the other hand, when expressed alone in the same conditions, IQGAP1 displayed strong localization at the plasma membrane, and was also seen in intracellular vesicles mostly concentrated in the vicinity of the nucleus (Fig. 3A, right panel). In the basal state, co-expression of the two proteins resulted in a DP1 intracellular vesicular distribution that was more spread out throughout the cytoplasm than when expressed alone (Fig. 3B, top left panel). In the presence of DP1, localization of IQGAP1 became more evenly distributed throughout the cytoplasm and still present at the plasma membrane (Fig. 3B, top middle panel). Co-localization between the two proteins can be seen in certain regions of the plasma membrane and in intracellular vesicles dispersed all through the cytoplasm (yellow pixels in Fig. 3B, top right panel). Stimulation with PGD_2 for 15 min, the time at which the interaction was maximally induced (Fig. 2A), resulted in the redistribution of the proteins and in their co-localization. DP1 was mainly detected in vesicles near the nucleus (Fig. 3B, bottom left panel). IQGAP1 was localized in punctate structures at the plasma membrane as well as in perinuclear vesicles (Fig. 3B, bottom middle panel). In these conditions, DP1 and IQGAP1 co-localized in vesicles in the vicinity of the nucleus (yellow pixels, Fig. 3B, bottom right panel).

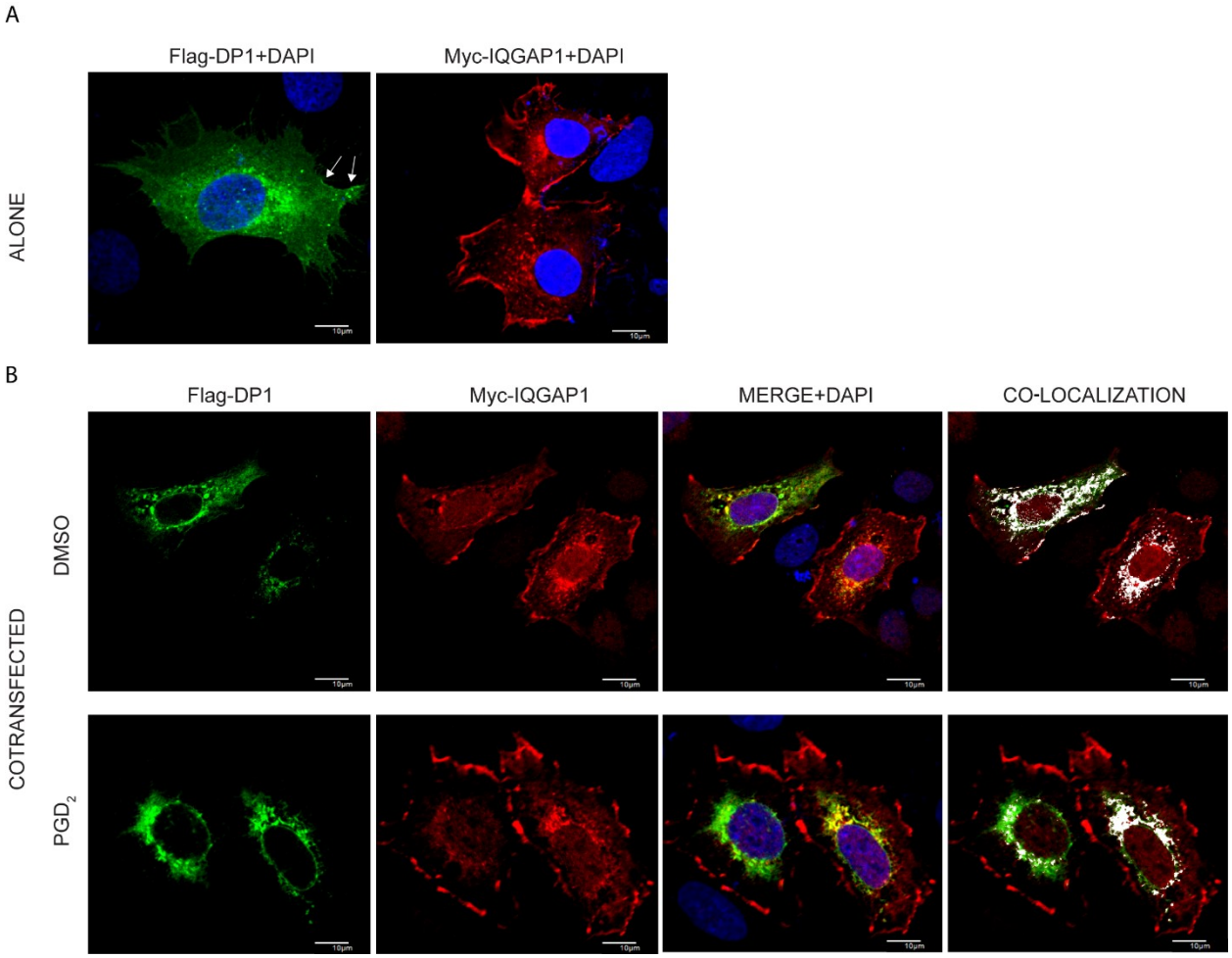

Fig. 3. Intracellular distribution of DP1 and IQGAP1. (A) HEK293 cells were transiently transfected with pcDNA3-FLAG-DP1 or pcDNA3-Myc-IQGAP1. The cells were then fixed and prepared for confocal microscopy as described in Materials and Methods. Myc-IQGAP1 was labelled with a Myc specific monoclonal antibody and an Alexa Fluor 546-conjugated anti-mouse IgG secondary antibody. It was visualized using a 543 nm emission laser line and an Alexa Fluor 546 detection filter (red). FLAGDP1 was labelled with a FLAG-specific polyclonal primary antibody and an Alexa Fluor 633-conjugated anti-rabbit IgG secondary antibody. It was visualized using a 633 nm emission laser line and an Alexa Fluor 633 detection filter (green). White arrows indicate DP1 at the plasma membrane. (B) HEK293 cells were transiently transfected with pcDNA3-FLAG-DP1 and pcDNA3-Myc-IQGAP1. The cells were then incubated with vehicle (upper panel) or with 1 µM PGD2 (lower panel) for 15 min. The cells were then processed for confocal microscopy, and FLAG-DP1 and IQGAP1 were visualized as indicated in (A). Overlays of the staining patterns of IQGAP1 and DP1 are presented (Merge) and the areas with high degree of co-localization appear in yellow. The "co-localization" panel shows the co-localizing pixels in white for easier observation. Nuclei were stained with DAPI. The images shown are single confocal slices and are representative of approximately 50 observed cells over three independent experiments. Bars, 10 µm.

3.4 *IQGAP1 regulates agonist-induced trafficking of DP1*

The role of IQGAP1 in the regulation of DP1 was then addressed. Considering that IQGAP1 can be involved in protein trafficking(Bamidele et al. 2015; Jessica M Smith et al. 2015) and the importance of trafficking in receptor signaling, we studied whether IQGAP1 modulated DP1 cell

surface expression after agonist stimulation. First, HEK293 cells transiently expressing FLAG-DP1 and Myc-IQGAP1 were subjected to a time-course of PGD_2 stimulation and FLAG-DP1 internalization was measured by ELISA as we described previously(Binda et al. 2014) (Fig. 4A). Co-expression of IQGAP1 promoted the PGD_2-induced internalization of DP1 throughout the time-course of receptor stimulation, with the largest effect at 30 min of agonist treatment where IQGAP1 increased receptor internalization by ~47%. A function for IQGAP1 in DP1 internalization was further explored with the use of two different DsiRNAs to knockdown endogenous IQGAP1 expression. Fig. 4B shows that depletion of endogenous IQGAP1 expression by both DsiRNAs caused a decrease in agonist-induced internalization of DP1 for the duration of the time-course, that was statistically different after 60 min of receptor stimulation. IQGAP1 expression knockdown by the two DsirRNAs is shown in Fig. 4C. Overexpression or depletion of IQGAP1 had no effect on total DP1 protein expression (see Fig. 5) or steady state levels of DP1 cell surface expression (data not shown). These data confirmed that IQGAP1 plays a positive role in agonist-mediated trafficking of DP1.

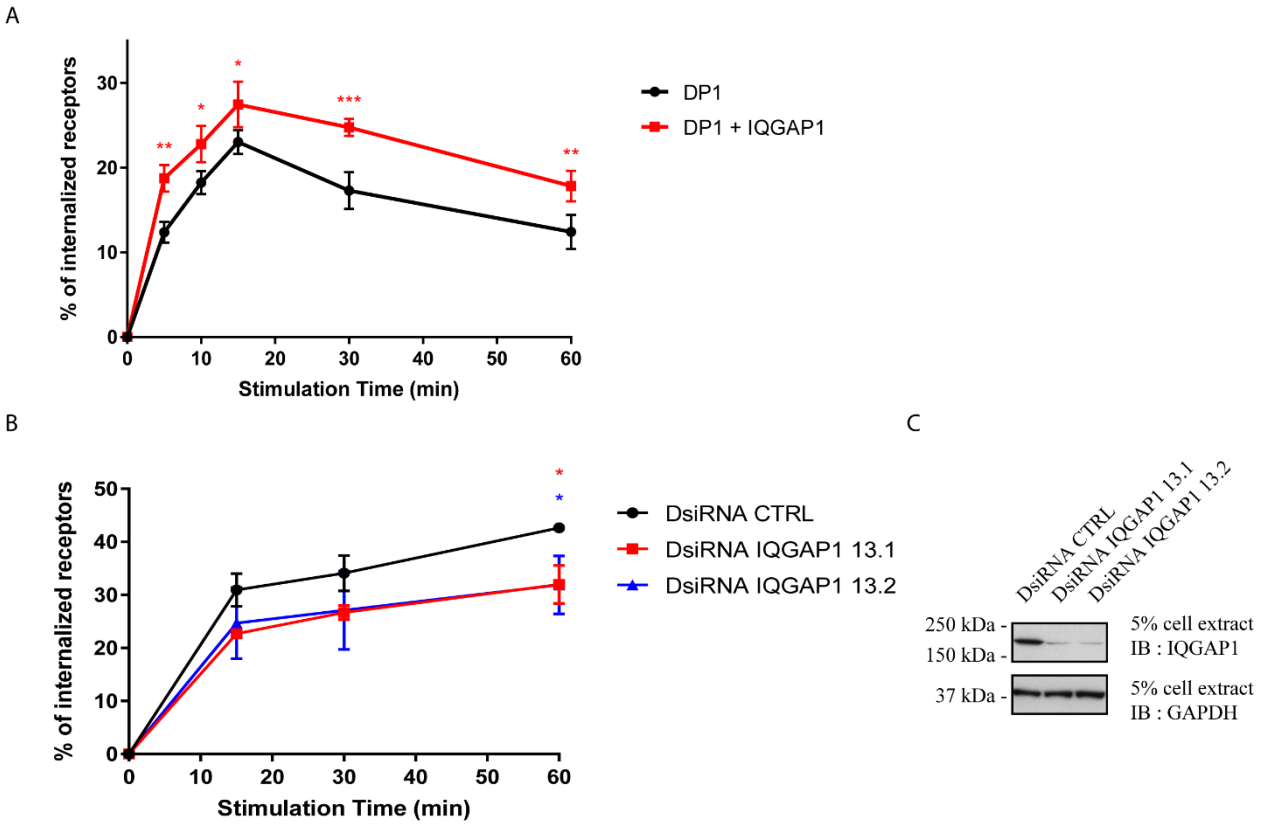

Fig. 4. IQGAP1 regulates the agonist-induced internalization of DP1. (A) Cell surface expression of the receptor was measured by ELISA in HEK293 cells transiently transfected with FLAG-DP1 in combination with pcDNA3 or pcDNA3-Myc-IQGAP1. 48 h post-transfection, cells were stimulated with 1 μM PGD2 for the indicated times, and the percentage of receptor internalization was calculated. (B) HEK293 cells were transfected with two different DsiRNAs targeting IQGAP1 or a negative control DsiRNA. 24 h after DsiRNAs transfection, cells were transiently transfected with pcDNA3-FLAG-DP1. 48 h after the second transfection, cells were treated with 1 μM PGD2 for the indicated times. Receptor cell surface expression was measured by ELISA, and the percentage of receptor internalization was calculated. (C) Immunoblotting (IB) of lysates from HEK293 cells that were transfected with the indicated DsiRNAs was performed with an IQGAP1-specific monoclonal antibody. Data from at least three independent experiments are presented as mean ± S.E. (error bars).

3.5 *IQGAP1 modulates DP1-induced ERK1/2 activation*

We next assessed the role of IQGAP1 in DP1-mediated ERK1/2 activation. Time-course analyses of ERK1/2 phosphorylation following DP1 stimulation were performed in HEK293 cells expressing FLAG-DP1 alone or in combination with Myc-IQGAP1 (Fig. 5A). ERK1/2 activation by DP1 expressed alone peaked between 5 and 10 min of receptor stimulation and gradually returned to near basal level. On the other hand, DP1-mediated ERK1/2 phosphorylation was promoted and sustained overtime by expression of IQGAP1 when compared to DP1 expressed alone. Knockdown of endogenous IQGAP1 expression resulted in a decrease in peak ERK1/2 activation after 5 min of DP1 stimulation (Fig. 5B). Interestingly, modulating the expression of IQGAP1 had no significant effect on p38, JNK and cAMP signaling following DP1 activation (not shown). Together, these data indicate that IQGAP1 participates selectively in ERK1/2 signaling mediated by DP1 activation.

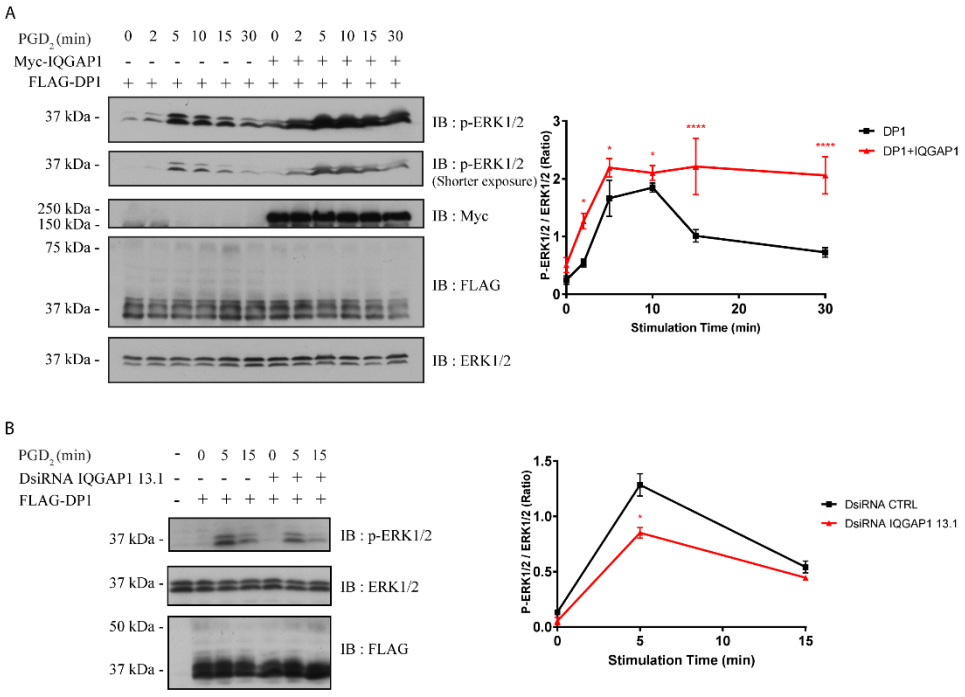

Fig. 5. IQGAP1 modulates DP1-induced ERK1/2 activation. (A) HEK293 cells were transiently transfected with pcDNA3-FLAG-DP1 and pcDNA3 or pcDNA3-Myc-IQGAP1. (B) HEK293 cells were transfected with IQGAP1 DsiRNA 12.1 or a negative control DsiRNA, and transiently transfected with pcDNA3-FLAG-DP1 24 h later. (A) and (B) 48 h after transfection of the receptor construct, cells were serum-starved for 3 h and stimulated with 1 µM PGD2 for the indicated times. Protein levels were assessed by Western blotting using FLAG, p-ERK1/2 and ERK1/2 antibodies. Densitometry analyses were performed on three different experiments. p-ERK1/2 pixels were normalized on ERK1/2 pixels, and results are presented as the ratio of these values (mean ± S.E. (error bars)).

3.6 *IQGAP2 and IQGAP3 regulate DP1-induced ERK1/2 activation*

We next wondered if the two other members of the IQGAP family, IQGAP2 and IQGAP3, were involved in the regulation of DP1 signaling. It was reported that the different IQGAPs may have diverse effects on particular signaling cascades(Jessica M Smith et al. 2015). Interestingly, knockdown of IQGAP2 expression promoted peak activation of ERK1/2 by DP1 stimulation (Fig. 6A and B), in contrast to IQGAP1. Conversely, depletion of IQGAP3 decreased DP1-mediated activation of ERK1/2 (Fig. 7A and B), similarly to IQGAP1. DsiRNA-mediated depletion of IQGAP2 and IQGAP3 expression is shown in Fig 6C and 7C, respectively. These results indicate that members of the IQGAP family have divergent roles in the regulation of ERK1/2 signaling by DP1.

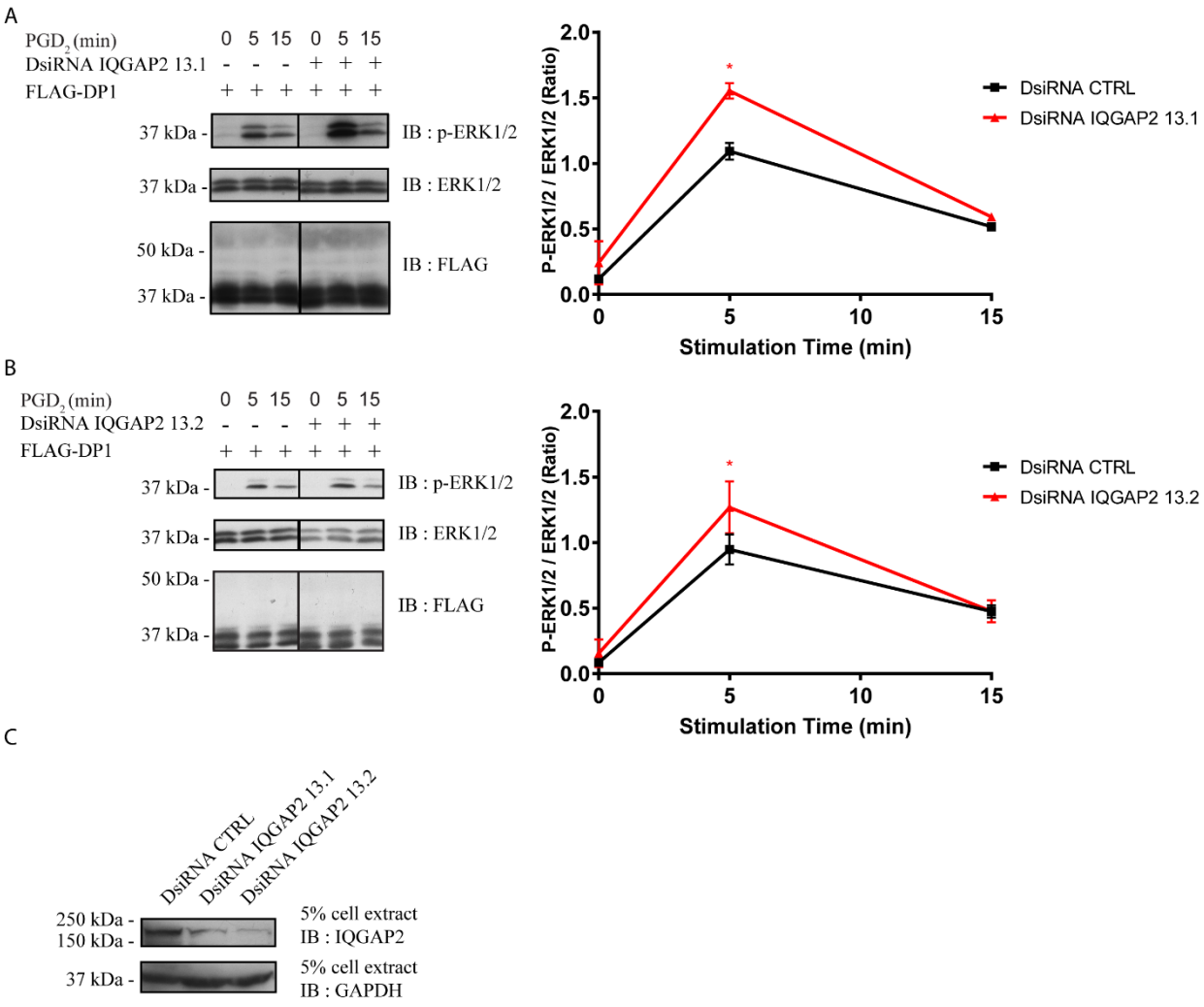

Fig. 6. IQGAP2 depletion increases DP1-induced ERK1/2 activation. (A) and (B) HEK293 cells were transfected with IQGAP2 DsiRNA 12.1, IQGAP2 DsiRNA 12.2 or a negative control DsiRNA, and transiently transfected with pcDNA3-FLAG-DP1 24 h later. 48 h after transfection of the receptor construct, cells were serum-starved for 3 h and stimulated with 1 µM PGD2 for the indicated times. Protein levels were assessed by Western blotting using FLAG, p-ERK1/2 and ERK1/2 antibodies. Densitometry analyses were performed on three different experiments. p-ERK1/2 pixels were normalized on ERK1/2 pixels, and results are presented as the ratio of these values (mean ± S.E. (error bars)). **, P ≤ 0,01. (C) HEK293 cells were transfected with negative control DsiRNAs, IQGAP2 DsiRNA 12.1 or IQGAP2 DsiRNA 12.2 for 72 h and mRNA expression levels was monitored with RNA extractions, followed by RT-PCR amplifications with specific primers for IQGAP2. RT-PCR of GAPDH mRNA was used as a control.

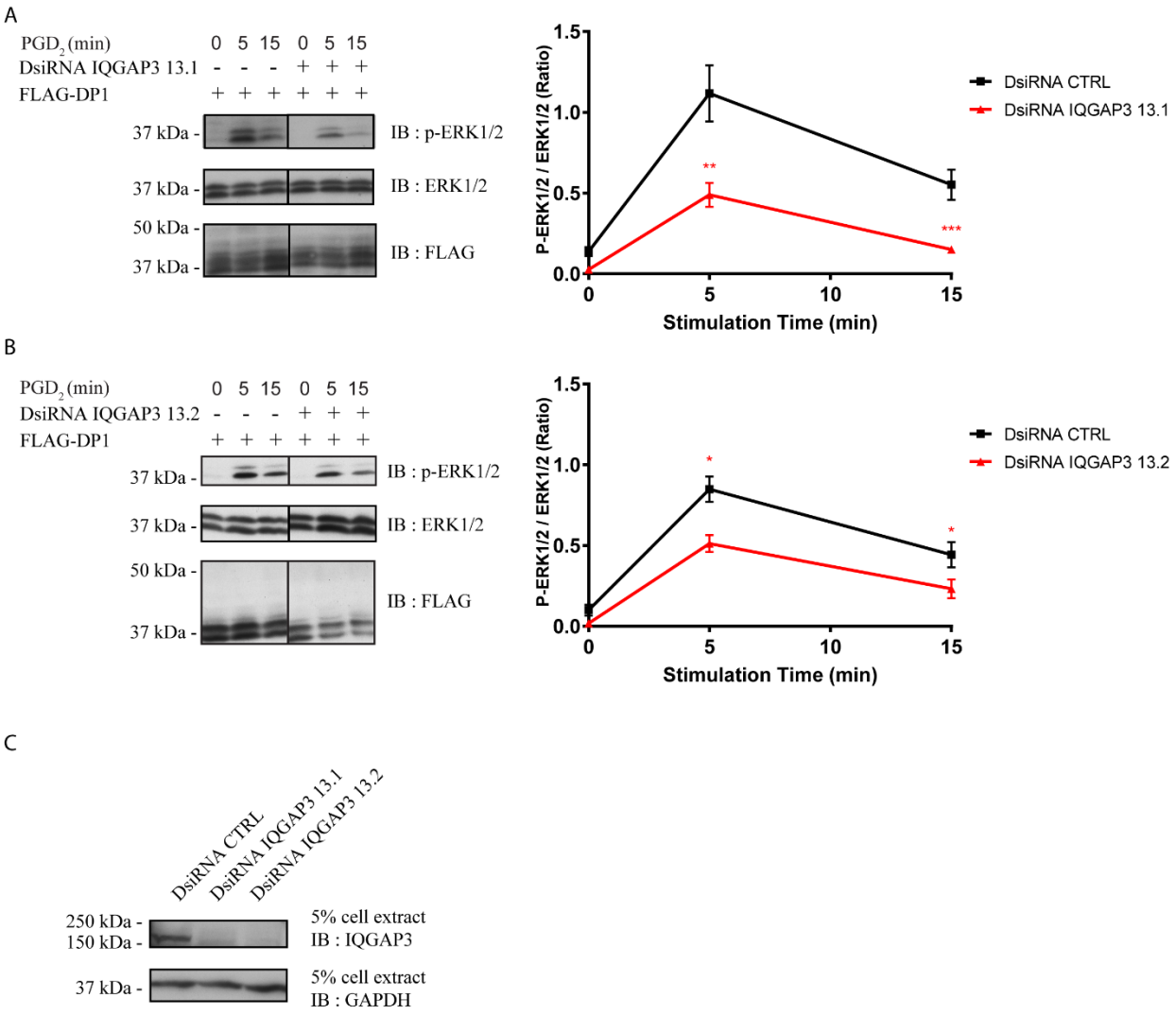

Fig. 7. Depletion of IQGAP3 reduces DP1-induced ERK1/2 activation. Depletion of IQGAP3 reduces DP1-induced ERK1/2 activation. (A) and (B) HEK293 cells were transfected with IQGAP3 DsiRNA 13.1, IQGAP3 DsiRNA 13.2 or a negative control DsiRNA, and transiently transfected with pcDNA3-FLAG-DP1 24 h later. 48 h after transfection of the receptor construct, cells were serum- starved for 3 h and stimulated with 1 µM PGD2 for the indicated times. Protein levels were assessed by Western blotting using anti-FLAG, p-ERK1/2 and ERK1/2 antibodies. Densitometry analyses were performed on three different experiments. p-ERK1/2 pixels were normalized on ERK1/2 pixels, and results are presented as the ratio of these values (mean ± S.E. (error bars)). **, P ≤ 0,01. (C) HEK293 cells were transfected with negative control DsiRNA, IQGAP3 DsiRNA 13.1 or IQGAP3 DsiRNA 13.2 for 72 h and protein expression was verified by Western blot with anti-IQGAP3 and GAPDH antibodies (GAPDH serves as control).

4. Discussion

Distinct spatial distribution and interacting proteins can dictate diverse signaling outputs for GPCRs, and thus determine various cell fates(Bhosle, Rivera, and Chemtob 2017; Calebiro and

Koszegi 2019; Eichel and von Zastrow 2018; Sposini and Hanyaloglu 2017). The DP1 receptor for PGD_2 is involved in a multitude of physiological and pathological processes (Ahmad 2014; Gustafsson et al. 2007a; Hammad et al. 2007b; Saleem et al. 2007; Vong et al. 2010). Although we and others reported on a number of DP1 interacting partners (Binda et al. 2014, 2019; Fréchette et al. 2020; Oláh et al. 2011; Sedej et al. 2011), the interactome and the regulation of this important GPCR remain poorly characterized. In the present study, we unraveled the protein-protein interaction network of DP1, classified the different interactors by subcellular localization and function, studied the DP1-IQGAP1 interaction and established its importance in DP1 signaling and trafficking.

Our LC-MS/MS approach is validated by the identification of previously described interactors of DP1, such as ERK1/2(Binda et al. 2014), APP(Oláh et al. 2011), PTGDR2(Sedej et al. 2011) and HSP90(Binda et al. 2014). It is further supported by the presence of proteins that are expected to interact with DP1 or known to be associated with GPCR functions. For example, DP1 is a $G\alpha_s$-coupled receptor, and accordingly, $G\alpha_s$ (GNAS) and Gγ subunits (GNG5, GNG10) are among the interacting proteins that were detected. Other predictable GPCR interactors revealed by our data include Regulators of G Protein Signaling (RGS1 and RGS10) and the Receptor for Activated C Kinase 1 (RACK1 or GNB2L1). While the appearance of RGS proteins *per se* is not surprising, the fact that, of all the RGS proteins, RGS1 and RGS10 were identified is interesting since these two proteins are potential targets in neuroinflammatory and neurodegenerative diseases(Lee and Bou Dagher 2016), just like DP1(Lima et al. 2012). For its part, the scaffolding protein RACK1 was previously characterized as a modulator of cell surface expression of three GPCRs in our laboratory, namely the TPβ, CXCR4 and AT1R receptors, but did not affect DP1 trafficking (Parent et al. 2008). It will be interesting to study whether RACK1 is involved in DP1-mediated signaling. Our group recently identified interacting partners of the delta opioid receptor (DOP) expressed at the endogenous level from brains of a FLAG-DOP knock-in mice(Degrandmaison et al. 2020). Several of the hits obtained for DP1 in the present study were also found in our FLAG-DOP mice KI study, such as ARF6, EXOC3, DNAJA2 and VPS33A.This indicates that, as expected, GPCRs share some common interactors but also further validates our present data obtained in HEK293 cells.

For decades, GPCRs were thought of plasma membrane proteins that transduce extracellular stimuli into a myriad of intracellular signaling pathways. Emerging data, however, indicate that GPCRs can localize to various intracellular compartments where they engage in signaling mechanisms that can be distinct from the cell surface (reviewed in (Y. J. I. Jong et al. 2018)). Results from analyses of the subcellular localization of identified interacting partners when performing GPCR interactome studies are inherently intriguing. Indeed, they can reveal unexpected intracellular localization of a given receptor and uncover the mechanisms by which the GPCR exerts its functions and how it is targeted to this compartment. As anticipated, the majority of the identified DP1 interacting partners presented here are known to localize in the cytosol and at the plasma membrane. However, a significant number of the interactors are also associated with the nucleus, the mitochondrion or the extracellular exosome. The possible localization of DP1 in exosomal membranes is worthy of note as PGD_2 was confirmed as an exosome cargo(Subra et al. 2010). Furthermore, the small GTPase Rab4 was described as being enriched in exosomes(Blanc and Vidal 2018), and was recently shown to interact with DP1 by our laboratory(Binda et al. 2019). Although nuclear(Bhosle et al. 2017), mitochondrial(Bénard et al. 2012) and exosomal(Verweij et al. 2018) compartments are all confirmed localizations for GPCRs, their targeting and function at these sites remain poorly characterized and is an exciting and expanding field of research. Interactome data such as ours will help in designing experiments to further our understanding of these questions.

In order to validate that our LC-MS/MS data led to the identification of functionally relevant interactions, we investigated the role of the IQGAP1 scaffold in DP1 trafficking and signaling. IQGAP1 is a multifunctional scaffold protein involved in a vast array of cellular functions(Hedman et al. 2015; Malarkannan et al. 2012; Jessica M Smith et al. 2015), including the regulation of cell-cell adhesion, the coordination of cell migration, the potentiation and crosstalk of signaling pathways, as well as the regulation of diverse nuclear functions and clathrin-dependent endocytosis. We confirmed the DP1-IQGAP1 interaction at the endogenous level in colon adenocarcinoma HT-29 cells. The DP1-IQGAP1 interaction is dynamic and was promoted by agonist treatment and peaked after 15 min of receptor stimulation in HEK293 cells. Previous DP1-interacting proteins were shown to bind to the C-terminal tail and to one of the intracellular loops of the receptor(Binda et al. 2014, 2019; Fréchette et al. 2020). On the other hand, IQGAP1

does not bind to the C-terminus but interacts with intracellular loops 2 and 3 of DP1, domains known to be involved in G protein binding and signaling (Wong 2003). Binding of IQGAP1 to two intracellular domains of DP1 is interesting but not unexpected when one considers the large size of the IQGAP1 protein and the 3D conformation of GPCRs. Moreover, work underway in our laboratory indicates that multiple domains of IQGAP1 are involved in its interaction with DP1. Further experiments will be necessary to completely understand the molecular determinants involved in the DP1/IQGAP1 interaction. Altogether, these observations prompted us to explore the possible modulation of ERK1/2 activation by IQGAP1 following DP1 activation. Overexpression and knockdown experiments demonstrated that IQGAP1 promotes DP1-mediated ERK1/2 signaling, analogously to what was reported for CXCR4 (Bamidele et al. 2015). Further experiments will be needed to delineate whether IQGAP1 interacts directly with DP1 or through an adaptor protein, and if it scaffolds proteins of the ERK1/2 signaling cascade in response to DP1 activation to favor ERK1/2 signaling.

As IQGAP1 can be involved in intracellular trafficking, we ascertained whether it modulated DP1 cell surface expression. IQGAP1 overexpression or knockdown had no effect on basal cell surface expression of DP1 but revealed that it is positively involved in agonist-induced trafficking of the receptor. This may be explained by the IQGAP1 interaction with ARF6(Magalhaes et al. 2012) and β-arrestins(Alemayehu et al. 2013), proteins that play important roles in GPCR trafficking and signaling. We showed previously that agonist-induced internalization of DP1 is promoted by β-arrestin1 and 2(Gallant et al. 2007). Since GPCR internalization is associated with ERK1/2 signaling in endosomes, IQGAP1 may be involved in promoting ERK1/2 activation following PGD_2 treatment by participating in DP1 internalization in endosomes and scaffolding the proteins of the ERK1/2 signaling cascade. In this regard, it is interesting to consider the confocal microscopy data. At the basal state, DP1 and IQGAP1 colocalized throughout the cells, from the perinuclear area to the plasma membrane. However, following agonist stimulation, a redistribution of DP1 and a subfraction of IQGAP1 to the perinuclear region was noticeable. IQGAP1's functions in the nuclear region include actin cytoskeleton organization at the cytoplasmic face of the nuclear envelope (Henderson 2012), nucleo-cytoplasmic trafficking(Rigothier et al. 2016) and formation of the MAP kinase signalosome(Malarkannan et al. 2012). Another subfraction of IQGAP1 remained at the plasma membrane after DP1

activation, which is not surprising considering the multiple roles of IQGAP1 in the coordination of the formation of the cytoskeleton and of adherens junctions (Li et al. 1999; Watanabe et al. 2004). It can be noticed that expected DP1 interactors like β-arrestins, as well as previously reported interacting proteins GGA3(Fréchette et al. 2020), Rab4(Binda et al. 2019) and L-PGDS(Binda et al. 2014) were not identified in our LC-MS/MS experiments. One of the possible explanations for this is that the LC-MS/MS experiments were carried out in absence of agonist stimulation, and in the case of L-PGDS, that the protein is not expressed in HEK293 cells(Binda et al. 2014).

IQGAP1 is the best-characterized and the only ubiquitously expressed member of the IQGAP family. IQGAP2 is mostly expressed in liver and stomach, whereas IQGAP3 is expressed in the brain, testis, lungs, small intestine and colon(C. White, Erdemir, and Sacks 2012). The three IQGAPs contain a calponin homology domain (CHD), WW domain, IQ domain, Ras GTPase-activating protein-related domain (GRD), and RasGAP C-terminus domain. The number of IQ motifs varies among IQGAPs which differ in function and subcellular localization(Jessica M Smith et al. 2015). For example, IQGAP2 is considered a tumor suppressor in breast cancer(Schmidt et al. 2008), as opposed to IQGAP1 and IQGAP3 that were found to be upregulated in a wide variety of cancers and to stimulate tumor growth and metastasis(Hayashi et al. 2010; White et al. 2009; Yang et al. 2014). Since IQGAP2 was detected in our LC-MS/MS experiments, we decided to test the impact of both IQGAP2 and IQGAP3 on DP1-mediated ERK1/2 activation. IQGAP2 knockdown resulted in increased ERK1/2 phosphorylation following DP1 activation, supporting its observed negative role in ERK1/2 signaling in MCF7 cells (Schmidt et al. 2008). On the other hand, IQGAP3 knockdown resulted in a decrease in DP1-mediated ERK1/2 activation, similarly to what was obtained when HeLa cells were stimulated with EGF(Yang et al. 2014). The differential effects of the IQGAP isoforms on DP1-mediated ERK1/2 signaling may be of significance in cancer cells. MAPK pathways are known pharmacological targets against cancer (Diab et al. 2014; Lee, Rauch, and Kolch 2020; De Luca et al. 2012). Considering the impact of DP1(Murata et al. 2008; Tippin et al. 2014; Vong et al. 2010) and IQGAP1(Hayashi et al. 2010; Liang et al. 2017; White et al. 2009) expression in colon cancer, further investigations concerning the relationship between these two molecular determinants will be needed.

5. Conclusion

In summary, we described the DP1 interactome in HEK293 cells and categorized the different interacting partners by function and localization. The IQGAP1 interaction and function were studied as a validation of our approach. IQGAP isoforms may play distinct roles in GPCR signaling. The identified putative DP1 interacting proteins open multiple lines of research in DP1 and GPCR biology in various cell compartments.

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3. Discussion

Au cours des deux dernières décennies, de nombreuses percées dans le domaine de la recherche sur les récepteurs couplés aux protéines G, autant au niveau de leur structure que de leur signalisation, ont ouvert la voie à la découverte de plus d'une centaine de molécules pharmacologiques ciblant les RCPG, en établissant ces derniers comme la famille des récepteurs membranaires les plus ciblés par la pharmacopée actuelle. Cependant, malgré le fait que cette famille de protéines comporte plus de 800 membres, seulement 134 de ces récepteurs sont ciblés par des médicaments prescrits ou en vente libre (Hauser et al. 2017). À ce nombre, on peut ajouter environ une cinquantaine de molécules ciblant des protéines directement liées aux RCPGs, telles que des transporteurs ou des enzymes pouvant modifier en amont l'activation des récepteurs, ou encore modifier la signalisation en aval du récepteur (Sriram and Insel 2018). Malgré ces connaissances, il apparaît évident, vu le nombre important de récepteurs dit orphelins ou peu étudiés, qu'il reste beaucoup de connaissances à acquérir afin d'ultimement améliorer la pharmacopée moderne. Les résultats de mes travaux de recherche apportent un nouvel éclairage sur les mécanismes de régulation du trafic et de la signalisation du récepteur à la prostaglandine D2 DP1, un RCPG peu étudié dans la littérature scientifique. Dans mon premier manuscrit, nous clarifions les rôles interdépendants de la GTPase RAB4, de la protéine adaptatrice GGA3 et de la prostaglandine synthase L-PGDS dans le trafic et la signalisation de DP1. De plus, nous caractérisons la nouvelle interaction entre DP1 et GGA3. Dans mon deuxième manuscrit, nous effectuons une analyse des différents partenaires d'interaction identifiés par chromatographie liquide couplé à de la spectrométrie de masse en tandem (LC-MS/MS). Nous

avons également déterminé la sous-localisation et la fonction cellulaire de ces interacteurs, caractérisé la modulation du trafic du récepteur DP1 par l'un de ces interacteurs (IQGAP1) et analysé la réponse différentielle de signalisation ERK1/2 par IQGAP1 ainsi que ses différents isoformes (IQGAP2 et IQGAP3). Cette discussion sera donc séparée en deux volets, un pour chacun des articles présentés dans cette thèse. Une synthèse des connaissances antérieures pertinentes, une analyse des nouvelles connaissances acquises ainsi que des perspectives futures seront discutés dans chacun de ces volets.

Premier article – Synthèse des connaissances antérieures pertinentes

Les informations concernant les mécanismes de régulation de l'internalisation et du recyclage du récepteur DP1 sont assez limitées, mais il a été précédemment démontré par notre laboratoire que DP1 recycle via des vésicules Rab4 positives (Gallant et al. 2007) et que la synthase de la prostaglandine D_2, L-PGDS, est un interacteur de cette GTPase et promeut son activation suite à l'activation du récepteur (Binda et al. 2019). Considérant que Rab4 a également été impliquée dans le recyclage du récepteur Met via un mécanisme nécessitant la protéine adaptatrice GGA3 et Arf6 (Parachoniak et al. 2011), nous avons décidé d'investiguer en premier lieu si le récepteur DP1 pouvait emprunter un mécanisme semblable pour le recyclage à la surface et en cas de résultat positif, vérifier l'importance de cette protéine sur une voie de signalisation activable connue de DP1, c'est-à-dire l'activation des ERK1/2 (Binda et al. 2014).

Premier article – Analyse des nouvelles connaissances acquises

De prime abord, il est intéressant de constater, au vu des articles mentionnés ci-haut et du premier manuscrit de cette thèse, la multiplicité de localisation et de fonction que peut exécuter une seule et même protéine. Les protéines de la famille des GGA ont initialement été connues comme des protéines effectuant exclusivement le transport vésiculaire entre les différents compartiments du TGN de manière dépendante de la protéine Arf1 (Dell'Angelica et al. 2000), puis comme étant capables d'effectuer le transport de protéines de type lectines du TGN jusqu'au compartiment lysosomale (R Puertollano et al. 2001). La reconnaissance et l'aide au

triage par GGA3 de récepteurs tyrosine kinase ubiquitinés ont été découvertes par la suite (Puertollano and Bonifacino 2004), puis de multiples autres cargos possibles tels qu'un RCPG (Maoxiang Zhang et al. 2016c) et des intégrines (Ratcliffe et al. 2016) ont été identifiés. Les résultats présentés dans le premier article de cette thèse développent le rôle de GGA3 dans le recyclage via un mécanisme Rab4-dépendant et sa capacité de moduler la signalisation d'un RCPG en plus de celle déjà connue du récepteur tyrosine kinase MET.

En ce qui concerne les RCPG, GGA3 n'était connue pour le moment que pour son rôle dans la voie sécrétoire du récepteur α2-adrénergique en augmentant son expression de surface, sans moduler son expression totale, ni son internalisation ou sa signalisation (Maoxiang Zhang et al. 2016a). Par opposition, nos résultats démontrent que GGA3, dans le cas du récepteur DP1, ne semble pas avoir d'effet sur son expression de surface, tel que démontré par les ELISA démontrant l'absence d'effet des DsiRNAs de GGA3 sur la présence du récepteur à la surface membranaire en condition basale. Par contre, les expériences d'internalisation et de recyclage ont démontré clairement un effet de GGA3 (via un mécanisme Rab4-dépendant) sur la dynamique post-stimulation du récepteur. De plus, GGA3 a distinctement un impact sur l'activation de la voie ERK1/2 suite à l'activation du récepteur, démontrant une importance de la protéine adaptatrice sur la signalisation en aval d'un RCPG. Bien que GGA3 ait déjà été reconnue dans la littérature comme pouvant moduler les voies de signalisation de certains récepteurs tyrosine kinase (Crupi et al. 2019; X. Li et al. 2015; Parachoniak et al. 2011) ou les récepteurs de type intégrines (Ratcliffe et al. 2016), c'est la première fois à ma connaissance qu'elle est reconnue comme modulateur dans une voie de signalisation d'un RCPG.

Une autre différence marquée par rapport à la littérature scientifique actuelle est l'absence probable d'implication d'une protéine de la famille des Arf dans l'action de GGA3 sur la dynamique de DP1. Classiquement, la famille des GGA nécessite une petite protéine G de type Arf pour avoir un effet sur l'internalisation de récepteurs, tel que démontré avec le récepteur Met (Parachoniak et al. 2011), avec la β1-intégrine (Ratcliffe et al. 2016) ou avec le récepteur TrkA (X. Li et al. 2015). Dans le cas du récepteur DP1, cependant, l'utilisation du mutant GGA3 N194A qui ne peut lier les protéines Arf démontre que l'action de GGA3 n'est pas, dans ce cas précis, dépendante des protéines Arf.

L'implication de la protéine Rab4 dans le recyclage de DP1 et de la synthase de PGD_2 L-PGDS dans le recrutement et l'activation de Rab4 dans le recyclage de DP1 a déjà été établie dans le laboratoire (Binda et al. 2019). C'est donc pour cette raison que nous avons vérifié si le mécanisme de recyclage de DP1 dû à GGA3 était dépendant de ces protéines. Les résultats obtenus démontrent une intéressante relation de dépendance entre ces trois protéines. Tel qu'attendu, GGA3 nécessite la présence de Rab4 afin d'effectuer son action sur le recyclage de DP1. Il est également très intéressant de constater que l'effet de GGA3 nécessite la L-PGDS afin d'avoir son effet et que l'effet de la L-PGDS est réciproquement dépendant de la présence de GGA3. Il est intriguant d'observer qu'une protéine adaptatrice nécessite la synthase produisant le ligand même du récepteur qu'elle transporte afin d'effectuer son action. Il s'agit en effet d'une nouvelle interaction et fonction pour L-PGDS, qui comme le laboratoire du Pr Parent a déjà démontré, est une synthase de prostaglandine qui peut également jouer un rôle de co-facteur de Hsp90 dans la maturation de DP1 et dans l'assemblage d'un complexe de signalisation entre DP1 et les protéines ERK1/2 (Binda et al. 2014). Dans ces travaux, il avait été observé que la L-PGDS augmentait le transport de DP1 à la surface cellulaire en interagissant avec Hsp90. De plus, l'interaction DP1-L-PGDS augmentait l'activité de production de PGD_2 par la synthase, révélant une boucle de signalisation intracrine entre un récepteur et l'enzyme produisant son agoniste.

Premier article – Perspectives futures

Les résultats obtenus dans ce premier manuscrit soulèvent quelques questions. Le premier point de discussion pouvant être apporté concerne la capacité de la protéine GGA3 N194A (qui ne peut pas lier les protéines Arf) à induire un recyclagede manière aussi efficace que la protéine non-mutée. Considérant que l'activation d'une protéine Arf est généralement nécessaire pour le recrutement d'une protéine adaptatrice tel que GGA3 à une membrane, cela soulève la question de l'identification d'une protéine pouvant effectuer ce recrutement. Un mécanisme potentiel est proposé à la fin de l'article selon lequel un complexe composé de DP1/L-PGDS/Rab4 serait formé dans un compartiment endosomal. L'activation subséquente de Rab 4 entraînerait le recrutement d'un effecteur de Rab4 au complexe, la Rabaptin-5, qui est elle-même déjà connue pour interagir avec GGA3 et participer à l'arrimage et la fusion des membranes endosomales. Alternativement, il serait également possible que la L-PGDS, favorisant l'activation de Rab4, soit

déjà liée à GGA3 et que cette interaction favorise le recrutement de la Rabaptin-5 afin de continuer le processus de recyclage. Une méthode qui pourrait nous permettre de contrôler la véracité de ce modèle *in cellulo* serait d'effectuer une immunoprécipitation suite à la stimulation de DP1 (idéalement dans un modèle cellulaire où DP1 est transfecté de manière stable) et vérifier si l'ajout d'ARN interférents de Rab4 et/ou de L-PGDS influencent le recrutement de GGA3 à DP1 lors d'une immunoprécipitation de cette dernière.

Dans le cas où l'ajout d'un ARN interférent de Rab4 diminue l'interaction de GGA3 avec DP1, il resterait à vérifier si l'interaction est dépendante de la Rabaptin-5. Une simple mutagenèse dirigée destinée à inactiver la région FGPLV (Région de la Rabaptin-5 permettant l'interaction avec GGA3) sur une construction surexprimée de la Rabaptin-5 permettrait par la suite de déterminer si la Rabaptin-5 est nécessaire au recrutement de GGA3 sur DP1.

Dans le cas où notre modèle ne serait pas confirmé, il serait approprié d'effectuer une étude du protéome de GGA3 suite à une stimulation de DP1 dans un contexte cellulaire, par une étude de spectrométrie de masse par exemple, ce qui pourrait également amener des pistes de solution à ce problème.

Une autre question intéressante pouvant se poser concerne la liaison entre le récepteur DP1 et la protéine GGA3. Il est répertorié dans la littérature que les protéines cargo prises en charge par GGA3 ont généralement une séquence de type DXXLL (Crupi et al. 2019; X. Li et al. 2015) ou une séquence RRR (M Zhang et al. 2016), séquences n'étant pas présentes chez le récepteur DP1. Une étude sur le récepteur Met (Parachoniak et al. 2011) a cependant démontré que l'interaction entre la protéine adaptatrice GGA3 et son cargo pouvait être médiée par l'intermédiaire de Crk. Bien que l'étude en question ne caractérise pas la région d'interaction entre Crk et le cargo, elle définit le domaine d'interaction de GGA3 avec Crk comme étant le domaine VHS. Considérant que les essais de GST-Pulldown en lysat cellulaire entre les domaines de GGA3 et DP1 du manuscrit 1 de cette thèse démontrent que DP1 interagit avec le domaine VHS de GGA3, il pourrait être pertinent de déterminer par co-immunoprécipitation ou Pulldown si la protéine Crk sert d'intermédiaire entre GGA3 et DP1.

Également, certains approfondissements sur la dynamique d'interaction entre les protéines étudiées dans cet article pourraient s'avérer intéressants au niveau physiopathologique. Bien que chacun des acteurs impliqués dans ce manuscrit ait un ou plusieurs rôles connus dans différents problèmes de santé connus chez l'humain, une étude plus approfondie permet de constater que les quatre protéines majeures étudiés ont tous un rôle à jouer dans la maladie d'Alzheimer. Bien que la physiopathologie de l'Alzheimer soit encore à ce jour très imparfaitement incomprise et qu'une multitude d'hypothèses soient présentement à l'étude quant à la genèse de cette maladie (Kocahan and Doğan 2017), une caractéristique majeure bien connue de cette pathologie est l'accumulation d'une protéine appelée amyloïde bêta dans les neurones (Sanabria-Castro, Alvarado-Echeverría, and Monge-Bonilla 2017). La production de cette protéine est dépendante d'une enzyme de la famille des protéases aspartiques, BACE-1, permettant le clivage du précurseur de la protéine amyloïde (APP) en bêta amyloïde. Cette protéine est surexprimée lors d'atteinte de l'organisme par la maladie d'Alzheimer (Zhong et al. 2007) et de manière intéressante, la protéine GGA3 est responsable du transport de cette dernière des endosomes précoces aux lysosomes. En effet, la perte d'expression de GGA3 mène à une accumulation de BACE-1 dans les endosomes (Kang et al. 2010) et à une augmentation de la production de bêta amyloïde (Sarajärvi et al. 2009). L'accumulation intra-cellulaire peut mener à l'apoptose de la cellule (Yao, Nguyen, and Pike 2005), activant alors plusieurs caspases dont la caspase-3, caspase ayant été démontrée comme ayant la capacité de cliver GGA3 et ainsi entraîner une rétro-activation de production de bêta amyloïde par BACE-1, bêta amyloïde qui sera ultimement rejeté dans le milieu extracellulaire (Vassar 2007). Ce rejet massif d'amyloïde pourra alors entraîner une réaction en chaîne dans l'environnement immédiat de la cellule, la bêta-amyloïde pouvant s'agglomérer en plaque amyloïde et nuire au fonctionnement normal des cellules neuronales environnantes (Chen et al. 2017). La protéine L-PGDS quant à elle a été démontrée comme neuroprotectrice dans la pathologie d'Alzheimer en ayant une activité chaperonne sur les agrégats de bêta-amyloïde et permettant une meilleurs solubilisation de ceux-ci (Kannaian et al. 2019), menant à une meilleure clairance des agrégats et une diminution de la cytotoxicité de ces derniers (Low, Phillips, and Pervushin 2020). Concernant la protéine Rab4, cette dernière est surexprimée dans les neurones de patients atteints d'Alzheimer et des dysfonctions dans le recyclage de plusieurs molécules y sont associées (Cataldo et al. 2000).

En ce qui a trait au récepteur DP1, les quelques résultats parus dans la littérature scientifique ne permettent pas d'avoir une réponse claire quant à son rôle dans la maladie d'Alzheimer. En effet, bien que l'activation de DP1 soit réputée avoir un effet neuroprotecteur sur les cellules neuronales (Liang et al. 2005), certains auteurs émettent l'hypothèse que ce récepteur pourrait avoir un rôle délétère dans la pathologie d'Alzheimer car son expression est régulée à la hausse de manière concomitante avec la hausse de bêta-amyloïde dans les cellules atteintes de cette maladie (Mohri et al. 2007). Quoi qu'il en soit réellement, il est clair que des recherches plus poussées sur le rôle de ce récepteur dans cette pathologie sont nécessaires. Les travaux effectués dans le premier manuscrit de cette thèse pourraient s'avérer être une base intéressante pour des recherches plus ciblées avec des modèles cellulaires adaptés et la dynamique entre ces protéines pourraient être approfondie afin de mieux comprendre leur rôles et fonctions en situation pathologique.

Deuxième article – Synthèse des connaissances antérieures pertinentes

Suite aux résultats obtenus dans le premier manuscrit, il apparaît pertinent de caractériser l'interactome du récepteur DP1 afin de pouvoir mieux analyser les liens entre les protéines interagissant avec le récepteur DP1. Cette analyse nous permettrait, entre autres, de mieux évaluer les voies de signalisation pouvant être modulées par DP1. Les récepteurs couplés aux protéines G sont des molécules étudiées depuis maintenant plusieurs années et les connaissances reliées à leur localisation, leur fonction et leur trafic se sont constamment développées au fil des années. Bien que ces derniers aient été initialement découverts à la surface membranaire, de nombreuses études montrent que ces récepteurs peuvent être également retrouvé aux niveaux des endomembranes biologiques. Nous savons maintenant que ces derniers sont présents et fonctionnels aux membranes de divers compartiments cellulaires, tels que les mitochondries, le noyau, le Golgi et les endosomes (Y.-J. I. Jong, Harmon, and O'Malley 2018). Il était déjà été établi que le récepteur DP1 a une localisation fortement intracellulaire en plus de sa localisation à la membrane plasmique (Binda et al. 2014; Labrecque, Sébastien J Roy, et al. 2013; Parent et al. 2010b; Roy et al. 2013). Sachant que les fonctions des protéines peuvent être différentes selon leur localisation cellulaire et que lesdites localisations peuvent être pertinentes dans plusieurs pathologies (Hung and Link 2011), nous

avons effectué une analyse de l'interactome du récepteur DP1 et caractérisé les différentes localisations des partenaires d'interaction dans la cellule. Également, étant au fait du rôle établi de DP1 dans la pathogenèse de certains cancers, nous avons vérifié l'implication des protéines identifiées comme possibles partenaires d'interaction et avons classifié à l'aide de la banque de données COSMIC (Catalogue of Somatic Mutations in Cancer) l'implication de ces partenaires dans différents types de cancer.

Deuxième article – Analyse des nouvelles connaissances acquises et perspectives futures

L'une des analyses les plus excitantes à effectuer suite à une analyse des partenaires d'interaction obtenus lors d'une analyse de type LC-MS/MS est de regrouper et classer les différents partenaires d'interaction selon des paramètres prédéterminés qui sont pertinents à l'atteinte de l'objectif de départ. Dans le cas de cet article, plusieurs objectifs étaient visés dans la réalisation de ce manuscrit. En premier lieu, la localisation des différents partenaires d'interaction afin de mieux comprendre la localisation fortement intracellulaire de DP1, ce qui permettra l'émission d'hypothèses de recherche mieux ciblées sur ce récepteur à l'avenir. En deuxième lieu, classifier les différentes protéines selon leurs rôles cellulaires connus permet d'effectuer un processus de déduction plus efficace lors d'éventuelles réflexions sur de futurs projets de recherche impliquant le récepteur DP1. Le prochain paragraphe traitera donc des différentes sous-localisations cellulaires des différentes protéines considérées comme partenaires d'interaction potentiels de DP1.

Tel que mentionné précédemment, le récepteur DP1 possède une forte localisation intracellulaire et l'on observe généralement une localisation périnucléaire constante lors d'essais de microscopie confocal. Il y a donc de réelles possibilités que le récepteur DP1 puisse être présent au noyau, surtout si l'on prend en compte que des récepteurs aux prostanoïdes ont déjà été répertoriés comme étant présents dans ce compartiment cellulaire (Gobeil 2002; Helliwell et al. 2004). Considérant que la localisation nucléaire des RCPGs commence à être bien établi dans la littérature (Bhosle et al. 2016, 2017; Mcardle et al. 2010), l'identification de protéines localisées au compartiment nucléaire pourrait être d'intérêt. Il est d'ailleurs très intéressant de constater dans la liste de partenaires d'interaction potentiels de DP1 que plus du tiers peuvent avoir une

localisation au noyau. Parmi ceux-ci, des régulateurs de facteurs de transcription, des protéines liant l'acide désoxyribonucléique (ADN) ainsi que de très nombreuses protéines ayant la capacité de lier l'acide ribonucléique (ARN). On peut d'ailleurs remarquer la présence de facteurs de transcriptions connus tel que NCOA2, un co-activateur transcriptionnel généralement associé aux récepteurs nucléaires liants de petites molécules hydrophobes (stéroïdes, hormones thyroïdienne, rétinoïdes ainsi que la vitamine D). Ce fait est intéressant car la L-PGDS, partenaire d'interaction de DP1, possède une activité lipocaline et a donc la capacité de transporter de tels ligands (Shimanuki et al. 2012; Takeda et al. 2010). Bien que l'interaction avec une protéine ayant la capacité d'être présente au noyau ne constitue en aucun cas une démonstration de la présence du RCPG dans ce compartiment, l'interaction du récepteur avec ces protéines soulèvent plusieurs questions intéressantes. En effet, il a été rapporté dans la littérature que les RCPGs pouvaient avoir de multiples fonctions en relation avec l'expression génique ainsi que la régulation du traitement des ARNm ou des ARNt. Concernant l'expression génique en particulier, il a été démontré qu'un RCPG et/ou ses protéines G associées pouvaient moduler directement des facteurs de transcription afin de moduler l'activité transcriptionnelle de gènes. Un exemple de ce phénomène serait le récepteur bêta-adrénergique présent à la membrane nucléaire de cellules de myocarde de rat ayant la capacité de moduler la transcription génique médiée par NFκB, par ERK1/2 et par la PKB suite à la stimulation à l'isoprotérénol (Vaniotis et al. 2011). Un autre exemple de RCPG présent à la membrane nucléaire serait le récepteur à l'endothéline ET-1, qui a la capacité de moduler les concentration intra-nucléaires de calcium suite à sa stimulation avec son ligand naturel dans plusieurs types cellulaires (Bkaily et al. 2011).

Du côté du traitement des ARNm et des ARNt, les RCPGs ont également la capacité de moduler la vitesse et la localisation des mécanismes de traduction par les ribosomes, phénomène particulièrement important dans les cellules neuronales où les ARNm à traduire au bout des dendrites ne sont pas nécessairement les mêmes que ceux présents au bout de l'axone (Ho et al. 2009; Tréfier et al. 2018). Ces différents mécanismes seront certainement à garder en tête si des études de transcriptomique sont tentées avec le récepteur DP1 comme modèle. Dans de telles expériences, ils seraient également intéressant de vérifier les séquences peptidiques du récepteur DP1 qui pourraient être impliquées dans de tels phénomènes. Une simple analyse bio-informatique à l'aide d'un outil tel que Eukaryotic Linear Motif (http://elm.eu.org/) nous permet

d'identifier des séquences d'acides aminés présentes sur une protéine étant connues pour avoir des fonctions particulières. Dans le cas de DP1, cette analyse nous permet d'identifier une séquence pouvant avoir un impact potentiel sur la transcription ou la traduction. Cette séquence de liaison consistant en une thréonine phosphorylée suivie d'un résidu acide en pT+3 s'appelle une séquence de liaison au forkhead-associated (FHA) et est située dans la queue C-terminale du récepteur. La séquence de liaison au FHA permet la liaison aux protéines ayant un domaine FHA, protéines ayant généralement une localisation nucléaire et ayant un rôle dans les mécanismes de contrôle du cycle cellulaire, dans les mécanismes de réparation de l'ADN ou dans la régulation de la transcription (Durocher et al. 2000). Une mutation ciblée sur le résidu p-thréonine pourrait donc être une stratégie intéressante dans le cadre d'expérimentations sur la capacité du récepteur DP1 à moduler d'éventuels mécanismes transcriptionnels.

Une autre localisation importante des partenaires d'interaction potentiels de DP1 est la mitochondrie, considérant que 17.1% des protéines considérées positives en spectrométrie de masse dans l'interaction avec le récepteur sont des protéines mitochondriales. Cette localisation potentielle est intéressante pour un récepteur aux prostanoïdes car une partie de l'oxydation des prostaglandines se déroule dans ce compartiment. De plus, des études récentes sur les différents récepteurs à la prostaglandine E_2 ont déterminé que ces derniers avaient plusieurs effets fonctionnels sur les mitochondries, tels que la régulation d'espèces réactives à l'oxygène (Cerioni et al. 2019), la régulation de la mitophagie (Ding et al. 2019) ainsi que l'activité métabolique de ces dernières (Ying et al. 2017). L'activation de la voie des MAP kinases à proximité de ce compartiment est également reconnue comme un facteur important de régulation de la fonction des mitochondries. En effet, l'activation de cette voie de signalisation peut influencer les phénomènes de fission des mitochondries, plusieurs voies métaboliques internes à celles-ci et moduler les différentes voies d'apoptoses dépendantes de la mitochondrie (Lavoie, Gagnon, and Therrien 2020). Le récepteur DP1 étant connu pour activer la voie des MAP kinases, tous ces mécanismes pourraient être étudiés dans le cadre d'une étude sur les conséquences fonctionnelles du récepteur dans le compartiment mitochondrial. De multiples RCPG sont déjà connus pour être présents dans le compartiment mitochondrial et leurs effets dans ce compartiment sont assez divers. Le récepteur aux purines $P2Y_1$-like à la capacité de moduler la concentration calcique intra-mitochondriale(Belous et al. 2006). Le récepteur AT-1R

régule la production d'anions superoxide et accroît la respiration mitochondriale (Valenzuela et al. 2016). Le récepteur CB_1 est également retrouvé dans ce compartiment et via sa protéine G_i associée, à la capacité de moduler le métabolisme énergétique de la mitochondrie (et de la cellule) (Bénard et al. 2012). Il pourrait être intéressant de vérifier l'effet de DP1 dans ce compartiment, surtout considérant que les protéines $G_{\alpha s}$, l'adénylate cyclase ainsi que les protéines $G_{\beta\gamma}$ ont été détectés dans ce compartiment(Mohammad Nezhady, Rivera, and Chemtob 2020) et que des protéines pouvant moduler le potentiel de membrane mitochondriale ont été détectées dans nos expériences de spectrométrie de masse (VDAC1-2-3).

Un autre compartiment cellulaire pour lequel beaucoup de protéines positives dans l'interaction avec le récepteur DP1 ont été identifiées dans nos essais de spectrométrie de masse sont les exosomes. Ce compartiment cellulaire est relativement moins connu que beaucoup d'organelles classiques de la cellule, mais de multiples études au cours des dernières années ont élucidé plusieurs des mécanismes menant à la formation de ces vésicules et permis la classification des différentes composantes structurelles de ces dernières. Un excellent résumé des différentes structures, fonctions ainsi que des futures perspectives médicales de ces vésicules est disponible dans le manuscrit de Kalluri et Lebleu (Kalluri and LeBleu 2020). Considérant la bonne proportion (23.7%) de partenaires potentiels du récepteur DP1 ayant une possible localisation exosomale, il me semble judicieux de mettre en perspective les différentes relations possibles entre les différents acteurs protéiques présentés dans mes deux manuscrits et ce compartiment cellulaire. En premier lieu, il convient de mentionner que certaines prostaglandines ont déjà été détectées dans les exosomes extra-cellulaires, dont la PGE_2 ainsi que la 15—deoxy-$\Delta^{12\text{-}14}$-prostaglandine J_2, un métabolite de la PGD_2 (Subra et al. 2010). Il apparaît dès lors un lien possible entre DP1, la L-PGDS et les exosomes. Ces derniers étant synthétisés de manière intracellulaire à partir des vésicules intraluminales des corps multivésiculaires (Kowal, Tkach, and Théry 2014) et le complexe DP1-LPGDS étant principalement intracellulaire (Binda et al. 2014), il n'est pas exclu que le complexe puisse participer d'une manière ou une autre à la formation et/ou le chargement des exosomes, surtout considérant que plusieurs de leurs partenaires communs d'interaction sont des cargos connus ou des protéines impliquées dans la synthèse ou la maturation de ces derniers. Ces partenaires sont Rab4, Hsp90, IQGAP1. Rab4 est connue pour être associée aux exosomes (Blanc and Vidal 2018) et est possiblement impliquée dans l'excrétion de ces derniers

(Moralès 2019) Hsp90 est impliquée dans la déformation membranaire nécessaire pour la relâche des vésicules exosomales (Lauwers et al. 2018), tandis que IQGAP1 coordonne les phénomènes de polymérisation d'actine nécessaires afin d'assurer le transport des exosomes des compartiments endosomaux (ainsi que des corps multivésiculaires) jusqu'à la membrane plasmique (Samson et al. 2017). Ayant ces informations en tête, plusieurs voies de recherches intéressantes sont possibles :

1) Pour plusieurs types de cancers, la relâche de métalloprotéinases dans les tissus environnants est un facteur important de pathogénicité (Kessenbrock, Plaks, and Werb 2010). Les facteurs moléculaires permettant la relâche des exosomes sont un important facteur dans la relâche de ces métalloprotéinases (Liu et al. 2009). Rab4 est connue pour également être un facteur nécessaire pour la relâche de ces métalloprotéinases (Frittoli et al. 2014). Il serait donc intéressant d'étudier si le récepteur DP1 ou la L-PGDS ont un rôle à jouer dans la relâche de ces vésicules.
2) Il a déjà été démontré que l'interaction entre DP1 et L-PGDS, qui augmente de manière basale la production de PGD_2, pouvait être partie constituante d'une boucle intracrine permettant l'export du récepteur DP1 à la surface cellulaire et permettant ainsi d'augmenter la signalisation cellulaire reliée à l'activation membranaire du récepteur (Binda et al. 2014). Il serait intéressant de vérifier si cette interaction promeut une possible voie de communication paracrine via la relâche d'exosomes. Tel que mentionné précédemment, la présence de métabolite de PGD_2 (15—deoxy-$\Delta^{12\text{-}14}$-prostaglandine J_2) a déjà été détecté dans certains exosomes. Ce métabolite est connu pour être un ligand du récepteur PPARγ (Peroxisome Proliferator-Activated Receptor Gamma) et l'activation de ce récepteur nucléaire pourrait expliquer certains effets anti-inflammatoires attribués au récepteur DP1 en situation pathologique (Hammad et al. 2007a; Maicas et al. 2012). De plus, il serait donc intéressant d'étudier si la présence de DP1 et/ou L-PGDS influence la formation d'exosomes, si la composition en 15-deoxy-$\Delta^{12\text{-}14}$-prostaglandine J_2 augmente lorsque ces derniers sont présents et si c'est le cas, vérifier un possible effet paracrine sur les cellules environnantes en vérifiant l'activation du récepteur PPARγ dans ces dernières.

Il est également pertinent de noter qu'il a été démontré que les RCPG eux-mêmes pouvaient subir un transfert vertical, c'est-à-dire être transférés d'une cellule à une autre et d'être fonctionnels une fois arrivé à destination (Bebelman et al. 2020).

Il a été démontré dans mon dernier manuscrit que les différents isoformes de IQGAP (1, 2 et 3) modulaient de différentes manières la voie des MAPK suite à l'activation de DP1. Considérant que l'activation de cette voie de signalisation est un facteur important dans la pathogenèse de plusieurs cancers (Braicu et al. 2019), il serait intéressant de vérifier d'une part, les différents domaines de liaison du récepteur aux différents isoformes de IQGAP et d'autre part, si la signalisation de DP1 est toujours modulée suite à la mutagénèse de ces régions d'interaction. Si la signalisation est abrogée, cela ouvrirait la porte à une possible conception de peptides pharmacologiques bloqueurs qui pourraient permettre de moduler la voie des MAPK induite par l'activation de DP1. Il serait également important de préciser à ce moment le rôle pro-oncogène ou suppresseur de tumeur de l'IQGAP impliqué dans la voie de signalisation. En effet, tel que discuté dans l'article 2 de cette thèse, IQGAP1 est généralement considéré comme un pro-oncogène dans plusieurs modèles animaux ou cellulaires de cancer mais ce rôle n'est pas universel dans tous les modèles étudiés. L'équipe du professeur Theodorescu, en étudiant dans un modèle de banque de tissus de cancer de la vessie, a effectivement découvert qu'un shRNA ciblant IQGAP1 avait un fort potentiel pro-oncogène. Des expériences ultérieures *in vitro* ont confirmées que la suppression de IQGAP1 entraînait une augmentation de la prolifération de cellules de cancer de la vessie T24 (Hensel et al. 2015). Le rôle précis des IQGAP devrait donc être établi de manière spécifique au type cellulaire étudié, en gardant en tête le fait qu'une protéine peut avoir de multiples rôles dans différents tissus.

Globalement, les nouvelles informations apportées par ces deux articles apportent un nouvel éclairage sur les différents mécanismes ainsi que de nouveaux partenaires d'interaction pouvant moduler le trafic et la signalisation des RCPG. Les résultats présentés démontrent que la signalisation des MAPK engendrée par le récepteur DP1 est modulable par plusieurs acteurs distincts ayant tous des effets différents sur l'intensité et la durée d'activation de cette voie de signalisation. Considérant la très grande diversité des localisations des protéines trouvées en spectrométrie de masse, l'une des informations qui serait pertinente à aller chercher dans des

études ultérieures serait la localisation de l'activation des ERK1/2 dans un modèle cellulaire où DP1 est réputé pertinent au niveau physiologique ou pathophysiologique.

4. Conclusion

Les RCPG étant souvent utilisés comme cibles pharmacologiques, il apparaît important de caractériser les interactions moléculaires de ces derniers afin de mieux comprendre leur fonctionnement et pouvoir raffiner les médicaments déjà existants. Nous avons approfondi les connaissances relatives à l'internalisation, le recyclage et la signalisation induite par DP1 dans le premier article en démontrant que GGA3 est un nouveau partenaire d'interaction s'insérant dans la dynamique du trafic de ce récepteur lorsqu'il est activé. Son interaction avec la synthase L-PGDS est également une nouveauté dans la littérature et pourra aider à une future caractérisation des mécanismes régissant le déplacement des synthases à l'intérieur de la cellule.

Le deuxième article apporte certes de nouveaux développements quant à la modulation du trafic et de la signalisation d'un RCPG par une protéine échafaud et ses isoformes, mais il apporte surtout de nouveaux questionnements avec les nombreux partenaires d'interactions provenant de multiples sous-localisations cellulaires différentes, qui pourront peut-être éventuellement contribuer à développer de nouveaux champs de recherche.

Mises ensembles, ces nouvelles connaissances ont le potentiel d'amener un nouvel éclairage sur plusieurs sujets d'importance. Si l'on prend en compte les différentes pathologies dans lesquelles le récepteur DP1 est impliqué, les différentes informations présentées dans cette thèse concernant le trafic, la signalisation ainsi que les domaines d'interaction entre DP1 et ses partenaires pourraient être d'un grand intérêt pour le développement de nouvelles molécules pharmacologiques. La caractérisation des interfaces d'interaction protéiques peut effectivement être utile pour la synthèse de petites molécules thérapeutiques, que ce soit de petits peptides pharmacologiques cyclisés stables ou encore des chaperonnes pharmacologiques. Ces différentes molécules pourraient être utilisés afin de favoriser le transport du récepteur DP1 à la surface membranaire (ou ailleurs!) dans les pathologies où la signalisation du récepteur pourrait être bénéfique dans un contexte thérapeutique, tel que l'Alzheimer, le cancer du côlon

ou l'ostéoporose. Des recherches devront cependant être fait sur la relation entre la localisation du récepteur et ses fonctions cellulaires. En effet, l'activation de certaines voies de signalisation à la surface membranaire n'a pas nécessairement la même conséquence fonctionnelle que l'activation de la même voie de signalisation à une autre localisation intracellulaire. De très nombreuses protéines partenaires ont été détectées en spectrométrie de masse et la localisation et la fonction de ces protéines apporte de nouvelles interrogations quant à la présence ainsi que la fonction des RCPG dans des compartiments cellulaires distincts de la membrane plasmique, tel que le noyau, les mitochondries ainsi que les exosomes. La recherche en sciences biologiques a souvent étudié les effets globaux d'une signalisation sur l'ensemble d'une cellule ou d'une population de cellule. Il y a fort à parier que la localisation précise d'une cascade de signalisation à l'intérieur de la cellule deviendra un sujet de recherche d'importance, particulièrement dans une époque où l'intérêt pour la médecine personnalisée est grandissant.

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Table S1. Potential DP1 interacting partners

∞ indicates that peptides were detected only in the Flag-DP1 condition. The CRAPOME (x/716) column indicates the number of times the protein was found in the 716 experiments catalogued in the CRAPOME database.

Gene Symbol	Protein name	Fold intensity Flag-DP1 / pcDNA3			CRAPOME (X/716)
		MS1	MS2	MS3	
AAAS	Aladin	∞	-	∞	65
ABCB4	Phosphatidylcholine translocator ABCB4	∞	∞	-	0

ABCB8	Mitochondrial potassium channel ATP-binding subunit	∞	-	2.4	0
ABCE1	ATP-binding cassette sub-family E member 1	∞	∞	-	121
ABCF2	ATP-binding cassette sub-family F member 2	∞	-	∞	137
ABLIM1	Actin-binding LIM protein 1	∞	∞	-	90
ACADM	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	∞	∞	-	83
ACAT1	Acetyl-CoA acetyltransferase, mitochondrial	∞	∞	-	161
ACLY	ATP-citrate synthase	∞	2.2	-	296
ACSL3	Long-chain-fatty-acid--CoA ligase 3	∞	∞	-	153
ADD1	Alpha-adducin	∞	3.2	-	140
ADPGK	ADP-dependent glucokinase	∞	2.1	-	10
AFF4	AF4/FMR2 family member 4	∞	∞	-	99
AFTPH	Aftiphilin	∞	∞	-	34

AGPS	Alkyldihydroxyacetonephosphate synthase, peroxisomal	∞	∞	-	56
AIG1	Androgen-induced gene 1 protein	∞	∞	-	2
ALDH18A1	Delta-1-pyrroline-5-carboxylate synthase	∞	∞	-	292
ALG1	Chitobiosyldiphosphodolichol beta-mannosyltransferase	∞	2.4	-	2
ALG11	GDP-Man:Man(3)GlcNAc(2)-PP-Dol alpha-1,2-mannosyltransferase	∞	-	∞	0
ALG2	Alpha-1,3/1,6-mannosyltransferase ALG2	∞	∞	-	0
ALG5	Dolichyl-phosphate beta-glucosyltransferase	∞	-	1.6	13
ALG8	Probable dolichyl pyrophosphate Glc1Man9GlcNAc2 alpha-1,3-glucosyltransferase	∞	-	2.4	7
ALKBH5	RNA demethylase ALKBH5	∞	∞	-	46
ANKLE2	Ankyrin repeat and LEM domain-containing protein 2	∞	∞	-	43
AP1G1	AP-1 complex subunit gamma-1	∞	∞	-	21
AP3D1	AP-3 complex subunit delta-1	∞	-	∞	198
APEX1	DNA-(apurinic or apyrimidinic site) endonuclease	∞	-	1.9	109
APH1A	Gamma-secretase subunit APH-1A	∞	-	∞	0
APOB	Apolipoprotein B-100	∞	2.4	-	18
APP	Amyloid-beta precursor protein	∞	∞	-	13

ARF6	ADP-ribosylation factor 6	∞	∞	-	27
ARL1	ADP-ribosylation factor-like protein 1	∞	-	∞	126
ARL8B	ADP-ribosylation factor-like protein 8B	∞	2.3	-	45
ASNS	Asparagine synthetase [glutamine-hydrolyzing]	∞	∞	-	131
ATG9A	Autophagy-related protein 9A	∞	∞	-	1
ATL2	Atlastin-2	∞	-	∞	12
ATL3	Atlastin-3	∞	2.4	-	1
ATP13A1	Manganese-transporting ATPase 13A1	∞	∞	-	27
ATP1A1	Sodium/potassium-transporting ATPase subunit alpha-1	∞	∞	-	335
ATP6AP2	Renin receptor	∞	2.7	-	5
ATP6V0A1	V-type proton ATPase 116 kDa subunit a1	∞	∞	∞	6
ATP6V0C	V-type proton ATPase 16 kDa proteolipid subunit	∞	2.0	-	6
ATP6V1A	V-type proton ATPase catalytic subunit A	∞	1.7	-	153
ATP6V1G1	V-type proton ATPase subunit G 1	∞	∞	-	48
AUP1	Ancient ubiquitous protein 1	∞	-	2.1	9
AURKA	Aurora kinase A	∞	-	2.3	24

BCAP31	B-cell receptor-associated protein 31	∞	∞	-	104
BCLAF1	Bcl-2-associated transcription factor 1	∞	∞	-	390
BUD23	Probable 18S rRNA (guanine-N(7))-methyltransferase	∞	-	∞	17
BYSL	Bystin	∞	∞	-	146
BZW2	Basic leucine zipper and W2 domain-containing protein 2	∞	2.1	-	22
C11ORF98	Uncharacterized protein C11orf98	∞	∞	-	88
C1ORF131	Uncharacterized protein C1orf131	∞	∞	-	40
C1QB	Complement C1q subcomponent subunit B	∞	1.7	-	2
C1QBP	Complement component 1 Q subcomponent-binding protein, mitochondrial	∞	2.4	-	420
CAD	CAD protein	∞	1.8	-	387
CALD1	Caldesmon	∞	∞	-	158
CALU	Calumenin	∞	1.6	-	147
CAND1	Cullin-associated NEDD8-dissociated protein 1	∞	∞	-	275
CANX	Calnexin	∞	∞	-	310
CAPZB	F-actin-capping protein subunit beta	∞	∞	-	366
CCAR1	Cell division cycle and apoptosis regulator protein 1	∞	5.5	-	103

CCDC47	Coiled-coil domain-containing protein 47	∞	∞	-	100
CCDC59	Thyroid transcription factor 1-associated protein 26	∞	∞	-	54
CCDC88A	Girdin	∞	-	2.3	14
CCNB1	G2/mitotic-specific cyclin-B1	∞	-	∞	33
CCT2	T-complex protein 1 subunit beta	∞	∞	-	428
CCT3	T-complex protein 1 subunit gamma	∞	∞	-	367
CCT7	T-complex protein 1 subunit eta	5.7	∞	-	360
CCT8	T-complex protein 1 subunit theta	3.1	1.8	-	451
CD247	T-cell surface glycoprotein CD3 zeta chain	4.4	1.9	-	1
CDIPT	CDP-diacylglycerol--inositol 3-phosphatidyltransferase	2.0	∞	∞	64
CDK1	Cyclin-dependent kinase 1	2.9	2.3	-	282
CDK2	Cyclin-dependent kinase 2	4.0	∞	-	234
CELSR1	Cadherin EGF LAG seven-pass G-type receptor 1	6.8	2.0	∞	0
CELSR3	Cadherin EGF LAG seven-pass G-type receptor 3	2.0	∞	-	0
CEP170	Centrosomal protein of 170 kDa	3.1	1.6	-	145
CERS2	Ceramide synthase 2	4.2	2.1	-	26

CHCHD1	Coiled-coil-helix-coiled-coil-helix domain-containing protein 1	3.4	∞	-	66
CHD4	Chromodomain-helicase-DNA-binding protein 4	5.6	2.4	-	256
CHID1	Chitinase domain-containing protein 1	3.1	-	∞	19
CHPT1	Cholinephosphotransferase 1	4.6	1.7	-	1
CIRBP	Cold-inducible RNA-binding protein	12.1	∞	-	208
CKAP2	Cytoskeleton-associated protein 2	6.9	2.1	-	120
CKAP5	Cytoskeleton-associated protein 5	7.4	∞	-	196
CLASP2	CLIP-associating protein 2	13.4	-	-	98
CLCC1	Chloride channel CLIC-like protein 1	3.0	∞	∞	103
CLCN3	H(+)/Cl(-) exchange transporter 3	2.9	-	∞	1
CLCN7	H(+)/Cl(-) exchange transporter 7	4.0	3.1	-	16
CLPB	Caseinolytic peptidase B protein homolog	3.4	2.1	-	63
CLPX	ATP-dependent Clp protease ATP-binding subunit clpX-like, mitochondrial	2.7	∞	-	51
CLTC	Clathrin heavy chain 1	5.3	2.3	-	406
CLUH	Clustered mitochondria protein homolog	8.4	∞	-	54
CMTM8	CKLF-like MARVEL transmembrane domain-containing protein 8	3.2	∞	-	0

CNIH4	Protein cornichon homolog 4	3.6	∞	-	54
CNOT9	CCR4-NOT transcription complex subunit 9	3.7	∞	-	31
COIL	Coilin	3.3	∞	-	143
COMT	Catechol O-methyltransferase	4.9	∞	-	32
COPA	Coatomer subunit alpha	16.9	3.7	-	202
COPB1	Coatomer subunit beta	9.6	∞	∞	278
COPS5	COP9 signalosome complex subunit 5	4.6	-	∞	42
COPS6	COP9 signalosome complex subunit 6	5.2	4.4	1.8	49
COQ8A	Atypical kinase COQ8A, mitochondrial	3.9	1.9	-	36
CPSF7	Cleavage and polyadenylation specificity factor subunit 7	2.6	∞	-	154
CPVL	Probable serine carboxypeptidase CPVL	3.6	∞	-	83
CRKL	Crk-like protein	1.6	∞	-	218
CSE1L	Exportin-2	6.4	∞	-	318
CSRP2	Cysteine and glycine-rich protein 2	14.9	∞	-	217
CTNNA1	Catenin alpha-1	3.9	-	2.2	114
CTNND1	Catenin delta-1	4.2	4.3	-	99

CTSA	Lysosomal protective protein	∞	∞	-	14
CTTN	Src substrate cortactin	5.8	-	3.1	318
CYFIP1	Cytoplasmic FMR1-interacting protein 1	8.1	∞	∞	217
DAD1	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit DAD1	∞	-	∞	27
DAP3	28S ribosomal protein S29, mitochondrial	2.0	-	2.2	96
DCAF1	DDB1- and CUL4-associated factor 1	6.1	∞	-	7
DCTN2	Dynactin subunit 2	6.2	7.3	∞	219
DCTN3	Dynactin subunit 3	1.6	2.7	-	38
DDB1	DNA damage-binding protein 1	1.9	∞	-	212
DDOST	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit	3.3	4.9	-	148
DDX1	ATP-dependent RNA helicase DDX1	21.3	-	∞	331
DDX17	Probable ATP-dependent RNA helicase DDX17	2.4	11.3	-	523
DDX21	Nucleolar RNA helicase 2	2.0	∞	-	438
DDX46	Probable ATP-dependent RNA helicase DDX46	3.2	∞	-	302
DDX5	Probable ATP-dependent RNA helicase DDX5	4.0	-	∞	528
DEGS1	Sphingolipid delta(4)-desaturase DES1	1.9	-	∞	1

DEK	Protein DEK	2.3	2.0	-	193
DERL1	Derlin-1	2.4	1.8	-	6
DHCR24	Delta(24)-sterol reductase	5.2	1.9	-	9
DHX16	Pre-mRNA-splicing factor ATP-dependent RNA helicase DHX16	4.0	∞	-	112
DIDO1	Death-inducer obliterator 1	3.2	∞	-	140
DNAAF5	Dynein assembly factor 5, axonemal	-	∞	∞	15
DNAJA1	DnaJ homolog subfamily A member 1	35.8	-	∞	243
DNAJA2	DnaJ homolog subfamily A member 2	2.6	2.2	-	210
DNAJC10	DnaJ homolog subfamily C member 10	7.8	∞	-	131
DNAJC2	DnaJ homolog subfamily C member 2	-	2.2	∞	29
DNAJC8	DnaJ homolog subfamily C member 8	12.0	∞	-	167
DOCK7	Dedicator of cytokinesis protein 7	10.9	-	∞	103
DPM1	Dolichol-phosphate mannosyltransferase subunit 1	9.3	∞	-	107
DRG1	Developmentally-regulated GTP-binding protein 1	155.4	4.0	-	172
DSC2	Desmocollin-2	∞	-	∞	19
DSP	Desmoplakin	7.0	∞	1.7	328

DYNC1H1	Cytoplasmic dynein 1 heavy chain 1	2.0	7.4	-	345
EBNA1BP2	Probable rRNA-processing protein EBP2	2.1	1.6	-	137
EBP	3-beta-hydroxysteroid-Delta(8),Delta(7)-isomerase	4.0	∞	-	47
EDC3	Enhancer of mRNA-decapping protein 3	6.8	2.0	-	52
EEF1A2	Elongation factor 1-alpha 2	1.8	3.2	1.7	645
EEF1B2	Elongation factor 1-beta	8.5	-	∞	379
EEF1G	Elongation factor 1-gamma	7.3	-	∞	461
EEF2	Elongation factor 2	20.9	∞	-	488
EIF2AK2	Interferon-induced, double-stranded RNA-activated protein kinase	6.0	∞	-	76
EIF2AK3	Eukaryotic translation initiation factor 2-alpha kinase 3	13.1	∞	∞	2
EIF3A	Eukaryotic translation initiation factor 3 subunit A	2.8	-	-	287
EIF3B	Eukaryotic translation initiation factor 3 subunit B	6.6	∞	-	282
EIF3D	Eukaryotic translation initiation factor 3 subunit D	-	∞	∞	249
EIF3E	Eukaryotic translation initiation factor 3 subunit E	3.0	4.6	-	209
EIF3F	Eukaryotic translation initiation factor 3 subunit F	9.5	5.0	-	272
EIF3I	Eukaryotic translation initiation factor 3 subunit I	8.0	1.7	-	280

EIF4A3	Eukaryotic initiation factor 4A-III	16.6	5.6	∞	418
EIF4B	Eukaryotic translation initiation factor 4B	2.5	∞	-	344
EIF4E2	Eukaryotic translation initiation factor 4E type 2	∞	∞	-	54
EIF4G1	Eukaryotic translation initiation factor 4 gamma 1	1.6	∞	∞	293
EIF4G2	Eukaryotic translation initiation factor 4 gamma 2	3.0	7.7	-	119
EIF4H	Eukaryotic translation initiation factor 4H	3.3	2.2	-	205
EIF5B	Eukaryotic translation initiation factor 5B	10.2	∞	-	200
EMC1	ER membrane protein complex subunit 1	2.0	∞	-	25
ENO1	Alpha-enolase	1.9	∞	-	478
ENY2	Transcription and mRNA export factor ENY2	12.0	3.0	-	84
ERH	Enhancer of rudimentary homolog	2.8	-	∞	454
ESF1	ESF1 homolog	1.6	4.4	-	101
ESYT1	Extended synaptotagmin-1	2.5	∞	-	173
ETFA	Electron transfer flavoprotein subunit alpha, mitochondrial	3.6	∞	-	148
EWSR1	RNA-binding protein EWS	8.4	∞	-	301
EXOC3	Exocyst complex component 3	-	∞	∞	23

EXOC6	Exocyst complex component 6	1.6	2.0	-	10
EXOSC6	Exosome complex component MTR3	1.9	1.8	-	179
EXOSC8	Exosome complex component RRP43	8.3	∞	-	93
EXOSC9	Exosome complex component RRP45	4.5	∞	-	171
FAF2	FAS-associated factor 2	4.7	-	∞	70
FAM126A	Hyccin	3.8	∞	-	4
FAM32A	Protein FAM32A	8.6	∞	-	112
FAM50A	Protein FAM50A	1.6	21.6	-	97
FAM91A1	Protein FAM91A1	3.5	1.8	-	81
FAM98A	Protein FAM98A	5.5	-	∞	112
FAM98B	Protein FAM98B	1.9	3.5	-	113
FARSB	Phenylalanine--tRNA ligase beta subunit	4.5	-	∞	139
FASN	Fatty acid synthase	9.4	∞	-	436
FAU	40S ribosomal protein S30	4.1	∞	-	320
FBL	rRNA 2'-O-methyltransferase fibrillarin	4.1	∞	-	387
FHL1	Four and a half LIM domains protein 1	-	∞	∞	177

FHOD1	FH1/FH2 domain-containing protein 1	15.2	12.1	-	37
FIP1L1	Pre-mRNA 3'-end-processing factor FIP1	5.4	∞	-	219
FKBP2	Peptidyl-prolyl cis-trans isomerase FKBP2	1.8	∞	-	7
FKBP8	Peptidyl-prolyl cis-trans isomerase FKBP8	2.6	-	∞	82
FLNA	Filamin-A	2.1	3.3	2.1	508
FMR1	Synaptic functional regulator FMR1	2.4	2.1	-	131
FOCAD	Focadhesin	13.9	∞	∞	2
FRAS1	Extracellular matrix protein FRAS1	2.8	2.2	-	4
FRG1	Protein FRG1	3.3	2.0	-	138
FUS	RNA-binding protein FUS	12.1	1.7	-	428
G3BP1	Ras GTPase-activating protein-binding protein 1	9.2	-	∞	353
G6PD	Glucose-6-phosphate 1-dehydrogenase	4.1	-	∞	89
GANAB	Neutral alpha-glucosidase AB	7.0	-	∞	216
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	1.8	∞	-	458
GAPVD1	GTPase-activating protein and VPS9 domain-containing protein 1	3.4	5.7	-	125
GBF1	Golgi-specific brefeldin A-resistance guanine nucleotide exchange factor 1	2.3	1.5	-	55

GCDH	Glutaryl-CoA dehydrogenase, mitochondrial	4.0	-	∞	24
GCN1	eIF-2-alpha kinase activator GCN1	1.7	∞	-	246
GFM1	Elongation factor G, mitochondrial	1.9	2.6	-	40
GFPT1	Glutamine--fructose-6-phosphate aminotransferase [isomerizing] 1	1.7	2.5	-	62
GGCX	Vitamin K-dependent gamma-carboxylase	3.0	2.3	-	6
GIGYF2	GRB10-interacting GYF protein 2	2.1	2.6	-	156
GLMN	Glomulin	1.9	8.5	-	28
GLRX5	Glutaredoxin-related protein 5, mitochondrial	1.6	2.7	-	20
GLUD1	Glutamate dehydrogenase 1, mitochondrial	2.0	-	∞	217
GNAS	Guanine nucleotide-binding protein G(s) subunit alpha isoforms short	3.5	2.0	-	207
GNPAT	Dihydroxyacetone phosphate acyltransferase	3.9	∞	-	14
GPAA1	Glycosylphosphatidylinositol anchor attachment 1 protein	3.4	2.6	-	0
GPATCH11	G patch domain-containing protein 11	77.0	1.6	-	34
GPD2	Glycerol-3-phosphate dehydrogenase, mitochondrial	2.3	2.1	-	47
GPR180	Integral membrane protein GPR180	2.4	1.8	-	1
GPX4	Phospholipid hydroperoxide glutathione peroxidase	3.7	∞	-	25

GRB10	Growth factor receptor-bound protein 10	3.8	2.5	-	3
GSTK1	Glutathione S-transferase kappa 1	2.2	-	∞	42
GTF2F1	General transcription factor IIF subunit 1	5.8	∞	-	132
GTF2I	General transcription factor II-I	4.5	∞	-	312
HACD3	Very-long-chain (3R)-3-hydroxyacyl-CoA dehydratase 3	7.8	∞	-	176
HADHA	Trifunctional enzyme subunit alpha, mitochondrial	6.5	-	∞	154
HADHB	Trifunctional enzyme subunit beta, mitochondrial	1.7	3.8	-	123
HAX1	HCLS1-associated protein X-1	5.8	∞	-	63
HDGF	Hepatoma-derived growth factor	5.3	∞	-	174
HDGFL2	Hepatoma-derived growth factor-related protein 2	6.1	∞	-	185
HEATR5B	HEAT repeat-containing protein 5B	4.9	∞	30.5	9
HELLS	Lymphoid-specific helicase	-	∞	∞	97
HIGD1A	HIG1 domain family member 1A, mitochondrial	2.3	2.0	∞	52
HLA-A	HLA class I histocompatibility antigen, A alpha chain	1.6	1.7	2.6	114
HLA-B	HLA class I histocompatibility antigen, B alpha chain	4.8	1.7	-	118
HMGB3	High mobility group protein B3	26.8	-	∞	87

HNRNPA2B1	Heterogeneous nuclear ribonucleoproteins A2/B1	4.8	2.4	-	536
HNRNPA3	Heterogeneous nuclear ribonucleoprotein A3	-	∞	∞	447
HNRNPAB	Heterogeneous nuclear ribonucleoprotein A/B	19.1	1.6	-	442
HNRNPD	Heterogeneous nuclear ribonucleoprotein D0	2.4	∞	-	489
HNRNPDL	Heterogeneous nuclear ribonucleoprotein D-like	9.3	∞	1.8	369
HNRNPF	Heterogeneous nuclear ribonucleoprotein F	1.6	∞	-	528
HNRNPK	Heterogeneous nuclear ribonucleoprotein K	3.1	2.7	-	581
HNRNPL	Heterogeneous nuclear ribonucleoprotein L	3.0	∞	-	460
HNRNPM	Heterogeneous nuclear ribonucleoprotein M	2.2	4.9	-	520
HOMER2	Homer protein homolog 2	6.0	3.6	-	18
HSD17B10	3-hydroxyacyl-CoA dehydrogenase type-2	2.1	2.3	-	290
HSD17B11	Estradiol 17-beta-dehydrogenase 11	2.6	2.9	-	4
HSD17B12	Very-long-chain 3-oxoacyl-CoA reductase	1.7	1.5	-	97
HSD17B4	Peroxisomal multifunctional enzyme type 2	4.7	2.8	-	139
HSDL1	Inactive hydroxysteroid dehydrogenase-like protein 1	18.8	3.0	-	9
HSDL2	Hydroxysteroid dehydrogenase-like protein 2	10.7	∞	-	79

HSP90AA1	Heat shock protein HSP 90-alpha	84.9	-	∞	565
HSP90AB1	Heat shock protein HSP 90-beta	-	∞	∞	573
HSP90B1	Endoplasmin	4.5	5.2	∞	460
HSPA1A	Heat shock 70 kDa protein 1A	3.6	∞	-	698
HSPA5	Endoplasmic reticulum chaperone BiP	27.2	∞	-	661
HSPA8	Heat shock cognate 71 kDa protein	1.7	11.5	-	703
HSPA9	Stress-70 protein, mitochondrial	9.5	-	∞	552
HSPD1	60 kDa heat shock protein, mitochondrial	4.3	2.5	-	520
HSPH1	Heat shock protein 105 kDa	4.1	∞	-	347
HTT	Huntingtin	1.6	-	1.8	19
IARS2	Isoleucine--tRNA ligase, mitochondrial	9.9	-	∞	66
IDH2	Isocitrate dehydrogenase [NADP], mitochondrial	7.4	∞	-	65
IDH3A	Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial	1.8	∞	-	80
IDH3B	Isocitrate dehydrogenase [NAD] subunit beta, mitochondrial	5.1	-	∞	69
IGF2BP1	Insulin-like growth factor 2 mRNA-binding protein 1	11.1	-	∞	343
IGF2R	Cation-independent mannose-6-phosphate receptor	3.0	∞	-	31

IK	Protein Red	3.0	-	∞	134
IL7R	Interleukin-7 receptor subunit alpha	2.1	2.8	-	0
ILF2	Interleukin enhancer-binding factor 2	2.3	5.7	-	313
ILVBL	2-hydroxyacyl-CoA lyase 2	-	∞	∞	39
IMPDH2	Inosine-5'-monophosphate dehydrogenase 2	9.0	-	∞	195
INPP5K	Inositol polyphosphate 5-phosphatase K	7.2	∞	-	1
INTS3	Integrator complex subunit 3	43.1	-	∞	29
IPO11	Importin-11	4.3	∞	-	63
IPO5	Importin-5	-	∞	∞	267
IPO7	Importin-7	4.2	4.9	-	191
IPO8	Importin-8	-	3.2	2.3	95
IPO9	Importin-9	-	∞	∞	120
IQGAP1	Ras GTPase-activating-like protein IQGAP1	1.9	2.2	-	197
IRS4	Insulin receptor substrate 4	2.7	2.1	-	378
ITIH6	Inter-alpha-trypsin inhibitor heavy chain H6	2.3	-	∞	1
JAK1	Tyrosine-protein kinase JAK1	2.5	2.2	-	14

KDELR1	ER lumen protein-retaining receptor 1	2.5	∞	-	31
KHDRBS1	KH domain-containing, RNA-binding, signal transduction-associated protein 1	6.5	∞	-	348
KHSRP	Far upstream element-binding protein 2	2.8	2.1	-	403
KIAA1522	Uncharacterized protein KIAA1522	2.2	∞	-	5
KIAA2013	Uncharacterized protein KIAA2013	3.7	8.7	-	1
KPNB1	Importin subunit beta-1	1.7	-	∞	418
KRAS	GTPase KRas	4.1	∞	-	24
KRTCAP2	Keratinocyte-associated protein 2	4.2	2.1	-	1
LAMTOR3	Ragulator complex protein LAMTOR3	10.8	5.3	-	5
LARP4B	La-related protein 4B	2.8	∞	-	86
LDHA	L-lactate dehydrogenase A chain	5.5	∞	-	304
LDHB	L-lactate dehydrogenase B chain	2.7	∞	-	340
LONP1	Lon protease homolog, mitochondrial	3.3	2.4	-	149
LPCAT1	Lysophosphatidylcholine acyltransferase 1	1.9	2.1	-	43
LPCAT2	Lysophosphatidylcholine acyltransferase 2	3.2	4.4	-	6
LRCH2	Leucine-rich repeat and calponin homology domain-containing protein 2	2.4	1.6	-	8

LRPAP1	Alpha-2-macroglobulin receptor-associated protein	4.0	1.9	-	31
LRPPRC	Leucine-rich PPR motif-containing protein, mitochondrial	3.4	2.9	-	249
LRRC47	Leucine-rich repeat-containing protein 47	4.0	1.9	-	82
LSG1	Large subunit GTPase 1 homolog	14.9	-	∞	85
LSM14A	Protein LSM14 homolog A	6.1	8.3	-	227
LUC7L3	Luc7-like protein 3	3.5	4.8	-	324
MACROD1	ADP-ribose glycohydrolase MACROD1	7.1	2.6	-	13
MAGED2	Melanoma-associated antigen D2	6.5	∞	-	133
MAGT1	Magnesium transporter protein 1	7.3	-	∞	13
MAP1B	Microtubule-associated protein 1B	2.1	10.2	-	260
MAP1S	Microtubule-associated protein 1S	1.8	3.7	-	33
MARK2	Serine/threonine-protein kinase MARK2	-	∞	∞	23
MATR3	Matrin-3	4.0	∞	-	441
MCM4	DNA replication licensing factor MCM4	10.6	-	∞	293
MCM5	DNA replication licensing factor MCM5	2.5	2.7	-	208
MDN1	Midasin	4.9	-	∞	85

METTL15	12S rRNA N4-methylcytidine (m4C) methyltransferase	55.7	∞	-	0
MFAP1	Microfibrillar-associated protein 1	13.0	∞	-	203
MGST2	Microsomal glutathione S-transferase 2	8.4	-	∞	2
MGST3	Microsomal glutathione S-transferase 3	17.5	5.2	-	9
MIA3	Transport and Golgi organization protein 1 homolog	17.1	16.0	-	51
MIOS	GATOR complex protein MIOS	8.1	∞	-	11
MOB4	MOB-like protein phocein	6.0	2.3	-	28
MORF4L1	Mortality factor 4-like protein 1	14.7	2.8	-	26
MPDU1	Mannose-P-dolichol utilization defect 1 protein	2.5	6.6	-	44
MPLKIP	M-phase-specific PLK1-interacting protein	1.7	1.7	-	3
MPP6	MAGUK p55 subfamily member 6	2.4	-	∞	10
MRM2	rRNA methyltransferase 2, mitochondrial	7.3	∞	-	0
MRPL11	39S ribosomal protein L11, mitochondrial	7.6	∞	-	38
MRPL15	39S ribosomal protein L15, mitochondrial	5.4	1.6	-	56
MRPL33	39S ribosomal protein L33, mitochondrial	22.3	-	∞	27
MRPL37	39S ribosomal protein L37, mitochondrial	6.2	∞	-	61

MRPL42	39S ribosomal protein L42, mitochondrial	2.2	∞	-	3
MRPL46	39S ribosomal protein L46, mitochondrial	5.1	2.6	-	62
MRPS23	28S ribosomal protein S23, mitochondrial	2.6	∞	-	85
MRPS26	28S ribosomal protein S26, mitochondrial	6.9	1.6	-	51
MRPS34	28S ribosomal protein S34, mitochondrial	4.3	4.1	-	58
MRPS7	28S ribosomal protein S7, mitochondrial	1.8	∞	-	76
MRRF	Ribosome-recycling factor, mitochondrial	1.9	∞	-	20
MSH2	DNA mismatch repair protein Msh2	1.9	29.5	-	202
MTDH	Protein LYRIC	14.2	2.5	-	179
MTHFD1	C-1-tetrahydrofolate synthase, cytoplasmic	2.2	3.4	-	311
MTHFD1L	Monofunctional C1-tetrahydrofolate synthase, mitochondrial	2.7	∞	-	150
MYBBP1A	Myb-binding protein 1A	1.9	6.3	-	301
MYH9	Myosin-9	2.9	∞	-	448
MYL4	Myosin light chain 4	2.5	∞	-	3
MYO1B	Unconventional myosin-Ib	3.6	-	∞	159
NASP	Nuclear autoantigenic sperm protein	2.3	∞	-	327

NCAPD2	Condensin complex subunit 1	13.6	-	∞	112
NCAPH	Condensin complex subunit 2	2.5	2.2	-	212
NCLN	Nicalin	3.5	3.5	-	41
NCOA2	Nuclear receptor coactivator 2	3.7	2.6	-	15
NDUFA10	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10, mitochondrial	1.7	1.6	-	67
NDUFA2	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 2	8.0	∞	-	11
NDUFB10	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 10	3.9	2.1	-	32
NDUFB4	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 4	4.9	-	∞	5
NDUFS2	NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial	2.4	∞	1.6	43
NDUFS5	NADH dehydrogenase [ubiquinone] iron-sulfur protein 5	3.2	∞	-	26
NDUFS6	NADH dehydrogenase [ubiquinone] iron-sulfur protein 6, mitochondrial	6.8	-	2.1	17
NDUFS8	NADH dehydrogenase [ubiquinone] iron-sulfur protein 8, mitochondrial	9.6	∞	-	42
NDUFV1	NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial	3.6	-	∞	7
NELFE	Negative elongation factor E	∞	∞	-	152
NIPSNAP1	Protein NipSnap homolog 1	2.8	∞	-	40
NIPSNAP2	Protein NipSnap homolog 2	2.5	∞	-	24

NMT1	Glycylpeptide N-tetradecanoyltransferase 1	2.9	∞	-	113
NOLC1	Nucleolar and coiled-body phosphoprotein 1	4.4	∞	-	297
NONO	Non-POU domain-containing octamer-binding protein	1.8	∞	-	505
NOP14	Nucleolar protein 14	4.2	-	∞	46
NOP2	Probable 28S rRNA (cytosine(4447)-C(5))-methyltransferase	3.9	∞	-	276
NPM3	Nucleoplasmin-3	2.4	5.0	-	209
NSDHL	Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating	4.0	∞	-	68
NSF	Vesicle-fusing ATPase	3.7	1.6	-	98
NSUN5	28S rRNA (cytosine-C(5))-methyltransferase	2.9	∞	-	12
NT5DC2	5'-nucleotidase domain-containing protein 2	3.9	∞	-	113
NUDT21	Cleavage and polyadenylation specificity factor subunit 5	2.8	2.5	-	295
NUP155	Nuclear pore complex protein Nup155	5.1	2.2	-	175
NUP188	Nucleoporin NUP188 homolog	4.1	∞	-	52
NUP205	Nuclear pore complex protein Nup205	1.7	∞	-	158
NUP93	Nuclear pore complex protein Nup93	-	∞	∞	211
OAT	Ornithine aminotransferase, mitochondrial	3.7	∞	-	202

ODR4	Protein odr-4 homolog	1.6	2.4	-	11
OPA1	Dynamin-like 120 kDa protein, mitochondrial	25.2	∞	-	41
PARS2	Probable proline--tRNA ligase, mitochondrial	21.5	∞	-	5
PCBP2	Poly(rC)-binding protein 2	5.7	-	∞	475
PCLAF	PCNA-associated factor	2.4	∞	-	41
PCMT1	Protein-L-isoaspartate(D-aspartate) O-methyltransferase	3.0	1.6	-	299
PCNA	Proliferating cell nuclear antigen	3.5	-	∞	268
PDAP1	28 kDa heat- and acid-stable phosphoprotein	2.6	∞	-	233
PDE12	2',5'-phosphodiesterase 12	5.6	-	∞	71
PDHA1	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial	2.4	-	∞	126
PDHB	Pyruvate dehydrogenase E1 component subunit beta, mitochondrial	2.0	-	∞	141
PDIA3	Protein disulfide-isomerase A3	99.3	∞	-	281
PDIA4	Protein disulfide-isomerase A4	5.0	-	∞	168
PDIA6	Protein disulfide-isomerase A6	-	3.0	2.2	357
PDS5A	Sister chromatid cohesion protein PDS5 homolog A	8.5	∞	-	136
PEX14	Peroxisomal membrane protein PEX14	∞	∞	-	99

PFKM	ATP-dependent 6-phosphofructokinase, muscle type	2.0	1.8	-	126
PHB	Prohibitin	2.0	2.2	-	269
PHF6	PHD finger protein 6	2.0	4.6	-	156
PHGDH	D-3-phosphoglycerate dehydrogenase	1.8	∞	-	394
PI4KA	Phosphatidylinositol 4-kinase alpha	1.8	6.2	-	30
PIGT	GPI transamidase component PIG-T	1.7	-	∞	7
PITPNB	Phosphatidylinositol transfer protein beta isoform	6.3	7.2	-	61
PKM	Pyruvate kinase PKM	2.5	4.2	-	536
PLS3	Plastin-3	3.2	2.6	∞	208
PPIA	Peptidyl-prolyl cis-trans isomerase A	2.4	2.1	-	439
PPIB	Peptidyl-prolyl cis-trans isomerase B	4.9	3.0	-	228
PPIG	Peptidyl-prolyl cis-trans isomerase G	11.0	∞	-	86
PPIL1	Peptidyl-prolyl cis-trans isomerase-like 1	4.3	∞	-	94
PPIL2	RING-type E3 ubiquitin-protein ligase PPIL2	2.7	∞	-	46
PPIL4	Peptidyl-prolyl cis-trans isomerase-like 4	61.1	∞	-	213
PPP1CA	Serine/threonine-protein phosphatase PP1-alpha catalytic subunit	5.1	∞	-	325

PPP1R12A	Protein phosphatase 1 regulatory subunit 12A	3.3	∞	-	145
PQBP1	Polyglutamine-binding protein 1	-	∞	∞	67
PRDX1	Peroxiredoxin-1	3.3	∞	-	549
PRDX2	Peroxiredoxin-2	2.5	∞	-	482
PRDX3	Thioredoxin-dependent peroxide reductase, mitochondrial	-	3.4	7.4	315
PRDX6	Peroxiredoxin-6	12.4	∞	-	388
PRKDC	DNA-dependent protein kinase catalytic subunit	5.5	-	∞	406
PRKRIP1	PRKR-interacting protein 1	3.4	∞	-	0
PRMT5	Protein arginine N-methyltransferase 5	3.5	3.0	-	285
PRPF31	U4/U6 small nuclear ribonucleoprotein Prp31	14.7	∞	∞	251
PRPF38A	Pre-mRNA-splicing factor 38A	2.6	∞	-	120
PRPF4B	Serine/threonine-protein kinase PRP4 homolog	12.5	∞	-	131
PRPF6	Pre-mRNA-processing factor 6	2.7	1.5	-	180
PRRC2A	Protein PRRC2A	12.0	-	∞	212
PRRC2C	Protein PRRC2C	9.9	2.0	-	223
PSIP1	PC4 and SFRS1-interacting protein	2.5	6.9	-	219

PSMC1	26S proteasome regulatory subunit 4	3.1	∞	-	195
PSMC3	26S proteasome regulatory subunit 6A	13.3	3.1	-	225
PSMC4	26S proteasome regulatory subunit 6B	7.9	-	2.1	210
PSMC6	26S proteasome regulatory subunit 10B	5.1	∞	-	179
PSMD1	26S proteasome non-ATPase regulatory subunit 1	3.4	2.2	-	217
PSMD11	26S proteasome non-ATPase regulatory subunit 11	2.4	5.6	-	204
PSMD12	26S proteasome non-ATPase regulatory subunit 12	1.7	9.1	-	221
PSMD13	26S proteasome non-ATPase regulatory subunit 13	1.5	2.9	-	160
PSMD14	26S proteasome non-ATPase regulatory subunit 14	2.3	3.2	-	168
PSMD2	26S proteasome non-ATPase regulatory subunit 2	2.3	∞	-	271
PSMD3	26S proteasome non-ATPase regulatory subunit 3	1.9	∞	-	269
PSMD4	26S proteasome non-ATPase regulatory subunit 4	1.9	2.8	-	220
PSMD6	26S proteasome non-ATPase regulatory subunit 6	2.8	∞	-	187
PSMD7	26S proteasome non-ATPase regulatory subunit 7	2.3	∞	-	144
PSME2	Proteasome activator complex subunit 2	1.6	∞	-	82
PTGDR	Prostaglandin D2 receptor	2.3	5.0	-	0

PTPN1	Tyrosine-protein phosphatase non-receptor type 1	4.5	2.1	-	124
PTPRF	Receptor-type tyrosine-protein phosphatase F	2.3	2.6	-	1
PTRH2	Peptidyl-tRNA hydrolase 2, mitochondrial	24.8	9.6	-	31
PYCR2	Pyrroline-5-carboxylate reductase 2	1.6	∞	-	98
PYCR3	Pyrroline-5-carboxylate reductase 3	1.9	4.2	-	10
QPCT	Glutaminyl-peptide cyclotransferase	3.0	4.2	-	122
RAB11FIP1	Rab11 family-interacting protein 1	3.3	∞	-	76
RAB21	Ras-related protein Rab-21	21.4	∞	-	131
RABL3	Rab-like protein 3	8.1	-	∞	30
RABL6	Rab-like protein 6	3.0	1.6	-	88
RACK1	Receptor of activated protein C kinase 1	2.2	6.3	-	352
RAN	GTP-binding nuclear protein Ran	2.6	1.6	-	440
RANGAP1	Ran GTPase-activating protein 1	4.1	3.0	-	283
RAVER1	Ribonucleoprotein PTB-binding 1	2.4	2.7	-	129
RBBP4	Histone-binding protein RBBP4	1.8	4.2	-	393
RBBP7	Histone-binding protein RBBP7	3.2	2.7	-	370

RBFOX2	RNA binding protein fox-1 homolog 2	5.5	11.3	-	43
RBM10	RNA-binding protein 10	2.2	2.0	-	327
RBM12B	RNA-binding protein 12B	3.2	6.5	-	12
RBM14	RNA-binding protein 14	2.4	5.7	-	293
RBM26	RNA-binding protein 26	3.3	6.7	-	146
RBM27	RNA-binding protein 27	1.8	2.9	-	165
RBM6	RNA-binding protein 6	1.9	2.1	-	80
RBM8A	RNA-binding protein 8A	1.9	1.7	-	123
RCN1	Reticulocalbin-1	2.1	5.0	-	107
RCN2	Reticulocalbin-2	5.9	2.5	-	208
RDH14	Retinol dehydrogenase 14	2.0	-	∞	3
RIOK1	Serine/threonine-protein kinase RIO1	4.7	∞	3.0	153
ROCK1	Rho-associated protein kinase 1	7.4	-	∞	57
RPL10A	60S ribosomal protein L10a	5.8	-	∞	280
RPL11	60S ribosomal protein L11	9.3	2.1	-	495
RPL12	60S ribosomal protein L12	∞	∞	-	397

RPL13	60S ribosomal protein L13	2.0	∞	-	474
RPL14	60S ribosomal protein L14	2.0	2.1	6.4	333
RPL22	60S ribosomal protein L22	6.9	∞	-	429
RPL22L1	60S ribosomal protein L22-like 1	5.2	1.9	-	56
RPL23A	60S ribosomal protein L23a	2.7	7.7	-	418
RPL31	60S ribosomal protein L31	∞	-	∞	335
RPL32	60S ribosomal protein L32	1.7	3.1	-	184
RPL34	60S ribosomal protein L34	2.8	∞	-	247
RPL35	60S ribosomal protein L35	3.0	3.7	-	302
RPL38	60S ribosomal protein L38	3.2	1.8	-	300
RPL6	60S ribosomal protein L6	14.0	1.7	-	432
RPL7	60S ribosomal protein L7	2.9	-	∞	335
RPL8	60S ribosomal protein L8	2.3	13.9	-	390
RPL9	60S ribosomal protein L9	1.7	-	∞	390
RPN1	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1	5.0	∞	-	246
RPN2	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2	1.8	11.6	-	179

RPS12	40S ribosomal protein S12	2.9	18.0	-	382
RPS13	40S ribosomal protein S13	2.0	10.5	-	311
RPS15A	40S ribosomal protein S15a	3.0	8.5	-	401
RPS19	40S ribosomal protein S19	3.5	19.3	-	334
RPS3A	40S ribosomal protein S3a	3.4	2.0	-	434
RPS4X	40S ribosomal protein S4, X isoform	2.6	∞	∞	451
RPS5	40S ribosomal protein S5	1.6	2.1	-	321
RPS6	40S ribosomal protein S6	1.7	3.3	-	466
RPS6KA2	Ribosomal protein S6 kinase alpha-2	11.4	3.0	-	15
RPS9	40S ribosomal protein S9	5.2	-	∞	388
RPTOR	Regulatory-associated protein of mTOR	6.1	-	3.4	14
RRP12	RRP12-like protein	6.6	∞	-	176
RTCB	RNA-splicing ligase RtcB homolog	2.2	60.6	-	290
SACM1L	Phosphatidylinositol-3-phosphatase SAC1	2.3	∞	-	22
SAMHD1	Deoxynucleoside triphosphate triphosphohydrolase SAMHD1	6.3	1.7	-	120
SART1	U4/U6.U5 tri-snRNP-associated protein 1	2.8	∞	-	233

SBDS	Ribosome maturation protein SBDS	13.4	-	∞	33
SCAMP2	Secretory carrier-associated membrane protein 2	3.3	∞	-	9
SCO1	Protein SCO1 homolog, mitochondrial	4.3	1.9	-	18
SDE2	Replication stress response regulator SDE2	10.4	∞	-	85
SDF4	45 kDa calcium-binding protein	7.5	1.8	-	45
SEC22A	Vesicle-trafficking protein SEC22a	5.6	-	2.1	0
SEC22B	Vesicle-trafficking protein SEC22b	6.5	-	∞	85
SEC31A	Protein transport protein Sec31A	5.5	2.5	-	79
SEC63	Translocation protein SEC63 homolog	8.0	3.3	-	64
SELENOI	Ethanolaminephosphotransferase 1	3.2	2.9	-	12
SELENOM	Selenoprotein M	8.3	3.8	-	8
SERBP1	Plasminogen activator inhibitor 1 RNA-binding protein	3.1	-	1.6	468
SERPINH1	Serpin H1	1.6	92.6	1.7	281
SF1	Splicing factor 1	3.6	∞	-	256
SF3A1	Splicing factor 3A subunit 1	3.4	2.1	-	313
SF3A2	Splicing factor 3A subunit 2	6.4	1.6	-	176

SF3B1	Splicing factor 3B subunit 1	9.0	∞	-	361
SF3B2	Splicing factor 3B subunit 2	-	∞	∞	317
SF3B3	Splicing factor 3B subunit 3	4.4	∞	-	322
SF3B5	Splicing factor 3B subunit 5	4.3	∞	-	141
SFSWAP	Splicing factor, suppressor of white-apricot homolog	5.0	∞	∞	100
SFT2D3	Vesicle transport protein SFT2C	10.7	1.5	-	0
SFXN1	Sideroflexin-1	2.7	2.7	-	140
SFXN3	Sideroflexin-3	2.3	2.4	3.3	31
SKIV2L	Helicase SKI2W	2.4	∞	-	18
SLAIN2	SLAIN motif-containing protein 2	3.8	1.7	-	62
SLC16A1	Monocarboxylate transporter 1	4.3	∞	-	172
SLC1A4	Neutral amino acid transporter A	4.5	∞	-	0
SLC1A5	Neutral amino acid transporter B(0)	13.6	-	∞	236
SLC24A1	Sodium/potassium/calcium exchanger 1	5.4	-	∞	0
SLC25A17	Peroxisomal membrane protein PMP34	2.1	-	∞	5
SLC25A24	Calcium-binding mitochondrial carrier protein SCaMC-1	3.3	∞	3.0	9

SLC25A3	Phosphate carrier protein, mitochondrial	∞	-	∞	362
SLC25A6	ADP/ATP translocase 3	∞	∞	-	495
SLC27A4	Long-chain fatty acid transport protein 4	1.9	11.1	-	5
SLC30A7	Zinc transporter 7	3.5	∞	-	2
SLC35F2	Solute carrier family 35 member F2	2.0	∞	-	0
SLC37A3	Sugar phosphate exchanger 3	1.9	10.2	-	0
SLC38A9	Sodium-coupled neutral amino acid transporter 9	2.6	3.4	-	0
SLC39A14	Metal cation symporter ZIP14	1.9	3.6	-	9
SLC39A6	Zinc transporter ZIP6	1.8	16.0	-	1
SLC3A2	4F2 cell-surface antigen heavy chain	1.5	∞	-	189
SLC4A1AP	Kanadaptin	3.1	∞	-	74
SLC4A2	Anion exchange protein 2	14.1	-	∞	0
SLC6A15	Sodium-dependent neutral amino acid transporter B(0)AT2	4.7	∞	-	31
SLC7A5	Large neutral amino acids transporter small subunit 1	3.0	∞	-	73
SLIRP	SRA stem-loop-interacting RNA-binding protein, mitochondrial	4.3	∞	-	113
SLU7	Pre-mRNA-splicing factor SLU7	12.6	1.6	-	118

SMC4	Structural maintenance of chromosomes protein 4	4.5	∞	-	253
SMG1	Serine/threonine-protein kinase SMG1	18.7	∞	-	14
SMNDC1	Survival of motor neuron-related-splicing factor 30	32.9	-	3.7	115
SND1	Staphylococcal nuclease domain-containing protein 1	6.9	1.5	-	265
SNRPA	U1 small nuclear ribonucleoprotein A	4.0	4.8	2.5	194
SNRPA1	U2 small nuclear ribonucleoprotein A'	4.9	-	∞	314
SNRPB2	U2 small nuclear ribonucleoprotein B''	27.5	∞	1.6	214
SNRPD1	Small nuclear ribonucleoprotein Sm D1	2.6	∞	-	356
SNRPD2	Small nuclear ribonucleoprotein Sm D2	4.6	∞	-	340
SNX7	Sorting nexin-7	3.4	1.6	-	0
SORT1	Sortilin	6.3	-	∞	4
SPCS3	Signal peptidase complex subunit 3	1.8	∞	-	20
SPIN1	Spindlin-1	8.8	-	∞	159
SPNS1	Protein spinster homolog 1	2.5	∞	-	14
SPTLC1	Serine palmitoyltransferase 1	7.2	∞	-	31
SRP9	Signal recognition particle 9 kDa protein	4.8	∞	-	208

SRRM1	Serine/arginine repetitive matrix protein 1	4.6	∞	-	240
SRRM2	Serine/arginine repetitive matrix protein 2	2.8	3.9	-	324
SRSF1	Serine/arginine-rich splicing factor 1	2.0	∞	-	280
SRSF11	Serine/arginine-rich splicing factor 11	15.4	1.5	-	243
SRSF7	Serine/arginine-rich splicing factor 7	3.4	∞	∞	351
SRSF9	Serine/arginine-rich splicing factor 9	11.7	∞	-	151
SSBP4	Single-stranded DNA-binding protein 4	2.8	6.8	-	4
SSR3	Translocon-associated protein subunit gamma	1.9	1.7	-	44
SSR4	Translocon-associated protein subunit delta	1.9	∞	∞	254
STK11IP	Serine/threonine-protein kinase 11-interacting protein	2.6	1.7	-	9
STT3A	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit STT3A	2.2	∞	-	119
STX17	Syntaxin-17	4.9	∞	-	4
SUCLG2	Succinate--CoA ligase [GDP-forming] subunit beta, mitochondrial	2.7	∞	-	38
SUPT16H	FACT complex subunit SPT16	3.3	-	∞	175
SV2A	Synaptic vesicle glycoprotein 2A	3.3	∞	-	1
SYMPK	Symplekin	6.1	∞	-	111

SYNCRIP	Heterogeneous nuclear ribonucleoprotein Q	6.3	3.8	-	459
SYNRG	Synergin gamma	-	∞	∞	56
SYVN1	E3 ubiquitin-protein ligase synoviolin	1.8	2.4	-	0
TACC3	Transforming acidic coiled-coil-containing protein 3	1.9	1.8	-	97
TACO1	Translational activator of cytochrome c oxidase 1	1.6	3.2	-	33
TAF15	TATA-binding protein-associated factor 2N	3.8	1.8	1.7	383
TAMM41	Phosphatidate cytidylyltransferase, mitochondrial	1.7	2.1	-	9
TBC1D10B	TBC1 domain family member 10B	6.5	∞	-	60
TBRG4	FAST kinase domain-containing protein 4	2.8	2.7	-	22
TCEA1	Transcription elongation factor A protein 1	4.1	2.0	-	47
TCERG1	Transcription elongation regulator 1	4.9	2.5	1.6	183
TCF25	Transcription factor 25	7.8	∞	-	1
TCP1	T-complex protein 1 subunit alpha	1.6	2.0	-	432
TECR	Very-long-chain enoyl-CoA reductase	3.0	∞	-	192
TEX10	Testis-expressed protein 10	51.8	∞	-	115
TFAM	Transcription factor A, mitochondrial	3.6	1.7	1.7	107

TFB1M	Dimethyladenosine transferase 1, mitochondrial	1.9	14.9	-	8
THOC2	THO complex subunit 2	14.8	-	∞	222
THRAP3	Thyroid hormone receptor-associated protein 3	2.8	-	∞	382
TIMM50	Mitochondrial import inner membrane translocase subunit TIM50	5.0	∞	-	354
TMA16	Translation machinery-associated protein 16	1.7	1.9	∞	85
TMCO1	Calcium load-activated calcium channel	14.7	∞	-	30
TMED10	Transmembrane emp24 domain-containing protein 10	2.9	2.0	-	66
TMED5	Transmembrane emp24 domain-containing protein 5	17.0	∞	-	6
TMED9	Transmembrane emp24 domain-containing protein 9	4.9	∞	-	23
TMEM11	Transmembrane protein 11, mitochondrial	2.0	∞	-	2
TMEM33	Transmembrane protein 33	2.4	∞	-	144
TMEM41B	Transmembrane protein 41B	6.5	-	2.6	3
TMEM63B	CSC1-like protein 2	1.6	5.4	-	1
TMEM70	Transmembrane protein 70, mitochondrial	9.8	2.2	-	3
TMX3	Protein disulfide-isomerase TMX3	1.8	11.5	-	17
TNRC6B	Trinucleotide repeat-containing gene 6B protein	7.4	∞	-	162

TOMM34	Mitochondrial import receptor subunit TOM34	1.9	-	∞	32
TOP1	DNA topoisomerase 1	10.7	-	∞	285
TOR3A	Torsin-3A	4.2	∞	-	0
TPM3	Tropomyosin alpha-3 chain	10.7	-	∞	354
TPP1	Tripeptidyl-peptidase 1	2.3	∞	-	37
TPT1	Translationally-controlled tumor protein	8.3	∞	-	65
TRA2B	Transformer-2 protein homolog beta	5.5	2.1	-	163
TRAP1	Heat shock protein 75 kDa, mitochondrial	8.3	∞	∞	478
TRAPPC3	Trafficking protein particle complex subunit 3	2.9	∞	-	17
TRIM28	Transcription intermediary factor 1-beta	6.9	3.3	-	466
TRIP6	Thyroid receptor-interacting protein 6	22.0	∞	-	85
TRMT10C	tRNA methyltransferase 10 homolog C	1.9	4.6	∞	76
TSPO	Translocator protein	2.4	1.5	∞	4
TTC28	Tetratricopeptide repeat protein 28	2.8	3.3	-	84
TUBB	Tubulin beta chain	7.8	∞	-	685
TUFM	Elongation factor Tu, mitochondrial	2.7	1.9	-	408

TXNDC5	Thioredoxin domain-containing protein 5	1.9	∞	∞	149
U2AF1	Splicing factor U2AF 35 kDa subunit	1.6	∞	-	351
U2AF2	Splicing factor U2AF 65 kDa subunit	2.6	1.9	-	231
UBAP2L	Ubiquitin-associated protein 2-like	5.2	28.6	-	322
UBE2L3	Ubiquitin-conjugating enzyme E2 L3	4.0	∞	-	95
UBIAD1	UbiA prenyltransferase domain-containing protein 1	6.5	∞	-	21
UBXN4	UBX domain-containing protein 4	2.5	∞	-	28
UFD1	Ubiquitin recognition factor in ER-associated degradation protein 1	7.1	∞	-	68
UFL1	E3 UFM1-protein ligase 1	5.3	∞	-	53
UGGT1	UDP-glucose:glycoprotein glucosyltransferase 1	3.6	2.7	-	69
UNC45A	Protein unc-45 homolog A	1.6	∞	-	136
UPF3B	Regulator of nonsense transcripts 3B	3.2	1.5	-	42
UQCR11	Cytochrome b-c1 complex subunit 10	2.4	2.7	-	7
UQCRC2	Cytochrome b-c1 complex subunit 2, mitochondrial	3.5	7.0	∞	190
USO1	General vesicular transport factor p115	3.5	-	∞	155
USP15	Ubiquitin carboxyl-terminal hydrolase 15	4.5	-	∞	182

UTP14A	U3 small nucleolar RNA-associated protein 14 homolog A	∞	∞	-	117
VCP	Transitional endoplasmic reticulum ATPase	18.1	∞	∞	314
VDAC1	Voltage-dependent anion-selective channel protein 1	4.5	∞	-	213
VDAC2	Voltage-dependent anion-selective channel protein 2	2.6	∞	-	256
VDAC3	Voltage-dependent anion-selective channel protein 3	7.1	∞	-	226
VEZT	Vezatin	2.7	6.6	-	2
VIM	Vimentin	6.5	3.4	-	543
VMP1	Vacuole membrane protein 1	1.5	-	∞	15
VPS16	Vacuolar protein sorting-associated protein 16 homolog	4.3	-	∞	5
VPS33A	Vacuolar protein sorting-associated protein 33A	2.4	4.1	-	2
VPS41	Vacuolar protein sorting-associated protein 41 homolog	4.4	-	3.2	0
VPS45	Vacuolar protein sorting-associated protein 45	6.0	-	6.5	2
VWA8	von Willebrand factor A domain-containing protein 8	3.5	-	4.5	8
WASHC4	WASH complex subunit 4	6.1	∞	-	17
WDR33	pre-mRNA 3' end processing protein WDR33	2.0	4.4	-	117
WDR49	WD repeat-containing protein 49	4.5	-	∞	0

WDR7	WD repeat-containing protein 7	3.8	-	∞	6
WDR77	Methylosome protein 50	-	∞	∞	250
WLS	Protein wntless homolog	2.1	2.0	-	1
WTAP	Pre-mRNA-splicing regulator WTAP	1.8	1.7	-	77
XPO1	Exportin-1	3.8	-	∞	237
XPO5	Exportin-5	3.2	∞	-	129
XRCC6	X-ray repair cross-complementing protein 6	19.4	3.9	-	388
XXYLT1	Xyloside xylosyltransferase 1	90.0	∞	-	0
YARS2	Tyrosine--tRNA ligase, mitochondrial	2.3	5.0	-	65
YBX1	Y-box-binding protein 1	8.2	∞	-	448
YIPF3	Protein YIPF3	22.8	1.6	-	0
YRDC	YrdC domain-containing protein, mitochondrial	6.9	∞	-	12
YWHAQ	14-3-3 protein theta	2.3	∞	-	410
ZC3H13	Zinc finger CCCH domain-containing protein 13	8.6	2.0	-	41
ZC3H15	Zinc finger CCCH domain-containing protein 15	2.5	∞	-	149
ZC3H4	Zinc finger CCCH domain-containing protein 4	2.3	1.6	-	134

ZMAT2	Zinc finger matrin-type protein 2	1.6	∞	-	53
ZNF207	BUB3-interacting and GLEBS motif-containing protein ZNF207	3.8	1.5	-	92
ZNF593	Zinc finger protein 593	2.0	1.7	-	36
ZRANB2	Zinc finger Ran-binding domain-containing protein 2	1.9	∞	-	168
ZSWIM5	Zinc finger SWIM domain-containing protein 5	1.9	2.0	-	0

Table S2. LC-MS / MS single hits

Gene Symbol	Protein name
41	Protein 4.1
1433E	14-3-3 protein epsilon
1433F	14-3-3 protein eta
1433Z	14-3-3 protein zeta/delta
2A5G	Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunit
2AAA	Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A
2AAB	Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A beta
2ABA	Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B
3BP5	SH3 domain-binding protein 5
3MG	DNA-3-methyladenine glycosylase
5NT1A	Cytosolic 5'-nucleotidase 1A
5NT3A	Cytosolic 5'-nucleotidase 3A {ECO:0000305|PubMed:15968458,
A1AT	Alpha-1-antitrypsin {ECO:0000305}
A1CF	APOBEC1 complementation factor
AAKG1	5'-AMP-activated protein kinase subunit gamma-1
AAPK1	5'-AMP-activated protein kinase catalytic subunit alpha-1
AAPK2	5'-AMP-activated protein kinase catalytic subunit alpha-2
AASS	Alpha-aminoadipic semialdehyde synthase, mitochondrial
AB17B	Alpha/beta hydrolase domain-containing protein 17B {ECO:0000305}
ABCA1	Phospholipid-transporting ATPase ABCA1 {ECO:0000305}
ABCA3	ATP-binding cassette sub-family A member 3
ABCA6	ATP-binding cassette sub-family A member 6
ABCAC	ATP-binding cassette sub-family A member 12
ABCB6	ATP-binding cassette sub-family B member 6, mitochondrial
ABCB7	ATP-binding cassette sub-family B member 7, mitochondrial
ABCBA	ATP-binding cassette sub-family B member 10, mitochondrial
ABCD3	ATP-binding cassette sub-family D member 3
ABCF1	ATP-binding cassette sub-family F member 1
ABD12	Lysophosphatidylserine lipase ABHD12 {ECO:0000305}
ABHGA	Phosphatidylserine lipase ABHD16A {ECO:0000305}
ABI1	Abl interactor 1
ABL1	Tyrosine-protein kinase ABL1
ABL2	Tyrosine-protein kinase ABL2
ACACA	Acetyl-CoA carboxylase 1 {ECO:0000303|PubMed:12810950}
ACAD9	Complex I assembly factor ACAD9, mitochondrial
ACADV	Very long-chain specific acyl-CoA dehydrogenase, mitochondrial
ACATN	Acetyl-coenzyme A transporter 1
ACDSB	Short/branched chain specific acyl-CoA dehydrogenase, mitochondrial
ACOD	Acyl-CoA desaturase
ACOT8	Acyl-coenzyme A thioesterase 8
ACOT9	Acyl-coenzyme A thioesterase 9, mitochondrial
ACOX1	Peroxisomal acyl-coenzyme A oxidase 1 {ECO:0000303|PubMed:8117268}

ACPM	Acyl carrier protein, mitochondrial
ACSF2	Medium-chain acyl-CoA ligase ACSF2, mitochondrial {ECO:0000305}
ACSL1	Long-chain-fatty-acid--CoA ligase 1 {ECO:0000305}

ACSL4	Long-chain-fatty-acid--CoA ligase 4 {ECO:0000305}
ACTB	Actin, cytoplasmic 1
ACTBL	Beta-actin-like protein 2
ACTG	Actin, cytoplasmic 2
ACTY	Beta-centractin
ACTZ	Alpha-centractin
ADA1B	Alpha-1B adrenergic receptor
ADCY3	Adenylate cyclase type 3
ADRM1	Proteasomal ubiquitin receptor ADRM1
ADRO	NADPH:adrenodoxin oxidoreductase, mitochondrial
ADT2	ADP/ATP translocase 2
AEN	Apoptosis-enhancing nuclease
AGAL	Alpha-galactosidase A
AGK	Acylglycerol kinase, mitochondrial {ECO:0000303|PubMed:15939762}
AGM1	Phosphoacetylglucosamine mutase {ECO:0000305}
AHNK	Neuroblast differentiation-associated protein AHNAK
AHNK2	Protein AHNAK2
AHSA1	Activator of 90 kDa heat shock protein ATPase homolog 1
AIF1L	Allograft inflammatory factor 1-like
AIFM1	Apoptosis-inducing factor 1, mitochondrial {ECO:0000305}
AIMP1	Aminoacyl tRNA synthase complex-interacting multifunctional protein 1
AIMP2	Aminoacyl tRNA synthase complex-interacting multifunctional protein 2
AKA11	A-kinase anchor protein 11
AKAP1	A-kinase anchor protein 1, mitochondrial
AKAP2	A-kinase anchor protein 2
AKAP6	A-kinase anchor protein 6
AKAP8	A-kinase anchor protein 8
AKIR2	Akirin-2
AKP8L	A-kinase anchor protein 8-like
AKT2	RAC-beta serine/threonine-protein kinase
AL1B1	Aldehyde dehydrogenase X, mitochondrial
AL1L2	Mitochondrial 10-formyltetrahydrofolate dehydrogenase
AL3A2	Aldehyde dehydrogenase family 3 member A2
ALDH2	Aldehyde dehydrogenase, mitochondrial
ALG13	Putative bifunctional UDP-N-acetylglucosamine transferase and
ALG3	Dol-P-Man:Man(5)GlcNAc(2)-PP-Dol alpha-1,3-mannosyltransferase
ALG6	Dolichyl pyrophosphate Man9GlcNAc2 alpha-1,3-glucosyltransferase
ALKB8	Alkylated DNA repair protein alkB homolog 8
AMFR	E3 ubiquitin-protein ligase AMFR
AMOT	Angiomotin
AMPL	Cytosol aminopeptidase
AN32A	Acidic leucine-rich nuclear phosphoprotein 32 family member A
AN34C	Ankyrin repeat domain-containing protein 34C
ANFY1	Rabankyrin-5 {ECO:0000303|PubMed:15328530}

ANGE1	Protein angel homolog 1
ANK3	Ankyrin-3 {ECO:0000303|PubMed:7836469}
ANKH1	Ankyrin repeat and KH domain-containing protein 1

ANLN	Anillin
ANM1	Protein arginine N-methyltransferase 1 {ECO:0000305}
ANM3	Protein arginine N-methyltransferase 3
ANO10	Anoctamin-10
ANO3	Anoctamin-3
ANO6	Anoctamin-6
ANR27	Ankyrin repeat domain-containing protein 27
ANR52	Serine/threonine-protein phosphatase 6 regulatory ankyrin repeat subunit
ANXA7	Annexin A7
AOC3	Membrane primary amine oxidase
AP1AR	AP-1 complex-associated regulatory protein
AP1B1	AP-1 complex subunit beta-1
AP1M1	AP-1 complex subunit mu-1
AP1S1	AP-1 complex subunit sigma-1A
AP1S2	AP-1 complex subunit sigma-2
AP2A1	AP-2 complex subunit alpha-1
AP2A2	AP-2 complex subunit alpha-2
AP2B1	AP-2 complex subunit beta
AP2M1	AP-2 complex subunit mu {ECO:0000305}
AP2S1	AP-2 complex subunit sigma
AP3B1	AP-3 complex subunit beta-1
AP3M1	AP-3 complex subunit mu-1
AP3S1	AP-3 complex subunit sigma-1
APC	Adenomatous polyposis coli protein
APC10	Anaphase-promoting complex subunit 10
APC5	Anaphase-promoting complex subunit 5
API5	Apoptosis inhibitor 5
APR	Phorbol-12-myristate-13-acetate-induced protein 1
AR13B	ADP-ribosylation factor-like protein 13B
AR6P6	ADP-ribosylation factor-like protein 6-interacting protein 6
ARF4	ADP-ribosylation factor 4
ARFG1	ADP-ribosylation factor GTPase-activating protein 1
ARG33	Rho guanine nucleotide exchange factor 33
ARH	Low density lipoprotein receptor adapter protein 1 {ECO:0000305}
ARHG2	Rho guanine nucleotide exchange factor 2
ARL10	ADP-ribosylation factor-like protein 10
ARL2	ADP-ribosylation factor-like protein 2
ARL8A	ADP-ribosylation factor-like protein 8A
ARMC1	Armadillo repeat-containing protein 1
ARMC6	Armadillo repeat-containing protein 6
ARMX3	Armadillo repeat-containing X-linked protein 3
ARNT	Aryl hydrocarbon receptor nuclear translocator
AROS	Active regulator of SIRT1
ARP2	Actin-related protein 2
ARPC3	Actin-related protein 2/3 complex subunit 3

ARRD1	Arrestin domain-containing protein 1 {ECO:0000305}
ASHWN	Ashwin

ASPH	Aspartyl/asparaginyl beta-hydroxylase
ASTER	Protein Asterix
ASTL	Astacin-like metalloendopeptidase
ASTRA	Protein Aster-A {ECO:0000250|UniProtKB:Q8VEF1}
AT11C	Phospholipid-transporting ATPase IG
AT132	Polyamine-transporting ATPase 13A2 {ECO:0000305|PubMed:31996848}
AT133	Probable cation-transporting ATPase 13A3
AT1B1	Sodium/potassium-transporting ATPase subunit beta-1
AT1B3	Sodium/potassium-transporting ATPase subunit beta-3
AT2A2	Sarcoplasmic/endoplasmic reticulum calcium ATPase 2
AT2B1	Plasma membrane calcium-transporting ATPase 1 {ECO:0000305}
AT2B4	Plasma membrane calcium-transporting ATPase 4 {ECO:0000305}
AT2C1	Calcium-transporting ATPase type 2C member 1
ATAD1	ATPase family AAA domain-containing protein 1
ATD3A	ATPase family AAA domain-containing protein 3A
ATD3B	ATPase family AAA domain-containing protein 3B
ATIF1	ATPase inhibitor, mitochondrial {ECO:0000305}
ATM	Serine-protein kinase ATM
ATP5J	ATP synthase-coupling factor 6, mitochondrial {ECO:0000305}
ATP5L	ATP synthase subunit g, mitochondrial {ECO:0000305}
ATP6	ATP synthase subunit a
ATP7B	Copper-transporting ATPase 2
ATP9A	Probable phospholipid-transporting ATPase IIA
ATPA	ATP synthase subunit alpha, mitochondrial {ECO:0000305}
ATPB	ATP synthase subunit beta, mitochondrial {ECO:0000305}
ATPF2	ATP synthase mitochondrial F1 complex assembly factor 2
ATRAP	Type-1 angiotensin II receptor-associated protein
ATRX	Transcriptional regulator ATRX
ATS2	A disintegrin and metalloproteinase with thrombospondin motifs 2
ATX10	Ataxin-10
ATX2	Ataxin-2
ATX2L	Ataxin-2-like protein
AVEN	Cell death regulator Aven
AZI2	5-azacytidine-induced protein 2
B2L12	Bcl-2-like protein 12
B2L13	Bcl-2-like protein 13
B3GA3	Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3
B3GT6	Beta-1,3-galactosyltransferase 6
B4GT5	Beta-1,4-galactosyltransferase 5
B4GT7	Beta-1,4-galactosyltransferase 7
B9D1	B9 domain-containing protein 1
BACE2	Beta-secretase 2
BAF	Barrier-to-autointegration factor
BAG2	BAG family molecular chaperone regulator 2
BAG6	Large proline-rich protein BAG6 {ECO:0000305}

BAK	Bcl-2 homologous antagonist/killer
BAP29	B-cell receptor-associated protein 29

BASI	Basigin
BAZ2A	Bromodomain adjacent to zinc finger domain protein 2A
BCCIP	BRCA2 and CDKN1A-interacting protein
BCS1	Mitochondrial chaperone BCS1
BEST3	Bestrophin-3
BET1L	BET1-like protein
BGAL	Beta-galactosidase
BGAT	Histo-blood group ABO system transferase
BGLR	Beta-glucuronidase
BICD2	Protein bicaudal D homolog 2
BIEA	Biliverdin reductase A
BIG1	Brefeldin A-inhibited guanine nucleotide-exchange protein 1
BIG2	Brefeldin A-inhibited guanine nucleotide-exchange protein 2
BIRC6	Baculoviral IAP repeat-containing protein 6
BL1S2	Biogenesis of lysosome-related organelles complex 1 subunit 2
BLK	Tyrosine-protein kinase Blk
BMP15	Bone morphogenetic protein 15
BORG4	Cdc42 effector protein 4
BORG5	Cdc42 effector protein 1
BPTF	Nucleosome-remodeling factor subunit BPTF
BRD2	Bromodomain-containing protein 2
BRD3	Bromodomain-containing protein 3
BRE1A	E3 ubiquitin-protein ligase BRE1A
BRE1B	E3 ubiquitin-protein ligase BRE1B
BRI3B	BRI3-binding protein
BRK1	Protein BRICK1
BRX1	Ribosome biogenesis protein BRX1 homolog
BSCL2	Seipin
BTF3	Transcription factor BTF3
BUB3	Mitotic checkpoint protein BUB3
BUD23	Probable 18S rRNA (guanine-N(7))-methyltransferase {ECO:0000305}
BZW1	Basic leucine zipper and W2 domain-containing protein 1
C1GLC	C1GALT1-specific chaperone 1
C1QA	Complement C1q subcomponent subunit A
C2C2L	Phospholipid transfer protein C2CD2L {ECO:0000305}
C2D1B	Coiled-coil and C2 domain-containing protein 1B
C560	Succinate dehydrogenase cytochrome b560 subunit, mitochondrial
C56D2	Cytochrome b561 domain-containing protein 2
CA122	Uncharacterized protein C1orf122
CAC1D	Voltage-dependent L-type calcium channel subunit alpha-1D
CACO1	Calcium-binding and coiled-coil domain-containing protein 1
CACO2	Calcium-binding and coiled-coil domain-containing protein 2
CAD11	Cadherin-11
CADH1	Cadherin-1
CADH2	Cadherin-2
CAF17	Putative transferase CAF17, mitochondrial

CAHD1	VWFA and cache domain-containing protein 1

CALB1	Calbindin
CAMLG	Calcium signal-modulating cyclophilin ligand
CAMP2	Calmodulin-regulated spectrin-associated protein 2 {ECO:0000305}
CAN9	Calpain-9
CAPR1	Caprin-1
CAPR2	Caprin-2
CAPS1	Calcium-dependent secretion activator 1
CASD1	N-acetylneuraminate 9-O-acetyltransferase {ECO:0000305}
CASP	Protein CASP
CASPE	Caspase-14
CASZ1	Zinc finger protein castor homolog 1
CATB	Cathepsin B
CATC	Dipeptidyl peptidase 1
CAZA1	F-actin-capping protein subunit alpha-1
CBLN1	Cerebellin-1
CBPA1	Carboxypeptidase A1 {ECO:0000305}
CBPD	Carboxypeptidase D
CBS	Cystathionine beta-synthase {ECO:0000305}
CBX5	Chromobox protein homolog 5
CC020	Uncharacterized protein C3orf20
CC116	Coiled-coil domain-containing protein 116
CC124	Coiled-coil domain-containing protein 124
CC134	Coiled-coil domain-containing protein 134
CC159	Coiled-coil domain-containing protein 159
CC28A	Coiled-coil domain-containing protein 28A
CCD12	Coiled-coil domain-containing protein 12
CCD22	Coiled-coil domain-containing protein 22
CCD50	Coiled-coil domain-containing protein 50
CCD63	Coiled-coil domain-containing protein 63
CCD69	Coiled-coil domain-containing protein 69 {ECO:0000305}
CCD73	Coiled-coil domain-containing protein 73
CCD80	Coiled-coil domain-containing protein 80
CCD93	Coiled-coil domain-containing protein 93
CCDC8	Coiled-coil domain-containing protein 8
CCL21	C-C motif chemokine 21
CCNA2	Cyclin-A2 {ECO:0000312|HGNC:HGNC:1578}
CCNL2	Cyclin-L2
CCNT1	Cyclin-T1
CCNY	Cyclin-Y
CCYL1	Cyclin-Y-like protein 1
CD050	Uncharacterized protein C4orf50
CD9	CD9 antigen {ECO:0000303|PubMed:1840589}
CDC20	Cell division cycle protein 20 homolog
CDC27	Cell division cycle protein 27 homolog
CDC5L	Cell division cycle 5-like protein
CDC73	Parafibromin

CDK4	Cyclin-dependent kinase 4

CDK5	Cyclin-dependent-like kinase 5
CDK9	Cyclin-dependent kinase 9
CDKAL	Threonylcarbamoyladenosine tRNA methylthiotransferase
CDO1	Cysteine dioxygenase type 1
CDS1	Phosphatidate cytidylyltransferase 1 {ECO:0000305}
CDS2	Phosphatidate cytidylyltransferase 2 {ECO:0000305}
CDV3	Protein CDV3 homolog
CE051	UPF0600 protein C5orf51
CE128	Centrosomal protein of 128 kDa
CEGT	Ceramide glucosyltransferase {ECO:0000305}
CELF2	CUGBP Elav-like family member 2
CENPE	Centromere-associated protein E
CENPF	Centromere protein F
CENPV	Centromere protein V
CEP89	Centrosomal protein of 89 kDa
CEP95	Centrosomal protein of 95 kDa
CEPT1	Choline/ethanolaminephosphotransferase 1 {ECO:0000305}
CF047	Uncharacterized protein C6orf47
CF089	Bombesin receptor-activated protein C6orf89
CF120	UPF0669 protein C6orf120
CFA20	Cilia- and flagella-associated protein 20
CFTR	Cystic fibrosis transmembrane conductance regulator
CG050	Uncharacterized protein C7orf50
CGB2	Choriogonadotropin subunit beta variant 2
CGNL1	Cingulin-like protein 1
CGT	2-hydroxyacylsphingosine 1-beta-galactosyltransferase
CH033	UPF0488 protein C8orf33
CHD9	Chromodomain-helicase-DNA-binding protein 9
CHERP	Calcium homeostasis endoplasmic reticulum protein
CHIP	E3 ubiquitin-protein ligase CHIP {ECO:0000305}
CHK1	Serine/threonine-protein kinase Chk1
CHM2A	Charged multivesicular body protein 2a
CHM2B	Charged multivesicular body protein 2b
CHM4B	Charged multivesicular body protein 4b
CHP1	Calcineurin B homologous protein 1
CHP3	Calcineurin B homologous protein 3
CHPF2	Chondroitin sulfate glucuronyltransferase
CHST5	Carbohydrate sulfotransferase 5
CHSTE	Carbohydrate sulfotransferase 14
CHSTF	Carbohydrate sulfotransferase 15
CHTOP	Chromatin target of PRMT1 protein
CI072	Guanine nucleotide exchange C9orf72 {ECO:0000305}
CISD1	CDGSH iron-sulfur domain-containing protein 1
CISD2	CDGSH iron-sulfur domain-containing protein 2
CISY	Citrate synthase, mitochondrial
CK098	Uncharacterized protein C11orf98 {ECO:0000305}

CK5P1	Mitochondrial tRNA methylthiotransferase CDK5RAP1

CK5P3	CDK5 regulatory subunit-associated protein 3 {ECO:0000312}
CKAP4	Cytoskeleton-associated protein 4
CKLF6	CKLF-like MARVEL transmembrane domain-containing protein 6
CKS1	Cyclin-dependent kinases regulatory subunit 1
CL065	Probable peptide chain release factor C12orf65, mitochondrial
CLAP1	CLIP-associating protein 1
CLASR	CLK4-associating serine/arginine rich protein
CLCA	Clathrin light chain A
CLD16	Claudin-16
CLGN	Calmegin
CLMN	Calmin
CLN3	Battenin {ECO:0000305}
CLN5	Ceroid-lipofuscinosis neuronal protein 5
CLN6	Ceroid-lipofuscinosis neuronal protein 6
CLP1L	Cleft lip and palate transmembrane protein 1-like protein
CLPT1	Cleft lip and palate transmembrane protein 1
CLUS	Clusterin
CMC1	Calcium-binding mitochondrial carrier protein Aralar1
CMC2	Calcium-binding mitochondrial carrier protein Aralar2
CMS1	Protein CMSS1
CMTD1	Catechol O-methyltransferase domain-containing protein 1
CN37	2',3'-cyclic-nucleotide 3'-phosphodiesterase
CND3	Condensin complex subunit 3
CNDD3	Condensin-2 complex subunit D3
CNGA4	Cyclic nucleotide-gated cation channel alpha-4
CNN3	Calponin-3
CNNM3	Metal transporter CNNM3
CNNM4	Metal transporter CNNM4
CNO10	CCR4-NOT transcription complex subunit 10
CNOT1	CCR4-NOT transcription complex subunit 1
CNOT8	CCR4-NOT transcription complex subunit 8
CNOT9	CCR4-NOT transcription complex subunit 9
CO040	UPF0235 protein C15orf40
CO3	Complement C3
COA1	Cytochrome c oxidase assembly factor 1 homolog
COA3	Cytochrome c oxidase assembly factor 3 homolog, mitochondrial
COF1	Cofilin-1
COF2	Cofilin-2
COG2	Conserved oligomeric Golgi complex subunit 2
COG4	Conserved oligomeric Golgi complex subunit 4
COG5	Conserved oligomeric Golgi complex subunit 5
COG6	Conserved oligomeric Golgi complex subunit 6
COG7	Conserved oligomeric Golgi complex subunit 7
COG8	Conserved oligomeric Golgi complex subunit 8
COMD9	COMM domain-containing protein 9
COPB2	Coatomer subunit beta'

COPD	Coatomer subunit delta

COPE	Coatomer subunit epsilon
COPG1	Coatomer subunit gamma-1
COPG2	Coatomer subunit gamma-2
COPT1	High affinity copper uptake protein 1
COPZ1	Coatomer subunit zeta-1
COQ2	4-hydroxybenzoate polyprenyltransferase, mitochondrial
COQ8A	Atypical kinase COQ8A, mitochondrial {ECO:0000305}
COX1	Cytochrome c oxidase subunit 1
COX14	Cytochrome c oxidase assembly protein COX14
COX15	Cytochrome c oxidase assembly protein COX15 homolog
COX16	Cytochrome c oxidase assembly protein COX16 homolog, mitochondrial
COX2	Cytochrome c oxidase subunit 2
COX41	Cytochrome c oxidase subunit 4 isoform 1, mitochondrial
COX5A	Cytochrome c oxidase subunit 5A, mitochondrial
COX6C	Cytochrome c oxidase subunit 6C
CP1A1	Cytochrome P450 1A1 {ECO:0000303|PubMed:11555828}
CP20A	Cytochrome P450 20A1
CP3A4	Cytochrome P450 3A4 {ECO:0000303|PubMed:15373842}
CP4FC	Cytochrome P450 4F12 {ECO:0000303|PubMed:11162645}
CP4X1	Cytochrome P450 4X1 {ECO:0000303|PubMed:18549450}
CP51A	Lanosterol 14-alpha demethylase
CPEB3	Cytoplasmic polyadenylation element-binding protein 3
CPLX1	Complexin-1
CPLX2	Complexin-2
CPNE3	Copine-3 {ECO:0000305}
CPSF3	Cleavage and polyadenylation specificity factor subunit 3
CPSF6	Cleavage and polyadenylation specificity factor subunit 6 {ECO:0000305}
CPT1A	Carnitine O-palmitoyltransferase 1, liver isoform
CQ080	Uncharacterized protein C17orf80
CRTC3	CREB-regulated transcription coactivator 3
CRY2	Cryptochrome-2
CS025	UPF0449 protein C19orf25
CSCL1	CSC1-like protein 1
CSDE1	Cold shock domain-containing protein E1 {ECO:0000305}
CSF1R	Macrophage colony-stimulating factor 1 receptor
CSK21	Casein kinase II subunit alpha
CSK22	Casein kinase II subunit alpha'
CSKP	Peripheral plasma membrane protein CASK
CSMD1	CUB and sushi domain-containing protein 1
CSMT1	Protein CCSMST1
CSN1	COP9 signalosome complex subunit 1
CSN2	COP9 signalosome complex subunit 2
CSN3	COP9 signalosome complex subunit 3
CSN4	COP9 signalosome complex subunit 4

CSTF1	Cleavage stimulation factor subunit 1
CSTF3	Cleavage stimulation factor subunit 3
CT027	UPF0687 protein C20orf27

CTBL1	Beta-catenin-like protein 1
CTL2	Choline transporter-like protein 2
CTNA2	Catenin alpha-2
CTNB1	Catenin beta-1
CTNL1	Alpha-catulin
CTR2	Cationic amino acid transporter 2
CTRO	Citron Rho-interacting kinase
CTTB2	Cortactin-binding protein 2
CUL1	Cullin-1
CUL4B	Cullin-4B
CUX1	Homeobox protein cut-like 1
CUX2	Homeobox protein cut-like 2
CWC15	Spliceosome-associated protein CWC15 homolog
CWC22	Pre-mRNA-splicing factor CWC22 homolog
CWC25	Pre-mRNA-splicing factor CWC25 homolog
CX056	UPF0428 protein CXorf56
CX7A2	Cytochrome c oxidase subunit 7A2, mitochondrial
CXA1	Gap junction alpha-1 protein
CXCR4	C-X-C chemokine receptor type 4
CY1	Cytochrome c1, heme protein, mitochondrial
CY24A	Cytochrome b-245 light chain
CYB5	Cytochrome b5
CYB5B	Cytochrome b5 type B
CYBP	Calcyclin-binding protein
CYC	Cytochrome c
CYFP2	Cytoplasmic FMR1-interacting protein 2
CYH3	Cytohesin-3
CYHR1	Cysteine and histidine-rich protein 1
CYTSB	Cytospin-B
D19L1	Probable C-mannosyltransferase DPY19L1
DAAF5	Dynein assembly factor 5, axonemal {ECO:0000303|PubMed:25232951,
DAZP1	DAZ-associated protein 1
DBLOH	Diablo homolog, mitochondrial
DC1I2	Cytoplasmic dynein 1 intermediate chain 2
DC1L1	Cytoplasmic dynein 1 light intermediate chain 1
DC2L1	Cytoplasmic dynein 2 light intermediate chain 1
DCAF1	DDB1- and CUL4-associated factor 1 {ECO:0000312|HGNC:HGNC:30911}
DCAF5	DDB1- and CUL4-associated factor 5
DCAKD	Dephospho-CoA kinase domain-containing protein
DCC	Netrin receptor DCC
DCK	Deoxycytidine kinase
DCNL2	DCN1-like protein 2
DCNL5	DCN1-like protein 5
DCP1A	mRNA-decapping enzyme 1A

DCP2	m7GpppN-mRNA hydrolase {ECO:0000305}
DCST1	E3 ubiquitin-protein ligase DCST1 {ECO:0000305}
DCTN1	Dynactin subunit 1

DCTN4	Dynactin subunit 4
DCXR	L-xylulose reductase
DDA1	DET1- and DDB1-associated protein 1 {ECO:0000303|PubMed:17452440}
DDC	Aromatic-L-amino-acid decarboxylase
DDRGK	DDRGK domain-containing protein 1 {ECO:0000305}
DDX18	ATP-dependent RNA helicase DDX18
DDX20	Probable ATP-dependent RNA helicase DDX20
DDX23	Probable ATP-dependent RNA helicase DDX23
DDX41	Probable ATP-dependent RNA helicase DDX41
DDX42	ATP-dependent RNA helicase DDX42
DDX47	Probable ATP-dependent RNA helicase DDX47
DDX51	ATP-dependent RNA helicase DDX51
DDX59	Probable ATP-dependent RNA helicase DDX59
DDX6	Probable ATP-dependent RNA helicase DDX6 {ECO:0000305}
DECR2	Peroxisomal 2,4-dienoyl-CoA reductase
DEFM	Peptide deformylase, mitochondrial
DEGS2	Sphingolipid delta(4)-desaturase/C4-monooxygenase DES2
DEN6A	Protein DENND6A
DENR	Density-regulated protein
DGKE	Diacylglycerol kinase epsilon
DGLB	Diacylglycerol lipase-beta {ECO:0000303|PubMed:14610053}
DHB7	3-keto-steroid reductase
DHB8	Estradiol 17-beta-dehydrogenase 8
DHCR7	7-dehydrocholesterol reductase {ECO:0000303|PubMed:9683613}
DHDDS	Dehydrodolichyl diphosphate synthase complex subunit DHDDS
DHR13	Dehydrogenase/reductase SDR family member 13
DHRS3	Short-chain dehydrogenase/reductase 3
DHRS7	Dehydrogenase/reductase SDR family member 7
DHX15	Pre-mRNA-splicing factor ATP-dependent RNA helicase DHX15
DHX30	ATP-dependent RNA helicase DHX30 {ECO:0000305}
DHX36	ATP-dependent DNA/RNA helicase DHX36 {ECO:0000305}
DHX40	Probable ATP-dependent RNA helicase DHX40
DHX57	Putative ATP-dependent RNA helicase DHX57
DHX8	ATP-dependent RNA helicase DHX8
DHX9	ATP-dependent RNA helicase A {ECO:0000305}
DIAP1	Protein diaphanous homolog 1
DIAP3	Protein diaphanous homolog 3
DIC	Mitochondrial dicarboxylate carrier
DICER	Endoribonuclease Dicer
DIEXF	Digestive organ expansion factor homolog
DIM1	Probable dimethyladenosine transferase
DIP2C	Disco-interacting protein 2 homolog C
DIRA1	GTP-binding protein Di-Ras1
DJB11	DnaJ homolog subfamily B member 11

DJB12	DnaJ homolog subfamily B member 12 {ECO:0000312|HGNC:HGNC:14891}
DJC11	DnaJ homolog subfamily C member 11
DJC13	DnaJ homolog subfamily C member 13

DJC16	DnaJ homolog subfamily C member 16
DKC1	H/ACA ribonucleoprotein complex subunit DKC1
DLG1	Disks large homolog 1 {ECO:0000305}
DLG2	Disks large homolog 2
DMD	Dystrophin
DMTF1	Cyclin-D-binding Myb-like transcription factor 1
DMXL1	DmX-like protein 1
DNJA3	DnaJ homolog subfamily A member 3, mitochondrial
DNJB1	DnaJ homolog subfamily B member 1
DNJB6	DnaJ homolog subfamily B member 6
DNJC1	DnaJ homolog subfamily C member 1
DNJC3	DnaJ homolog subfamily C member 3
DNJC7	DnaJ homolog subfamily C member 7
DNJC9	DnaJ homolog subfamily C member 9
DNM1L	Dynamin-1-like protein
DNM3A	DNA (cytosine-5)-methyltransferase 3A
DNMT1	DNA (cytosine-5)-methyltransferase 1
DNPEP	Aspartyl aminopeptidase
DOC11	Dedicator of cytokinesis protein 11 {ECO:0000305}
DOCK2	Dedicator of cytokinesis protein 2
DOCK8	Dedicator of cytokinesis protein 8
DOLK	Dolichol kinase
DPM3	Dolichol-phosphate mannosyltransferase subunit 3
DPOD1	DNA polymerase delta catalytic subunit {ECO:0000305}
DPOLA	DNA polymerase alpha catalytic subunit
DPYD	Dihydropyrimidine dehydrogenase [NADP(+)]
DREB	Drebrin
DRS7B	Dehydrogenase/reductase SDR family member 7B
DSC3	Desmocollin-3
DSG1	Desmoglein-1
DSG2	Desmoglein-2
DSRAD	Double-stranded RNA-specific adenosine deaminase
DTNA	Dystrobrevin alpha
DTNB	Dystrobrevin beta
DTX1	E3 ubiquitin-protein ligase DTX1
DUS5	Dual specificity protein phosphatase 5
DX39A	ATP-dependent RNA helicase DDX39A
DX39B	Spliceosome RNA helicase DDX39B
DYH10	Dynein heavy chain 10, axonemal
DYH17	Dynein heavy chain 17, axonemal {ECO:0000305}
DYH3	Dynein heavy chain 3, axonemal
DYH8	Dynein heavy chain 8, axonemal {ECO:0000305}
DYHC2	Cytoplasmic dynein 2 heavy chain 1
DYLT1	Dynein light chain Tctex-type 1
DYM	Dymeclin
DYN2	Dynamin-2

DYST	Dystonin

E41L2	Band 4.1-like protein 2
E41L3	Band 4.1-like protein 3
EAA1	Excitatory amino acid transporter 1 {ECO:0000303|PubMed:16042756,
EAA5	Excitatory amino acid transporter 5
ECHD1	Ethylmalonyl-CoA decarboxylase
ECHP	Peroxisomal bifunctional enzyme {ECO:0000305}
ECI2	Enoyl-CoA delta isomerase 2 {ECO:0000305}
EDC4	Enhancer of mRNA-decapping protein 4
EDEM3	ER degradation-enhancing alpha-mannosidase-like protein 3
EDF1	Endothelial differentiation-related factor 1
EEA1	Early endosome antigen 1
EED	Polycomb protein EED {ECO:0000305}
EF1D	Elongation factor 1-delta
EFR3A	Protein EFR3 homolog A {ECO:0000305}
EFTS	Elongation factor Ts, mitochondrial {ECO:0000255|HAMAP-
EGR1	Early growth response protein 1 {ECO:0000303|PubMed:2377485}
EHD1	EH domain-containing protein 1 {ECO:0000305}
EHD4	EH domain-containing protein 4 {ECO:0000305}
EHMT2	Histone-lysine N-methyltransferase EHMT2
EI24	Etoposide-induced protein 2.4 homolog
EI2BD	Translation initiation factor eIF-2B subunit delta
EI2BE	Translation initiation factor eIF-2B subunit epsilon
EIF2A	Eukaryotic translation initiation factor 2A
EIF3K	Eukaryotic translation initiation factor 3 subunit K {ECO:0000255|HAMAP-
EIF3L	Eukaryotic translation initiation factor 3 subunit L {ECO:0000255|HAMAP-
EIF3M	Eukaryotic translation initiation factor 3 subunit M {ECO:0000255|HAMAP-
EKI2	Ethanolamine kinase 2
ELAV1	ELAV-like protein 1
ELL	RNA polymerase II elongation factor ELL
ELMO1	Engulfment and cell motility protein 1
ELOV1	Elongation of very long chain fatty acids protein 1 {ECO:0000255|HAMAP-
ELOV5	Elongation of very long chain fatty acids protein 5 {ECO:0000255|HAMAP-
EM55	55 kDa erythrocyte membrane protein
EMAL4	Echinoderm microtubule-associated protein-like 4
EMC10	ER membrane protein complex subunit 10
EMC2	ER membrane protein complex subunit 2
EMC3	ER membrane protein complex subunit 3
EMC4	ER membrane protein complex subunit 4
EMC6	ER membrane protein complex subunit 6
EMC7	ER membrane protein complex subunit 7
EMC8	ER membrane protein complex subunit 8

EMD	Emerin
EMX2	Homeobox protein EMX2
ENASE	Cytosolic endo-beta-N-acetylglucosaminidase
ENDOV	Endonuclease V
ENL	Protein ENL
ENOB	Beta-enolase

ENPP1	Ectonucleotide pyrophosphatase/phosphodiesterase family member 1
EPHA4	Ephrin type-A receptor 4
EPHB1	Ephrin type-B receptor 1
EPIPL	Epiplakin {ECO:0000303|PubMed:11278896}
EPN4	Clathrin interactor 1
EPT1	Ethanolaminephosphotransferase 1 {ECO:0000305}
ERAL1	GTPase Era, mitochondrial
ERAP1	Endoplasmic reticulum aminopeptidase 1
ERC2	ERC protein 2
ERC6L	DNA excision repair protein ERCC-6-like
ERCC2	General transcription and DNA repair factor IIH helicase subunit XPD
ERD22	ER lumen protein-retaining receptor 2
ERD23	ER lumen protein-retaining receptor 3
ERF3A	Eukaryotic peptide chain release factor GTP-binding subunit ERF3A
ERF3B	Eukaryotic peptide chain release factor GTP-binding subunit ERF3B
ERG1	Squalene monooxygenase
ERG24	Delta(14)-sterol reductase TM7SF2
ERGI1	Endoplasmic reticulum-Golgi intermediate compartment protein 1
ERGI3	Endoplasmic reticulum-Golgi intermediate compartment protein 3
ERI3	ERI1 exoribonuclease 3
ERLEC	Endoplasmic reticulum lectin 1
ERLN1	Erlin-1 {ECO:0000303|PubMed:16835267}
ERLN2	Erlin-2
ERMP1	Endoplasmic reticulum metallopeptidase 1
ERN1	Serine/threonine-protein kinase/endoribonuclease IRE1 {ECO:0000305}
ERP29	Endoplasmic reticulum resident protein 29
ERR1	Steroid hormone receptor ERR1
ESIP1	Epithelial-stromal interaction protein 1
EST3	Carboxylesterase 3
ESYT2	Extended synaptotagmin-2 {ECO:0000305}
ETFB	Electron transfer flavoprotein subunit beta {ECO:0000305}
EXD2	Exonuclease 3'-5' domain-containing protein 2
EXOC1	Exocyst complex component 1
EXOC2	Exocyst complex component 2
EXOC4	Exocyst complex component 4
EXOC5	Exocyst complex component 5
EXOC7	Exocyst complex component 7
EXOC8	Exocyst complex component 8
EXOS2	Exosome complex component RRP4 {ECO:0000305}
EXOS4	Exosome complex component RRP41
EXT2	Exostosin-2
F1142	Protein FAM114A2
F120A	Constitutive coactivator of PPAR-gamma-like protein 1
F120C	Constitutive coactivator of PPAR-gamma-like protein 2
F135A	Protein FAM135A

F162A	Protein FAM162A
F184A	Protein FAM184A

F207A	Protein FAM207A
F210B	Protein FAM210B, mitochondrial {ECO:0000305}
F214B	Protein FAM214B
F262	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2
F263	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3
F90AK	Putative protein FAM90A20P
FA8A1	Protein FAM8A1
FACD2	Fanconi anemia group D2 protein
FACE1	CAAX prenyl protease 1 homolog
FACE2	CAAX prenyl protease 2
FACR1	Fatty acyl-CoA reductase 1 {ECO:0000305|PubMed:15220348}
FADS1	Acyl-CoA (8-3)-desaturase {ECO:0000305}
FADS2	Acyl-CoA 6-desaturase {ECO:0000305|PubMed:12713571}
FAK2	Protein-tyrosine kinase 2-beta
FAKD2	FAST kinase domain-containing protein 2, mitochondrial
FAKD5	FAST kinase domain-containing protein 5, mitochondrial
FAM3A	Protein FAM3A
FANK1	Fibronectin type 3 and ankyrin repeat domains protein 1 {ECO:0000305}
FARP1	FERM, ARHGEF and pleckstrin domain-containing protein 1
FARP2	FERM, ARHGEF and pleckstrin domain-containing protein 2
FAT3	Protocadherin Fat 3
FBLN2	Fibulin-2
FBN3	Fibrillin-3
FBRS	Probable fibrosin-1
FBW1B	F-box/WD repeat-containing protein 11
FBX50	F-box only protein 50
FBXL7	F-box/LRR-repeat protein 7
FDFT	Squalene synthase
FEN1	Flap endonuclease 1 {ECO:0000255|HAMAP-Rule:MF_03140}
FGD4	FYVE, RhoGEF and PH domain-containing protein 4
FIBB	Fibrinogen beta chain
FIS1	Mitochondrial fission 1 protein
FITM2	Fat storage-inducing transmembrane protein 2
FKBP3	Peptidyl-prolyl cis-trans isomerase FKBP3
FLII	Protein flightless-1 homolog
FLIP1	Filamin-A-interacting protein 1
FLOT1	Flotillin-1
FLOT2	Flotillin-2
FLT3L	Fms-related tyrosine kinase 3 ligand
FLVC1	Feline leukemia virus subgroup C receptor-related protein 1
FNBP1	Formin-binding protein 1
FND3A	Fibronectin type-III domain-containing protein 3A
FOLC	Folylpolyglutamate synthase, mitochondrial
FOLH1	Glutamate carboxypeptidase 2
FOXK2	Forkhead box protein K2 {ECO:0000305}

FPPS	Farnesyl pyrophosphate synthase {ECO:0000305}
FRPD3	FERM and PDZ domain-containing protein 3

FRS2	Fibroblast growth factor receptor substrate 2
FRS3	Fibroblast growth factor receptor substrate 3
FRYL	Protein furry homolog-like
FSD1L	FSD1-like protein
FSIP2	Fibrous sheath-interacting protein 2
FUBP3	Far upstream element-binding protein 3
FUND2	FUN14 domain-containing protein 2
FUT3	3-galactosyl-N-acetylglucosaminide 4-alpha-L-fucosyltransferase FUT3
FUT8	Alpha-(1,6)-fucosyltransferase
FWCH2	FLYWCH family member 2
FXR1	Fragile X mental retardation syndrome-related protein 1
FXR2	Fragile X mental retardation syndrome-related protein 2
FXRD1	FAD-dependent oxidoreductase domain-containing protein 1
FXRD2	FAD-dependent oxidoreductase domain-containing protein 2
FYN	Tyrosine-protein kinase Fyn
G3BP2	Ras GTPase-activating protein-binding protein 2
G3PT	Glyceraldehyde-3-phosphate dehydrogenase, testis-specific
G45IP	Growth arrest and DNA damage-inducible proteins-interacting protein 1
G6PC3	Glucose-6-phosphatase 3
G6PT1	Glucose-6-phosphate exchanger SLC37A4
GABPA	GA-binding protein alpha chain
GABR2	Gamma-aminobutyric acid type B receptor subunit 2
GALK2	N-acetylgalactosamine kinase
GALT1	Polypeptide N-acetylgalactosaminyltransferase 1
GALT2	Polypeptide N-acetylgalactosaminyltransferase 2
GALT8	Probable polypeptide N-acetylgalactosaminyltransferase 8
GAN	Gigaxonin
GAPR1	Golgi-associated plant pathogenesis-related protein 1
GAR1	H/ACA ribonucleoprotein complex subunit 1
GBG10	Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-10
GBG5	Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-5
GBP2	Guanylate-binding protein 2
GBRB3	Gamma-aminobutyric acid receptor subunit beta-3
GBX1	Homeobox protein GBX-1
GCN1	eIF-2-alpha kinase activator GCN1 {ECO:0000250|UniProtKB:E9PVA8}
GCP2	Gamma-tubulin complex component 2
GCP3	Gamma-tubulin complex component 3
GCP4	Gamma-tubulin complex component 4
GCP6	Gamma-tubulin complex component 6
GCP60	Golgi resident protein GCP60
GCSP	Glycine dehydrogenase (decarboxylating), mitochondrial
GDPD1	Lysophospholipase D GDPD1 {ECO:0000305}
GDPD3	Lysophospholipase D GDPD3 {ECO:0000305}

GDS1	Rap1 GTPase-GDP dissociation stimulator 1
GEMI4	Gem-associated protein 4
GEMI5	Gem-associated protein 5
GET4	Golgi to ER traffic protein 4 homolog {ECO:0000305}

GGT7	Glutathione hydrolase 7
GHC1	Mitochondrial glutamate carrier 1
GHDC	GH3 domain-containing protein
GIT2	ARF GTPase-activating protein GIT2
GL8D1	Glycosyltransferase 8 domain-containing protein 1
GLBL2	Beta-galactosidase-1-like protein 2
GLI2	Zinc finger protein GLI2 {ECO:0000305}
GLI3	Transcriptional activator GLI3
GLPK2	Glycerol kinase 2
GLRX3	Glutaredoxin-3
GLSK	Glutaminase kidney isoform, mitochondrial
GLT14	Polypeptide N-acetylgalactosaminyltransferase 14
GLUT4	Solute carrier family 2, facilitated glucose transporter member 4
GLYM	Serine hydroxymethyltransferase, mitochondrial
GNA11	Guanine nucleotide-binding protein subunit alpha-11
GNA13	Guanine nucleotide-binding protein subunit alpha-13
GNA15	Guanine nucleotide-binding protein subunit alpha-15
GNAI1	Guanine nucleotide-binding protein G(i) subunit alpha-1
GNAI2	Guanine nucleotide-binding protein G(i) subunit alpha-2
GNAI3	Guanine nucleotide-binding protein G(i) subunit alpha
GNAZ	Guanine nucleotide-binding protein G(z) subunit alpha
GNL1	Guanine nucleotide-binding protein-like 1
GNL3	Guanine nucleotide-binding protein-like 3
GOGA2	Golgin subfamily A member 2
GOGA5	Golgin subfamily A member 5
GOGA7	Golgin subfamily A member 7
GOGB1	Golgin subfamily B member 1
GOLI4	Golgi integral membrane protein 4
GOLM1	Golgi membrane protein 1
GOLP3	Golgi phosphoprotein 3
GOSR1	Golgi SNAP receptor complex member 1
GOSR2	Golgi SNAP receptor complex member 2
GOT1B	Vesicle transport protein GOT1B
GP108	Protein GPR108
GP179	Probable G-protein coupled receptor 179
GPBP1	Vasculin
GPD1L	Glycerol-3-phosphate dehydrogenase 1-like protein
GPDA	Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic {ECO:0000305}
GPER1	G-protein coupled estrogen receptor 1 {ECO:0000305}
GPI8	GPI-anchor transamidase
GPR3	G-protein coupled receptor 3
GPT	UDP-N-acetylglucosamine--dolichyl-phosphate N-
GPTC4	G patch domain-containing protein 4
GPX8	Probable glutathione peroxidase 8
GRP2	RAS guanyl-releasing protein 2

GRPE2	GrpE protein homolog 2, mitochondrial
GRWD1	Glutamate-rich WD repeat-containing protein 1

GSAP	Gamma-secretase-activating protein
GSK3B	Glycogen synthase kinase-3 beta
GSLG1	Golgi apparatus protein 1
GSTP1	Glutathione S-transferase P {ECO:0000305}
GTPB1	GTP-binding protein 1
GTPB3	tRNA modification GTPase GTPBP3, mitochondrial
GTPB6	Putative GTP-binding protein 6
GTPB8	GTP-binding protein 8
GTR1	Solute carrier family 2, facilitated glucose transporter member 1
GUAA	GMP synthase [glutamine-hydrolyzing]
GUF1	Translation factor GUF1, mitochondrial {ECO:0000255|HAMAP-
GXLT1	Glucoside xylosyltransferase 1
GYS1	Glycogen [starch] synthase, muscle
GYS2	Glycogen [starch] synthase, liver
H90B2	Putative heat shock protein HSP 90-beta 2
HACD3	Very-long-chain (3R)-3-hydroxyacyl-CoA dehydratase 3 {ECO:0000305}
HAGHL	Hydroxyacylglutathione hydrolase-like protein
HAKAI	E3 ubiquitin-protein ligase Hakai {ECO:0000305}
HBAZ	Hemoglobin subunit zeta
HBS1L	HBS1-like protein
HDAC1	Histone deacetylase 1 {ECO:0000305}
HDGR2	Hepatoma-derived growth factor-related protein 2
HEAT1	HEAT repeat-containing protein 1
HEG1	Protein HEG homolog 1
HEMH	Ferrochelatase, mitochondrial
HEMO	Hemopexin
HERP1	Homocysteine-responsive endoplasmic reticulum-resident ubiquitin-like
HES7	Transcription factor HES-7
HGS	Hepatocyte growth factor-regulated tyrosine kinase substrate
HIP1	Huntingtin-interacting protein 1
HIP1R	Huntingtin-interacting protein 1-related protein
HIPK1	Homeodomain-interacting protein kinase 1
HLAC	HLA class I histocompatibility antigen, C alpha chain
HLAG	HLA class I histocompatibility antigen, alpha chain G
HM13	Minor histocompatibility antigen H13
HMDH	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HMGA2	High mobility group protein HMGI-C
HMGB1	High mobility group protein B1
HMGB2	High mobility group protein B2
HMGCL	Hydroxymethylglutaryl-CoA lyase, mitochondrial
HMGN1	Non-histone chromosomal protein HMG-14
HMOX1	Heme oxygenase 1
HMOX2	Heme oxygenase 2
HMR1	Major histocompatibility complex class I-related gene protein

HMSD	Serpin-like protein HMSD
HMSDV	Minor histocompatibility protein HMSD variant form
HNF1A	Hepatocyte nuclear factor 1-alpha

HNRH1	Heterogeneous nuclear ribonucleoprotein H
HNRH2	Heterogeneous nuclear ribonucleoprotein H2
HNRH3	Heterogeneous nuclear ribonucleoprotein H3
HNRPR	Heterogeneous nuclear ribonucleoprotein R
HNRPU	Heterogeneous nuclear ribonucleoprotein U
HOOK3	Protein Hook homolog 3
HPBP1	Hsp70-binding protein 1 {ECO:0000305}
HPRT	Hypoxanthine-guanine phosphoribosyltransferase
HS2ST	Heparan sulfate 2-O-sulfotransferase 1
HSP74	Heat shock 70 kDa protein 4
HTSF1	HIV Tat-specific factor 1
HUWE1	E3 ubiquitin-protein ligase HUWE1
HVCN1	Voltage-gated hydrogen channel 1
HXK1	Hexokinase-1 {ECO:0000305}
HXK2	Hexokinase-2 {ECO:0000305}
HYAL2	Hyaluronidase-2
HYEP	Epoxide hydrolase 1 {ECO:0000305}
HYOU1	Hypoxia up-regulated protein 1
I17RA	Interleukin-17 receptor A
I5P1	Inositol polyphosphate-5-phosphatase A
ICLN	Methylosome subunit pICln
ICMT	Protein-S-isoprenylcysteine O-methyltransferase
IF2A	Eukaryotic translation initiation factor 2 subunit 1
IF2B	Eukaryotic translation initiation factor 2 subunit 2
IF2B2	Insulin-like growth factor 2 mRNA-binding protein 2
IF2B3	Insulin-like growth factor 2 mRNA-binding protein 3
IF2M	Translation initiation factor IF-2, mitochondrial
IF3M	Translation initiation factor IF-3, mitochondrial
IF4E	Eukaryotic translation initiation factor 4E
IF5	Eukaryotic translation initiation factor 5
IF5A1	Eukaryotic translation initiation factor 5A-1
IFG15	Torsin-1A-interacting protein 2, isoform IFRG15
IFM2	Interferon-induced transmembrane protein 2
IFN14	Interferon alpha-14
IFT57	Intraflagellar transport protein 57 homolog
IGHG1	Immunoglobulin heavy constant gamma 1
IGS23	Immunoglobulin superfamily member 23
IGSF2	Immunoglobulin superfamily member 2
IGSF3	Immunoglobulin superfamily member 3
IKIP	Inhibitor of nuclear factor kappa-B kinase-interacting protein
ILEU	Leukocyte elastase inhibitor
ILF3	Interleukin enhancer-binding factor 3
ILK	Integrin-linked protein kinase
IMA1	Importin subunit alpha-1 {ECO:0000305}
IN80E	INO80 complex subunit E
INO80	Chromatin-remodeling ATPase INO80 {ECO:0000305}

INT12	Integrator complex subunit 12

INT7	Integrator complex subunit 7
IPIL1	Inositol 1,4,5-trisphosphate receptor-interacting protein-like 1
IPO4	Importin-4
IPPK	Inositol-pentakisphosphate 2-kinase
IQGAP2	Ras GTPase-activating-like protein IQGAP2
IR3IP	Immediate early response 3-interacting protein 1
ISCU	Iron-sulfur cluster assembly enzyme ISCU, mitochondrial
ITB1	Integrin beta-1
ITCH	E3 ubiquitin-protein ligase Itchy homolog
ITM2B	Integral membrane protein 2B
ITM2C	Integral membrane protein 2C
ITPR1	Inositol 1,4,5-trisphosphate receptor type 1
ITPR3	Inositol 1,4,5-trisphosphate receptor type 3
JAGN1	Protein jagunal homolog 1 {ECO:0000305}
JAM2	Junctional adhesion molecule B
JIP4	C-Jun-amino-terminal kinase-interacting protein 4
JPH1	Junctophilin-1
K0100	Protein KIAA0100
K1210	Acrosomal protein KIAA1210 {ECO:0000305}
KAD2	Adenylate kinase 2, mitochondrial {ECO:0000255|HAMAP-Rule:MF_03168}
KAD4	Adenylate kinase 4, mitochondrial {ECO:0000255|HAMAP-Rule:MF_03170}
KANL3	KAT8 regulatory NSL complex subunit 3
KAP2	cAMP-dependent protein kinase type II-alpha regulatory subunit
KATL2	Katanin p60 ATPase-containing subunit A-like 2 {ECO:0000255|HAMAP-
KBL	2-amino-3-ketobutyrate coenzyme A ligase, mitochondrial
KC1A	Casein kinase I isoform alpha
KCNH1	Potassium voltage-gated channel subfamily H member 1
KCNH4	Potassium voltage-gated channel subfamily H member 4
KCNH8	Potassium voltage-gated channel subfamily H member 8
KCT2	Keratinocyte-associated transmembrane protein 2
KCTD5	BTB/POZ domain-containing protein KCTD5
KDIS	Kinase D-interacting substrate of 220 kDa
KDM5A	Lysine-specific demethylase 5A
KDM7A	Lysine-specific demethylase 7A
KI2S5	Killer cell immunoglobulin-like receptor 2DS5
KIF11	Kinesin-like protein KIF11
KIF2A	Kinesin-like protein KIF2A
KIF3A	Kinesin-like protein KIF3A
KIF5A	Kinesin heavy chain isoform 5A
KIF5C	Kinesin heavy chain isoform 5C
KIN17	DNA/RNA-binding protein KIN17
KINH	Kinesin-1 heavy chain
KISHA	Protein kish-A

KISHB	Protein kish-B
KLC1	Kinesin light chain 1
KLC2	Kinesin light chain 2
KLDC4	Kelch domain-containing protein 4

KLH17	Kelch-like protein 17
KLH34	Kelch-like protein 34
KLK5	Kallikrein-5 {ECO:0000312|HGNC:HGNC:6366}
KLOT	Klotho
KMT2C	Histone-lysine N-methyltransferase 2C
KMT2D	Histone-lysine N-methyltransferase 2D
KPCD	Protein kinase C delta type
KPRA	Phosphoribosyl pyrophosphate synthase-associated protein 1
KPRB	Phosphoribosyl pyrophosphate synthase-associated protein 2
KRA59	Keratin-associated protein 5-9
KRI1	Protein KRI1 homolog
KRR1	KRR1 small subunit processome component homolog
KS6A1	Ribosomal protein S6 kinase alpha-1
KS6B1	Ribosomal protein S6 kinase beta-1
KS6B2	Ribosomal protein S6 kinase beta-2
KSR1	Kinase suppressor of Ras 1
KTHY	Thymidylate kinase
KTN1	Kinectin
KTNA1	Katanin p60 ATPase-containing subunit A1 {ECO:0000255|HAMAP-
KTNB1	Katanin p80 WD40 repeat-containing subunit B1 {ECO:0000255|HAMAP-
KV401	Immunoglobulin kappa variable 4-1 {ECO:0000303|PubMed:11549845,
KY	Kyphoscoliosis peptidase
L10K	Leydig cell tumor 10 kDa protein homolog
L2GL1	Lethal(2) giant larvae protein homolog 1
L2HDH	L-2-hydroxyglutarate dehydrogenase, mitochondrial
LACTB	Serine beta-lactamase-like protein LACTB, mitochondrial {ECO:0000305}
LAGE3	EKC/KEOPS complex subunit LAGE3 {ECO:0000305}
LAMB4	Laminin subunit beta-4
LAMC1	Laminin subunit gamma-1
LANC1	Glutathione S-transferase LANCL1 {ECO:0000250|UniProtKB:O89112}
LANC2	LanC-like protein 2
LAP2A	Lamina-associated polypeptide 2, isoform alpha
LAP2B	Lamina-associated polypeptide 2, isoforms beta/gamma
LAP4B	Lysosomal-associated transmembrane protein 4B {ECO:0000305}
LARP1	La-related protein 1
LARP4	La-related protein 4
LAS1L	Ribosomal biogenesis protein LAS1L
LASP1	LIM and SH3 domain protein 1
LBN	Limbin
LBR	Delta(14)-sterol reductase LBR
LC7L2	Putative RNA-binding protein Luc7-like 2

LCA5L	Lebercilin-like protein
LCAP	Leucyl-cystinyl aminopeptidase
LCLT1	Lysocardiolipin acyltransferase 1
LETM1	Mitochondrial proton/calcium exchanger protein {ECO:0000305}
LGAT1	Acyl-CoA:lysophosphatidylglycerol acyltransferase 1
LGMN	Legumain

LHX6	LIM/homeobox protein Lhx6
LICH	Lysosomal acid lipase/cholesteryl ester hydrolase
LIMD2	LIM domain-containing protein 2 {ECO:0000305}
LIMS1	LIM and senescent cell antigen-like-containing domain protein 1
LIN7A	Protein lin-7 homolog A
LIN7C	Protein lin-7 homolog C
LIPA1	Liprin-alpha-1
LIPB1	Liprin-beta-1
LIPS	Hormone-sensitive lipase
LLPH	Protein LLP homolog
LMAN1	Protein ERGIC-53
LMAN2	Vesicular integral-membrane protein VIP36
LMBD1	Lysosomal cobalamin transport escort protein LMBD1
LMBD2	G-protein coupled receptor-associated protein LMBRD2
LMBR1	Limb region 1 protein homolog
LMF2	Lipase maturation factor 2
LMNB1	Lamin-B1
LMNB2	Lamin-B2
LMO7	LIM domain only protein 7
LMTK2	Serine/threonine-protein kinase LMTK2
LONP2	Lon protease homolog 2, peroxisomal {ECO:0000255|HAMAP-
LR10B	Leucine-rich repeat-containing protein 10B
LRAD4	Low-density lipoprotein receptor class A domain-containing protein 4
LRC40	Leucine-rich repeat-containing protein 40
LRC59	Leucine-rich repeat-containing protein 59
LRC8A	Volume-regulated anion channel subunit LRRC8A
LRC8C	Volume-regulated anion channel subunit LRRC8C
LRCH3	DISP complex protein LRCH3 {ECO:0000305|PubMed:29467281}
LRP5	Low-density lipoprotein receptor-related protein 5
LRRC1	Leucine-rich repeat-containing protein 1
LRRF1	Leucine-rich repeat flightless-interacting protein 1
LS14B	Protein LSM14 homolog B
LSM12	Protein LSM12 homolog
LSM4	U6 snRNA-associated Sm-like protein LSm4
LSR	Lipolysis-stimulated lipoprotein receptor
LTBP1	Latent-transforming growth factor beta-binding protein 1
LTOR1	Ragulator complex protein LAMTOR1
LTOR2	Ragulator complex protein LAMTOR2
LTOR4	Ragulator complex protein LAMTOR4
LTOR5	Ragulator complex protein LAMTOR5
LYAG	Lysosomal alpha-glucosidase
LYAR	Cell growth-regulating nucleolar protein
LYN	Tyrosine-protein kinase Lyn
LYPA2	Acyl-protein thioesterase 2
M2OM	Mitochondrial 2-oxoglutarate/malate carrier protein
M4K4	Mitogen-activated protein kinase kinase kinase kinase 4

MA1A1	Mannosyl-oligosaccharide 1,2-alpha-mannosidase IA

MA1A2	Mannosyl-oligosaccharide 1,2-alpha-mannosidase IB
MA1B1	Endoplasmic reticulum mannosyl-oligosaccharide 1,2-alpha-mannosidase
MAD1	Max dimerization protein 1
MADL2	Myeloid-associated differentiation marker-like protein 2
MAGB5	Melanoma-associated antigen B5
MALD1	MARVEL domain-containing protein 1
MANF	Mesencephalic astrocyte-derived neurotrophic factor
MAP12	Methionine aminopeptidase 1D, mitochondrial {ECO:0000255|HAMAP-
MAP2	Methionine aminopeptidase 2 {ECO:0000255|HAMAP-Rule:MF_03175}
MAP4	Microtubule-associated protein 4
MARCO	Macrophage receptor MARCO
MARCS	Myristoylated alanine-rich C-kinase substrate
MARK1	Serine/threonine-protein kinase MARK1
MARK3	MAP/microtubule affinity-regulating kinase 3
MAST1	Microtubule-associated serine/threonine-protein kinase 1
MATN2	Matrilin-2
MAVS	Mitochondrial antiviral-signaling protein {ECO:0000305}
MBD3	Methyl-CpG-binding domain protein 3
MBOA2	Lysophospholipid acyltransferase 2
MBOA5	Lysophospholipid acyltransferase 5
MBOA7	Lysophospholipid acyltransferase 7 {ECO:0000305}
MCAT	Mitochondrial carnitine/acylcarnitine carrier protein
MCCB	Methylcrotonoyl-CoA carboxylase beta chain, mitochondrial
MCE1	mRNA-capping enzyme
MCL1	Induced myeloid leukemia cell differentiation protein Mcl-1
MCM2	DNA replication licensing factor MCM2
MCM3	DNA replication licensing factor MCM3
MCM6	DNA replication licensing factor MCM6
MCM7	DNA replication licensing factor MCM7
MCMBP	Mini-chromosome maintenance complex-binding protein
MCTS1	Malignant T-cell-amplified sequence 1
MCU	Calcium uniporter protein, mitochondrial
MDC1	Mediator of DNA damage checkpoint protein 1
MDHM	Malate dehydrogenase, mitochondrial
MED1	Mediator of RNA polymerase II transcription subunit 1
MED22	Mediator of RNA polymerase II transcription subunit 22
MEP1A	Meprin A subunit alpha
MERL	Merlin
MESD	LRP chaperone MESD {ECO:0000305}
MET7A	Methyltransferase-like protein 7A
MEX3B	RNA-binding protein MEX3B
MFAP3	Microfibril-associated glycoprotein 3
MFF	Mitochondrial fission factor

MFN1	Mitofusin-1
MFN2	Mitofusin-2
MFR1L	Mitochondrial fission regulator 1-like
MFS10	Major facilitator superfamily domain-containing protein 10

MFS12	Major facilitator superfamily domain-containing protein 12
MFSD1	Major facilitator superfamily domain-containing protein 1
MFSD3	Major facilitator superfamily domain-containing protein 3
MFSD5	Molybdate-anion transporter
MFSD8	Major facilitator superfamily domain-containing protein 8
MFTC	Mitochondrial folate transporter/carrier
MGAT2	Alpha-1,6-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltransferase
MGME1	Mitochondrial genome maintenance exonuclease 1 {ECO:0000255|HAMAP-
MGN2	Protein mago nashi homolog 2
MGST1	Microsomal glutathione S-transferase 1
MGT4B	Alpha-1,3-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase B
MIB1	E3 ubiquitin-protein ligase MIB1
MIC19	MICOS complex subunit MIC19
MIC25	MICOS complex subunit MIC25
MIC26	MICOS complex subunit MIC26 {ECO:0000303|PubMed:25764979}
MIC27	MICOS complex subunit MIC27
MIC60	MICOS complex subunit MIC60
MICU2	Calcium uptake protein 2, mitochondrial
MINT	Msx2-interacting protein
MIRO2	Mitochondrial Rho GTPase 2
MITOK	Mitochondrial potassium channel {ECO:0000303|PubMed:31435016}
MK03	Mitogen-activated protein kinase 3
MK67I	MKI67 FHA domain-interacting nucleolar phosphoprotein
MLEC	Malectin
MLKL	Mixed lineage kinase domain-like protein
MMGT1	Membrane magnesium transporter 1
MMP17	Matrix metalloproteinase-17
MMP8	Neutrophil collagenase
MMS19	MMS19 nucleotide excision repair protein homolog
MMTA2	Multiple myeloma tumor-associated protein 2
MO4L2	Mortality factor 4-like protein 2
MOC2A	Molybdopterin synthase sulfur carrier subunit {ECO:0000255|HAMAP-
MOC2B	Molybdopterin synthase catalytic subunit {ECO:0000255|HAMAP-
MOGS	Mannosyl-oligosaccharide glucosidase
MON1B	Vacuolar fusion protein MON1 homolog B
MON2	Protein MON2 homolog
MOT13	Monocarboxylate transporter 13
MOT8	Monocarboxylate transporter 8
MOXD1	DBH-like monooxygenase protein 1
MP2K1	Dual specificity mitogen-activated protein kinase kinase 1 {ECO:0000305}
MP2K2	Dual specificity mitogen-activated protein kinase kinase 2
MPC2	Mitochondrial pyruvate carrier 2
MPP10	U3 small nucleolar ribonucleoprotein protein MPP10

MPP2	MAGUK p55 subfamily member 2
MPP5	MAGUK p55 subfamily member 5
MPP7	MAGUK p55 subfamily member 7
MRCKG	Serine/threonine-protein kinase MRCK gamma

MRM2	rRNA methyltransferase 2, mitochondrial
MRP	MARCKS-related protein
MRP1	Multidrug resistance-associated protein 1 {ECO:0000305}
MRP4	Multidrug resistance-associated protein 4
MRP5	Multidrug resistance-associated protein 5
MRP7	Multidrug resistance-associated protein 7
MRT4	mRNA turnover protein 4 homolog {ECO:0000250|UniProtKB:P33201}
MS3L1	Male-specific lethal 3 homolog
MSH5	MutS protein homolog 5
MSMO1	Methylsterol monooxygenase 1 {ECO:0000303|PubMed:23583456}
MT1G	Metallothionein-1G
MT1M	Metallothionein-1M
MT4	Metallothionein-4
MTCH1	Mitochondrial carrier homolog 1
MTCH2	Mitochondrial carrier homolog 2
MTDC	Bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase,
MTEF3	Transcription termination factor 3, mitochondrial
MTFP1	Mitochondrial fission process protein 1
MTFR1	Mitochondrial fission regulator 1
MTG1	Mitochondrial ribosome-associated GTPase 1
MTMRE	Myotubularin-related protein 14
MTNB	Methylthioribulose-1-phosphate dehydratase {ECO:0000255|HAMAP-
MTOR	Serine/threonine-protein kinase mTOR
MTX1	Metaxin-1
MTX2	Metaxin-2
MTX3	Metaxin-3
MUC2	Mucin-2
MUC4	Mucin-4
MUS81	Crossover junction endonuclease MUS81
MY18A	Unconventional myosin-XVIIIa
MYBPP	MYCBP-associated protein
MYCB2	E3 ubiquitin-protein ligase MYCBP2 {ECO:0000305}
MYEF2	Myelin expression factor 2
MYH10	Myosin-10
MYH11	Myosin-11
MYH6	Myosin-6
MYO10	Unconventional myosin-X
MYO1C	Unconventional myosin-Ic
MYO7A	Unconventional myosin-VIIa
MYO7B	Unconventional myosin-VIIb
MYOME	Myomegalin
NAA10	N-alpha-acetyltransferase 10
NAA15	N-alpha-acetyltransferase 15, NatA auxiliary subunit
NAA40	N-alpha-acetyltransferase 40 {ECO:0000303|PubMed:19660095,
NAA50	N-alpha-acetyltransferase 50 {ECO:0000305}

NAAA	N-acylethanolamine-hydrolyzing acid amidase
NAC2	Sodium/calcium exchanger 2

NACA	Nascent polypeptide-associated complex subunit alpha
NACAM	Nascent polypeptide-associated complex subunit alpha, muscle-specific
NAKD2	NAD kinase 2, mitochondrial
NAL13	NACHT, LRR and PYD domains-containing protein 13
NALP7	NACHT, LRR and PYD domains-containing protein 7
NARR	Ras-related protein Rab-34, isoform NARR
NAT10	RNA cytidine acetyltransferase {ECO:0000255|HAMAP-Rule:MF_03211,
NAT14	N-acetyltransferase 14
NB5R1	NADH-cytochrome b5 reductase 1
NB5R3	NADH-cytochrome b5 reductase 3
NBAS	Neuroblastoma-amplified sequence
NC2A	Dr1-associated corepressor
NCBP1	Nuclear cap-binding protein subunit 1
NCDN	Neurochondrin
NCEH1	Neutral cholesterol ester hydrolase 1
NCF4	Neutrophil cytosol factor 4
NCKP1	Nck-associated protein 1
NCOR2	Nuclear receptor corepressor 2 {ECO:0000305}
NCPR	NADPH--cytochrome P450 reductase {ECO:0000255|HAMAP-
NCTR3	Natural cytotoxicity triggering receptor 3
NDC1	Nucleoporin NDC1
NDE1	Nuclear distribution protein nudE homolog 1
NDOR1	NADPH-dependent diflavin oxidoreductase 1 {ECO:0000255|HAMAP-
NDUA1	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 1
NDUA4	Cytochrome c oxidase subunit NDUFA4
NDUA5	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 5
NDUA6	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 6
NDUA7	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 7
NDUA8	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8
NDUA9	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9,
NDUAB	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 11
NDUAC	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12
NDUAD	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 13
NDUB1	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 1
NDUB3	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 3
NDUB5	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 5,
NDUB6	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 6
NDUB8	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 8,
NDUB9	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 9
NDUBB	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11,
NDUC2	NADH dehydrogenase [ubiquinone] 1 subunit C2
NDUF3	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex assembly factor 3
NDUF4	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex assembly factor 4

NDUS1	NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial
NDUS3	NADH dehydrogenase [ubiquinone] iron-sulfur protein 3, mitochondrial
NDUS4	NADH dehydrogenase [ubiquinone] iron-sulfur protein 4, mitochondrial
NDUS7	NADH dehydrogenase [ubiquinone] iron-sulfur protein 7, mitochondrial

NDUV2	NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial
NDUV3	NADH dehydrogenase [ubiquinone] flavoprotein 3, mitochondrial
NEBL	Nebulette
NEBU	Nebulin
NED4L	E3 ubiquitin-protein ligase NEDD4-like
NEK1	Serine/threonine-protein kinase Nek1
NEK8	Serine/threonine-protein kinase Nek8
NELFA	Negative elongation factor A
NELFB	Negative elongation factor B
NELFD	Negative elongation factor C/D
NELL2	Protein kinase C-binding protein NELL2
NEMF	Nuclear export mediator factor NEMF
NEP	Neprilysin
NEP1	Ribosomal RNA small subunit methyltransferase NEP1
NEUA	N-acylneuraminate cytidylyltransferase
NEUM	Neuromodulin
NEUT	Neurotensin/neuromedin N
NF2IP	NFATC2-interacting protein
NFIP2	NEDD4 family-interacting protein 2
NFM	Neurofilament medium polypeptide
NFRKB	Nuclear factor related to kappa-B-binding protein
NFS1	Cysteine desulfurase, mitochondrial
NFXL1	NF-X1-type zinc finger protein NFXL1
NGBR	Dehydrodolichyl diphosphate synthase complex subunit NUS1
NHP2	H/ACA ribonucleoprotein complex subunit 2
NHRF2	Na(+)/H(+) exchange regulatory cofactor NHE-RF2
NHSL1	NHS-like protein 1
NICA	Nicastrin
NICN1	Nicolin-1
NIN	Ninein
NIP7	60S ribosome subunit biogenesis protein NIP7 homolog
NIPA4	Magnesium transporter NIPA4
NIPS2	Protein NipSnap homolog 2
NISCH	Nischarin
NKRF	NF-kappa-B-repressing factor
NKTR	NK-tumor recognition protein {ECO:0000305|PubMed:8421688}
NLK	Serine/threonine-protein kinase NLK
NLTP	Non-specific lipid-transfer protein
NMU	Neuromedin-U
NO40	Nucleolar protein of 40 kDa
NOB1	RNA-binding protein NOB1
NOC4L	Nucleolar complex protein 4 homolog
NOD1	Nucleotide-binding oligomerization domain-containing protein 1
NOG1	Nucleolar GTP-binding protein 1
NOG2	Nucleolar GTP-binding protein 2
NOL10	Nucleolar protein 10

NOL9	Polynucleotide 5'-hydroxyl-kinase NOL9

NOMO1	Nodal modulator 1
NOP16	Nucleolar protein 16
NOP56	Nucleolar protein 56
NOP58	Nucleolar protein 58
NOSIP	Nitric oxide synthase-interacting protein
NOTC2	Neurogenic locus notch homolog protein 2 {ECO:0000305}
NP1L1	Nucleosome assembly protein 1-like 1
NP1L4	Nucleosome assembly protein 1-like 4
NPC1	NPC intracellular cholesterol transporter 1
NPCL1	NPC1-like intracellular cholesterol transporter 1
NPL4	Nuclear protein localization protein 4 homolog
NPM	Nucleophosmin
NPRL2	GATOR complex protein NPRL2 {ECO:0000305}
NRIP1	Nuclear receptor-interacting protein 1
NRL	Neural retina-specific leucine zipper protein
NS1BP	Influenza virus NS1A-binding protein
NSL1	Kinetochore-associated protein NSL1 homolog
NSMA3	Sphingomyelin phosphodiesterase 4 {ECO:0000305}
NSRP1	Nuclear speckle splicing regulatory protein 1
NSUN2	RNA cytosine C(5)-methyltransferase NSUN2 {ECO:0000305}
NTH	Endonuclease III-like protein 1 {ECO:0000255|HAMAP-Rule:MF_03183}
NTPCR	Cancer-related nucleoside-triphosphatase
NU107	Nuclear pore complex protein Nup107
NU160	Nuclear pore complex protein Nup160
NU1M	NADH-ubiquinone oxidoreductase chain 1
NU2M	NADH-ubiquinone oxidoreductase chain 2
NU4M	NADH-ubiquinone oxidoreductase chain 4
NU5M	NADH-ubiquinone oxidoreductase chain 5
NU6M	NADH-ubiquinone oxidoreductase chain 6
NUB1	NEDD8 ultimate buster 1
NUCKS	Nuclear ubiquitous casein and cyclin-dependent kinase substrate 1
NUDC	Nuclear migration protein nudC
NUDT6	Nucleoside diphosphate-linked moiety X motif 6
NUMB	Protein numb homolog
NUP35	Nucleoporin NUP35 {ECO:0000312|HGNC:HGNC:29797}
NUP43	Nucleoporin Nup43
NUP85	Nuclear pore complex protein Nup85
NUP98	Nuclear pore complex protein Nup98-Nup96
NXF1	Nuclear RNA export factor 1
NXT2	NTF2-related export protein 2
NYNRI	Protein NYNRIN
O52E4	Olfactory receptor 52E4
O5AC2	Olfactory receptor 5AC2
OBI1	ORC ubiquitin ligase 1 {ECO:0000305}
OCLN	Occludin

OCRL	Inositol polyphosphate 5-phosphatase OCRL {ECO:0000305}
ODC	Mitochondrial 2-oxodicarboxylate carrier

OGFD3	2-oxoglutarate and iron-dependent oxygenase domain-containing protein 3
OR2G3	Olfactory receptor 2G3
OR4X1	Olfactory receptor 4X1
OR6Y1	Olfactory receptor 6Y1
OR7D2	Olfactory receptor 7D2
OR9A2	Olfactory receptor 9A2
ORC6	Origin recognition complex subunit 6
ORML1	ORM1-like protein 1
ORML3	ORM1-like protein 3
ORNT1	Mitochondrial ornithine transporter 1
OS9	Protein OS-9
OSB11	Oxysterol-binding protein-related protein 11
OSBL6	Oxysterol-binding protein-related protein 6
OSBL8	Oxysterol-binding protein-related protein 8
OSBL9	Oxysterol-binding protein-related protein 9
OSER1	Oxidative stress-responsive serine-rich protein 1
OSTC	Oligosaccharyltransferase complex subunit OSTC
OTU7A	OTU domain-containing protein 7A
OTUD4	OTU domain-containing protein 4
OVCH1	Ovochymase-1
OXA1L	Mitochondrial inner membrane protein OXA1L
OXSR1	Serine/threonine-protein kinase OSR1
P4HA2	Prolyl 4-hydroxylase subunit alpha-2
P4K2A	Phosphatidylinositol 4-kinase type 2-alpha
P53	Cellular tumor antigen p53
P5CR1	Pyrroline-5-carboxylate reductase 1, mitochondrial
P5CR3	Pyrroline-5-carboxylate reductase 3 {ECO:0000312|HGNC:HGNC:25846}
P66B	Transcriptional repressor p66-beta
P85A	Phosphatidylinositol 3-kinase regulatory subunit alpha
PA2G3	Group 3 secretory phospholipase A2
PA2G4	Proliferation-associated protein 2G4
PAB4L	Polyadenylate-binding protein 4-like
PABP1	Polyadenylate-binding protein 1
PABP2	Polyadenylate-binding protein 2
PABP4	Polyadenylate-binding protein 4
PACN3	Protein kinase C and casein kinase substrate in neurons protein 3
PAF1	RNA polymerase II-associated factor 1 homolog
PAF15	PCNA-associated factor {ECO:0000305}
PAI1	Plasminogen activator inhibitor 1
PAK4	Serine/threonine-protein kinase PAK 4
PALB2	Partner and localizer of BRCA2
PANK4	4'-phosphopantetheine phosphatase {ECO:0000303|PubMed:27322068}
PAQR1	Adiponectin receptor protein 1 {ECO:0000303|PubMed:12802337}

PAR14	Protein mono-ADP-ribosyltransferase PARP14 {ECO:0000305}
PAR16	Protein mono-ADP-ribosyltransferase PARP16 {ECO:0000305}
PAR4	Proteinase-activated receptor 4
PARP1	Poly [ADP-ribose] polymerase 1

PARP4	Protein mono-ADP-ribosyltransferase PARP4 {ECO:0000305}
PATE4	Prostate and testis expressed protein 4
PATL1	Protein PAT1 homolog 1
PAWR	PRKC apoptosis WT1 regulator protein
PBIP1	Pre-B-cell leukemia transcription factor-interacting protein 1
PCBP1	Poly(rC)-binding protein 1
PCD20	Protocadherin-20
PCDAB	Protocadherin alpha-11
PCDBE	Protocadherin beta-14
PCFT	Proton-coupled folate transporter
PCH2	Pachytene checkpoint protein 2 homolog
PCID2	PCI domain-containing protein 2
PCKGM	Phosphoenolpyruvate carboxykinase [GTP], mitochondrial
PCLO	Protein piccolo
PCM1	Pericentriolar material 1 protein
PCNP	PEST proteolytic signal-containing nuclear protein
PCY1A	Choline-phosphate cytidylyltransferase A
PD2R2	Prostaglandin D2 receptor 2
PDC10	Programmed cell death protein 10
PDC6I	Programmed cell death 6-interacting protein
PDCD6	Programmed cell death protein 6
PDE5A	cGMP-specific 3',5'-cyclic phosphodiesterase
PDIA1	Protein disulfide-isomerase
PDIA2	Protein disulfide-isomerase A2
PDIA5	Protein disulfide-isomerase A5
PDIP2	Polymerase delta-interacting protein 2 {ECO:0000303|PubMed:26984527}
PDYN	Proenkephalin-B
PDZD8	PDZ domain-containing protein 8 {ECO:0000305}
PECR	Peroxisomal trans-2-enoyl-CoA reductase
PEF1	Peflin {ECO:0000303|PubMed:10486255}
PEG3	Paternally-expressed gene 3 protein
PELO	Protein pelota homolog
PELP1	Proline-, glutamic acid- and leucine-rich protein 1
PESC	Pescadillo homolog {ECO:0000255|HAMAP-Rule:MF_03028}
PEX16	Peroxisomal membrane protein PEX16
PEX26	Peroxisome assembly protein 26
PEX3	Peroxisomal biogenesis factor 3
PEX5	Peroxisomal targeting signal 1 receptor
PFKAL	ATP-dependent 6-phosphofructokinase, liver type {ECO:0000255|HAMAP-
PG12A	Group XIIA secretory phospholipase A2
PGAM5	Serine/threonine-protein phosphatase PGAM5, mitochondrial
PGDH	15-hydroxyprostaglandin dehydrogenase [NAD(+)] {ECO:0000305}
PGRC1	Membrane-associated progesterone receptor component 1
PHAG1	Phosphoprotein associated with glycosphingolipid-enriched

	microdomains
PHB2	Prohibitin-2
PHF5A	PHD finger-like domain-containing protein 5A
PHKG2	Phosphorylase b kinase gamma catalytic chain, liver/testis isoform

PHLB1	Pleckstrin homology-like domain family B member 1
PI3R4	Phosphoinositide 3-kinase regulatory subunit 4
PI42C	Phosphatidylinositol 5-phosphate 4-kinase type-2 gamma
PI51A	Phosphatidylinositol 4-phosphate 5-kinase type-1 alpha
PI51C	Phosphatidylinositol 4-phosphate 5-kinase type-1 gamma
PICAL	Phosphatidylinositol-binding clathrin assembly protein
PIGA	Phosphatidylinositol N-acetylglucosaminyltransferase subunit A
PIGG	GPI ethanolamine phosphate transferase 2
PIGM	GPI mannosyltransferase 1
PIGO	GPI ethanolamine phosphate transferase 3
PIGS	GPI transamidase component PIG-S
PIGU	Phosphatidylinositol glycan anchor biosynthesis class U protein
PIN1	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1
PIN4	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 4
PIPSL	Putative PIP5K1A and PSMD4-like protein
PISD	Phosphatidylserine decarboxylase proenzyme, mitochondrial
PITC1	Cytoplasmic phosphatidylinositol transfer protein 1
PITM2	Membrane-associated phosphatidylinositol transfer protein 2
PIWL1	Piwi-like protein 1
PIWL2	Piwi-like protein 2
PK3CD	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta
PKHG4	Puratrophin-1
PKHS1	Pleckstrin homology domain-containing family S member 1
PKN1	Serine/threonine-protein kinase N1
PKN2	Serine/threonine-protein kinase N2
PKP2	Plakophilin-2
PKP4	Plakophilin-4
PLAC1	Placenta-specific protein 1
PLAK	Junction plakoglobin
PLCA	1-acyl-sn-glycerol-3-phosphate acyltransferase alpha
PLCB	1-acyl-sn-glycerol-3-phosphate acyltransferase beta
PLCC	1-acyl-sn-glycerol-3-phosphate acyltransferase gamma
PLCD3	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase delta-3
PLCE	1-acyl-sn-glycerol-3-phosphate acyltransferase epsilon
PLCL1	Inactive phospholipase C-like protein 1
PLD2	Phospholipase D2
PLD3	5'-3' exonuclease PLD3 {ECO:0000305}
PLIN4	Perilipin-4
PLK1	Serine/threonine-protein kinase PLK1
PLK4	Serine/threonine-protein kinase PLK4
PLOD1	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1
PLOD2	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 {ECO:0000305}
PLPL6	Patatin-like phospholipase domain-containing protein 6 {ECO:0000305}
PLXA2	Plexin-A2
PLXA4	Plexin-A4

PLXB2	Plexin-B2
PMYT1	Membrane-associated tyrosine- and threonine-specific cdc2-inhibitory

PNKD	Probable hydrolase PNKD
PNO1	RNA-binding protein PNO1
PO210	Nuclear pore membrane glycoprotein 210
PO3F1	POU domain, class 3, transcription factor 1
POGZ	Pogo transposable element with ZNF domain
POLI	DNA polymerase iota
POMT2	Protein O-mannosyl-transferase 2
PON2	Serum paraoxonase/arylesterase 2
POP1	Ribonucleases P/MRP protein subunit POP1
POTEA	POTE ankyrin domain family member A
PP1B	Serine/threonine-protein phosphatase PP1-beta catalytic subunit
PP1G	Serine/threonine-protein phosphatase PP1-gamma catalytic subunit
PP1RA	Serine/threonine-protein phosphatase 1 regulatory subunit 10
PPAC	Low molecular weight phosphotyrosine protein phosphatase
PPARG	Peroxisome proliferator-activated receptor gamma
PPE1	Serine/threonine-protein phosphatase with EF-hands 1
PPIF	Peptidyl-prolyl cis-trans isomerase F, mitochondrial
PPIL3	Peptidyl-prolyl cis-trans isomerase-like 3
PPIP1	Proline-serine-threonine phosphatase-interacting protein 1
PPM1G	Protein phosphatase 1G
PPP6	Serine/threonine-protein phosphatase 6 catalytic subunit
PPT1	Palmitoyl-protein thioesterase 1
PR38B	Pre-mRNA-splicing factor 38B
PR40A	Pre-mRNA-processing factor 40 homolog A
PRAF2	PRA1 family protein 2
PRAF3	PRA1 family protein 3
PRDM5	PR domain zinc finger protein 5
PREB	Prolactin regulatory element-binding protein
PRI1	DNA primase small subunit
PRI2	DNA primase large subunit
PRKRA	Interferon-inducible double-stranded RNA-dependent protein kinase
PRP16	Pre-mRNA-splicing factor ATP-dependent RNA helicase PRP16
PRP18	Pre-mRNA-splicing factor 18
PRP19	Pre-mRNA-processing factor 19 {ECO:0000305}
PRP8	Pre-mRNA-processing-splicing factor 8
PRPF3	U4/U6 small nuclear ribonucleoprotein Prp3
PRR11	Proline-rich protein 11
PRR13	Proline-rich protein 13
PRS7	26S proteasome regulatory subunit 7
PRS8	26S proteasome regulatory subunit 8
PRUN2	Protein prune homolog 2
PSA	Puromycin-sensitive aminopeptidase
PSA2	Proteasome subunit alpha type-2
PSA4	Proteasome subunit alpha type-4
PSA5	Proteasome subunit alpha type-5
PSD2	PH and SEC7 domain-containing protein 2

PSMD8	26S proteasome non-ATPase regulatory subunit 8

PSME3	Proteasome activator complex subunit 3
PSMG1	Proteasome assembly chaperone 1
PSN1	Presenilin-1
PSN2	Presenilin-2
PTBP1	Polypyrimidine tract-binding protein 1
PTCD3	Pentatricopeptide repeat domain-containing protein 3, mitochondrial
PTH	Probable peptidyl-tRNA hydrolase
PTK7	Inactive tyrosine-protein kinase 7
PTN11	Tyrosine-protein phosphatase non-receptor type 11
PTN13	Tyrosine-protein phosphatase non-receptor type 13
PTN2	Tyrosine-protein phosphatase non-receptor type 2
PTN9	Tyrosine-protein phosphatase non-receptor type 9
PTPM1	Phosphatidylglycerophosphatase and protein-tyrosine phosphatase 1
PTSS1	Phosphatidylserine synthase 1
PTSS2	Phosphatidylserine synthase 2
PUF60	Poly(U)-binding-splicing factor PUF60
PUM1	Pumilio homolog 1 {ECO:0000305}
PUR2	Trifunctional purine biosynthetic protein adenosine-3
PUR6	Multifunctional protein ADE2
PUR8	Adenylosuccinate lyase {ECO:0000303|PubMed:8404037}
PURA	Transcriptional activator protein Pur-alpha
PWP2	Periodic tryptophan protein 2 homolog
PX11B	Peroxisomal membrane protein 11B
PXMP2	Peroxisomal membrane protein 2
PYC	Pyruvate carboxylase, mitochondrial
PYRG1	CTP synthase 1 {ECO:0000305}
PYRG2	CTP synthase 2
QCR1	Cytochrome b-c1 complex subunit 1, mitochondrial
QCR8	Cytochrome b-c1 complex subunit 8
QCR9	Cytochrome b-c1 complex subunit 9
QOR	Quinone oxidoreductase
QPCTL	Glutaminyl-peptide cyclotransferase-like protein
QSOX2	Sulfhydryl oxidase 2
R113A	E3 ubiquitin-protein ligase RNF113A
RAB10	Ras-related protein Rab-10
RAB12	Ras-related protein Rab-12
RAB13	Ras-related protein Rab-13
RAB14	Ras-related protein Rab-14
RAB18	Ras-related protein Rab-18
RAB2A	Ras-related protein Rab-2A
RAB34	Ras-related protein Rab-34
RAB5A	Ras-related protein Rab-5A
RAB5C	Ras-related protein Rab-5C
RAB7A	Ras-related protein Rab-7a
RAB7L	Ras-related protein Rab-7L1
RAB8B	Ras-related protein Rab-8B

RAB9A	Ras-related protein Rab-9A

RAB9B	Ras-related protein Rab-9B
RAC3	Ras-related C3 botulinum toxin substrate 3 {ECO:0000305}
RACK1	Receptor of activated protein C kinase 1
RAD54	DNA repair and recombination protein RAD54-like
RAP1A	Ras-related protein Rap-1A
RAP2B	Ras-related protein Rap-2b
RARG	Retinoic acid receptor gamma
RASL1	RasGAP-activating-like protein 1 {ECO:0000305}
RB33B	Ras-related protein Rab-33B
RB39A	Ras-related protein Rab-39A
RB3GP	Rab3 GTPase-activating protein catalytic subunit
RBGP1	Rab GTPase-activating protein 1
RBGPR	Rab3 GTPase-activating protein non-catalytic subunit
RBM12	RNA-binding protein 12
RBM15	RNA-binding protein 15 {ECO:0000305}
RBM25	RNA-binding protein 25
RBM28	RNA-binding protein 28
RBM3	RNA-binding protein 3
RBM33	RNA-binding protein 33
RBM5	RNA-binding protein 5
RBM7	RNA-binding protein 7 {ECO:0000305}
RBMS2	RNA-binding motif, single-stranded-interacting protein 2
RBMX	RNA-binding motif protein, X chromosome
RBMX2	RNA-binding motif protein, X-linked 2
RBP2	E3 SUMO-protein ligase RanBP2
RBX1	E3 ubiquitin-protein ligase RBX1
RCC1	Regulator of chromosome condensation
RCC2	Protein RCC2
RCOR2	REST corepressor 2
RDH10	Retinol dehydrogenase 10
RDH11	Retinol dehydrogenase 11
RDH13	Retinol dehydrogenase 13 {ECO:0000305}
RECQ4	ATP-dependent DNA helicase Q4
RECQ5	ATP-dependent DNA helicase Q5
REEP4	Receptor expression-enhancing protein 4
REN3A	Regulator of nonsense transcripts 3A
RENT2	Regulator of nonsense transcripts 2
RER1	Protein RER1
RETST	All-trans-retinol 13,14-reductase
REV3L	DNA polymerase zeta catalytic subunit
RFA3	Replication protein A 14 kDa subunit
RFC1	Replication factor C subunit 1
RFC2	Replication factor C subunit 2
RFC3	Replication factor C subunit 3
RFC4	Replication factor C subunit 4
RFC5	Replication factor C subunit 5

RFIP5	Rab11 family-interacting protein 5

RFT1	Protein RFT1 homolog
RGL2	Ral guanine nucleotide dissociation stimulator-like 2
RGS1	Regulator of G-protein signaling 1
RGS10	Regulator of G-protein signaling 10
RHBL4	Rhomboid-related protein 4
RHG05	Rho GTPase-activating protein 5
RHG22	Rho GTPase-activating protein 22
RHOG	Rho-related GTP-binding protein RhoG
RINT1	RAD50-interacting protein 1
RISC	Retinoid-inducible serine carboxypeptidase
RL10	60S ribosomal protein L10 {ECO:0000305}
RL13A	60S ribosomal protein L13a
RL15	60S ribosomal protein L15
RL17	60S ribosomal protein L17
RL18	60S ribosomal protein L18
RL18A	60S ribosomal protein L18a
RL19	60S ribosomal protein L19
RL1D1	Ribosomal L1 domain-containing protein 1
RL21	60S ribosomal protein L21
RL23	60S ribosomal protein L23
RL24	60S ribosomal protein L24
RL27	60S ribosomal protein L27
RL27A	60S ribosomal protein L27a
RL28	60S ribosomal protein L28
RL29	60S ribosomal protein L29
RL3	60S ribosomal protein L3
RL30	60S ribosomal protein L30
RL35A	60S ribosomal protein L35a
RL36	60S ribosomal protein L36
RL37A	60S ribosomal protein L37a
RL4	60S ribosomal protein L4
RL5	60S ribosomal protein L5
RL7A	60S ribosomal protein L7a
RLA1	60S acidic ribosomal protein P1
RLA2	60S acidic ribosomal protein P2
RM01	39S ribosomal protein L1, mitochondrial
RM04	39S ribosomal protein L4, mitochondrial
RM09	39S ribosomal protein L9, mitochondrial
RM10	39S ribosomal protein L10, mitochondrial
RM12	39S ribosomal protein L12, mitochondrial
RM14	39S ribosomal protein L14, mitochondrial
RM17	39S ribosomal protein L17, mitochondrial
RM18	39S ribosomal protein L18, mitochondrial
RM19	39S ribosomal protein L19, mitochondrial
RM21	39S ribosomal protein L21, mitochondrial
RM22	39S ribosomal protein L22, mitochondrial

RM23	39S ribosomal protein L23, mitochondrial

RM24	39S ribosomal protein L24, mitochondrial
RM27	39S ribosomal protein L27, mitochondrial
RM30	39S ribosomal protein L30, mitochondrial
RM32	39S ribosomal protein L32, mitochondrial
RM38	39S ribosomal protein L38, mitochondrial
RM40	39S ribosomal protein L40, mitochondrial
RM44	39S ribosomal protein L44, mitochondrial
RM45	39S ribosomal protein L45, mitochondrial
RM48	39S ribosomal protein L48, mitochondrial
RM49	39S ribosomal protein L49, mitochondrial
RM50	39S ribosomal protein L50, mitochondrial
RM53	39S ribosomal protein L53, mitochondrial
RM54	39S ribosomal protein L54, mitochondrial
RMD3	Regulator of microtubule dynamics protein 3
RN121	RING finger protein 121
RN138	E3 ubiquitin-protein ligase RNF138 {ECO:0000305}
RN170	E3 ubiquitin-protein ligase RNF170
RN185	E3 ubiquitin-protein ligase RNF185
RNC	Ribonuclease 3
RNF25	E3 ubiquitin-protein ligase RNF25
RNF31	E3 ubiquitin-protein ligase RNF31
RNF5	E3 ubiquitin-protein ligase RNF5
RNH2B	Ribonuclease H2 subunit B
RNPS1	RNA-binding protein with serine-rich domain 1
ROCK2	Rho-associated protein kinase 2
ROGDI	Protein rogdi homolog
ROMO1	Reactive oxygen species modulator 1
RPA49	DNA-directed RNA polymerase I subunit RPA49
RPAB1	DNA-directed RNA polymerases I, II, and III subunit RPABC1
RPAB4	DNA-directed RNA polymerases I, II, and III subunit RPABC4
RPAC1	DNA-directed RNA polymerases I and III subunit RPAC1
RPAP2	Putative RNA polymerase II subunit B1 CTD phosphatase RPAP2
RPAP3	RNA polymerase II-associated protein 3
RPB2	DNA-directed RNA polymerase II subunit RPB2
RPGF3	Rap guanine nucleotide exchange factor 3
RPOM	DNA-directed RNA polymerase, mitochondrial {ECO:0000305}
RPP30	Ribonuclease P protein subunit p30
RPP38	Ribonuclease P protein subunit p38
RRAS2	Ras-related protein R-Ras2
RRBP1	Ribosome-binding protein 1
RRP1	Ribosomal RNA processing protein 1 homolog A
RRP1B	Ribosomal RNA processing protein 1 homolog B
RRP44	Exosome complex exonuclease RRP44
RS11	40S ribosomal protein S11
RS14	40S ribosomal protein S14
RS15	40S ribosomal protein S15

RS16	40S ribosomal protein S16

RS18	40S ribosomal protein S18
RS2	40S ribosomal protein S2
RS20	40S ribosomal protein S20
RS21	40S ribosomal protein S21
RS23	40S ribosomal protein S23
RS24	40S ribosomal protein S24
RS27	40S ribosomal protein S27
RS27L	40S ribosomal protein S27-like
RS3	40S ribosomal protein S3
RS4Y1	40S ribosomal protein S4, Y isoform 1
RS7	40S ribosomal protein S7
RS8	40S ribosomal protein S8
RSAD1	Radical S-adenosyl methionine domain-containing protein 1, mitochondrial
RSPRY	RING finger and SPRY domain-containing protein 1
RSRC2	Arginine/serine-rich coiled-coil protein 2
RT02	28S ribosomal protein S2, mitochondrial
RT05	28S ribosomal protein S5, mitochondrial
RT06	28S ribosomal protein S6, mitochondrial
RT09	28S ribosomal protein S9, mitochondrial
RT10	28S ribosomal protein S10, mitochondrial
RT11	28S ribosomal protein S11, mitochondrial
RT12	28S ribosomal protein S12, mitochondrial
RT14	28S ribosomal protein S14, mitochondrial
RT15	28S ribosomal protein S15, mitochondrial
RT16	28S ribosomal protein S16, mitochondrial
RT17	28S ribosomal protein S17, mitochondrial
RT18B	28S ribosomal protein S18b, mitochondrial
RT18C	28S ribosomal protein S18c, mitochondrial
RT21	28S ribosomal protein S21, mitochondrial
RT22	28S ribosomal protein S22, mitochondrial
RT25	28S ribosomal protein S25, mitochondrial
RT27	28S ribosomal protein S27, mitochondrial {ECO:0000305}
RT28	28S ribosomal protein S28, mitochondrial
RT30	39S ribosomal protein S30, mitochondrial
RT31	28S ribosomal protein S31, mitochondrial
RT35	28S ribosomal protein S35, mitochondrial
RT36	28S ribosomal protein S36, mitochondrial
RTCA	RNA 3'-terminal phosphate cyclase
RTF1	RNA polymerase-associated protein RTF1 homolog
RTL1	Retrotransposon-like protein 1
RTN1	Reticulon-1
RTN2	Reticulon-2
RTN3	Reticulon-3
RTN4	Reticulon-4 {ECO:0000305}
RTTN	Rotatin

RU17	U1 small nuclear ribonucleoprotein 70 kDa
RU1C	U1 small nuclear ribonucleoprotein C {ECO:0000255|HAMAP-

RUFY1	RUN and FYVE domain-containing protein 1
RUFY2	RUN and FYVE domain-containing protein 2
RUSD3	Mitochondrial mRNA pseudouridine synthase RPUSD3
RUVB1	RuvB-like 1
RUVB2	RuvB-like 2
RUXE	Small nuclear ribonucleoprotein E
RUXF	Small nuclear ribonucleoprotein F
RYR1	Ryanodine receptor 1
S10AA	Protein S100-A10
S12A2	Solute carrier family 12 member 2
S12A3	Solute carrier family 12 member 3
S12A4	Solute carrier family 12 member 4
S12A7	Solute carrier family 12 member 7
S12A9	Solute carrier family 12 member 9
S14L3	SEC14-like protein 3
S15A1	Solute carrier family 15 member 1
S15A3	Solute carrier family 15 member 3
S15A4	Solute carrier family 15 member 4
S17A5	Sialin
S18B1	MFS-type transporter SLC18B1
S19A1	Reduced folate transporter {ECO:0000305}
S19A2	Thiamine transporter 1
S20A1	Sodium-dependent phosphate transporter 1
S23A2	Solute carrier family 23 member 2
S23IP	SEC23-interacting protein
S2611	Sodium-independent sulfate anion transporter
S26A2	Sulfate transporter
S26A6	Solute carrier family 26 member 6
S26A7	Anion exchange transporter
S27A1	Long-chain fatty acid transport protein 1 {ECO:0000305}
S27A2	Very long-chain acyl-CoA synthetase
S27A3	Solute carrier family 27 member 3 {ECO:0000312|HGNC:HGNC:10997}
S29A1	Equilibrative nucleoside transporter 1
S29A3	Equilibrative nucleoside transporter 3
S30BP	SAP30-binding protein
S35A2	UDP-galactose translocator
S35A3	UDP-N-acetylglucosamine transporter
S35A5	Probable UDP-sugar transporter protein SLC35A5
S35B1	Solute carrier family 35 member B1
S35B2	Adenosine 3'-phospho 5'-phosphosulfate transporter 1
S35B4	UDP-xylose and UDP-N-acetylglucosamine transporter
S35D3	Solute carrier family 35 member D3
S35E1	Solute carrier family 35 member E1
S35F5	Solute carrier family 35 member F5
S38A1	Sodium-coupled neutral amino acid transporter 1

S38A2	Sodium-coupled neutral amino acid transporter 2
S38A7	Putative sodium-coupled neutral amino acid transporter 7

S38A8	Putative sodium-coupled neutral amino acid transporter 8
S38AA	Putative sodium-coupled neutral amino acid transporter 10
S39A1	Zinc transporter ZIP1
S39A3	Zinc transporter ZIP3
S39A7	Zinc transporter SLC39A7
S39AA	Zinc transporter ZIP10
S39AB	Zinc transporter ZIP11
S41A3	Solute carrier family 41 member 3
S45A3	Solute carrier family 45 member 3
S4A7	Sodium bicarbonate cotransporter 3
S52A2	Solute carrier family 52, riboflavin transporter, member 2
S61A1	Protein transport protein Sec61 subunit alpha isoform 1
S61A2	Protein transport protein Sec61 subunit alpha isoform 2
S6OS1	Protein SIX6OS1
SAAL1	Protein SAAL1
SAFB1	Scaffold attachment factor B1
SAM50	Sorting and assembly machinery component 50 homolog
SAPC2	Suppressor APC domain-containing protein 2 {ECO:0000305}
SAR1A	GTP-binding protein SAR1a
SARM1	NAD(+) hydrolase SARM1 {ECO:0000305}
SART3	Squamous cell carcinoma antigen recognized by T-cells 3 {ECO:0000305}
SAS10	Something about silencing protein 10
SC11A	Signal peptidase complex catalytic subunit SEC11A
SC16A	Protein transport protein Sec16A
SC23A	Protein transport protein Sec23A {ECO:0000305}
SC23B	Protein transport protein Sec23B {ECO:0000305}
SC24B	Protein transport protein Sec24B {ECO:0000305}
SC24C	Protein transport protein Sec24C {ECO:0000305}
SC24D	Protein transport protein Sec24D {ECO:0000305}
SC5A3	Sodium/myo-inositol cotransporter
SC5A5	Sodium/iodide cotransporter
SC5A6	Sodium-dependent multivitamin transporter
SC5AB	Sodium/myo-inositol cotransporter 2
SC5D	Lathosterol oxidase {ECO:0000305}
SC61B	Protein transport protein Sec61 subunit beta
SC61G	Protein transport protein Sec61 subunit gamma
SC6A1	Sodium- and chloride-dependent GABA transporter 1
SCAF8	SR-related and CTD-associated factor 8 {ECO:0000303|PubMed:9528809}
SCAM1	Secretory carrier-associated membrane protein 1
SCAM3	Secretory carrier-associated membrane protein 3
SCAM4	Secretory carrier-associated membrane protein 4
SCAP	Sterol regulatory element-binding protein cleavage-activating protein
SCD5	Stearoyl-CoA desaturase 5 {ECO:0000303|PubMed:22745828}
SCFD1	Sec1 family domain-containing protein 1

SCFD2	Sec1 family domain-containing protein 2
SCG2	Secretogranin-2
SCN1A	Sodium channel protein type 1 subunit alpha

SCO2	Protein SCO2 homolog, mitochondrial
SCPDL	Saccharopine dehydrogenase-like oxidoreductase
SCRB2	Lysosome membrane protein 2
SCRIB	Protein scribble homolog
SCYL2	SCY1-like protein 2
SDC2	Syndecan-2
SDF2L	Stromal cell-derived factor 2-like protein 1
SDHA	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
SDHB	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial
SE1L1	Protein sel-1 homolog 1
SE6L1	Seizure 6-like protein
SEC20	Vesicle transport protein SEC20
SELM	Selenoprotein M {ECO:0000303|PubMed:27645994}
SEM6D	Semaphorin-6D
SEN2	tRNA-splicing endonuclease subunit Sen2
SF3A3	Splicing factor 3A subunit 3
SF3B4	Splicing factor 3B subunit 4
SF3B6	Splicing factor 3B subunit 6
SFPQ	Splicing factor, proline- and glutamine-rich
SFXN4	Sideroflexin-4 {ECO:0000303|PubMed:15489334}
SG196	Protein O-mannose kinase
SGMR1	Sigma non-opioid intracellular receptor 1
SGMR2	Sigma intracellular receptor 2 {ECO:0000305}
SGPL1	Sphingosine-1-phosphate lyase 1 {ECO:0000305}
SGPP1	Sphingosine-1-phosphate phosphatase 1 {ECO:0000305}
SHB	SH2 domain-containing adapter protein B
SHF	SH2 domain-containing adapter protein F
SHOC2	Leucine-rich repeat protein SHOC-2
SHPRH	E3 ubiquitin-protein ligase SHPRH
SI1L1	Signal-induced proliferation-associated 1-like protein 1
SIG11	Sialic acid-binding Ig-like lectin 11
SIK3	Serine/threonine-protein kinase SIK3 {ECO:0000305}
SIM20	Small integral membrane protein 20
SIN1	Target of rapamycin complex 2 subunit MAPKAP1
SKIL	Ski-like protein
SKP1	S-phase kinase-associated protein 1
SL7A1	High affinity cationic amino acid transporter 1
SL9A2	Sodium/hydrogen exchanger 2
SL9A6	Sodium/hydrogen exchanger 6
SL9A7	Sodium/hydrogen exchanger 7
SLIK5	SLIT and NTRK-like protein 5
SLIT2	Slit homolog 2 protein
SLK	STE20-like serine/threonine-protein kinase
SLMAP	Sarcolemmal membrane-associated protein

SLTM	SAFB-like transcription modulator
SMAP1	Stromal membrane-associated protein 1
SMC1A	Structural maintenance of chromosomes protein 1A

SMC2	Structural maintenance of chromosomes protein 2
SMC5	Structural maintenance of chromosomes protein 5
SMCE1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin
SMCR8	Guanine nucleotide exchange protein SMCR8 {ECO:0000305}
SMD3	Small nuclear ribonucleoprotein Sm D3
SMIM7	Small integral membrane protein 7
SMIM8	Small integral membrane protein 8
SMN	Survival motor neuron protein
SMRCD	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin
SNAA	Alpha-soluble NSF attachment protein
SNAG	Gamma-soluble NSF attachment protein
SNAPN	SNARE-associated protein Snapin
SNG1	Synaptogyrin-1 {ECO:0000305}
SNG2	Synaptogyrin-2 {ECO:0000305}
SNIP1	Smad nuclear-interacting protein 1
SNP29	Synaptosomal-associated protein 29 {ECO:0000312|HGNC:HGNC:11133}
SNP47	Synaptosomal-associated protein 47
SNTB1	Beta-1-syntrophin
SNTB2	Beta-2-syntrophin
SNUT2	U4/U6.U5 tri-snRNP-associated protein 2
SNW1	SNW domain-containing protein 1
SNX1	Sorting nexin-1
SNX12	Sorting nexin-12
SNX27	Sorting nexin-27
SNX3	Sorting nexin-3
SNX4	Sorting nexin-4
SNX5	Sorting nexin-5
SNX6	Sorting nexin-6
SNX8	Sorting nexin-8
SO1A2	Solute carrier organic anion transporter family member 1A2
SOAT1	Sterol O-acyltransferase 1 {ECO:0000305}
SOLH2	Spermatogenesis- and oogenesis-specific basic helix-loop-helix-containing
SON	Protein SON
SP100	Nuclear autoantigen Sp-100
SPAG1	Sperm-associated antigen 1
SPB1	pre-rRNA 2'-O-ribose RNA methyltransferase FTSJ3 {ECO:0000255|HAMAP-
SPB7	Serpin B7
SPB8	Serpin B8
SPCS1	Signal peptidase complex subunit 1
SPCS2	Signal peptidase complex subunit 2
SPF27	Pre-mRNA-splicing factor SPF27
SPF45	Splicing factor 45

SPG21	Maspardin
SPIDR	DNA repair-scaffolding protein
SPIN3	Spindlin-3
SPIT2	Kunitz-type protease inhibitor 2
SPRE	Sepiapterin reductase

SPT2	Protein SPT2 homolog
SPT4H	Transcription elongation factor SPT4
SPTC2	Serine palmitoyltransferase 2 {ECO:0000305}
SPTN2	Spectrin beta chain, non-erythrocytic 2
SQSTM	Sequestosome-1
SR140	U2 snRNP-associated SURP motif-containing protein
SREK1	Splicing regulatory glutamine/lysine-rich protein 1
SRGP3	SLIT-ROBO Rho GTPase-activating protein 3
SRP14	Signal recognition particle 14 kDa protein
SRP54	Signal recognition particle 54 kDa protein
SRP68	Signal recognition particle subunit SRP68
SRP72	Signal recognition particle subunit SRP72
SRPK1	SRSF protein kinase 1
SRPRB	Signal recognition particle receptor subunit beta
SRRT	Serrate RNA effector molecule homolog
SRSF2	Serine/arginine-rich splicing factor 2
SRSF3	Serine/arginine-rich splicing factor 3
SRSF5	Serine/arginine-rich splicing factor 5
SRSF6	Serine/arginine-rich splicing factor 6
SSBP	Single-stranded DNA-binding protein, mitochondrial
SSF1	Suppressor of SWI4 1 homolog
SSRA	Translocon-associated protein subunit alpha
ST1B1	Sulfotransferase family cytosolic 1B member 1
ST38L	Serine/threonine-protein kinase 38-like
STABP	STAM-binding protein
STAR3	StAR-related lipid transfer protein 3 {ECO:0000305}
STAR7	StAR-related lipid transfer protein 7, mitochondrial
STAT3	Signal transducer and activator of transcription 3
STAU1	Double-stranded RNA-binding protein Staufen homolog 1
STBD1	Starch-binding domain-containing protein 1
STEA3	Metalloreductase STEAP3
STIL	SCL-interrupting locus protein
STIM1	Stromal interaction molecule 1
STK3	Serine/threonine-protein kinase 3
STK33	Serine/threonine-protein kinase 33
STK38	Serine/threonine-protein kinase 38
STML2	Stomatin-like protein 2, mitochondrial
STMN1	Stathmin
STOM	Erythrocyte band 7 integral membrane protein
STR3N	STARD3 N-terminal-like protein {ECO:0000303|PubMed:24105263}
STRC	Stereocilin
STRN	Striatin
STRN3	Striatin-3
STT3B	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit
STX18	Syntaxin-18

STX2	Syntaxin-2
STX4	Syntaxin-4

STX7	Syntaxin-7
STX8	Syntaxin-8
STXB1	Syntaxin-binding protein 1
STXB3	Syntaxin-binding protein 3
SUCA	Succinate--CoA ligase [ADP/GDP-forming] subunit alpha, mitochondrial
SUCB1	Succinate--CoA ligase [ADP-forming] subunit beta, mitochondrial
SUGP2	SURP and G-patch domain-containing protein 2
SUMO1	Small ubiquitin-related modifier 1
SUMO2	Small ubiquitin-related modifier 2 {ECO:0000305}
SURF4	Surfeit locus protein 4
SUSD5	Sushi domain-containing protein 5
SVIP	Small VCP/p97-interacting protein
SWT1	Transcriptional protein SWT1
SYCE3	Synaptonemal complex central element protein 3
SYCM	Probable cysteine--tRNA ligase, mitochondrial
SYDM	Aspartate--tRNA ligase, mitochondrial
SYEM	Probable glutamate--tRNA ligase, mitochondrial
SYF2	Pre-mRNA-splicing factor SYF2
SYFA	Phenylalanine--tRNA ligase alpha subunit
SYFM	Phenylalanine--tRNA ligase, mitochondrial
SYIC	Isoleucine--tRNA ligase, cytoplasmic
SYJ2B	Synaptojanin-2-binding protein
SYLM	Probable leucine--tRNA ligase, mitochondrial
SYMC	Methionine--tRNA ligase, cytoplasmic
SYMM	Methionine--tRNA ligase, mitochondrial
SYNC	Asparagine--tRNA ligase, cytoplasmic
SYNE2	Nesprin-2
SYNPO	Synaptopodin
SYPL1	Synaptophysin-like protein 1
SYRM	Probable arginine--tRNA ligase, mitochondrial
SYSM	Serine--tRNA ligase, mitochondrial
SYT14	Synaptotagmin-14
SYT16	Synaptotagmin-16
SYTM	Threonine--tRNA ligase, mitochondrial
SYVC	Valine--tRNA ligase
SYWC	Tryptophan--tRNA ligase, cytoplasmic {ECO:0000305}
SZT2	KICSTOR complex protein SZT2 {ECO:0000305}
T106B	Transmembrane protein 106B
T106C	Transmembrane protein 106C
T126A	Transmembrane protein 126A
T132C	Transmembrane protein 132C
T161A	Transmembrane protein 161A
T184C	Transmembrane protein 184C
T22D3	TSC22 domain family protein 3
T2EB	Transcription initiation factor IIE subunit beta

T2FB	General transcription factor IIF subunit 2
T4S20	Transmembrane 4 L6 family member 20

TAB1	TGF-beta-activated kinase 1 and MAP3K7-binding protein 1
TAB3	TGF-beta-activated kinase 1 and MAP3K7-binding protein 3
TAC2N	Tandem C2 domains nuclear protein
TACAN	Ion channel TACAN {ECO:0000303|PubMed:32084332}
TACC1	Transforming acidic coiled-coil-containing protein 1
TADBP	TAR DNA-binding protein 43
TAF2	Transcription initiation factor TFIID subunit 2
TAF8	Transcription initiation factor TFIID subunit 8
TAGL2	Transgelin-2
TAU	Microtubule-associated protein tau
TB10A	TBC1 domain family member 10A
TBB2A	Tubulin beta-2A chain
TBB2B	Tubulin beta-2B chain
TBB4A	Tubulin beta-4A chain
TBB4B	Tubulin beta-4B chain
TBB6	Tubulin beta-6 chain
TBC15	TBC1 domain family member 15
TBC20	TBC1 domain family member 20
TBC24	TBC1 domain family member 24
TBCD	Tubulin-specific chaperone D
TBCD4	TBC1 domain family member 4
TBCD5	TBC1 domain family member 5
TBD2B	TBC1 domain family member 2B
TBL2	Transducin beta-like protein 2
TBL3	Transducin beta-like protein 3
TC1D1	Tctex1 domain-containing protein 1
TCAL4	Transcription elongation factor A protein-like 4
TCF23	Transcription factor 23
TCPD	T-complex protein 1 subunit delta
TCPE	T-complex protein 1 subunit epsilon
TCPW	T-complex protein 1 subunit zeta-2
TCPZ	T-complex protein 1 subunit zeta
TDRKH	Tudor and KH domain-containing protein
TEFF1	Tomoregulin-1
TELO2	Telomere length regulation protein TEL2 homolog
TENN	Tenascin-N {ECO:0000312|HGNC:HGNC:22942}
TENS4	Tensin-4
TEX14	Inactive serine/threonine-protein kinase TEX14
TEX35	Testis-expressed protein 35
TF3C1	General transcription factor 3C polypeptide 1
TFAP4	Transcription factor AP-4
TFE2	Transcription factor E2-alpha
TFR1	Transferrin receptor protein 1
TGFA1	Transforming growth factor-beta receptor-associated protein 1
TGFB1	Transforming growth factor beta-1 proprotein
TGFR1	TGF-beta receptor type-1

TGM3	Protein-glutamine gamma-glutamyltransferase E

THADA	Thyroid adenoma-associated protein
THEM6	Protein THEM6
THIK	3-ketoacyl-CoA thiolase, peroxisomal
THIO	Thioredoxin
THOC3	THO complex subunit 3
THOC4	THO complex subunit 4
THTR	Thiosulfate sulfurtransferase
THYN1	Thymocyte nuclear protein 1
TI17A	Mitochondrial import inner membrane translocase subunit Tim17-A
TI17B	Mitochondrial import inner membrane translocase subunit Tim17-B
TIAM1	T-lymphoma invasion and metastasis-inducing protein 1
TICRR	Treslin
TIDC1	Complex I assembly factor TIMMDC1, mitochondrial
TIF1A	Transcription intermediary factor 1-alpha
TIM13	Mitochondrial import inner membrane translocase subunit Tim13
TIM14	Mitochondrial import inner membrane translocase subunit TIM14
TIM16	Mitochondrial import inner membrane translocase subunit TIM16
TIM21	Mitochondrial import inner membrane translocase subunit Tim21
TIM22	Mitochondrial import inner membrane translocase subunit Tim22
TIM44	Mitochondrial import inner membrane translocase subunit TIM44
TIRR	Tudor-interacting repair regulator protein
TISB	mRNA decay activator protein ZFP36L1 {ECO:0000305}
TITIN	Titin
TLCD1	TLC domain-containing protein 1
TLN2	Talin-2
TLS1	Telomere length and silencing protein 1 homolog
TM101	Transmembrane protein 101
TM104	Transmembrane protein 104
TM109	Transmembrane protein 109
TM115	Transmembrane protein 115 {ECO:0000305}
TM117	Transmembrane protein 117
TM128	Transmembrane protein 128
TM140	Transmembrane protein 140
TM147	Transmembrane protein 147
TM165	Transmembrane protein 165
TM168	Transmembrane protein 168
TM177	Transmembrane protein 177
TM181	Transmembrane protein 181
TM192	Transmembrane protein 192
TM199	Transmembrane protein 199 {ECO:0000303|PubMed:26833330}
TM201	Transmembrane protein 201
TM205	Transmembrane protein 205
TM214	Transmembrane protein 214
TM223	Transmembrane protein 223
TM245	Transmembrane protein 245
TM248	Transmembrane protein 248

TM254	Transmembrane protein 254

TM258	Transmembrane protein 258
TM38B	Trimeric intracellular cation channel type B
TM39A	Transmembrane protein 39A
TM41A	Transmembrane protein 41A
TM45A	Transmembrane protein 45A
TM9S2	Transmembrane 9 superfamily member 2
TM9S3	Transmembrane 9 superfamily member 3
TM9S4	Transmembrane 9 superfamily member 4
TMED1	Transmembrane emp24 domain-containing protein 1
TMED2	Transmembrane emp24 domain-containing protein 2
TMED3	Transmembrane emp24 domain-containing protein 3
TMED4	Transmembrane emp24 domain-containing protein 4
TMEM9	Transmembrane protein 9
TMF1	TATA element modulatory factor
TMLH	Trimethyllysine dioxygenase, mitochondrial
TMM43	Transmembrane protein 43
TMM44	Transmembrane protein 44
TMM59	Transmembrane protein 59
TMM68	Transmembrane protein 68
TMTC3	Protein O-mannosyl-transferase TMTC3 {ECO:0000305}
TMUB1	Transmembrane and ubiquitin-like domain-containing protein 1
TMUB2	Transmembrane and ubiquitin-like domain-containing protein 2
TMX1	Thioredoxin-related transmembrane protein 1
TMX2	Thioredoxin-related transmembrane protein 2
TNAP2	Tumor necrosis factor alpha-induced protein 2
TNFL4	Tumor necrosis factor ligand superfamily member 4
TNNI1	Troponin I, slow skeletal muscle
TNPO1	Transportin-1
TNPO2	Transportin-2
TNPO3	Transportin-3 {ECO:0000303|PubMed:23667635}
TNR16	Tumor necrosis factor receptor superfamily member 16
TNR6A	Trinucleotide repeat-containing gene 6A protein
TNR6C	Trinucleotide repeat-containing gene 6C protein
TOIP1	Torsin-1A-interacting protein 1
TOIP2	Torsin-1A-interacting protein 2
TOLIP	Toll-interacting protein
TOM20	Mitochondrial import receptor subunit TOM20 homolog
TOM22	Mitochondrial import receptor subunit TOM22 homolog
TOM40	Mitochondrial import receptor subunit TOM40 homolog
TOM5	Mitochondrial import receptor subunit TOM5 homolog
TOP2A	DNA topoisomerase 2-alpha
TOR1A	Torsin-1A
TOR1B	Torsin-1B
TOR2A	Torsin-2A
TOR2X	Prosalusin
TP4A1	Protein tyrosine phosphatase type IVA 1

TP4A2	Protein tyrosine phosphatase type IVA 2

TPC	Mitochondrial thiamine pyrophosphate carrier
TPC11	Trafficking protein particle complex subunit 11
TPC12	Trafficking protein particle complex subunit 12 {ECO:0000305}
TPC2L	Trafficking protein particle complex subunit 2-like protein
TPC6B	Trafficking protein particle complex subunit 6B
TPPC1	Trafficking protein particle complex subunit 1
TPPC4	Trafficking protein particle complex subunit 4
TPPC5	Trafficking protein particle complex subunit 5
TPPC8	Trafficking protein particle complex subunit 8
TPR	Nucleoprotein TPR
TR10A	Tumor necrosis factor receptor superfamily member 10A
TR112	Multifunctional methyltransferase subunit TRM112-like protein
TRABD	TraB domain-containing protein
TRAM1	Translocating chain-associated membrane protein 1
TRHY	Trichohyalin
TRI18	E3 ubiquitin-protein ligase Midline-1
TRI23	E3 ubiquitin-protein ligase TRIM23
TRI29	Tripartite motif-containing protein 29
TRI33	E3 ubiquitin-protein ligase TRIM33
TRI50	E3 ubiquitin-protein ligase TRIM50
TRIO	Triple functional domain protein
TRIPC	E3 ubiquitin-protein ligase TRIP12
TRM1L	TRMT1-like protein
TRM6	tRNA (adenine(58)-N(1))-methyltransferase non-catalytic subunit TRM6
TRM7	Putative tRNA (cytidine(32)/guanosine(34)-2'-O)-methyltransferase
TRPM3	Transient receptor potential cation channel subfamily M member 3
TRUA	tRNA pseudouridine synthase A
TSC2	Tuberin
TSN	Translin
TSN3	Tetraspanin-3
TSR1	Pre-rRNA-processing protein TSR1 homolog
TTBK2	Tau-tubulin kinase 2
TTC16	Tetratricopeptide repeat protein 16
TTC22	Tetratricopeptide repeat protein 22
TTC3	E3 ubiquitin-protein ligase TTC3
TTC37	Tetratricopeptide repeat protein 37
TTC7B	Tetratricopeptide repeat protein 7B
TTC9C	Tetratricopeptide repeat protein 9C
TTF2	Transcription termination factor 2
TTYH3	Protein tweety homolog 3
TULP1	Tubby-related protein 1
TWF1	Twinfilin-1
TX101	Testis-expressed protein 101 {ECO:0000305}
TX264	Testis-expressed protein 264
TXD12	Thioredoxin domain-containing protein 12

TXN4A	Thioredoxin-like protein 4A
TXTP	Tricarboxylate transport protein, mitochondrial

TYRP2	L-dopachrome tautomerase
U520	U5 small nuclear ribonucleoprotein 200 kDa helicase
U5S1	116 kDa U5 small nuclear ribonucleoprotein component
UB2G2	Ubiquitin-conjugating enzyme E2 G2
UB2J1	Ubiquitin-conjugating enzyme E2 J1
UBA1	Ubiquitin-like modifier-activating enzyme 1
UBAC1	Ubiquitin-associated domain-containing protein 1
UBAC2	Ubiquitin-associated domain-containing protein 2
UBAP2	Ubiquitin-associated protein 2
UBC12	NEDD8-conjugating enzyme Ubc12
UBC9	SUMO-conjugating enzyme UBC9
UBE2S	Ubiquitin-conjugating enzyme E2 S
UBE2T	Ubiquitin-conjugating enzyme E2 T
UBE3C	Ubiquitin-protein ligase E3C
UBE4A	Ubiquitin conjugation factor E4 A {ECO:0000305}
UBF1	Nucleolar transcription factor 1
UBIP1	Upstream-binding protein 1
UBL4A	Ubiquitin-like protein 4A {ECO:0000305}
UBP10	Ubiquitin carboxyl-terminal hydrolase 10
UBP16	Ubiquitin carboxyl-terminal hydrolase 16 {ECO:0000255|HAMAP-
UBP19	Ubiquitin carboxyl-terminal hydrolase 19
UBP20	Ubiquitin carboxyl-terminal hydrolase 20
UBP22	Ubiquitin carboxyl-terminal hydrolase 22
UBP24	Ubiquitin carboxyl-terminal hydrolase 24
UBP33	Ubiquitin carboxyl-terminal hydrolase 33
UBP7	Ubiquitin carboxyl-terminal hydrolase 7
UBQLN	Ubiquilin-like protein
UBR4	E3 ubiquitin-protein ligase UBR4
UBR5	E3 ubiquitin-protein ligase UBR5
UBX11	UBX domain-containing protein 11
UBXN1	UBX domain-containing protein 1
UBXN8	UBX domain-containing protein 8
UCK2	Uridine-cytidine kinase 2
UCP5	Brain mitochondrial carrier protein 1
UFC1	Ubiquitin-fold modifier-conjugating enzyme 1
UFD1	Ubiquitin recognition factor in ER-associated degradation protein 1
UFM1	Ubiquitin-fold modifier 1
UGGG2	UDP-glucose:glycoprotein glucosyltransferase 2
UHRF1	E3 ubiquitin-protein ligase UHRF1
UMPS	Uridine 5'-monophosphate synthase
UN93B	Protein unc-93 homolog B1
UQCC2	Ubiquinol-cytochrome-c reductase complex assembly factor 2
USE1	Vesicle transport protein USE1
USP9X	Probable ubiquitin carboxyl-terminal hydrolase FAF-X
UTRO	Utrophin
UXS1	UDP-glucuronic acid decarboxylase 1

VA0D1	V-type proton ATPase subunit d 1

VAC14	Protein VAC14 homolog
VAMP4	Vesicle-associated membrane protein 4
VAMP7	Vesicle-associated membrane protein 7
VANG1	Vang-like protein 1
VAPA	Vesicle-associated membrane protein-associated protein A
VAPB	Vesicle-associated membrane protein-associated protein B/C
VAS1	V-type proton ATPase subunit S1
VAT1	Synaptic vesicle membrane protein VAT-1 homolog
VATB2	V-type proton ATPase subunit B, brain isoform
VATE2	V-type proton ATPase subunit E 2
VATH	V-type proton ATPase subunit H
VIGLN	Vigilin
VIR	Protein virilizer homolog {ECO:0000305}
VISL1	Visinin-like protein 1
VKOR1	Vitamin K epoxide reductase complex subunit 1
VKORL	Vitamin K epoxide reductase complex subunit 1-like protein 1
VMA21	Vacuolar ATPase assembly integral membrane protein VMA21
VMA5A	von Willebrand factor A domain-containing protein 5A
VMAT1	Chromaffin granule amine transporter
VOPP1	Vesicular, overexpressed in cancer, prosurvival protein 1
VP13C	Vacuolar protein sorting-associated protein 13C
VP26A	Vacuolar protein sorting-associated protein 26A
VP26B	Vacuolar protein sorting-associated protein 26B
VPP2	V-type proton ATPase 116 kDa subunit a2
VPS11	Vacuolar protein sorting-associated protein 11 homolog
VPS18	Vacuolar protein sorting-associated protein 18 homolog
VPS25	Vacuolar protein-sorting-associated protein 25
VPS29	Vacuolar protein sorting-associated protein 29
VPS35	Vacuolar protein sorting-associated protein 35
VPS39	Vam6/Vps39-like protein
VPS4A	Vacuolar protein sorting-associated protein 4A
VTI1A	Vesicle transport through interaction with t-SNAREs homolog 1A
VTI1B	Vesicle transport through interaction with t-SNAREs homolog 1B
WASC4	WASH complex subunit 4 {ECO:0000312|HGNC:HGNC:29174}
WBP11	WW domain-binding protein 11
WDR11	WD repeat-containing protein 11
WDR18	WD repeat-containing protein 18
WDR26	WD repeat-containing protein 26
WDR3	WD repeat-containing protein 3
WDR41	WD repeat-containing protein 41 {ECO:0000305}
WDR43	WD repeat-containing protein 43
WDR59	GATOR complex protein WDR59 {ECO:0000305}
WDR5B	WD repeat-containing protein 5B
WDR6	WD repeat-containing protein 6
WDR75	WD repeat-containing protein 75
WFS1	Wolframin

WIPI3	WD repeat domain phosphoinositide-interacting protein 3

WWOX	WW domain-containing oxidoreductase
WWP2	NEDD4-like E3 ubiquitin-protein ligase WWP2
XPOT	Exportin-T
XRCC5	X-ray repair cross-complementing protein 5
XRN1	5'-3' exoribonuclease 1
YBOX3	Y-box-binding protein 3
YES	Tyrosine-protein kinase Yes
YIF1A	Protein YIF1A
YIF1B	Protein YIF1B {ECO:0000305}
YIPF2	Protein YIPF2
YIPF4	Protein YIPF4
YIPF5	Protein YIPF5
YIPF6	Protein YIPF6
YKT6	Synaptobrevin homolog YKT6
YLAT2	Y+L amino acid transporter 2
YLPM1	YLP motif-containing protein 1
YMEL1	ATP-dependent zinc metalloprotease YME1L1
YTDC1	YTH domain-containing protein 1 {ECO:0000305}
YTDC2	3'-5' RNA helicase YTHDC2 {ECO:0000305}
YTHD1	YTH domain-containing family protein 1 {ECO:0000305}
YTHD2	YTH domain-containing family protein 2 {ECO:0000305}
Z3H7A	Zinc finger CCCH domain-containing protein 7A
Z585B	Zinc finger protein 585B
Z705G	Putative zinc finger protein 705G
ZBT16	Zinc finger and BTB domain-containing protein 16
ZBT47	Zinc finger and BTB domain-containing protein 47
ZC11A	Zinc finger CCCH domain-containing protein 11A
ZC3H8	Zinc finger CCCH domain-containing protein 8
ZC3HE	Zinc finger CCCH domain-containing protein 14
ZCCHL	Zinc finger CCCH-type antiviral protein 1-like
ZCCHV	Zinc finger CCCH-type antiviral protein 1
ZCHC8	Zinc finger CCHC domain-containing protein 8
ZCPW1	Zinc finger CW-type PWWP domain protein 1
ZCPW2	Zinc finger CW-type PWWP domain protein 2
ZDH13	Palmitoyltransferase ZDHHC13 {ECO:0000305}
ZDH17	Palmitoyltransferase ZDHHC17 {ECO:0000305}
ZDH22	Palmitoyltransferase ZDHHC22
ZFAN6	AN1-type zinc finger protein 6
ZFP69	Zinc finger protein 69 homolog {ECO:0000250|UniProtKB:A2A761}
ZFPL1	Zinc finger protein-like 1
ZFY16	Zinc finger FYVE domain-containing protein 16
ZMY11	Zinc finger MYND domain-containing protein 11 {ECO:0000305}
ZMYM2	Zinc finger MYM-type protein 2
ZN112	Zinc finger protein 112
ZN224	Zinc finger protein 224
ZN236	Zinc finger protein 236

ZN251	Zinc finger protein 251

ZN283	Zinc finger protein 283
ZN302	Zinc finger protein 302
ZN326	DBIRD complex subunit ZNF326
ZN407	Zinc finger protein 407
ZN415	Zinc finger protein 415
ZN582	Zinc finger protein 582
ZN598	E3 ubiquitin-protein ligase ZNF598 {ECO:0000305}
ZN628	Zinc finger protein 628
ZN706	Zinc finger protein 706 {ECO:0000305}
ZN749	Zinc finger protein 749
ZNF12	Zinc finger protein 12
ZNT5	Zinc transporter 5
ZNT6	Zinc transporter 6
ZNT9	Zinc transporter 9
ZO2	Tight junction protein ZO-2
ZSCA1	Zinc finger and SCAN domain-containing protein 1
ZSWM6	Zinc finger SWIM domain-containing protein 6
ZW10	Centromere/kinetochore protein zw10 homolog

Table S3. Cytosolic positive hits

UniProt ID	Protein name
1433T_HUMAN	14-3-3 protein theta
4F2_HUMAN	4F2 cell-surface antigen heavy chain
A4_HUMAN	Amyloid-beta precursor protein
AAAS_HUMAN	Aladin
ABCE1_HUMAN	ATP-binding cassette sub-family E member 1
ACLY_HUMAN	ATP-citrate synthase
ADAS_HUMAN	Alkyldihydroxyacetonephosphate synthase, peroxisomal
ADDA_HUMAN	Alpha-adducin
AFTIN_HUMAN	Aftiphilin
ALEX_HUMAN	Protein ALEX
ALG2_HUMAN	Alpha-1,3/1,6-mannosyltransferase ALG2
ALKB5_HUMAN	RNA demethylase ALKBH5
ANM5_HUMAN	Protein arginine N-methyltransferase 5
AP1G1_HUMAN	AP-1 complex subunit gamma-1
APOB_HUMAN	Apolipoprotein B-100
ARF6_HUMAN	ADP-ribosylation factor 6
ARL1_HUMAN	ADP-ribosylation factor-like protein 1
ASNS_HUMAN	Asparagine synthetase [glutamine-hydrolyzing]
AURKA_HUMAN	Aurora kinase A
BAP31_HUMAN	B-cell receptor-associated protein 31
BIP_HUMAN	Endoplasmic reticulum chaperone BiP
BYST_HUMAN	Bystin
C1QBP_HUMAN	Complement component 1 Q subcomponent-binding protein, mitochondrial
C1TC_HUMAN	C-1-tetrahydrofolate synthase, cytoplasmic
CALD1_HUMAN	Caldesmon
CAND1_HUMAN	Cullin-associated NEDD8-dissociated protein 1
CAPZB_HUMAN	F-actin-capping protein subunit beta
CCNB1_HUMAN	G2/mitotic-specific cyclin-B1
CDK1_HUMAN	Cyclin-dependent kinase 1
CDK2_HUMAN	Cyclin-dependent kinase 2
CE170_HUMAN	Centrosomal protein of 170 kDa
CH60_HUMAN	60 kDa heat shock protein, mitochondrial
CHCH1_HUMAN	Coiled-coil-helix-coiled-coil-helix domain-containing protein 1
CKAP2_HUMAN	Cytoskeleton-associated protein 2
CKAP5_HUMAN	Cytoskeleton-associated protein 5
CLAP2_HUMAN	CLIP-associating protein 2
CLH1_HUMAN	Clathrin heavy chain 1
CLPX_HUMAN	ATP-dependent Clp protease ATP-binding subunit clpX-like, mitochondrial
CND1_HUMAN	Condensin complex subunit 1
CND2_HUMAN	Condensin complex subunit 2
CNOT9_HUMAN	CCR4-NOT transcription complex subunit 9
COMT_HUMAN	Catechol O-methyltransferase
COPA_HUMAN	Coatomer subunit alpha
COPB_HUMAN	Coatomer subunit beta

CRKL_HUMAN	Crk-like protein

CSN5_HUMAN	COP9 signalosome complex subunit 5
CSN6_HUMAN	COP9 signalosome complex subunit 6
CTNA1_HUMAN	Catenin alpha-1
CTND1_HUMAN	Catenin delta-1
CYFP1_HUMAN	Cytoplasmic FMR1-interacting protein 1
DCTN2_HUMAN	Dynactin subunit 2
DCTN3_HUMAN	Dynactin subunit 3
DDX1_HUMAN	ATP-dependent RNA helicase DDX1
DDX17_HUMAN	Probable ATP-dependent RNA helicase DDX17
DDX21_HUMAN	Nucleolar RNA helicase 2
DHB11_HUMAN	Estradiol 17-beta-dehydrogenase 11
DHB4_HUMAN	Peroxisomal multifunctional enzyme type 2
DHC24_HUMAN	Delta(24)-sterol reductase
DNJA1_HUMAN	DnaJ homolog subfamily A member 1
DNJA2_HUMAN	DnaJ homolog subfamily A member 2
DNJC2_HUMAN	DnaJ homolog subfamily C member 2
DNJC8_HUMAN	DnaJ homolog subfamily C member 8
DRG1_HUMAN	Developmentally-regulated GTP-binding protein 1
DYHC1_HUMAN	Cytoplasmic dynein 1 heavy chain 1
E2AK2_HUMAN	Interferon-induced, double-stranded RNA-activated protein kinase
EDC3_HUMAN	Enhancer of mRNA-decapping protein 3
EF1B_HUMAN	Elongation factor 1-beta
EF1G_HUMAN	Elongation factor 1-gamma
EF2_HUMAN	Elongation factor 2
EIF3A_HUMAN	Eukaryotic translation initiation factor 3 subunit A
EIF3B_HUMAN	Eukaryotic translation initiation factor 3 subunit B
EIF3D_HUMAN	Eukaryotic translation initiation factor 3 subunit D
EIF3E_HUMAN	Eukaryotic translation initiation factor 3 subunit E
EIF3F_HUMAN	Eukaryotic translation initiation factor 3 subunit F
EIF3I_HUMAN	Eukaryotic translation initiation factor 3 subunit I
ENOA_HUMAN	Alpha-enolase
ENPL_HUMAN	Endoplasmin
EXOC3_HUMAN	Exocyst complex component 3
EXOC6_HUMAN	Exocyst complex component 6
EXOS6_HUMAN	Exosome complex component MTR3
EXOS8_HUMAN	Exosome complex component RRP43
EXOS9_HUMAN	Exosome complex component RRP45
FAS_HUMAN	Fatty acid synthase
FHL1_HUMAN	Four and a half LIM domains protein 1
FHOD1_HUMAN	FH1/FH2 domain-containing protein 1
FKBP8_HUMAN	Peptidyl-prolyl cis-trans isomerase FKBP8
FLNA_HUMAN	Filamin-A
FMR1_HUMAN	Synaptic functional regulator FMR1
FUBP2_HUMAN	Far upstream element-binding protein 2
G3BP1_HUMAN	Ras GTPase-activating protein-binding protein 1
G3P_HUMAN	Glyceraldehyde-3-phosphate dehydrogenase

G6PD_HUMAN	Glucose-6-phosphate 1-dehydrogenase

GAPD1_HUMAN	GTPase-activating protein and VPS9 domain-containing protein 1
GBF1_HUMAN	Golgi-specific brefeldin A-resistance guanine nucleotide exchange factor 1
GCN1_HUMAN	eIF-2-alpha kinase activator GCN1
GFPT1_HUMAN	Glutamine--fructose-6-phosphate aminotransferase [isomerizing] 1
GGYF2_HUMAN	GRB10-interacting GYF protein 2
GNAS1_HUMAN	Guanine nucleotide-binding protein G(s) subunit alpha isoforms XLas
GNAS2_HUMAN	Guanine nucleotide-binding protein G(s) subunit alpha isoforms short
GNPAT_HUMAN	Dihydroxyacetone phosphate acyltransferase
GPX4_HUMAN	Phospholipid hydroperoxide glutathione peroxidase
GRB10_HUMAN	Growth factor receptor-bound protein 10
GRDN_HUMAN	Girdin
GSTK1_HUMAN	Glutathione S-transferase kappa 1
HAP28_HUMAN	28 kDa heat- and acid-stable phosphoprotein
HD_HUMAN	Huntingtin
HNRDL_HUMAN	Heterogeneous nuclear ribonucleoprotein D-like
HNRPD_HUMAN	Heterogeneous nuclear ribonucleoprotein D0
HNRPF_HUMAN	Heterogeneous nuclear ribonucleoprotein F
HNRPL_HUMAN	Heterogeneous nuclear ribonucleoprotein L
HOME2_HUMAN	Homer protein homolog 2
HS105_HUMAN	Heat shock protein 105 kDa
HS71A_HUMAN	Heat shock 70 kDa protein 1A
HS90A_HUMAN	Heat shock protein HSP 90-alpha
HS90B_HUMAN	Heat shock protein HSP 90-beta
HSP7C_HUMAN	Heat shock cognate 71 kDa protein
HTR5B_HUMAN	HEAT repeat-containing protein 5B
HYCCI_HUMAN	Hyccin
IDHP_HUMAN	Isocitrate dehydrogenase [NADP], mitochondrial
IF2B1_HUMAN	Insulin-like growth factor 2 mRNA-binding protein 1
IF2P_HUMAN	Eukaryotic translation initiation factor 5B
IF4A3_HUMAN	Eukaryotic initiation factor 4A-III
IF4B_HUMAN	Eukaryotic translation initiation factor 4B
IF4E2_HUMAN	Eukaryotic translation initiation factor 4E type 2
IF4G1_HUMAN	Eukaryotic translation initiation factor 4 gamma 1
IF4G2_HUMAN	Eukaryotic translation initiation factor 4 gamma 2
IF4H_HUMAN	Eukaryotic translation initiation factor 4H
IMB1_HUMAN	Importin subunit beta-1
IMDH2_HUMAN	Inosine-5'-monophosphate dehydrogenase 2
INP5K_HUMAN	Inositol polyphosphate 5-phosphatase K
IPO11_HUMAN	Importin-11
IPO7_HUMAN	Importin-7
IPO8_HUMAN	Importin-8
IPO9_HUMAN	Importin-9
IQGA1_HUMAN	Ras GTPase-activating-like protein IQGAP1
IRS4_HUMAN	Insulin receptor substrate 4
JAK1_HUMAN	Tyrosine-protein kinase JAK1
KHDR1_HUMAN	KH domain-containing, RNA-binding, signal transduction-associated protein 1

KPYM_HUMAN	Pyruvate kinase PKM

KS6A2_HUMAN	Ribosomal protein S6 kinase alpha-2
LAR4B_HUMAN	La-related protein 4B
LAT1_HUMAN	Large neutral amino acids transporter small subunit 1
LDHA_HUMAN	L-lactate dehydrogenase A chain
LDHB_HUMAN	L-lactate dehydrogenase B chain
LONM_HUMAN	Lon protease homolog, mitochondrial
LS14A_HUMAN	Protein LSM14 homolog A
LSG1_HUMAN	Large subunit GTPase 1 homolog
MAGD2_HUMAN	Melanoma-associated antigen D2
MAP1B_HUMAN	Microtubule-associated protein 1B
MAP1S_HUMAN	Microtubule-associated protein 1S
MCM5_HUMAN	DNA replication licensing factor MCM5
MDN1_HUMAN	Midasin
MDR3_HUMAN	Phosphatidylcholine translocator ABCB4
MEP50_HUMAN	Methylosome protein 50
MIO_HUMAN	GATOR complex protein MIOS
MYH9_HUMAN	Myosin-9
MYL4_HUMAN	Myosin light chain 4
MYPT1_HUMAN	Protein phosphatase 1 regulatory subunit 12A
NDUV1_HUMAN	NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial
NMT1_HUMAN	Glycylpeptide N-tetradecanoyltransferase 1
NPM3_HUMAN	Nucleoplasmin-3
NSF_HUMAN	Vesicle-fusing ATPase
OPA1_HUMAN	Dynamin-like 120 kDa protein, mitochondrial
P5CR3_HUMAN	Pyrroline-5-carboxylate reductase 3
PAIRB_HUMAN	Plasminogen activator inhibitor 1 RNA-binding protein
PCBP2_HUMAN	Poly(rC)-binding protein 2
PDE12_HUMAN	2',5'-phosphodiesterase 12
PDIA6_HUMAN	Protein disulfide-isomerase A6
PDS5A_HUMAN	Sister chromatid cohesion protein PDS5 homolog A
PFKAM_HUMAN	ATP-dependent 6-phosphofructokinase, muscle type
PHOCN_HUMAN	MOB-like protein phocein
PI4KA_HUMAN	Phosphatidylinositol 4-kinase alpha
PIMT_HUMAN	Protein-L-isoaspartate(D-aspartate) O-methyltransferase
PLST_HUMAN	Plastin-3
PP1A_HUMAN	Serine/threonine-protein phosphatase PP1-alpha catalytic subunit
PPIA_HUMAN	Peptidyl-prolyl cis-trans isomerase A
PPIG_HUMAN	Peptidyl-prolyl cis-trans isomerase G
PPIL4_HUMAN	Peptidyl-prolyl cis-trans isomerase-like 4
PQBP1_HUMAN	Polyglutamine-binding protein 1
PRC2A_HUMAN	Protein PRRC2A
PRC2C_HUMAN	Protein PRRC2C
PRDX1_HUMAN	Peroxiredoxin-1
PRDX2_HUMAN	Peroxiredoxin-2
PRDX3_HUMAN	Thioredoxin-dependent peroxide reductase, mitochondrial
PRDX6_HUMAN	Peroxiredoxin-6

PRKDC_HUMAN	DNA-dependent protein kinase catalytic subunit

PRS10_HUMAN	26S proteasome regulatory subunit 10B
PRS4_HUMAN	26S proteasome regulatory subunit 4
PRS6A_HUMAN	26S proteasome regulatory subunit 6A
PRS6B_HUMAN	26S proteasome regulatory subunit 6B
PSD11_HUMAN	26S proteasome non-ATPase regulatory subunit 11
PSD12_HUMAN	26S proteasome non-ATPase regulatory subunit 12
PSD13_HUMAN	26S proteasome non-ATPase regulatory subunit 13
PSDE_HUMAN	26S proteasome non-ATPase regulatory subunit 14
PSIP1_HUMAN	PC4 and SFRS1-interacting protein
PSMD1_HUMAN	26S proteasome non-ATPase regulatory subunit 1
PSMD2_HUMAN	26S proteasome non-ATPase regulatory subunit 2
PSMD3_HUMAN	26S proteasome non-ATPase regulatory subunit 3
PSMD4_HUMAN	26S proteasome non-ATPase regulatory subunit 4
PSMD6_HUMAN	26S proteasome non-ATPase regulatory subunit 6
PSMD7_HUMAN	26S proteasome non-ATPase regulatory subunit 7
PSME2_HUMAN	Proteasome activator complex subunit 2
PTH2_HUMAN	Peptidyl-tRNA hydrolase 2, mitochondrial
PTN1_HUMAN	Tyrosine-protein phosphatase non-receptor type 1
PYR1_HUMAN	CAD protein
RAB21_HUMAN	Ras-related protein Rab-21
RABL6_HUMAN	Rab-like protein 6
RACK1_HUMAN	Receptor of activated protein C kinase 1
RAGP1_HUMAN	Ran GTPase-activating protein 1
RAN_HUMAN	GTP-binding nuclear protein Ran
RASK_HUMAN	GTPase KRas
RBBP4_HUMAN	Histone-binding protein RBBP4
RBBP7_HUMAN	Histone-binding protein RBBP7
RBM8A_HUMAN	RNA-binding protein 8A
REN3B_HUMAN	Regulator of nonsense transcripts 3B
RFIP1_HUMAN	Rab11 family-interacting protein 1
RFOX2_HUMAN	RNA binding protein fox-1 homolog 2
RIOK1_HUMAN	Serine/threonine-protein kinase RIO1
RL10A_HUMAN	60S ribosomal protein L10a
RL11_HUMAN	60S ribosomal protein L11
RL12_HUMAN	60S ribosomal protein L12
RL13_HUMAN	60S ribosomal protein L13
RL14_HUMAN	60S ribosomal protein L14
RL22_HUMAN	60S ribosomal protein L22
RL23A_HUMAN	60S ribosomal protein L23a
RL31_HUMAN	60S ribosomal protein L31
RL32_HUMAN	60S ribosomal protein L32
RL34_HUMAN	60S ribosomal protein L34
RL35_HUMAN	60S ribosomal protein L35
RL38_HUMAN	60S ribosomal protein L38
RL6_HUMAN	60S ribosomal protein L6
RL7_HUMAN	60S ribosomal protein L7

RL8_HUMAN	60S ribosomal protein L8

RL9_HUMAN	60S ribosomal protein L9
ROCK1_HUMAN	Rho-associated protein kinase 1
RPN1_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1
RPTOR_HUMAN	Regulatory-associated protein of mTOR
RRP12_HUMAN	RRP12-like protein
RS12_HUMAN	40S ribosomal protein S12
RS13_HUMAN	40S ribosomal protein S13
RS15A_HUMAN	40S ribosomal protein S15a
RS19_HUMAN	40S ribosomal protein S19
RS30_HUMAN	40S ribosomal protein S30
RS3A_HUMAN	40S ribosomal protein S3a
RS4X_HUMAN	40S ribosomal protein S4, X isoform
RS5_HUMAN	40S ribosomal protein S5
RS6_HUMAN	40S ribosomal protein S6
RS9_HUMAN	40S ribosomal protein S9
RTCB_HUMAN	RNA-splicing ligase RtcB homolog
SBDS_HUMAN	Ribosome maturation protein SBDS
SC31A_HUMAN	Protein transport protein Sec31A
SDE2_HUMAN	Replication stress response regulator SDE2
SEC63_HUMAN	Translocation protein SEC63 homolog
SERA_HUMAN	D-3-phosphoglycerate dehydrogenase
SKIV2_HUMAN	Helicase SKI2W
SLAI2_HUMAN	SLAIN motif-containing protein 2
SLU7_HUMAN	Pre-mRNA-splicing factor SLU7
SMC4_HUMAN	Structural maintenance of chromosomes protein 4
SMD1_HUMAN	Small nuclear ribonucleoprotein Sm D1
SMD2_HUMAN	Small nuclear ribonucleoprotein Sm D2
SMG1_HUMAN	Serine/threonine-protein kinase SMG1
SND1_HUMAN	Staphylococcal nuclease domain-containing protein 1
SNUT1_HUMAN	U4/U6.U5 tri-snRNP-associated protein 1
SORT_HUMAN	Sortilin
SPIN1_HUMAN	Spindlin-1
SRC8_HUMAN	Src substrate cortactin
SRP09_HUMAN	Signal recognition particle 9 kDa protein
SRRM1_HUMAN	Serine/arginine repetitive matrix protein 1
STX17_HUMAN	Syntaxin-17
SYFB_HUMAN	Phenylalanine--tRNA ligase beta subunit
SYIC_HUMAN	Isoleucine--tRNA ligase, cytoplasmic
SYIM_HUMAN	Isoleucine--tRNA ligase, mitochondrial
SYMC_HUMAN	Methionine--tRNA ligase, cytoplasmic
SYMPK_HUMAN	Symplekin
SYNC_HUMAN	Asparagine--tRNA ligase, cytoplasmic
SYVC_HUMAN	Valine--tRNA ligase
SYWC_HUMAN	Tryptophan--tRNA ligase, cytoplasmic
SYYM_HUMAN	Tyrosine--tRNA ligase, mitochondrial
TACC3_HUMAN	Transforming acidic coiled-coil-containing protein 3

TB10B_HUMAN	TBC1 domain family member 10B

TCPA_HUMAN	T-complex protein 1 subunit alpha
TCPB_HUMAN	T-complex protein 1 subunit beta
TCPG_HUMAN	T-complex protein 1 subunit gamma
TCPH_HUMAN	T-complex protein 1 subunit eta
TCPQ_HUMAN	T-complex protein 1 subunit theta
TCTP_HUMAN	Translationally-controlled tumor protein
TERA_HUMAN	Transitional endoplasmic reticulum ATPase
TFAM_HUMAN	Transcription factor A, mitochondrial
TMED9_HUMAN	Transmembrane emp24 domain-containing protein 9
TNR6B_HUMAN	Trinucleotide repeat-containing gene 6B protein
TOM34_HUMAN	Mitochondrial import receptor subunit TOM34
TPM3_HUMAN	Tropomyosin alpha-3 chain
TPPC3_HUMAN	Trafficking protein particle complex subunit 3
TRIP6_HUMAN	Thyroid receptor-interacting protein 6
UB2L3_HUMAN	Ubiquitin-conjugating enzyme E2 L3
UBP15_HUMAN	Ubiquitin carboxyl-terminal hydrolase 15
UBXN4_HUMAN	UBX domain-containing protein 4
UFD1_HUMAN	Ubiquitin recognition factor in ER-associated degradation protein 1
UFL1_HUMAN	E3 UFM1-protein ligase 1
UN45A_HUMAN	Protein unc-45 homolog A
USO1_HUMAN	General vesicular transport factor p115
UT14A_HUMAN	U3 small nucleolar RNA-associated protein 14 homolog A
VATA_HUMAN	V-type proton ATPase catalytic subunit A
VATG1_HUMAN	V-type proton ATPase subunit G 1
VEZA_HUMAN	Vezatin
VIME_HUMAN	Vimentin
VIR_HUMAN	Protein virilizer homolog
VPP1_HUMAN	V-type proton ATPase 116 kDa subunit a1
VPS41_HUMAN	Vacuolar protein sorting-associated protein 41 homolog
WLS_HUMAN	Protein wntless homolog
XPO1_HUMAN	Exportin-1
XPO2_HUMAN	Exportin-2
XPO5_HUMAN	Exportin-5
XRCC6_HUMAN	X-ray repair cross-complementing protein 6
YBOX1_HUMAN	Y-box-binding protein 1
ZC3H4_HUMAN	Zinc finger CCCH domain-containing protein 4
ZC3HF_HUMAN	Zinc finger CCCH domain-containing protein 15

Table S4. Nucleus positive hits

UniProt ID	Protein name
A4_HUMAN	Amyloid-beta precursor protein
AAAS_HUMAN	Aladin
ACADM_HUMAN	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial
ADDA_HUMAN	Alpha-adducin
ADT3_HUMAN	ADP/ATP translocase 3
AFF4_HUMAN	AF4/FMR2 family member 4
ALG2_HUMAN	Alpha-1,3/1,6-mannosyltransferase ALG2
ALKB5_HUMAN	RNA demethylase ALKBH5
ANM5_HUMAN	Protein arginine N-methyltransferase 5
APEX1_HUMAN	DNA-(apurinic or apyrimidinic site) endonuclease
ATPB_HUMAN	ATP synthase subunit beta, mitochondrial
AURKA_HUMAN	Aurora kinase A
BCLF1_HUMAN	Bcl-2-associated transcription factor 1
BIP_HUMAN	Endoplasmic reticulum chaperone BiP
BYST_HUMAN	Bystin
C1QBP_HUMAN	Complement component 1 Q subcomponent-binding protein, mitochondrial
CAND1_HUMAN	Cullin-associated NEDD8-dissociated protein 1
CCAR1_HUMAN	Cell division cycle and apoptosis regulator protein 1
CCNB1_HUMAN	G2/mitotic-specific cyclin-B1
CDK1_HUMAN	Cyclin-dependent kinase 1
CDK2_HUMAN	Cyclin-dependent kinase 2
CHID1_HUMAN	Chitinase domain-containing protein 1
CIRBP_HUMAN	Cold-inducible RNA-binding protein
CND1_HUMAN	Condensin complex subunit 1
CNOT9_HUMAN	CCR4-NOT transcription complex subunit 9
COIL_HUMAN	Coilin
CPSF5_HUMAN	Cleavage and polyadenylation specificity factor subunit 5
CPSF7_HUMAN	Cleavage and polyadenylation specificity factor subunit 7
CSN5_HUMAN	COP9 signalosome complex subunit 5
CSRP2_HUMAN	Cysteine and glycine-rich protein 2
CTND1_HUMAN	Catenin delta-1
DCAF1_HUMAN	DDB1- and CUL4-associated factor 1
DDB1_HUMAN	DNA damage-binding protein 1
DDX1_HUMAN	ATP-dependent RNA helicase DDX1
DDX17_HUMAN	Probable ATP-dependent RNA helicase DDX17
DDX46_HUMAN	Probable ATP-dependent RNA helicase DDX46
DDX5_HUMAN	Probable ATP-dependent RNA helicase DDX5
DEK_HUMAN	Protein DEK
DESP_HUMAN	Desmoplakin
DHC24_HUMAN	Delta(24)-sterol reductase
DHX16_HUMAN	Pre-mRNA-splicing factor ATP-dependent RNA helicase DHX16
DIDO1_HUMAN	Death-inducer obliterator 1
DNJA1_HUMAN	DnaJ homolog subfamily A member 1
DNJC2_HUMAN	DnaJ homolog subfamily C member 2

DNJC8_HUMAN	DnaJ homolog subfamily C member 8

DPM1_HUMAN	Dolichol-phosphate mannosyltransferase subunit 1
DRG1_HUMAN	Developmentally-regulated GTP-binding protein 1
E2AK2_HUMAN	Interferon-induced, double-stranded RNA-activated protein kinase
EF1G_HUMAN	Elongation factor 1-gamma
EF2_HUMAN	Elongation factor 2
EIF3E_HUMAN	Eukaryotic translation initiation factor 3 subunit E
ENOA_HUMAN	Alpha-enolase
ENPL_HUMAN	Endoplasmin
EWS_HUMAN	RNA-binding protein EWS
EXOS8_HUMAN	Exosome complex component RRP43
EXOS9_HUMAN	Exosome complex component RRP45
FA50A_HUMAN	Protein FAM50A
FA98B_HUMAN	Protein FAM98B
FBRL_HUMAN	rRNA 2'-O-methyltransferase fibrillarin
FHL1_HUMAN	Four and a half LIM domains protein 1
FHOD1_HUMAN	FH1/FH2 domain-containing protein 1
FL2D_HUMAN	Pre-mRNA-splicing regulator WTAP
FLNA_HUMAN	Filamin-A
FMR1_HUMAN	Synaptic functional regulator FMR1
FUS_HUMAN	RNA-binding protein FUS
G3BP1_HUMAN	Ras GTPase-activating protein-binding protein 1
G3P_HUMAN	Glyceraldehyde-3-phosphate dehydrogenase
G6PD_HUMAN	Glucose-6-phosphate 1-dehydrogenase
GLRX5_HUMAN	Glutaredoxin-related protein 5, mitochondrial
GNAS3_HUMAN	Neuroendocrine secretory protein 55
GPX4_HUMAN	Phospholipid hydroperoxide glutathione peroxidase
GTF2I_HUMAN	General transcription factor II-I
HD_HUMAN	Huntingtin
HDGF_HUMAN	Hepatoma-derived growth factor
HDGR2_HUMAN	Hepatoma-derived growth factor-related protein 2
HELLS_HUMAN	Lymphoid-specific helicase
HNRDL_HUMAN	Heterogeneous nuclear ribonucleoprotein D-like
HNRPD_HUMAN	Heterogeneous nuclear ribonucleoprotein D0
HNRPF_HUMAN	Heterogeneous nuclear ribonucleoprotein F
HNRPK_HUMAN	Heterogeneous nuclear ribonucleoprotein K
HNRPL_HUMAN	Heterogeneous nuclear ribonucleoprotein L
HNRPM_HUMAN	Heterogeneous nuclear ribonucleoprotein M
HNRPQ_HUMAN	Heterogeneous nuclear ribonucleoprotein Q
HS105_HUMAN	Heat shock protein 105 kDa
HS71A_HUMAN	Heat shock 70 kDa protein 1A
HS90A_HUMAN	Heat shock protein HSP 90-alpha
HS90B_HUMAN	Heat shock protein HSP 90-beta
HSP7C_HUMAN	Heat shock cognate 71 kDa protein
IDH3A_HUMAN	Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial
IDH3B_HUMAN	Isocitrate dehydrogenase [NAD] subunit beta, mitochondrial
IF4A3_HUMAN	Eukaryotic initiation factor 4A-III

IF4G1_HUMAN	Eukaryotic translation initiation factor 4 gamma 1

ILF2_HUMAN	Interleukin enhancer-binding factor 2
IMB1_HUMAN	Importin subunit beta-1
IMDH2_HUMAN	Inosine-5'-monophosphate dehydrogenase 2
INP5K_HUMAN	Inositol polyphosphate 5-phosphatase K
INT3_HUMAN	Integrator complex subunit 3
IPO5_HUMAN	Importin-5
IQGA1_HUMAN	Ras GTPase-activating-like protein IQGAP1
JAK1_HUMAN	Tyrosine-protein kinase JAK1
KHDR1_HUMAN	KH domain-containing, RNA-binding, signal transduction-associated protein 1
KPYM_HUMAN	Pyruvate kinase PKM
KS6A2_HUMAN	Ribosomal protein S6 kinase alpha-2
LC7L3_HUMAN	Luc7-like protein 3
LDHA_HUMAN	L-lactate dehydrogenase A chain
LPPRC_HUMAN	Leucine-rich PPR motif-containing protein, mitochondrial
LYRIC_HUMAN	Protein LYRIC
MACD1_HUMAN	ADP-ribose glycohydrolase MACROD1
MAP1S_HUMAN	Microtubule-associated protein 1S
MATR3_HUMAN	Matrin-3
MBB1A_HUMAN	Myb-binding protein 1A
MCM4_HUMAN	DNA replication licensing factor MCM4
MCM5_HUMAN	DNA replication licensing factor MCM5
MDN1_HUMAN	Midasin
MEP50_HUMAN	Methylosome protein 50
MFAP1_HUMAN	Microfibrillar-associated protein 1
MPLKI_HUMAN	M-phase-specific PLK1-interacting protein
MSH2_HUMAN	DNA mismatch repair protein Msh2
MYH9_HUMAN	Myosin-9
NASP_HUMAN	Nuclear autoantigenic sperm protein
NCOA2_HUMAN	Nuclear receptor coactivator 2
NELFE_HUMAN	Negative elongation factor E
NONO_HUMAN	Non-POU domain-containing octamer-binding protein
ODPA_HUMAN	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial
ODPB_HUMAN	Pyruvate dehydrogenase E1 component subunit beta, mitochondrial
PAF15_HUMAN	PCNA-associated factor
PAIRB_HUMAN	Plasminogen activator inhibitor 1 RNA-binding protein
PCBP2_HUMAN	Poly(rC)-binding protein 2
PCNA_HUMAN	Proliferating cell nuclear antigen
PDIA3_HUMAN	Protein disulfide-isomerase A3
PDS5A_HUMAN	Sister chromatid cohesion protein PDS5 homolog A
PEX14_HUMAN	Peroxisomal membrane protein PEX14
PFKAM_HUMAN	ATP-dependent 6-phosphofructokinase, muscle type
PHB_HUMAN	Prohibitin
PP1A_HUMAN	Serine/threonine-protein phosphatase PP1-alpha catalytic subunit
PPIA_HUMAN	Peptidyl-prolyl cis-trans isomerase A
PPIB_HUMAN	Peptidyl-prolyl cis-trans isomerase B
PPIG_HUMAN	Peptidyl-prolyl cis-trans isomerase G

PPIL1_HUMAN	Peptidyl-prolyl cis-trans isomerase-like 1

PPIL2_HUMAN	RING-type E3 ubiquitin-protein ligase PPIL2
PPIL4_HUMAN	Peptidyl-prolyl cis-trans isomerase-like 4
PQBP1_HUMAN	Polyglutamine-binding protein 1
PR38A_HUMAN	Pre-mRNA-splicing factor 38A
PRDX1_HUMAN	Peroxiredoxin-1
PRDX6_HUMAN	Peroxiredoxin-6
PRKDC_HUMAN	DNA-dependent protein kinase catalytic subunit
PRP31_HUMAN	U4/U6 small nuclear ribonucleoprotein Prp31
PRP4B_HUMAN	Serine/threonine-protein kinase PRP4 homolog
PRP6_HUMAN	Pre-mRNA-processing factor 6
PRS10_HUMAN	26S proteasome regulatory subunit 10B
PRS4_HUMAN	26S proteasome regulatory subunit 4
PRS6A_HUMAN	26S proteasome regulatory subunit 6A
PRS6B_HUMAN	26S proteasome regulatory subunit 6B
PSD11_HUMAN	26S proteasome non-ATPase regulatory subunit 11
PSD13_HUMAN	26S proteasome non-ATPase regulatory subunit 13
PSDE_HUMAN	26S proteasome non-ATPase regulatory subunit 14
PSIP1_HUMAN	PC4 and SFRS1-interacting protein
PSMD1_HUMAN	26S proteasome non-ATPase regulatory subunit 1
PSMD2_HUMAN	26S proteasome non-ATPase regulatory subunit 2
PSMD3_HUMAN	26S proteasome non-ATPase regulatory subunit 3
PSMD4_HUMAN	26S proteasome non-ATPase regulatory subunit 4
PSMD7_HUMAN	26S proteasome non-ATPase regulatory subunit 7
PYR1_HUMAN	CAD protein
RABL6_HUMAN	Rab-like protein 6
RACK1_HUMAN	Receptor of activated protein C kinase 1
RAN_HUMAN	GTP-binding nuclear protein Ran
RAVR1_HUMAN	Ribonucleoprotein PTB-binding 1
RBBP4_HUMAN	Histone-binding protein RBBP4
RBBP7_HUMAN	Histone-binding protein RBBP7
RBM10_HUMAN	RNA-binding protein 10
RBM14_HUMAN	RNA-binding protein 14
RBM26_HUMAN	RNA-binding protein 26
RBM27_HUMAN	RNA-binding protein 27
RBM6_HUMAN	RNA-binding protein 6
RBM8A_HUMAN	RNA-binding protein 8A
RBP56_HUMAN	TATA-binding protein-associated factor 2N
RDH14_HUMAN	Retinol dehydrogenase 14
RED_HUMAN	Protein Red
REN3B_HUMAN	Regulator of nonsense transcripts 3B
RFOX2_HUMAN	RNA binding protein fox-1 homolog 2
RL10A_HUMAN	60S ribosomal protein L10a
RL13_HUMAN	60S ribosomal protein L13
RL22_HUMAN	60S ribosomal protein L22
RL23A_HUMAN	60S ribosomal protein L23a
RL6_HUMAN	60S ribosomal protein L6

RL7_HUMAN	60S ribosomal protein L7

RL9_HUMAN	60S ribosomal protein L9
ROA2_HUMAN	Heterogeneous nuclear ribonucleoproteins A2/B1
ROA3_HUMAN	Heterogeneous nuclear ribonucleoprotein A3
ROAA_HUMAN	Heterogeneous nuclear ribonucleoprotein A/B
RS13_HUMAN	40S ribosomal protein S13
RS3A_HUMAN	40S ribosomal protein S3a
RS6_HUMAN	40S ribosomal protein S6
RS9_HUMAN	40S ribosomal protein S9
RTCB_HUMAN	RNA-splicing ligase RtcB homolog
RU2A_HUMAN	U2 small nuclear ribonucleoprotein A'
RU2B_HUMAN	U2 small nuclear ribonucleoprotein B''
SAMH1_HUMAN	Deoxynucleoside triphosphate triphosphohydrolase SAMHD1
SBDS_HUMAN	Ribosome maturation protein SBDS
SDE2_HUMAN	Replication stress response regulator SDE2
SF01_HUMAN	Splicing factor 1
SF3A1_HUMAN	Splicing factor 3A subunit 1
SF3A2_HUMAN	Splicing factor 3A subunit 2
SF3B1_HUMAN	Splicing factor 3B subunit 1
SF3B2_HUMAN	Splicing factor 3B subunit 2
SF3B3_HUMAN	Splicing factor 3B subunit 3
SF3B5_HUMAN	Splicing factor 3B subunit 5
SFSWA_HUMAN	Splicing factor, suppressor of white-apricot homolog
SKIV2_HUMAN	Helicase SKI2W
SLIRP_HUMAN	SRA stem-loop-interacting RNA-binding protein, mitochondrial
SLU7_HUMAN	Pre-mRNA-splicing factor SLU7
SMC4_HUMAN	Structural maintenance of chromosomes protein 4
SMD1_HUMAN	Small nuclear ribonucleoprotein Sm D1
SMD2_HUMAN	Small nuclear ribonucleoprotein Sm D2
SMG1_HUMAN	Serine/threonine-protein kinase SMG1
SND1_HUMAN	Staphylococcal nuclease domain-containing protein 1
SNUT1_HUMAN	U4/U6.U5 tri-snRNP-associated protein 1
SPF30_HUMAN	Survival of motor neuron-related-splicing factor 30
SPIN1_HUMAN	Spindlin-1
SRRM1_HUMAN	Serine/arginine repetitive matrix protein 1
SRRM2_HUMAN	Serine/arginine repetitive matrix protein 2
SRS11_HUMAN	Serine/arginine-rich splicing factor 11
SRSF1_HUMAN	Serine/arginine-rich splicing factor 1
SRSF7_HUMAN	Serine/arginine-rich splicing factor 7
SRSF9_HUMAN	Serine/arginine-rich splicing factor 9
SSBP4_HUMAN	Single-stranded DNA-binding protein 4
SYWC_HUMAN	Tryptophan--tRNA ligase, cytoplasmic
T2FA_HUMAN	General transcription factor IIF subunit 1
TBB5_HUMAN	Tubulin beta chain
TCF25_HUMAN	Transcription factor 25
TCRG1_HUMAN	Transcription elongation regulator 1
TCTP_HUMAN	Translationally-controlled tumor protein

TECR_HUMAN	Very-long-chain enoyl-CoA reductase

TERA_HUMAN	Transitional endoplasmic reticulum ATPase
TFAM_HUMAN	Transcription factor A, mitochondrial
TIF1B_HUMAN	Transcription intermediary factor 1-beta
TM10C_HUMAN	tRNA methyltransferase 10 homolog C
TMA16_HUMAN	Translation machinery-associated protein 16
TOM34_HUMAN	Mitochondrial import receptor subunit TOM34
TOP1_HUMAN	DNA topoisomerase 1
TR150_HUMAN	Thyroid hormone receptor-associated protein 3
TRA2B_HUMAN	Transformer-2 protein homolog beta
TRIP6_HUMAN	Thyroid receptor-interacting protein 6
U2AF2_HUMAN	Splicing factor U2AF 65 kDa subunit
UB2L3_HUMAN	Ubiquitin-conjugating enzyme E2 L3
UBIA1_HUMAN	UbiA prenyltransferase domain-containing protein 1
UBP15_HUMAN	Ubiquitin carboxyl-terminal hydrolase 15
UBP2L_HUMAN	Ubiquitin-associated protein 2-like
UFD1_HUMAN	Ubiquitin recognition factor in ER-associated degradation protein 1
VDAC1_HUMAN	Voltage-dependent anion-selective channel protein 1
VDAC2_HUMAN	Voltage-dependent anion-selective channel protein 2
VDAC3_HUMAN	Voltage-dependent anion-selective channel protein 3
WDR33_HUMAN	pre-mRNA 3' end processing protein WDR33
XPO1_HUMAN	Exportin-1
XPO2_HUMAN	Exportin-2
XPO5_HUMAN	Exportin-5
XRCC6_HUMAN	X-ray repair cross-complementing protein 6
YBOX1_HUMAN	Y-box-binding protein 1
ZC3H4_HUMAN	Zinc finger CCCH domain-containing protein 4
ZMAT2_HUMAN	Zinc finger matrin-type protein 2
ZN207_HUMAN	BUB3-interacting and GLEBS motif-containing protein ZNF207
ZRAB2_HUMAN	Zinc finger Ran-binding domain-containing protein 2

Table S5. Exosome positive hits

UniProt ID	Protein name
1433T_HUMAN	14-3-3 protein theta
4F2_HUMAN	4F2 cell-surface antigen heavy chain
A4_HUMAN	Amyloid-beta precursor protein
AAAT_HUMAN	Neutral amino acid transporter B(0)
ACLY_HUMAN	ATP-citrate synthase
APOB_HUMAN	Apolipoprotein B-100
ARF6_HUMAN	ADP-ribosylation factor 6
ARL8B_HUMAN	ADP-ribosylation factor-like protein 8B
AT1A1_HUMAN	Sodium/potassium-transporting ATPase subunit alpha-1
ATPA_HUMAN	ATP synthase subunit alpha, mitochondrial
ATPB_HUMAN	ATP synthase subunit beta, mitochondrial
AUP1_HUMAN	Ancient ubiquitous protein 1
BIP_HUMAN	Endoplasmic reticulum chaperone BiP
C1TC_HUMAN	C-1-tetrahydrofolate synthase, cytoplasmic
CAB45_HUMAN	45 kDa calcium-binding protein
CALX_HUMAN	Calnexin
CAND1_HUMAN	Cullin-associated NEDD8-dissociated protein 1
CAPZB_HUMAN	F-actin-capping protein subunit beta
CDK1_HUMAN	Cyclin-dependent kinase 1
CH60_HUMAN	60 kDa heat shock protein, mitochondrial
CHID1_HUMAN	Chitinase domain-containing protein 1
CLH1_HUMAN	Clathrin heavy chain 1
COMT_HUMAN	Catechol O-methyltransferase
COPA_HUMAN	Coatomer subunit alpha
CPVL_HUMAN	Probable serine carboxypeptidase CPVL
CTND1_HUMAN	Catenin delta-1
CYFP1_HUMAN	Cytoplasmic FMR1-interacting protein 1
DCTN2_HUMAN	Dynactin subunit 2
DDB1_HUMAN	DNA damage-binding protein 1
DDX5_HUMAN	Probable ATP-dependent RNA helicase DDX5
DESP_HUMAN	Desmoplakin
DNJA1_HUMAN	DnaJ homolog subfamily A member 1
DNJA2_HUMAN	DnaJ homolog subfamily A member 2
DSC2_HUMAN	Desmocollin-2
DYHC1_HUMAN	Cytoplasmic dynein 1 heavy chain 1
EF1G_HUMAN	Elongation factor 1-gamma
EF2_HUMAN	Elongation factor 2
EFTU_HUMAN	Elongation factor Tu, mitochondrial
EIF3B_HUMAN	Eukaryotic translation initiation factor 3 subunit B
EIF3E_HUMAN	Eukaryotic translation initiation factor 3 subunit E
EIF3I_HUMAN	Eukaryotic translation initiation factor 3 subunit I
ENOA_HUMAN	Alpha-enolase
ENPL_HUMAN	Endoplasmin
EXOS9_HUMAN	Exosome complex component RRP45

FAS_HUMAN	Fatty acid synthase

FBRL_HUMAN	rRNA 2'-O-methyltransferase fibrillarin
FLNA_HUMAN	Filamin-A
G3P_HUMAN	Glyceraldehyde-3-phosphate dehydrogenase
G6PD_HUMAN	Glucose-6-phosphate 1-dehydrogenase
GANAB_HUMAN	Neutral alpha-glucosidase AB
GFPT1_HUMAN	Glutamine--fructose-6-phosphate aminotransferase [isomerizing] 1
GNAS1_HUMAN	Guanine nucleotide-binding protein G(s) subunit alpha isoforms XLas
GNAS2_HUMAN	Guanine nucleotide-binding protein G(s) subunit alpha isoforms short
GPX4_HUMAN	Phospholipid hydroperoxide glutathione peroxidase
GRP75_HUMAN	Stress-70 protein, mitochondrial
GSTK1_HUMAN	Glutathione S-transferase kappa 1
HLAA_HUMAN	HLA class I histocompatibility antigen, A alpha chain
HLAB_HUMAN	HLA class I histocompatibility antigen, B alpha chain
HNRPK_HUMAN	Heterogeneous nuclear ribonucleoprotein K
HNRPL_HUMAN	Heterogeneous nuclear ribonucleoprotein L
HNRPM_HUMAN	Heterogeneous nuclear ribonucleoprotein M
HS105_HUMAN	Heat shock protein 105 kDa
HS71A_HUMAN	Heat shock 70 kDa protein 1A
HS90A_HUMAN	Heat shock protein HSP 90-alpha
HS90B_HUMAN	Heat shock protein HSP 90-beta
HSP7C_HUMAN	Heat shock cognate 71 kDa protein
IDHP_HUMAN	Isocitrate dehydrogenase [NADP], mitochondrial
IMB1_HUMAN	Importin subunit beta-1
IMDH2_HUMAN	Inosine-5'-monophosphate dehydrogenase 2
IQGA1_HUMAN	Ras GTPase-activating-like protein IQGAP1
KPYM_HUMAN	Pyruvate kinase PKM
LAT1_HUMAN	Large neutral amino acids transporter small subunit 1
LDHA_HUMAN	L-lactate dehydrogenase A chain
LDHB_HUMAN	L-lactate dehydrogenase B chain
LTOR3_HUMAN	Ragulator complex protein LAMTOR3
MDR3_HUMAN	Phosphatidylcholine translocator ABCB4
MOT1_HUMAN	Monocarboxylate transporter 1
MPCP_HUMAN	Phosphate carrier protein, mitochondrial
MPP6_HUMAN	MAGUK p55 subfamily member 6
MPRI_HUMAN	Cation-independent mannose-6-phosphate receptor
MYH9_HUMAN	Myosin-9
MYO1B_HUMAN	Unconventional myosin-Ib
PAIRB_HUMAN	Plasminogen activator inhibitor 1 RNA-binding protein
PCBP2_HUMAN	Poly(rC)-binding protein 2
PCNA_HUMAN	Proliferating cell nuclear antigen
PDIA3_HUMAN	Protein disulfide-isomerase A3
PDIA6_HUMAN	Protein disulfide-isomerase A6
PHB_HUMAN	Prohibitin
PI4KA_HUMAN	Phosphatidylinositol 4-kinase alpha
PIMT_HUMAN	Protein-L-isoaspartate(D-aspartate) O-methyltransferase
PKRI1_HUMAN	PRKR-interacting protein 1

PP1A_HUMAN	Serine/threonine-protein phosphatase PP1-alpha catalytic subunit

PPGB_HUMAN	Lysosomal protective protein
PPIA_HUMAN	Peptidyl-prolyl cis-trans isomerase A
PPIB_HUMAN	Peptidyl-prolyl cis-trans isomerase B
PRC2A_HUMAN	Protein PRRC2A
PRDX1_HUMAN	Peroxiredoxin-1
PRDX2_HUMAN	Peroxiredoxin-2
PRDX6_HUMAN	Peroxiredoxin-6
PRS10_HUMAN	26S proteasome regulatory subunit 10B
PSD12_HUMAN	26S proteasome non-ATPase regulatory subunit 12
PSMD2_HUMAN	26S proteasome non-ATPase regulatory subunit 2
PSMD3_HUMAN	26S proteasome non-ATPase regulatory subunit 3
PSMD7_HUMAN	26S proteasome non-ATPase regulatory subunit 7
PSME2_HUMAN	Proteasome activator complex subunit 2
PTPRF_HUMAN	Receptor-type tyrosine-protein phosphatase F
PYR1_HUMAN	CAD protein
QPCT_HUMAN	Glutaminyl-peptide cyclotransferase
RAB21_HUMAN	Ras-related protein Rab-21
RACK1_HUMAN	Receptor of activated protein C kinase 1
RAN_HUMAN	GTP-binding nuclear protein Ran
RENR_HUMAN	Renin receptor
RL10A_HUMAN	60S ribosomal protein L10a
RL11_HUMAN	60S ribosomal protein L11
RL12_HUMAN	60S ribosomal protein L12
RL14_HUMAN	60S ribosomal protein L14
RL22_HUMAN	60S ribosomal protein L22
RL23A_HUMAN	60S ribosomal protein L23a
RL31_HUMAN	60S ribosomal protein L31
RL34_HUMAN	60S ribosomal protein L34
ROA2_HUMAN	Heterogeneous nuclear ribonucleoproteins A2/B1
RS13_HUMAN	40S ribosomal protein S13
RS15A_HUMAN	40S ribosomal protein S15a
RS19_HUMAN	40S ribosomal protein S19
RS3A_HUMAN	40S ribosomal protein S3a
RS4X_HUMAN	40S ribosomal protein S4, X isoform
RS5_HUMAN	40S ribosomal protein S5
RS9_HUMAN	40S ribosomal protein S9
SATT_HUMAN	Neutral amino acid transporter A
SCAM2_HUMAN	Secretory carrier-associated membrane protein 2
SERA_HUMAN	D-3-phosphoglycerate dehydrogenase
SMD2_HUMAN	Small nuclear ribonucleoprotein Sm D2
SND1_HUMAN	Staphylococcal nuclease domain-containing protein 1
SRSF7_HUMAN	Serine/arginine-rich splicing factor 7
SSRD_HUMAN	Translocon-associated protein subunit delta
SYIC_HUMAN	Isoleucine--tRNA ligase, cytoplasmic
SYMC_HUMAN	Methionine--tRNA ligase, cytoplasmic
SYNC_HUMAN	Asparagine--tRNA ligase, cytoplasmic

SYWC_HUMAN	Tryptophan--tRNA ligase, cytoplasmic

TBB5_HUMAN	Tubulin beta chain
TCPA_HUMAN	T-complex protein 1 subunit alpha
TCPB_HUMAN	T-complex protein 1 subunit beta
TCPG_HUMAN	T-complex protein 1 subunit gamma
TCPH_HUMAN	T-complex protein 1 subunit eta
TCPQ_HUMAN	T-complex protein 1 subunit theta
TCTP_HUMAN	Translationally-controlled tumor protein
TERA_HUMAN	Transitional endoplasmic reticulum ATPase
THIL_HUMAN	Acetyl-CoA acetyltransferase, mitochondrial
TMED9_HUMAN	Transmembrane emp24 domain-containing protein 9
TOR3A_HUMAN	Torsin-3A
TPM3_HUMAN	Tropomyosin alpha-3 chain
TPP1_HUMAN	Tripeptidyl-peptidase 1
TR150_HUMAN	Thyroid hormone receptor-associated protein 3
TSPO_HUMAN	Translocator protein
TXND5_HUMAN	Thioredoxin domain-containing protein 5
UGGG1_HUMAN	UDP-glucose:glycoprotein glucosyltransferase 1
VATA_HUMAN	V-type proton ATPase catalytic subunit A
VATG1_HUMAN	V-type proton ATPase subunit G 1
VATL_HUMAN	V-type proton ATPase 16 kDa proteolipid subunit
VDAC1_HUMAN	Voltage-dependent anion-selective channel protein 1
VDAC3_HUMAN	Voltage-dependent anion-selective channel protein 3
VIME_HUMAN	Vimentin
VPP1_HUMAN	V-type proton ATPase 116 kDa subunit a1
WLS_HUMAN	Protein wntless homolog
XPO2_HUMAN	Exportin-2
YBOX1_HUMAN	Y-box-binding protein 1

Table S6. Mitochondrion positive hits

UniProt ID	Protein name
1433T_HUMAN	14-3-3 protein theta
A4_HUMAN	Amyloid-beta precursor protein
ABCE1_HUMAN	ATP-binding cassette sub-family E member 1
ACADM_HUMAN	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial
ADAS_HUMAN	Alkyldihydroxyacetonephosphate synthase, peroxisomal
ADT3_HUMAN	ADP/ATP translocase 3
APEX1_HUMAN	DNA-(apurinic or apyrimidinic site) endonuclease
APH1A_HUMAN	Gamma-secretase subunit APH-1A
ATIF1_HUMAN	ATPase inhibitor, mitochondrial
ATP5J_HUMAN	ATP synthase-coupling factor 6, mitochondrial
ATP5L_HUMAN	ATP synthase subunit g, mitochondrial
ATPA_HUMAN	ATP synthase subunit alpha, mitochondrial
ATPB_HUMAN	ATP synthase subunit beta, mitochondrial
BAP31_HUMAN	B-cell receptor-associated protein 31
BIP_HUMAN	Endoplasmic reticulum chaperone BiP
C1QBP_HUMAN	Complement component 1 Q subcomponent-binding protein, mitochondrial
C1TC_HUMAN	C-1-tetrahydrofolate synthase, cytoplasmic
C1TM_HUMAN	Monofunctional C1-tetrahydrofolate synthase, mitochondrial
CDK1_HUMAN	Cyclin-dependent kinase 1
CH60_HUMAN	60 kDa heat shock protein, mitochondrial
CHCH1_HUMAN	Coiled-coil-helix-coiled-coil-helix domain-containing protein 1
CLPB_HUMAN	Caseinolytic peptidase B protein homolog
CLPX_HUMAN	ATP-dependent Clp protease ATP-binding subunit clpX-like, mitochondrial
COQ8A_HUMAN	Atypical kinase COQ8A, mitochondrial
DDX1_HUMAN	ATP-dependent RNA helicase DDX1
DDX21_HUMAN	Nucleolar RNA helicase 2
DEGS1_HUMAN	Sphingolipid delta(4)-desaturase DES1
DHE3_HUMAN	Glutamate dehydrogenase 1, mitochondrial
DNJA1_HUMAN	DnaJ homolog subfamily A member 1
ECHA_HUMAN	Trifunctional enzyme subunit alpha, mitochondrial
ECHB_HUMAN	Trifunctional enzyme subunit beta, mitochondrial
EFGM_HUMAN	Elongation factor G, mitochondrial
EFTU_HUMAN	Elongation factor Tu, mitochondrial
ENY2_HUMAN	Transcription and mRNA export factor ENY2
ETFA_HUMAN	Electron transfer flavoprotein subunit alpha, mitochondrial
FAKD4_HUMAN	FAST kinase domain-containing protein 4
FKBP8_HUMAN	Peptidyl-prolyl cis-trans isomerase FKBP8
GBF1_HUMAN	Golgi-specific brefeldin A-resistance guanine nucleotide exchange factor 1
GCDH_HUMAN	Glutaryl-CoA dehydrogenase, mitochondrial
GLRX5_HUMAN	Glutaredoxin-related protein 5, mitochondrial
GPDM_HUMAN	Glycerol-3-phosphate dehydrogenase, mitochondrial
GPX4_HUMAN	Phospholipid hydroperoxide glutathione peroxidase
GRP75_HUMAN	Stress-70 protein, mitochondrial
GSTK1_HUMAN	Glutathione S-transferase kappa 1

HAX1_HUMAN	HCLS1-associated protein X-1

HCD2_HUMAN	3-hydroxyacyl-CoA dehydrogenase type-2
HIG1A_HUMAN	HIG1 domain family member 1A, mitochondrial
HS71A_HUMAN	Heat shock 70 kDa protein 1A
HS90B_HUMAN	Heat shock protein HSP 90-beta
HSDL1_HUMAN	Inactive hydroxysteroid dehydrogenase-like protein 1
HSDL2_HUMAN	Hydroxysteroid dehydrogenase-like protein 2
IDH3A_HUMAN	Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial
IDH3B_HUMAN	Isocitrate dehydrogenase [NAD] subunit beta, mitochondrial
IDHP_HUMAN	Isocitrate dehydrogenase [NADP], mitochondrial
KPYM_HUMAN	Pyruvate kinase PKM
LONM_HUMAN	Lon protease homolog, mitochondrial
LPPRC_HUMAN	Leucine-rich PPR motif-containing protein, mitochondrial
MARK2_HUMAN	Serine/threonine-protein kinase MARK2
MITOS_HUMAN	Mitochondrial potassium channel ATP-binding subunit
MPCP_HUMAN	Phosphate carrier protein, mitochondrial
MRM2_HUMAN	rRNA methyltransferase 2, mitochondrial
NDUAA_HUMAN	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10, mitochondrial
NDUB4_HUMAN	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 4
NDUS2_HUMAN	NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial
NDUS5_HUMAN	NADH dehydrogenase [ubiquinone] iron-sulfur protein 5
NDUS8_HUMAN	NADH dehydrogenase [ubiquinone] iron-sulfur protein 8, mitochondrial
NDUV1_HUMAN	NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial
NIPS1_HUMAN	Protein NipSnap homolog 1
NIPS2_HUMAN	Protein NipSnap homolog 2
NMT1_HUMAN	Glycylpeptide N-tetradecanoyltransferase 1
OAT_HUMAN	Ornithine aminotransferase, mitochondrial
ODPA_HUMAN	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial
ODPB_HUMAN	Pyruvate dehydrogenase E1 component subunit beta, mitochondrial
OPA1_HUMAN	Dynamin-like 120 kDa protein, mitochondrial
P5CR2_HUMAN	Pyrroline-5-carboxylate reductase 2
P5CS_HUMAN	Delta-1-pyrroline-5-carboxylate synthase
PDE12_HUMAN	2',5'-phosphodiesterase 12
PHB_HUMAN	Prohibitin
PRDX3_HUMAN	Thioredoxin-dependent peroxide reductase, mitochondrial
PRDX6_HUMAN	Peroxiredoxin-6
PTH2_HUMAN	Peptidyl-tRNA hydrolase 2, mitochondrial
QCR2_HUMAN	Cytochrome b-c1 complex subunit 2, mitochondrial
RACK1_HUMAN	Receptor of activated protein C kinase 1
RASK_HUMAN	GTPase KRas
RM11_HUMAN	39S ribosomal protein L11, mitochondrial
RM15_HUMAN	39S ribosomal protein L15, mitochondrial
RM33_HUMAN	39S ribosomal protein L33, mitochondrial
RM37_HUMAN	39S ribosomal protein L37, mitochondrial
RM42_HUMAN	39S ribosomal protein L42, mitochondrial
RM46_HUMAN	39S ribosomal protein L46, mitochondrial
RRFM_HUMAN	Ribosome-recycling factor, mitochondrial

RT23_HUMAN	28S ribosomal protein S23, mitochondrial

RT26_HUMAN	28S ribosomal protein S26, mitochondrial
RT29_HUMAN	28S ribosomal protein S29, mitochondrial
RT34_HUMAN	28S ribosomal protein S34, mitochondrial
SCMC1_HUMAN	Calcium-binding mitochondrial carrier protein SCaMC-1
SCO1_HUMAN	Protein SCO1 homolog, mitochondrial
SFXN1_HUMAN	Sideroflexin-1
SFXN3_HUMAN	Sideroflexin-3
SLIRP_HUMAN	SRA stem-loop-interacting RNA-binding protein, mitochondrial
STX17_HUMAN	Syntaxin-17
SUCB2_HUMAN	Succinate--CoA ligase [GDP-forming] subunit beta, mitochondrial
SYIM_HUMAN	Isoleucine--tRNA ligase, mitochondrial
SYPM_HUMAN	Probable proline--tRNA ligase, mitochondrial
SYYM_HUMAN	Tyrosine--tRNA ligase, mitochondrial
TACO1_HUMAN	Translational activator of cytochrome c oxidase 1
TFAM_HUMAN	Transcription factor A, mitochondrial
THIL_HUMAN	Acetyl-CoA acetyltransferase, mitochondrial
TIM50_HUMAN	Mitochondrial import inner membrane translocase subunit TIM50
TM10C_HUMAN	tRNA methyltransferase 10 homolog C
TMM11_HUMAN	Transmembrane protein 11, mitochondrial
TMM70_HUMAN	Transmembrane protein 70, mitochondrial
TOM34_HUMAN	Mitochondrial import receptor subunit TOM34
TRAP1_HUMAN	Heat shock protein 75 kDa, mitochondrial
UBP15_HUMAN	Ubiquitin carboxyl-terminal hydrolase 15
VDAC1_HUMAN	Voltage-dependent anion-selective channel protein 1
VDAC2_HUMAN	Voltage-dependent anion-selective channel protein 2
VDAC3_HUMAN	Voltage-dependent anion-selective channel protein 3
VWA8_HUMAN	von Willebrand factor A domain-containing protein 8
YRDC_HUMAN	YrdC domain-containing protein, mitochondrial

Table S7. Endoplasmic reticulum positive hits

UniProt ID	Protein name
ACSL3_HUMAN	Long-chain-fatty-acid--CoA ligase 3
ADPGK_HUMAN	ADP-dependent glucokinase
ALG1_HUMAN	Chitobiosyldiphosphodolichol beta-mannosyltransferase
AMRP_HUMAN	Alpha-2-macroglobulin receptor-associated protein
ANKL2_HUMAN	Ankyrin repeat and LEM domain-containing protein 2
APEX1_HUMAN	DNA-(apurinic or apyrimidinic site) endonuclease
APH1A_HUMAN	Gamma-secretase subunit APH-1A
AT1A1_HUMAN	Sodium/potassium-transporting ATPase subunit alpha-1
ATLA2_HUMAN	Atlastin-2
ATLA3_HUMAN	Atlastin-3
BAP31_HUMAN	B-cell receptor-associated protein 31
BIP_HUMAN	Endoplasmic reticulum chaperone BiP
CAB45_HUMAN	45 kDa calcium-binding protein
CALU_HUMAN	Calumenin
CALX_HUMAN	Calnexin
CCD47_HUMAN	Coiled-coil domain-containing protein 47
CERS2_HUMAN	Ceramide synthase 2
CLCC1_HUMAN	Chloride channel CLIC-like protein 1
CNIH4_HUMAN	Protein cornichon homolog 4
DEGS1_HUMAN	Sphingolipid delta(4)-desaturase DES1
DERL1_HUMAN	Derlin-1
DHB11_HUMAN	Estradiol 17-beta-dehydrogenase 11
DHC24_HUMAN	Delta(24)-sterol reductase
DJC10_HUMAN	DnaJ homolog subfamily C member 10
DPM1_HUMAN	Dolichol-phosphate mannosyltransferase subunit 1
E2AK3_HUMAN	Eukaryotic translation initiation factor 2-alpha kinase 3
EBP_HUMAN	3-beta-hydroxysteroid-Delta(8),Delta(7)-isomerase
ECHB_HUMAN	Trifunctional enzyme subunit beta, mitochondrial
ENPL_HUMAN	Endoplasmin
ERD21_HUMAN	ER lumen protein-retaining receptor 1
ESYT1_HUMAN	Extended synaptotagmin-1
FAF2_HUMAN	FAS-associated factor 2
FKBP2_HUMAN	Peptidyl-prolyl cis-trans isomerase FKBP2
FKBP8_HUMAN	Peptidyl-prolyl cis-trans isomerase FKBP8
GGYF2_HUMAN	GRB10-interacting GYF protein 2
GRDN_HUMAN	Girdin
HACD3_HUMAN	Very-long-chain (3R)-3-hydroxyacyl-CoA dehydratase 3
HAX1_HUMAN	HCLS1-associated protein X-1
HD_HUMAN	Huntingtin
HLAA_HUMAN	HLA class I histocompatibility antigen, A alpha chain
HLAB_HUMAN	HLA class I histocompatibility antigen, B alpha chain
HNRPQ_HUMAN	Heterogeneous nuclear ribonucleoprotein Q
HS71A_HUMAN	Heat shock 70 kDa protein 1A
INP5K_HUMAN	Inositol polyphosphate 5-phosphatase K

LSG1_HUMAN	Large subunit GTPase 1 homolog

LYRIC_HUMAN	Protein LYRIC
MAGT1_HUMAN	Magnesium transporter protein 1
MESD_HUMAN	LRP chaperone MESD
MGST2_HUMAN	Microsomal glutathione S-transferase 2
MGST3_HUMAN	Microsomal glutathione S-transferase 3
NSDHL_HUMAN	Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating
OST48_HUMAN	ichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa sub
PCAT1_HUMAN	Lysophosphatidylcholine acyltransferase 1
PCAT2_HUMAN	Lysophosphatidylcholine acyltransferase 2
PDIA3_HUMAN	Protein disulfide-isomerase A3
PDIA4_HUMAN	Protein disulfide-isomerase A4
PDIA6_HUMAN	Protein disulfide-isomerase A6
PPGB_HUMAN	Lysosomal protective protein
PPIB_HUMAN	Peptidyl-prolyl cis-trans isomerase B
PTN1_HUMAN	Tyrosine-protein phosphatase non-receptor type 1
RCN1_HUMAN	Reticulocalbin-1
RCN2_HUMAN	Reticulocalbin-2
RDH14_HUMAN	Retinol dehydrogenase 14
RL13_HUMAN	60S ribosomal protein L13
RL34_HUMAN	60S ribosomal protein L34
RPN1_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit
RS3A_HUMAN	40S ribosomal protein S3a
RS6_HUMAN	40S ribosomal protein S6
S39A6_HUMAN	Zinc transporter ZIP6
SAC1_HUMAN	Phosphatidylinositol-3-phosphatase SAC1
SC22B_HUMAN	Vesicle-trafficking protein SEC22b
SC31A_HUMAN	Protein transport protein Sec31A
SEC63_HUMAN	Translocation protein SEC63 homolog
SERPH_HUMAN	Serpin H1
SPCS3_HUMAN	Signal peptidase complex subunit 3
SPTC1_HUMAN	Serine palmitoyltransferase 1
SSRG_HUMAN	Translocon-associated protein subunit gamma
SV2A_HUMAN	Synaptic vesicle glycoprotein 2A
SYVN1_HUMAN	E3 ubiquitin-protein ligase synoviolin
TECR_HUMAN	Very-long-chain enoyl-CoA reductase
TERA_HUMAN	Transitional endoplasmic reticulum ATPase
TMCO1_HUMAN	Calcium load-activated calcium channel
TMED5_HUMAN	Transmembrane emp24 domain-containing protein 5
TMED9_HUMAN	Transmembrane emp24 domain-containing protein 9
TMEDA_HUMAN	Transmembrane emp24 domain-containing protein 10
TMM33_HUMAN	Transmembrane protein 33
TOR3A_HUMAN	Torsin-3A
TPPC3_HUMAN	Trafficking protein particle complex subunit 3
TSPO_HUMAN	Translocator protein
TXND5_HUMAN	Thioredoxin domain-containing protein 5
UBIA1_HUMAN	UbiA prenyltransferase domain-containing protein 1
UBXN4_HUMAN	UBX domain-containing protein 4

unit

UFL1_HUMAN	E3 UFM1-protein ligase 1
UGGG1_HUMAN	UDP-glucose:glycoprotein glucosyltransferase 1
USO1_HUMAN	General vesicular transport factor p115
VMP1_HUMAN	Vacuole membrane protein 1
WLS_HUMAN	Protein wntless homolog

Table S8. Golgi apparatus positive hits

UniProt ID	Protein name
A4_HUMAN	Amyloid-beta precursor protein
ACSL3_HUMAN	Long-chain-fatty-acid--CoA ligase 3
AFTIN_HUMAN	Aftiphilin
ALKB5_HUMAN	RNA demethylase ALKBH5
AMRP_HUMAN	Alpha-2-macroglobulin receptor-associated protein
ANM5_HUMAN	Protein arginine N-methyltransferase 5
AP1G1_HUMAN	AP-1 complex subunit gamma-1
AP3D1_HUMAN	AP-3 complex subunit delta-1
APH1A_HUMAN	Gamma-secretase subunit APH-1A
ARF6_HUMAN	ADP-ribosylation factor 6
ARL1_HUMAN	ADP-ribosylation factor-like protein 1
AT1A1_HUMAN	Sodium/potassium-transporting ATPase subunit alpha-1
CAB45_HUMAN	45 kDa calcium-binding protein
CALU_HUMAN	Calumenin
CAND1_HUMAN	Cullin-associated NEDD8-dissociated protein 1
CDIPT_HUMAN	CDP-diacylglycerol--inositol 3-phosphatidyltransferase
CH60_HUMAN	60 kDa heat shock protein, mitochondrial
CHPT1_HUMAN	Cholinephosphotransferase 1
CLAP2_HUMAN	CLIP-associating protein 2
CLCN3_HUMAN	H(+)/Cl(-) exchange transporter 3
COPB_HUMAN	Coatomer subunit beta
EPT1_HUMAN	Ethanolaminephosphotransferase 1
ERD21_HUMAN	ER lumen protein-retaining receptor 1
EXOC3_HUMAN	Exocyst complex component 3
FAS_HUMAN	Fatty acid synthase
GANAB_HUMAN	Neutral alpha-glucosidase AB
GBF1_HUMAN	Golgi-specific brefeldin A-resistance guanine nucleotide exchange factor 1
GGYF2_HUMAN	GRB10-interacting GYF protein 2
GRDN_HUMAN	Girdin
HD_HUMAN	Huntingtin
HLAA_HUMAN	HLA class I histocompatibility antigen, A alpha chain
HLAB_HUMAN	HLA class I histocompatibility antigen, B alpha chain
MEP50_HUMAN	Methylosome protein 50
MPLKI_HUMAN	M-phase-specific PLK1-interacting protein
MPRI_HUMAN	Cation-independent mannose-6-phosphate receptor
PCAT1_HUMAN	Lysophosphatidylcholine acyltransferase 1
PHOCN_HUMAN	MOB-like protein phocein
RS12_HUMAN	40S ribosomal protein S12
SAC1_HUMAN	Phosphatidylinositol-3-phosphatase SAC1
SCAM2_HUMAN	Secretory carrier-associated membrane protein 2
SDE2_HUMAN	Replication stress response regulator SDE2
SELM_HUMAN	Selenoprotein M
SNUT1_HUMAN	U4/U6.U5 tri-snRNP-associated protein 1
SORT_HUMAN	Sortilin

SRC8_HUMAN	Src substrate cortactin

SYNRG_HUMAN	Synergin gamma
TCPA_HUMAN	T-complex protein 1 subunit alpha
TMED5_HUMAN	Transmembrane emp24 domain-containing protein 5
TMED9_HUMAN	Transmembrane emp24 domain-containing protein 9
TMEDA_HUMAN	Transmembrane emp24 domain-containing protein 10
TPP1_HUMAN	Tripeptidyl-peptidase 1
TPPC3_HUMAN	Trafficking protein particle complex subunit 3
UN45A_HUMAN	Protein unc-45 homolog A
USO1_HUMAN	General vesicular transport factor p115
VPP1_HUMAN	V-type proton ATPase 116 kDa subunit a1
VPS41_HUMAN	Vacuolar protein sorting-associated protein 41 homolog
VPS45_HUMAN	Vacuolar protein sorting-associated protein 45
WLS_HUMAN	Protein wntless homolog
YIPF3_HUMAN	Protein YIPF3
ZNT7_HUMAN	Zinc transporter 7

Table S9. Membrane positive hits

UniProt ID	Protein name
1433T_HUMAN	14-3-3 protein theta
4F2_HUMAN	4F2 cell-surface antigen heavy chain
A4_HUMAN	Amyloid-beta precursor protein
AAAS_HUMAN	Aladin
AAAT_HUMAN	Neutral amino acid transporter B(0)
ABCE1_HUMAN	ATP-binding cassette sub-family E member 1
ABCF2_HUMAN	ATP-binding cassette sub-family F member 2
ACLY_HUMAN	ATP-citrate synthase
ACSL3_HUMAN	Long-chain-fatty-acid--CoA ligase 3
ADAS_HUMAN	Alkyldihydroxyacetonephosphate synthase, peroxisomal
ADPGK_HUMAN	ADP-dependent glucokinase
AIG1_HUMAN	Androgen-induced gene 1 protein
ALEX_HUMAN	Protein ALEX
ALG1_HUMAN	Chitobiosyldiphosphodolichol beta-mannosyltransferase
ALG11_HUMAN	GDP-Man:Man(3)GlcNAc(2)-PP-Dol alpha-1,2-mannosyltransferase
ALG2_HUMAN	Alpha-1,3/1,6-mannosyltransferase ALG2
ALG5_HUMAN	Dolichyl-phosphate beta-glucosyltransferase
ANKL2_HUMAN	Ankyrin repeat and LEM domain-containing protein 2
AP1G1_HUMAN	AP-1 complex subunit gamma-1
AP3D1_HUMAN	AP-3 complex subunit delta-1
APH1A_HUMAN	Gamma-secretase subunit APH-1A
ARF6_HUMAN	ADP-ribosylation factor 6
ARL8B_HUMAN	ADP-ribosylation factor-like protein 8B
AT131_HUMAN	Manganese-transporting ATPase 13A1
AT1A1_HUMAN	Sodium/potassium-transporting ATPase subunit alpha-1
ATG9A_HUMAN	Autophagy-related protein 9A
ATLA2_HUMAN	Atlastin-2
ATLA3_HUMAN	Atlastin-3
ATPA_HUMAN	ATP synthase subunit alpha, mitochondrial
ATPB_HUMAN	ATP synthase subunit beta, mitochondrial
AUP1_HUMAN	Ancient ubiquitous protein 1
B3A2_HUMAN	Anion exchange protein 2
BAP31_HUMAN	B-cell receptor-associated protein 31
BIP_HUMAN	Endoplasmic reticulum chaperone BiP
BYST_HUMAN	Bystin
BZW2_HUMAN	Basic leucine zipper and W2 domain-containing protein 2
C1QBP_HUMAN	Complement component 1 Q subcomponent-binding protein, mitochondrial
C1TC_HUMAN	C-1-tetrahydrofolate synthase, cytoplasmic
C1TM_HUMAN	Monofunctional C1-tetrahydrofolate synthase, mitochondrial
CAB45_HUMAN	45 kDa calcium-binding protein
CALU_HUMAN	Calumenin
CALX_HUMAN	Calnexin
CAND1_HUMAN	Cullin-associated NEDD8-dissociated protein 1
CCD47_HUMAN	Coiled-coil domain-containing protein 47

CCNB1_HUMAN	G2/mitotic-specific cyclin-B1

CDIPT_HUMAN	CDP-diacylglycerol--inositol 3-phosphatidyltransferase
CDK1_HUMAN	Cyclin-dependent kinase 1
CERS2_HUMAN	Ceramide synthase 2
CH60_HUMAN	60 kDa heat shock protein, mitochondrial
CHD4_HUMAN	Chromodomain-helicase-DNA-binding protein 4
CHID1_HUMAN	Chitinase domain-containing protein 1
CHPT1_HUMAN	Cholinephosphotransferase 1
CKAP5_HUMAN	Cytoskeleton-associated protein 5
CLAP2_HUMAN	CLIP-associating protein 2
CLCC1_HUMAN	Chloride channel CLIC-like protein 1
CLCN3_HUMAN	H(+)/Cl(-) exchange transporter 3
CLCN7_HUMAN	H(+)/Cl(-) exchange transporter 7
CLH1_HUMAN	Clathrin heavy chain 1
CND1_HUMAN	Condensin complex subunit 1
CND2_HUMAN	Condensin complex subunit 2
CNOT9_HUMAN	CCR4-NOT transcription complex subunit 9
COIL_HUMAN	Coilin
COMT_HUMAN	Catechol O-methyltransferase
COPA_HUMAN	Coatomer subunit alpha
COPB_HUMAN	Coatomer subunit beta
CPSF7_HUMAN	Cleavage and polyadenylation specificity factor subunit 7
DAD1_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit DAD1
DCTN2_HUMAN	Dynactin subunit 2
DDX1_HUMAN	ATP-dependent RNA helicase DDX1
DDX17_HUMAN	Probable ATP-dependent RNA helicase DDX17
DDX21_HUMAN	Nucleolar RNA helicase 2
DDX46_HUMAN	Probable ATP-dependent RNA helicase DDX46
DDX5_HUMAN	Probable ATP-dependent RNA helicase DDX5
DEGS1_HUMAN	Sphingolipid delta(4)-desaturase DES1
DERL1_HUMAN	Derlin-1
DESP_HUMAN	Desmoplakin
DHB4_HUMAN	Peroxisomal multifunctional enzyme type 2
DHC24_HUMAN	Delta(24)-sterol reductase
DJC10_HUMAN	DnaJ homolog subfamily C member 10
DNJA1_HUMAN	DnaJ homolog subfamily A member 1
DNJA2_HUMAN	DnaJ homolog subfamily A member 2
DPM1_HUMAN	Dolichol-phosphate mannosyltransferase subunit 1
DRG1_HUMAN	Developmentally-regulated GTP-binding protein 1
DYHC1_HUMAN	Cytoplasmic dynein 1 heavy chain 1
E2AK2_HUMAN	Interferon-induced, double-stranded RNA-activated protein kinase
E2AK3_HUMAN	Eukaryotic translation initiation factor 2-alpha kinase 3
EDC3_HUMAN	Enhancer of mRNA-decapping protein 3
EF1G_HUMAN	Elongation factor 1-gamma
EF2_HUMAN	Elongation factor 2
EFTU_HUMAN	Elongation factor Tu, mitochondrial
EIF3A_HUMAN	Eukaryotic translation initiation factor 3 subunit A

EIF3D_HUMAN	Eukaryotic translation initiation factor 3 subunit D

EIF3E_HUMAN	Eukaryotic translation initiation factor 3 subunit E
EIF3F_HUMAN	Eukaryotic translation initiation factor 3 subunit F
ENOA_HUMAN	Alpha-enolase
ENPL_HUMAN	Endoplasmin
ESYT1_HUMAN	Extended synaptotagmin-1
EXOC6_HUMAN	Exocyst complex component 6
FAS_HUMAN	Fatty acid synthase
FBRL_HUMAN	rRNA 2'-O-methyltransferase fibrillarin
FHOD1_HUMAN	FH1/FH2 domain-containing protein 1
FKBP8_HUMAN	Peptidyl-prolyl cis-trans isomerase FKBP8
FLNA_HUMAN	Filamin-A
FMR1_HUMAN	Synaptic functional regulator FMR1
FUBP2_HUMAN	Far upstream element-binding protein 2
G3P_HUMAN	Glyceraldehyde-3-phosphate dehydrogenase
G6PD_HUMAN	Glucose-6-phosphate 1-dehydrogenase
GANAB_HUMAN	Neutral alpha-glucosidase AB
GBF1_HUMAN	Golgi-specific brefeldin A-resistance guanine nucleotide exchange factor 1
GCN1_HUMAN	eIF-2-alpha kinase activator GCN1
GGYF2_HUMAN	GRB10-interacting GYF protein 2
GNAS1_HUMAN	Guanine nucleotide-binding protein G(s) subunit alpha isoforms XLas
GNAS2_HUMAN	Guanine nucleotide-binding protein G(s) subunit alpha isoforms short
GNPAT_HUMAN	Dihydroxyacetone phosphate acyltransferase
GPAA1_HUMAN	Glycosylphosphatidylinositol anchor attachment 1 protein
GRDN_HUMAN	Girdin
GSTK1_HUMAN	Glutathione S-transferase kappa 1
GTF2I_HUMAN	General transcription factor II-I
HACL2_HUMAN	2-hydroxyacyl-CoA lyase 2
HLAA_HUMAN	HLA class I histocompatibility antigen, A alpha chain
HLAB_HUMAN	HLA class I histocompatibility antigen, B alpha chain
HNRPF_HUMAN	Heterogeneous nuclear ribonucleoprotein F
HNRPK_HUMAN	Heterogeneous nuclear ribonucleoprotein K
HNRPL_HUMAN	Heterogeneous nuclear ribonucleoprotein L
HNRPM_HUMAN	Heterogeneous nuclear ribonucleoprotein M
HNRPQ_HUMAN	Heterogeneous nuclear ribonucleoprotein Q
HS90A_HUMAN	Heat shock protein HSP 90-alpha
HS90B_HUMAN	Heat shock protein HSP 90-beta
HSDL2_HUMAN	Hydroxysteroid dehydrogenase-like protein 2
HSP7C_HUMAN	Heat shock cognate 71 kDa protein
HTR5B_HUMAN	HEAT repeat-containing protein 5B
IF4A3_HUMAN	Eukaryotic initiation factor 4A-III
IF4G1_HUMAN	Eukaryotic translation initiation factor 4 gamma 1
IF4G2_HUMAN	Eukaryotic translation initiation factor 4 gamma 2
IF4H_HUMAN	Eukaryotic translation initiation factor 4H
ILF2_HUMAN	Interleukin enhancer-binding factor 2
IMB1_HUMAN	Importin subunit beta-1
IMDH2_HUMAN	Inosine-5'-monophosphate dehydrogenase 2

INP5K_HUMAN	Inositol polyphosphate 5-phosphatase K

IPO5_HUMAN	Importin-5
IPO7_HUMAN	Importin-7
IPO9_HUMAN	Importin-9
JAK1_HUMAN	Tyrosine-protein kinase JAK1
K2013_HUMAN	Uncharacterized protein KIAA2013
KHDR1_HUMAN	KH domain-containing, RNA-binding, signal transduction-associated protein 1
LAR4B_HUMAN	La-related protein 4B
LAT1_HUMAN	Large neutral amino acids transporter small subunit 1
LDHA_HUMAN	L-lactate dehydrogenase A chain
LDHB_HUMAN	L-lactate dehydrogenase B chain
LONM_HUMAN	Lon protease homolog, mitochondrial
LPPRC_HUMAN	Leucine-rich PPR motif-containing protein, mitochondrial
LSG1_HUMAN	Large subunit GTPase 1 homolog
MAGD2_HUMAN	Melanoma-associated antigen D2
MAGT1_HUMAN	Magnesium transporter protein 1
MARK2_HUMAN	Serine/threonine-protein kinase MARK2
MATR3_HUMAN	Matrin-3
MBB1A_HUMAN	Myb-binding protein 1A
MCM4_HUMAN	DNA replication licensing factor MCM4
MCM5_HUMAN	DNA replication licensing factor MCM5
MDN1_HUMAN	Midasin
MDR3_HUMAN	Phosphatidylcholine translocator ABCB4
MGST2_HUMAN	Microsomal glutathione S-transferase 2
MGST3_HUMAN	Microsomal glutathione S-transferase 3
MOT1_HUMAN	Monocarboxylate transporter 1
MPCP_HUMAN	Phosphate carrier protein, mitochondrial
MPP6_HUMAN	MAGUK p55 subfamily member 6
MPRI_HUMAN	Cation-independent mannose-6-phosphate receptor
MPU1_HUMAN	Mannose-P-dolichol utilization defect 1 protein
MSH2_HUMAN	DNA mismatch repair protein Msh2
MYH9_HUMAN	Myosin-9
NCKX1_HUMAN	Sodium/potassium/calcium exchanger 1
NCLN_HUMAN	Nicalin
NONO_HUMAN	Non-POU domain-containing octamer-binding protein
NOP14_HUMAN	Nucleolar protein 14
NU155_HUMAN	Nuclear pore complex protein Nup155
NU188_HUMAN	Nucleoporin NUP188 homolog
NU205_HUMAN	Nuclear pore complex protein Nup205
NUP93_HUMAN	Nuclear pore complex protein Nup93
OPA1_HUMAN	Dynamin-like 120 kDa protein, mitochondrial
OST48_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit
PAIRB_HUMAN	Plasminogen activator inhibitor 1 RNA-binding protein
PCAT1_HUMAN	Lysophosphatidylcholine acyltransferase 1
PCBP2_HUMAN	Poly(rC)-binding protein 2
PEX14_HUMAN	Peroxisomal membrane protein PEX14
PFKAM_HUMAN	ATP-dependent 6-phosphofructokinase, muscle type

PHB_HUMAN	Prohibitin

PI4KA_HUMAN	Phosphatidylinositol 4-kinase alpha
PIGT_HUMAN	GPI transamidase component PIG-T
PM34_HUMAN	Peroxisomal membrane protein PMP34
PPGB_HUMAN	Lysosomal protective protein
PPIA_HUMAN	Peptidyl-prolyl cis-trans isomerase A
PPIB_HUMAN	Peptidyl-prolyl cis-trans isomerase B
PRC2A_HUMAN	Protein PRRC2A
PRC2C_HUMAN	Protein PRRC2C
PRDX6_HUMAN	Peroxiredoxin-6
PRKDC_HUMAN	DNA-dependent protein kinase catalytic subunit
PRP6_HUMAN	Pre-mRNA-processing factor 6
PRS10_HUMAN	26S proteasome regulatory subunit 10B
PRS4_HUMAN	26S proteasome regulatory subunit 4
PRS6A_HUMAN	26S proteasome regulatory subunit 6A
PRS6B_HUMAN	26S proteasome regulatory subunit 6B
PSD11_HUMAN	26S proteasome non-ATPase regulatory subunit 11
PSD12_HUMAN	26S proteasome non-ATPase regulatory subunit 12
PSD13_HUMAN	26S proteasome non-ATPase regulatory subunit 13
PSMD1_HUMAN	26S proteasome non-ATPase regulatory subunit 1
PSMD2_HUMAN	26S proteasome non-ATPase regulatory subunit 2
PSMD3_HUMAN	26S proteasome non-ATPase regulatory subunit 3
PSMD7_HUMAN	26S proteasome non-ATPase regulatory subunit 7
PSME2_HUMAN	Proteasome activator complex subunit 2
PTH2_HUMAN	Peptidyl-tRNA hydrolase 2, mitochondrial
PYR1_HUMAN	CAD protein
RAN_HUMAN	GTP-binding nuclear protein Ran
RASK_HUMAN	GTPase KRas
RDH14_HUMAN	Retinol dehydrogenase 14
RL10A_HUMAN	60S ribosomal protein L10a
RL11_HUMAN	60S ribosomal protein L11
RL12_HUMAN	60S ribosomal protein L12
RL13_HUMAN	60S ribosomal protein L13
RL14_HUMAN	60S ribosomal protein L14
RL31_HUMAN	60S ribosomal protein L31
RL32_HUMAN	60S ribosomal protein L32
RL35_HUMAN	60S ribosomal protein L35
RL6_HUMAN	60S ribosomal protein L6
RL7_HUMAN	60S ribosomal protein L7
RL8_HUMAN	60S ribosomal protein L8
RL9_HUMAN	60S ribosomal protein L9
ROA2_HUMAN	Heterogeneous nuclear ribonucleoproteins A2/B1
RPN1_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1
RPN2_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2
RS12_HUMAN	40S ribosomal protein S12
RS13_HUMAN	40S ribosomal protein S13
RS15A_HUMAN	40S ribosomal protein S15a

RS19_HUMAN	40S ribosomal protein S19

RS4X_HUMAN	40S ribosomal protein S4, X isoform
RS5_HUMAN	40S ribosomal protein S5
RS6_HUMAN	40S ribosomal protein S6
RS9_HUMAN	40S ribosomal protein S9
S27A4_HUMAN	Long-chain fatty acid transport protein 4
SATT_HUMAN	Neutral amino acid transporter A
SEC63_HUMAN	Translocation protein SEC63 homolog
SLU7_HUMAN	Pre-mRNA-splicing factor SLU7
SND1_HUMAN	Staphylococcal nuclease domain-containing protein 1
STT3A_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit STT3A
SYFB_HUMAN	Phenylalanine--tRNA ligase beta subunit
SYIC_HUMAN	Isoleucine--tRNA ligase, cytoplasmic
SYMC_HUMAN	Methionine--tRNA ligase, cytoplasmic
SYVN1_HUMAN	E3 ubiquitin-protein ligase synoviolin
TGO1_HUMAN	Transport and Golgi organization protein 1 homolog
TOM34_HUMAN	Mitochondrial import receptor subunit TOM34
TRAP1_HUMAN	Heat shock protein 75 kDa, mitochondrial
UBIA1_HUMAN	UbiA prenyltransferase domain-containing protein 1
UFL1_HUMAN	E3 UFM1-protein ligase 1
USO1_HUMAN	General vesicular transport factor p115
VDAC1_HUMAN	Voltage-dependent anion-selective channel protein 1
VKGC_HUMAN	Vitamin K-dependent gamma-carboxylase
VMP1_HUMAN	Vacuole membrane protein 1
VPS41_HUMAN	Vacuolar protein sorting-associated protein 41 homolog
XPO1_HUMAN	Exportin-1
XPO2_HUMAN	Exportin-2
XRCC6_HUMAN	X-ray repair cross-complementing protein 6
YRDC_HUMAN	YrdC domain-containing protein, mitochondrial

Table S10. Plasma membrane positive hits

UniProt ID	Protein name
4F2_HUMAN	4F2 cell-surface antigen heavy chain
A4_HUMAN	Amyloid-beta precursor protein
AAAT_HUMAN	Neutral amino acid transporter B(0)
ACLY_HUMAN	ATP-citrate synthase
ADDA_HUMAN	Alpha-adducin
AIG1_HUMAN	Androgen-induced gene 1 protein
ALEX_HUMAN	Protein ALEX
AMRP_HUMAN	Alpha-2-macroglobulin receptor-associated protein
APH1A_HUMAN	Gamma-secretase subunit APH-1A
APOB_HUMAN	Apolipoprotein B-100
ARF6_HUMAN	ADP-ribosylation factor 6
AT1A1_HUMAN	Sodium/potassium-transporting ATPase subunit alpha-1
ATPA_HUMAN	ATP synthase subunit alpha, mitochondrial
ATPB_HUMAN	ATP synthase subunit beta, mitochondrial
B3A2_HUMAN	Anion exchange protein 2
BIP_HUMAN	Endoplasmic reticulum chaperone BiP
C1QBP_HUMAN	Complement component 1 Q subcomponent-binding protein, mitochondrial
CAB45_HUMAN	45 kDa calcium-binding protein
CALD1_HUMAN	Caldesmon
CD3Z_HUMAN	T-cell surface glycoprotein CD3 zeta chain
CDIPT_HUMAN	CDP-diacylglycerol--inositol 3-phosphatidyltransferase
CELR1_HUMAN	Cadherin EGF LAG seven-pass G-type receptor 1
CELR3_HUMAN	Cadherin EGF LAG seven-pass G-type receptor 3
CH60_HUMAN	60 kDa heat shock protein, mitochondrial
CKAP5_HUMAN	Cytoskeleton-associated protein 5
CLAP2_HUMAN	CLIP-associating protein 2
CLCN3_HUMAN	H(+)/Cl(-) exchange transporter 3
CLH1_HUMAN	Clathrin heavy chain 1
COMT_HUMAN	Catechol O-methyltransferase
COPB_HUMAN	Coatomer subunit beta
CSCL2_HUMAN	CSC1-like protein 2
CTNA1_HUMAN	Catenin alpha-1
CTND1_HUMAN	Catenin delta-1
DEGS1_HUMAN	Sphingolipid delta(4)-desaturase DES1
DESP_HUMAN	Desmoplakin
DSC2_HUMAN	Desmocollin-2
EF2_HUMAN	Elongation factor 2
ENOA_HUMAN	Alpha-enolase
ENPL_HUMAN	Endoplasmin
EWS_HUMAN	RNA-binding protein EWS
EXOC6_HUMAN	Exocyst complex component 6
FAS_HUMAN	Fatty acid synthase
FHL1_HUMAN	Four and a half LIM domains protein 1
FLNA_HUMAN	Filamin-A

FRAS1_HUMAN	Extracellular matrix protein FRAS1

G3P_HUMAN	Glyceraldehyde-3-phosphate dehydrogenase
GAPD1_HUMAN	GTPase-activating protein and VPS9 domain-containing protein 1
GNAS2_HUMAN	Guanine nucleotide-binding protein G(s) subunit alpha isoforms short
GRB10_HUMAN	Growth factor receptor-bound protein 10
GRDN_HUMAN	Girdin
HAP28_HUMAN	28 kDa heat- and acid-stable phosphoprotein
HAX1_HUMAN	HCLS1-associated protein X-1
HCD2_HUMAN	3-hydroxyacyl-CoA dehydrogenase type-2
HLAA_HUMAN	HLA class I histocompatibility antigen, A alpha chain
HLAB_HUMAN	HLA class I histocompatibility antigen, B alpha chain
HNRPF_HUMAN	Heterogeneous nuclear ribonucleoprotein F
HOME2_HUMAN	Homer protein homolog 2
HS71A_HUMAN	Heat shock 70 kDa protein 1A
HS90A_HUMAN	Heat shock protein HSP 90-alpha
HS90B_HUMAN	Heat shock protein HSP 90-beta
HSP7C_HUMAN	Heat shock cognate 71 kDa protein
HYCCI_HUMAN	Hyccin
IL7RA_HUMAN	Interleukin-7 receptor subunit alpha
INP5K_HUMAN	Inositol polyphosphate 5-phosphatase K
IQGA1_HUMAN	Ras GTPase-activating-like protein IQGAP1
IRS4_HUMAN	Insulin receptor substrate 4
LAT1_HUMAN	Large neutral amino acids transporter small subunit 1
LTOR3_HUMAN	Ragulator complex protein LAMTOR3
MAGT1_HUMAN	Magnesium transporter protein 1
MAP1B_HUMAN	Microtubule-associated protein 1B
MARK2_HUMAN	Serine/threonine-protein kinase MARK2
MDR3_HUMAN	Phosphatidylcholine translocator ABCB4
MESD_HUMAN	LRP chaperone MESD
MGST2_HUMAN	Microsomal glutathione S-transferase 2
MOT1_HUMAN	Monocarboxylate transporter 1
MPP6_HUMAN	MAGUK p55 subfamily member 6
MPRI_HUMAN	Cation-independent mannose-6-phosphate receptor
MYH9_HUMAN	Myosin-9
MYO1B_HUMAN	Unconventional myosin-Ib
MYPT1_HUMAN	Protein phosphatase 1 regulatory subunit 12A
NADAP_HUMAN	Kanadaptin
NCKX1_HUMAN	Sodium/potassium/calcium exchanger 1
NELFE_HUMAN	Negative elongation factor E
NMT1_HUMAN	Glycylpeptide N-tetradecanoyltransferase 1
NSF_HUMAN	Vesicle-fusing ATPase
OPA1_HUMAN	Dynamin-like 120 kDa protein, mitochondrial
OST48_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit
PAIRB_HUMAN	Plasminogen activator inhibitor 1 RNA-binding protein
PCAT1_HUMAN	Lysophosphatidylcholine acyltransferase 1
PD2R_HUMAN	Prostaglandin D2 receptor
PDIA6_HUMAN	Protein disulfide-isomerase A6

PDS5A_HUMAN	Sister chromatid cohesion protein PDS5 homolog A

PHB_HUMAN	Prohibitin
PI4KA_HUMAN	Phosphatidylinositol 4-kinase alpha
PLST_HUMAN	Plastin-3
PP1A_HUMAN	Serine/threonine-protein phosphatase PP1-alpha catalytic subunit
PPIL2_HUMAN	RING-type E3 ubiquitin-protein ligase PPIL2
PRC2A_HUMAN	Protein PRRC2A
PTPRF_HUMAN	Receptor-type tyrosine-protein phosphatase F
RASK_HUMAN	GTPase KRas
RENR_HUMAN	Renin receptor
RM42_HUMAN	39S ribosomal protein L42, mitochondrial
ROCK1_HUMAN	Rho-associated protein kinase 1
RRP12_HUMAN	RRP12-like protein
S27A4_HUMAN	Long-chain fatty acid transport protein 4
S39A6_HUMAN	Zinc transporter ZIP6
S39AE_HUMAN	Metal cation symporter ZIP14
S6A15_HUMAN	Sodium-dependent neutral amino acid transporter B(0)AT2
SAMH1_HUMAN	Deoxynucleoside triphosphate triphosphohydrolase SAMHD1
SATT_HUMAN	Neutral amino acid transporter A
SDE2_HUMAN	Replication stress response regulator SDE2
SORT_HUMAN	Sortilin
SRC8_HUMAN	Src substrate cortactin
SUCB2_HUMAN	Succinate--CoA ligase [GDP-forming] subunit beta, mitochondrial
SV2A_HUMAN	Synaptic vesicle glycoprotein 2A
SYMPK_HUMAN	Symplekin
TB10B_HUMAN	TBC1 domain family member 10B
TCPG_HUMAN	T-complex protein 1 subunit gamma
TMEDA_HUMAN	Transmembrane emp24 domain-containing protein 10
TMX3_HUMAN	Protein disulfide-isomerase TMX3
TRIP6_HUMAN	Thyroid receptor-interacting protein 6
VATA_HUMAN	V-type proton ATPase catalytic subunit A
VATG1_HUMAN	V-type proton ATPase subunit G 1
VATL_HUMAN	V-type proton ATPase 16 kDa proteolipid subunit
VDAC1_HUMAN	Voltage-dependent anion-selective channel protein 1
VIME_HUMAN	Vimentin
VMP1_HUMAN	Vacuole membrane protein 1
VPP1_HUMAN	V-type proton ATPase 116 kDa subunit a1
WLS_HUMAN	Protein wntless homolog
YIPF3_HUMAN	Protein YIPF3

Table S11. Protein folding and chaperones

UniProt ID	Protein name
AP1G1_HUMAN	AP-1 complex subunit gamma-1
BAP31_HUMAN	B-cell receptor-associated protein 31
CKLF8_HUMAN	CKLF-like MARVEL transmembrane domain-containing protein 8
CLH1_HUMAN	Clathrin heavy chain 1 {ECO:0000303 | PubMed:26822784,
CNIH4_HUMAN	Protein cornichon homolog 4
COPA_HUMAN	Coatomer subunit alpha
COPB_HUMAN	Coatomer subunit beta
ERD21_HUMAN	ER lumen protein-retaining receptor 1
EXOC3_HUMAN	Exocyst complex component 3
EXOC6_HUMAN	Exocyst complex component 6
GRDN_HUMAN	Girdin
MPRI_HUMAN	Cation-independent mannose-6-phosphate receptor
NSF_HUMAN	Vesicle-fusing ATPase
OPA1_HUMAN	Dynamin-like 120 kDa protein, mitochondrial
SC31A_HUMAN	Protein transport protein Sec31A
SORT_HUMAN	Sortilin
STX17_HUMAN	Syntaxin-17 {ECO:0000303 | PubMed:21545355}
TGO1_HUMAN	Transport and Golgi organization protein 1 homolog {ECO:0000305}
TMED5_HUMAN	Transmembrane emp24 domain-containing protein 5
TMED9_HUMAN	Transmembrane emp24 domain-containing protein 9
TMEDA_HUMAN	Transmembrane emp24 domain-containing protein 10
USO1_HUMAN	General vesicular transport factor p115
VP33A_HUMAN	Vacuolar protein sorting-associated protein 33A
VPS41_HUMAN	Vacuolar protein sorting-associated protein 41 homolog
VPS45_HUMAN	Vacuolar protein sorting-associated protein 45

Table S12. Transporters

UniProt ID	Protein name
AAAT_HUMAN	Neutral amino acid transporter B(0)
AP3D1_HUMAN	AP-3 complex subunit delta-1
AT1A1_HUMAN	Sodium/potassium-transporting ATPase subunit alpha-1
ATP5J_HUMAN	ATP synthase-coupling factor 6, mitochondrial {ECO:0000305}
B3A2_HUMAN	Anion exchange protein 2
CLCN3_HUMAN	H(+)/Cl(-) exchange transporter 3
DERL1_HUMAN	Derlin-1 {ECO:0000303|PubMed:15215855}
HD_HUMAN	Huntingtin
IMB1_HUMAN	Importin subunit beta-1
IPO11_HUMAN	Importin-11
IPO5_HUMAN	Importin-5
IPO7_HUMAN	Importin-7
IPO8_HUMAN	Importin-8
IPO9_HUMAN	Importin-9
MDR3_HUMAN	Phosphatidylcholine translocator ABCB4 {ECO:0000305}
MITOS_HUMAN	Mitochondrial potassium channel ATP-binding subunit {ECO:0000305}
MOT1_HUMAN	Monocarboxylate transporter 1
NCKX1_HUMAN	Sodium/potassium/calcium exchanger 1
NU155_HUMAN	Nuclear pore complex protein Nup155
NUP93_HUMAN	Nuclear pore complex protein Nup93
PEX14_HUMAN	Peroxisomal membrane protein PEX14
PIPNB_HUMAN	Phosphatidylinositol transfer protein beta isoform
PLST_HUMAN	Plastin-3
S27A4_HUMAN	Long-chain fatty acid transport protein 4 {ECO:0000305}
S38A9_HUMAN	Sodium-coupled neutral amino acid transporter 9 {ECO:0000305}
S39A6_HUMAN	Zinc transporter ZIP6
S39AE_HUMAN	Metal cation symporter ZIP14 {ECO:0000305|PubMed:18270315}
S6A15_HUMAN	Sodium-dependent neutral amino acid transporter B(0)AT2
SATT_HUMAN	Neutral amino acid transporter A
SCMC1_HUMAN	Calcium-binding mitochondrial carrier protein SCaMC-1
SFXN1_HUMAN	Sideroflexin-1 {ECO:0000250|UniProtKB:Q99JR1}
SFXN3_HUMAN	Sideroflexin-3 {ECO:0000303|PubMed:30442778}
SPNS1_HUMAN	Protein spinster homolog 1
VATA_HUMAN	V-type proton ATPase catalytic subunit A
VATG1_HUMAN	V-type proton ATPase subunit G 1
VATL_HUMAN	V-type proton ATPase 16 kDa proteolipid subunit
VDAC1_HUMAN	Voltage-dependent anion-selective channel protein 1
VDAC2_HUMAN	Voltage-dependent anion-selective channel protein 2
VDAC3_HUMAN	Voltage-dependent anion-selective channel protein 3
VPP1_HUMAN	V-type proton ATPase 116 kDa subunit a1
XPO1_HUMAN	Exportin-1
XPO2_HUMAN	Exportin-2
XPO5_HUMAN	Exportin-5

Table S13. Intracellular trafficking related proteins

UniProt ID	Protein name
AP1G1_HUMAN	AP-1 complex subunit gamma-1
BAP31_HUMAN	B-cell receptor-associated protein 31
CKLF8_HUMAN	CKLF-like MARVEL transmembrane domain-containing protein 8
CLH1_HUMAN	Clathrin heavy chain 1 {ECO:0000303 | PubMed:26822784,
CNIH4_HUMAN	Protein cornichon homolog 4
COPA_HUMAN	Coatomer subunit alpha
COPB_HUMAN	Coatomer subunit beta
ERD21_HUMAN	ER lumen protein-retaining receptor 1
EXOC3_HUMAN	Exocyst complex component 3
EXOC6_HUMAN	Exocyst complex component 6
GRDN_HUMAN	Girdin
MPRI_HUMAN	Cation-independent mannose-6-phosphate receptor
NSF_HUMAN	Vesicle-fusing ATPase
OPA1_HUMAN	Dynamin-like 120 kDa protein, mitochondrial
SC31A_HUMAN	Protein transport protein Sec31A
SORT_HUMAN	Sortilin
STX17_HUMAN	Syntaxin-17 {ECO:0000303 | PubMed:21545355}
TGO1_HUMAN	Transport and Golgi organization protein 1 homolog {ECO:0000305}
TMED5_HUMAN	Transmembrane emp24 domain-containing protein 5
TMED9_HUMAN	Transmembrane emp24 domain-containing protein 9
TMEDA_HUMAN	Transmembrane emp24 domain-containing protein 10
USO1_HUMAN	General vesicular transport factor p115
VP33A_HUMAN	Vacuolar protein sorting-associated protein 33A
VPS41_HUMAN	Vacuolar protein sorting-associated protein 41 homolog
VPS45_HUMAN	Vacuolar protein sorting-associated protein 45

Table S14. Translational proteins

UniProt ID	Protein name
ABCF2_HUMAN	ATP-binding cassette sub-family F member 2
CLU_HUMAN	Clustered mitochondria protein homolog {ECO:0000255|HAMAP-
CSN6_HUMAN	COP9 signalosome complex subunit 6
EF1A2_HUMAN	Elongation factor 1-alpha 2
EF1B_HUMAN	Elongation factor 1-beta
EF2_HUMAN	Elongation factor 2
EFTU_HUMAN	Elongation factor Tu, mitochondrial
EIF3A_HUMAN	Eukaryotic translation initiation factor 3 subunit A
EIF3B_HUMAN	Eukaryotic translation initiation factor 3 subunit B
EIF3D_HUMAN	Eukaryotic translation initiation factor 3 subunit D
EIF3E_HUMAN	Eukaryotic translation initiation factor 3 subunit E
EIF3F_HUMAN	Eukaryotic translation initiation factor 3 subunit F
EIF3I_HUMAN	Eukaryotic translation initiation factor 3 subunit I
FMR1_HUMAN	Synaptic functional regulator FMR1 {ECO:0000305}
IF2P_HUMAN	Eukaryotic translation initiation factor 5B
IF4B_HUMAN	Eukaryotic translation initiation factor 4B
IF4E2_HUMAN	Eukaryotic translation initiation factor 4E type 2
IF4G1_HUMAN	Eukaryotic translation initiation factor 4 gamma 1
IF4G2_HUMAN	Eukaryotic translation initiation factor 4 gamma 2
IF4H_HUMAN	Eukaryotic translation initiation factor 4H
LRC47_HUMAN	Leucine-rich repeat-containing protein 47
PSMD7_HUMAN	26S proteasome non-ATPase regulatory subunit 7
RL10A_HUMAN	60S ribosomal protein L10a
RL11_HUMAN	60S ribosomal protein L11
RL12_HUMAN	60S ribosomal protein L12
RL13_HUMAN	60S ribosomal protein L13
RL14_HUMAN	60S ribosomal protein L14
RL22_HUMAN	60S ribosomal protein L22
RL22L_HUMAN	60S ribosomal protein L22-like 1
RL23A_HUMAN	60S ribosomal protein L23a
RL31_HUMAN	60S ribosomal protein L31
RL32_HUMAN	60S ribosomal protein L32
RL35_HUMAN	60S ribosomal protein L35
RL38_HUMAN	60S ribosomal protein L38
RL6_HUMAN	60S ribosomal protein L6
RL7_HUMAN	60S ribosomal protein L7
RL8_HUMAN	60S ribosomal protein L8
RL9_HUMAN	60S ribosomal protein L9
RM11_HUMAN	39S ribosomal protein L11, mitochondrial
RM15_HUMAN	39S ribosomal protein L15, mitochondrial
RM37_HUMAN	39S ribosomal protein L37, mitochondrial
RM42_HUMAN	39S ribosomal protein L42, mitochondrial
RM46_HUMAN	39S ribosomal protein L46, mitochondrial
RRFM_HUMAN	Ribosome-recycling factor, mitochondrial

RS12_HUMAN	40S ribosomal protein S12

RS13_HUMAN	40S ribosomal protein S13
RS15A_HUMAN	40S ribosomal protein S15a
RS19_HUMAN	40S ribosomal protein S19
RS3A_HUMAN	40S ribosomal protein S3a {ECO:0000255|HAMAP-Rule:MF_03122}
RS4X_HUMAN	40S ribosomal protein S4, X isoform
RS5_HUMAN	40S ribosomal protein S5
RS6_HUMAN	40S ribosomal protein S6 {ECO:0000303|PubMed:29563586}
RS9_HUMAN	40S ribosomal protein S9
RT07_HUMAN	28S ribosomal protein S7, mitochondrial
RT23_HUMAN	28S ribosomal protein S23, mitochondrial
RT26_HUMAN	28S ribosomal protein S26, mitochondrial
RT29_HUMAN	28S ribosomal protein S29, mitochondrial
SYFB_HUMAN	Phenylalanine--tRNA ligase beta subunit
SYIM_HUMAN	Isoleucine--tRNA ligase, mitochondrial
SYPM_HUMAN	Probable proline--tRNA ligase, mitochondrial
SYYM_HUMAN	Tyrosine--tRNA ligase, mitochondrial

Table S15. Nucleic acid binding proteins

UniProt ID	Protein name
BCLF1_HUMAN	Bcl-2-associated transcription factor 1
COIL_HUMAN	Coilin
CPSF5_HUMAN	Cleavage and polyadenylation specificity factor subunit 5
CPSF7_HUMAN	Cleavage and polyadenylation specificity factor subunit 7
DDB1_HUMAN	DNA damage-binding protein 1
DHX16_HUMAN	Pre-mRNA-splicing factor ATP-dependent RNA helicase DHX16
DIDO1_HUMAN	Death-inducer obliterator 1
EWS_HUMAN	RNA-binding protein EWS
EXOS6_HUMAN	Exosome complex component MTR3
EXOS8_HUMAN	Exosome complex component RRP43
EXOS9_HUMAN	Exosome complex component RRP45
FA98A_HUMAN	Protein FAM98A {ECO:0000305}
FA98B_HUMAN	Protein FAM98B
FRG1_HUMAN	Protein FRG1
FUBP2_HUMAN	Far upstream element-binding protein 2
FUS_HUMAN	RNA-binding protein FUS
G3BP1_HUMAN	Ras GTPase-activating protein-binding protein 1
HNRPF_HUMAN	Heterogeneous nuclear ribonucleoprotein F
HNRPK_HUMAN	Heterogeneous nuclear ribonucleoprotein K
HNRPM_HUMAN	Heterogeneous nuclear ribonucleoprotein M
HNRPQ_HUMAN	Heterogeneous nuclear ribonucleoprotein Q
IF2B1_HUMAN	Insulin-like growth factor 2 mRNA-binding protein 1
KHDR1_HUMAN	KH domain-containing, RNA-binding, signal transduction-associated protein
LAR4B_HUMAN	La-related protein 4B
LS14A_HUMAN	Protein LSM14 homolog A
MCM4_HUMAN	DNA replication licensing factor MCM4
MCM5_HUMAN	DNA replication licensing factor MCM5 {ECO:0000303 | Ref.3}
MSH2_HUMAN	DNA mismatch repair protein Msh2
NADAP_HUMAN	Kanadaptin
NONO_HUMAN	Non-POU domain-containing octamer-binding protein
NOP14_HUMAN	Nucleolar protein 14
PAIRB_HUMAN	Plasminogen activator inhibitor 1 RNA-binding protein {ECO:0000305}
PCBP2_HUMAN	Poly(rC)-binding protein 2
PCNA_HUMAN	Proliferating cell nuclear antigen
PDE12_HUMAN	2',5'-phosphodiesterase 12
PHF6_HUMAN	PHD finger protein 6
PRC2A_HUMAN	Protein PRRC2A
PRC2C_HUMAN	Protein PRRC2C
PRP31_HUMAN	U4/U6 small nuclear ribonucleoprotein Prp31
PRP6_HUMAN	Pre-mRNA-processing factor 6
RAVR1_HUMAN	Ribonucleoprotein PTB-binding 1
RB12B_HUMAN	RNA-binding protein 12B
RBM14_HUMAN	RNA-binding protein 14
RBM26_HUMAN	RNA-binding protein 26

RBM27_HUMAN	RNA-binding protein 27

RBP56_HUMAN	TATA-binding protein-associated factor 2N
RFOX2_HUMAN	RNA binding protein fox-1 homolog 2
RU2A_HUMAN	U2 small nuclear ribonucleoprotein A'
RU2B_HUMAN	U2 small nuclear ribonucleoprotein B''
SBDS_HUMAN	Ribosome maturation protein SBDS
SDE2_HUMAN	Replication stress response regulator SDE2 {ECO:0000305}
SF01_HUMAN	Splicing factor 1
SF3A1_HUMAN	Splicing factor 3A subunit 1
SF3A2_HUMAN	Splicing factor 3A subunit 2
SF3B1_HUMAN	Splicing factor 3B subunit 1
SF3B2_HUMAN	Splicing factor 3B subunit 2
SF3B3_HUMAN	Splicing factor 3B subunit 3
SFSWA_HUMAN	Splicing factor, suppressor of white-apricot homolog
SLU7_HUMAN	Pre-mRNA-splicing factor SLU7
SMD1_HUMAN	Small nuclear ribonucleoprotein Sm D1
SNRPA_HUMAN	U1 small nuclear ribonucleoprotein A
SRP09_HUMAN	Signal recognition particle 9 kDa protein
SRRM1_HUMAN	Serine/arginine repetitive matrix protein 1
SRS11_HUMAN	Serine/arginine-rich splicing factor 11
SRSF1_HUMAN	Serine/arginine-rich splicing factor 1
SRSF7_HUMAN	Serine/arginine-rich splicing factor 7
SRSF9_HUMAN	Serine/arginine-rich splicing factor 9
T2FA_HUMAN	General transcription factor IIF subunit 1
TCEA1_HUMAN	Transcription elongation factor A protein 1
TCRG1_HUMAN	Transcription elongation regulator 1
TFB1M_HUMAN	Dimethyladenosine transferase 1, mitochondrial
TM10C_HUMAN	tRNA methyltransferase 10 homolog C {ECO:0000305}
TNR6B_HUMAN	Trinucleotide repeat-containing gene 6B protein
TOP1_HUMAN	DNA topoisomerase 1
TR150_HUMAN	Thyroid hormone receptor-associated protein 3
U2AF1_HUMAN	Splicing factor U2AF 35 kDa subunit
UT14A_HUMAN	U3 small nucleolar RNA-associated protein 14 homolog A
WDR33_HUMAN	pre-mRNA 3' end processing protein WDR33
XRCC6_HUMAN	X-ray repair cross-complementing protein 6
ZN207_HUMAN	BUB3-interacting and GLEBS motif-containing protein ZNF207
ZRAB2_HUMAN	Zinc finger Ran-binding domain-containing protein 2

Table S16. Signaling-related proteins

UniProt ID	Protein name
A4_HUMAN	Amyloid-beta precursor protein {ECO:0000305}
ACLY_HUMAN	ATP-citrate synthase
ACSL3_HUMAN	Long-chain-fatty-acid--CoA ligase 3 {ECO:0000305}
ADPGK_HUMAN	ADP-dependent glucokinase
AFF4_HUMAN	AF4/FMR2 family member 4
ALEX_HUMAN	Protein ALEX
ALG1_HUMAN	Chitobiosyldiphosphodolichol beta-mannosyltransferase
ALG5_HUMAN	Dolichyl-phosphate beta-glucosyltransferase
ALG8_HUMAN	Probable dolichyl pyrophosphate alpha-1,3-glucosyltransferase
ARF6_HUMAN	ADP-ribosylation factor 6
ARL1_HUMAN	ADP-ribosylation factor-like protein 1
ASNS_HUMAN	Asparagine synthetase [glutamine-hydrolyzing]
ATIF1_HUMAN	ATPase inhibitor, mitochondrial {ECO:0000305}
ATLA2_HUMAN	Atlastin-2
ATLA3_HUMAN	Atlastin-3
BUD23_HUMAN	Probable 18S rRNA (guanine-N(7))-methyltransferase {ECO:0000305}
CCAR1_HUMAN	Cell division cycle and apoptosis regulator protein 1
CCNB1_HUMAN	G2/mitotic-specific cyclin-B1
CDIPT_HUMAN	CDP-diacylglycerol--inositol 3-phosphatidyltransferase {ECO:0000305}
CHPT1_HUMAN	Cholinephosphotransferase 1 {ECO:0000305}
CND1_HUMAN	Condensin complex subunit 1
COMT_HUMAN	Catechol O-methyltransferase {ECO:0000305}
DAD1_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit
DEK_HUMAN	Protein DEK
DHC24_HUMAN	Delta(24)-sterol reductase
DHE3_HUMAN	Glutamate dehydrogenase 1, mitochondrial
DOCK7_HUMAN	Dedicator of cytokinesis protein 7
DPM1_HUMAN	Dolichol-phosphate mannosyltransferase subunit 1
EBP_HUMAN	3-beta-hydroxysteroid-Delta(8),Delta(7)-isomerase {ECO:0000305}
ECHA_HUMAN	Trifunctional enzyme subunit alpha, mitochondrial
ECHB_HUMAN	Trifunctional enzyme subunit beta, mitochondrial
ENOA_HUMAN	Alpha-enolase
EPT1_HUMAN	Ethanolaminephosphotransferase 1 {ECO:0000305}
ERH_HUMAN	Enhancer of rudimentary homolog
ETFA_HUMAN	Electron transfer flavoprotein subunit alpha, mitochondrial
FAS_HUMAN	Fatty acid synthase
FBRL_HUMAN	rRNA 2'-O-methyltransferase fibrillarin
G3P_HUMAN	Glyceraldehyde-3-phosphate dehydrogenase
G6PD_HUMAN	Glucose-6-phosphate 1-dehydrogenase
GANAB_HUMAN	Neutral alpha-glucosidase AB
GAPD1_HUMAN	GTPase-activating protein and VPS9 domain-containing protein 1
GFPT1_HUMAN	Glutamine--fructose-6-phosphate aminotransferase [isomerizing] 1
GLRX5_HUMAN	Glutaredoxin-related protein 5, mitochondrial
GNAS1_HUMAN	Guanine nucleotide-binding protein G(s) subunit alpha isoforms XLas

GNAS2_HUMAN	Guanine nucleotide-binding protein G(s) subunit alpha isoforms short

GNAS3_HUMAN	Neuroendocrine secretory protein 55
GPDM_HUMAN	Glycerol-3-phosphate dehydrogenase, mitochondrial {ECO:0000305}
GPX4_HUMAN	Phospholipid hydroperoxide glutathione peroxidase
GSTK1_HUMAN	Glutathione S-transferase kappa 1
HACL2_HUMAN	2-hydroxyacyl-CoA lyase 2 {ECO:0000303 | PubMed:28289220}
HCD2_HUMAN	3-hydroxyacyl-CoA dehydrogenase type-2
HDGF_HUMAN	Hepatoma-derived growth factor
HDGR2_HUMAN	Hepatoma-derived growth factor-related protein 2
IDH3A_HUMAN	Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial
IDH3B_HUMAN	Isocitrate dehydrogenase [NAD] subunit beta, mitochondrial
IL7RA_HUMAN	Interleukin-7 receptor subunit alpha
ILF2_HUMAN	Interleukin enhancer-binding factor 2
IMDH2_HUMAN	Inosine-5'-monophosphate dehydrogenase 2 {ECO:0000255 | HAMAP-
INP5K_HUMAN	Inositol polyphosphate 5-phosphatase K {ECO:0000305}
IQGA1_HUMAN	Ras GTPase-activating-like protein IQGAP1
ITIH6_HUMAN	Inter-alpha-trypsin inhibitor heavy chain H6
LDHA_HUMAN	L-lactate dehydrogenase A chain
LDHB_HUMAN	L-lactate dehydrogenase B chain
MAGT1_HUMAN	Magnesium transporter protein 1
MBB1A_HUMAN	Myb-binding protein 1A
MET15_HUMAN	12S rRNA N4-methylcytidine (m4C) methyltransferase
MGST2_HUMAN	Microsomal glutathione S-transferase 2
MGST3_HUMAN	Microsomal glutathione S-transferase 3 {ECO:0000305}
MO4L1_HUMAN	Mortality factor 4-like protein 1
MPP6_HUMAN	MAGUK p55 subfamily member 6
MYPT1_HUMAN	Protein phosphatase 1 regulatory subunit 12A
NDUA2_HUMAN	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 2
NDUAA_HUMAN	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10,
NDUB4_HUMAN	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 4
NDUBA_HUMAN	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 10
NDUS2_HUMAN	NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial
NDUS6_HUMAN	NADH dehydrogenase [ubiquinone] iron-sulfur protein 6, mitochondrial
NDUS8_HUMAN	NADH dehydrogenase [ubiquinone] iron-sulfur protein 8, mitochondrial
NMT1_HUMAN	Glycylpeptide N-tetradecanoyltransferase 1
NSDHL_HUMAN	Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating
NT5D2_HUMAN	5'-nucleotidase domain-containing protein 2
OAT_HUMAN	Ornithine aminotransferase, mitochondrial
OST48_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa
P5CS_HUMAN	Delta-1-pyrroline-5-carboxylate synthase
PCAT1_HUMAN	Lysophosphatidylcholine acyltransferase 1
PCAT2_HUMAN	Lysophosphatidylcholine acyltransferase 2
PD2R_HUMAN	Prostaglandin D2 receptor
PDS5A_HUMAN	Sister chromatid cohesion protein PDS5 homolog A
PFKAM_HUMAN	ATP-dependent 6-phosphofructokinase, muscle type
PHOCN_HUMAN	MOB-like protein phocein
PI4KA_HUMAN	Phosphatidylinositol 4-kinase alpha

PIMT_HUMAN	Protein-L-isoaspartate(D-aspartate) O-methyltransferase

PPIL1_HUMAN	Peptidyl-prolyl cis-trans isomerase-like 1
PPIL2_HUMAN	RING-type E3 ubiquitin-protein ligase PPIL2 {ECO:0000305}
PRDX1_HUMAN	Peroxiredoxin-1
PRDX2_HUMAN	Peroxiredoxin-2
PRDX3_HUMAN	Thioredoxin-dependent peroxide reductase, mitochondrial
PRDX6_HUMAN	Peroxiredoxin-6
PSIP1_HUMAN	PC4 and SFRS1-interacting protein
PYR1_HUMAN	CAD protein
QCR10_HUMAN	Cytochrome b-c1 complex subunit 10
QPCT_HUMAN	Glutaminyl-peptide cyclotransferase
RABL6_HUMAN	Rab-like protein 6
RAGP1_HUMAN	Ran GTPase-activating protein 1
RAN_HUMAN	GTP-binding nuclear protein Ran
RASK_HUMAN	GTPase KRas
RDH14_HUMAN	Retinol dehydrogenase 14 {ECO:0000305}
RED_HUMAN	Protein Red {ECO:0000303 | PubMed:10216252}
RENR_HUMAN	Renin receptor
RPN1_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1
RPN2_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2
SAMH1_HUMAN	Deoxynucleoside triphosphate triphosphohydrolase SAMHD1
SCO1_HUMAN	Protein SCO1 homolog, mitochondrial
SERA_HUMAN	D-3-phosphoglycerate dehydrogenase
SERPH_HUMAN	Serpin H1
SF01_HUMAN	Splicing factor 1
SP16H_HUMAN	FACT complex subunit SPT16
SPTC1_HUMAN	Serine palmitoyltransferase 1
SSRD_HUMAN	Translocon-associated protein subunit delta
SSRG_HUMAN	Translocon-associated protein subunit gamma
STT3A_HUMAN	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit
SUCB2_HUMAN	Succinate--CoA ligase [GDP-forming] subunit beta, mitochondrial
TB10B_HUMAN	TBC1 domain family member 10B
TECR_HUMAN	Very-long-chain enoyl-CoA reductase {ECO:0000305}
THIL_HUMAN	Acetyl-CoA acetyltransferase, mitochondrial
THOC2_HUMAN	THO complex subunit 2
UBIA1_HUMAN	UbiA prenyltransferase domain-containing protein 1
UGGG1_HUMAN	UDP-glucose:glycoprotein glucosyltransferase 1
VMP1_HUMAN	Vacuole membrane protein 1
ZC3H4_HUMAN	Zinc finger CCCH domain-containing protein 4
ZC3HF_HUMAN	Zinc finger CCCH domain-containing protein 15
ZN593_HUMAN	Zinc finger protein 593