



The Lipocalin Apolipoprotein D Functional Portrait: A Systematic Review

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Apolipoprotein D is a chordate gene early originated in the Lipocalin protein family. Among other features, regulation of its expression in a wide variety of disease conditions in humans, as apparently unrelated as neurodegeneration or breast cancer, have called for attention on this gene. Also, its presence in different tissues, from blood to brain, and different subcellular locations, from HDL lipoparticles to the interior of lysosomes or the surface of extracellular vesicles, poses an interesting challenge in deciphering its physiological function: Is ApoD a moonlighting protein, serving different roles in different cellular compartments, tissues, or organisms? Or does it have a unique biochemical mechanism of action that accounts for such apparently diverse roles in different physiological situations? To answer these questions, we have performed a systematic review of all primary publications where ApoD properties have been investigated in chordates. We conclude that ApoD ligand binding in the Lipocalin pocket, combined with an antioxidant activity performed at the rim of the pocket are properties sufficient to explain ApoD association with different lipid-based structures, where its physiological function is better described as lipid-management than by long-range lipid-transport. Controlling the redox state of these lipid structures in particular subcellular locations or extracellular structures, ApoD is able to modulate an enormous array of apparently diverse processes in the organism, both in health and disease. The new picture emerging from these data should help to put the physiological role of ApoD in new contexts and to inspire well-focused future research.

Keywords: protein physiology, lipid peroxidation, membrane management, oxidative stress, lipoprotein particles, extracellular vesicles, lysosome, ApoD

INTRODUCTION

ApoD, identified and named almost 50 years ago, is a protein belonging to the Lipocalin family. Experimental research on ApoD has been accumulating, encouraged by numerous findings of ApoD relationship to many human diseases, from cancer to cardiovascular, metabolic or neurodegenerative conditions. This affluence of scientific reports has described many aspects of ApoD functional features, but a fundamental question remains to be responded: does ApoD moonlight, performing different biochemical functions in different biological contexts? or does it display a distinctive biochemical role that is being used in several physiological systems?

Along this half-a-century of ApoD research many reviews focused on this protein have been published. All of them are narrative in nature and many concentrate on specific details of ApoD

such as its relationship to disease, often underlining partial and not critically assessed views on many aspects of ApoD biology.

Aiming at answering the central questions posed above, we have performed a systematic review of all primary research published until January 2021 where ApoD properties have been investigated in the chordate phylum. Reports were tagged and classified according to their contributions to “molecular properties,” “gene data,” “regulation of expression,” “disease-related,” “cellular trafficking,” “tissue and organ function,” and “protein physiology.” The level and quality of experimental evidence were critically evaluated to try to identify cause-effect relationships. The picture emerging from this approach should help to understand the physiological role of ApoD and to inspire well-focused future research.

METHODS

To assess the current knowledge on the physiology of ApoD, we performed a literature review of primary publications in a systematic manner, searching the National Library of Medicine database with the PubMed engine (published until January 31, 2021). Using the search query “Apolipoprotein D” OR Apo-D OR ApoD, we recovered 851 entries from which 39 narrative reviews were excluded. Following a Title/Keywords screen, we selected 787 entries for further assessment. Following exclusion criteria we finally selected 417 articles reporting research on the Lipocalin ApoD in chordates as the final review sources, and stored them in a Zotero (v5.0.88) collection. The complete collection is available in the **Supplementary Tables 1–8**. According to the abstract information, articles were tagged with the following terms: Disease-related (DR, $n = 216$), Regulation of Expression (RE, $n = 186$), Gene Data (GD, $n = 37$), Molecular Properties (MP, $n = 59$), Cellular Trafficking (CT, $n = 33$), Tissue and Organ Function (TOF, $n = 36$), and Protein Physiology (PP, $n = 35$). **Figure 1** summarizes the review process workflow and outcome.

Following full article reading, we classified each tagged report with subheading terms to guide the organization of the review. We then performed an evaluation of the conclusions statements of each report based on technical and argumentative consistency, according to existing state-of-the-art standards and required experimental controls. In cases of uncertainty, experts in each field were contacted and asked for their objective judgement.

The following databases and *in silico* prediction platforms and tools were used in this work: ProtParam (<https://web.expasy.org/protparam/>); DeepLoc-1.0 (<http://www.cbs.dtu.dk/services/DeepLoc/>); Gene Ontology database (<http://geneontology.org/>);

Abbreviations: AA: arachidonic acid; BCF: breast cyst fluid; CSF: cerebrospinal fluid; E-3M2H: E-3-methyl-2-hexenoic acid; ECs: endothelial cells; EM: electron microscopy; EVs: extracellular vesicles; GuHCl: guanidine hydrochloride; HDX-MS: amide hydrogen-deuterium exchange mass spectrometry; LPC: lysophosphatidylcholine; LPS: bacterial lipopolysaccharide; MCs: blood vessel mural cells; MSCs: bone marrow stem cells; OS: oxidative stress; RER: rough endoplasmic reticulum; ROS: reactive oxygen species; SAXS: small-angle X-ray scattering; STR: short-tandem repeats; TG: triglycerides; UTRs: gene untranslated regions.

Human Protein Atlas (<https://www.proteinatlas.org/>); Mouse gene expression (<http://www.informatics.jax.org/expression.shtml>); miRNA database (mirdb.org). The ApoD multiple sequence alignment was generated with ClustalX2 (<http://www.clustal.org>), and the 3D structure of ApoD was visualized with ViewerLite 4.2 (<https://chemweb.ir/accelrys-viewerlite/>). A model of HApoD with sugars attached was built with GlyProt (<http://glycosciences.de/modeling/glyprot/php/main.php>).

RESULTS AND DISCUSSION

ApoD is an early-diverging member of the Lipocalin family, with its phylogenetic origins traced back to the origin of chordates (Ganfornina et al., 2000; Diez-Hermano et al., 2021). Furthermore, ApoD is the chordate Lipocalin most similar to those in other phyla. ApoD primary structure is well-conserved in chordates, as deduced from a multiple sequence alignment of 22 chordate species (**Figure 2A**; **Table 1**), with an average 67% identity (range: 55–90%) in mature protein sequence. An intriguing aspect of this alignment is a favored residue conservation of the region encompassing the first three β -strands of the protein primary structure (**Figure 2A**).

Molecular Properties

ApoD is a monodomain globular glycoprotein with two intramolecular disulfide bonds, which are molecular properties suitable for working in extracellular non-reducing milieus. ApoD shows an N-terminal signal peptide in all chordates that lets the nascent protein to enter the endoplasmic reticulum. The protein can therefore follow a canonical secretion pathway, and is glycosylated along this path.

Protein Parameters

Since early characterization studies of ApoD, its apparent electrophoretic mobility, density of ApoD-positive fractions and behavior in size exclusion chromatography, suggested the existence of post-translational modifications (glycosylation), a potential for oligomerization, and an association with lipids. The predicted acidic isoelectric point (**Table 1**) implicates that ApoD polypeptide would have its lowest solubility in aqueous-salt solutions at the pH of acidic organelles in the cell, while at neutral pH the ApoD polypeptide would show a net negative charge. ApoD displays four conserved cysteine residues, while an additional cysteine (Cys116) is present only in humans (absent even in other primates) and allows for inter-molecular disulfide bond formation (**Figures 2A, 3B,E**; **Table 1**).

References contributing to this section are listed in **Reference Collection 1, Supplementary Table 2**.

Protein Structure

The ApoD 3D crystal structure has been solved for the human protein after modification of several residues that rendered the protein prone to aggregation. The unique human Cys116 is close to one of the hydrophobic loops, and was also mutated to facilitate crystallization. The structure reveals a typical

Lipocalin fold (Skerra, 2000) composed of an eight-stranded β -barrel structure with an adjacent C-terminal α -helix. It has a closed end, and an open end with access to a pocket able to bind mostly hydrophobic ligands. Two intra-molecular disulfide bonds stabilize the structure. Three out of four loops at the barrel open-end are hydrophobic, making these regions candidate for interaction with hydrophobic surfaces, and contain residues relevant for ApoD antioxidant properties (see section Protein Physiology). Two N-glycosylation sites (Figures 2A, 3F) are located on the side and bottom of the calyx, away from the ligand-binding pocket opening. Figures 3A,B show a surface representation of the ApoD monomer structure with charged or hydrophobic surface highlighted in color. Other relevant residues are shown in Figures 3C–E.

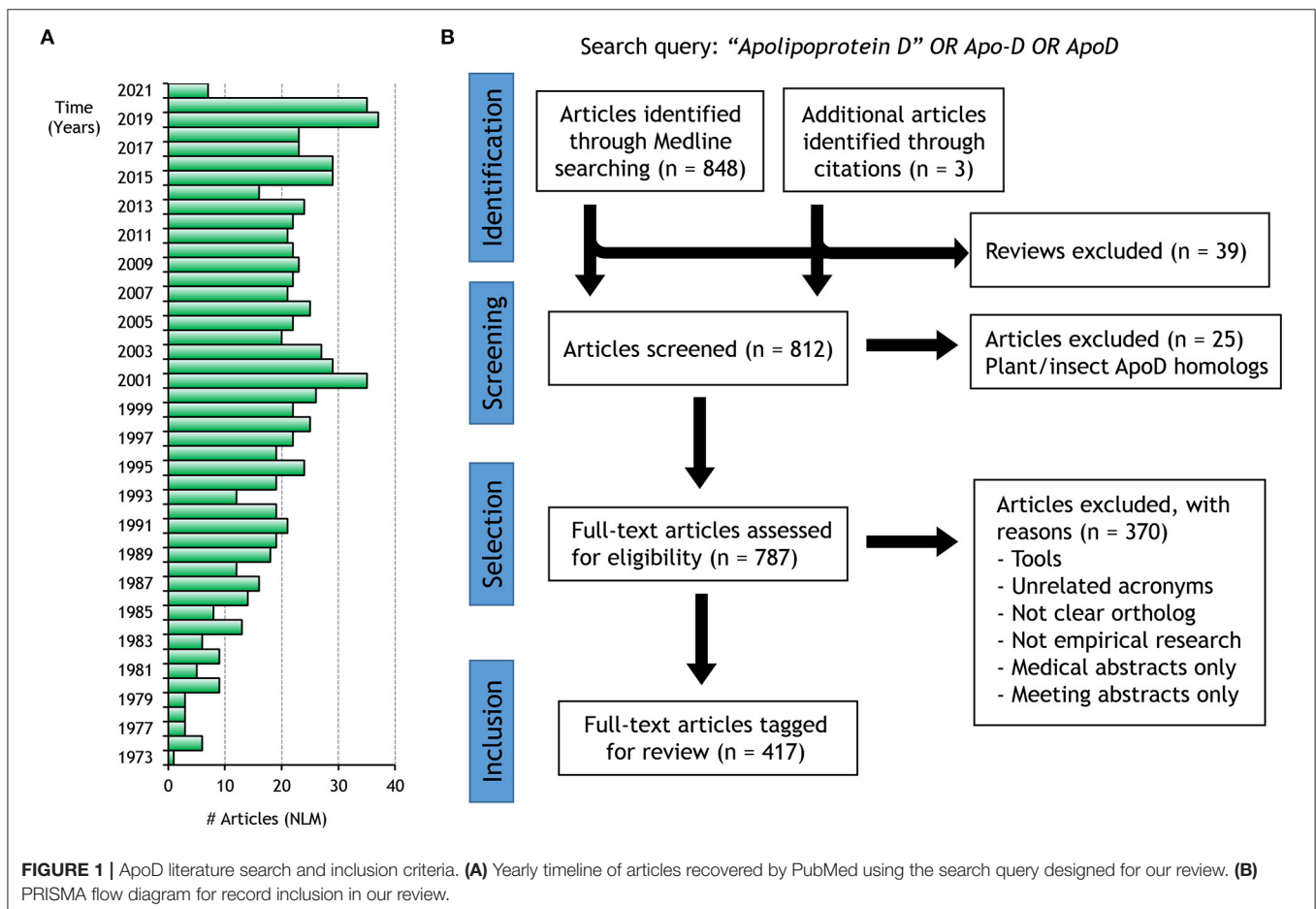
The presence of a ligand inside the pocket did not modify the general crystal structure of ApoD. When explored by amide hydrogen-deuterium exchange mass spectrometry (HDX-MS) or small-angle X-ray scattering (SAXS) in solution, interesting conformational changes elicited by ligand binding were detected, resulting in further ordering of the already stable Lipocalin fold. ApoD structure is also stable upon protein oxidation with H_2O_2 . Dynamic information extrapolated from the crystal structure has allowed further modeling of ApoD binding to small ligands, lipoprotein particles or membranes.

These studies help to understand a methionine-dependent lipid antioxidant mechanism (see below) and to study the influence of glycosylation on these functional properties. In addition, the ApoD monomer crystal structure, combined with modeled glycosylation conformations, was used to generate coherent models for the conformations of ApoD oligomers (Figures 3G,H) later confirmed experimentally (see below).

References contributing to this section are listed in Reference Collection 2, Supplementary Table 2.

Protein Glycosylation

As mentioned above, sugars were soon revealed to be linked to ApoD, with a relevant carbohydrate contribution (~15–22%) to its apparent molecular weight. Two asparagine sites were experimentally demonstrated to be glycosylated, and *in silico* studies of human ApoD revealed no interference of sugars with binding pocket access. Figure 3F depicts a model of the N-linked oligosaccharides. The Asn45 glycosylation site is conserved in birds and mammals, but the second glycosylation site shows variations in position (Figure 2A). In ApoD of human plasma, Asn45 contains primarily trisialo-triantennary oligosaccharides, and Asn78 contains fucosylated disialo-biantennary oligosaccharides. The presence of negatively



charged sialic acid in native ApoD sugar moiety contributes to its net negative charge in neutral pH environments.

Interesting variations of ApoD carbohydrate moiety have been reported between species (e.g., humans vs. other primates or rodents), between various tissues in a single species (brain tissue, cerebrospinal fluid, inner ear perilymph or plasma), within a tissue, or between health and disease conditions. Patterns of glycosylation have also been demonstrated to be sex-dependent (e.g., BCF in females, or axillary secretion in males). For example, less glycosylated forms of ApoD are present in mouse/human brain tissue compared to plasma, with differences in both terminal sialic acid and core N-linked oligosaccharides. A clear increase in α 2-3 sialoglycosylation of plasma ApoD distinguishes, with high sensitivity, children with Autism Spectrum Disorder

from healthy controls. Within a single tissue (cerebrospinal fluid; CSF) there is also variegation in the degree of ApoD sialylation. These variations generate size and charge heterogeneities with potential functional consequences worth exploring.

References contributing to this section are listed in **Reference Collection 3, Supplementary Table 2.**

Protein Oligomerization

Covalent and non-covalent homodimers and tetramers of ApoD have been detected in various experimental and biological systems. All studies of ApoD oligomerization have been focused so far on the human protein. Crystallization of bacterial recombinant human ApoD revealed that the protein tends to aggregate due to hydrophobic surface patches. This property

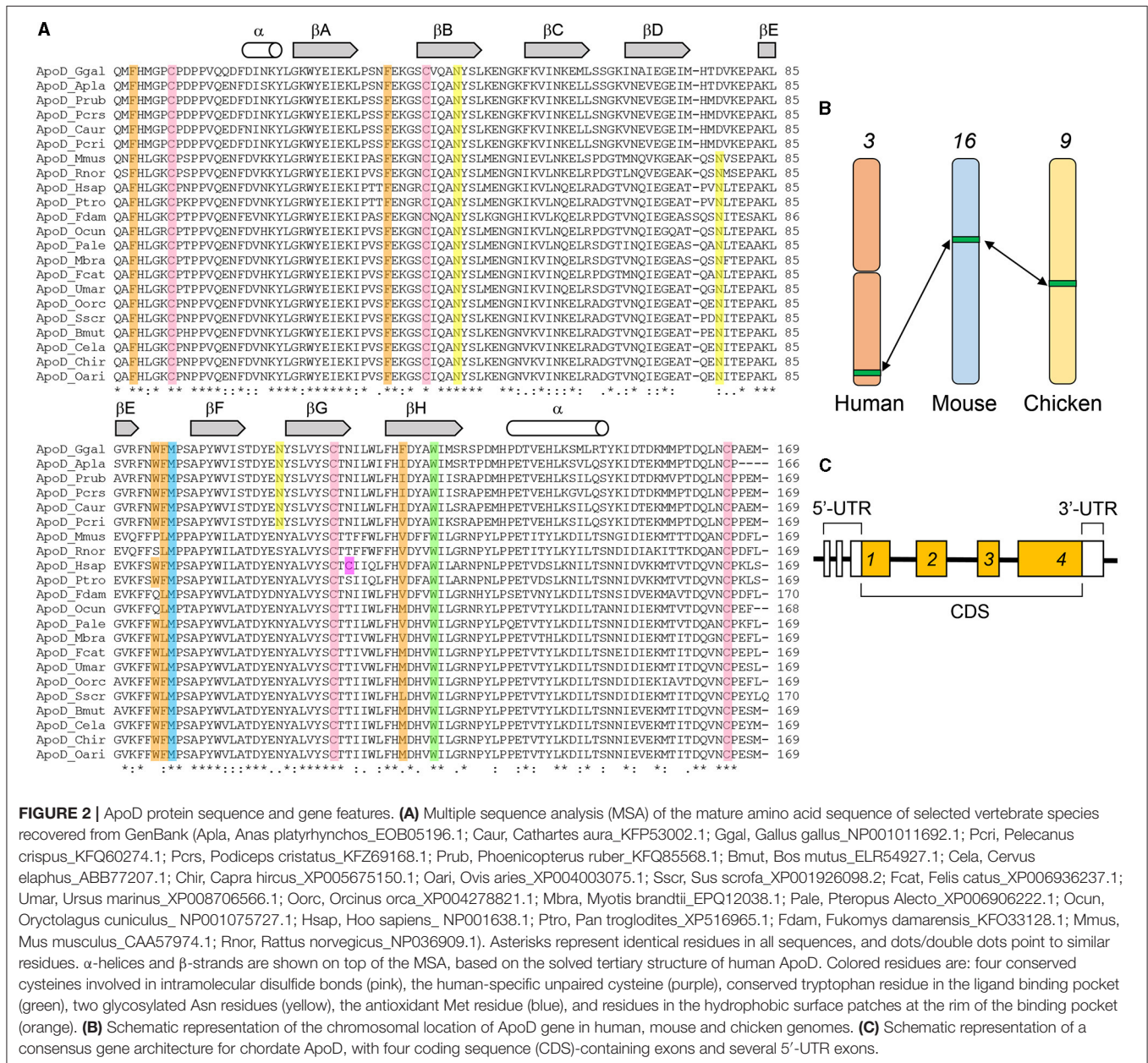


FIGURE 2 | ApoD protein sequence and gene features. **(A)** Multiple sequence analysis (MSA) of the mature amino acid sequence of selected vertebrate species recovered from GenBank (Apla, *Anas platyrhynchos*_EOB05196.1; Caur, *Cathartes aura*_KFP53002.1; Ggal, *Gallus gallus*_NP001011692.1; Pcri, *Pelecanus crispus*_KFQ60274.1; Pcrs, *Podiceps cristatus*_KFZ69168.1; Prub, *Phoenicopterus ruber*_KFQ85568.1; Bmut, *Bos mutus*_ELR54927.1; Cela, *Cervus elaphus*_ABB77207.1; Chir, *Capra hircus*_XP005675150.1; Oari, *Ovis aries*_XP004003075.1; Sscr, *Sus scrofa*_XP001926098.2; Fcat, *Felis catus*_XP006936237.1; Umar, *Ursus marinus*_XP008706566.1; Oorc, *Orcinus orca*_XP004278821.1; Mbra, *Myotis brandtii*_EPQ12038.1; Pale, *Pteropus Alecto*_XP006906222.1; Ocu, *Crytolagus culiculus*_NP00107527.1; Hsap, *Hoo sapiens*_NP001638.1; Ptro, *Pan troglodites*_XP516965.1; Fdam, *Fukomya damarensis*_KFO33128.1; Mmus, *Mus musculus*_CAA57974.1; Rnor, *Rattus norvegicus*_NP036909.1). Asterisks represent identical residues in all sequences, and dots/double dots point to similar residues. α -helices and β -strands are shown on top of the MSA, based on the solved tertiary structure of human ApoD. Colored residues are: four conserved cysteines involved in intramolecular disulfide bonds (pink), the human-specific unpaired cysteine (purple), conserved tryptophan residue in the ligand binding pocket (green), two glycosylated Asn residues (yellow), the antioxidant Met residue (blue), and residues in the hydrophobic surface patches at the rim of the binding pocket (orange). **(B)** Schematic representation of the chromosomal location of ApoD gene in human, mouse and chicken genomes. **(C)** Schematic representation of a consensus gene architecture for chordate ApoD, with four coding sequence (CDS)-containing exons and several 5'-UTR exons.

TABLE 1 | ApoD protein parameters.

| Acc. number | Class/order | Common name | Species name | # Residues mature protein | Theor. Mw | Theor. pl | # Disulfide bonds | # Cys | N-linked sugars | Met-93 | Mature protein sequence |
|---------------|--------------------------|---------------------|-----------------------------|---------------------------|-----------|-----------|-------------------|-------|-----------------|--------|---|
| EOB05196.1 | Aves/Anseriformes | Mallard | <i>Anas platyrhynchos</i> | 166 | 19,412 | 5.35 | 2 | 4 | 2 | Yes | QMFHMGPCDPPVQENFDISKYLKGYEIEKLPSSFEGKSCIQANYSKLENG KFKVINKELSSGKVNVEVEGEIMHTDVKPEAKLSVRFNWFMPSPAPYWWISTDY ENYSLVYSCTNIIWLFHIDYAWIMSRTPDMHPETVEHLKSVLQSYKIDTEKMM TDQLNCP |
| KFP53002.1 | Aves/Cathartiformes | Turkey vulture | <i>Cathartes aura</i> | 169 | 19,750 | 5.23 | 2 | 4 | 2 | Yes | QMFHMGPCDPPVQEDFNINKYLKGYEIEKLPSSFEGKSCIQANYSKLENG KFKVINKELSSGKVNVEVEGEIMHMDVKEPAKLGVRFNWFMPSPAPYWWISTD YENYSLVYSCTNIIWLFHIDYAWILSRAPEMHPETVEHLKSVLQSYKIDTEKMM PTDQLNCPAEM |
| NP001011692.1 | Aves/Galliformes | Chicken | <i>Gallus gallus</i> | 169 | 19,780 | 5.51 | 2 | 4 | 2 | Yes | QMFHMGPCDPPVQDQDFDINKYLKGYEIEKLPSSFEGKSCVQANYSKLENG GKFKVINKELSSGKINAIEGEIMHTDVKPEAKLGVRFNWFMPSPAPYWWISTDY ENYSLVYSCTNIIWLFHIDYAWIMSRSPDMHPDTEHLKSMRLTYKIDTDKM MPTDQLNCPAEM |
| KFQ60274.1 | Aves/Pelecaniformes | Dalmatian pelican | <i>Pelecanus crispus</i> | 169 | 19,778 | 5.23 | 2 | 4 | 2 | Yes | QMFHMGPCDPPVQEDFDINKYLKGYEIEKLPSSFEGKSCIQANYSKLENG KFKVINKELSSGKVNVEVEGEIMHMDVKEPAKLGVRFNWFMPSPAPYWWISTD YENYSLVYSCTNIIWLFHIDYAWIKSRAPEMHPETVEHLKSVLQSYKIDTEKMM PTDQLNCPPEM |
| KFZ69168.1 | Aves/Podicipediformes | Great crested grebe | <i>Podiceps cristatus</i> | 169 | 19,719 | 5.09 | 2 | 4 | 2 | Yes | QMFHMGPCDPPVQEDFDINKYLKGYEIEKLPSSFEGKSCIQANYSKLENG KFKVINKELSSGKVNVEVEGEIMHMDVKEPAKLGVRFNWFMPSPAPYWWISTD YENYSLVYSCTNIIWLFHIDYAWIISRAPEMHPETVEHLKSVLQSYKIDTDKMM PTDQLNCPPEM |
| KFQ85568.1 | Aves/Phoenicopteriformes | American flamingo | <i>Phoenicopterus ruber</i> | 169 | 19,731 | 5.08 | 2 | 4 | 2 | Yes | QMFHMGPCDPPVQEDFDINKYLKGYEIEKLPSSFEGKSCIQANYSKLENG KFKVINKELSSGKVNVEVEGEIMHMDVKEPAKLGVRFNWFMPSPAPYWWISTDY ENYSLVYSCTNIIWLFHIDYAWIISRAPDMHPETVEHLKSVLQSYKIDTDKMMVPT DQLNCPPEM |
| ELR54927.1 | Mammalia/Artiodactyla | Wild yak | <i>Bos mutus</i> | 169 | 19,466 | 5.07 | 2 | 4 | 2 | Yes | QAFHLGKCPHPPVQENFDVNYKLGWYIEKIPVSEFKGSCIQANYSKLENGN VKVINKELRADGTVNQIEGEATPENITEPAKLVKFFWFMPSPAPYWWLATDYEN YALVYSCTTIIWLFHMDHVVILGRNPYLPPEVTYTKDILTSNIEVEKMTITDQV NCPESM |
| ABB77207.1 | Mammalia/Artiodactyla | Red deer | <i>Cervus elaphus</i> | 169 | 19,564 | 4.96 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFDVNYKLGWYIEKIPVSEFKGSCIQANYSKLENGN VKVINKELRADGTVNQIEGEATQENITEPAKLVKFFWFMPSPAPYWWLATDYE NYALVYSCTTIIWLFHMDHVVILGRNPYLPPEVTYTKDILTSNIEVEKMTITD QVNCPEYM |
| XP005675150.1 | Mammalia/Artiodactyla | Goat | <i>Capra hircus</i> | 169 | 19,488 | 4.96 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFDVNYKLGWYIEKIPVSEFKGSCIQANYSKLENGN VKVINKELRADGTVNQIEGEATQENITEPAKLVKFFWFMPSPAPYWWLATDYE NYALVYSCTTIIWLFHMDHVVILGRNPYLPPEVTYTKDILTSNIEVEKMTITD QVNCPESM |
| XP004003075.1 | Mammalia/Artiodactyla | Sheep | <i>Ovis aries</i> | 169 | 19,488 | 4.96 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFDVNYKLGWYIEKIPVSEFKGSCIQANYSKLENGN VKVINKELRADGTVNQIEGEATQENITEPAKLVKFFWFMPSPAPYWWLATDYE NYALVYSCTTIIWLFHMDHVVILGRNPYLPPEVTYTKDILTSNIEVEKMTITD QVNCPESM |
| XP001926098.2 | Mammalia/Artiodactyla | Swine | <i>Sus scrofa</i> | 170 | 19,592 | 4.83 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFDVNYKLGWYIEKIPVSEFKGSCIQANYSKLENGN IKVINKELRADGTVNQIEGEATPDNITEPAKLVKFFWLMPSAPYWWLATDYE YALVYSCTTIIWLFHLDHVVILGRNPYLPPEVTYTKDILTSNDIDIEKMTITDQV NCPPEYLQ |
| XP006936237.1 | Mammalia/Carnivora | Domestic cat | <i>Felis catus</i> | 169 | 19,474 | 4.82 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFDVNYKLGWYIEKIPVSEFKGSCIQANYSKLENGN IKVINQELRPDGTVMNIEGEATQANLITEPAKLVKFFWLMPSAPYWWLATDYE NYALVYSCTTIIWLFHMDHVVILGRNPYLPPEVTYTKDILTSNEIDIEKMTITD QVNCPEPL |
| XP008706566.1 | Mammalia/Carnivora | Polar bear | <i>Ursus maritimus</i> | 169 | 19,371 | 4.71 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFDVNYKLGWYIEKIPVSEFKGSCIQANYSKLENGN IKVINQELRSDGTVMNIEGEATQANLITEPAKLVKFFWLMPSAPYWWLATDYE NYALVYSCTTIIWLFHMDHVVILGRNPYLPPEVTYTKDILTSNDIDIEKMTITD QVNCPESL |

(Continued)

TABLE 1 | Continued

| Acc. number | Class/order | Common name | Species name | # Residues mature protein | Theor. Mw | Theor. pl | # Disulfide bonds | # Cys | N-linked sugars | Met-93 | Mature protein sequence |
|---------------|---------------------|---------------------|------------------------------|---------------------------|---------------|-------------|-------------------|-------|-----------------|--------|---|
| XP004278821.1 | Mammalia/Cetacea | Killer whale | <i>Orcinus orca</i> | 169 | 19,500 | 4.74 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFDVNKYLGRWYEIEKIPVSFEKGSQIQANYSLMENG NIKVLNQLRADGTVNQIEGEATQENITEPAKLVKFFWFMPSAPYWWLATDYE NYALVYSCTTIWLFHMDHWILGRNPYLPPEVTYTKDILTSNDIDIEKIAVTDQ VNCPEFL |
| EPQ12038.1 | Mammalia/Chiroptera | Brandt's bat | <i>Myotis brandtii</i> | 169 | 19,380 | 4.9 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFDVNKYLGRWYEIEKIPVSFEKGSQIQANYSLMENG IKVINQELRSDGTVNQIEGEASQSNFTEPAKLVKFFWFMPSAPYWWLATDYE NYALVYSCTTIWLFHMDHWILGRNPYLPPEVTYTKDILTSNDIDIEKMTITD QGNCPDFL |
| XP006906222.1 | Mammalia/Chiroptera | Black flying fox | <i>Pteropus alecto</i> | 169 | 19,359 | 5.35 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFDVNKYLGRWYEIEKIPVSFEKGSQIQANYSLMENG IKVLNQLRSDGTINQIEGEASQANLTAAPKLVKFFWFMPSAPYWWLATDYK NYALVYSCTTIWLFHMDHWILGRNPYLPQETVYTKDILTSNDIDIEKMTVTD QANCPKFL |
| NP001075727.1 | Mammalia/Lagomorpha | Rabbit | <i>Oryctolagus cuniculus</i> | 168 | 19,433 | 5.15 | 2 | 4 | 2 | Yes | QAFHLGRCPTPPVQENFDVHKYLGRWYEIEKIPVSFEKGNQIQANYSLMENG NIKVLNQLRDPGTVNQIEGQATQSNLTPAKLVKFFQMLMPTAPYWWLATDY ENYALVYSCTTIWLFHMDHWILGRNRYLPPEVTYTKDILTANNIDIEKMTVT DQVNCPEF |
| NP001638.1 | Mammalia/Primates | Human | <i>Homo sapiens</i> | 169 | 19,303 | 5.2 | 2 | 5 | 2 | Yes | QAFHLGKCPNPPVQENFDVNKYLGRWYEIEKIPTTFENGRCIQANYSLMENG KIKVLNQLRDPGTVNQIEGEATPVNLTEPAKLVKFFWFMPSAPYWWLATDYE NYALVYSCTCIQLFHVDFAWILARNPNLPPEVTVDSLKNILTSNNIDVKKMTVTD QVNCPKLS |
| XP516965.1 | Mammalia/Primates | Chimpanzee | <i>Pan troglodytes</i> | 169 | 19,301 | 5.43 | 2 | 4 | 2 | Yes | QAFHLGKCPKPPVQENFDVNKYLGRWYEIEKIPTTFENGRCIQANYSLMENG KIKVLNQLRADGTVNQIEGEATPVNLTEPAKLVKFFWFMPSAPYWWLATDYE NYALVYSCTSIQLFHVDFAWILARNPNLPPEVTVDSLKNILTSNNIDVKKMTVTD QVNCPKLS |
| KFO33128.1 | Mammalia/Rodentia | Damaraland mole-rat | <i>Fukomys damarensis</i> | 170 | 19,458 | 5.16 | 2 | 4 | 2 | Yes | QAFHLGKCPNPPVQENFVNKYLGRWYEIEKIPASFEKGNQIQANYSLKNGG HIKVLNQLRDPGTVNQIEGEASSQSNITESAKLEVKFFQMLMPSAPYWWLATDY DNYALVYSCTNIWLFHVDVFWILGRNHYLPSETVNYLTKDILTSNSIDVEKMAVT DQVNCPDFL |
| CAA57974.1 | Mammalia/Rodentia | House mouse | <i>Mus musculus</i> | 169 | 19,478 | 4.71 | 2 | 4 | 2 | Yes | QNFHLGKCPSPVQENFDVKKYLGRWYEIEKIPASFEKGNQIQANYSLMENG NIEVLNKLSPDGTMNQVKGAKQSNVSEPAKLEVQFFPLMPPAPYWWLATDY ENYALVYSCTTFFWLFHVDVFWILGRNPYLPPEVTYTKDILTSNGIDIEKMTTDD QANCPDFL |
| NP036909.1 | Mammalia/Rodentia | Rat | <i>Rattus norvegicus</i> | 169 | 19,584 | 5.04 | 2 | 4 | 2 | Yes | QSFHLGKCPSPVQENFDVKKYLGRWYEIEKIPVSFEKGNQIQANYSLMENG NIKVLNQLRDPGTNLNQEVEGAKQSNMSEPAKLEVQFFSLMPPAPYWWLATDY ESYALVYSCTTFFWFFHVDVYWWILGRNPYLPPEVTYTKYLTSNDIDIAKITTKDQ ANCPDFL |
| | | | Min | 166 | 19,301 | 4.71 | | | | | |
| | | | Max | 170 | 19,780 | 5.51 | | | | | |
| | | | Average | 169 | 19,519 | 5.07 | | | | | |

In silico prediction (see section Methods) of molecular weight, pl and N-linked oligosaccharides, or experimentally tested (disulfide bonds and antioxidant Met-93 of human ApoD). ApoD from birds and mammals analyzed.

could promote self-association or association with lipid-based structures *in vivo* (Figures 3J,K).

Homodimers due to intermolecular disulfide bonds, evidenced by comparing electrophoretic mobility under reducing/non-reducing conditions, have been detected in urine and tear fluids. Experiments with sulfhydryl-trapping reagents during handling indicate that new disulfide bonds were not introduced along the experimental procedure. However, other forms of oligomerization are possible and compatible with these results, resulting from non-covalent stable binding between ApoD monomers. Figures 3G,H summarize the different forms of ApoD self-interaction.

Exposure of human ApoD to oxidized lipids promote dimerization and further oligomerization, in a way dependent on the oxidation state of particular methionine residues (Met93, see below), as demonstrated with recombinant ApoD, mutated at specific Met residues, and produced in a human cell line. Oxidation-dependent ApoD dimerization is resistant to guanidine hydrochloride (GuHCl) but not to urea, indicating that it is based on non-covalent intermolecular bonds. This property has allowed to detect ApoD dimers in specific brain regions of Alzheimer's disease patients (e.g., hippocampus, but not cerebellum) that also correlate with disease progression. In contrast, GuHCl extracts from healthy control brains show only monomeric forms of ApoD.

A tetrameric stable form of native ApoD in BCF, but not in plasma or CSF, has been demonstrated and characterized by multi-angle laser light scattering, analytical ultracentrifugation, HDX-MS and SAXS. Experimental data using progesterone as a ligand and the native ~100 kDa ApoD tetramer from BCF, supports a particular tetramer conformation among those predicted by molecular modeling, where the binding pocket opening is accessible and the sugar moieties do not interfere in the inter-subunit interface (Figure 3H). Monomers interact with each other through the C-terminal α -helix and three β -sheets in close proximity, while glycosylated surfaces and Met93 are exposed in the tetramer. Oligomerization does not preclude ligand binding, and is not significantly altered upon binding of various ligands (biliverdin, palmitic acid, progesterone and sphingomyelin) or by *in vitro* protein oxidation with H₂O₂. The putative contribution of intermolecular disulfide bonds in the tetramer (involving human Cys116) has not been explored.

References contributing to this section are listed in Reference Collection 4, Supplementary Table 2.

Small Ligand Binding

The ability to bind progesterone was a defining feature of the most abundant protein in BCF, therefore named progesterone-binding cyst protein (PBCP) or gross cystic disease fluid protein 24 (GCDFF-24). Later on, this protein was demonstrated to be identical to ApoD purified from plasma HDL particles. Ligand-protein interaction at the ApoD binding pocket induces conformational changes leading to a more ordered structure, but does not result in major structural changes or altered oligomerization. These dynamic changes, though subtle, might have implications for ApoD interactions with other proteins

or lipoprotein particles. Ligand binding reports are grouped in Reference Collections 5, 6, Supplementary Table 2.

Progesterone accommodation in the pocket involves a tryptophan residue heavily conserved in the Lipocalin family (Trp127 in human ApoD; Figures 2A, 3C), whose fluorescence (Ex. λ = 295 nm) changes upon binding. This element in the pocket makes Trp-fluorescence titration a valid method to test a variety of ligands for ApoD (Table 2). All *in vitro* ligand-binding experiments have been performed with the human protein, using either recombinant ApoD (expressed by bacteria or eukaryotic cells) or native protein purified from BCF or plasma HDL. Arachidonic acid (AA) shows the highest affinity, while various AA derivatives (e.g., prostaglandins, 12-HETE or 5,15-diHETE) show no binding by Trp-fluorescence titration.

Cholesterol, a reasonable candidate because of its high presence in plasma lipoprotein particles, has been repeatedly tested, and reported to have no binding, or a very low affinity one (Table 2). A series of works (Reference Collection 6, Supplementary Table 2) demonstrate that ApoD has no cholesterol-transfer activity, a hypothesis originated by ApoD co-purification with lecithin-cholesterol acyltransferase (LCAT), whose activity is in fact modulated by ApoD (see section Protein Physiology) by a mechanism discarding ApoD as a cholesterol provider for LCAT.

Only one ligand has been identified bound to ApoD and extracted from the protein after purification from a natural source. E-3-methyl-2-hexenoic acid (E-3M2H), a male axillary precursor of odorants, was identified by gas chromatography-mass spectrometry (GC/MS) after temperature/pH switch and chloroform extraction from purified ApoD.

Interestingly, various ligands (e.g., bilirubin or E-3M2H) whose interaction with ApoD has been demonstrated by a different technique, do not alter Trp-fluorescence, raising the possibility of other sites of interaction. Molecular dynamics simulations infer flexible binding of oxidized derivatives of AA (5s-, 12s-, and 15s-HpETE) around the conserved Met93 at one of the hydrophobic patches at the entrance of the pocket. This particular form of lipoperoxide binding to ApoD is not expected to produce changes in fluorescence of Trp-127, located at the bottom of the binding pocket. A proof of interaction is experimentally supported by site-directed mutagenesis combined with HPLC-detection of reduced lipids (HETEs) after exposure to ApoD. This interaction underlies the antioxidant activity of ApoD (see below). Figure 3I summarizes in cartoon form this new view of small ligand-binding sites of ApoD, not restricted to the Lipocalin pocket.

Protein-Protein Interactions

Interactions of ApoD to higher-order lipid structures, like lipoprotein particles or cellular membranes, are particularly relevant since they determine the range of sites and biological contexts where ApoD function can be performed. They might depend on protein-protein or protein-lipid contacts.

As mentioned above, co-purification of ApoD with LCAT might indicate the potential for a protein-protein interaction

in nascent HDL particles, but a clear demonstration of ApoD-LCAT complex is not available. In contrast, a clear protein-protein interaction does account for human ApoD presence in HDL particles. An intermolecular disulfide link between ApoD Cys116 and ApoA-II Cys6 has been demonstrated by peptide digestion followed by sequencing and mass spectrometry (MS). This interaction, however, is an exclusive property of human ApoD due to its unique unpaired cysteine.

A putative disulfide-linked ApoD-ApoB100 complex was also proposed, but evidence is based on predictions from electrophoretic mobility in reducing/non-reducing conditions and immunoblot detection with anti-ApoD antibodies only, or with antibodies raised against LDL particles. An almost full characterization of 23 out of 25 cysteine residues in ApoB-100 by MS-analysis and peptide sequencing found no bonds with ApoD (Yang et al., 1990), strongly arguing against a disulfide-mediated interaction. Alternative mechanisms of ApoD interactions with plasma lipoprotein particles are therefore open to consideration.

Other potential interactions of ApoD have been explored with classic two-hybrid systems, where protein-protein contact takes place in the cell nuclei or cytoplasm, both requiring ectopic expression of ApoD in non-native biological compartments unsuitable for disulfide linked proteins (see sections Protein Structure and Cellular Trafficking). Alternatively, co-immunoprecipitation *in vitro* with or without crosslinking agents has been a method of choice. Using these approaches, ApoD has been proposed to interact with the extracellular glycoprotein Osteopontin (OPN), the intracellular domain of the Leptin Receptor (OB-Rb), the transmembrane glycoprotein Basigin (BSG), and the Scavenger receptor class B type 1 (SRB1).

The weak interaction reported between ApoD and the intracellular domain of OB-Rb, combined with its presumed topology within the cell, should discard this finding as a biologically relevant interaction for ApoD unless it is replicated. For membrane proteins such as BSG and SRB1, proposed as putative membrane receptors for ApoD, co-localization by

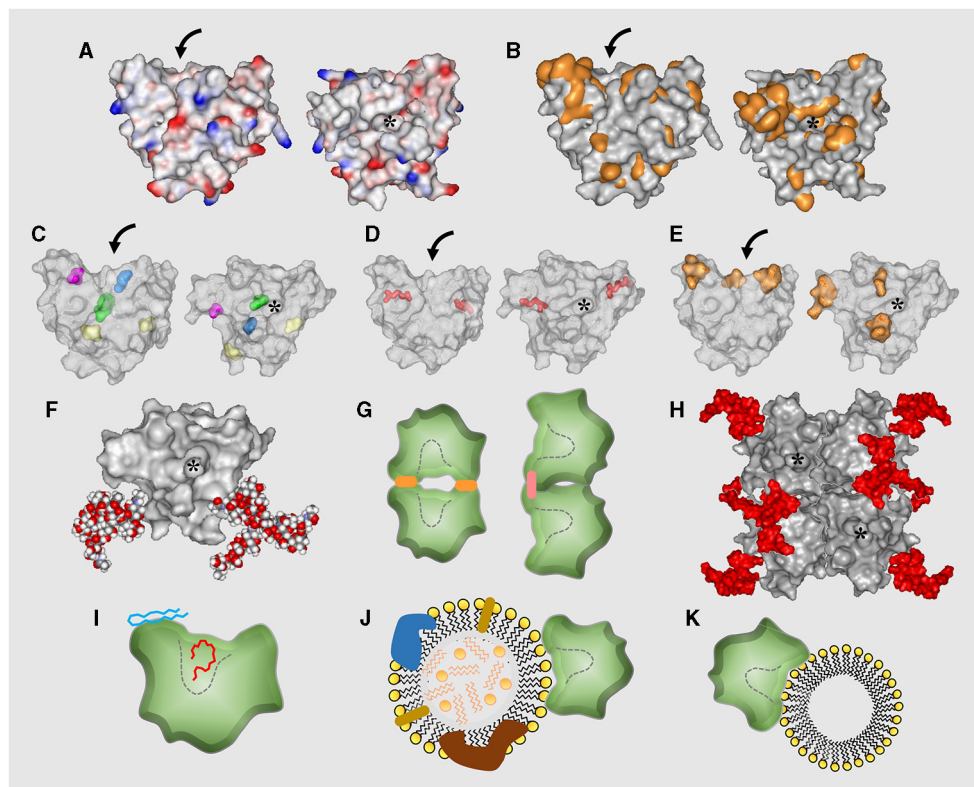


FIGURE 3 | Molecular features of ApoD. **(A,B)** Graycolored space-filled views of the human ApoD tertiary structure (modelled from PDB ID:2HZQ) showing charged residues in A (positive, red; negative, blue) and hydrophobic residues in B (orange). Side view of the β -barrel (left image; curved arrows point to the pocket entrance) and top view (right image) looking into the hydrophobic pocket (asterisk). **(C–E)** Human ApoD (PDB ID:2HZQ) side and top views with highlighted relevant residues. Colored residues in **(C)** are the antioxidant Met93 (blue); the human-specific unpaired Cys116 (purple); the conserved ligand binding pocket Trp127 (green); and the two glycosylated Asn45/Asn78 (yellow). Pink-colored residues in D are the four cysteines forming two intramolecular disulfide bonds. Orange-colored residues in E are those forming three hydrophobic loops around the pocket entrance. **(F)** Space-filled view of human ApoD with reported oligosaccharides linked to Asn45 and Asn78, as modelled by GlyProt (see Methods). **(G)** Cartoon representations of human ApoD dimers formed by hydrophobic patches (orange) or by intermolecular Cys116 disulfide bonds (pink). Variations of the particular configuration shown are possible. Dashed lines delineate the ligand pocket. **(H)** Representation of the best supported tetrameric structure of human ApoD found in BCF. Asterisks mark the ligand pocket accessible in all subunits (two facing back). Oligosaccharides shown in red. **(I)** Cartoon illustration of a side view of human ApoD with AA (red) and HpETE (blue) positioned into the hydrophobic pocket (marked by a dashed line) and interacting with the Met93-containing hydrophobic patch respectively. **(J,K)** Cartoon illustration of human ApoD interacting with higher-order lipid structures via the hydrophobic patches at rim of the pocket; **(J)** HDL particle; **(K)** Unilamellar vesicle (liposome).

TABLE 2 | ApoD ligand binding *in vitro* assays.

| Ligand | Apparent Kd (μM) | Apparent Kd (μM) | Apparent Kd (μM) | Apparent Kd (μM) | Apparent Kd (μM) |
|----------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| References | Morais Cabral et al., 1995 | Vogt and Skerra, 2001 | Breustedt et al., 2006 | Ruiz et al., 2013 | García-Mateo et al., 2014 |
| All- <i>trans</i> -retinoic acid | | | 2.8 | 4.0 \pm 2.6 | |
| Retinol | | | 0.08 \pm 0.04 | 0.2 \pm 0.1 | |
| Arachidonic acid | 0.006 \pm 0.004 | 3.2 \pm 0.2 | | | |
| 2-Arachidonoyl-glycerol | | | | n.d. | |
| 12-HETE | n.d. | | | | |
| 5,15-diHETE | n.d. | | | | |
| Prostaglandins (D2, E1, F2a) | n.d. | | | | |
| Lysophosphatidylcholine | | | | | 1.13 \pm 0.05 |
| Linoleic acid | n.d. | | | | |
| Oleic acid | n.d. | | | | |
| Palmitic acid | n.d. | | | 3.3 \pm 0.6 | |
| Palmitoyl sphingomyelin | | | | 1.3 \pm 0.5 | |
| Cholesterol | n.d. | | | n.d. | |
| Pregnenolone | | n.d. | | | |
| Progesterone | 0.4 \pm 0.1 | 1.7 \pm 0.02 | | | |
| Dihydrotestosterone | | n.d. | | | |
| β -Estradiol | | | | n.d. | |
| E-3M2H | | n.d. | | | |
| Anandamide | | | | 1.6 \pm 1.3 | |
| Bilirubin | 2.6 \pm 0.5 | n.d. | | | |

Ligands tested by tryptophan fluorescence-based assays *in vitro*. Apparent Kd (μM) average \pm SD are shown. "n.d." = no binding detected.

confocal imaging is often used as additional evidence. However, protein-complexes are below the resolution of standard co-labeling techniques, and methods relying on distance-dependent energy transfer, super-resolution or immunoelectron microscopy would be desirable as further evidence in relevant *in vivo* conditions. Other candidate ApoD receptors (LDLR and CXCR-4) are predicted from physiological contexts, where downstream consequences of ApoD exposure are modified by antagonists of these receptors. However, a direct interaction with these receptors has not been explored.

References contributing to this section are listed in **Reference Collection 7, Supplementary Table 2**.

Binding to Lipid-Rich Structures

The presence of ApoD in plasma lipoprotein particles lies at the base of its discovery in humans. ApoD was initially visualized as a "thin-line" polypeptide in immune-double diffusion analyses of plasma HDL particles, and was then identified as a low-abundance component of HDL₃ particles (defined as small-dense HDLs, $d = 1.12\text{--}1.27$ g/ml). Analysis of HDLs separated by electrophoretic mobility in non-denaturing PAGE followed by in-gel trypsinization, identified ApoD within the HDL- $\alpha 2$ type, in a 1:100 ratio with respect to ApoA-I. The presence of ApoD in HDLs has been confirmed also in human CSF and in baboon and mouse plasma. Additionally, plasma ApoB-100 positive LDL particles contain ApoD as well, but at lower concentrations (~ 8 ng ApoD/ μg LDL vs. ~ 69 ng ApoD/ μg HDL₃). The generalized interaction with different lipoparticles in several species suggests that ApoD-lipoparticle interactions must rely

on a mechanism independent of ApoD-ApoA-II disulfide bond, a human HDL rarity. The fact that ApoD-LDL interaction is prevented by detergents, and do not take place with recombinant ApoD where hydrophobic surface residues have been mutated (to favor crystallization), suggests a hydrophobicity-dependent ApoD-lipoparticle binding mechanism (**Figure 3J**).

Also, direct binding of ApoD to unilamellar phospholipid vesicles (liposomes) further demonstrates its ability to bind to lipidic structures without requiring a protein-protein interaction. These unilamellar vesicles represent a simplified version of the outer phospholipid layer of HDLs, LDLs or a membrane bilayer (**Figure 3K**). In addition, ApoD has recently been identified in extracellular vesicles, characterized by the presence of CD81, CD63, and flotillin-1, and a density of $d = 1.17\text{--}1.23$ g/ml. The hydrophobic patches of ApoD at the entrance of the binding pocket are the likely site of interaction with liposomes or biological membranes, as indicated by experiments combining ApoD capacity to reduce oxidized liposomes with mutagenesis of Met residues that in fact contribute to the hydrophobicity of those patches.

The knowledge accrued on ApoD protein structure, its glycosylation and oligomerization properties, as well as its interactions with small ligands and other lipidic structures are relevant for its physiological roles in lipid management, and should help to get a global picture of how these molecular properties are put to work in various physiological contexts.

References contributing to this section are listed in **Reference Collection 8, Supplementary Table 2**.

Gene Data and Genomic Properties

Chromosomal Position and Gene Structure

The gene coding for ApoD locates in an autosomic chromosome that shows ample synteny in chordates (Sanchez et al., 2006), reflecting a strong evolutionary conservation of this genomic region (**Figure 2B**). The ApoD gene shows a standard metazoan exon-intron architecture, with a coding sequence interspersed in four exons that is conserved in chordates (Sánchez et al., 2003). Moreover, the gene upstream and downstream untranslated regions (UTRs) are also composed of several exons, mainly in the 5'-UTR, a property well-preserved in mammals (Mejias et al., 2019) (**Figure 2C**).

References contributing to this section are listed in **Reference Collection 9, Supplementary Table 3**.

Transcriptional Control of Gene Expression

The promoter region and elements controlling the expression of ApoD have been studied in detail for the human gene. The human promoter shows a canonic TATA-box upstream of the transcription start site. Several promoter elements and nuclear factors have been predicted to potentially regulate ApoD transcription in a number of organisms.

Experimental proof of a regulatory potential of human ApoD has been gathered for SRE1, AP-1, APR-3, NFκB, PARP1, HnRNP-U, and APEX-1 in cultured cells subjected to inflammation (LPS) and metabolic stress (serum deprivation). Also, the transactivator TAp73 mediates ApoD expression upon cell differentiation. The mouse ApoD promoter region has been recently assessed experimentally, and an alternative promoter region has been related to OS-induced ApoD expression.

DNA methylation, inferred from the CpG content of the gene promoter region, is also an important regulatory mechanism for ApoD transcription, with an inverse relationship between level of DNA methylation and ApoD gene transcription. This gene regulation mechanism has been shown in different physiological or pathological contexts: in esophageal, colorectal and astrocytic cancers, in the expression profile defining Th17 lymphocytes, and for the androgen receptor-response in male sexual development.

References contributing to this section are listed in **Reference Collection 10, Supplementary Table 3**.

Post-transcriptional and Translational Control of Gene Expression

The mRNA 3'-UTR is known to influence its stability and translation efficiency. ApoD 3'-UTRs show a high degree of conservation in mammals, and display shorter lengths and higher G+C content than those observed in average mammalian gene UTRs. These differences have been proposed to underlie a tight regulatory control of ApoD translation. In this context, a number of miRNAs have been predicted to control ApoD translation, possibly by binding to the 3'-UTR. Some of these miRNAs, like miR-229b-3p, miR-423-3p, and miR-490-3p, have been experimentally tested and implicated in the post-transcriptional downregulation of ApoD expression in rat male reproductive system upon metabolic dysfunction.

The 5'-UTR of ApoD also presents relevant properties for the regulation of ApoD expression. It is rich in short-tandem

repeats (STR), specifically in primates. Long stretches of STRs are predicted to affect transcription and translation, which might have contributed to the neurodevelopmental changes that underlie primate evolution. Furthermore, mammalian ApoD genes show several alternative 5'-UTRs forms, possibly arising from alternative splicing. The alternative 5'-UTRs of the mouse ApoD gene have been experimentally tested and shown to underlie differential protein expression in several mouse tissues, with a particular 5'-UTR variant being strongly induced upon OS. Moreover, *in silico* analyses of these 5'-UTR variants in mouse and human ApoD show upstream initiation codons, upstream open reading frames, and predicted secondary structures that suggest a tight control on ApoD gene expression.

References contributing to this section are listed in **Reference Collection 11, Supplementary Table 3**.

Gene Polymorphisms

In terms of genetic variation for the ApoD gene, over 4,600 variants have been found in the GRCH38.p12 (annotation Release 109) assembly of the human genome, while 187 are reported in the short variants (dbSNP) and structural variants (dbVar) databases. Six variants that involve missense, intron insertions and 3'-UTR insertions, are predicted to involve molecular consequences. Some of these variants have been linked with variable support to human cancer, metabolic or neurological diseases (see **Supplementary Table 18**, and section ApoD-Disease Relationships), but a final proof of their clinical significance is currently missing.

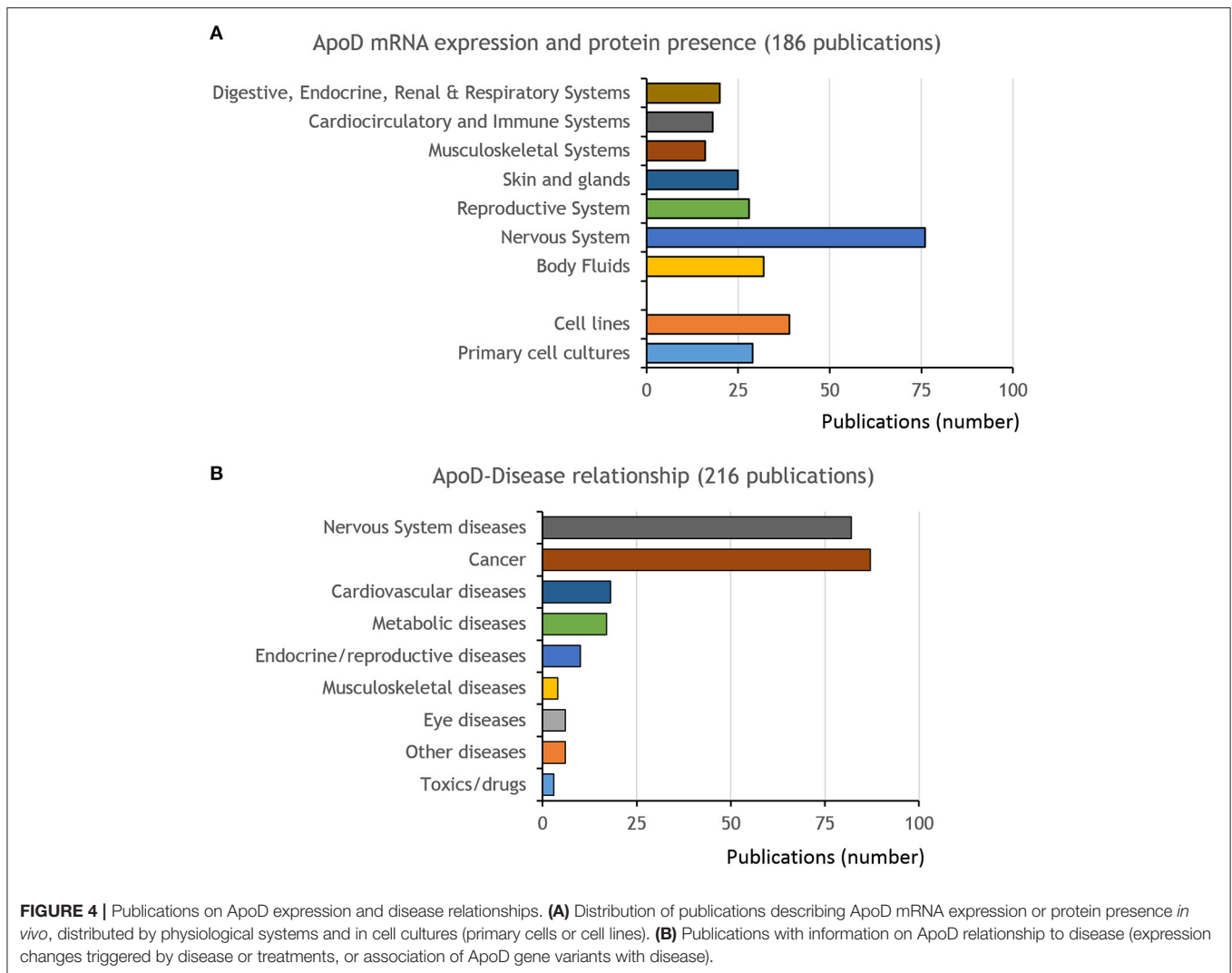
References contributing to this section are listed in **Reference Collection 12, Supplementary Table 3**.

Regulation of Expression

A total of 186 primary publications (**Figure 4A**) were labeled with the *regulation of expression* (RE) tag for this systematic review (details recorded in **Supplementary Tables 9–17**). We combined our analysis with current data compiled in human and mouse expression atlases (see Methods section; **Supplementary Figures 1, 2**).

ApoD in Body Fluids

Since its discovery in plasma HDL particles, ApoD protein and/or mRNA have been found in almost every organ, tissue or fluid. In addition to plasma, ApoD protein is present CSF, perilymph, urine, and secretions from exocrine glands (sweat, tears and mammary secretions) (**Supplementary Table 9**). The cellular origin of ApoD protein in each of these body fluids is not fully elucidated. With the exception of Th17 lymphocytes, blood cells in general do not express ApoD mRNA, and liver and intestine (major sites of HDL biogenesis) are among the ApoD low-expressing tissues both in humans and mice (**Supplementary Figures 1, 2**). Plasma ApoD protein (~128 mg/l) is approximately 25 times the concentration of CSF ApoD (~5 mg/l) in healthy adult men, and they are uncorrelated, suggesting that a separate pool of ApoD protein is managed in these barrier-separated compartments.



Avian egg fluids are also rich in ApoD, with the interesting property that egg white ApoD positively correlates with egg freshness.

References contributing to this section are listed in **Reference Collection 13, Supplementary Table 4**.

Tissue and Cellular Expression Patterns and Response to Stimuli

The analysis of tissue expression pattern leads to a general conclusion: in spite of its wide distribution, ApoD is never ubiquitously expressed, never in all cell types in a tissue, or at all times in a given cell type. ApoD is expressed in most tissues with a salt-and-pepper spatiotemporal pattern, suggesting a fine control that depends on particular physiological cell states. Furthermore, all tissues bear ApoD-expressing cells and cells able to endocytose ApoD protein from the extracellular milieu (see section Cellular Trafficking). These expression features, along with ApoD being a very stable protein, result in a high protein abundance when measured in high-throughput analyses, and in a lack of exact fit between mRNA and protein

expression in a given tissue or cell (**Supplementary Figure 1; Reference Collections 14–16; Supplementary Table 4**). While tissues as the female breast present high levels of ApoD mRNA and protein, organs like the liver show high abundance of ApoD protein, but barely detectable ApoD mRNA both in human and mice. At the other end of the spectrum, blood cells and immune system-related organs are among those with low levels or no expression of ApoD, either mRNA or protein.

Organs and tissues involved in both male and female reproductive physiology express ApoD (**Supplementary Table 10**). The high expression of ApoD in breast has been located to the glandular epithelium (**Supplementary Figure 1**), and breast cysts accumulate high amounts of ApoD protein, making BCF a useful experimental source of native ApoD protein. ApoD mRNA is detected at all stages of the spermatogenesis process in testis and in ovarian theca cells. Along the female cycle, stromal and epithelial cells of the endometrium express ApoD mRNA and protein during the secretory phase. ApoD is also expressed during

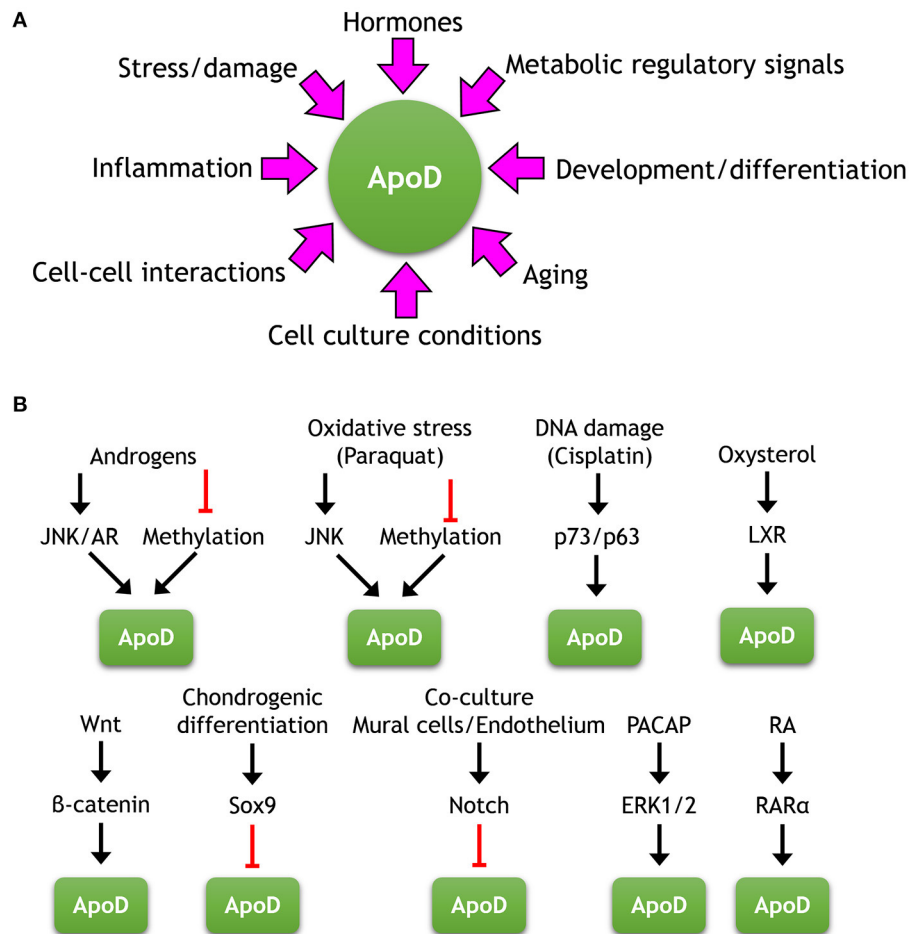


FIGURE 5 | Factors and pathways regulating the expression of ApoD. **(A)** Diverse stimuli regulate ApoD expression in a variety of cells and physiological conditions. **(B)** Summary of upstream regulatory pathways regulating ApoD expression where elements of the signaling cascade have been identified.

corpus luteum maturation in the ovary. Gestation alters ApoD abundance in plasma as well (**Supplementary Table 9**), with a decrease during a healthy pregnancy followed by a fast recovery if the mother breastfeeds her baby. ApoD expression in breast secretions and skin is also altered upon establishment of menopause.

These temporal patterns of expression are due to hormone regulation, as demonstrated by both *in vivo* and *in vitro* studies (**Supplementary Tables 10, 16, 17**; **Reference Collection 17**). Upregulation of ApoD by androgens is well documented in different preparations like breast explants, male genital fibroblasts or primary epithelial cells from male axillary apocrine glands. This regulation is mediated by nuclear androgen receptor (AR), and ApoD is being used as an AR activity assay (**Figure 5B**). Estrogens and progesterone, alone or in combination, also change ApoD expression in several experimental settings, with more variation in the final outcome depending on cell type (e.g., breast cancer cell lines up-regulate ApoD upon exposure to 17β -estradiol, while prostate cancer cell lines down-regulate it, **Supplementary Table 17**). Sex hormone-regulation of ApoD is also present in birds, in the context of oviposition cycles or

egg fertilization, thus representing relevant biological stimuli for ApoD spatiotemporal regulation throughout evolution (**Figure 5, Supplementary Table 10**).

Expression in the nervous system (**Supplementary Table 11**) has been amply explored for ApoD, with primary publications doubling those devoted to other tissues or systems (**Figure 4**). All evidences support a prominent and consistent ApoD expression in the nervous system, where myelinating glial cells (oligodendrocytes and Schwann cells) constitute the main sites of expression in control conditions, followed by a more disseminated expression in astrocytes. ApoD protein abundance in the nervous system is accounted for by the fact that ApoD associates to myelin itself, a structure representing a large proportion of the vertebrate nervous system volume. As mentioned above, only subsets of cells express ApoD at a given time or location for each cell type (**Reference Collection 16, Supplementary Table 4**).

In addition to glial cells, ApoD has been found in meninges and the vascular system of the nervous system (**Supplementary Table 11**), particularly in pial and perivascular cells (mural cells or pericytes) associated to the capillary beds.

During mouse embryogenesis, ApoD has been detected in both pericytes and endothelial cells, and mRNA expression in the latter is under the control of Wnt/ β -catenin signaling during the time interval of blood-brain-barrier formation (Figure 5B). ApoD-positive pericytes and other perivascular cells are also reported in the adult nervous system. RNAseq analyses of acutely isolated cortical cells show endothelial cells as second to myelinating oligodendrocytes in ApoD enrichment.

Although neuronal expression has been subject to debate (Supplementary Table 11), unambiguous detection of ApoD mRNA in neurons has been reported only in the developing brain. In contrast, detection of ApoD protein in some neurons has been reported at various ages in healthy control situations, while this finding is more abundant upon aging or disease. Neuronal uptake of ApoD upon disease has a certain degree of specificity. It is frequently found in the brain of Alzheimer's, but not in Parkinson's disease patients. Animal models of brain traumatic injury, stroke and Niemann-Pick type A disease do show neurons that have internalized ApoD protein, while they are not found in the Niemann-Pick type C mouse model. Transfer of ApoD from astroglial cells to neurons has been demonstrated in cell culture preparations, and shown to be mediated by extracellular vesicles (Supplementary Table 17; see section Cellular Trafficking).

A well-established fact with strong support from different studies is that ApoD expression increases throughout brain aging (Reference Collection 18, Supplementary Tables 4, 11), a pattern conserved in several species analyzed with just one exception: a study documenting a decrease in ApoD mRNA in the aging avian hippocampus. A higher ApoD expression in cortex and brainstem in comparison with hippocampus or cerebellum are well-supported regional differences within the brain (Supplementary Table 11). In the highly-expressing prefrontal cortex, the increase of ApoD mRNA and protein throughout life positively correlates with proteins involved in antioxidant defense.

The expression data obtained from healthy individuals is coherent with an ApoD gene response to diverse experimental stress or injury paradigms (Reference Collections 19–20, Supplementary Table 4) that include oxidative stress (OS), peripheral nerve or traumatic brain injury, kainate excitotoxicity, damage by middle cerebral artery occlusion or by viral infection and experimental inflammation. All of the above results in increased ApoD expression *in vivo*. This ApoD stress response is mostly, but not exclusively, documented in the nervous system (e.g., OS-triggered upregulation is also observed in the cardiovascular system). These patterns of response can be extended to the many disease situations reviewed in section ApoD-Disease Relationships. In addition to the abundant correlative data from human diseases, experiments in animal models of disease analyzed *in vivo*, primary cell cultures and cell lines support a major conclusion: ApoD is a key player in the endogenous response to a variety of potentially harmful stimuli. The damage and stress responsive p73/p63 and JNK pathways have been demonstrated to up-regulate ApoD (Supplementary Tables 16, 17 and Figure 5), while the particular signaling cascades regulating ApoD upon other

stress or inflammation inducers (e.g., H₂O₂, UV light or LPS) remains to be elucidated. Not all stressful conditions trigger ApoD expression (Supplementary Table 17), underscoring the specificity of pathways regulating ApoD (Figure 5). Moreover, a fine regulation of ApoD upon OS seems necessary, since it involves various non-exclusive mechanisms like DNA demethylation, the use of alternative promoters or 5'-UTR specific mRNA variants (see section Gene Data and Genomic Properties).

Nutritional and metabolic states also regulate ApoD expression (Reference Collection 21, Supplementary Table 4), and ApoD upregulation under caloric restriction or ADCY5 loss-of-function seems to be part of a common signature leading to lifespan extension. Curiously, these results derived from *in vivo* studies agree with ApoD upregulation upon serum starvation in cell culture systems (Reference Collection 22, Supplementary Table 4). New studies on how metabolic switches can modulate ApoD in different contexts, and searching for the specific signaling pathways that trigger ApoD expression are therefore valuable. A particular lipid-managing pathway is known to control ApoD expression: ApoD is a target gene for LXR in liver, skeletal muscle, adipocytes and endothelial cells, thus becoming part of the response to oxysterol stimulation.

Pathways involved in development and cell differentiation are also known to regulate ApoD expression (Reference Collection 23; Supplementary Tables 4, 16, 17). In addition to its regulation by the Wnt/ β -catenin pathway mentioned above, ApoD is downstream of Sox9 during chondrogenic differentiation, and of PACAP/Erk signaling during adipocyte differentiation. Also, particular cell-cell interactions regulate ApoD expression in one of the cellular partners, like endothelial-mural cell interactions relevant during the angiogenesis process. In this scenario, ApoD is downregulated in mural cells by contact-dependent (Notch-3) and contact-independent mechanisms.

Finally, confluency and senescence in cell cultures also trigger ApoD expression (Reference Collection 22, Supplementary Table 4). These culture conditions parallel steady-state situations of cells in their physiological tissue environment and the *in vivo* upregulation by aging, respectively. Both conditions concur with a halt in cell division, as it is also the case for serum starvation conditions. The good prognosis of some types of cancers where ApoD increases, also relates its expression to low cell-division rate (see section ApoD-Disease Relationships). Retinoic acid induction of ApoD expression, mediated specifically by RAR α in breast cancer cells, correlates with the anti-proliferative action of this signaling pathway. However, the potential role of ApoD in regulating cell division (see section Protein Physiology) must be dependent on the physiological/pathological context. For example, in the model of pericyte-endothelium interactions mentioned above, mural cells decrease ApoD expression upon interaction with endothelial cells, when they would stop dividing to generate mature capillary structures.

Figure 5 summarizes stimuli regulating ApoD expression and the particular upstream signaling pathways known to date.

ApoD-Disease Relationships

The reports in this section either study the expression of ApoD in response to disease and therapies, or evaluate association of ApoD gene variants with disease. Information was accrued from a total of 216 primary publications (**Figure 4B**; details in **Supplementary Table 18**).

That ApoD is part to the endogenous response to a wide range of diseases, with diverse primary causes, is uncontentious. Data support the existence of common factors underlying diverse disease situations that cause ApoD expression changes, and OS is the strongest candidate. The ApoD upregulation upon experimental stress or injury reviewed above is coherent with prominent examples concurring in the nervous system (**Reference Collection 27, Supplementary Table 5**), where 85% of 66 reports on degenerative/psychiatric diseases or naturally occurring injury identify an over-expression of ApoD. Exceptions are the down-regulation observed in neurotransmission-centered diseases, like depression and a DOPA-decarboxylase deficiency.

Cancer is the other major disease where changes in ApoD expression have been analyzed (82 reports). A clear negative correlation between ApoD expression and malignancy has been found in nervous system tumors, fibrosarcomas, breast, colorectal, hepatic, renal and cervical cancers. The general association of a good prognosis with high ApoD expression strongly suggests a protective anti-tumoral function for this Lipocalin. While studies of prostate cancer have not evidenced unambiguously such a pattern, some studies show regional ApoD expression differences (high in juxta-tumoral tissue) that are still compatible with a defensive tissue response to neoplastic transformation. ApoD tumor-suppressing activity has been experimentally tested and an inverse relationship between ApoD promoter methylation, ApoD expression and outcome is supported by various reports (**Supplementary Table 18**). Whether a common mechanism of ApoD function can promote survival of damaged postmitotic cells in neurodegenerative diseases, and also prevents proliferation of cancerous cells deserves further analysis.

Cardiovascular and metabolic diseases (particularly diabetes) as well as infection or injury, are also accompanied by ApoD upregulation. Again, OS might be a common link to ApoD response to these diseases, for instance in atherosclerotic plaques depending on disease progression, or upon oxidative degradation of glycosylated proteins in diabetes.

In contrast to the many diseases where ApoD expression changes have been reported, few genetic variations of ApoD have been widely or robustly linked to disease risk or prognosis (see section Gene Polymorphisms and **Supplementary Table 18**). Among the few cases reported, it is striking that most of them occur in non-coding sequences (introns or UTRs) revealing that pathogenic variations in ApoD protein sequence must be too deleterious to survive in extant populations.

Cellular Trafficking

The consistent finding of ApoD in body fluids and the signal sequence present in the translated polypeptide indicate that ApoD is exocytosed from cells expressing the protein. A consistent set of experimental work supports the association

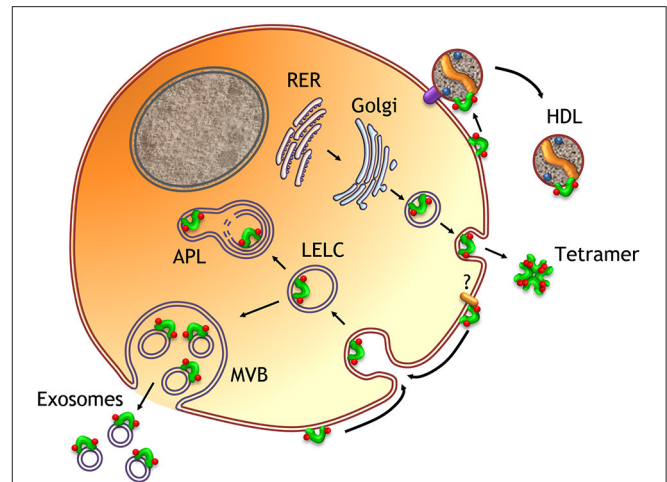


FIGURE 6 | Schematic representation of ApoD subcellular traffic. A model of an ApoD-expressing cell is represented. Canonical exocytosis through the RER-Golgi pathway generates the mature, glycosylated (red dots) protein. The tetrameric form identified in the breast cyst fluid is represented as the format detected in extracellular fluids. Once at the plasma membrane, ApoD can be endocytosed (by non-expressing cells as well) and targeted to lysosomes and autophagolysosomes. When endolysosomes develop into multivesicular bodies, ApoD would be carried on the outer surface of exosomes. Finally, ApoD can be transferred to HDL during their biogenesis, or during their lipid-efflux activity (upon HDL-receptor interaction).

of ApoD to the rough endoplasmic reticulum (ER), the signal peptide removal in the protein sorting process, the N-linked oligosaccharide modification carried out in RER-Golgi, and a secretion of the mature glycoprotein to the extracellular environment in several tissues and cultured cells. All these data make ApoD a typical soluble extracellular protein undergoing a canonical secretory pathway, a consensus attained by subcellular localization prediction algorithms and data present in gene ontology databases (see Methods). Additionally, subcellular traffic of ApoD can also lead to its exportation out of the cell in different formats that include ApoD tetramers, HDL-associated ApoD and extracellular vesicle-associated ApoD (**Figure 6**).

However, several reports have interpreted their findings about ApoD biological roles on the basis of protein partitioning in cytoplasm and/or nuclear compartments. Aside of technical issues questioning those results, some reports use overexpression of fusion-tagged proteins, which are known to undergo unnatural compartmentalization or degradation. Also, strategies based on *in vitro* interaction assays that were designed for proteins naturally occurring in the cytoplasmic or nuclear compartments (like the classic two-hybrid assays) preclude the finding of functionally relevant interactions for ApoD. An alleged cytosolic ApoD would likely be non-glycosylated and improperly folded in the absence of its intramolecular disulfide bonds.

Intracellular Traffic

A number of studies have shown the presence of ApoD in RER and vesicular compartments of different eukaryotic cells. Immunoelectron microscopy (EM) of nervous system cell types has unambiguously identified ApoD in the outer

nuclear membrane-RER membrane complex and in lysosomes. Lysosomes isolated from placental cells, monitored with biochemical techniques, contain ApoD. Likewise, clathrin-coated vesicles isolated from hen's ovaries also contain ApoD.

Recently, the subcellular location of ApoD has been studied in detail in basal conditions and under experimental stimuli, either by immunogold-EM microscopy, or by fluorescence immunocytochemistry combined with established cell compartment markers and monitored by well-documented standardized confocal microscopy. These studies have detected the presence of ApoD in RER, the Golgi apparatus, endosomes, lysosomes, autophagosomes, multivesicular bodies, as well as in the outer side of plasma membrane, clathrin-coated vesicles and caveolae. The protein does not localize to mitochondria or peroxisomes, and has not been immunolocalized inside cell nuclei. Lysosomal ApoD localization has been demonstrated in astrocytes, oligodendrocytes, Schwann cells, fibroblasts, and neurons.

Although those experiments were performed at a fixed time point, serial-time experiments demonstrated that the presence of ApoD in the endosome-lysosome compartment is stable and dynamically enriched upon OS exposure. Long-lasting lysosomal location of ApoD depends on its glycosylation and hydrophobicity, as mutated bacterial recombinant ApoD is maintained in lysosomes only transiently. Targeting of ApoD to the lysosomal compartment occurs not only in ApoD-expressing cells, but also in non-expressing neurons upon exposure to exogenous ApoD or when co-cultured with astrocytes. The fact that ApoD is a stable component of subsets of lysosomes at a given time, connects many of the apparently diverse physiological roles of ApoD (see section Protein Physiology).

References contributing to this section are listed in **Reference Collection 33, Supplementary Table 6**.

Exocytosis

It is undoubtedly established, as discussed above, that ApoD is being secreted to the extracellular environment following a canonical secretory pathway (**Figure 6**). However, whether this pathway leads to actual secretion of ApoD in monomeric form has not been established. In addition, extracellular vesicles (EVs) constitute an alternative exocytotic path for ApoD (see section Binding to Lipid-Rich Structures). Proteomic analyses have identified ApoD in EVs from human plasma and CSF. Experimental characterization of EVs produced by a human astroglial cell line and by mouse primary astrocytes, identified the ApoD-positive vesicles as exosomes originated from multivesicular bodies, according to their size (~100 nm), density (1.17–1.23 g/ml) and molecular markers. When exported by glial cells in exosomes, ApoD must be located on the external surface of these EVs (**Figure 6**).

A third mechanism by which ApoD becomes extracellular is by traveling in HDL particles. ApoD-HDL association can take place during HDL biogenesis, or ApoD can associate to HDLs while the lipoparticles bind to cell membranes and perform their lipid efflux activity. However, these mechanistic details and the particular subcellular origin of the HDL-associated ApoD detected in body fluids need to be investigated. The plasma

membrane location of both ApoA-I dependent HDL biogenesis (Denis et al., 2008) and ABCA1-dependent cholesterol efflux activity (Phillips, 2018), makes it a likely location for the origin of ApoD-positive HDL particles (**Figure 6**).

References contributing to this section are listed in **Reference Collection 34, Supplementary Table 6**.

Endocytosis

The immunolocalization of ApoD in cells not expressing the gene (see section Tissue and Cellular Expression Patterns and Response to Stimuli), as well as the internalization of ApoD by cells cultured in the presence of its native or recombinant forms, are the experimental basis supporting the endocytosis of this Lipocalin. It takes place both under control conditions and in response to specific biological stimuli. ApoD endocytosis appears as a general property of this protein, as it has been reported in birds and mammals. Particularly, in glia-neuron co-cultures ApoD is found to be exclusively transported in EVs from astrocytes to neurons, where it gets internalized. The current view of several extracellular formats of ApoD (HDL, EVs or tetramers in solution) makes it worth to study whether different membrane interaction mechanisms or endocytosis paths are used for ApoD internalization.

ApoD association to the extracellular side of the plasma membrane is coherent with both, its traffic from RER to plasma membrane by the canonical exocytotic path and with its cell contact before internalization. ApoD-plasma membrane interaction has been experimentally demonstrated and is currently considered an established localization for ApoD in human cells (<https://www.proteinatlas.org/ENSG00000189058-APOD/cell>). Whether ApoD-membrane association is mediated by protein-protein or protein-lipid interactions requires further research (see sections Protein-Protein Interactions and Binding to Lipid-Rich Structures). **Figure 6** summarizes ApoD intra and extracellular traffic as currently known.

References contributing to this section are listed in **Reference Collection 35, Supplementary Table 6**.

Tissue and Organ Function

The reports tagged in this section were selected because they study the function of ApoD by experimentally altering ApoD natural expression levels, or by subjecting cells or tissues to defined concentrations of the protein in a controlled experimental situation. A critical review of these reports aims at uncovering common and distinct roles for ApoD in different physiological organ and cellular systems.

ApoD Functions in Cardiovascular System

The process of angiogenesis has been a focus of interest to study the role of ApoD, given its reported expression by blood vessel mural cells (MCs: smooth muscle cells and pericytes). Both in embryonic development and during the remodeling process of wound healing, ApoD increased expression is causally linked to undifferentiated mural cells migration, though is not consistently related to cell proliferation (as it is often found in cancer cells; see section ApoD-Disease Relationships). A crosstalk between endothelial cells (ECs) and MCs governs the switch of

the angiogenic cellular process from a proliferative/migratory state to a differentiation state, characterized by quiescence and adhesion. This switch is essential for vessel morphogenesis. Blood vessel angiogenesis involves reactive oxygen species (ROS), EC-derived PDGF-BB, JAGGED1 and NO, as well as MC-expressed NOTCH3. These secreted and cell contact-mediated signaling downregulates ApoD in MCs, a process linked to blood vessel maturation. Experimental manipulation of ApoD levels demonstrates that ApoD regulates the adhesion of MCs to the extracellular matrix, and low levels of ApoD promote Zyxin- and Vinculin-positive focal adhesion contacts. Concordant effects have been reported in retinal choroid vessels: ApoD-KO mice show neovascularization with increased permeability.

Myocardial cells show slight expression of ApoD under normal circumstances, but the tissue surrounding an injured/infarcted area promptly upregulates ApoD. The study of this process in ApoD-KO mice indicates that ApoD is associated to protection from cell death in the injured tissue. This ApoD protective role on cardiomyocytes is dependent on a proper protein fold and strongly correlates with its antioxidant activity (see sections Binding to Lipid-Rich Structures and Protein Physiology). In this experimental paradigm, the protective activity is attained by increasing ApoD in plasma, though it is unclear whether ApoD levels are also elevated in the infarcted tissue. We thus propose that ApoD function in myocardial tissue protection and remodeling might be based on: (1) A modulation of cell viability in cardiomyocytes and vessel ECs, possibly due to internalization of plasma-derived ApoD, and/or (2) a regulation of cell differentiation related to the angiogenic response described above, organized by ECs and MCs.

References contributing to this section are listed in **Reference Collection 36, Supplementary Table 7.**

Roles of ApoD in Metabolism Regulation

The role of ApoD in metabolism has been analyzed *in vivo* by using two different ApoD-KO mouse lines and a transgenic mouse (hApoD-Tg) driving the expression of human ApoD under the control of the human THY1 gene. This hApoD-Tg mouse ectopically expresses hApoD mostly in neurons, but the protein is present in plasma and other organs physiologically relevant to metabolism. Also, adenovirus-driven liver production of mouse ApoD has been used as a paradigm of acute overexpression, leading to elevated protein levels in plasma.

The metabolic consequences of altering ApoD levels have been evaluated mostly in plasma and liver, although also in retina, and measured in a variety of experimental settings: fasting or non-fasting conditions, different feeding diets, and different sex or age of animals. No clear pattern can be extracted for the role of ApoD on carbohydrate metabolism, where reports describe varied outcomes on glucose tolerance or insulin resistance depending on experimental conditions. Some consistency is observed in the effects on triglycerides (TG): Loss of ApoD leads to decreased hepatic TG content and increased plasma TG, while overexpression leads to elevated TG levels in liver and unaltered or decreased triglyceridemia (depending on the strategy used for ApoD overexpression). On the other hand, variations in plasma cholesterol levels are also reported, with

various outcomes upon ApoD loss or overexpression. Also, association of ApoD polymorphisms have been found with both increased and decreased HDL-cholesterol species. The finding of ApoD being able to mediate binding of HDL to LDL, and of HDL particles to actively dividing carcinoma cells, suggests that it can regulate lipid traffic indirectly by influencing lipoparticle dynamics. Variations in local physiological contexts of this traffic mechanism might contribute in very different ways to the final systemic outputs measured in the experimental settings studied *in vivo*. However, more work is needed to derive definitive evidence for understanding the role of ApoD in lipid and carbohydrate metabolism. So far, the relevant results indicate that the functional relationship of ApoD with various metabolic parameters is, at most, indirect and dependent on other physiological conditions.

References contributing to this section are listed in **Reference Collection 37, Supplementary Table 7.**

ApoD Functions in Skeletal System

Bone cells, from bone marrow stem cells (MSCs) to osteoblasts, are reported to express ApoD in cell culture systems (**Supplementary Tables 16, 17**), and two reports have focused on testing the effects of experimental manipulations of ApoD levels on bone formation and remodeling. Relevant sex and hormone-related patterns have been found using ApoD-KO or hApoD-Tg mice and cell culture systems. With both approaches ApoD appears as an osteogenic factor. Lack of ApoD in mice reduces bone volume and thickness. These effects are observed in trabecular and cortical bone in females, but only in cortical bone in males. Enhanced bone turnover in female ApoD-KO mice is indicated by increased osteoblast surface and osteoclast numbers. Primary MSCs from ApoD-KO mice have lower survival and proliferation, and increased osteoclastogenesis, but an uptake of exogenous hApoD partially reverts their osteogenic potential. When osteoporosis is modeled by glucocorticoid (dexamethasone) treatment after osteogenic induction of MSCs, overexpression of ApoD reverts the effects of dexamethasone, as measured by PI3K/Akt pathway activity and downstream osteogenic gene expression, thus promoting the osteogenic process. Osteogenesis is accompanied by SOD and catalase upregulation, and oxidative damage is associated with glucocorticoid-induced osteoporosis, thus linking ApoD function in this context to its antioxidant activity.

References contributing to this section are listed in **Reference Collection 38, Supplementary Table 7.**

ApoD Functions in the Nervous System

As presented above, the current evidence supports a general view in which non-neuronal cells become the source of ApoD in response to different stimuli, and neurons count on the Lipocalin for its cellular functions by internalizing ApoD. Neurotransmission is one of those functions modulated by ApoD. Analysis of downstream effects in gene expression in the brain of ApoD-KO or hApoD-Tg mice, reveal an enrichment of genes related to synaptic transmission. Particularly, changes in glutamate, somatostatin,

dopamine and acetylcholine neurotransmission have been independently documented by receptor binding assays, HPLC determination of neurotransmitters or their catabolites, or receptor immunodetection. These effects might underlie the behavioral phenotypes related to locomotor function, motor and spatial learning, and retinal function observed in mice with altered expression levels of ApoD.

ApoD addition to cultured neurons results in neuritogenesis and synaptogenesis, which are crucial during neuronal development and underlie neuronal plasticity of established circuits. Neuritogenesis is promoted in immature neurons in culture by the combined addition of ApoD and retinoic acid in the absence of serum. Experiments combining ApoD addition with receptor antagonists indicate that ApoD-dependent neurite extension can be mediated by LDLR, and possibly also by CXCR4 activation, pathways known to be involved in neuronal differentiation.

Another general function of ApoD, extensively analyzed in loss-of-function and transgenic mice, is its role in the glial response to dyshomeostatic changes in the nervous system due to oxidative, metabolic or traumatic stresses. Many studies have reported an acute regulation of ApoD expression under these insults, either experimental or triggered by disease (see sections Regulation of Expression and ApoD-Disease Relationships), supporting an overall neuroprotective role now widely accepted as a functional label for this Lipocalin. Both astrocytes and oligodendrocytes express and secrete ApoD in response to stress. The protein exerts an autocrine and paracrine neural tissue protection, which results in functional preservation of OS-challenged dopaminergic systems, of neurons affected by kainate excitotoxicity or suffering from A β -related degeneration. Astrocytes, although not an abundant source of ApoD in basal conditions, quickly respond to OS with a JNK-dependent expression of ApoD, which is secreted to the extracellular milieu as cargo on the surface of extracellular vesicles (**Figure 6**). The protein is internalized by glial and neuronal cells, improving their viability thanks to a control by ApoD of OS-dependent lipid peroxide accumulation. Moreover, a surge of ApoD in a stressed neural tissue behaves as an off-signal limiting the dimension and duration of gliosis and inflammation. The inflammatory response is linked to OS due to increased PLA2 expression and AA production, among other factors. Quenching of AA is proposed as part of this inflammation control by ApoD (see section Protein Physiology).

A long-lasting homeostasis maintenance role for ApoD has been also proposed in the process of physiological aging of the nervous system, where this protein has been shown as the most consistently overexpressed in primates and rodents. Also, life-expanding strategies in model organisms, like caloric restriction, promote ApoD expression not only in the nervous system but also in cardiac and skeletal muscle (**Supplementary Table 11**). The homeostatic role predicted by the expression pattern is supported by the phenotypes exhibited by aged ApoD-KO mice, which do not display altered lifespan but do present signs of early neurodegeneration at 3 months of age, with oxidative damage and proteostasis defects in cortex and hippocampus. These alterations underlie cognitive defects

and a hyperkinetic phenotype evident in old (21 months) ApoD-KO mice.

The predominant expression of ApoD in myelinating cells under control conditions (oligodendrocytes in CNS and Schwann cells in PNS; see section Regulation of Expression) has prompted experimental studies, using cultured primary cells and ApoD-KO and hApoD-Tg mice, that clearly support the implication of ApoD in the myelination process during development, in the lifelong maintenance of the myelin sheath, and in the remyelination that occurs in response to environmental insults. These processes have been analyzed in the mouse brain corpus callosum as well as in the peripheral sciatic nerve. ApoD is required for a proper and timely response to a crush injury in PNS nerves, helping to recover locomotor function. ApoD promotes myelin clearance and regulates angiogenesis and macrophages recruitment to the wound site, processes that are essential for subsequent axonal regeneration and remyelination. ApoD contributes to optimize myelin clearance, carried out by transdifferentiated Schwann cells and infiltrating macrophages, through two complementary actions: control of lipid-mediated inflammatory signaling and optimization of the phagocytosis process itself. Data indicates that ApoD regulates and control the tissue levels of AA and lysophosphatidylcholine (both *in vitro*-demonstrated ApoD ligands, **Table 2**). They are needed for an adequate cytokine inflammatory response and recruitment of bone marrow-derived macrophages. Although macrophages do not express ApoD, the levels of this Lipocalin in the injured nerve environment influence their phagocytic activity, since myelin-associated ApoD is phagocytosed as well. Flow cytometry experiments with primary macrophages demonstrated that ApoD affects the initiation and efficacy of phagocytosis.

A dynamic spatiotemporal regulation of ApoD expression is apparent in myelinating cells, with a prominent increase at the height of postnatal myelination followed by continuous rise throughout life. The absence of ApoD results in a defective and irreversible compaction, mostly in the extracellular leaflet of both CNS and PNS myelin. This altered myelin structure results in a decreased conduction velocity, reported for the sciatic nerve, and compromises motor learning tasks. As downstream effects, both the mTORC1-dependent lipogenic switch and the ERK-mediated growth pathways are altered in the absence of ApoD. A lack of myelin compaction is due to inadequate removal of myelin glycocalyx, mostly affecting gangliosides GM1-2b, GD1b, and GT1b content and distribution. This role of ApoD on glycocalyx physiology was demonstrated to be linked to the adequate subcellular localization of lysosomal and plasma membrane sialidase (Neu1 and Neu3) and of the regulatory Fyn kinase. This mechanism requires preservation of lysosomal membrane integrity (see section Protein Physiology).

References contributing to this section are listed in **Reference Collection 39, Supplementary Table 7**.

Protein Physiology

In this final section we aim at discussing the available knowledge, derived from state-of-the-art research critically assessed in this

review, to give a plausible answer to the central question posed in the Introduction: In order to achieve its pleiotropic roles, does ApoD moonlight between different biochemical functions when expressed in different contexts, or instead ApoD displays a distinctive biochemical role that works on varied physiological situations?

The presence of ApoD in extracellular formats such as lipoprotein particles and exosomes evidences its ability to associate to higher-order lipid structures. According to our systematic search no unambiguous evidence exists for the secretion of protein monomers in native conditions. Non-denaturing electrophoresis analysis of CSF revealed only high-molecular weight ApoD oligomers, while in plasma it has been repeatedly identified in lipoprotein particles preparations. In the particular case of BCF, where an extremely high concentration of ApoD is produced, the protein assembles in tetramers through protein-protein interactions. Finally, ApoD secreted by cultured astrocytes is internalized by neurons only if the conditioned extracellular media has not been depleted of extracellular vesicles. A protein region encompassing the first three β -strands, highly conserved in chordates (**Figure 2A**), and several hydrophobic patches located at the protein pocket entrance (**Figure 3E**) are proposed to underlie ApoD self-association and ApoD-lipid structure interactions, respectively.

These results shed doubts on a view of ApoD widely cited (a functional tag in most databases for this Lipocalin) as a “lipid transporter,” a task that a secreted globular monomer could easily achieve.

Unquestionably though, it is the ability of ApoD to bind small hydrophobic ligands of varied shapes inside its β -barrel pocket. However, when free ligands (e.g., AA) have been mechanistically related to ApoD function, binding data are compatible with a buffering or quenching function, or a very local shuttling of the ligand at the most, rather than to a generalized long-range ligand transport between cells. A curious case is the expression of ApoD in feather follicles of pheasants, only in skin areas with specific plumage colors, suggestive of a pigment-retention function. Similarly, the ligand bound to ApoD in sweat from human axilla could be the source of slowly released volatile odor molecules. These ligand-retention functions compare well with that of crustacean ApoD homologs, also linked to their carapace coloration (Wade et al., 2009).

In a different context, ligand shuttling has been repeatedly proposed for ApoD in the cholesterol transfer to LCAT. However, ApoD has been demonstrated not to bind cholesterol, not to contribute to LCAT-cholesterol transfer and not to show a direct interaction with LCAT. On the contrary, experimental data suggests that ApoD exerts “stabilizing effects” on LCAT activity. After reviewing the relevant information on this issue, we propose a different view that can guide new testable hypotheses: ApoD binds lysophosphatidylcholine (LPC), a LCAT reaction product that exerts a negative feedback on LCAT activity. By quenching LPC, ApoD would maintain LCAT activity over a wide range of LPC product concentration. This specific LPC quenching function is compatible with the small amounts of ApoD recovered from HDLs, since only a transitory presence of ApoD

might be needed when LCAT is adding cholesterol to the lipoparticle. As for the HDL-LDL interaction (see section Roles of ApoD in Metabolism Regulation), the putative consequences of ApoD presence in HDLs on cholesterol management in the organism would therefore be of an indirect nature, and could explain the lack of correlation between ApoD and cholesterol content in many physiological or pathological situations.

A fundamental advance in defining ApoD molecular function was its role in organismal protection against OS, achieved by a control of the magnitude of lipid peroxidation, measured at tissue or cellular levels. This role has received strong experimental support from *in vitro* biochemical assays, cellular experimental systems, and *in vivo* experiments with animal models where ApoD expression was manipulated. Moreover, further validation for this role comes from experimental approaches testing the expression of human ApoD in evolutionary distant organisms. Overexpression of human ApoD in *Drosophila* increases lifespan in both normal and pro-oxidative experimental conditions. Also, replacement in plants of the native chloroplast Lipocalin (LCNP) by human ApoD, targeted to thylakoids, rescues drought and OS sensitivity of the mutant. Lipid peroxidation control is evidenced in both reports as the mechanism mediating the organism response.

An ApoD antioxidant mechanism has been demonstrated using oxidized AA-derivatives in solution or auto-oxidized liposomes. ApoD is able to reduce free radical-generating lipid hydroperoxides to inert lipid hydroxides. In this reaction, the residue Met93 exposed on one of the surface hydrophobic patches of the protein (**Figure 3C**) is converted to Met93-sulfoxide. This residue is preserved in ApoD chordate orthologs (**Figure 2A**) and contributes to the functional differentiation of ApoD from its closest Lipocalin relative, RBP4, where that position is occupied by charged (Lys or Arg) residues (Diez-Hermano et al., 2021). To maintain ApoD antioxidant activity, the action of a methionine sulfoxide reductase (MRS) would be required. However, oxidized ApoD tends to self-associate. Interesting data from Alzheimer's disease brain samples reveal that hippocampal (but not cerebellar) MRS levels decrease with disease progression, while ApoD oligomerization increases. This suggests that the ApoD redox cycling might be blocked if Met93 does not return to its native form and the protein self-associates. This effect sets an upper limit to ApoD antioxidant activity, since it would result in the consumption of ApoD-Met93. Whether this depletion triggers a feedback regulatory loop promoting ApoD gene expression under OS situations in different physiological and pathological contexts would be an interesting aspect to explore. In this context, we must keep in mind that ApoD structure is stable under pro-oxidative situations, making it suitable for the biological contexts where ApoD function is beneficial (from neurodegenerative conditions to cancer). Also, ApoD ligand binding ability is preserved at low pH and its glycosylation prevents a rapid degradation, both good assets to perform its ligand binding and antioxidant functions inside the endolysosomal compartment.

The direct antioxidant activity of ApoD and its demonstrated stable location in the lysosomal compartment put forward a new

view of ApoD protein physiology that holds high explanatory power in the understanding of a number of apparently varied ApoD roles.

ApoD control of redox state can be performed directly on both, cell membranes and lipoprotein particles. The unilamellar vesicles where ApoD-reducing activity has been demonstrated are a good experimental model for both types of lipid-based structures. Lipid peroxide products are mainly derived from cellular membranes, which are a major target for cell-generated ROS. The ability of ApoD to keep low levels of membrane-originated lipid peroxides, together with the positive correlation of ApoD content in HDLs with their antioxidant capacity, and the promotion of HDL-LDL interaction by exogenously-added native ApoD, support the protective action of ApoD in both types of lipidic structures (membranes and lipoparticles). Additional evidence comes from the existence of ApoD insect homologs stably anchored to cell membranes (Ganfornina et al., 1995; Ruiz García, 2013), which suggests that membrane interaction is part of an ancestral ApoD property.

In addition to the immediate effects on the redox state of membranes and other lipid structures, ApoD can give rise to indirect effects when performing its antioxidant function in the lysosome. The lysosome is considered a “lipid-controlling” cellular hub. ApoD maintenance of lysosomal membrane redox balance and integrity results in the control of plasma membrane composition. This is for example the case for plasma membrane glycolipids, with important consequences for membrane-membrane interactions like those required in the process of myelin compaction. Lysosomal membrane stability can, by extension, influence the lipid export/import balance in cells, another way of ApoD indirectly conditioning the organism lipid metabolism. Altered ApoD expression in response to mutations of the lysosomal cholesterol transporters (as in Niemann-Pick type C disease) supports this notion. Plasma membrane modulation is also coherent with the observed correlation of ApoD content in HDLs and their ABCA1-dependent cholesterol efflux capability in macrophages, or the subtle changes in lipid content in lipoprotein particles of subjects with ApoD polymorphisms. Through its influence on membranes and lipoparticle dynamics, without a need of binding cholesterol, ApoD can modulate its flux within and between cells.

Additionally, the lysosome is a “cell death/survival controller” by its fundamental recycling, detoxifying and proteostatic functions. Lysosomal ApoD would condition whether a failure in the lysosomal compartment takes place upon a wide array of disease/injury situations, thus contributing to the final cell fate. This ApoD-dependent cell fate decision can be extended to developmental processes as well.

Finally, a role of ApoD in innate immunity has been frequently reported, while no mechanistic link to the protein physiology was proposed. We suggest that ApoD, with its lysosomal optimization mechanism, can modulate the efficiency of phagocytic cells, like it has been demonstrated in injury-recruited macrophages, therefore influencing many of the maintenance and immune responses of the organism.

This view makes us to propose that ApoD lipid-binding properties are more related to management of lipid-based

structures composition (membranes or lipoparticles) and a control of their redox state, than to lipid transport. Whether similar membrane-stabilizing properties endow ApoD-positive exosomes with resistance properties to be efficient cargo transporters in disease or tissue damage situations, would be worth studying.

A different aspect of ApoD physiology scarcely studied is the role of its demonstrated N-linked glycosylation, which has been proven to be tissue and species specific, and to be essential for both, ApoD interaction with lipoparticles and for its cellular localization in the endolysosomal compartment. This is particularly important because of the association between redox signaling and glycan profiles, which in turn could affect several signaling pathways (Khoder-Agha and Kietzmann, 2021). In relation to this, modulation of signaling pathways by ApoD has been confirmed in endothelial cells and osteoblasts (PI3K-Akt pathway) and nervous tissue (pERK). How ApoD controls signaling cascades is open to discussion. Although several protein candidates have been proposed as ApoD membrane receptor, no clear demonstration is available for a receptor-mediated signaling transduction. Alternatively, ApoD might not require a protein receptor and trigger a unique signaling cascade. Instead, it could be working as a quencher of lipid modulators (e.g., AA), or conditioning the membrane partitioning of signaling complexes that are known to be dependent on membrane lipids distribution.

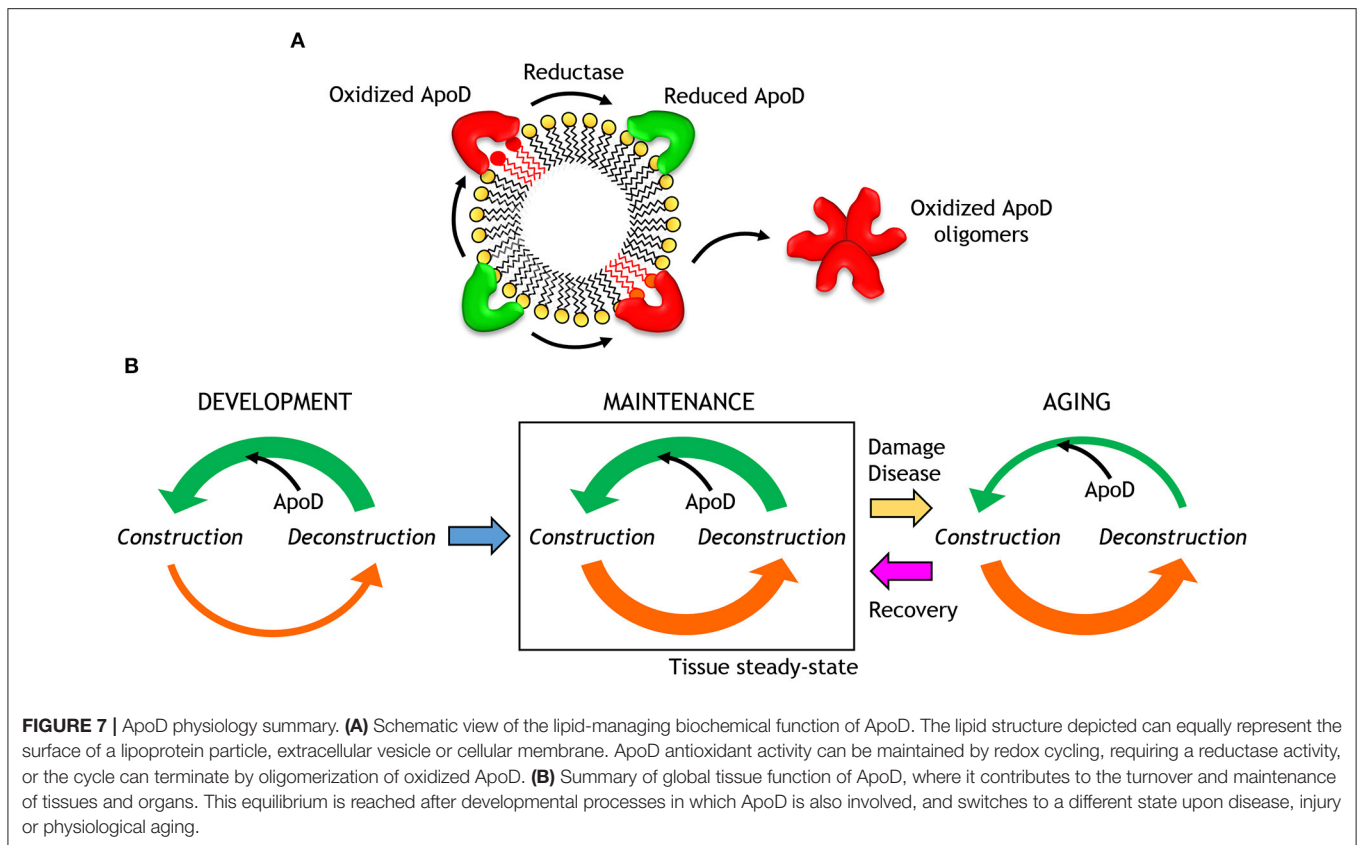
In summary, the available information supports a parsimonious hypothesis for the biological function of ApoD, with a unique biochemical role related to the management and redox state of lipid cellular and extracellular structures. This proposition is compatible with the wealth of experimental results showing that multiple stimuli in varied cellular contexts trigger ApoD expression with a tight spatiotemporal regulatory control. The protein can then become associated with the challenged membranes or being exported to the extracellular milieu to act in a paracrine fashion. Both direct and indirect downstream effects, depending on the cell type affected, would explain pleiotropy at the organismal level with a single biochemical function.

The proposed unique molecular mechanism also explains ApoD biological role in response to tissue/organ damage and disease, where homeostatic maintenance is disturbed and ApoD will contribute to restore the equilibrium through tissue repair/reconstruction. Under this paradigm, we can also explain ApoD roles in organismal developmental processes implying building-deconstruction cycles. **Figure 7** summarizes the new view on ApoD physiology. References contributing to this section are listed in **Reference collection 40, Supplementary Table 8**.

Future Goals for ApoD Biology

In spite of the explanatory power of our proposed biological role for ApoD, many questions keep been unresolved and many others are likely to arise, which can spur and guide new research programs. A few of them follow:

- (1) To explore the functional relationship between the protein antioxidant capacity and the pocket ligand binding. In this



- respect, the hypothesis of ApoD working on oxidized lipid “whiskers” (Greenberg et al., 2008; Del Caño-Espinel, 2014) on cell membrane bilayers or lipoparticles is appealing and worth contrasting.
- (2) To test whether ApoD downstream effects on signaling pathways rely on a canonical receptor-mediated transduction, or alternatively they depend on the modulation of the lipid context of signaling elements (e.g., PI3K). Findings in *Drosophila* reveal that loss of an ApoD homolog alters PI3K association to the plasma membrane (Hull-Thompson et al., 2009).
 - (3) To test whether oligomeric vs. monomeric forms of ApoD underlie its managing function on cell membranes or lipoparticles.
 - (4) To characterize the extent of ApoD redox cycle, maintaining antioxidant ApoD activity thanks to the intervention of reductases, and the implications of a potential upper limit to this mechanism due to ApoD oligomerization. This aspect can be key to fully understand ApoD function in aging and disease.
 - (5) To analyze the effects of differential glycosylation on ApoD interactions and functions.
 - (6) Recent studies on a *Drosophila* homolog (Yin et al., 2021) point to lipid droplets as another higher-order lipid structure susceptible to be modulated by ApoD. Searching for lipid droplet-managing functions of vertebrate ApoD is therefore pertinent.

- (1) At a more general tissue/organ level, several functions are relevant to be studied in more depth, such as the ApoD role on feather and skin physiology, neuronal synaptic function, and metabolism.
- (8) Finally, it is worth to analyze the potential exchange between the nervous system and systemic pools of extracellular ApoD in its different formats, not only to fully understand its roles in the organism, but also for a potential therapeutic use of ApoD in nervous system diseases.

ApoD SYSTEMATIC REVIEW. REFERENCE COLLECTIONS

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Reference Collection 2 (Eichinger et al., 2007; Oakley et al., 2012; Kielkopf et al., 2018, 2019, 2021).

Reference Collection 3 (McConathy and Alaupovic, 1976, 1986; Bojanovski et al., 1980; Yang et al., 1994; Schindler et al., 1995; Zeng et al., 1996; Sun et al., 1998; Perdomo and Henry Dong, 2009; Li et al., 2016; Qin et al., 2017).

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DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

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AUTHOR CONTRIBUTIONS

MG and DS: conceptualization, writing, review, and editing. Both authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphys.2021.738991/full#supplementary-material>

Supplementary Figure 1 | ApoD mRNA and protein expression summary of the Human Protein Atlas.

Supplementary Figure 2 | ApoD mRNA and protein expression summary of the Mouse Gene Expression Database.

Supplementary Table 1 | Complete ApoD Reference Library.

Supplementary Tables 2–8 | References organized by subheadings within each tag (MP, GD, RE, DR, CT, TOF, and PP).

Supplementary Tables 9–15 | Analysis of primary papers describing ApoD mRNA expression or protein detection *in vivo* in different physiological systems: body fluids, reproductive system, nervous system, skin and glands, musculoskeletal system, cardiovascular and immune systems, and other functional systems (digestive system, liver, pancreas, adipose tissue, kidney).

Supplementary Tables 16, 17 | Analysis of primary papers describing ApoD mRNA expression or protein detection in primary cultures and cell lines.

Supplementary Table 18 | Analysis of primary papers describing ApoD relationships to disease (expression regulation by disease or treatment, genetic variations associated to disease).

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