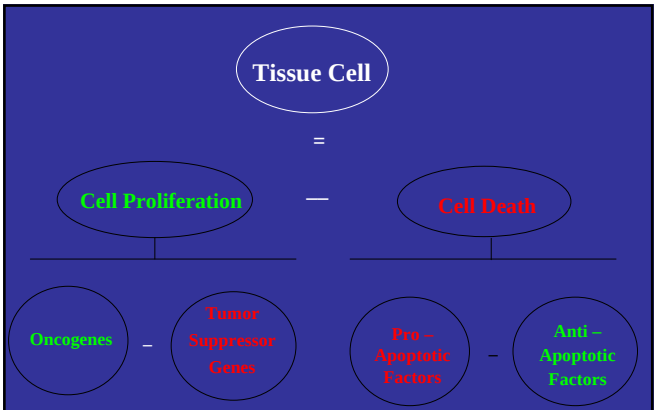
MOLECULAR BIOLOGY OF CANCER

- Gain-of-function **(dominant)** mutations can activate **oncogenes**, which are positive effectors of transformation
- Loss of function **(recessive)** mutations can inactivate **tumor suppressor genes** products which are negative growth regulators



FUNCTIONS OF ONCOGENES & TUMOR SUPPRESSOR GENES

- Cells are chronically faced with decisions to:
  - **Divide**
  - **Differentiate**
  - Undergo programmed cell death (**apoptosis**)
- All three outcomes affect the net cell number
- These decision pathways are primary targets for action of oncogenes and tumor suppressor genes

ONCOGENES IN RNA TUMOUR RETROVIRUSES

- Acutely transforming retroviruses can form tumors in animals within weeks to months
- This type of retrovirus carries within its genome an oncogenic **gene (v-ONC)** that was captured **(transduced)** from the genetic material of a host cell in an earlier cycle of infection
  - v-ONC: first oncogenes to be identified
  - v-ONC: placed under altered regulatory (viral) control
  - v-ONC: mutated alleles of normal cellular genes **(proto-oncogenes)** with remarkable conservation between species

Figure 28.8 Each transforming retrovirus carries an oncogene derived from a cellular gene. Viruses have names and abbreviations reflecting the history of their isolation and the types of tumor they cause. This list shows some representative examples of the retroviral oncogenes.

Virus	Name	Species	Tumor	Oncogene
Rous sarcoma	RSV	chicken	sarcoma	*src*
Harvey murine sarcoma	Ha-MuSV	rat	sarcoma & erythroleukemia	*H-ras*
Kirsten murine sarcoma	Ki-MuSV	rat	sarcoma & erythroleukemia	*K-ras*
Moloney murine sarcoma	Mo-MuSV	mouse	sarcoma	*mos*
FBJ murine osteosarcoma	FBJ-MuSV	mouse	chondrosarcoma	*fos*
Simian sarcoma	SSV	monkey	sarcoma	*sis*
Feline sarcoma	PI-FeSV	cat	sarcoma	*sis*
Feline sarcoma	SM-FeSV	cat	fibrosarcoma	*fms*
Feline sarcoma	ST-FeSV	cat	fibrosarcoma	*fes*
Avian sarcoma	ASV-17	chicken	fibrosarcoma	*jun*
Fujinami sarcoma	FuSV	chicken	sarcoma	*fps*
Avian myelocytomatosis	MC29	chicken	carcinoma, sarcoma, & myelocytoma	*myc*
Abelson leukemia	MuLV	mouse	B cell lymphoma	*abl*
Reticuloendotheliosis	REV-T	turkey	lymphatic leukemia	*rel*
Avian erythroblastosis	AEV	chicken	erythroleukemia & fibrosarcoma	*erbB, erbA*
Avian myeloblastosis	AMV	chicken	myeloblastic leukemia	*myb*

Transforming Viruses Carry Oncogenes

Transformation may result from tumor virus infection thus "oncogenes"

> Polyomavirus/dsDNA/6Kb/T antigen/Early viral gene/Inactivate tumor suppressor gene

> Human papillomavirus/dsDNA/8Kb/E6 & E7 genes/Early viral genes/Inactivate tumor suppressor gene

> Adenovirus/dsDNA/37Kb/E1A & E1B genes/Early viral genes/Inactivate tumor suppressor gene

> Retrovirus(acute)/ssRNA/6-9Kb/Individual genes/Cellular origin/Activate oncogenic pathway

Transformation occurs in non-permissive infection (vs. productive infection in permissive hosts) [Fig 28-4]

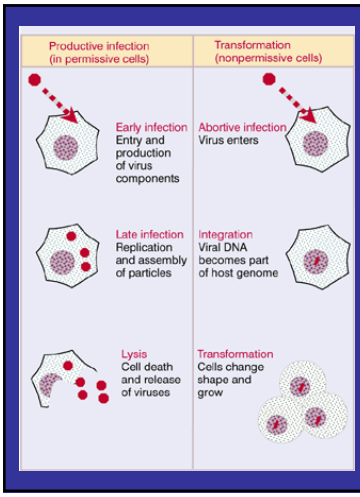


Figure 28.4 Permissive cells are productively infected by a DNA tumor virus that enters the lytic cycle, while nonpermissive cells are transformed to change their phenotype.

Transforming Viruses Carry Oncogenes

Common mechanism of DNA tumor virus transformation

Early genes with oncogenic potential
Integration of viral oncogenes into host genomes
Oncogene proteins always interact with host cellular proteins
[Cell transformation by polyomavirus/adenovirus]

Polyoma & SV40 produce T-antigens early in infection
T-antigen has transforming activity
Papillomaviruses produce E6 & E7 oncoproteins

EBV immortalized human B lymphocytes
EBV oncogene unknown

ONCOGENES

- Protooncogenes are important **regulators of biologic processes**
- Despite their name, they do not reside in the genome for the sole purpose of promoting the neoplastic phenotype
- They are essential to normal biologic processes (more than 100 identified)
- They play diverse roles in the **control of cellular growth,** including **proliferation, apoptosis, genome stability, and differentiation**

ONCOGENE ACTIVATION

- Genetic damage: **activation of protooncogenes**
- Qualitative or quantitative changes
- Mechanisms:
  - **Retroviral insertion mutagenesis**
  - **Point mutation**
  - **Gene amplification**
  - **Gene translocation**

ONCOGENES: Mechanism of action

- Four major biochemical mechanisms of action:
  - Abnormal signaling: structurally abnormal **cytokine/growth factor**
  - Aberrant phosphorylation of proteins: altered receptors and other **signal transducer kinases**
  - Abnormal transmission of signals: **G proteins**
  - Disturbed regulation of gene transcription: abnormal **transcription factors**

CLASSES OF ONCOGENES

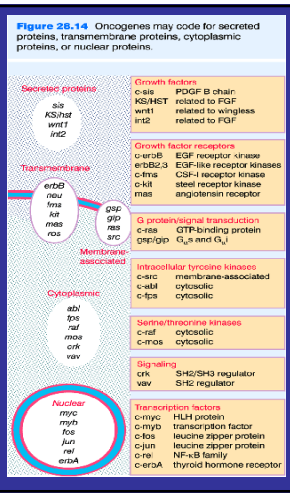
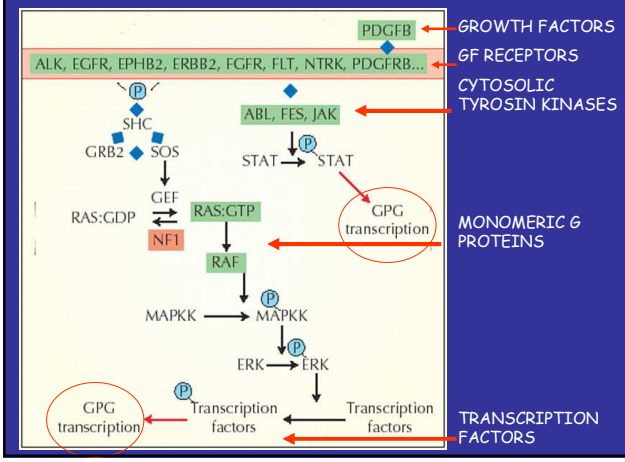


Figure 28.14 Oncogenes may code for secreted proteins, transmembrane proteins, cytoplasmic proteins, or nuclear proteins.



ONCOGENES & SIGNAL TRANSDUCTION PATHWAYS

- Oncogene products can override growth factor dependency by functioning as:
  - constitutively active **ligands**
  - constitutively active **receptors**
  - constitutively active **downstream elements**

ONCOGENES & SIGNAL TRANSDUCTION PATHWAYS

- Each control point can be the target of **deregulation** by oncoproteins:
  - **over-expression**
  - **ectopic expression** (no alteration in their normal structure)
  - **point mutations or truncations**
- By causing deregulation of the signaling, oncoproteins can force a cell into **uncontrolled cell division** or invasive growth

ONCOGENES AS EXTRACELLUALR GROWTH FACTORS

- A number of other growth factor genes have been activated through promoter insertion in experimental viral systems (e.g. interleukins 2 and 3 and granulocyte/macrophage colony-stimulating factor)

ONCOGENES AS EXTRACELLUALR GROWTH FACTORS

- The first oncogene product with an explicit function was the v-SIS protein, a modified form of platelet-derived growth factor (PDGF)
- Infection of cells with simian sarcoma virus, which harbors v-SIS, results in production of functional PDGF

  This **autocrine stimulation** generates a chronic growth stimulus for PDGF-responsive cells

ONCOGENES AS RECEPTOR TYROSINE KINASES

- Receptor oncogenes are activated in human cancers by gene amplification (which leads to over-expression), rearrangements, and point mutations
- Both N- and C-terminal **deletions** can partly **activate** the **transforming potential** of receptor tyrosine kinases

ONCOGENES AS RECEPTOR TYROSINE KINASES

- Mutations in the RET gene: responsible for inherited cancer syndromes:
- MEN IIA and familial medullary thyroid cancer mutations
  - elimination of conserved cysteins in the extracellular domain
  - formation of disulfide-linked receptor dimers
- MEN IIB is associated with mutation of the tyrosine kinase domain

ONCOGENES & RAS FAMILY

- RAS functions analogously to other G proteins that cycle between inactive guanine diphosphate (GDP)-bound states and active GTP-bound forms
- The GTP-bound forms activate downstream signaling proteins until GTP hydrolysis which is mediated by the intrinsic activity of RAS returns the system to the basal state
- **Transforming mutants of RAS are resistant to the GTPase**

Mutational Activation of Ras Proto-oncogenes

Quantitative changes (amplification or over-expression) of *c-ras* gene can also transform normal cells

ras protein is a monomeric guanine nucleotide-binding protein
has intrinsic GTPase activity
interconverts between active and inactive *ras* proteins

Constitutive activation of *ras* may be oncogenic

Mutations that create oncogenic *ras*
inhibition of GTPase activity

ONCOGENES & RAS FAMILY

- Activations of one of the three human RAS genes Ha-, Ki-, or N-RAS are the **most common dominant mutations in human cancer**
- Point mutations that activate RAS genes are **clustered** in the regions encoding amino acids 12, 13, and 59 to 61
- These mutations act by interfering with the guanine triphosphate (GTP) hydrolysis step of the RAS-GNP cycle

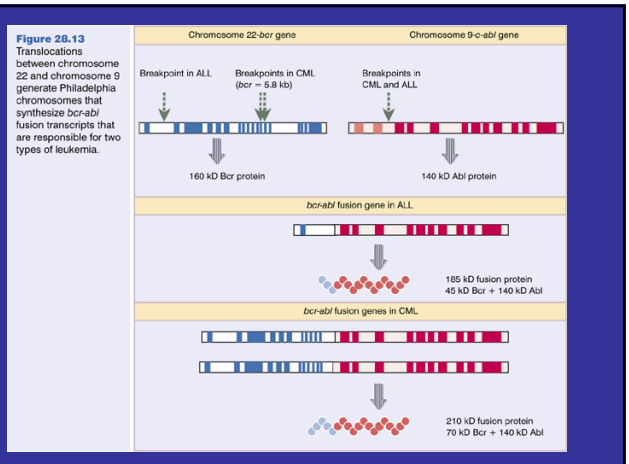
Translocation

Translocation can generate hybrid oncogenes & human cancers

[CML & Philadelphia chromosome]

c-abl gene on chromosome 9 and *bcr* gene on chromosome 22

Why is the hybrid *bcr-abl* protein oncogenic?
Activation of *ras* pathway for transformation



ONCOGENES AS TRANSCRIPTION FACTORS

- Four basic types of effects:
  - ✓progression from G1 to S phase in the cell cycle
  - ✓apoptosis
  - ✓genome stability
  - ✓cellular maturation

Amplification, Insertion, or Translocation

Genomic changes (amplification, insertion & translocation) that cause proto-oncogene activation:

Amplification: *c-myc, c-abl, c-myb, c-erbB, c-K-ras, mdm-2*
- presence of known oncogenes in amplified region
- amplification of same oncogenes in many cancers

Insertion: insertion of retrovirus LTR over-expresses *c-myc*
- [Insertion of ALV activates *c-myc* gene; Fig 28-11]

Translocation:
- [reciprocal translocation by illegitimate recombination; Fig 28-12]
- immunoglobulin or TCR gene and *c-myc* oncogene
- Increased *c-myc* expression after translocation

c-myc coding sequences are unaltered in all cases

ONCOGENES AS TRANSCRIPTION FACTORS

- Growth factor-stimulated cells: rapid rise in **"immediate early"** mRNAs for **nuclear proteins: Myc, Fos, Jun**
  - ✓regulation of gene expression: cell proliferation and differentiation
  - ✓bind DNA in a site-specific manner
  - ✓activate or repress gene transcription

ONCOGENES AS TRANSCRIPTION FACTORS

- **c-MYC**
  - ✓Cell culture and animal models: Oncogene cooperation between c-MYC and activated Ha-RAS: neither oncogene is fully oncogenic
  - ✓Unlike other oncogenes: inappropriately regulated expression of c-MYC, rather than mutations in the protein, contributes to tumorigenesis

ONCOGENES AS TRANSCRIPTION FACTORS

- **c-MYC**
  - ✓Initial discovery as a viral oncogene in the avian myelocytomatosis virus
  - ✓c-MYC activation by chromosomal **translocation** in **Burkitt's** lymphoma
  - ✓**Amplification** of c-MYC or of MYC family members (N-MYC) in numerous human tumors, including neuroblastomas, and retinoblastomas

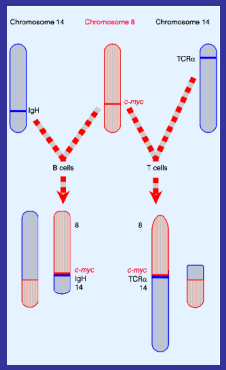


Figure 28.12 A chromosomal translocation is a reciprocal event that exchanges parts of two chromosomes. Translocations that activate the human *c-myc* proto-oncogene involve Ig loci in B cells and TCR loci in T cells.

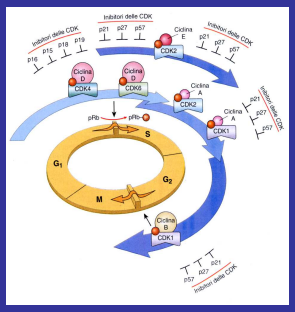
ONCOGENES AS TRANSCRIPTION FACTORS

- **JUN, FOS, and AP1**

  FOS and JUN form dimers that initiate gene transcription of targeted genes

ONCOGENES AS REGULATORS OF THE CELL CYCLE

- **Cyclins and CDKs** are the core apparatus of cell cycle progression
- ✓ In mantle cell lymphoma, a reciprocal translocation between 11q13 and 14q32 places cyclin D under regulatory control of Ig heavy chain sequences
- ✓ Cyclin D expression is also frequently upregulated through demethylation of the gene, permitting transcriptional activation.



ONCOGENES AS ANTI-APOPTOTIC GENES (BCL-2)

- **BCL-2 overexpression can block apoptosis** that is induced by any of a number of signals, including radiation, chemotherapeutic agents, growth factor withdrawal, steroids, and heat shock

ONCOGENES AS ANTI-APOPTOTIC GENES (BCL-2)

- Follicular lymphomas: t(14;18) that puts the BCL-2 gene (on chr 18) under transcriptional control of the Ig heavy chain gene (on chr 14), resulting in BCL-2 overexpression
- In transgenic animals, BCL-2 overexpression in lymphoid cells results in increased survival of these cells and immune dysfunction, rather than increased cellular proliferation

ONCOGENES AS INHIBITORS OF CELLULAR DIFFERENTIATION

- Human cancers typically arise after long latency and accrue multiple abnormalities in their control over cellular growth and phenotype
- One distinguishing feature of malignant cells is their **inability** to attain a normal, functional, **terminally differentiated state**

ONCOGENES AS INHIBITORS OF CELLULAR DIFFERENTIATION

- **The nuclear oncogene v-ERBA** was isolated, along with v-ERBB, as one of two viral oncogenes in the chicken erythroblastosis virus
- The cellular homologue, **c-ERBA**, is a **nuclear receptor for the thyroid hormones**
- v-ERBA by itself does not appear to express transforming potential, but its presence potentiates the transforming potential of v-ERBB (which encodes a truncated and constitutively active EGF receptor) by specifically interrupting the differentiation of erythroblasts

ONCOGENES AS INHIBITORS OF CELLULAR DIFFERENTIATION

- The v-ERBA product is thought to **alter** the expression of genes that play an important role in **erythroid differentiation**
- **v-ERBA** gene does not bind triiodothyronine or thyroxine and is therefore **ligand independent**, but it can either suppress or transactivate certain promoters

ONCOGENES AS INHIBITORS OF CELLULAR DIFFERENTIATION

- **Acute promyelocytic leukemia**, the M3 subtype of AML, is associated with a **block** at the promyelocyte stage **of differentiation**
  - High doses of **retinoic acid** can induce a hematologic remission, which is accompanied by a release of the block to **cellular maturation**
  - The tumor typically occurs with a **t(15;17)** that involves two genes - **PML** (for promyelocyte) on chromosome 15 and the retinoic acid receptor alpha **(RARalpha)** gene on chromosome 17

ONCOGENES AS INHIBITORS OF CELLULAR DIFFERENTIATION

- PML is a gene of unknown function that localizes to the nucleus and may act as a factor regulating apoptosis
- RARalpha is one of three nuclear receptors for retinoic acid and is a ligand-dependent transcription factor
- In a cell culture assay, the PML-RARalpha chimeric protein can block the differentiation of human promyelocytic cells, and overexpression of the chimeric protein in the myeloid compartment of mice results in massive overproduction of immature myeloid cells and, at lower frequency, myeloid leukemias

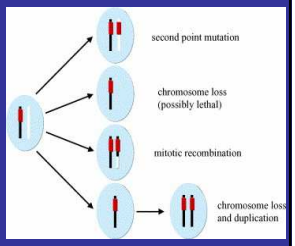
ONCOGENES AS INHIBITORS OF CELLULAR DIFFERENTIATION

- It is likely that the PML-RARalpha chimera inappropriately represses or activates key targets that play a role in myeloid maturation and that this results in a block to the differentiation process
- With pharmacologic dosing of retinoic acid, it is possible to overcome this block, most likely by alleviating the effect of this oncogenic chimera

TUMOUR GENE SUPPRESSORS

ONCOSUPPRESSOR GENES

In general, oncosuppressor genes act as recessive genes. It followes that if only one allele is mutated or deleted, the wild-type allele compensates and no altered phenotype is apparent. Thus, in heterozigousy oncosuppressor genes are not effective as long as the other allele is functional. Loss of Heterozigousy (LOH) is a condition in which the normal allele is deleted or not expressed (silenced !): in this case the combination with the mutated allele determines a loss-of-function leading to the transformed phenotype. Haploinsufficient oncosuppressors manifest their effect also when only one allele is mutated.



MOST IMPORTANT ONCO-SUPPRESSORS

NEGATIVE REGULATORS OF CELL CYCLE

p-53
RB-1 (p110RB)
WT-1 p46-49WT
MTS-1 (p16) inhibitor of cdk-4/ciclina D
MTS-2 (p15) inhibitor of cdk-4-6, it releases p27
p21/WAF inhibitor of cdk-2/cyclin D/E
NOTCH

INHIBITORS OF SIGNAL TRANSDUCTION

NF-1 (Neurofibromin) GPTase GAP (inactivates Ras)
PCSK inhibitor of Tyrosin kinase p66 Scr
PTEN Protein -Lipid phosphatase (downregulates AKT pathway)
TSC1/2 inhibitor of mTOR

CYTOSKELETON ASSOCIATED PROTEINS

DCC (proteina N-CAM)
NF-2 (shwannina)
ARK-1 (ovomorulina)
APC (it binds to β-catenin)

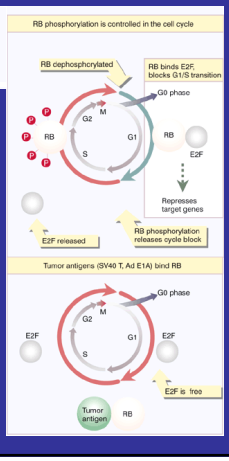
REGULATORS OF AUTOPHAGY

BECN1 (Beclin1, it binds and activates PI3k III)

TUMOR SUPPRESSOR GENE RB PRODUCT p105-RB:
A Nuclear Phosphoprotein Involved in Cell Cycle Regulation

- RB is a gene that was first identified as a tumor suppressor gene **mutated in** the **familial** cancer, **retinoblastoma**
- RB mutations are not restricted to familial retinoblastomas; they occur in **many human cancers**
- Loss-of-function mutations in RB, or production of DNA tumor virus RB binding proteins, **abrogate the need for a major cyclin D function**, which is the cell cycle-dependent phosphorylation of RB

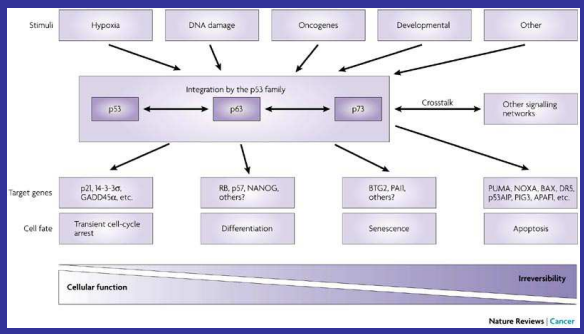
Figure 28.22 A block to the cell cycle is released when RB is phosphorylated (in the normal cycle) or when it is sequestered by a tumor antigen (in a transformed cell).



G0/G1 phase: nonphosphorylated
S phase: phosphorylated by cyclin/cdk

Target of Rb: E2F group of transcription factors, which activate genes that are essential for the S phase
Rb prevents cells from entering S phase; Released E2F prompts the cell to enter S phase
Viral tumor antigens (SV40's T Ag, Adenovirus E1A and HPV E6) bind specifically to Rb
Inactivation of Rb is needed for the cell to cycle, which can be done by cyclic phosphorylation or by sequestering by tumor antigens
Over-expression of Rb impeded cell growth

INVOLVEMENT of p53 in the CONTROL OF CELL PROLIFERATION



p53 suppresses growth or triggers apoptosis

>50% of cancers lost p53 or have mutations in p53 gene
- p53 protein level ↑ in many tumor cells; Oncogene?
- Mutant protein acted as dominant negative mutants ← tetramer

Loss of p53:
- Cell growth advantage; not tissue-specific (many cancers)
- [Wild type p53 restrains cell growth]

Implication: p53 inhibits normal cells' capacity of unrestrained growth?

Evidence that p53 is indeed a tumor suppressor gene:
- p53- mice develop a variety of tumors early in life
- p53 DNA inhibits transformation by oncogenes in cultured cells
- Human Li-Fraumeni Syndrome (rare inherited cancer; heterozygous p53 mutation acted as dominant negative or autosomal dominant)

P53 Suppresses Growth or Triggers Apoptosis

p53 protects cells from consequences of DNA damages p53 ↑
(repair it or destroy if it is unable to repair!)

Activation of p53 → growth arrest or apoptosis
Depends on cell cycle

Other molecular activities of p53
p53 can also activate various pathways
as a transcription factor
Cellular oncoprotein mdm2 inhibits p53 activity
forms a negative feedback circuitry
How p53 trigger apoptosis? Separable from growth arrest

Is p53 function essential for survival?

P53 Suppresses Growth or Triggers Apoptosis

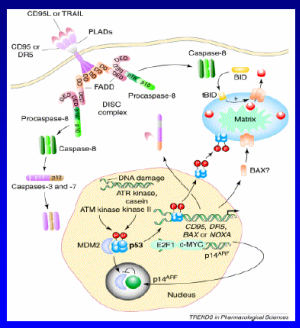
How p53 trigger apoptosis?
separable from growth arrest at the G1 checkpoint

Connection between tumorigenesis & loss of apoptosis
apoptosis inhibits tumorigenesis by eliminating tumorigenic cells

p53 function is probably not essential for survival $p53^-$ animals
Definitive proof the p53 & Rb suppress tumorigenesis still lacking

P53 acts as a sensor that integrates information from many pathways that affect the cell's ability to divide

p53-Mediated Apoptosis



Bratton & Cohen (2001)

Models of p53 action:

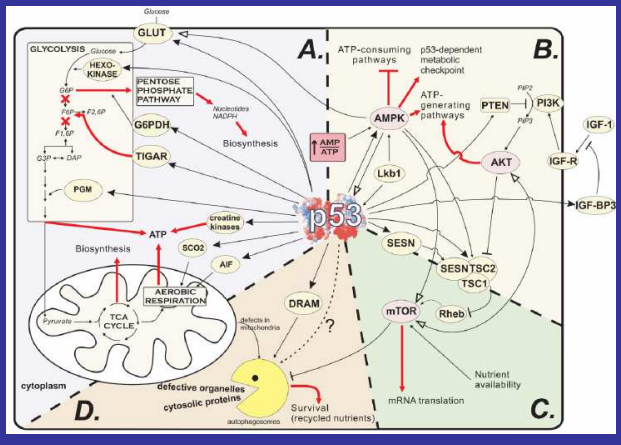
- Transcriptional upregulation of pro-apoptotic genes
  - Pro-apoptotic Bcl-2 members
  - Death receptors (e.g. CD95 & DR5)
- Transcription-independent activation of Bax (BH3-like activity), initiating cyto c release.

p53 and Drug Resistance

- Loss of normal p53 function reduces drug-induced apoptosis and tumor regression.
  - *p53* mutations
  - Defects in the p53 pathway
    Functional mutations or altered expression of its downstream effectors (*PTEN, Bax, Bak,* and *Apaf-1*) or upstream regulators (*ATM, Chk2, Mdm2* and *INK4a/ARF*)
- In many tumor cells, pro-apoptotic signaling via BH3-only proteins is impaired, typically due to mutations in *p53* (e.g., Bak, Bax, Puma, and Noxa)
- Effects of p53 on drug-induced apoptosis is determined by a variety of factors.
- Functional p53 does not appear to be a general determinant of anticancer drug activity in solid tumors.

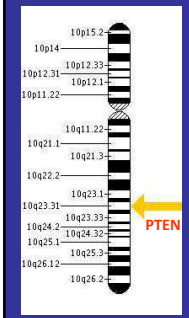
TUMOR SUPPRESSOR GENE p53

- In many tumors, both p53 alleles are deleted and there is no p53
- However, malignant transformation can also occur when certain mutants of p53 are expressed in a cell containing at least one normal p53 allele. These mutations, referred to as **dominant negative**, probably act by binding to and inhibiting the function of the normal p53 protein.
- (most frequent mutation R273H)
-



PTEN

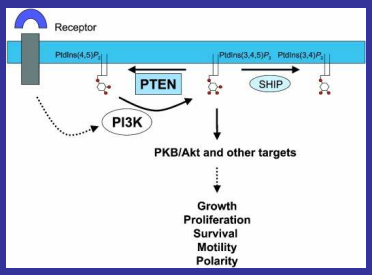
- **PTEN** phosphatase and tensin homolog deleted on chromosome 10
- **MMAC1** mutated in multiple advanced cancers
- **TEP-1** TGFβ-regulated and epithelial cell enriched phosphatase



- PTEN protein is found in almost all tissues in the body
- Is a tumor suppressor gene localized to chromosome 10q23.3
- Is a dual-specificity phosphatase — protein phosphatase / lipid phosphatase
- Acts to suppress cell growth, proliferation, survival and in a more cell sepecific manner plays a role in the establishment of polarity and inhibits the migration of several mammalian cell types
- the human genome contains at least seven gene-like sequences with significant identity to PTEN, including the PI 3-phosphatase TPIP (TPTE and PTEN homologous inositol lipid phosphatase), and also TPTE (transmembrane phosphatase with tensin homology), which appears to lack this activity, expressed sequence tags derived from many of the other gene copies appear to contain frameshift mutations or lack requisite parts of the phosphatase and C2 domains, indicating that these may be pseudogenes.

Lipid phosphatase activity

- lipid phosphatase is a ubiquitous regulator of the cellular PI (phosphoinositide) 3-kinase signalling pathway
- PTEN antagonizes PI 3-kinase signalling by dephosphorylating the 3-position of the inositol ring of PtdIns(3,4,5)P_3 and thus inactivating downstream signalling



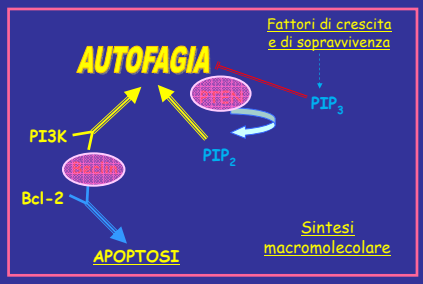
Deregulation of PTEN function in disease

alterations in the expression and activity of the phosphatase have been proposed to play a causal role in the development of several conditions other than cancer, including rheumatoid arthritis, chronic obstructive pulmonary disease and pulmonary fibrosis

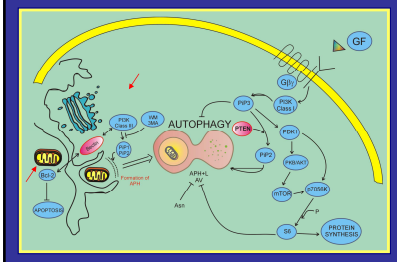
Evidence for mutation of the *PTEN* coding sequence in many diverse tumour types strongly support the status of PTEN as an important tumour suppressor for many types of cancer. In addition, soon after the identification of PTEN, it was discovered that inherited mutations in *PTEN* can cause several human disorders, including Cowden disease, Bannayan–Riley–Ruvalcaba syndrome and *Proteus* syndrome .
Cowden disease in particular is accompanied by an increased cancer risk, specifically of breast and thyroid tumours
Of the 150 or so mutations in PTEN that have been identified in patients suffering from these inherited disorders, none have been described in the C-terminal tail

loss of PTEN drives tumour development through deregulation of PI 3-kinase signalling and, in turn, processes including cell growth, proliferation and survival

PTEN AND P53 ONCOSUPRESSORS REGULATE AUTOPHAGY

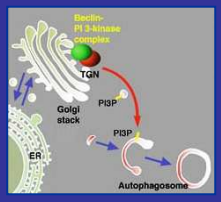


PTEN AND P53 ONCOSUPRESSORS REGULATE BOTH AUTOPHAGY AND CELL SURVIVAL



aa 88 to aa150 in BECLIN 1 mediates the interaction with anti-apoptotic BCL2

BECLIN1 interacts with PI3-K class III to trigger AUTOPHAGY



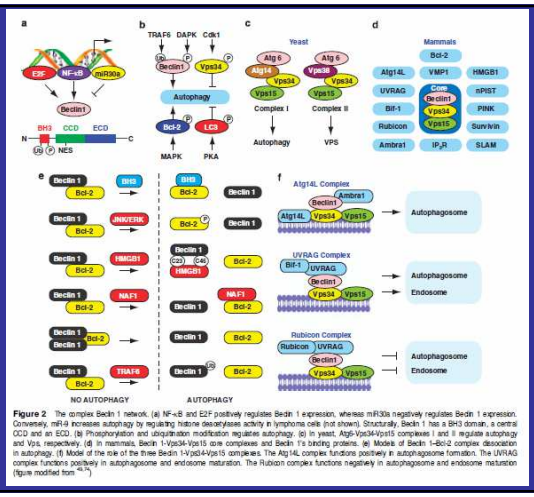
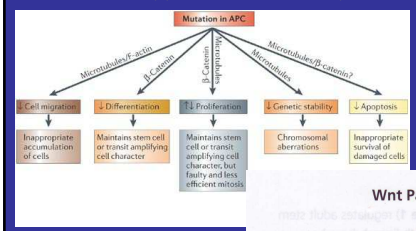
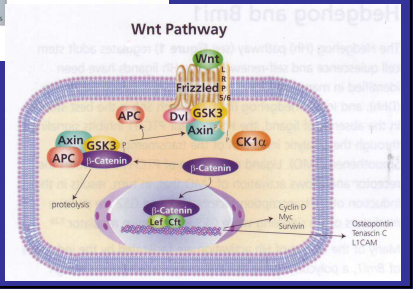


Figure 2 The complex Beclin 1 network. (a) NF-κB and E2F positively regulates Beclin 1 expression, whereas miR30a negatively regulates Beclin 1 expression. Conversely, miR-9 increases autophagy by regulating histone deacetylases activity in lymphoma cells (not shown). Structurally, Beclin 1 has a BH3 domain, a central CCD and an ECD. (b) Phosphorylation and ubiquitination modification regulates autophagy. (c) In yeast, Atg6-Vps34-Vps15 complexes I and II regulate autophagy and Vps, respectively. (d) In mammals, Beclin 1-Vps34-Vps15 core complexes and Beclin 1's binding proteins. (e) Models of Beclin 1–Bcl-2 complex dissociation in autophagy. (f) Model of the role of the three Beclin 1-Vps34-Vps15 complexes. The Atg14L complex functions positively in autophagosome formation. The UVRAG complex functions positively in autophagosome and endosome maturation. The Rubicon complex functions negatively in autophagosome and endosome maturation (figure modified from [42,71])

APC oncosuppressor: its Loss promotes intestinal tumours





BRCA-1 and BRCA-2

BRCA = *Breast Cancer*

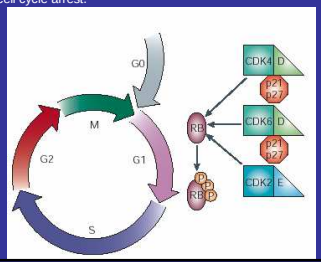
- ✓ Deletion and Loss-Of-Function mutations of both alleles increases the risk of cancers (breast, ovary)
- ✓ 5-10% of breast cancers are familial: 80% of these cancers present with mutations in BCRAdei tumori alla mammella sono famigliari. (BRCA mutations are rare in sporadic breast cancers)
- ✓ BRCA proteins are involved in Double-Strand break DNA repair.

ATM

- Analysis of families carrying the trait suggests that ATM heterozygotes are at a somewhat greater risk for cancer development, notably breast cancer
- Ataxia-telangiectasia mutant cells show **defects in the G1/S, S, and G2/M checkpoints**, indicating that ATM is a common element in all three of these responses

INHIBITORS OF CYCLIN-DEPENDENT KINASES IN CANCER

- Inhibitors of cell cycle progression are candidate tumor suppressor genes since they function normally to restrain cell division
- There are several inhibitors of cyclin-dependent protein kinases
- The genes encoding two related CDKIs, **p15 and p16**, are located in the neighborhood of a tumor suppressor locus involved in familial melanoma and other cancers, and several alleles of p16 derived from tumors are deficient in p16-mediated cell cycle arrest.



COOPERATION BETWEEN ONCOGENES & TUMOR SUPPRESSOR GENES

- Inappropriate advancement of the cell cycle (e.g. following viral infection, oncogene activation, or loss of tumor suppressors that regulate the cell cycle) can trigger apoptosis:
  - ✓Following adenovirus infection, the adenovirus protein E1A can cause G1 to S transition, in part by binding to and inactivating RB
  - ✓A normal cell responds to this by initiating apoptosis
  - ✓thus, by itself, E1A is not a potent oncogene in normal cells because its expression can cause cell death
  - ✓However, in the case of oncosuppressor loss, E1A can induce a tumoral phenotype (E1A is transforming when p53 or RB is inactivated)
- A similar effect is seen with loss of RB or overexpression of E2F.

COOPERATION BETWEEN ONCOGENES & TUMOR SUPPRESSOR GENES

- Also other oncogenes, such as MYC and FOS, encode proteins that can cause advancement of the cell cycle. In normal cells, the cellular response to these alterations is apoptosis, while in cells lacking certain oncosuppressor the hyper-expression of MYC or FOS can lead to trasnformation.
- Note: MYC also cooperate with RAS !!!

COOPERATION BETWEEN ONCOGENES & TUMOR SUPPRESSOR GENES

- The **combination of a stimulus to the cell cycle and an anti-apoptotic factor** or gene results in cell growth, usually at a more rapid rate than their normal counterparts, and often with an altered, or transformed morphology
- This is a possible explanation for many instances of **oncogene cooperativity** that occurs when two different genes can fully transform primary cells, whereas each gene on its own cannot