CANCER

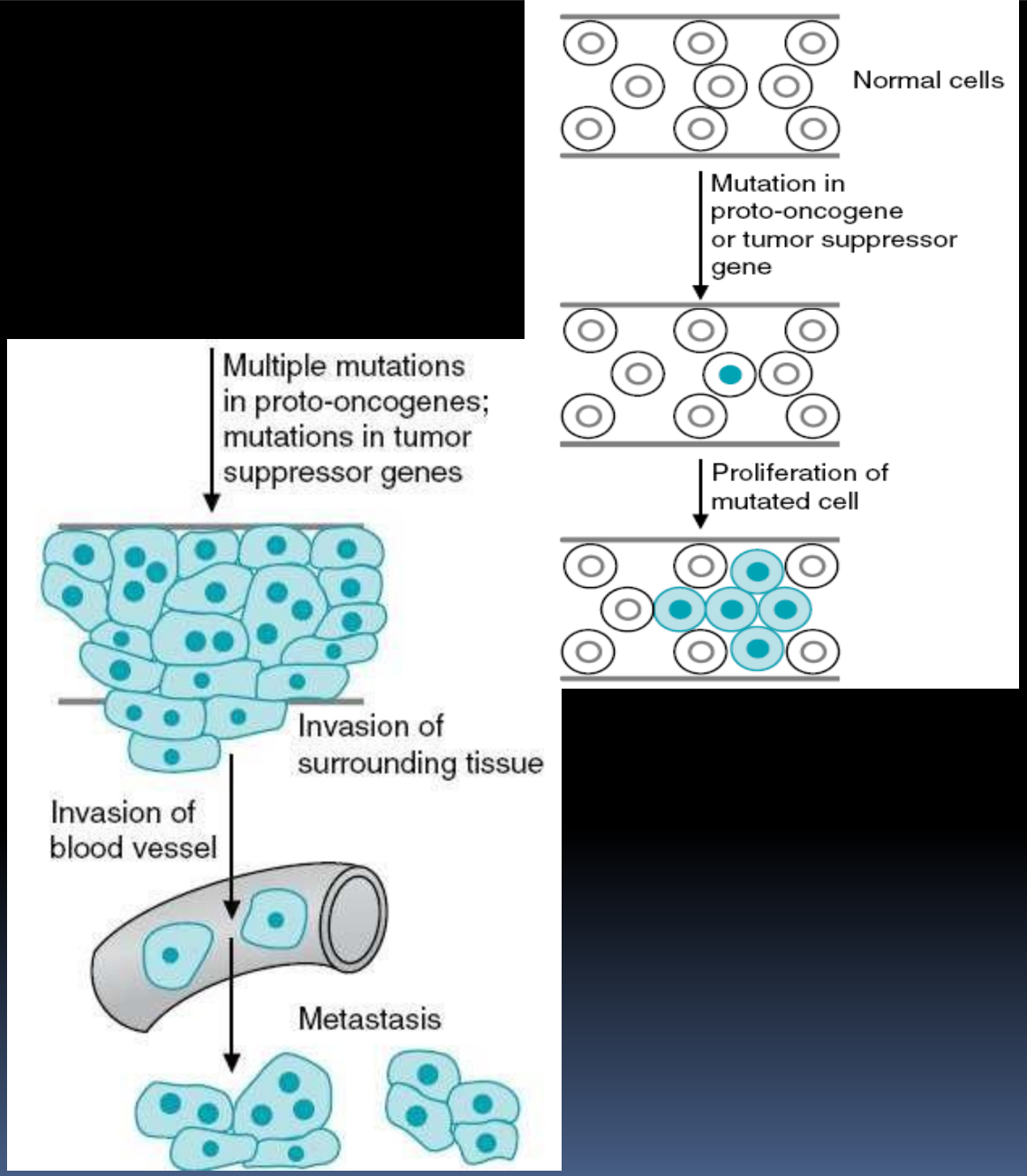
MUNMUN
CHATTERJEE

•The term cancer applies to a group of diseases which cells grow abnormally and form a malignant tumor.

•Malignant cells can nearby tissues and metastasize (establish y areas of growth).

•This aberrant growth pattern results from mutations in genes tha egulate proliferation, differen tion, and vival of cells in a multicellular organism.

• Because of these genetic changes canc no longer respond to that g vern growth of normal cells


Normal cells
Mutation in proto-oncogene or tumor suppressor gene
Proliferation of mutated cell
Multiple mutations in proto-oncogenes; mutations in tumor suppressor genes
Invasion of surrounding tissue
Invasion of blood vessel
Metastasis

- *Oncogenes* – The genes involved in the development of cancer

  normal cells do contain DNA sequence similar to viral oncognenes

To distinguish these two genes: V-src (viral gene) and C-src (cellular gene)

- Protooncogenes – normal constituents of cells whose function is to promote proliferation or cell survival.

These genes can code for growth factors, growth factor receptors, signal transduction proteins, intracellular kinases and transcription factors.

- Tumor suppressor genes (normal growth suppressor genes) -- encode proteins that inhibit proliferation, promote cell death, or repair DNA

Activation of oncogenes or absence /inactivation of tumor suppressor genes can lead to cancer.

Protooncogenes are regulatory genes

- Products of many oncogene are polypeptide growth factor

  ex: sis gene produce PDGF - normal wound healing.

- Product act as receptor for growth factor

  ex: erb-B produces receptor for EGF

- Some act on key IC pathway involved in growth control

  ex: Src Product → receptor of EGF, insulin, PDGF.

- C-oncogenes are under the control of regulatory genes & expressed only when required.

- When virus enters, an extra oncogene is inserted so as to produce continuous expression of gene leading to uncontrolled cellular activity & malignant transformation.

Table 51.7. Some important growth factors

Growth factor	Abbre-viation	Mol. wt. kilo D	Chromo-some no.	Produced by location	Function
Epidermal growth factor	EGF	6	7	Fibroblasts, submaxillary gland	Stimulates epidermal and epithelial cells
Transforming growth factor-a	TGF-α	5.6	-	Tumor cells, placenta	Similar to EGF
Transforming growth factor-b	TGF-β	25	-	Platelets, placenta	Inhibition of fibroblasts
Platelet derived growth factor	PDGF	32	5	Platelets	Accelerates wound healing
Nerve growth factor	NGF	26	1	Submaxillary gland	Growth of sensory neurons
Insulin-like growth factor	IGF-1	11	15	Serum	Sulfation into cartilage
Erythropoietin	EP	39	7	Kidney	Stimulates erythropoiesis
Granulocyte macrophage colony stimulating factor	GMCSF	18-30	5	Endothelial cells, and T cells	Stimulates granulocytes, monocytes,magakaryocytes
Granulocyte colony stimulating factor	GCSF	20	17	Endothelial cells, and fibroblasts	Stimulates granulocytes
Monocyte colony stimulating factor	MCSF	70-90	5	Endothelial cells	Stimulates monocytes
Tumor necrosis factor- alpha	TNF-α	17	6	Monocyte	Necrosis of tumor cells, proliferation of leukocytes

Many factor activate protooncogenes

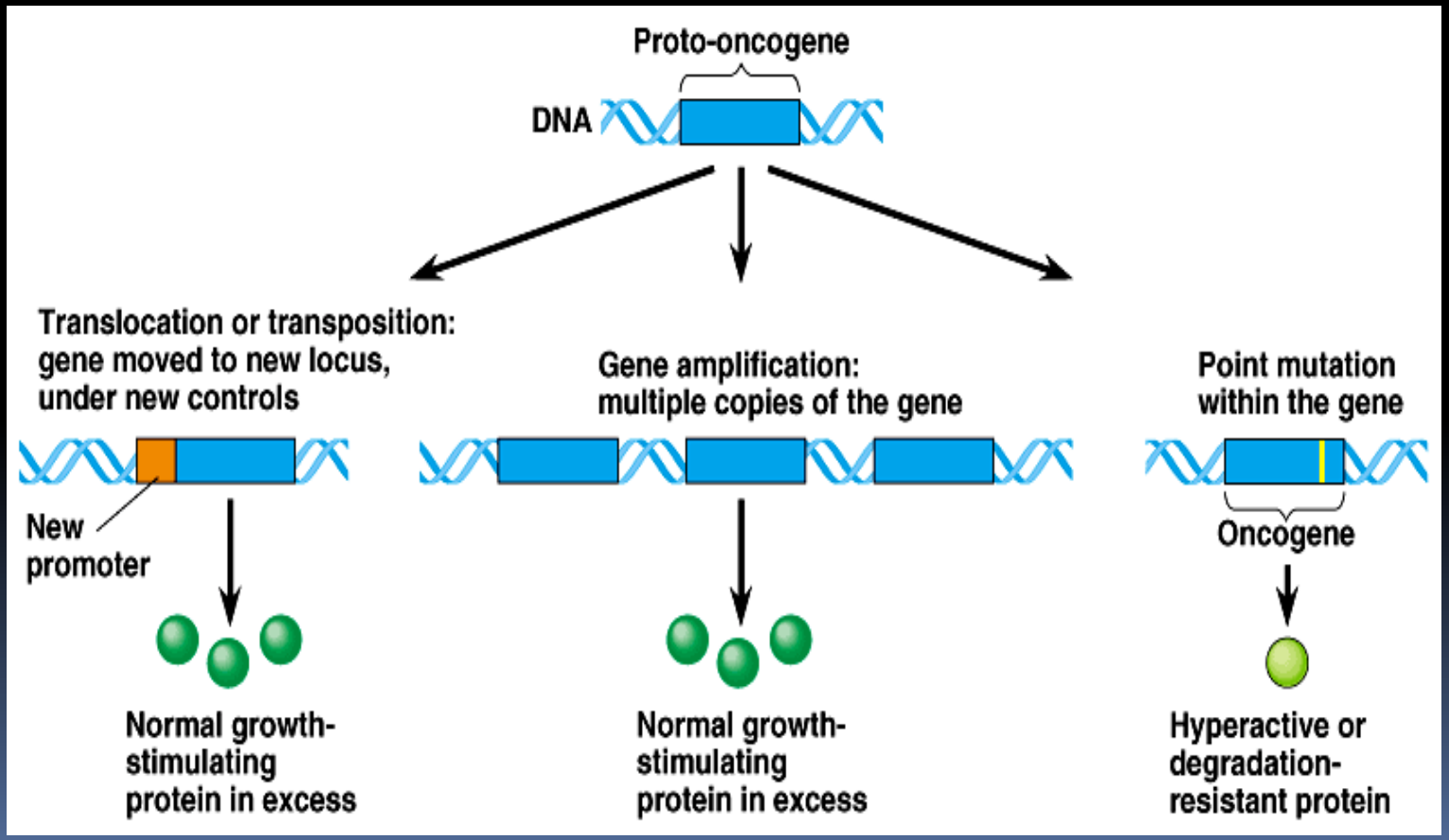
Virus
Chemical carcinogens
Chromosomal translocation
γ-rays
Spontaneous mutation

All such factors may converge into one biochemical abnormalities "Activation of protooncogenes" leading to malignancy

- Because neoplasia is a multistep process, more than one of these mechanisms often contribute to the genesis of human tumors by altering a number of cancer-associated genes.
- Full expression of the neoplastic phenotype, including the capacity for metastasis, usually involves a combination of protooncogene activation and inactivation tumor suppressor gene.

- 5 mechanisms of activation :

1. Promoter insertion
2. Enhancer insertion
3. Chromosomal translocation
4. Gene amplification
5. Point mutations



1. Promoter Insertion

- Certain retro viruses lack oncogenes (eg : avian leukemia viruses) but may cause cancer over a long period of time.

Viral insertion into chromosomes:

- In retrovirus, cDNA is made from their RNA by enzyme reverse transcriptase.
- cDNA gets inserted into host genome
- Integrated dscDNA → provirus
- This proviral DNA takes over the control of transcription of cellular chromosomal DNA & transforms the cell.

  eg: Avian leukemia

2. Enhancer Insertion

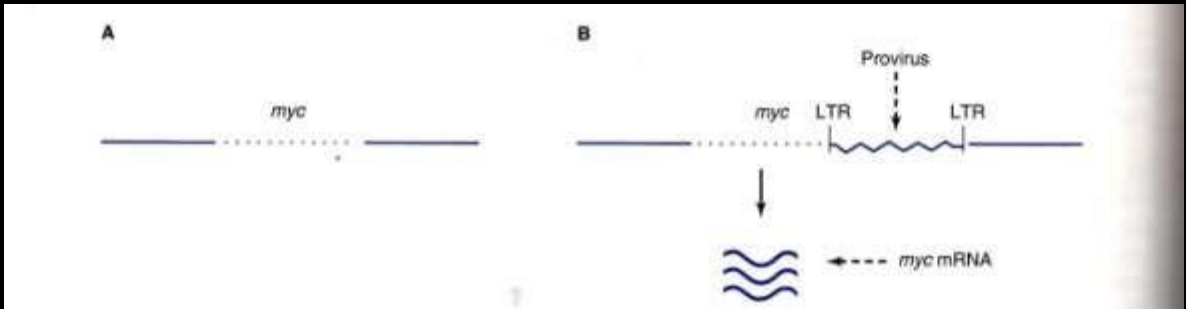


Figure 62–4. Schematic representation showing how enhancer insertion may activate a proto-oncogene. **A:** Normal chicken chromosome, showing an inactive *myc* gene. **B:** An avian leukemia virus has integrated in the chromosome in its proviral form, adjacent to the *myc* gene. However, in this instance, the site of integration is just downstream of the *myc* gene and it cannot act as a promoter (Figure 62–6). Instead, a certain proviral sequence acts as an enhancer element, leading to activation of the upstream *myc* gene and its transcription. For simplicity, only one strand of DNA is depicted and other details have been omitted.

3. Chromosomal translocation

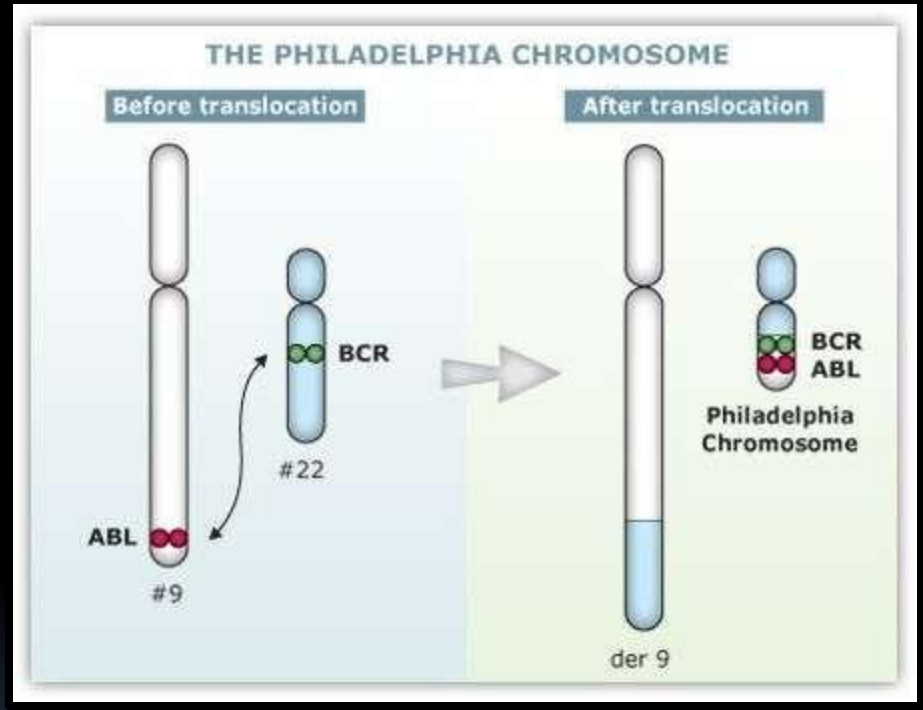
- Rearrangement of genetic material by splitting off a small fragment of chromosome which is joined to another chromosome.

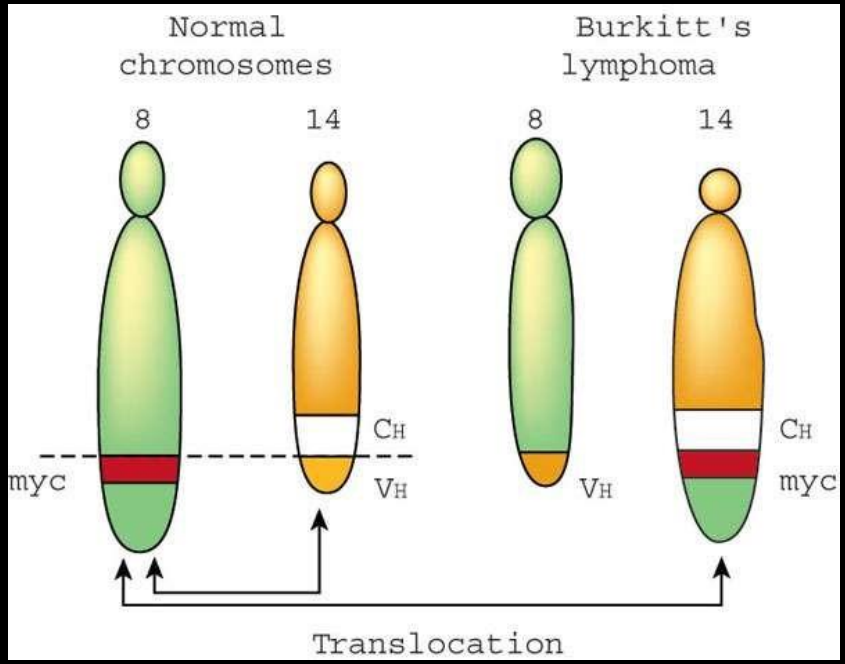
- Over expression of proto oncogenes

  eg: Burkitts lymphoma

  Chronic myeloid leukemia

Thebcr/abl fusion, created on the chromosome 22, encodes a chimeric protein of 210 kDa, with increased tyrosine kinase activity and abnormal cellular localization. 20% of cases of ALL. Overexpression of the bcl-2 protein inhibits apoptosis, leading to an imbalance between lymphocyte proliferation and programmed cell death.





- c-myc finds itself in a region of active gene transcription, and it may simply be the overproduction of the c-myc product (a transcription factor essential for cell division) that propels the lymphocyte down the pathway towards cancer.

4. Gene amplification

- Certain DNA sequence is amplified several fold in some cancers.

- Gene amplification was first discovered as a mechanism by which some tumor cell lines can acquire resistance to growth-inhibiting drugs. Methotrexate becomes inactive due to gene amplification resulting in a several fold increase in activity of DHR.

- Studies then demonstrated that three protooncogene families-myc, erb B, and ras-are amplified in a significant number of human tumors.

- About 20% to 30% of breast and ovarian cancers and some types of SCC show c-myc amplification.

- Amplification of N-myc correlates strongly with advanced tumor stage in neuroblastoma

5. Mutations:

- Mutations activate protooncogenes through structural alterations. These alterations, which usually involve critical protein regulatory regions, often lead to the uncontrolled, continuous activity of the mutated protein.

- Various types of mutations, such as base substitutions, deletions, and insertions, are capable of activating protooncogenes.

- **In human tumors the most characterized oncogene mutations are base substitutions (point mutations) that change a single amino acid within the protein.**

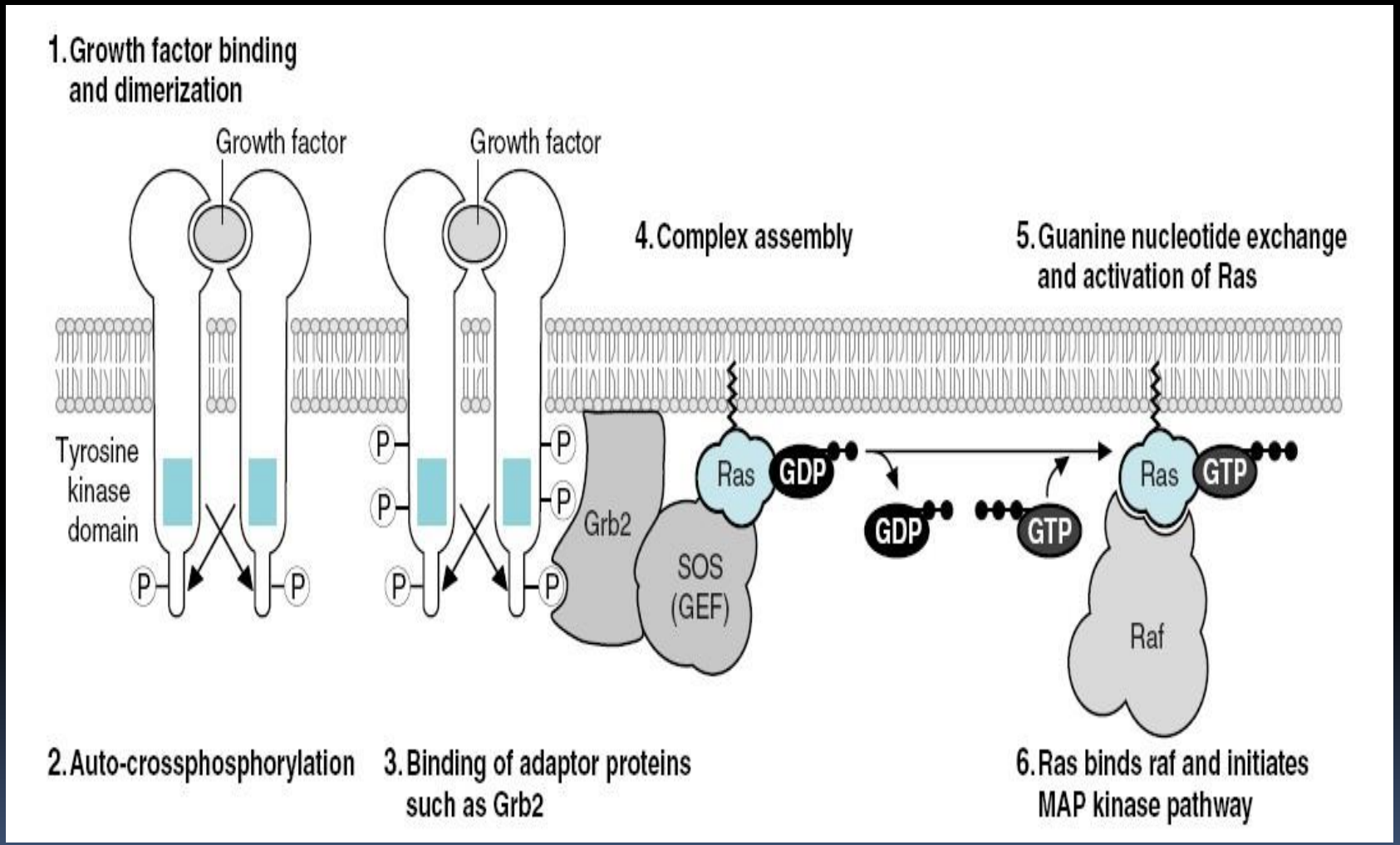
- Mutations in DNA that give rise to cancer may be inherited or caused by chemical carcinogens, radiation, viruses, and by replication errors that are not repaired.

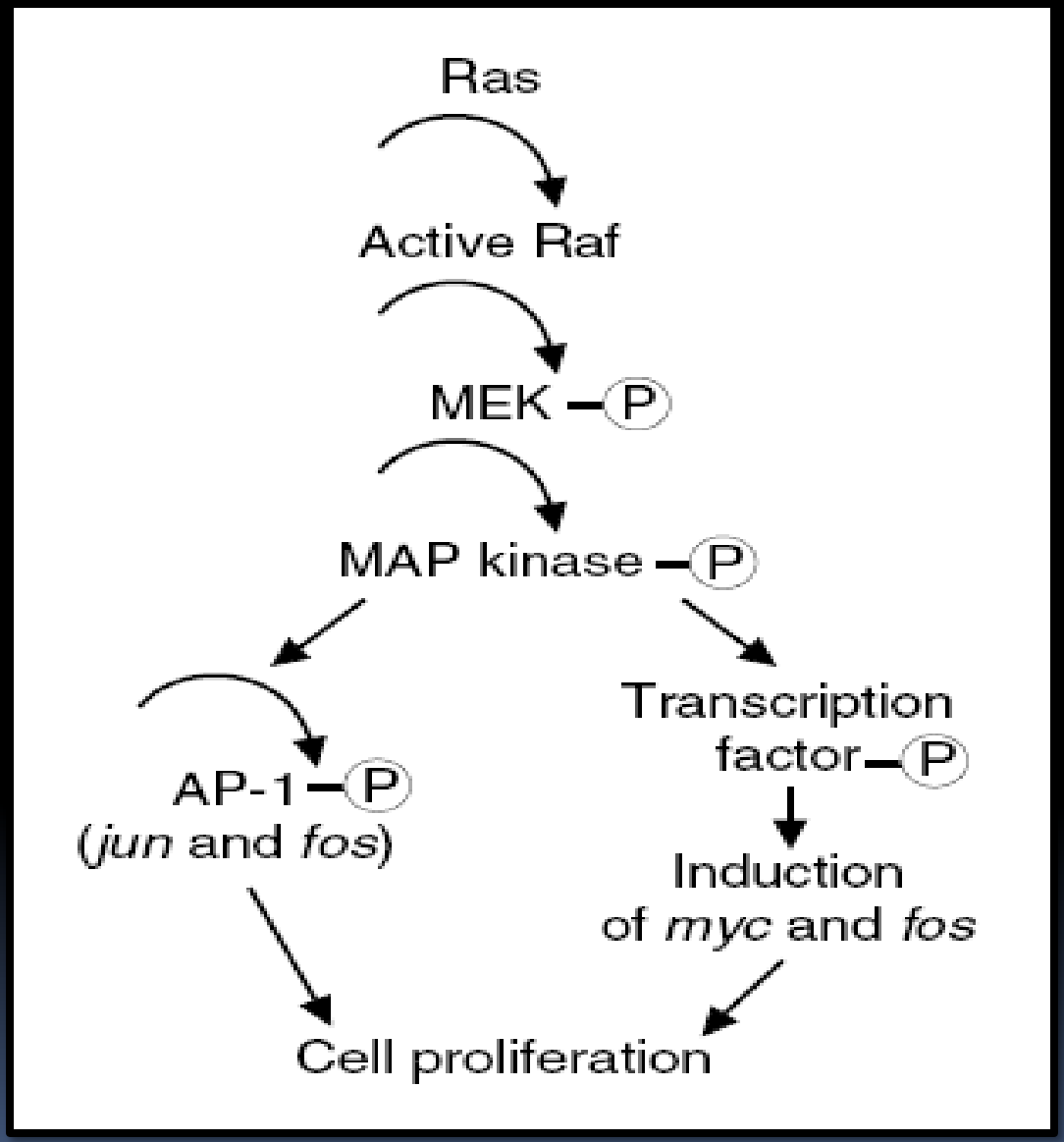
Point mutation

- Point mutations are frequently detected in the ras family of protooncogenes (K-ras, H-ras, and N-ras).
- Single most dominant cause of many human tumor.
- Ras protein M.W 21000(P_{21})

- Inactive ras is in bound state with GDP.

- When cells are stimulated by GF, ras P_{21} get activated by exchanging GDP for GTP.
- In normal cells, the activity of ras P_{21} is short lived because of GTPase activity.
- Point mutation cause altered ras P_{21} lacking GTPase activity


1. Growth factor binding and dimerization
Growth factor
Growth factor
Tyrosine kinase domain
P
P
P
P
P
P
P
P
Grb2
SOS (GEF)
4. Complex assembly
Ras
GDP
GDP
GTP
5. Guanine nucleotide exchange and activation of Ras
Ras
GTP
Raf
2. Auto-crossphosphorylation
3. Binding of adaptor proteins such as Grb2
6. Ras binds raf and initiates MAP kinase pathway


Ras
Active Raf
MEK – P
MAP kinase – P
AP-1 – P
(jun and fos)
Transcription
factor – P
Induction
of myc and fos
Cell proliferation

- Studies have found K-ras mutations in about 30% of lung adenocarcinomas, 50% of colon carcinomas, and 90% of carcinomas of the pancreas.

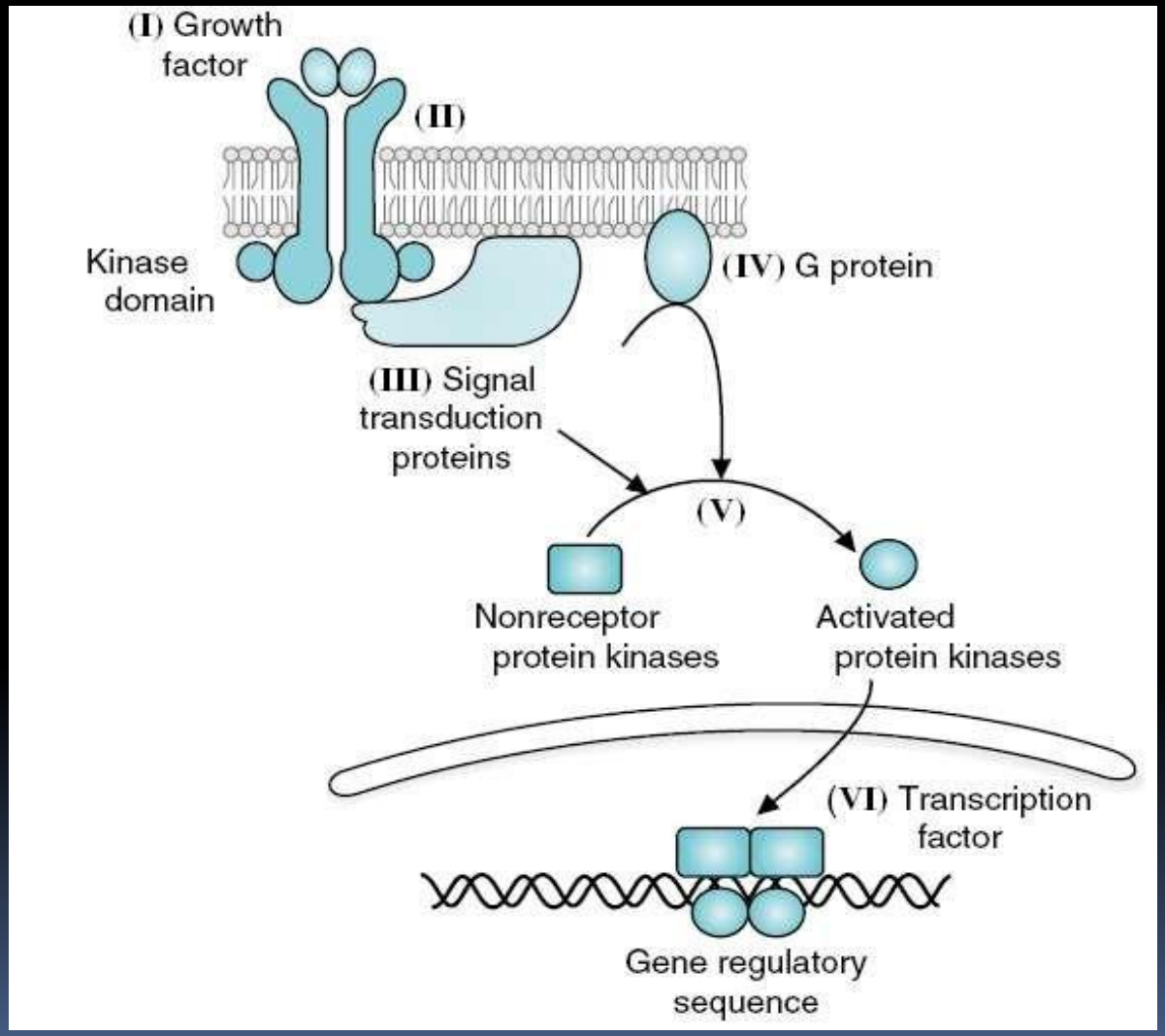
- N-ras mutations – hematologic malignancies

- Another significant example of activating point mutations is represented by those affecting the ret protooncogene in multiple endocrine neoplasia type 2A syndrome (MEN2A)

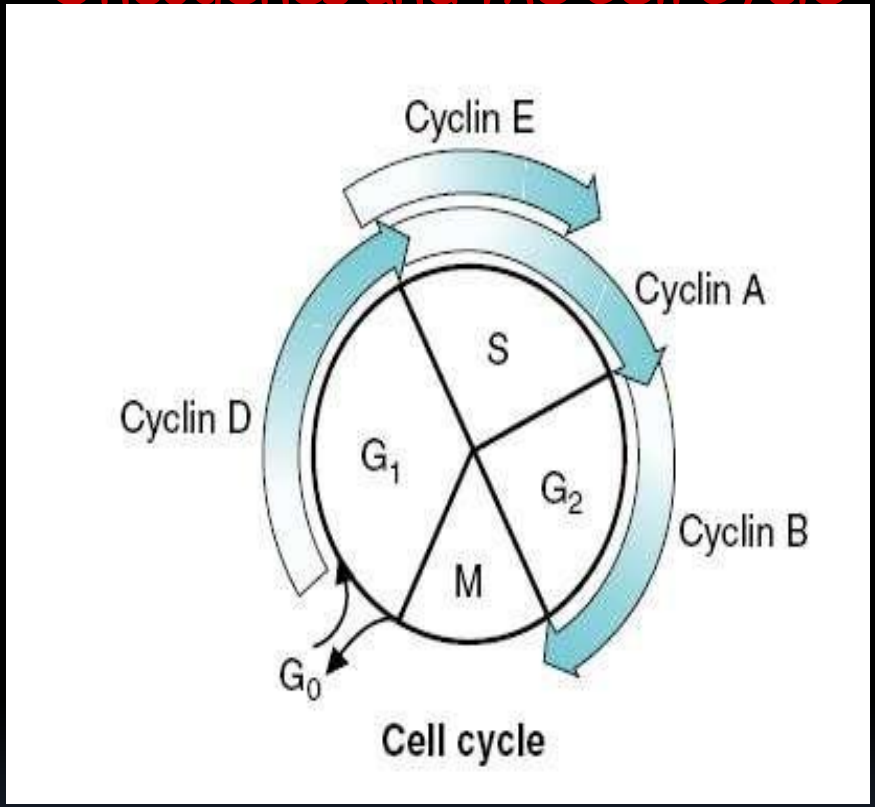
Growth factors

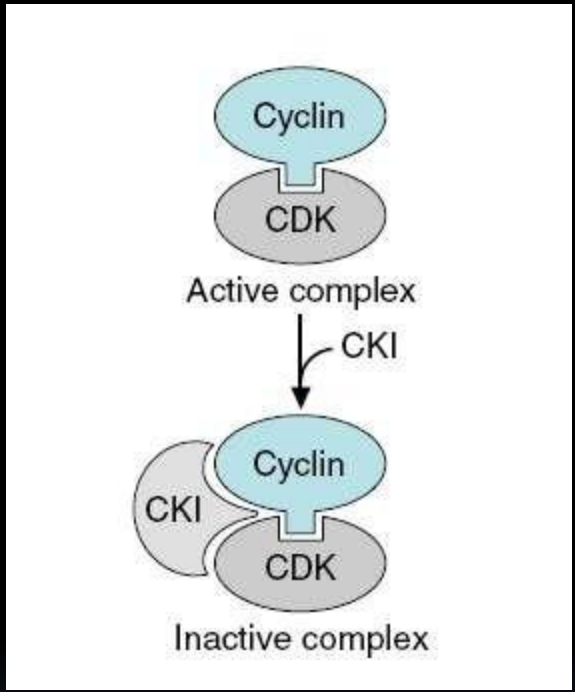
- The genes for both growth factors and growth factor receptors are oncogenes.
- Growth factors generally regulate growth by serving as ligands that bind to cellular receptors located on the plasma membrane (cell-surface receptors) .
- Binding of ligands to these receptors stimulates a signal transduction pathway in the cell activating the transcription of certain genes.
- If too much of a growth factor or a growth factor receptor is produced, the target cells may respond by proliferating inappropriately.
- Growth factors receptors may also become oncogenic through translocation or point mutations.

Mechanism of action of oncogens



Oncogenes and the Cell Cycle





- Because the cell is committed to DNA replication and division once it enters the S phase, multiple regulatory proteins are involved in determining whether the cell is ready to pass this checkpoint.
- These regulatory proteins include:
- cdk4 and cdk6 -which are constitutively produced throughout the cell Cycle
- cyclin D - whose synthesis is only induced after growth factor stimulation of a quiescent cell
- the retinoblastoma gene product (Rb),
- and a class of transcription factors known collectively as E2F.

Failure of check point in cell cycle result in cancer :

- Intrinsic error rate
- After a period of arrest even though damage remains unpaired, the cell may resume the cycle.
- Check point may be mutated leading to unchecked growth cancer ⟶

Antioncogenes / oncosuppressor genes

- Normally protect the individual from getting the cancer by inhibiting the proliferation in response to certain signals such as DNA damage.

- When this gene is deleted or mutated, cancer results.

- Antioncogenes acts by :
- directly regulating the cell cycle.
- Affect the receptors and signal transduction
- Affect cell adhesion.

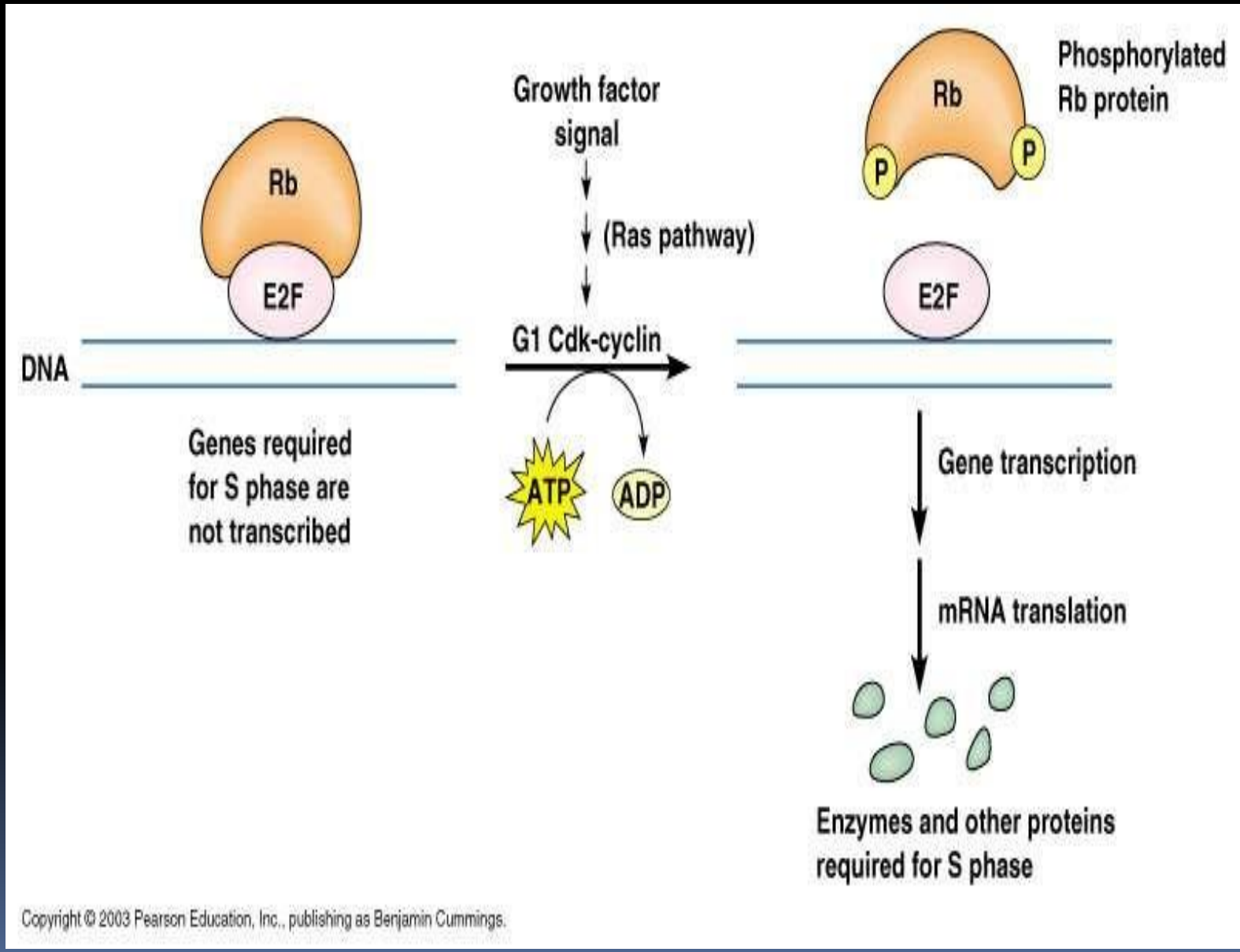
Table 51.6. Important oncosuppressor genes

Name of the oncosuppressor	Abbre-viation	Chromosome no.
Retinoblastoma	RB	13
Wilms' tumor	WT	11
Familal adenomatous polyposis	FAP	5
Deleted in colon cancer	DCC	18
Gene for protein-53	p53	17
Familial breast cancer	BRAC	3
von Hippel-Lindau gene	VHL	3

PTEN -- Detected in gliomas, prostate cancer.
NF-1 -- neurofibromatosis

RETINOBLASTOMA (rb) GENE

- Isolated from pt of retinoblastoma
- In binds and in activates E_2F a transcription factor
- rb inhibits cell cycle at G_1phase.
- Cyclin D inactivates Rb which is normal mechanism to over come G_1 arrest by Rb.
- Certain tumour antigens combine with rb
- So Rb cannot inhibit cell cycle leading to continuous cell division cancer.


Rb
E2F
DNA
Genes required
for S phase are
not transcribed
Growth factor
signal
(Ras pathway)
G1 Cdk-cyclin
ATP
ADP
Rb
P
P
Phosphorylated
Rb protein
E2F
Gene transcription
mRNA translation
Enzymes and other proteins
required for S phase
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- P_{53}

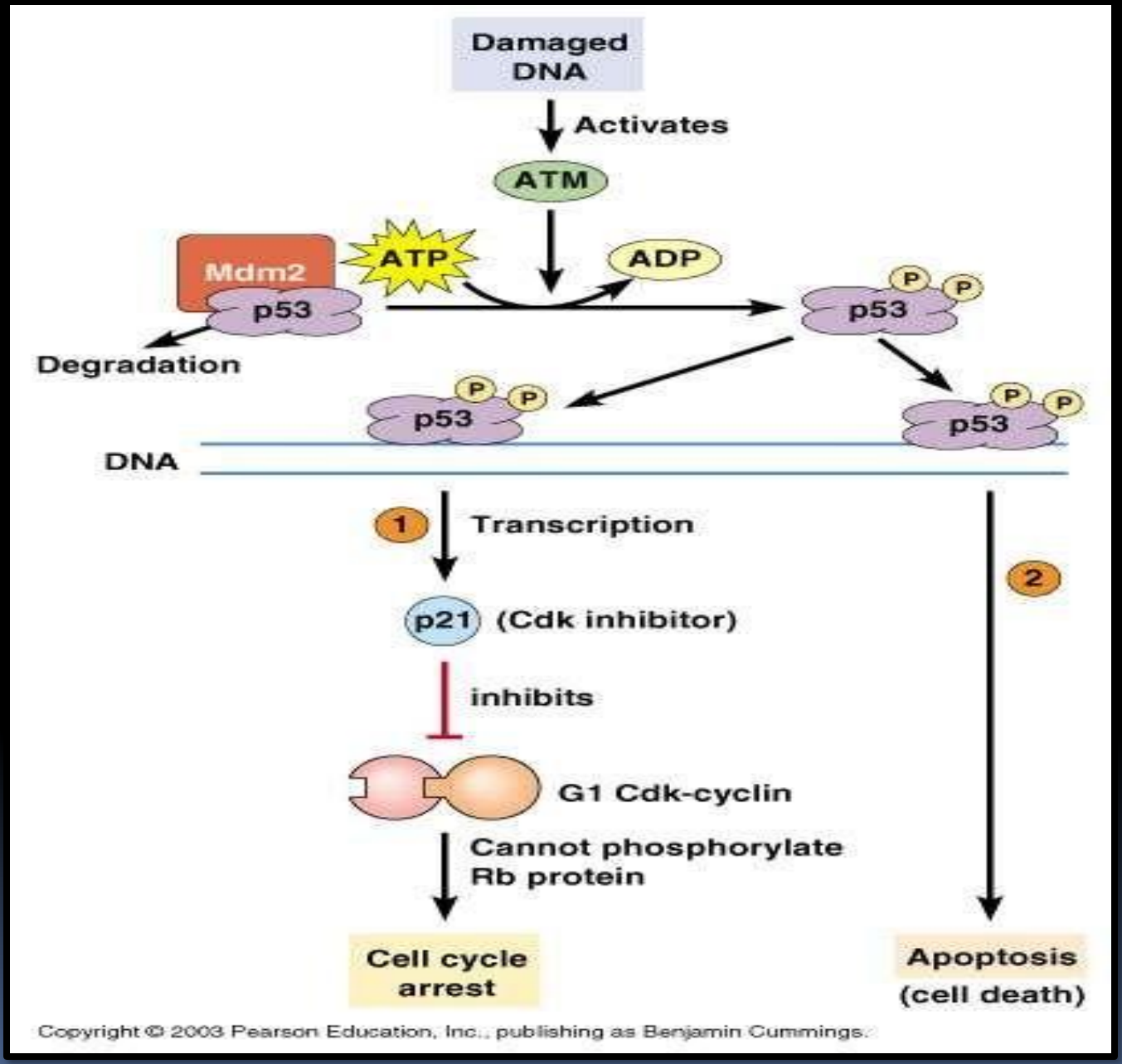
- Gene encodes a phosphoprotein with MW 53,000 with 375 a.a
- **The guardian of the genome**

- It is a transcription factor regulating the cell cycle and apoptosis.

- It block the cells that have damaged DNA by triggering the production of another protein P_{21}, which blocks cell division until the damage is repaired.

- **If DNA damage is serve, P_{53} directs the cell to commit suicide by apoptosis program**

- Most tumors have a complete absence of P_{53} ,other show mutation that lead to non function P_{53}
- **Inheritance of a mutation in p53 leads to Li-Fraumeni syndrome.**



GADD (Growth Arrest DNA Damage)

Activates two apoptotic gene bax and IGFBP3

NF-1 regulates ras by activating GTPase activity

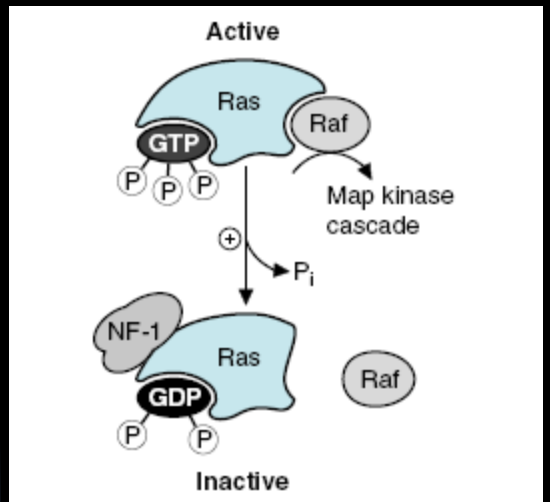
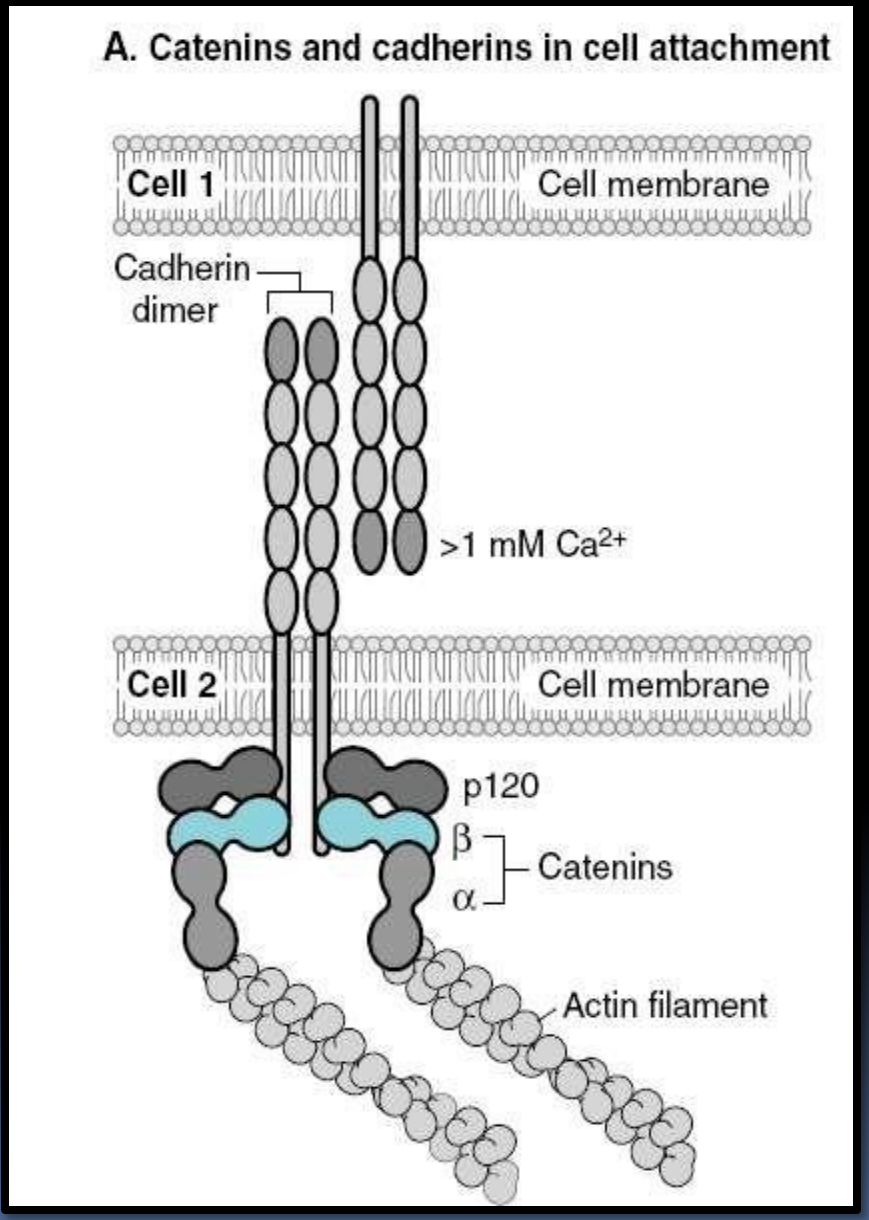
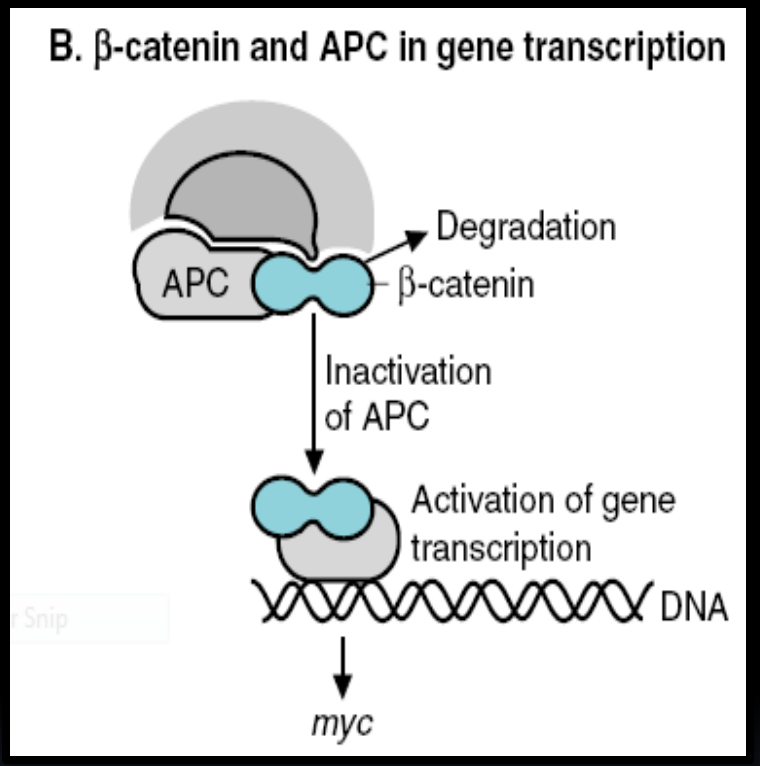


Fig.18.11. NF-1 (neurofibromin) binds to Ras and activates its GTPase activity, thereby decreasing cell proliferation. A mutation in neurofibromin leads to prolonged GTP binding and activation of Ras.

Tumor Suppressor Genes affect Cell Adhesion





Inherited mutation in APC – familial adenomatosis polyposis

Table 62–6. Some differences between oncogenes and tumor suppressor genes.[1]

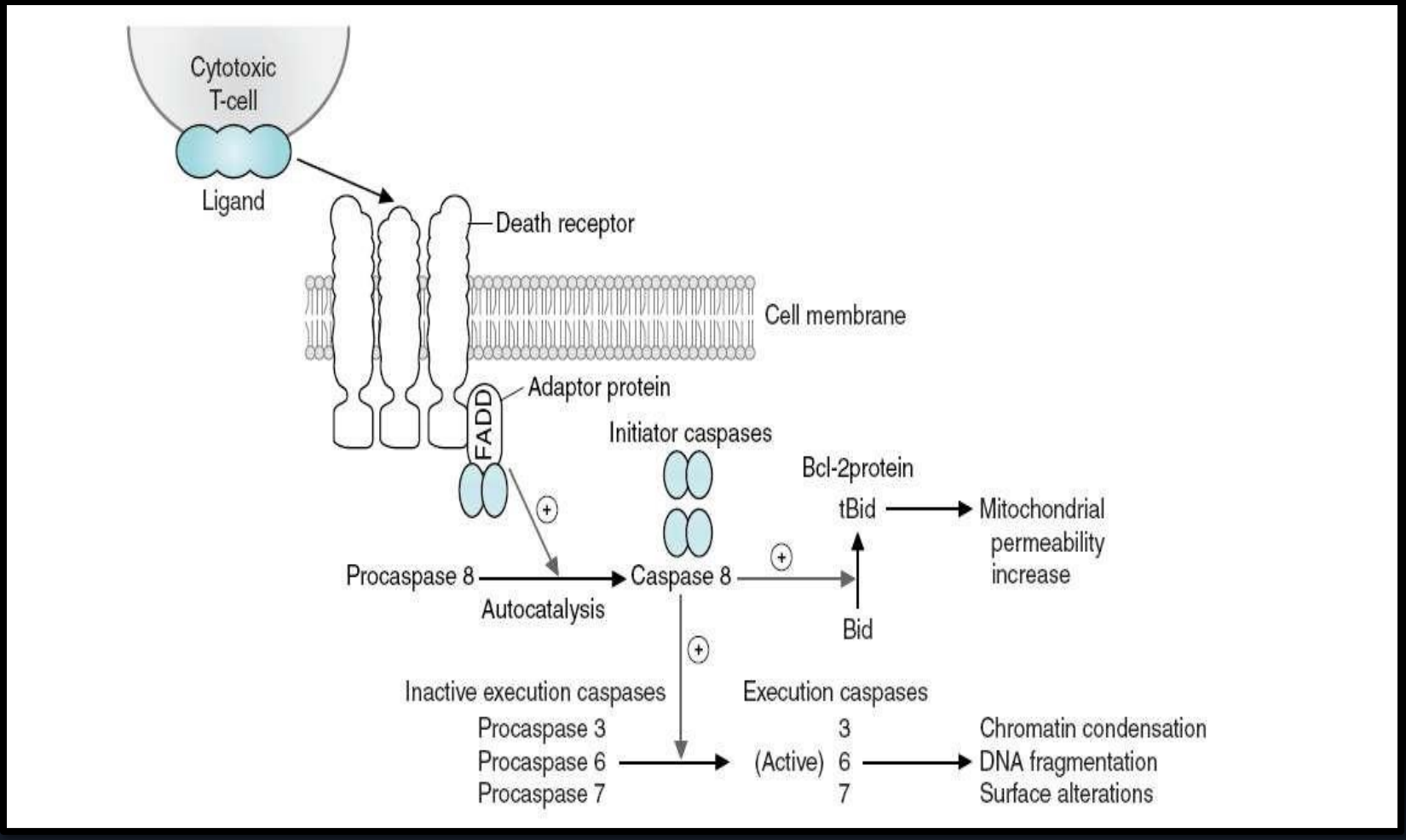
Oncogenes	Tumor Suppressor Genes
Mutation in one of the two alleles sufficient for activity; act dominant to wild-type	Mutations in both alleles or a mutation in one followed by a loss of or reduction to homozygosity in the second
"Gain of function" of a protein that signals cell division	Loss of function of a protein
Mutation arises in somatic tissue, not inherited	Mutation present in germ cell (can be inherited) or somatic cell
Some tissue preference	Strong tissue preference (eg, effect of *RB1* gene in the retina)

Apoptosis

- Cell Cycle Suppression and Apoptosis. Normal cell growth depends on a balanced regulation of cell cycle progression and apoptosis (programmed cell death) by proto-oncogenes and growth suppressor genes.

- At checkpoints in the products of tumor suppressor genes slow growth in response to signals from the cell's environment, including external growth inhibitory factors, or to allow time for repair of damaged DNA, or in response to other adverse circumstances in cells.

- Alternately, cells with damaged DNA are targeted for apoptosis so that they will not proliferate. Many growth-stimulatory pathways involving proto-oncogene.



Apoptotic mediating gene – c-fos, p53, rb

Antiapoptotic gene – bcl-2 , bcl-x, bcl-w

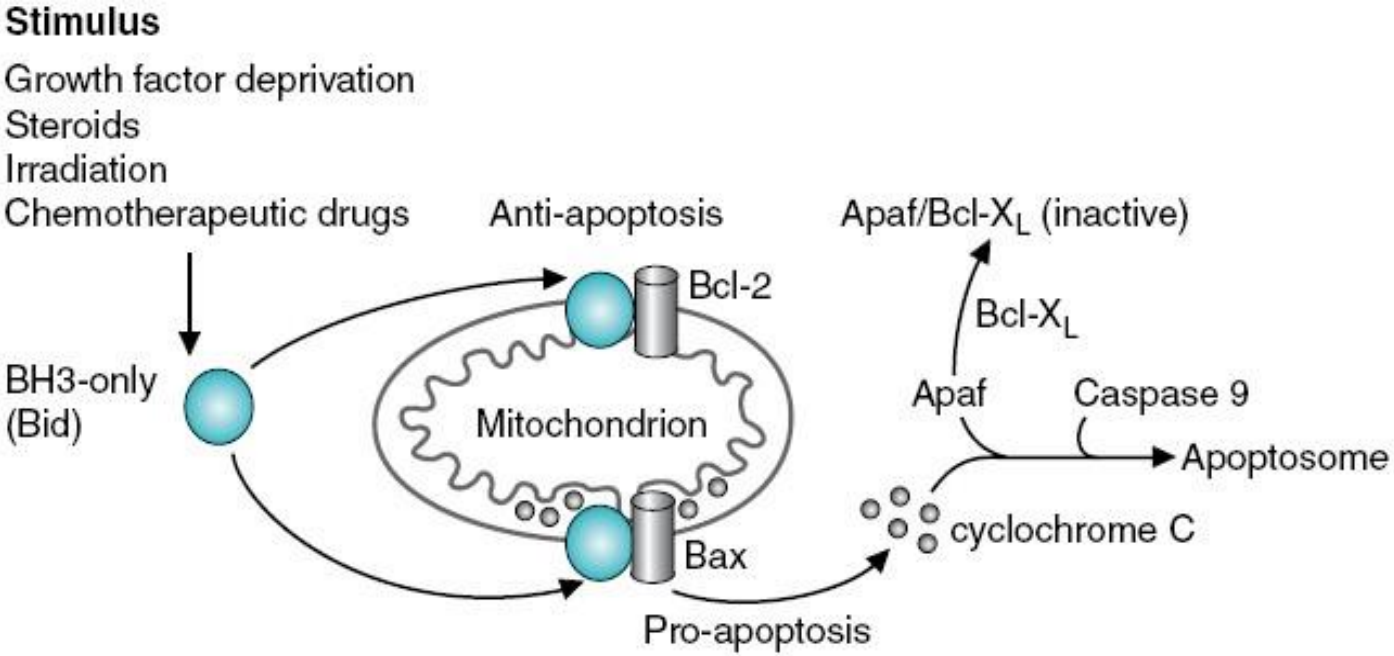


Fig. 18.16. Roles of the Bcl-2 family members in regulating apoptosis. Bcl-2, which is anti-apoptotic, binds Bid (or tBid) and blocks formation of channels that allow cytochrome c release from the mitochondria. Death signals result in activation of a BH3-only protein such as Bid, which can lead to mitochondrial pore formation, swelling, and release of cytochrome c. Bid binds to and activates the membrane ion-channel protein Bax, activating cytochrome c release, which binds to Apaf and leads to formation of the apoptosome.

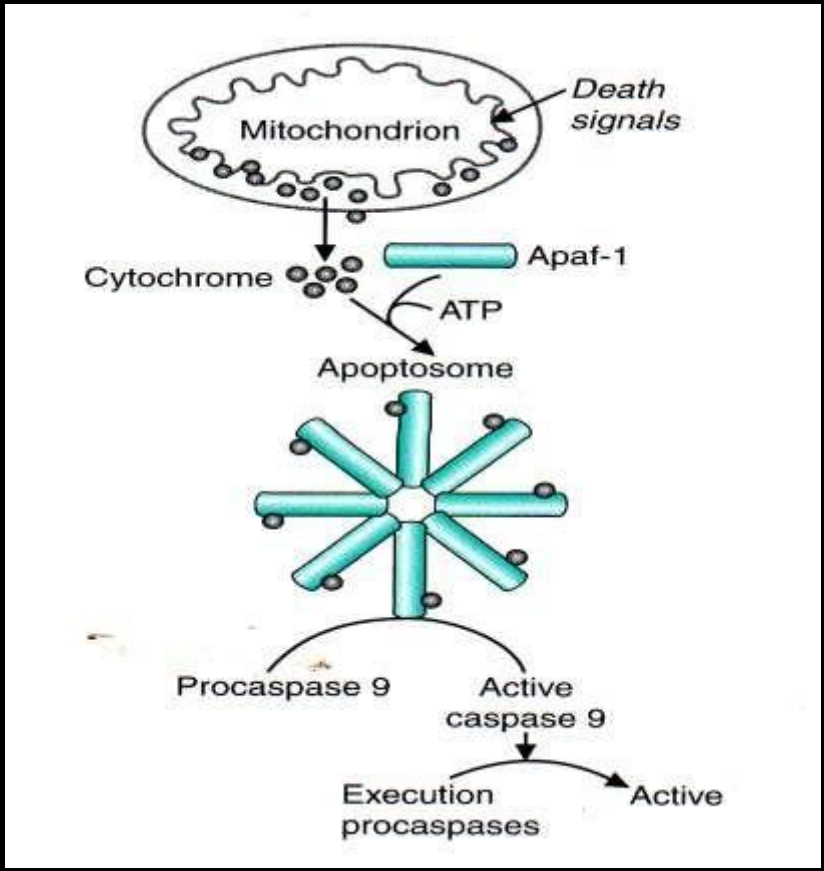


Fig. 18.15. The mitochondrial integrity pathway releases cytochrome c, which binds to Apaf and forms a multimeric complex called the apoptosome. The apoptosome converts procaspase 9 to active caspase, which it releases into the cytosol.

Cancer Cells Bypass Apoptosis

•activation of growth factor–dependent signaling pathways that inhibit apoptosis **" PDGF/Akt/BAD pathway"**.

• phosphorylation of the pro-apoptotic BH3-only protein BAD, which inactivates apoptosis.

•One of the features of neoplastic transformation is loss of GF dependence for survival.

Mutations in Repair Enzymes

- DNA repair enzymes are tumor suppressor genes in the sense that errors repaired before replication do not become mutagenic.
- If DNA repair enzymes are absent, mutations accumulate much more rapidly
- once a mutation develops in a growth regulatory gene, a cancer may arise.
- Ex: inherited mutations in the tumor suppressor genes brca1 and brca2 predispose women to the development of breast cancer.
- HNPCC (hereditary non-polyposis colon cancer) – due to inherited mutations in enzymes involved in the DNA mismatch repair system.
- --

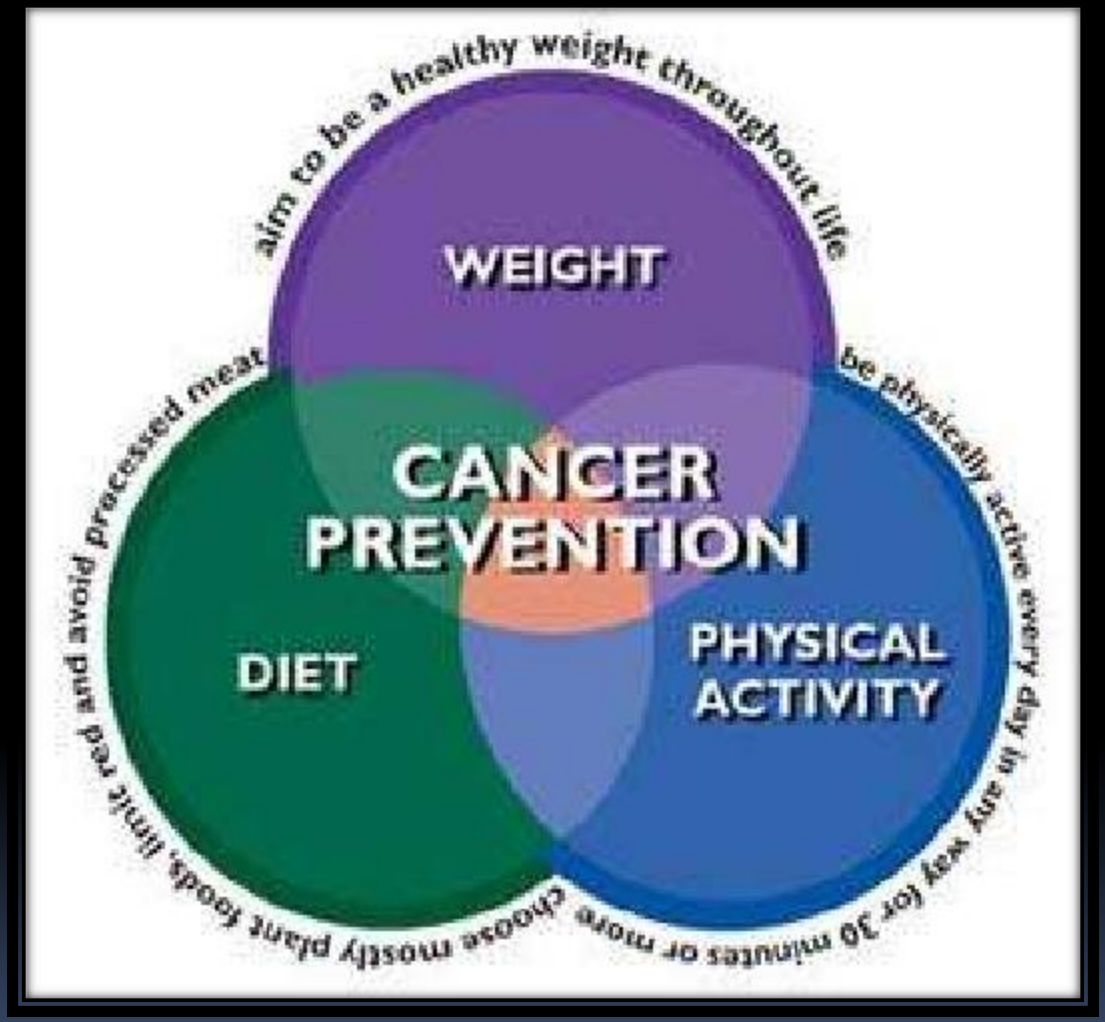
Telomerase

- DNA polymerase is unable to replicate the ends of chromosomes , resulting in loss of DNA at specialized ends of chromosomes called telomere.
- Telomeres composed of tandem repeats of six nucleotide sequences (TTAGGG)
- Telomere binds with specialized telomere binding proteins to form a T loop structure that prevents the ends of chromosomes from being recognized as broken or damaged DNA.
- Loss of telomere repeats with each cell division cycle causes gradual telomere shortening leading to growth arrest.

- Critically short telomere triggers a p53 regulated DNA damage check point , this is called replicative senescence .
- Cells can bypass this growth arrest if rb or p53 are nonfunctional
- Cancer cells activate the enzyme telomerase thus telomere length is maintained throughout multiple cell division.
- In certain cancer , telomerase activation caused cancer – Dyskeratosis congenita
- **Telomerase is an attractive target for cancer chemotherapy**.

	Normal cell	Tumor cell
1. Tumor kinetics	1% cells are in dividing state	2-5% cells are in cell cycle.
2. Doubling time	Cellular proliferation ratio is less	more the Ratio, more aggressive is the cancer
3. Contact inhibition	Multiplication stops when cell come into contact	This property is lost, & adjacent cells continue to multiply to form multilayer
4. Sialicacid content	Carry less negative change on cell surface	More, Tend to repel each other Cause metastatic penetration & invasiveness

5. Anchorage dependence	Firmly adhere to cell surface (Vinculin)	Loss of anchorage dependence Tyrosine kinase cause abnormal phosphorylation of vinculin
6. Cell fusion	Fertilization ,immune response ,tissue repair & regeneration	Initiation & progression of cancer.
7. Metastasis & secondaries	-----	Collagenase & stromolysin released by cells penetrate surrounding areas.
8. Apoptosis	number of cells newly produced will be equal to number of cells died	bypass Mutation in oncogenes create apoptotic resistance cells
9. Metabolic attention in cancer cells	----	Are shown to delete different enzymes or even whole metabolic activity.


aim to be a healthy weight throughout life
WEIGHT
be physically active every day in any way for 30 minutes or more
CANCER PREVENTION
PHYSICAL ACTIVITY
DIET
choose mostly plant foods, limit red and avoid processed meat