NEOPLASIA : 3
MOLECULAR BASIS OF CANCER

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Mechanism of oncogenesis

Proto-oncogene: normal gene that can undergo a genetic change to become cancerous.

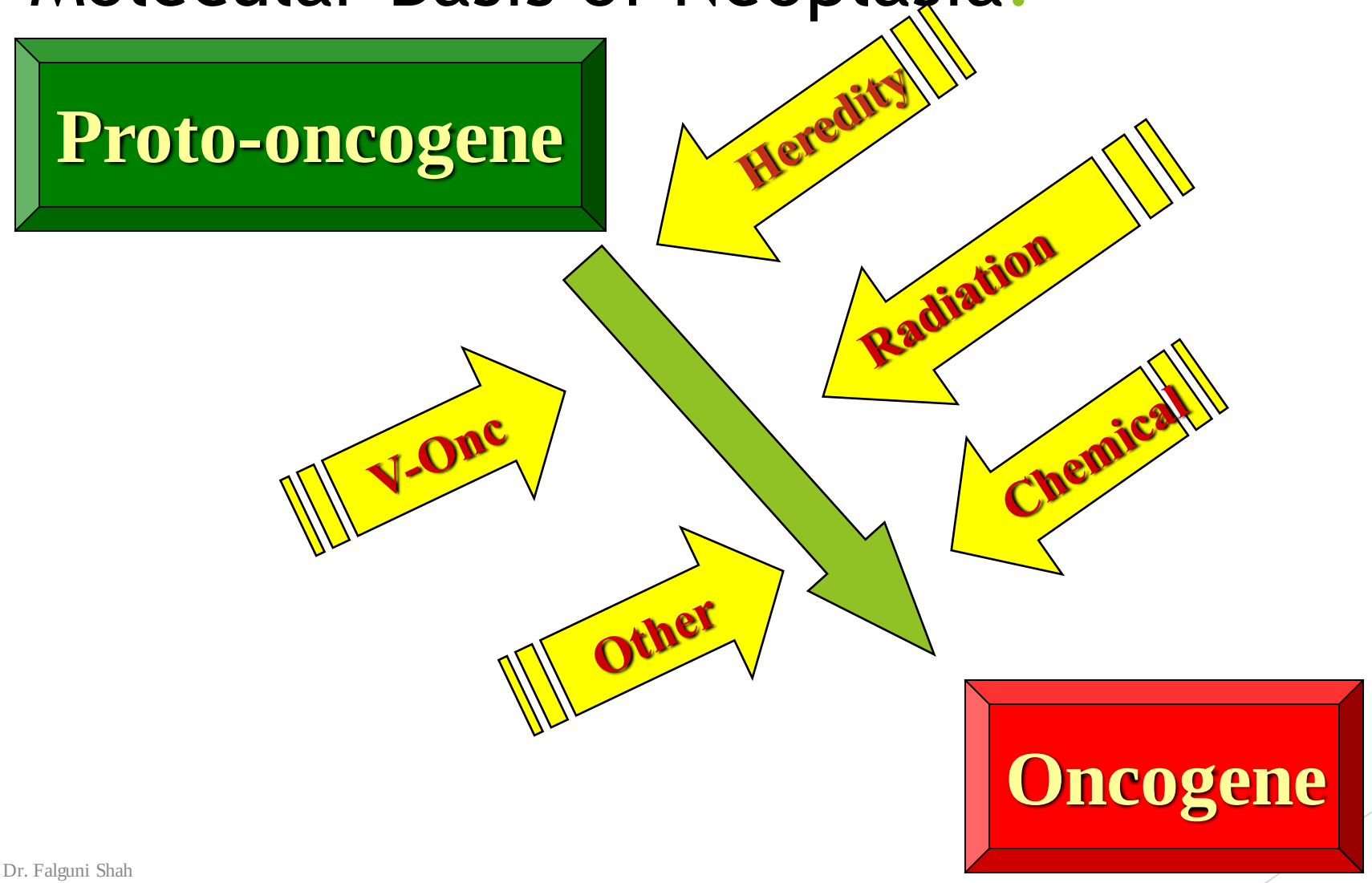
Oncogene: a gene with a single dominant (gain of function) mutation that causes a normal gene to become cancerous.Protein product of it called Oncoprotein

Tumor suppressor gene: a recessive (loss of function) mutation in an inhibitory gene. Often associated with inherited germ line syndromes.

Genes of Apoptosis: Dominent or recessive

DNA repair gene: Defective in ability to repair damaged DNA

Molecular Basis of Neoplasia:



Molecular Basis of Carcinogenesis

- Nonlethal genetic damage lies at the heart of carcinogenesis
- Four classes of regulatory genes.
  1. Growth Promoters – Proto-oncogenes
  2. Inhibitors – Cancer-suppressor genes
  3. Genes regulating Apoptosis.
  4. DNA repair genes.

Hallmarks of Cancer

"Cancer genes" cause bad things in cells:

- Cell sufficiency in growth signals
- Insensitivity to growth-inhibitory signals
- Evasion of apoptosis
- Limitless replicative potential
- Sustained angiogenesis
- Invasion and metastasis
- Altered cellular metabolism
- Ability to evade the host immune response

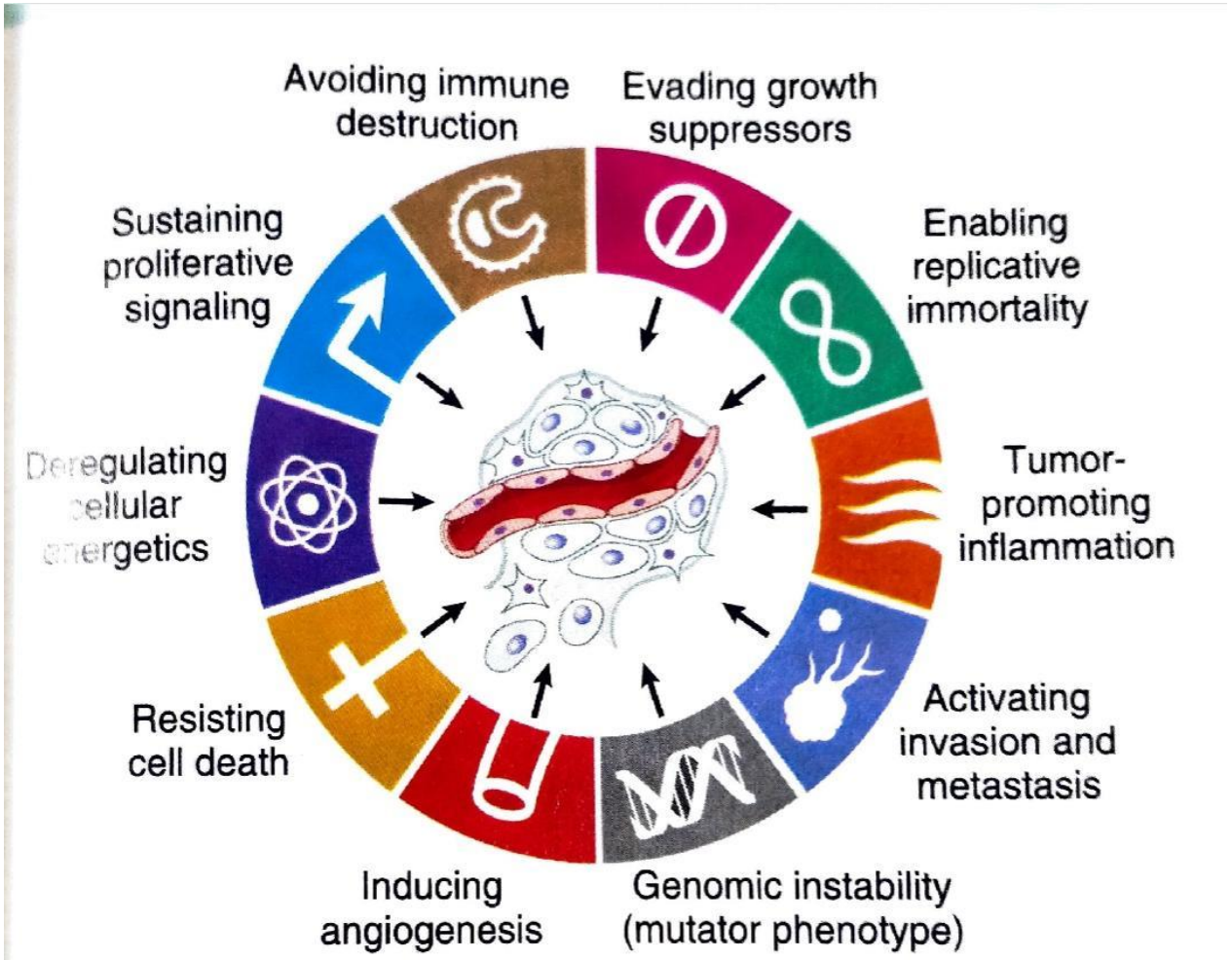


Figure 7-24 Hallmarks of cancer. (Adapted from Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646.)

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

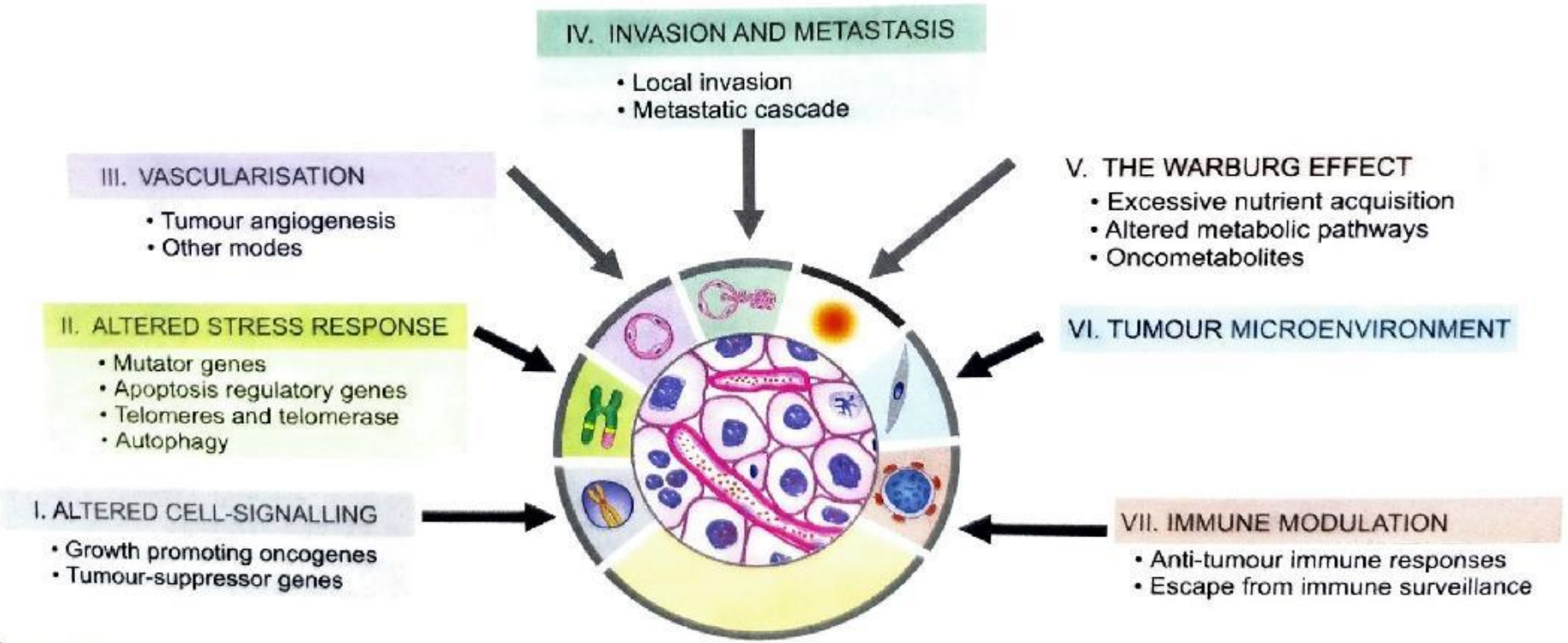


Figure 7.19 Schematic representation of revised hallmarks of cancer in terms of molecular carcinogenesis (depicted left to right clockwise).

Figure courtesy reference : Textbook of PATHOLOGY, Harsh Mohan, Edition 8th

Autonomous Growth

In normal cells…

- Growth factor binds to receptor
- Receptor activates signal-transducing protein
- Signal-transducing protein activates 2nd messenger
- 2nd messenger talks to nuclear transcription factors
- Nuclear transcription factors start DNA transcription
- Entry and progression of the cell into the cell cycle

↓

Cell division

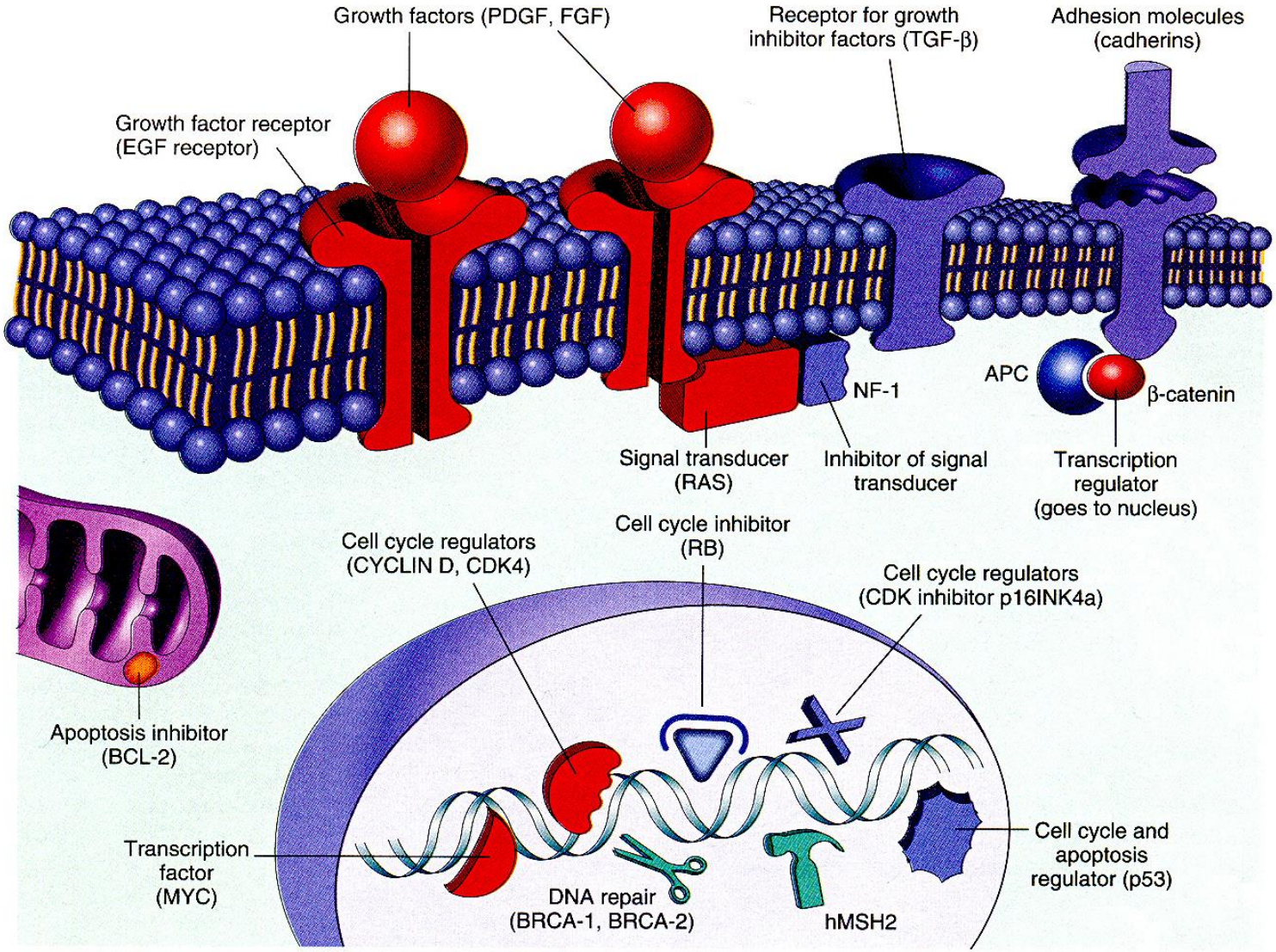


Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Self sufficiency in growth signals

GROWTH FACTORS

- All normal cells require stimulation by growth factors to undergo proliferation.
- Many cancer cells acquire growth self sufficiency by acquiring the ability to synthesize the same growth factors to which they are responsive e.g. PDGF,TGF-a related to Astrocytoma
- In many cases, the products of other oncogenes (eg.RAS genes) cause overexpression of growth factors such as TGF-alpha.
- Homologues of fibroblast growth factors FGF-3have been detected in several gastrointestinal and breast tumors.
- Hepatocyte growth factor & its receptor-MET overexpressed in follicular carcinoma of thyroid

Table 7.5 Selected Oncogenes, Their Mode of Activation, and Associated Human Tumors

Category	Proto-Oncogene	Mode of Activation in Tumor	Associated Human Tumor
Growth Factors			
PDGF-β	*PDGFB*	Overexpression	Astrocytoma
Fibroblast growth factors	*HST1* *FGF3*	Overexpression Amplification	Osteosarcoma Stomach cancer Bladder cancer Breast cancer Melanoma
TGF-α	*TGFA*	Overexpression	Astrocytomas
HGF	*HGF*	Overexpression	Hepatocellular carcinomas Thyroid cancer
Growth Factor Receptors			
EGF-receptor family	*ERBB1 (EGFR)* *ERBB2 (HER)*	Mutation Amplification	Adenocarcinoma of lung Breast carcinoma
FMS-like tyrosine kinase 3	*FLT3*	Point mutation or small duplications	Leukemia
Receptor for neurotrophic factors	*RET*	Point mutation	Multiple endocrine neoplasia 2A and B, familial medullary thyroid carcinomas
PDGF receptor	*PDGFRB*	Amplification, translocation	Gliomas, leukemias
Receptor for KIT ligand	*KIT*	Point mutation	Gastrointestinal stromal tumors, seminomas, leukemias
ALK receptor	*ALK*	Translocation Point mutation	Adenocarcinoma of lung, certain lymphomas Neuroblastoma
Proteins Involved in Signal Transduction			
GTP-binding (G) proteins	*KRAS* *HRAS* *NRAS* *GNAQ* *GNAS*	Point mutation Point mutation Point mutation Point mutation Point mutation	Colon, lung, and pancreatic tumors Bladder and kidney tumors Melanomas, hematologic malignancies Uveal melanoma Pituitary adenoma, other endocrine tumors
Nonreceptor tyrosine kinase	*ABL*	Translocation	Chronic myelogenous leukemia Acute lymphoblastic leukemia
RAS signal transduction	*BRAF*	Point mutation	Melanomas, leukemias, colon carcinoma, others
Notch signal transduction	*NOTCH1*	Point mutation, translocation	Leukemias, lymphomas, breast carcinoma
JAK/STAT signal transduction	*JAK2*	Point mutation, translocation	Myeloproliferative disorders Acute lymphoblastic leukemia
Nuclear Regulatory Proteins			
Transcriptional activators	*MYC* *NMYC*	Translocation Amplification	Burkitt lymphoma Neuroblastoma
Cell Cycle Regulators			
Cyclins	*CCND1* (cyclin D1)	Translocation Amplification	Mantle cell lymphoma, multiple myeloma Breast and esophageal cancers
Cyclin-dependent kinase	*CDK4*	Amplification or point mutation	Glioblastoma, melanoma, sarcoma

Figure reference : Robbins and Cotran, Pathologic Basis of Disease, Edition 10th

Growth factor receptors

- Mutations causing constitutive demerization & activation without binding to growth factor & deliver continuous mitogenic signals to cell
- Over expression – More common
- Can render cancer cells hyper responsive to normal levels of the growth factors, a level that would normally not trigger proliferation. E.g. : EGF Receptor family
  - ERBB 1 – over expressed in 80 % SCC Lung
  - HER 2 – (ERBB 2) is amplified in 25 % of breast Ca and Adenocarcinoma of Lung, Ovary and Salivary Glands
  - Point mutation that activate c-FMS, gene encoding the colony stimulating factor receptor detected in myeloid leukemia

- The significance of HER 2 – Clinical benefit by blocking the extracellular domains of this receptor with anti – HER 2 antibody in treatment of Breast cancer

Signal transducing proteins

- Many signaling proteins are associated with the inner leaflet of the plasma membrane where they receive signals from activated growth factor receptors and transmit them to the nucleus. E.g. RAS and ABL gene products

- RAS is a signal transduction protein –single dominant oncogene in human tumor - 15% to 30%
- Point mutation of RAS – Codons 12,59 or 61
- H RAS-Bladder Ca, K RAS- Colon & Pancreas,

  N RAS- Hematopoietic Ca respectively

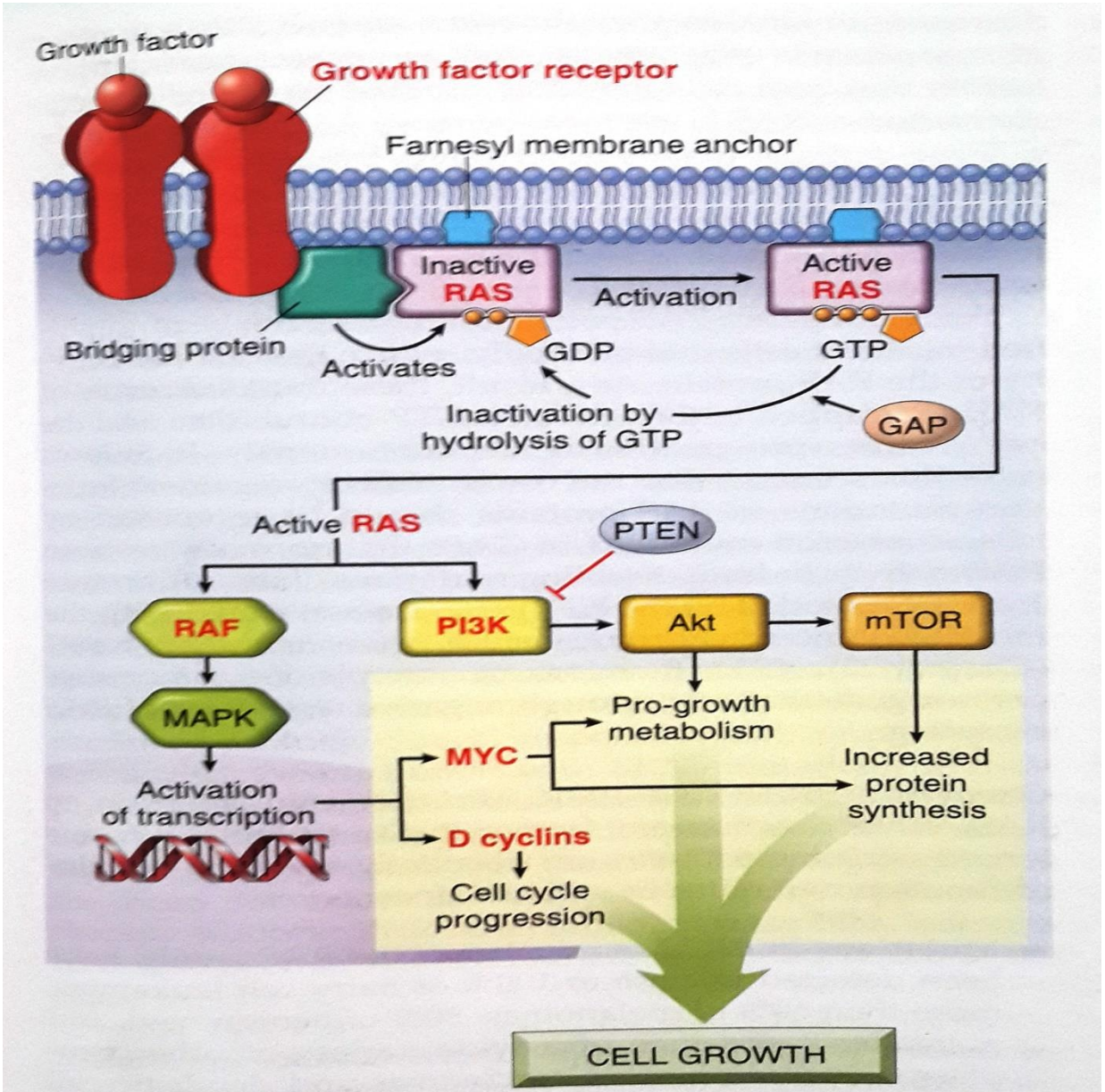


Figure 7-25 Growth factor signaling pathways in cancer. Growth factor receptors, RAS, PI3K, MYC, and D cyclins are oncoproteins that are activated by mutations in various cancers. GAPs apply brakes to RAS activation, and PTEN serves the same function for PI3K.

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

- RAS activated by exchanging GDP for GTP. Active RAS in turn acts on MAP kinase pathway & target nuclear transcription factors and promote mitogenesis . GTPase activity accelerated by GTPase- activating protein(GAPs) leading to hydrolysis of GTP to GDP & prevent uncontrolled RAS activity Mutant RAS protein can bind GAPs but their GTPase activity fails to be augmented ,thus the cell is continue to proliferate
- RAS protein indirectly regulate levels of cyclins by activating MAP kinase pathway

Alteration in nonreceptor Tyrosine kinases

- ABL proto oncogene has tyrosine kinase activity that is dampened by negative regulatory domains eg.in CML & certain Acute Leukemias, the ABL gene is translocated from 9 to 22 chromosome Where it fuses with part of BCR gene.
- The BCR-ABL hybrid gene has potent tyrosine kinase activity

Translocation of ABL-BCR gene

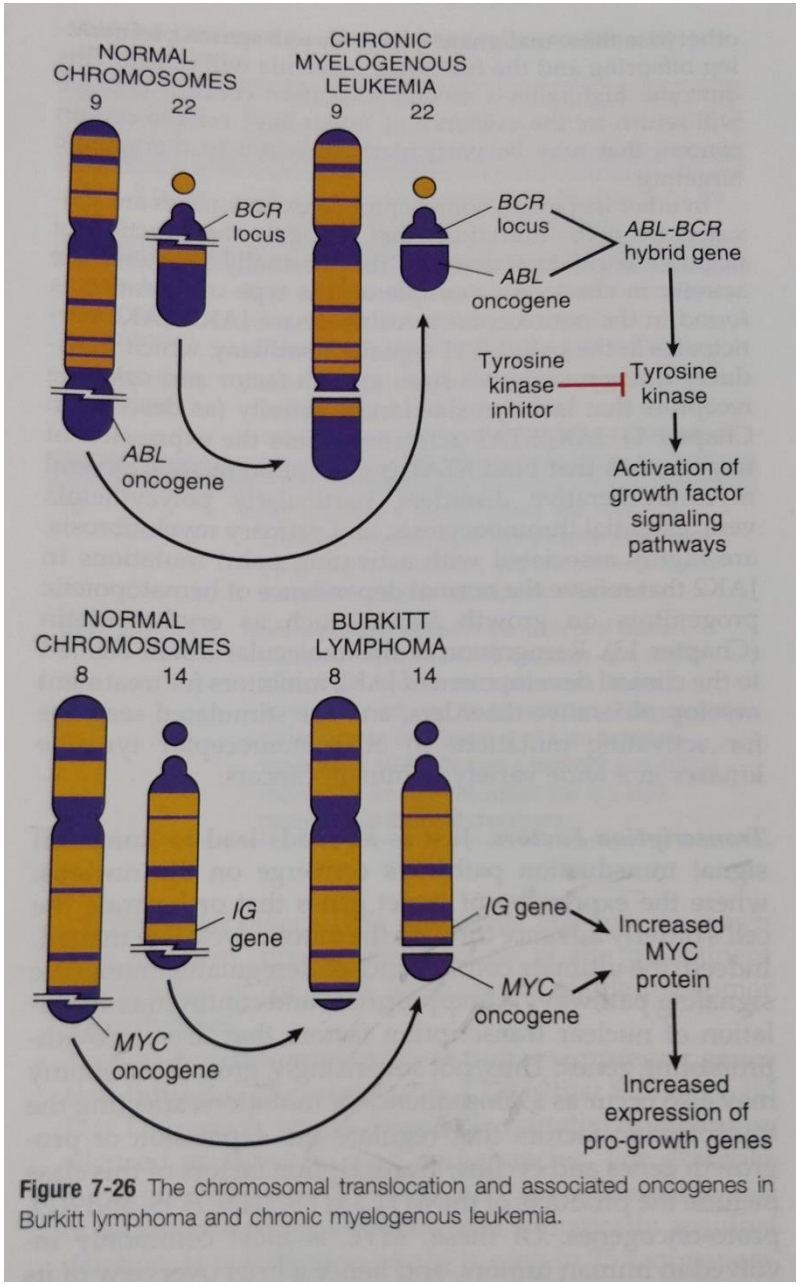


Figure 7-26 The chromosomal translocation and associated oncogenes in Burkitt lymphoma and chronic myelogenous leukemia.

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Nuclear transcription factors

- Ultimately, all signal transduction pathways enter the nucleus and have an impact on a large bank of responder genes that orchestrate the cells orderly advance through the mitotic cycle.
- Mutation of genes that regulate transcription of DNA result into growth autonomy. E.g. MYC, MYB, JUN, FOS oncogene. MYC is the most common oncogene in tumors.
- MYC protein rapidly translocated to nucleus, sometimes as a dimer with another protein MAX binds to the DNA, causing transcriptional activation of several growth related genes including cyclin dependent kinases.

- MYC gene are associated with persistent expression or overexpression,--sustained proliferation of tumor cells. E.g.. Deregulation of MYC gene by t(8:14) translocation in Burkitt lymphoma, B-cell tumor.
- MYC is amplified in breast, colon, lung ca.
- N-MYC –amplified in neuroblastoma
- L-MYC- amplified in small cell ca lung.

Evasion of Apoptosis

Many proteins involved in apoptosis:

- Fas (the “death receptor”)
- Executioner caspases - Bak, Bax & Bim
- p53 (the “guardian”)Gene BAX

Antiapoptotic protein

BCL-2 family – BCL-2/BCL-x

- If genes for these proteins are mutated, the cell becomes immortal!

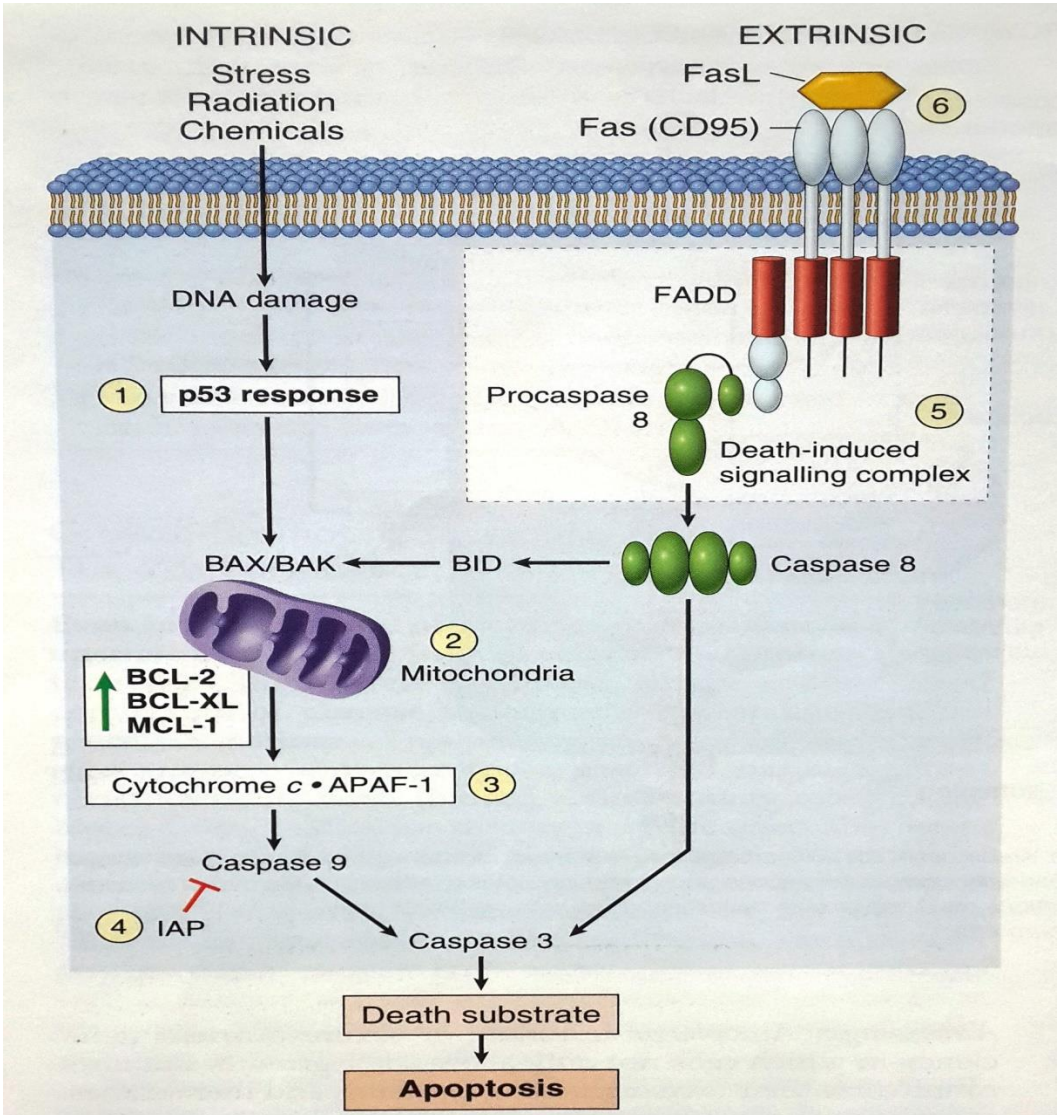


Figure 7-33 Intrinsic and extrinsic pathways of apoptosis and mechanisms used by tumor cells to evade cell death. (1) Loss of p53, leading to reduced function of pro-apoptotic factors such as BAX. (2) Reduced egress of cytochrome *c* from mitochondria as a result of upregulation of anti-apoptotic factors such as BCL2, BCL-XL, and MCL-1. (3) Loss of apoptotic peptidase activating factor 1 (APAF1). (4) Upregulation of inhibitors of apoptosis (IAP). (5) Reduced CD95 level. (6) Inactivation of death-induced signaling complex. FADD, Fas-associated via death domain.

Figure courtesy reference :
Robbins & Cotran,
Pathologic Basis of Disease,
South Asia Edition, 2017

- BCL-2 is localized on outer leaflet of mitochondrial membrane, endoplasmic reticulum, and nuclear-membrane.
- BCL-2 family of proteins regulate proteolytic enzyme (Caspases) responsible for Apoptosis
- Proapoptotic action of p53 gene is mediated by up regulation of BAX gene-this counteracts Antiapoptotic action of BCL-2.

- 85% of B cell Follicular Lymphomas carry t(14,18)- like Burkitt lymphoma.(14 q,32 site where Ig Heavy chain genes are found).
- Juxtaposition of transcriptionally active locus with BCL-2 causes OVEREXPRESSION of BCL-2 protein.
- OVEREXPRESSION of BCL-2 protects lymphocytes from Apoptosis and allows them to survive for long periods.
- Over expression of BCL-2 can rescue cells from c-MYC initiated apoptosis. Thus c- MYC triggers proliferation and BCL-2 prevents cell death, even if growth factors are limited
- Steady accumulation of B lymphocytes results in Lymphadenopathy and marrow infiltration.
- BCL-2 over expressing lymphomas result from reduced cell death rather than explosive cell proliferation- *INDOLENT tumor*.

Limitless Replication

- Normal human cells: only 60-70 doublings
- Telomeres keep getting shorter…
- …leading to cell cycle arrest (via p53 check points, causing proliferative arrest or apoptosis
- Stem cells and cancer cells use telomerase activity to maintain telomere length and keep replicating!

Sustained Angiogenesis

Definitions- Tumors stimulate growth of host blood vessels, process called Angiogenesis

- Tumor cells need blood too!
- Can't grow >1-2 mm in diameter or thickness without new vessels due to hypoxia induced cell death
- Neovascularization- dual effect- perfusion & produce growth factors by endothelial cells, so continue tumor growth and metastasis
- Angiogenic factors-VEGF & basic fibroblast growth factor(bFGF) produced by tumor cells & macrophages

- P53 inhibits angiogenesis by inducing synthesis of thrombospondin-1
- angiostatin, endostatin & tumstatin derived by proteolytic cleavage of plasminogen & collagen
- tumor growth controlled by balance between angiogenic & antiangiogenic factors
- focused on use of angiogenic inhibitors(endostatin) as adjuncts to therapy
- Trials - antibodies to VEGF as antitumor effect being conducted

Failure of DNA repair

- We swim in a Sea of Carcinogens.
- We are constantly exposed to mutagenic agents (sunlight, radiation, chemicals)!!
- We don’t get very many cancers because normal cells are able to REPAIR DNA damage!!
- In addition to environmental damage, DNA of normal dividing cells is susceptible to alterations resulting from "Spontaneous Errors" occurring during DNA replication
- Many systems for DNA repair exist.
- If you inherit a defect in any of these systems, you’ll be more likely to get cancer.

HNPCC- Hereditary Nonpolyposis Colon Cancer Syndrome

- Familial Carcinomas of Caecum and Proximal Colon.
- HNPCC results from defects in genes involved in DNA Mismatch Repair.
- When a strand of DNA is replicating , mismatch repair genes act as Spell-Checkers. e.g.in case of erroneous pairing of GT as against normal AT. Mismatch repair genes correct the defect. Without Proof Reading, the errors slowly accumulate in several genes including Proto-Oncogene and tumor Suppressor Genes.

- DNA repair genes themselves are not oncogenic BUT they allow mutation in other genes during the process of normal cell division.
- Cells with defects in DNA Repair are said to have RER Phenotype (Replication Error) documented by examination of *Micro satellite Sequences* in tumor cell DNA.

- Xeroderma Pigmentosum
  - failure of nucleotide excision repair(NER) system
  - sun exposure (UV rays) leads to skin cancers

BRCA-1 AND BRCA-2 GENES

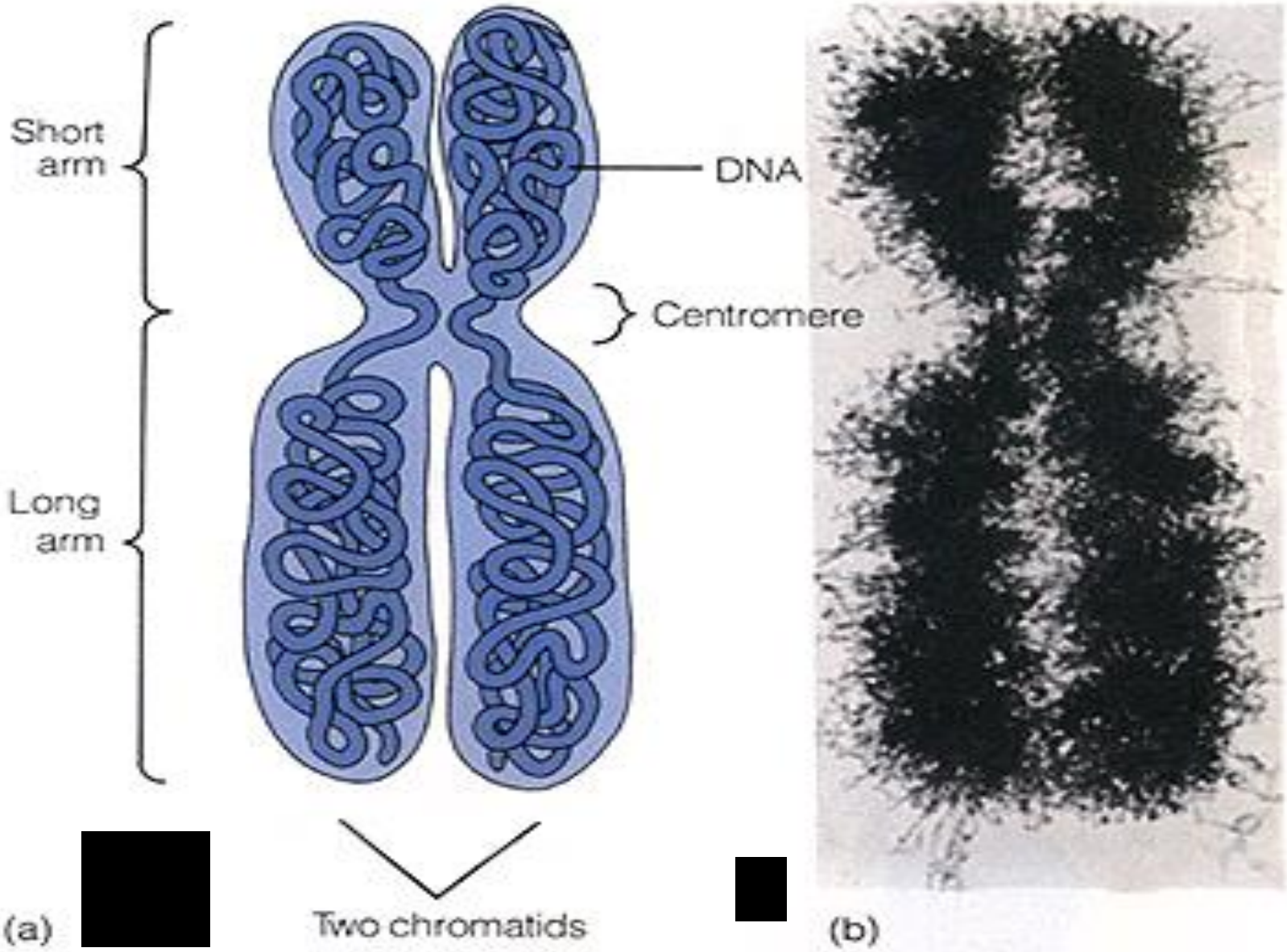
- BRCA-1 on 17q,12-21; BRCA-2 on 13q
- Tumor suppressor genes associated with Breast and other Cancers.
- Germ line mutation in BRCA-1 - ++ risk of epithelial ovarian cancers , prostate & colon cancers.
- BRCA-2 mutation - ++risk for Carcinomas of Male Breast, Ovary, Prostate, Pancreas and Larynx.
- 5-10% breast Carcinomas are familial and BRCA- 1 & 2 mutations account for 80% familial cancers.
- Protein products of these genes are localized to nuclear transcriptional regulation.
- Both participate in process of homologous recombination of DNA repair

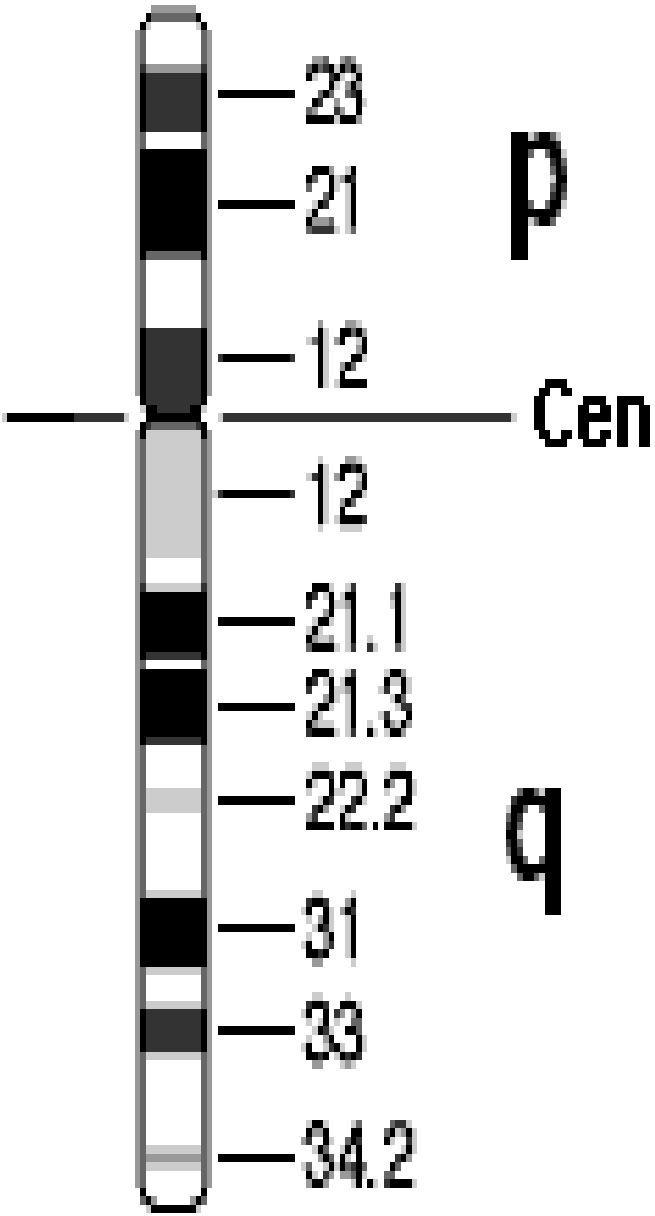
Chromosomal Changes

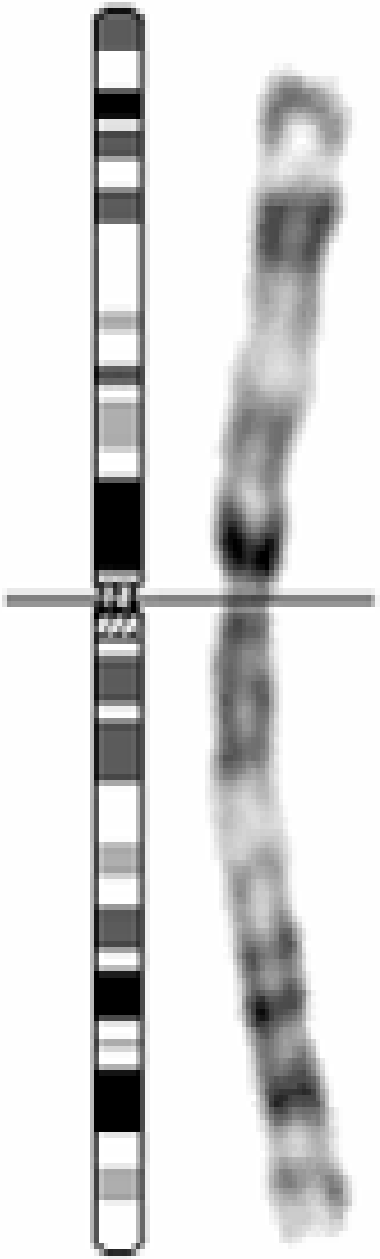
- Genetic damage can be:
  - subtle, invisible on a karyotype (point mutation)
  - large, visible in a karyotype
- Some karyotypic abnormalities occur predictably in certain tumors
  - leukemias, lymphomas
  - solid tumors

Mechanisms of activation of cellular proto-oncogenes

1. Point mutation
2. Deletion
3. Chromosomal translocation
4. Gene amplification
5. Over expression of signaling proteins


Short arm
Long arm
DNA
Centromere
Two chromatids
(a)
(b)





Chromosome banding

- Balanced translocations
  - Common!
  - Either put proto-oncogene next to a promotor…
  - …or create a fusion gene that makes a bad, growth-promoting product
  - Most common in hematopoietic tumors
  - Example: Ph chromosome

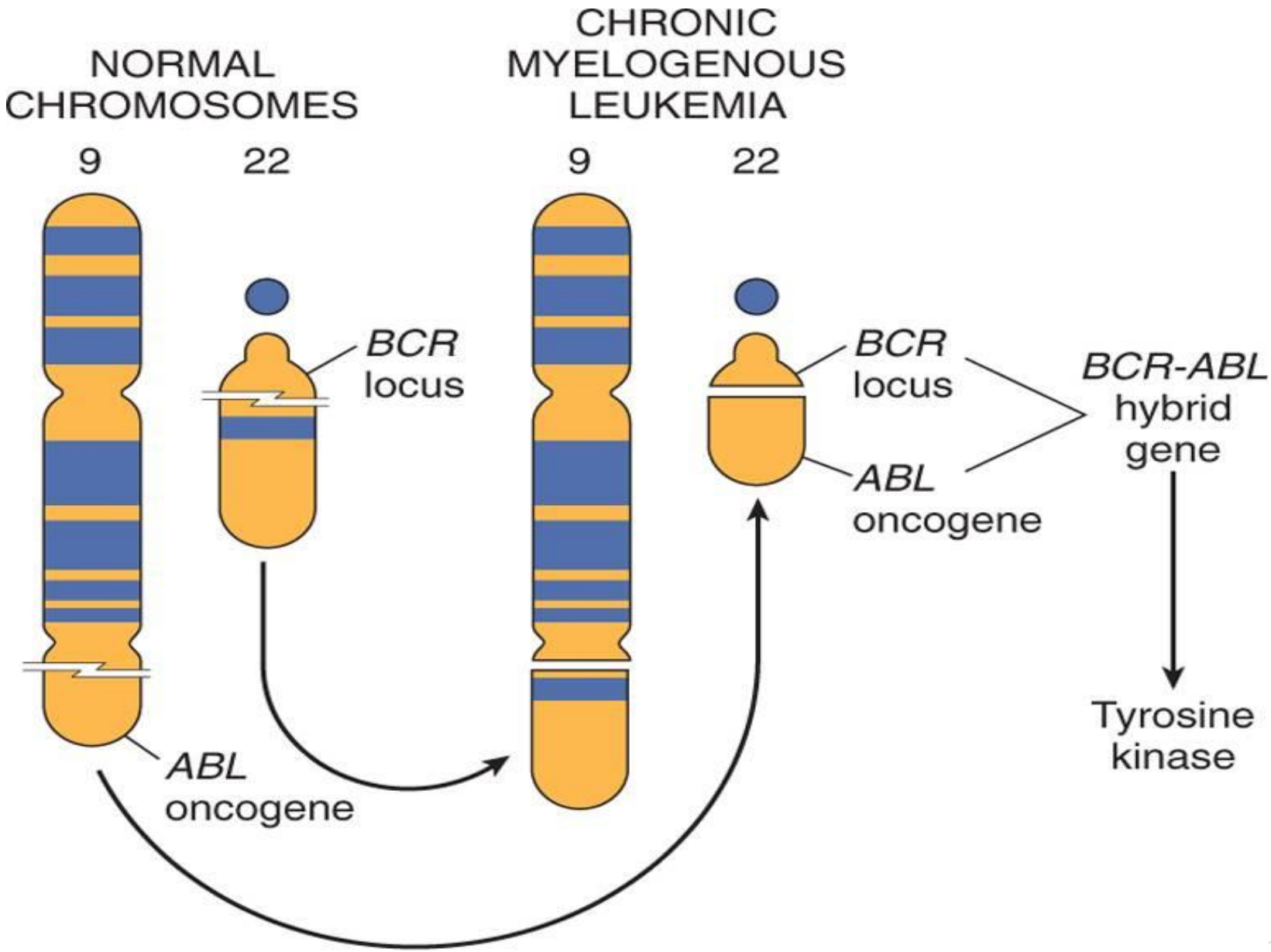


Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

- Deletions
  - Deletion of part or all of a chromosome
  - Usually: deletion of a tumor-suppressor gene
  - Most common in solid tumors
  - Example: del 13q14 in retinoblastoma

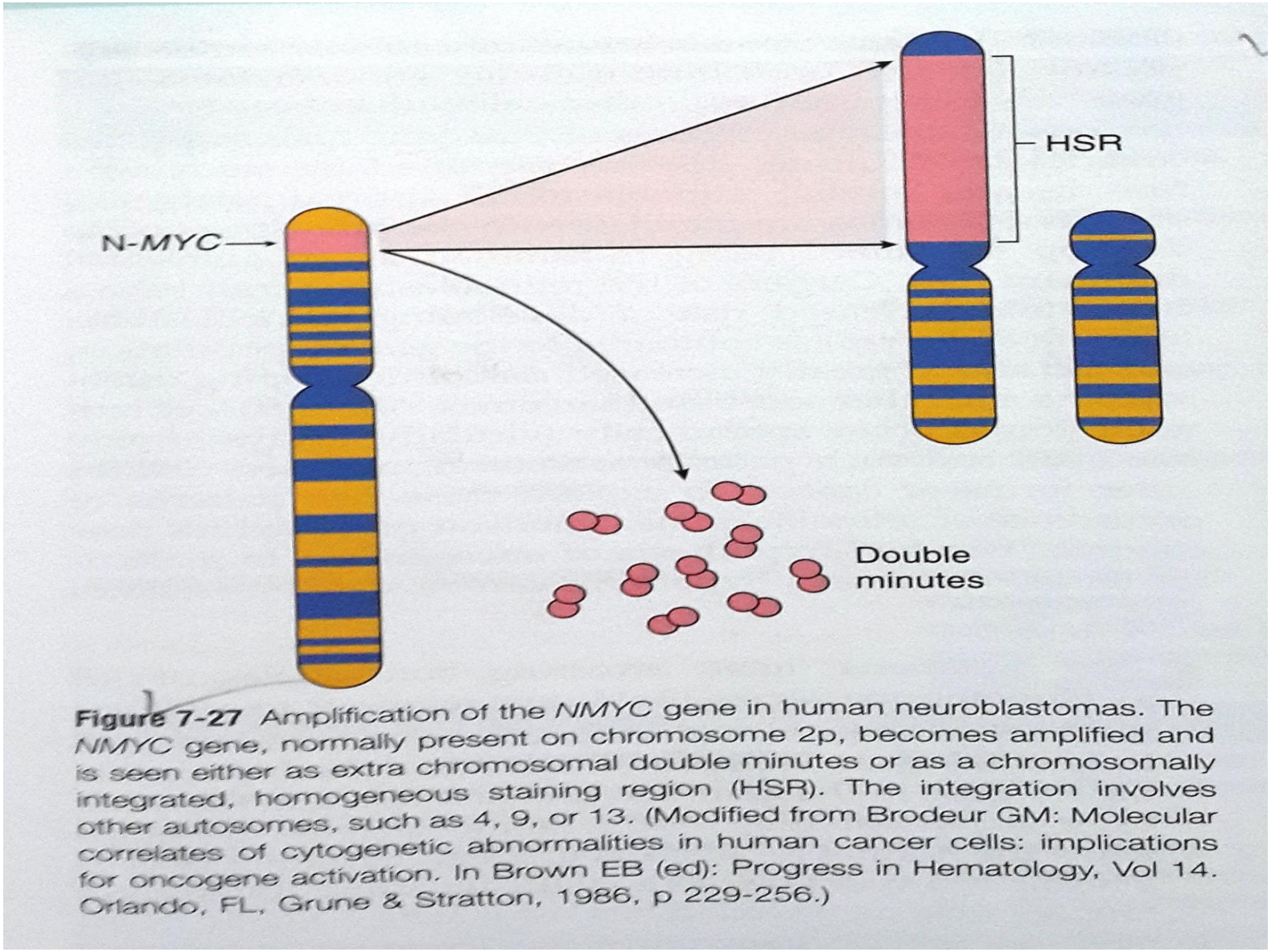


Figure 7-27 Amplification of the *NMYC* gene in human neuroblastomas. The *NMYC* gene, normally present on chromosome 2p, becomes amplified and is seen either as extra chromosomal double minutes or as a chromosomally integrated, homogeneous staining region (HSR). The integration involves other autosomes, such as 4, 9, or 13. (Modified from Brodeur GM: Molecular correlates of cytogenetic abnormalities in human cancer cells: implications for oncogene activation. In Brown EB (ed): Progress in Hematology, Vol 14. Orlando, FL, Grune & Stratton, 1986, p 229-256.)

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

NEOPLASIA :4
MOLECULAR BASIS OF CANCER

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Insensitivity to Growth-Inhibitory Signals

LOSS OF FUNCTION OF THESE GENES
IS KEY EVENT IN ALL TUMORS
RB & P53gene

- RB gene product stops cells at G_1 checkpoint
- Mutant RB is inactive; lets cells pass through G_1!
- Patients with two mutant RB genes have:
  - increased risk of retinoblastoma
  - Increased risk of other tumors (sarcoma)

Tumor suppressor genes

Have been

theoretically predicted

by Alfred Knudson

in 1971

(Two-hit hypothesis)

The Cell Cycle

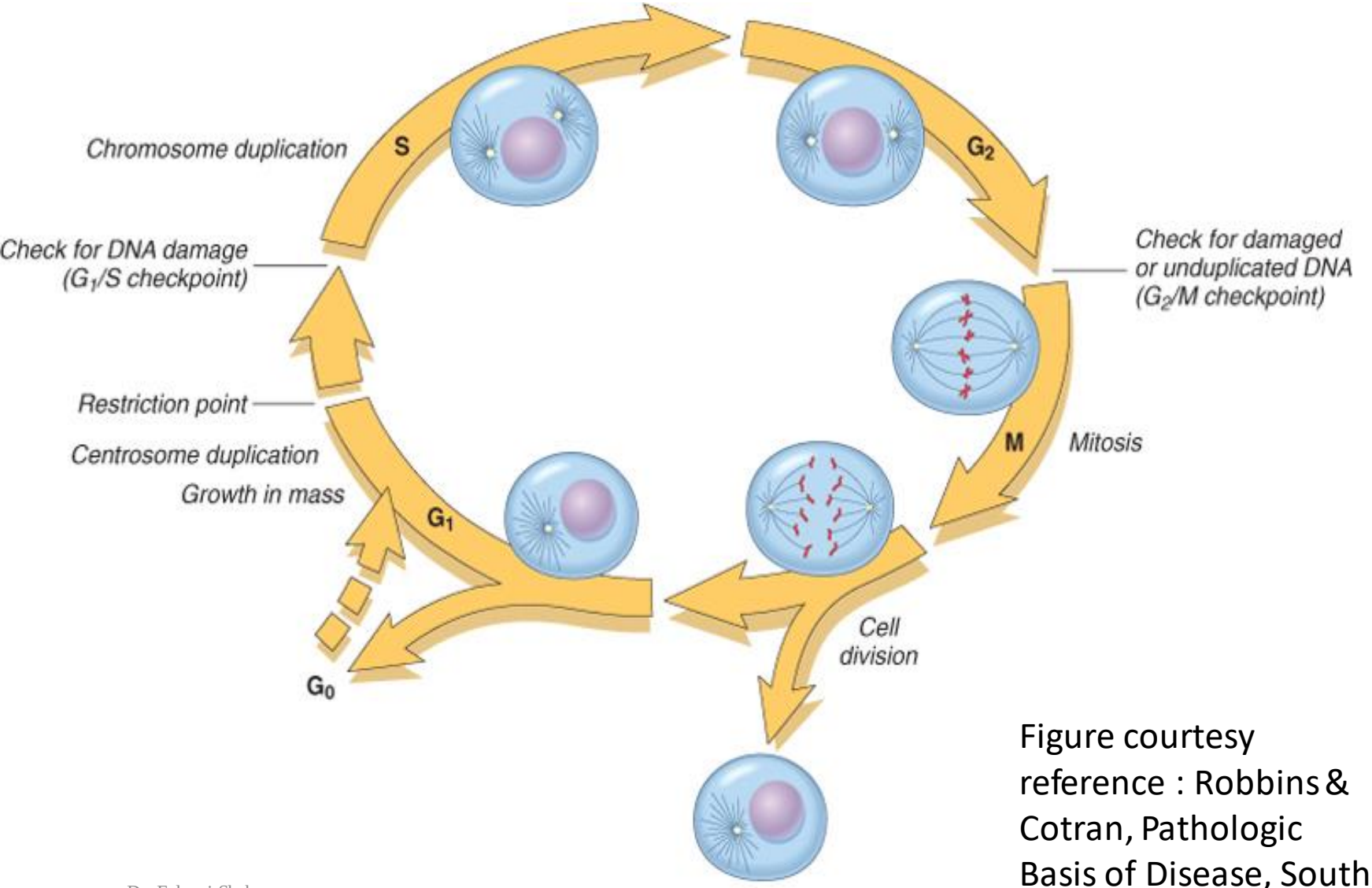


Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

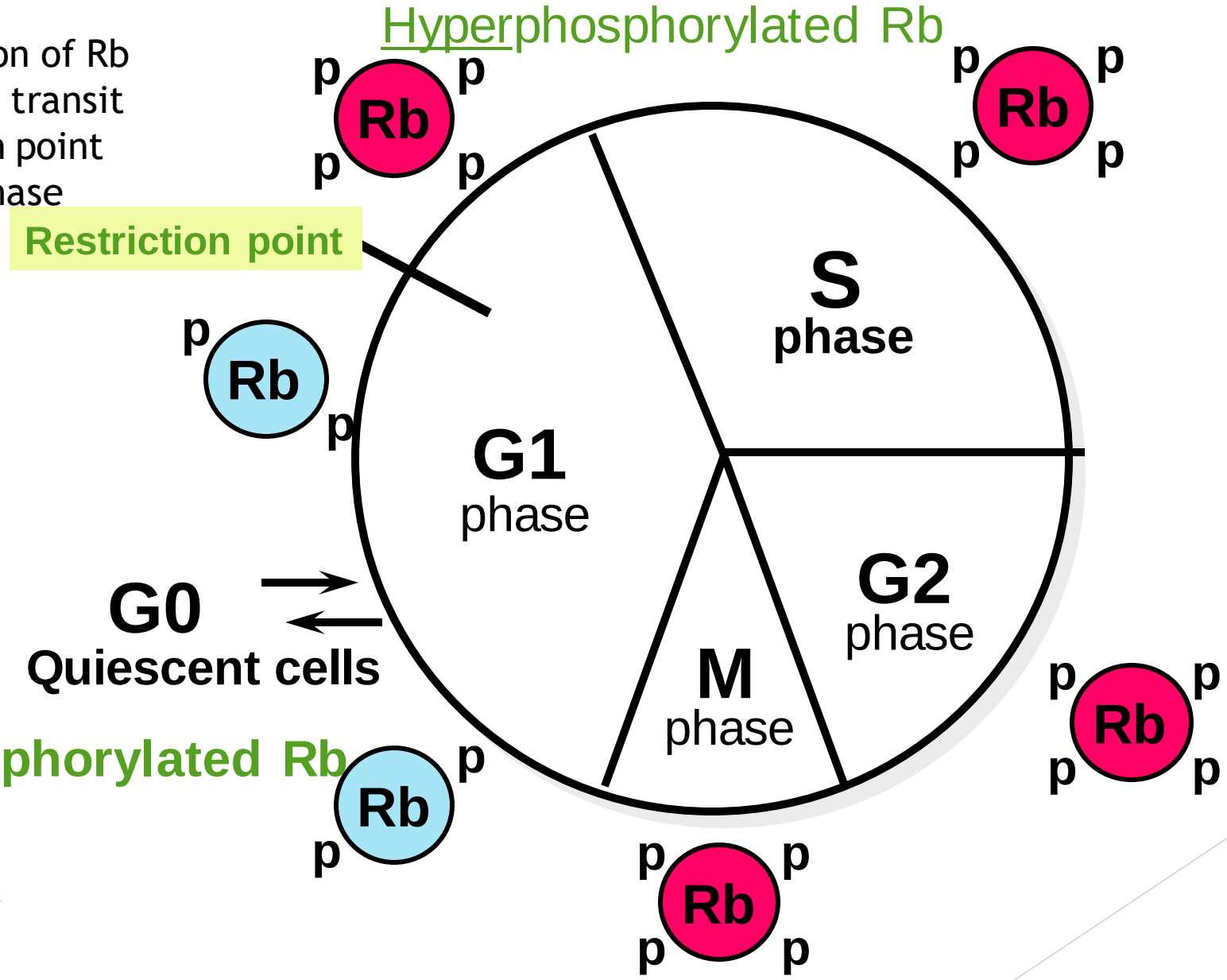
Table 7-6 Cell Cycle Components and Inhibitors That Are Frequently Mutated in Cancer

Cell Cycle Component	Main Function
Cyclins and Cyclin-Dependent Kinases	
CDK4; D cyclins	Form a complex that phosphorylates RB, allowing the cell to progress through the G_1 restriction point
Cell Cycle Inhibitors	
CIP/KIP family: p21, p27 (CDKN1A-D)	Block the cell cycle by binding to cyclin-CDK complexes p21 is induced by the tumor suppressor p53 p27 responds to growth suppressors such as TGF-β
INK4/ARF family (CDKN2A-C)	p16/INK4a binds to cyclin D-CDK4 and promotes the inhibitory effects of RB p14/ARF increases p53 levels by inhibiting MDM2 activity
Cell Cycle Checkpoint Components	
RB	Tumor suppressive "pocket" protein that binds E2F transcription factors in its hypophosphorylated state, preventing G_1/S transition; also interacts with several transcription factors that regulate differentiation
p53	Tumor suppressor altered in the majority of cancers; causes cell cycle arrest and apoptosis. Acts mainly through p21 to cause cell cycle arrest. Causes apoptosis by inducing the transcription of pro-apoptotic genes such as *BAX*. Levels of p53 are negatively regulated by MDM2 through a feedback loop. p53 is required for the G_1/S checkpoint and is a main component of the G_2/M checkpoint.

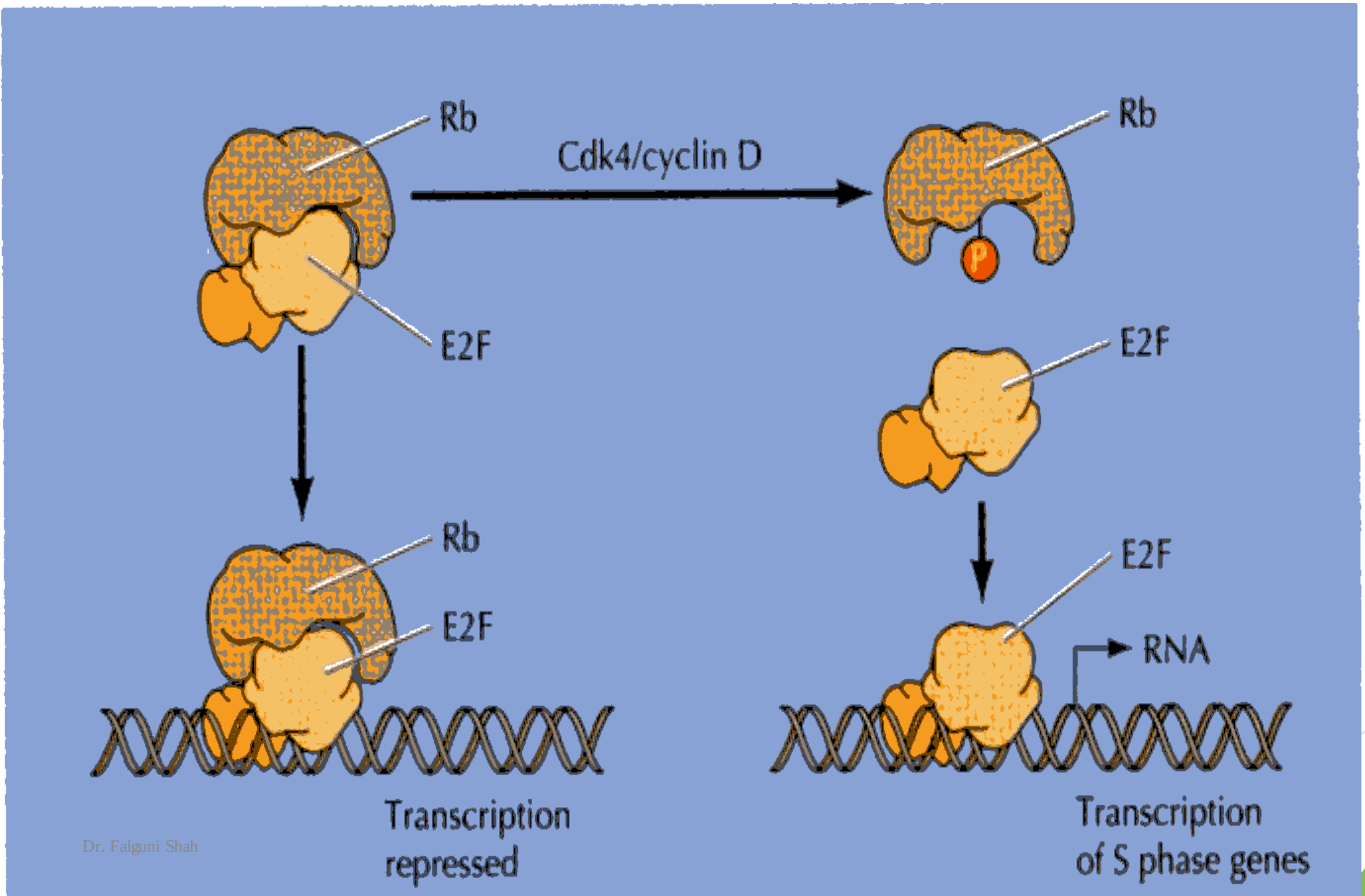
Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Cell-cycle dependent phosphorylation of Rb

Phosphorylation of Rb allows cells to transit the restriction point and enter S phase



Phosphorylation of Rb genes



RETINOBLASTOMA GENE

- Two hit hypothesis
- Two mutations (hits) are required to produce Retinoblastoma.
- These involve RB gene on chromosome No. 13q.
- Both normal alleles should be inactivated (two hits) for development of retinoblastoma.
- In familial form, all cells inherit ONE mutant gene from a carrier parent.
- The SECOND mutation affects the RB locus in one of the retinal cells after birth.
- Therefore, familial transmission follows an autosomal dominant pattern.
- In SPORADIC cases BOTH normal alleles of RB gene are lost by somatic mutation.

Retinoblastoma appearance

Retinoblastoma may be unifocal or multifocal.
About 60% of patients have unilateral RB with a mean age of diagnosis of 24 months;
About 40% have bilateral RB with a mean age of diagnosis of 15 months.

Secondary tumors-osteosarcomas and rhabdomyosarcomas

4,4% have secondary tumor in 10 years, 18,3% in 20 years; 26,1 % in 30 years

70% of patients have point mutations in RB1 gene;
10% -- partial deletion of RB1 gene;
20% -- causes unknown; appearance is the same

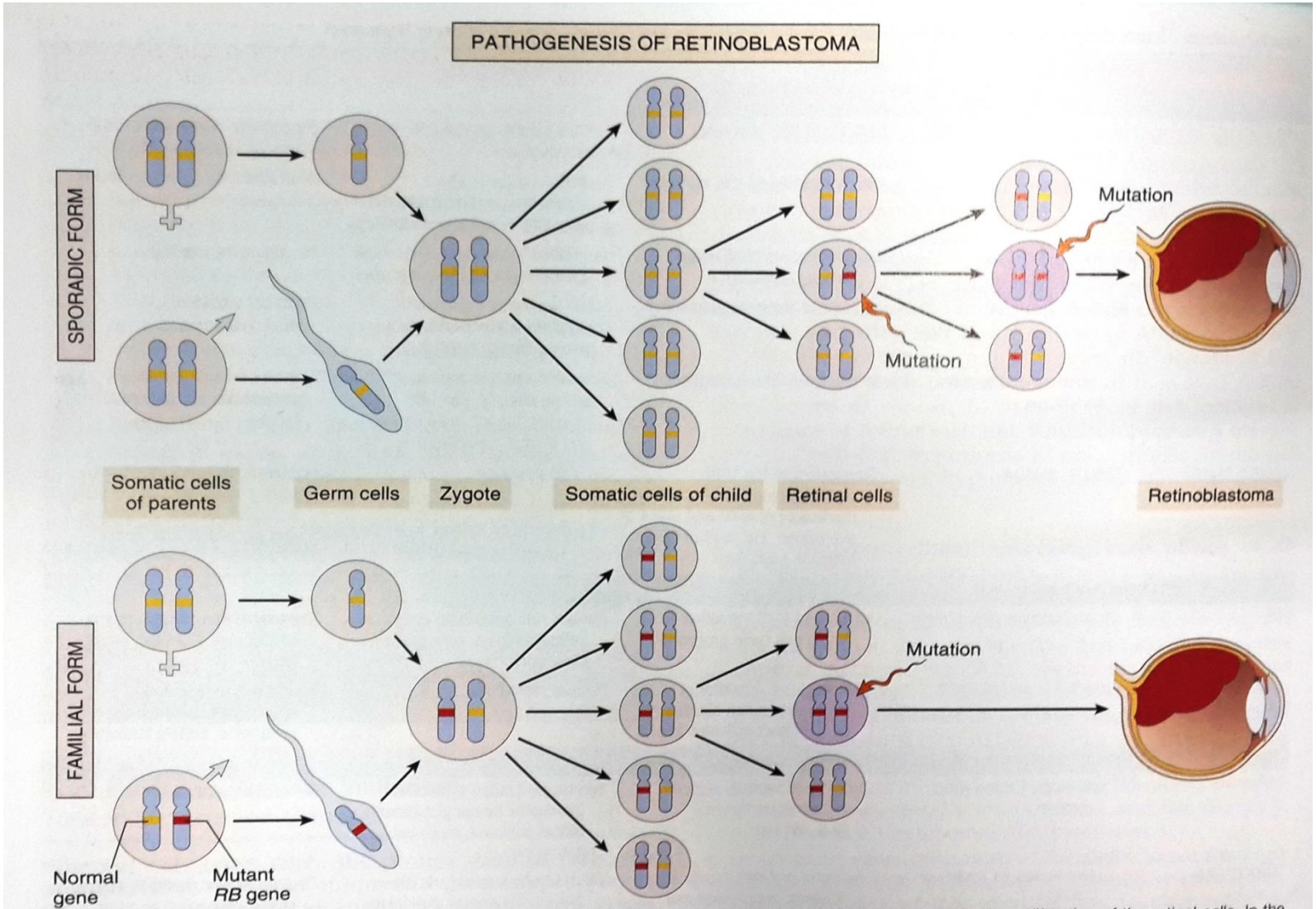
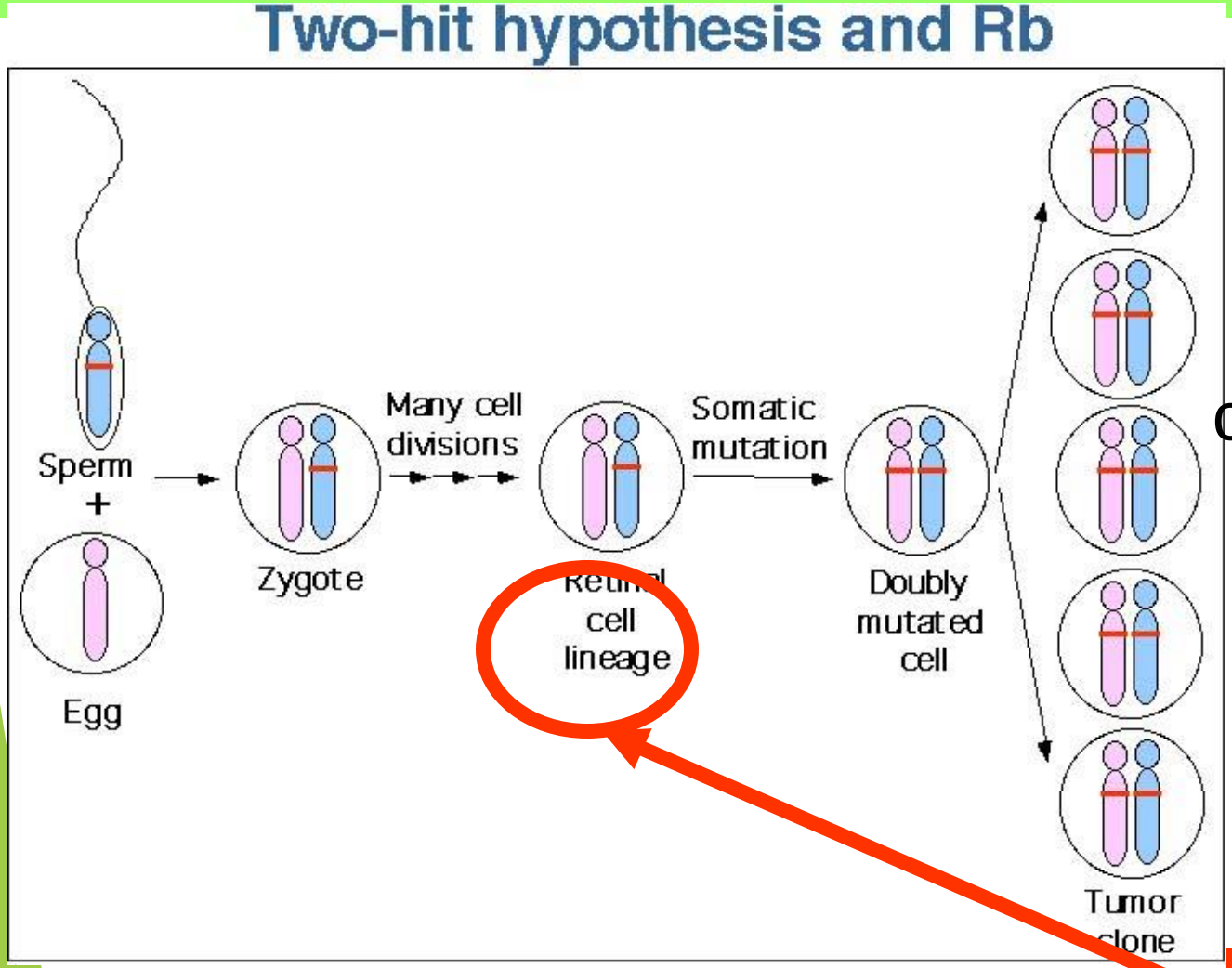


Figure 7-28 Pathogenesis of retinoblastoma. Two mutations of the *RB* locus on chromosome 13q14 lead to neoplastic proliferation of the retinal cells. In the sporadic form, both *RB* mutations in the tumor-founding retinal cell are acquired. In the familial form, all somatic cells inherit one mutated copy of *RB* gene from a carrier parent, and as a result only one additional *RB* mutation in a retinal cell is required for complete loss of RB function.

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Mutation should be in retinal cell



If 2nd mutation arises in connective tissue

Osteosarcoma

Retinoblastoma

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

p53 Gene

- p53 senses DNA damage, and induces G1 arrest and induces DNA repair process.
- Cell with un-repairable DNA is directed to apoptosis by p53 gene.
- “P53 is a **guardian of the genome.”**
- Its homozygous loss leads to accumulation of damaged DNA may result in malignancy”
- Homozygous loss of p53 is seen in virtually every type of cancer.
- Over half of human malignant cells show loss of p53 gene by special tests.

- located on chromosome 17 p 13.1
- 50% human cancers show mutation

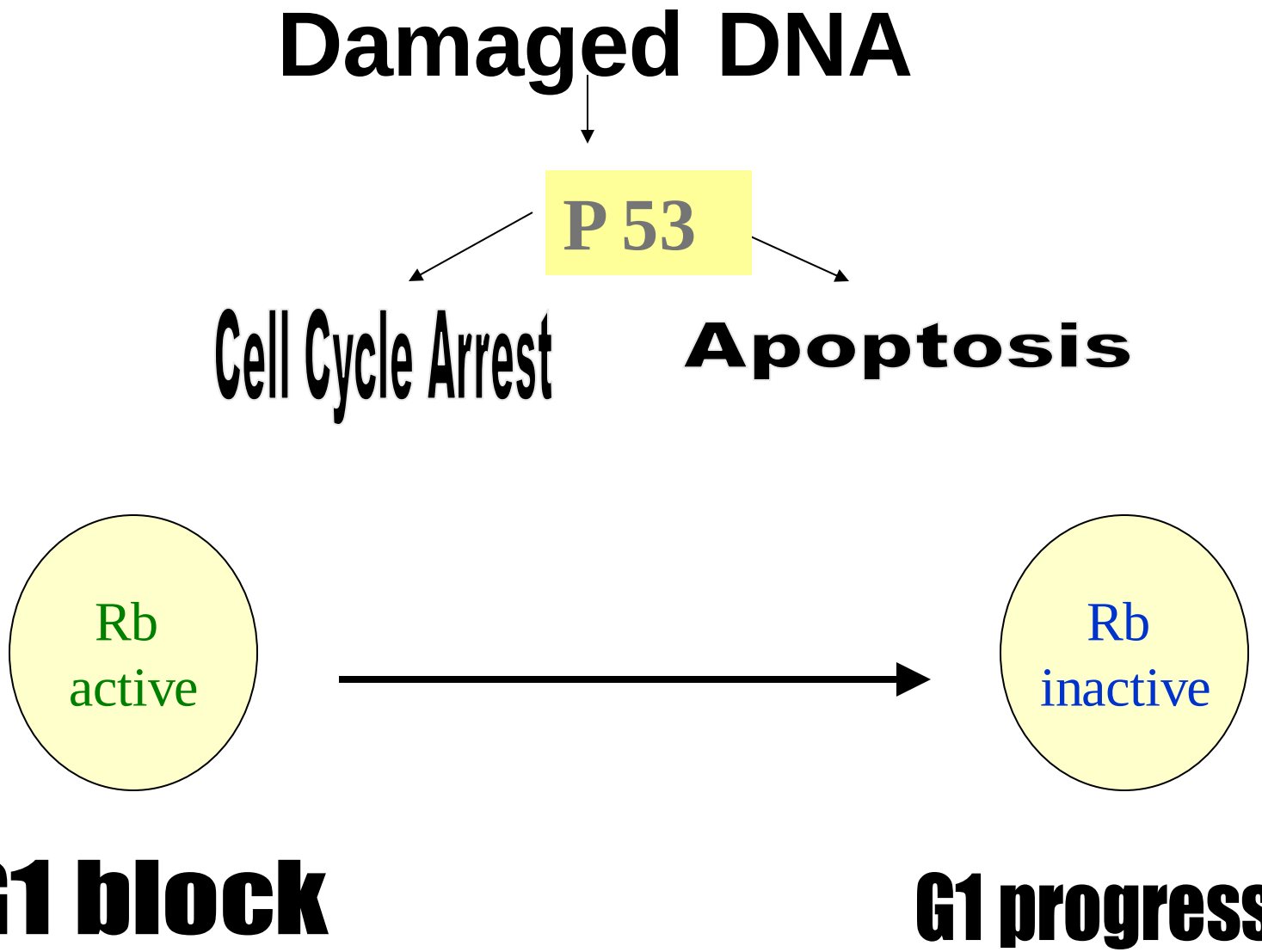
  (homozygous loss) of P53 Gene
- Inactivating mutations in most cases acquired
- less commonly mutant allele inherited- Li - Fraumeni syndrome- 25 fold greater chance of developing malignant tumor by 50 yrs age
- common tumors- sarcomas, Breast carcinoma, Leukemia, Brain tumors.

P 53 Molecular policeman

- P53 protein localized to -nucleus-functions primarily by controlling transcription of several other genes.
- Normally, p53 has a short half life (20 minutes) and hence unlike RB can't police normal cell cycle
- BUT When DNA damaged 'cause of radiation, UV light or chemicals-it applies BRAKES- Rapid ++ in p53 levels& activation of p53 as a transcription factor.
- p53 binds to DNA-stimulates transcription of several genes mediating TWO MAJOR EFFECTS

THREE MAJOR EFFECTS:

- i. **Cell cycle arrest**
- ii. **Apoptosis** Cell cycle arrest in late G1 phase-caused by p53 dependent transcription of CDK inhibitor p21-inhibits cyclin/CDK complexes. Thus prevents phosphorylation of RB necessary for cells to enter S phase. So allows cells the time to repair DNA damage.
- iii. **Cell senescence**


Damaged DNA
P 53
Cell Cycle Arrest
Apoptosis
Rb
active
Rb
inactive
G1 block
G1 progression

- P53 also induces transcription of GADD 45 (Growth Arrest & DNA Damage) , a protein involved in DNA repair.
- If damaged DNA is repaired, p53 activates a gene called MDM2 whose product binds to & down regulates p53 thus relieving cell cycle block.
- If during pause, DNA can't be repaired, p53 induces activation of Apoptosis inducing genes, BAX carry cell death commands of p53.
- BAX binds to & antagonizes apoptosis inhibiting protein BCL-2.

- If p53 is normal, tumor cells undergo apoptosis BUT if p53 gene is mutated, cells don't die resulting in tumor.
- P53 Function can also be inactivated by transforming proteins of HPV.
- MDM2 (Cellular p53 binding protein) is OVREXPRESSED in a subset of human soft tissue sarcoma as a result of gene amplification
- Childhood ALL and Teratocarcinoma retaining normal p53 respond better to radiation then lung and ovarian Ca carrying mutant p53 alleles.

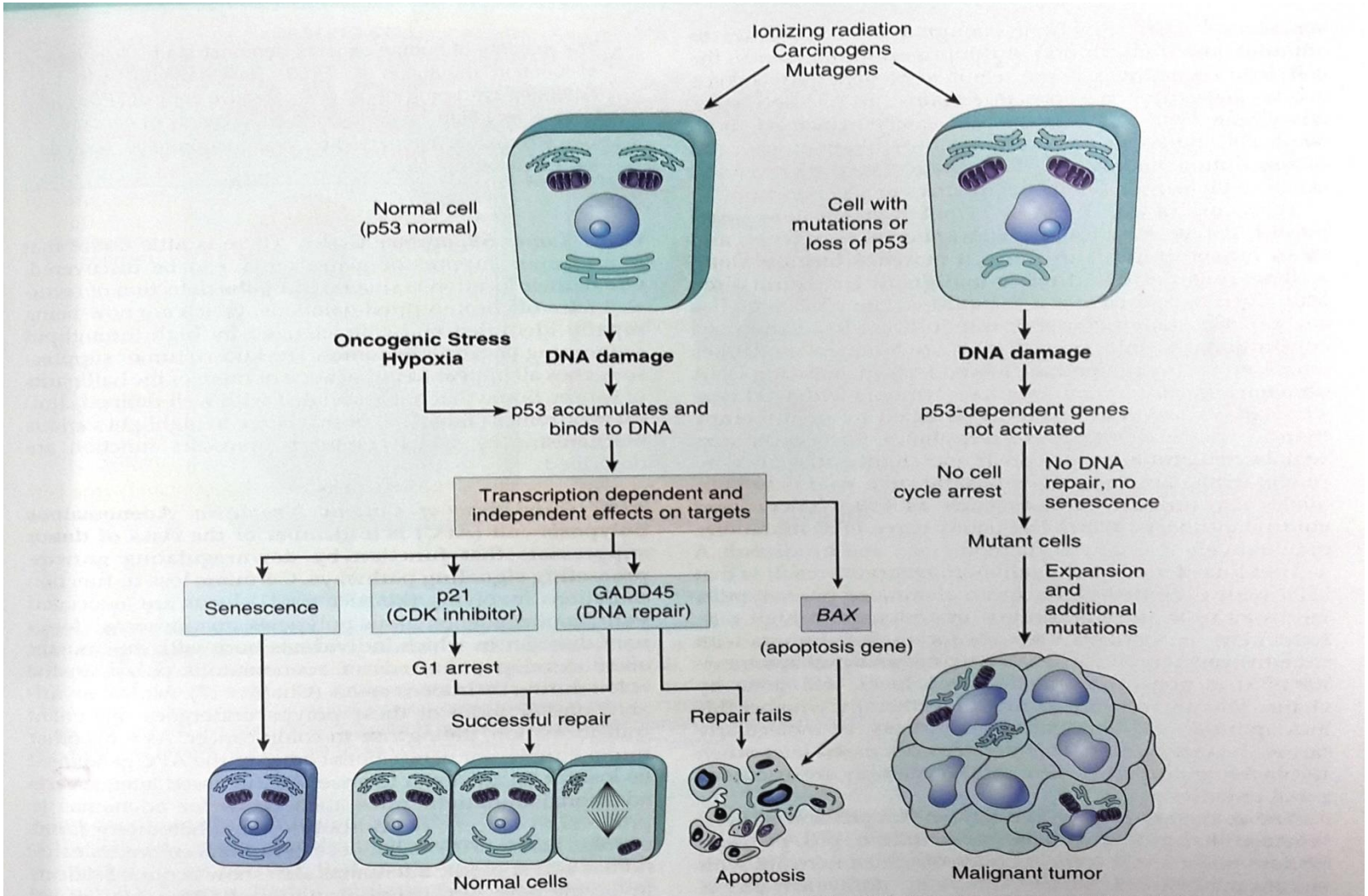


Figure 7-30 The role of p53 in maintaining the integrity of the genome. Activation of normal p53 by DNA-damaging agents or by hypoxia leads to cell cycle arrest in G_1 and induction of DNA repair by transcriptional upregulation of the cyclin-dependent kinase inhibitor *CDKN1A* (encoding the cyclin-dependent kinase inhibitor p21) and the *GADD45* genes. Successful repair of DNA allows cells to proceed with the cell cycle; if DNA repair fails, p53 triggers either apoptosis or senescence. In cells with loss or mutations of the p53 gene, DNA damage does not induce cell cycle arrest or DNA repair, and genetically damaged cells proliferate, giving rise eventually to malignant neoplasms.

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Other genes that function as Tumor suppressors

- NF-1 Hereditary neurofibromatosis type 1. NF-1 (normal) gene encodes a GTPase activating protein that facilitates conversion of active RAS into inactive RAS.
- Mutation of one copy of NF-1 gene leads to benign neurofibromas while inactivation of second gene leads to malignant neurofibrosarcomas.
- APC- Adenomatous Polyposis coli gene behaves in the similar fashion.APC/beta catenin pathway -APC degrade beta- catenin which is nuclear transcription factor
- DCC- Deleted in colon Ca. DCC gene product is involved in transmission of negative signals responsible for contact inhibition.
- NF-2 gene, VHL ,Catherin, TGF-beta pathway etc.

Inherited Conditions That Increase Risk For Certain Cancers

Inherited Conditions That Increase Risk for Cancer	
Name of Condition	**Type of Cancer**
Hereditary retinoblastoma	Retinoblastoma
Xeroderma pigmentosum	Skin
Wilms' tumor	Kidney
Li-Fraumeni syndrome	Sarcomas, brain, breast, leukemia
Familial adenomatous polyposis	Colon, rectum
Paget's disease of bone	Bone
Fanconi's – aplastic anemia	Leukemia, liver, skin

Tumor growth kinetics is different for gatekeepers and caretakers

Gatekeeper genes

is altered through mutation,
Oncogenes & tumor suppressor genes directly control tumor growth. Regulate entry of cell into tumorigenic path

Caretaker genes

that do not directly control tumor growth but affect genomic instability - DNA repair genes
Increased mutations of all genes
and the process of tumorigenesis is accelerated.

Multi-step Theory

- Stage of initiation
- Latent stage
- Stage of promotion
- Stage of malignant transformation

Multi-step Process

- Tumor initiation and progression results from stepwise accumulation of DNA mutations.
- Several characters of malignant neoplasm are the result of multiple genetic defects.
- Initial steps reversible(e.g. dysplasia), but final Malignant transformation is irreversible. **“Hit & Run”**

Steps to Cancer

- Every tumor results from the accumulation of a bunch of mutations
- Average: 90!
- Normally, body fixes or gets rid of mutated cells (RB, p53)!
- For a tumor cell to grow, one of its mutations must be within these checkpoint/guardian genes.

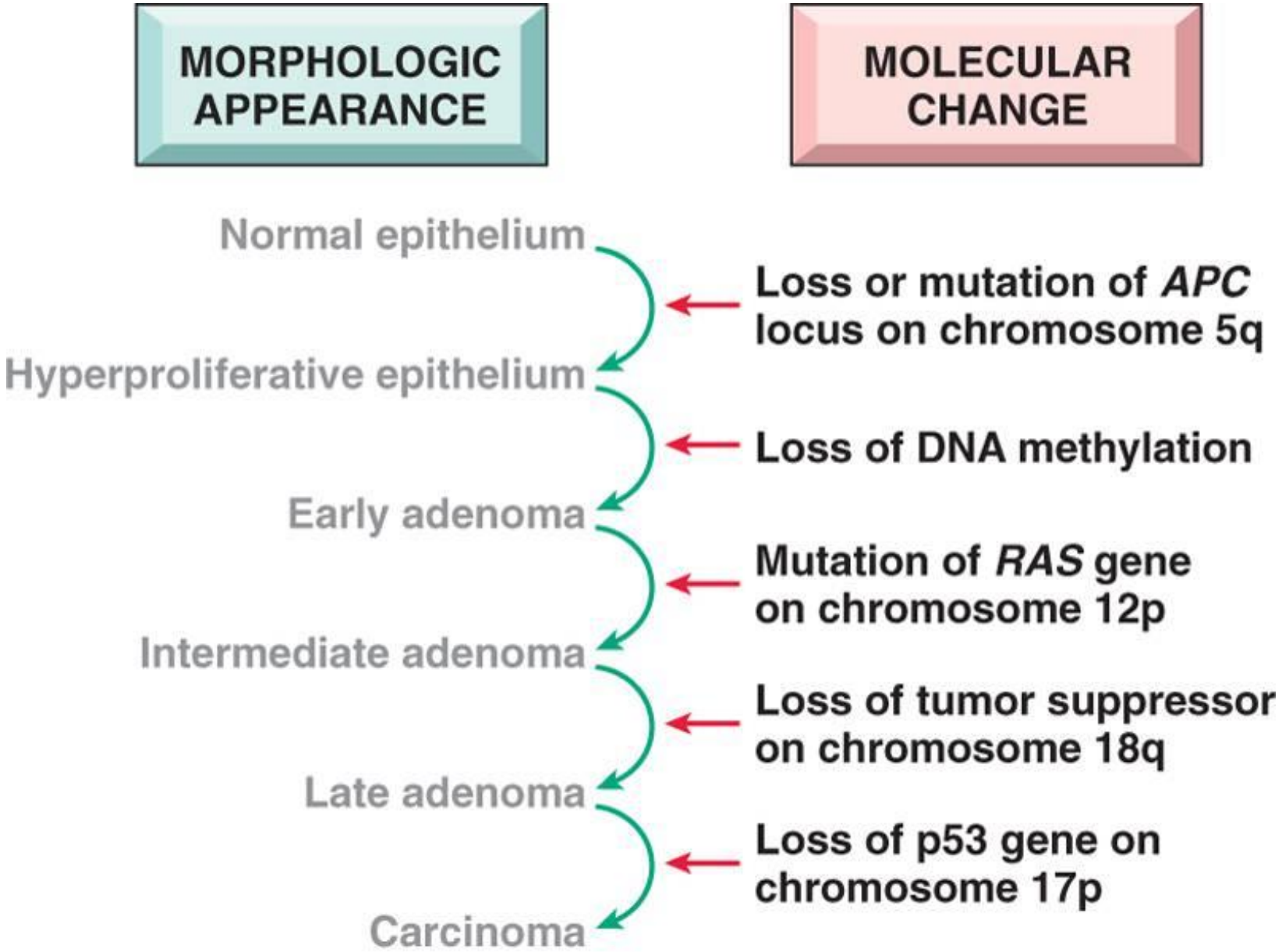


Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Multistep theory

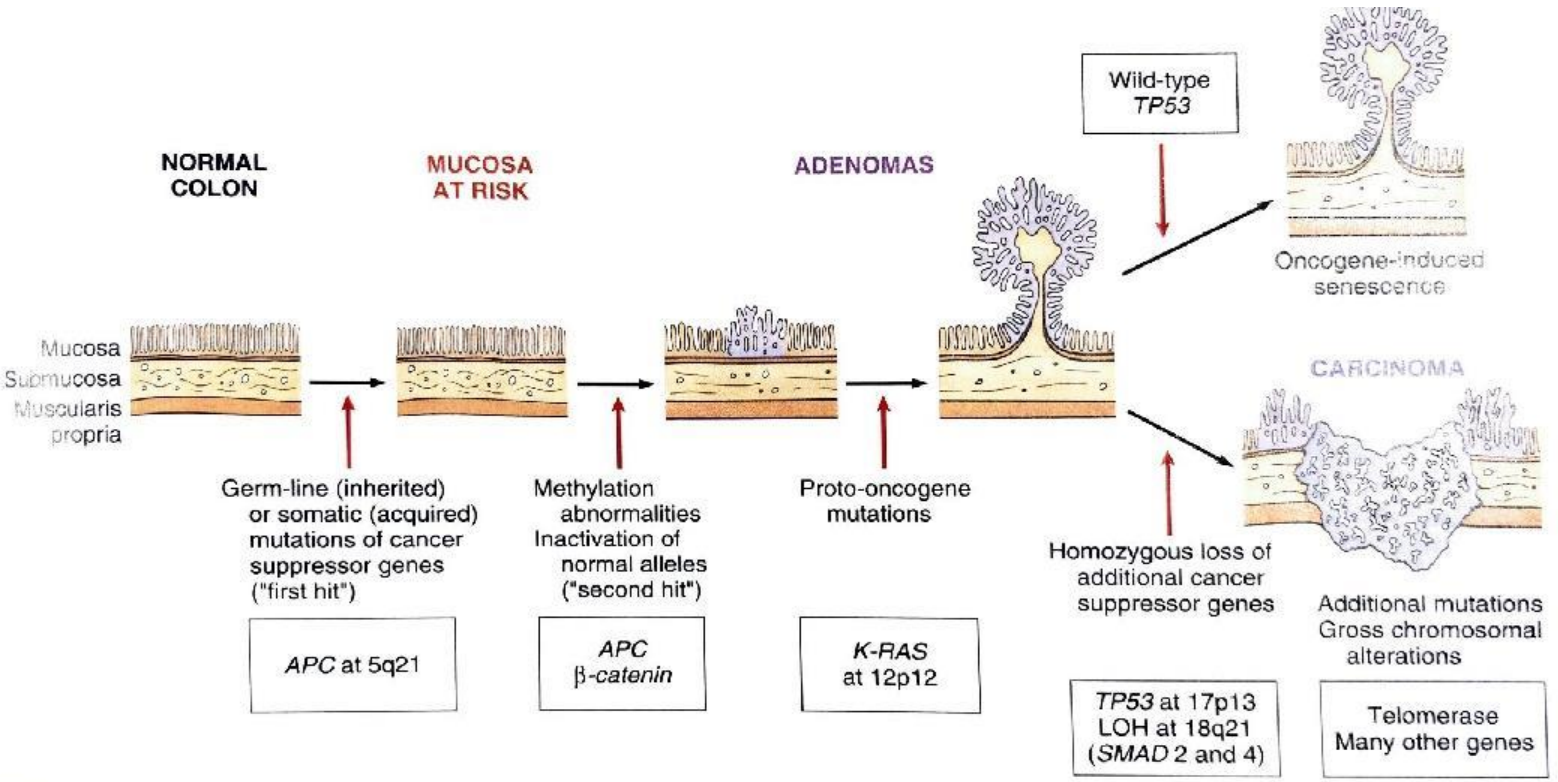


Figure 7-42 Molecular model for the evolution of colorectal cancers through the adenoma-carcinoma sequence. Although *APC* mutation is an early event and loss of *TP53* occurs late in the process of tumorigenesis, the timing for the other changes may be variable. Note also that individual tumors may not have all of the changes listed. *Top right*, cells that gain oncogene signaling without loss of *TP53* eventually enter oncogene-induced senescence. LOH, loss-of-heterozygosity.

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Programmed cell death in carcinogenesis

TRANSFORMATION

Initial event

Immortalization

Inhibition of apoptosis

PROMOTION

Altered DNA repair

Successive accumulation of mutations

Cell cycle promotion

Inhibition of apoptosis

PROGRESSION

Genomic instability

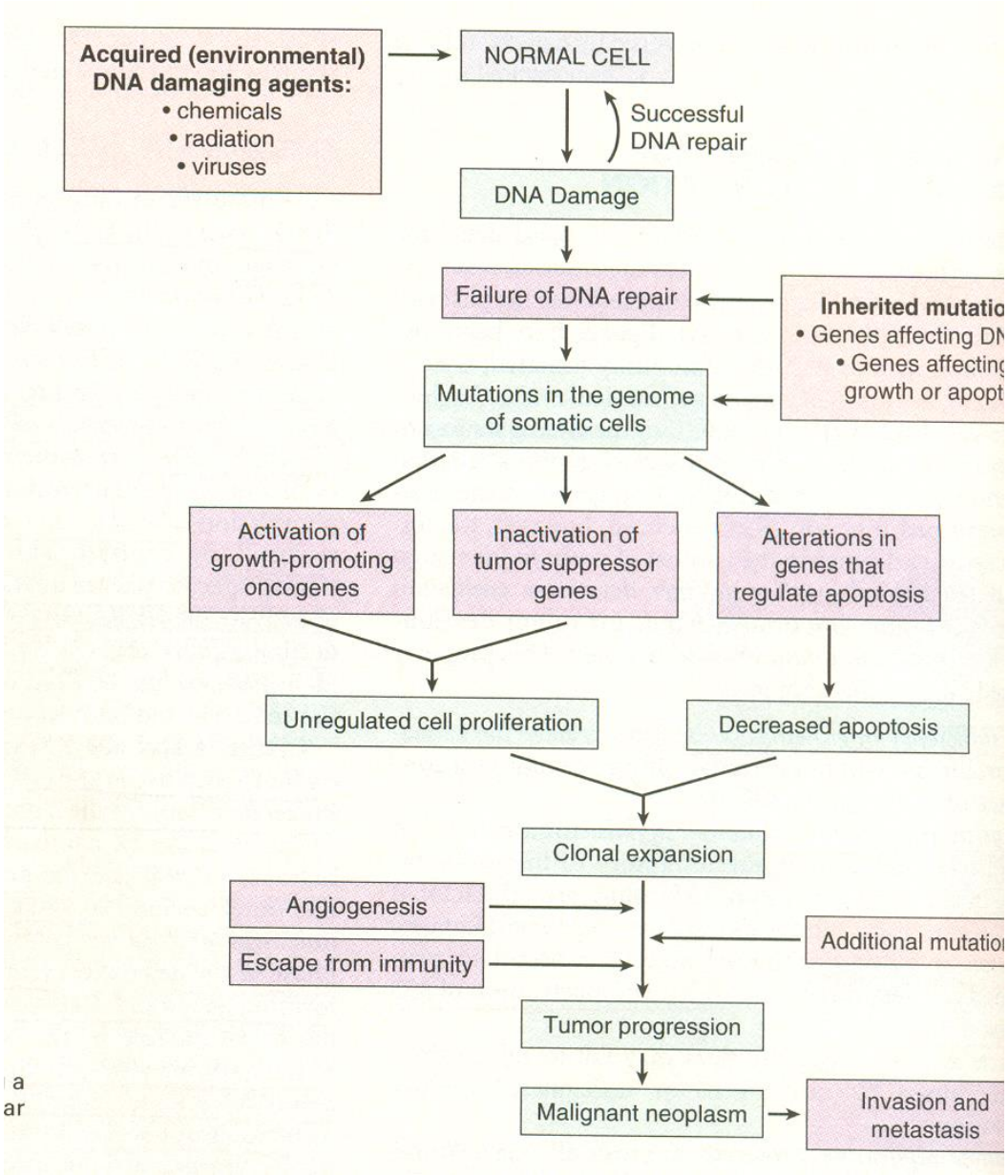
Other mutations

Irregular expression of apoptosis

Drug resistance

Summary

- DNA damage - loss of control over cell division.
- Radiation, Chemicals & Viral infections are some known causes of cancers.
- Cancer evolves in multiple steps by sequentially acquiring different DNA damages.
- Initiation, Latent stage, Promotion and Malignant transformation are recognizable stages in carcinogenesis.
- Each character of malignancy depends on unique DNA alteration.


Acquired (environmental) DNA damaging agents:
• chemicals
• radiation
• viruses
NORMAL CELL
Successful DNA repair
DNA Damage
Failure of DNA repair
Inherited mutatio
• Genes affecting DN
• Genes affecting
growth or apopt
Mutations in the genome of somatic cells
Activation of growth-promoting oncogenes
Inactivation of tumor suppressor genes
Alterations in genes that regulate apoptosis
Unregulated cell proliferation
Decreased apoptosis
Clonal expansion
Angiogenesis
Escape from immunity
Additional mutatio
Tumor progression
Malignant neoplasm
Invasion and metastasis