Molecular Basis of Cancer

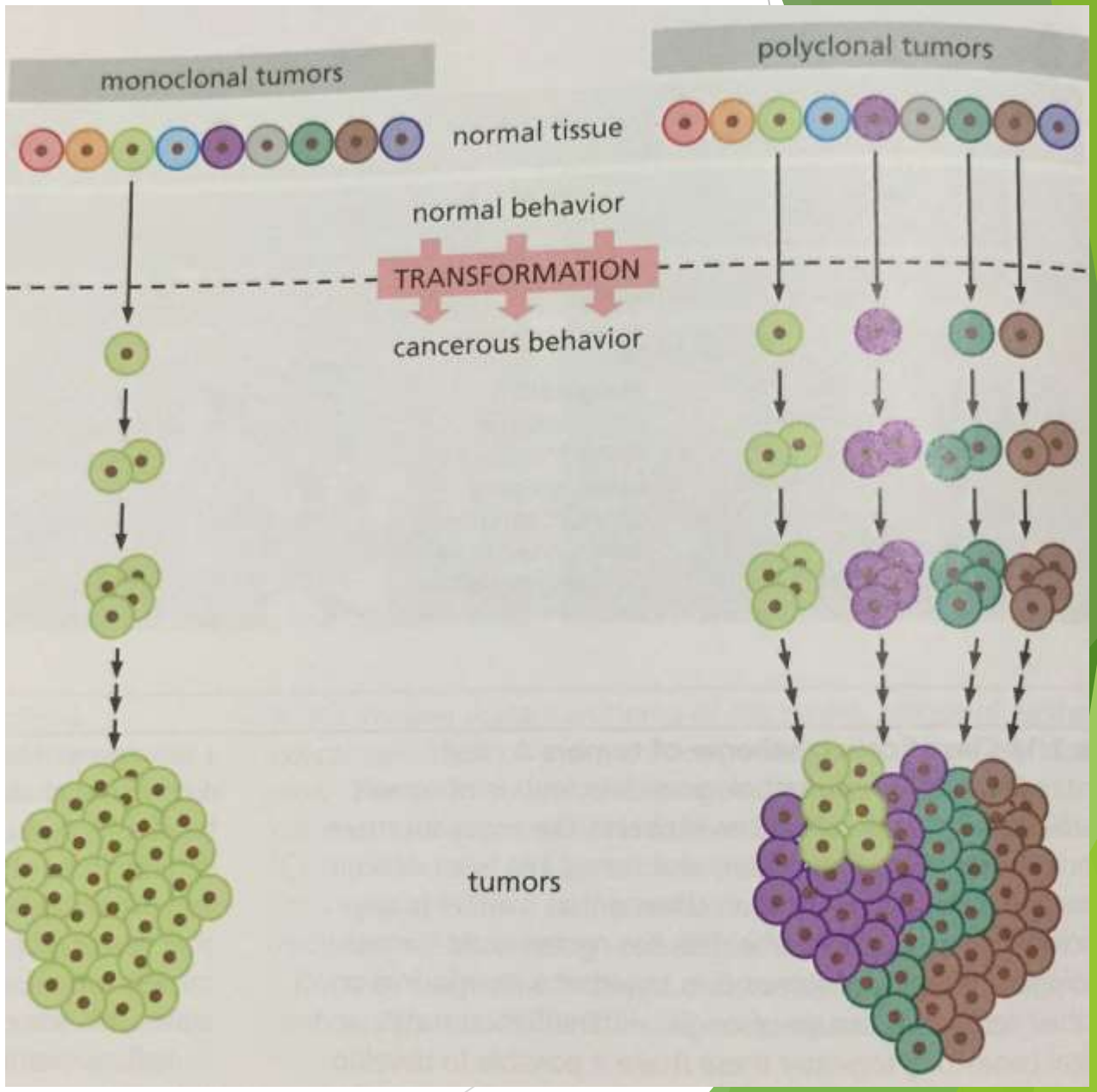
Dian Yuliartha Lestari

Pinsip dasar moleculer cancer

- Beberapa kerusakan genetik awal didapatkan dari paparan lingkungan (kimiawi, virus, radiasi)
- Terbentuk nya tumor dari ekspansi klonal 1 sel prekursor yang mengalami kerusakan genetik
- 4 kelompok gen regulator yang merupakan target kerusakan genetik :
  - Growth proto-oncogen
  - Growth inhibiting tumor suppressor gene
  - Gene regulated apoptosis
  - Gene involved in DNA repair
- Carcinogenesis merupakan suatu hasil akumulasi mutasi yang berasal dari proses multistep

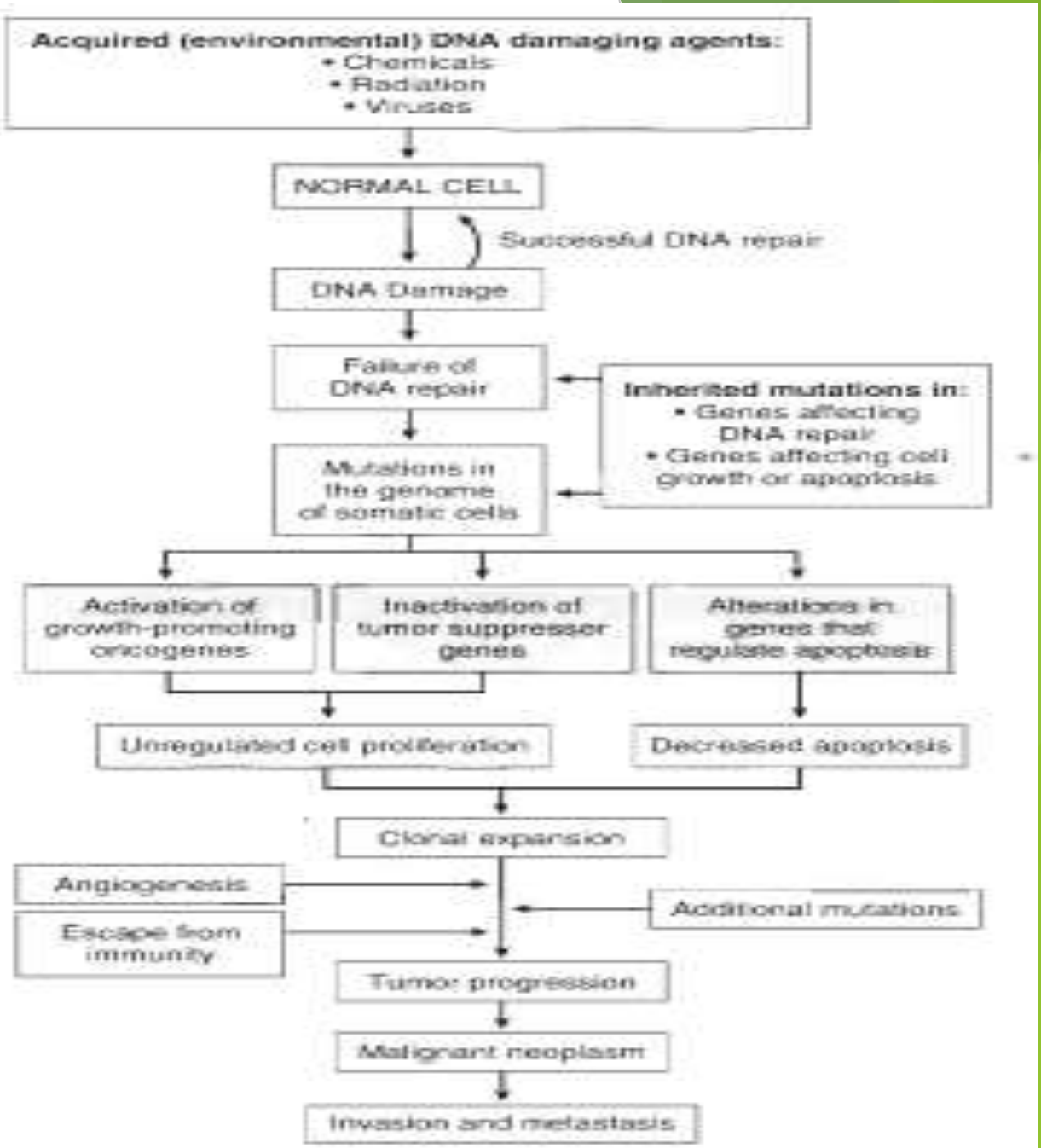
monoclonality

- Monoclonal → hanya satu sel yang mengalami transformasi maligna dan tumbuh progresive
- Polyclonal → beberapa sel yang berbeda asal genetikanya mengalami transformasi maligna membentuk suatu massa sehingga tidak dapat ditentukan asal sel nya



Genetic Regulation

- 4 classes or normal regulatory genes are :
  - proto-oncogenes
  - tumor-suppressor genes
  - regulate apoptosis
  - regulate DNA repair
- In cancer :
  - Activasi oncogen
  - Inhibisi tumor suppressor gene
  - Abnormal apoptosis regulatory gene
  - Failure of DNA repair



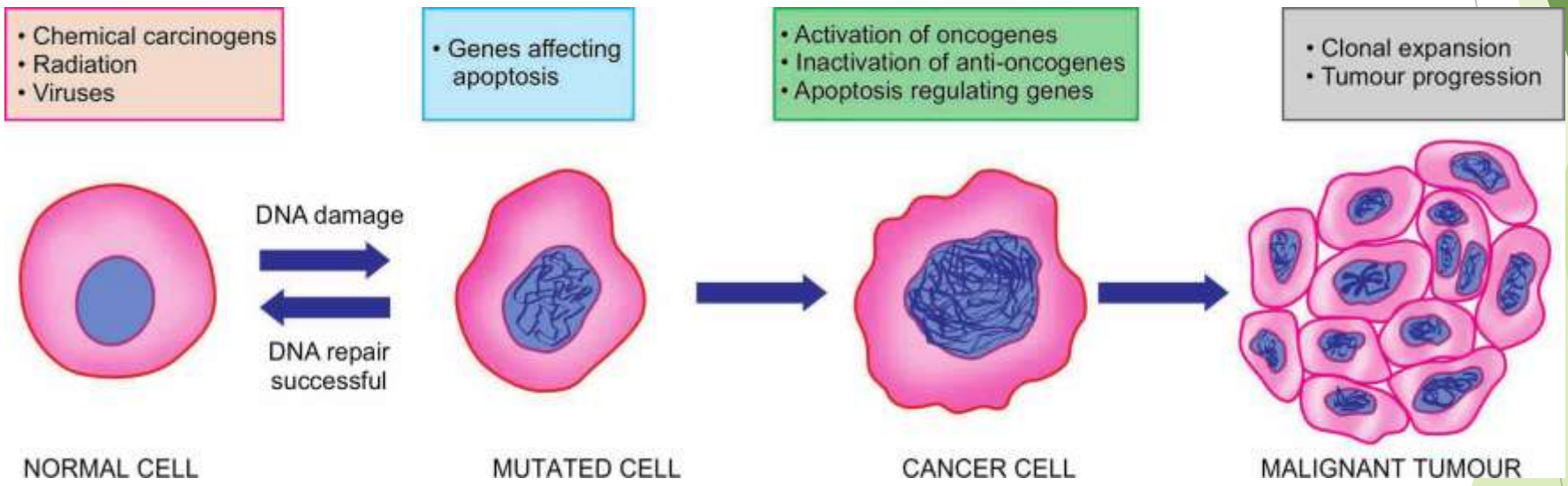


Figure 7.17 Schematic illustration to show molecular basis of cancer.

Hallmark of cancer

1. Self-sufficiency in growth signals
2. Insensitivity to growth-inhibitory signal
3. Altered celluler metabolism (warburg effect)
4. Evasion of apoptosis
5. Limitless replicative potential (immortality)
6. Sustained angiogenesis
7. Ability to invade and metastazise
8. Ability to evade the host imune response

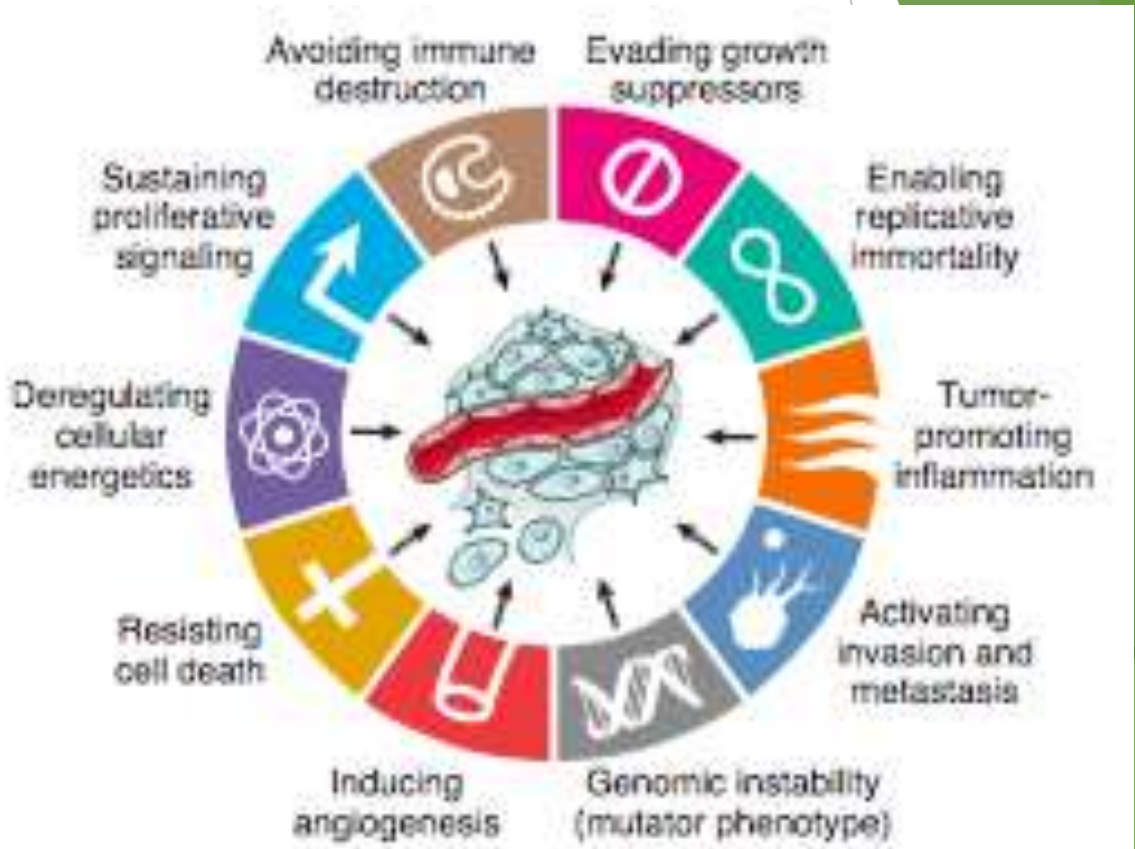


Figure 7-24 Hallmarks of cancer. (Adapted from Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646.)

Self-sufficiency in growth signals : Oncogens

- Oncogen → gene that promotes autonomous cell growth in cancer
- Oncogen terjadi akibat mutasi dari proto-oncogen
- Oncogen mengkode protein yang disebut : Oncoprotein
- Fungsi oncoprotein adalah tetap meningkatkan pertumbuhan sel tumor meskipun tidak mendapatkan growth signal yang normal

Growth signal normal :

- Ikatan antara growth factor dengan growth receptor
- Ikatan tersebut mengaktivasi signal transducing protein
- Transmisi signal transduksi ke inti sel melewati signal transduksi molekul
- Induksi dan aktivasi inti sel mencetuskan DNA transkripsi
- Ekspresi factor yang mencetuskan Sel untuk memasuki siklus sel
- Perubahan dari ekspresi gen lain untuk mensupport sel dan metabolisme nya untuk perkembangan yang optimal

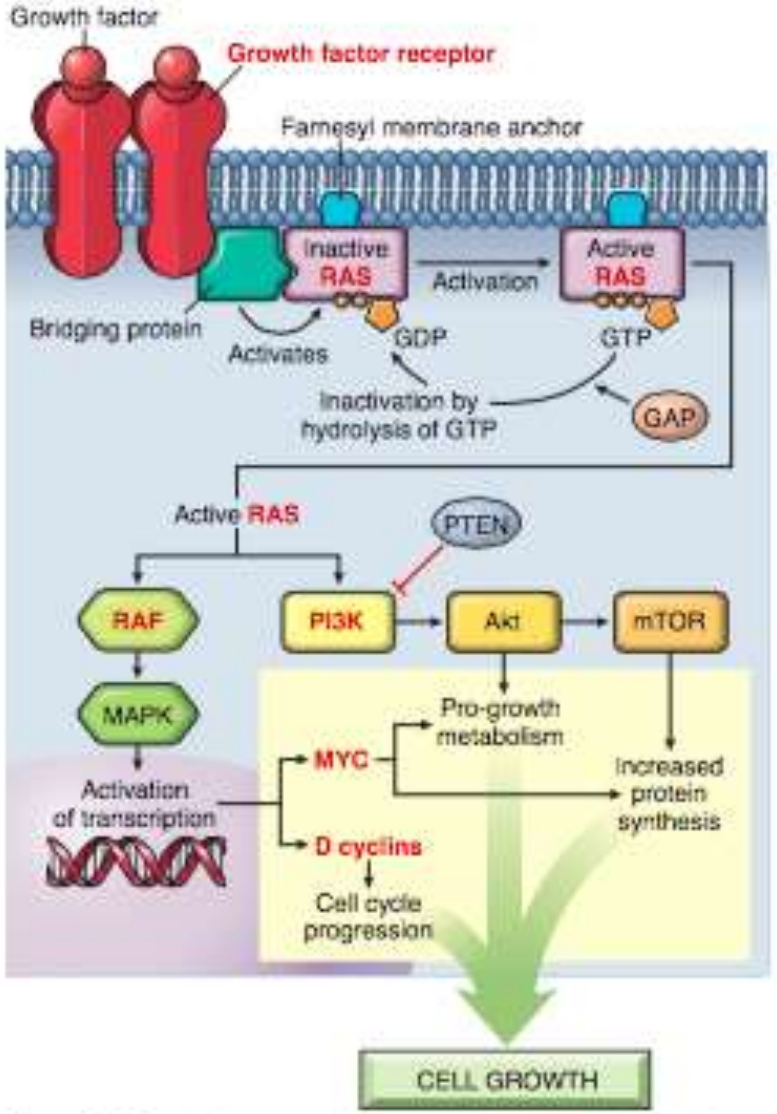


Figure 7-25 Growth factor signaling pathways in cancer. Growth factor receptors, RAS, PI3K, MYC, and D cyclins are oncoproteins that are activated by mutations in various cancers. GAPs apply brakes to RAS activation, and PTEN serves the same function for PI3K.

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 chain	*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	Leukemia
Receptor for neurotrophic factors	*RET*	Point mutation	Multiple endocrine neoplasia 2A and B, familial medullary thyroid carcinomas
PDGF receptor	*PDGFRB*	Overexpression, translocation	Gliomas, leukemias
Receptor for KIT ligand	*KIT*	Point mutation	Gastrointestinal stromal tumors, seminomas, leukemias
ALK receptor	*ALK*	Translocation, fusion gene formation 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 Point mutation	Chronic myelogenous leukemia Acute lymphoblastic leukemia
RAS signal transduction	*BRAF*	Point mutation, Translocation	Melanomas, leukemias, colon carcinoma, others
Notch signal transduction	*NOTCH1*	Point mutation, Translocation Gene rearrangement	Leukemias, lymphomas, breast carcinoma
JAK/STAT signal transduction	*JAK2*	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

Growth Factor – Growth Factor Receptor

- Secara normal, sel membutuhkan stimulasi growth factor agar dapat proliferasi
- Ikatan antara GF dengan GFR dapat mengaktifkan thyrosin-kinase pathway melalui jalur RAS
- Aktif nya RAS dapat mengkatifkan MAPK dan PI3K sehingga terjadi proses transkripsi DNA pada inti sel
- Pada malignancy → overekspresi GF
  - PDGF → glioblastoma
  - TGF-α → sarcoma
  - EGFR/ERBB1 → ca paru
  - ERBB2 → ca mamma

RAS mutation

- Protein RAS merupakan anggota dari protein G pada membran yang berikatan dengan GTP (guanasine triphosphat) and GDP (guanasine diphosphat)
- Stimulasi pada thyrosin kinase mengubah GDP menjadi GTP sehingga mengaktifkan RAS
- RAS memiliki intrinsik GTP-activiting protein (GAP) dimana berfungsi mengha,mbat RAS yang tidak terkontrol
- Didapatkan 3 gen pengkode RAS pada manusia
  - HRAS
  - KRAS
  - NRAS
- Teraktivasi akibat infeksi retrovirus
- 15-25% tumor → ekspresi RAS mutation
- 90% pada ca pancreas dan cholangio ca
- 50% pada colon, endometrium, thyroid
- Mutasi pada GAP → NF 1

Oncogenic BRAF dan PI3K mutation

- Mutasi BRAF
  - 100 % → hairy cell leukemia
  - 60% → melanoma
  - 80% → nevus
- Mutasi PI3K
  - 30% → ca mamma

MYC oncogen

- MYC merupakan salah satu faktor transkripsi pada inti
- Mekanisme MYC sampai sekarang masih belum jelas
- Aktivitas MYC :
  - Mengkespresikan beberapa gen yang berperan pada pertumbuhan sel
  - Meningkatkan upregulasi dari ekspresi telomerase
  - Salah satu faktor trkskripsi yang dapat bekerja untuk mengaktifkan somatic cell menjadi pluripotent stem cell
- MYC translocation :
  - Burkit’s lymphoma
  - neuroblastoma

Cyclin - CDK

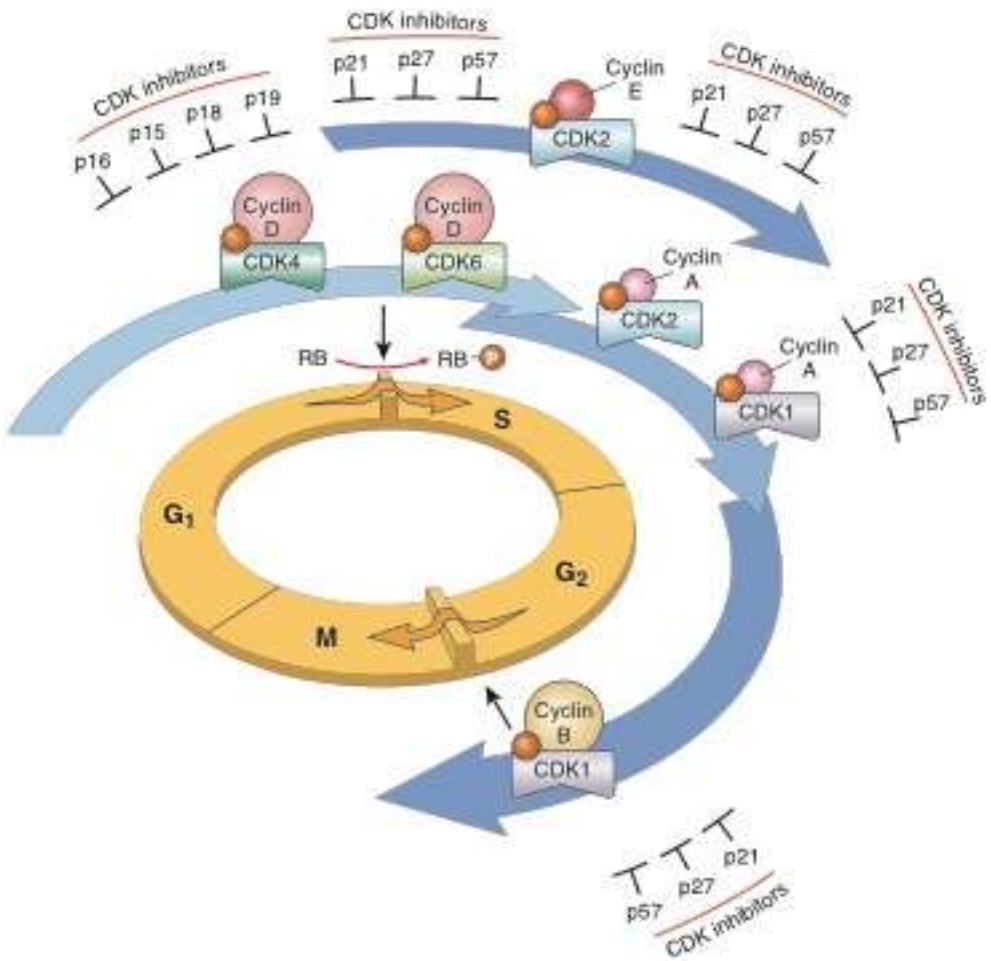


Table 7-6 Cell Cycle Components and Inhibitors That Are Frequently Mutated in Cancer

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.

Mutations in growth factor receptors, non-receptor tyrosine kinases, or downstream signaling molecules that lead to constitutive signaling, such as:

- Activation of the EGF receptor tyrosine kinase by point mutations (lung cancer); activation of the HER2 receptor tyrosine kinase by gene amplification (breast cancer) ; activation of the JAK2 tyrosine kinase by point muta- tions (myeloproliferative disorders)
- Activation of the ABL nonreceptor tyrosine kinase by chromosomal translocation and creation of a BCR-ABL fusion gene (chronic myelogenous leukemia, acute lym- phoblastic leukemia)
- Activation of RAS by point mutations (many cancers)
- Activation of the PI3K and BRAF serine/threonine kinases by point mutations (many cancers)

Insensitivity to growth inhibition : Tumor Suppressor gene

- Disebut juga Anti Oncogen
- Berfungsi untuk menekan pertumbuhan atau menghambat proliferasi sel tumor
- Saat normal gen ini berperan dalam siklus sel
- Jika terjadi mutasi → maka hambatan proliferasi menjadi hilang → sel tumbuh tidak teratur
- Contoh : p53, pRb

Gene	Protein	Function	Familial Syndromes	Sporadic Cancers
Inhibitors of Mitogenic Signaling Pathways				
APC	Adenomatous polyposis coli protein	Inhibitor of WNT signaling	Familial colonic polyps and carcinomas	Carcinomas of stomach, colon, pancreas; melanoma
NF1	Neurofibromin-1	Inhibitor of RAS/MAPK signaling	Neurofibromatosis type 1 (neurofibromas and malignant peripheral nerve sheath tumors)	Neuroblastoma, juvenile myeloid leukemia
NF2	Merlin	Cytoskeletal stability, Hippo pathway signaling	Neurofibromatosis type 2 (acoustic schwannoma and meningioma)	Schwannoma, meningioma
PTCH	Patched	Inhibitor of Hedgehog signaling	Gorlin syndrome (basal cell carcinoma, medulloblastoma, several benign tumors)	Basal cell carcinoma, medulloblastoma
PTEN	Phosphatase and tensin homologue	Inhibitor of PI3K/AKT signaling	Cowden syndrome (variety of benign skin, GI, and CNS growths; breast, endometrial, and thyroid carcinoma)	Diverse cancers, particularly carcinomas and lymphoid tumors
SMAD2, SMAD4	SMAD2, SMAD4	Component of the TGFβ signaling pathway, repressors of MYC and CDK4 expression, inducers of CDK inhibitor expression	Juvenile polyposis	Frequently mutated (along with other components of the TGFβ signaling pathway) in colonic and pancreatic carcinoma

Inhibitors of Cell Cycle Progression				
RB	Retinoblastoma (RB) protein	Inhibitor of G1/S transition during cell cycle progression	Familial retinoblastoma syndrome (retinoblastoma, osteosarcoma, other sarcomas)	Retinoblastoma; osteosarcoma carcinomas of breast, colon, lung
CDKN2A	p16/INK4a and p14/ARF	p16: Negative regulator of cyclin-dependent kinases; p14, indirect activator of p53	Familial melanoma	Pancreatic, breast, and esophageal carcinoma, melanoma, certain leukemias
Inhibitors of "Pro-growth" Programs of Metabolism and Angiogenesis				
VHL	Von Hippel Lindau (VHL) protein	Inhibitor of hypoxia-induced transcription factors (e.g., HIF1α)	Von Hippel Lindau syndrome (cerebellar hemangioblastoma, retinal angioma, renal cell carcinoma)	Renal cell carcinoma
STK11	Liver kinase B1 (LKB1) or STK11	Activator of AMPK family of kinases; suppresses cell growth when cell nutrient and energy levels are low	Peutz-Jeghers syndrome (GI polyps, GI cancers, pancreatic carcinoma and other carcinomas)	Diverse carcinomas (5%-20% of cases, depending on type)
SDHB, SDHD	Succinate dehydrogenase complex subunits B and D	TCA cycle, oxidative phosphorylation	Familial paraganglioma, familial pheochromocytoma	Paraganglioma

Inhibitors of Invasion and Metastasis				
CDH1	E-cadherin	Cell adhesion, inhibition of cell motility	Familial gastric cancer	Gastric carcinoma, lobular breast carcinoma
Enablers of Genomic Stability				
TP53	p53 protein	Cell cycle arrest and apoptosis in response to DNA damage	Li-Fraumeni syndrome (diverse cancers)	Most human cancers
DNA Repair Factors				
BRCA1, BRCA2	Breast cancer-1 and breast cancer-2 (BRCA1 and BRCA2)	Repair of double-stranded breaks in DNA	Familial breast and ovarian carcinoma; carcinomas of male breast; chronic lymphocytic leukemia (BRCA2)	Rare
MSH2, MLH1, MSH6	MSH1, MLH1, MSH6	DNA mismatch repair	Hereditary nonpolyposis colon carcinoma	Colonic and endometrial carcinoma
Unknown Mechanisms				
WT1	Wilms tumor-1 (WT1)	Transcription factor	Familial Wilms tumor	Wilms tumor, certain leukemias
MEN1	Menin	Transcription factor	Multiple endocrine neoplasia-1 (MEN1; pituitary, parathyroid, and pancreatic endocrine tumors)	Pituitary, parathyroid, and pancreatic endocrine tumors

Rb : Genome of proliferation

RB, a key negative regulator of the G_1/S cell cycle transition, is directly or indirectly inactivated in most human cancers.

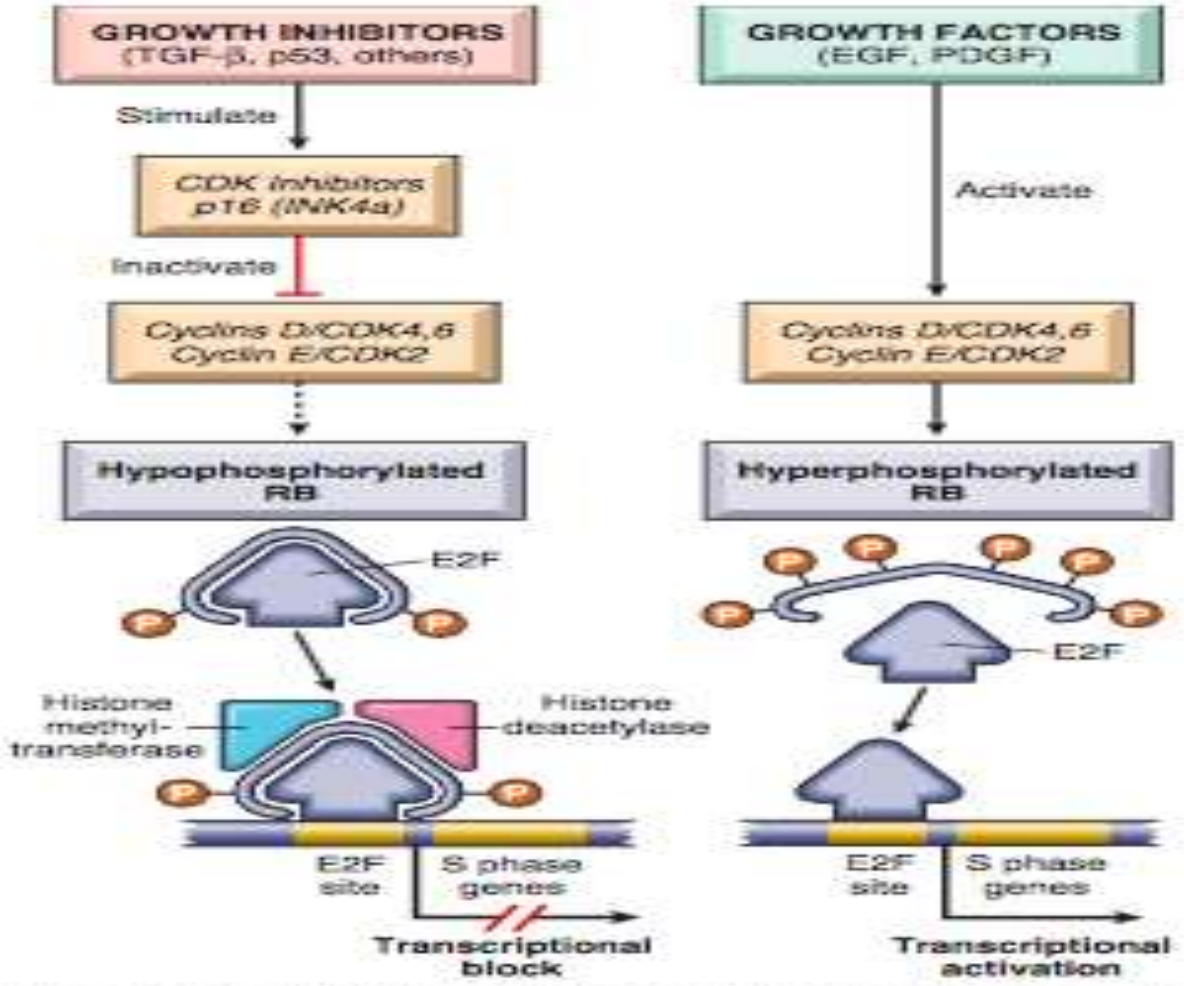


Figure 7-29 The role of RB in regulating the G_1-S checkpoint of the cell cycle. Hypophosphorylated RB in complex with the E2F transcription factors binds to DNA, recruits chromatin-remodeling factors (histone deacetylases and histone methyltransferases), and inhibits transcription of genes whose products are required for the S phase of the cell cycle. When RB is phosphorylated by the cyclin D-CDK4, cyclin D-CDK6, and cyclin E-CDK2 complexes, it releases E2F. The latter then activates transcription of S-phase genes. The phosphorylation of RB is inhibited by cyclin-dependent kinase inhibitors, because they inactivate cyclin-CDK complexes. Virtually all cancer cells show dysregulation of the G_1-S checkpoint as a result of mutation in one of four genes that regulate the phosphorylation of RB; these genes are *RB*, *CDK4*, the genes encoding cyclin D proteins, and *CDKN2A* (p16). TGF-β, transforming growth factor-β.

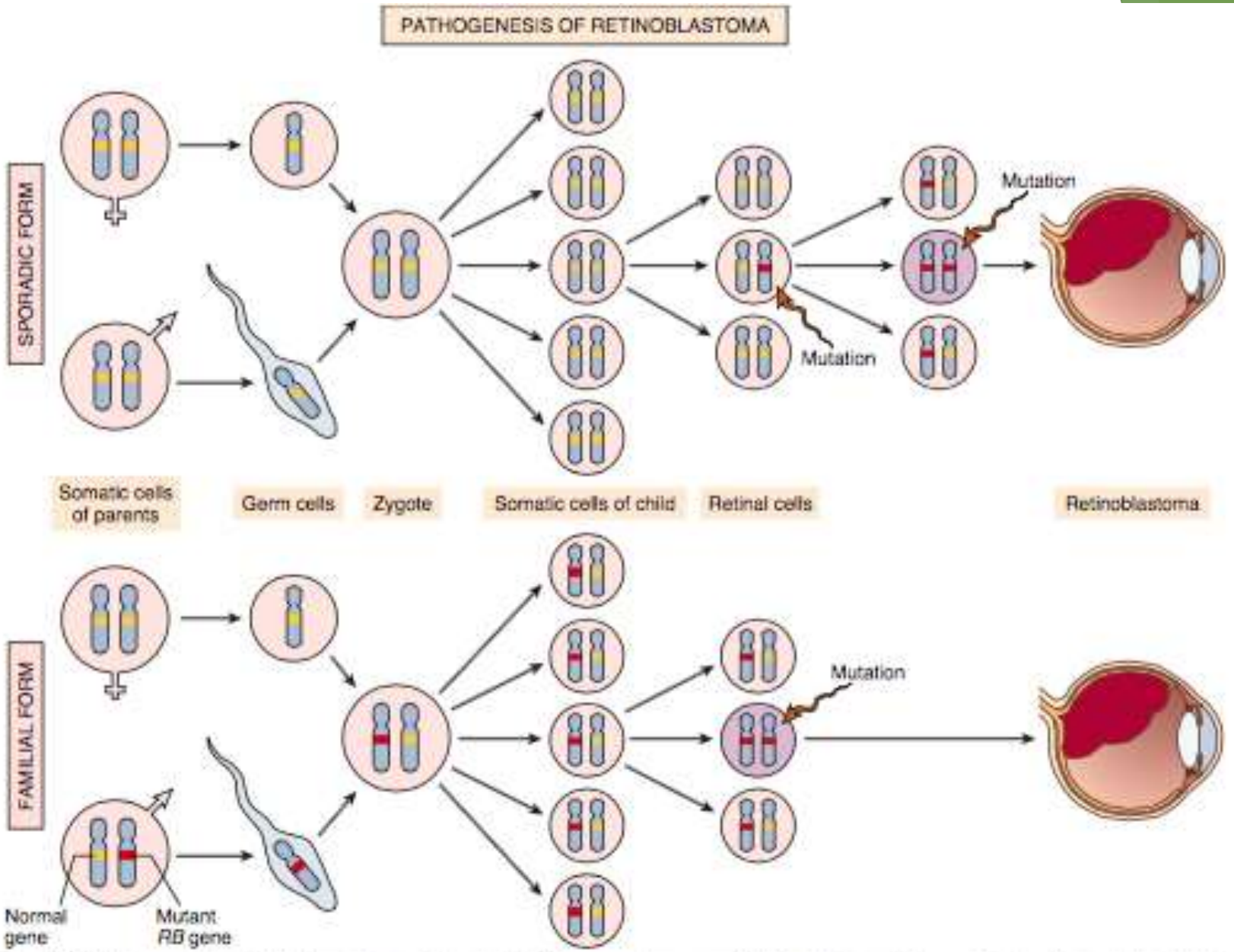


Figure 7-28 Pathogenesis of retinoblastoma. Two mutations of the *RB* locus on chromosome 13q14 lead to neoplastic proliferation of the retinal cells. In the sporadic form, both *RB* mutations in the tumor-founding retinal cell are acquired. In the familial form, all somatic cells inherit one mutated 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.

The antiproliferative effect of RB is abrogated in cancers through a variety of mechanisms, including:

- Loss-of-function mutations affecting *RB*
- Gene amplifications of CDK4 and cyclin D genes
- Loss of cyclin-dependent kinase inhibitors (p16/INK4a)
- Viral oncoproteins that bind and inhibit RB (E7 protein of HPV)

TP_{53} : Guardian of the Genome

***TP53*, a tumor suppressor gene that regulates cell cycle progression, DNA repair, cellular senescence, and apoptosis, is the most frequently mutated gene in human cancers.**

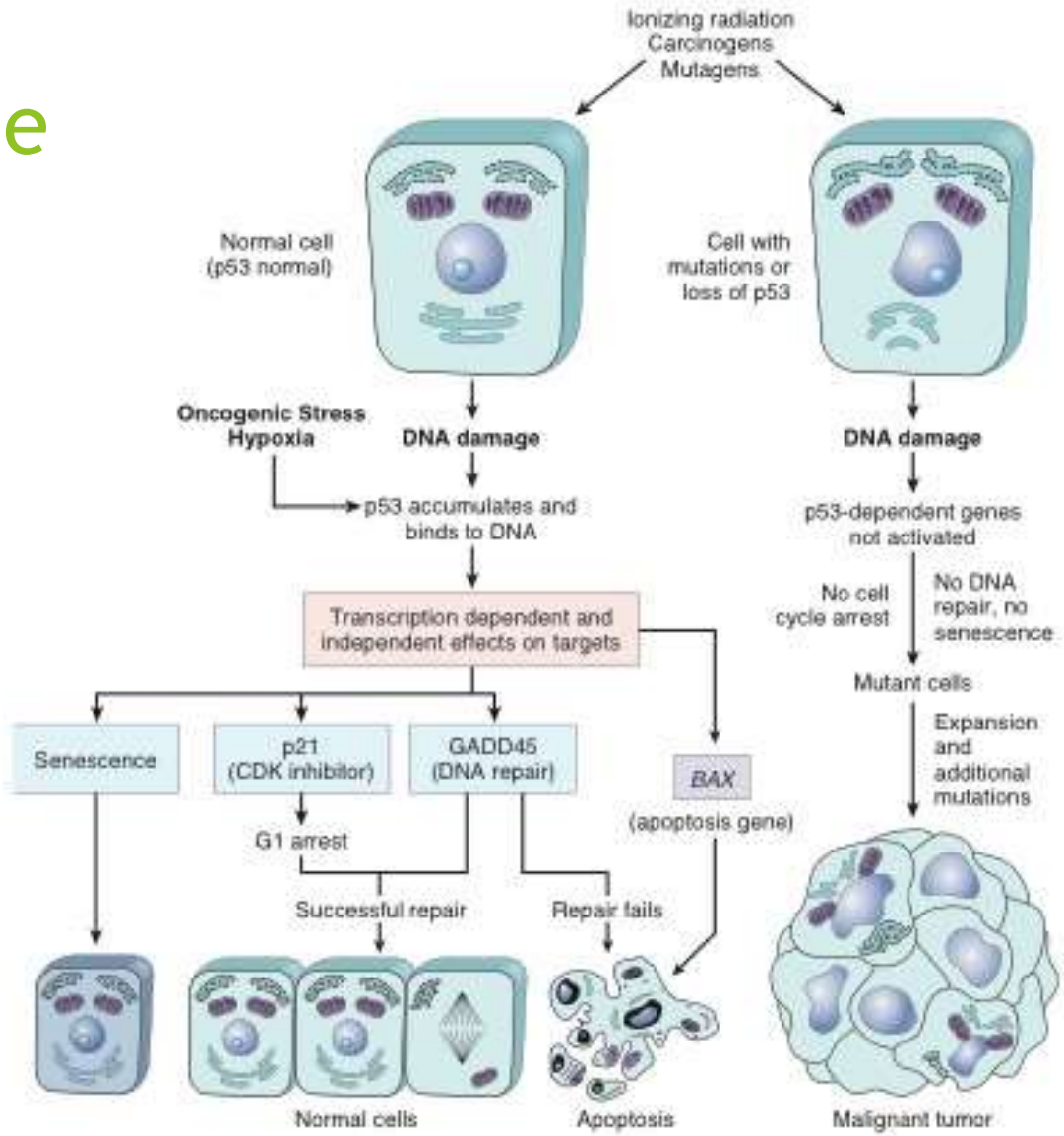


Figure 7-30 The role of p53 in maintaining the integrity of the genome. Activation of normal p53 by DNA-damaging agents or by hypoxia leads to cell cycle arrest in G_1 and induction of DNA repair by transcriptional upregulation of the cyclin-dependent kinase inhibitor *CDKN1A* (encoding the cyclin-dependent 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.

- 50% kanker → Mutasi pada TP53 terjadi pada kromosom 17p13.1
- 3 kanker terbanyak : paru, colon, breast → mutasi TP53
- Mirip dengan Prb, Mutasi TP53 yang terjadi hanya satu alelmerupakan “first hit”
- TP53 mengkode protein p53 yang berfungsi dalam berbagai tahapan di sklus sel, dan mengaktifakan beberapa protein lain, salah satu nya MDM2
- MDM 2 berfungsi untuk mendegradasi TP53, sehingga jika ditemukan TP53 yang abnormal, maka akan didapatkan peningkatan MDM2
- Sama seperti pRB, transformasi TP53 akibat ikatan DNA dengan virus (E6 HPV)
- Secara normal, TP53 undetectable, jika terjadi overstress, TP53 disekresikan akibat inhibisi dari MDM2 lewat 2 mekanisme :
  1. DNA damage dan hypoxia
  2. Oncogenic stress
- Keluarga p53 : p63 (sel epitelial), p73 (strong apoptotic agent)

APC : Gatekeeper of Colonic Neoplasia

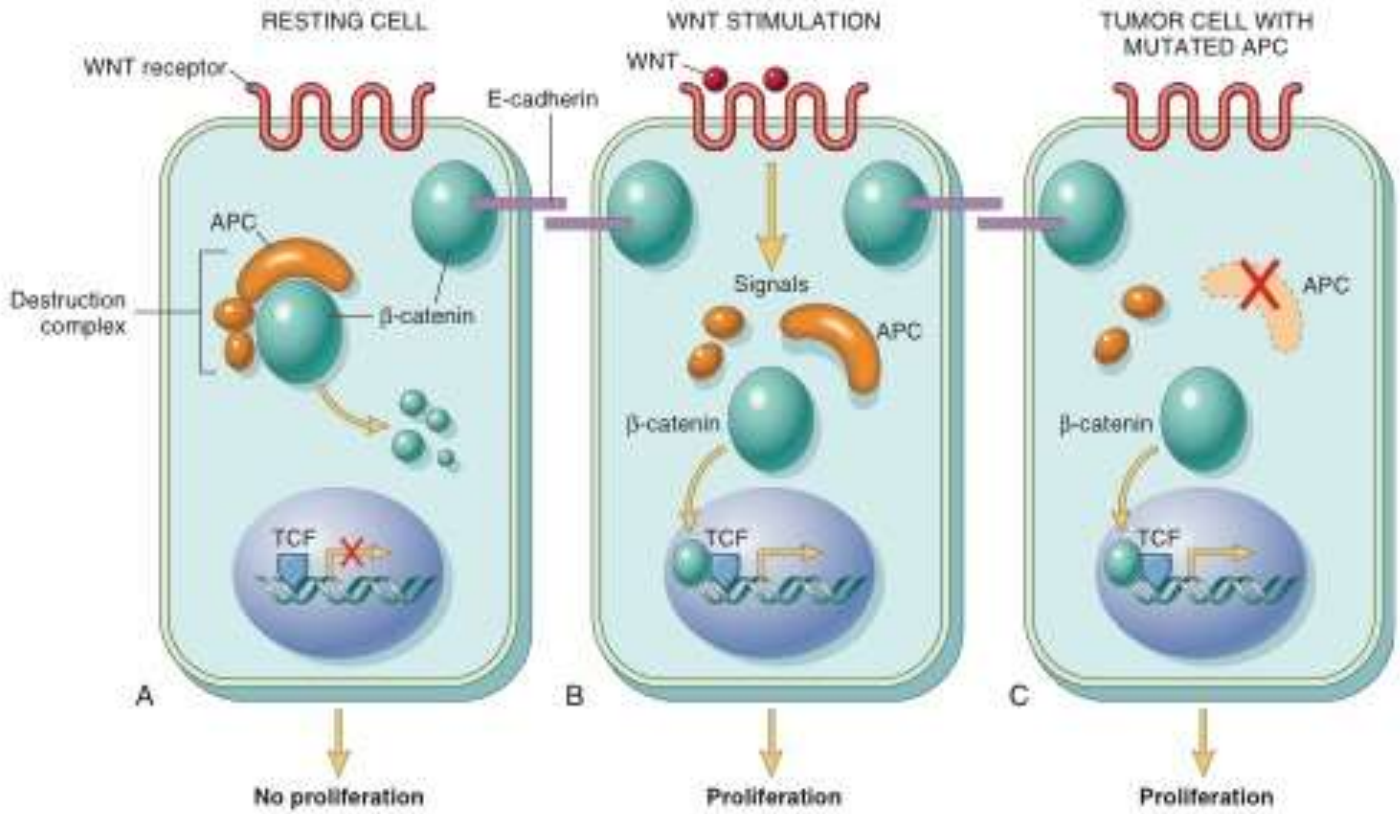


Figure 7-31 The role of APC in regulating the stability and function of β-catenin. APC and β-catenin are components of the WNT signaling pathway. **A,** In resting colonic epithelial cells (not exposed to WNT), β-catenin forms a macromolecular complex containing the APC protein. This complex leads to the destruction of β-catenin, and intracellular levels of β-catenin are low. **B,** When normal colonic epithelial cells are stimulated by WNT molecules, the destruction complex is deactivated, β-catenin degradation does not occur, and cytoplasmic levels increase. β-catenin translocates to the nucleus, where it binds to TCF, a transcription factor that activates genes involved in cell cycle progression. **C,** When APC is mutated or absent, as frequently occurs in colonic polyps and cancers, the destruction of β-catenin cannot occur. β-catenin translocates to the nucleus and coactivates genes that promote entry into the cell cycle, and cells behave as if they are under constant stimulation by the WNT pathway.

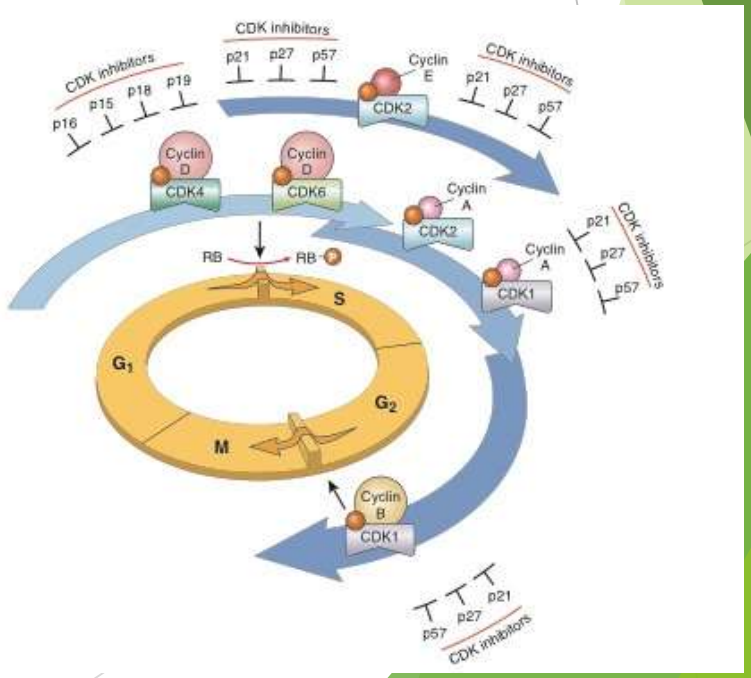
- Mutasi APC (adenomatous poliposis coli) pada kromosom 5q21 → terjadi pada pasien adenomatous colon yang mengalami 1 alele mutasi
- APC merupakan salah satu komponen dari WnT signaling pathway, dimana berperan sebagai :
  - Kontrol perkembangan sel
  - Kontrol adhesi
  - Dan kontrol polaritas selama fase embriogenic
- Fungsi utama dari APC adalah menahan B-catenin → jika WnT tidak terstimulasi maka APC menyebabkan degradasi dari B-catenin
- Jika Wnt terstimulasi maka terjadi hambatan proses destruksi oleh APC, sehingga B-catenin berikatan dengan TCF mengaktifkan transkripsi sel
- Jika APC tidak ada, maka B-catenin masuk ke dalam nukleus dan berikatan dengan TCF
- Mutasi pada APC/B-catenin terjadi pada 50% hepatoblastoma, dan 20% hepatoma

E-chaderin

- Merupakan protein permukaan sel yang berperan pada ikatan antar sel
- Hilangnya ikatan antar sel menyebabkan peningkatan translokasi B-catenin ke dalam nukleus, dan menstimulasi proliferasi sel
- Secara normal, hilangnya ikatan B-catenin/E-chaderin terjadi pada trauma di sel epitelial
- Mutasi pada B-catenin/E-chaderin menyebabkan proliferasi sel terus menerus
- Dengan hilangnya E-chaderin maka kemungkinan tumor invasi dan metastasis akan lebih tinggi
- Mutasi E chaderin = CDH1 → gastric carcinoma

CDKN2A

- Mengkode 2 protein :
  1. p16/INK4a CDKi → menghambat ikatan CDK4/Cyclin-D → pRb teraktivasi
  2. P14/ARF → mengambat MDM2 → tidak terjadi destruksi p53 → p53 aktif
- Mutasi pada CDKN2A dapat berpengaruh pada pRb dan p53
- Mutasi CDKN2A : melanoma maligna, bladder ca, ALL, head and neck tumor, cholangio ca



PTEN (phosphatase dan tensin homologue)

- Menghambat ikatan PI3K/Akt pada thyrosin kinase pathway
- Akibatnya tidak terjadi proliferasi sel
- Mutasi pada PTEN → Cowden syndrome

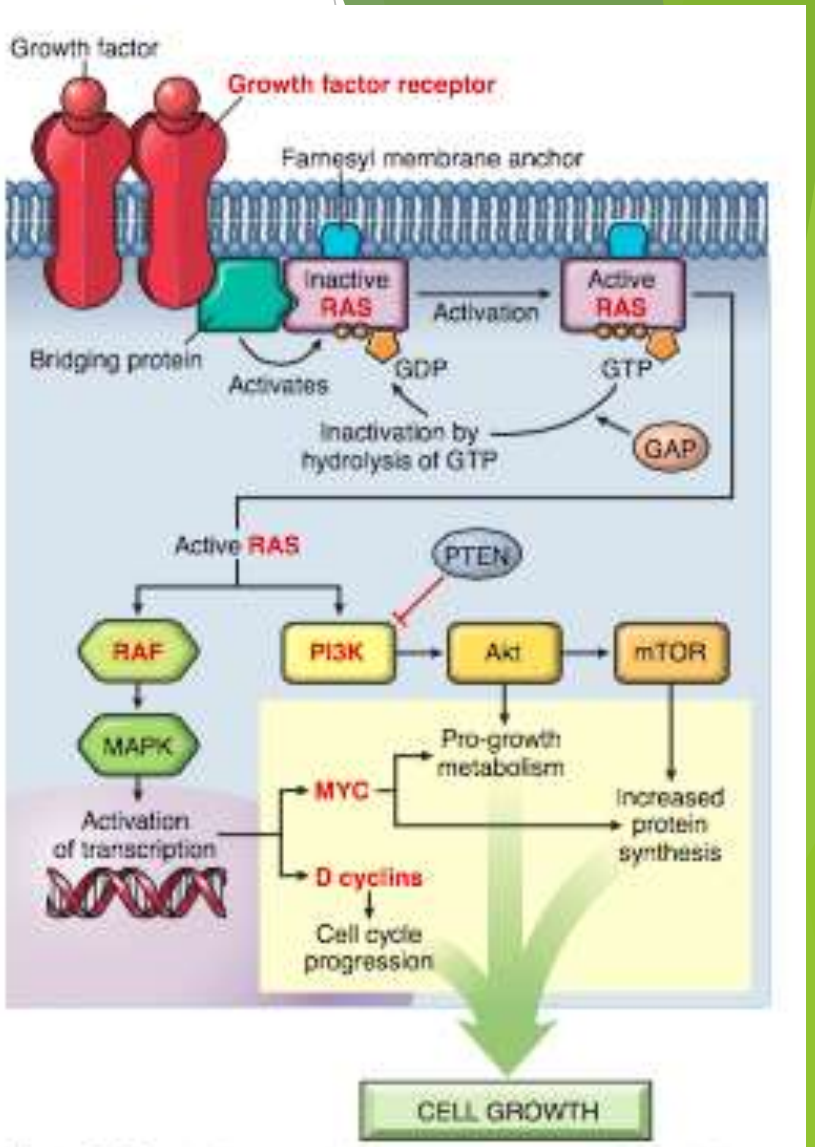


Figure 7-25 Growth factor signaling pathways in cancer. Growth factor receptors, RAS, PI3K, MYC, and D cyclins are oncoproteins that are activated by mutations in various cancers. GAPs apply brakes to RAS activation, and PTEN serves the same function for PI3K.

GROWTH PROMOTING METABOLIC ALTERATION : WARBURG EFFECT

- Even in the presence of ample oxygen, cancer cells demonstrate a distinctive form of cellular metabolism charac- terized by high levels of glucose uptake and increased conversion of glucose to lactose (fermentation) via the glycolytic pathway.
- This phenomenon called : Warburg Effect → aerobic glycolysis
- aerobic glycolysis provides rapidly dividing tumor cells with metabolic intermediates that are needed for the synthesis of cellular components, whereas mitochondrial oxidative phosphorylation does not.
- metabolic reprogramming is produced by signaling cascades downstream of growth factor receptors, the very same pathways that are deregulated by mutations in oncogenes and tumors suppressor genes in cancers.

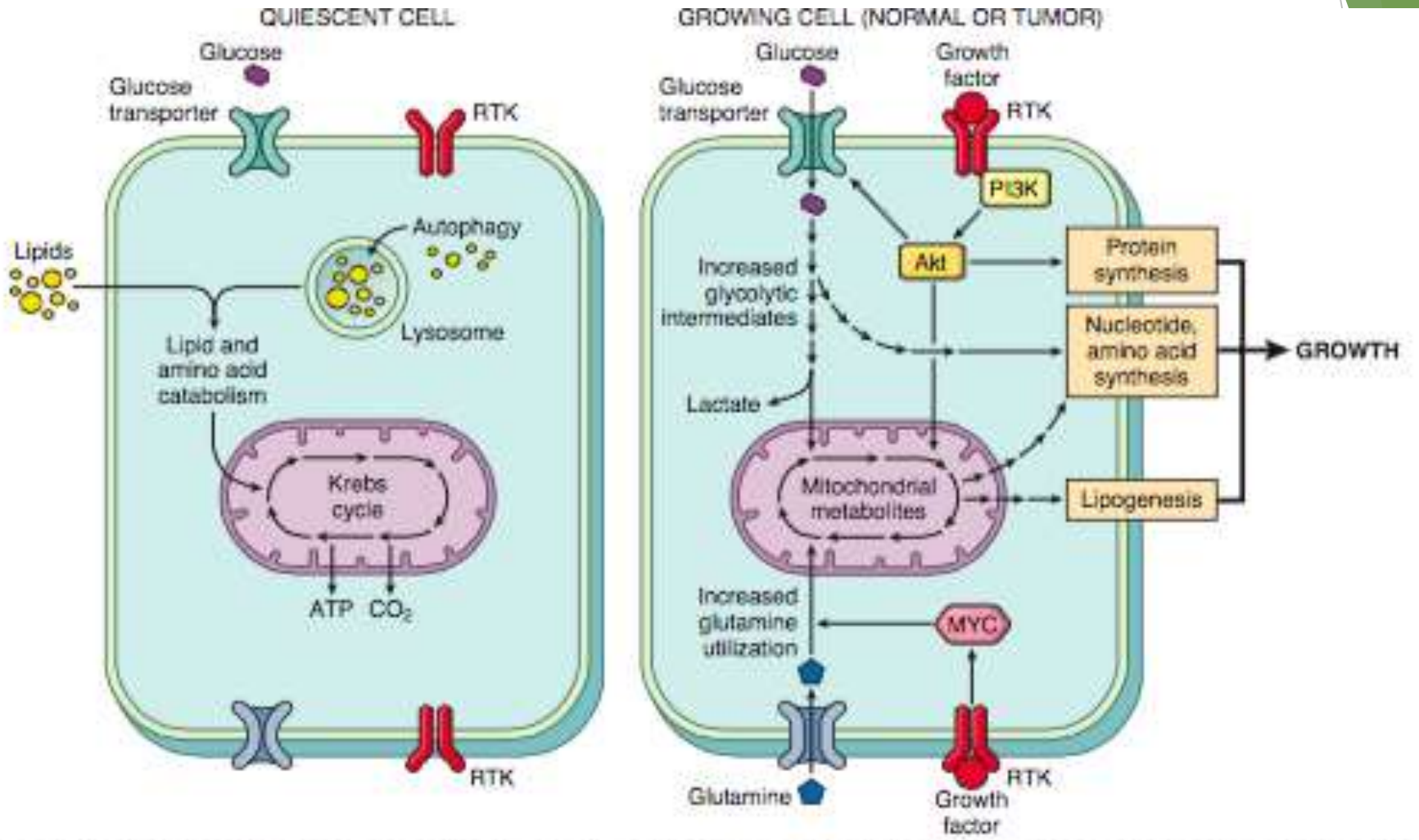


Figure 7-32 Metabolism and cell growth. Quiescent cells rely mainly on the Krebs cycle for ATP production; if starved, autophagy (self-eating) is induced to provide a source of fuel. When stimulated by growth factors, normal cells markedly upregulate glucose and glutamine uptake, which provide carbon sources for synthesis of nucleotides, proteins, and lipids. In cancers, oncogenic mutations involving growth factor signaling pathways and other key factors such as MYC deregulate these metabolic pathways, an alteration known as the *Warburg effect*.

Evasion of Programmed Cell Death : Apoptosis

- Gen yang berfungsi untuk mengatur apaptosis
- Saat keadaan normal berperan di dalam siklus sel
- Jika terjadi mutasi
  - → maka sel tidak akan mati, dan sel akan proliferasi terus menerus
- Mutasi tersering → jalur intrinsik
- Integritas dari membran mitokondria diatur oleh protein pro-apoptotic dan anti-apoptotic
- Pro apptotic → BAX/BAK
- Anti apoptotic → BCL2, BCL-XL, MCL1
- Mutasi pada BCL 2 → malignant lymphoma

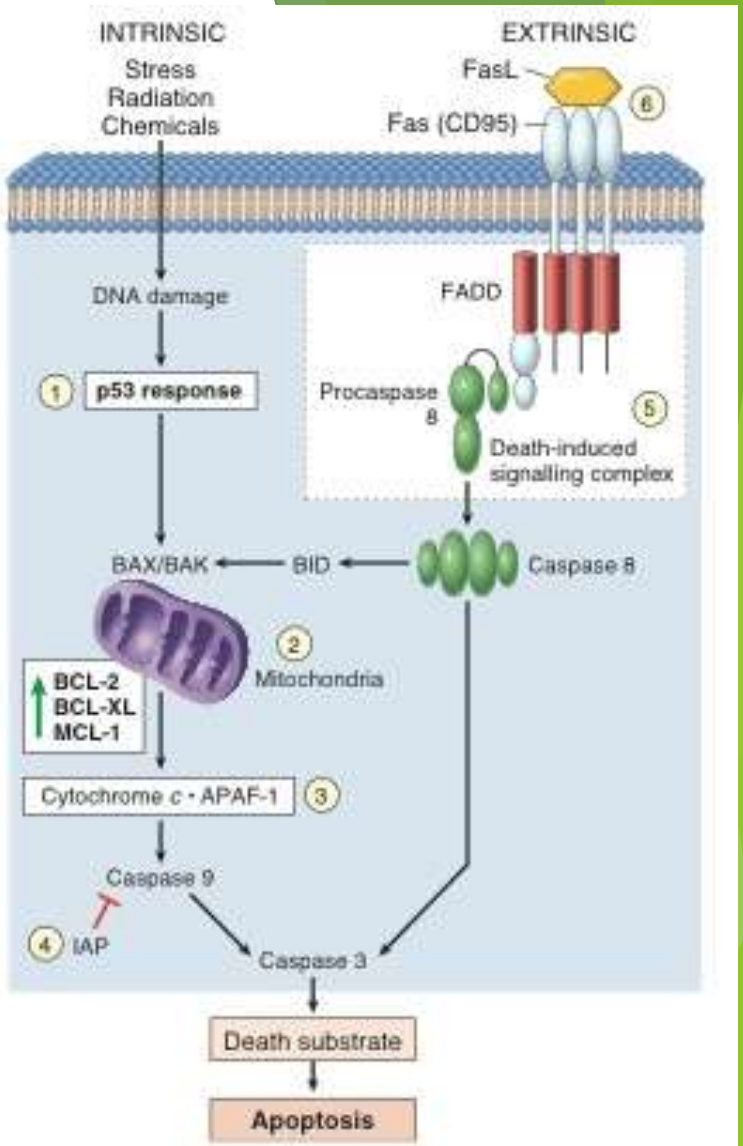


Figure 7-33 Intrinsic and extrinsic pathways of apoptosis and mechanisms used by tumor cells to evade cell death. (1) Loss of p53, leading to reduced function of pro-apoptotic factors such as BAX. (2) Reduced egress of cytochrome c from mitochondria as a result of upregulation of anti-apoptotic factors 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.

Limitless Replicative Potential : The Stem-Cell like Properties of Cancer Cells

- All cancers contain cells that are immortal and have limitless replicative potential
- Immortality of cancer cells :
  - Evasions of senescence
  - Evasions of mitotic crisis
  - The capacity of self-renewal
- Contoh : AML, CML

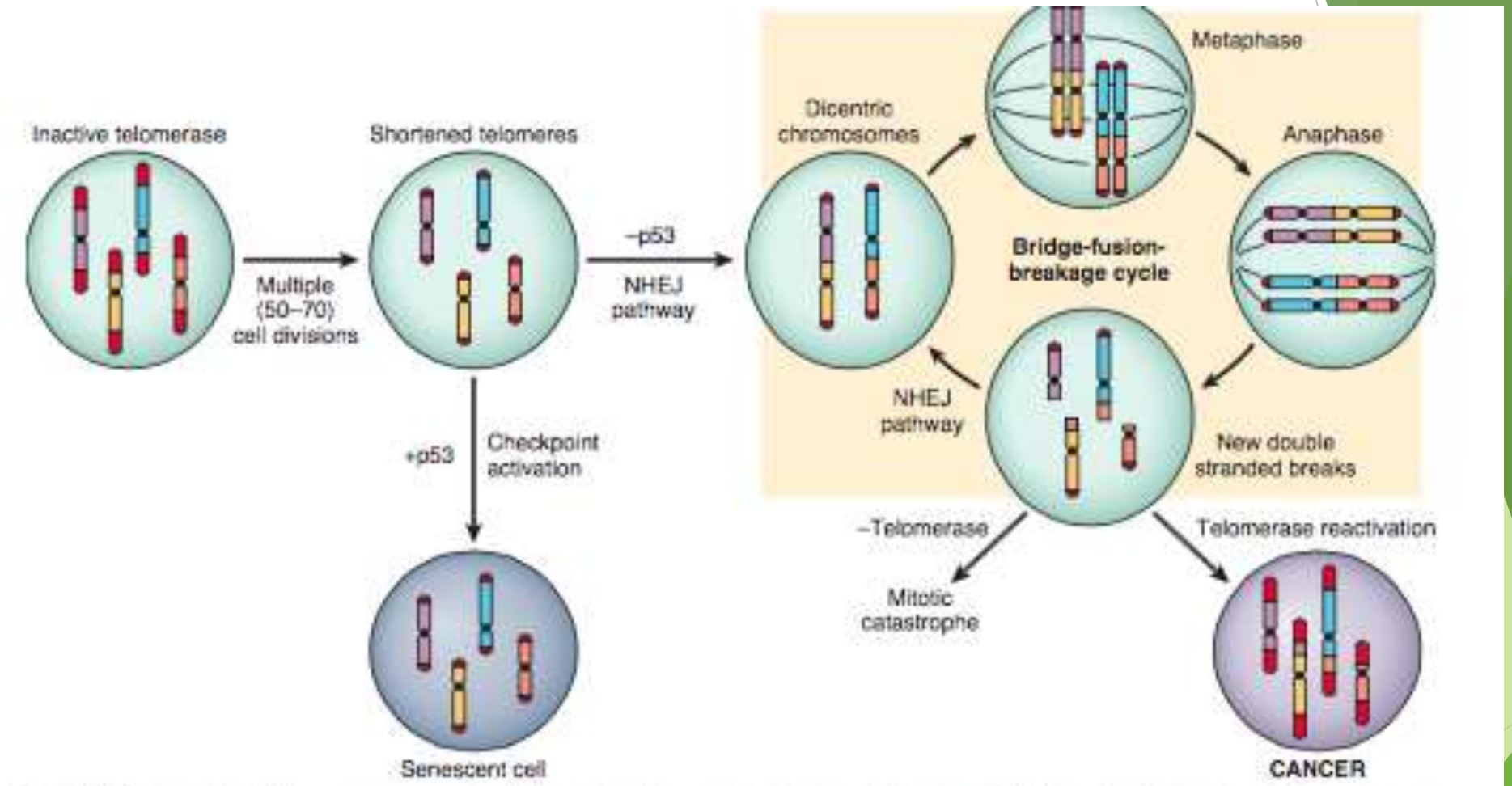


Figure 7-34 Escape of cells from senescence and mitotic catastrophe caused by telomere shortening. Replication of somatic cells, which do not express telomerase, leads to shortened telomeres. In the presence of competent checkpoints, cells undergo arrest and enter nonreplicative senescence. In the absence of checkpoints, DNA repair pathways, such as the nonhomologous end-joining (NHEJ) pathway are inappropriately activated, leading to the formation of dicentric chromosomes. At mitosis the dicentric chromosomes are pulled apart, generating random double-stranded breaks, which then activate DNA-repair pathways, leading to the random association of double-stranded ends and the formation, again, of dicentric chromosomes. Cells undergo numerous rounds of this bridge-fusion-breakage cycle, which generates massive chromosomal instability and numerous mutations. If cells fail to reexpress telomerase, they eventually undergo mitotic catastrophe and death. Reexpression of telomerase allows the cells to escape the bridge-fusion-breakage cycle, thus promoting their survival and tumorigenesis.

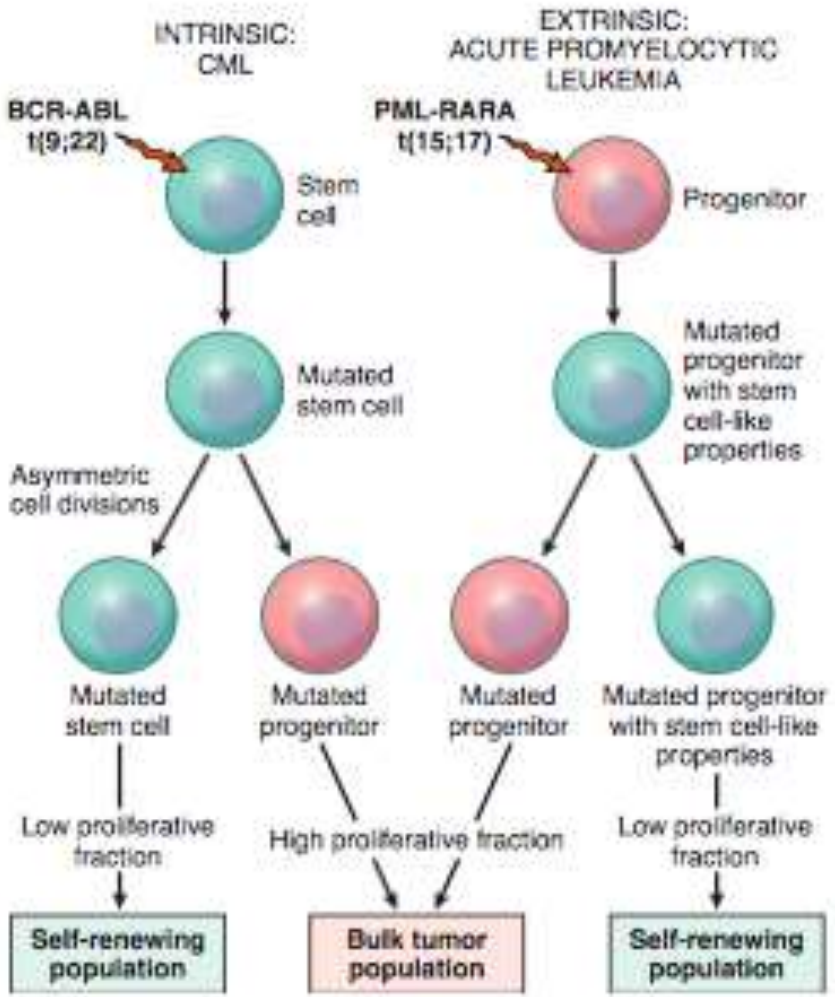


Figure 7-35 Origins of cells with self-renewing capacity in cancer. Cancer stem cells can arise from transformed tissue stem cells (e.g., hematopoietic stem cells in chronic myelogenous leukemia, CML) with intrinsic "stemness" or from proliferating cells that acquire a mutation that confers "stemness" (e.g., granulocyte progenitors in acute promyelocytic leukemia). In both instances, the cancer stem cells undergo asymmetric cell divisions that give rise to committed progenitors that proliferate more rapidly than the cancer stem cells; as a result, most of the malignant cells in both tumors lack self-renewing capacity.

Terima kasih