NEOPLASIA 2

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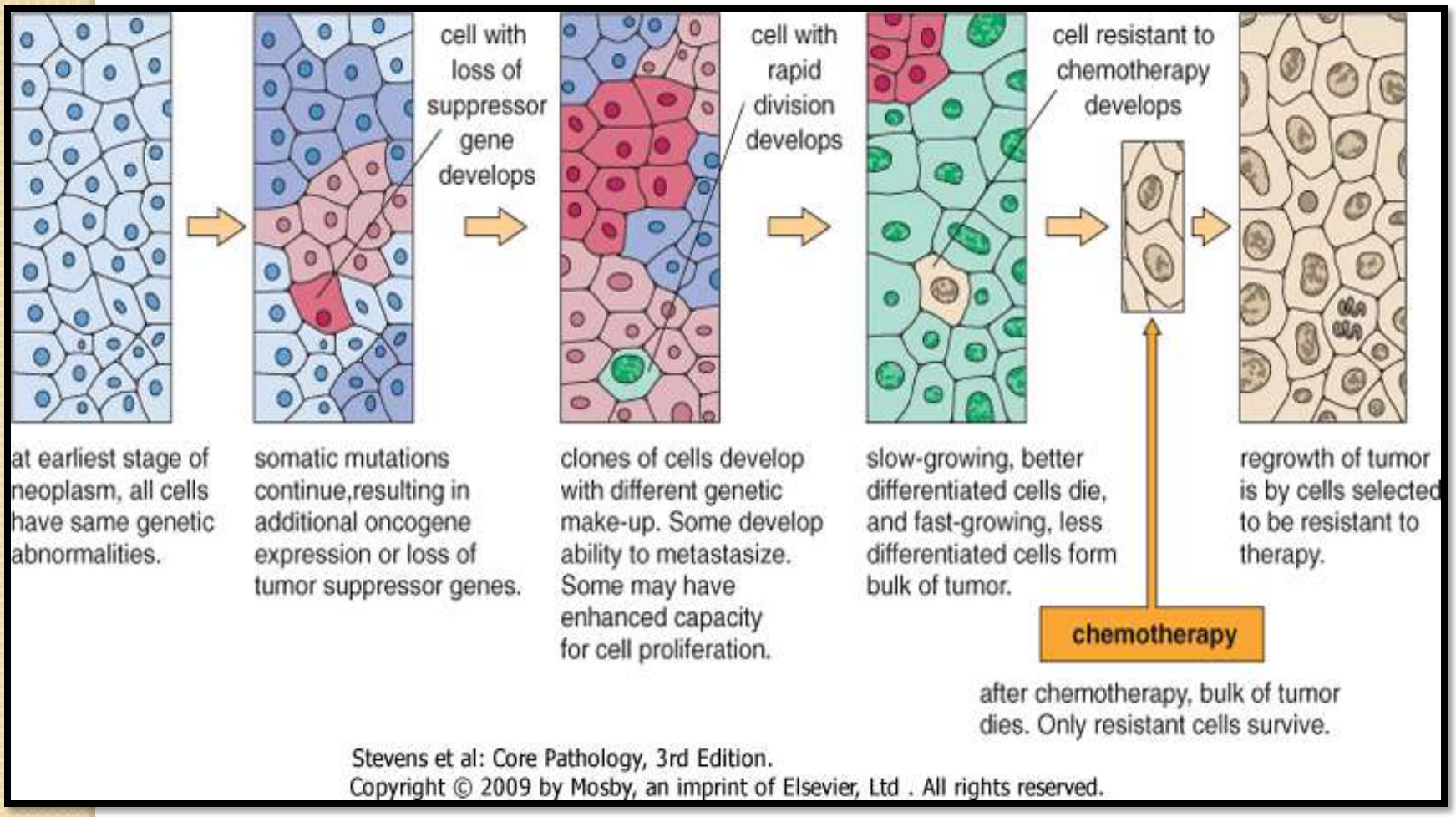
Principles

1. ***Non-lethal genetic damage lies at the heart of carcinogenesis.***

   - **May be acquired (environmental agents or viruses) OR inherited in the germ line**
   - **Environmental – exogenous agents or endogenous products of cell metabolism**

2. ***A tumor is formed by the clonal expansion of a single precursor cell that has incurred the genetic damage → tumors are monoclonal***

   - **As tumors develop they undergo further somatic mutation → tumor composed of a set of slightly different cells (tumor heterogeneity) → growth control more abnormal and facilitate metastasis**



Stevens et al: Core Pathology, 3rd Edition.

3. Four classes of regulatory genes are the principal targets of genetic damage.

a) Protooncogenes (*p-oncs*)

- Genes that code for proteins involved in the control of cell growth (e.g. Growth factors, growth factor receptors, signal transducers)
- Mutant alleles dominant → transform cells despite presence of normal counterpart → phenotype affected even if one allele is present

3. Four classes of regulatory genes are the principal targets of genetic damage.

b) Tumor suppressor genes

- Genes that produce products that inhibits cell growth → control G_1 to S phase of cell cycle & nuclear transcription
- Both normal alleles must be damaged for transformation to occur → *recessive oncogenes* → malignant phenotype only develops if both alleles fail to suppress growth

3. Four classes of regulatory genes are the principal targets of genetic damage.

c) Apoptosis genes

- **Regulate programmed cell death**
- **Example: *BAX* apoptosis gene**
  - ✓ **Activated by TP53 if DNA damage is excessive**
  - ✓ **BAX protein inactivates the *BCL2* anti-apoptosis gene**
  - ✓ **Mutation of TP53 → inactivate BAX → no apoptosis**

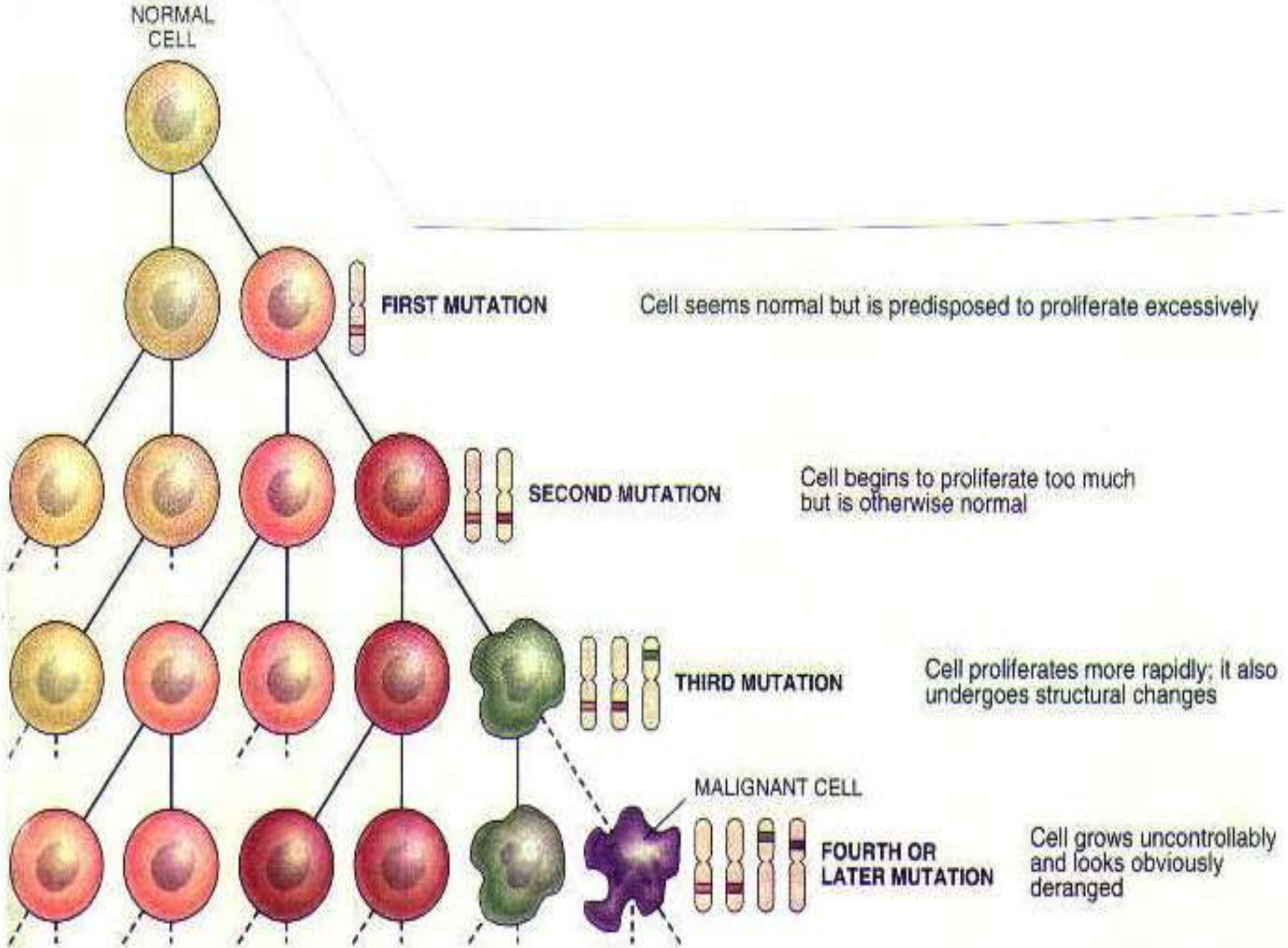
3. Four classes of regulatory genes are the principal targets of genetic damage.

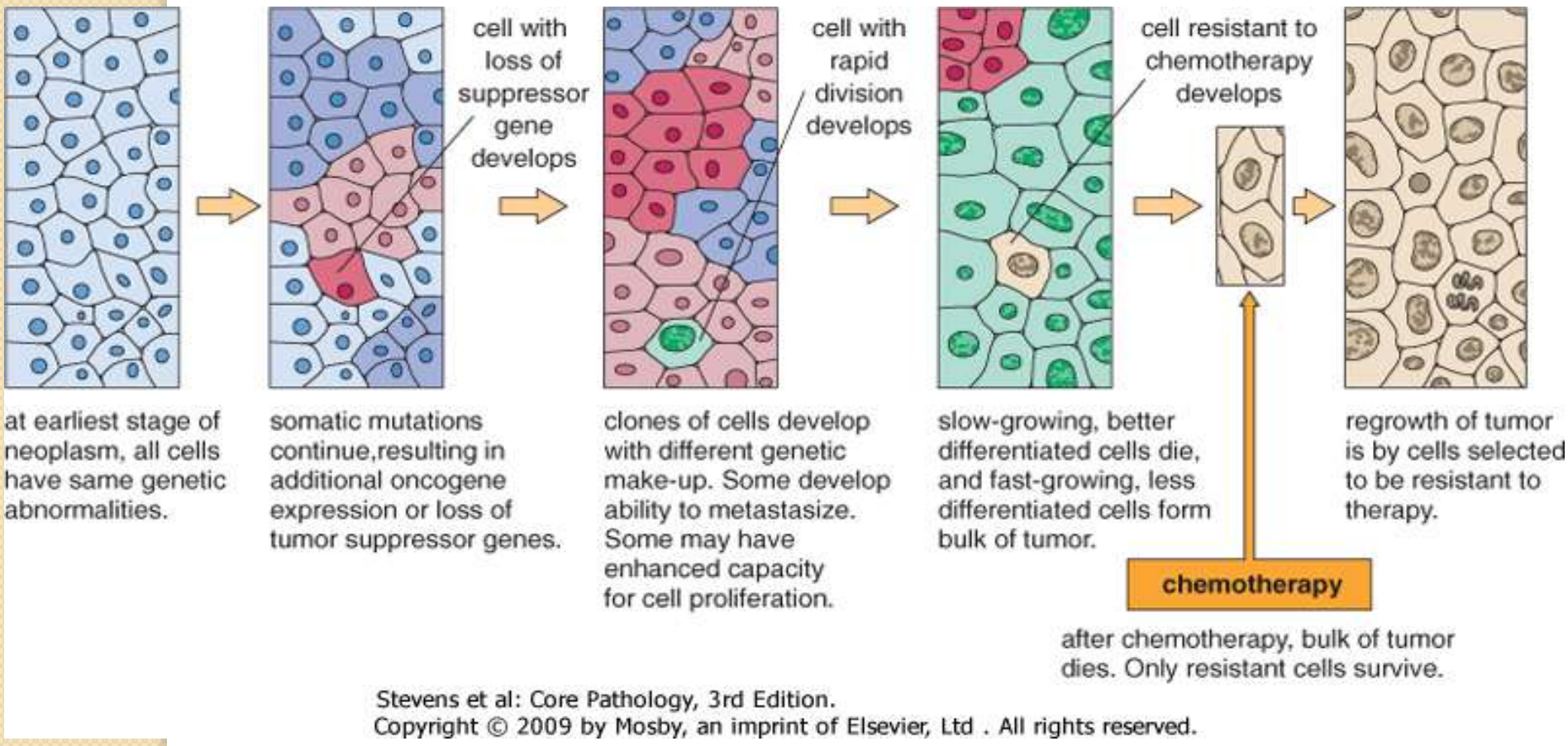
d) Genes involved in DNA repair

- **Loss of activity → DNA instability → somatic mutations in oncogenes or tumor suppressor genes**
- **Both alleles must be inactivated**

4. Carcinogenesis is a multistep process at both the phenotypic and the genetic levels

- **Phenotypic attributes of malignant neoplasms are acquired in a step-wise fashion → called tumor progression**
- **Progression results from accumulation of genetic lesions (multiple mutations)**


NORMAL CELL
FIRST MUTATION
Cell seems normal but is predisposed to proliferate excessively
SECOND MUTATION
Cell begins to proliferate too much but is otherwise normal
THIRD MUTATION
Cell proliferates more rapidly; it also undergoes structural changes
MALIGNANT CELL
FOURTH OR LATER MUTATION
Cell grows uncontrollably and looks obviously deranged



Tumor progression and genetic heterogeneity. As tumors develop they undergo further somatic mutation, which causes abnormalities in other oncogenes. Mutations may also lead to cell death. A mutation that puts a cell at a survival disadvantage will cause that clone to be eliminated. A tumor will ultimately consist of many different subclones of cells, those with greater growth potential gradually coming to dominate the lesion.

MOLECULAR BASIS

Fundamental Changes in Cell Physiology That Determine Malignant Phenotype

1. *Self-sufficiency in growth signals*
2. *Insensitivity to growth-inhibiting signals*
3. *Evasion of apoptosis*
4. *Limitless replicative potential*
5. *Sustained angiogenesis*
6. *Ability to invade and metastasize*
7. *Defects in DNA repair*

MOLECULAR BASIS

Self-sufficiency in growth signals

A. Oncogenes

- **Genes that promote autonomous growth in cancer cells**
- **Unmutated counterparts called proto-oncogenes**
- **Created by mutations in proto-oncogenes**
- **Products similar to normal counter-parts but lacks important internal regulatory elements → endow the cell with self-sufficiency in growth**

MOLECULAR BASIS

Self-sufficiency in growth signals

Normal Cell Proliferation

Binding of growth factor to receptor

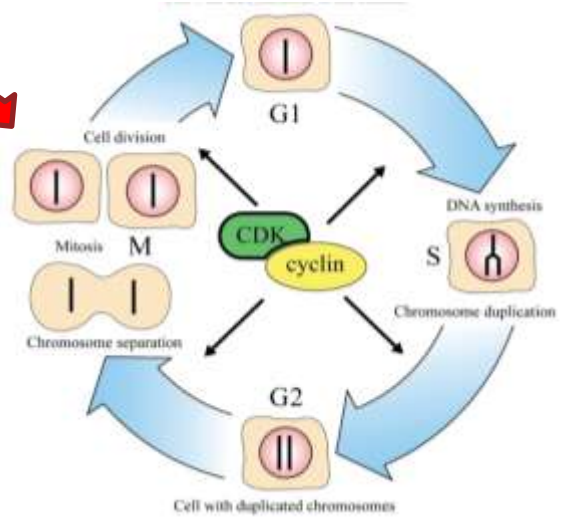
Activation of signal-transducing proteins on inner leaflet of plasma membrane

Transmission of signal across cytosol → nucleus

Induction and activation of nuclear regulatory factors

Initiate DNA transcription

Entry and progression into cell cycle



Self-sufficiency in growth signals

Role of Oncoproteins

1. Growth factors

- **Most soluble growth factors made by one cell type and act on a neighboring cell to stimulate proliferation → paracrine action**
- **Most cancer cells able to synthesize the same growth factors to which they are responsive in an autocrine loop**

Self-sufficiency in growth signals

Role of Oncoproteins

2. Growth factor receptors

- **Normal transmembrane receptors: cytoplasmic tyrosine kinase transiently activated → followed by receptor dimerization and tyrosine phosphorylation**
- **Oncogenic version: with constitutive dimerization and activation without binding to the growth factor → continuous mitogenic signal to cell even in the absence of growth factors in the environment**

Self-sufficiency in growth signals

Role of Oncoproteins

2. Growth factor receptors

- **Mechanisms of constitutive activation of GFRs:**

a) Mutations and gene rearrangements

✓ ***RET* protein → normally expressed in neuroendocrine cells**

- ***Point mutation in extracellular domain → MEN 2A (thyroid, adrenal, and parathyroid tumors)***
- ***Point mutations in cytoplasmic domain → MEN 2B (thyroid and adrenal tumors)***

Self-sufficiency in growth signals

Role of Oncoproteins

2. **Growth factor receptors**
   - **Mechanisms of constitutive activation of GFRs:**
     a) **Mutations and gene rearrangements**
        - ✓ ***FLT3* gene → code for FMS-like tyrosine kinase 3 receptor**
          - ***Point mutation → myeloid leukemias***

Self-sufficiency in growth signals

Role of Oncoproteins

2. **Growth factor receptors**
   - **Mechanisms of constitutive activation of GFRs:**
     b) **Overexpression of normal forms of GFRs**
     - ✓ **More common**
     - ✓ ***ERBB1*** **(EGF receptor gene) → 80% of squamous cell Ca of lungs**
     - ✓ ***ERBB2 (HER-2/NEU)*** **→ breast Ca, adenocarcinoma of ovary**

Self-sufficiency in growth signals

Role of Oncoproteins

3. Signal-Transducing Proteins

- **Located on inner leaflet of the plasma membrane → receive signals from outside the cell → transmit to cell's nucleus**
- ***Most well studied is RAS family of GTP-binding proteins (G proteins)***

MOLECULAR BASIS

Self-sufficiency in growth signals

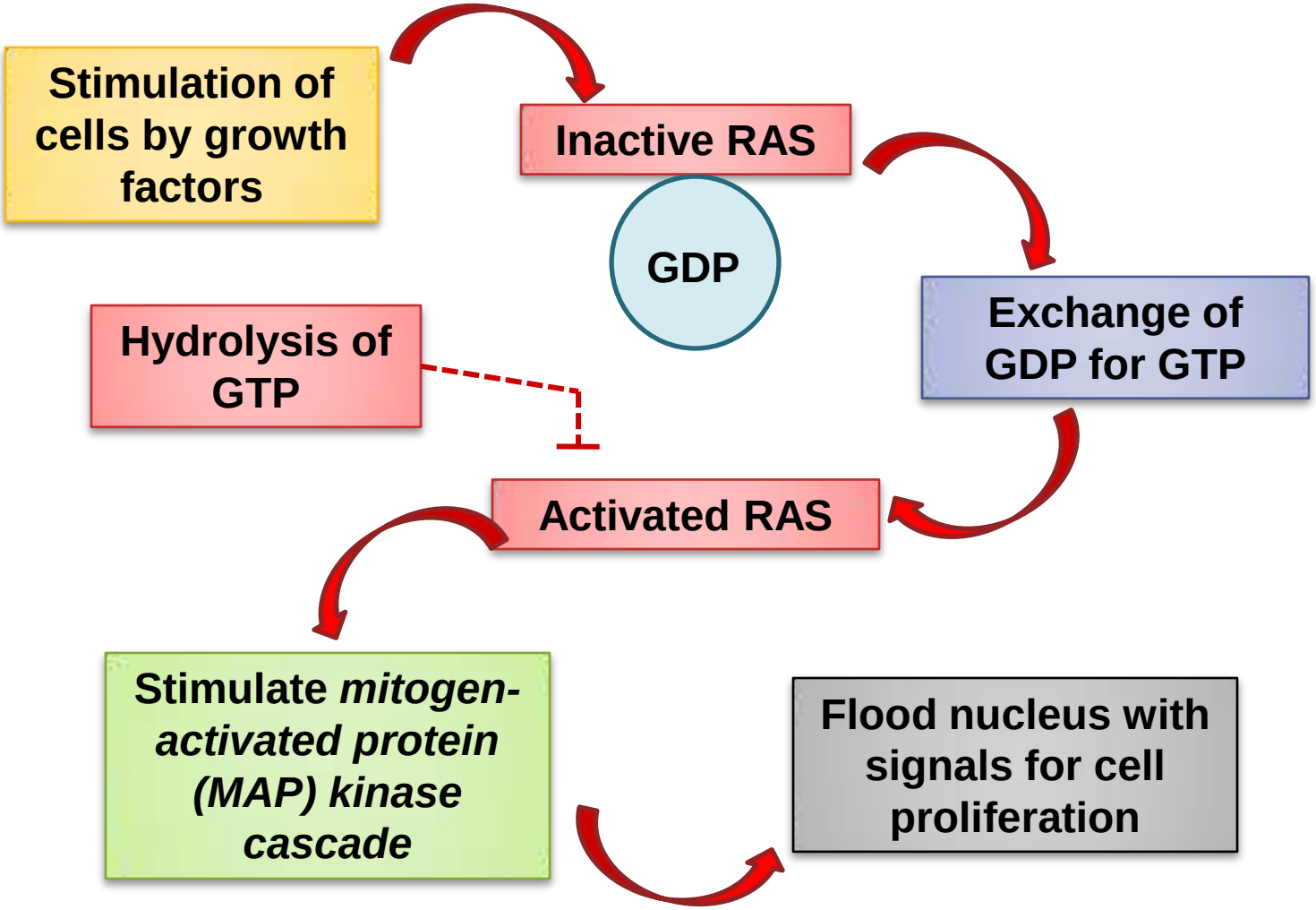
RAS Oncogone (HRAS, KRAS, NRAS)

- **Point mutation of proto-oncogene the single most common abnormality in human tumors**
- **Located at cytoplasmic aspect of plasma membrane as well as membranes of ER and Golgi**
- **RAS proteins bind guanosine nucleotides**

MOLECULAR BASIS

Self-sufficiency in growth signals

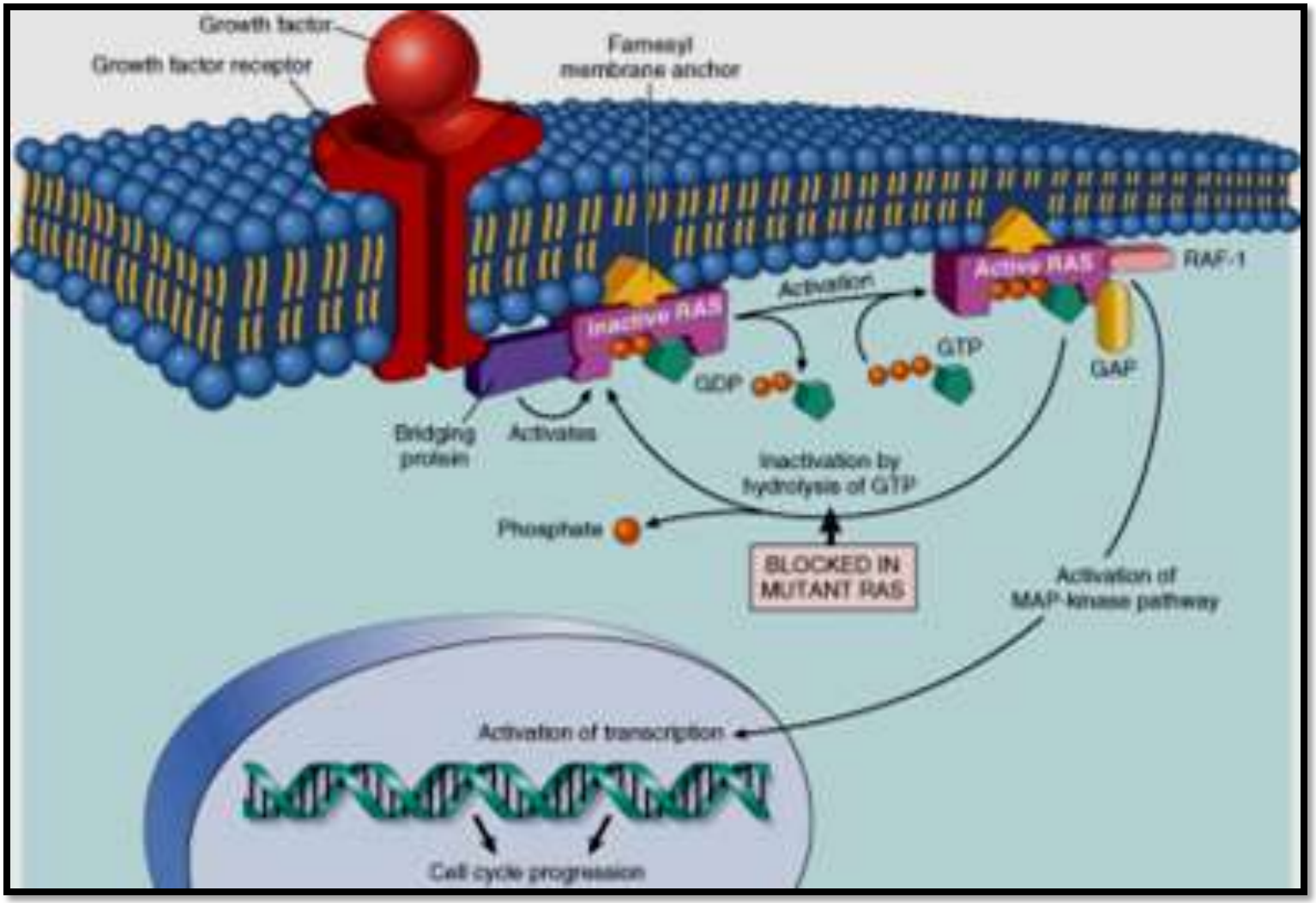
RAS Oncogone



MOLECULAR BASIS

Self-sufficiency in growth signals

RAS Oncogone

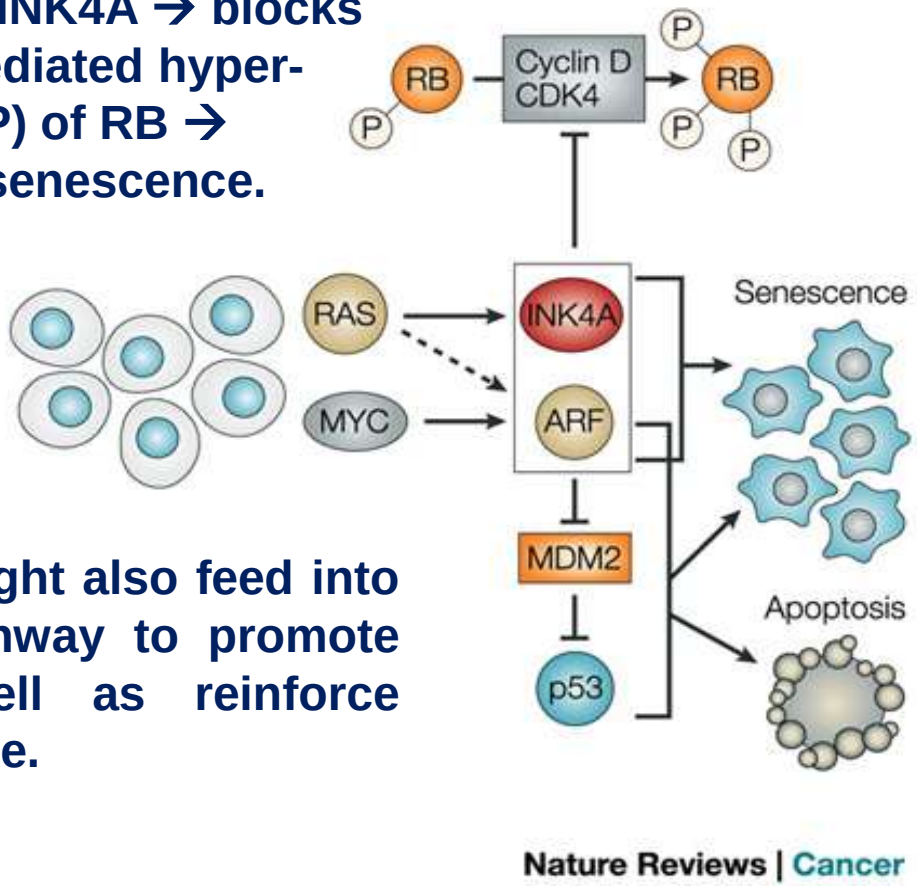


MOLECULAR BASIS

Self-sufficiency in growth signals

RAS Oncogone

Activation of oncogenic RAS leads to upregulation of INK4A → blocks cyclin-D–CDK4-mediated hyper-phosphorylation (P) of RB → provokes cellular senescence.



RAS signalling might also feed into the ARF–p53 pathway to promote apoptosis as well as reinforce cellular senescence.

MOLECULAR BASIS

Self-sufficiency in growth signals

RAS Oncogone

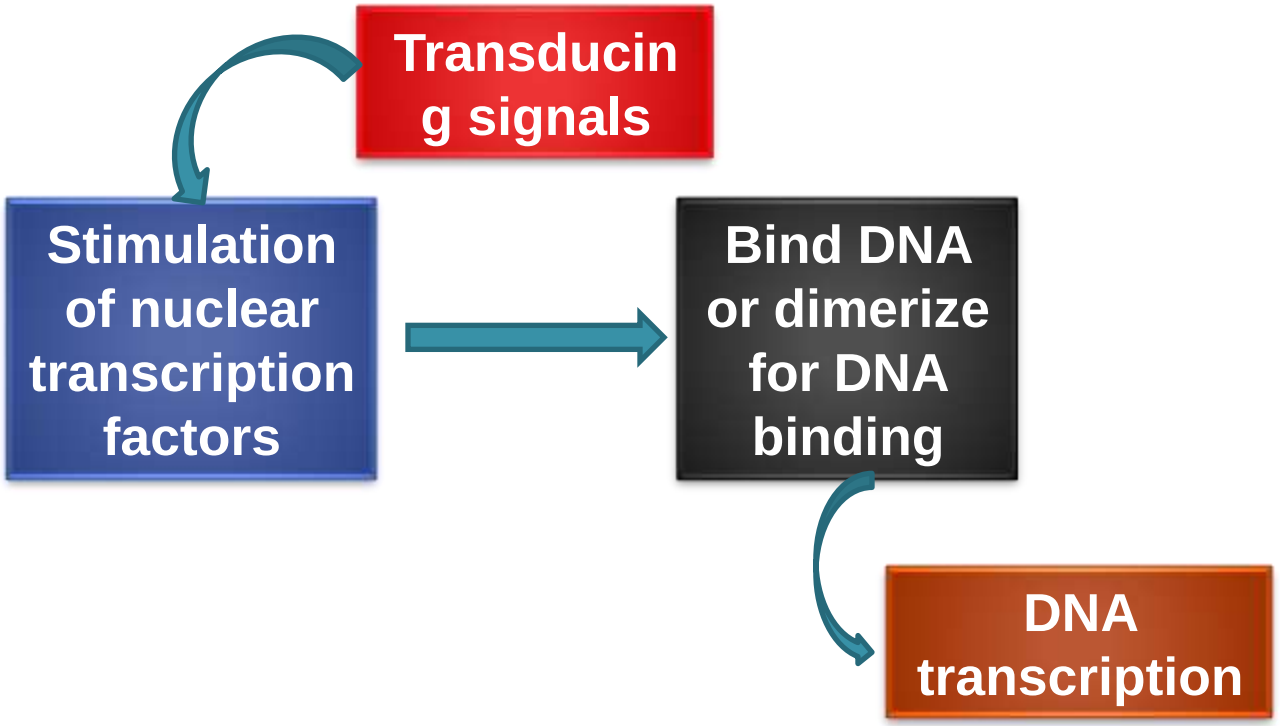
- **Mutated RAS trapped in its activated GTP-bound form due to inactivation of GTP hydrolysis → cell forced into a continuous proliferative state**

- ***Mutations of KRAS → carcinomas of colon and pancreas***
- ***Mutations of HRAS → bladder tumors***
- ***Mutations of NRAS → hematopoietic tumors***

Self-sufficiency in growth signals

Role of Oncoproteins

4. Transcription factors



Self-sufficiency in growth signals

Role of Oncoproteins

4. Transcription factors

- ***Ultimate consequence of signalling through oncogenes is inappropriate and continuous stimulation of nuclear transcription factors***
- ***Growth autonomy occurs as a consequence of mutations affecting genes that regulate transcription (e.g. MYC)***

Self-sufficiency in growth signals

MYC Oncogone

- **Proto-oncogene expressed in all eukaryotic cells → immediate response genes → rapidly induced when quiescent cells receive signal to divide**
- ***Target genes of oncogene:*** **include ornithine decarboxylase and cyclin D2 → associated with cell proliferation**

Self-sufficiency in growth signals

MYC Oncogone

- **Range of activities modulated by *MYC*:**

1. ***Histone acetylation***
2. ***Reduced cell adhesion***
3. ***Increased cell motility***
4. ***Increased telomerase activity***
5. ***Increased protein synthesis***
6. ***Decreased proteinase activity***

Self-sufficiency in growth signals

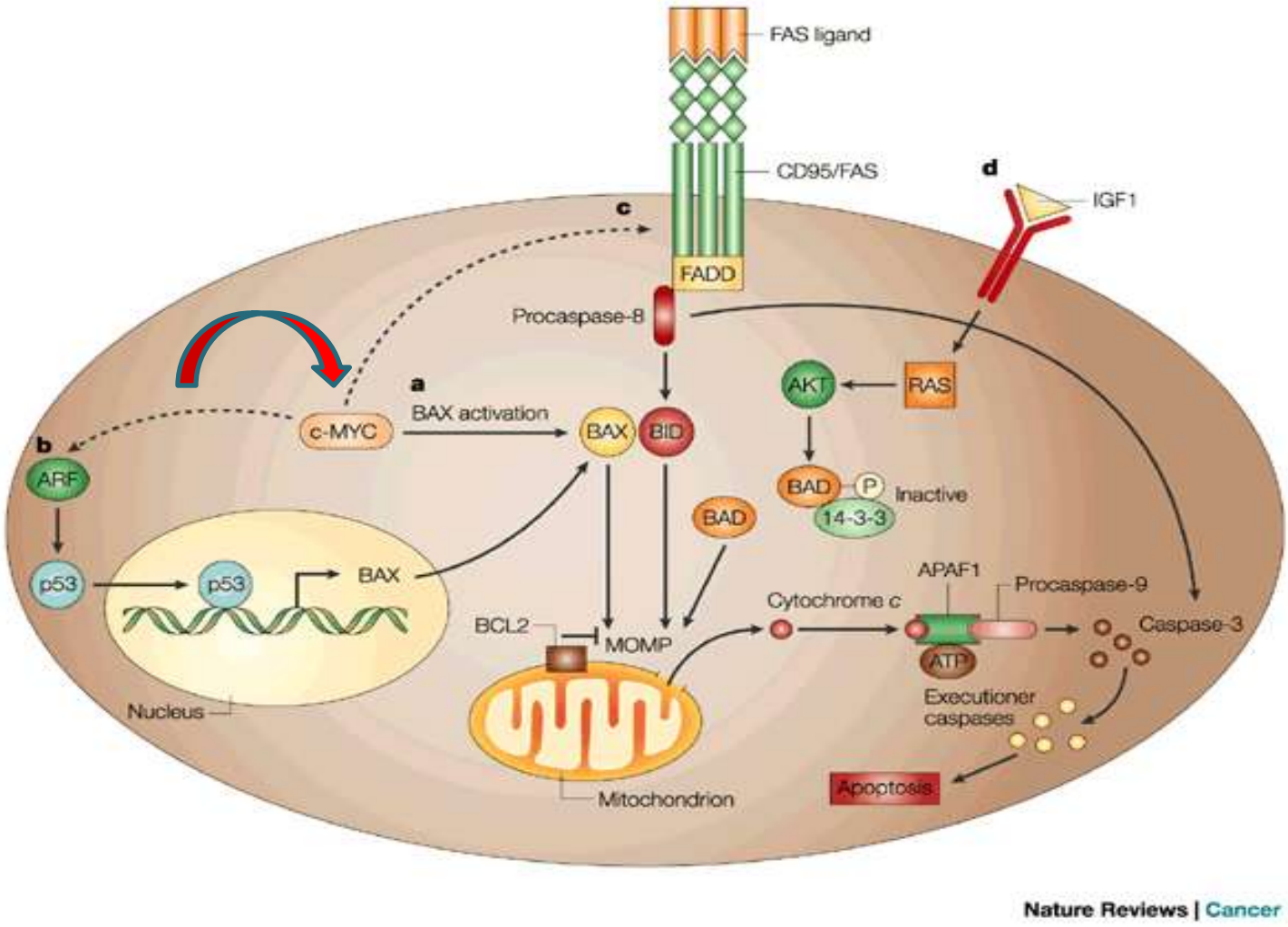
MYC Oncogone

- **Range of activities modulated by *MYC*:**
  7. ***Selection of origins of replication - overexpression → more origins of replication needed for normal cell replication***
  8. ***Bypass checkpoints involved in replication***
  9. ***Re-programming of cells into pluripotent stem cells***
  10. ***Enhance self-renewal, block differentiation or both***

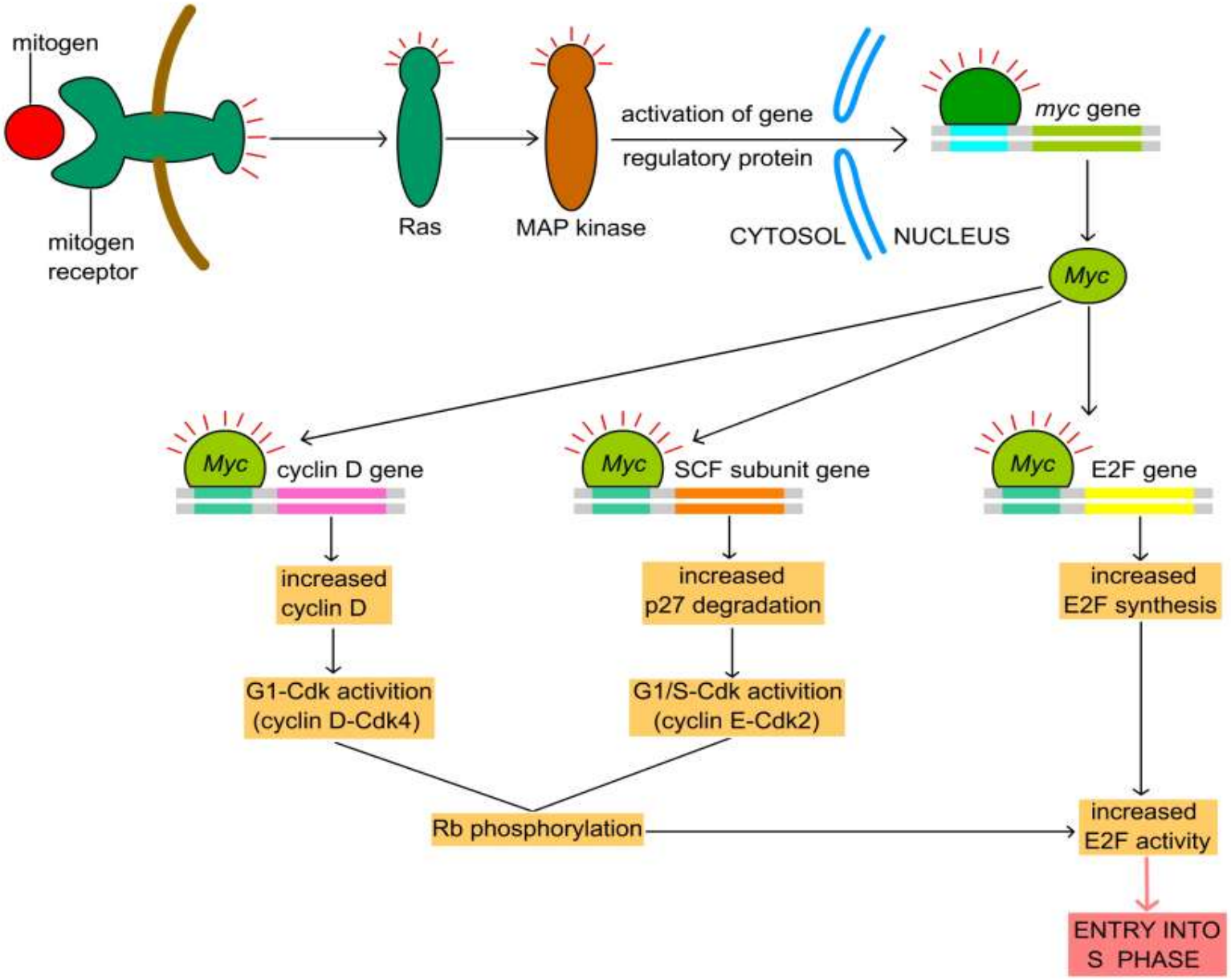
Self-sufficiency in growth signals

MYC Oncogone

- **Persistent expression commonly found in tumors**
- ***Translocation → Burkitt's lymphoma***
- ***Amplification → carcinoma of breast, colon, lungs, and other carcinomas***



c-MYC sensitizes cells to a wide range of pro-apoptotic stimuli. During apoptosis, c-MYC induces release of cytochrome c from the mitochondria into the cytosol, possibly through activation of the pro-apoptotic molecule BAX


mitogen
mitogen receptor
Ras
MAP kinase
activation of gene
regulatory protein
CYTOSOL
NUCLEUS
myc gene
Myc
Myc
cyclin D gene
Myc
SCF subunit gene
Myc
E2F gene
increased cyclin D
increased p27 degradation
increased E2F synthesis
G1-Cdk activition (cyclin D-Cdk4)
G1/S-Cdk activition (cyclin E-Cdk2)
Rb phosphorylation
increased E2F activity
ENTRY INTO S PHASE

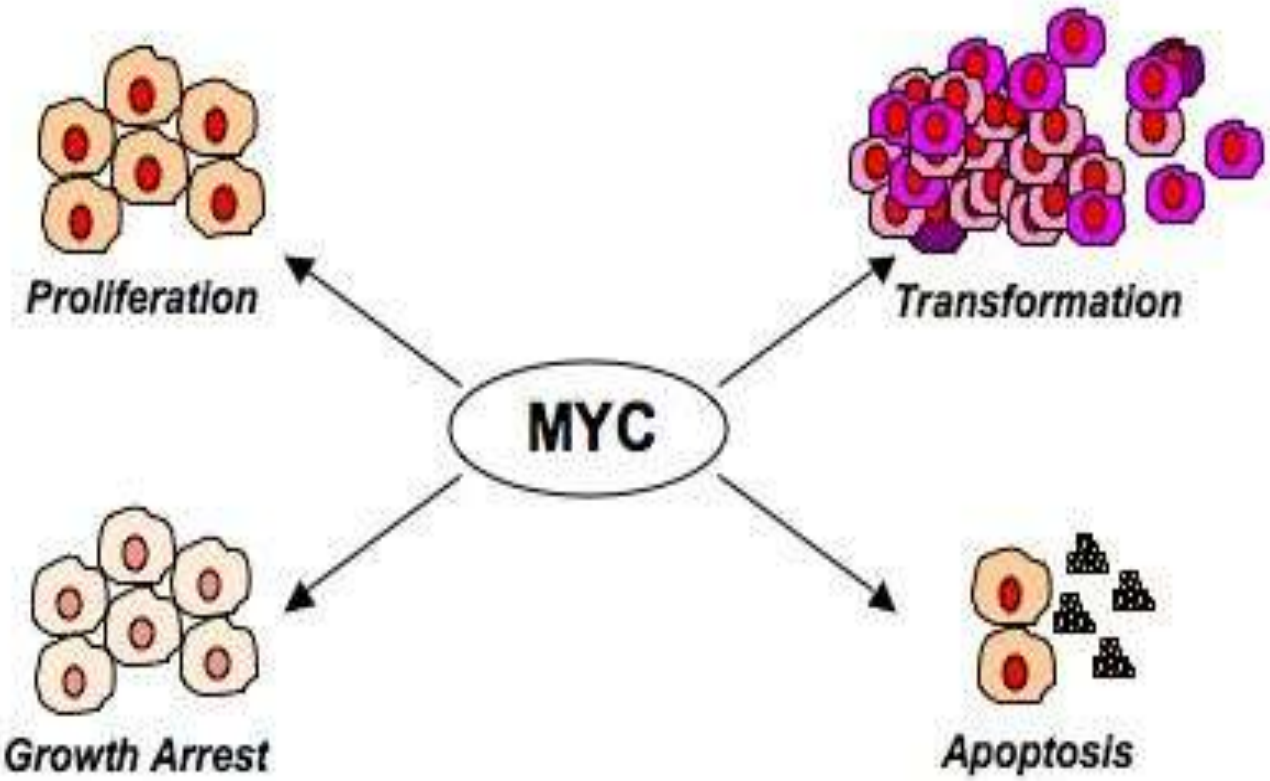
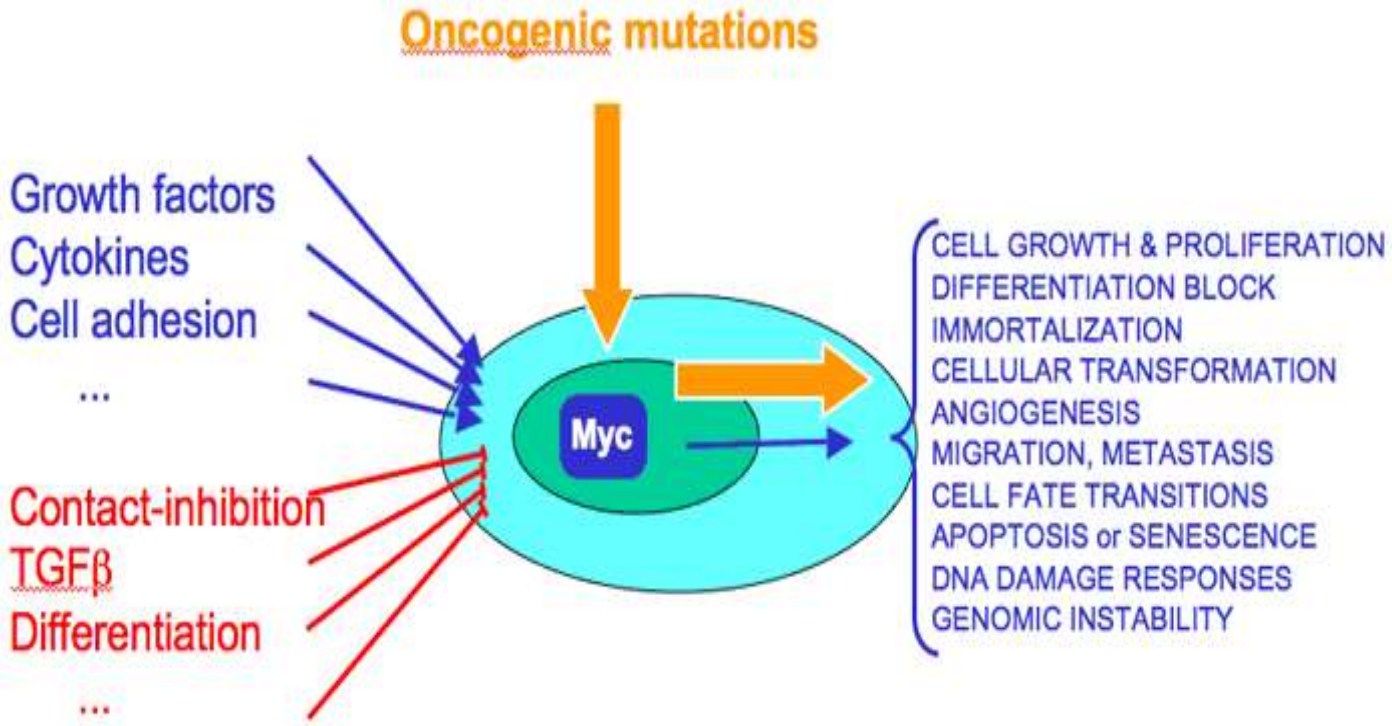


Figure 1. c-Myc induces cell proliferation, cell transformation, growth arrest and apoptosis. The biological response to c-Myc is dependent on the cell lineage and environment.

Myc is an intracellular sensor and transducer of extracellular stimuli



Self-sufficiency in growth signals

B. Dysregulated activity of cyclins & CDKs

Normal Cell Cycle:

- **Orderly progression of cells through cell cycle orchestrated by CDKs bound to cyclins**
- **CDK-cyclin complexes phosphorylate crucial target proteins that drive the cell through the cell cycle**
- **Cyclins D, E, A, and B appear sequentially during the cell cycle and bind to one or more CDKs**

Self-sufficiency in growth signals

B. Dysregulated activity of cyclins & CDKs

Normal Cell Cycle:

- **Inhibitors of CDKs (CDKIs)**
  1. **CIP/WAP family → inhibit CDKs broadly**
     - **p21, p27, p57**
  2. **INK4 family → with selective action on cyclin D/CDK4 and cyclin D/CDK6**
     - **p15, p16, p18, p19**

Self-sufficiency in growth signals

B. Dysregulated activity of cyclins & CDKs

Normal Cell Cycle:

- **Cell cycle checkpoints**
  1. **G_1/S checkpoint**
     - **Checks for DNA damage → prevent replication of cells with defects in DNA**
  2. **G_2/M checkpoint**
     - **Monitors completion of DNA & checks whether cell can safely initiate mitosis → important in cells exposed to ionizing radiation**

Self-sufficiency in growth signals

B. Dysregulated activity of cyclins & CDKs

Normal Cell Cycle:

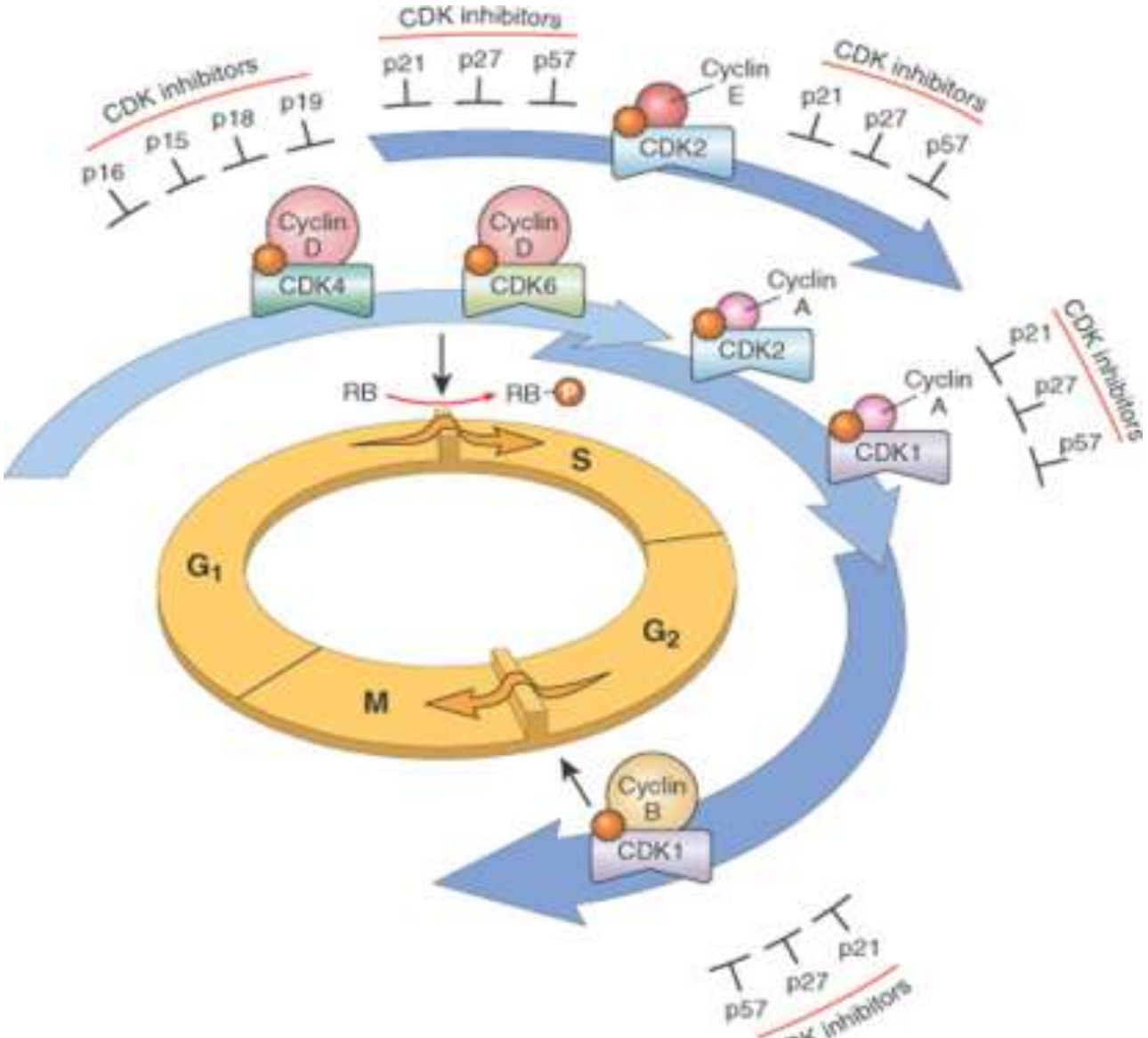
- **Cell cycle checkpoints**
  - ✓ **Require:**
    1. **Sensors of DNA damage**
       - ➢ **Proteins of RAD family & ataxia telangiectasia mutated (ATM)**
    2. **Signal transducers**
       - ➢ **CHK kinase family**

Self-sufficiency in growth signals

B. Dysregulated activity of cyclins & CDKs

Normal Cell Cycle:

- **Cell cycle checkpoints**
  - ✓ **Require:**
    3. **Effector molecules**
       - ➢ **G_1/S → p53 and p21**
       - ➢ **G_2/M → p53-dependent and p53-independent mechanisms**



Self-sufficiency in growth signals

B. Dysregulated activity of cyclins & CDKs

- Mutations that dysregulate activity of cyclins and CDKs favor cell proliferation

- Mutations affecting expression of cyclin D or CDK4 common in neoplastic transformation
  - ✓ Cyclin D overexpression → Ca of breast, esophagus, liver, lymphomas
  - ✓ Amplification of CDK4 → melanomas, sarcomas,

Self-sufficiency in growth signals

B. Dysregulated activity of cyclins & CDKs

- **CDKIs frequently mutated or otherwise silenced in many human malignancies**
  - ✓ **Somatically acquired deletion or inactivation of p16 → pancreatic Ca, glioblastomas, esophageal cancers, ALL, bladder cancers**
  - ✓ **Germline mutations of p16 → melanoma**

Self-sufficiency in growth signals

B. Dysregulated activity of cyclins & CDKs

- ***Defects in cell cycle checkpoint components are a major cause of genetic instability in cancer cells.***

Insensitivity to growth inhibition & escape from senescence

Tumor Suppressor Genes

- **Apply breaks to cell proliferation → prevent uncontrolled growth**
- **Recognize genotoxic stress → shut down cell proliferation**
- **Expression of oncogene in a normal cell → lead to quiescence or permanent cell cycle arrest (oncogene-induced senescence)**

Tumor Suppressor Genes: RB (retinoblastoma)

- **RB protein a ubiquitously expressed nuclear phosphoprotein**
- **Exists in an *active hypophosphorylated state* in quiescent cells and an *inactive hyperphosphorylated state* in the G_1/*S* cell cycle transition**

Tumor Suppressor Genes: RB (retinoblastoma)

- **Important in its enforcement of G_1 → cells can exit the cell cycle either temporarily (quiescence), or permanently (senescence) → induce senescence**
- **RB also controls stability of the cell cycle inhibitor p27**

Tumor Suppressor Genes: RB (retinoblastoma)

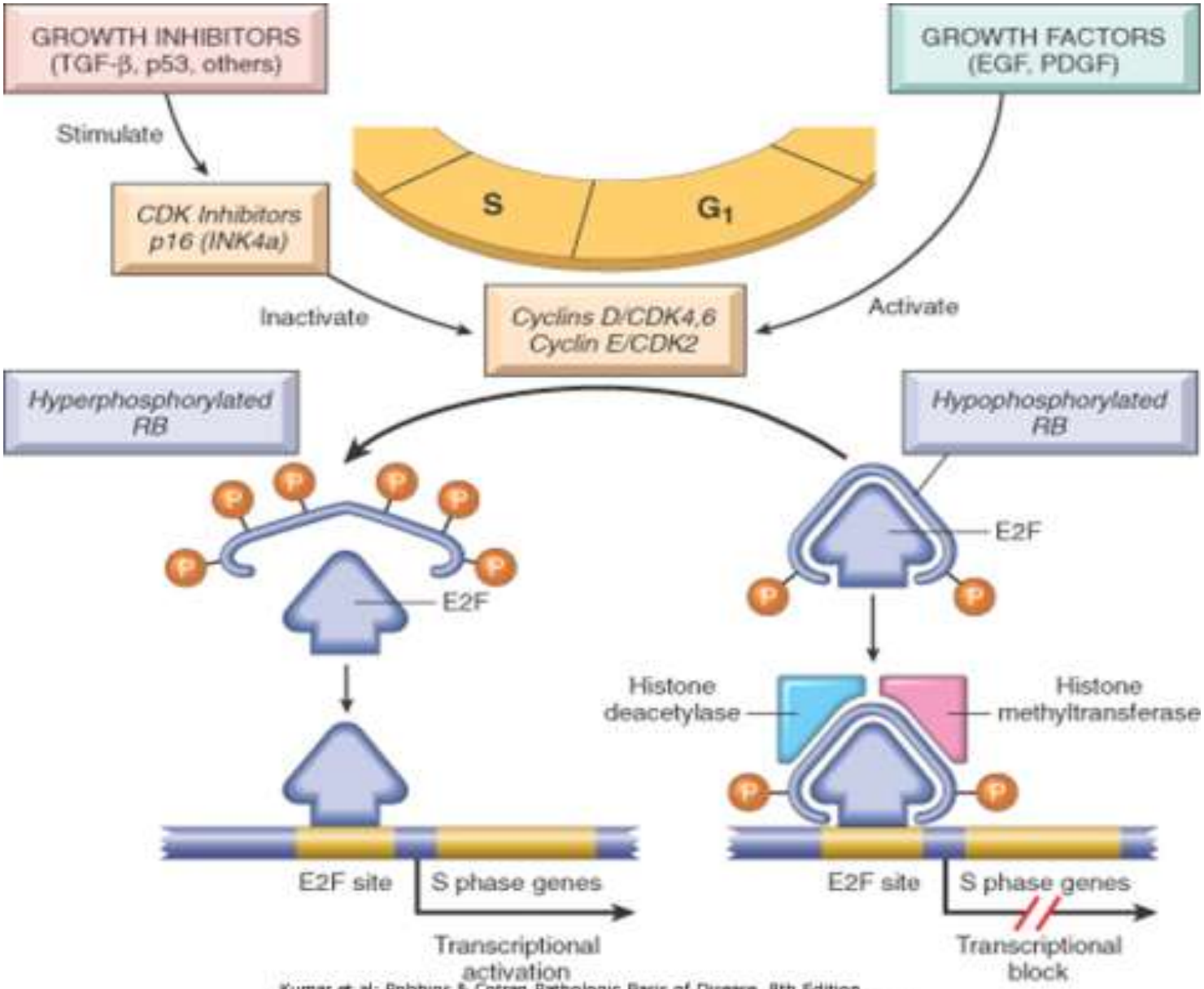
- **Blocks E2F-mediated transcription by:**
  1. ***E2F sequestration*** → **prevent E2F from interacting with other transcriptional activators**
  2. ***Recruitment of chromatin-remodelling proteins*** **(histone deacetylases & histone methyl-transferases)** → **bind to E2F-responsive genes (e.g. Cyclin E)**

MOLECULAR BASIS

Tumor Suppressor Genes: RB (retinoblastoma)

- **Hypophosphorylated (active) RB → binds to and inhibits E2F → no cyclin E transcription → progression to S phase inhibited**

- **Hyperphosphorylated RB → inactive RB → release of E2F → (+) transcription of cyclin E → (+) DNA replication and progression through cell cycle**



Tumor Suppressor Genes: RB (retinoblastoma)

- **Absent RB due to gene mutation → no regulation of E2F transcription factors → (+) DNA replication and continuous progression through cell cyle**

Tumor Suppressor Genes: RB (retinoblastoma)

- **Mutations in other genes that control RB phosphorylation can mimic the effect of *RB* loss**
  - ✓ **Mutational activation of cyclin D or CDK4 → facilitate RB phosphory-lation**
  - ✓ **Mutational inactivation of CDKIs → unregulated activation of cyclins and CDKs**

MOLECULAR BASIS

- ***Loss of normal cell cycle control is central to malignant transformation.***

- ***At least one of the following regulators of the cell cycle is dysregulated in majority of human cancers:***

  1. ***p16/INK4a***
  2. ***cyclin D***
  3. ***CDK4***
  4. ***RB***

Tumor Suppressor Genes: p53

- ***TP53*** **gene located at chr. 17p13.1**
- **Most common target for genetic alterations in human tumors**
- **Sense cellular stress, such as DNA damage, shortened telomeres, and hypoxia**
- **Functions as a critical gatekeeper against the formation of cancer → *"molecular policeman"* or *"guardian of the genome"***

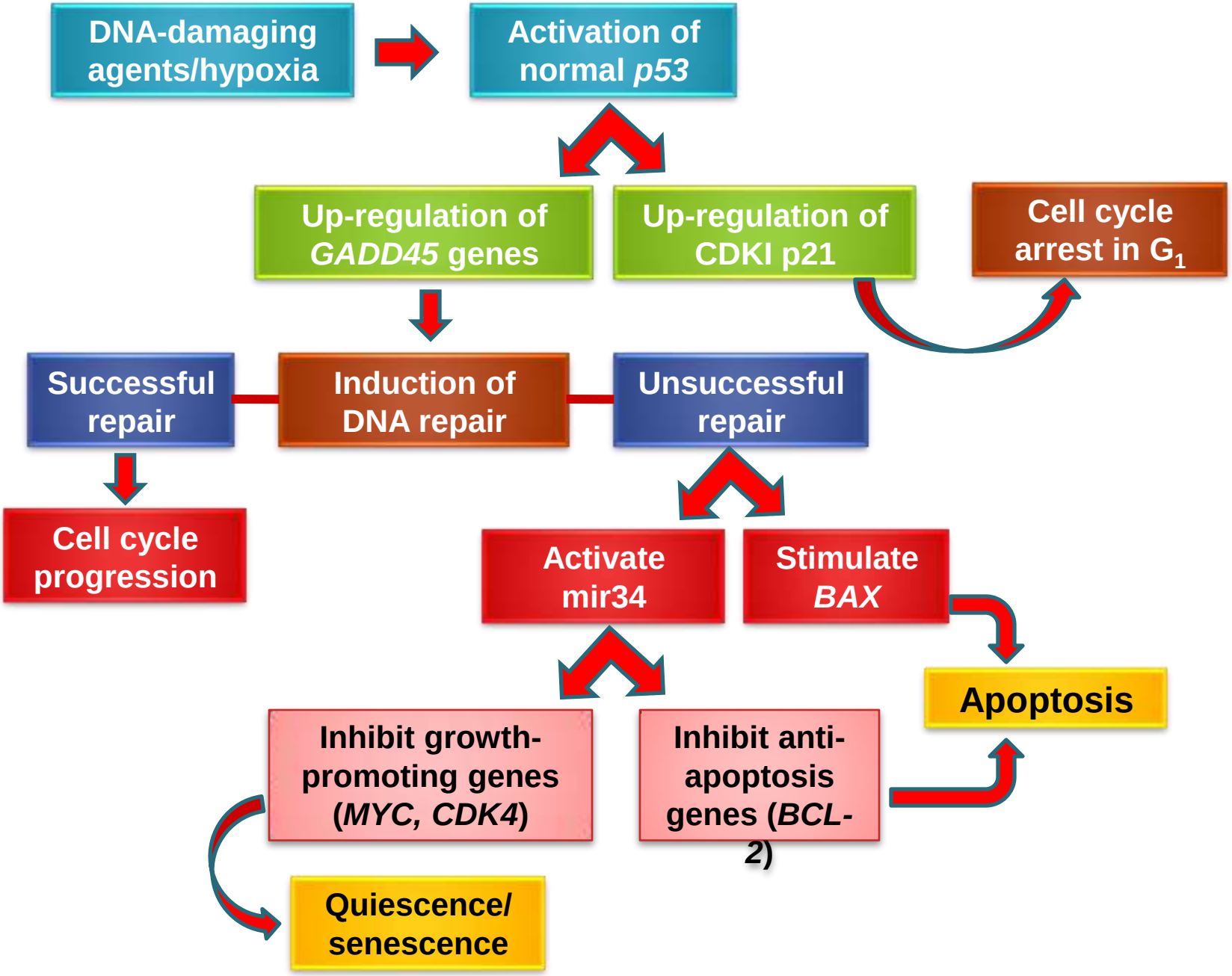
Tumor Suppressor Genes: p53

- **p63 and p73 → p53 collaborators**
  - ✓ **p53 ubiquitously expressed while p63 and p73 with more tissue specificity**
  - ✓ **p63 essential for differentiation of stratified squamous epithelia**
  - ✓ **p73 with strong pro-apoptotic effects after DNA damage from chemotherapeutic agents**

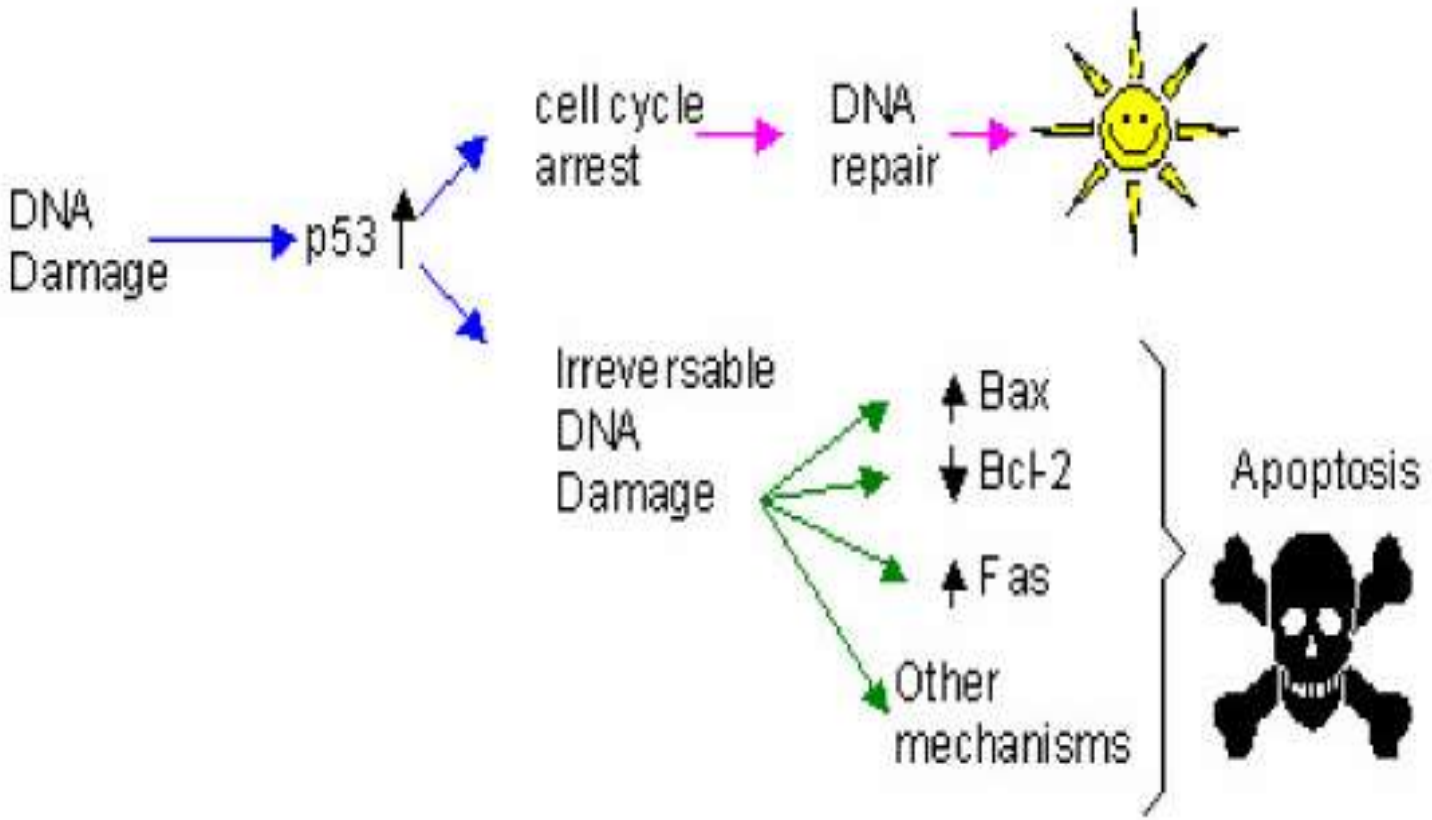
Tumor Suppressor Genes: p53

- **Prevents malignant transformation by:**
  1. **Activation of temporary cell cycle arrest (quiescence)**
  2. **Induction of permanent cell cycle arrest (senescence)**
  3. **Triggering of programmed cell death (apoptosis)**

MOLECULAR BASIS

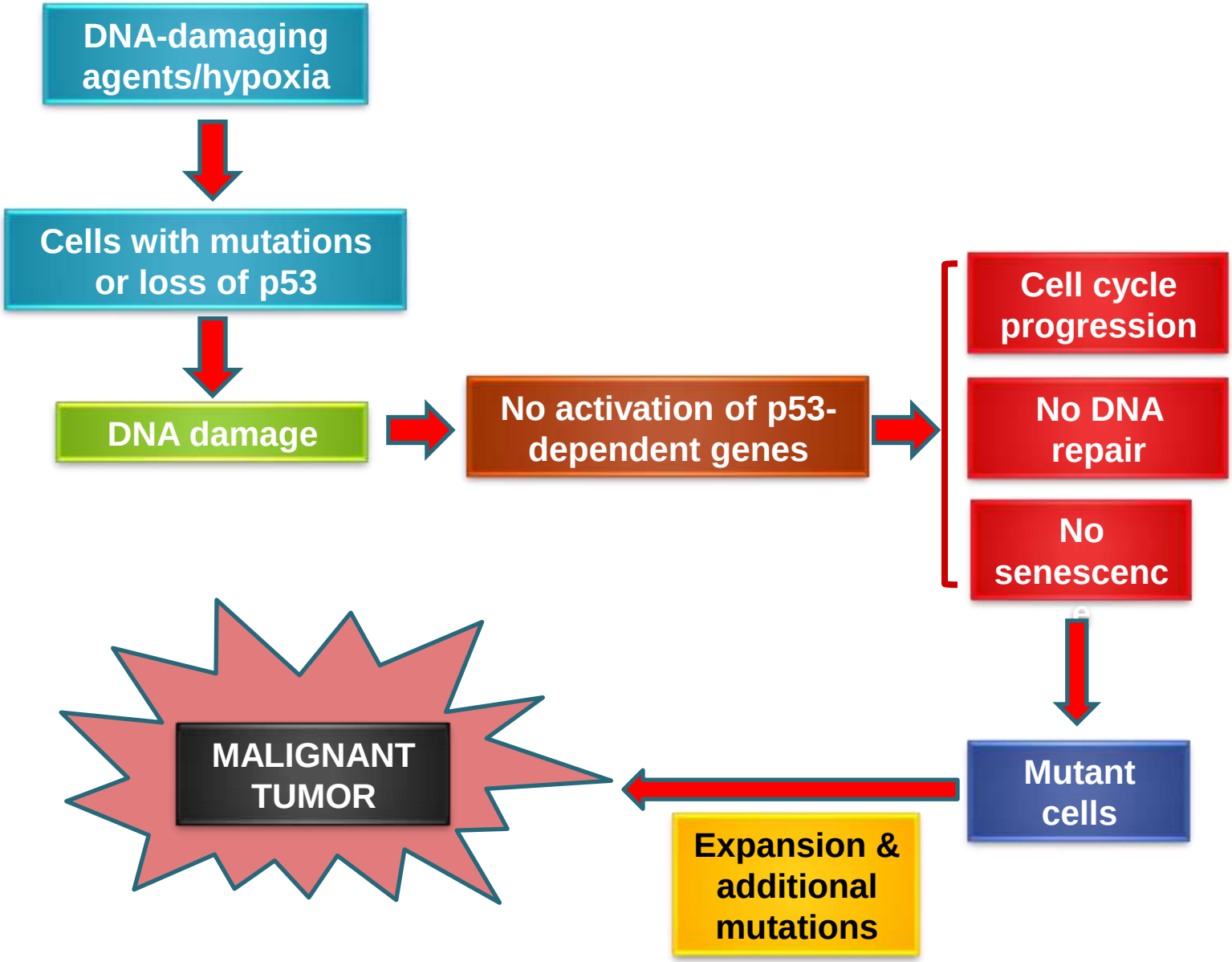


MOLECULAR BASIS



Summary of the mechanism of action of the tumor suppressor protein, p53.

MOLECULAR BASIS



MOLECULAR BASIS

Tumor Suppressor Genes: p53

- ***Homozygous loss of p53 occurs in virtually every type of cancer***
  - ✓ ***In most cases, inactivating mutations affect both p53 alleles and are acquired in somatic cells.***

- ***Approximately 80% of p53 point mutations present in human cancers are located in the DNA-binding domain of the protein***

Tumor Suppressor Genes: p53

- ***In the majority of tumors without p53 mutations, the function of the p53 pathway is blocked by mutation in another gene that regulates p53 function***
  - ✓ ***MDM2 and MDMX → stimulate degradation of p53 → overexpressed in malignancies***
    - ❖ ***Amplification of MDM2 → human sarcomas***

Tumor Suppressor Genes: p53

- *mir34 microRNAs important to p53 response → targets include pro-proliferative genes such as cyclins and anti-apoptotic genes (BCL-2)*
  - ✓ *Inhibition or blockage of mir34 → impaired p53 response*
  - ✓ *Ectopic expression of mir34 without p53 activation → growth arrest and apoptosis*

MOLECULAR BASIS

Tumor Suppressor Genes: APC/ß-Catenin Pathway

Adenomatous polyposis coli genes (APC)

- **Main function is down-regulation of growth-promoting signals**
- **Loci found at chr. 5q21**
- **Component of *WNT signalling pathway***
- **Important function of the *APC* protein is to down-regulate ß-catenin**

Tumor Suppressor Genes: APC/ß-Catenin Pathway

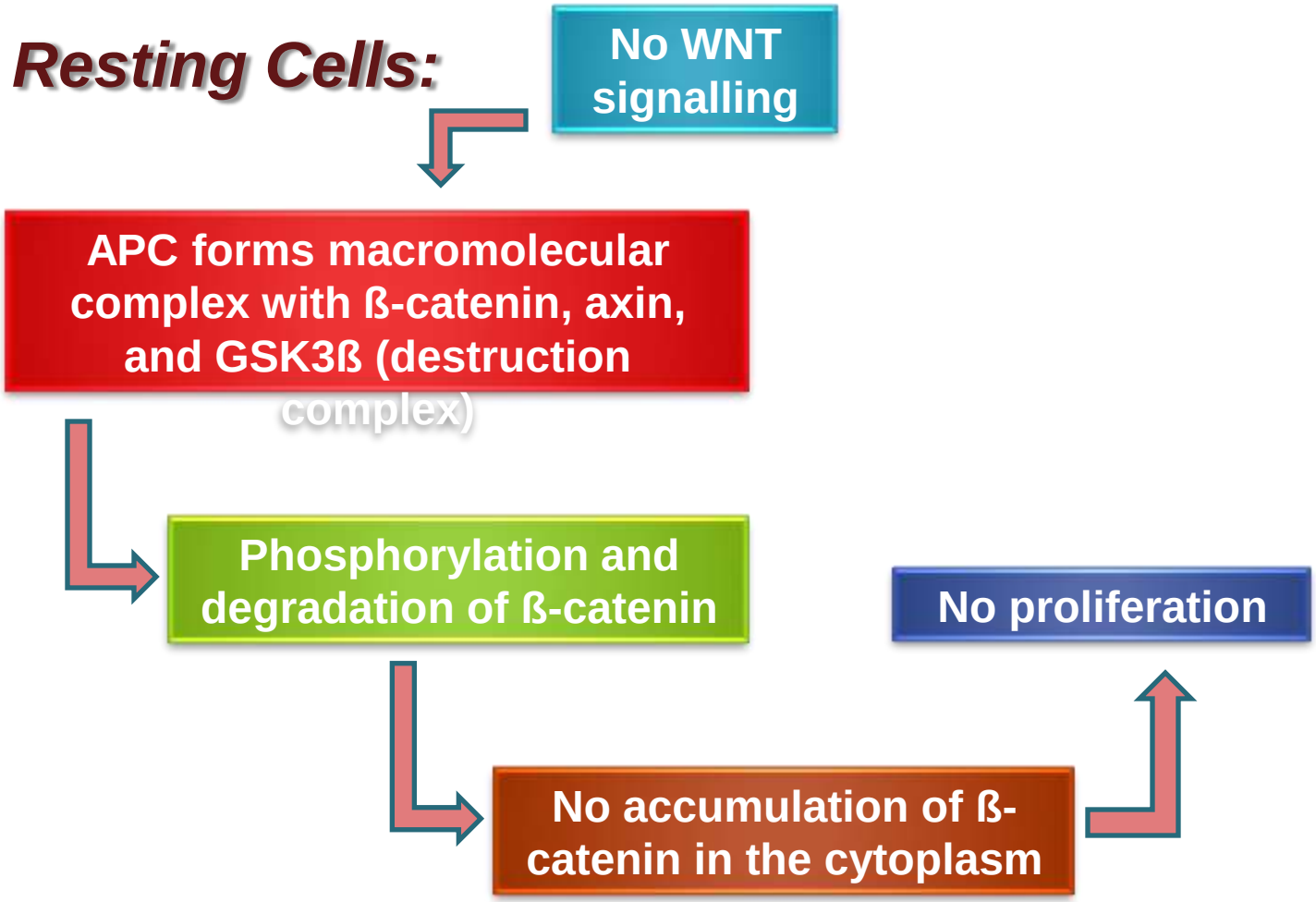
WNT Signalling Pathway

- **Major role in controlling cell fate, adhesion, and cell polarity during embryonic development**
- **Required for self-renewal of hemato-poietic stem cells**
- **Signals through cell surface receptors called frizzled (FRZ)**

MOLECULAR BASIS

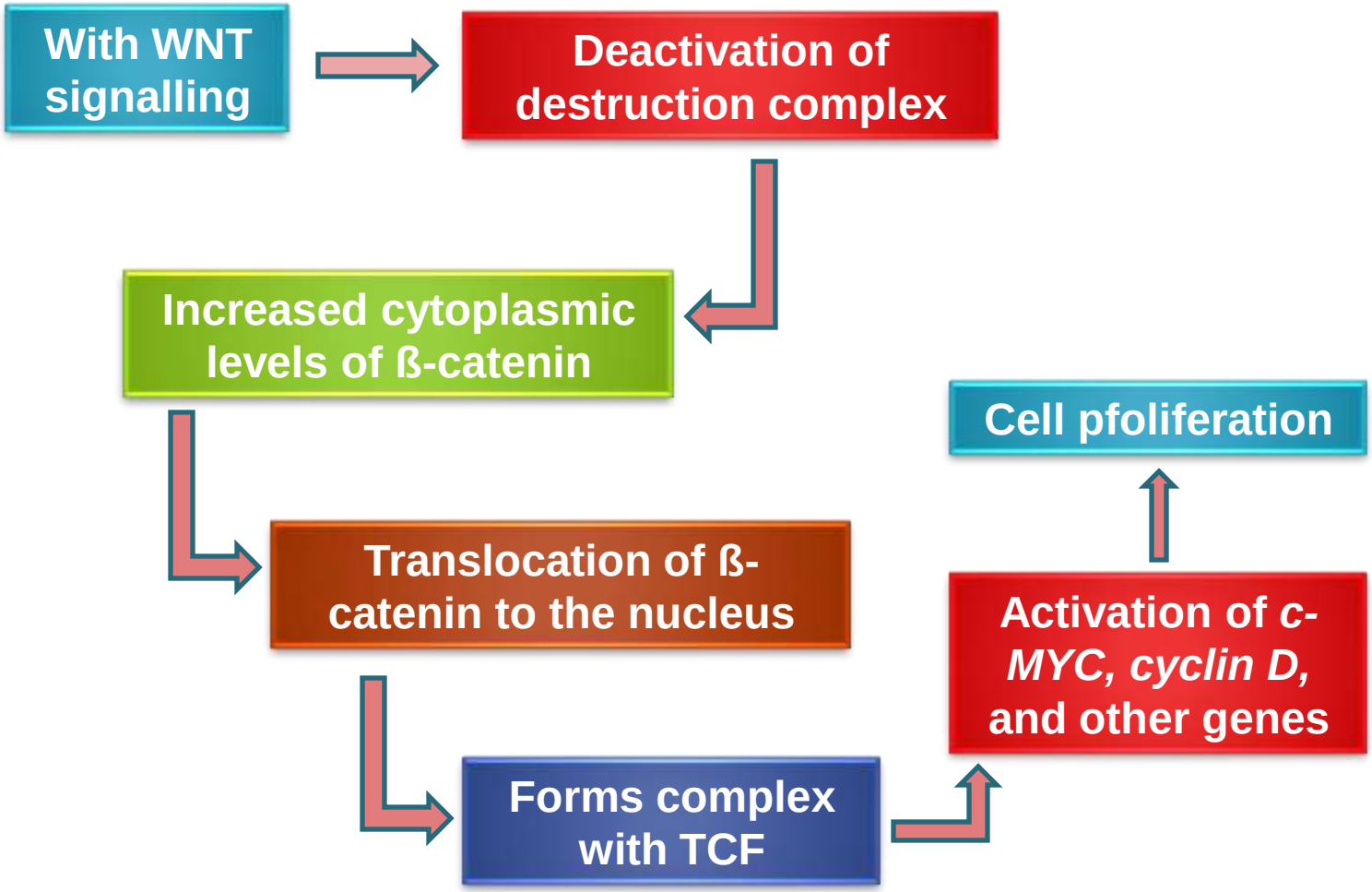
Tumor Suppressor Genes: APC/ß-Catenin Pathway

In Resting Cells:



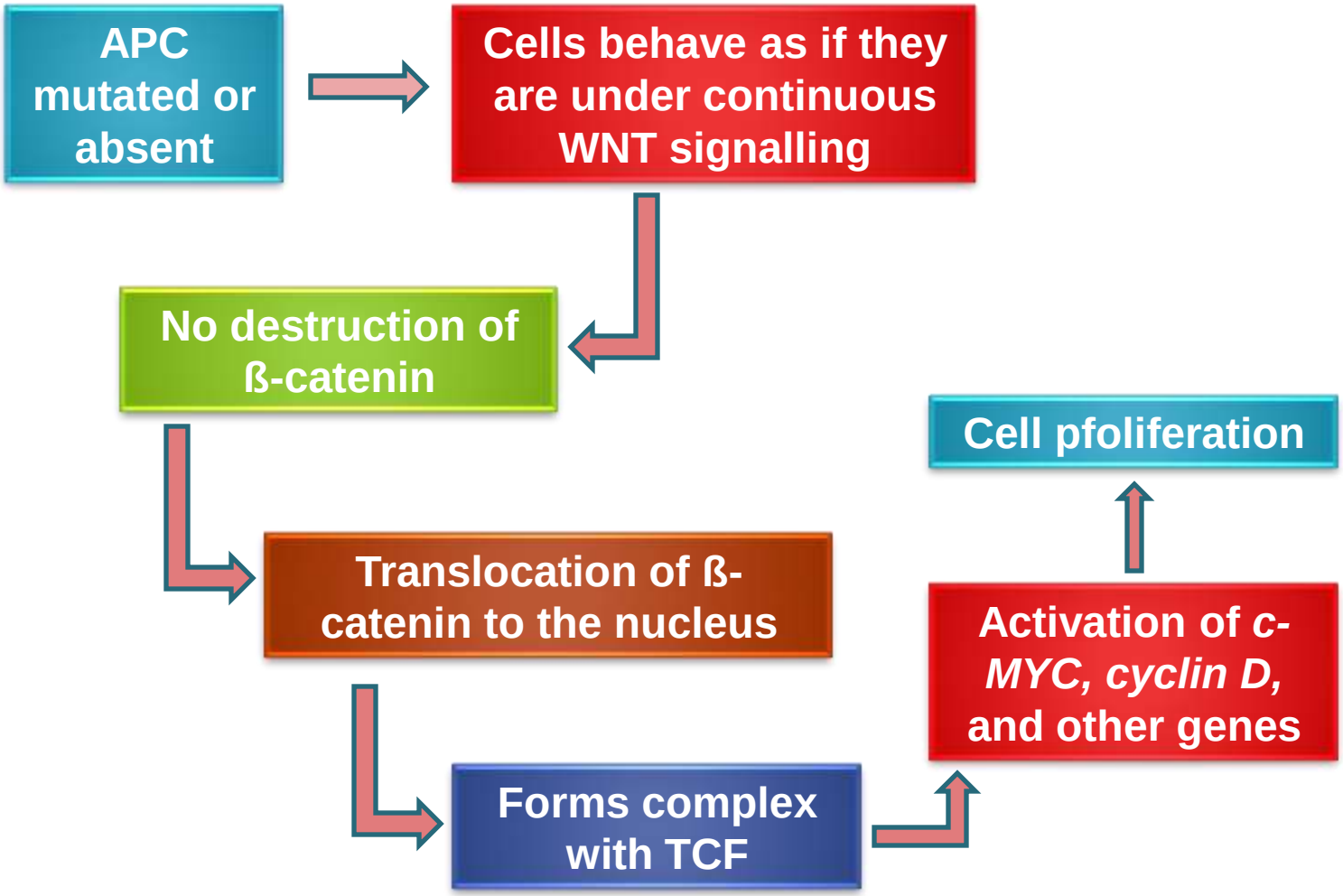
MOLECULAR BASIS

Tumor Suppressor Genes: APC/ß-Catenin Pathway



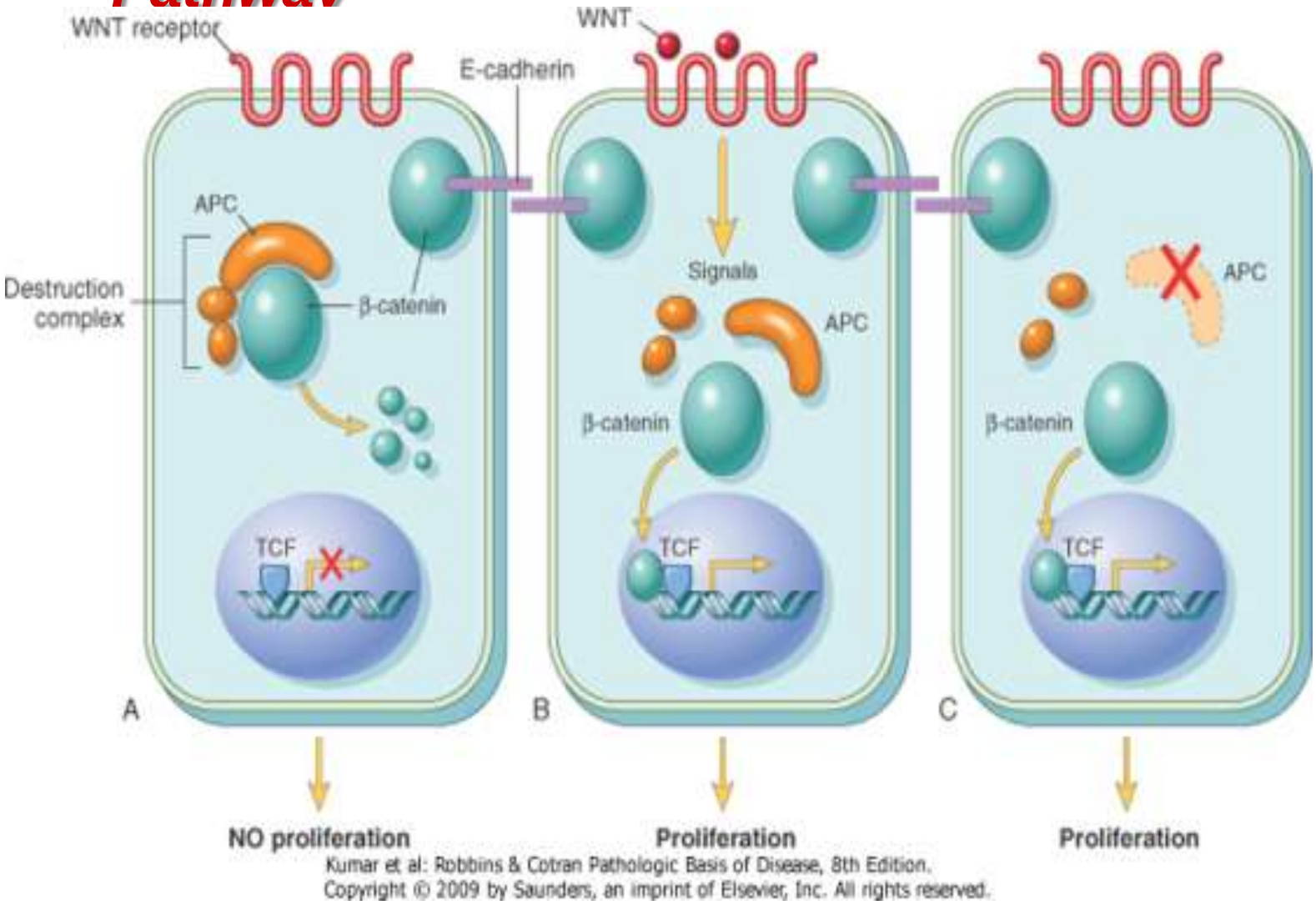
MOLECULAR BASIS

Tumor Suppressor Genes: APC/ß-Catenin Pathway



MOLECULAR BASIS

Tumor Suppressor Genes: APC/ß-Catenin Pathwav



MOLECULAR BASIS

Tumor Suppressor Genes: APC/ß-Catenin Pathway

Significance:

- ***Colon tumors → normal APC genes with mutations in ß-catenin → no destruction of ß-catenin by APC***

- ***Mutations in ß-catenin gene present in more than 50% of hepatoblastomas and approx. 20% of hepatocellular carcinoma***

MOLECULAR BASIS

Tumor Suppressor Genes: APC/ß-Catenin Pathway

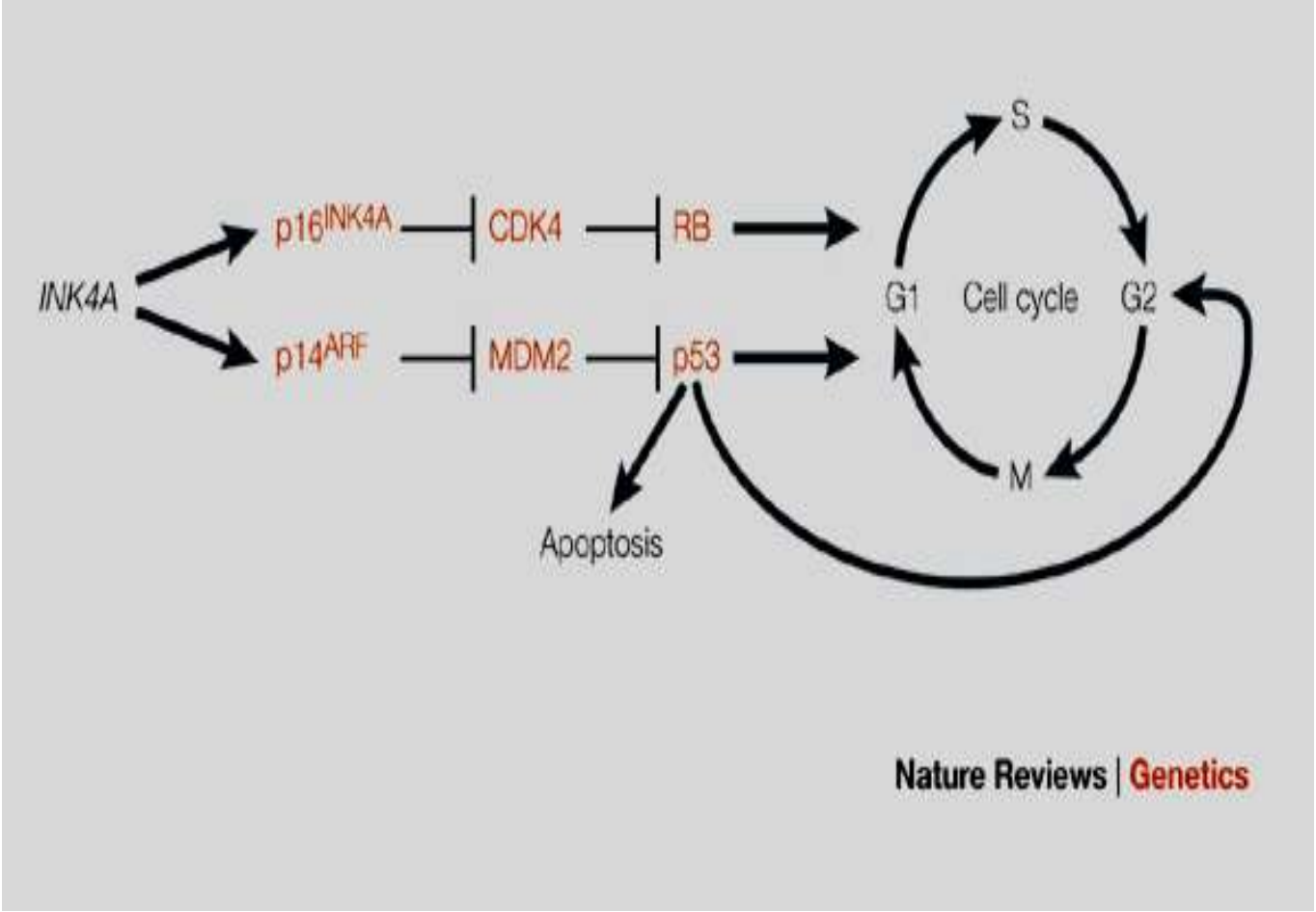
Significance:

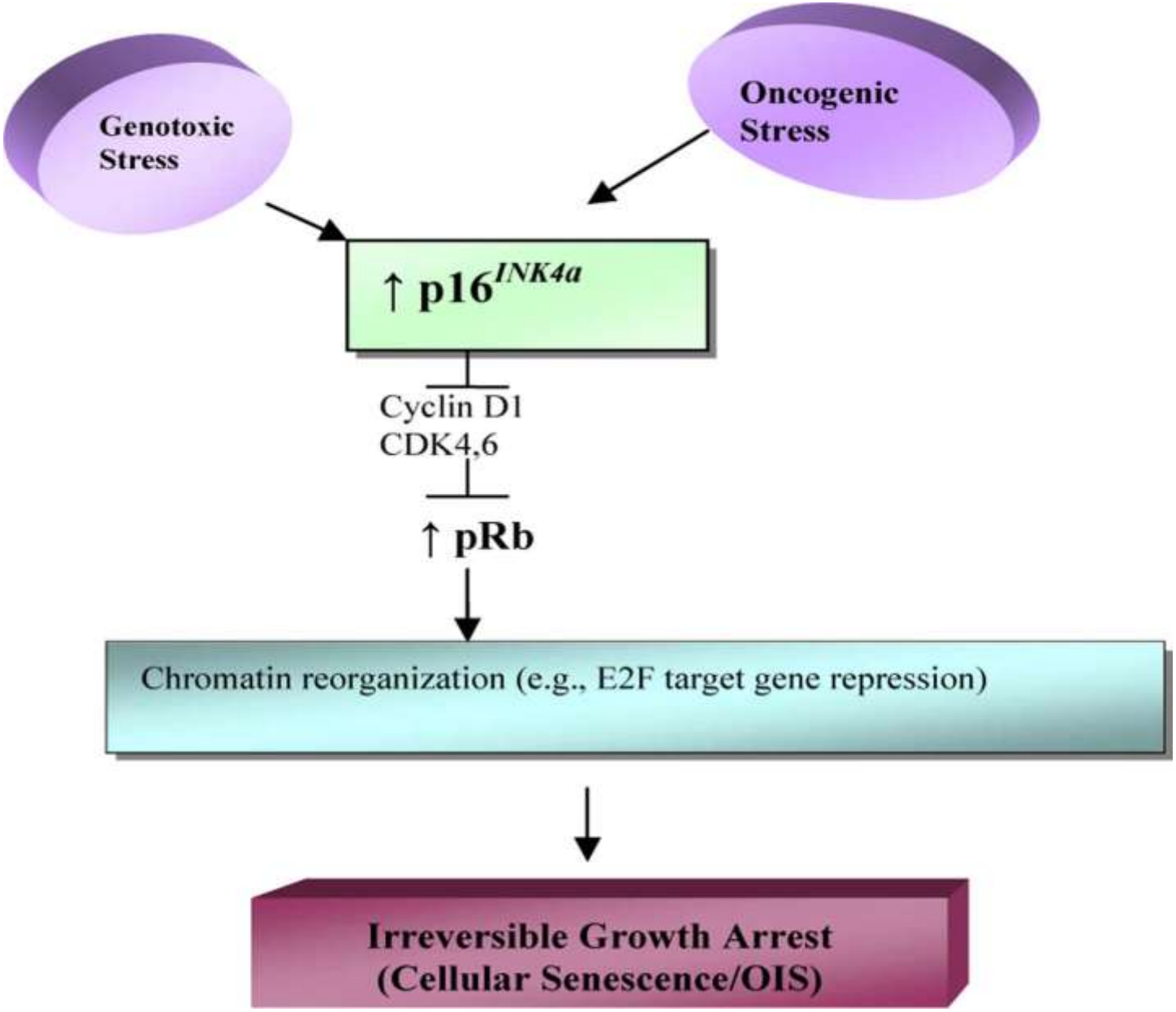
- *ß-catenin normally binds to the cytoplasmic tail of E-cadherin → maintain intercellular adhesiveness*
  - ✓ *Mutation of ß-catenin/E-cadherin axis → loss of contact inhibition → easy disaggregation of cells → favor malignant phenotype*
  - ✓ *Mutation of ß-catenin/E-cadherin axis → ß-catenin translocates to nucleus → cell proliferation*

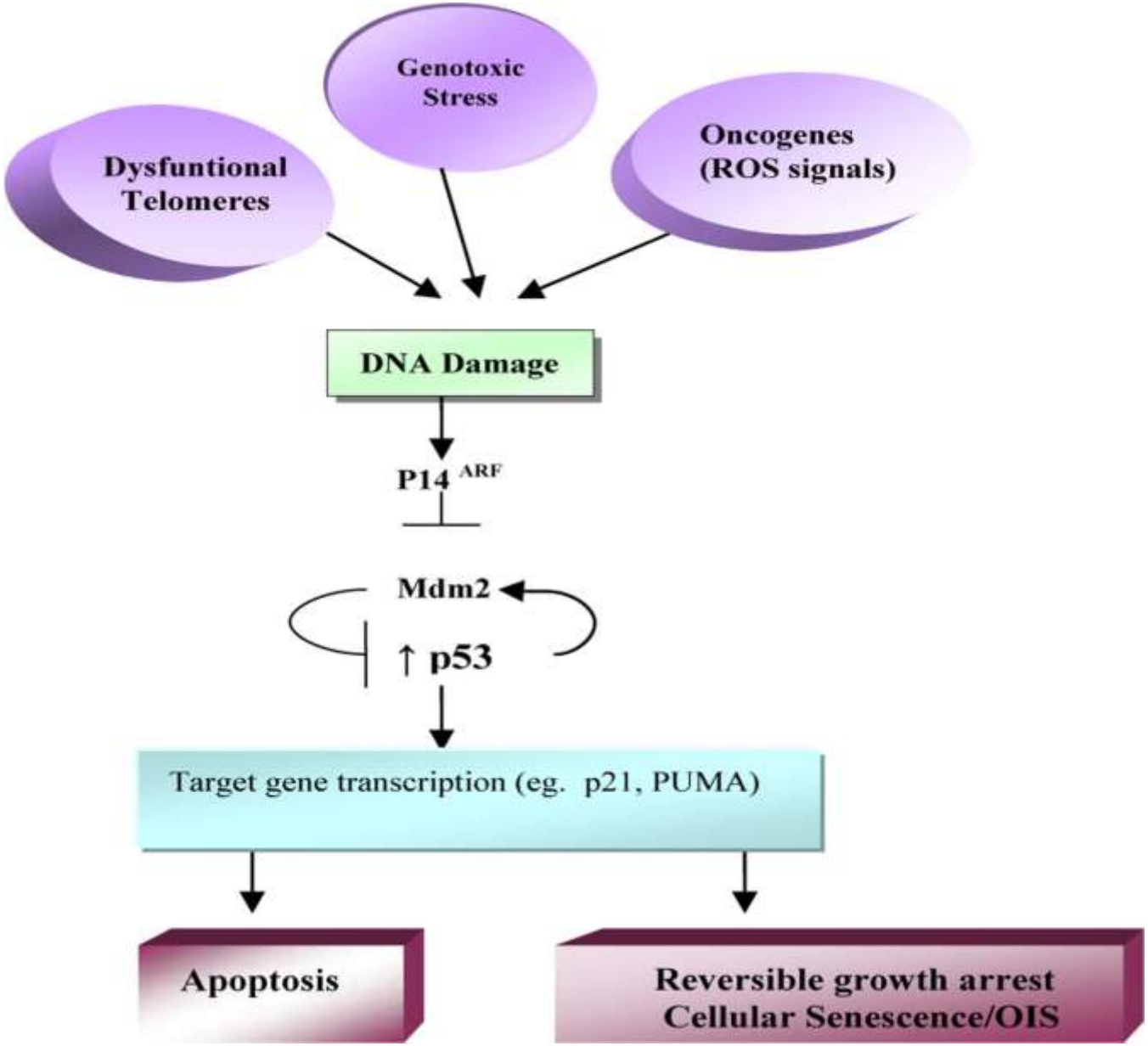
Other Genes That Function as Tumor Suppressors

INK4a/ARF

- **Also called *CDKN2A* gene locus**
- **Two protein products:**
  1. **p16/INK4a CDKI → block cyclin D/ CDK2-mediated phosphorylation of RB; crucial for induction of senescence; silenced by hyper-methylation of the genes**
  2. **p14/ARF → inhibit MDM2 → prevent destruction of p53**


INK4A
p16INK4A
CDK4
RB
p14ARF
MDM2
p53
Apoptosis
S
G1
Cell cycle
G2
M
Nature Reviews | Genetics


Genotoxic Stress
Oncogenic Stress
↑ p16INK4a
Cyclin D1
CDK4,6
↑ pRb
Chromatin reorganization (e.g., E2F target gene repression)
Irreversible Growth Arrest
(Cellular Senescence/OIS)


Genotoxic Stress
Dysfuntional Telomeres
Oncogenes (ROS signals)
DNA Damage
P14 ARF
Mdm2
↑ p53
Target gene transcription (eg. p21, PUMA)
Apoptosis
Reversible growth arrest
Cellular Senescence/OIS

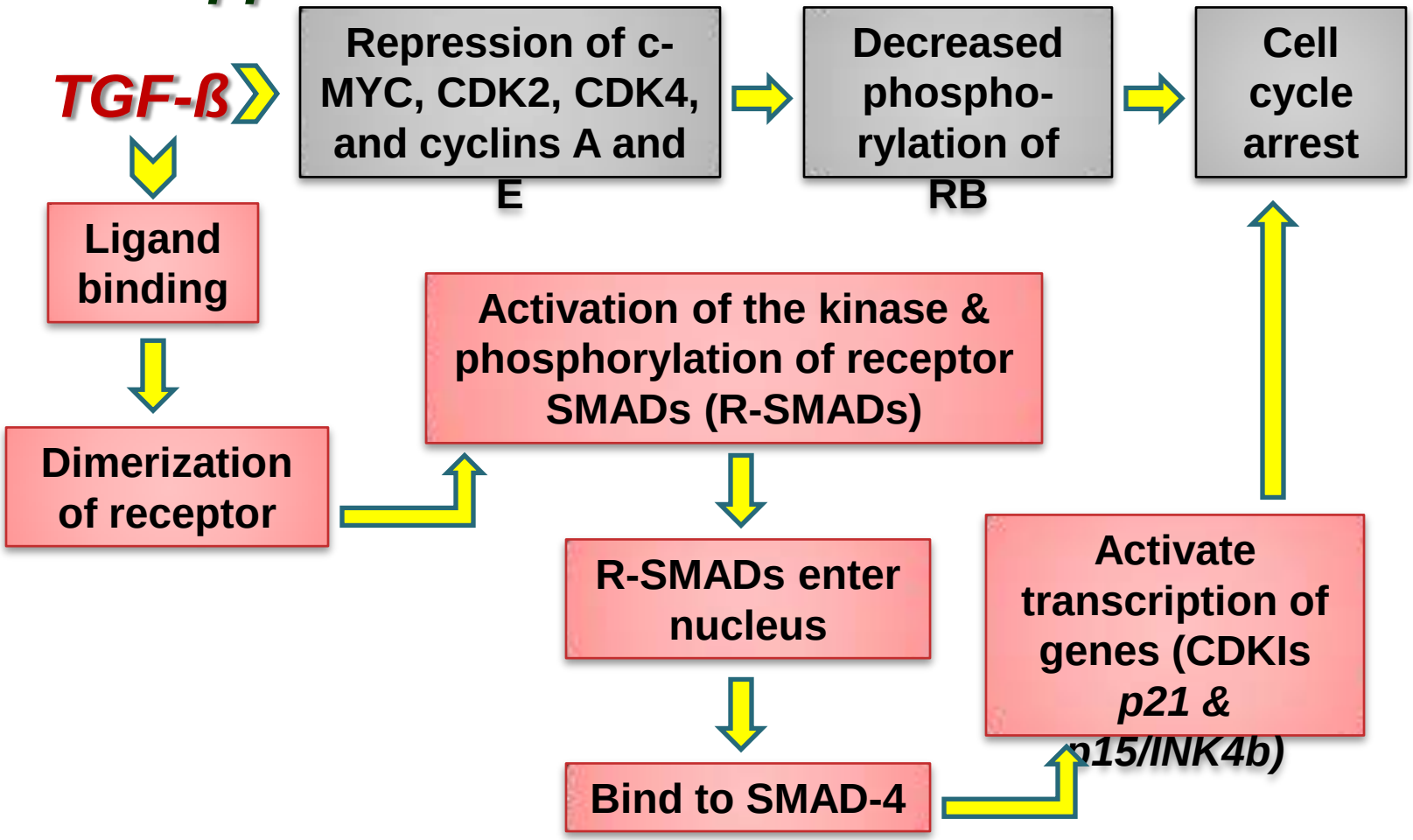
Other Genes That Function as Tumor Suppressors

TGF-ß

- **Potent inhibitor of proliferation in most normal epithelial, endothelial, and hematopoietic cells**
- **Regulates cellular processes by binding to a serine-threonine kinase complex composed of TGF-ß receptors I and II**

MOLECULAR BASIS

Other Genes That Function as Tumor Suppressors



Other Genes That Function as Tumor Suppressors

TGF-ß

- *Can prevent or promote tumor growth depending on the state of other genes in the cell*
- *Mutations affecting type II TGF-ß receptor → cancer of colon, stomach, endometrium*
- *Mutational inactivation of SMAD4 → pancreatic cancer*

Other Genes That Function as Tumor Suppressors

PTEN (Phosphatase and tensin homologue)

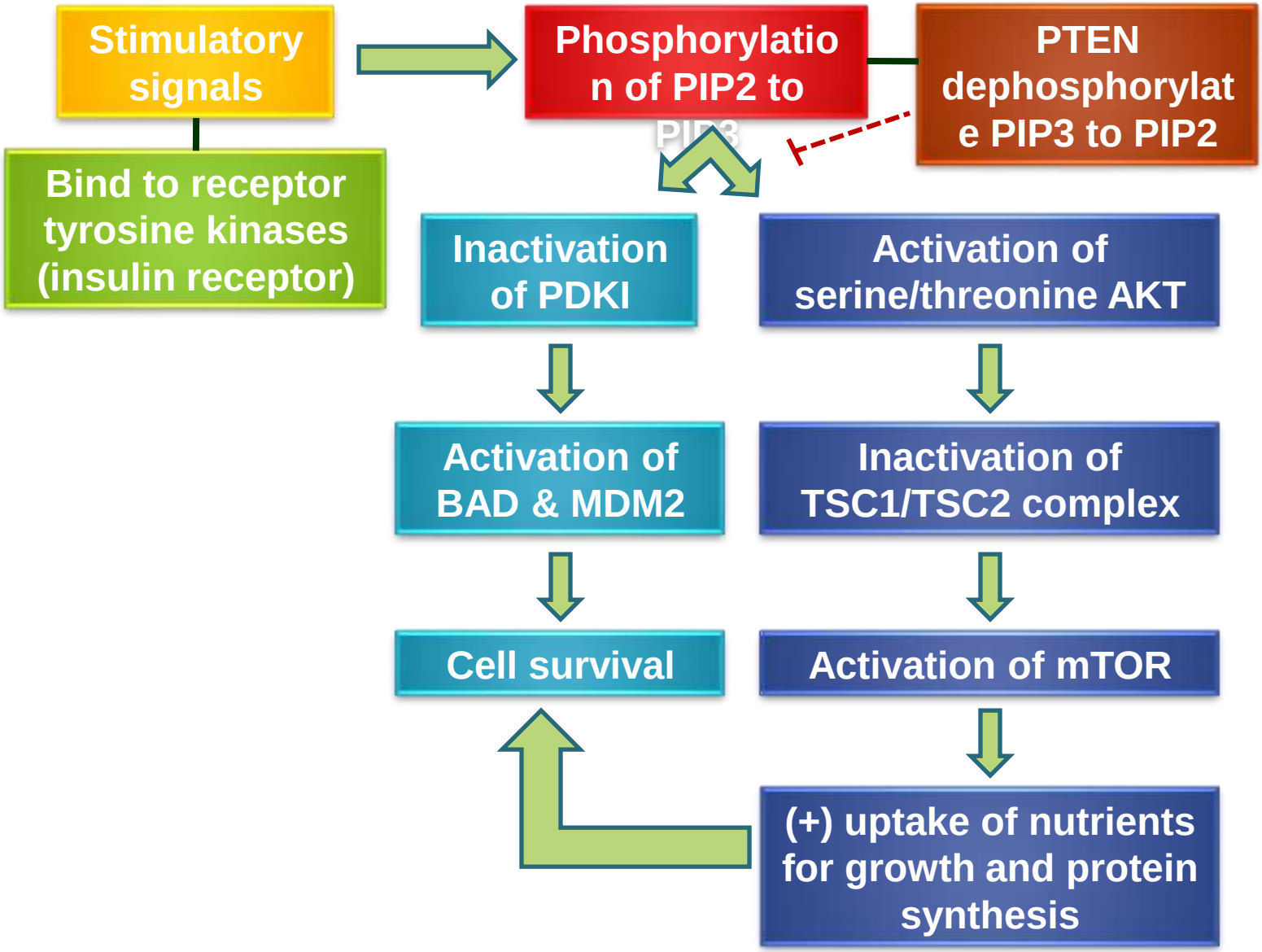
- **Gene on chr. 10q23**
- **Membrane-associated phosphatase → acts as a brake on the pro-survival/ pro-growth PI3K/AKT pathway → most commonly mutated pathway in human cancer**

Other Genes That Function as Tumor Suppressors

PTEN (Phosphatase and tensin homologue)

- **Mutated in Cowden syndrome → autosomal dominant; frequent benign growths (tumors of skin appendages) and increased incidence of epithelial cancers (breast, endometrium, thyroid)**

MOLECULAR BASIS



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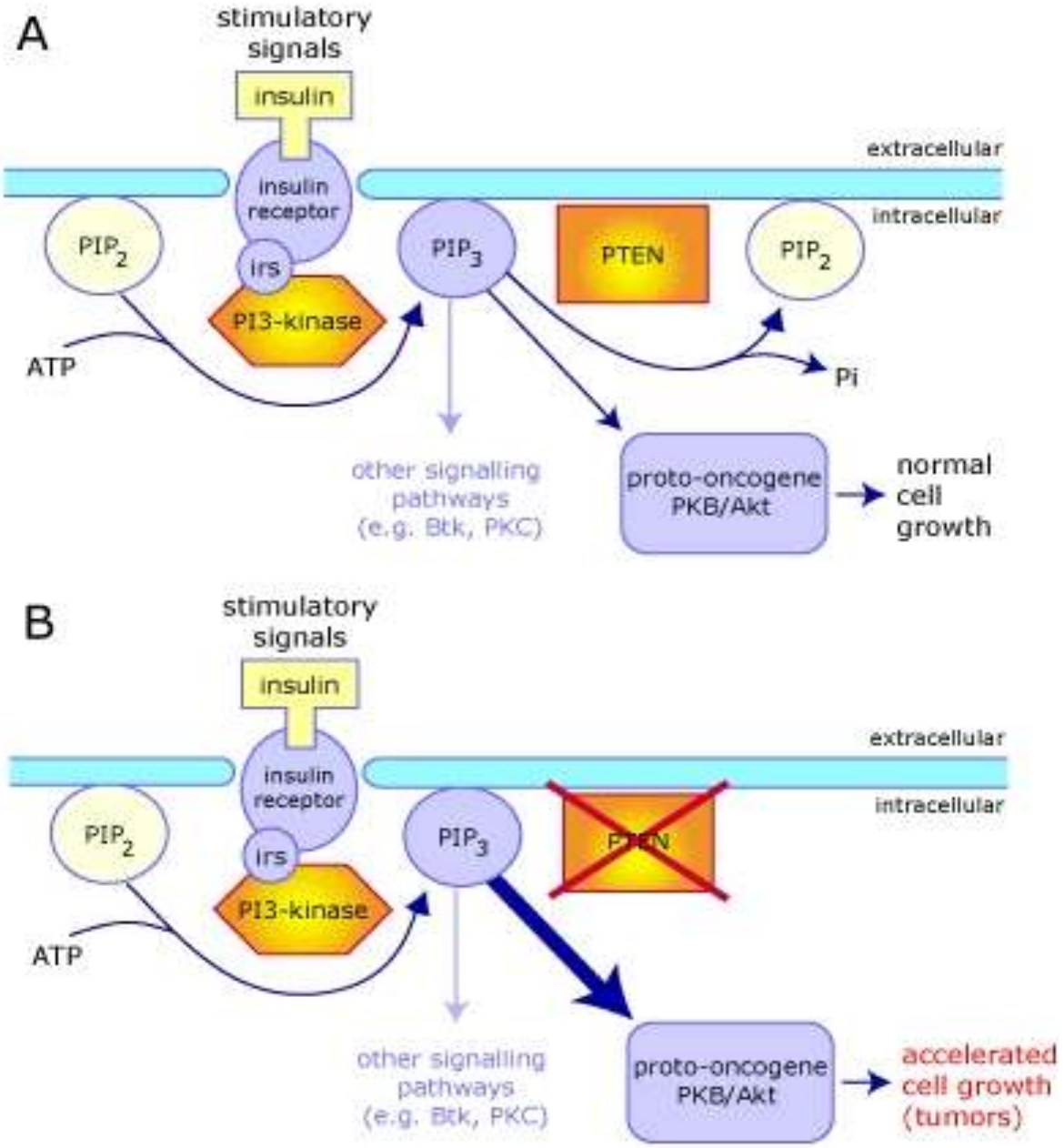


Other Genes That Function as Tumor Suppressors

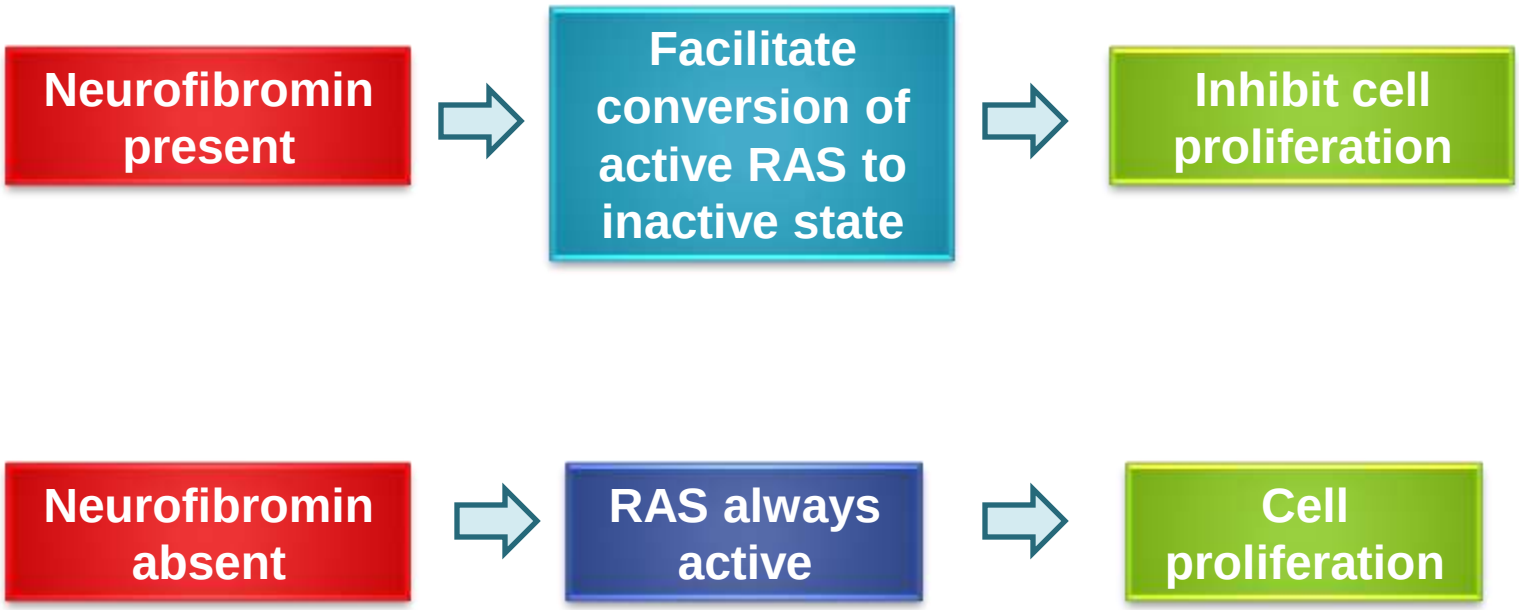
NF1 (Neurofibromatosis 1)

- **Inheritance of one mutant allele → benign neurofibromas and optic nerve glioma → neurofibromatosis type 1**
- **Protein product called neurofibromin**

MOLECULAR BASIS

Other Genes That Function as Tumor Suppressors

NF1 (Neurofibromatosis 1)



Other Genes That Function as Tumor Suppressors

NF2 (Neurofibromatosis 2)

- **Germline mutation → benign bilateral schwannomas of acoustic nerve → neurofibromatosis type 2**
- **Somatic mutations of both alleles → sporadic meningiomas and ependymomas**

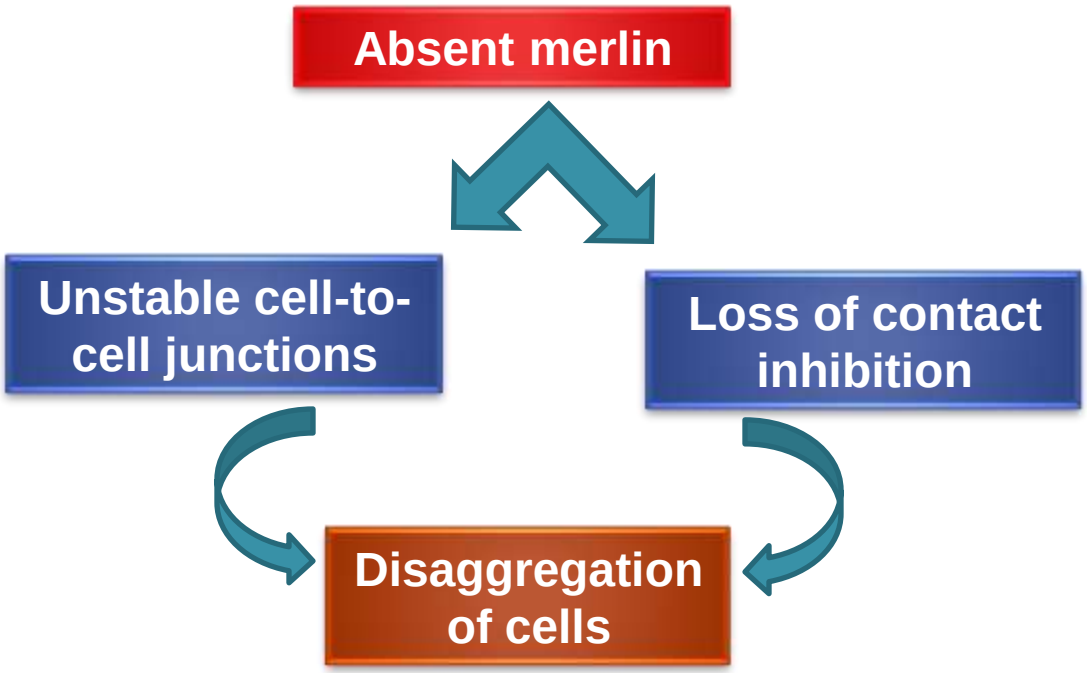
Other Genes That Function as Tumor Suppressors

NF2 (Neurofibromatosis 2)

- **Protein product: neurofibromin 2 or merlin → part of Salvador-Warts-Hippo (SWH) tumor suppressor pathway**
- **Homologous to red cell membrane cytoskeletal protein**

Other Genes That Function as Tumor Suppressors

NF2 (Neurofibromatosis 2)



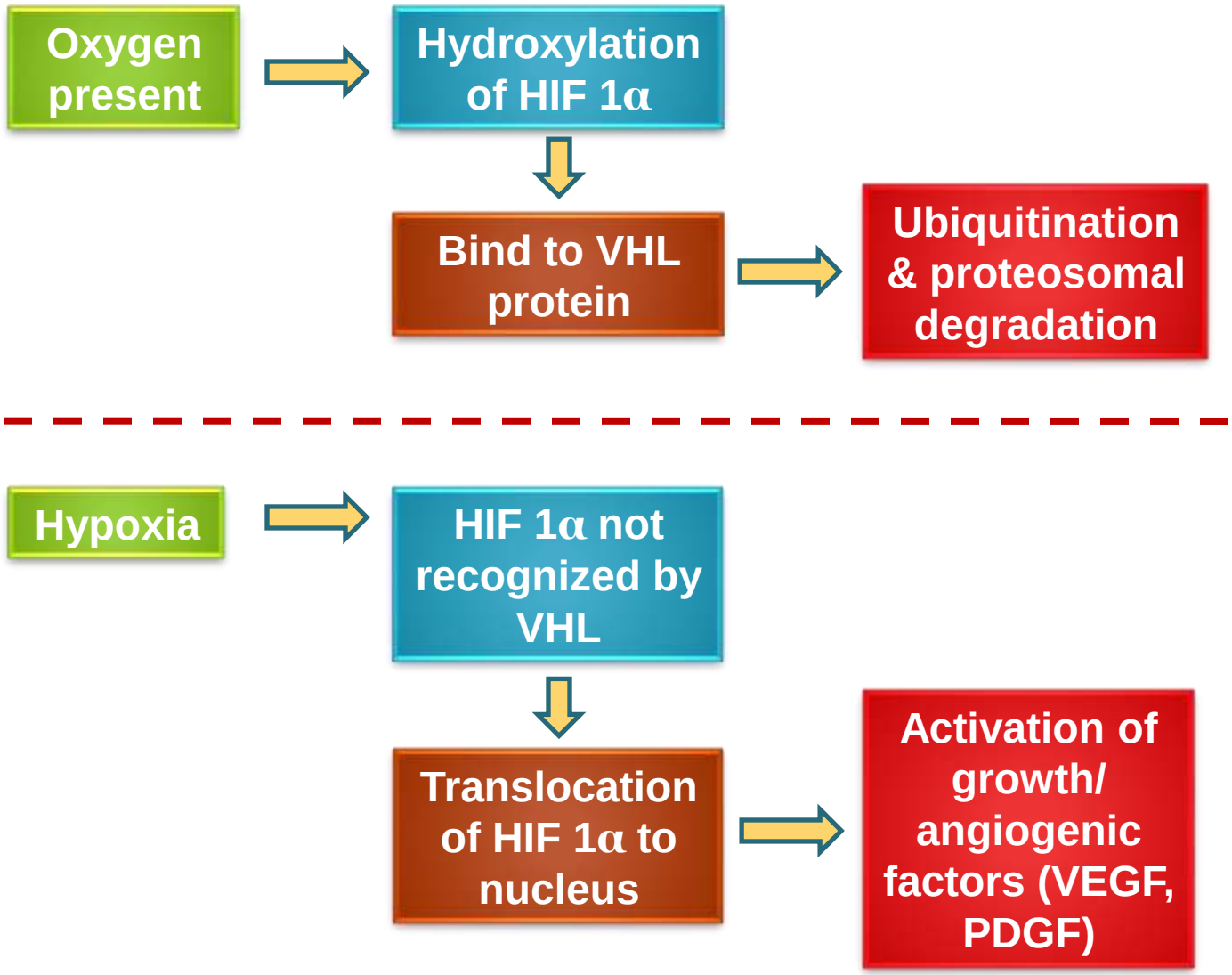
Other Genes That Function as Tumor Suppressors

VHL (von Hippel-Lindau gene)

- **Chromosome 3p**
- **VHL protein part of ubiquitin ligase complex → critical substrate is hypoxia-inducible transcription factor 1α (HIF 1α)**
- **Germline mutation → hereditary renal cell cancers, retinal angioma, renal cyst, pheochromocytoma, hemangioblastomas of CNS**

MOLECULAR BASIS

VHL (von Hippel-Lindau gene)



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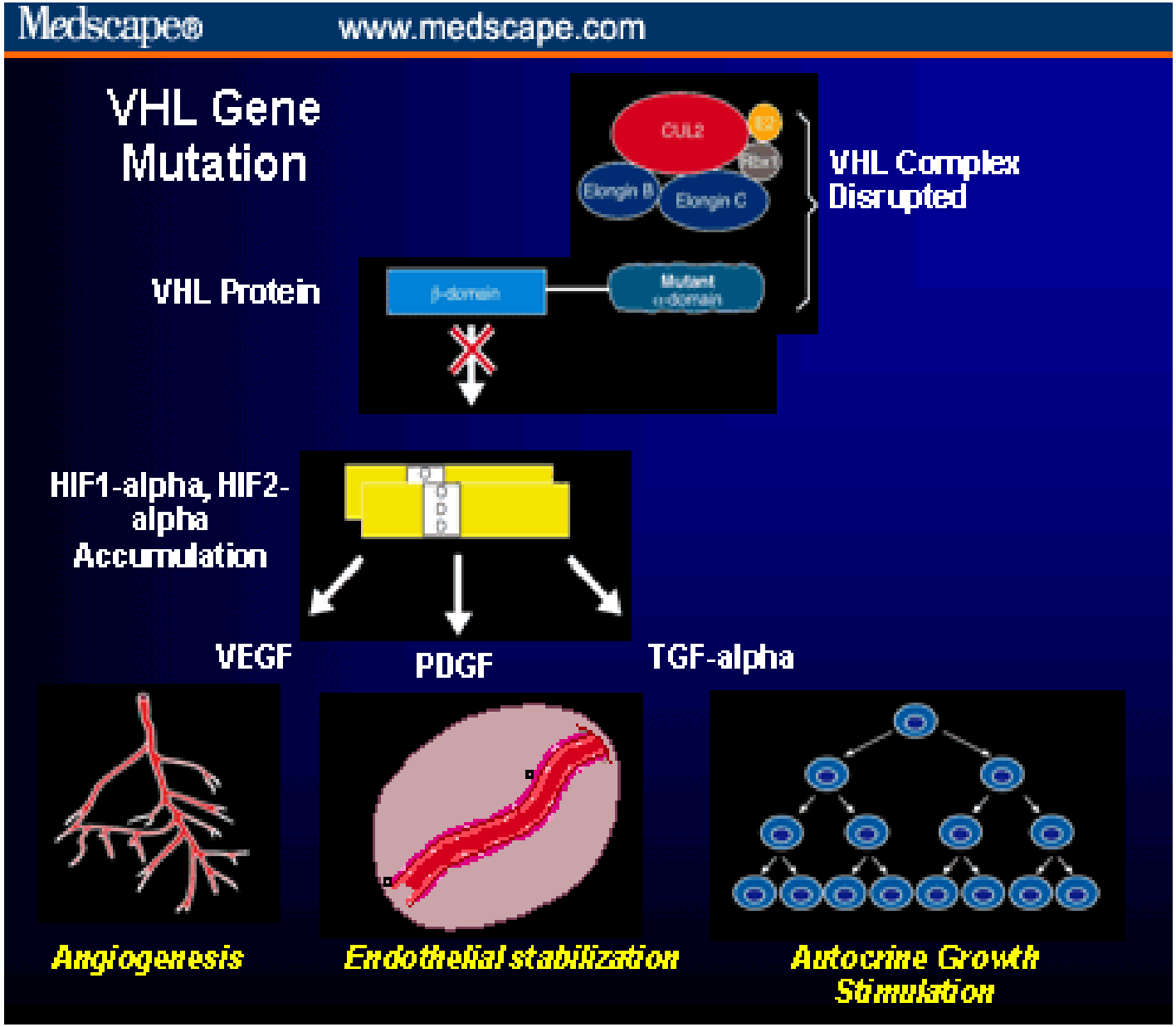


Other Genes That Function as Tumor Suppressors

WT-1 (Wilms' Tumor-1 gene)

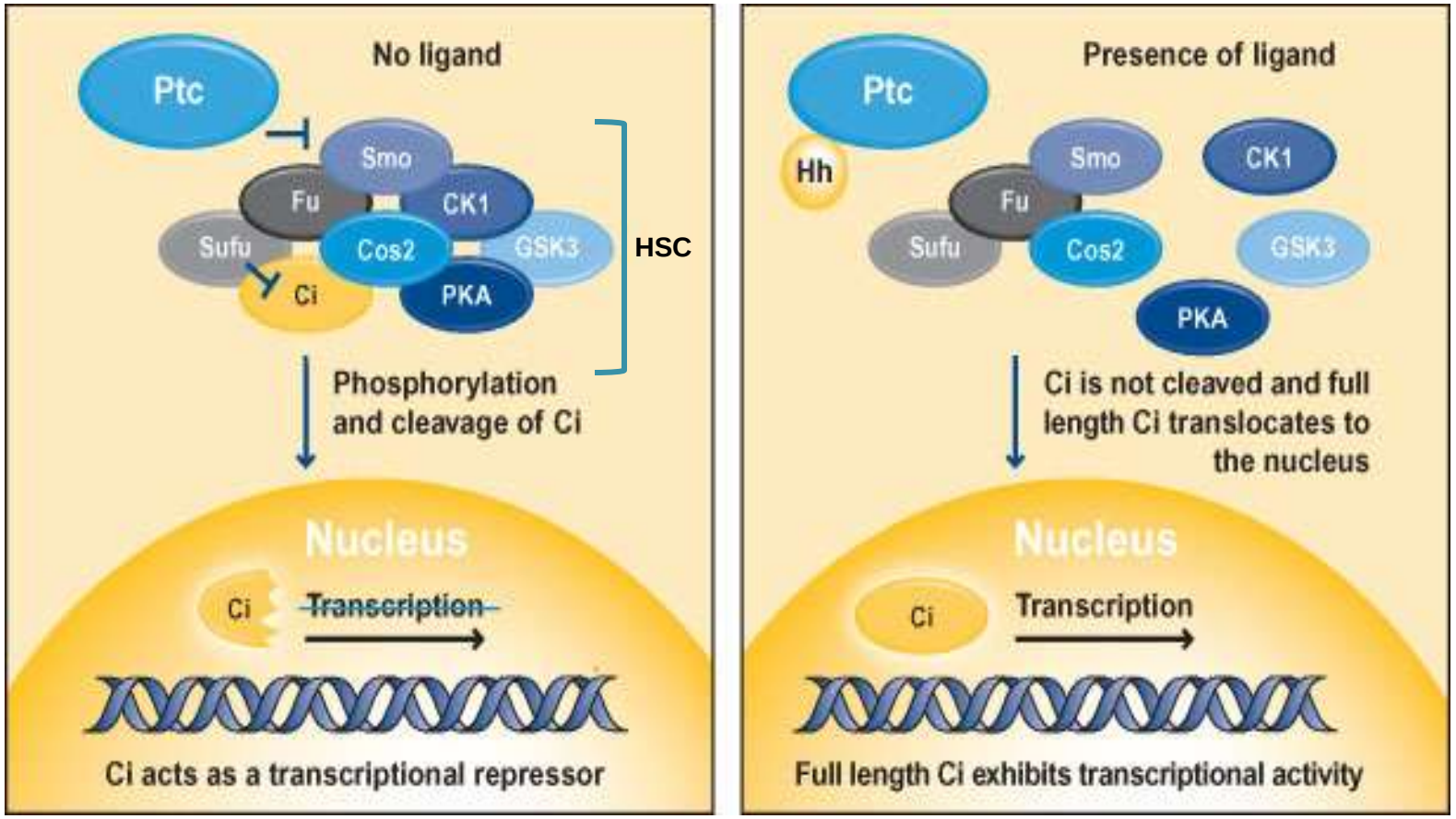
- **Chromosome 11p13**
- **Protein product a transcriptional activator of genes involved in renal and gonadal differentiation**
- **Overexpression → Wilms' tumor and a variety of adult cancers (leukemias and breast Ca)**

Other Genes That Function as Tumor Suppressors

Patched (PTCH-1 & PTCH-2)

- **Protein product (PTCH) is a cell membrane protein → functions as receptor for family of proteins called *hedgehog***
- **Hedgehog/PATCHED pathway regulates *TGF-ß, PDGFRA and PDGFRB* genes**

MOLECULAR BASIS



Ptc – Patched; Hh – hedgehog; Smo – smoothened; Ci – cubitus interruptus (transcription factor); Fu – fused (serine/threonine kinase); Cos2 – costal 2 (kinesin-like molecule); PKA – protein kinase A; CK 1 – protein kinase CK 1; Sufu – suppressor of fused; GSK3 – glycogen synthase kinase 3; HSC – hedgehog signalling complex

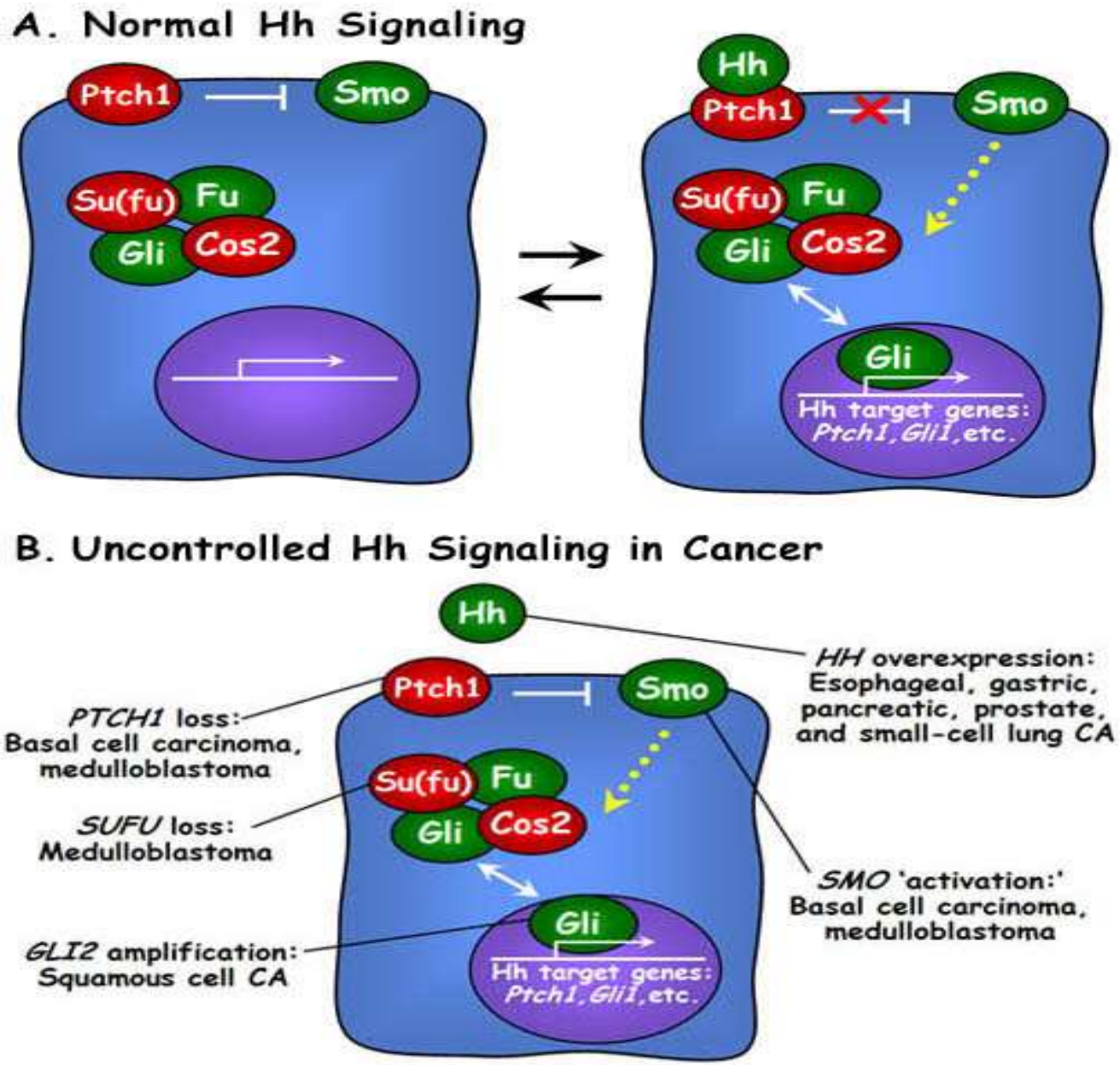
MOLECULAR BASIS

Other Genes That Function as Tumor Suppressors

Patched (PTCH-1 & PTCH-2)

- **Mutations in *PTCH* → Gorlin synd. → nevoid basal carcinoma synd.**
- ***PTCH* mutations present in 20% to 50% of sporadic cases of basal cell carcinoma**
- **50% of mutations caused by UV exposure**

MOLECULAR BASIS



END of PART 2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search ID: mban2063
"The brain tumor's incurable, but let me give you something for that dandruff."