Pathology

Subject :

Lec no : lec-25-

Done By : Hala AL Beshtawe

وَقُل رَّبِّ زِدْنِي عِلْمًا

NEOPLASIA

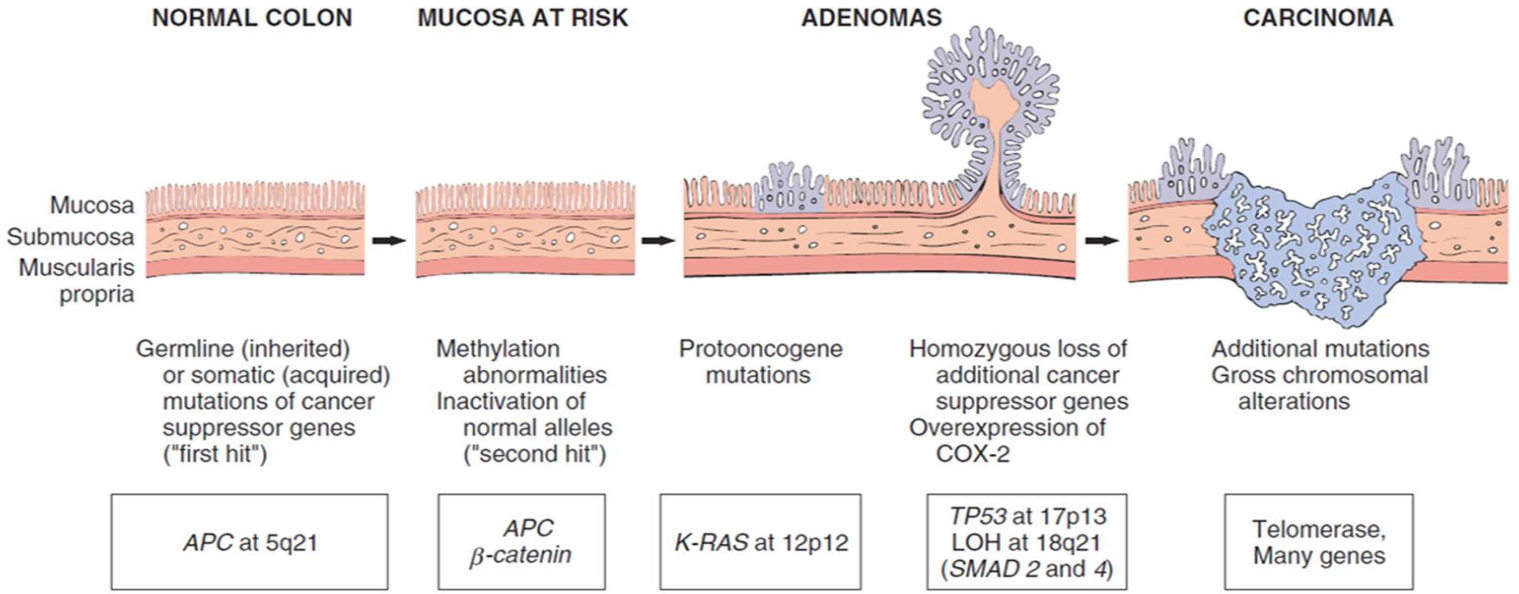
Dr. Ola Abu Al Karsaneh

Carcinogenesis

- Carcinogenesis is a multistep process resulting from the accumulation of multiple genetic alterations that collectively give rise to the transformed phenotype and all of its associated hallmarks.

* تحتاج الكثير من الطفرات لحدوث كانسر (هيث ان طفره جينيه واحده غير كافيه لحدوث سرطان)

In most cases, no single mutation is sufficient to transform a normal cell into a cancer cell.



Tumor Progression:

This is the stepwise accumulation of mutations resulting in increasing features of malignancy:

- More Aggressive
- Less responsive to therapy

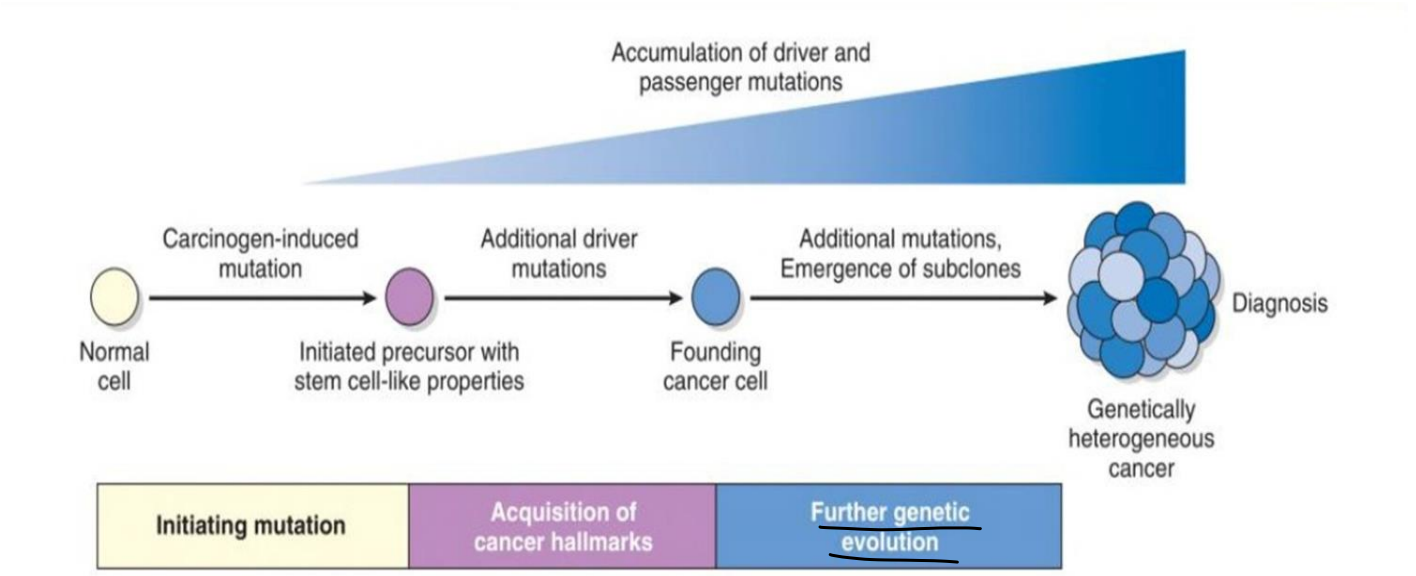


Fig. 6.16 Development of cancer through stepwise accumulation of complementary driver mutations. The order in which various driver mutations occur is usually unknown and may vary from tumor to tumor.

Hallmarks of Cancer

- All cancers appear to display eight fundamental changes in cell physiology and two enabling factors (genomic instability and tumor-promoting inflammation) that promote cellular transformation and subsequent tumor progression.

1. Self-sufficiency in growth signals
2. Insensitivity to growth-inhibitory signals
3. Altered cellular metabolism
4. Evasion of apoptosis
5. Limitless replicative potential (Immortality)
6. Sustained angiogenesis
7. Ability to invade & metastasize
8. Evasion of immune surveillance

سنتحدث عنهم بالتفصيل لاحقًا

1. Self-sufficiency in growth signals

* يحدث (mutation) متسبب الخلية لا تتوقع (GF) ← mutation ← Gain function

- Gain of function mutation in Genes coding for growth: Classified by the site of action

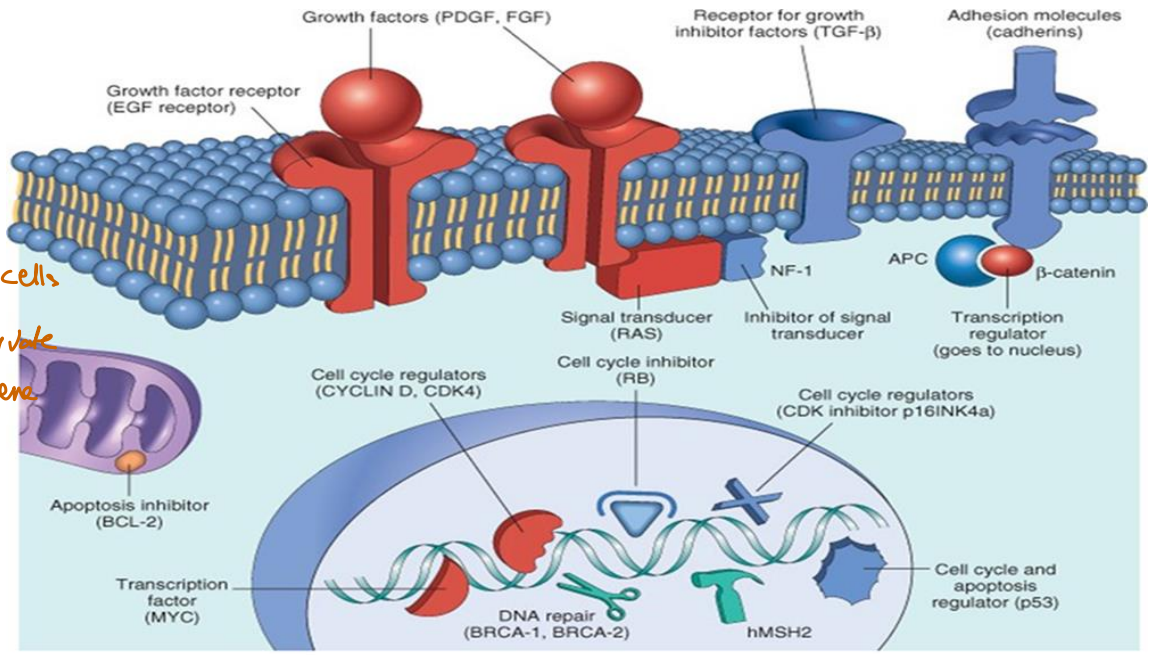
- Proto-oncogenes: Normal.
- Oncogenes: Mutant/overexpressed
- oncogenes ➡ oncoproteins (promote cell growth, even without normal growth-promoting Signals).
- They include genes coding:

1. Growth factors
2. Cell surface receptors

} active receptor

3. Signal transduction proteins } send signals inside the cells
4. Nuclear transcription factors } occurs in the nucleus & activate transcription of the gene
5. Cell cycle proteins → excepretion of protein
6. Inhibitors of apoptosis

over excepretion of proto-oncogene → inhibit apoptosis



cancer cells can synthesize their own growth factors Autocrine
or activate other normal cells to synthesize growth factor paracrine

1- Oncogenes coding Growth Factors

- Some cancers acquire the ability to synthesize the same growth factors (GF) to which they are responsive (autocrine) or send signals to activate normal cells in the supporting stroma to synthesize the same GF to which they are responsive (paracrine).
  - Platelet-derived growth factor (PDGF) seen in glioblastomas → malignant tumor in the brain
  - Transforming Growth Factor (TGF- α) in sarcomas
- Products of other oncogenes (e.g. RAS) may cause overexpression of GF.

* طريقة اخرى كبيرة جدا ال GF في malignant cells هي حدوث mutations في receptors الذي يرتبط بـ (GF)
overexpression for receptors

2- Oncogenes coding Growth Factor Receptors

- **Many of the growth factor receptors function as oncoproteins when they:**

- Mutant receptor ⟹ continuous signals even in the absence of GF…

Or Normal but overexpressed ⟹ hypersensitive to GF…

- Epidermal GF receptor family:

ERBB1 overexpressed in sq. CA lung

ERBB2 (Her2) amplified in breast Ca → GF receptor on cell membrain → we use hormonal therapy to inhibition of (Her 2)

- Increase = POOR PROGNOSIS

* قد تكون المشكلة في الخطوة (3) اي في الجينات المسؤولة عن ال transduction

3- Oncogenes in signal transduction

- The signals are transmitted to the nucleus through various signal transduction molecules.

- Two important oncoproteins in the category of signaling molecules:

1. RAS

2.ABL

* الـ(RAS) في الحالة الطبيعية يكون مرتبط بـ(GDP) فيكون (Inactive) فيحتاج إلى تنشيط لتحويله إلى active عن طريق ارتباطه بـ(GTP) ← مما يجعل الخلية تدخل عليه (proliferation)

1. RAS

- RAS proteins **are inactive when bound to GDP**
- Stimulation of cells by growth factors: exchange of GDP for GTP and generate active RAS.
- Intrinsic guanosine triphosphatase (GTPase) of RAS hydrolyzes GTP to GDP, releasing a phosphate group and returning RAS to its quiescent GDP-bound state.
- The GTPase (يحول الـ(RAS) الـ Inactive) protein is magnified dramatically by a family of GTPase-activating proteins (GAPs).

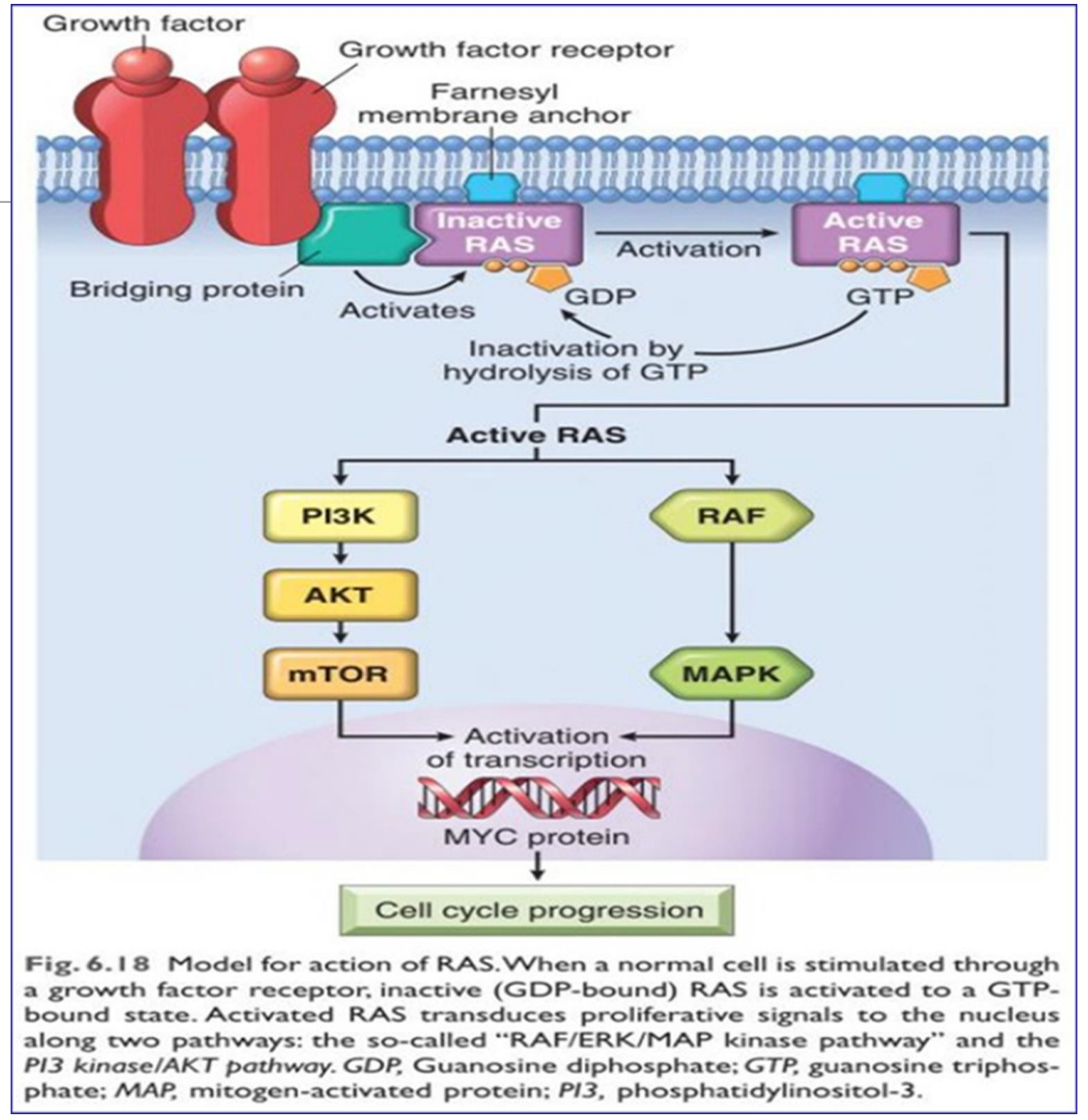


Fig. 6.18 Model for action of RAS. When a normal cell is stimulated through a growth factor receptor, inactive (GDP-bound) RAS is activated to a GTP-bound state. Activated RAS transduces proliferative signals to the nucleus along two pathways: the so-called "RAF/ERK/MAP kinase pathway" and the *PI3 kinase/AKT pathway*. *GDP*, Guanosine diphosphate; *GTP*, guanosine triphosphate; *MAP*, mitogen-activated protein; *PI3*, phosphatidylinositol-3.

- Active RAS → Signal transduction (RAF/MAP-K or PI3-K/AKT pathways) → transcription activation

- RAS most commonly is activated by point mutations in amino acid residues that are either within the GTP binding pocket or in the enzymatic region that carries out GTP hydrolysis

-Activated RAS stimulates downstream regulators of proliferation by several interconnected pathways.

RAS

- Commonest oncogene mutation in human tumors.

- Point mutations in codons 12, 13 are present in 30% of cancers, especially CA pancreas & Colon.

translocation يتجه (over activation) يحدث له
in philadelphia chromosome

فقط المخطوط

2. ABL: present in cytoplasm

- Non-receptor tyrosine kinase function as signal transduction molecule
- The ABL proto- oncogene has tyrosine kinase activity dampened by internal negative regulatory domain

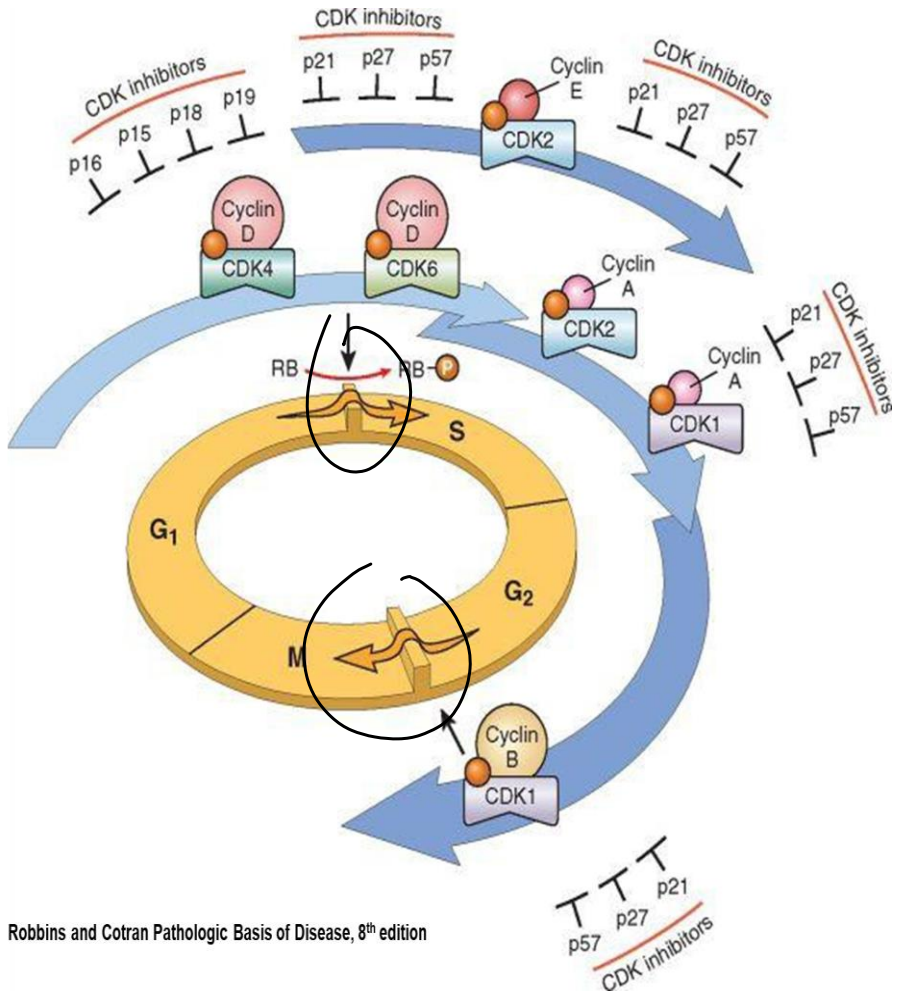
- Chronic myeloid leukemia: t(9;22) → BCR ABL hybrid gene
- This new gene protein is retained in the cytoplasm where it has tyrosine kinase activity activates all of the signals downstream of RAS → cell proliferation

4- Nuclear Transcription Factors:

- DNA transcription regulated by genes e.g. MYC, JUN,….etc. that regulate the expression of growth-promoting genes, such as cyclins → initiation of cell cycle
- MYC mutation ⇒ sustained activation
- Examples:
  - Dysregulation of *MYC* in Burkitt lymphoma

5- Cyclins & Cyclin Dependent – Kinases regulate cell cycle phases

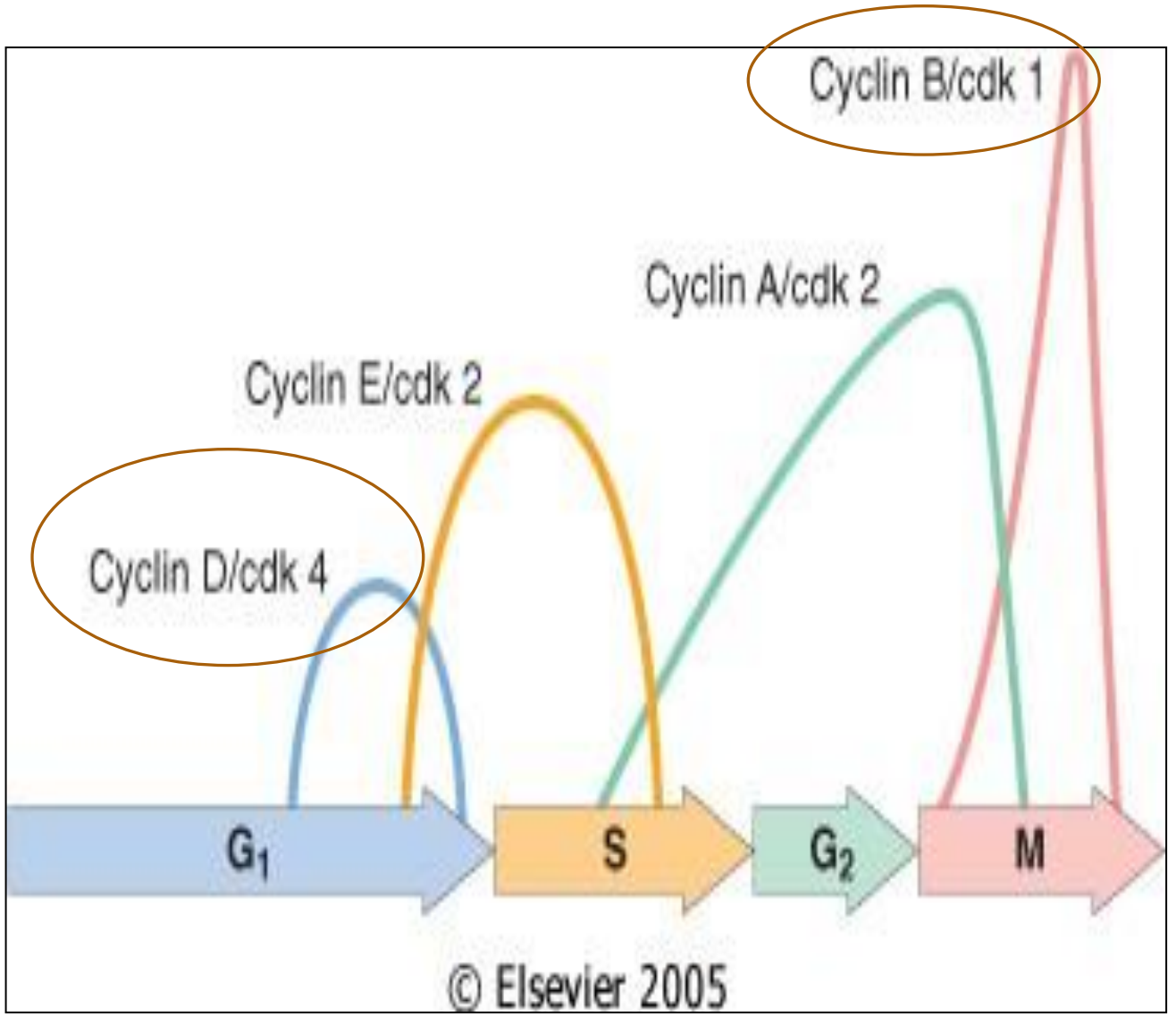
- Family of proteins that control entry of the cells at specific phases of cell cycle (D, E, A, B….etc.)
- Level of a specific cyclin increases at a specific phase, then decreases rapidly after the cell departs that phase
- Function by **phosphorylating certain proteins (e.g. RB protein)**
- Cyclins bind to CDKs, activating them



Robbins and Cotran Pathologic Basis of Disease, 8th edition

Two important checkpoints, each of which is tightly regulated by a balance of growth-promoting and growth-suppressing factors, as well as by sensors of DNA damage:

- **G1 - S phase checkpoint:**
Cyclin D family---CDK4 & CDK6
- **G2 - M transition:** Cyclin B-CDK1



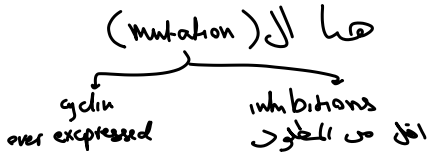
- CDK inhibitors regulate the activity of CDK/ Cyclin.

- Selective or nonselective inhibition.

- Examples: p21, p27 & p57 inhibit all CDKs while INK4 Inhibitors (p15, p16, p18 & p19) inhibit CDK4 & CDK6.

selective

- The tumor suppressor protein p53 controls expression of p21.



Mutations that dysregulate activity of cyclins & CDKs → Gain-of-function mutations and cell proliferation:

e.g.: Cyclin D is overexpressed in breast

Loss-of-function mutations involving CDKIs → cell proliferation:

- Disabling mutations of CDKN2A (encoding p16): germline (in melanoma)
- Acquired deletion or inactivation of *CDKN2A* is seen in pancreatic carcinomas

A final consideration :

- The increased production of oncoproteins does not by itself lead to a sustained proliferation of cancer cells.

- There are two built-in mechanisms, **cell senescence and apoptosis**, that oppose oncogene-mediated cell growth.

- Therefore, genes that regulate these two braking mechanisms must be disabled to allow the action of oncogenes to proceed unopposed.

2.Insensitivity to growth-inhibitory signals

tumor suppressor gene لا يستجيبوا إلى

- **Disruption in Cancer Suppressor Genes**

tumor suppressor gene أمثلة

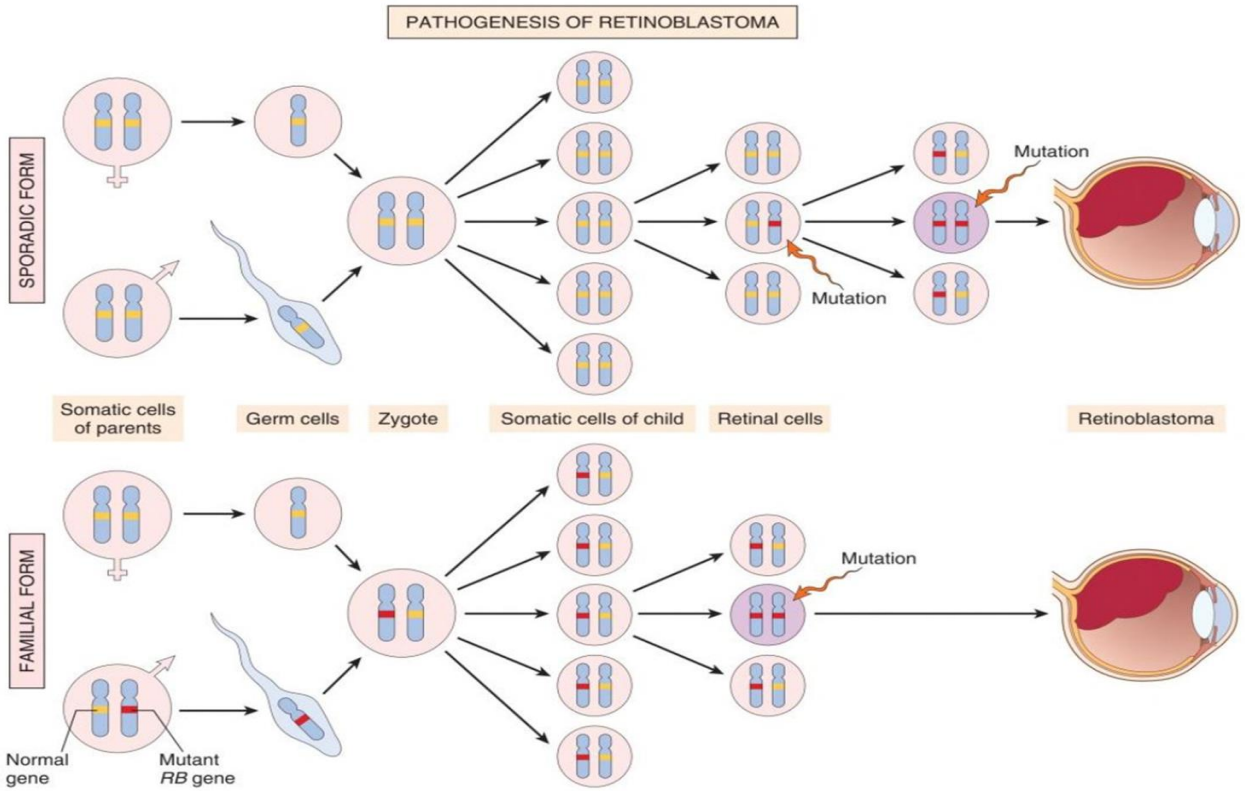
- Growth inhibitory pathway by:

1. **RB gene**: Regulate cell cycle
2. **TP53 gene**: Regulate cycle & apoptosis
3. **TGF- β:** Block GF signals
4. **APC gene**: regulates β –catenin

1- *RB* gene (Governor of cell cycle):

- The first tumor **suppressor** gene to be discovered
- First studied in Retinoblastoma
- *RB* gene ⟹ RB protein
- Both copies of the gene must be lost for neoplastic transformation to occur
- This is called loss of heterozygosity
- Familial (*RB* ⇨ *RB*) or
  - here we have one inherited defected copy and the other copy defected by a carcinogen
- Sporadic (*RB* ⇨ *RB* ⇨ *RB*)
  - here there is a carcinogen defect one copy and after that other carcinogen affect the other copy

* لازم يكون السحتين من الجين defected سواء كان familial او sporadic لـ tumor suppressor gene لانه عمل اي



Mode of action of *RB* gene:

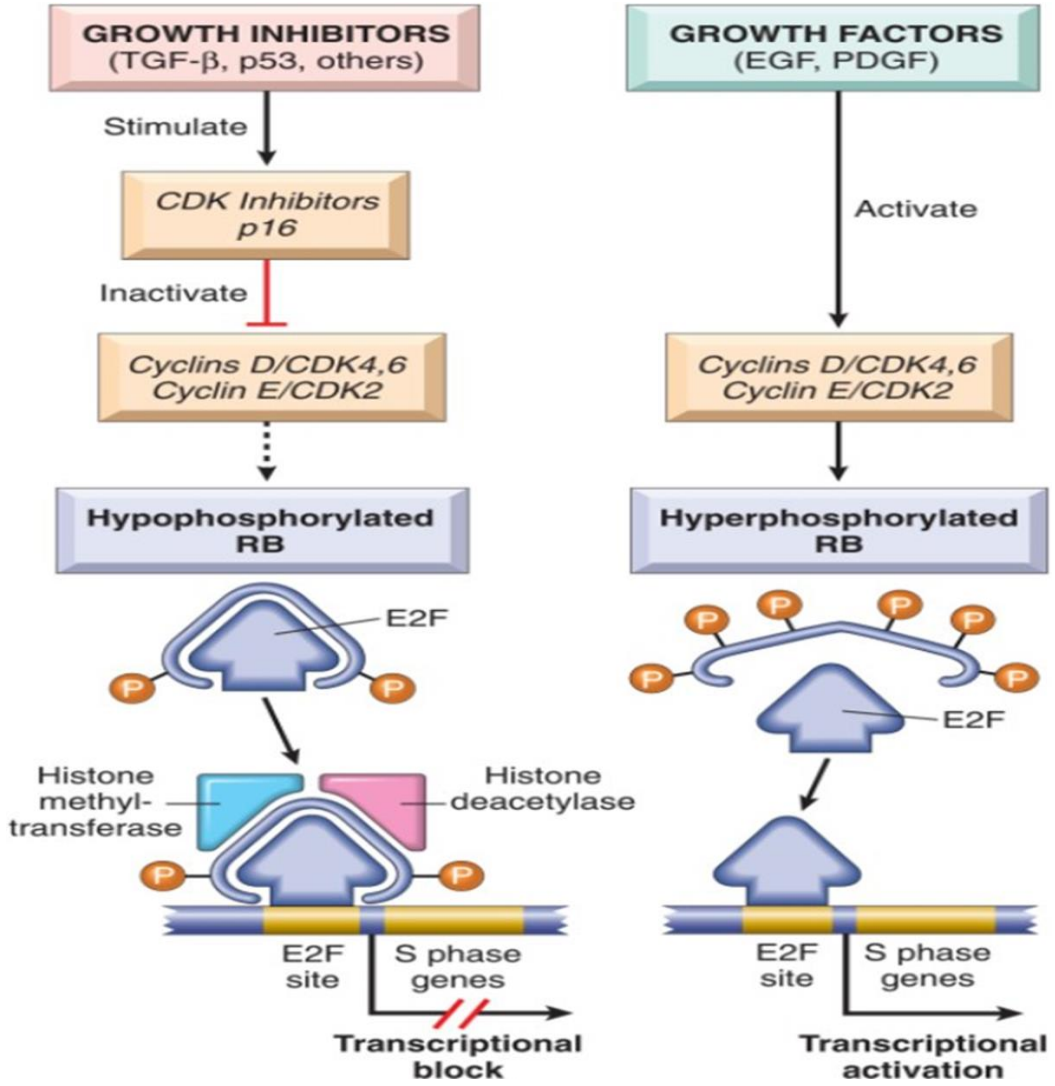
- **The function of the RB protein is to regulate the G1/S checkpoint**, the portal through which cells must pass before DNA replication commences.

- G1 – S transition and DNA replication require the activity of cyclin E/CDK2

- Cyclin E is dependent on the E2F family of transcription factors

- **Active hypophosphorylated RB** binds to & inhibits the E2F family of transcription factors --- NO TRANSCRIPTION of cyclin E

Growth factor signaling leads to cyclin D expression and activation of cyclin D- CDK4/6 complexes, which ⟹ phosphorylate RB, inactivating the protein and releasing E2F ⟹ induce target genes such as cyclin E. TRANSCRIPTION (G1 -- S phase)



Retinoblastoma:

- Sporadic in 60% of cases
- Familial (40%), AD
- In familial form, patients carry one mutation in their genome, followed by a second mutation in retinal cells
- No tumor develops unless two alleles in chr. 13 become mutant (two hit theory)
- Familial form: ↑ incidence of bilateral ret., osteosarcoma, and other tumors

2- TP53 (Guardian of Genome)

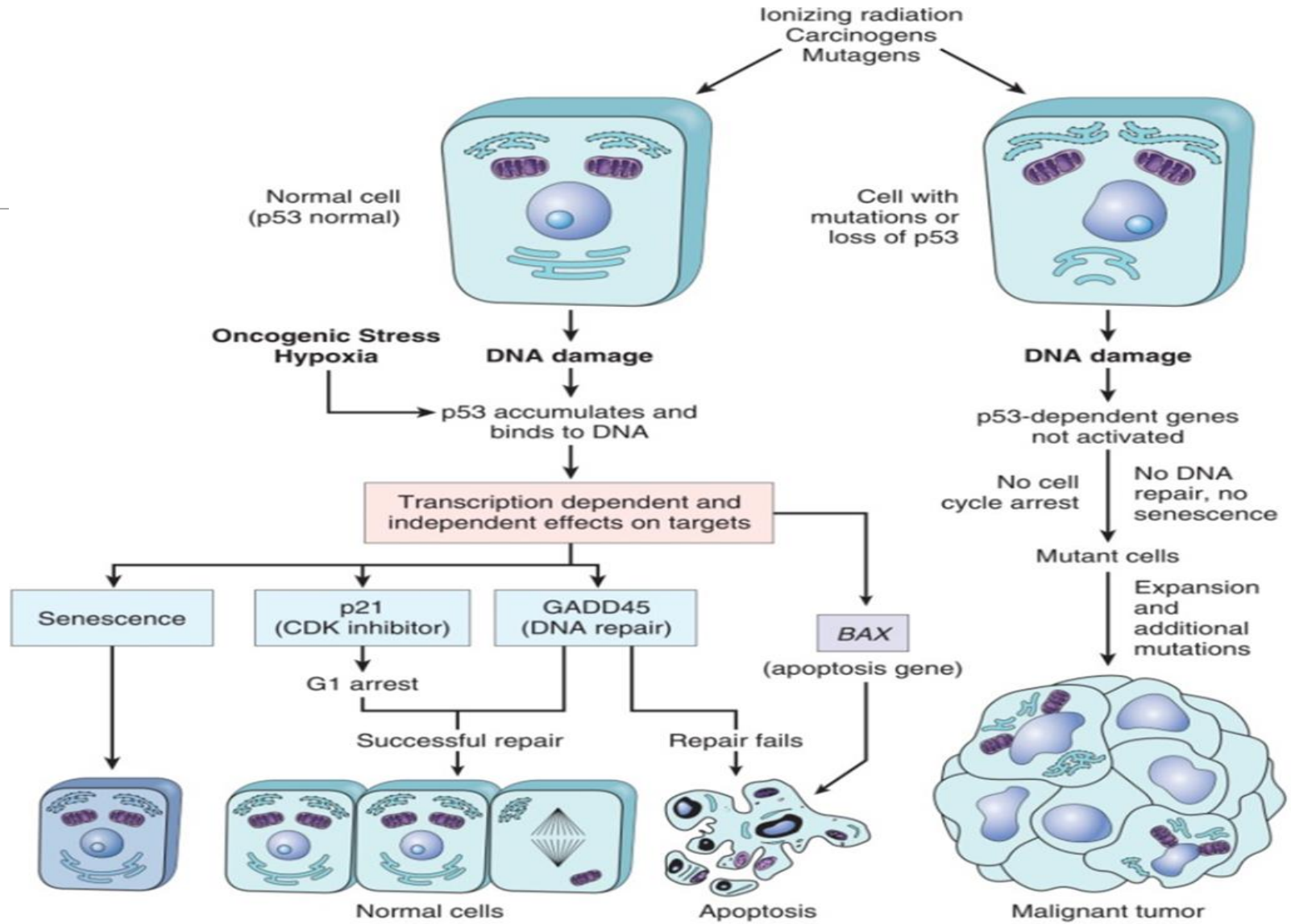
- **The most commonly mutated gene (and suppressor gene) in human cancer.**
- Homozygous loss in 70% of cancers
- *TP53* is a negative regulator of the cell cycle (protein product is p53).
- 'Guardian of the Genome' OR (Policeman) preventing genetically damaged cells from progressing through a new cycle.
- p53 is inactivated by MDM2.
- Upon DNA damage or other stresses, various pathways will dissociate the p53 and MDM2 complex.

Mode of activation & action:

- p53 senses DNA damage or other stresses through various sensors, like protein kinases e.g. ATM protein
- p53 released from MDM2 & activated with longer half-life →
  - Transcription of CDKI gene (p21) → cell cycle arrest at G1 (Quiescence) ---Result: more time for repair --- Normal

OR

- If repair fails ----Senescence (permanent cell cycle arrest) or Apoptosis (p53 is a positive regulator of apoptosis)
- **OR** *Fixed mutation* --- ***NEOPLASIA***


Ionizing radiation
Carcinogens
Mutagens
Normal cell
(p53 normal)
Cell with
mutations or
loss of p53
Oncogenic Stress
Hypoxia
DNA damage
DNA damage
p53 accumulates and
binds to DNA
p53-dependent genes
not activated
No cell
cycle arrest
No DNA
repair, no
senescence
Transcription dependent and
independent effects on targets
Mutant cells
Expansion
and
additional
mutations
Senescence
p21
(CDK inhibitor)
GADD45
(DNA repair)
BAX
(apoptosis gene)
G1 arrest
Successful repair
Repair fails
Normal cells
Apoptosis
Malignant tumor

❑ Significance of TP53 mutation:

- Acquired mutation in many cancers

  e.g. colon, lung, …etc

- Inherited mutation in one allele---

  Li-Fraumeni syndrome – 25-fold ---malignancy: sarcoma, breast carcinoma….. etc

متلازمة اشخاصها يورثوا defected (p53)

3- Transforming Growth Factor-β (TGF-B):

A potent inhibitor of proliferation (Antiproliferative activity): -

Act by binding to a complex composed of TGF-β receptors I and II, resulting in the transcriptional activation of **CDKIs** with growth-suppressing activity and **repression** of growth-promoting genes.

- Mutations may alter the **type II TGF-β receptor.**

-Mutational inactivation of TGF-β components seen in a very high percent of pancreatic carcinoma

4- Contact Inhibition, APC:

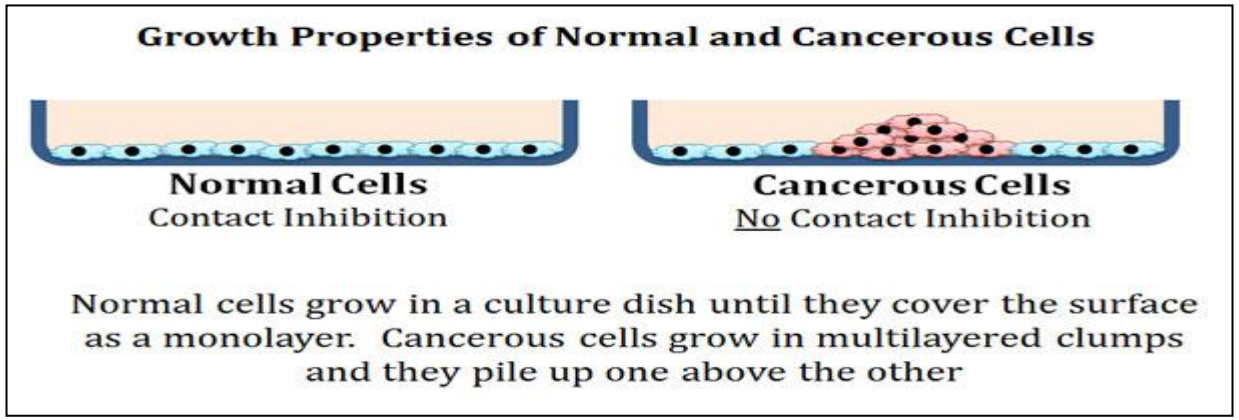
- Cell–cell contacts in many tissues are mediated by homodimeric interactions between transmembrane proteins called **cadherins**.
  - **E-cadherin** (E for epithelial) mediates cell–cell contact in epithelial layers.

- **Contact inhibition** enables noncancerous cells to cease proliferation and growth when they form confluent monolayers and **contact** each other.

- **Two mechanisms have been proposed to explain how E-cadherin maintains contact inhibition:**

1-Tumor suppressor gene *NF2*

2- **APC** gene and **B catenin** (a key component of the **WNT signaling pathway**).



-This characteristic is lost when cells undergo malignant transformation, leading to uncontrolled proliferation and solid tumor formation.

By:

-E-cadherins are reduced in many cancers. ← اي ان في حاله السرطانات لا يكون هناك اي اعتبار لمساحه المكان الموجوده للتكاثر في الخلايا

- Mutant APC. → Continuous proliferation for the cell cycle

لا يعمل

ACTION OF APC GENE:

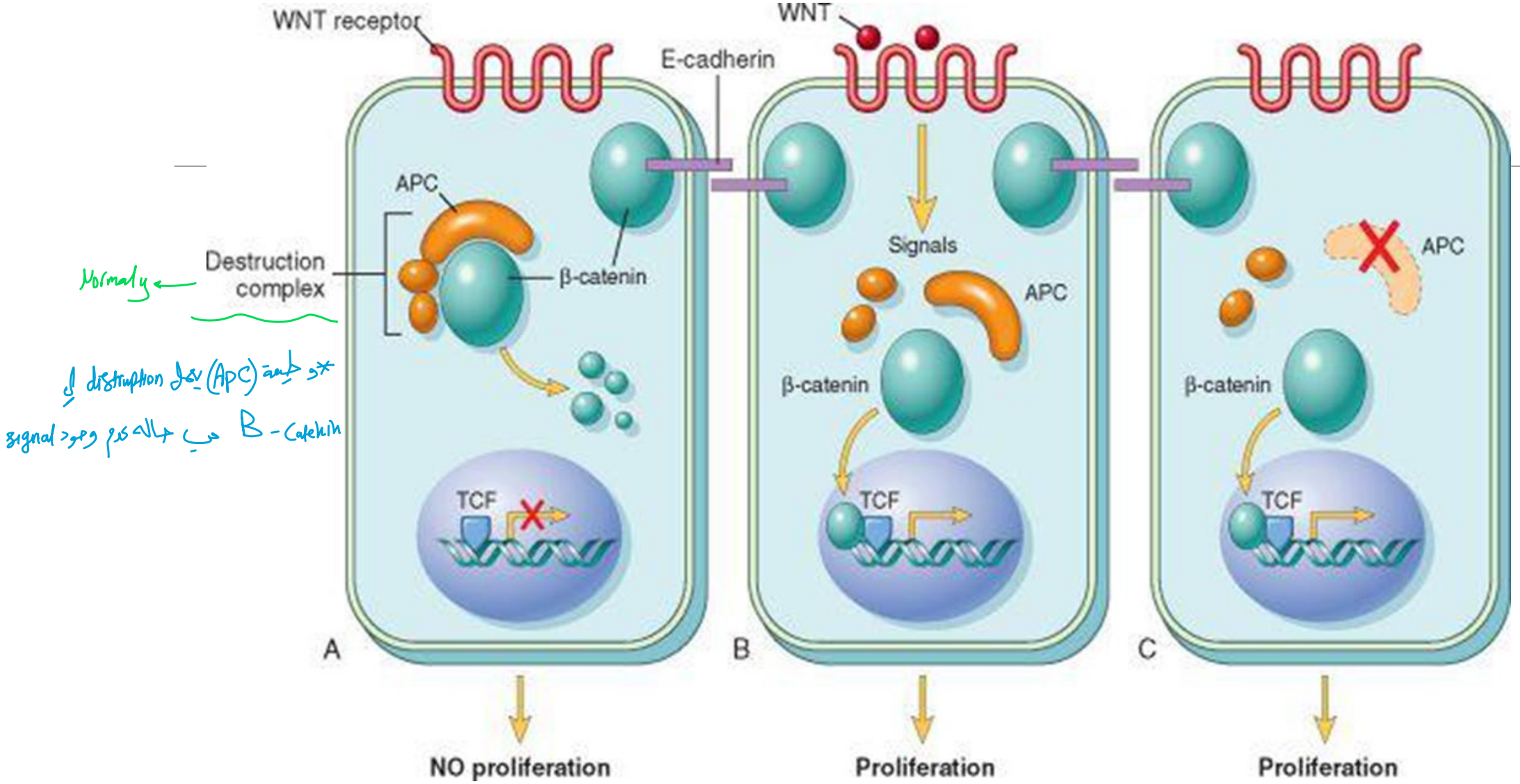
- Gene product is a cytoplasmic protein that acts in adhesion by regulating the destruction of **β-catenin** in the cytoplasm.

- In quiescent cells that have not been exposed to WNT, cytoplasmic β-catenin is degraded by a *destruction complex, so no proliferation of cells occur.*

E-Cadherin+ APC + β-catenin → **Destruction Complex**

- With the loss of APC (in malignant cells), β-catenin degradation is prevented, and the WNT signaling response is inappropriately activated in the absence of

WNT ⟶ transcription of growth-promoting genes as well as transcriptional regulators that repress E-cadherin expression and thus reduce contact inhibition and proliferation.



Normaly ←

* طبيعة الـ distruption بيكون (APC) في حالة عدم وجود signal في حالة B-Catenin

Clinical significance of APC

Familial Adenomatous Polyposis Coli (FAP)

- AD syndrome.
-Individuals with inherited one mutant allele of APC develop 100s to 1000s of adenomatous polyps by their teens or twenties.

-Additional mutations → colonic carcinoma (100% ↑↑ risk).

-70-80% of sporadic colonic carcinoma show mutant APC.

-Colonic cancers with normal APC have activating mutations of **β-catenin.**