جامعة الملك سعود
King Saud University

pathology
MED 439

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Carcinogenesis

Objectives:-
No objectives

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Color Index:
Slides
Important
Male's slides only
Female's slides only
Notes
Extra information

Carcinogenesis

- It is a multistep process at both the phenotypic and the genetic levels.
- single cell which has the genetic damage undergoes neoplastic proliferation (clonal expansion) forming the tumor mass.

Genetic damage
(Leads to mutation)

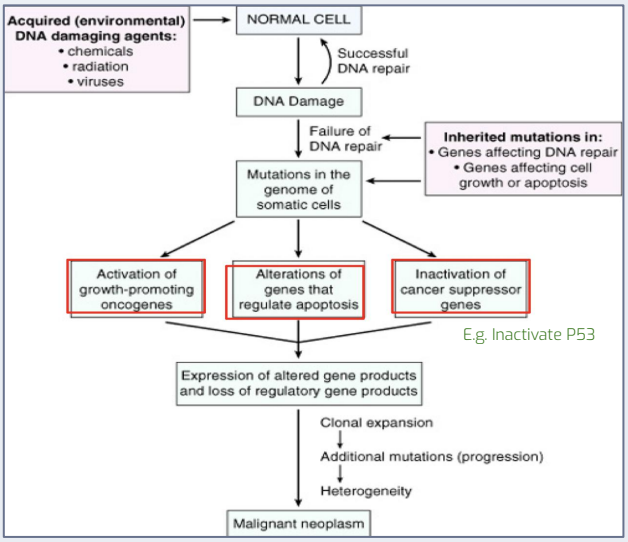
causes:

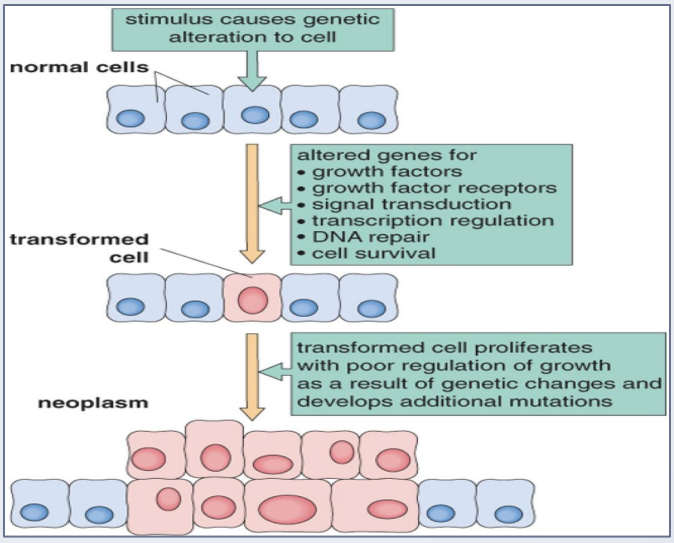
- **Environmental:** Chemical, Radiation, infectious
- **Inherited**

Targets:
(Four regulatory genes)

- **Growth promoting Protooncogenes:**
- **Growth inhibiting (suppressors) genes**
- **Genes regulating apoptosis**
- **DNA repair genes**

Protooncogene → mutation → oncogene.





Main changes in the cell physiology that lead to formation of the malignant phenotype: (each point will be explained in details)

- **A- Self-sufficiency in growth signals**
- **B- Insensitivity to growth-inhibitory signals**
- **C- Evasion of apoptosis**
- **D- Limitless replicative potential**
- **E- Sustained angiogenesis**
- **F- Ability to invade and metastsize**

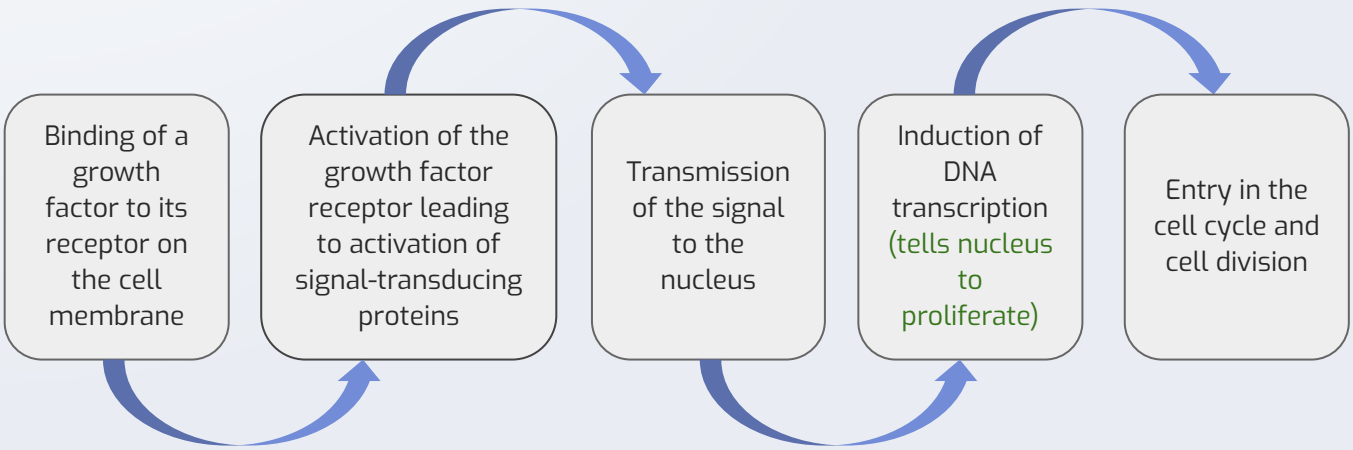
Main changes in the cell physiology that lead to formation of the malignant phenotype:

A- Self-sufficiency in growth signals

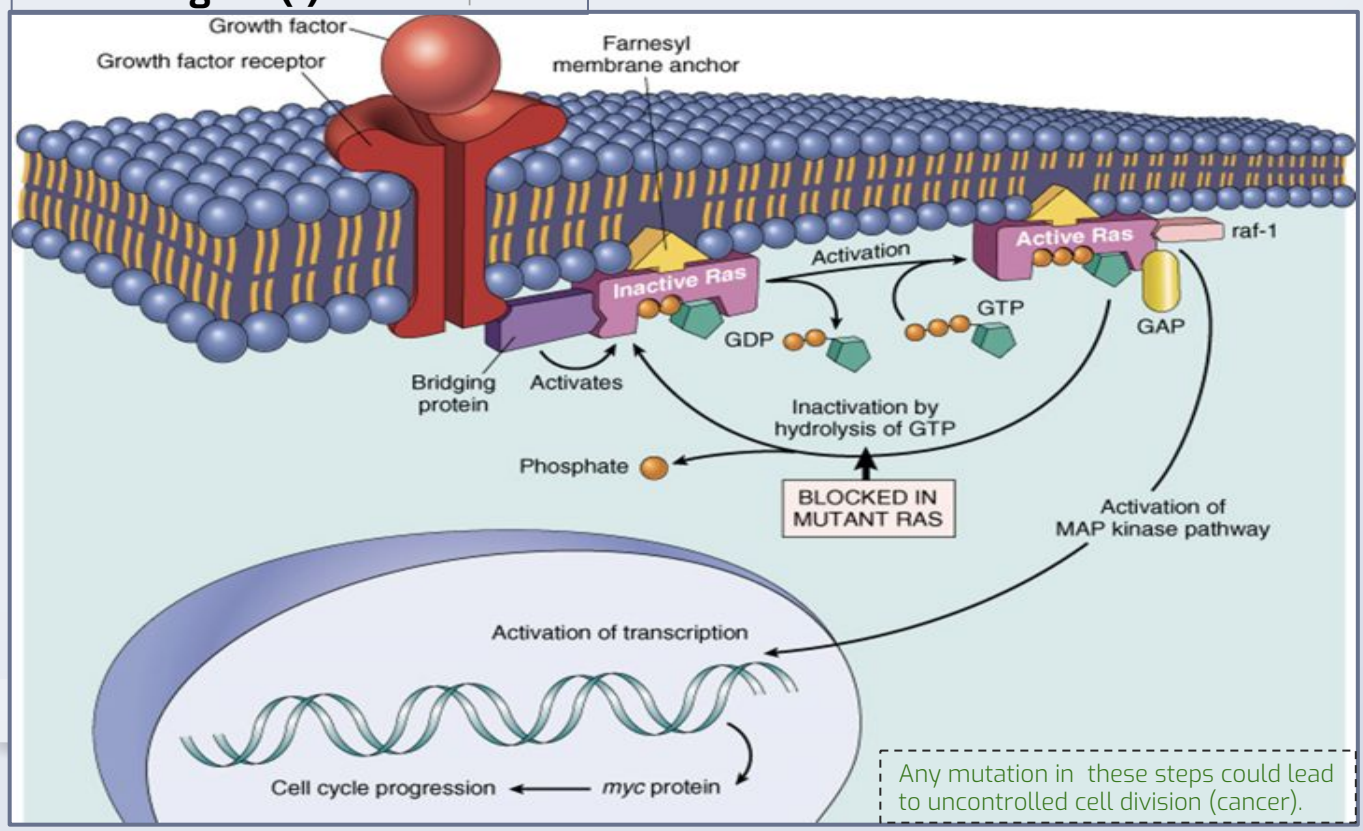
✳ **Oncogene**: *Gene that promote autonomous cell growth in cancer cells* (causes cancer).

- Derived by mutations in protooncogenes.
- Characterized by the ability to promote cell growth in the absence of normal growth-promoting signals.
- **Oncoproteins**: The products.

✳ **CELL CYCLE:**



reference **Figure (1)** Extra & Helpful



Any mutation in these steps could lead to uncontrolled cell division (cancer).

How do cancer cells acquire self-sufficiency in growth signals?

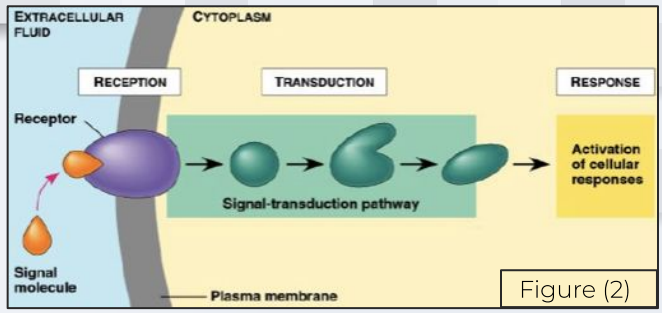


Figure (2)

1- Growth factors (binds to the receptor):

- Cancer cells are capable to synthesize the same growth factors to which they are responsive, E.g:
  - Sarcomas → TGF-a
  - Glioblastoma → PDGF

2-Growth factors receptors:

- Mutation:
  - continuous signals to cells and uncontrolled growth.
- Overexpression:
  - cells become very sensitive thus becoming hyperresponsive to normal levels of growth factors
- Eg : Epidermal Growth Factor (EGF) Receptor family:
  - **HER2** :
    - Amplified in breast cancers and other tumors.
    - High levels of HER2 in **breast cancer** indicate poor prognosis
    - Anti- HER2 antibodies are used in treatment.

HER2: tells the nucleus to make more cells (proliferate) which leads to breast cancer. It can be tested to detect others types of cancer.

3- Signal-transducing proteins (in the cytoplasm):

- They receive signals from activated growth factors receptors and transmits them to the nucleus. E.g :

1

- RAS (Female: not important):
- 30% of all human tumors contain mutated RAS gene.
  E.g. colon, Pancreas cancers
- Mutations of the RAS gene is the most common oncogene abnormality in human tumors
- Mutations in RAS → cells continue to proliferate

*Figure (1)

2

- ABL gene
  - ABL proto-oncogene has a tyrosine kinase activity
  - ts activity is controlled by negative regulatory mechanism
  - E.g. chronic myeloid leukemia (CML) :
    - t(9,22)→ABL gene transferred from ch. 9 to ch. 22
    - Fusion with BCR→BCR-ABL
    - BCR-ABL has tyrosine kinase activity (oncogene).

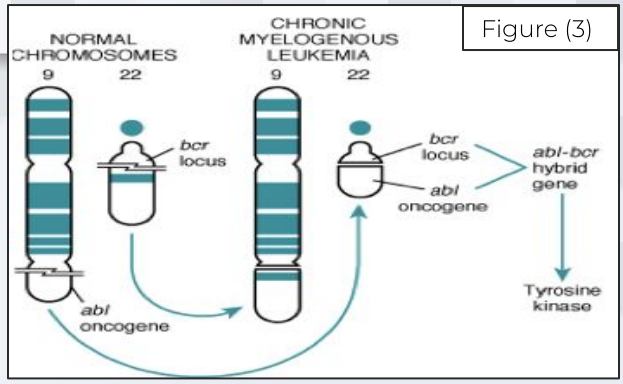
*Figure (3) in the next slide...

cont.

...ABL Gene

(not important)
CML patients are treated with (Gleevec) which is inhibitor (intracellular) of ABL kinase

Figure (3)



4- Nuclear transcription factors :

Figure (1)

- Mutations may affect genes that regulate transcription of DNA → growth autonomy
  - E.g. MYC **(in the nucleus)**: (it increase when the cell want to divide and decrease when the cell cycle starts)
    - MYC proto-oncogene produce MYC protein when cell receives growth signals.
    - MYC protein binds to DNA leading to activation of growth-related genes.
- Normally, MYC decrease when cell cycle begins but in tumors there is sustained expression of MYC → continuous proliferation
  - E.g. Burkitt Lymphoma; MYC is dysregulated due to t(8,14).

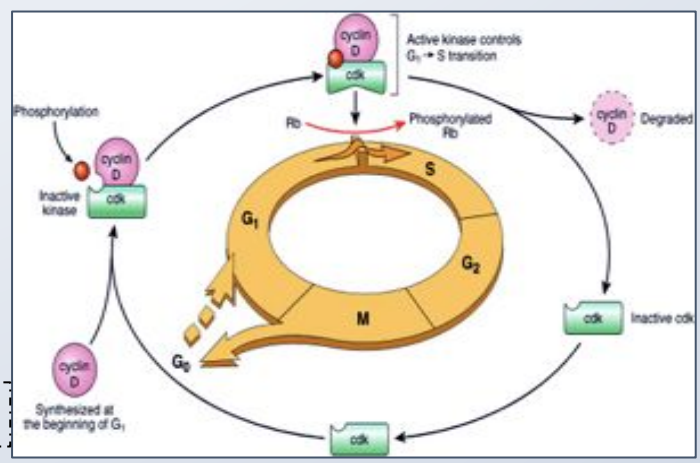
5- Cyclins and cyclins- dependent kinases (CDKs):

Just know what's underlined here

- <u>Progression of cells through cell cycles is regulated by CDKs after they are activated by binding with cyclins.</u>

- <u>Mutations that dysregulate cyclins and CDKs will lead to cell proliferation</u> E.g.
  - Cyclin D genes are overexpressed in breast, esophagus and liver cancers.
  - CDK4 is amplified in melanoma and sarcomas.

Remember:
the gene (MYC) is associated with Burkitt lymphoma (aggressive) and t(8,14)



Every action is controlled by a gene

Main changes in the cell physiology that lead to formation of the malignant phenotype:

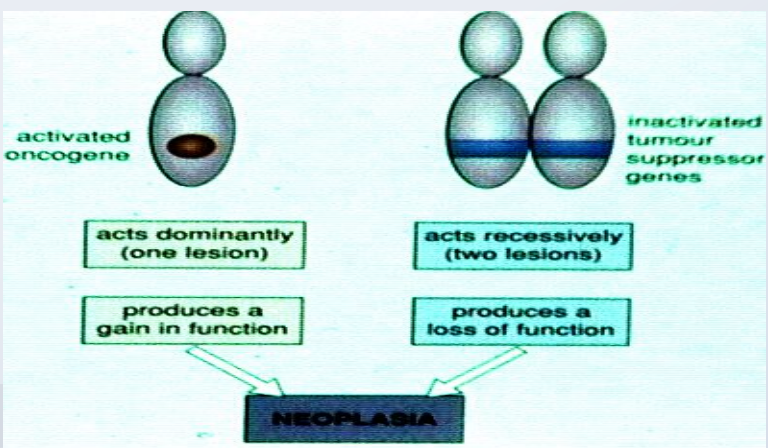
B- Insensitivity to growth-inhibitory signals:

* Tumor suppressor genes control (apply brakes) cells proliferation

If mutation caused disruption to them → cell becomes insensitive to growth inhibition → uncontrolled proliferation.

Examples:
(Will be explained in details in the next slides)

- P53 * most popular example
- RB (retinoblastoma) gene
- APC (Adenomatous Polyposis Coli – B Catenin pathway)
- TGF-B (Transforming Growth Factor- B pathways)



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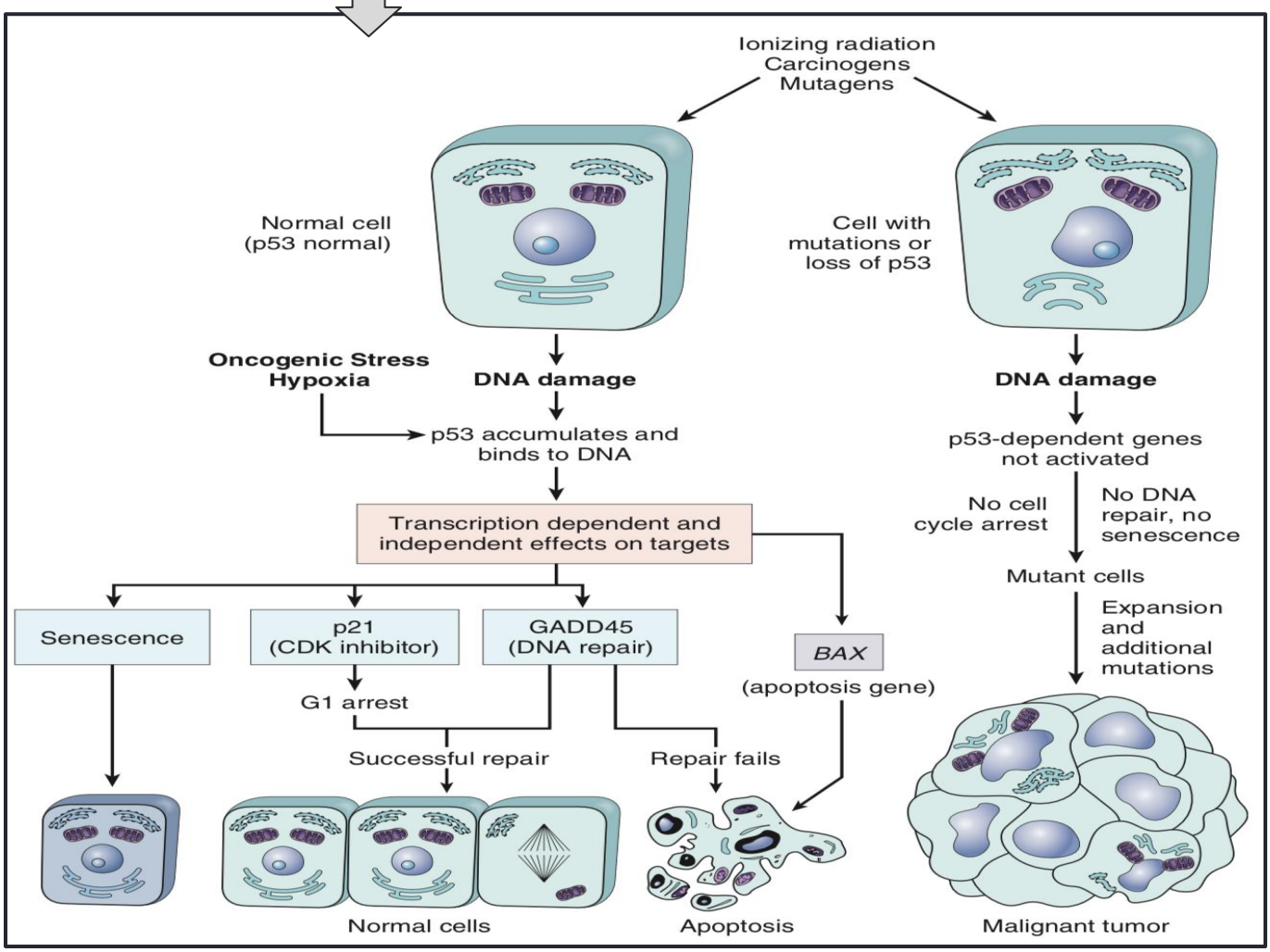
P53

- It has multiple functions Mainly:
  - Tumor suppressor gene (anti-proliferative)
  - Regulates apoptosis.

- P53 is also responsible for repair gene.
- P53 senses DNA damage.
- Causes G1 arrest to give chance for DNA repair.
- Induce DNA repair genes.
- If a cell with damaged DNA cannot be repaired, it will be directed by P53 to undergo apoptosis.
- With loss of P53, DNA damage goes unrepaired.
- Mutations will be fixed in the dividing cells, leading to malignant transformation:



- **P53 is called the "guardian of the genome".**
- 70% of human cancers have a defect in P53.
- It has been reported with almost all types of cancers : e.g. lung, colon, breast.
- In most cases, mutations are acquired, but can be inherited, e.g : Li-Fraumeni syndrome.

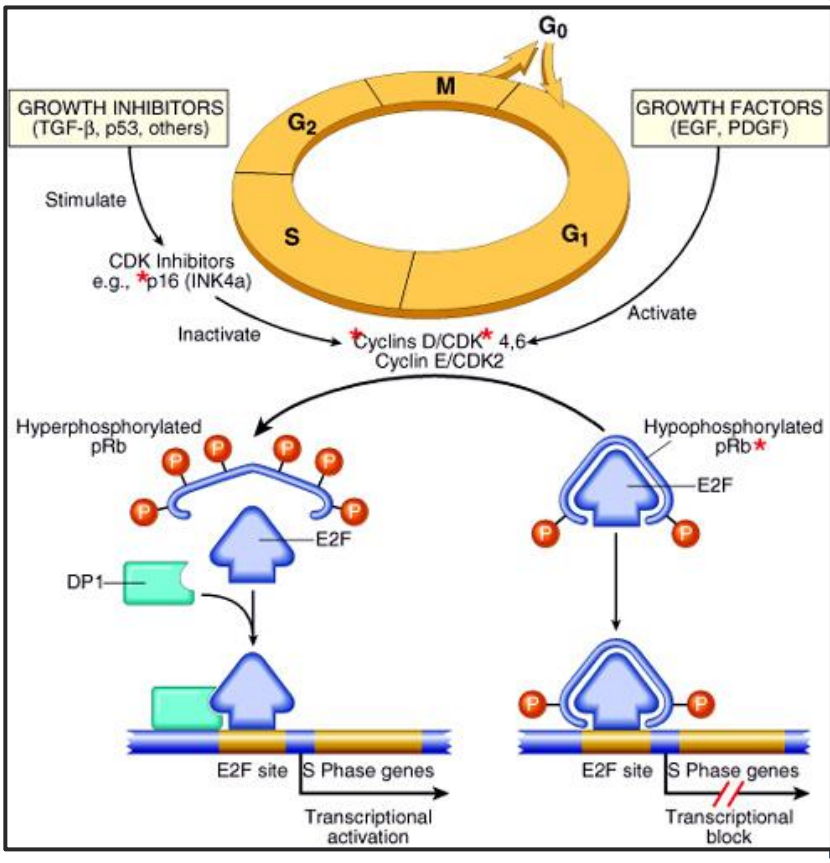
RB (*Retinoblastoma*) gene

ركزوا على الكلام، الفيقرز للتوضيح والفهم <- مفيدة.

- First tumor suppressor gene discovered.
- Discovered initially in retinoblastomas.
- Found in other tumors, e.g. breast cancer.
- DNA-binding protein located on chromosome 13.
- Exists in "active" and "inactive" forms.

* If active ⬆

→ will stop the advancing from G1 to S phase in cell cycle.

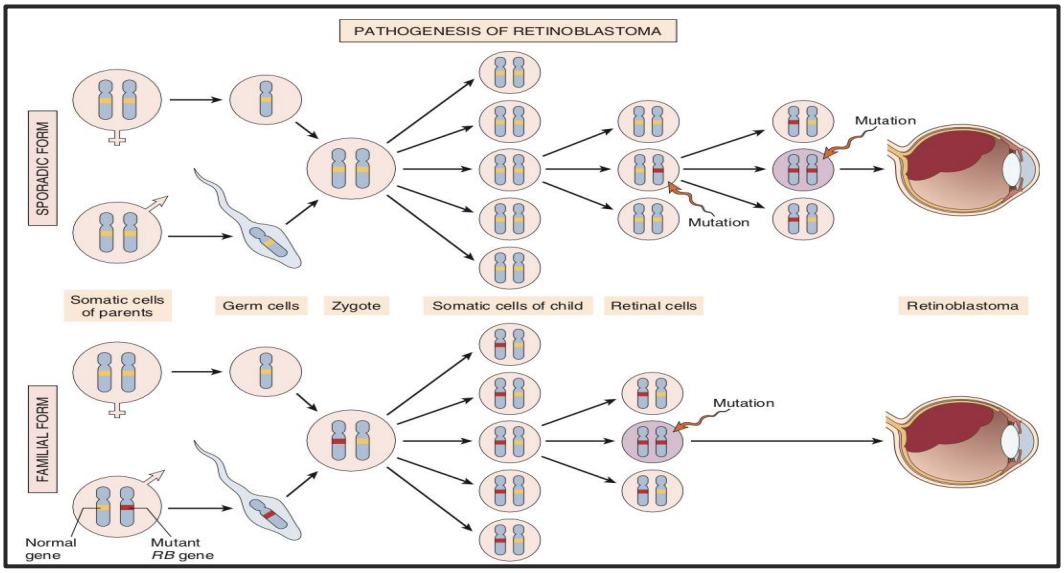


* If cell is stimulated by growth factors ⬇

→inactivation of RB gene → brake is released → *cells start cell cycle* (G1 →S→M) then RB gene is activated again.

- Retinoblastoma is an uncommon childhood tumor.
  - ➢ either sporadic (60%) or familial (40%).

- Two mutations required to produce retinoblastoma (one is not enough).
- Both normal copies of the gene should be lost to produce retinoblastoma.



APC (Adenomatous Polyposis Coli – B Catenin pathway)

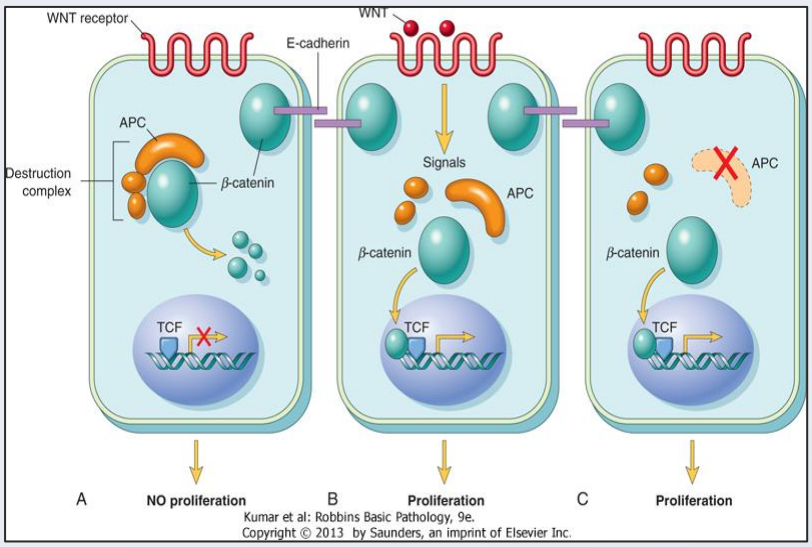
- APC is tumor suppressor gene
- APC gene loss is very common in colon cancers (just focus on this)
- It has anti-proliferative action through inhibition of b-Catenin which activate cell proliferation
- Individuals with mutant APC develop thousands of colonic polyps
- One or more of the polyps will progress to colonic carcinoma
- APC mutations are seen in 70% to 80% of sporadic colon cancers

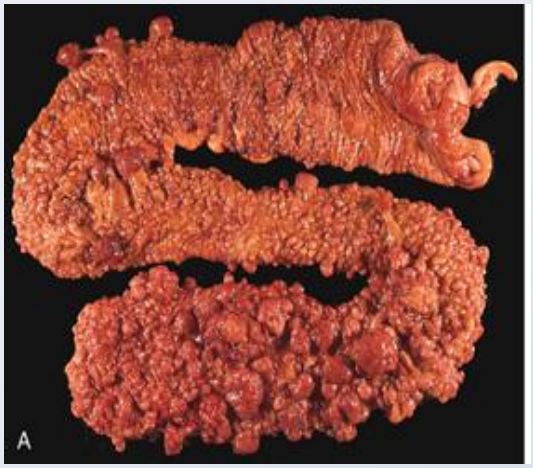
TGF-B (Transforming Growth Factor- B pathways)

- It is an inhibitor of proliferation
- It regulate RB pathway
- Inactivation of TGF-B lead to cell proliferation

Mutations in TGF-B pathway are present in:
100% of pancreatic cancers
83% of colon cancers

Female: Not important





Main changes in the cell physiology that lead to formation of the malignant phenotype:

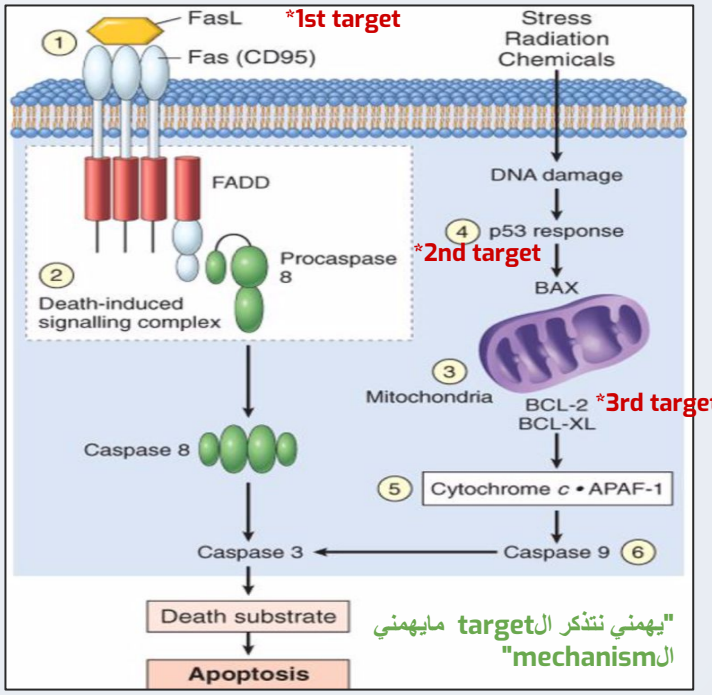
Not able to undergo *apoptosis* (programmed cell death)

C. Evasion of apoptosis

- Mutations in the genes regulating apoptosis are factors in malignant transformation.
- Cell survival is controlled by genes that promote and inhibit apoptosis.

- Reduce CD95 level inactivate death-**inducing signaling cascade** that **cleaves DNA to cause death**---> tumor cells are less susceptible to apoptosis
- DNA damage induce apoptosis (with the action of P53) can be blocked in tumors
- Loss of P53 and up-regulation of BCL2 prevent apoptosis **e.g. follicular lymphoma**

Targets of gene mutation in evasion of apoptosis :
1.CD95 2. P53 3. BCL2



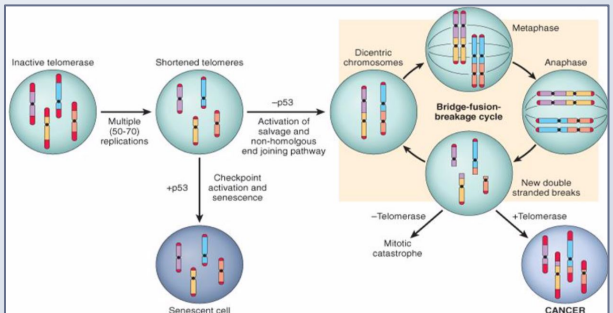
Main changes in the cell physiology that lead to formation of the malignant phenotype:

Cells of the body don't normally have the ability to divide indefinitely, in this case the cell will divide indefinitely

D. Limitless replicative potential

- Normally there is progressive shortening of <u>telomeres</u> at the ends of chromosomes
- Telomerase is *active* in normal <u>stem</u> cells but *absent* in <u>somatic</u> cells
- **In tumor cells:** activation of the enzyme telomerase, which can maintain normal telomere length

As a cell begins to become cancerous, it divides more often, and its telomeres become very short. If its telomeres get too short, the cell may die. Often times, these cells escape death by making more telomerase enzyme, which prevents the telomeres from getting even shorter



Main changes in the cell physiology that lead to formation of the malignant phenotype:

It has the ability to develop new blood vessel to get nutrients easily (Facilitate growth)

E. Sustained angiogenesis

* Neovascularization has two main effects:

1. Perfusion supplies oxygen and nutrients
2. Newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors, e.g. PDGF, IL1

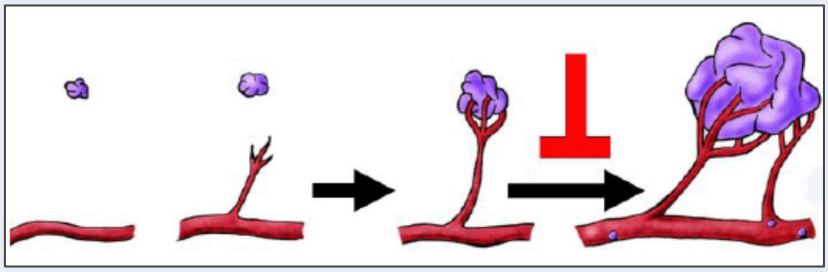
* Angiogenesis is required for metastasis
* purpose is to feed cancer

How do tumors develop a blood supply?

Female: Not important

* Tumor associated angiogenic factor (produced by the tumor)
* These factors may be produced by tumor cells or by inflammatory cells infiltrating the tumor e.g. macrophages

* **Important factors :**
- Vascular endothelial growth factor (VEGF) (Male: most important example)
- Fibroblast growth factor



as the growth increase the stimulation increase

As cancer cells divide, a tumour will develop and grow. Cancer cells have the same needs as normal cells. They need a blood supply to bring oxygen and nutrients to grow and survive. When a tumour is very small, it can easily grow, and it gets oxygen and nutrients from nearby blood vessels

Main changes in the cell physiology that lead to formation of the malignant phenotype:

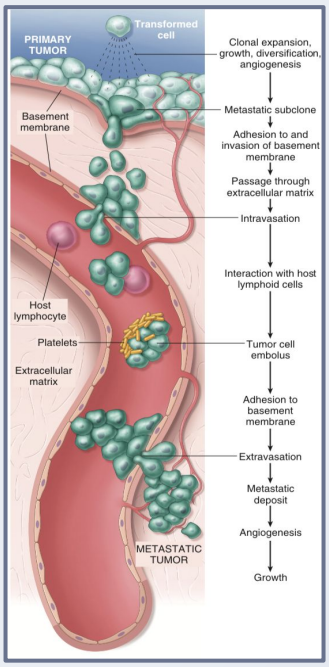
F. Ability to invade and metastasize Female Dr: Not important

Invasion and metastasis result from complex reactions involving cancer cells, stromal cells and the extracellular matrix (ECM). These metastatic cascades are subdivided into two phases

Phases of invasion and metastasis

Phase one: invasion of extracellular matrix

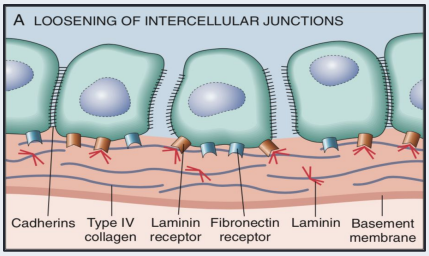
- Tumor cells must interact with ECM at several stages during this phase. They are divided into four stages



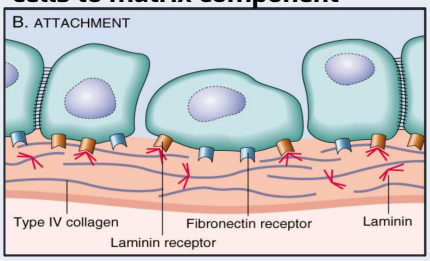
1) Malignant cells first breach the underlying basement membrane
2) Enter and traverse the interstitial tissue
3) Penetrate the vascular basement membrane
4) Gain access to the circulation

- Invasion of the ECM has four steps:

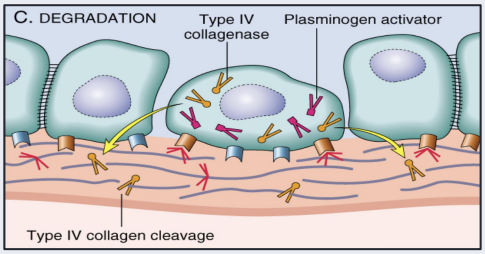
1. Detachment of tumor cells from each other



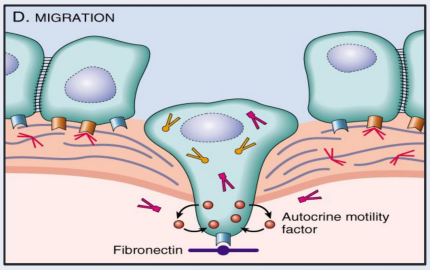
2. Attachments of tumor cells to matrix component



3. Degradation of ECM by collagenase enzyme



4. Migration of tumor cells



Phase two: vascular dissemination and homing of tumor cells

Some features of tumor cells in the circulation:

- ❑ May form emboli
- ❑ Most travel as single cells
- ❑ Adhesion to vascular endothelium
- ❑ Extravasation

Emboli are single tumor cells that adhered and accumulated with platelets

Genomic instability

Both copies of BRCA1 and BRCA2 must be inactivated for cancer to develop

- Enabler of malignancy
- Occurs as a result of defect in DNA repair genes
- Examples:

  - Hereditary nonpolyposis colon carcinoma (HNPCC)

  -Xeroderma pigmentosum

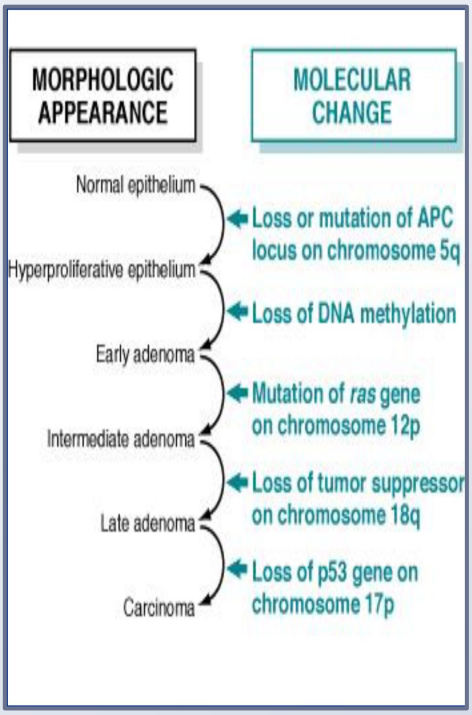
  - Familial breast cancer:

  Due to mutations in BRCA1 and BRCA2 genes. These genes regulate DNA repair and account for 80% of familial breast cancer. They are also involved in other malignancies, e.g. epithelial ovarian cancers

Molecular basis of multistep carcinogenesis

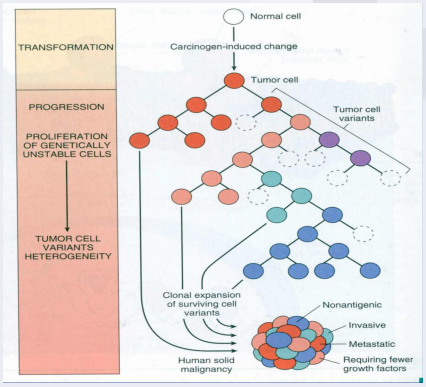
Any morphological change correspond with molecular change

- Cancer results from accumulation of multiple mutations
- All cancers have multiple genetic alterations, involving activation of several oncogenes and loss of two or more tumor suppressor genes
- One mutation does not lead to cancer
- Damage to cancer-regulating hormones will not necessarily cause malignant tumors



Tumor progression

- Many tumors become more aggressive and acquire greater malignant potential, this is called “tumor progression”
- By time, the tumor becomes clinically evident; their constituent cells are extremely *heterogeneous* (differentiated)



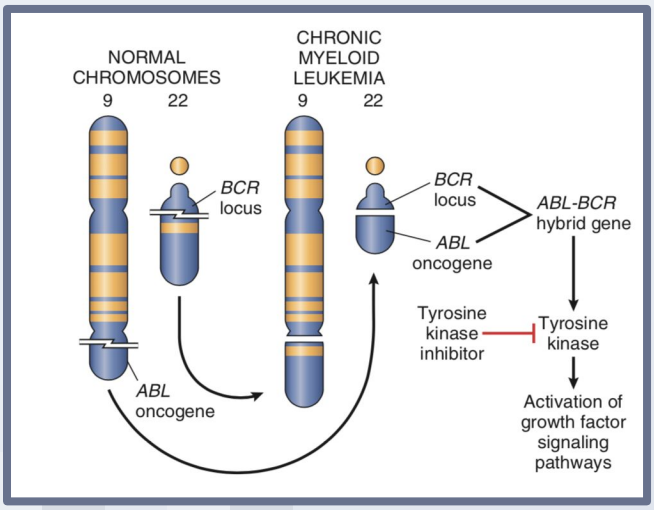
Karyotypic changes in tumor

- Translocations:
  In chronic myeloid leukemia/CML: t(9,22), occurs on the Philadelphia chromosome
  In Burkitt lymphoma: t(8,14)
  In follicular lymphoma: t(14,18)
- Deletions
- Gene amplification: Breast cancer: HER-2

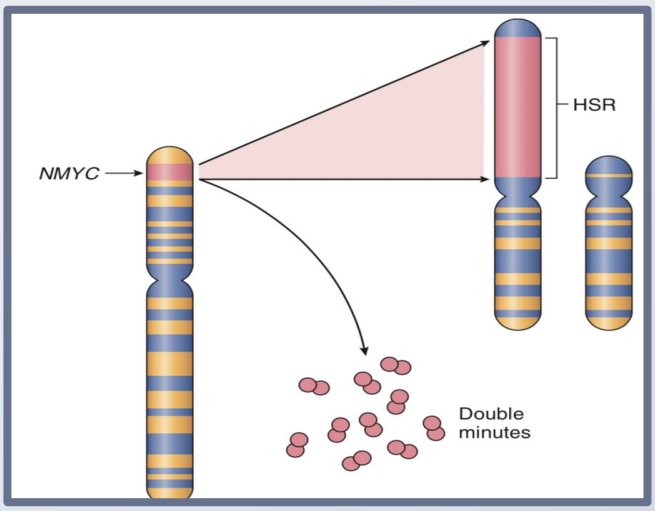
the mutated chromosome (22) is called the Philadelphia chromosome

Amplification produces several hundred copies of the gene

Translocation in CML



Gene amplification



MCQs

1- What is the gene that causes cancer?			
a- oncogene	B- suppressors genes	C- protoogene	D- P53
2- Example of epidermal growth factor receptor ?			
A- ABL	B- HER2	C-RAS	D-HER3
3- Angiogenesis is required for:			
A- Apoptosis	B- Evasion of apoptosis	C- Metastasis	D- Growth
4- Which one of these factors is a tumor associated angiogenic factor			
A-BCL2	B- CD95	C- VEGF	D- P53
5- Familial breast cancer is caused by which gene?			
A- BRKA1	B- HNPCC	C- BRCA1	D- HER-2
6- Malignant cell gain entry to the circulation by			
A- Extravasation	B- Degrading basement membrane	C- Diapedesis	D- Angiogenesis

MCQ: 1-A, 2-B, 3-C ,4-C ,5-C ,6-B

SAQs

1- What is the disease MYC involved with ?
2- How do tumors develop a blood supply?
3- How many mutations are required to produce retinoblastoma ?
4- What type of chromosomal change occurs in chronic myeloid leukemia?

SAQ:
1. burkitt lymphoma
2. Tumor associated angiogenic factor
3. Two mutations
4. Translocation

- غادة العثمان
- ماجد العسكر

- البندري العنزي
- بنان القاضي
- رغد خالد سويعد
- رغد العسيري
- روان باقادر
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- محمد السنيدي
- محمد السياري
- محمد القهيدان
- محمد الوهيبي
- مشعل الثنيان
- نايف آل الشيخ

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للتواصل والإقتراحات:
pathology439@gmail.com

Editing File