Carcinogenesis

Editing File

Objectives: No objectives.

Color Code:

Female's Notes
Male's Notes
Important
Extra

Pathology Team 441

MED441 KING SAUD UNIVERSITY

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Carcinogenesis

- Carcinogenesis 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)

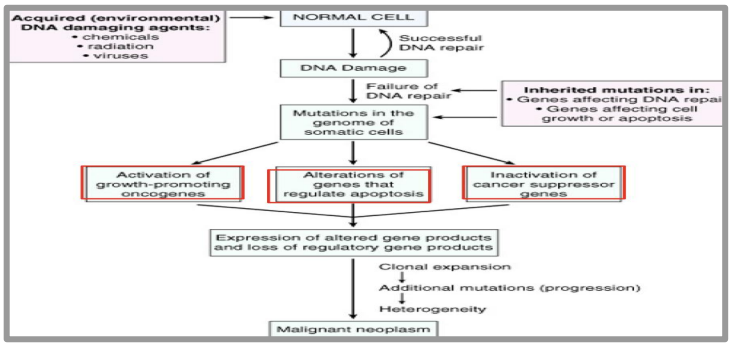
Causes

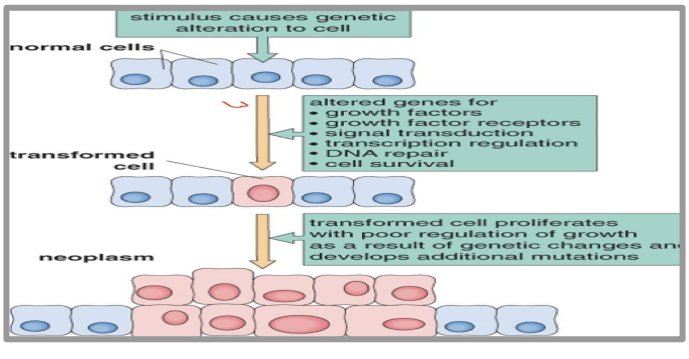
- **Environmental :** chemical.Radiation.infectious.
- **Inherited**

Targets (Four regulatory genes)

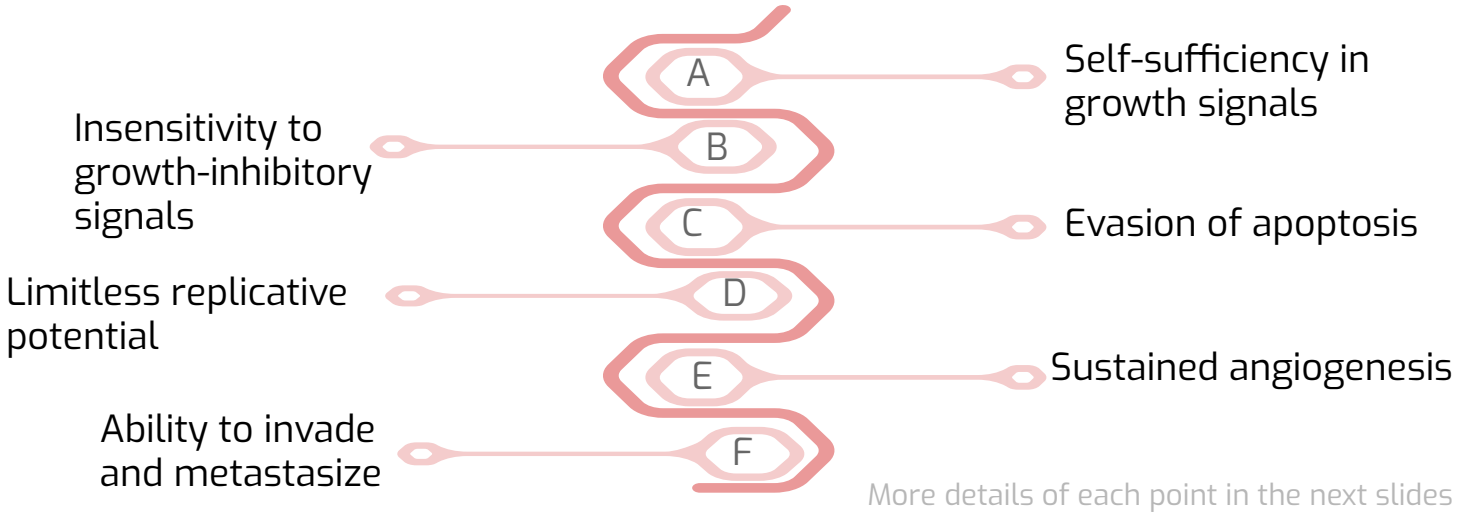
- DNA repair genes
- Growth promoting Protooncogenes
- Growth inhibiting (suppressors) genes
- Genes regulating apoptosis

Protooncogene → mutation → oncogene





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



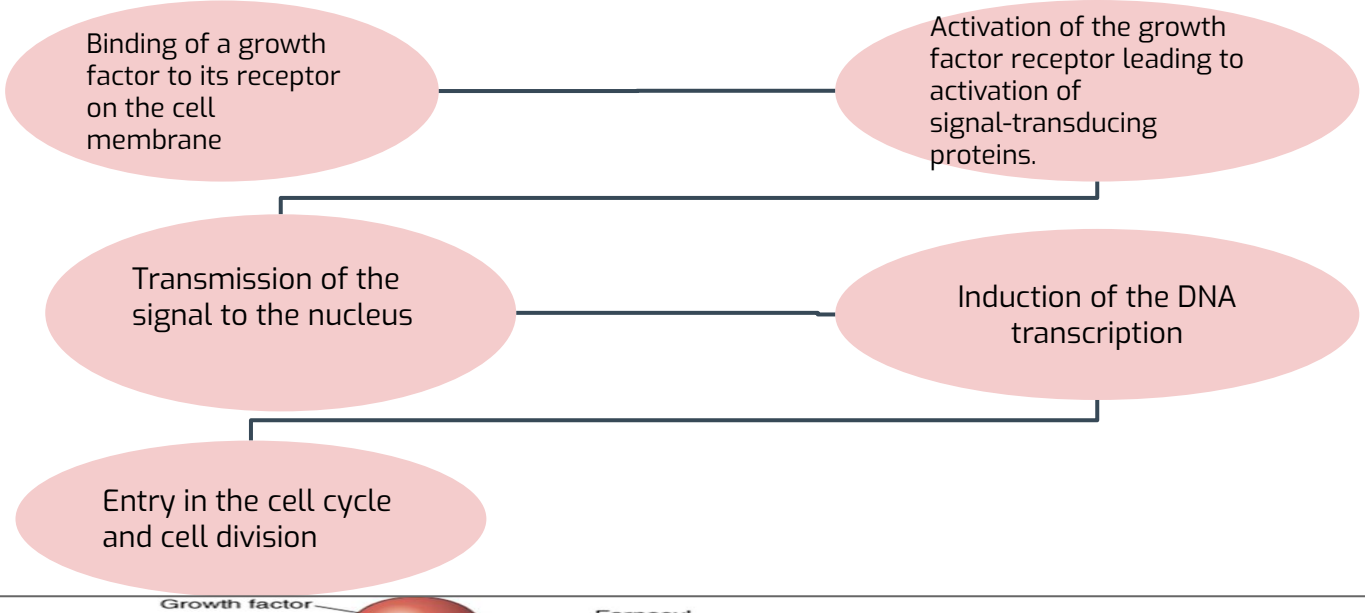
More details of each point in the next slides

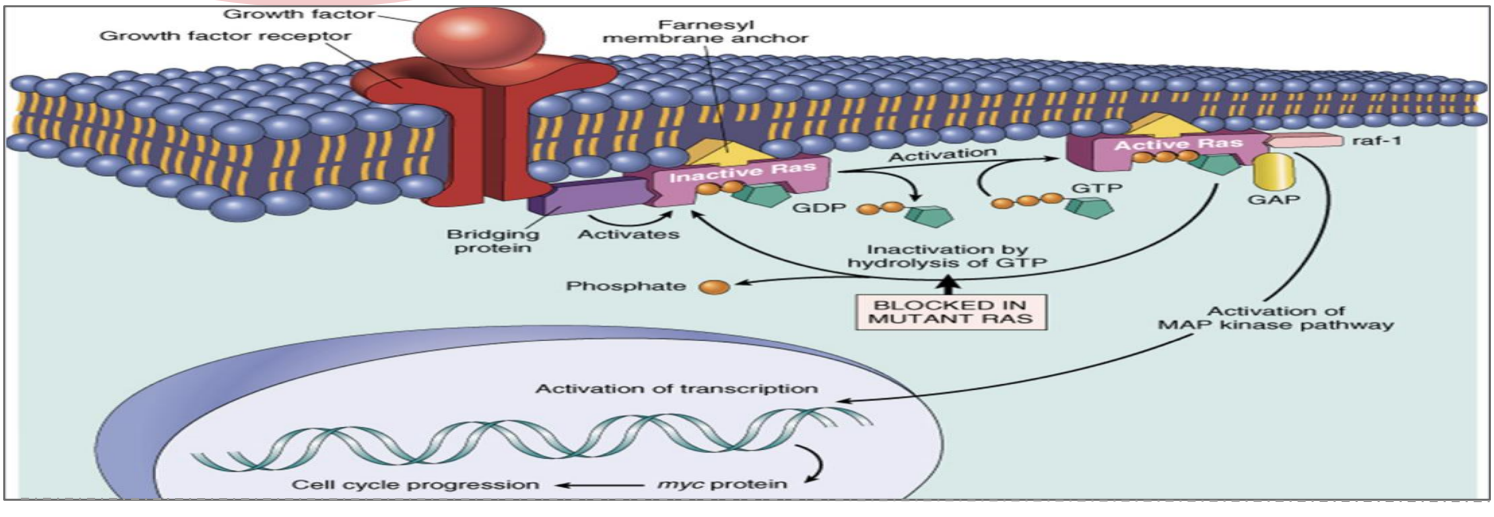
A- Self-sufficiency in growth signals

★ **Oncogene** : Gene that promote autonomous cell growth in cancer cells

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

★ **Remember cell cycle**





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

1.Growth factor

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

Cont.

2.Growth factor receptors:

- **mutation** :continuous signals to cells and uncontrolled growth
- **overexpression** : -cells become very sensitive 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 n
- Anti- HER2 antibodies are used in treatment

3.Signal transducing proteins :

- They receive signals from activated growth factors receptors and transmit them to the nucleus.
- Eg :

1) **RAS** :

- 30% of all human tumors contain mutated RAS gene. E.g. colon and Pancreas cancers.
- Mutations of the RAS gene is the most common oncogene abnormality in human tumors
- Mutations in RAS > cells continue to proliferate

2) **ABL**:

- ABL protooncogene has a tyrosine kinase activity
- Its 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 (oncogenic)

4.Nuclear transcription factors:

- Mutations may affect genes that regulate transcription of DNA → growth autonomy

E.g. MYC (in the nucleus) Med439's note: (it increase when the cell want to divide and decrease when the cell cycle starts)

- MYC protooncogene 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.
- Eg. Burkitt Lymphoma : MYC is dysregulated due to t(8,14).

Cont.

5- Cyclins and cyclins- dependent kinases (CDKs)

- Progression of cells through cell cycles is regulated by CDKs after they are activated by binding with cyclins.
- Mutations that dysregulate cyclins and CDKs will lead to cell proliferation.

- E.g :

1. Cyclin D genes are overexpressed in breast, esophagus and liver cancers.
2. CDK4 is amplified in melanoma and sarcomas.

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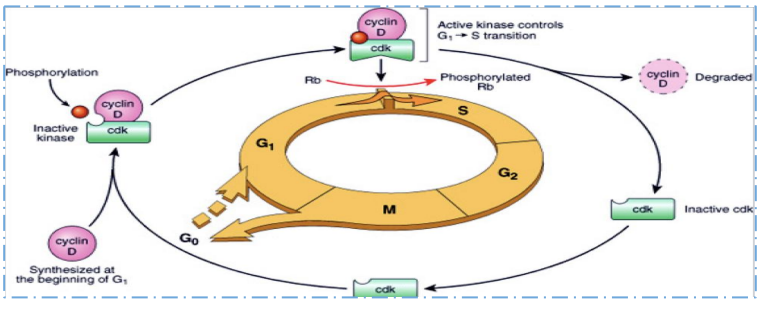
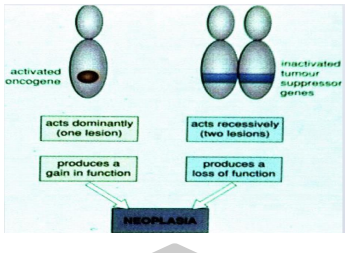
Remember: the gene (MYC) is associated with Burkitt lymphoma (aggressive) and t(8,14)



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 :**

More details in the next slides

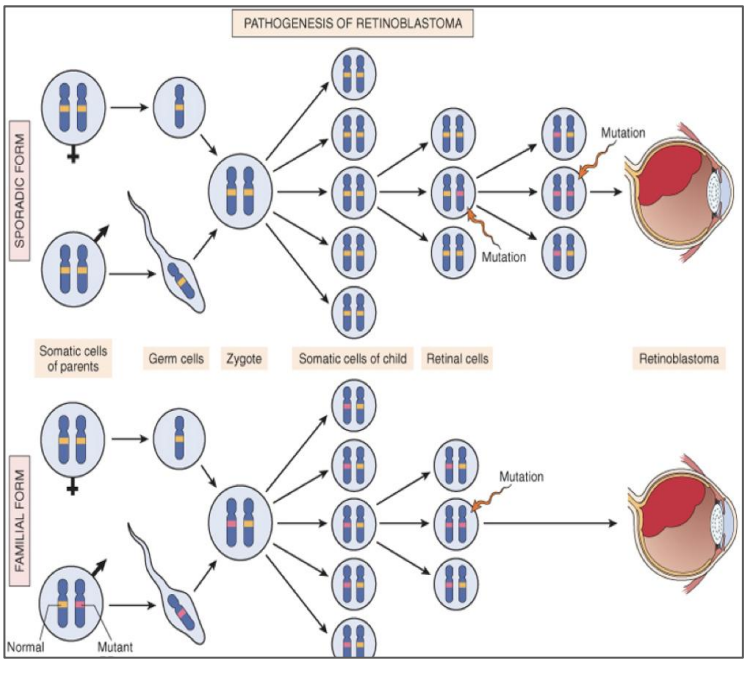
P53	RB gene	APC	TGF-B
*The most popular example Med439's note	(Retinoblastoma) gene	(Adenomatous Polyposis Coli – B Catenin pathway)	Transforming Growth Factor- B pathways)

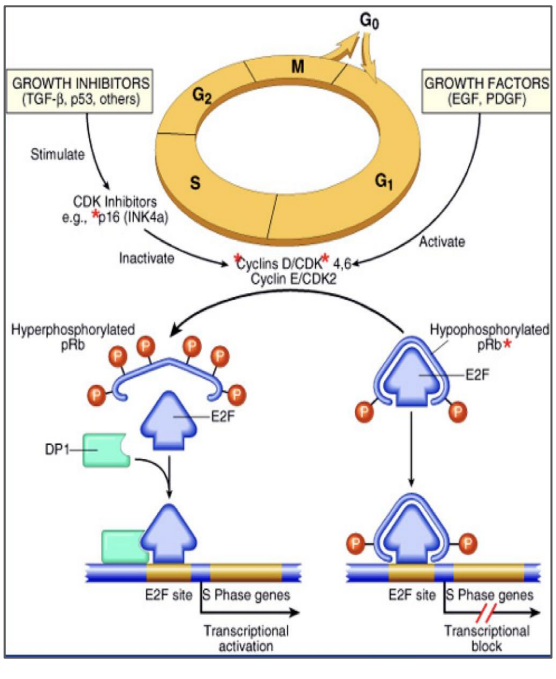
Cont.

RB
(retinoblastoma) gene

- ★ First tumor supressor gene discovered.
- ★ It was discovered initially in retinoblastomas
- ★ Found in other tumors. Eg: breast ca.
- ★ RB gene is a DNA-binding protein.
- ★ RB is located on chromosome 13.
- ★ It's an uncommon childhood tumor
- ★ Retinoblastoma is either sporadic (60%) or familial (40%)
- ★ Two mutations required to produce retinoblastoma
- ★ Both normal copies of the gene should be lost to produce retinoblastoma.
- ★ RB gene exists in "active" and " inactive" form.
- ★ 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 release** → **cells start cell cycle G1>S>M then RB gene is activated again**





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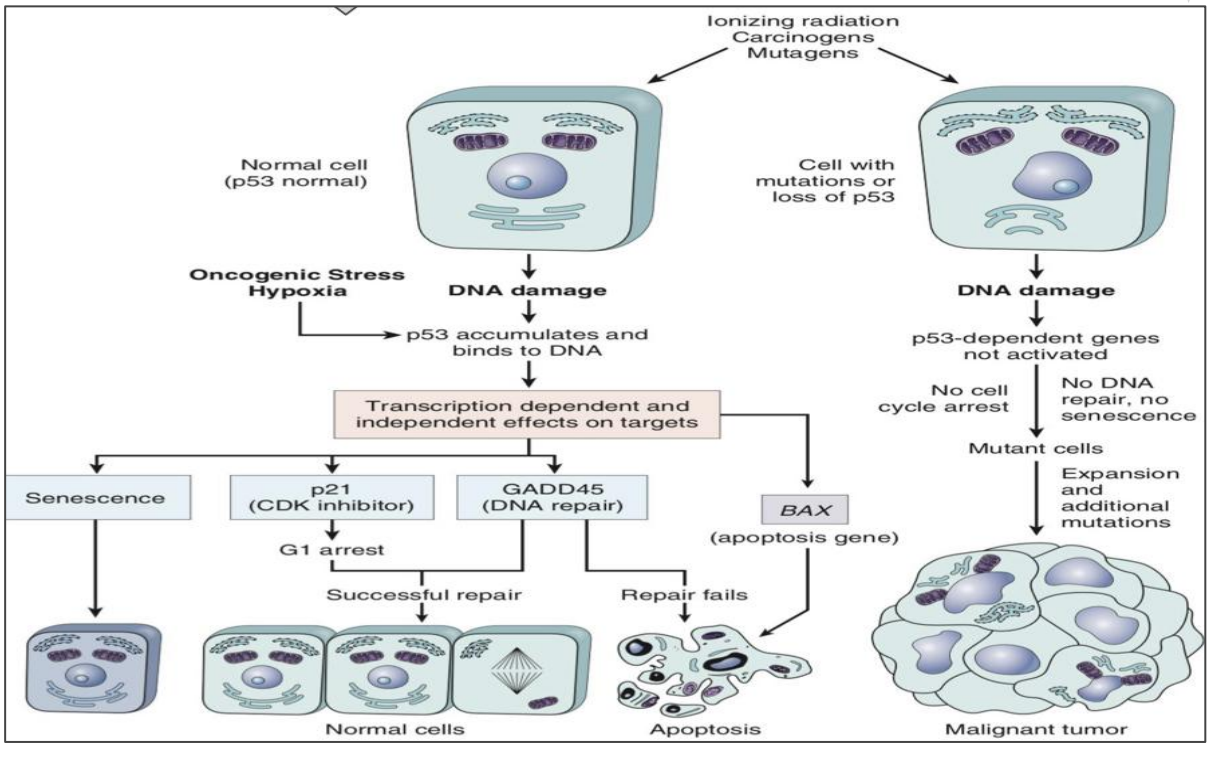
P53

★ It has multiple functions
- Mainly :

1.Tumor suppressor gene (anti-proliferative).
2.Regulates apoptosis.

★ 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.



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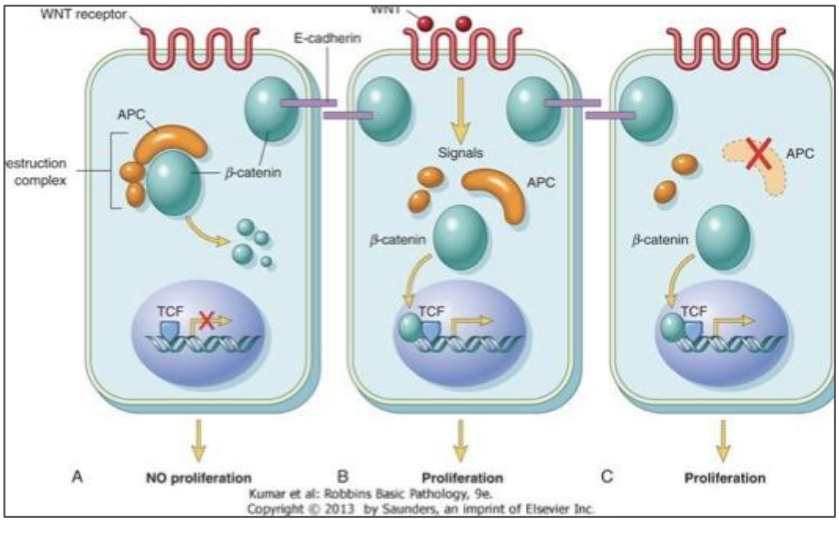
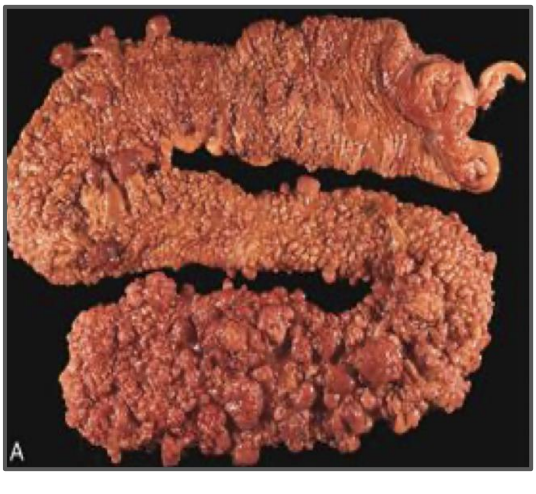
APC

- ★ APC (Adenomatous Polyposis Coli – B Catenin pathway)
- ★ APC gene loss is very common in colon cancers
- ★ 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

- ★ 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.





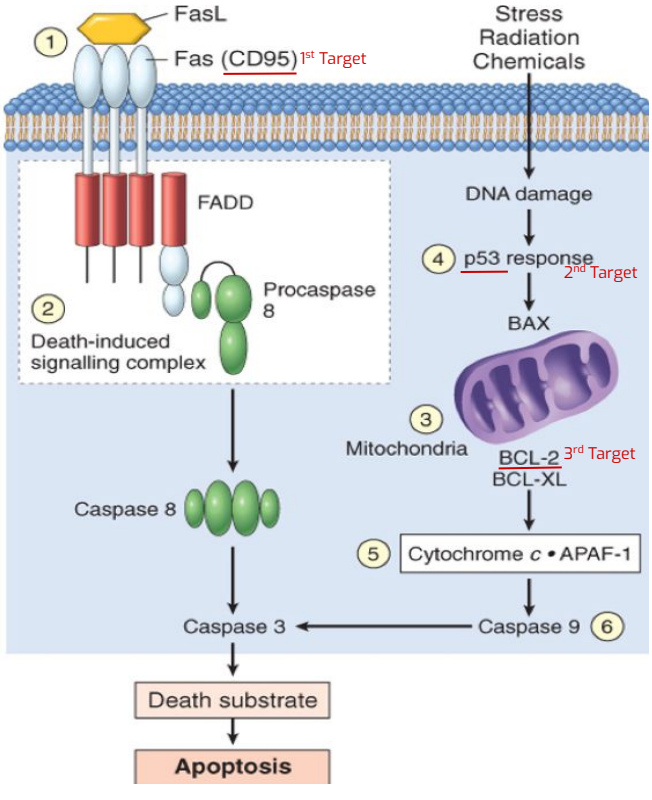
C - Evasion of apoptosis

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

- Reduced CD95 level inactivate death – **induced signaling cascade that cleaves DNA to cause death** ⟶ tumor cells are less susceptible to apoptosis.
- DNA damage induced 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.

If the tumour cells are not going through apoptosis as it normally should, we will have a cell proliferation and it will lead to the formation of cancer.

Targets of gene mutation in evasion of apoptosis :

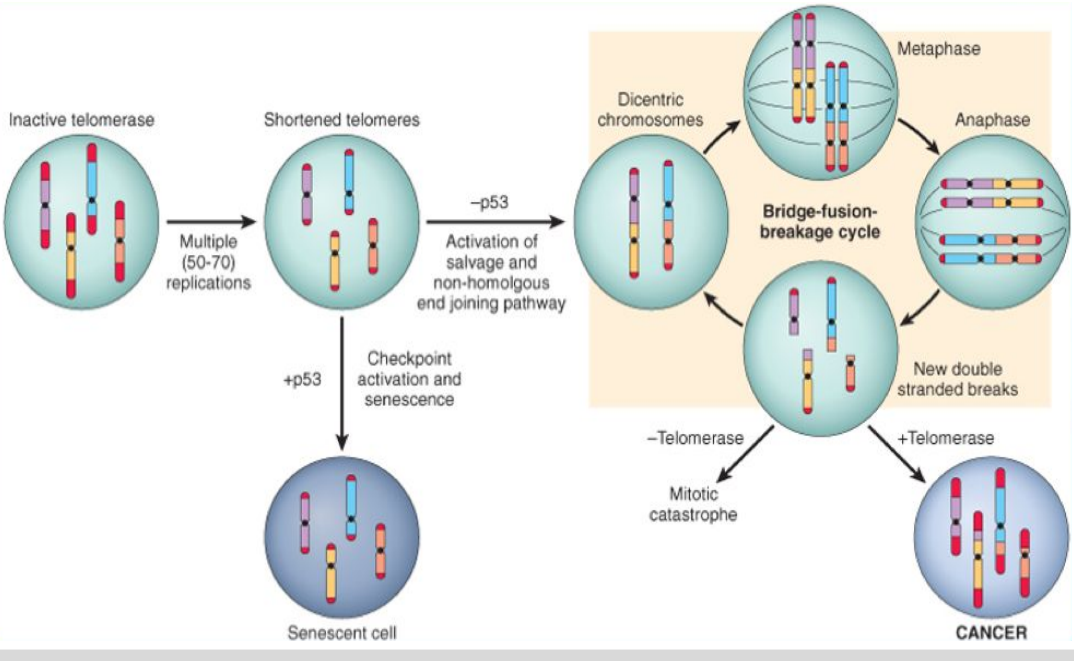


D- Limitless replicative potential

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

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

439 note: 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.



E - Sustained angiogenesis

★ Neovascularization has two main effects:

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

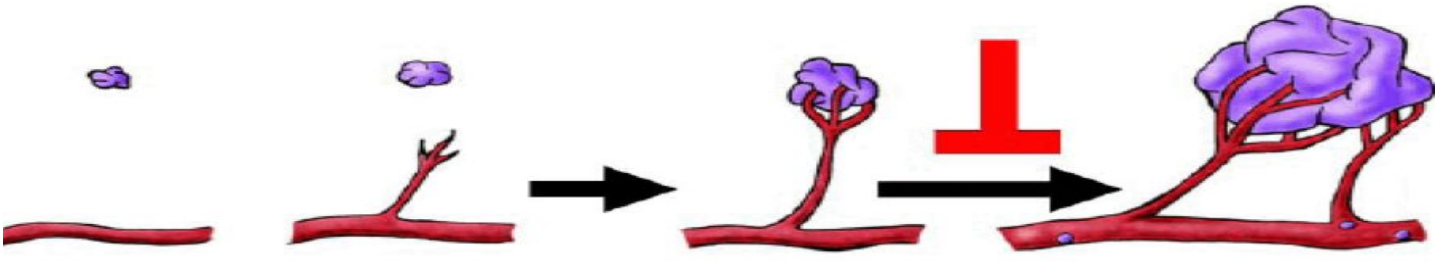
★ Angiogenesis is required for metastasis.

How blood supply cancer and keep it grow?
Either by 1. Supplies more oxygen and nutrients, or by 2. More growth factors.

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

How do tumors develop a blood supply?

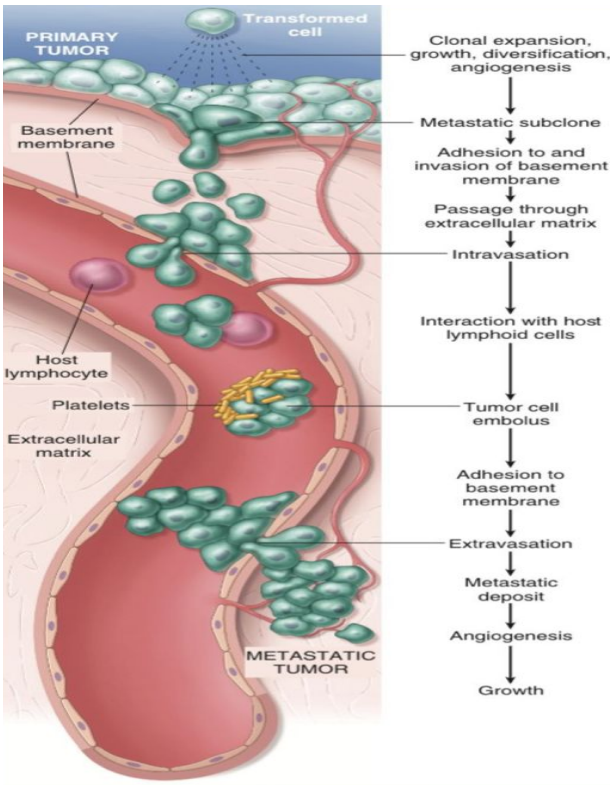
★ Tumor-associated angiogenic factors.
★ These factors may be produced by tumor cells or by inflammatory cells infiltrating the tumor e.g. macrophages.
★ Important factors :
1-Vascular endothelial growth factor (VEGF)
2-Fibroblast growth factor.



F- Ability to invade and metastsize

Phase one invasion of extracellular matrix (ECM)

★ Malignant cells first breach the underlying basement membrane.
★ Traverse the interstitial tissue
★ Penetrate the vascular basement membrane.
★ Gain access to the circulation.



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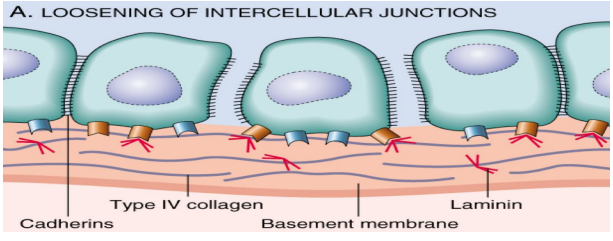
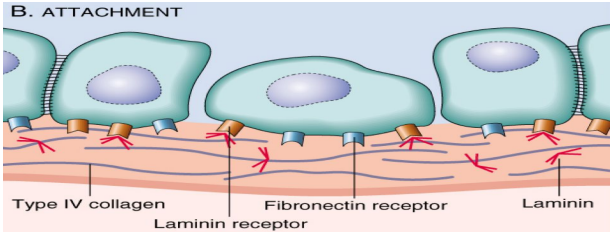
Invasion of the ECM has four steps:

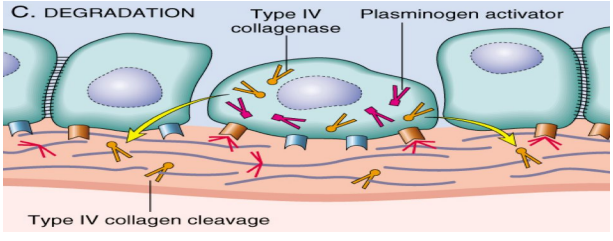
1. Detachment of tumor cells from each other.



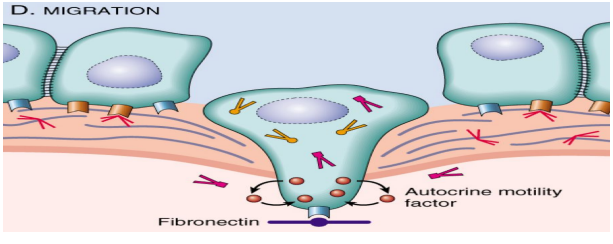
2. Attachments of tumor cells to matrix components.



3. Degradation of ECM by collagenase enzyme.



4. Migration of tumor cells.



Phase two Vascular dissemination and homing of tumor cells.

- ★ May form emboli.
- ★ Most travel as single cells.

One cell is enough to cause metastasize.

- ★ Adhesion to vascular endothelium.
- ★ extravasation.

Genomic Instability

- ★ Enabler of malignancy.
- ★ Due to defect in DNA repair genes.
- ★ Examples:

1. Hereditary Nonpolyposis colon carcinoma(HNPCC)
2. Xeroderma pigmentosum.
3. **Familial breast cancer:**

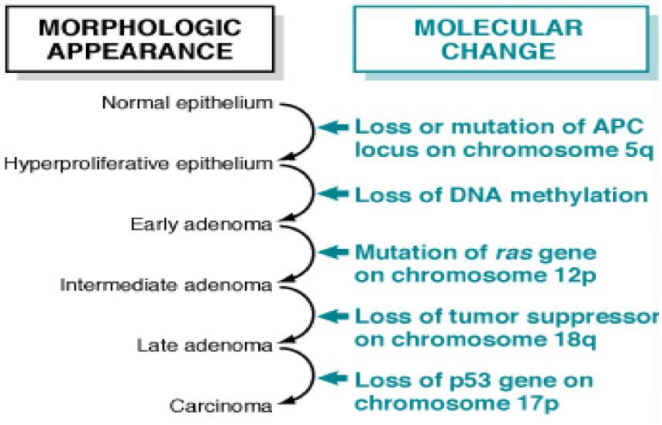
- Due to mutations in BRCA1 and BRCA2 genes, These genes regulate DNA repair.
- They are account for 80% of familial breast cancer.
- They are also involved in other malignancies.

439 note: Both copies of BRCA1 and BRCA2 must be inactivated for cancer to develop.

Molecular Basis of multistep Carcinogenesis

★ Cancer results from accumulation of multiple mutations.

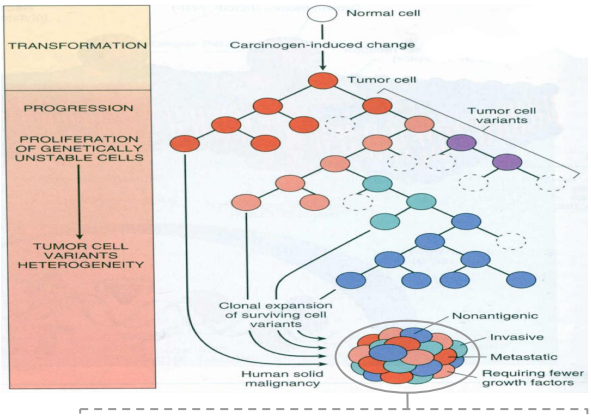
★ All cancers have multiple genetic alterations, involving activation of several oncogenes and loss of two or more tumor suppressor genes.



Tumor progression

★ Many tumors become more aggressive and acquire greater malignant potential, this is called "tumor progression"
- not increase in size!! But increase in number.

★ By the time, the tumor become clinically evident, their constituent cells are extremely heterogeneous.



Heterogeneous: collection of multiple abnormal cancer cells.

Karyotypic Changes in Tumors

★ Translocations:
- In CML : t(9,22) ..." Philadelphia chromosome"
- In Burkitt Lymphoma : t(8,14)
- In Follicular Lymphoma : t(14,18)

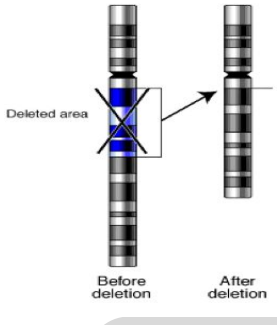
Diagnosed by karyotype.

★ Deletions

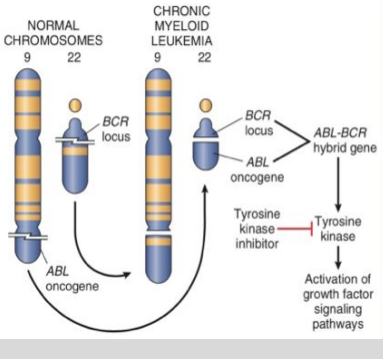
★ Gene amplification:
- Breast cancer : HER-2

One gene has multiple number of copies of that gene

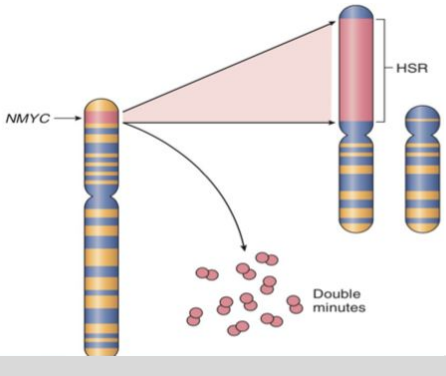
Deletions



Translocations In CML



Gene amplification



★ MCQs

1) What type of chromosomal change occurs in chronic myeloid leukemia?			
A) Translocations	B) Deletions	C) Gene amplification	D) Inversion
2) In which cells is telomerase present?			
A) Somatic cells	B) Stem cells	C) Tumor cells	D) B and C
3) Which one of these Tumor suppressors genes is called "guardian of the genome"?			
A) PB	B) P53	C) APC	D) TGF-B
4) RB (retinoblastoma) gene is located on chromosome...			
A) 13	B) 7	C) 9	D) 1

★ SAQ

1) What are the genes that cause familial breast cancer?

2) Give 2 examples of signal-transducing proteins

Answers:
1) BRCA1 and BRCA2 2) RAS gene and ABL gene

Answers : 1)A 2) D 3) B 4) A

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