CARCINOGENESIS

CARCINOGENESIS: Multistep process at both
- Phenotype (الشكل المظهري)
- Genotype (الشكل الجيني)

CARCINOGENESIS start with genetic damage
- Environmental
  - Chemical
  - Radiation
  - Viral
- Inherited

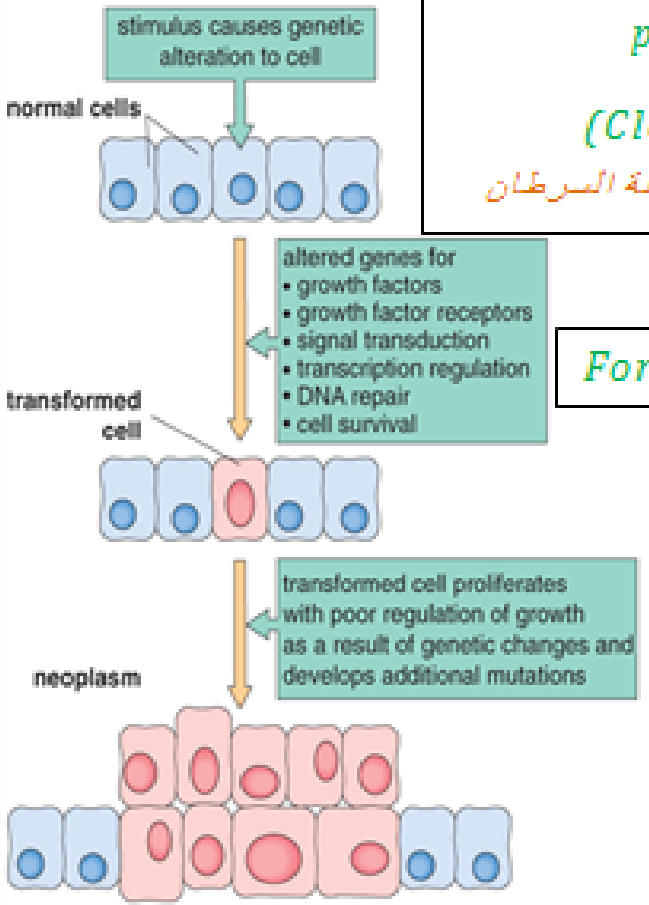
Leads to mutation

Undergoes neoplastic proliferations

(Clonal expansion)

توسع الأعضاء بسبب تكون كتلة السرطان

Forming TUMOR mass.



Where are the targets of the genetic damage??

Four regulatory genes are the main targets

- Growth promoting genes (proto-oncogenes)
- Growth inhibiting (suppressor) genes
- Genes regulating apoptosis
- DNA repair genes

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

- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory signals
- Evasion of apoptosis
- Limitless replicative potential
- Sustained angiogenesis
- Ability to invade and metastasize

Oncogenes → Promote autonomous cell growth in cancer cells

Derived by mutations in (proto-oncogenes) → **Function** → **Ability to promote cell growth in the absence of normal growth-promoting signals** → **Produce** → **Oncoprotein**

HOW CANCER CELLS ACQUIRE SELF-SUFFICIENCY IN GROWTH SIGNALS??

Some depend on cell cycle
Refer to lecture

1- Growth factors:

Cancer cells synthesize growth factors to which they are responsive.

E.g.

Sarcomas -> (TGF-α)

Glioblastoma -> (PDGF)

2-Growth factors receptors:

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

3- Signal-transducing proteins:

RAS

30% of tumors

E.g : colon . Pancreas cancers

ABL gene

*ABL proto-oncogene has a tyrosine kinase activity

*Its activity is controlled by -tive regulatory mechanism

E.g. : chronic myeloid leukemia (CML) due to ABL gene chromosome trans. (9,22) treated with (Gleevec)

4- Nuclear transcription factors:

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

E.g. MYC

*MYC proto-oncogene produce MYC protein → cell receives growth signals

*MYC protein binds to DNA leading to activation of growth-related genes.

*More MYC → continuous proliferation.

E.g. Burkitt Lymphoma due to t(8.14)

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 → lead to cell proliferation … E.g. :

*Cyclin D genes are overexpressed in breast, esophagus and liver cancers.

*CDK4 is amplified in melanoma and sarcomas

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For Example:

(RB) retinoblastoma gene:

Info about RB:

* Uncommon childhood tumor.
*1st tumor suppressor gene discovered .
*It was discovered initially in retinoblastomas.
*Found in other tumors, e.g. breast cancer.
*RB gene is a DNA-binding protein.
*RB is located on chromosome 13
*Can be "active"and " inactive"
*Sporadic (60%) *Familial (40%)
*2 mutations required to produce RB

RB function:

If active→ stop cell cycle in G1 to S phase
if inactive→ start cell cycle→ active RB

(TGF-β)Transforming Growth Factor- β pathway:

(TGF-β) functions:

1) tumor suppressor gene
2) Regulate RB pathway.
3) Inactivation of TGF-b lead to cell proliferation

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

(APC)Adenomatous Polyposis Coli-β Catenin pathway: (Colon)

(APC) Functions:

1) tumor suppressor gene
2) loss is very common in colon cancers
3) Has **anti-proliferative action** through **inhibition of b-Catenin** => activate cell proliferation.
4) **mutant APC** develop thousands of colonic polyps

Polyps => colonic carcinoma

70% to 80% of sporadic colon cancers

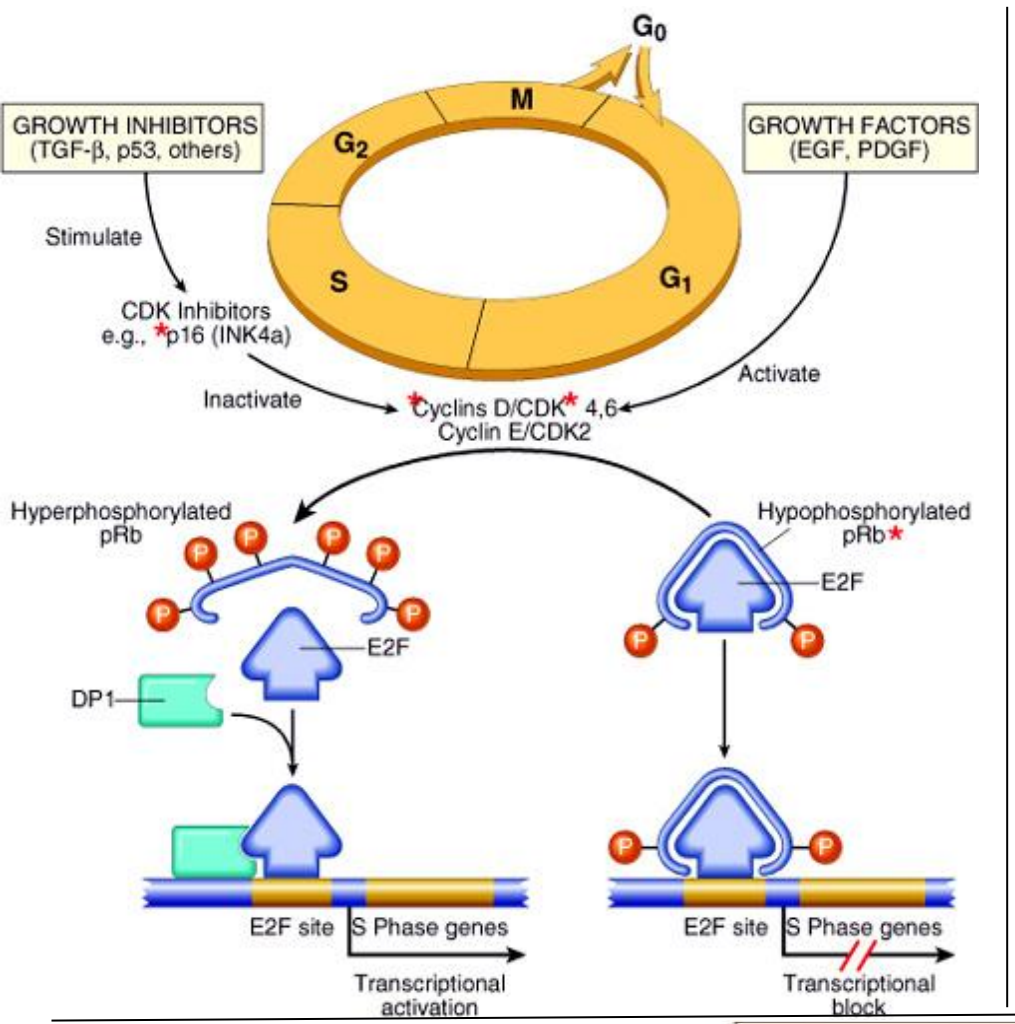
(P53)

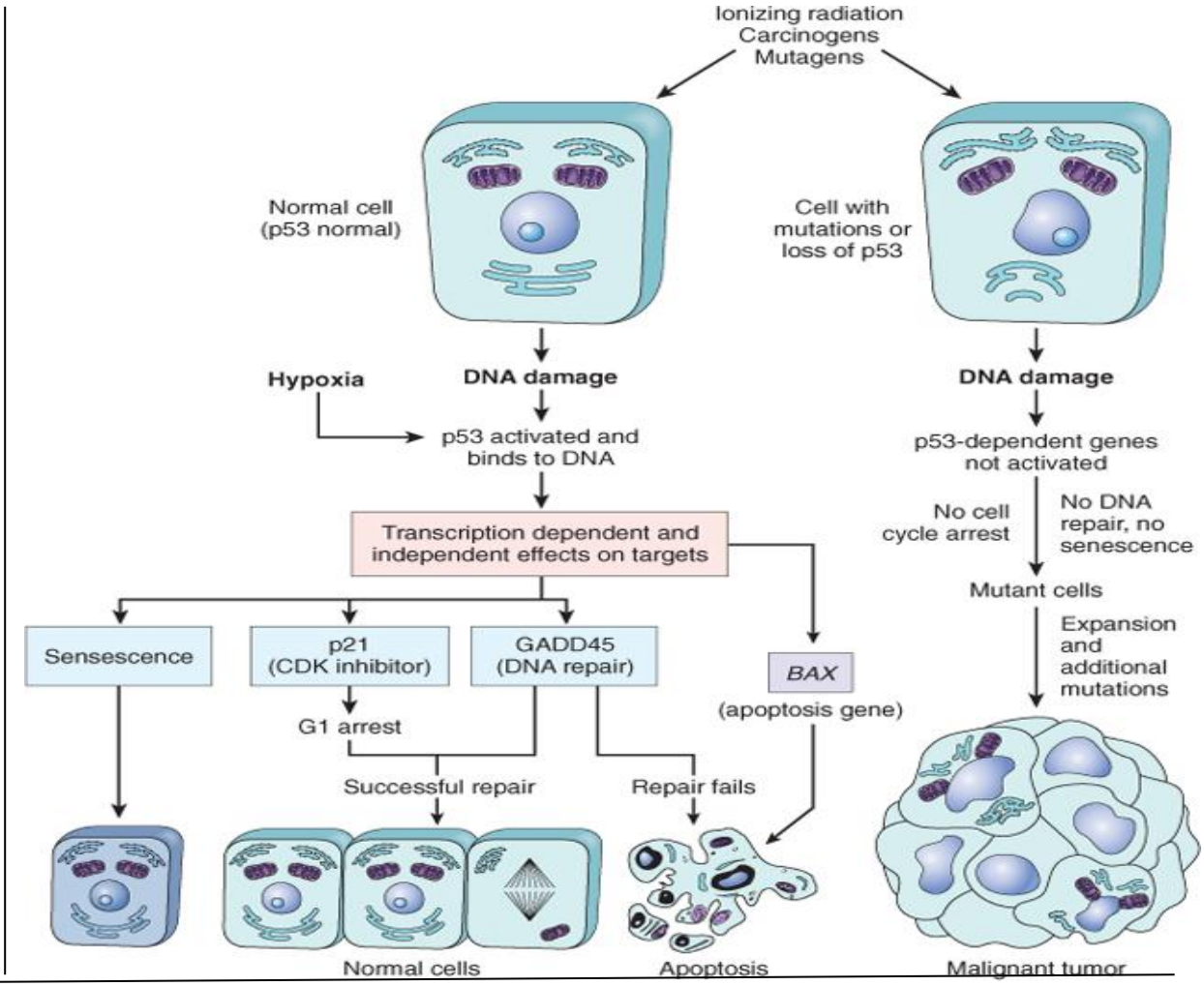
(P53) functions:

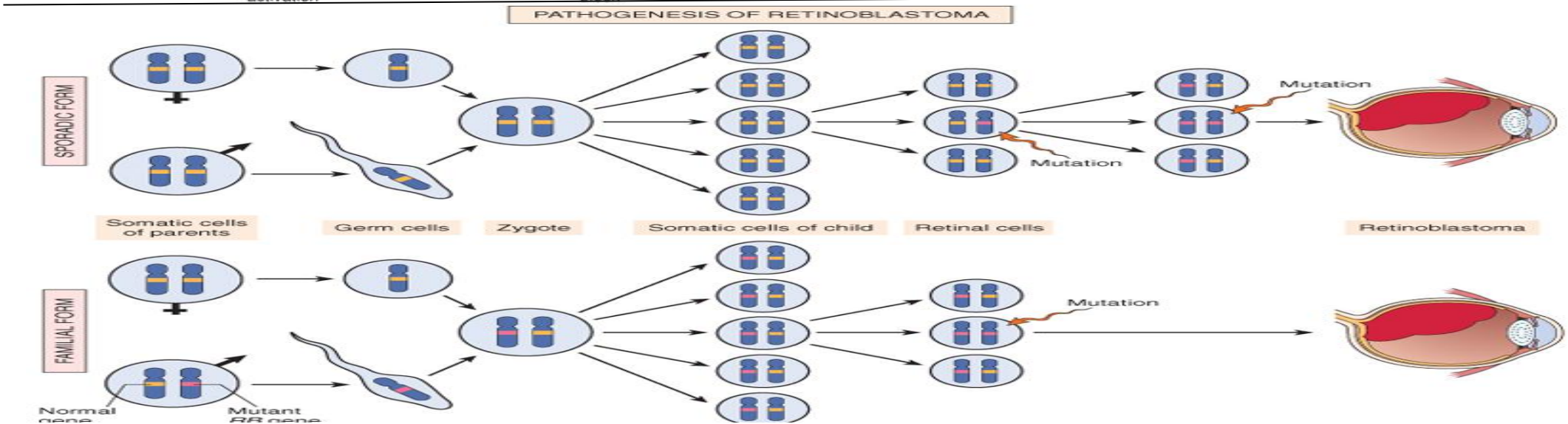
1) Tumor suppressor gene (anti-proliferative).
2) Regulates apoptosis.

*P53 senses DNA damage.
*stop G1 to give chance for DNA repair.
*If DNA cannot be repaired, P53 undergo apoptosis.
*Loss of P53, DNA damage.
*Called "guardian of the genome".
*70% of tumors.
*most cases, mutations are acquired, can be inherited, **e.g : Li-Fraumeni syndrome**

الرسم يوضح


G0
M
G2
S
G1
GROWTH INHIBITORS
(TGF-β, p53, others)
GROWTH FACTORS
(EGF, PDGF)
Stimulate
CDK Inhibitors
e.g., *p16 (INK4a)
Inactivate
Activate
Cyclins D/CDK 4,6
Cyclin E/CDK2
Hyperphosphorylated
pRb
Hypophosphorylated
pRb*
E2F
DP1
E2F site
S Phase genes
Transcriptional
activation
E2F site
S Phase genes
Transcriptional
block


Ionizing radiation
Carcinogens
Mutagens
Normal cell
(p53 normal)
Cell with
mutations or
loss of p53
Hypoxia
DNA damage
DNA damage
p53 activated 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
Sensescence
p21
(CDK inhibitor)
GADD45
(DNA repair)
BAX
(apoptosis gene)
G1 arrest
Successful repair
Repair fails
Normal cells
Apoptosis
Malignant tumor


PATHOGENESIS OF RETINOBLASTOMA
SPORADIC FORM
Mutation
Mutation
Somatic cells
of parents
Germ cells
Zygote
Somatic cells of child
Retinal cells
Retinoblastoma
FAMILIAL FORM
Mutation
Normal
gene
Mutant
RB gene

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- **Evasion of apoptosis**
- Limitless replicative potential
- Sustained angiogenesis
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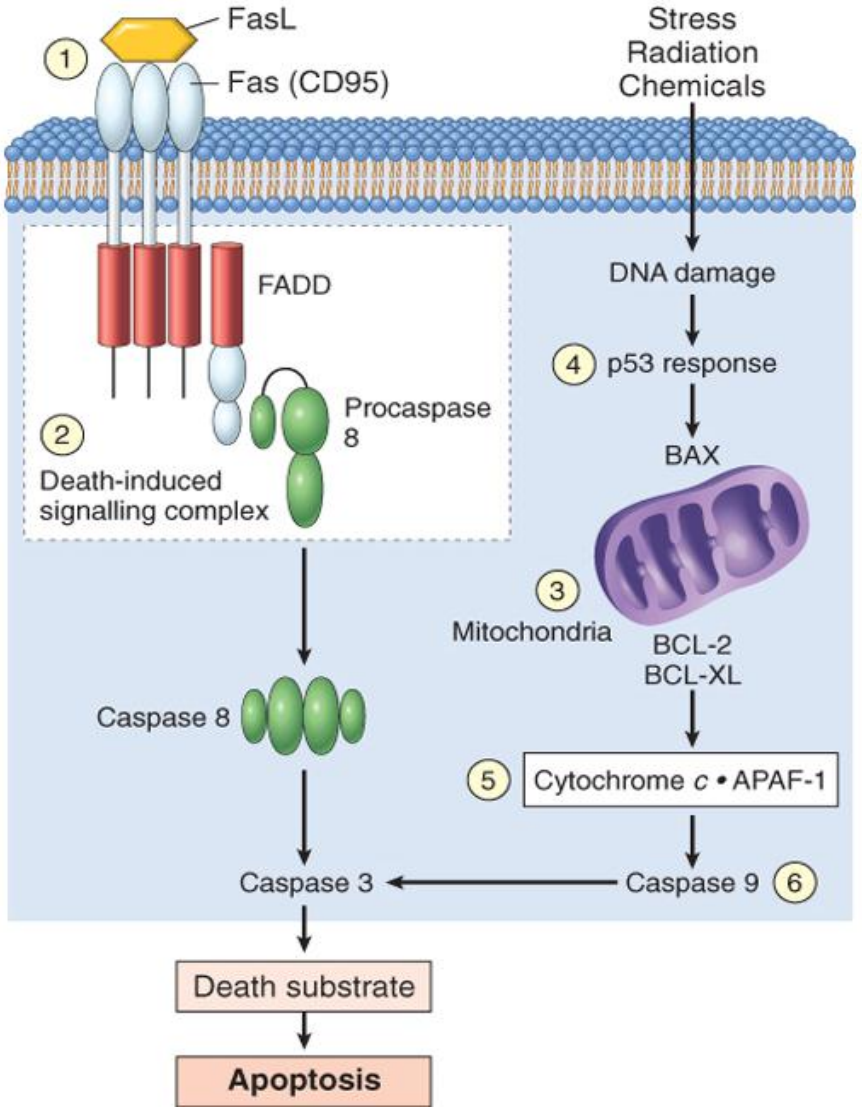
Cell survival is controlled by genes that promote and inhibit apoptosis

Reduced ↓ (CD95) inactivate death –induced signaling → tumor is 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



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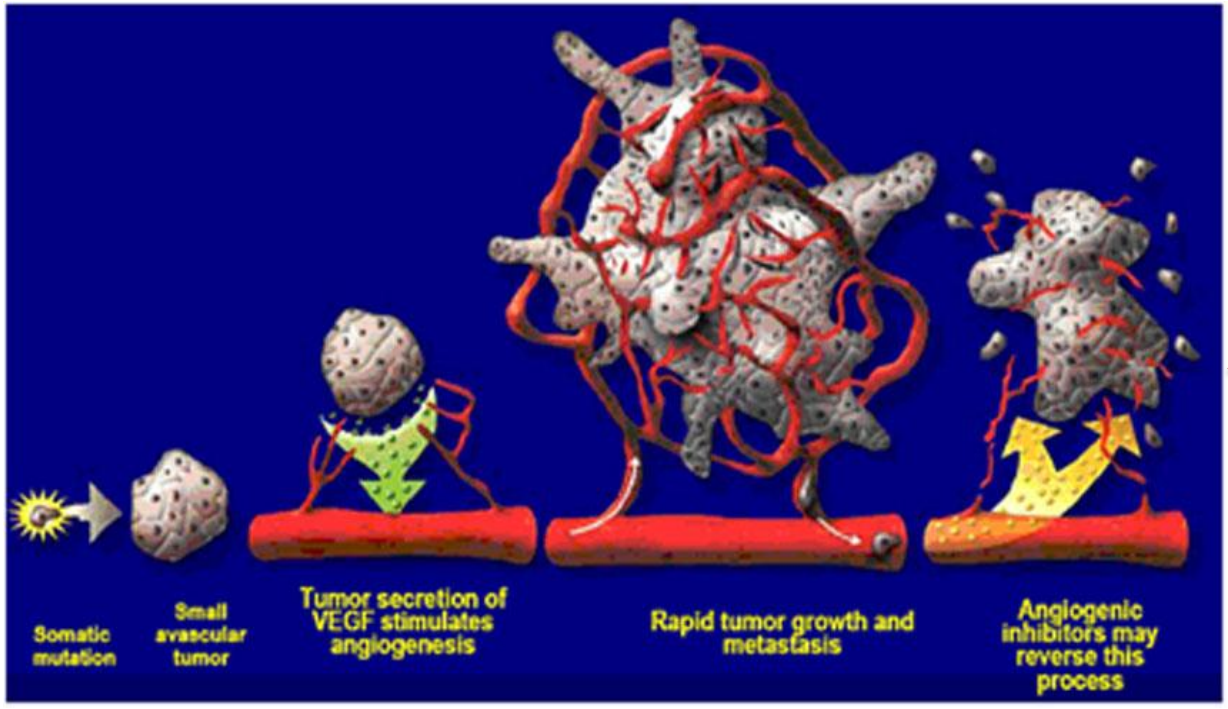
*normally there a Progressive shortening of telomeres at the ends of chromosomes

*Telomerase is active in normal stem cells but absent in somatic cells

*In tumor cells: activation of telomerase, which can maintain normal telomere length



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, IL-1

Angiogenesis is required for metastasis

How do tumors develop a blood supply?

By tumor-associated angiogenic factors:

1) Vascular endothelial growth factor(VEGF)
2) Fibroblast growth factor

These factors may be produced by

a) Tumor cells b) or by inflammatory cells infiltrating the tumor e.g. macrophages

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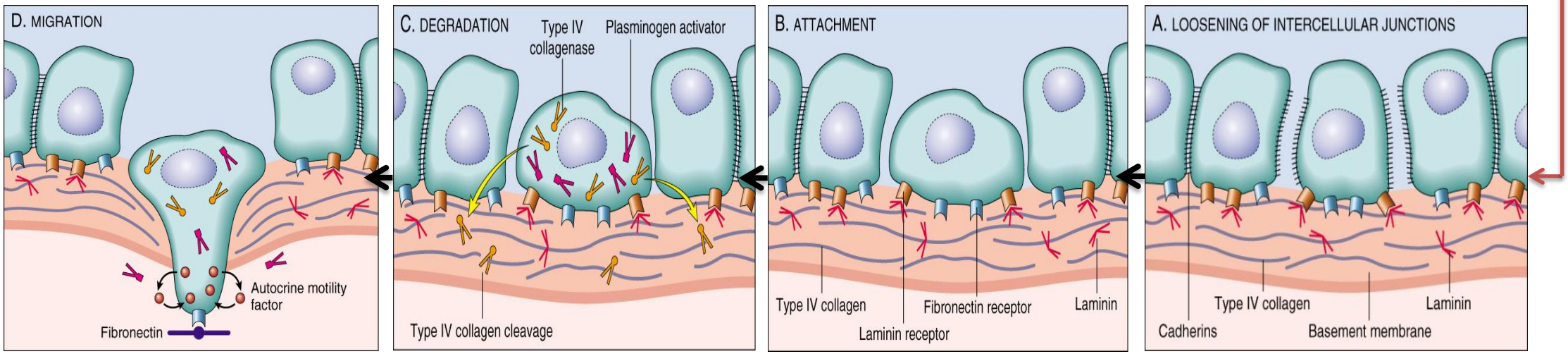
1) Invasion of extracellular matrix (ECM)

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

Invasion of the ECM has 4 steps:



2) Vascular dissemination and homing of tumor cells

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

Genomic Instability
(عدم الإتزان الجيني)

*Enabler of malignancy, due to defect in DNA repair genes

Examples:

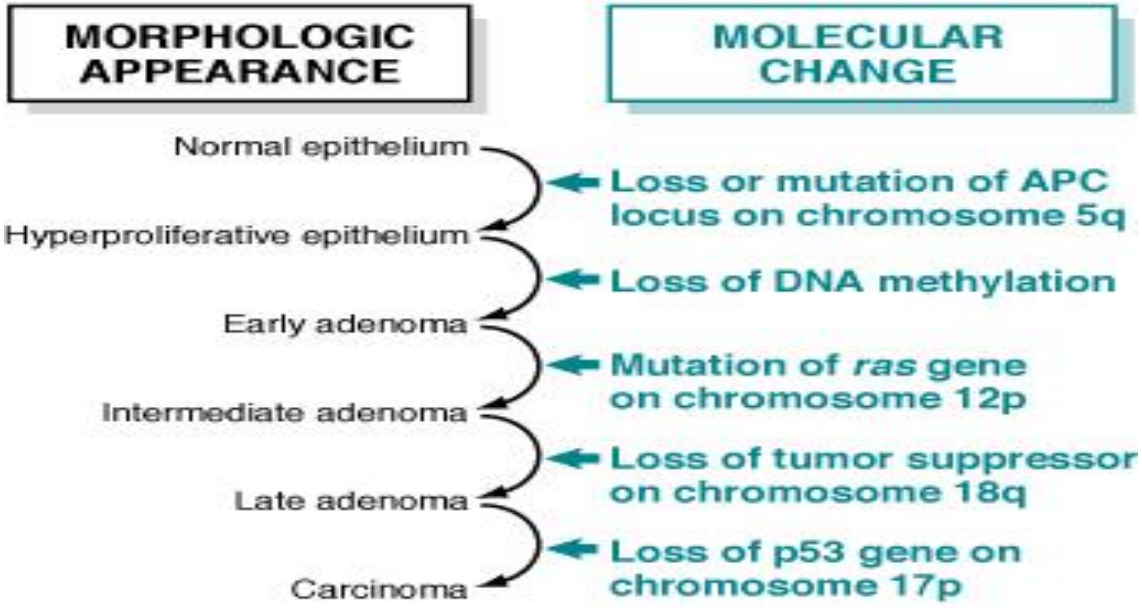
- Hereditary Non-polyposis colon carcinoma (HNPCC)
- Xeroderma pigmentosum
- Familial breast cancer

Familial breast cancer:

- ✓ Due to mutations in BRCA1 and BRCA2 genes
- ✓ These genes regulate DNA repair
- ✓ 80% of familial breast cancer

Molecular Basis of multistep Carcinogenesis

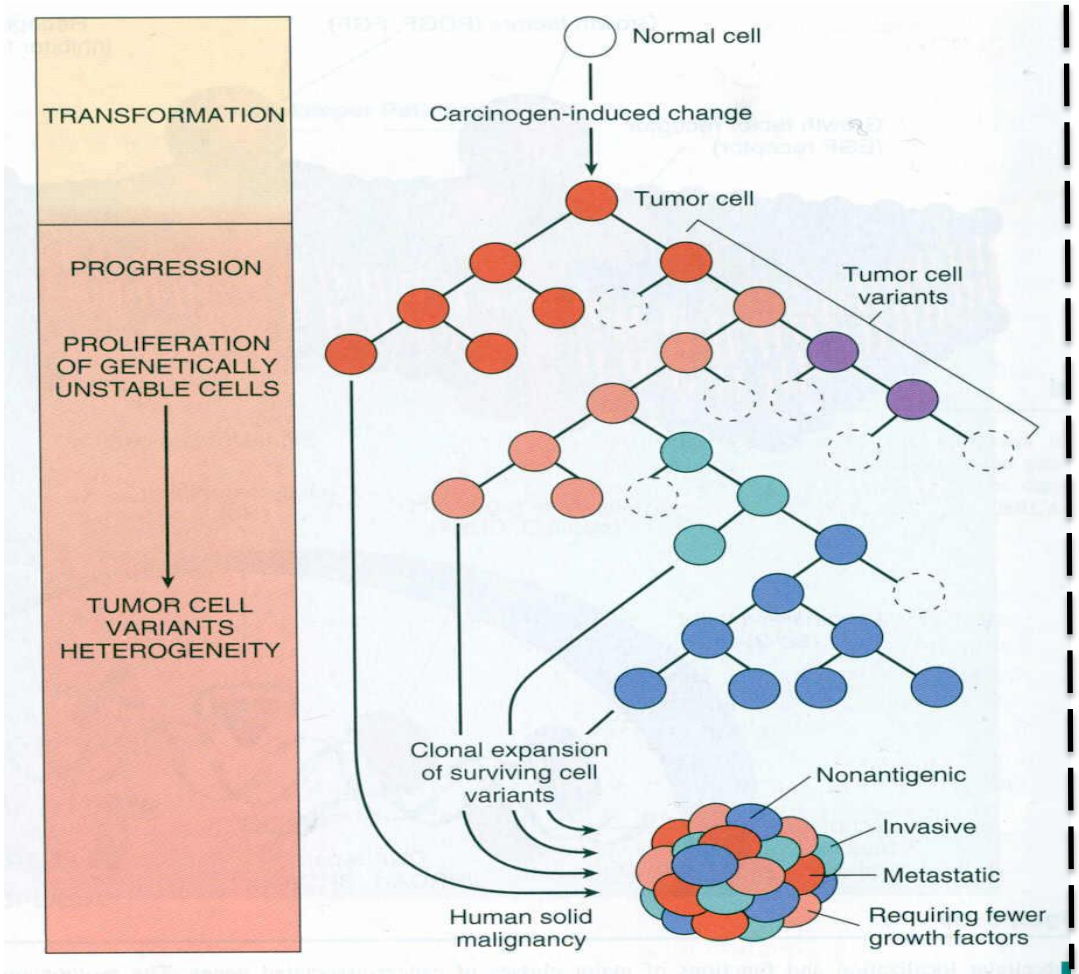
- ✓ Cancer results from accumulation of multiple mutations
- ✓ All cancers have multiple genetic alterations, involving activation of several oncogenes and loss of two or more tumor suppressor genes



Tumor progression

***It means tumors <u>become aggressive</u> <u>not</u> increased in size.**

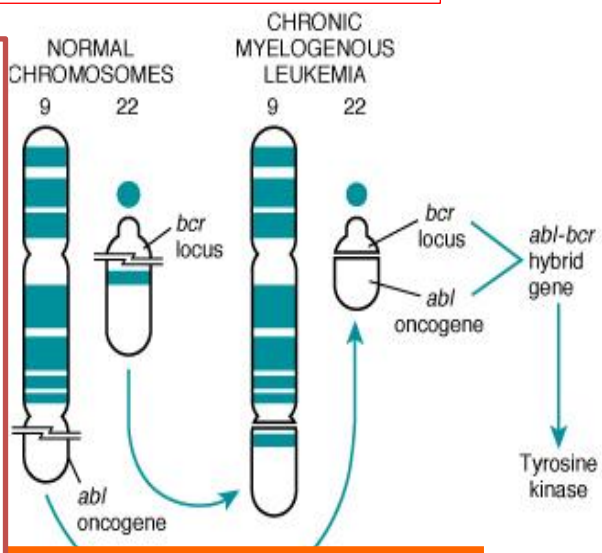
By the time, the tumor become clinically evident, their constituent cells are <u>extremely heterogeneous</u>



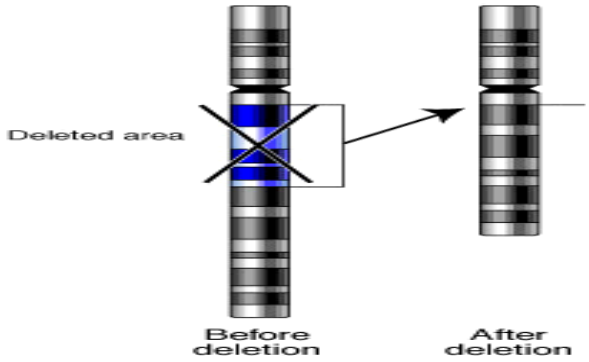
Karyotype Changes in Tumors

A) Translocations:

- **In CML : t(9,22) …" Philadelphia chromosome"**
- **In Burkitt Lymphoma : t(8,14)**
- **In Follicular Lymphoma : t(14,18)**

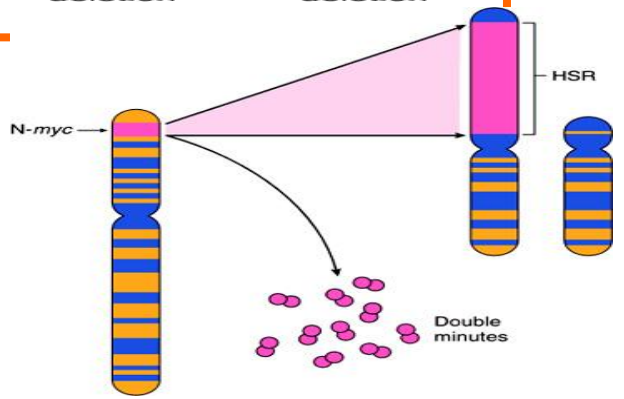


B) Deletions



C) Gene amplification:

Breast cancer : HER-2



Some questions from Dr. Maha's lecture :

1) At which site or part of cell cycle RB work to stop the cell cycle?

   A) G1 to S B) S to G1 C) M to S

2) Which one of the following is tumor suppressor gene?

   A) RAS B) MYC C) TGF-B

3) Which of the following gene mutation is common in Adenomatous polyposis coli-B?

   A) P53 B) APC C) TGF-B

4) In (CML) chronic myeloid leukemia, ABL gene trans chromosomes from:

   A) t(9,22) B) t(14,18) C) t(8,14)

5) What the mutated gene that causes CML?

   A) APC B) MYC C) ABL

6) The treatment of breast cancer is working on which gene receptors?

   A) HER2 B) P53 C) APC

What is the Deference between sporadic and familial cancer?

Sporadic => needs 1 allele affected and cell need 2 mutations to develop cancer

Familial => needs 2 allele affected and cell need 1 mutation to develop cancer

See RB development picture in page 4