PATHOLOGY TEAMWORK

MED444

Carcinogenesis

OBJECTIVES

- Define carcinogenesis
- List causes of cancer
- Identify the major genetic properties and hallmarks of cancer
- List examples of oncogenes, tumor suppressor genes and genes involved in apoptosis, limitless replicative potential, angiogenesis and ability to invade and metastasize
- Discuss the theory of molecular basis of multistep carcinogenesis
- List the karyotype changes in tumors

Editing file

COLOR INDEX:

MAIN TEXT (BLACK)

FEMALE SLIDES (PINK)

MALE SLIDES (BLUE)

IMPORTANT (RED)

DR'S NOTE (GREEN)

EXTRA INFO (GREY)

How to study this lecture

- Males and females slides are totally different, so the best way to study it is to focus on the females slides (it includes everything according to Dr. Osama) + understand important key information from Dr. Osama revision

- Check Dr. Osama's revision (9-41)

- Check Dr. Maha's revision file (revisions → pathology)

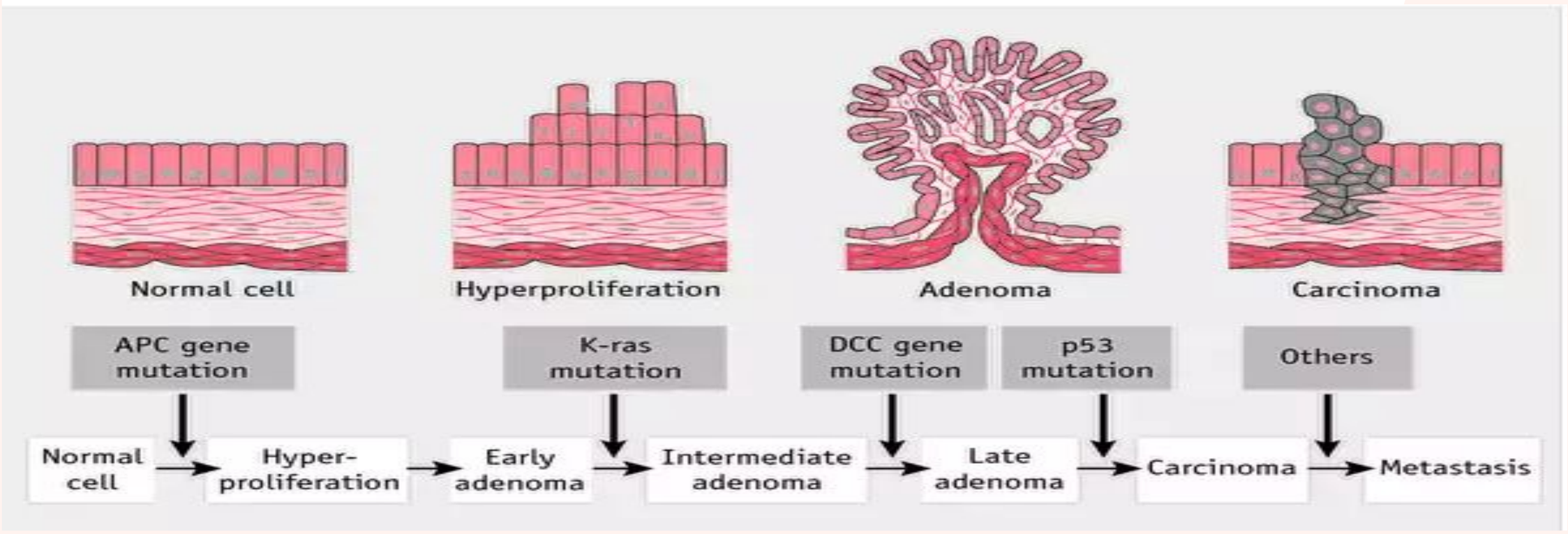
- understand the text highlighted in yellow to cover males slides

-هذه المحاضره اعتمدوا على محاضره دكتور اسامه(سلايدات العيال) والاشياء الزياده الي في سلايدات البنات اقرأوها احتياطا

Carcinogenesis

DEFINITION

- A mechanism of induction of tumor. It is a multistep process at both the phenotypic and the genetic levels



Causes

In the germ line

Inherited

Environmental

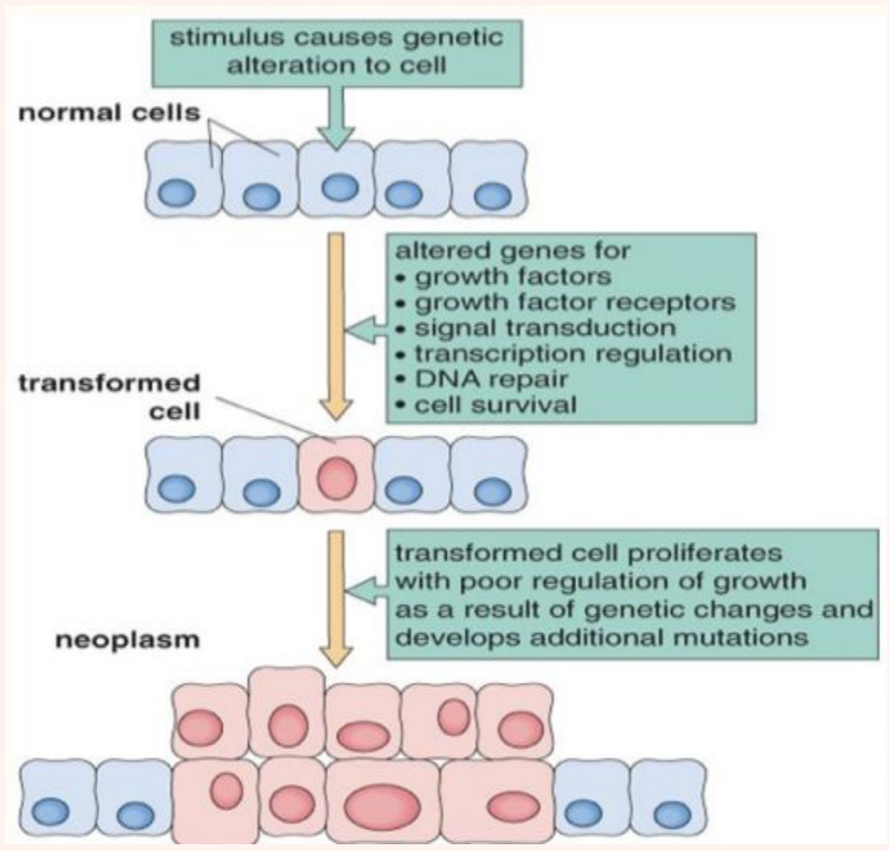
Chemical :
- Smoking →lung CA
- Benzidine → urinary bladder CA
- Arinsic compounds → skin CA
- Vinyl chloride → liver CA

Radiation exposure:
- Leukemia
- Thyroid CA
- Skin cancer

Biological:
- Viral :
  - HPV
  - Viral hepatitis B and C
- parasite :
  - Schistosomia

Genetic damage → mutation:
- Responsible for the generation of malignant cells.
- Single cell which has the genetic damage undergoes neoplastic proliferation (clonal expansion) forming tumor mass.

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

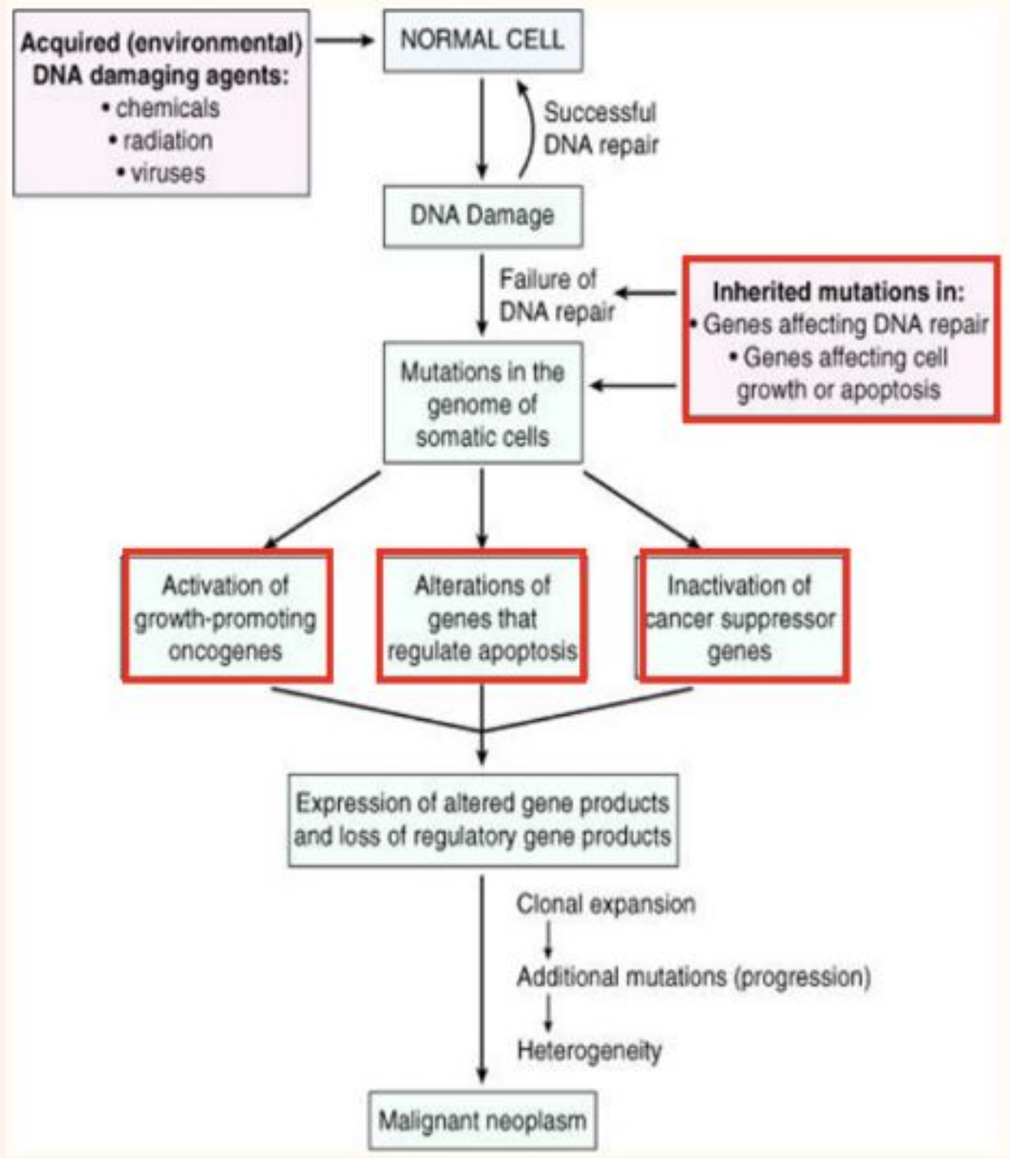


- Homeostasis of cells is a process to keep between proliferating and programmed cell death.

- Mutation in the DNA result in disturbance of regulation of the process

Changes in the cell

- The genetic hypothesis of cancer implies that a tumor mass results from the clonal expansion of a single progenitor cell that has incurred genetic damage (i.e., tumors are monoclonal).
- Not every mutation results in loss of gene functionality.
- Some mutations may lead to gain and overexpression.
- Mutant alleles of proto-oncogenes are called oncogenes.
- They are considered dominant because mutation of a single allele can lead to cellular transformation.
- Loss of gene function does not necessarily lead to cell death.
- It might have a proliferation impact on the cell.
- It has become clear that cancer is a disease caused by mutations that alter the function of a finite subset of 20,000 or so human genes
- We will refer to these genes s cancer genes and the usually fall under four major classes



Protooncogene → mutation → oncogene

Growth promoting proto-oncogenes

• Oncogenes are genes that induce a transformed phenotype when expressed in cells by promoting increased cell growth.
• A major discovery in cancer was the realization that oncogenes are mutated or overexpressed versions of normal cellular genes, which are called proto-oncogenes.
• Most oncogenes encode transcription factors (c-MYC), factors that participate in pro-growth signaling pathways, or factors that enhance cell survival.
• They are considered dominant genes because a mutation involving a single allele is sufficient to produce a pro-oncogenic effect.

1

Growth inhibiting (Tumor suppressor) genes

• Tumor suppressor genes are genes that normally prevent uncontrolled growth and, when mutated or lost from a cell, allow the transformed phenotype to develop.
• Often both normal alleles of tumor suppressor genes must be damaged for transformation to occur, autosomal recessive, (exception TP53 in Ch17, Rb in Ch13).
• Tumor suppressor genes can be placed into two general groups,
○ "Governors" that act as important brakes on cellular proliferation.
○ "Guardians" that are responsible for sensing genomic damage.

2

Genes regulating apoptosis

• Genes that regulate apoptosis primarily act by enhancing cell survival, rather than stimulating proliferation.
• Understandably, genes of this class that protect against apoptosis are often overexpressed in cancer cells, whereas those that promote apoptosis tend to be underexpressed or functionally inactivated by mutations.

3

DNA repair genes

● Genes that regulate interactions between tumor cells and host cells, as these genes are also recurrently mutated or functionally altered in certain cancers.
● Particularly important are genes that enhance or inhibit recognition of tumors cells by the host immune system.

4

Major genetic properties (Hallmarks of cancer)

Eight cancer hallmarks and two enabling factors (genomic instability and tumor- promoting inflammation). Most cancer cells acquire these properties during their development, typically due to mutations in critical genes.

Main changes in cell physiology that leads to formation of malignant cells

- Self sufficiency in growth signals
  - Growth factors
  - Growth factors receptors
  - Signal transduction proteins
- Evasion of apoptosis
  - Nuclear transcription factor
  - Cyclins and cyclin dependent kinases
- Limitless replicative potential
- Sustained angiogenesis
- Ability to invade and metastsize
- Insensitivity to growth inhibitory signals
  - Retinoblastoma gene
  - P-53
  - TGF-B
  - (APC)-B catenin pathway
- Genomic instability (mutator phenotype)
- Avoiding immune distruction
- Tumor promoting inflammation
- deregulating cellular energetics

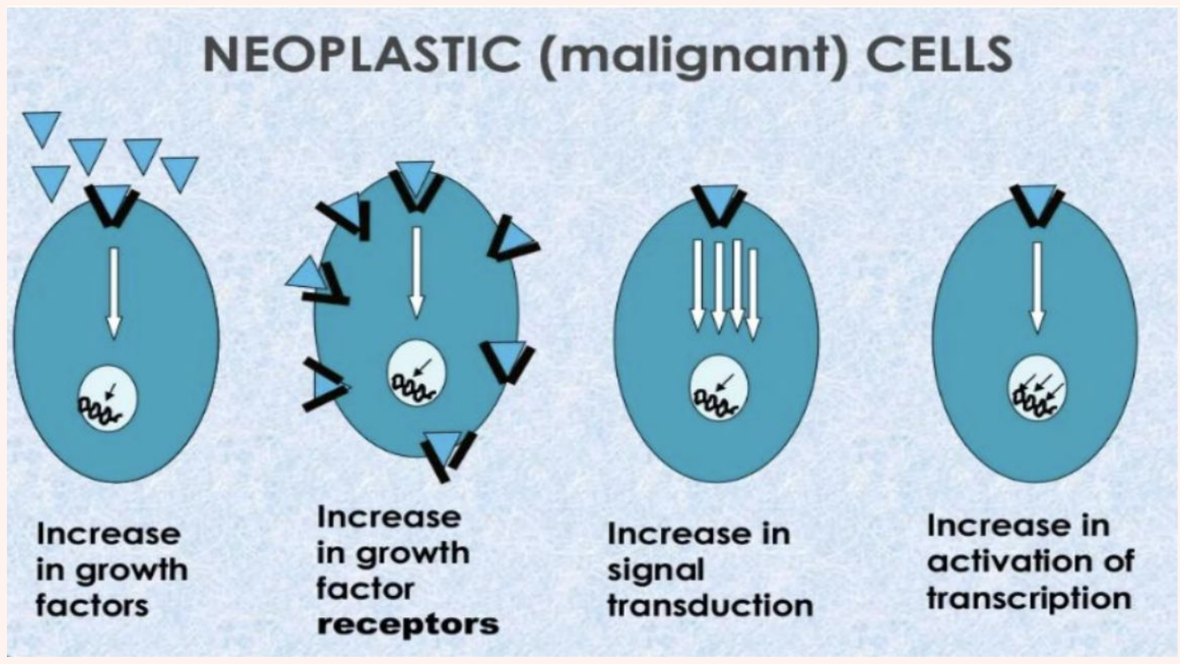
Self sufficiency in growth signals

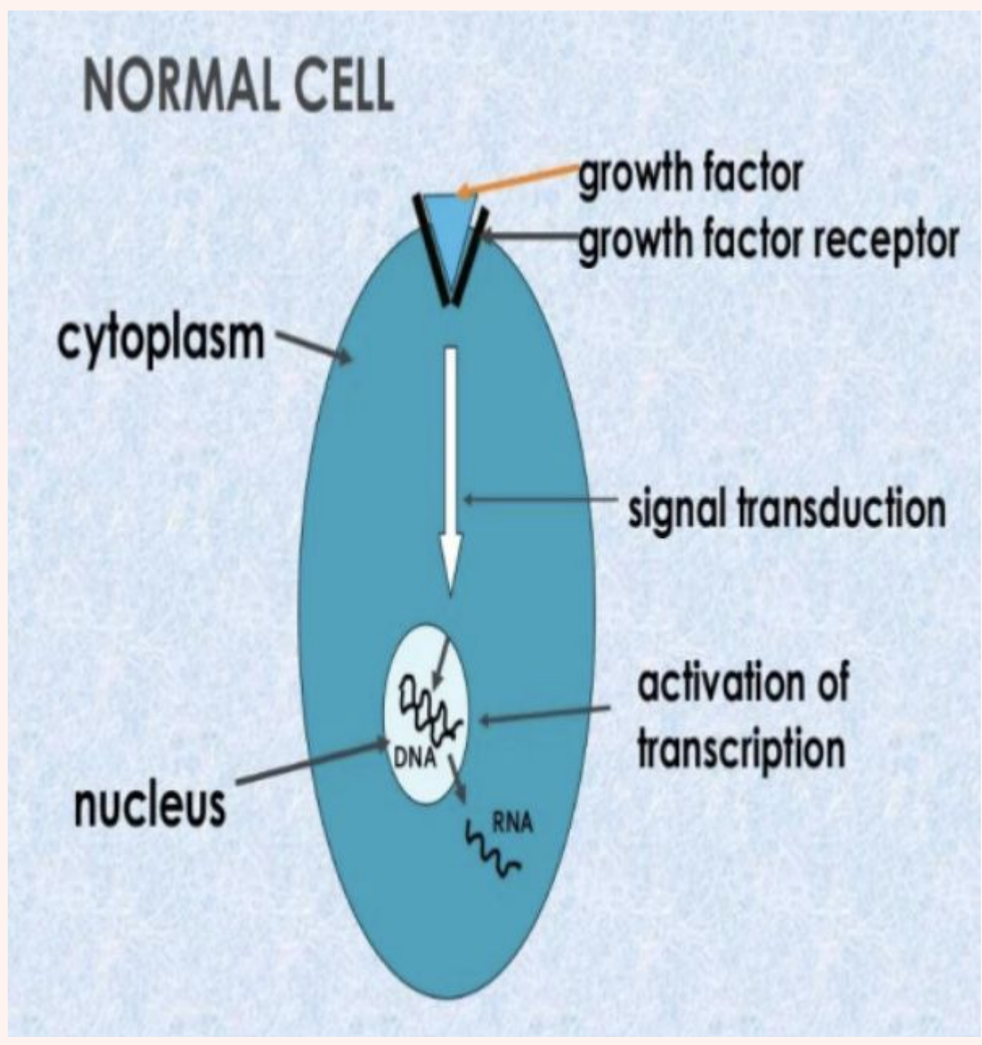
Female slides only

- Oncogene: Gene that promote autonomous cell growth in cancer cells
- They are derived by mutations in protooncogenes
- They are characterized by the ability to promote cell growth in the absence of normal growth-promoting signals
- Oncoproteins : are the products

Normal cell Cycle (from book):

1. Binding of a growth factor to its specific receptor on the cell membrane
2. Transient and limited activation of the growth factor receptor, which in turn activates several signal-transducing proteins
3. Transmission of the signal across to the nucleus
4. Induction and activation of nuclear regulatory factors that initiate and regulate DNA transcription
5. Entry into the cell cycle, resulting ultimately in cell division





Self sufficiency in growth signals cont.

GIRL'S SLIDES

1. Growth factors:

- Cancer cells are capable to synthesize the same growth factors to which they are responsive
- E.g. 1. Sarcomas → TGF-α 2. Glioblastoma → PDGF

2. Growth Factor receptors:

Receptors → mutation → continuous signals to cells and uncontrolled growth
Receptors → overexpression → cells become very sensitive→hyperresponsive to normal levels of growth factors

Example of Growth factors receptors:
Epidermal Growth Factor (EGF) Receptor family (HER2)

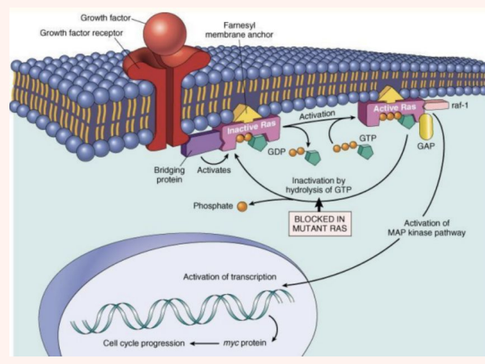
- Amplified in breast cancers and other tumors
- High levels of HER2 in breast cancer indicate poor prognosis
- Anti- HER2 targeted therapies (Tratuzaumab) in positive cases

3. Signal Transducing proteins :

They receive signals from activated growth factors receptors and transmit them to the nucleus. Examples : RAS and ABL

1. RAS gene:

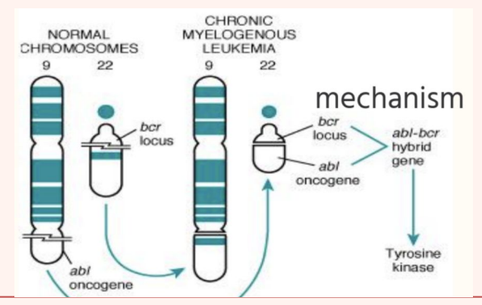
a. 30% of all human tumors contain mutated RAS gene E.g : colon and pancreas cancers
b. Mutations of the RAS gene is the most common oncogene abnormality in human tumors
c. Mutations in RAS → cells continue to proliferate



1. ABL gene:

a. ABL protooncogene has a tyrosine kinase activity
b. Its activity is controlled by negative regulatory mechanism
c. E.g. : chronic myeloid leukemia (CML) :
i. t(9,22) → ABL gene transferred from ch. 9 to ch. 22

ii. Fusion with BCR → BCR-ABL
Iii. BCR-ABL has tyrosine kinase activity →(oncogene)
➔ CML patients are treated with (Gleevec) which is inhibitor of kinase



4. Nuclear Transcription factors :

-Mutations may affect genes that regulate transcription of DNA, growth autonomy
E.g. MYC

- MYC protooncogene produce MYC protein when cell receives growth signals
- MYC protein binds to DNA leading to activation of growth-related genes

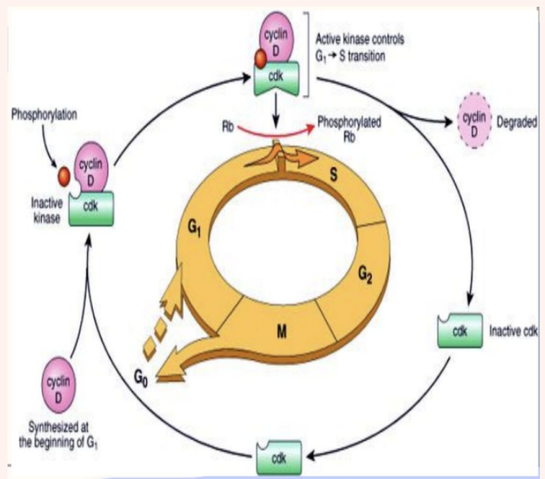
-In tumors there is sustained expression of MYC → continuous proliferation
-E.g. Burkitt Lymphoma; MYC is dysregulated due to t(8,14)

5. Cyclins and Cyclins-Dependent Kinases (CDKs)

-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.

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



Insensitivity to growth-inhibitory signals

GIRL'S SLIDES

- Tumor suppressor genes control (apply breaks) cell proliferation.

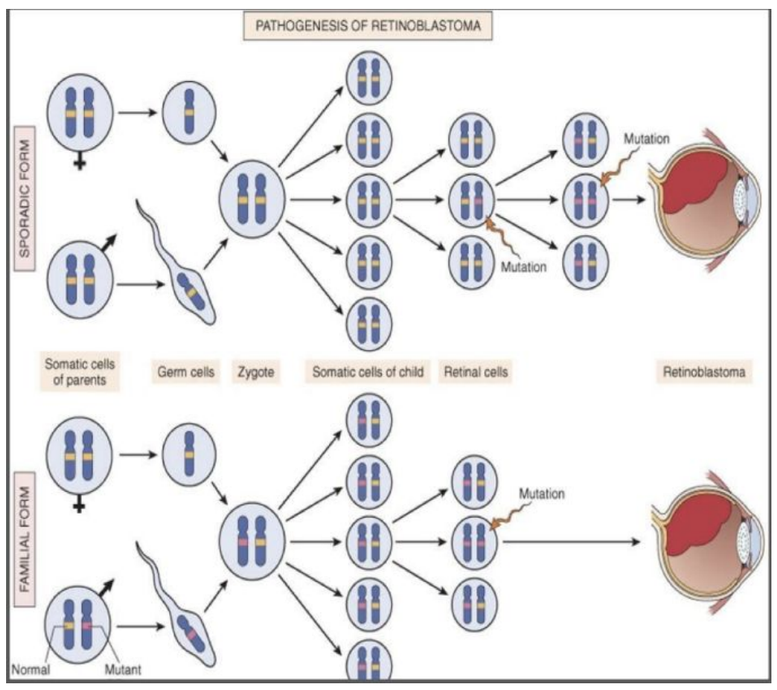
Mutation causes disruption

Cell becomes insensitive to growth inhibition

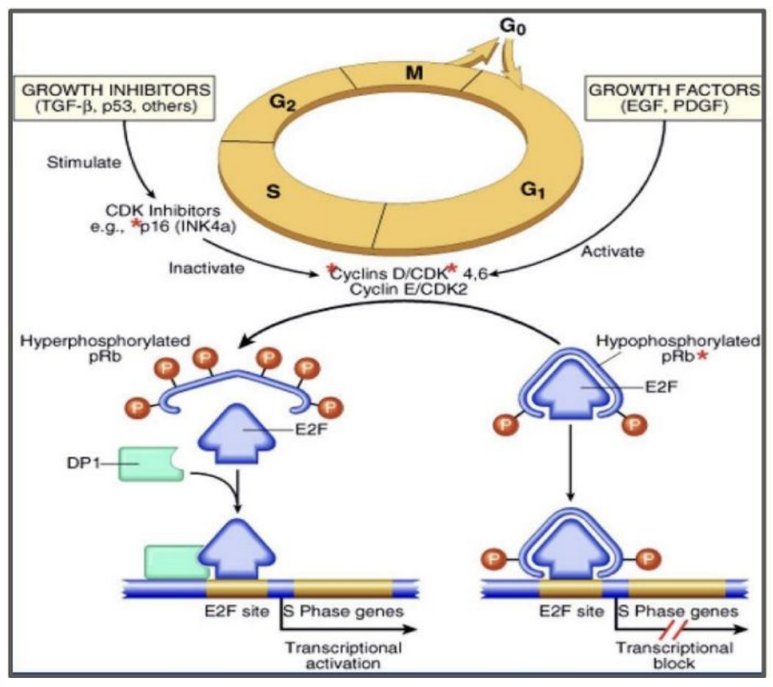
Uncontrolled proliferation

- Examples

P53	RB	ABC	TGF-B
The most popular example (439 note)	Retinoblastoma gene	(Adenomatous Polyposis Coli – B Catenin pathway)	Transforming Growth Factor- B pathways)



- Retinoblastoma
  - First 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
  - Retinoblastoma is 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

Insensitivity to growth-inhibitory signals Cont.

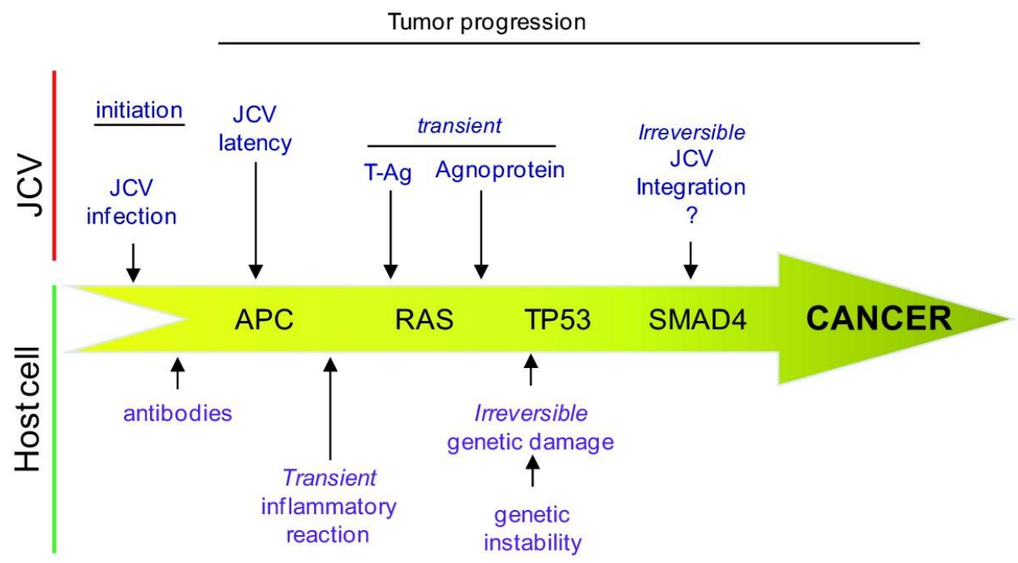
GIRL'S SLIDES

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.

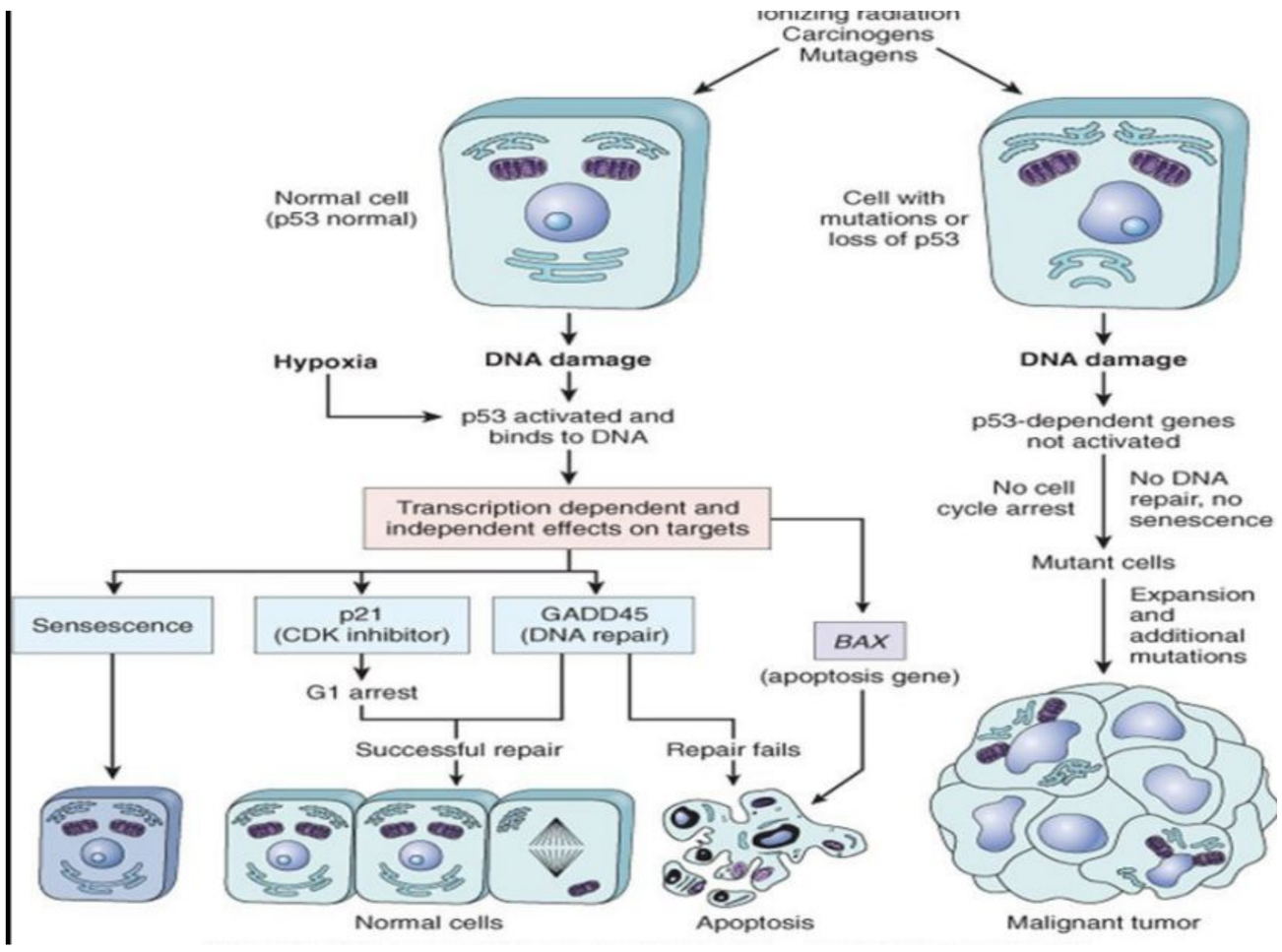
APC

- 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.



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



GIRL'S SLIDES

Evasion of apoptosis

- Mutation in the genes regulating apoptosis are factors in malignant transformation
- Cell survival is controlled by genes that promote and inhibit apoptosis
- Apoptosis in normal cell is guided by :

Cell death receptors (CD95)- activation lead to DNA damage

Pro-apoptotic factors (BAD, BAX and p53).

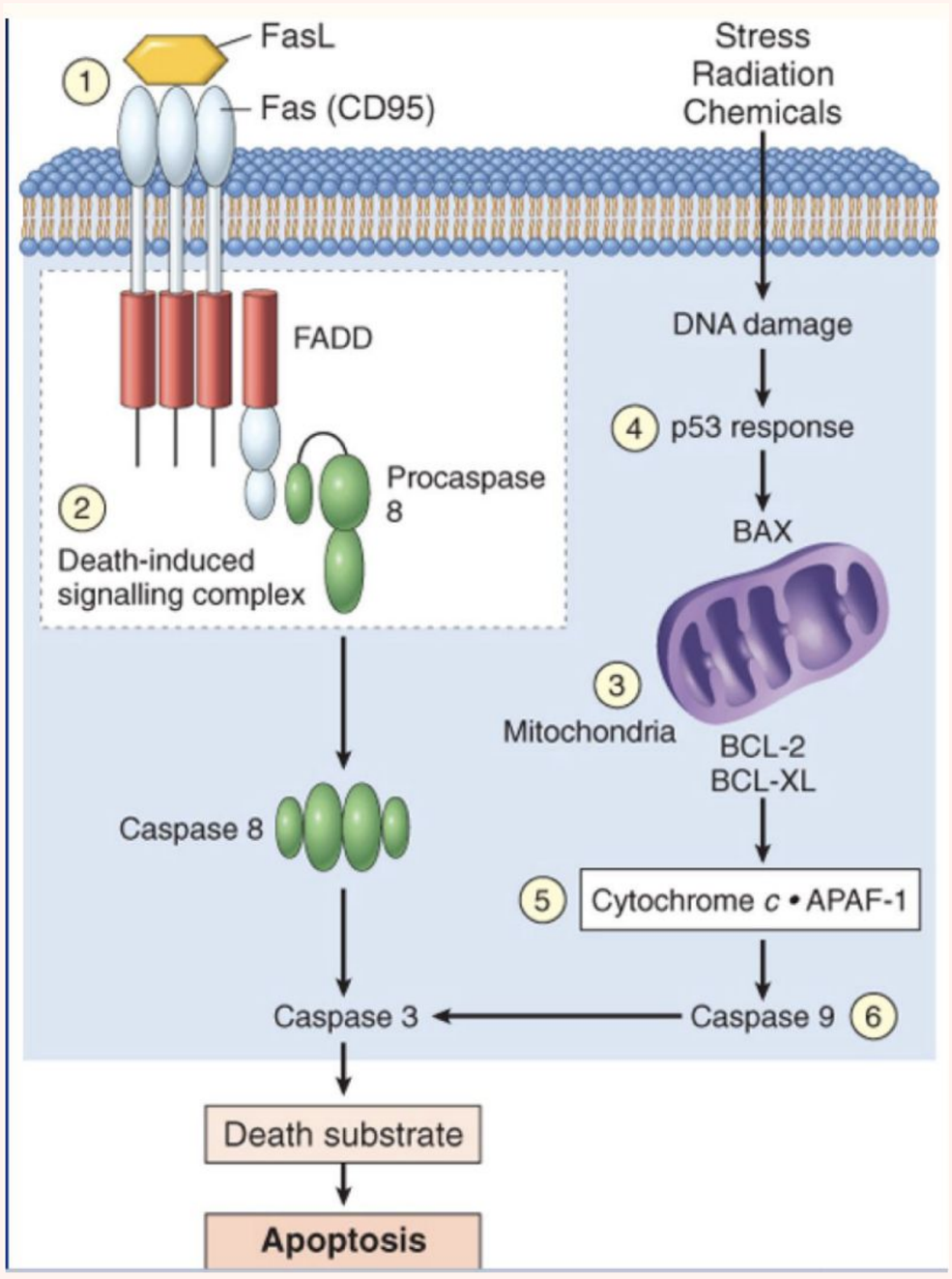
Apoptosis inhibitors (BCL2 and BCL-X)

❏ Reduce CD95 level inactivate death inducing signalling 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

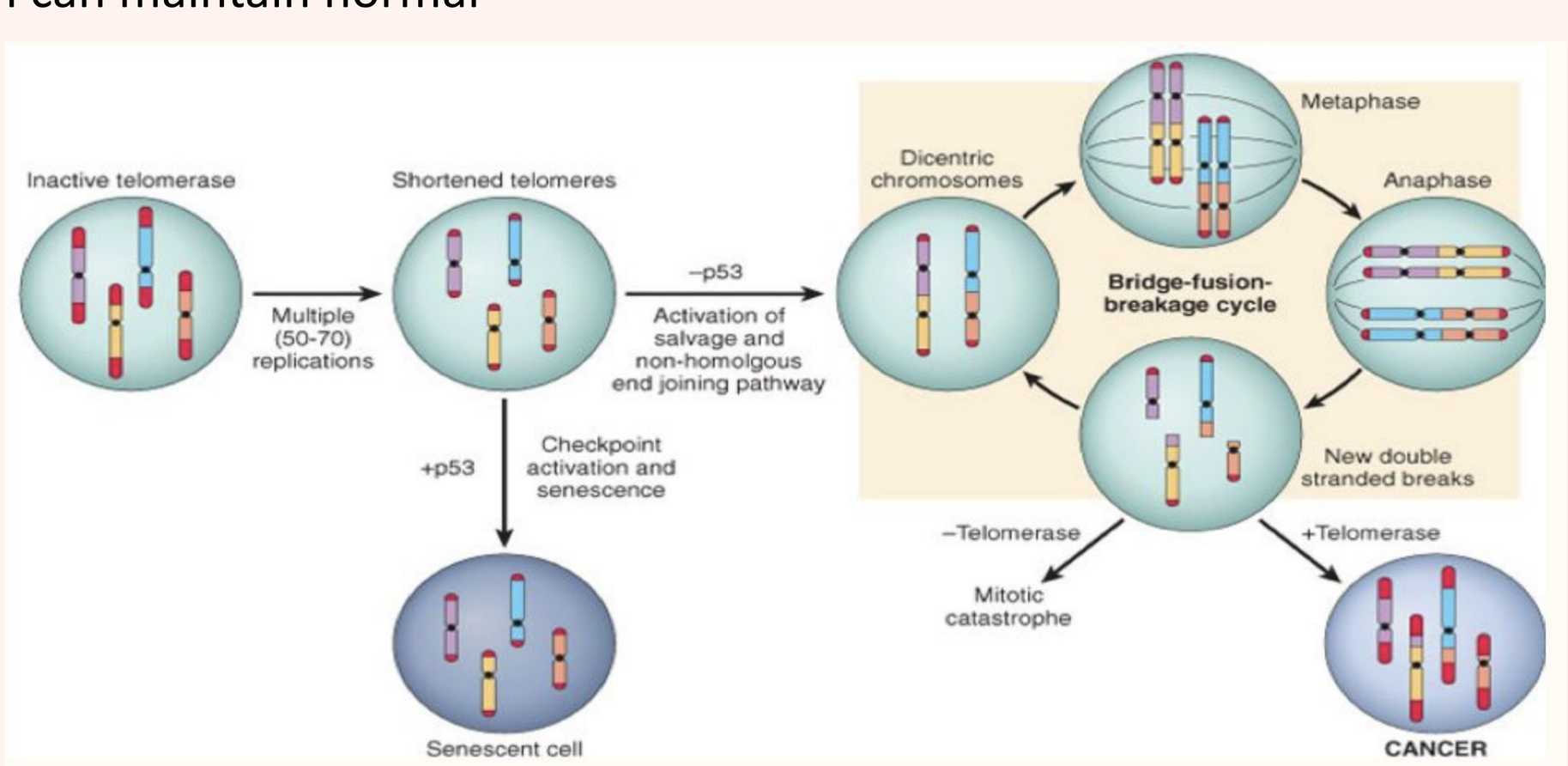


Limitless replicative potential

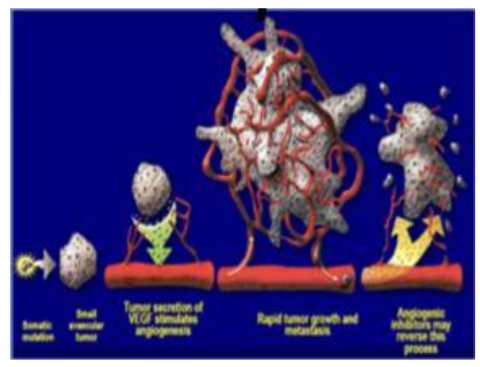
- Normally there is progressive shortening of telomeres at the ends of chromosomes

- 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



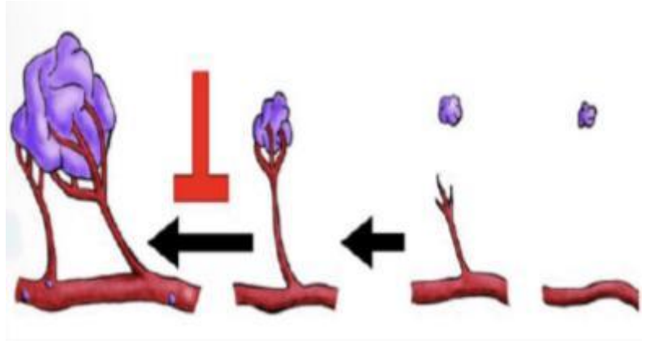
Sustained angiogenesis



- 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, IL-1.

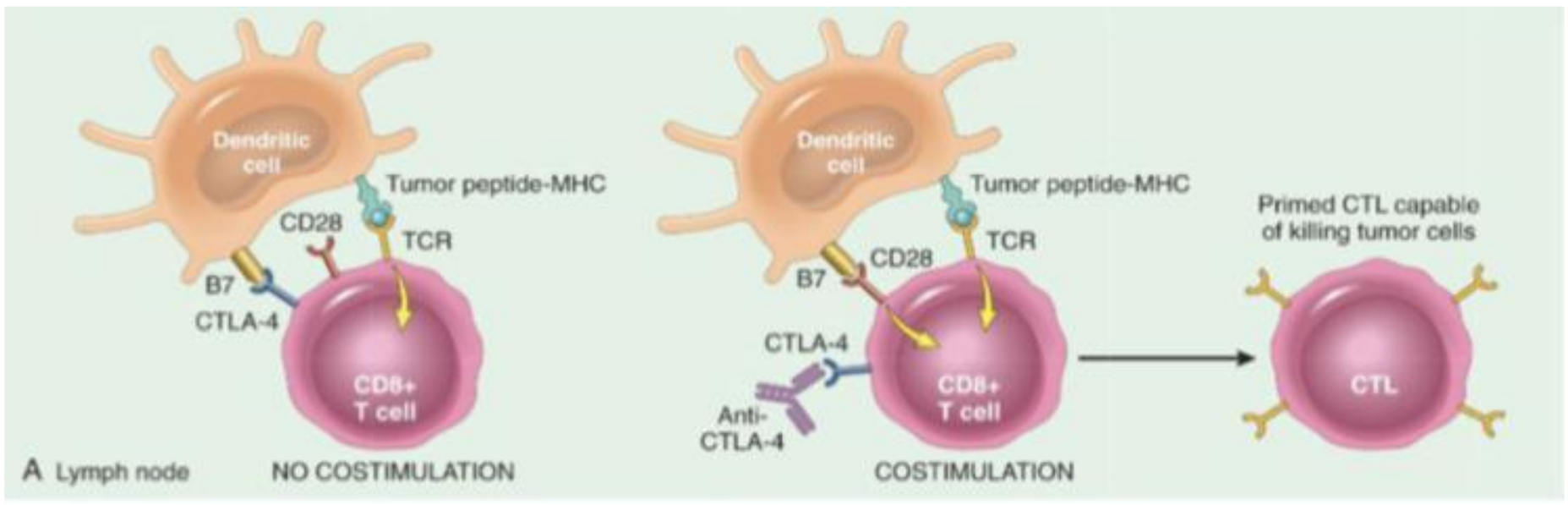
- Angiogenesis is required for metastasis

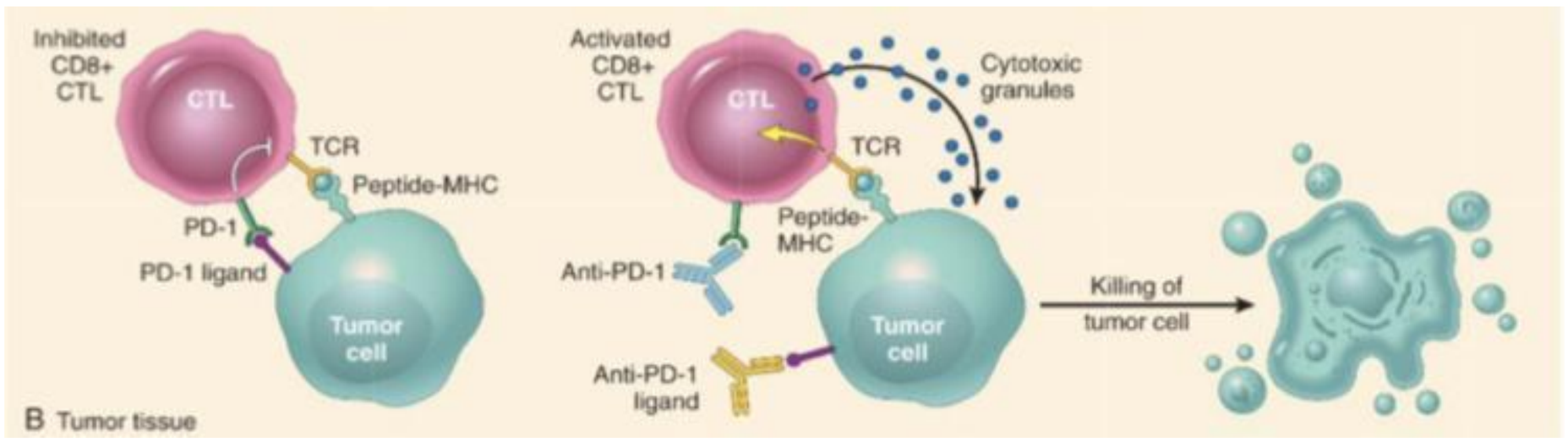


How do tumors develop a blood supply?

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

Avoiding immune destruction





GIRL'S SLIDES

Ability to invade and metastasize

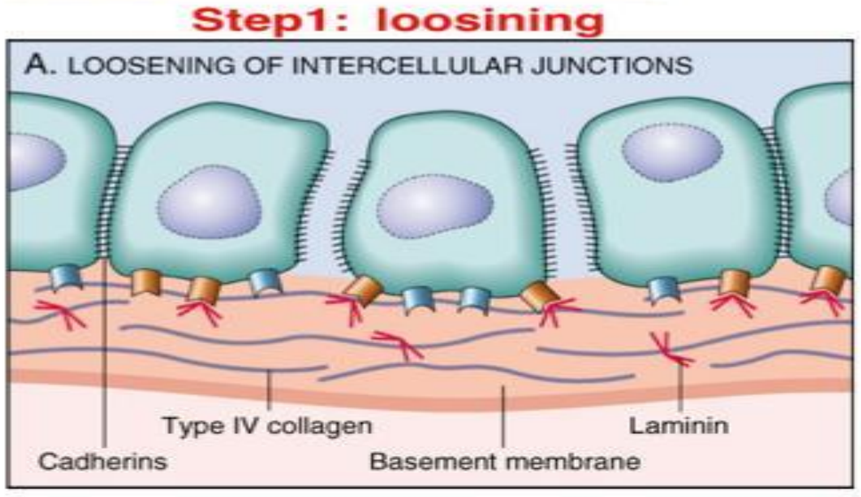
2 phases

01 Invasion of Extracellular material

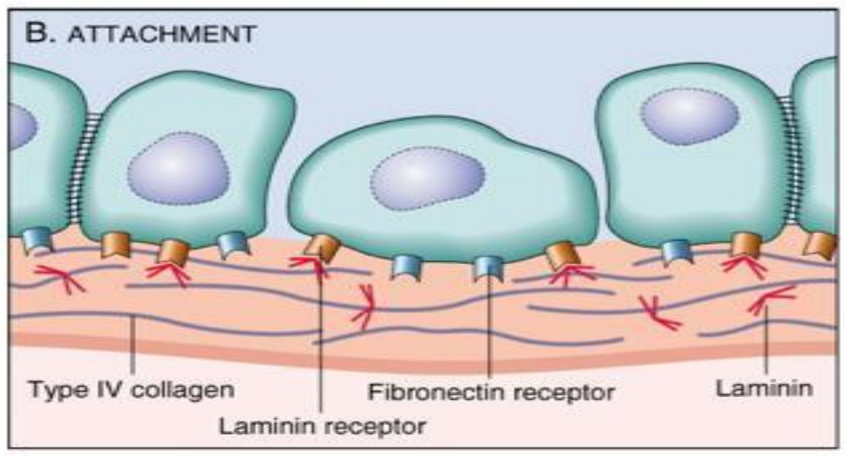
- Malignant cells first breach the underlying basement membrane.
- Traverse the interstitial tissue.
- Penetrate vascular basement membrane to gain access to circulation. (To spread and metastasize)

Ability to invade and metastsize

Step1: loosining

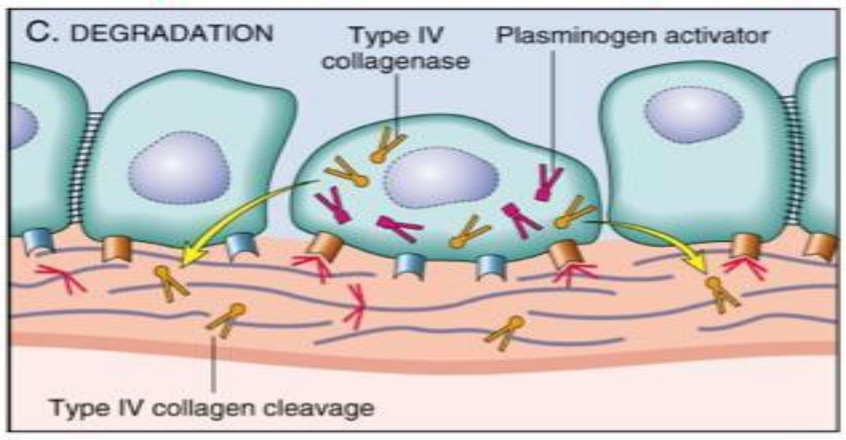


Step2: Attachment to ECM

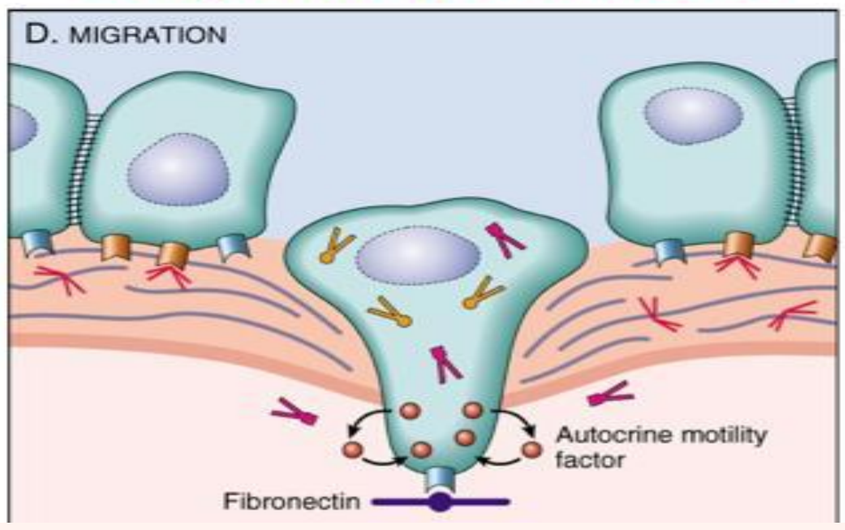


Ability to invade and metastsize

Step 3. Degradation by collagenase



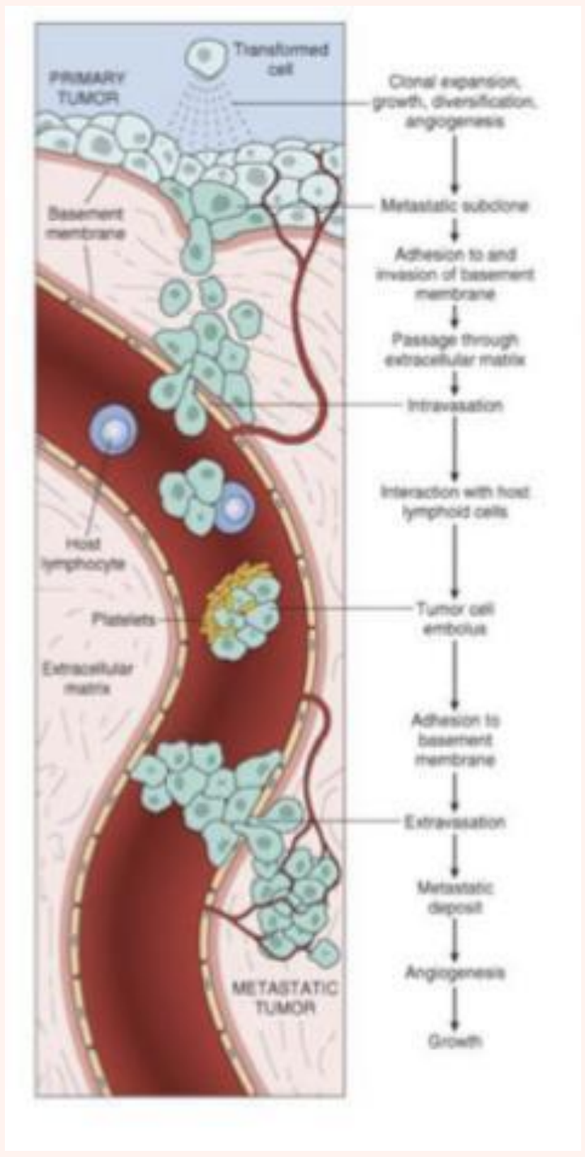
4. Migration of tumor cells



GIRL'S SLIDES

Ability to invade and metastasize

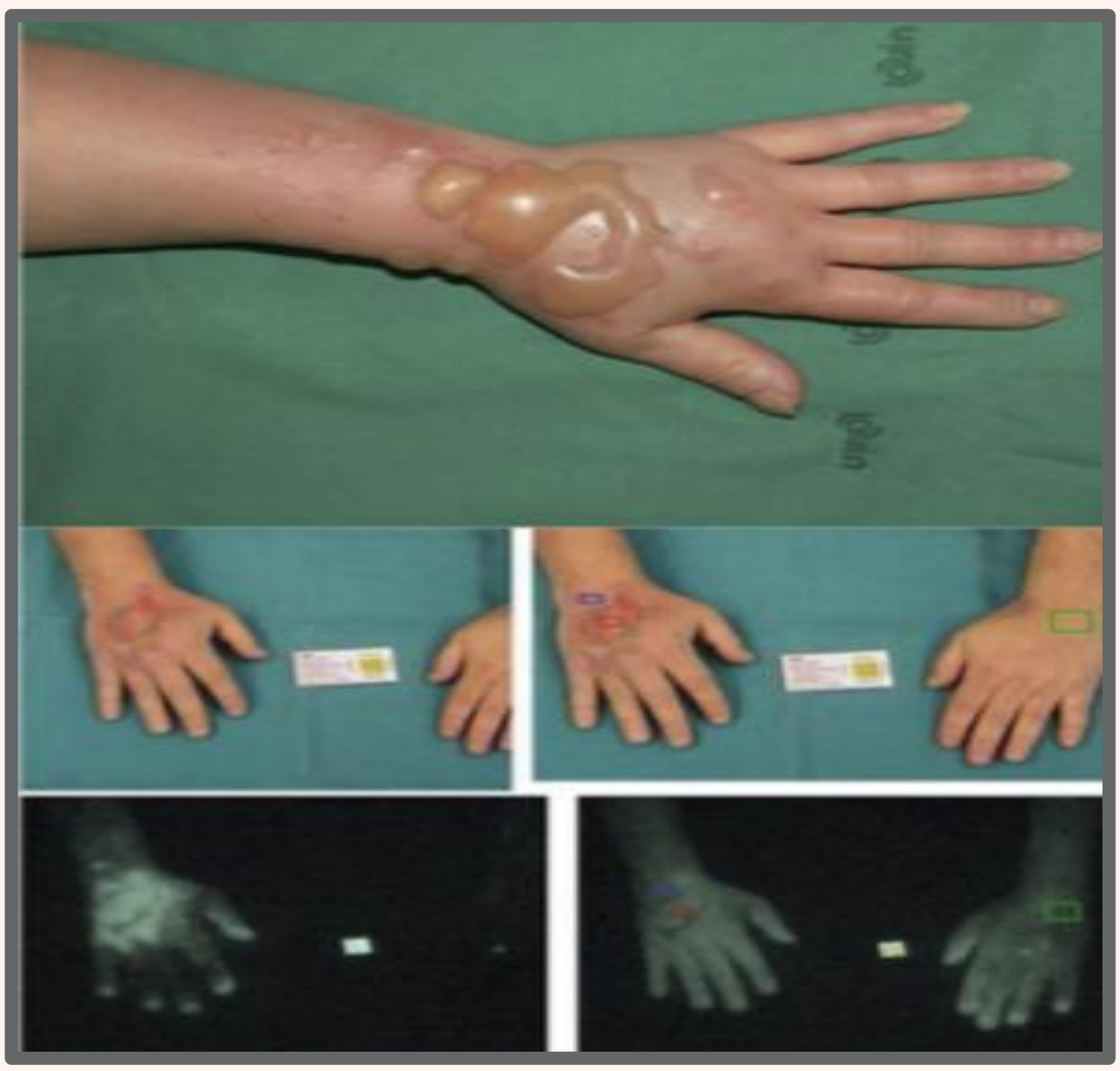
2 phases



02

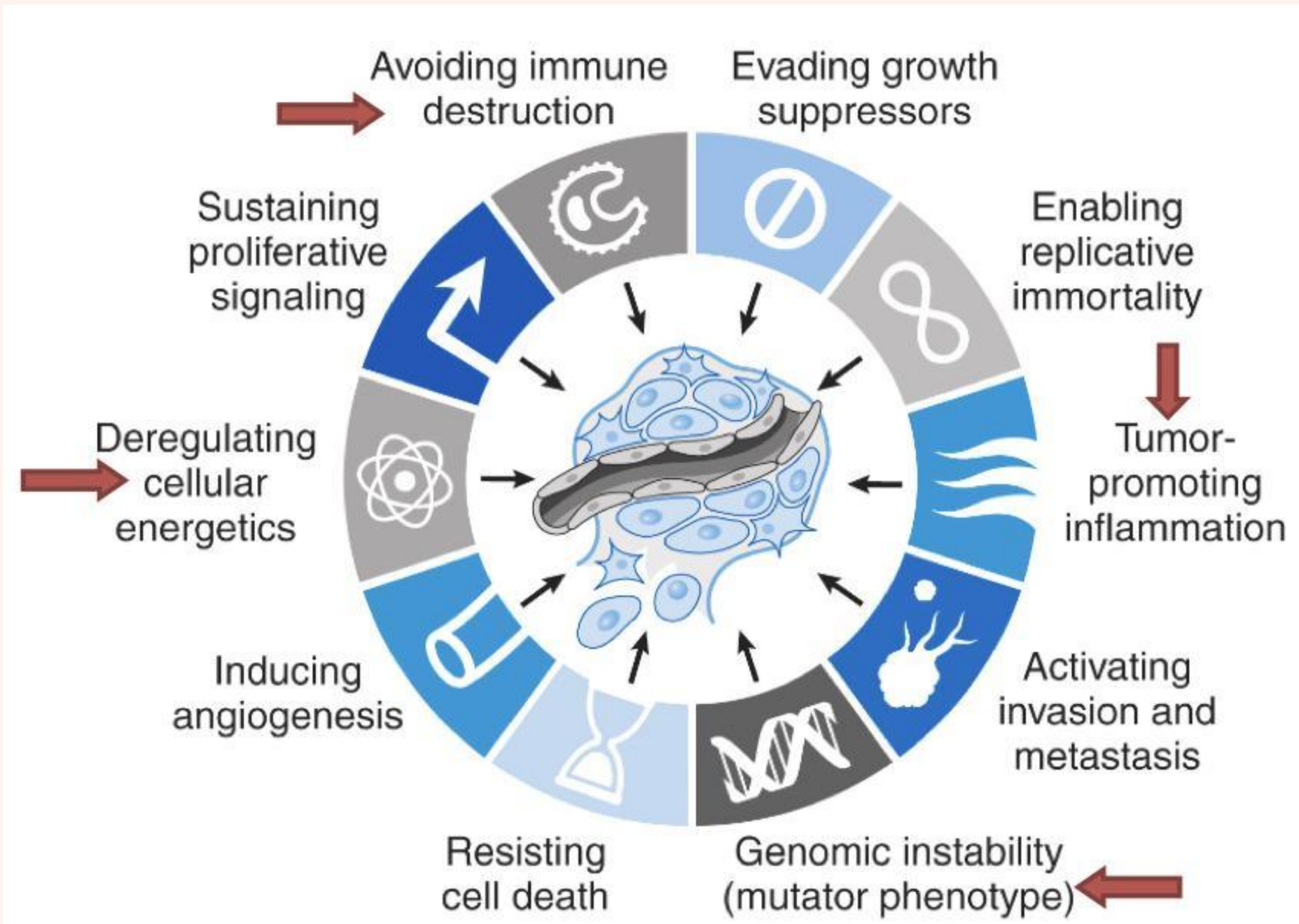
Vascular dissemination and homing of tumor cells

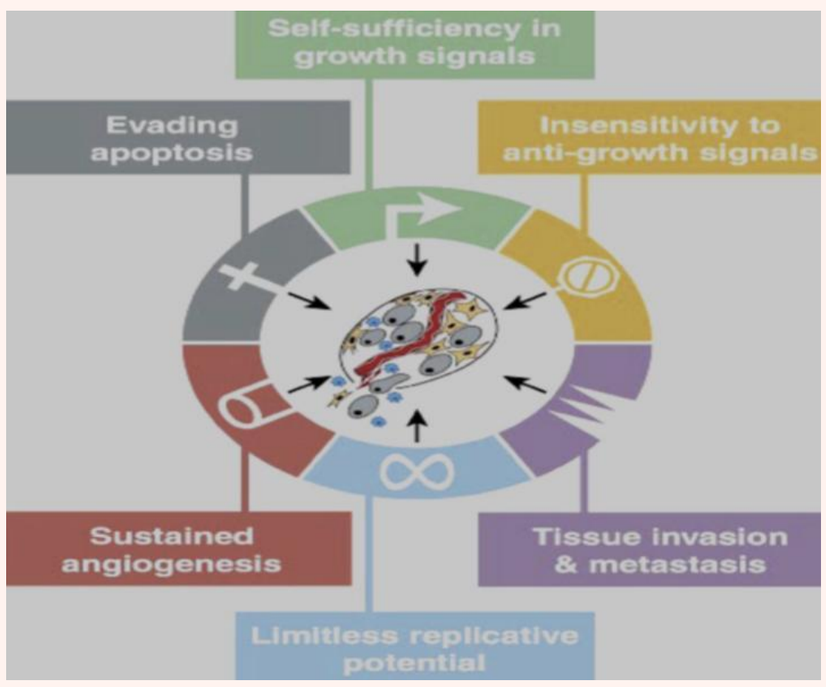
- May form emboli.
- Most travel a single cells. (one cell is enough to cause metastasis).
- The tumor cells adhere to the vascular endothelium (can lead to the formation of an embolus as mentioned above).
- Extravasation (leakage of blood or any fluid).



GIRL'S SLIDES

Hallmarks of cancer





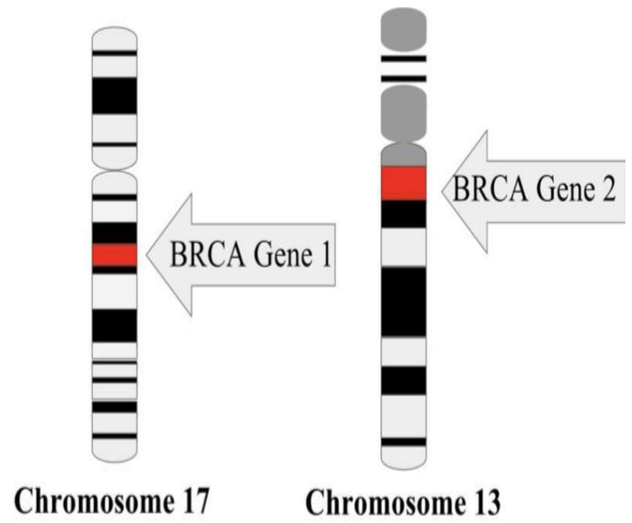
GIRL'S SLIDES

Genomic instability

- The enabler of malignancy.
- Caused by a defect in the DNA repair genes.

Examples:

Hereditary Nonpolyposis Colon Carcinoma	Xeroderma pigmentosum	Familial Breast Cancers



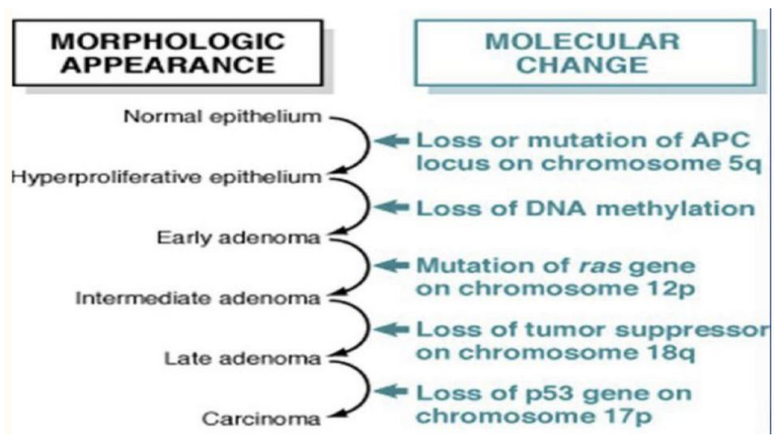
Familial breast cancer is caused by:
Mutations in BRCA 1 and BRCA 2 genes which regulate DNA repairs.
- These genes account for 80% of familial breast cancer.
- They are also involved in other malignancies.

In females it increases the risk of breast cancer and pancreatic cancer.
In men it increases the risk of prostate cancer and pancreatic cancer.

439 note:
Both copies of BRCA1 and BRCA2 must be inactive for cancer to occur.

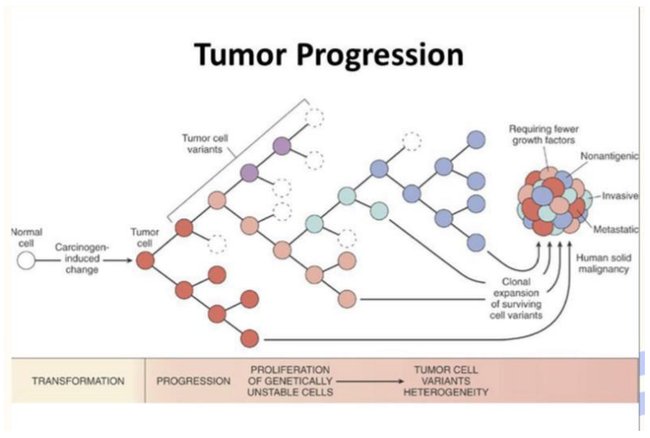
Molecular basis of multistep carcinogenesis

1. Cancer result from the accumulation of multiple mutations
2. All Types of cancer have multiple genetic alterations, involving activation of several oncogenes and the 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 (it's not an increase in size but in number) similar to hyperplasia "in concept".
- By the time the tumor becomes evident, their constituent cells become extremely Heterogeneous.



Genetic Lesions in Cancer

- The genetic changes found in cancers vary from point mutations (Molecular lab) involving single nucleotides to abnormalities large enough to produce gross changes in chromosome structure (Cytogenetics lab).
- Driver mutations are mutations that alter the function of cancer genes and thereby directly contribute to the development or progression of a given cancer.
- Passenger mutations are acquired mutations that are neutral and do not affect cellular behavior but proven to be important in cancer.
- Passenger mutations greatly outnumber driver mutations.

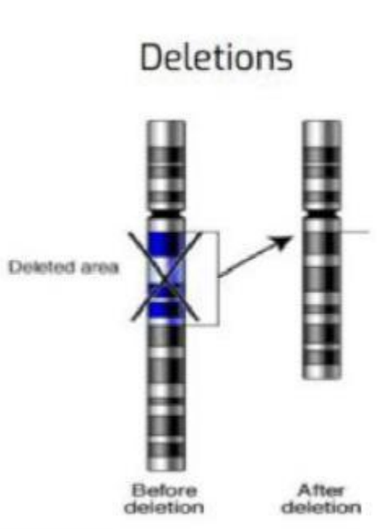
Point mutations

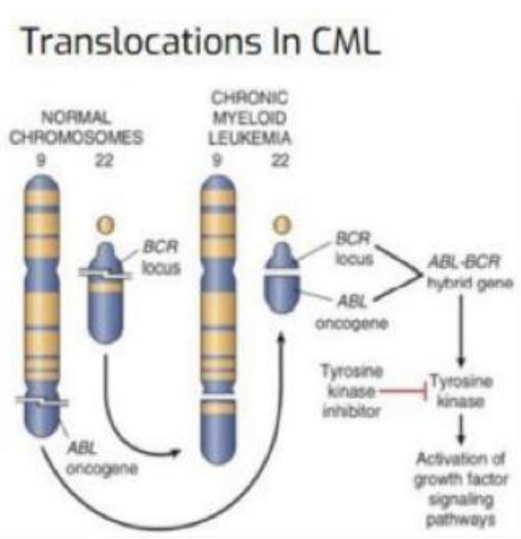
- Point mutations can either activate or inactivate the protein products of the affected genes depending on their precise position and consequence.
- Point mutations that convert proto-oncogenes into oncogenes (class 1) generally produce a gain-of-function, like RAS gene into a cancer gene, one of the most comment events in human cancers, KRAS in Ch 12 develop colon cancer.
- By contrast, point mutations (as well as larger aberrations, such as insertions and deletions) in tumor suppressor genes (class 2) reduce or disable the function of the encoded protein, like TP53, a prototypical "guardian" type tumor suppressor gene.

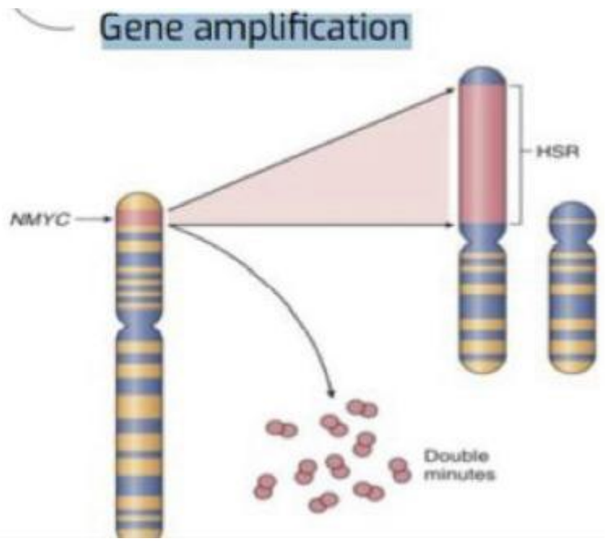
Will a mutation of RAS gene lead to cancer? information not enough, it might be a silent mutation.
Overexpression of RAS → cancer, down regulation → it will not develop.

Gene rearrangement (Diagnosed by karyotyping)

- Gene rearrangements may be produced by chromosomal translocations or inversions.
- Specific chromosomal translocations and inversions are highly associated with certain malignancies, particularly neoplasms derived from hematopoietic cells and other kinds of mesenchymal cells.
- Some gene rearrangements result in overexpression of proto- oncogenes leading to highly active promoter or enhancer like in >90% cases of **Burkitt lymphoma; t(8;14),** CMYC-IHG.
- Other oncogenic gene rearrangements create fusion genes encoding novel chimeric proteins Most notable is the Philadelphia (Ph) chromosome in **chronic myeloid leukemia (CML), t(9;22), BCR-ABL1.**
- In Follicular lymphoma: t(14,18)





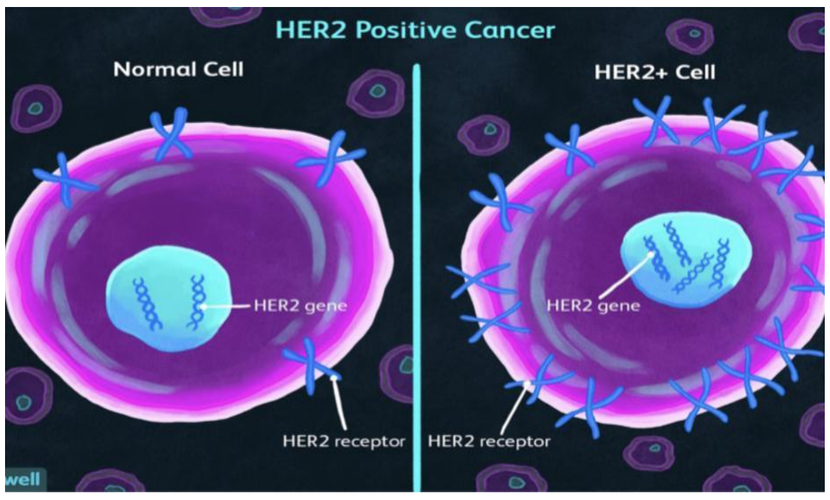


Gene amplification

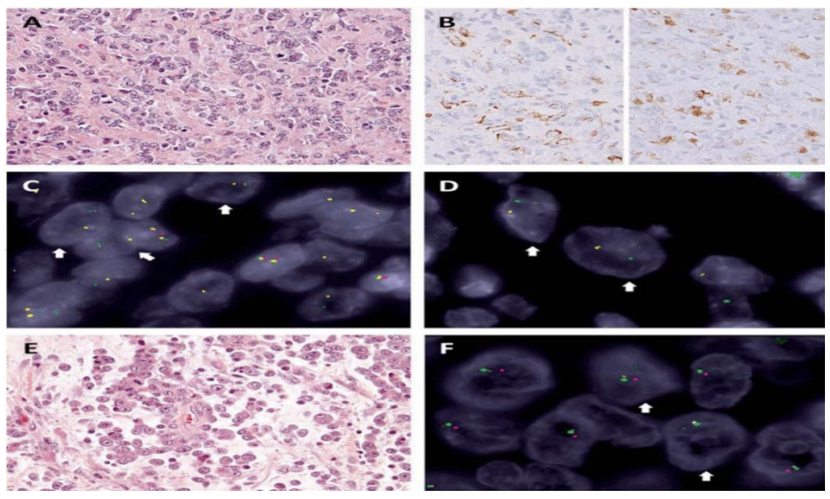
- Proto-oncogenes may be converted to oncogenes by gene amplification, with consequent overexpression and hyperactivity of otherwise normal proteins by producing several hundred copies of the gene, a change in copy number that can be readily detected by molecular hybridization (FISH or CGH-array) with appropriate DNA probes.
- Two mutually exclusive patterns are seen:

1. Multiple small, extra-chromosomal structures called double minutes
2. Homogeneously staining regions (HSR) derives from the insertion of the amplified genes into new chromosomal locations (might be detected by G-banded karyotype), like in Neuroblastoma (N-MYC, Ch2)

Breast cancer: HER-2



Deletion



Aneuploidy

- Aneuploidy is defined as a number of chromosomes that is not a multiple of the haploid state; for humans, that is a chromosome number that is not a multiple of 23.
- Aneuploidy is remarkably common in cancers.
- Mechanistic data establishing aneuploidy as a cause of carcinogenesis,rather than a consequence.

- However, tumor development and progression may be molded by changes in chromosome numbers that enhance the dosage of oncogenes while restricting the activity of tumor suppressor genes.

MicroRNAS and cancer

- MicroRNAs (miRNAs) are noncoding, single-stranded RNAs, approximately 22 nucleotides in length, that function as negative regulators of genes .
- They inhibit gene expression post-transcriptionally by repressing translation or, in some cases, by messenger RNA (mRNA).
- Specifically, if the target of a miRNA is a tumor suppressor gene, then overactivity of the miRNA can reduce the tumor suppressor protein.
- Downregulation or deletion of certain miRNAs in some leukemias and lymphomas results in increased expression of **BCL2**, an **anti-apoptotic gene** (also in RAS and MYC oncogenes)

DR'S NOTE

If a mutation happened to microRNAs what will it lead to?
Depends on the type of mutation and the gene it affects .

DR'S NOTE

↑miRNA ———> ↓BCL2 ———> Apoptosis ———> no tumors

↓miRNA ———> ↑BCL2 ———> proliferatio ———> tumor

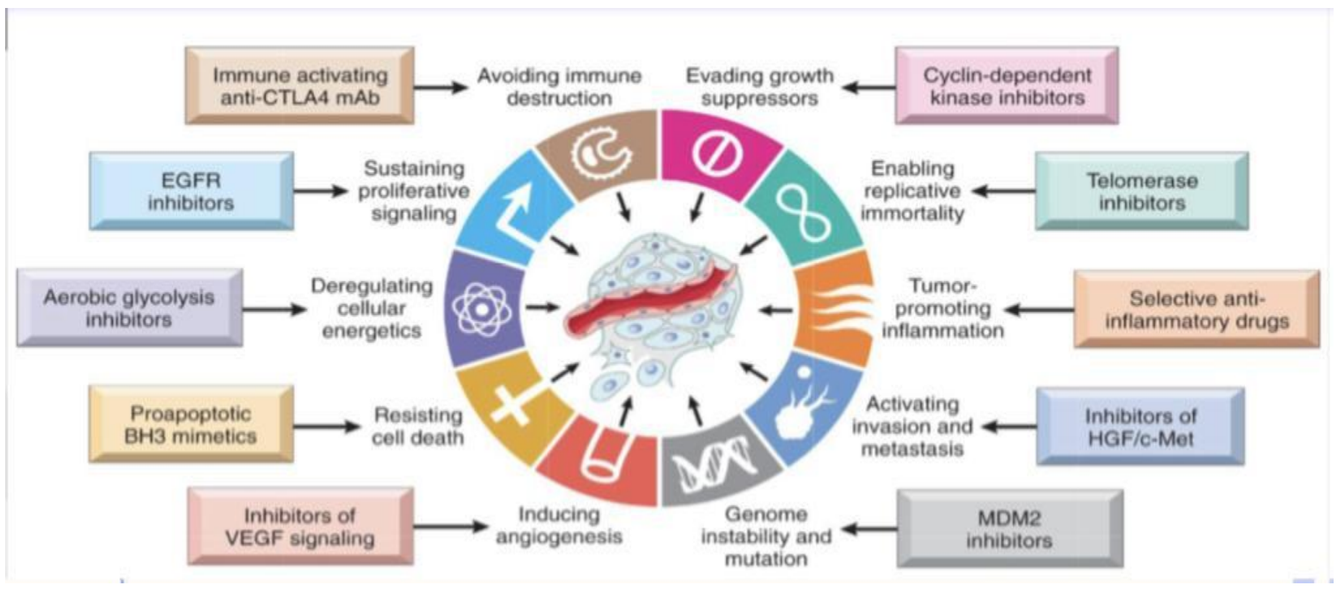
BOY'S SLIDES

Epigenetic Modifications and Cancer

- Epigenetics refers to reversible, heritable changes in gene expression that occur without mutation. Such changes involve posttranslational modifications of histones and DNA methylation.
- The epigenetic state of particular cell types dictates their response to signals that control growth and differentiation. For example,the NOTCH1 gene has an oncogenic role in T-cell leukemia.

Therapeutic targeting of the hallmarks of cancer

- Eight cancer hallmarks and two enabling factors (genomic instability and tumor- promoting inflammation). Most cancer cells acquire these properties during their development, typically due to mutations in critical genes.



BOY'S SLIDES

Summary

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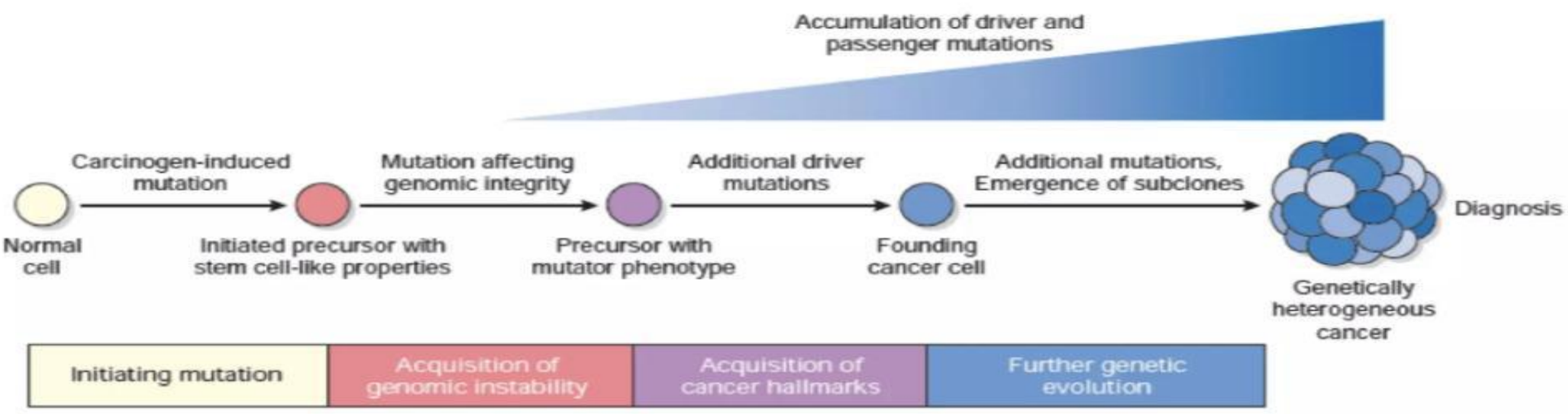
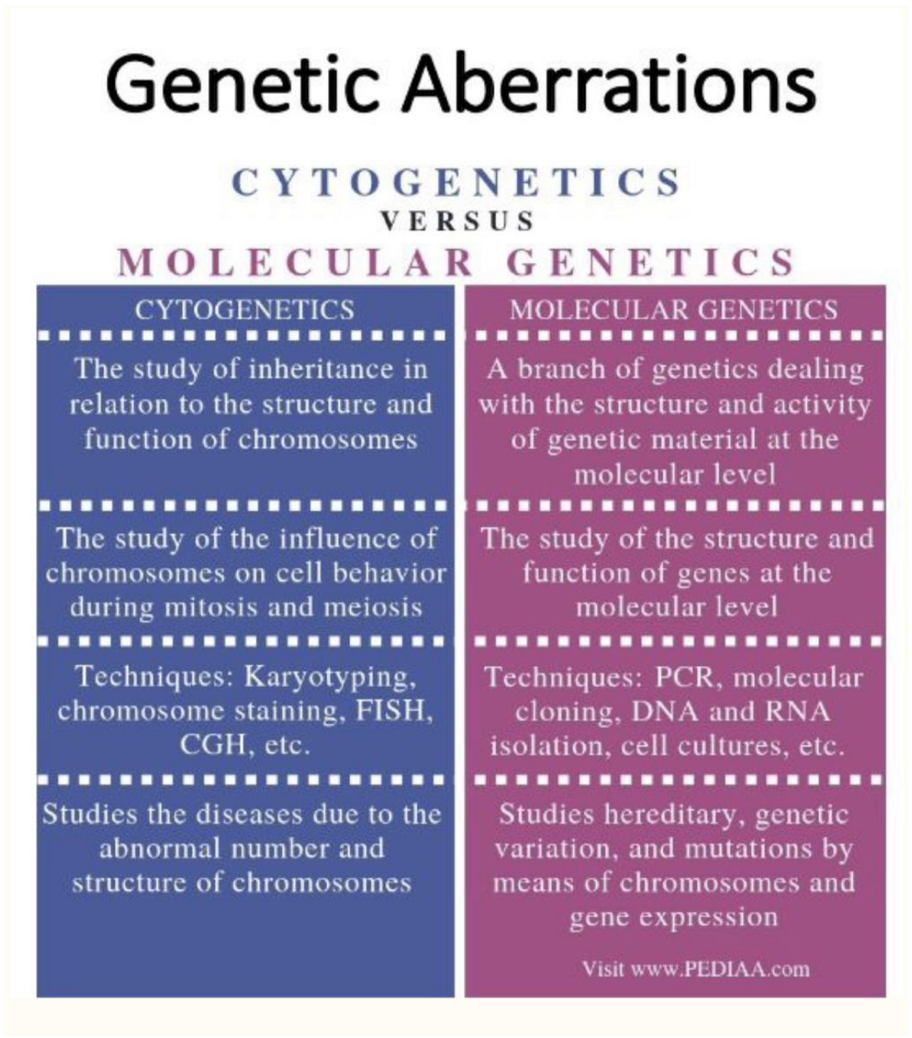
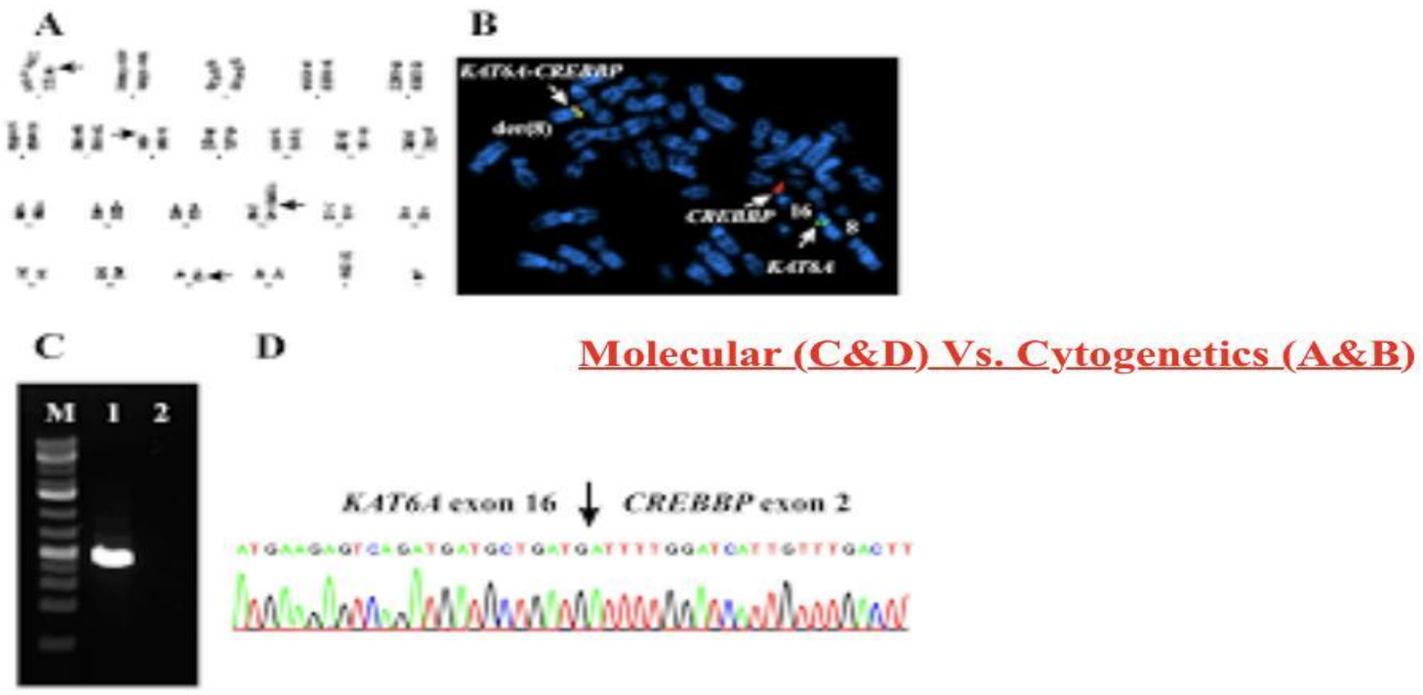
- Mutations in cancer cells fall into two major classes,
  - driver (pathogenic) mutations and
  - passenger (neutral) mutations.
- Passenger mutations may become driver mutations if selective pressure on the tumor changes, for example, in the setting of treatment with an effective therapeutic drug.
- Tumor cells acquire driver mutations through several means, including point mutations and nonrandom chromosomal abnormalities that contribute to malignancy; these include gene rearrangements, deletions, and amplifications.
- Gene rearrangements (usually caused by translocations, but sometimes by inversions of other more complex events) contribute to carcinogenesis by overexpression of oncogenes or generation of novel fusion proteins with altered signaling capacity. Deletions frequently affect tumor suppressor genes, whereas gene amplification increases the expression of oncogenes.
- Overexpression of miRNAs can contribute to carcinogenesis by reducing the expression of tumor suppressors, while deletion or loss of expression of miRNAs can lead to overexpression of proto-oncogenes.
- Tumor suppressor genes and DNA repair genes also may be silenced by epigenetic changes, which involve reversible, heritable changes in gene expression that occur not by mutation but by methylation of the promoter.



BOY'S SLIDES



Inherited Predisposition	Gene(s)
Autosomal Dominant Cancer Syndromes	
Retinoblastoma	*RB*
Li-Fraumeni syndrome (various tumors)	*TP53*
Melanoma	*CDKN2A*
Familial adenomatous polyposis/colon cancer	*APC*
Neurofibromatosis 1 and 2	*NF1, NF2*
Breast and ovarian tumors	*BRCA1, BRCA2*
Multiple endocrine neoplasia 1 and 2	*MEN1, RET*
Hereditary nonpolyposis colon cancer	*MSH2, MLH1, MSH6*
Nevoid basal cell carcinoma syndrome	*PTCH1*
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum	Diverse genes involved in nucleotide excision repair
Ataxia-telangiectasia	*ATM*
Bloom syndrome	*BLM*
Fanconi anemia	Diverse genes involved in repair of DNA cross-links



Molecular (C&D) Vs. Cytogenetics (A&B)

BOY'S SLIDES

cancer Genes

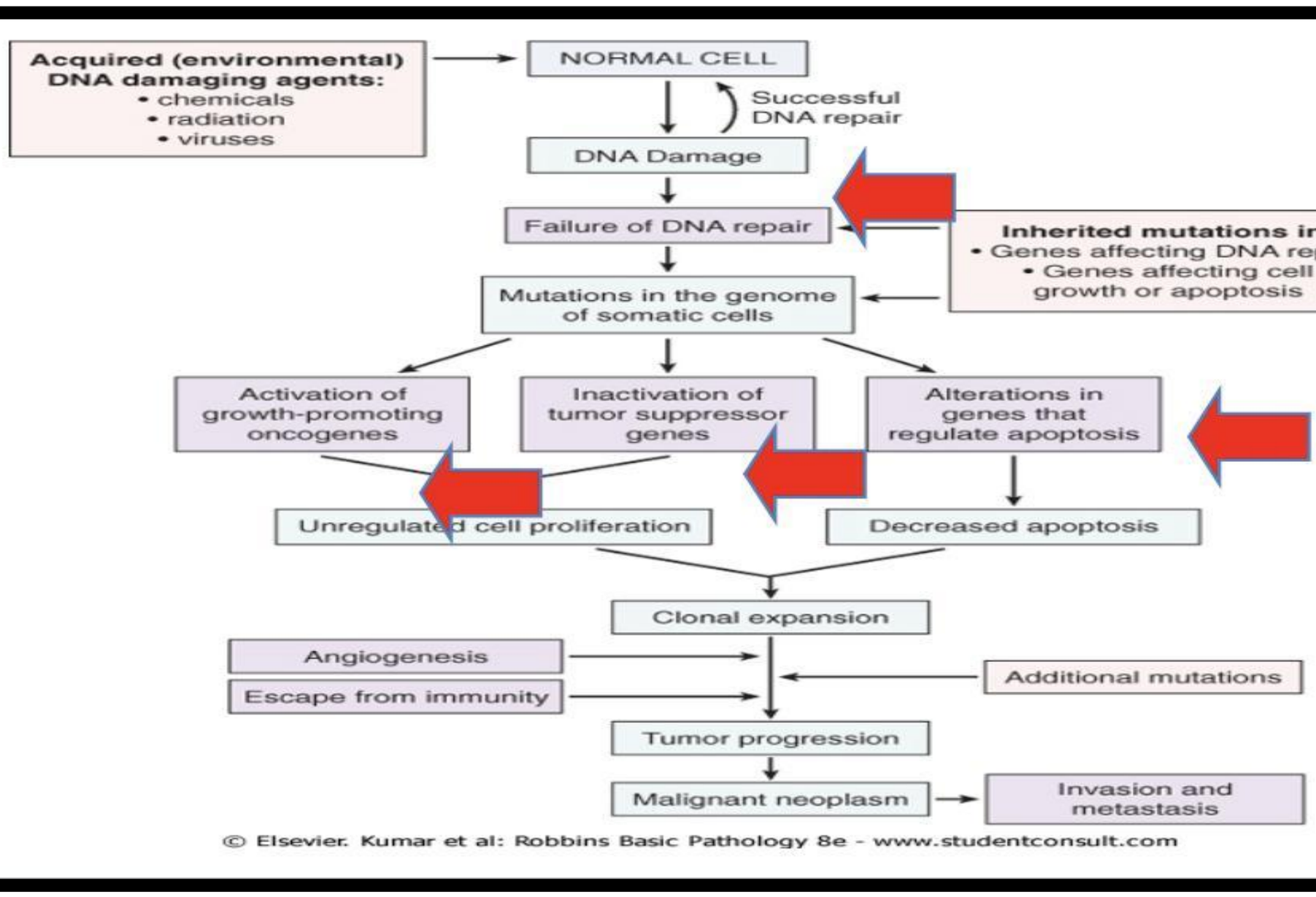
- It has become eminently clear that cancer is a disease caused by mutations that alter the function of a finite subset of the 20,000 or so human genes.

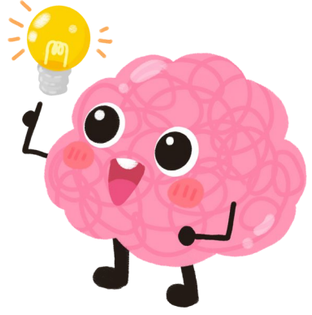
- For simplicity, we will refer to these genes as cancer genes and usually they fall into one of four major functional classes:
  1.Oncogenes,
  2.Tumor suppressor genes,
  3.Genes that regulate apoptosis,
  4.Genes that regulate interactions between tumor cells and host cells

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

- Mutation may be acquired by the action of environmental agents, such as chemicals, radiation, or viruses, or it may be inherited in the germ line.

- The genetic hypothesis of cancer implies that a tumor mass results from the clonal expansion of a single progenitor cell that has incurred genetic damage (i.e., tumors are monoclonal).





KEYWORDS

t(9,22)	Chronic myeloid leukemia is associated with t(9,22)
TP53	Li-Fraumni Syndrome is due to defect in TP53
BCL2	BCL2 is Anti-apoptosis factor
Telomerase	Normally active enzyme in stem cells
Overexpression	Cells become very sensitive hyperresponsive to normal levels of growth factors
Translocation	is a type of chromosomal change occurs in chronic myeloid leukemia
Tumor cells	In Tumor cells telomerase is present
P53	this Tumor suppressors genes is called “guardian of the genome

MCQ

Answer:
1-B 6-A
2-D 7-D
3-C 8-B
4-C
5-D

1- Chronic myeloid leukemia is associated with..?			
A)HER2	**B)t(9,22)**	**C)t(8,14)**	**D)none**
2- Li-Fraumni Syndrome is due to defect in?			
A)Rb	**B)MLH1**	**C)APC**	**D)TP53**
3- Anti-apoptosis factor?			
A)CD95	**B)MYC**	**C)BCL2**	**D)TP53**
4-Normally active enzyme in stem cells?			
A)COX	**B)Phospholipase**	**C)Telomerase**	**D)Tyrosine Kinase**
5- Cells become very sensitive hyperresponsive to normal levels of growth factors?			
A)Oncogene	**B)protooncogene**	**C)HER2**	**D)Overexpression**

MCQ

Answer:
6-A
7-D
8-B

6- What type of chromosomal change occurs in chronic myeloid leukemia?

A)Translocation	B)Deletions	C)Gene amplification	D)Inversion

7- In which cells is telomerase present?

A)Somatic cells	B)Stem cells	C)Tumor cells	D)B and C

8- Which one of these Tumor suppressors genes is called “guardian of the genome”?

A)PB	B)P53	C)APC	D)TGF-B

PATHOLOGY TEAM 444

PATHOLOGY TEAMWORK

MED444

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