

# Neoplasia

## Lecture 3

CARCINOGENESIS

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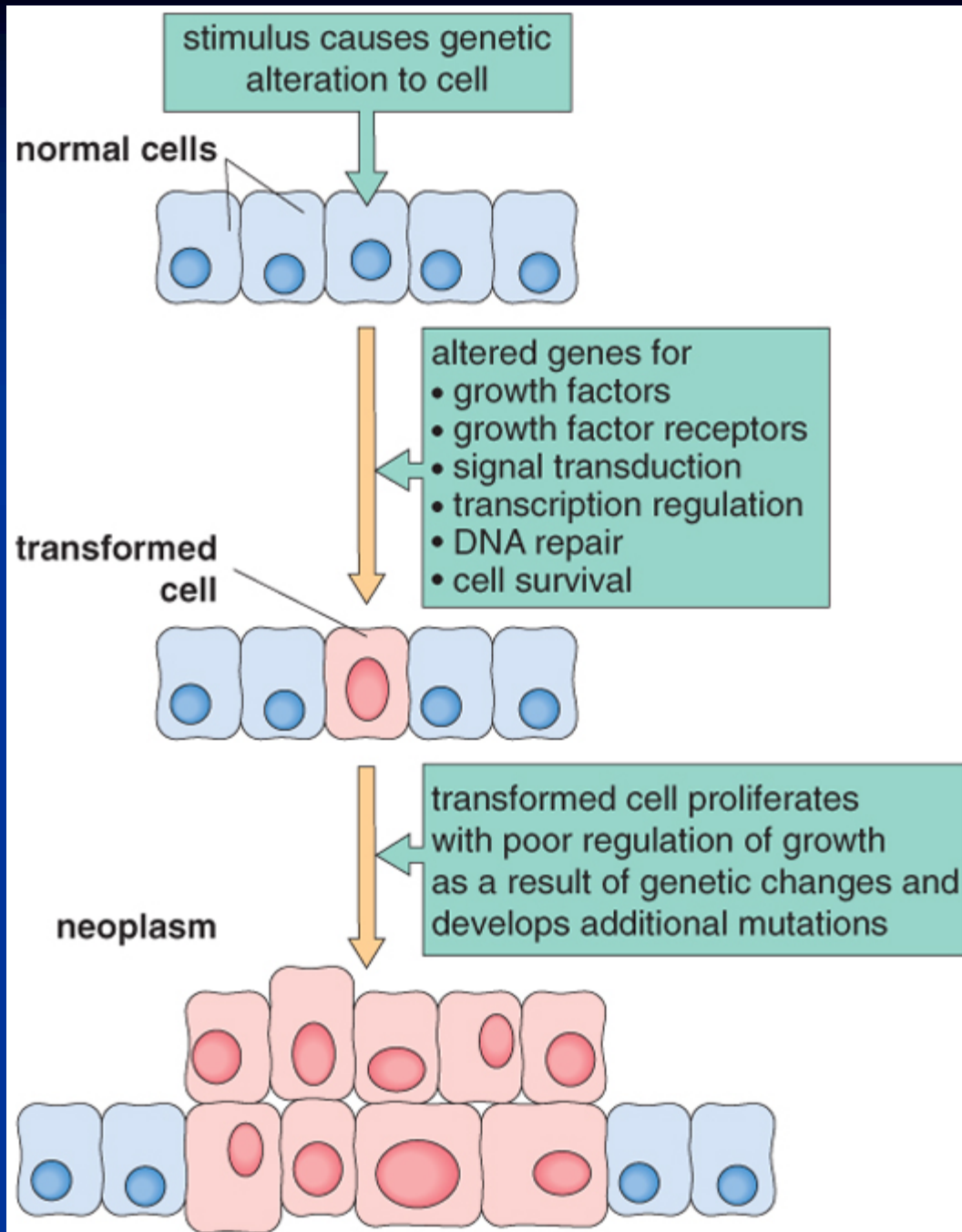
Foundation block 2014  
Pathology

# CARCINOGENESIS

- Carcinogenesis is a multistep process at both the phenotypic and the genetic levels.
- It starts with a genetic damage:
  - Environmental
    - Chemical
    - Radiation
    - Infectious
  - Inherited

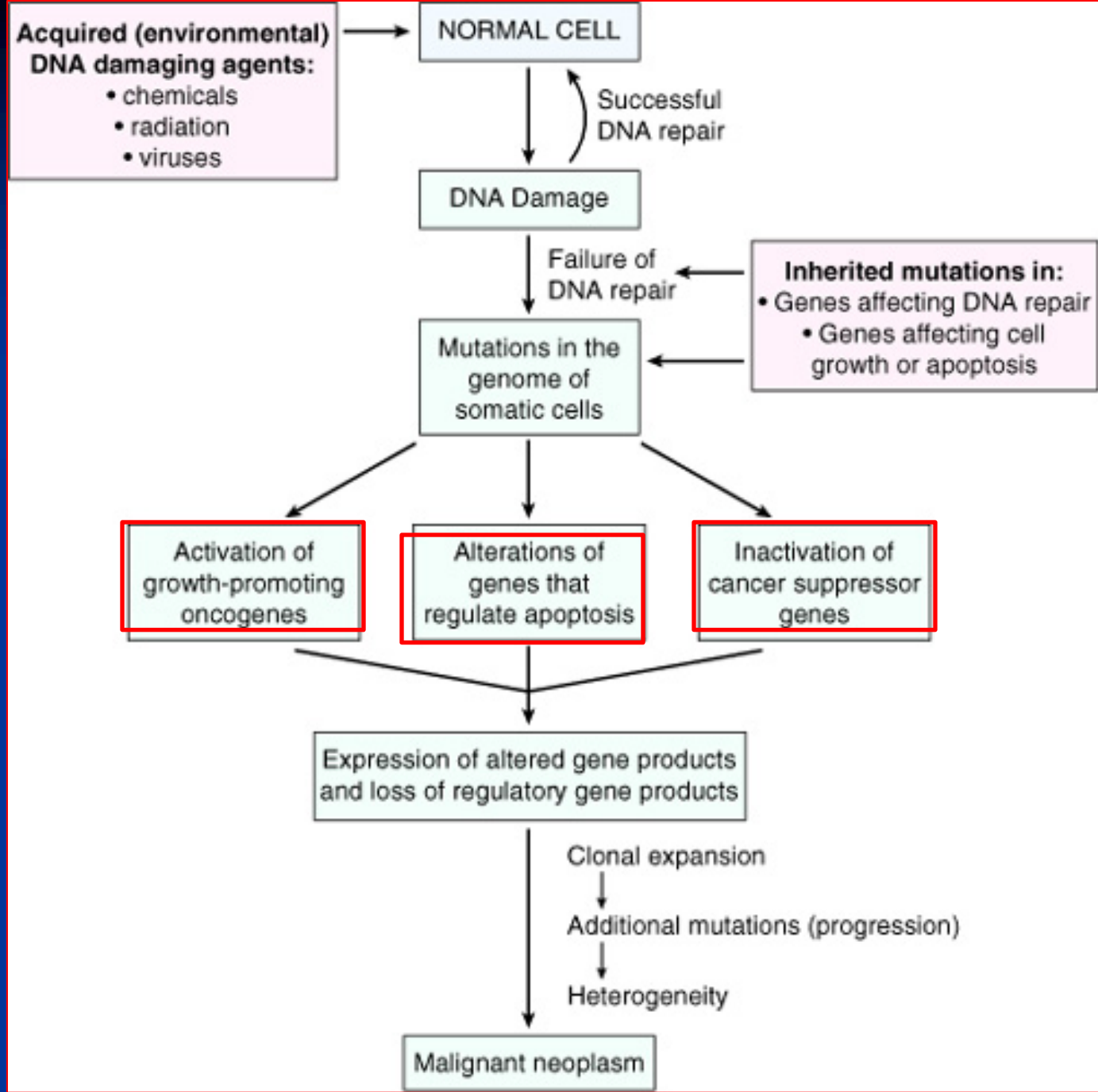
# Carcinogenesis

- Genetic damage lead to “mutation”
- single cell which has the genetic damage undergoes neoplastic proliferation ( clonal expansion) forming the tumor mass



# Carcinogenesis

- Where are the targets of the genetic damage??
- Four regulatory genes are the main targets:
  - Growth promoting protooncogenes
    - Protooncogene > mutation > oncogene
  - Growth inhibiting (supressors) genes
  - Genes regulating apoptosis
  - DNA repair genes



# Carcinogenesis

- 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

# Carcinogenesis

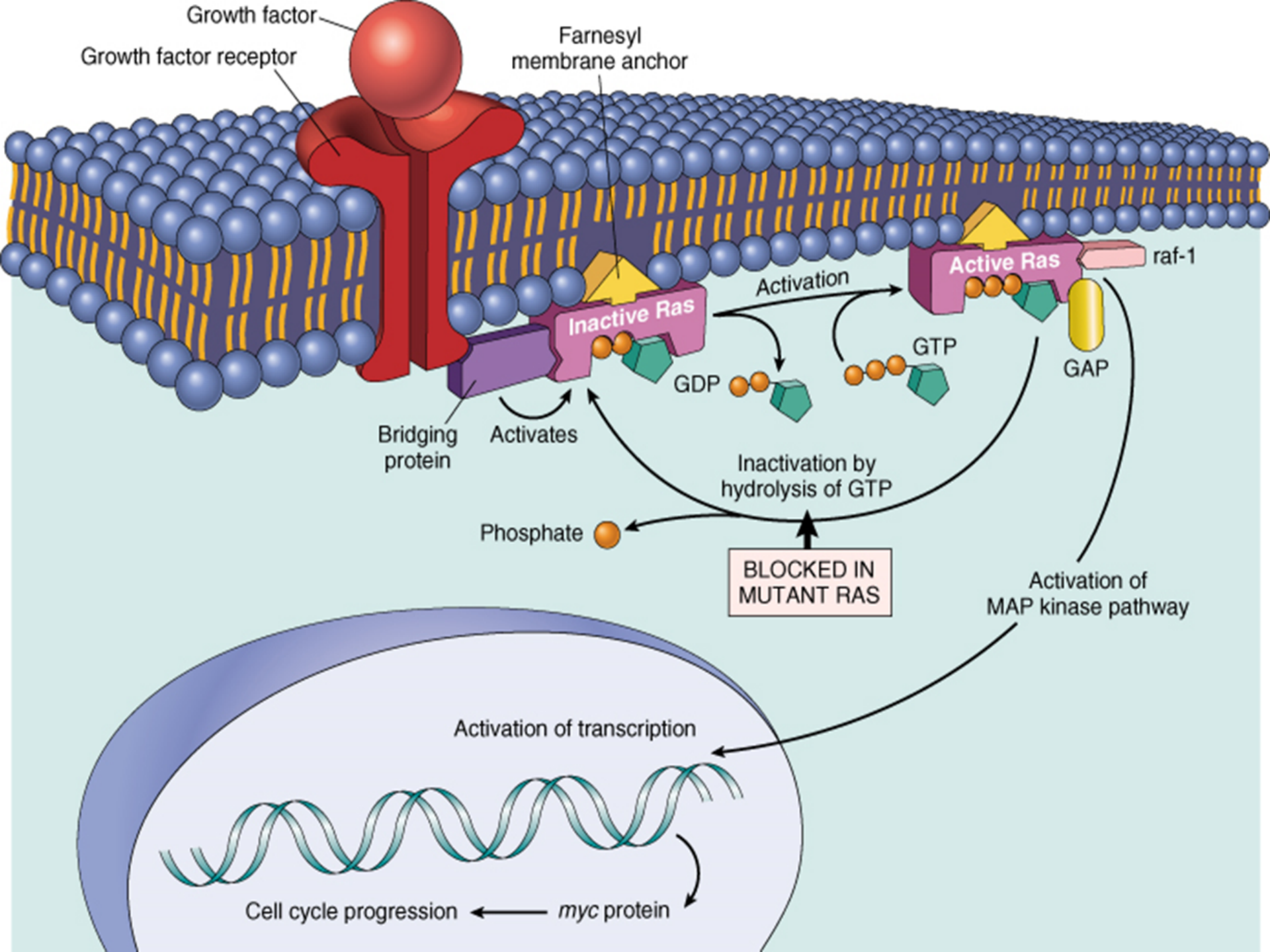
## A - Self-sufficiency in Growth signals:

- 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



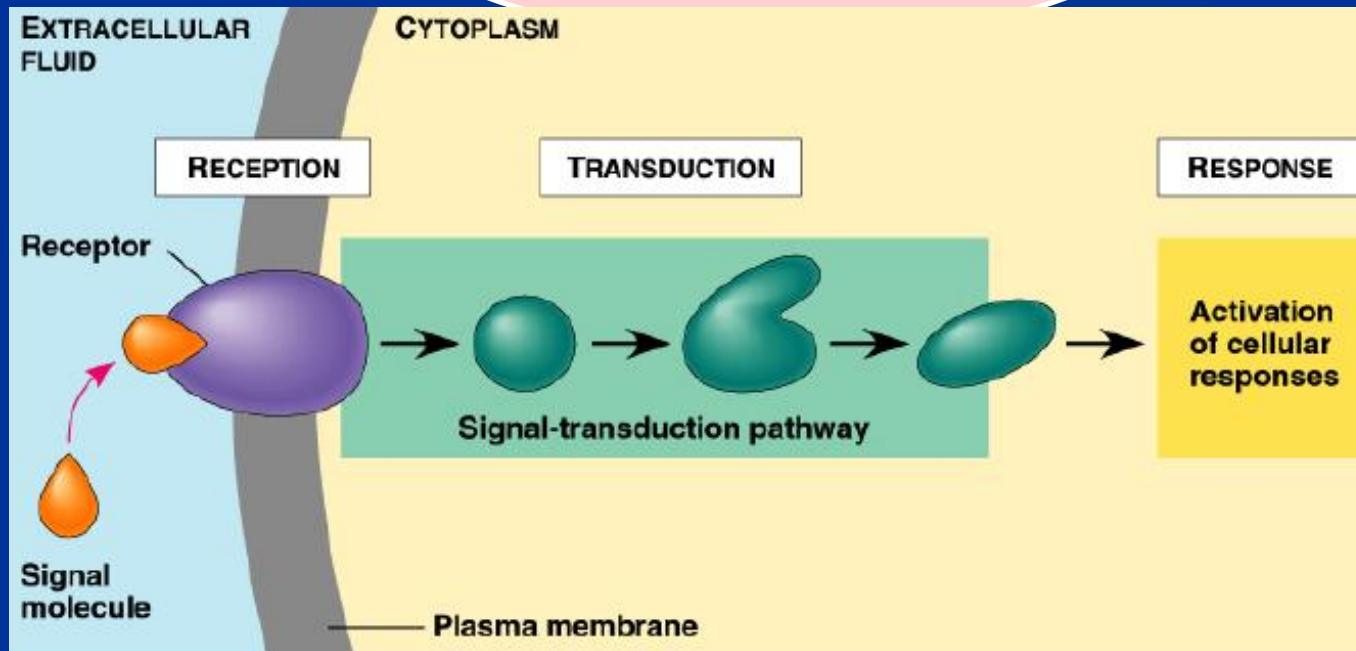
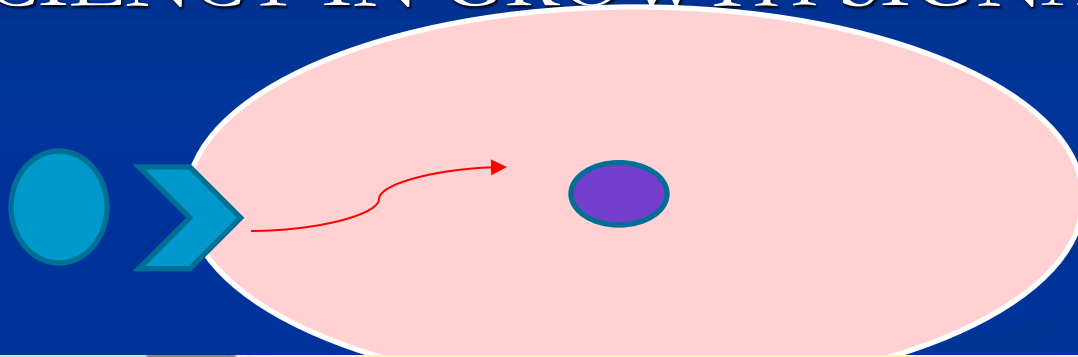
# Carcinogenesis

- Remember the cell cycle !!
  - Binding of a growth factor to its receptor on the cell membrane
  - Activation of the growth factor receptor leading to activation of signal-transducing proteins
  - Transmission of the signal to the nucleus
  - Induction of the DNA transcription
  - Entry in the cell cycle and cell division



# Carcinogenesis

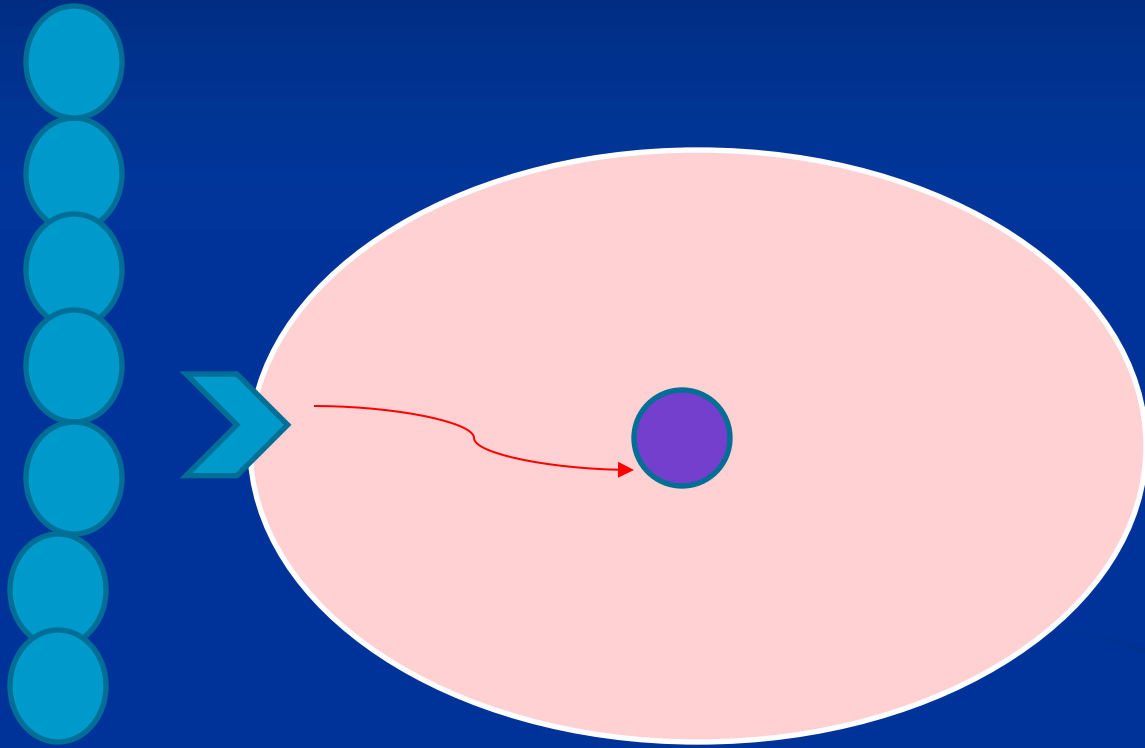
- HOW CANCER CELLS ACQUIRE SELF-SUFFICIENCY IN GROWTH SIGNALS??



# Carcinogenesis

## 1- Growth factors:

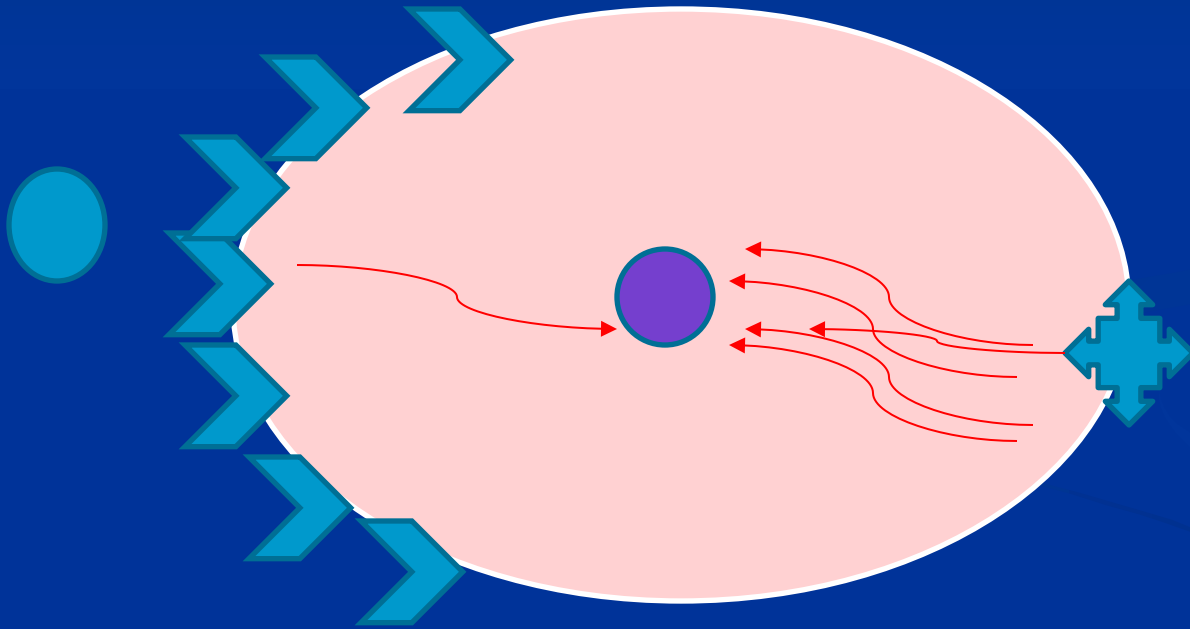
- Cancer cells are capable to synthesize the same growth factors to which they are responsive
  - E.g. Sarcomas ---- > TGF- $\alpha$   
Glioblastoma-----> PDGF



# Carcinogenesis

## 2-Growth factors receptors:

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



# Carcinogenesis

- Example :
  - 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



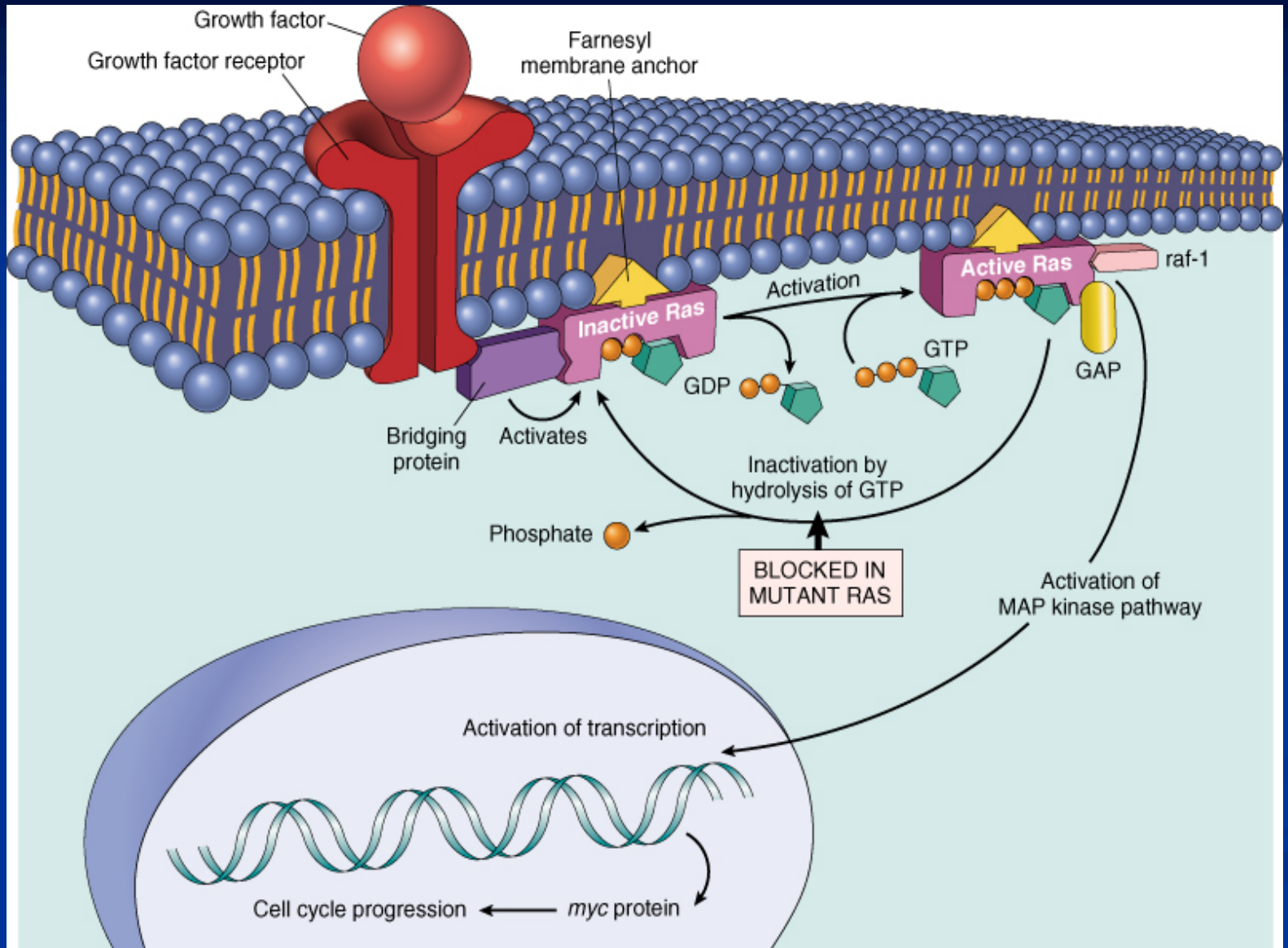
# Carcinogenesis

## 3- Signal-transducing proteins :

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

# Carcinogenesis

- RAS :
  - 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

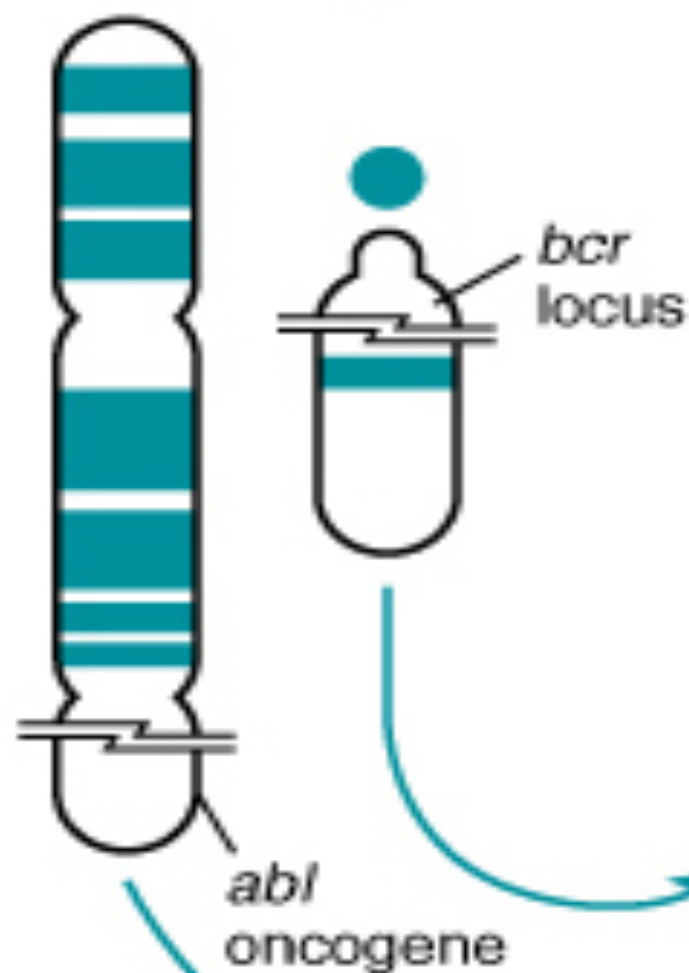


# Carcinogenesis

- ABL gene
  - 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 ---( oncogenec)

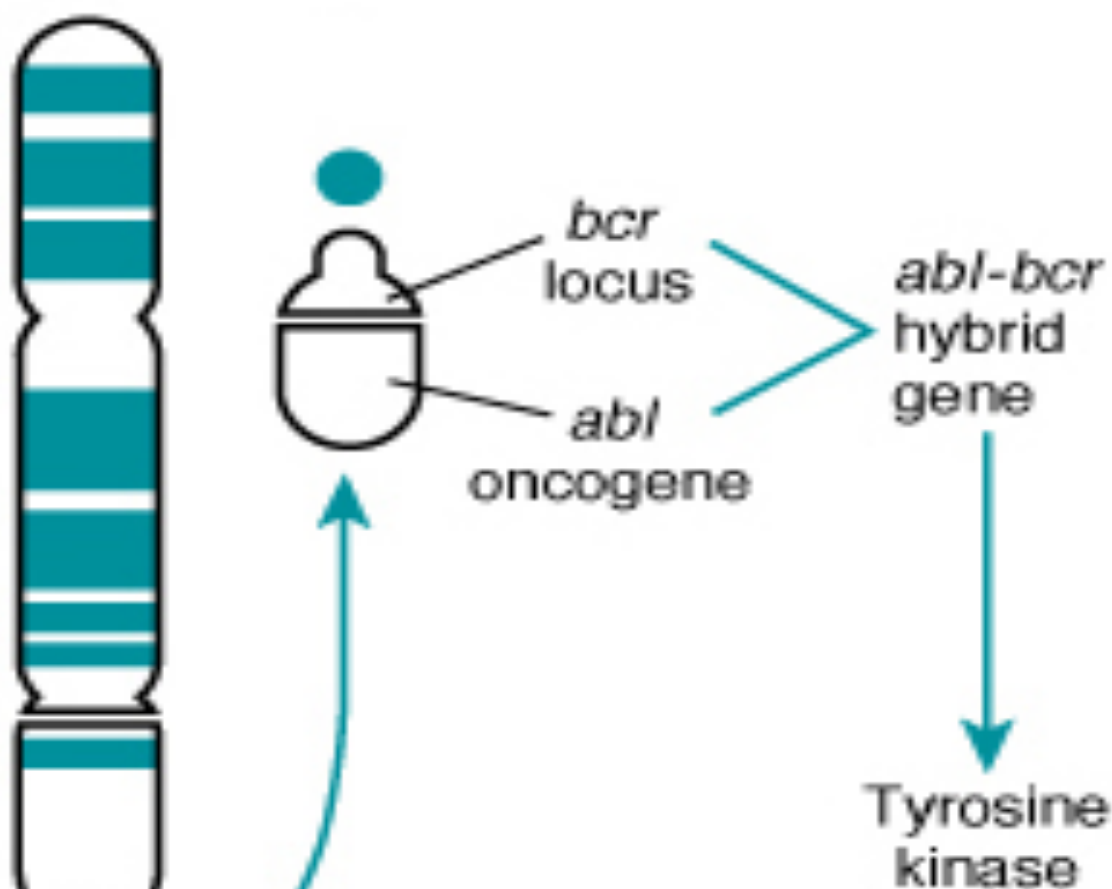
NORMAL  
CHROMOSOMES

9 22



CHRONIC  
MYELOGENOUS  
LEUKEMIA

9 22



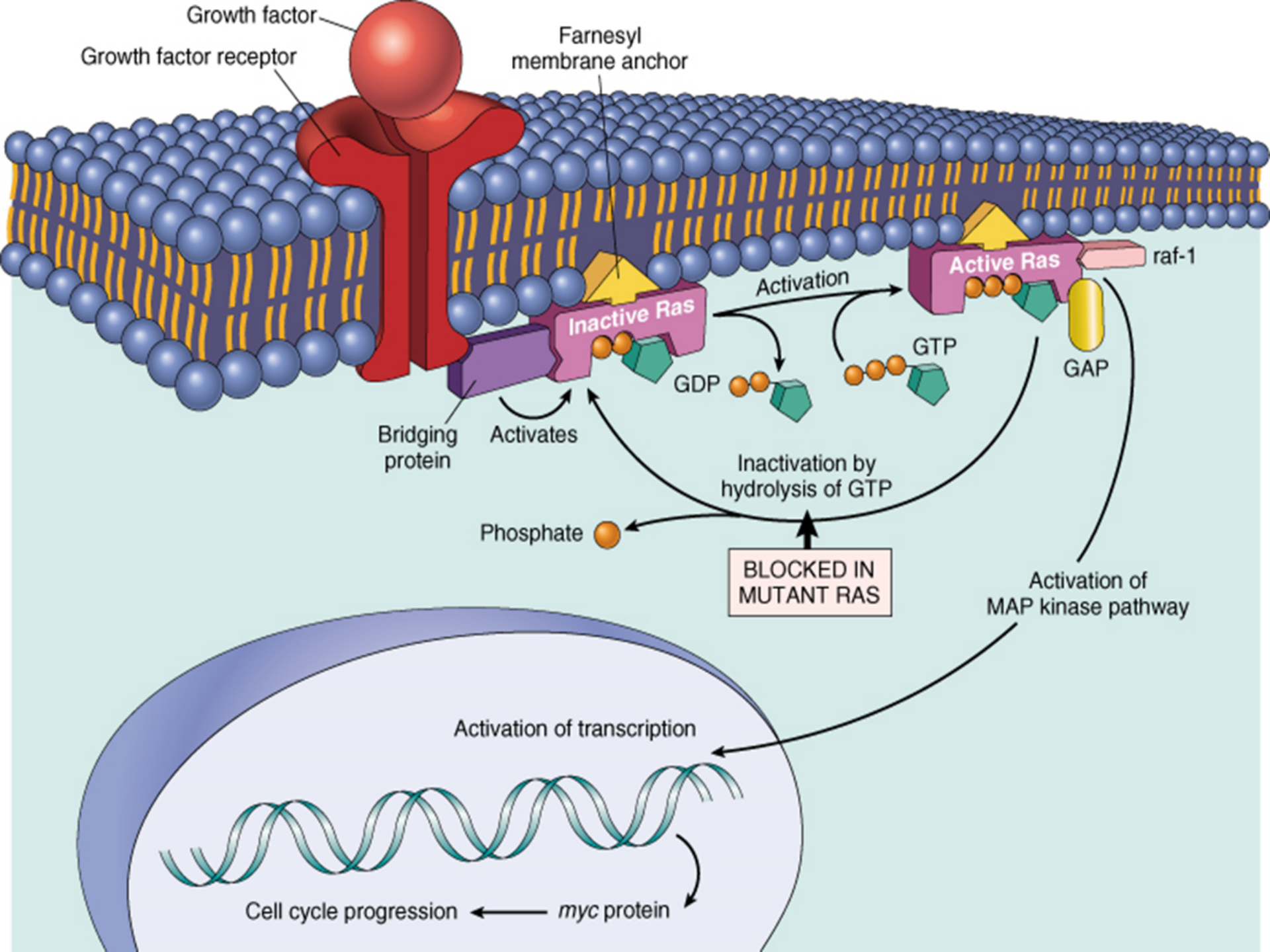
# Carcinogenesis

- CML patients are treated with ( Gleevec) which is inhibitor of ABL kinase

# Carcinogenesis

## 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



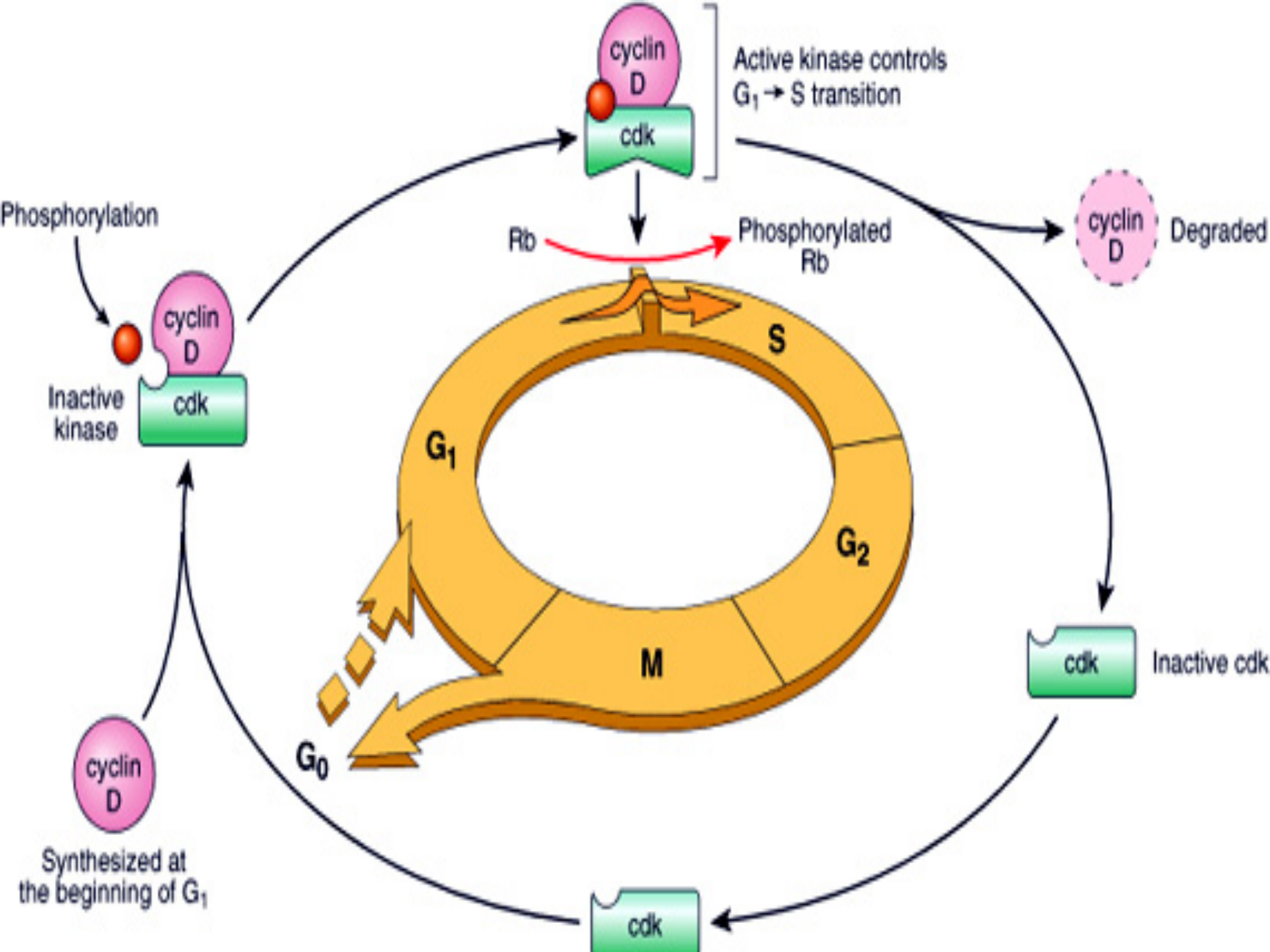


# Carcinogenesis

- 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  $t(8,14)$

# Carcinogenesis

- 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



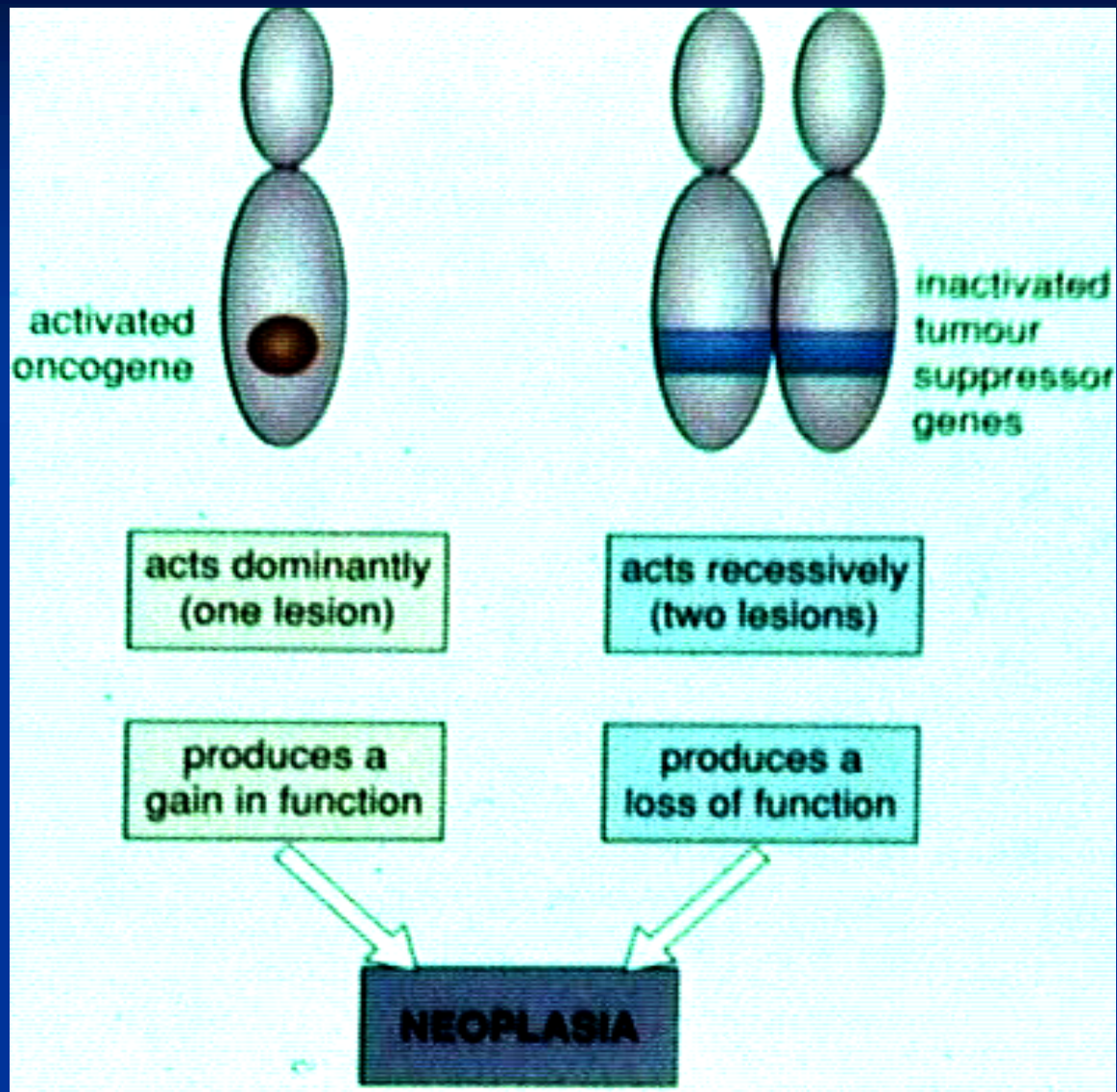
# Carcinogenesis

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

# Carcinogenesis

## 2. 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: RB, TGF- $\beta$ , APC, P53



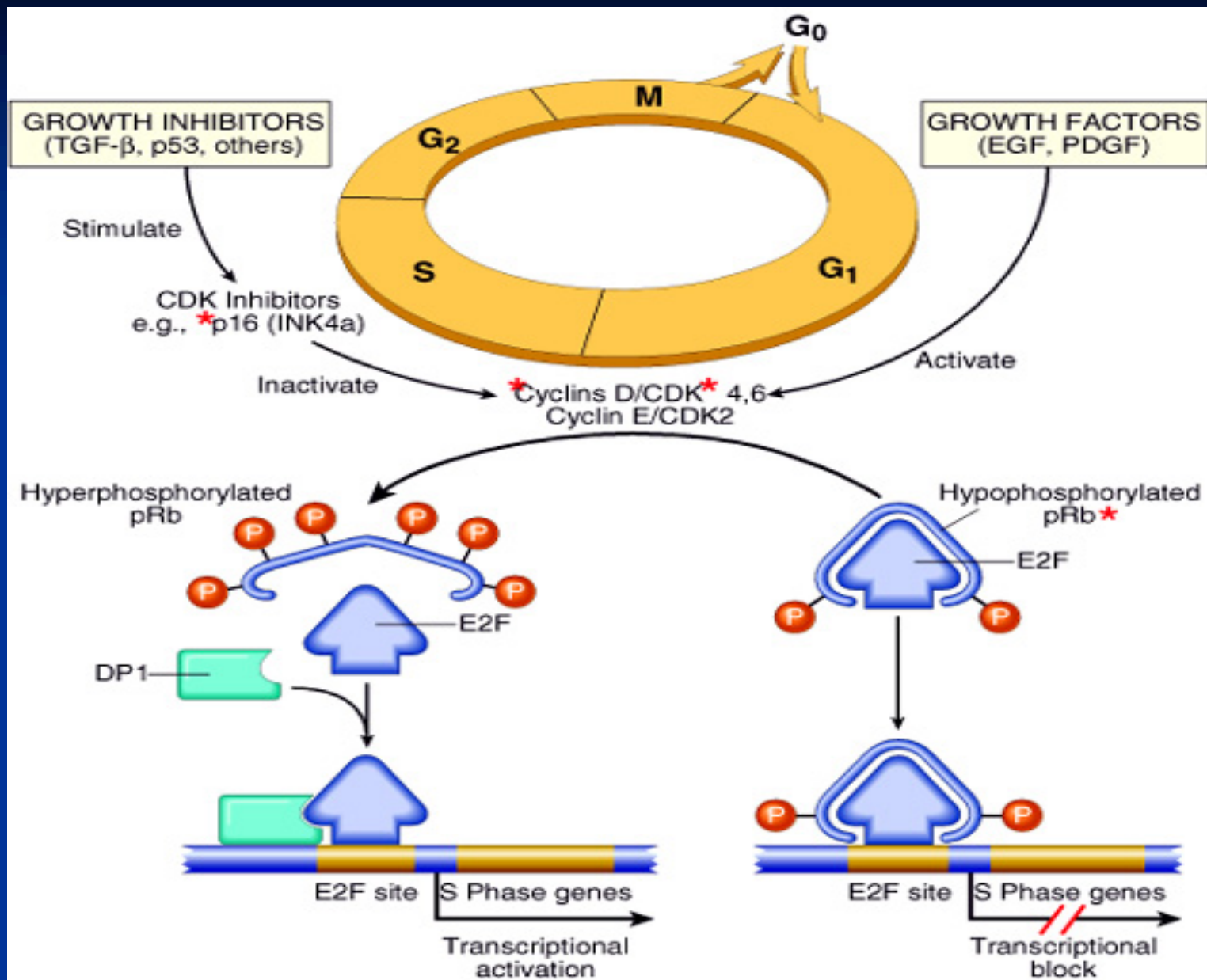
# Carcinogenesis

- RB ( retinoblastoma ) gene :
  - First tumor supressor gene discovered
  - It was discovered initially in retinoblastomas
  - Found in other tumors, e.g. breast ca
  - RB gene is a DNA-binding protein
  - RB is located on chromosome 13

# Carcinogenesis

- RB gene 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



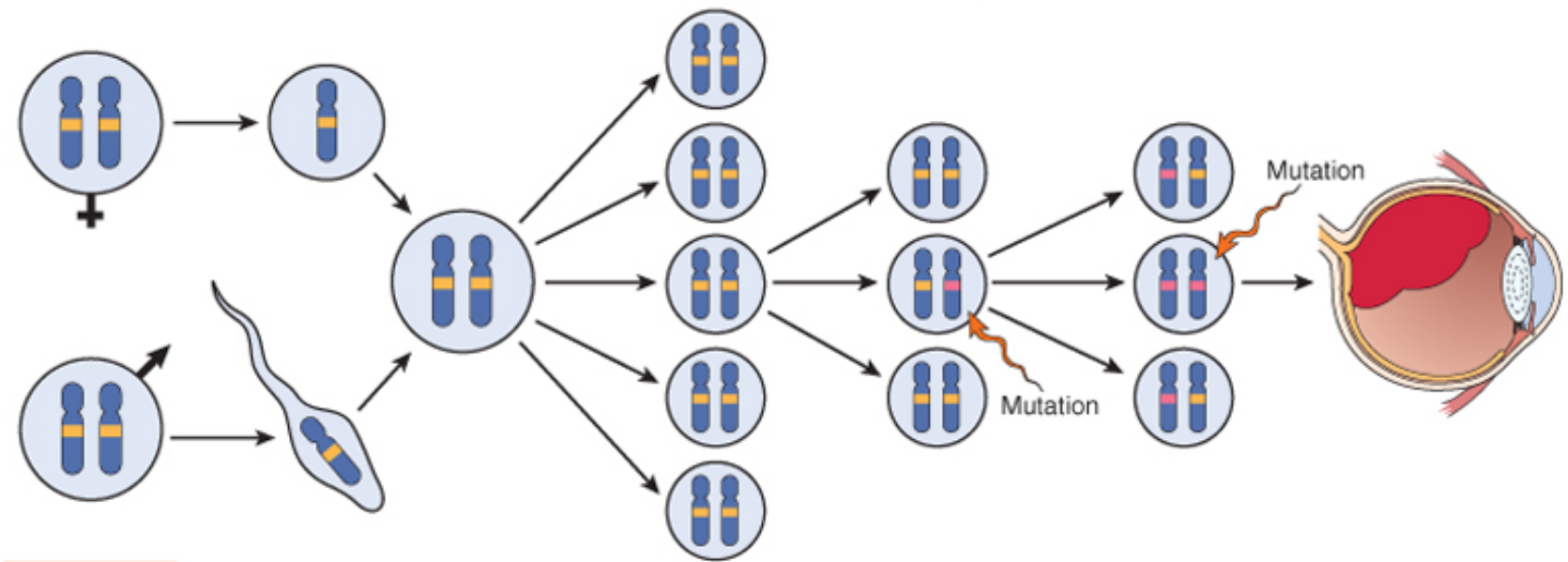


# Carcinogenesis

- 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

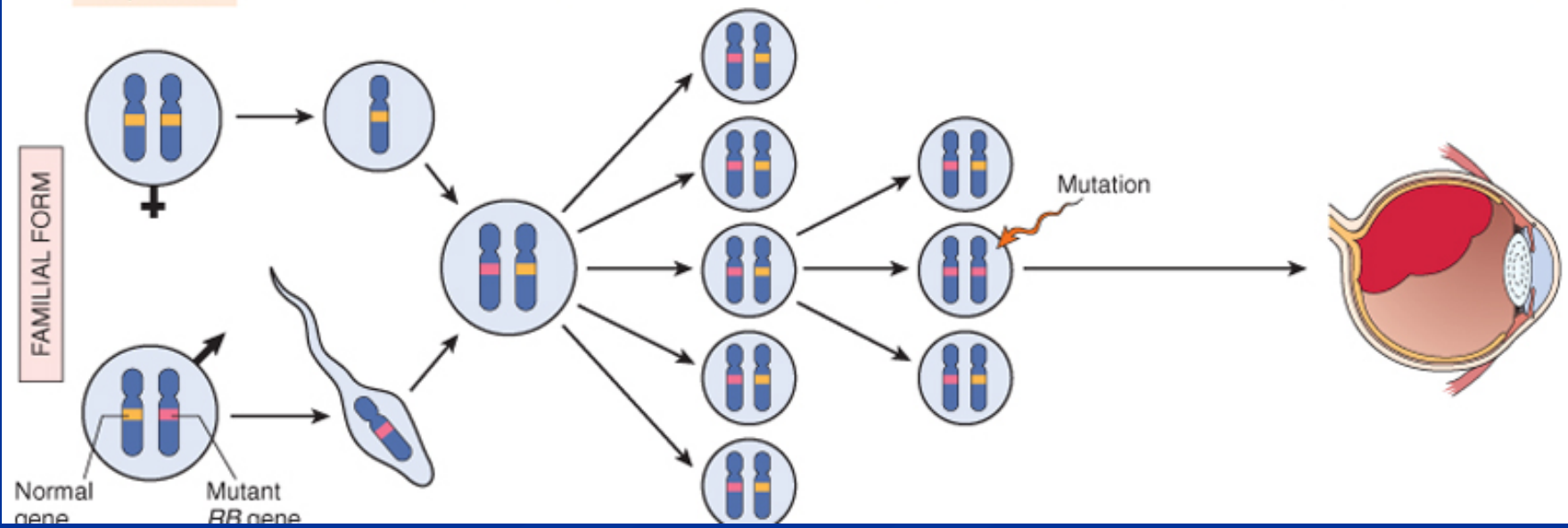
# PATHOGENESIS OF RETINOBLASTOMA

SPORADIC FORM



Somatic cells of parents      Germ cells      Zygote      Somatic cells of child      Retinal cells      Retinoblastoma

FAMILIAL FORM



Normal gene      Mutant RB gene

# Carcinogenesis

- Transforming Growth Factor-  $\beta$  pathway:
  - TGF- $\beta$  is an inhibitor of proliferation
  - It regulate RB pathway
  - Inactivation of TGF- $\beta$  lead to cell proliferation

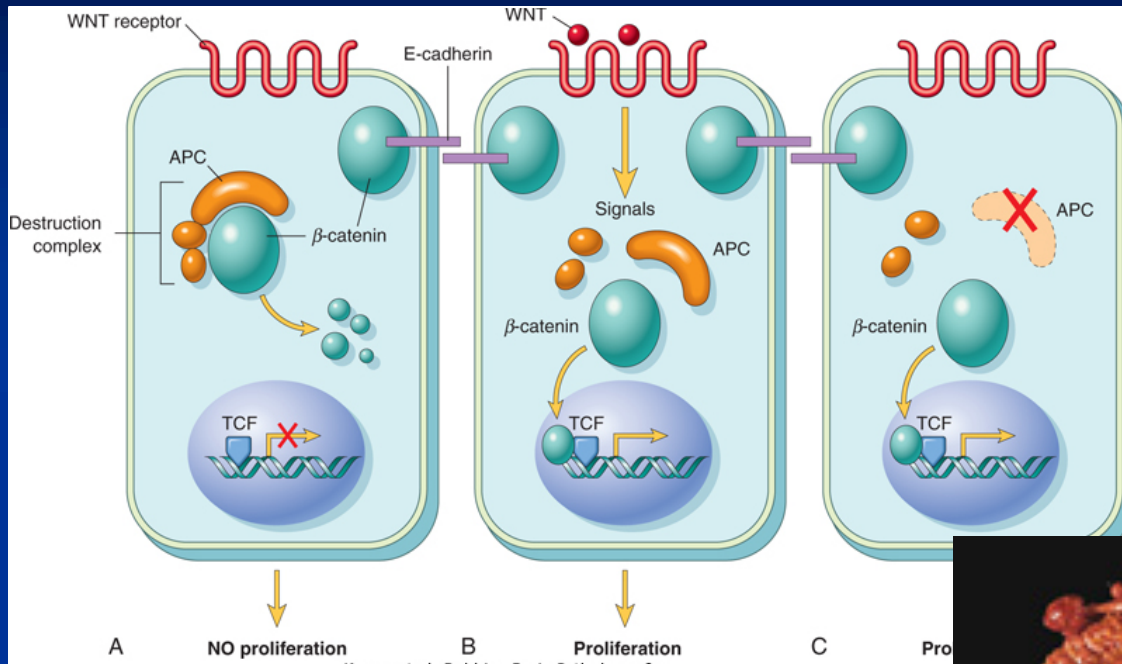
Mutations in TGF- $\beta$  pathway are present in :

- 100% of pancreatic cancers
- 83% of colon cancers

# Carcinogenesis

- Adenomatous Polyposis Coli –  $\beta$  Catenin pathway:
  - APC is tumor suppressor gene
  - APC gene loss is very common in colon cancers
  - It has anti-proliferative action through inhibition of  $\beta$ -Catenin which activate cell proliferation
  - Individuals with mutant APC develop thousands of colonic polyps

# Adenomatous Polyposis Coli



# Carcinogenesis

- One or more of the polyps will progress to colonic carcinoma
- APC mutations are seen in 70% to 80% of sporadic colon cancers

# Carcinogenesis

- P53
  - It has multiple functions
  - Mainly :
    - Tumor suppressor gene ( anti-proliferative )
    - Regulates apoptosis

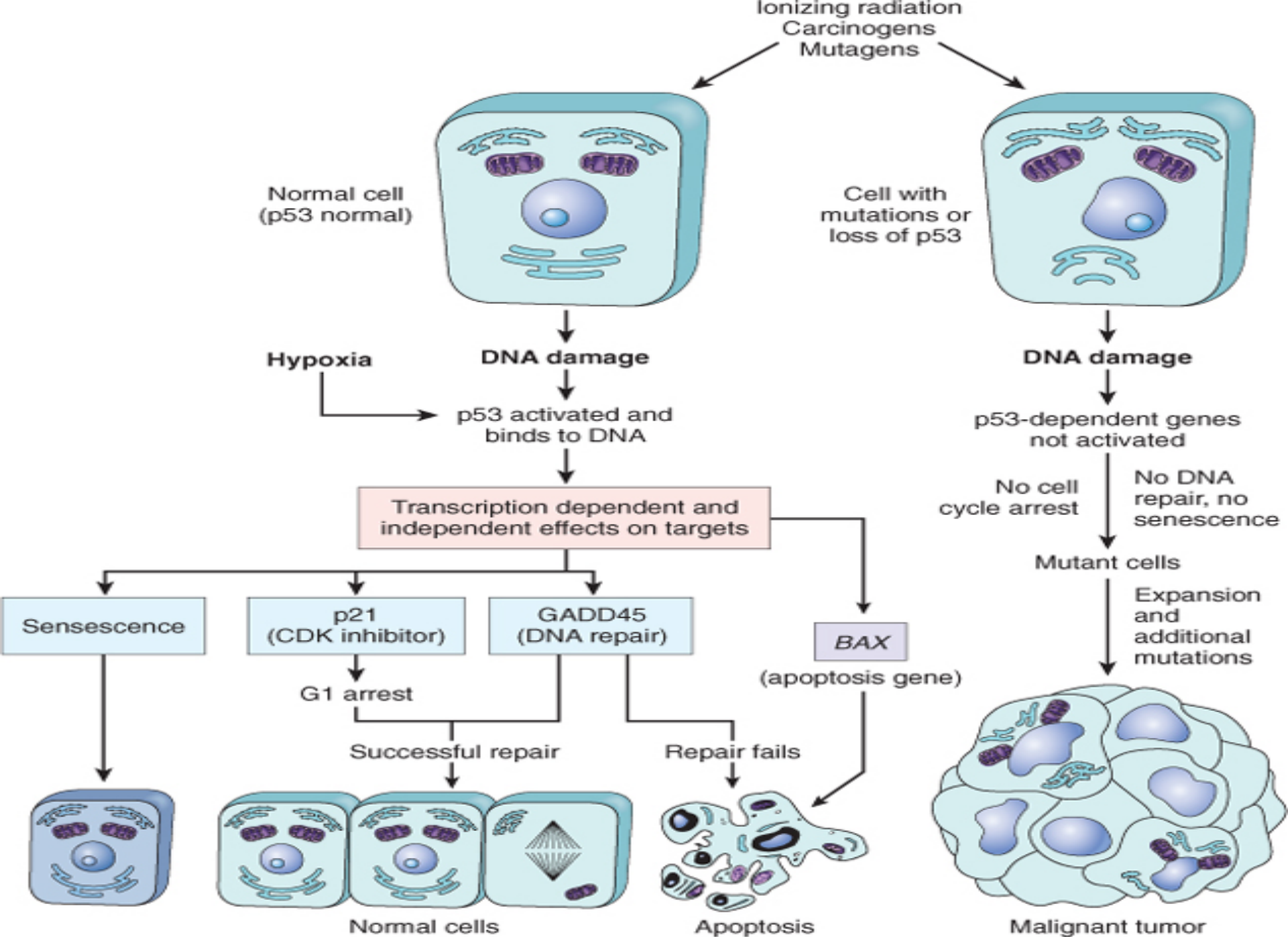


# Carcinogenesis

- 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

# Carcinogenesis

- With loss of P53, DNA damage goes unrepaired
- Mutations will be fixed in the dividing cells, leading to malignant transformation



# Carcinogenesis

- 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

# Carcinogenesis

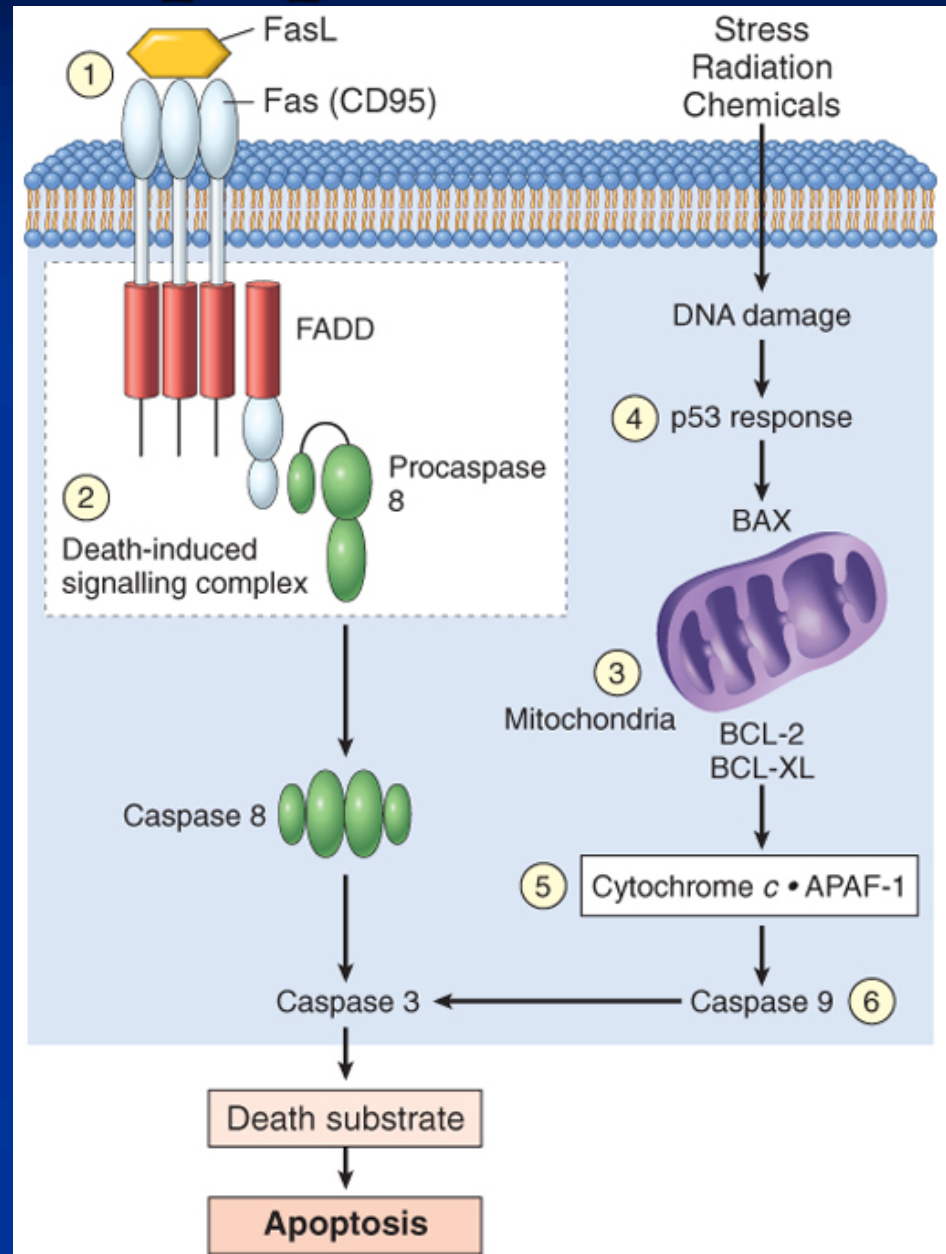
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  - E- Sustained angiogenesis
  - F- Ability to invade and metastasize

# Carcinogenesis

- **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

# Evasion of 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



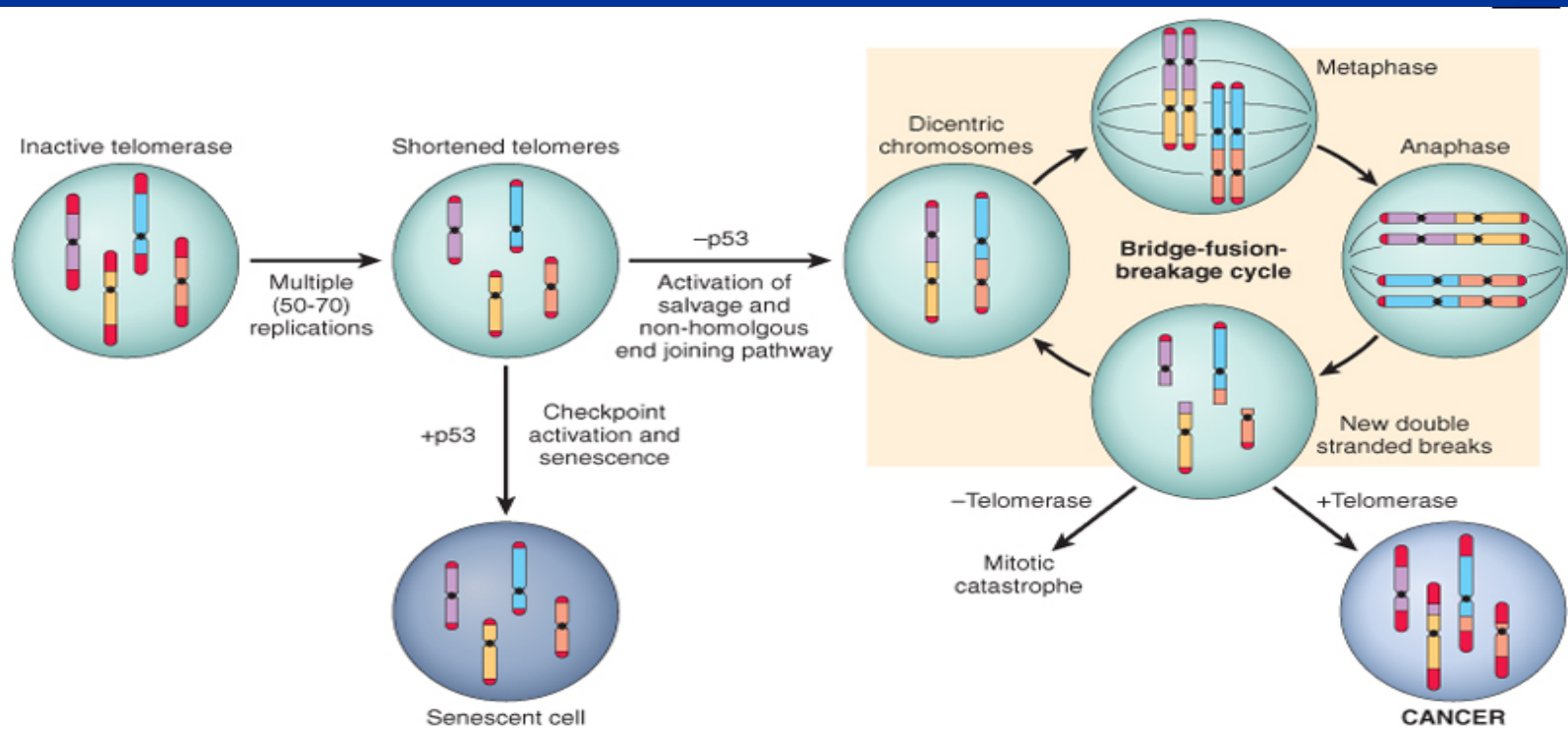
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## ■ Limitless replicative potential:

- 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



# Carcinogenesis

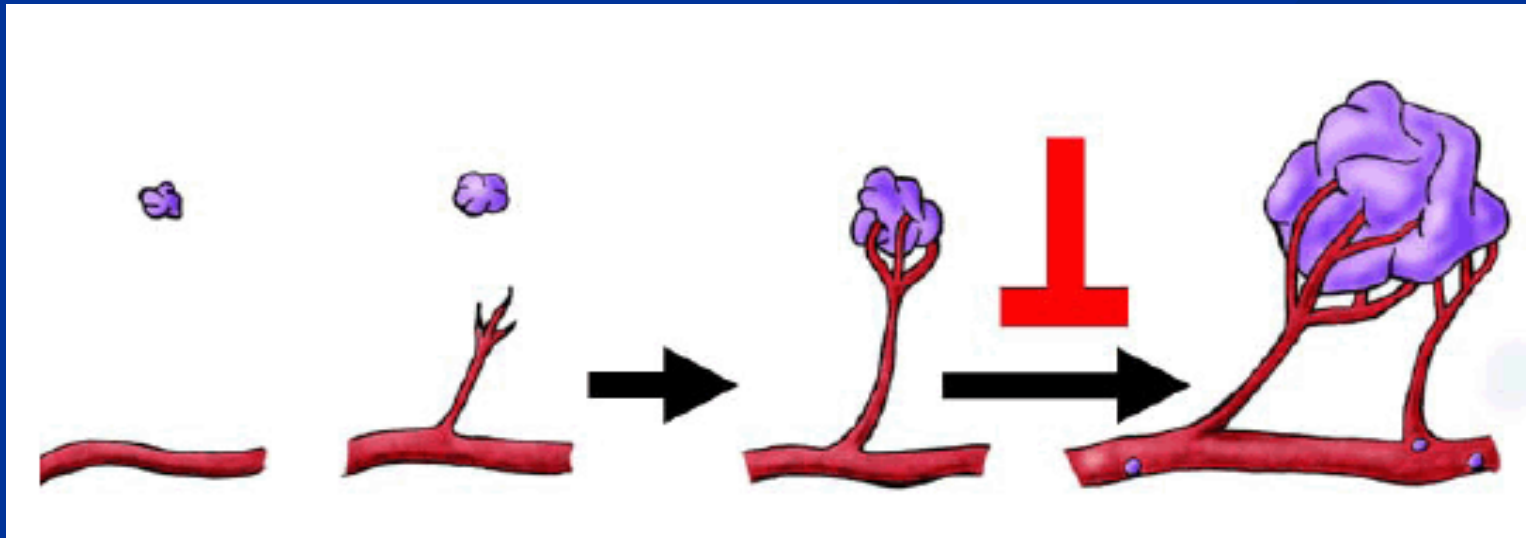
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# Carcinogenesis

## ■ Sustained angiogenesis

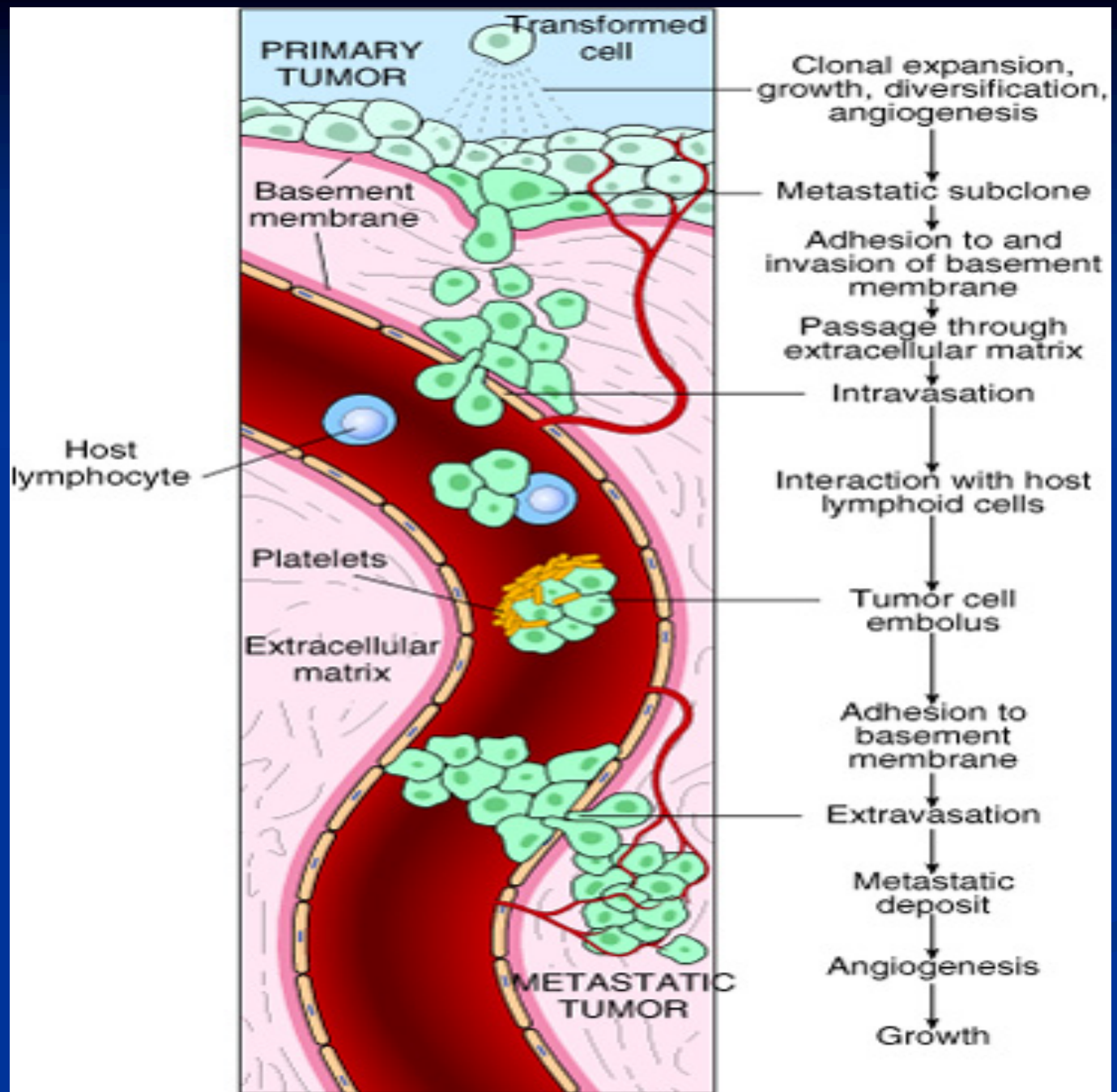
- Neovascularization has two main effects:
  - Perfusion supplies oxygen and nutrients
  - Newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors, e.g : PDGF, IL-1
- Angiogenesis is required for metastasis

- How 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 :
    - Vascular endothelial growth factor( VEGF )
    - Fibroblast growth factor



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# Carcinogenesis

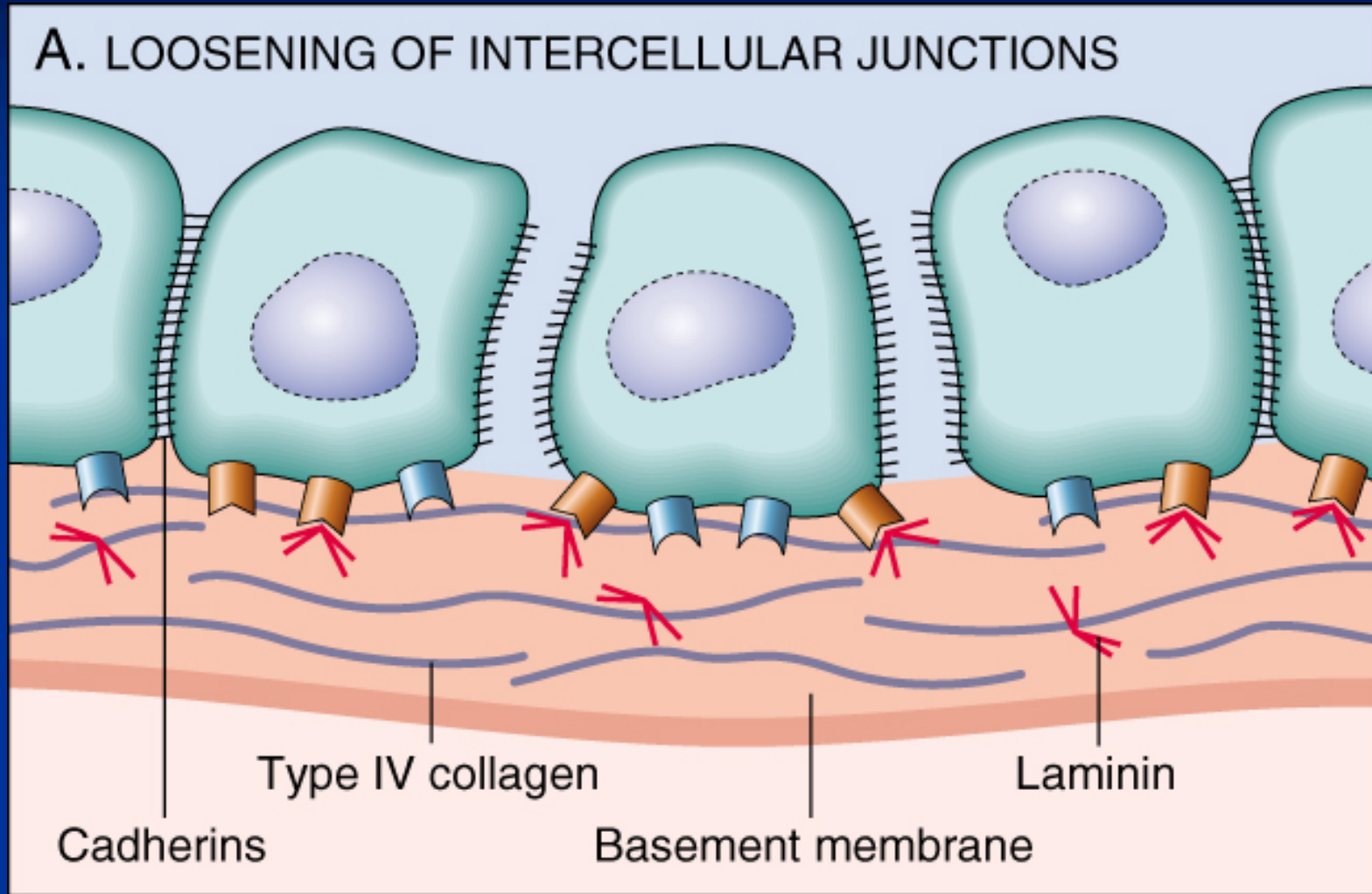
- **Ability to invade and metastasize:**
  - Two phases :
    - Invasion of extracellular matrix
    - Vascular dissemination and homing of tumor cells

# Carcinogenesis

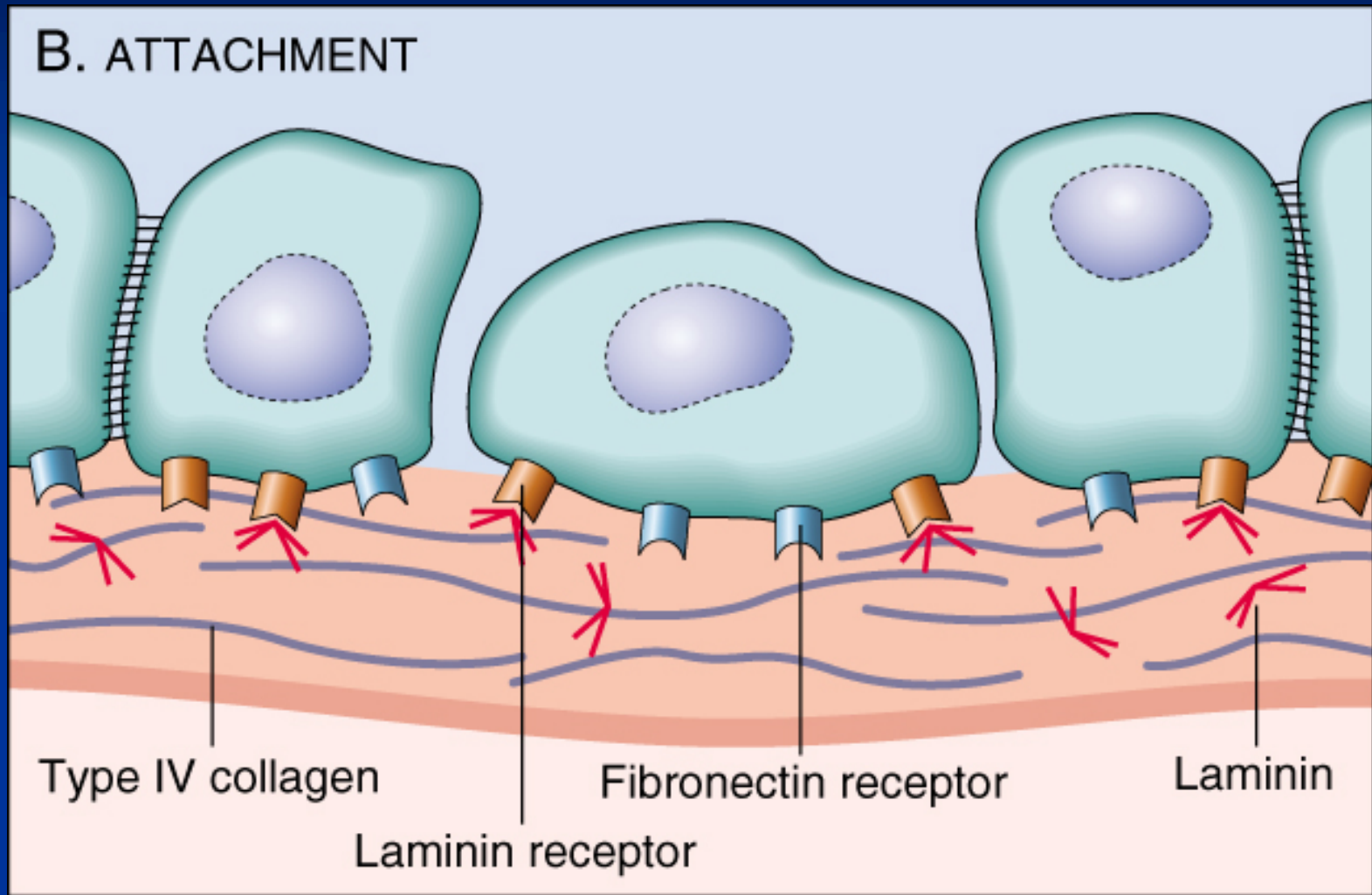
- Invasion of ECM:
  - Malignant cells first breach the underlying basement membrane
  - Traverse the interstitial tissue
  - Penetrate the vascular basement membrane
  - Gain access to the circulation
- ❖ Invasion of the ECM has four steps:



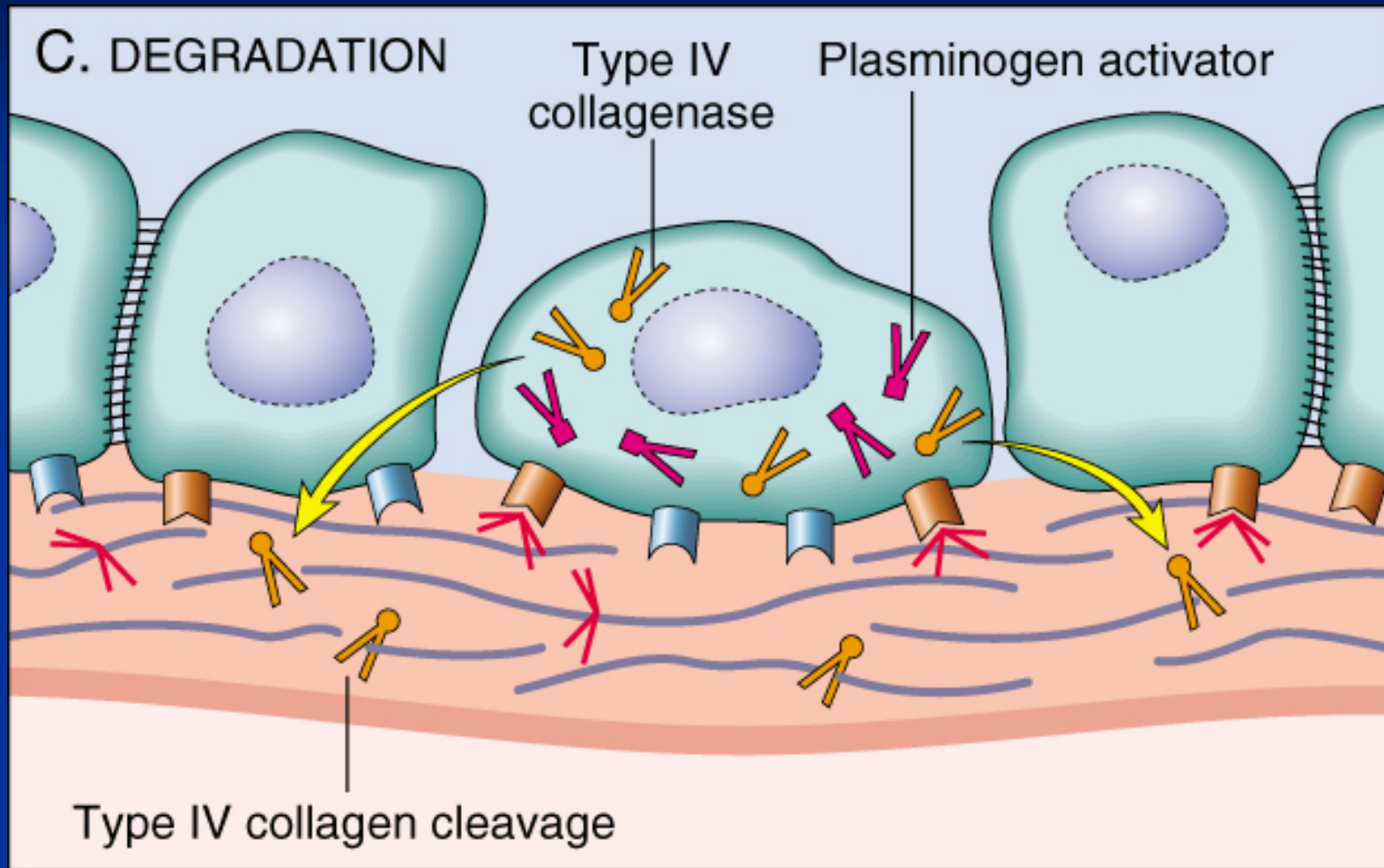
# 1. Detachment of tumor cells from each other



## 2. Attachments of tumor cells to matrix components



### 3. Degradation of ECM by collagenase enzyme





# Carcinogenesis

- Vascular dissemination and homing of tumor cells:
  - May form emboli
  - Most travel as single cells
  - Adhesion to vascular endothelium
  - extravasation

# Carcinogenesis

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# Genomic Instability

- Enabler of malignancy
- Due to defect in DNA repair genes
- Examples:
  - Hereditary Nonpolyposis colon carcinoma(HNPCC)
  - Xeroderma pigmentosum
  - Familial breast cancer

# Genomic Instability

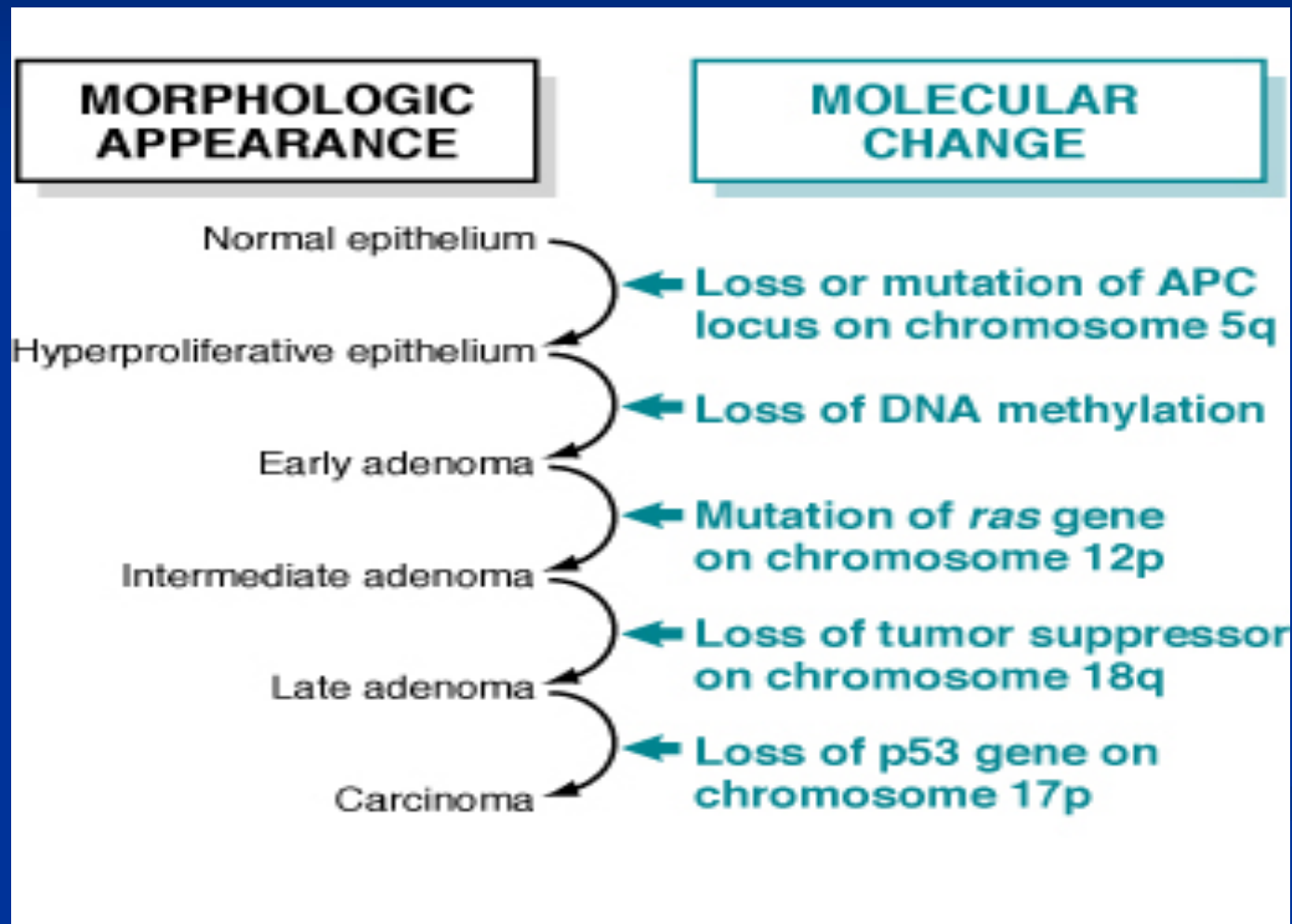
- Familial breast cancer:
  - Due to mutations in BRCA1 and BRCA2 genes
  - These genes regulate DNA repair
  - Account for 80% of familial breast cancer
  - They are also involved in other malignancies



# 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

# Molecular Basis of multistep Carcinogenesis



# Tumor progression

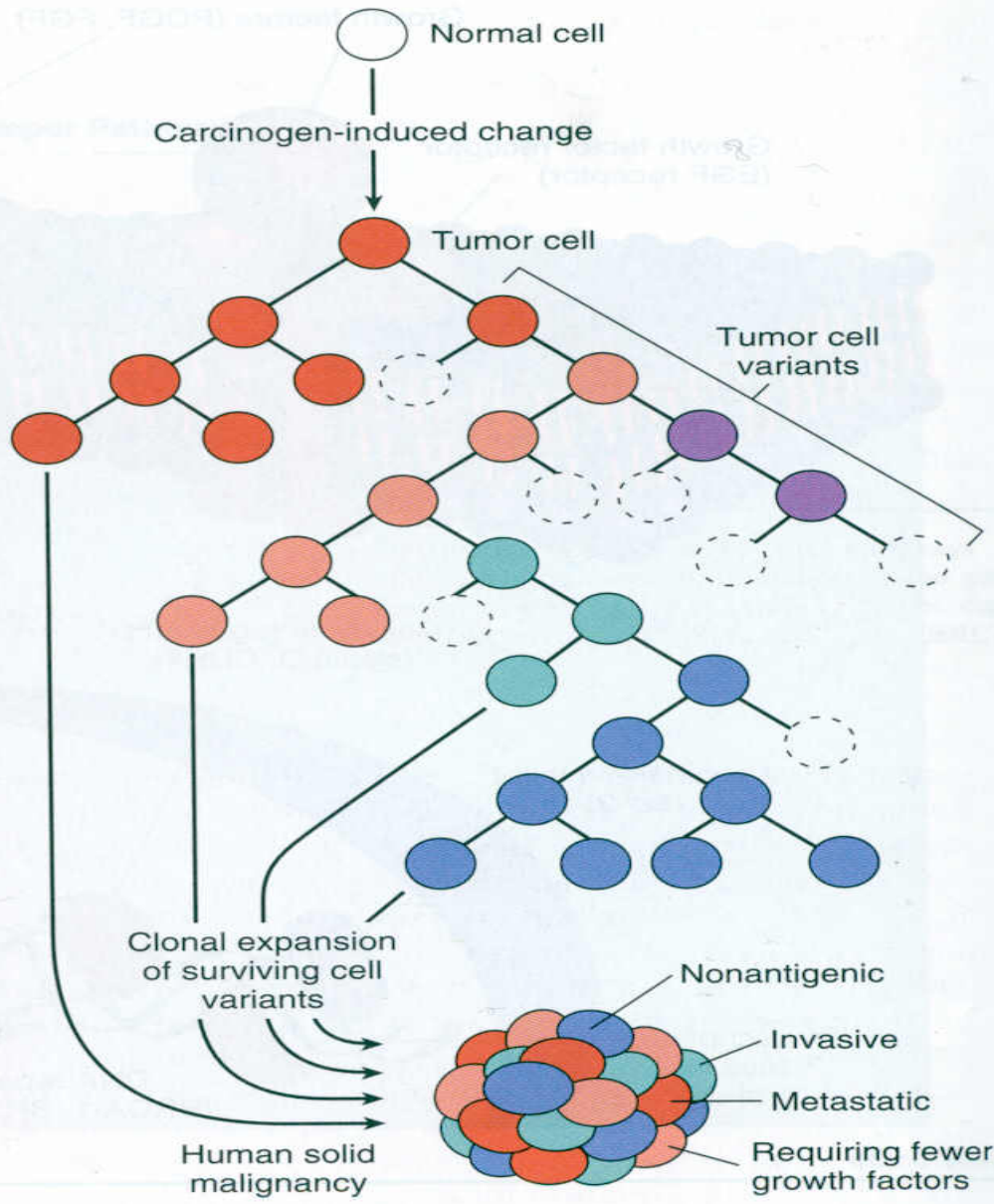
- Many tumors become more aggressive and acquire greater malignant potential...this is called “tumor progression” ...not increase in size!!
- By the time, the tumor become clinically evident, their constituent cells are extremely heterogeneous

TRANSFORMATION

PROGRESSION

PROLIFERATION OF GENETICALLY UNSTABLE CELLS

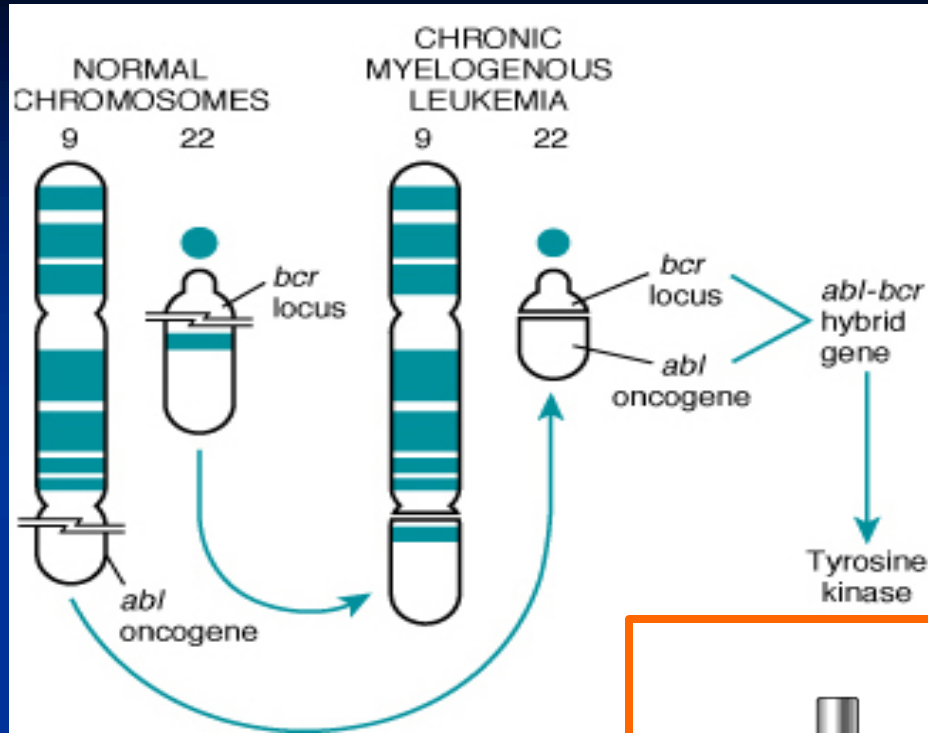
TUMOR CELL VARIANTS HETEROGENEITY



# Karyotypic Changes in Tumors

- Translocations:
  - In CML : t(9,22) ...” Philadelphia chromosome”
  - In Burkitt Lymphoma : t(8,14)
  - In Follicular Lymphoma : t(14,18)
- Deletions
- Gene amplification:
  - Breast cancer : HER-2

# Translocations



# Gene amplification

