Neoplasia
Lecture 3

CARCINOGENESIS

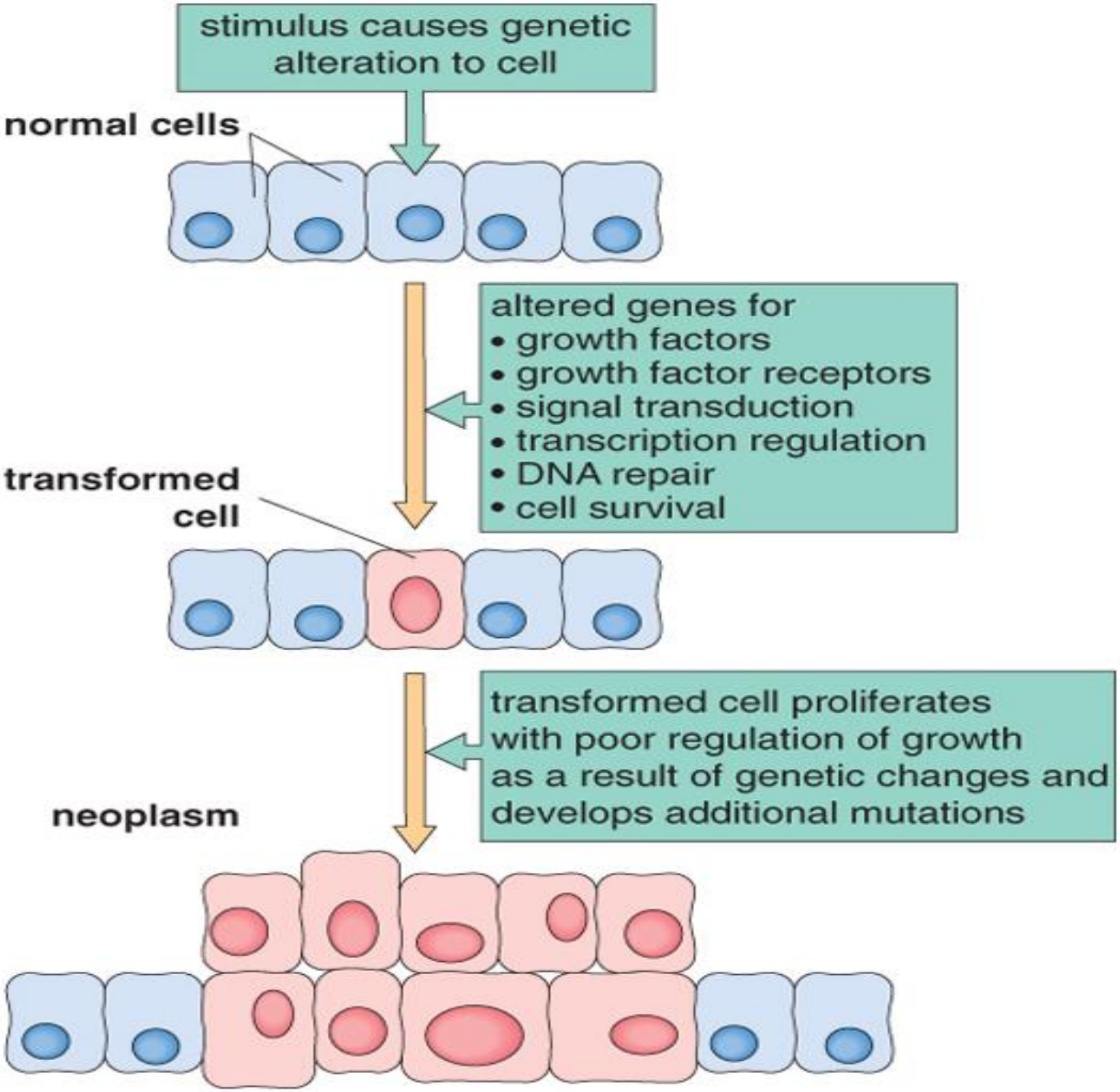
Dr. Abdulmalik Alsheikh, M.D

CARCINOGENESIS

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

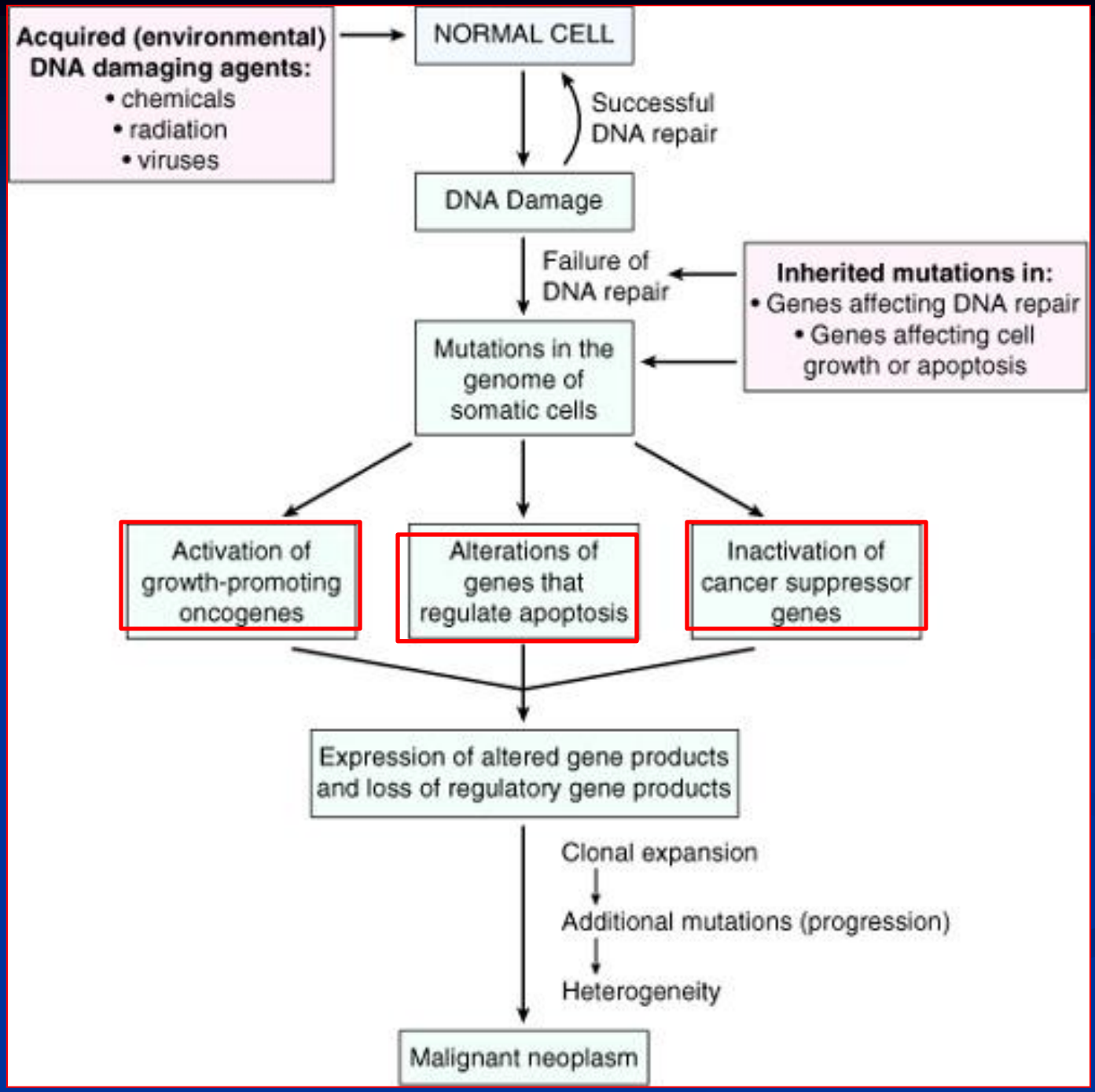
Carcinogenesis

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


stimulus causes genetic alteration to cell
normal cells
altered genes for
• growth factors
• growth factor receptors
• signal transduction
• transcription regulation
• DNA repair
• cell survival
transformed cell
transformed cell proliferates with poor regulation of growth as a result of genetic changes and develops additional mutations
neoplasm

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


Acquired (environmental) DNA damaging agents:
• chemicals
• radiation
• viruses
NORMAL CELL
Successful DNA repair
DNA Damage
Failure of DNA repair
Inherited mutations in:
• Genes affecting DNA repair
• Genes affecting cell growth or apoptosis
Mutations in the genome of somatic cells
Activation of growth-promoting oncogenes
Alterations of genes that regulate apoptosis
Inactivation of cancer suppressor genes
Expression of altered gene products and loss of regulatory gene products
Clonal expansion
Additional mutations (progression)
Heterogeneity
Malignant neoplasm

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 metastsize

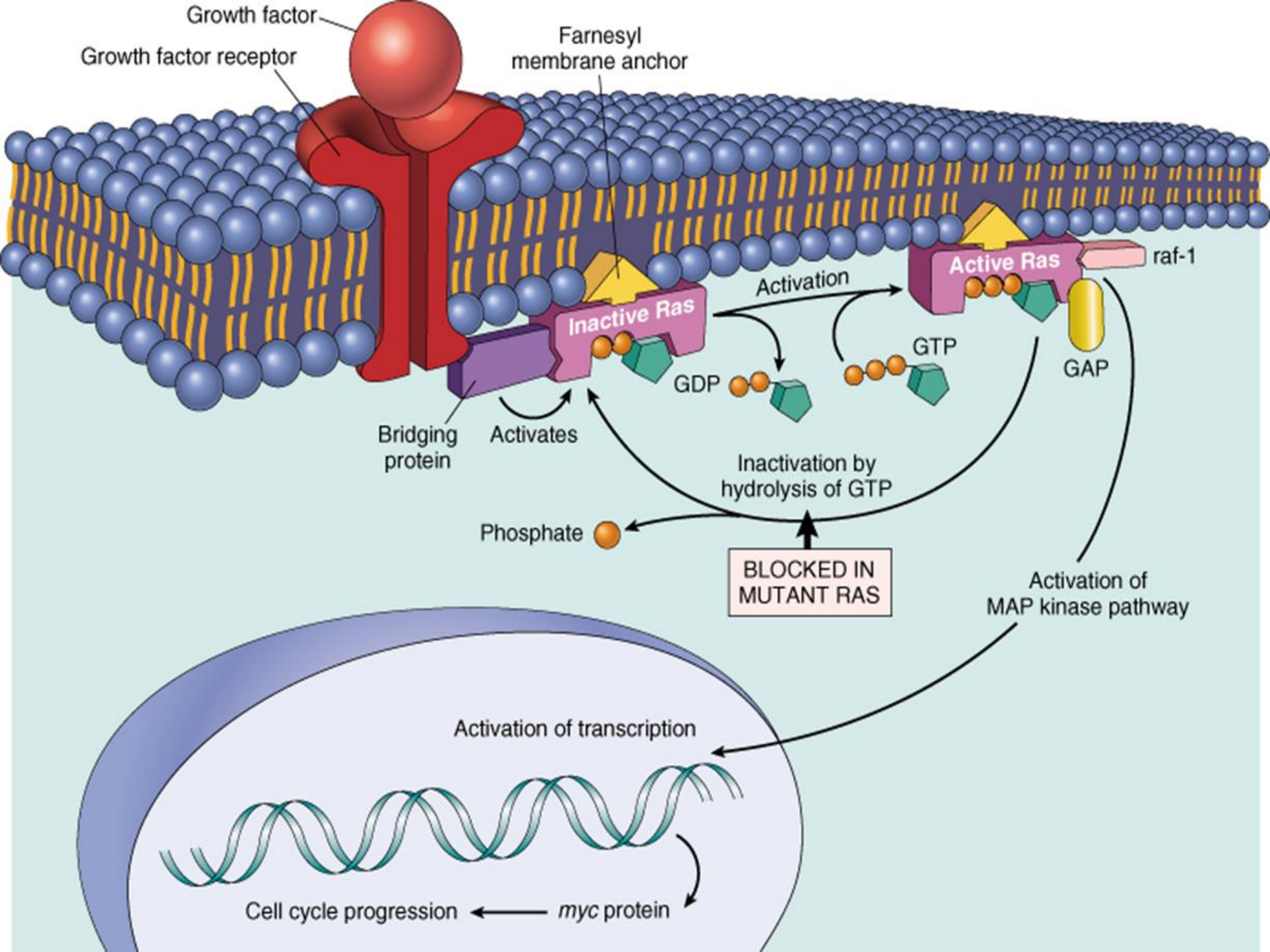
Carcinogenesis

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

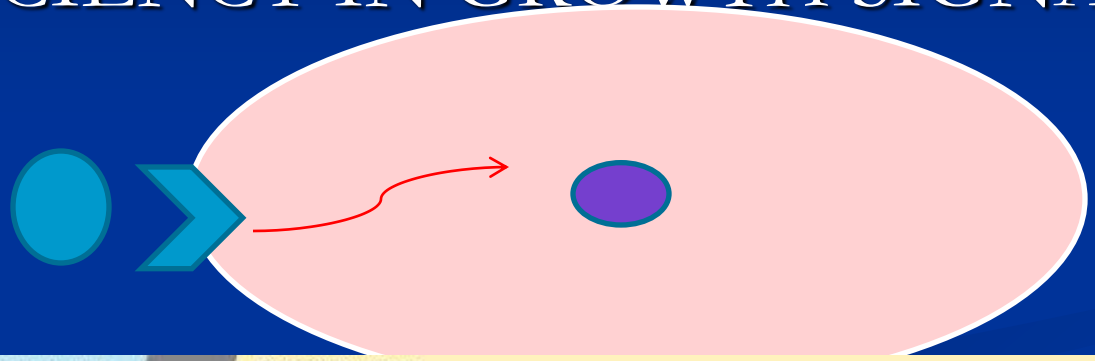
Carcinogenesis

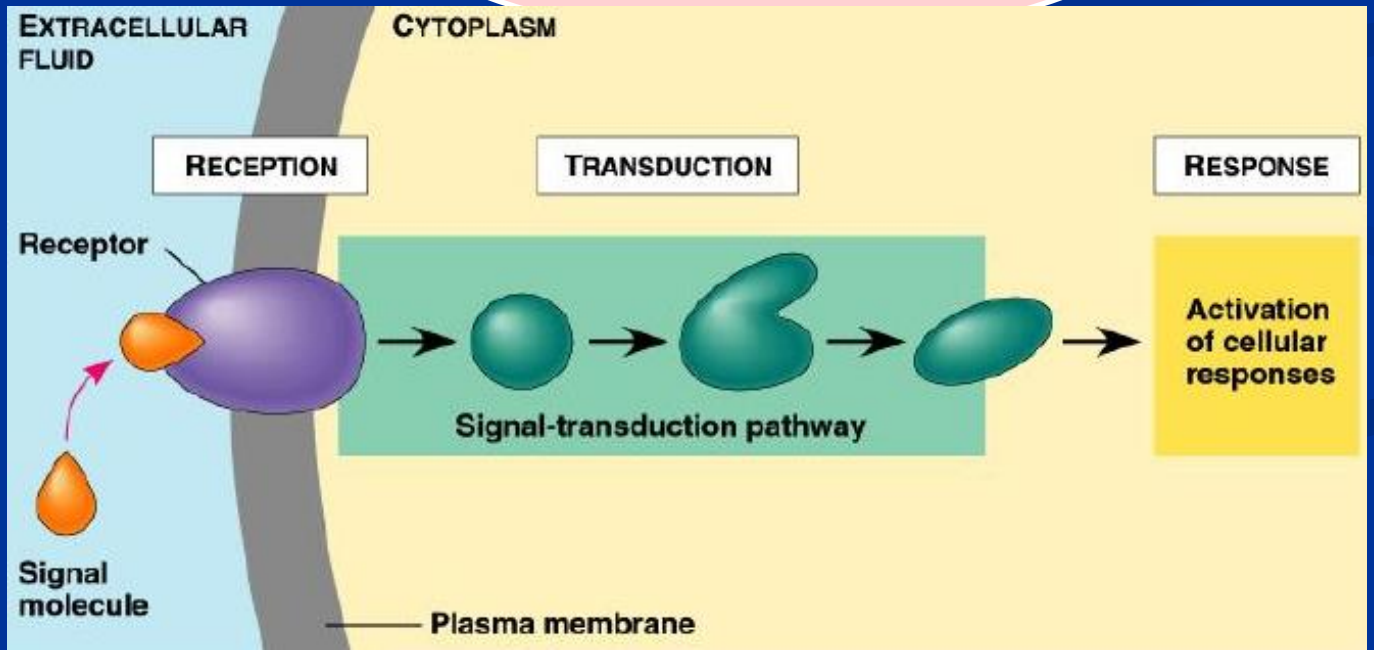
- Remember the cell cycle !!
  - Binding of a growth factor to its receptor on the cell membrane
  - Activation of the growth factor receptor leading to activation of signal-transducing proteins
  - Transmission of the signal to the nucleus
  - Induction of the DNA transcription
  - Entry in the cell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


Growth factor
Growth factor receptor
Farnesyl membrane anchor
Inactive Ras
Activation
Active Ras
raf-1
GTP
GDP
GAP
Bridging protein
Activates
Inactivation by hydrolysis of GTP
Phosphate
BLOCKED IN MUTANT RAS
Activation of MAP kinase pathway
Activation of transcription
Cell cycle progression
myc protein

Carcinogenesis

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



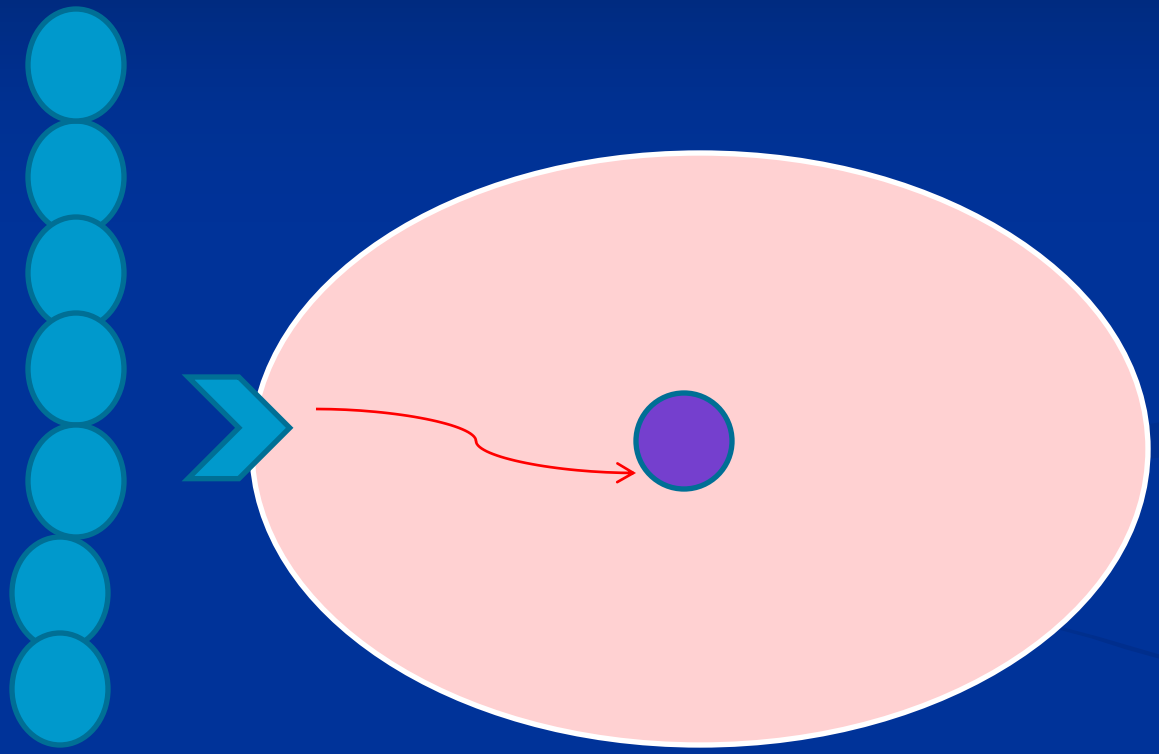


Carcinogenesis

1- Growth factors:

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

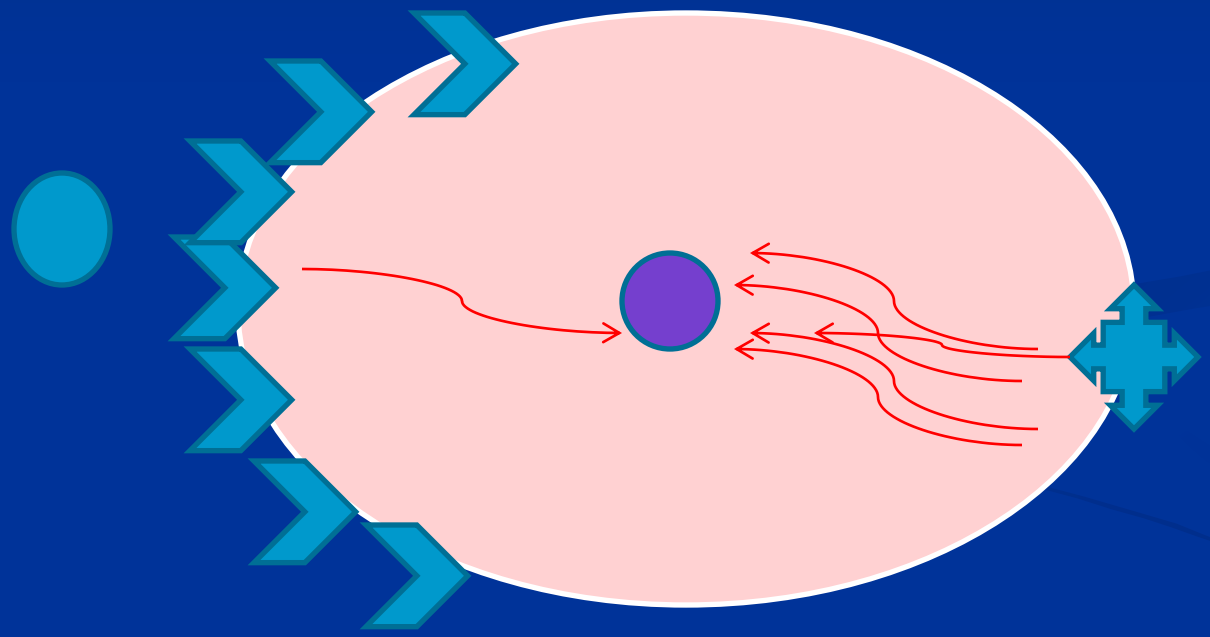
    Glioblastoma-----> PDGF



Carcinogenesis

2-Growth factors receptors:

- Receptors --- mutation ----continous signals to cells and uncontroled 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

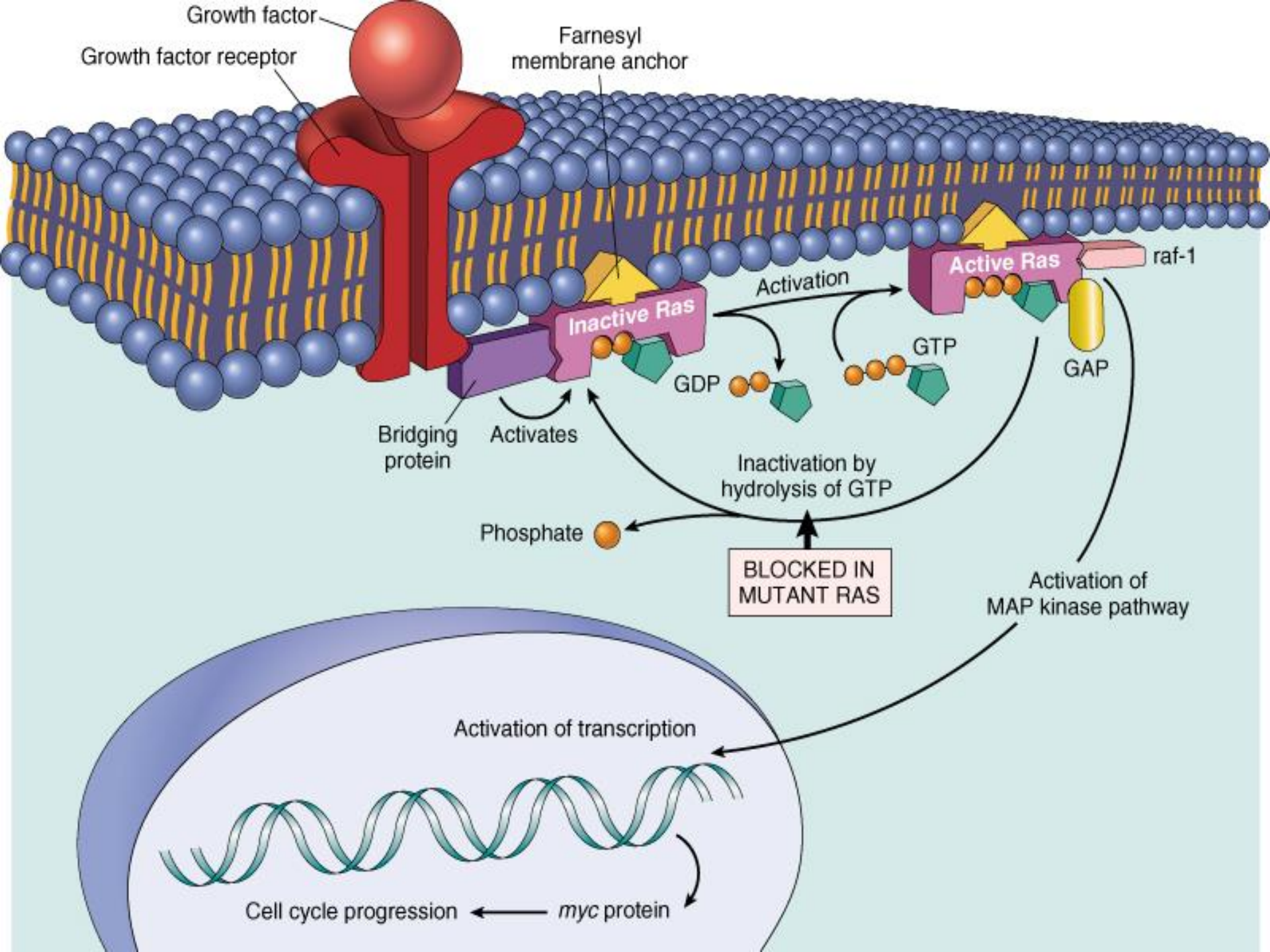
Carcinogenesis

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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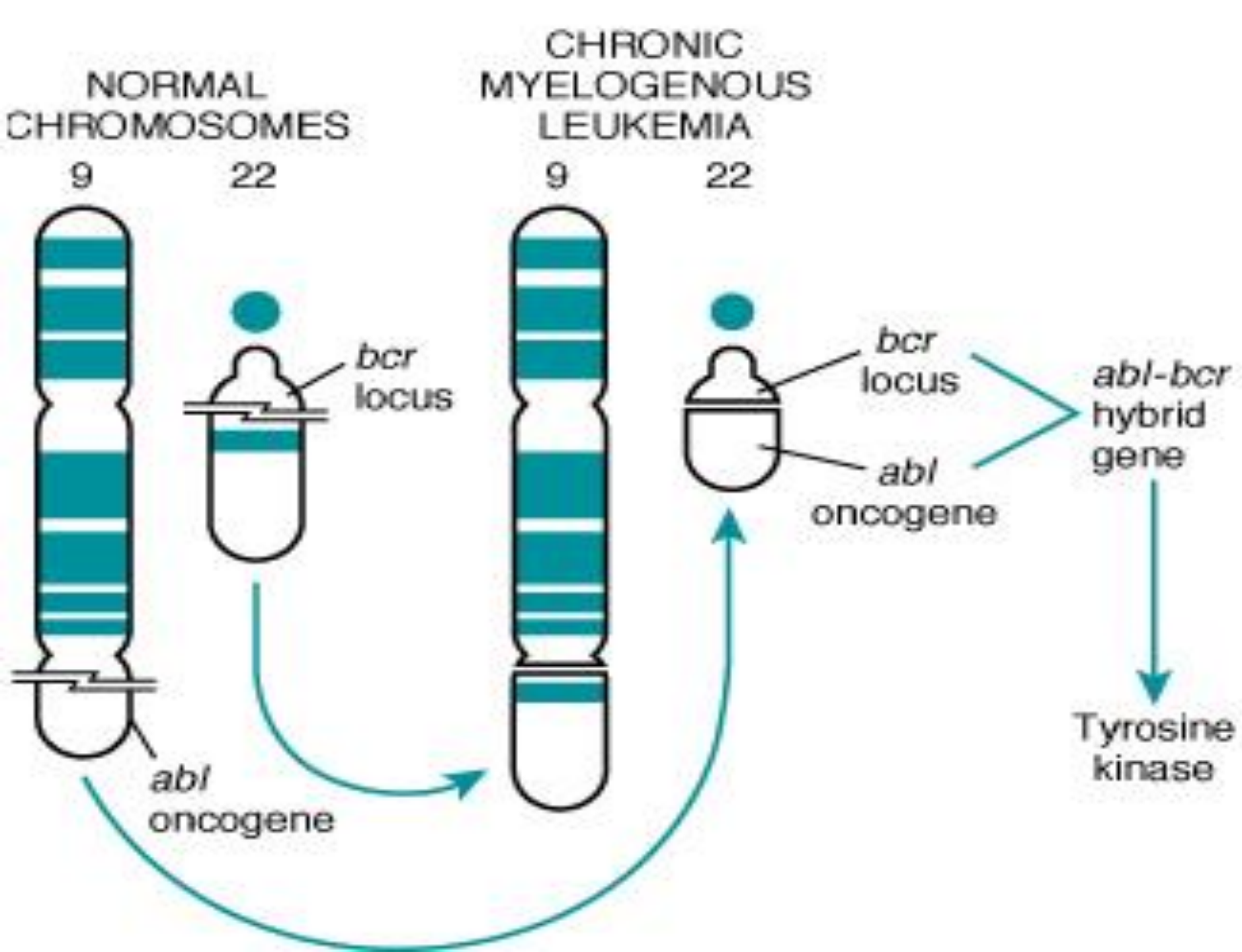
Activation of transcription
Cell cycle progression
myc protein

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 acttivity ---(oncogenec)


NORMAL
CHROMOSOMES
9
22
CHRONIC
MYELOGENOUS
LEUKEMIA
9
22
bcr
locus
abl
oncogene
bcr
locus
abl
oncogene
abl-bcr
hybrid
gene
Tyrosine
kinase

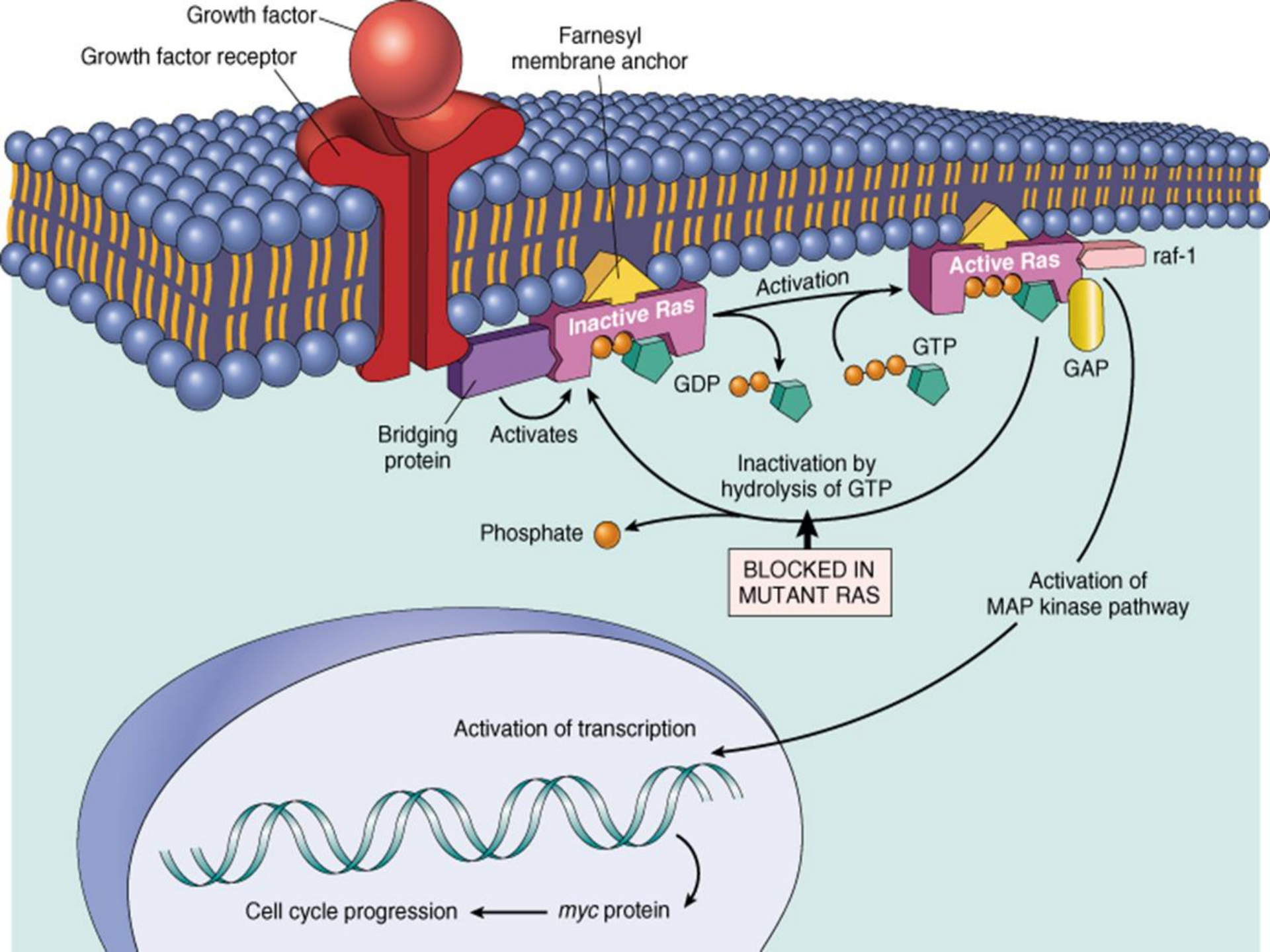
Carcinogenesis

- 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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Activation of MAP kinase pathway
Activation of transcription
Cell cycle progression
myc protein

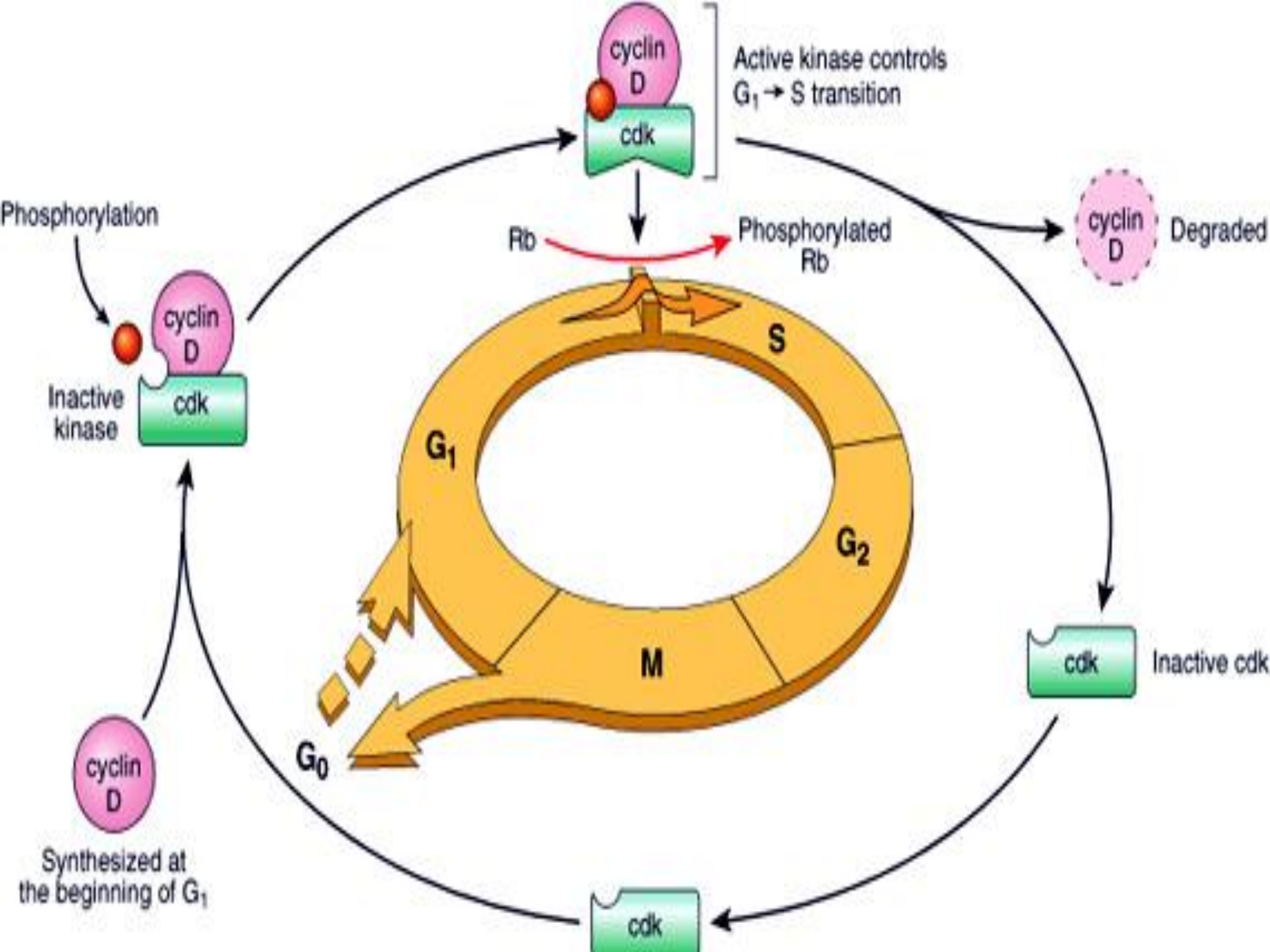
Carcinogenesis

- 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


cyclin D
cdk
Active kinase controls $G_1 \rightarrow S$ transition
Phosphorylation
Rb
Phosphorylated Rb
cyclin D
Degraded
cyclin D
cdk
Inactive kinase
S
G_1
G_2
M
G_0
cdk
Inactive cdk
cyclin D
Synthesized at the beginning of G_1
cdk

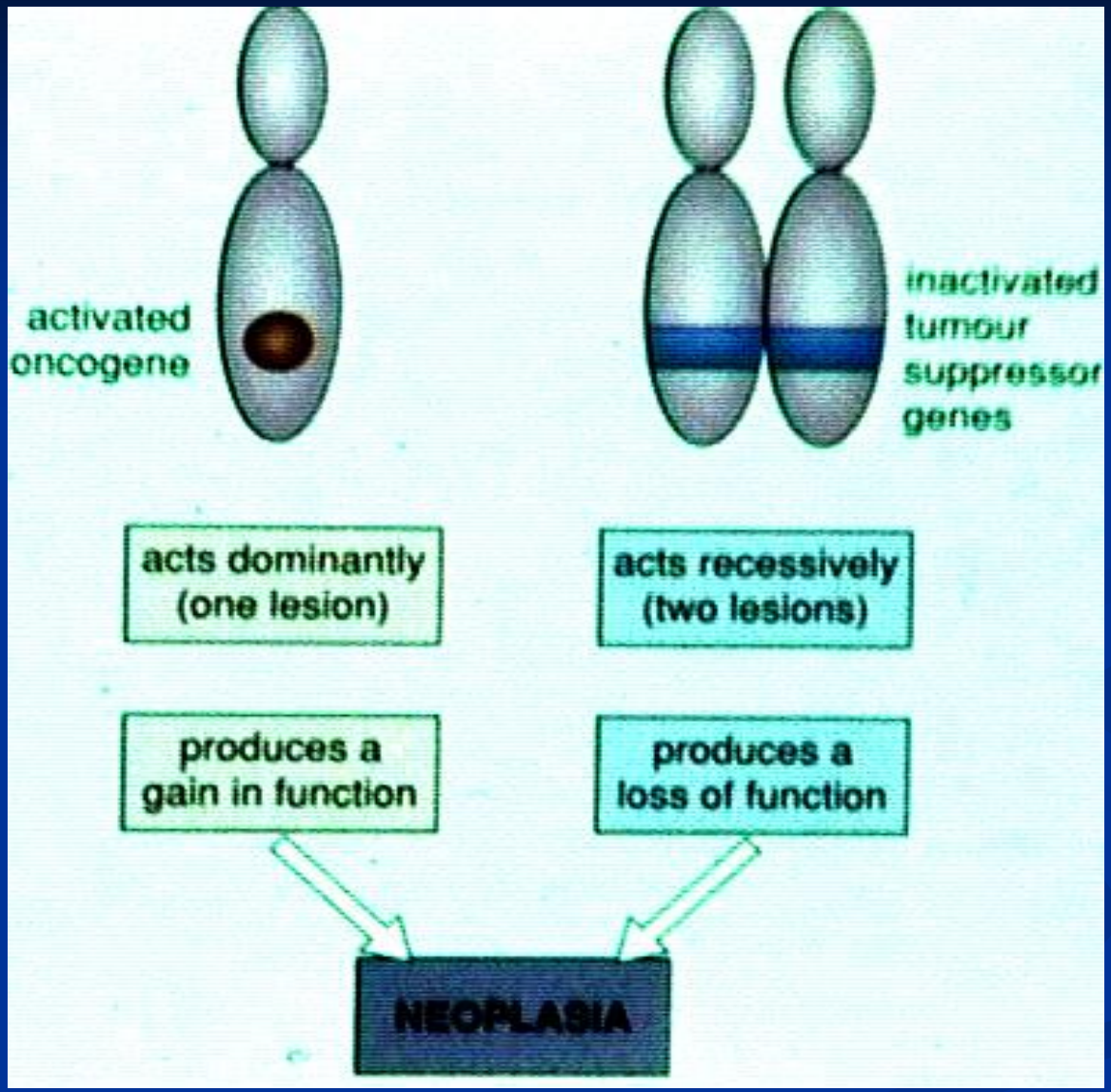
Carcinogenesis

- 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 metastsize

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-β, APC, P53

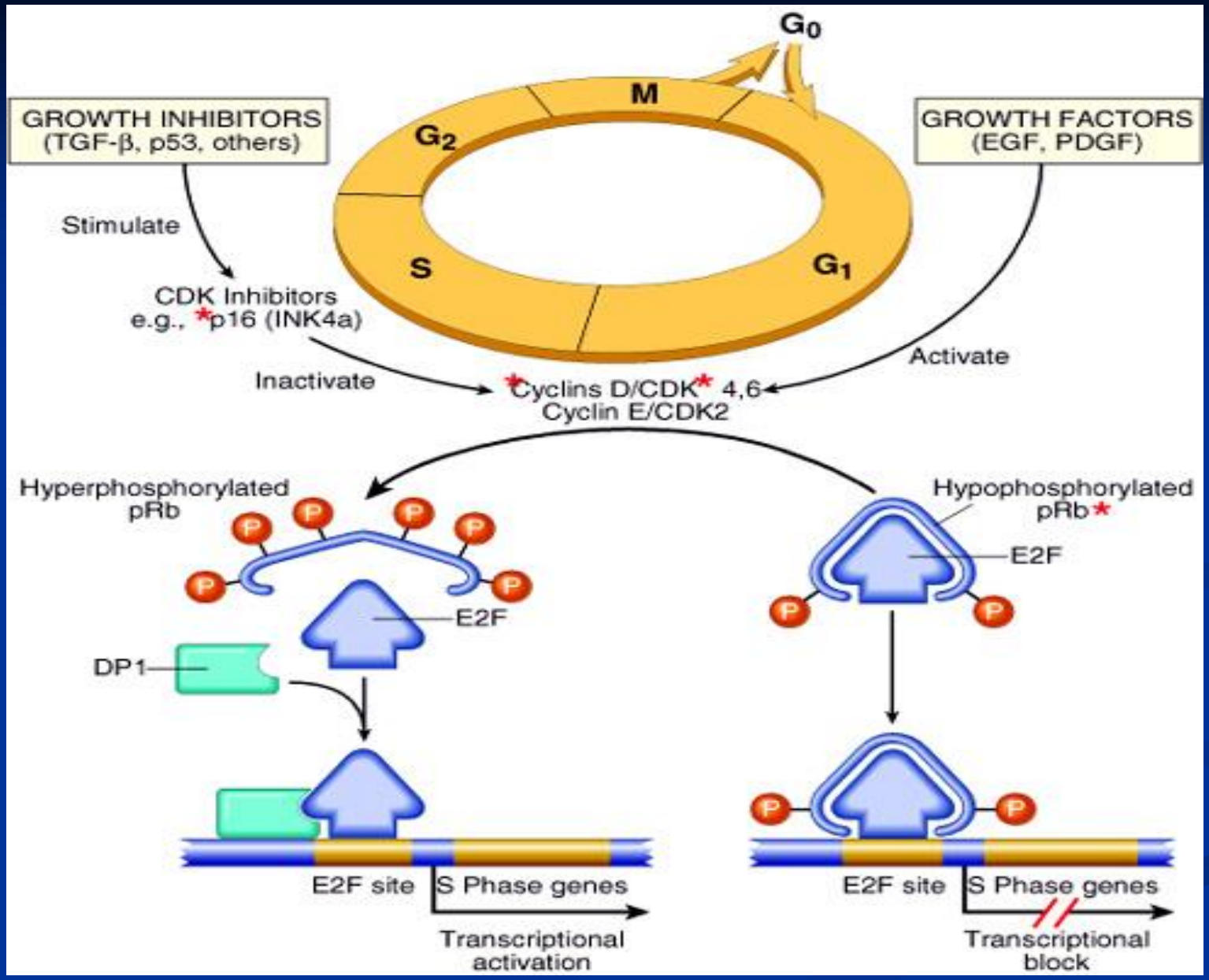

activated oncogene
inactivated tumour suppressor genes
acts dominantly (one lesion)
acts recessively (two lesions)
produces a gain in function
produces a loss of function
NEOPLASIA

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

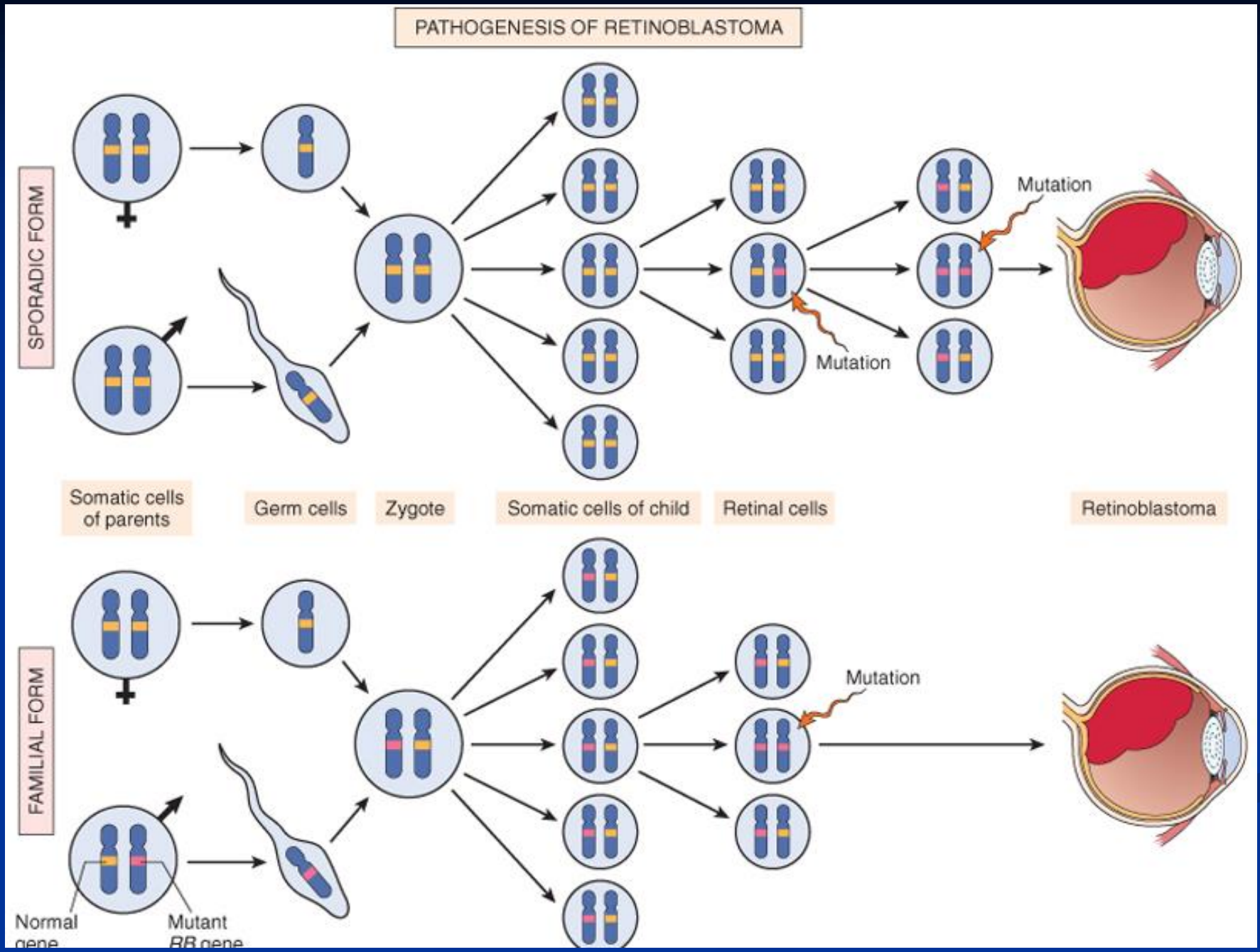
Carcinogenesis

- 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


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
E2F
DP1
Hypophosphorylated
pRb*
E2F
E2F site
S Phase genes
Transcriptional
activation
E2F site
S Phase genes
Transcriptional
block

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

Carcinogenesis

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

Mutations in TGF-β pathway are present in :

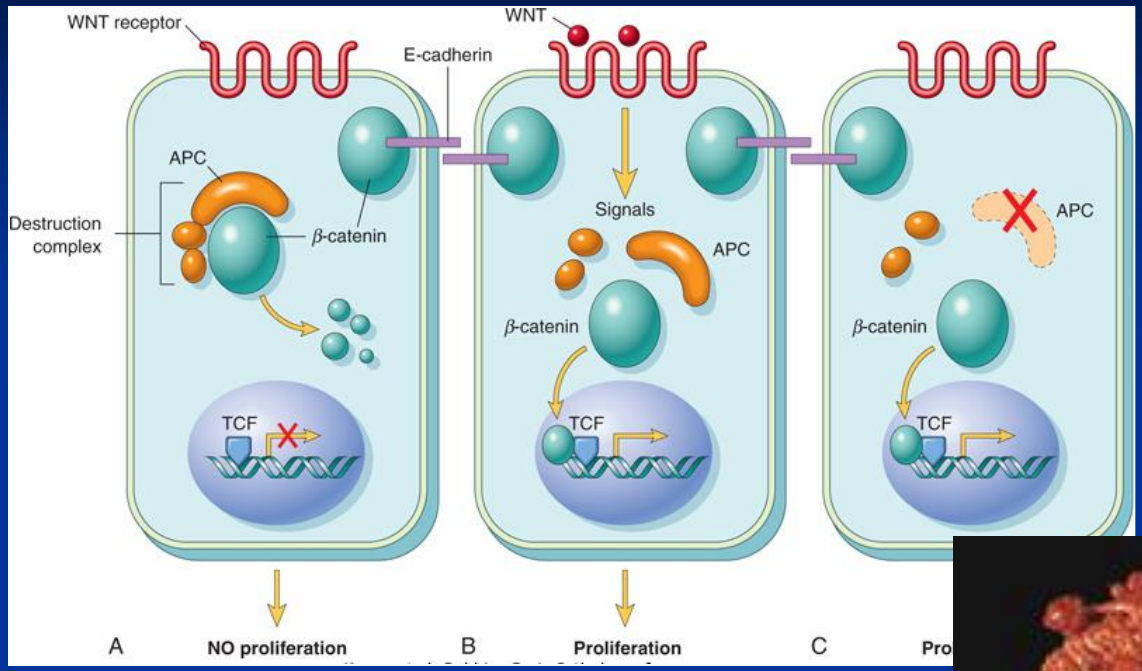
100% of pancreatic cancers

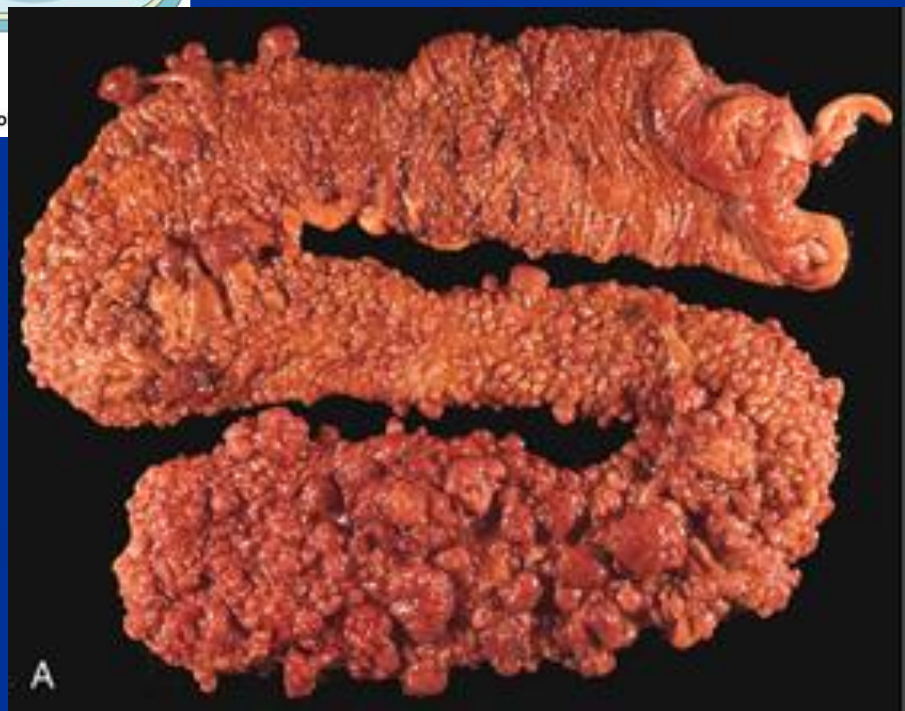
83% of colon cancers

Carcinogenesis

- Adenomatous Polyposis Coli – β Catenin pathway:
  - APC is tumor supressor gene
  - APC gene loss is very common in colon cancers
  - It has anti-proliferative action through inhibition of β–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

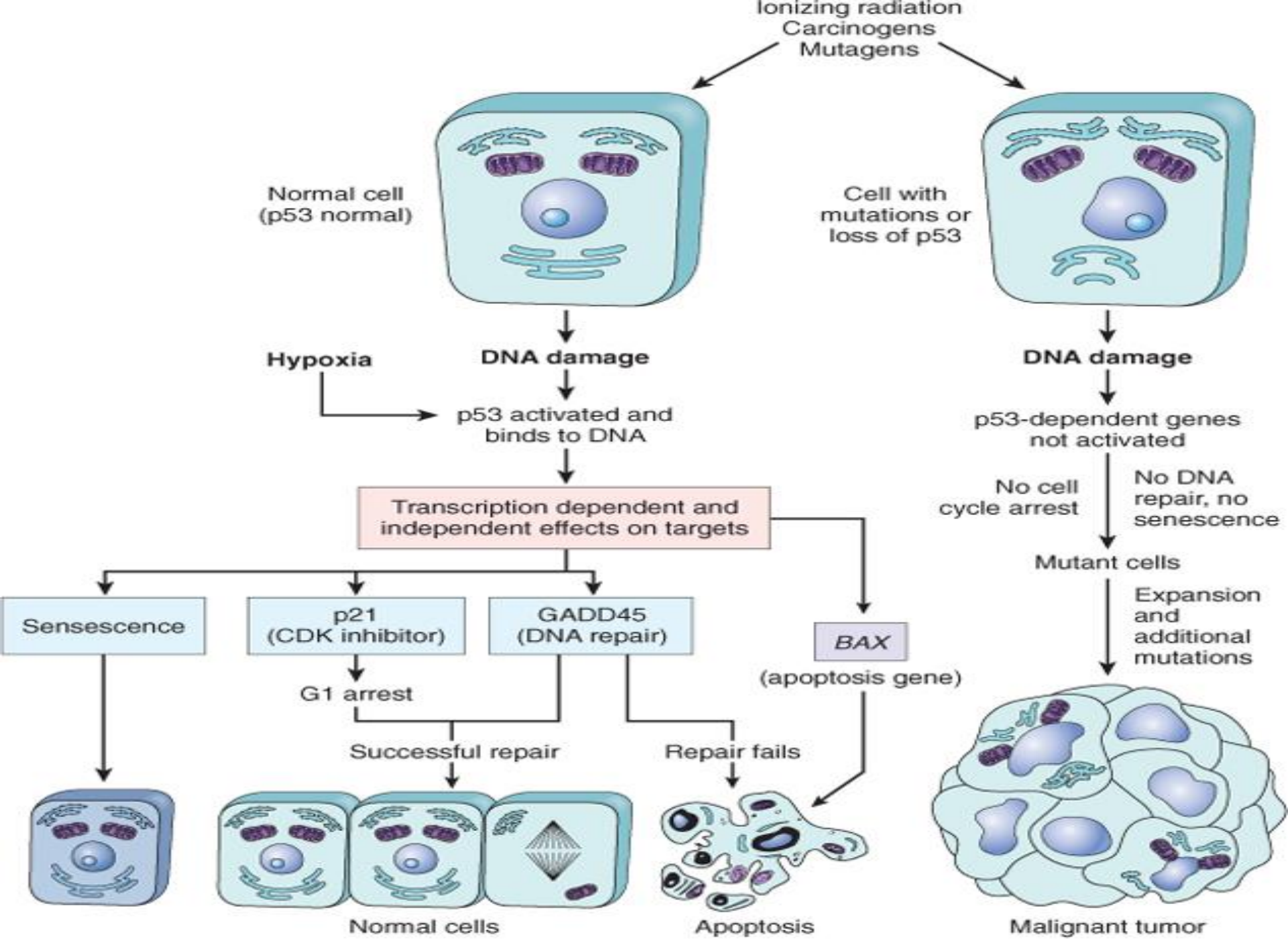
- P53
  - It has multiple functions
  - Mainly :
    - Tumor suppressor gene (anti-proliferative)
    - Regulates apoptosis

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



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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 inhereted, e.g : Li-Fraumeni syndrome

Carcinogenesis

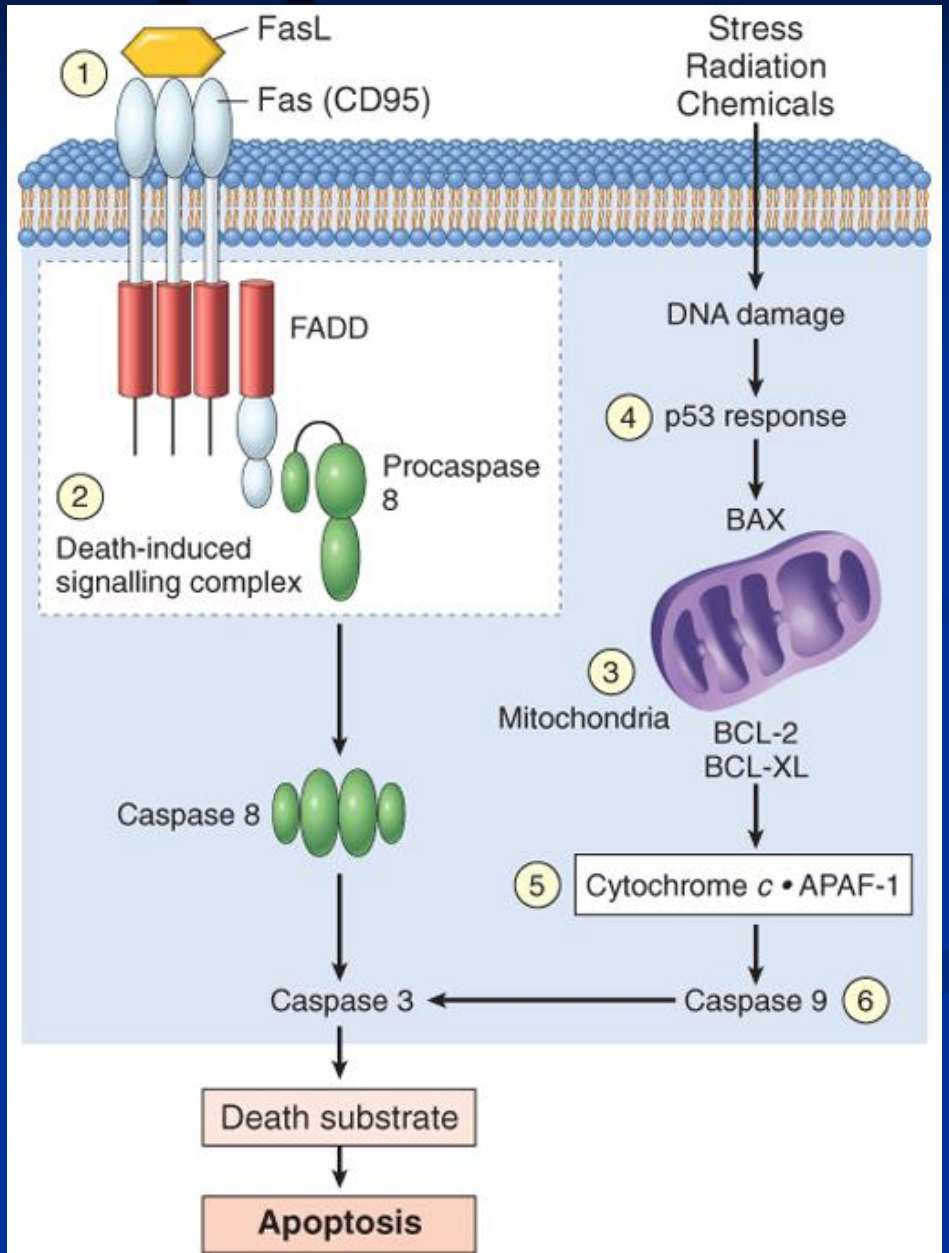
- Main changes in the cell physiology that lead to formation of the malignant phenotype:
  - A- Self-sufficiency in growth signals
  - B- Insensitivity to growth-inhibitory signals
  - **C- Evasion of apoptosis**
  - D- Limitless replicative potential
  - E- Sustained angiogenesis
  - F- Ability to invade and metastsize

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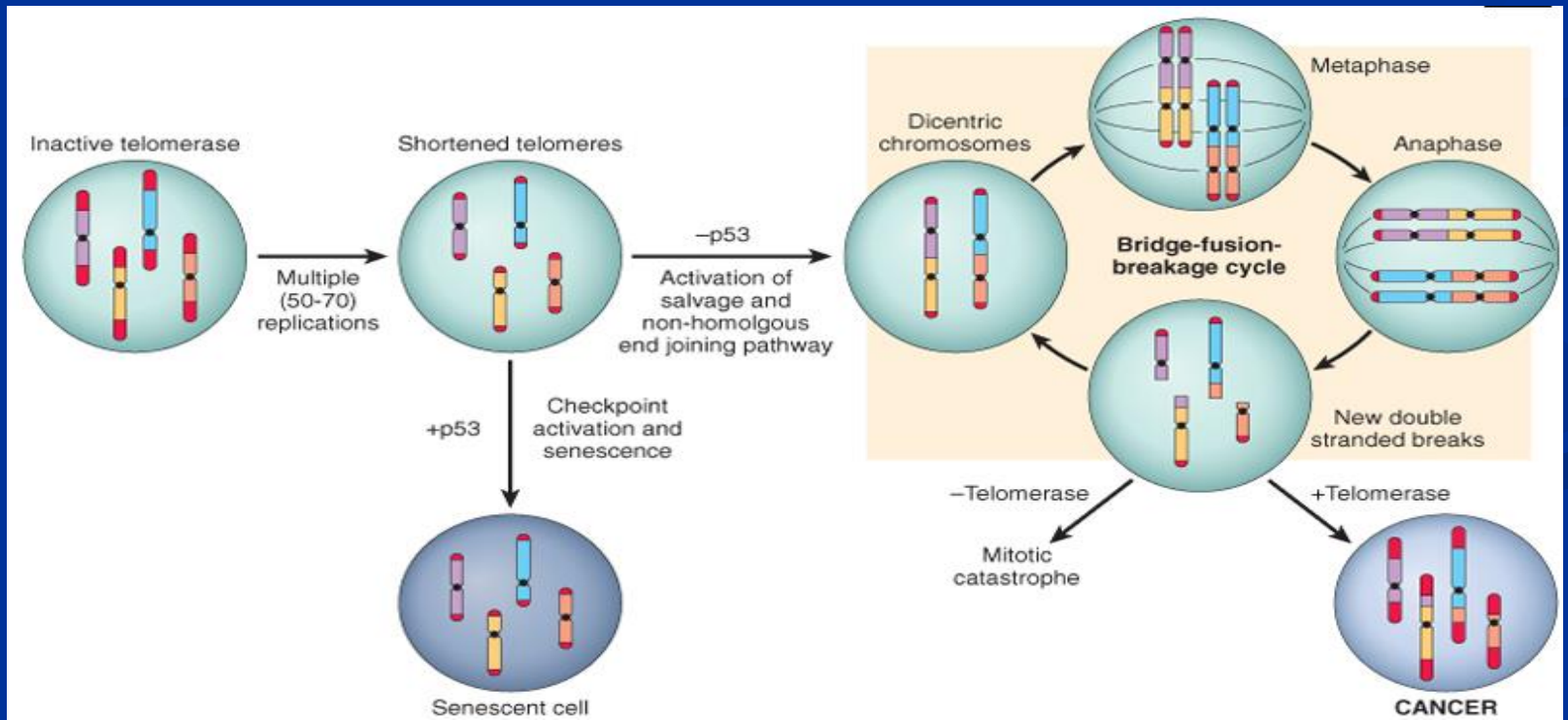
- **Limitless replicative potential:**
  - Normally there is progressive shortening of telomeres at the ends of chromosomes
  - Telomerase is active in normal stem cells but absent in somatic cells
  - In tumor cells : activation of the enzyme telomerase, which can maintain normal telomere length



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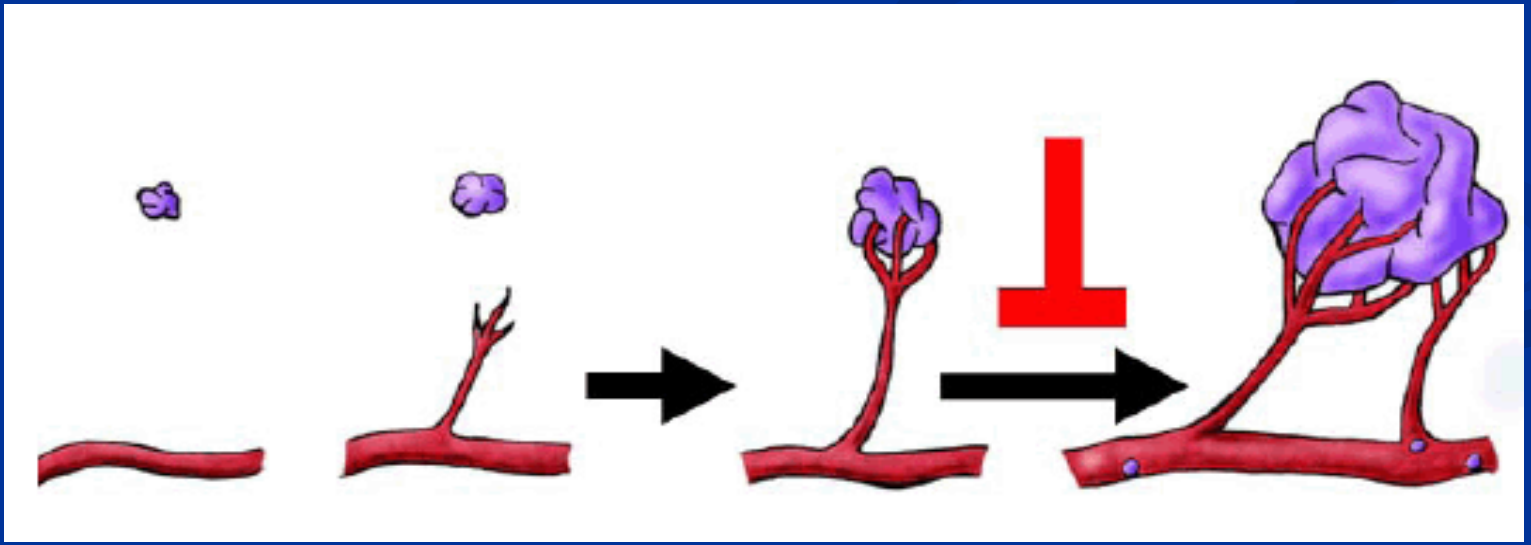
Carcinogenesis

- **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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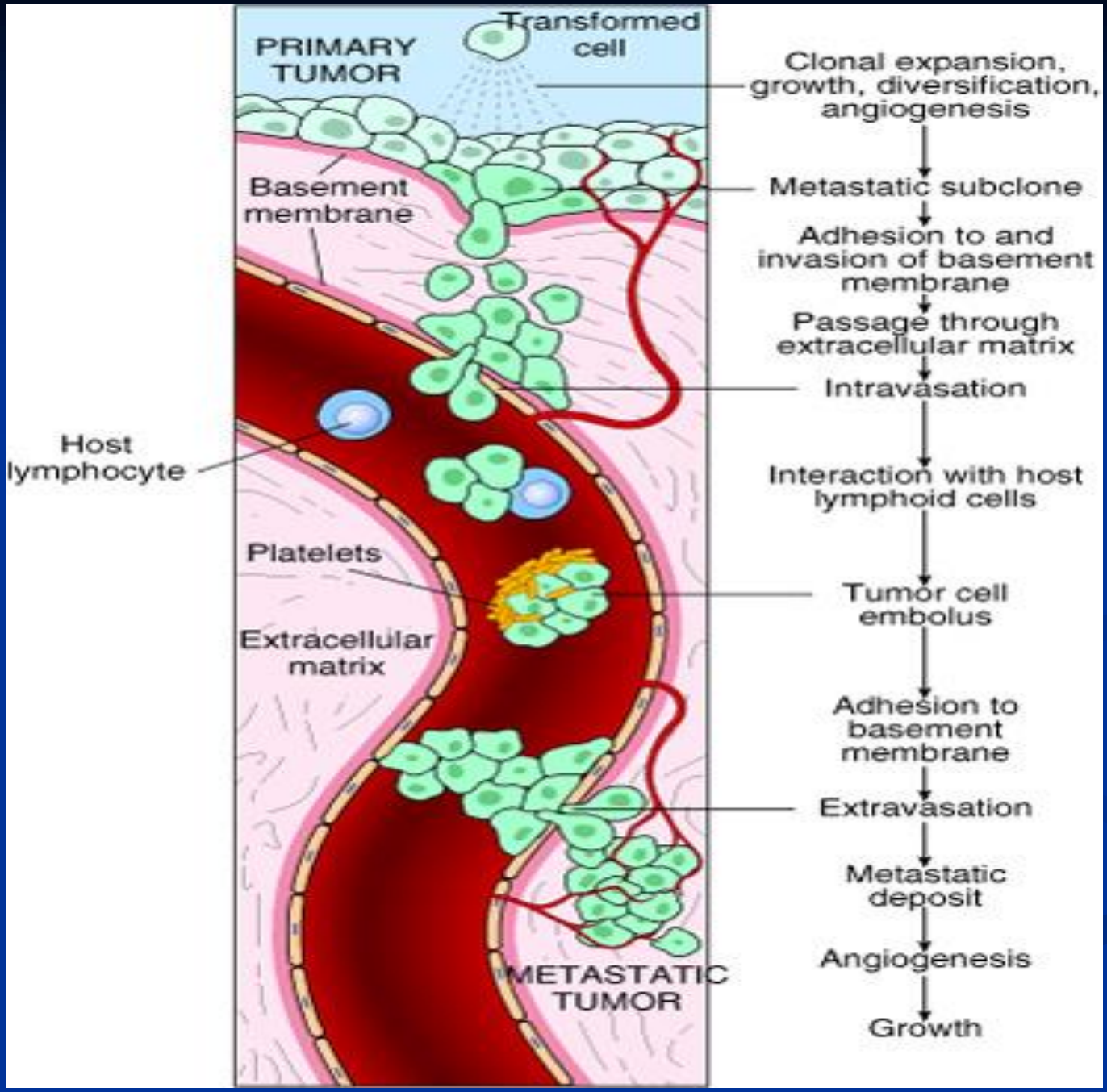

PRIMARY TUMOR
Transformed cell
Clonal expansion, growth, diversification, angiogenesis
Basement membrane
Metastatic subclone
Adhesion to and invasion of basement membrane
Passage through extracellular matrix
Intravasation
Host lymphocyte
Interaction with host lymphoid cells
Platelets
Tumor cell embolus
Extracellular matrix
Adhesion to basement membrane
Extravasation
Metastatic deposit
Angiogenesis
METASTATIC TUMOR
Growth

Carcinogenesis

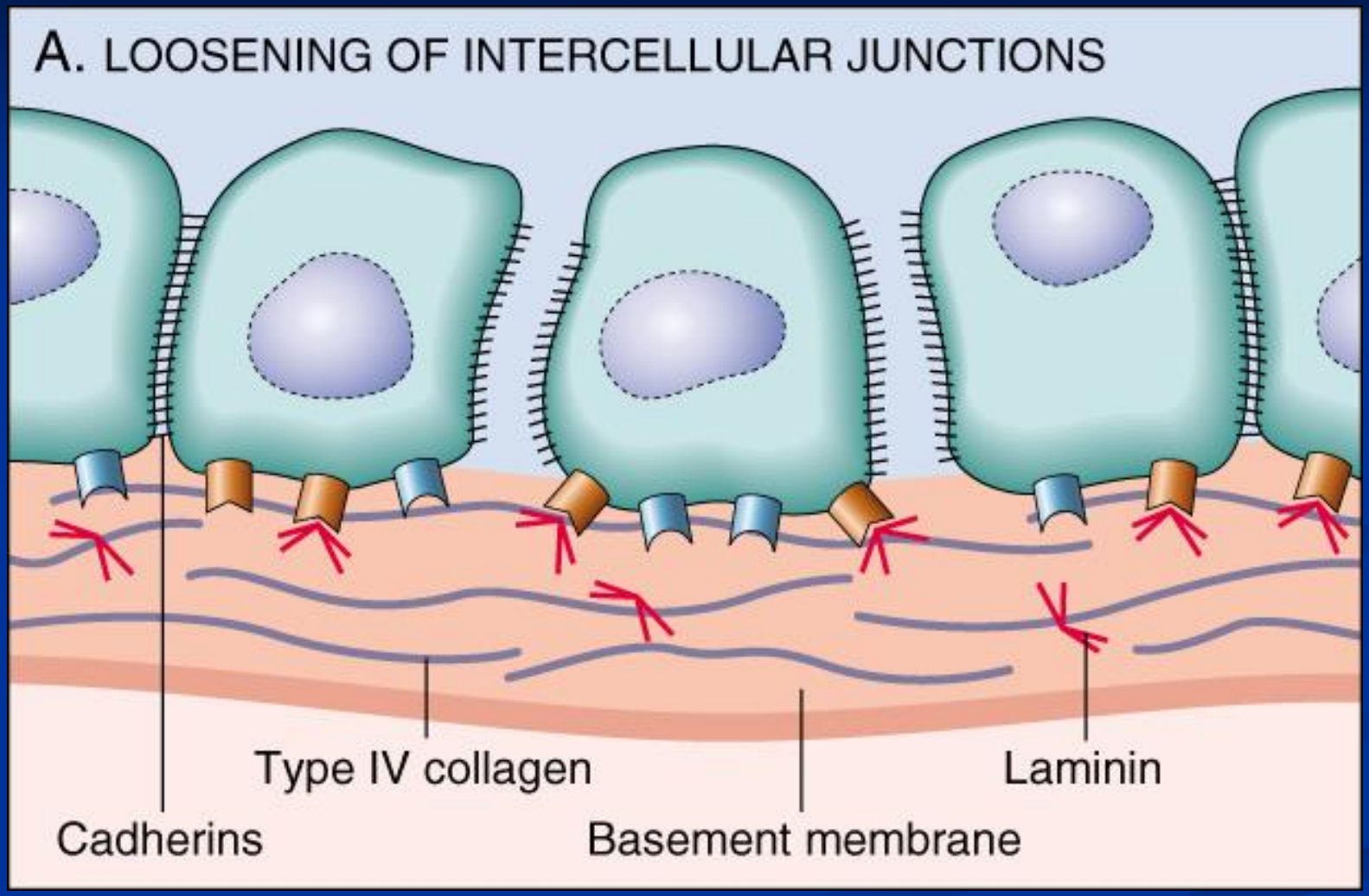
- **Ability to invade and metastsize:**
  - Two phases :
    - Invasion of extracellular matrix
    - Vascular dissimenation and homing of tumor cells

Carcinogenesis

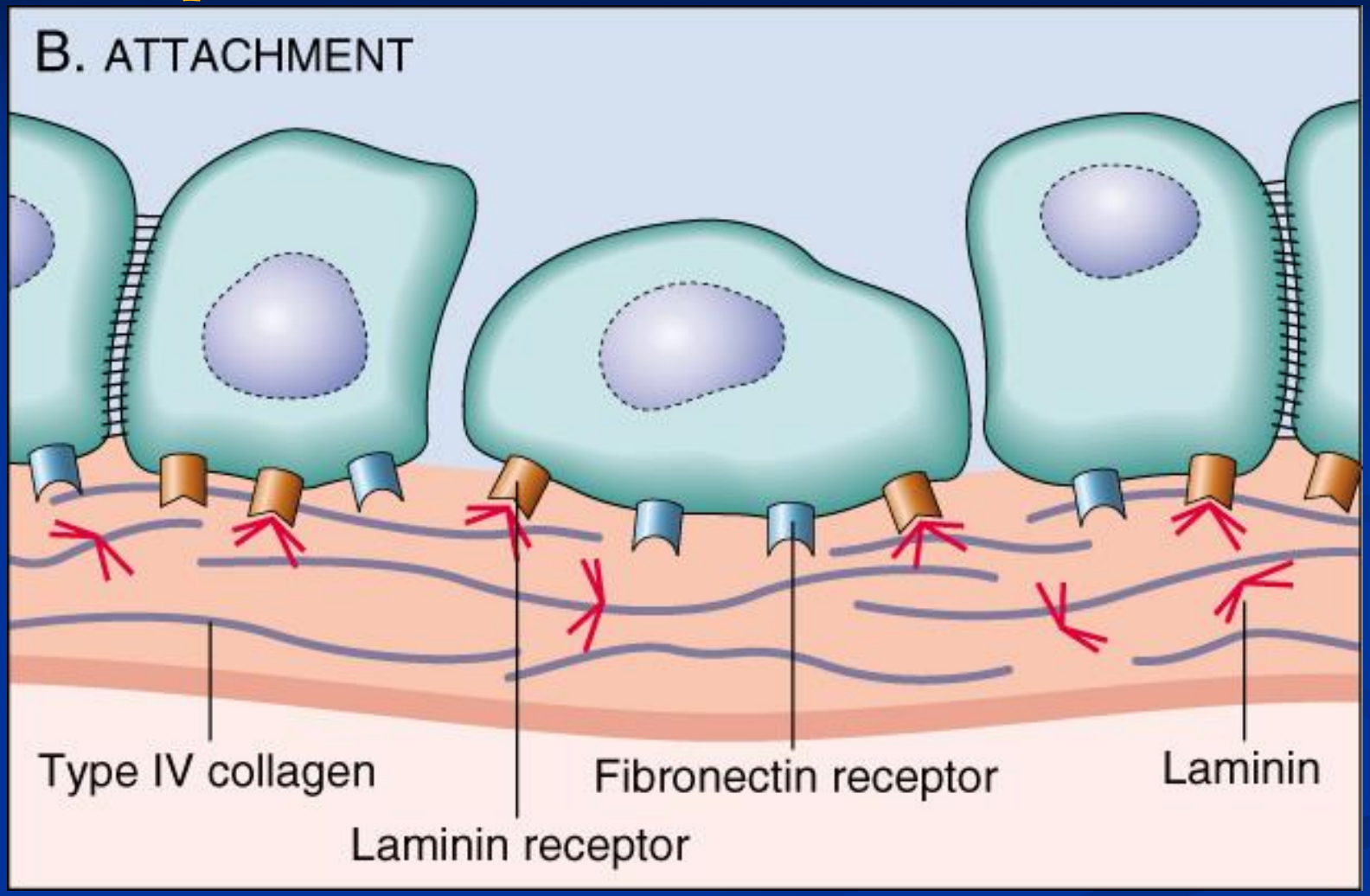
- Invasion of ECM:
  - Malignant cells first breach the underlying basement membrane
  - Traverse the interstitial tissue
  - Penetrate the vascular basement membrane
  - Gain access to the circulation

  - Invasion of the ECM has four steps:

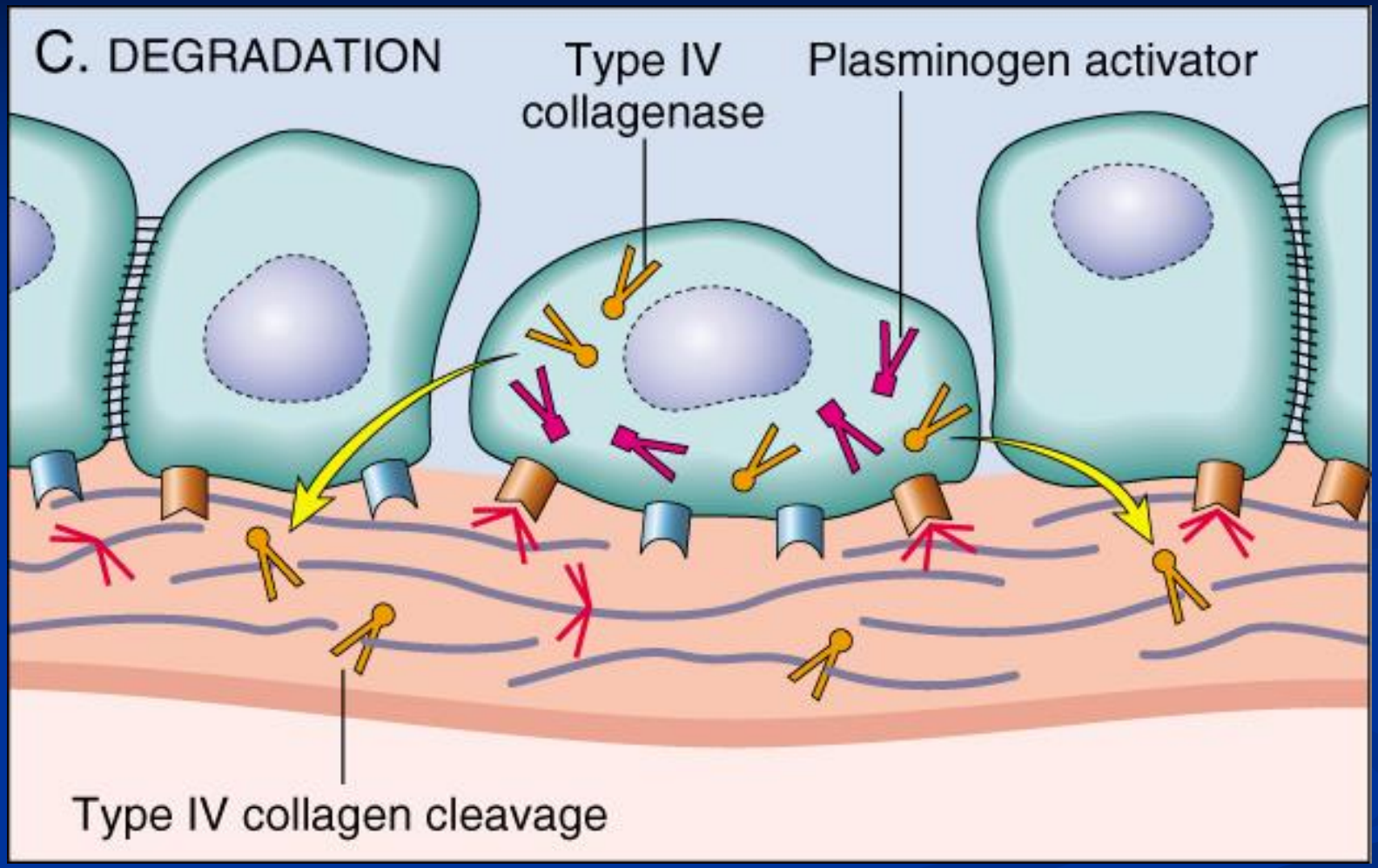
1. Detachment of tumor cells from each other



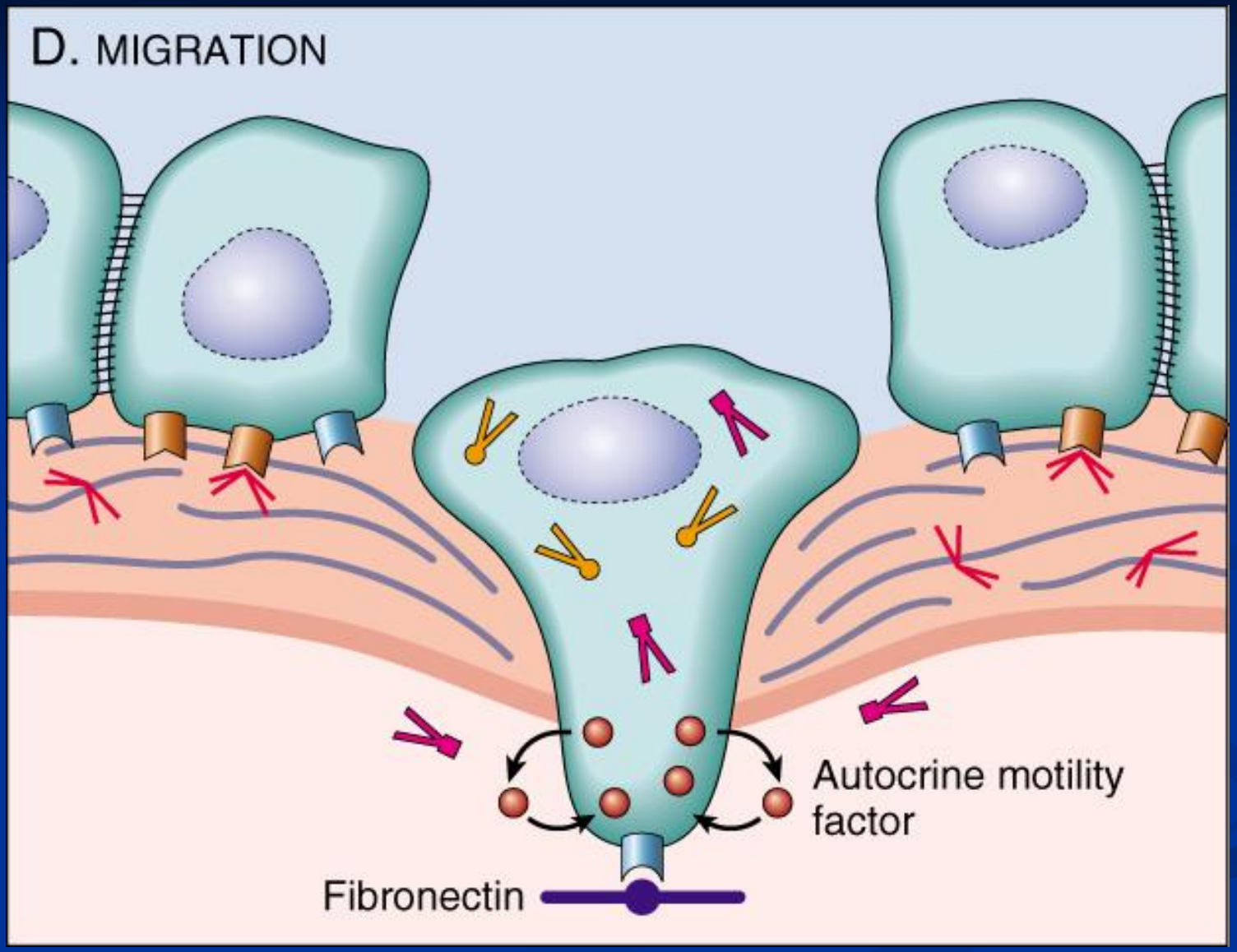
2. Attachments of tumor cells to matrix components



3. Degradation of ECM by collagenase enzyme



4. Migration of tumor cells



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

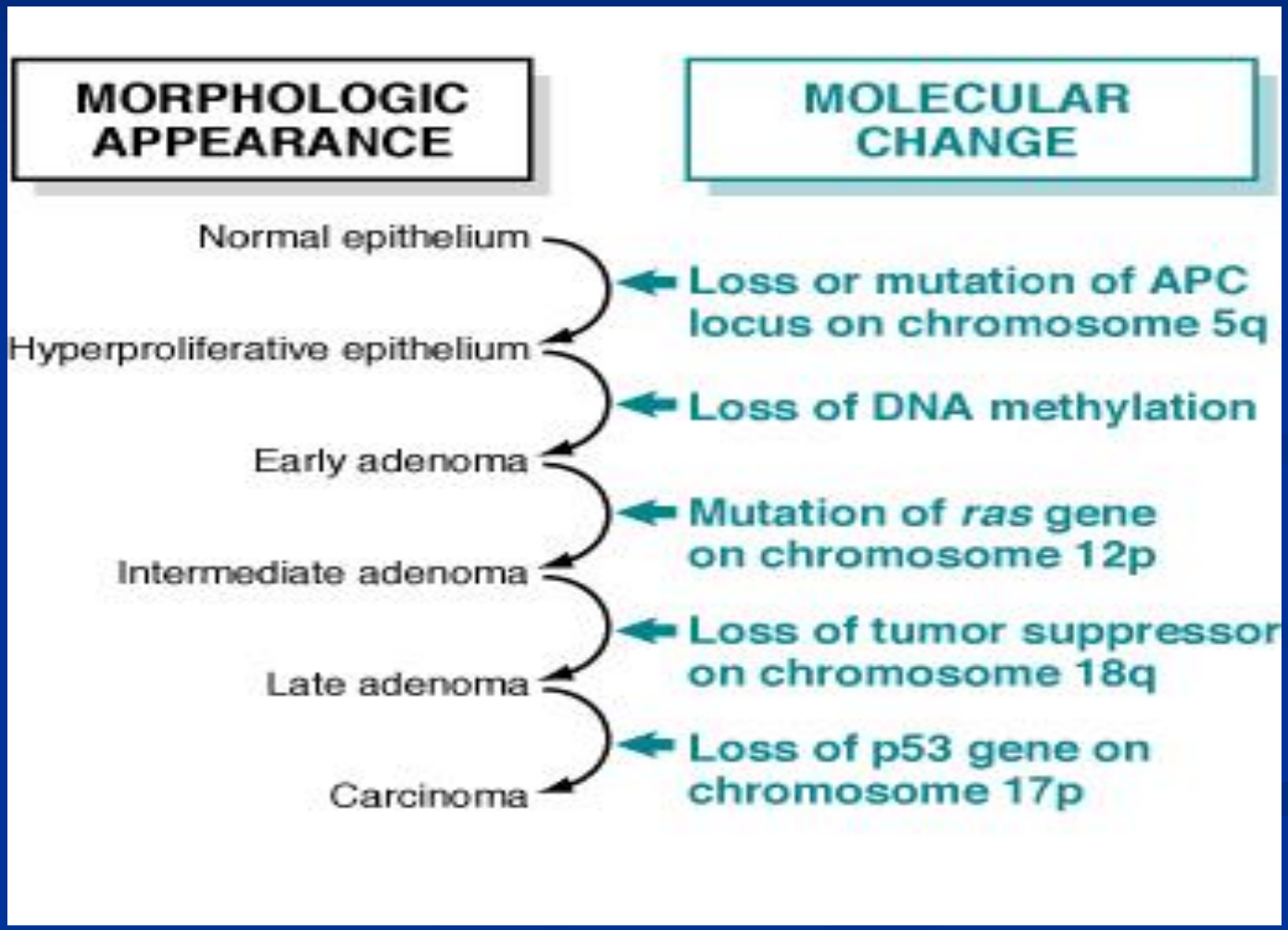
Genomic Instability

- 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

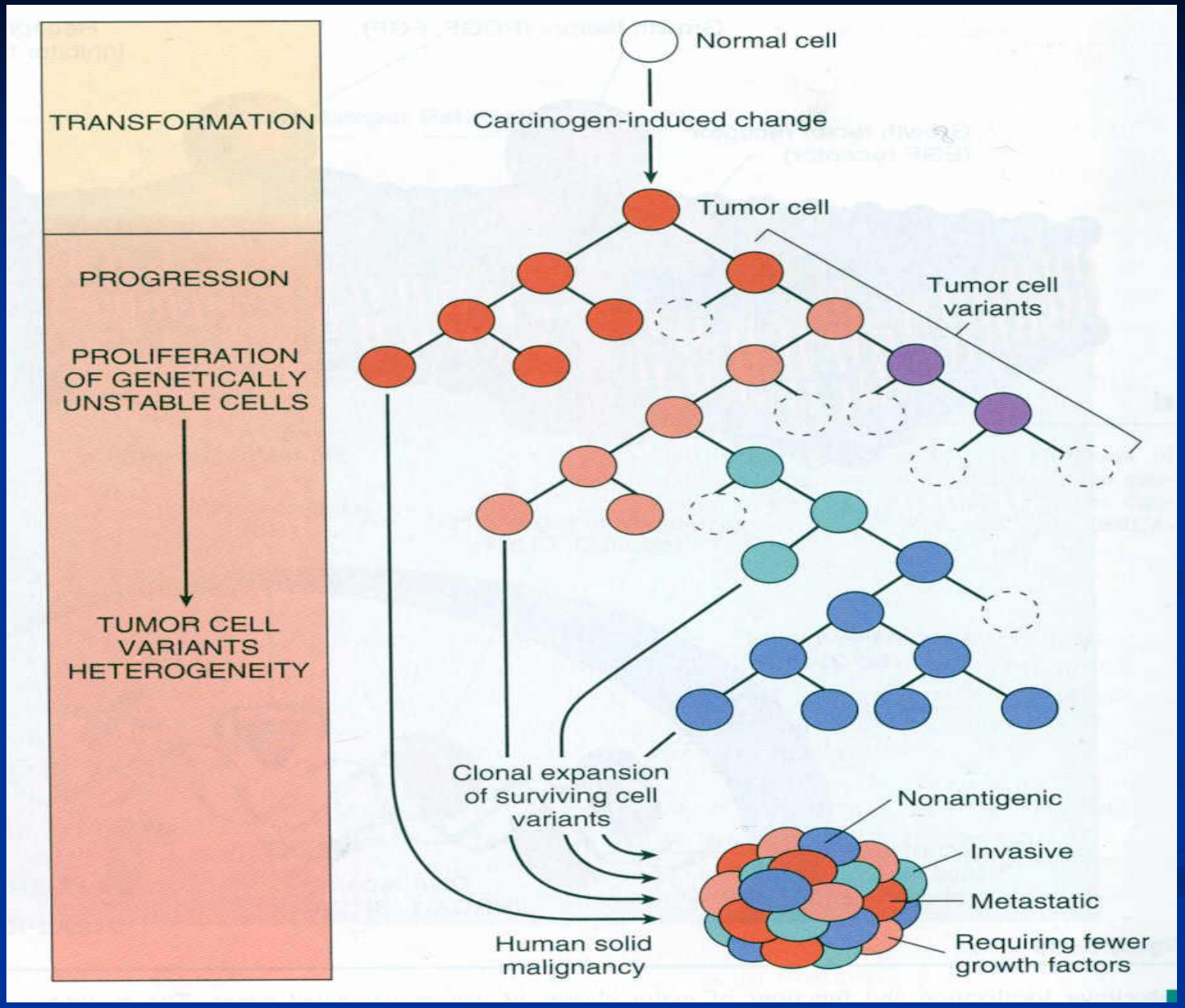
- Cancer results from accumulation of multiple mutations
- All cancers have multiple genetic alterations, involving activation of several oncogenes and loss of two or more tumor suppressor genes

Molecular Basis of multistep Carcinogenesis



Tumor progression

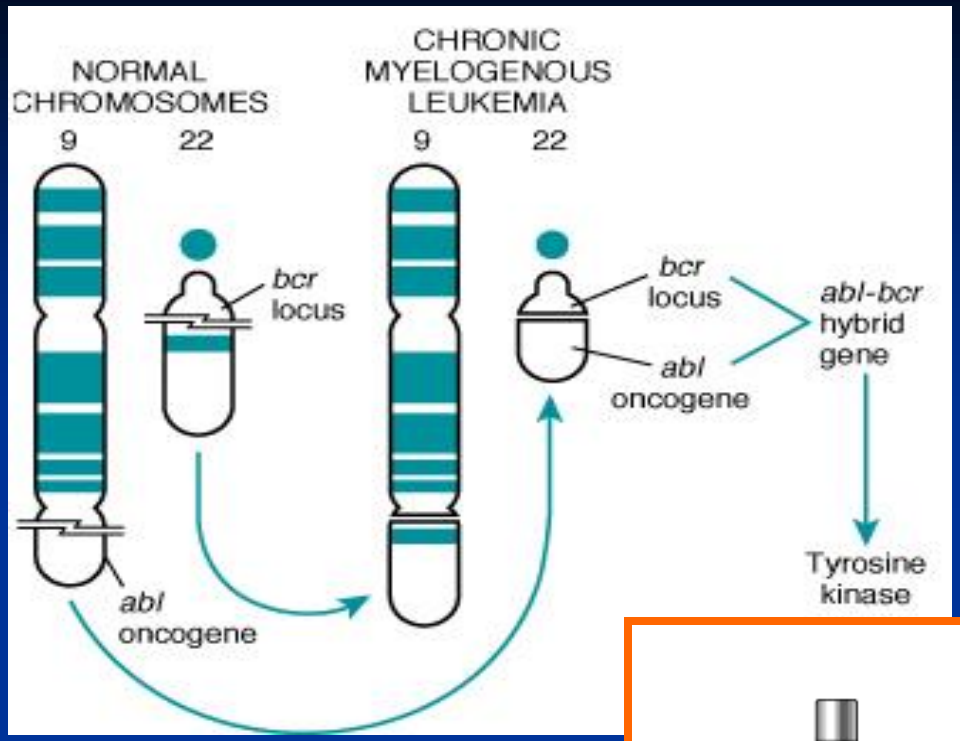
- Many tumors become more aggressive and acquire greater malignant potential…this is called “ tumor progression” …not increase in size!!
- By the time, the tumor become clinically evident, their constituent cells are extremely heterogeneous


TRANSFORMATION
PROGRESSION
PROLIFERATION OF GENETICALLY UNSTABLE CELLS
TUMOR CELL VARIANTS HETEROGENEITY
Normal cell
Carcinogen-induced change
Tumor cell
Tumor cell variants
Clonal expansion of surviving cell variants
Nonantigenic
Invasive
Metastatic
Requiring fewer growth factors
Human solid malignancy

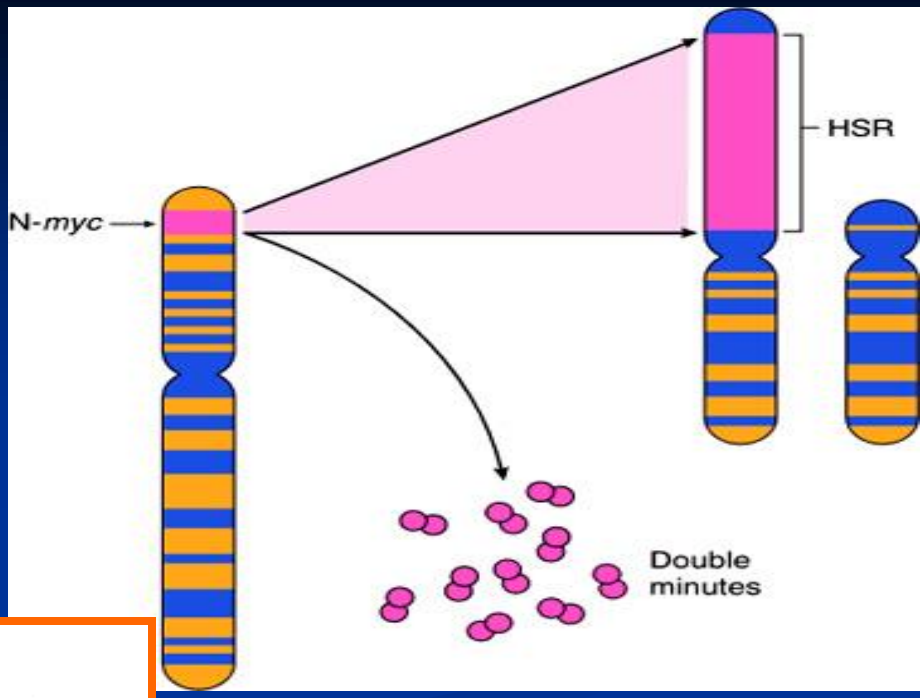
Karyotypic Changes in Tumors

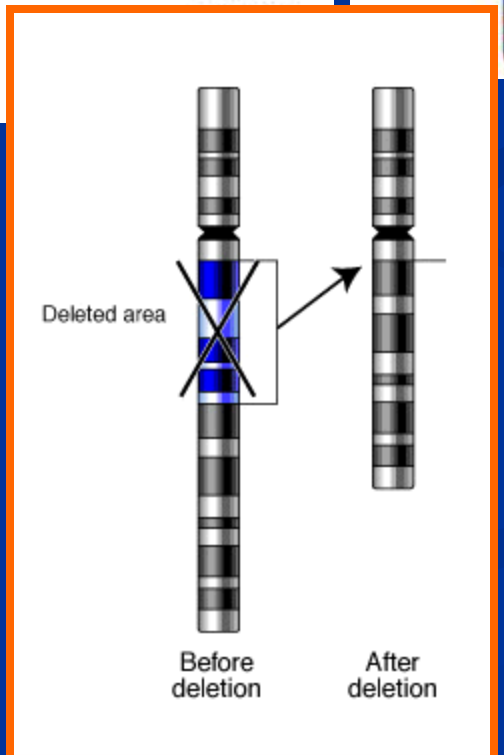
- Translocations:
  - In CML : t(9,22) …" Philadelphia chromosome"
  - In Burkitt Lymphoma : t(8,14)
  - In Follicular Lymphoma : t(14,18)
- Deletions
- Gene amplification:
  - Breast cancer : HER-2

Translocations



Gene amplification





NEOPLASIA

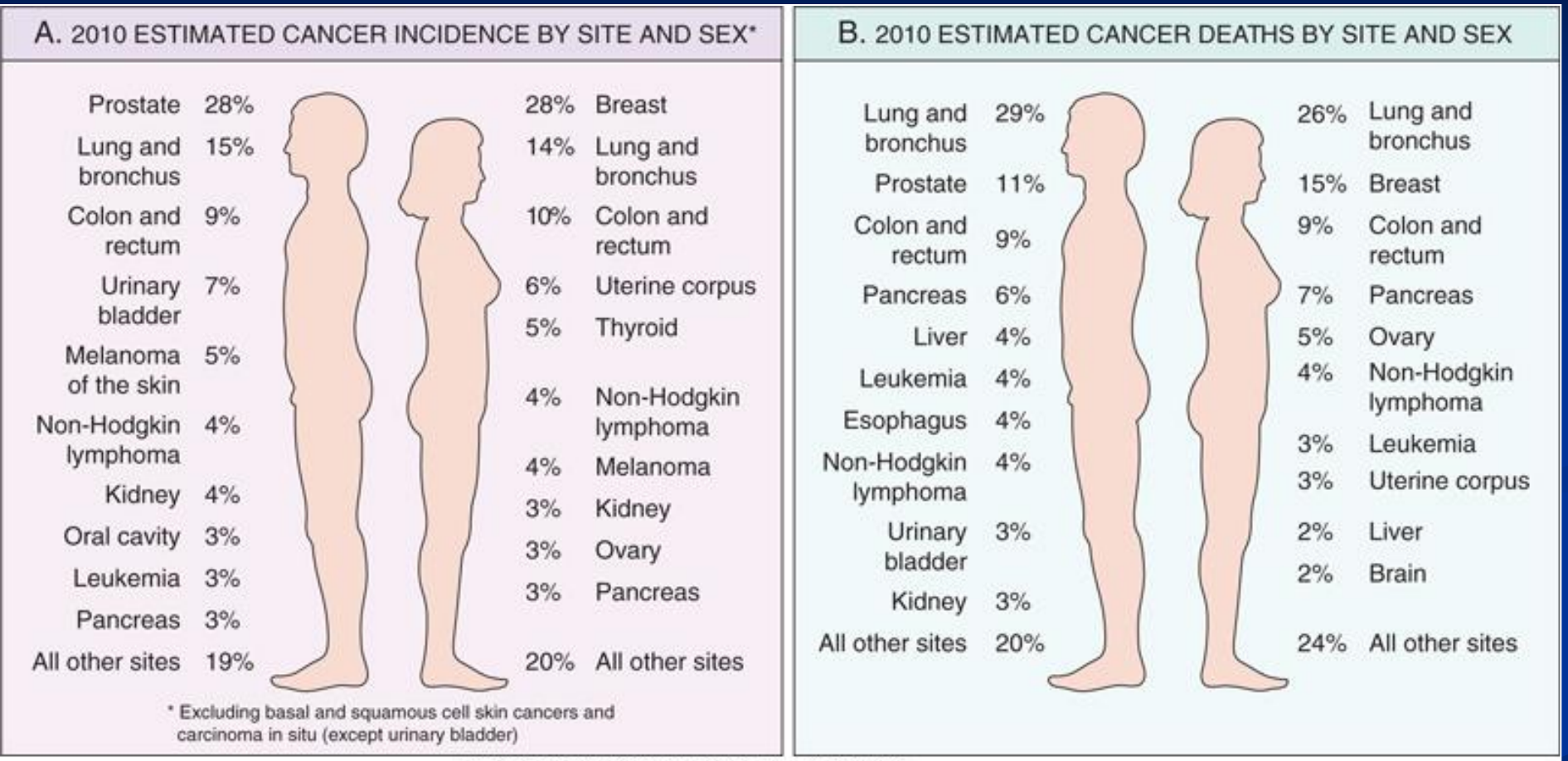
Lecture 4

ETIOLOGY OF CANCER:
CARCINOGENIC AGENTS

Abdulmalik Alsheikh, M.D.

Neoplasia

- Epidemiology
  - **Will help to discover aetiology**
  - **Planning of preventive measures**
  - **To know what is common and what is rare.**
  - **Development of screening methods for early diagnosis**



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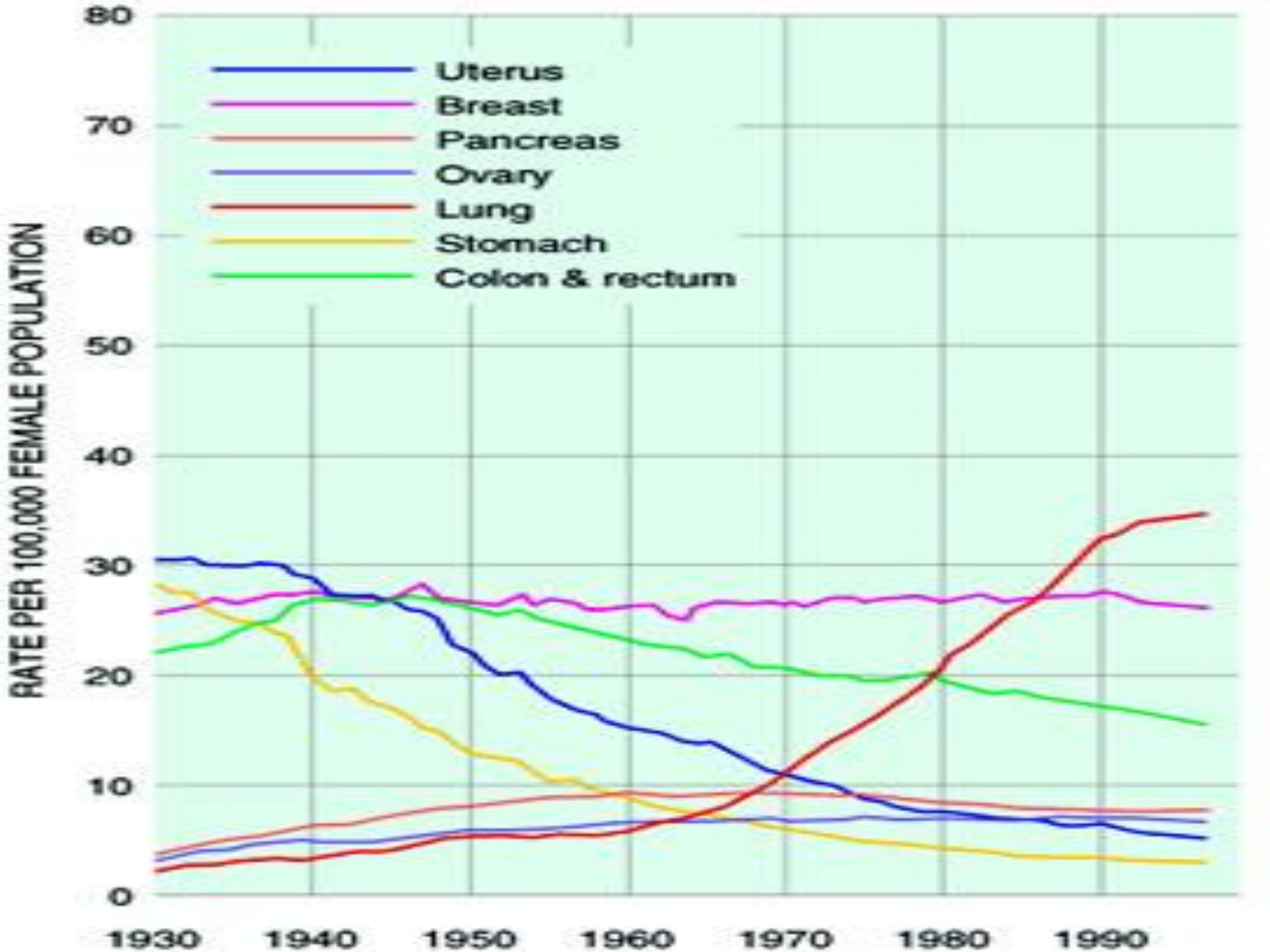
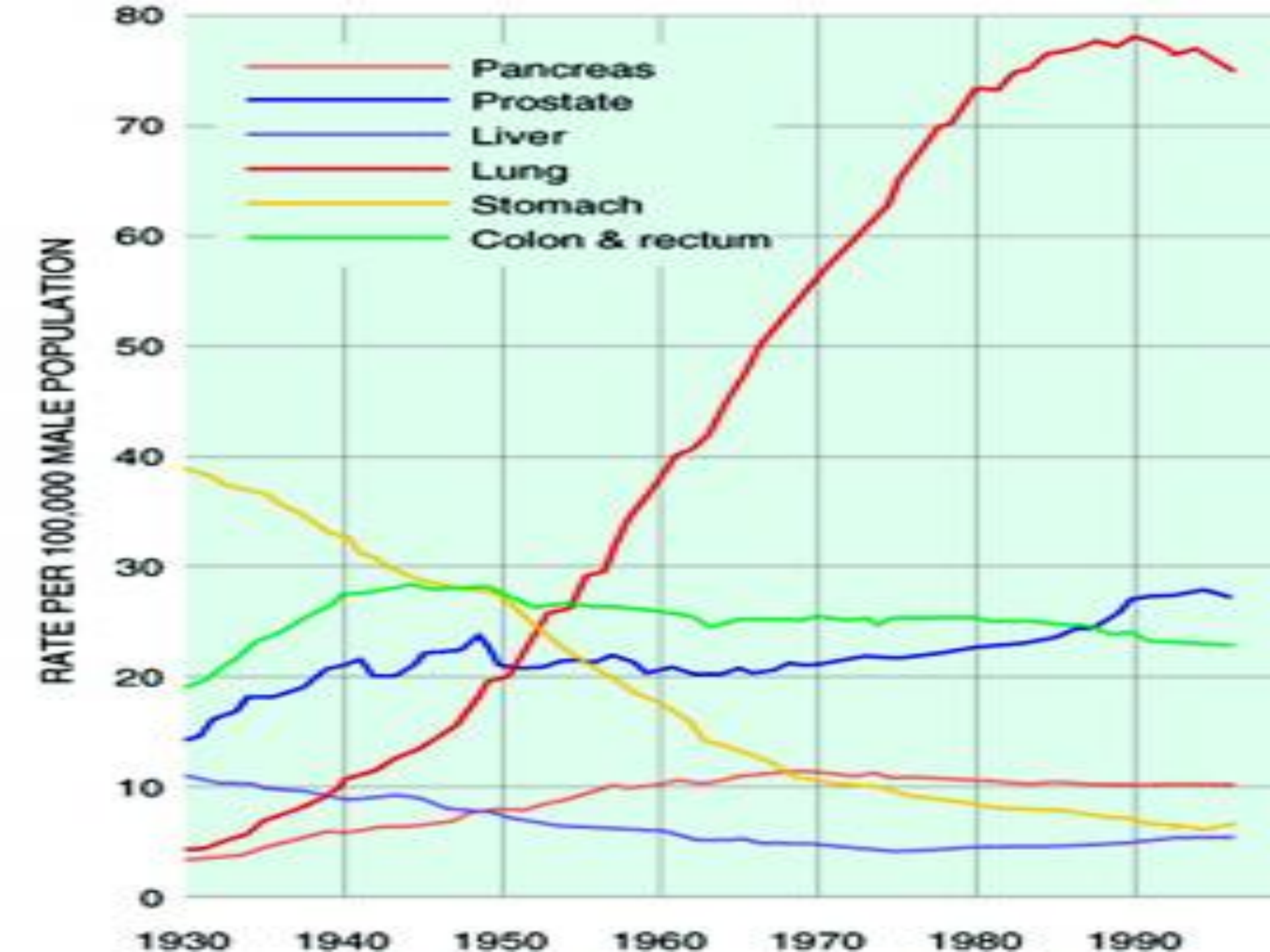

Uterus
Breast
Pancreas
Ovary
Lung
Stomach
Colon & rectum
RATE PER 100,000 FEMALE POPULATION
80
70
60
50
40
30
20
10
0
1930
1940
1950
1960
1970
1980
1990


Pancreas
Prostate
Liver
Lung
Stomach
Colon & rectum
RATE PER 100,000 MALE POPULATION
80
70
60
50
40
30
20
10
0
1930
1940
1950
1960
1970
1980
1990

Neoplasia

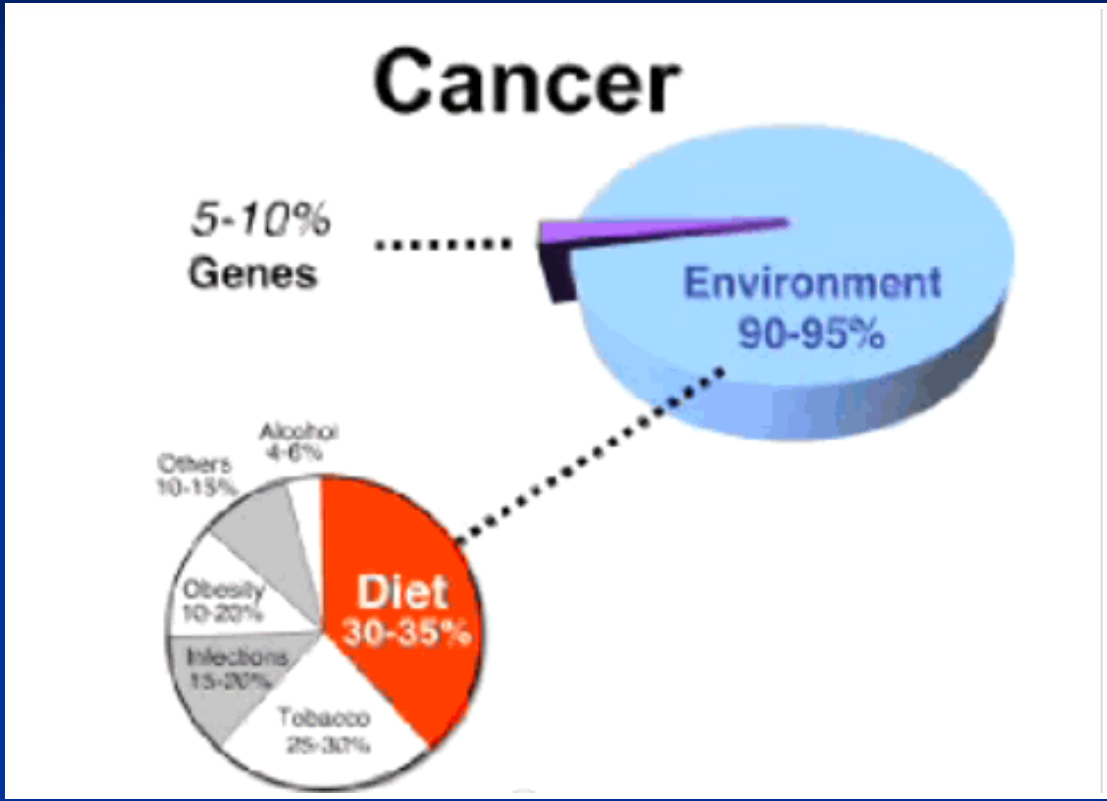
- Factors affecting incidence of cancer
  - **Geographic and Environmental**
  - Age
  - Heredity
  - Aquired preneoplastic disorders

Neoplasia

- Factors affecting incidence of cancer
  - **Geographic and Environmental**
  - Age
  - Heredity
  - Aquired preneoplastic disorders

Neoplasia

- Geographic and Environmental factors:
  - Rate of stomach carcinoma in Japan is seven times the rate in North America and Europe.
  - Breast carcinoma is five times higher in North America comparing to Japan
  - Liver cell carcinoma is more common in African populations


Cancer
5-10%
Genes
Environment
90-95%
Alcohol
4-6%
Others
10-15%
Diet
30-35%
Obesity
10-20%
Infections
15-20%
Tobacco
25-30%

Neoplasia

- Geographic and **Environmental** factors:
  - Asbestos : mesothelioma
  - Smoking : lung cancer
  - Multiple sexual partners: cervical cancer
  - Fatty diets : colonic cancer

Please see table 6-3 for occupational cancers

Neoplasia

- Factors affecting incidence of cancer
  - Geographic and Environmental
  - **Age**
  - Heredity
  - Aquired preneoplastic disorders

Neoplasia

- Age:
  - Generally, the frequency of cancer increases with age.
  - Most cancer mortality occurs between 55 and 75.
  - Cancer mortality is also increased during childhood
  - Most common tumors of children: Leukemia, tumors of CNS, Lymphomas, soft tissue and bone sarcomas.

Neoplasia

- Factors affecting incidence of cancer
  - Geographic and Environmental
  - Age
  - **Heredity**
  - Aquired preneoplastic disorders

Neoplasia

- Heredity
  - Inherited Cancer Syndromes
  - Familial Cancers
  - Autosomal Recessive Syndromes of Defective DNA repair

Heredity

- Inherited Cancer Syndromes:
  - Inheritance of a single mutant gene greatly increases the risk of developing neoplasm
  - E.g. Retinoblastoma in children :
    - 40% of Retinoblastomas are familial
    - carriers of the gene have 10000 fold increase in the risk of developing Retinoblastoma
  - E.g. multiple endocrine neoplasia

Heredity

- Familial Cancers:
  - All common types of cancers occur in familial form
  - E.g. breast, colon, ovary,brain
  - Familial cancers usually have unique features:
    - Start at early age
    - Multiple or bilateral
    - Two or more relatives

Heredity

- Autosomal Recessive Syndromes of Defective DNA repair :
  - Small group of autosomal recessive disorders
  - Characterized by DNA instability

Please see table 6-4 for more examples

Neoplasia

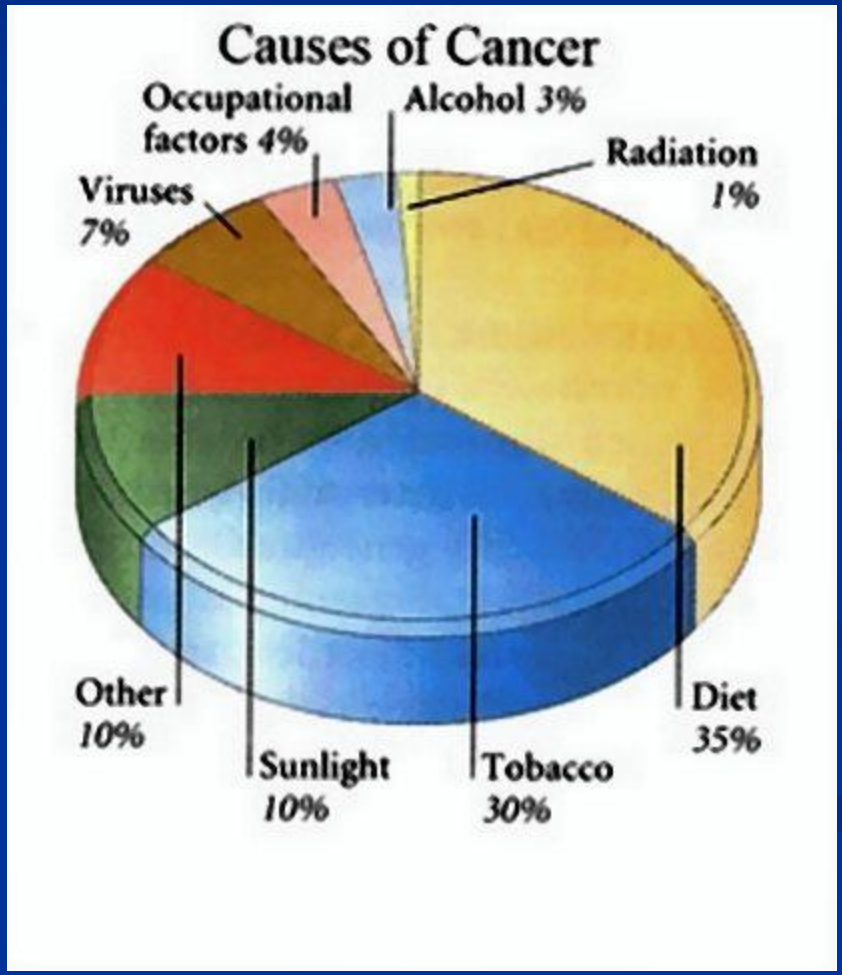
- Factors affecting incidence of cancer
  - Geographic and Environmental
  - Age
  - Heredity
  - **Aquired preneoplastic disorders**

Neoplasia

- **Aquired preneoplastic disorders:** Some Clinical conditions that predispose to cancer
  - Dysplastic bronchial mucosa in smokers→ lung carcinoma
  - Liver cirrhosis → liver cell carcinoma
  - Margins of chronic skin fistula → squamous cell carcinoma

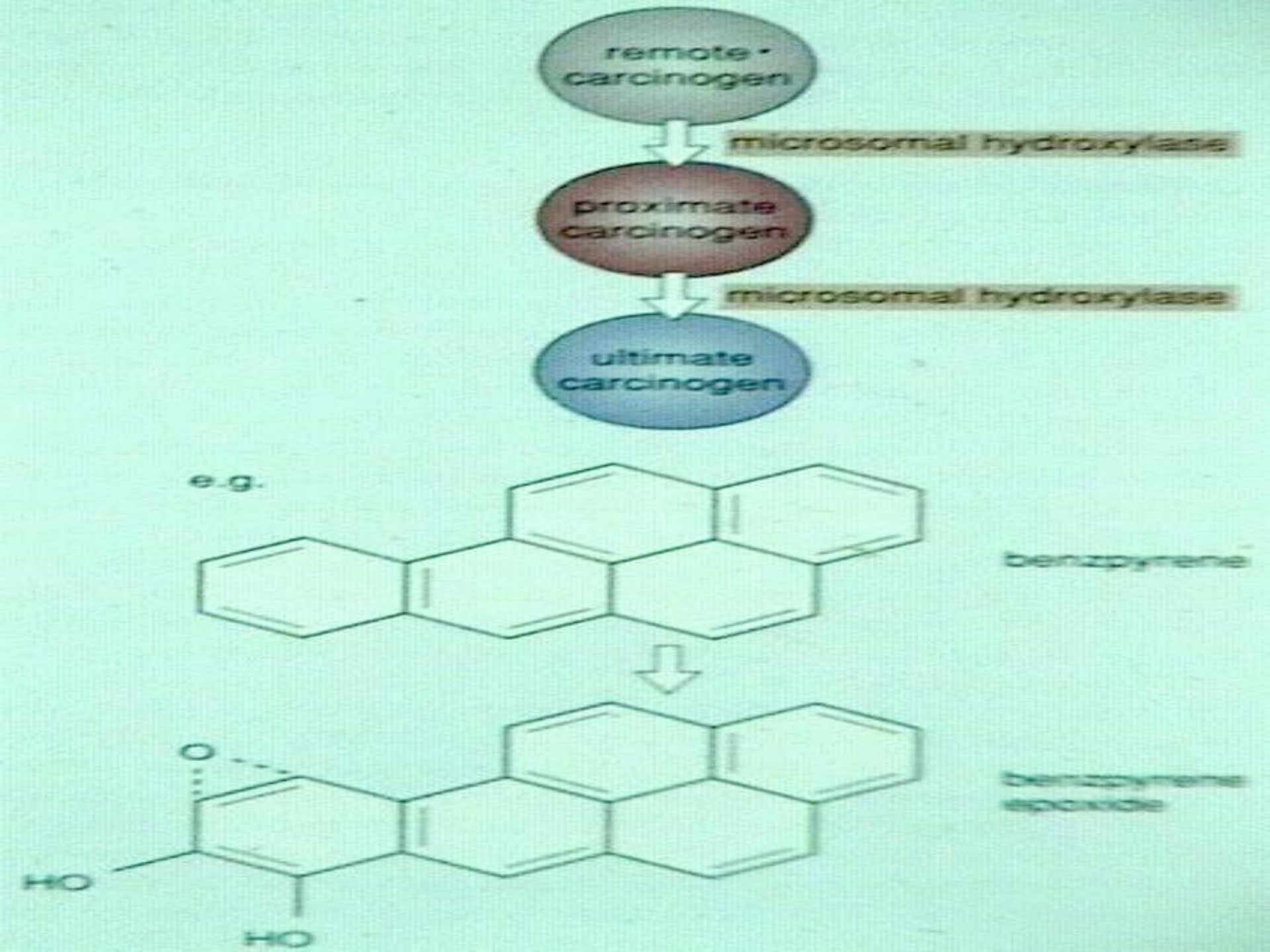
Carcinogenic Agents

- Chemicals
- Radiation
- Microbial agents



Carcinogenic Agents
Chemical Carcinogens

- Natural or synthetic
- Direct reacting or indirect
- Indirect → need metabolic conversion to be active and carcinogenic
- Indirect chemicals are called " procarcinogens " and their active end products are called " ultimate carcinogens"


remote carcinogen
microsomal hydroxylase
proximate carcinogen
microsomal hydroxylase
ultimate carcinogen
e.g.
benzpyrene
O
HO
HO

Carcinogenic Agents
Chemical Carcinogens

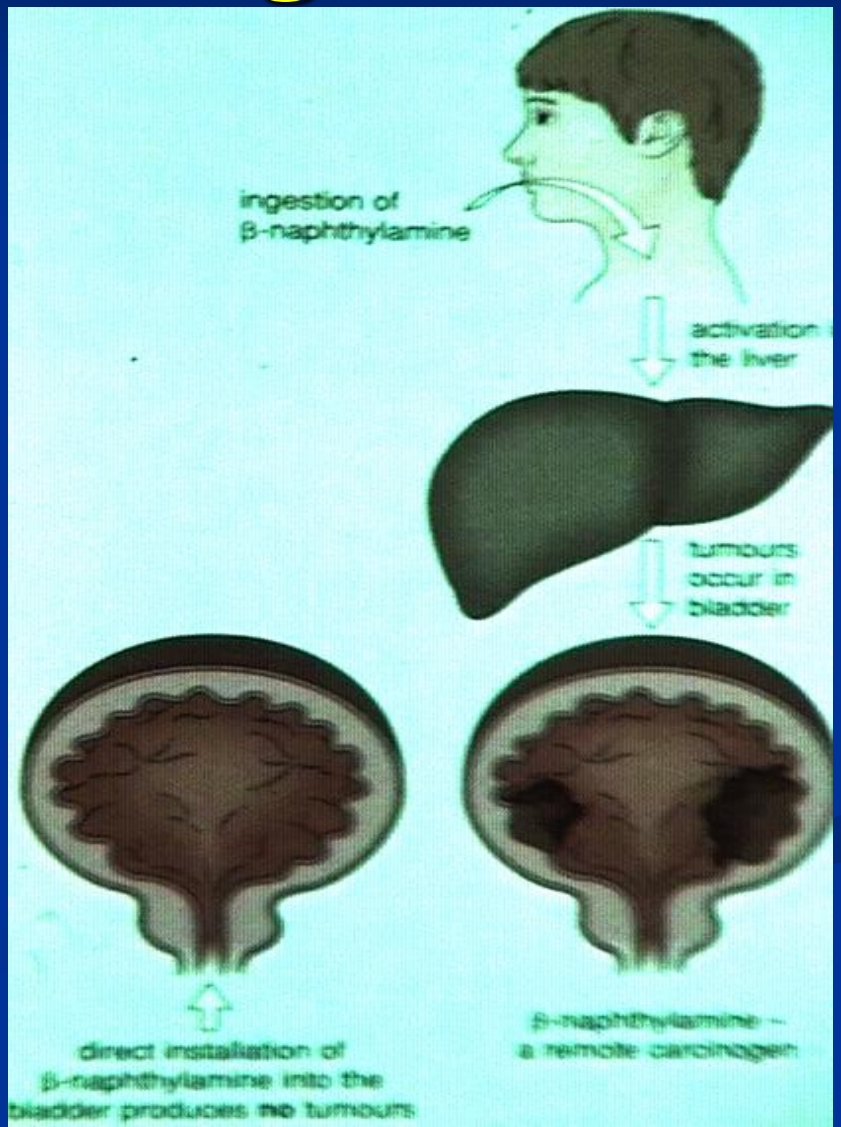
- All direct reacting and ultimate chemical carcinogens are highly reactive as they have electron-deficient atoms
- They react with the electron rich atoms in RNA, DNA and other cellular proteins

Carcinogenic Agents
Chemical Carcinogens

- Examples:
  - Alkylating agents
  - Polycyclic hydrocarbons:
    - Cigarette smoking
    - Animal fats during broiling meats
    - Smoked meats and fish

Carcinogenic Agents
Chemical Carcinogens

- Aromatic amines and azo dyes:
  - B-naphthylamine cause bladder cancer in rubber industries and aniline dye
  - Some azo dyes are used to color food also can cause bladder cancer



Carcinogenic Agents
Chemical Carcinogens

- Other substances:
  - Nitrosamines and nitrosamides are used as preservatives. They cause gastric cancer.
  - Aflatoxin B: produced by aspirigillus growing on improperly stored grains. It cause hepatocellular carcinoma

Carcinogenic Agents
Chemical Carcinogens

- Mechanism of action of chemical carcinogens:
  - Most of them are mutagenic. i.e. cause mutations
  - RAS and P53 are common targets

Carcinogenic Agents
Radiation Carcinogenesis

- UV rays of sunlight
- X-rays
- Nuclear radiation
- Therapeutic irradiations

- Radiation has mutagenic effects: chromosomes breakage, translocations, and point mutations

Carcinogenic Agents
Radiation Carcinogenesis

- UV rays of sunlight :
  - Can cause skin cancers: melanoma, squamous cell carcinoma, and basal cell carcinoma
  - It is capable to damage DNA
  - With extensive exposure to sunlight, the repair system is overwhelmed→ skin cancer
  - They cause mutations in P53 gene

Carcinogenic Agents

- Viral and Microbial oncogenesis
  - DNA viruses
  - RNA viruses
  - other organisms

Carcinogenic Agents
Viral Carcinogenesis

- carry genes that induce cell replication as part of the viral life cycle
- host cell has endogenous genes that maintain the normal cell-cycle
- Viral infection mimics or blocks these normal cellular signals necessary for growth regulation

Carcinogenic Agents
Viral Carcinogenesis

RNA Oncogenic viruses

Human T-Cell Leukemia Virus type 1 (HTLV-1)

- RNA retrovirus targets / transforms T-cells
- causes T-Cell leukemia/Lymphoma
- Endemic in Japan and Caribbean
- Transmitted like HIV but only 1% of infected develop T-Cell leukemia/Lymphoma
- 20-30 year latent period

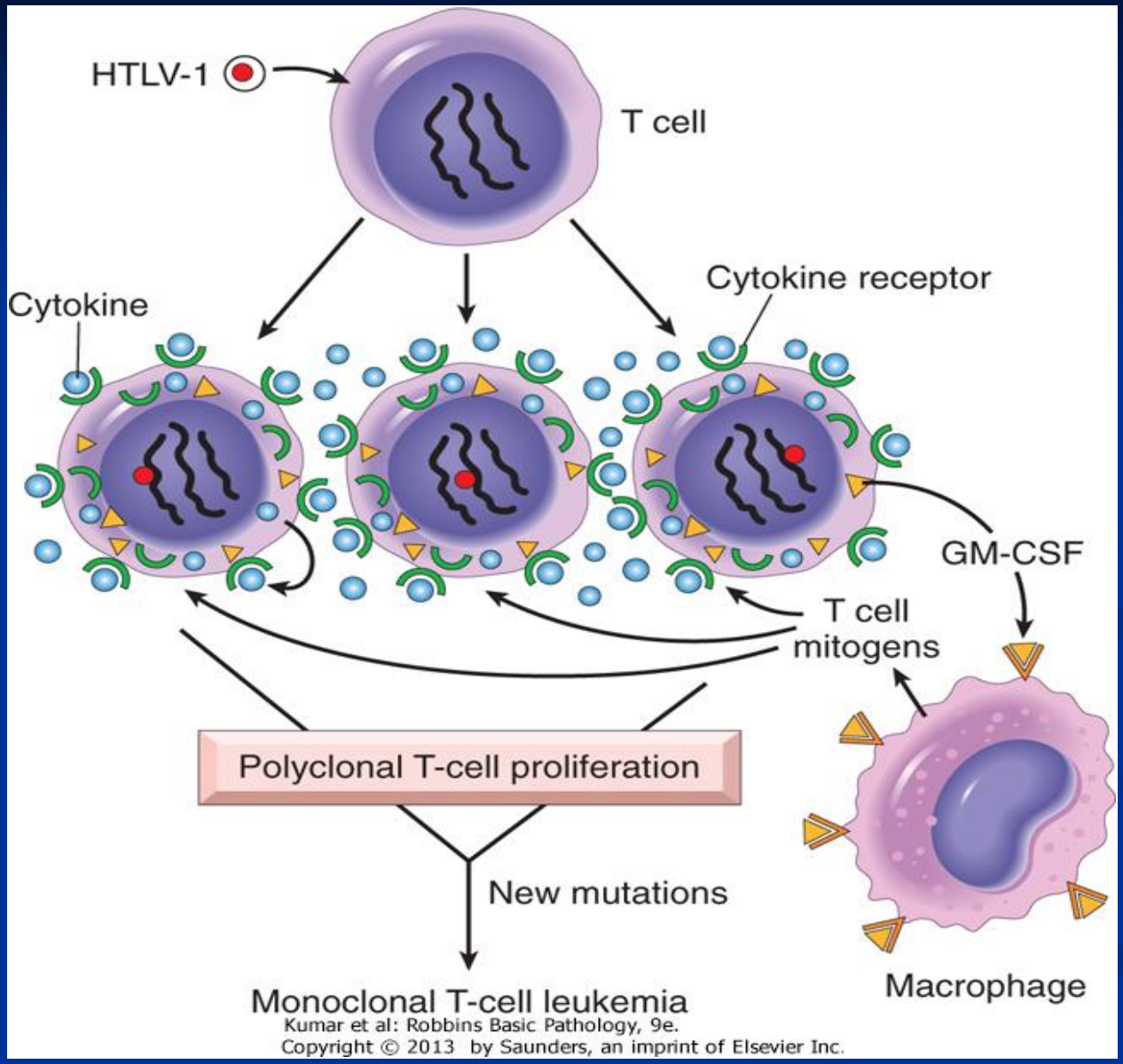
Carcinogenic Agents

Viral Carcinogenesis

RNA Oncogenic viruses

Human T-Cell Leukemia Virus type 1 (HTLV-1)

- No cure or vaccine
- Treatment : chemotherapy with common relapse


HTLV-1
T cell
Cytokine
Cytokine receptor
GM-CSF
T cell
mitogens
Polyclonal T-cell proliferation
New mutations
Monoclonal T-cell leukemia
Macrophage
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Carcinogenic Agents
Viral Carcinogenesis

DNA Oncogenic Viruses

- virus DNA forms stable association with host's DNA
- transcribed viral DNA transforms host cell

Examples: papilloma viruses

Epstein-Barr (EBV)

Hepatitis B (HBV)

Kaposi sarcoma herpes virus

Carcinogenic Agents
Viral Carcinogenesis

Human Papillomavirus (HPV)

- 70 types
- squamous cell carcinoma of
  - cervix
  - anogenital region
  - mouth
  - larynx

Carcinogenic Agents Human Papillomavirus (HPV)

- sexually transmitted
- Cervical cancer
  - 85% have types 16 and 18
- Genital warts
  - types 6 and 11

Carcinogenic Agents
Human Papillomavirus (HPV)

- HPV causing benign tumors:
  - types 6, 11
- HPV causing malignant tumors :
  - types 16, 18, 31
  - vDNA integrates w/ host

Carcinogenic Agents
Viral Carcinogenesis

- HPV (types 16 and 18)
  - over-expression of Exon 6 and 7
    - E6 protein binds to Rb tumor suppressor
      - replaces normal transcription factors
      - decreases Rb synthesis
    - E7 protein binds to P53
      - facilitates degradation of P53

Carcinogenic Agents
Viral Carcinogenesis

- HPV infection alone is not sufficient -
  - other risk factors:
    - cigarette smoking
    - coexisting infections
    - hormonal changes

Carcinogenic Agents
Viral Carcinogenesis

- Epstein-Barr Virus
- common virus worldwide
- Infects B lymphocytes and epithelial cells of oropharynx
- causes infectious mononucleosis
- EBV infection may cause malignancy
  - Burkitt's Lymphoma
  - B cell lymphoma in immunosuppressed
  - Nasopharyngeal carcinoma

Carcinogenic Agents
Viral Carcinogenesis
Epstein-Barr Virus related

- **Nasopharyngeal carcinoma**
  - Cancer of nasopharygeal epithelium
  - Endemic in South China, parts of Africa
  - 100% of tumors contain EBV genome in endemic areas

Carcinogenic Agents
Viral Carcinogenesis
Epstein-Barr Virus related

- Burkitt Lymphoma
  - highly malignant B cell tumor
  - sporadic rare occurrence worldwide
  - most common childhood tumor in Africa
  - all cases have t(8:14)

Carcinogenic Agents
Viral Carcinogenesis
Epstein-Barr Virus related

- causes B lymphocyte cell proliferation
- loss of growth regulation
- predisposes to mutation, esp. t(8:14)

Carcinogenic Agents
Viral Carcinogenesis

- Hepatitis B virus (HBV)
  - Strong association with Liver Cancer
  - World-wide, but HBV infection is most common in Far East and Africa
  - HBV infection incurs up to 200-fold risk

Carcinogenic Agents

- Helicobacter Pylori
- bacteria infecting stomach
- implicated in:
  - peptic ulcers
  - gastric lymphoma
    - Mucosal Associated Lymphoid Tumor (MALT)
  - gastric carcinoma

NEOPLASIA
Lecture 5

Host defense
Effect of a tumor on the host
Laboratory Diagnosis

Abdulmalik Alsheikh, M.D.

Objectives

- Define host defense against cancer
- Define tumor grade and clinical stage.
- Define cachexia and its cause.
- Define paraneoplastic syndrome, and know examples of tumors associated with endocrinopathies, osseous changes, and vascular and hematologic changes.
- Be familiar with the general principles, value, procedures, and applications of biopsy, exfoliative and aspiration cytology, and frozen section.
- List some examples of tests used to diagnose cancer by immunohistochemistry and flowcytometry.
- Discuss the use of molecular diagnostic testing in the setting of cancer diagnosis and prognosis.

Host defense

- Tumor Antigens:
  - Tumor-specific antigens: present only on tumor cells
  - Tumor-associated antigens: present on tumor cells and some normal cells

Host defense

- Tumor antigens may:
  - Result from gene mutations: P53, RAS
  - Be products of amplified genes: HER-2
  - Viral antigens: from oncogenic viruses
  - Be differentiation specific: PSA in prostate
  - Oncofetal antigens: CEA, Alpha fetoprotein
    - normal embryonic antigen but absent in adults….in some tumors it will be re-expressed, e.g: colon ca, liver cancer

Host defense

- Antitumor mechanisms involve:
  - Cytotoxic T lymphocytes
  - Natural killer cells
  - Macrophages
  - Humoral mechanisms :
    - Complement system
    - Antibodies

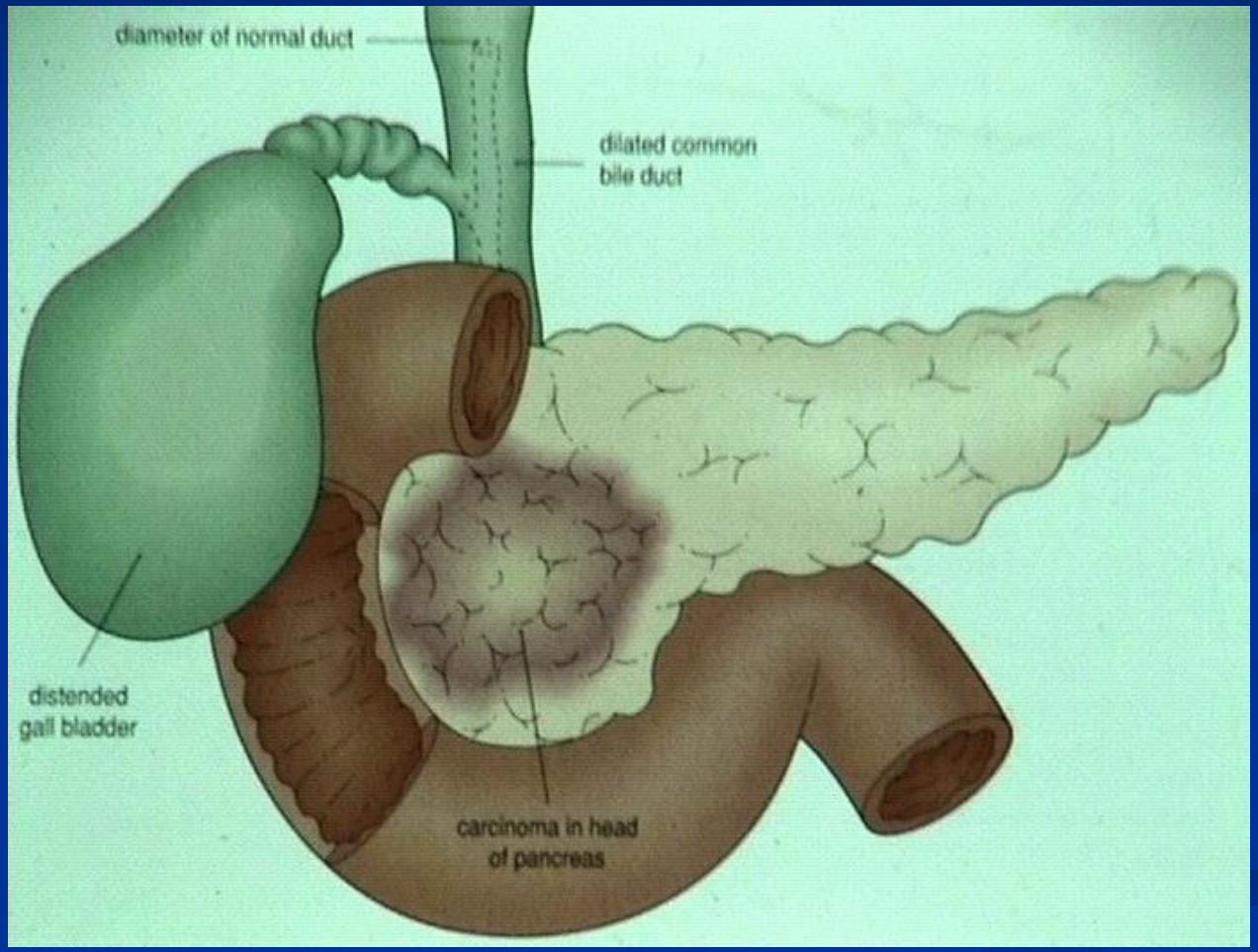
Clinical features

- Tumours cause problems because :
  - Location and effects on adjacent structures:

(1cm pituitary adenoma can compress and destroy the surrounding tissue and cause hypopituitarism).

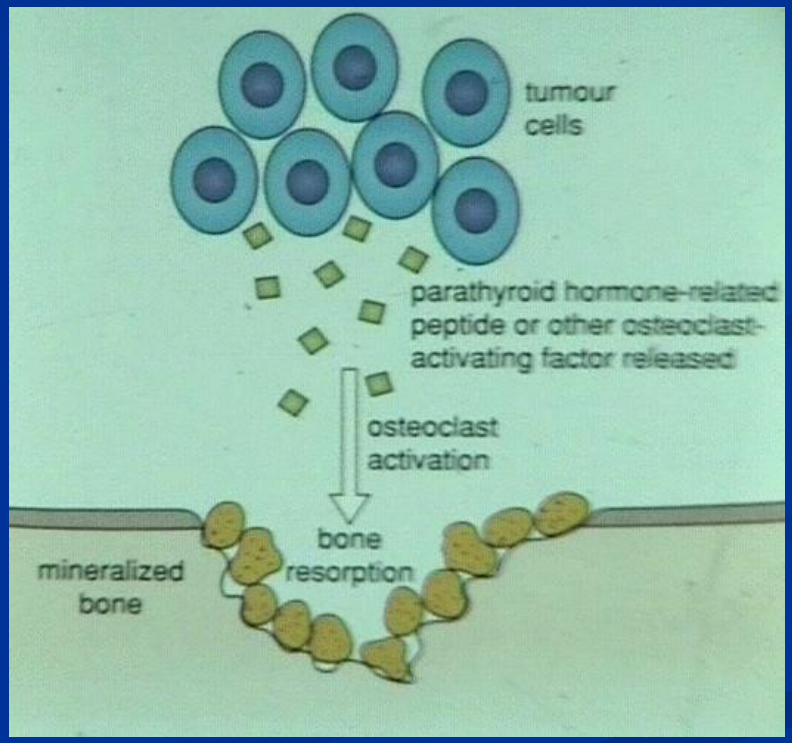
(0.5 cm leiomyoma in the wall of the renal artery may lead to renal ischemia and serious hypertension).

  - Tumors may cause bleeding and secondary infections
    - lesion ulcerates adjacent tissue and structures


diameter of normal duct
dilated common bile duct
distended gall bladder
carcinoma in head of pancreas

EFFECT OF A TUMOR ON THE HOST

- Secondary fracture



Clinical features

- Effects on functional activity
  - hormone synthesis occurs in neoplasms arising in endocrine glands:
  - adenomas and carcinomas of β cells of the islets of the pancreas produce hyperinsulinism.
  - Some adenomas and carcinomas of the adrenal cortex elaborate corticosteroids.
    - aldosterone induces sodium retention, hypertension and hypokalemia
  - Usually such activity is associated with benign tumors more than carcinomas.

Clinical features

Cancer cachexia

- Usually accompanied by weakness, anorexia and anemia
- Severity of cachexia, generally, is correlated with the size and extend of spread of the cancer.
- The origins of cancer cachexia are multifactorial:
  - anorexia (reduced calorie intake)
  - increased basal metabolic rate and calorie expenditure remains high.
  - **general metabolic disturbance**

Clinical features

Paraneoplastic syndromes

- They are symptoms that occur in cancer patients and cannot be explained.
- They are diverse and are associated with many different tumors.
- They appear in 10% to 15% of pateints.
- They may represent the earliest manifestation of an occult neoplasm.
- They may represent significant clinical problems and may be lethal.
- They may mimic metastatic disease.

Clinical features

- **The most common paraneoplastic syndrome are:**
  - Hypercalcemia
  - Cushing syndrome
  - Nonbacterial thrombotic endocarditis
- **The most often neoplasms associated with these syndromes:**
  - Lung and breast cancers and hematologic malignancies

P araneoplastic syndromes

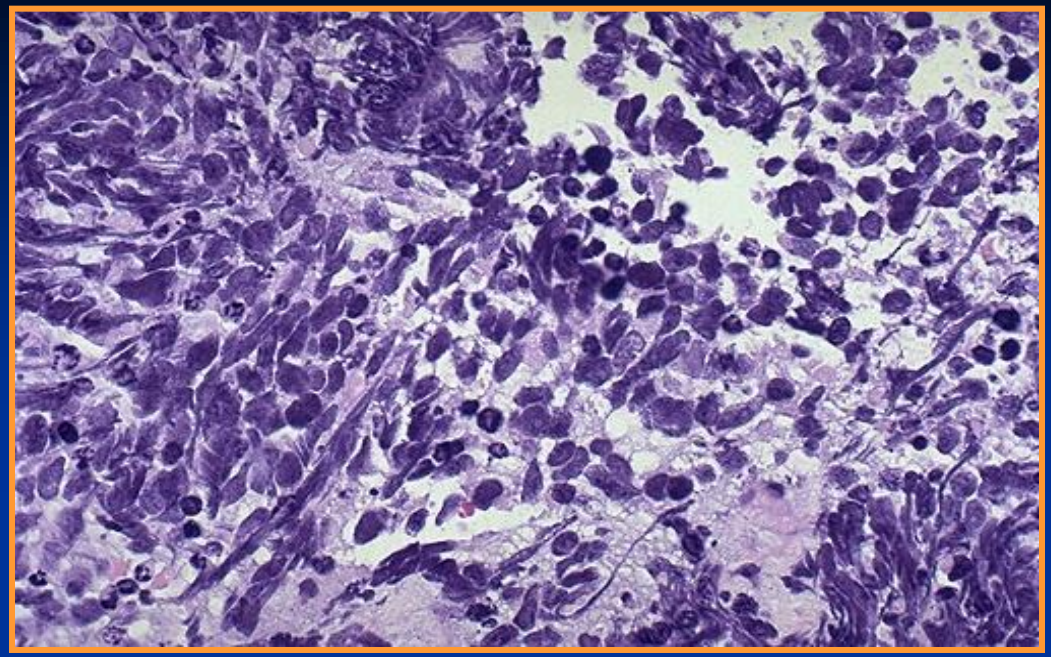
Syndrome	Mechanism	Example
Cushing's Syndrome	ACTH -like substance	Lung oat cell carcinoma
Hypercalcemia	Parathormone -like substance	Lung squamous cell carcinoma Renal cell carcinoma Breast carcinoma
Hyponatremia	Inappropriate ADH secretion	Lung oat cell carcinoma
Polycythemia	Erythropoietin -like substance	Cerebellar haemangioma Renal cell carcinoma
Trousseau's Syndrome	Hypercoagulable state	Various carcinomas
Hypoglycemia	Insulin -like substance	Various carcinomas and sarcomas
Carcinoid Syndrome	-5hydroxy -indoleacetic acid) 5 - HIAA (	Metastatic malignant carcinoid tumors

Clinical Features

- Grading :
  - Grade I, II, III, IV
  - Well, moderately, poorly differentiated, anaplastic
- Staging :
    - Size
    - Regional lymph nodes involvement
    - Presence or absence of distant metastasis
  - TNM system

Grading of Malignant Neoplasms

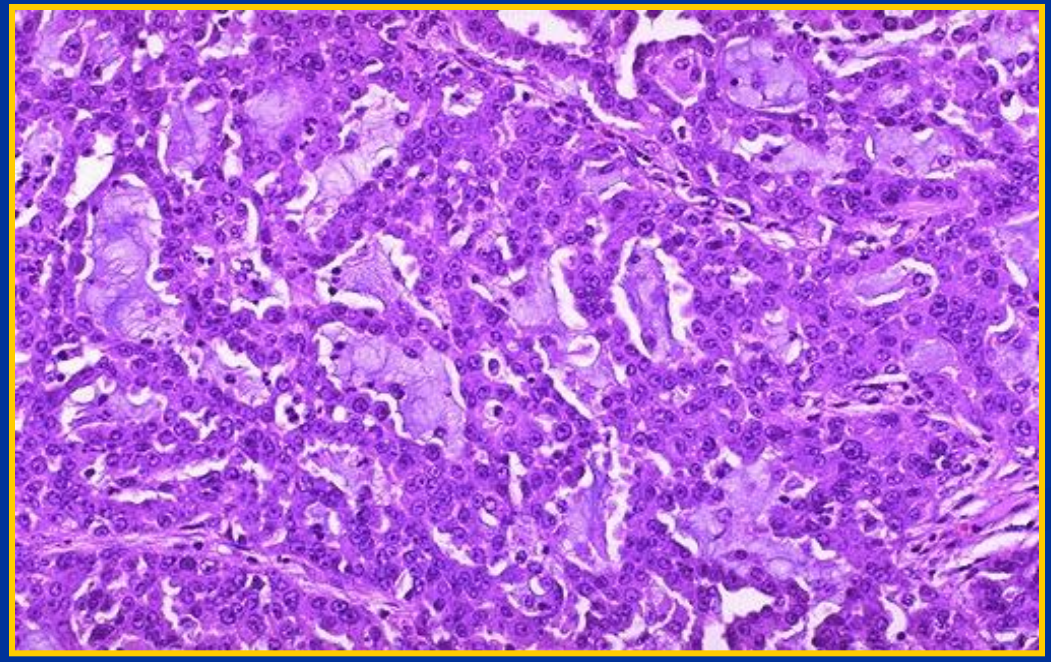
Grade	Definition
I	Well differentiated
II	Moderately differentiated
III	Poorly differentiated
IV	Nearly anaplastic



Oat cell carcinima of the lung
Undifferenciated carcinoma
Grade IV

Poorly differentiated neoplasms have cells that are difficult to recognize as to their cell of origine

Higher grade means:
a lesser degree of differentiation
and the worse the
biologic behavior



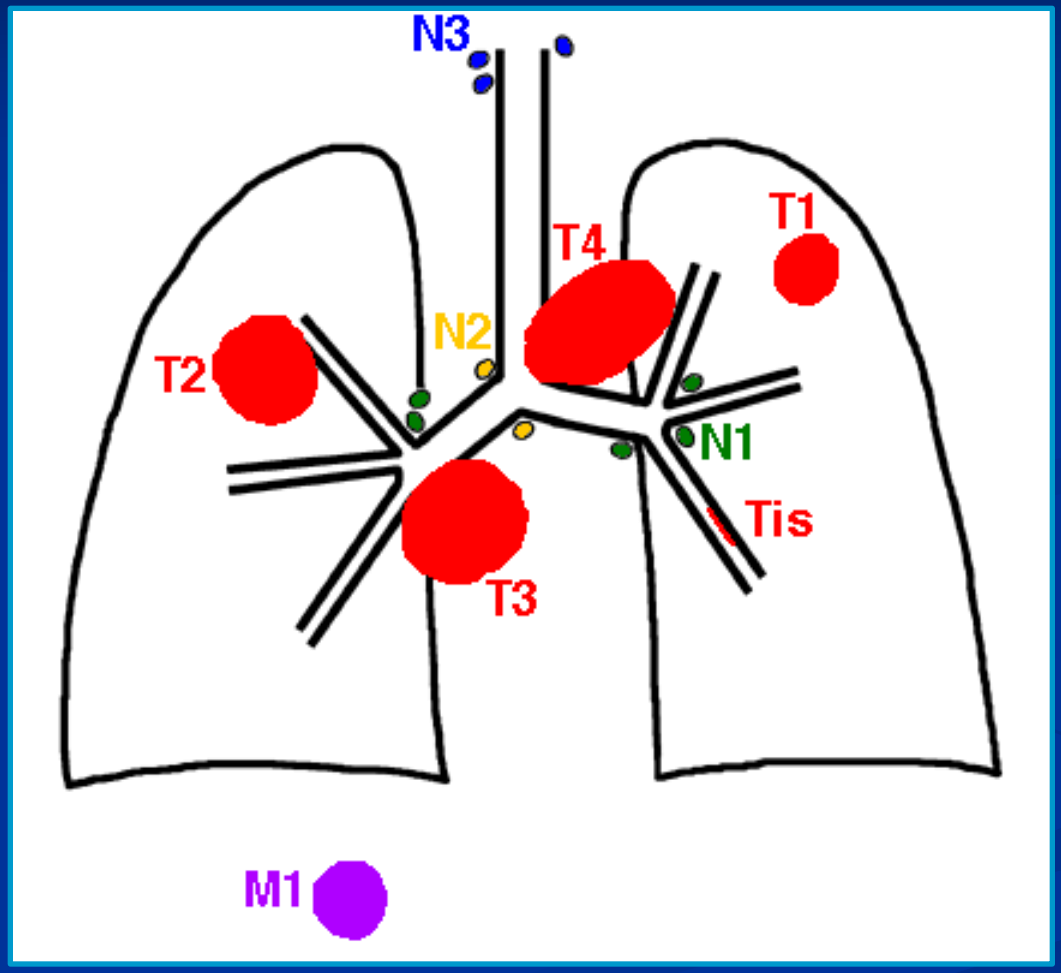
Adenocarcinoma of the colon
Well differenciated carcinoma

A well differentiated neoplasm is composed of cells that closely resemble the cell of origin.

Clinical Staging

- T (primary tumor): T1, T2, T3, T4
- N (regional lymph nodes): N0, N1, N2, N3
- M (metastasis): M0, M1

TNM staging system in cancer



Staging of Malignant Neoplasms

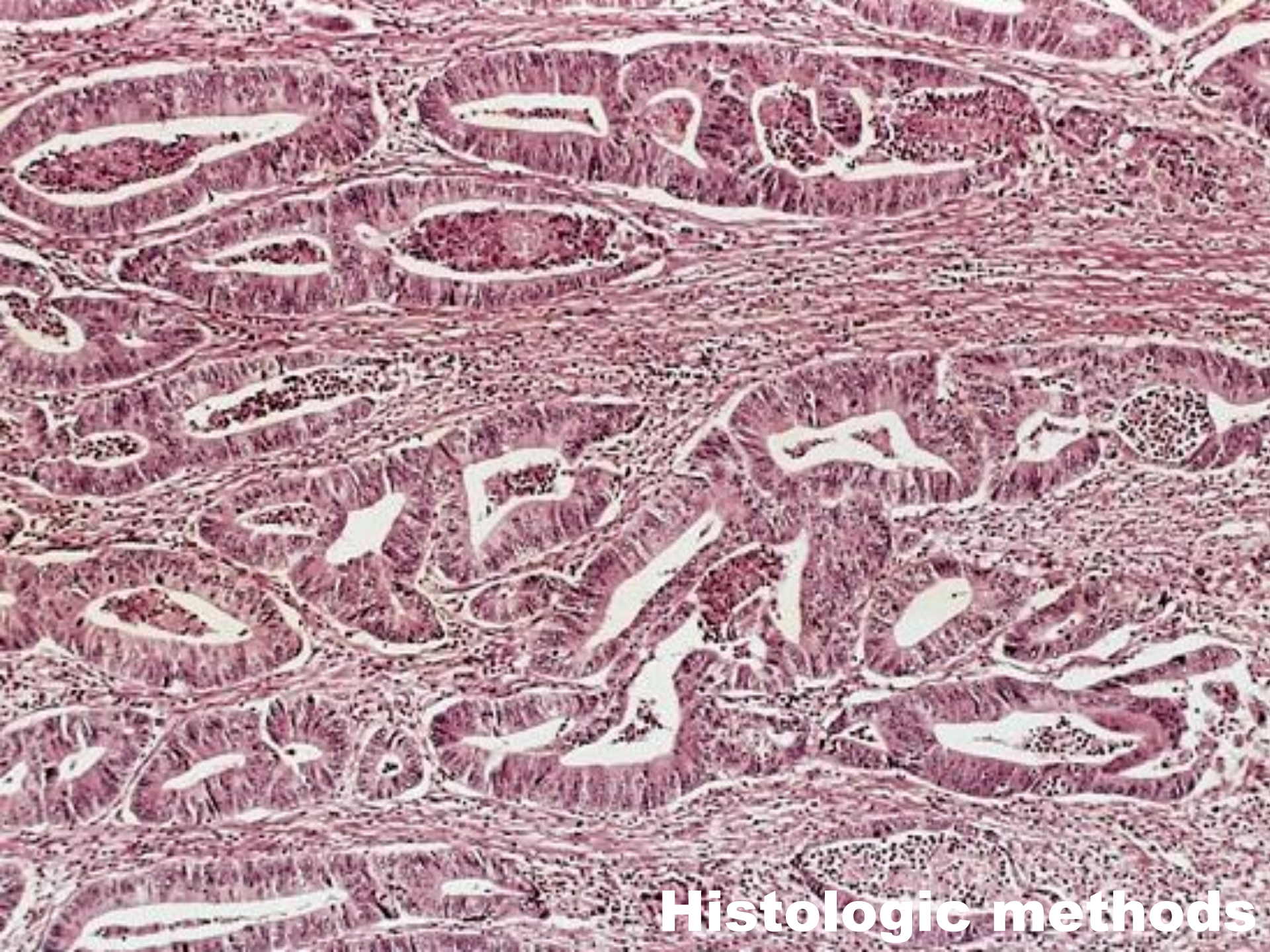
Stage	Definition
Tis	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present

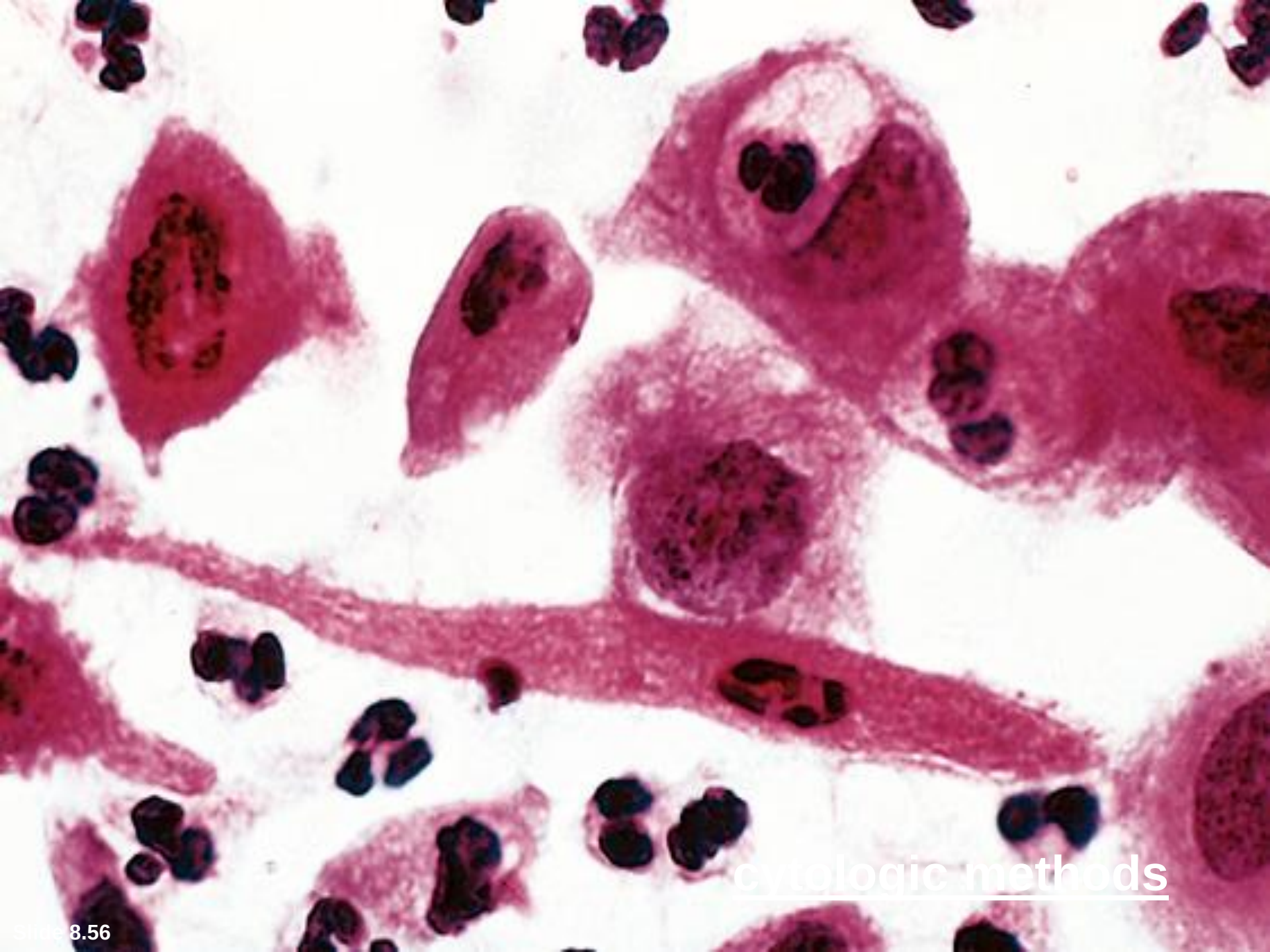
Laboratory Diagnosis

- Morphologic methodes
- Biochemical assays
- Molecular diagnosis

Laboratory Diagnosis

- **Microscopic Tissue Diagnosis**
  - the gold standard of cancer diagnosis.
  - Several sampling approaches are available:
    - Excision or biopsy
      - Frozen section
    - fine-needle aspiration
    - Cytologic smears


Histologic methods



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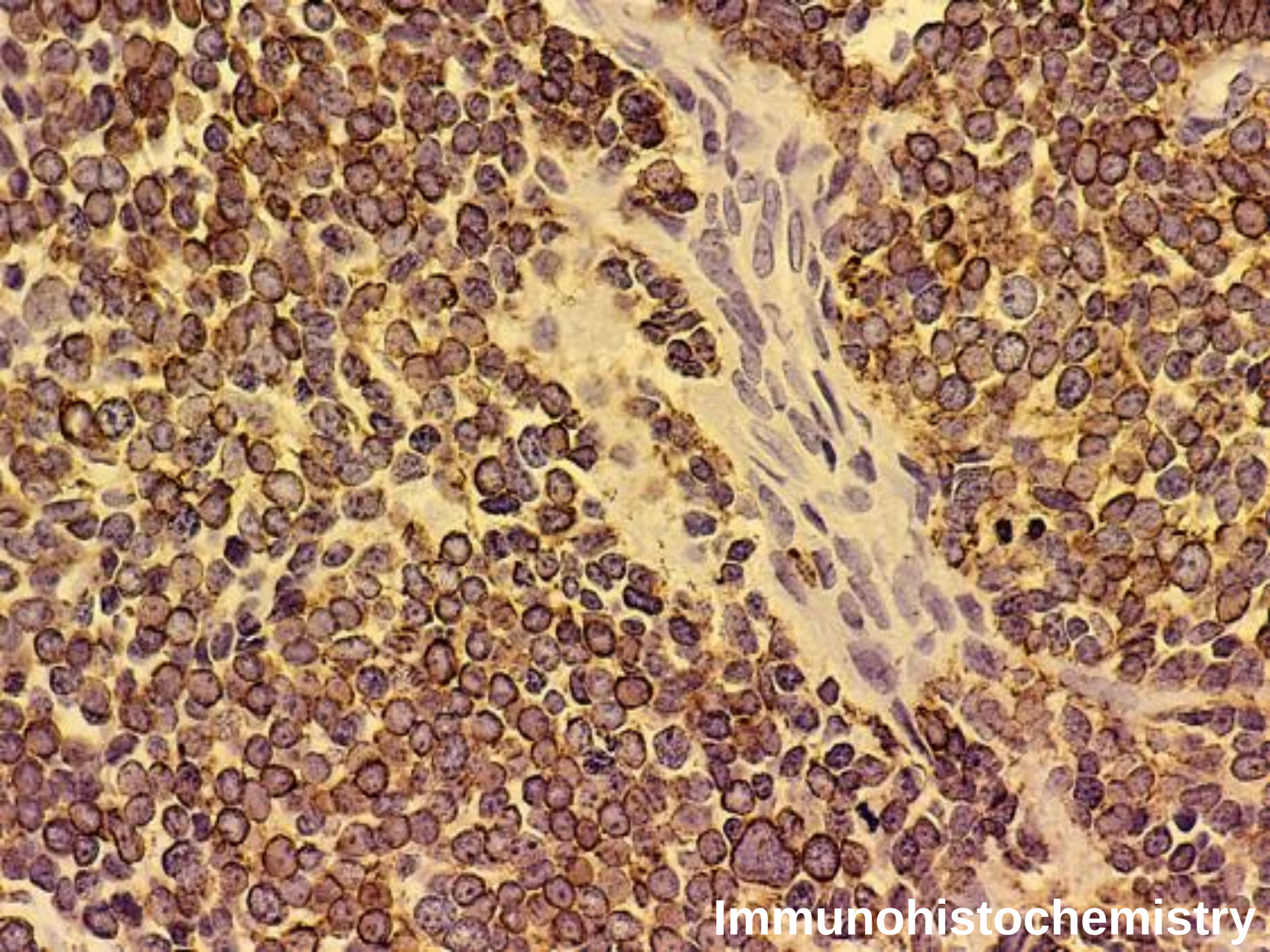
Immunohistochemistry

Laboratory Diagnosis

- **Biochemical assays:**
- Useful for measuring the levels of tumor associated enzymes, hormones, and tumor markers in serum.
- Useful in determining the effectiveness of therapy and detection of recurrences after excision
- Elevated levels may not be diagnostic of cancer (PSA).
- Only few tumor markers are proved to be clinically useful, example CEA and α- fetoprotein.

Laboratory Diagnosis

- **Molecular diagnosis**
- Polymerase chain reaction (PCR)

  example: detection of BCR-ABL transcripts in chronic myeloid leukemia.
- Fluorescent in situ hybridization (fish)

  it is useful for detecting chromosomes translocation characteristic of many tumors

Both PCR and Fish can show amplification of oncogenes (HER2 and N-MYC)

Molecular diagnosis

DNA microarray analysis

- Expression of thousands of genes are studied.
- Different tissue has different pattern of gene expression.
- Powerful tool useful for subcategorization of disease e.g. Lymphoma

- confirmation of morphologic diagnosis
- illustration of genes involved in certain disease and possible therapy.