Neoplasia

BY:

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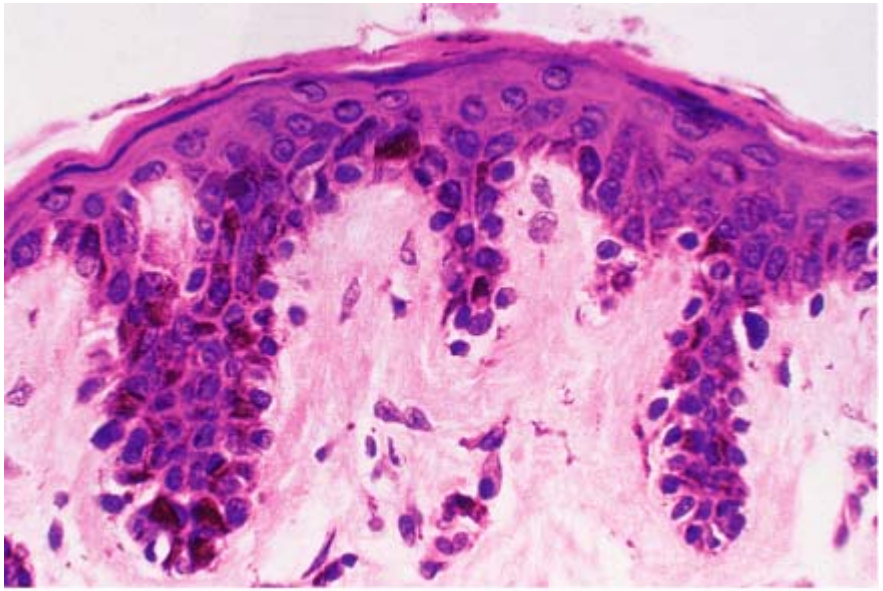
Neoplasia

- New growth-Neoplasm
- Tumour- Swelling
- Oncology Oncos-study of tumour neoplasms
- Cancer- Malignant tumours[crab]

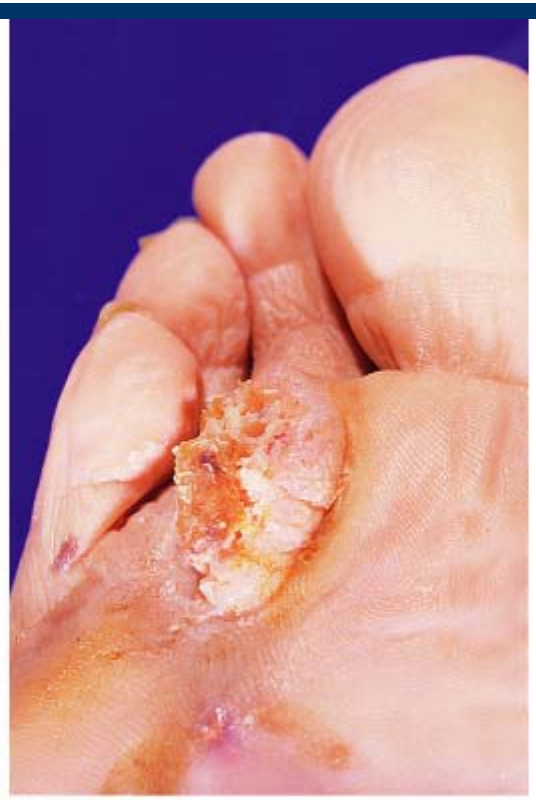
Neoplasia

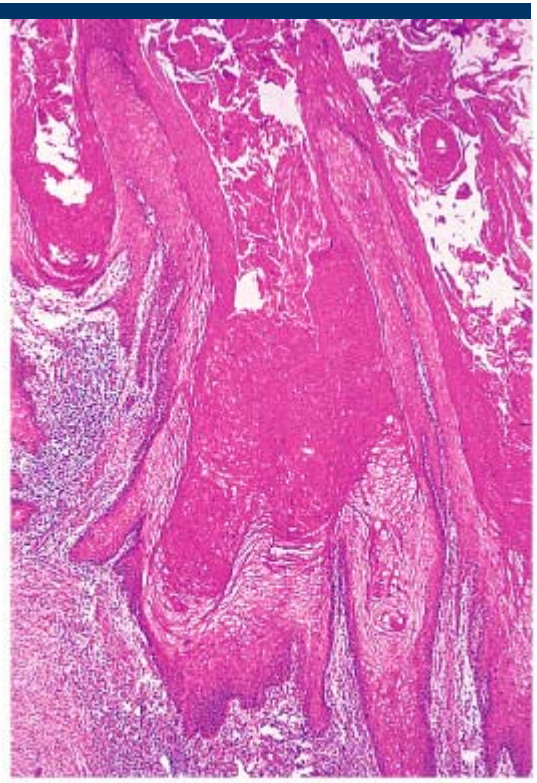
- Definition-Abnormal mass of tissue the growth of which exceeds & is uncoordinated with that of normal tissue & persists in the same excessive manner after cessation of stimuli
- Heritable genetic alteration –passed to progeny of tumour cells
- Autonomous
- Clonal

Non-neoplastic skin tissue



Neoplasia (abnormal tissue mass, Excessive growth)





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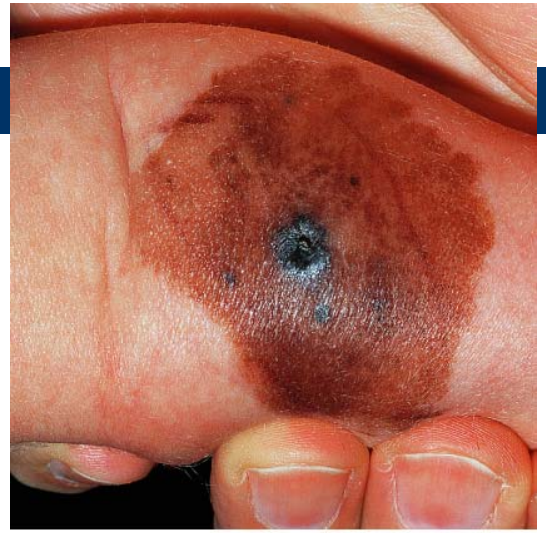

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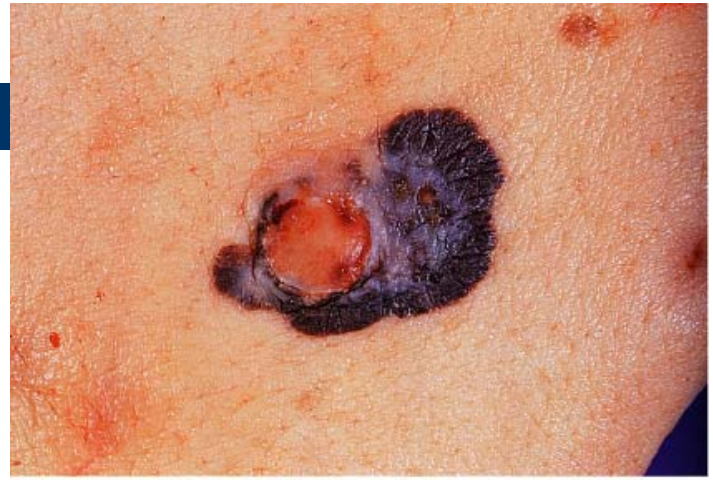

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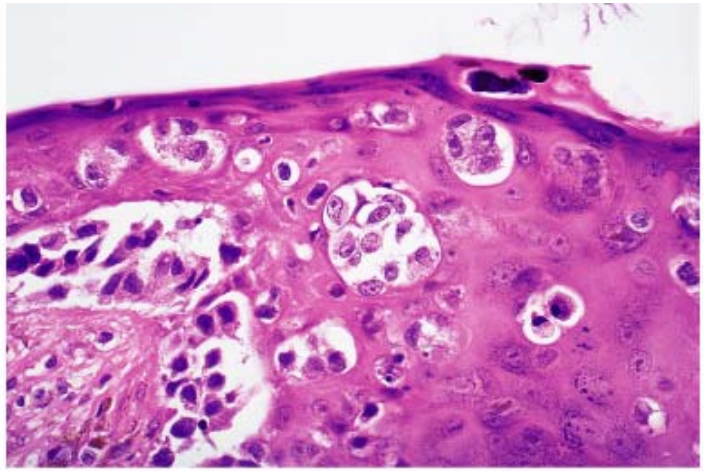

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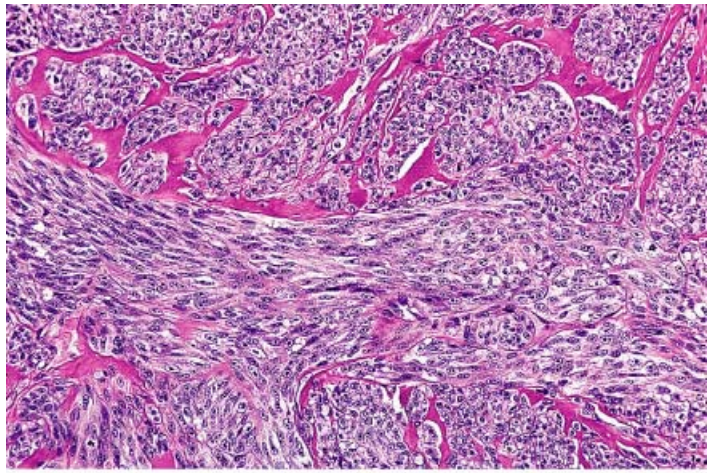

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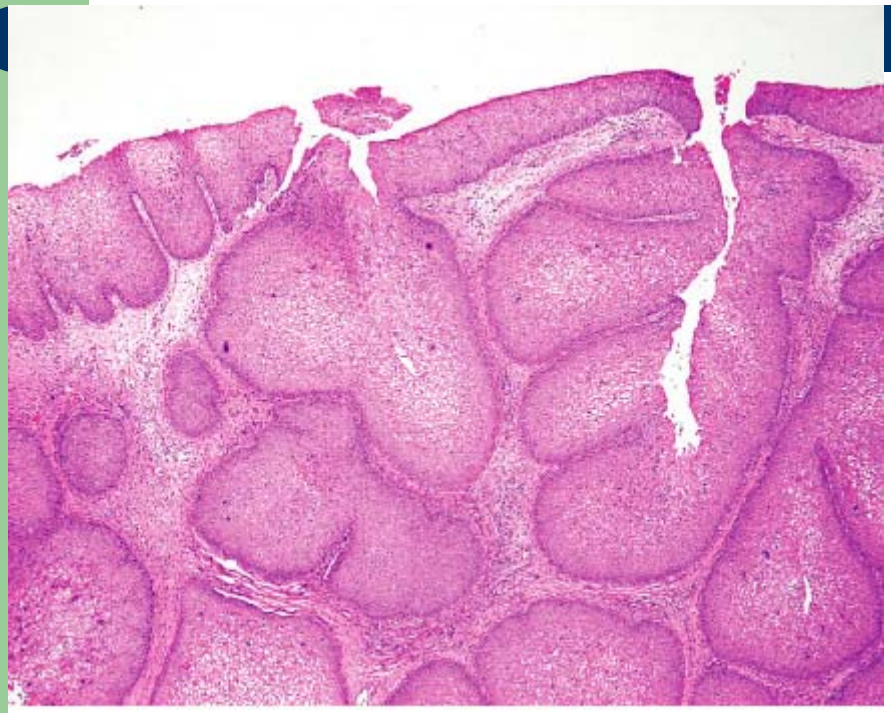
Neoplasia-Uncoordinated (Autonomous)Growth



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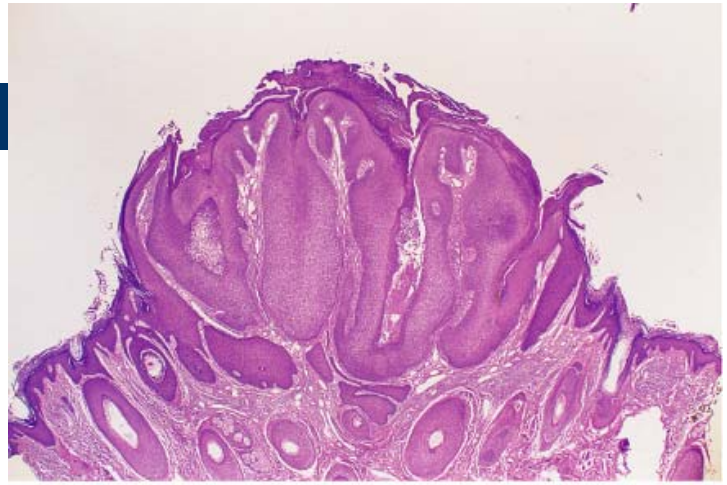

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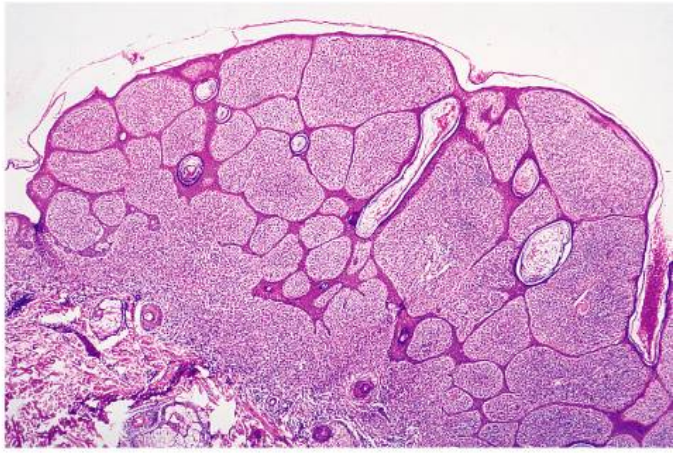

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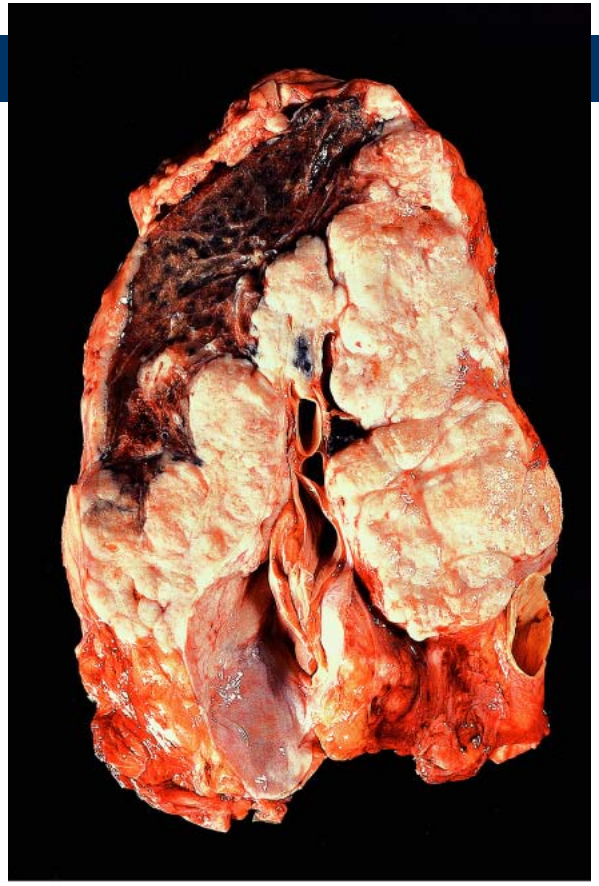
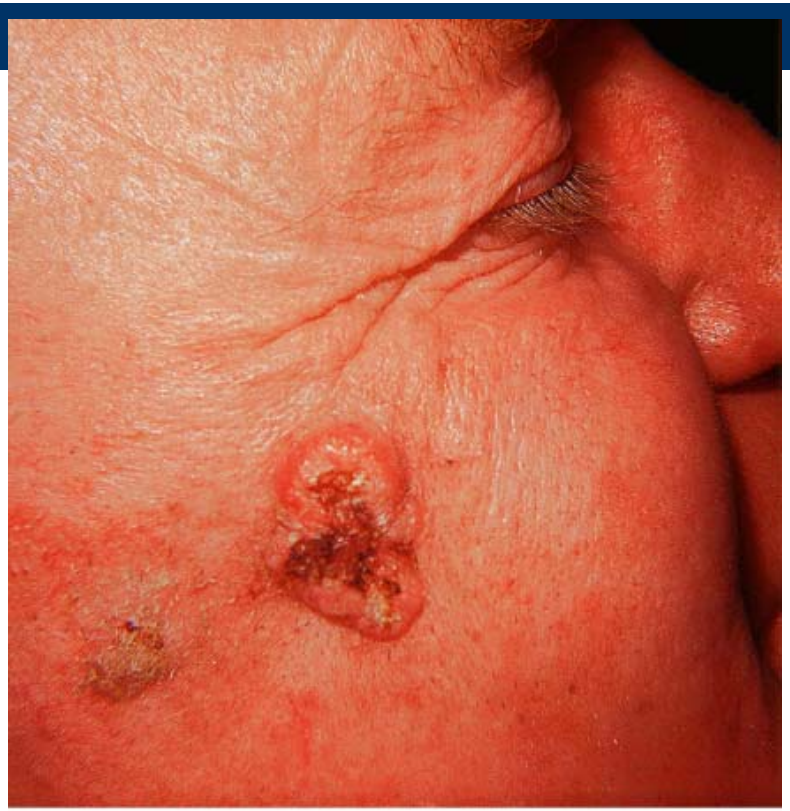
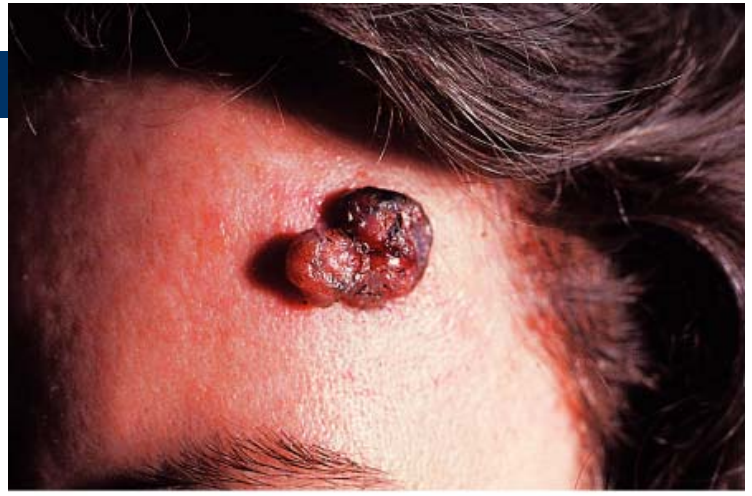
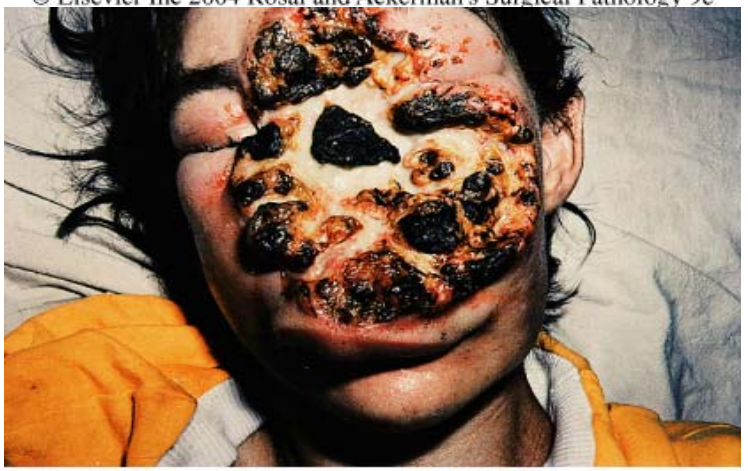
Neoplasia **persists** even after initiating event (stimulus)no longer exists



Neoplasia parasitic upon host tissues

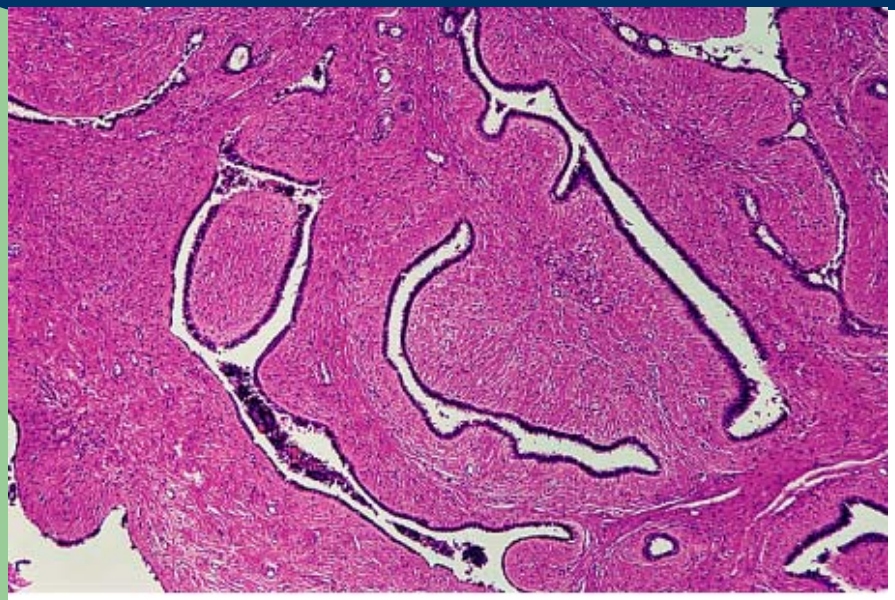






Neoplasia

- Benign Malignant
  - Parenchyma[proliferating neoplastic cells]-cutting edge&behaviour of tumour
  - Supporting storma[C.T&bld.vessles]-growth&evolution of tu &framework-
  - soft&fleshy
  - Schirrous



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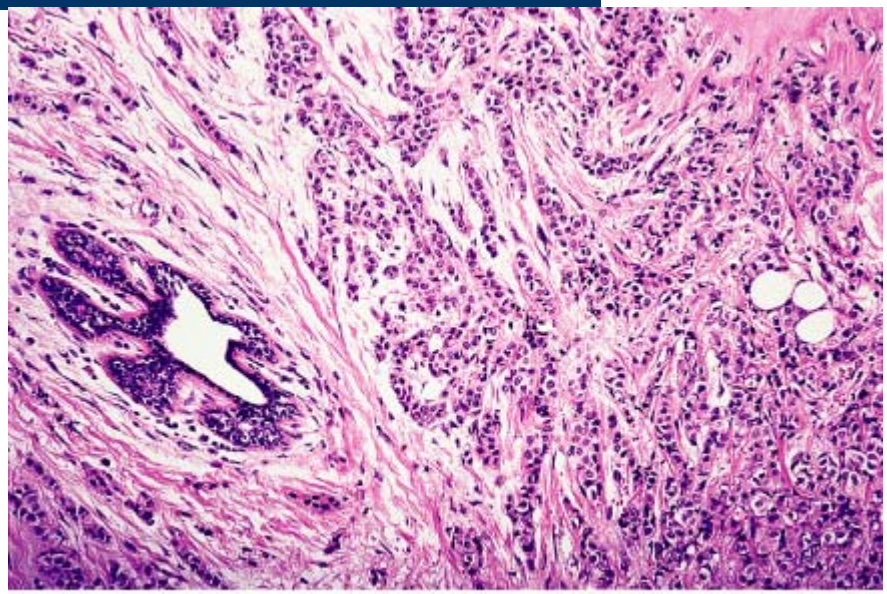

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Neoplasia

- **Benign tumours-suffix –oma to cell of origin**
  - **Mesenchymal tumours- Chondroma,Fibroma**
  - **Epithelial-complex**

    --Adenoma-form glandular structures/arise from Glandular structures

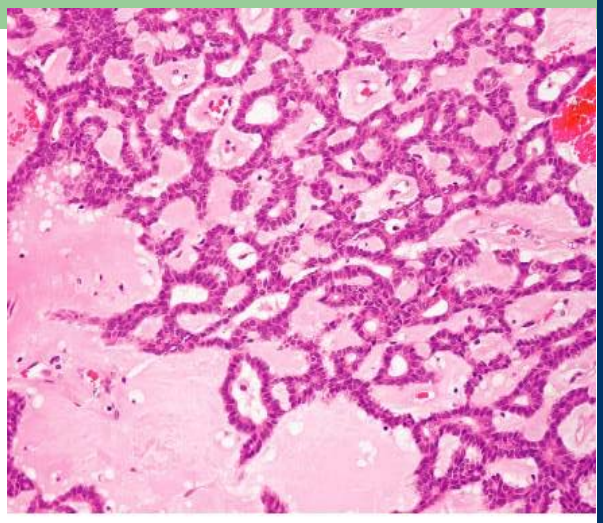
    Renal Adenoma&Adrenal cortical adenoma

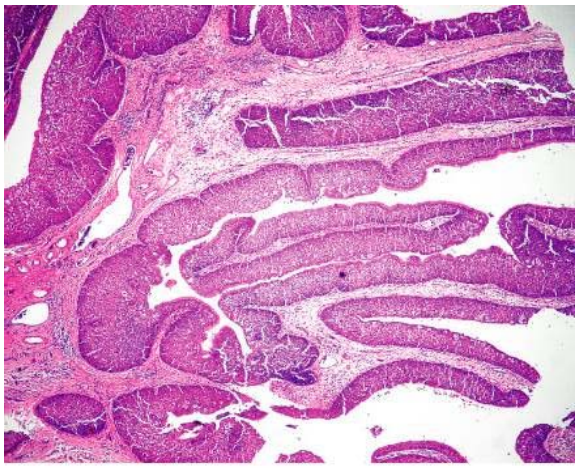
    --Papilloma

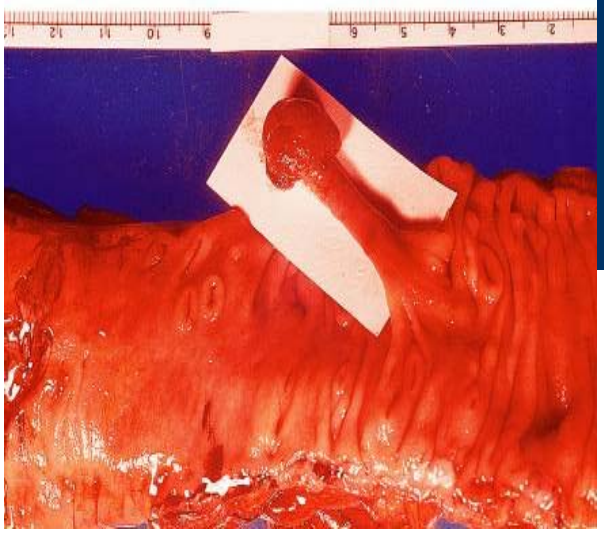
    --Cystadenoma

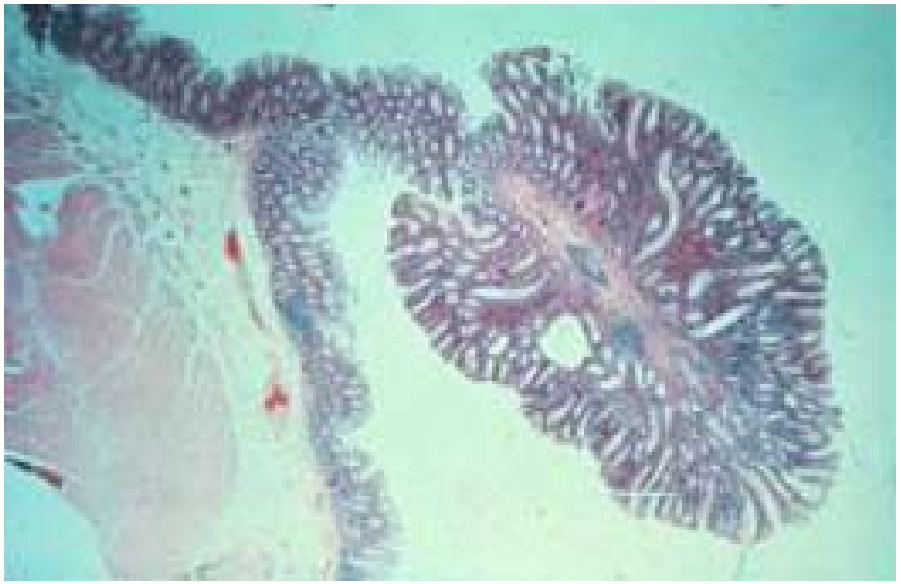
    ---Papillary Cystadenoma

    ---Polyp









Malignant tumors nomenclature:

-**Mesenchymal cancers-Sarcomas** (Fleshy)

-Rhabdosarcoma, Liposarcoma, Fibrosarcoma, Osteosarcoma, Chondrosarcoma

-**Epithelial cancers (Epithelium of any 3 germ layers) -Carcinomas**

(further qualified as differentiated/ site of origin)

-Adenocarcinoma, Squamous cell carcinoma, Renal cell carcinoma, Hepatocellularcarcinoma

-Undifferentiated malignant tumor

-Cancer of undifferentiated cells of unknown tissue origin

Nomenclature of neoplasms

Tumours of Mesenchymal Tissues

	BENIGN	MALIGNANT
• C.T.&derivatives	Fibroma lipoma	fibrosarcoma,
• Endothelial.&derivatives	Haemangioma	
• Blood cells		leukaemia,lymphoma
• Muscle	leiomyoma,Rhabdomyoma	

Tumours of epithelial tissues

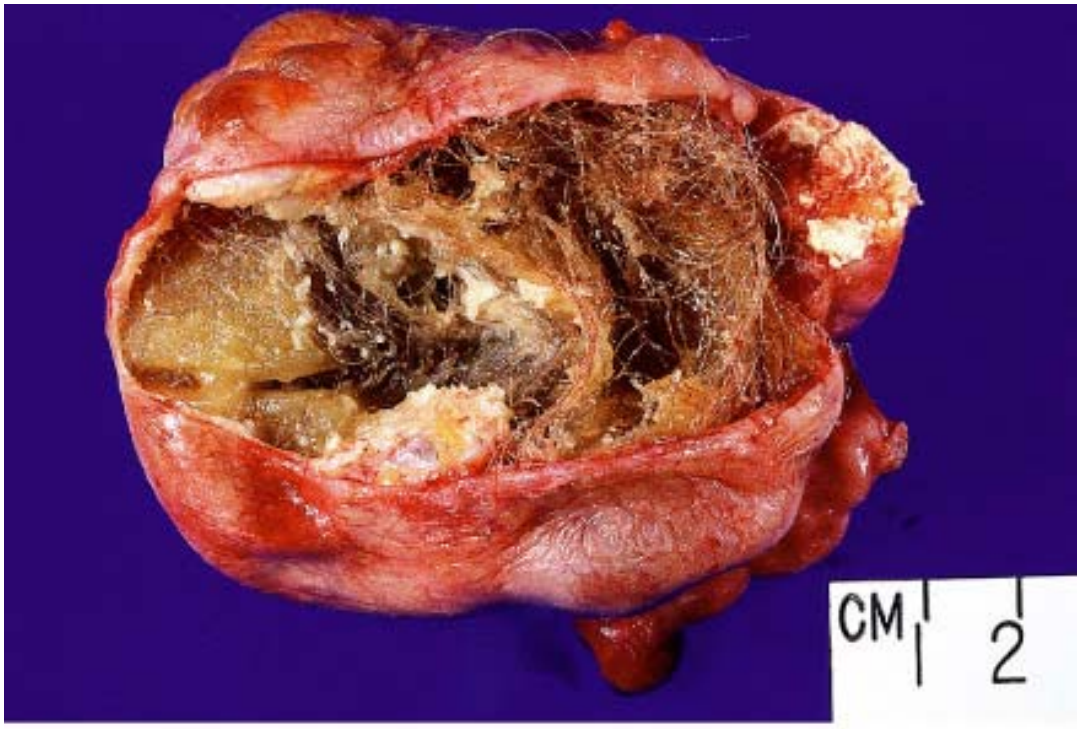
• Squamous cells		Sq.Cell.Ca
• Basal cells	Papilloma	Basal C.ell Ca.
• Epi. lining of glands	Adenoma,papilloma. Cystadenoma	Adeno Ca.
• Resp .	Bronchogenic Ca.	
• Liver		Hepatocellular Ca
• Placenta	Adenoma H.Mole.	Choriocarcinoma.

.

- **Mixed tumours-**divergent diff. of a single line of parenchymal cells into another tissue

  eg Pleomorphic adenoma

- **Teratoma-** A variety of parenchymal cells from more than 1 germ layer



Neoplasia-basic concepts & definitions

Nomenclature Exceptions: Tumors

-Malignant tumors & suffix-oma

~Melanoma (cancers of Melanocytes)

~Lymphoma (cancers of Lymphoid tissue)

~Seminoma (cancers of Gonadal germ cells)

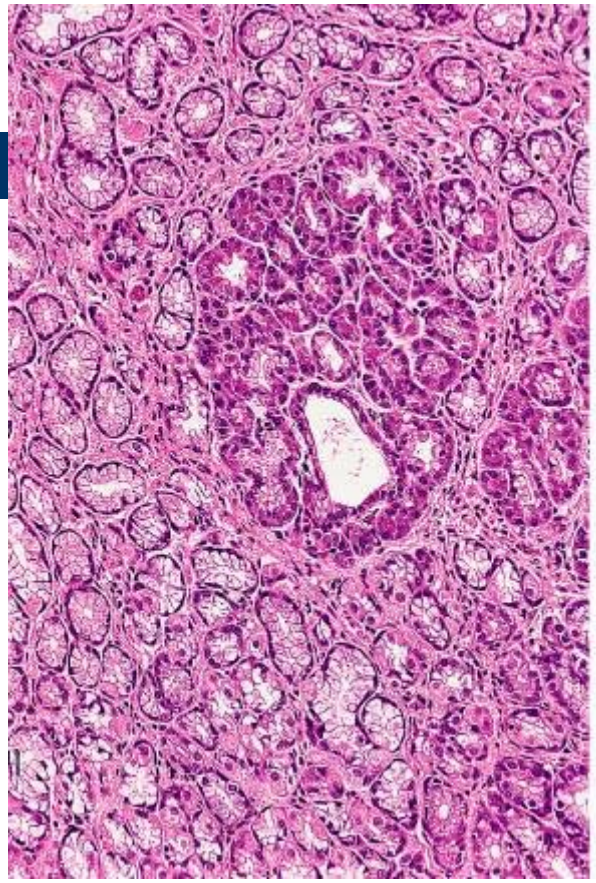
~Hepatoma (Hepatocellularcarcinoma)

~Myeloma (Malignancy of Plasma cells)

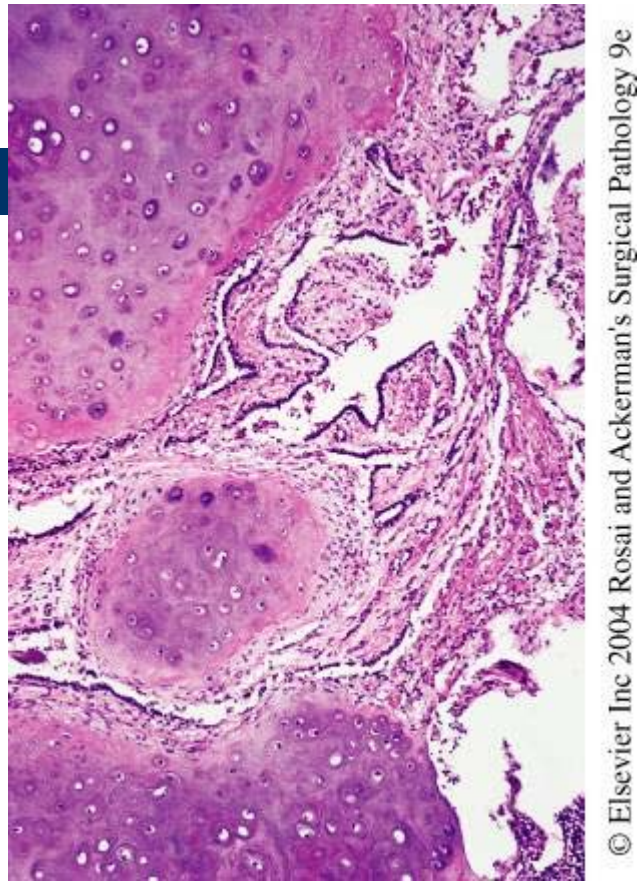
Neoplasia

Choriostoma-An ectopic Rest of normal tissue
E.g Adrenal cells under kidney capsule
Pancreatic rests-Gastric mucosa

Hamartoma-Mass of disorganised but mature cells/tissue indigneous to that site; Lungs-cartilage,b.v.,bronchial structures lymhoid tissue



Choristoma- Pancreatic acini in gastric mucosa



Lung Hamartoma

Characteristics of benign &malignant neoplasms

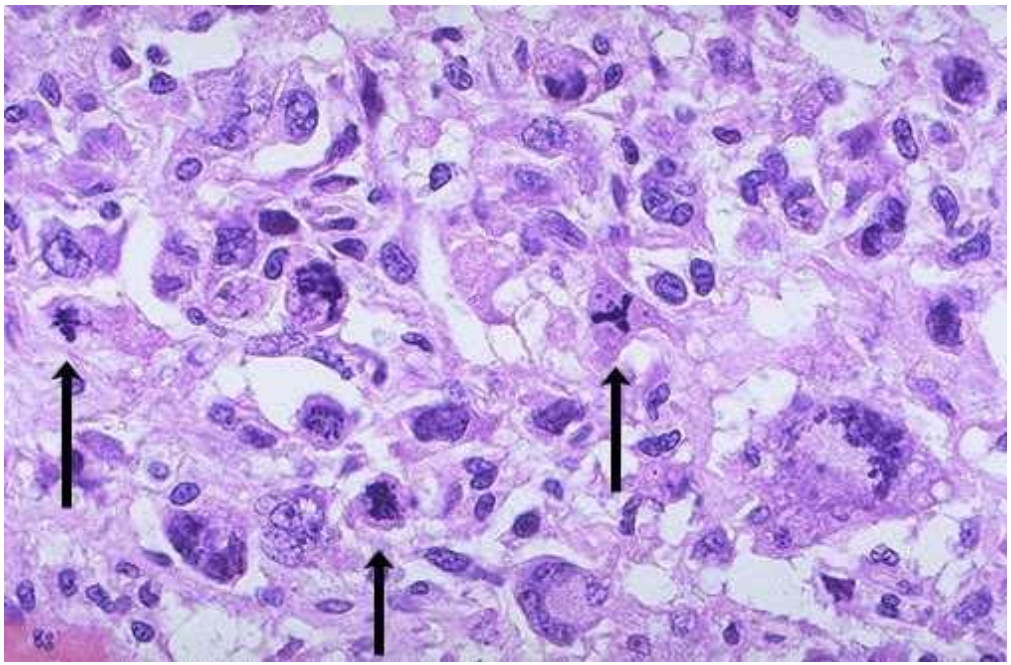
- Differentiation &Anaplasia
- Rate of Growth
- Local Invasion
- Metastasis

Characteristics of benign &malignant neoplasms

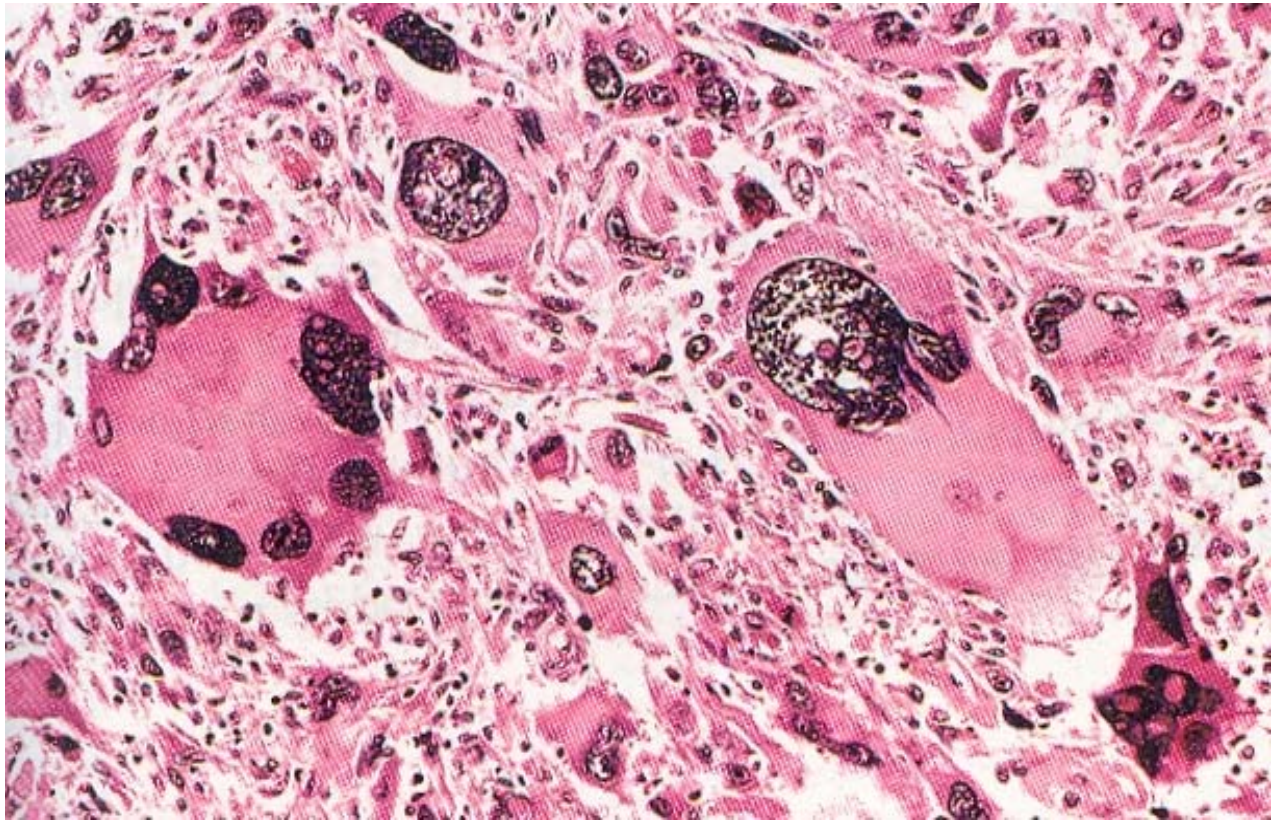
- Differentiation&Anaplasia-Refers to extent to which parenchymal cells resemble comparable normal cells of that tissue –morhphology.& function.
- Benign-well differentiated. E.g Leiomyoma
- Malignant-well differentiated,Mod.diff.Poorly differentiated.
- Anaplasia is lack of differentiation.-Hallmark of MALIGNANCY
- Cancer-stem cells in specialized tissues
- Well diff.- Maturation of proliferating cells-
- Poorly differentiated. proliferation without maturation

Characteristics of benign &malignant neoplasms

- **Morphological features of Anaplasia**
  - Pleomorphism-variation in size &shape
  - Hyperchromasia
  - Nuclear shape
  - Clumped chromatin
  - Prominent nucleoli
  - Increased mitosis
  - Tu giant cells
  - Loss of orientation
  - Central necrosis



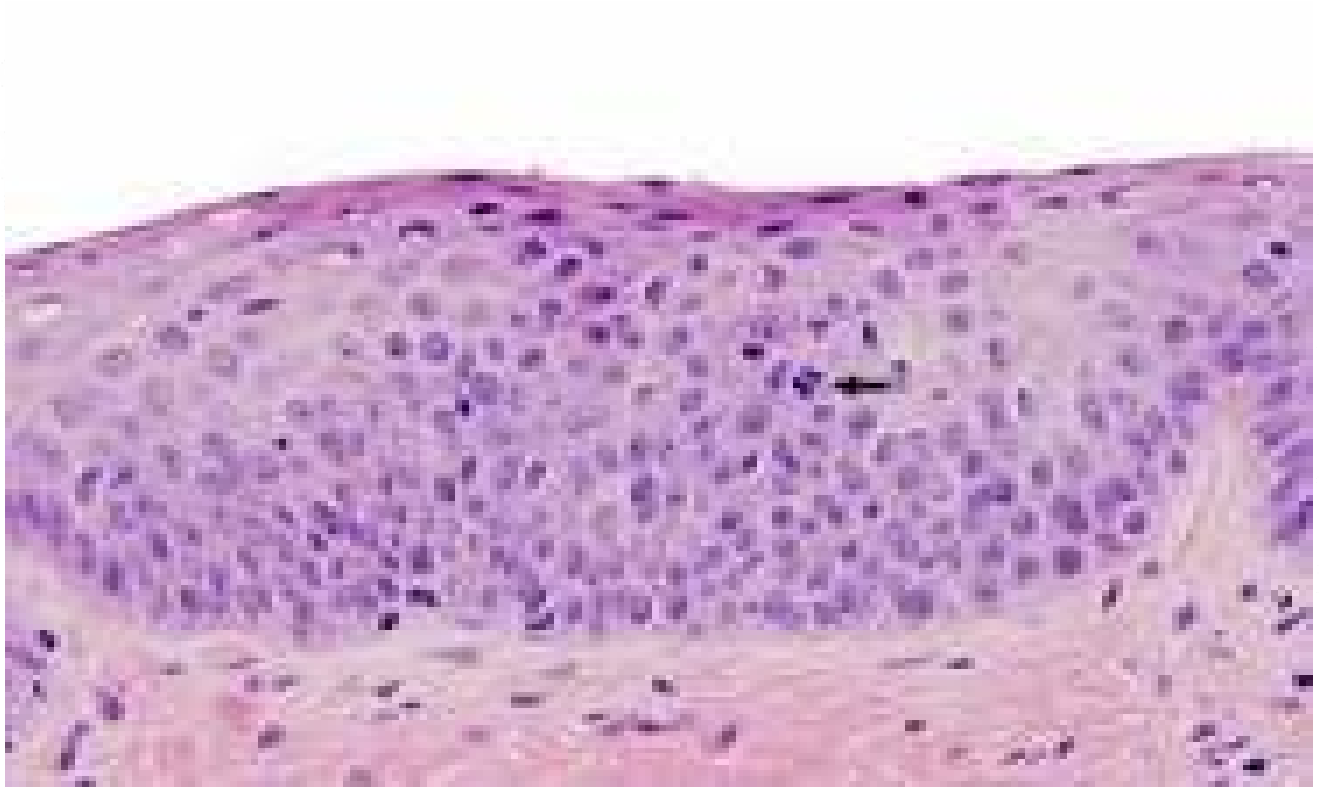
Characteristics of Benign & Malignant neoplasms

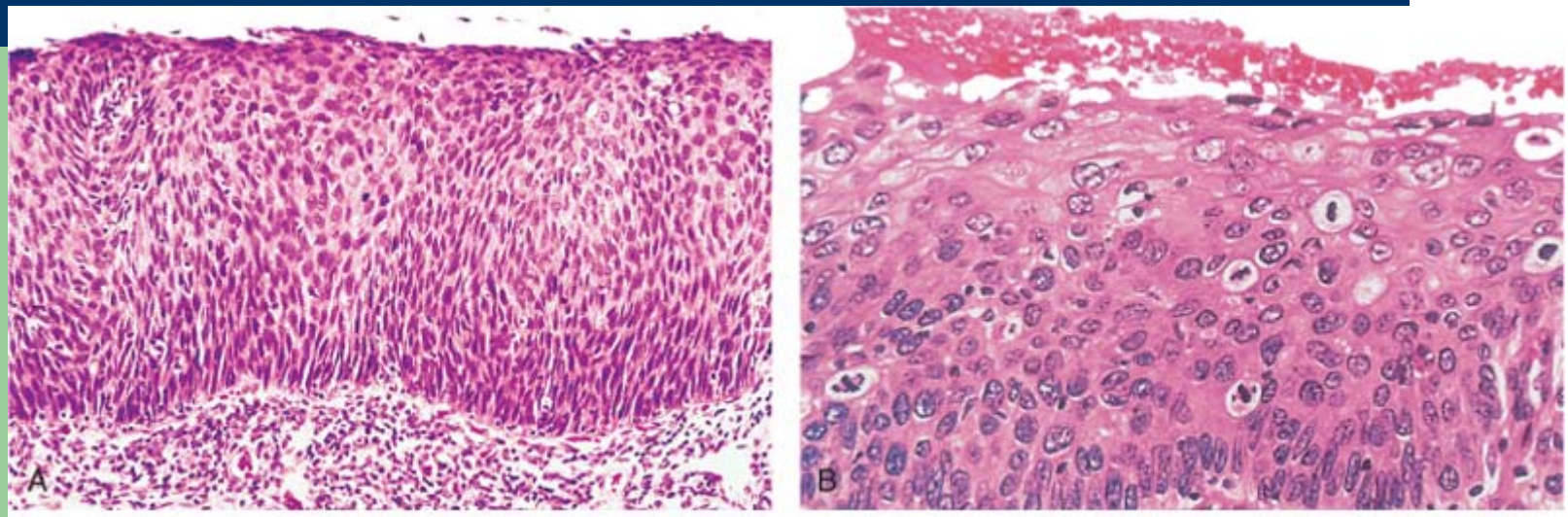


Characteristics of Benign &Malignant neoplasms

- **Dysplasia-disorderded growth**

- **Loss of uniformity of individual cells**
- **Loss in architectural pattern**
- **Mild, moderate,severe**
- **Mild, moderate-reversible**
- **FUNCTIONAL changes- well differentiated retain function.**
  - **Poorly differentiated-loss of function, emergence of other fn.-fetal protein,ectopic hormone production.**





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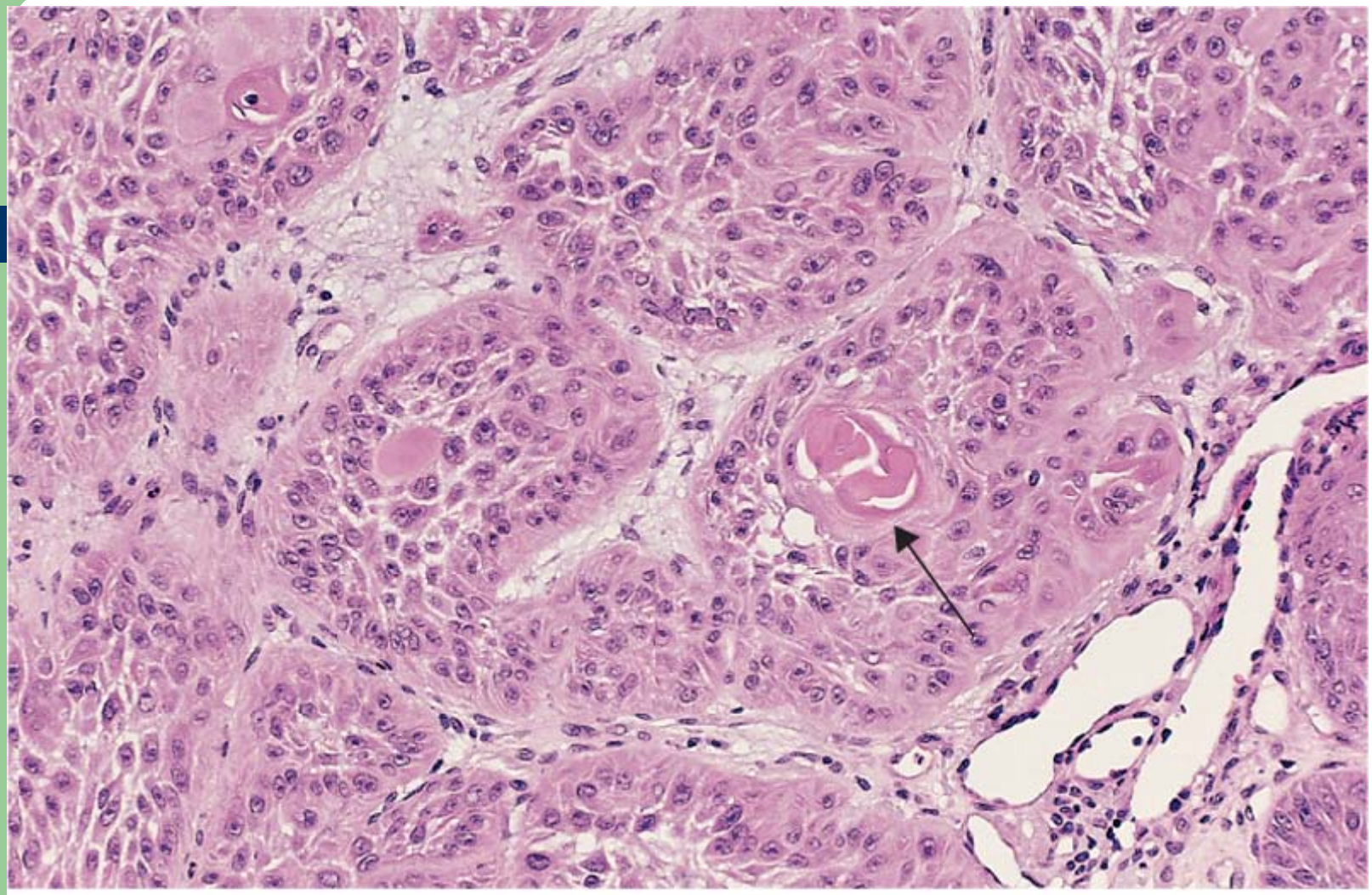


Characteristics of Benign &Malignant neoplasms

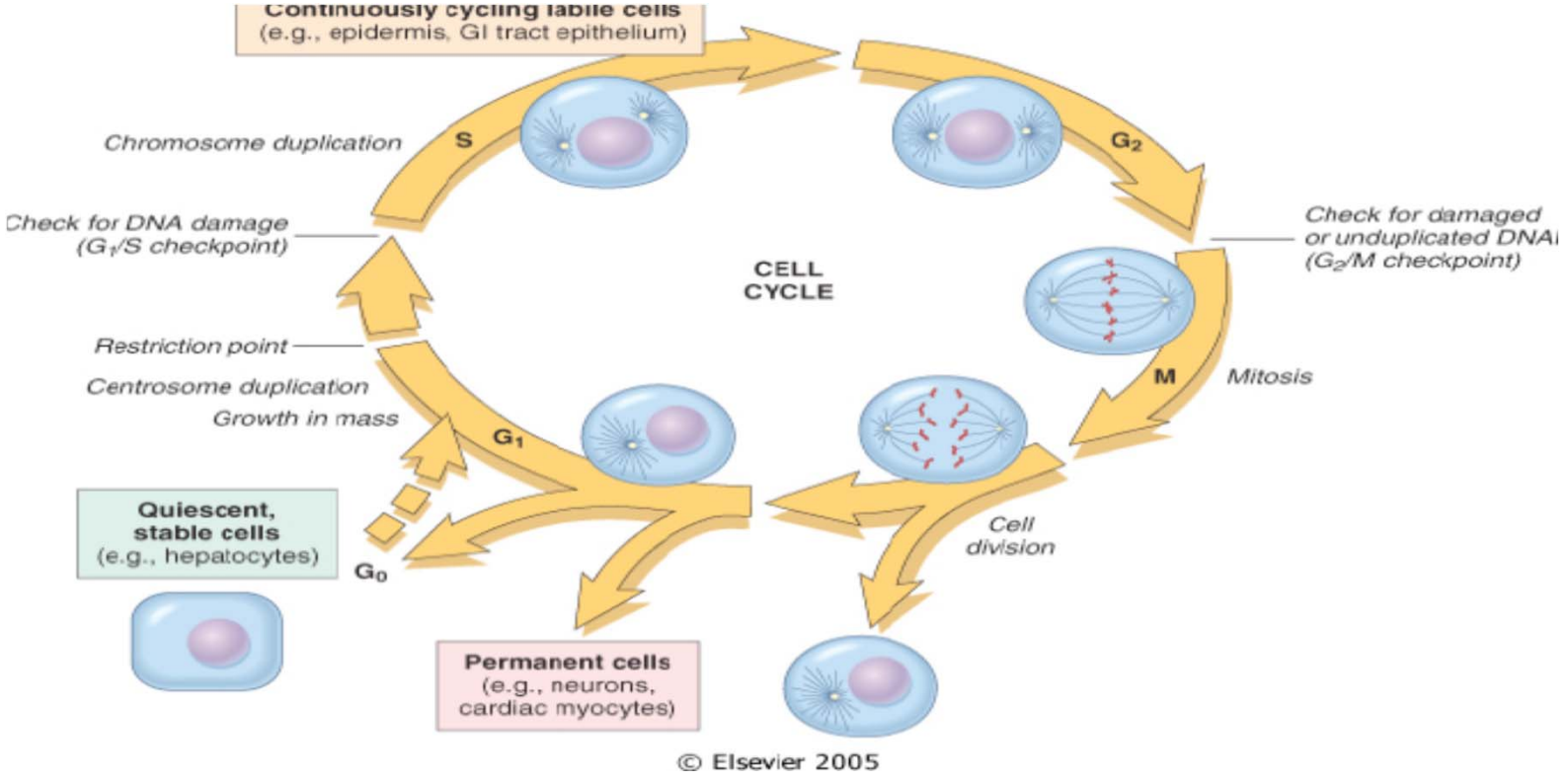
Rate of growth :Prognosis & t/t outcome

determined by 3 factors:

- Fraction of tumour cells in replicating pool
- Doubling time of tumour cells
- Rate at which cells are lost in growing lesion

Cell cycle constraints –lost in tumours but cell cycle is not shortened

Normal Cell Cycle



Characteristics of Benign & Malignant neoplasms

- Proportion of cells with in tu. That are in proliferation pool-Growth fraction
- Submicroscopic level → transformed cells in proliferating pool → vast majority of grow,most leave cell cycle

shedding

Decreased nutrients

Apoptosis

Differentiation

G_O

Characteristics of Benign &Malignant neoplasms

Rapidly proliferating tumour- G. fraction-20%

- **Cell production>cell loss**
  - **Rapid- leukemia/lymphoma/lung ca**
  - **Slow-Ca breast, colon**
- **G fraction determines response to chemotherapy**
  - **Rapid- meltaway by chemo**
  - **Slow (5%)-debulking – increases G fraction**

Characteristics of Benign & Malignant neoplasms

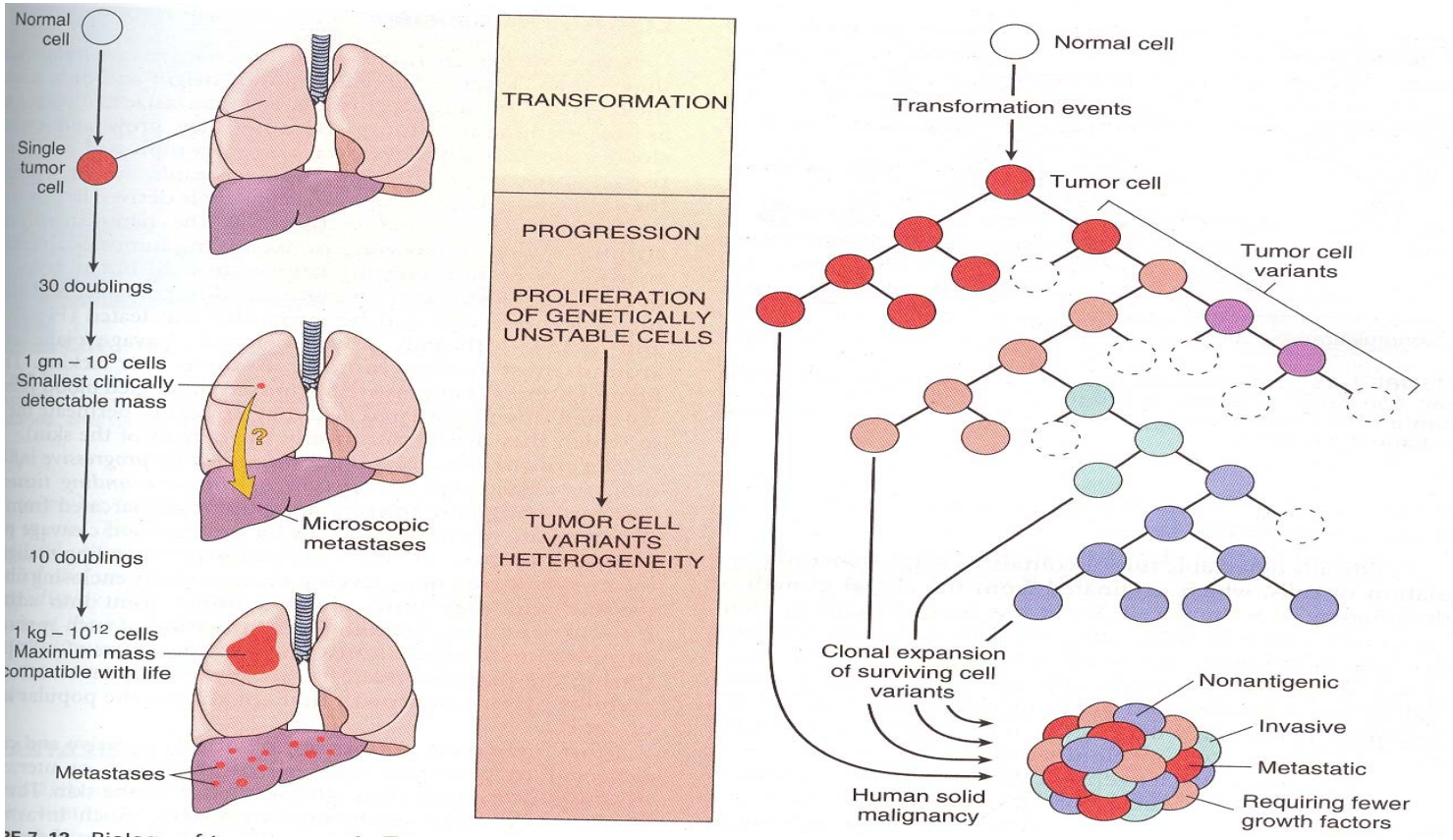
Doubling time- clinically detectable tumour (approx 1gm =10^9 cells) requires 30 population doublings

for 1kg (10^{12} cells)- only 10 more doublings

Doubling time variable

Rate of growh –not constant

Characteristics of Benign & Malignant neoplasms



Characteristics of Benign & Malignant neoplasms

Local Invasion

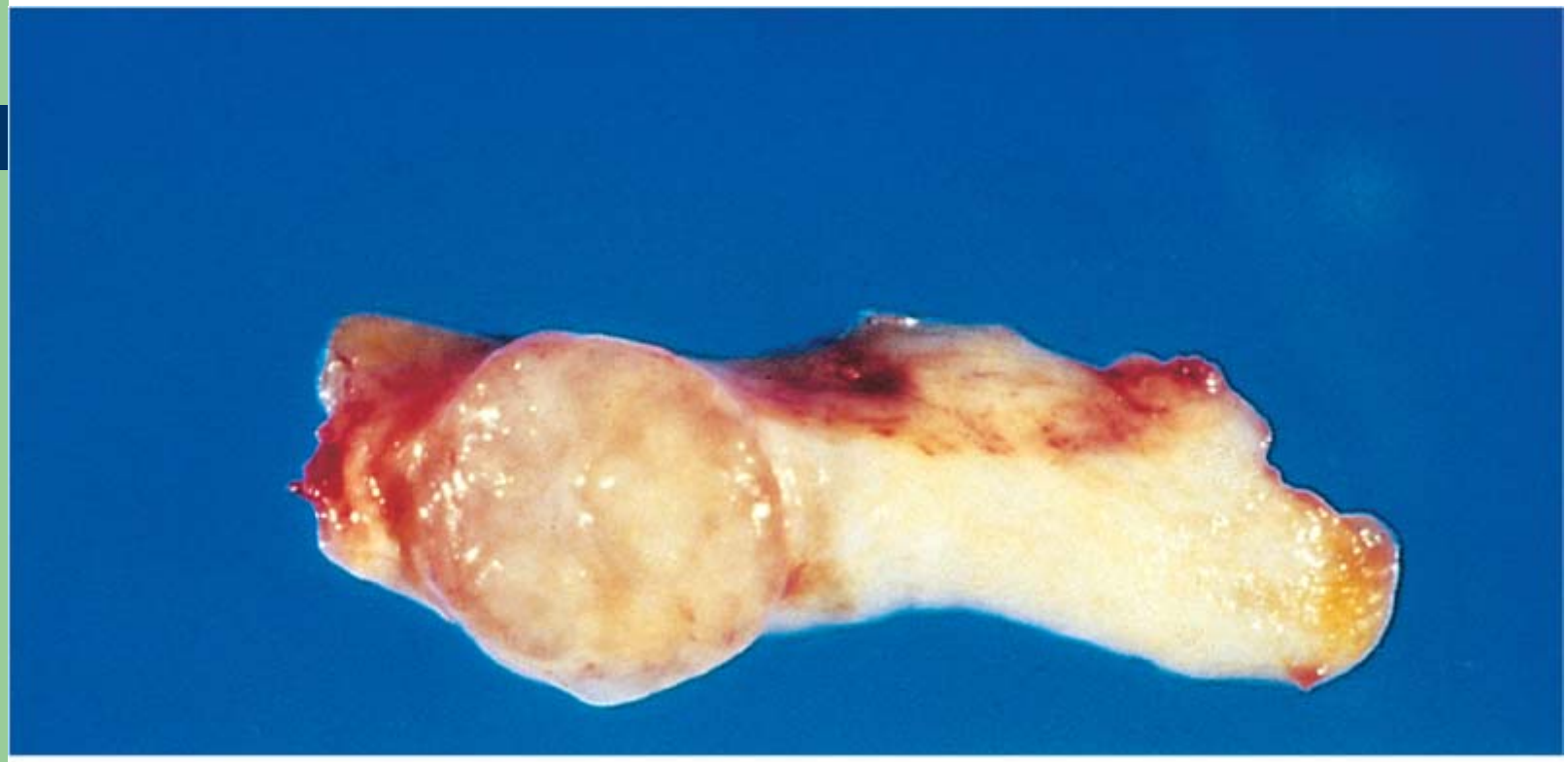
Infiltration of adjacent normal tissue

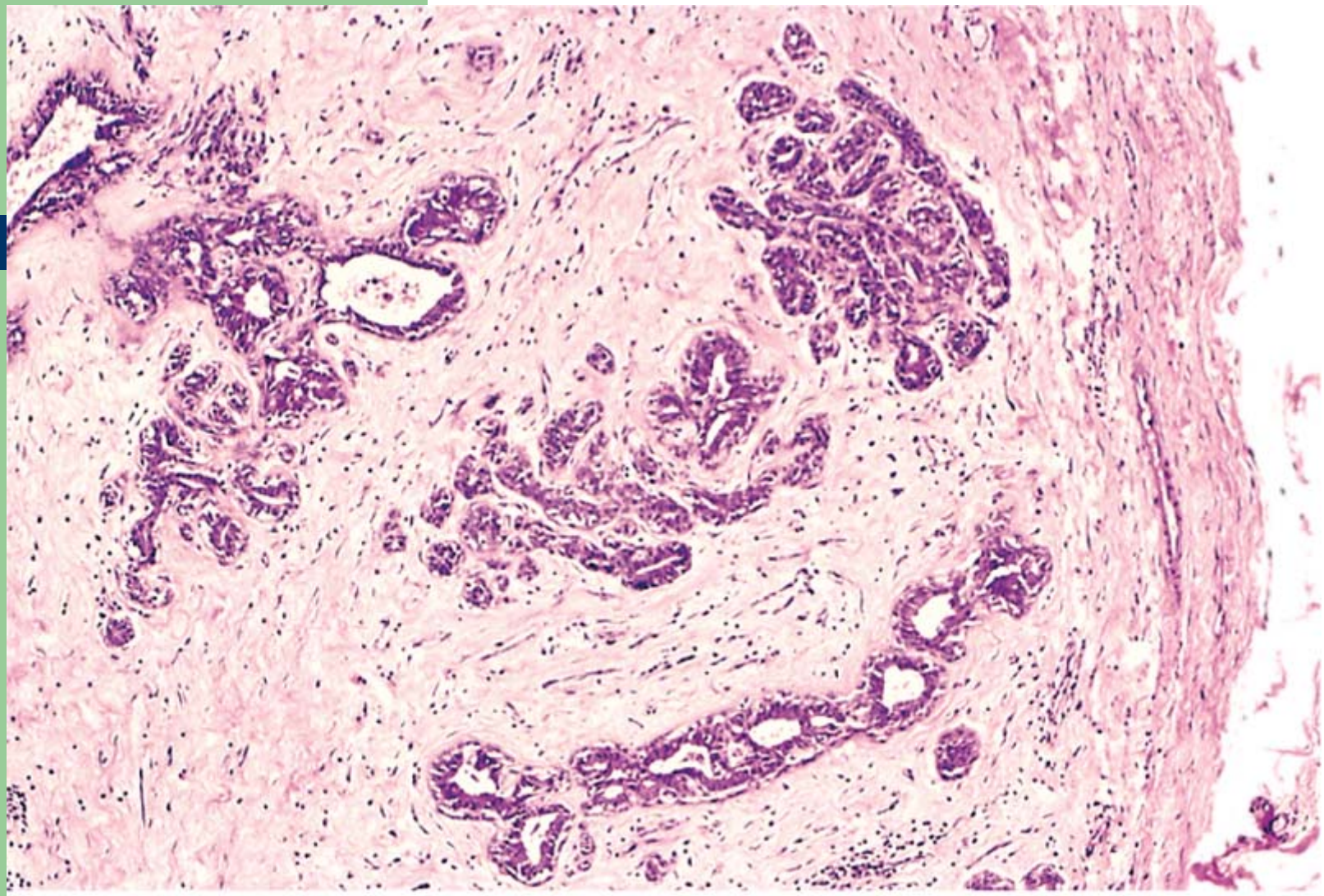
- **Nearly all benign tumors grow as cohesive expansile masses that remain localized to their site of origin**
- **Next to the development of metastases, invasiveness is the most reliable feature that differentiates malignant from benign tumors.**

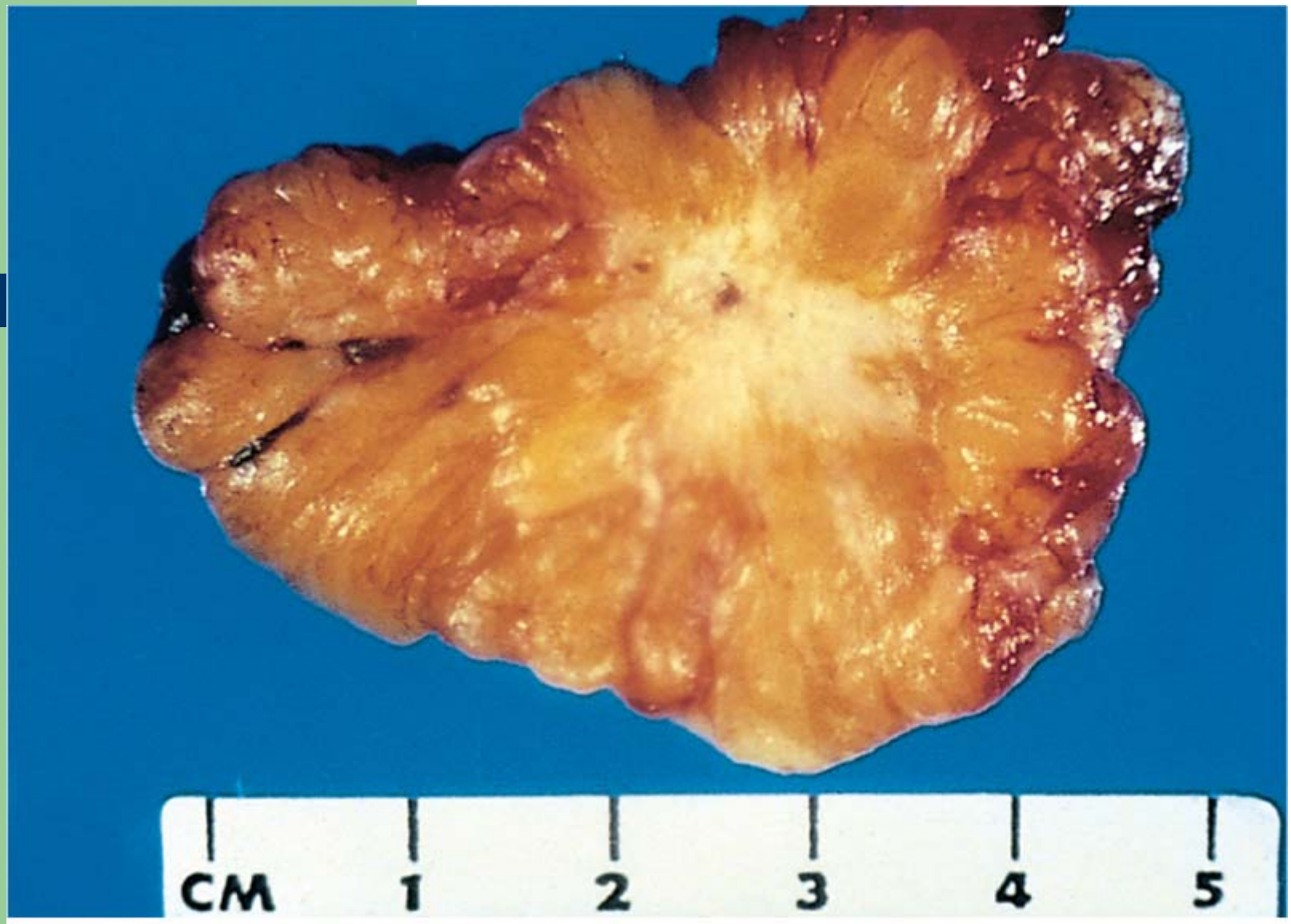
Characteristics of Benign &Malignant neoplasms

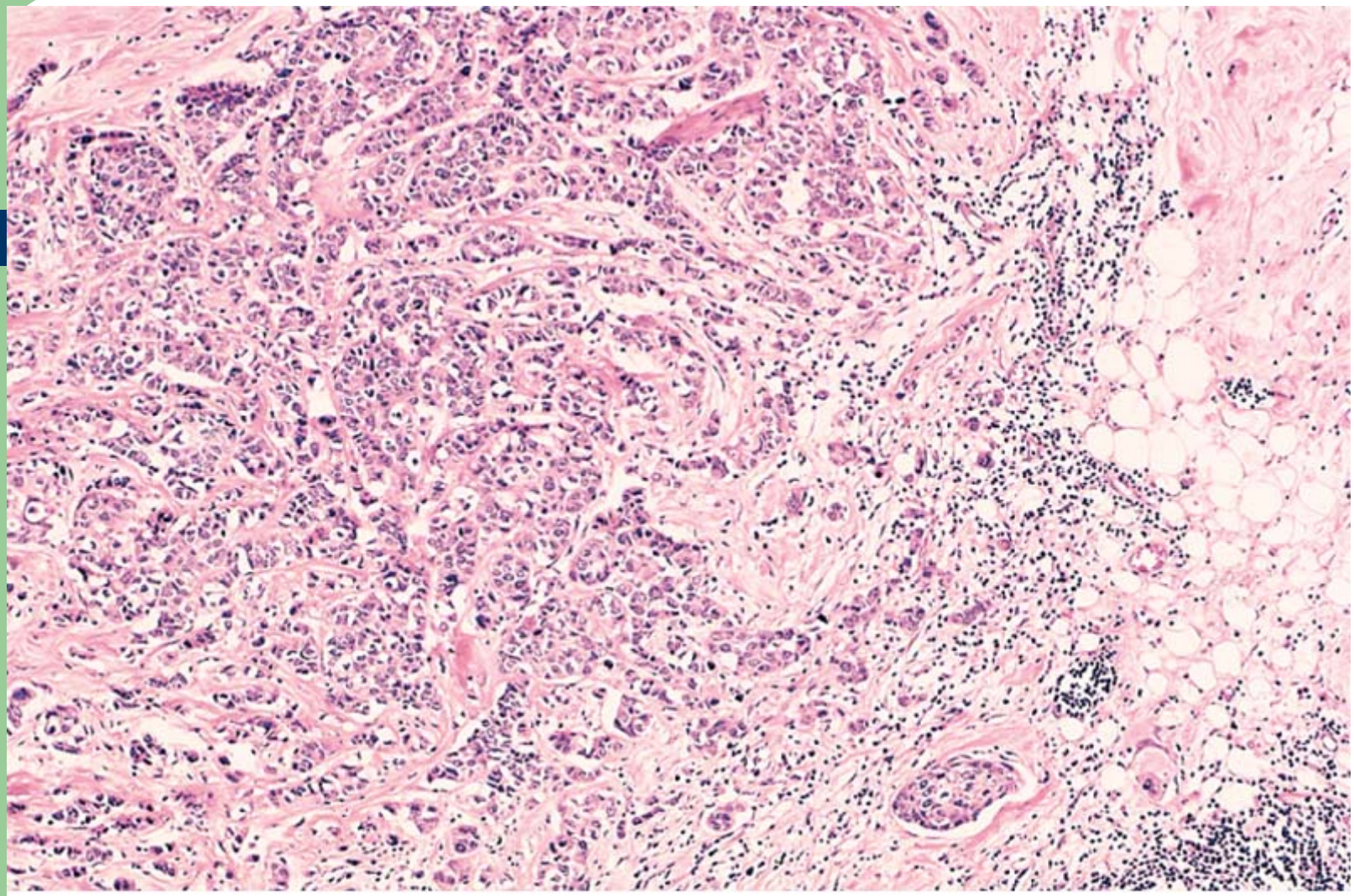
- The growth of cancers is accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue.

- In general, malignant tumors are poorly demarcated from the surrounding normal tissue, and a well-defined cleavage plane is lacking









Characteristics of Benign &Malignant neoplasms

Metastasis

- Metastases are tumor implants discontinuous with the

primary tumor, taking up residence at some distance

- Metastasis unequivocally marks a tumor as malignant

because benign neoplasms do not metastasize

- With few exceptions, all cancers can metastasize

Characteristics of Benign &Malignant neoplasms

- The major exceptions are gliomas in the CNS and basal cell carcinomas of the skin
- In general, the more aggressive, the more rapidly growing, and the larger the primary neoplasm, the greater the likelihood that it will metastasize or already has metastasized

Pathways of spread

1. **Direct seeding of body cavities & surfaces**
   - Open field
   - Pseudomyxoma peritonei

2. **Lymphatic spread**

Dissemination of ca,no fntional lymphatics;

Pattern of L.N.-natural routes of lymphatics

CA BREAST-Upper outer quadrant-axillary L.Ns;inner quadrant – internal mammary,Lung ca-perihilar,tracheobronchial ,medistinal L.Ns.

- skip metastasis

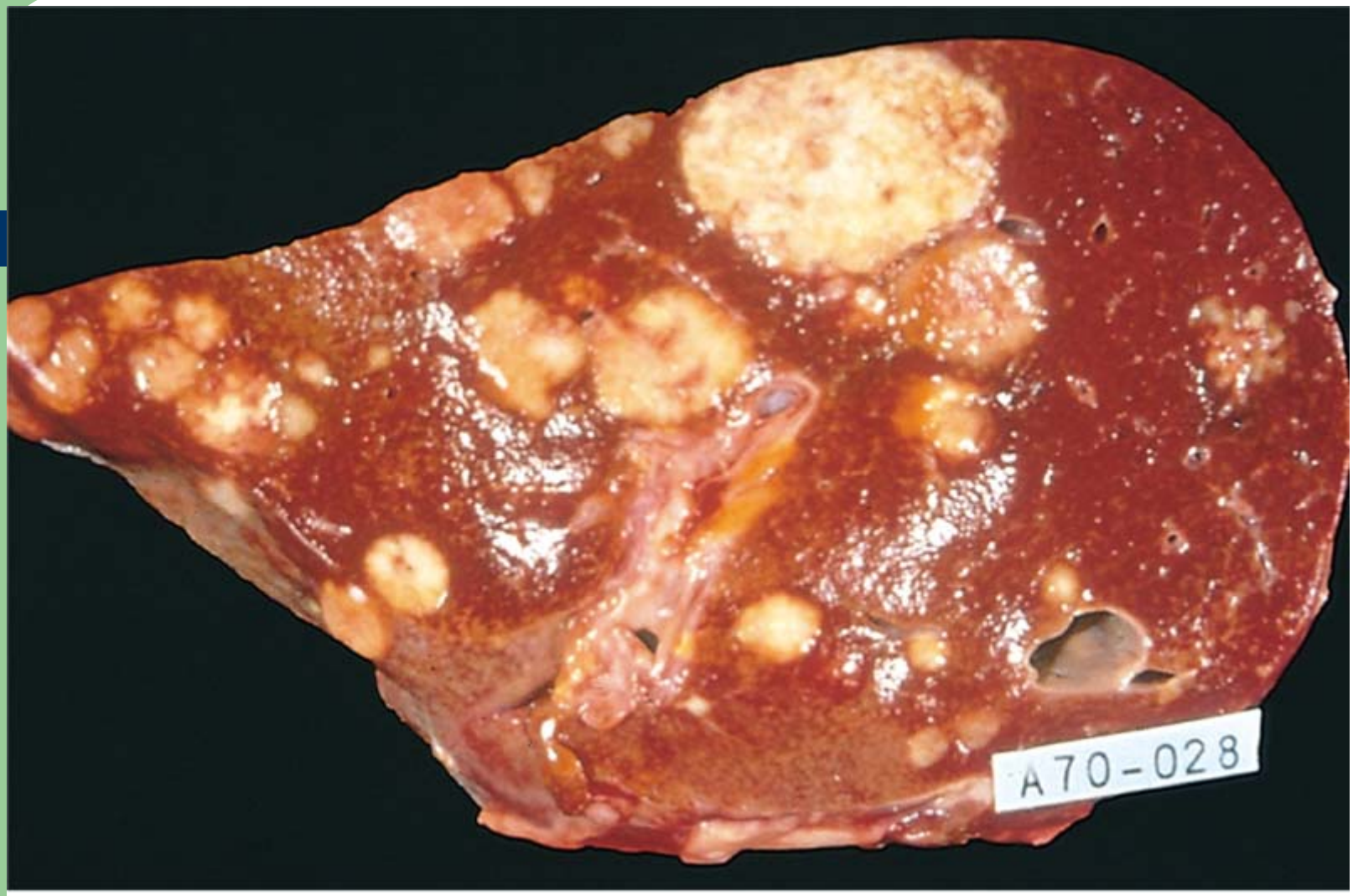
- **Prognostic marker**

- **Sentinal L.N.-FIRSt L.N.in lymphatic drainage from pr. Tu.**
- **Effective barrier**
- **L.N. enlargement**

Pathways of spread

3. Haematogenous spread

- Sarcomas
- Arteries resistant- pulmonary capillary bed
  pulmonary arteriovenous shunt
- Venous invasion follows the route of venous drainage
  lungs- caval
  liver- portal
  vertebral venous plexus- thyroid, prostate
- Carcinoma – RCC,HCC
- Gross-multiple,round lesions



Molecular basis of invasion and metastasis

INVASION AND METASTASIS

- Invasion and metastasis are biologic hallmarks of malignant tumors.
- They are the major cause of cancer-related morbidity and mortality
- A clear understanding of the origin of metastasis is of major importance for the management of cancer patients and the development of effective therapies to prevent tumor spread
- Subclones of tumour cells,metastatic signature
  - prop. Intrinsic to tu. Cells
  - components of stroma

Molecular basis of invasion and metastasis

- The metastatic cascade: Two phases
- Invasion of Extracellular Matrix
- Vascular Dissemination and Homing of Tumor cells

Molecular basis of invasion and metastasis

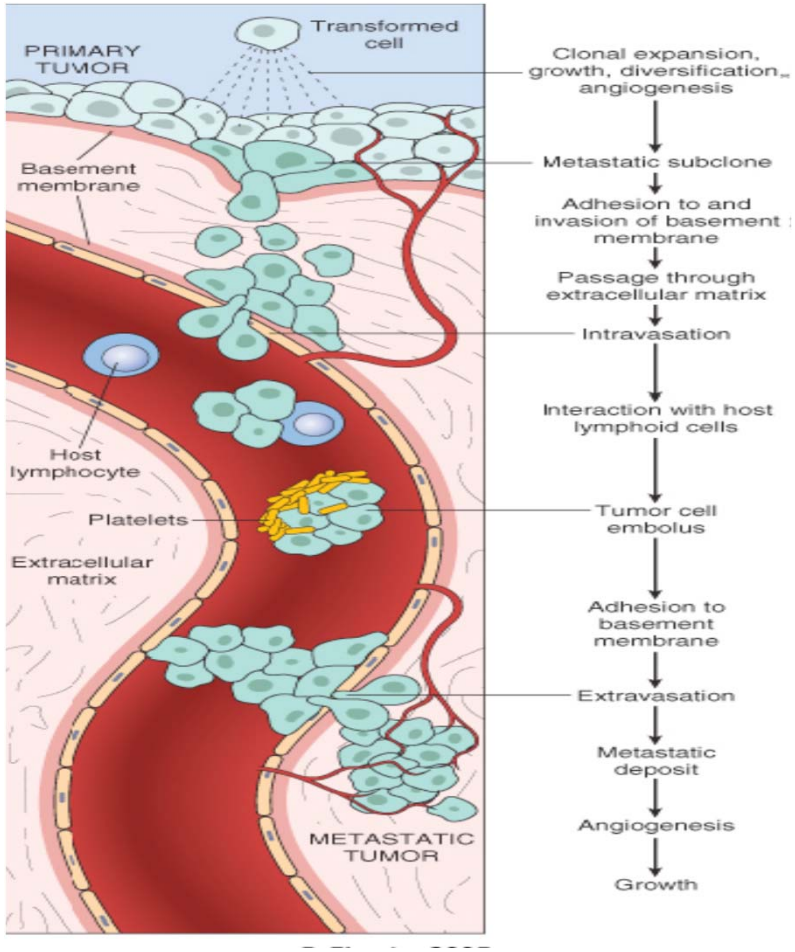
- **TUMOR STROMA**
- COMPOSITION OF THE STROMA

  EC connective tissue consisting of collagen, proteoglycans, blood vessels, stromal fibroblasts, inflammatory and immune cells,, etc.
- TUMOR-STROMAL INTERACTIONS

Molecular basis of invasion and metastasis

Steps of Invasion

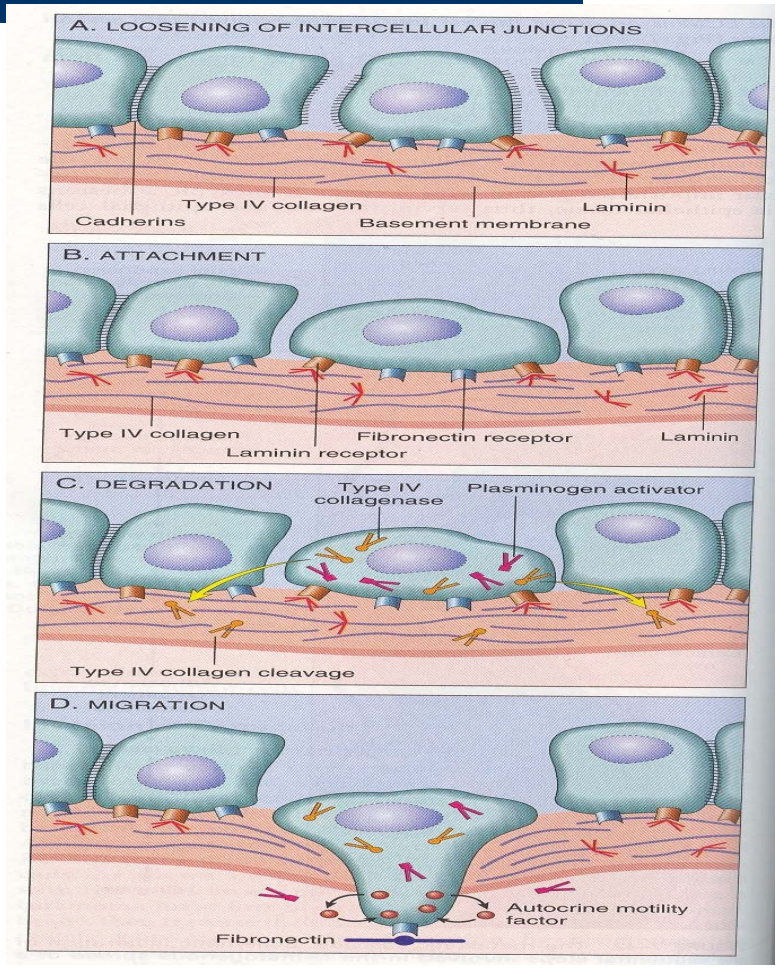
- loss of tumor cell-cell adhesion
- invasion of basement membrane and extracellular matrix
- adherence to matrix
- secretion of proteolytic enzymes
- cell locomotion
- invasion of blood vessels and lymphatics



Molecular basis of invasion and metastasis

Invasion of Extracellular Matrix[active process]

- Detachment ("loosening up") of the tumor cells from each other
- Attachment to matrix components
- Degradation of ECM
- Migration of tumor cells



Molecular basis of invasion and metastasis

- Normal cells-cadherins[E-cadherins],catenins
- Receptor mediated attachement of tu. Cells tolaminin ,collagen IV[integrins,Igs family]
- Increase integrins ,laminin receptors
- Different integrins [$\alpha_4\beta_1$ integrins]

Molecular basis of invasion and metastasis

Invasion of ECM:

- Enzymatic Degradation of Matrix: Invasion of the ECM is not merely due to passive growth pressure but requires active enzymatic degradation of the ECM components.
- Tumor cells secrete proteolytic enzymes themselves or induce host cells (e.g., stromal fibroblasts and infiltrating macrophages) to elaborate proteases such as plasminogen activators, collagenases. etc.
- Serine, cystine, matrix metalloproteinases-MMP-9,MMP-2
- Inhibitors of MMPs

Molecular basis of invasion and metastasis

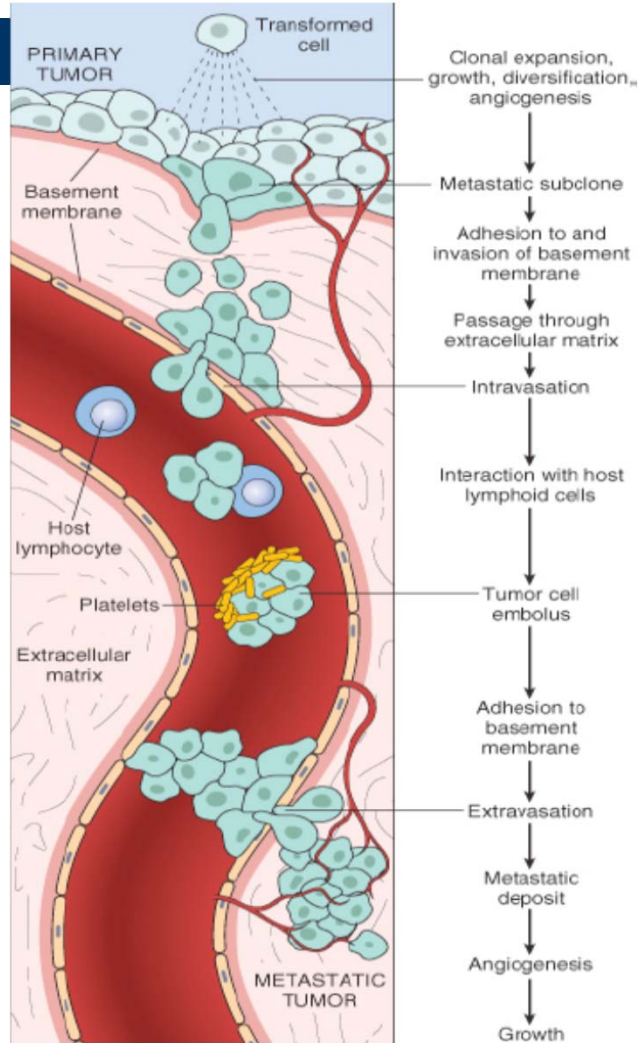
- While the most obvious effect of matrix destruction is to create a path for invasion by tumor cells
- cleavage products of matrix components ,derived from collagen and proteoglycans, also have growth promoting,angiogenic, and chemotactic activities
- Degradation of collagen IV exposes cryptic domains-angiogenesis
- Antiangiogenesis-endostatin,tumststin

Molecular basis of invasion and metastasis

Tumor Metastasis

Steps of Extravasation

- circulating tumor cells
- formation of tumor clumps
- adhesion to endothelium
- penetration of basement membrane



Molecular basis of invasion and metastasis

Vascular Dissemination and Homing of Tumor Cells

- Once in the circulation, tumor cells are particularly vulnerable to destruction by innate and adaptive immune defenses.
  - Within the circulation, tumor cells tend to aggregate in clumps.
  - This is favored by homotypic adhesions among tumor cells as well as heterotypic adhesion between tumor cells and blood cells, particularly platelets.
  - Formation of platelet-tumor aggregates may enhance tumor cell survival and implantability.

Molecular basis of invasion and metastasis

Vascular Dissemination and Homing of Tumor Cells

- **Arrest and extravasation of tumor emboli at distant sites involve adhesion to the endothelium, followed by egress through the basement membrane.**
- **Involved in these processes are adhesion molecules (integrins, laminin receptors) and proteolytic enzymes.**

Molecular basis of invasion and metastasis

- **Sites of Tumor Metastasis**
  - Proximity to tumor site
  - --regional lymph nodes
  - --Tumor specific targets e.g. prostate carcinoma mets to bone
- ✓ Organ-specific adhesion molecules?
- ✓ Growth factor secretion
- ✓ Suitable environment

Molecular basis of invasion and metastasis

Mechanism of Organ Tropism

- Because the first step in extravasation is adhesion to the endothelium, tumor cells may have **adhesion molecules** whose ligands are expressed preferentially on the endothelial cells of the target organ.
- The endothelial cells of the vascular beds of various tissues differ in their expression of ligands for adhesion molecules.

Molecular basis of invasion and metastasis

- **Chemokines** have a very important role in determining the target tissues for metastasis.e.g. Some breast cancer cells express the chemokine receptorsCXCR4 and CCR7. The chemokines that bind to these receptors are highly expressed in tissues to which breast cancers commonly metastasize.
- Some target organs may liberate chemoattractants that tend to recruit tumor cells to the site. Examples include insulin-like growth factors I and II.

Molecular basis of invasion and metastasis

Mechanism of Organ Tropism

In some cases, the target tissue may be an **unpermissive environment-unfavorable soil**, for the growth of tumor seedlings.e.g.,although well vascularized, skeletal muscles are rarely the site of metastases.

Staging of Malignant Neoplasms

TNM Staging [UICC] Union int. contre cancer

T_o 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

Staging

- AJC staging
- Stage O-IV
- All 3 components of UICC

Grading

- Grading schems are based upon the microscopic appearance of a neoplasm with H&E staining.
- Degree of differentiation and no. of mitosis
- Most grading systems have three or four grades (designated with numbers or roman numerals).
- Broders' for sq. cell ca

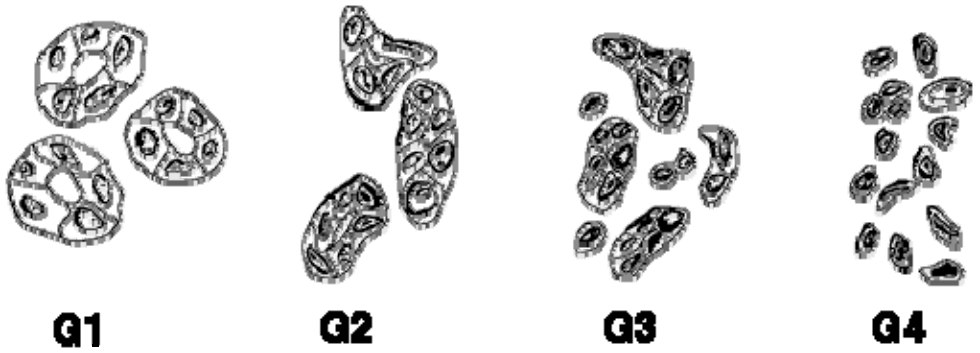
  Grade I-Well diff.-less than 25% anaplastic cells

  Grade II-Mod. Diff.-25%-50% anaplastic cells

  GradeIII- Mod. Diff-50%-75% anaplastic cells

  Grade IV-Poorly diff.-more than 75% anaplastic cells
- In the diagram utilizing an adenocarcinoma as an example, the principles of grading are illustrated:

Grading



Prognostic Markers

- Clinical Prognostic Markers

  Size,grade, vascular invasion,nodal involvement

- Molecular markers

  Expression of oncogene C-met, c-ras

  CD44

  Estrogen receptors

  EGF receptor

  Angiogenesis factors

Epidemiology and predisposing factors to Neoplasia

- Incidence-20-23% of all mortality
- Most common ca in males-lung,prostate,colorectal
- Most common ca in females-breast,lung,colorectal
- **Age-males-6-8 decade**

  females-4 6 decade

  children [less than 15]-leukaemia,lymphoma,wilms Tu.,retinoblastoma,neuroblastoma,medulloblastoma, rhabdomyosarcoma,hepatoblastoma

Predisposing factors

Racial and geographical factors

- Japanese– ca stomach<7-8 fold>
- Europeans and Americans– Ca lung,Breast ,Colon
- Black africans– Ca skin, cervix,penis
- South east asians—Nasophar.ca
- Indians – oral cavity,upper aero digestive

Predisposing factors

Environmental and cultural

- Smoking ,Alcohol,Betel nut,Diet
- Carcinoma cervix—early marriage, parity ,and multiple partners
- Penile Cancer – Rare in Jews and muslims,smegma-carcinogenic

- **arsenic compounds**

--Lung, skin, hemangiosarcoma

Byproduct of metal smelting. Component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips

- **Asbestos**

--Lung, mesothelioma; gastrointestinal tract (esophagus, stomach, large intestine)

--Formerly used for many applications because of fire, heat, and friction resistance; still found in existing construction as well as fire-resistant textiles, friction materials (i.e., brake linings)

- **Benzene**

--Leukemia, Hodgkin lymphoma

--Principal component of light oil.

Although use as solvent is discouraged, many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents, fumigant

- **Beryllium and beryllium compounds**

--Lung

--Missile fuel and space vehicles.

- Cadmium and cadmium compounds

--Prostate

--. Used in batteries and as alloy and in metal platings and coatings

- **Cadmium and cadmium compounds**

--Prostate

--. Used in batteries and as alloy and in metal platings and coatings

- **Chromium compounds**

--Lung

--Component of metal alloys, paints, pigments, and preservatives

- **Ethylene oxide**

---Leukemia

---Ripening agent for fruits and nuts. Used in rocket propellant and chemical synthesis, in fumigants for foodstuffs and textiles, and in sterilants for hospital equipme

- **Nickel compounds**

---Nose, lung

---Nickel plating. Component of ferrous alloys, ceramics, and batteries.

- **Radon and its decay products**

--Lung

--From decay of minerals--containing uranium. Can be serious hazard in quarries and mines

- **Vinyl chloride**

--Angiosarcoma, liver

--Refrigerant. Monomer for vinyl polymers. Adhesive for plastics.

Hormones And Cancer

- Estrogen—Endometrial ca, Vaginal Ca
- Contraceptive pills-ca breast, Liver Adenomas
- Anabolic Steroids ---liver tumors

Heredity

Hereditary forms of cancer can be divided into three categories

- Inherited Cancer Syndromes
- Familial Cancers
- Inherited Autosomal Recessive Syndromes of Defective DNA Repair

Inherited cancer syndromes

- Inherited cancer syndromes include several well-defined cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor.
- The predisposition to these tumors shows an autosomal dominant pattern of inheritance.
- ``Childhood retinoblastoma -- Approximately 40% of retinoblastomas are familial.
- Carriers of this gene have a 10,000-fold increased risk of developing retinoblastoma, usually bilaterally.
- greatly increased risk of developing a second cancer, particularly osteogenic sarcoma.

Familial adenomatous polyposis ---an extraordinarily high risk of cancer.

Individuals who inherit the autosomal dominant mutation have, at birth or soon thereafter, innumerable polypoid adenomas of the colon, and virtually **100% of patients develop a carcinoma of the colon by age 50 p53**

--- Li-Fraumeni syndrome (various tumors**)**

- Tumors within this group often are associated with a specific marker phenotype.
- There may be multiple benign tumors in the affected tissue, as occurs in familial polyposis of the colon and in multiple endocrine neoplasia.
- Sometimes, there are abnormalities in tissue that are not the target of transformation (e.g., Lisch nodules and café-au-lait spots in neurofibromatosis

Familial Cancers

- Familial clustering of cases, but role of inherited predisposition not clear for each individual
- Breast cancer (not linked to BRCA1 or BRCA2
- Ovarian cancer
- Pancreatic cancer

Familial cancers

- Virtually all the common types of cancers that occur sporadically have been reported to occur in familial forms
- Features that characterize familial cancers include

  early age at onset

  tumors arising in two or more close relatives of the index case

  sometimes multiple or bilateral tumors.

- Familial cancers are not associated with specific marker phenotypes. For example, in contrast to the familial adenomatous polyposis syndrome, familial colonic cancers do not arise in preexisting benign polyps.
- The transmission pattern of familial cancers is not clear. In general, siblings have a relative risk between 2 and 3 times.
- Segregation analysis of large families usually reveals that predisposition to the tumors is dominant, but multifactorial inheritance cannot be easily ruled out

Inherited Autosomal Recessive Syndromes

- Inherited Autosomal Recessive Syndromes of Defective DNA Repair
- Xeroderma pigmentos
- Ataxia-telangiectasia
- Bloom syndrome
- Fanconi anemia

Acquired Preneoplastic Disorders

- certain clinical conditions have well-recognized predispositions to the development of malignant neoplasia and are referred to as preneoplastic disorders.

This designation is unfortunate

- ✓ Persistent regenerative cell replication

  --(e.g., squamous cell carcinoma in the margins of a chronic skin fistula or in a long-unhealed skin wound

  -- hepatocellular carcinoma in cirrhosis of the liver)

- ✓ Hyperplastic and dysplastic proliferations
  - - endometrial carcinoma in atypical endometrial hyperplasia
  - - bronchogenic carcinoma in the dysplastic bronchial mucosa of habitual cigarette smokers)
  - -Chronic atrophic gastritis (e.g., gastric carcinoma in pernicious anemia or following long-standing Helicobacter pylori infection)
  - - an increased incidence of colorectal carcinoma in long-standing disease Chronic ulcerative colitis)

- increased risk of squamous cell carcinoma following Leukoplakia of the oral cavity, vulva, or penis
- Villous adenomas of the colon (e.g., high risk of transformation to colorectal carcinoma)

- **ALL BENIGN TU—INHERENT RISK:NEVER TO FREQUENT**

MOLECULAR BASIS OF CANCER

- **Nonlethal genetic damage (or mutation) lies at the heart of carcinogenesis. Cancer is a genetic disease,**

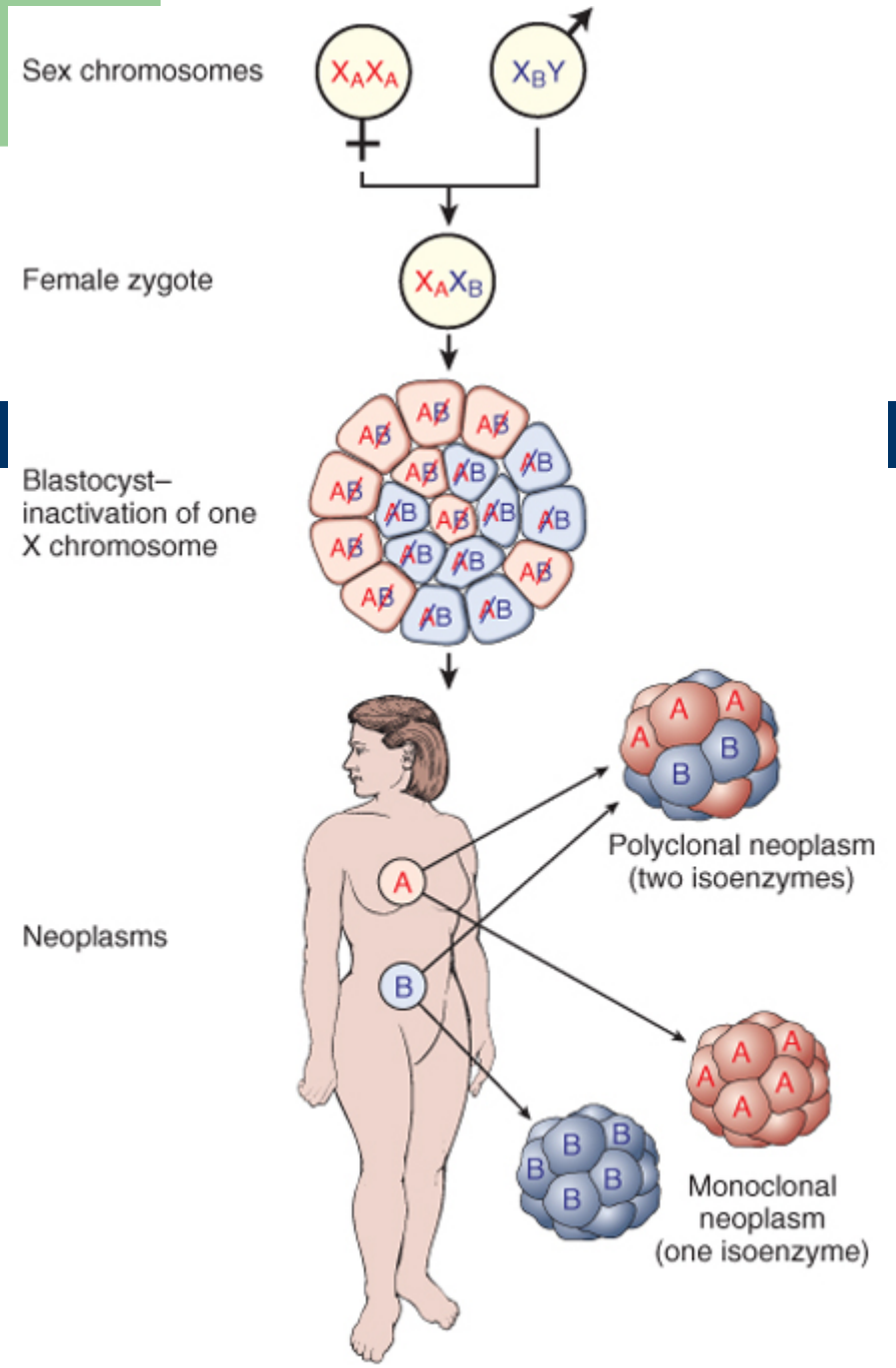
  Envt. Damage

  Germ Line

- **A tumor is formed by the clonal expansion of a single precursor cell that has incurred the genetic damage (i.e., tumors are monoclonal)**

  -- Clonality of tumors is assessed readily in women who are heterozygous for polymorphic X-linked markers, such as the enzyme glucose-6-phosphate dehydrogenase

  --HUMARA



- Four classes of normal regulatory genes –
  - proto-oncogenes
  - tumor suppressor genes
  - apoptosis-regulating genes
  - genes involved in DNA repair

the principal targets of genetic damage

- Mutant alleles of proto-oncogenes are called oncogenes. They are considered dominant because mutation of a single allele can lead to cellular transformation.
- typically both normal alleles of tumor suppressor genes must be damaged for transformation to occur, so this family of genes is sometimes referred to as recessive oncogenes.

    in some cases, loss of a single allele of a tumor suppressor gene can promote transformation (haploinsufficiency).

- Genes that regulate apoptosis may be dominant, as are proto-oncogenes, or they may behave as tumor suppressor genes.

MOLECULAR BASIS OF CANCER

- DNA repair genes affect cell proliferation or survival indirectly by influencing the ability of the organism to repair nonlethal damage in other genes, including protooncogenes, tumor suppressor genes, and genes that regulate apoptosis
- **Carcinogenesis is a multistep process at both the phenotypic and the genetic levels**
  - TOMOUR PROGRESSION

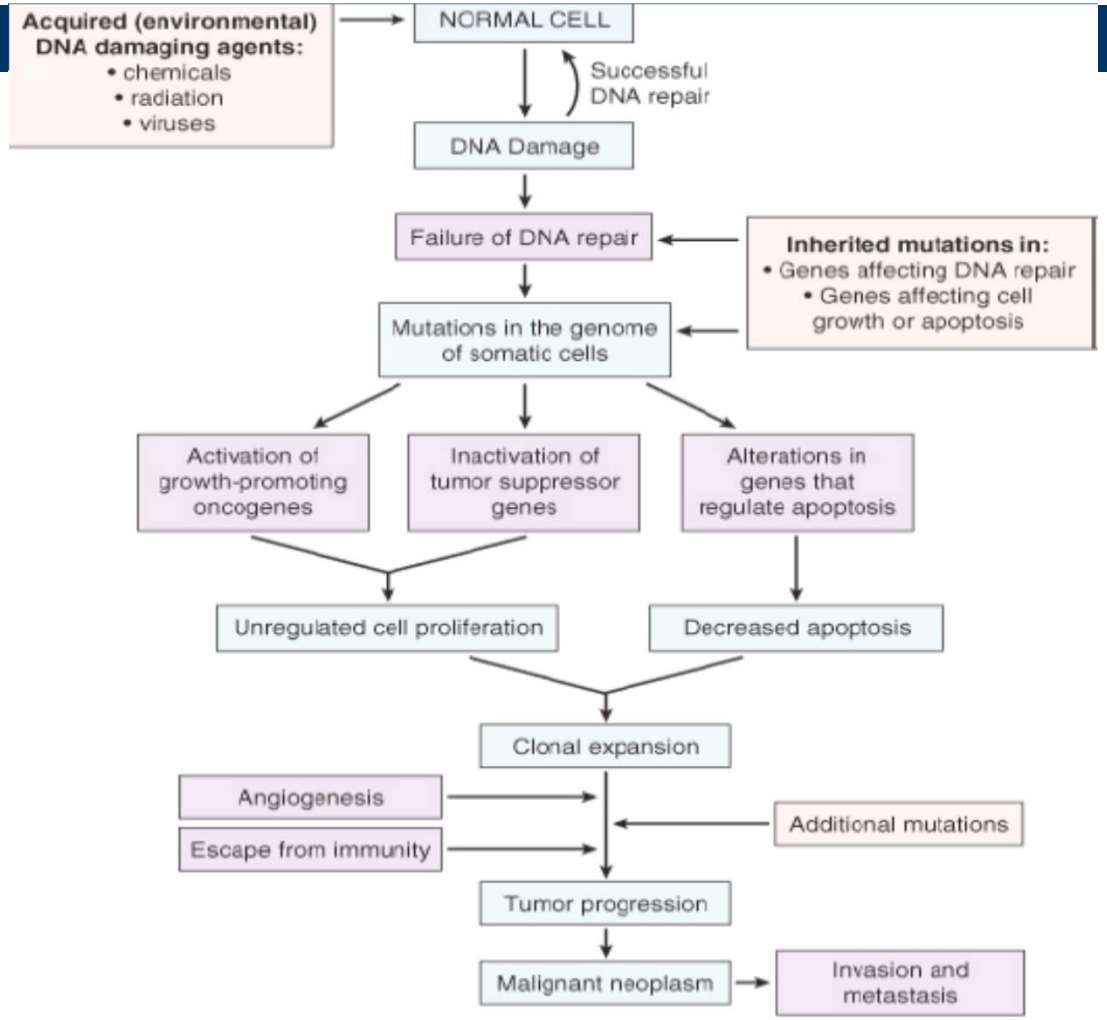
Principal Targets of Genetic Damage: 4 Classes of Normal Regulatory Genes

- Growth-promoting protooncogenes
- Growth-inhibiting tumor suppressor genes
- Apoptosis-regulating genes; genes that regulate the programmed cell death
- DNA repair genes

Essential Alterations for Malignant Transformation

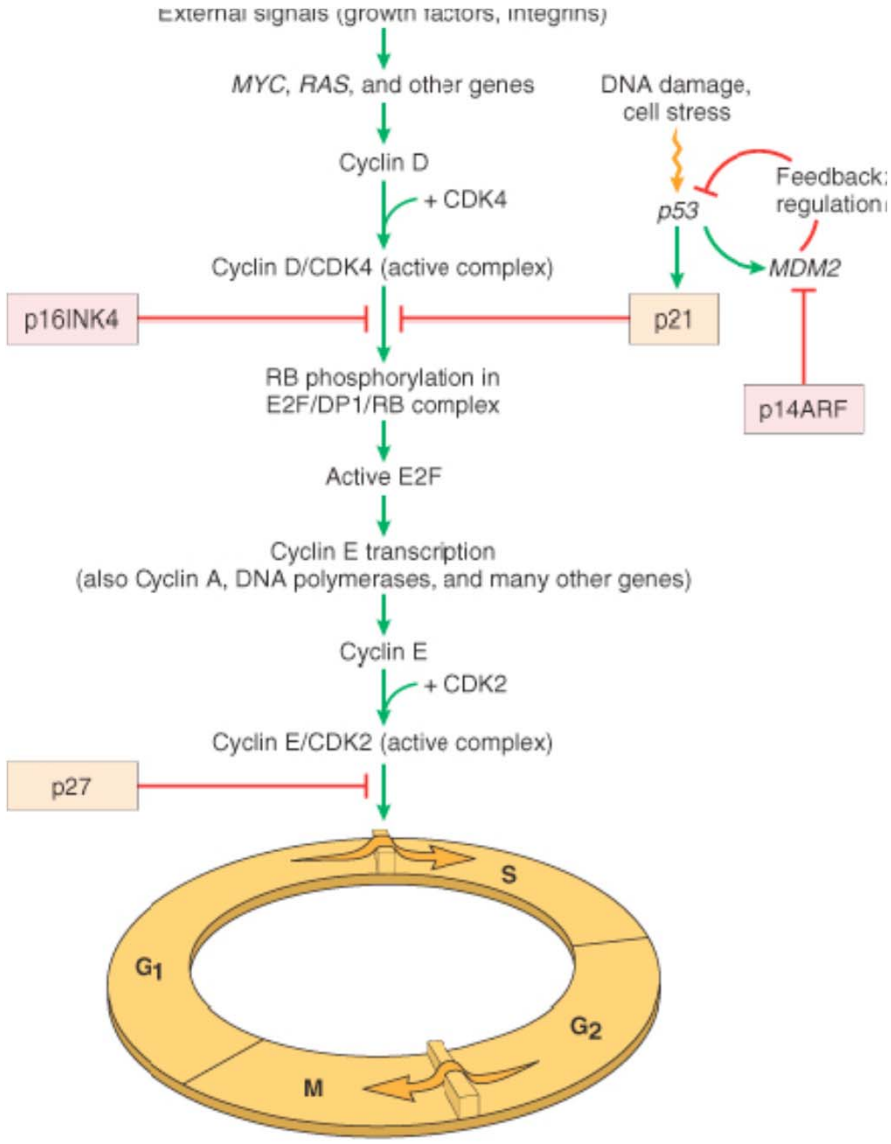
- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory signals
- Evasion of apoptosis
- Defects in DNA repair
- Ligmitless replicative potential
- Sustained angiogenesis
- Ability to invade and metastasize

Simplified flow chart of the molecular basis of cancer



Normal Cell Cycle

- It is important to understand the molecular regulation of the normal cell cycle, since cell cycle abnormalities are fundamental to cancer growth and many of the genes that cause cancer perturb the cell cycle.
- The orderly progression of cells through the various phases of cell cycle is orchestrated by cyclins and cyclin-dependent kinases (CDKs), and by their inhibitors.



Main Cell-Cycle Components and Their Inhibitors

- Cyclin-Dependent Kinases (CDK)
- CDK Inhibitors
- Checkpoint Components

Cell-Cycle Inhibitors

- The activity of cyclin-CDK complexes is tightly regulated by inhibitors, called CDK inhibitors.
- Two main classes of CDK inhibitors: the Cip/Kip
- These inhibitors function as tumor suppressors and and the INK4/ARF families are frequently altered in tumors
- Cip/Kip-p21 p27 p57
- INK4/ARF- p16INK4, p14ARF

Cell-Cycle Checkpoints

- The cell cycle has its own internal controls, called checkpoints.
- Two main checkpoints: One at the G1/S transition and another at the G2/M.
- To function properly, cell-cycle checkpoints require sensors of DNA damage, signal transducers, and effector molecules.

G1/S Checkpoint

- The S phase is the point of no return in the cell cycle, and before a cell makes the final commitment to replicate, the G1/S checkpoint checks for DNA damage.
- If DNA damage is present, the DNA repair machinery and mechanisms that arrest the cell cycle are put in motion.
- The delay in cell-cycle progression provides the time needed for DNA repair; if the damage is not repairable, apoptotic pathwaysare activated to kill the cell.
- Thus, the G1/S checkpoint prevents the replication of cells that have defects in DNA, which would be perpetuated as mutations or chromosomal breaks in the progeny of thecell.
- DNA damaged after its replication can still be repaired aslong as the chromatids have not separated.

G2/M Checkpoint

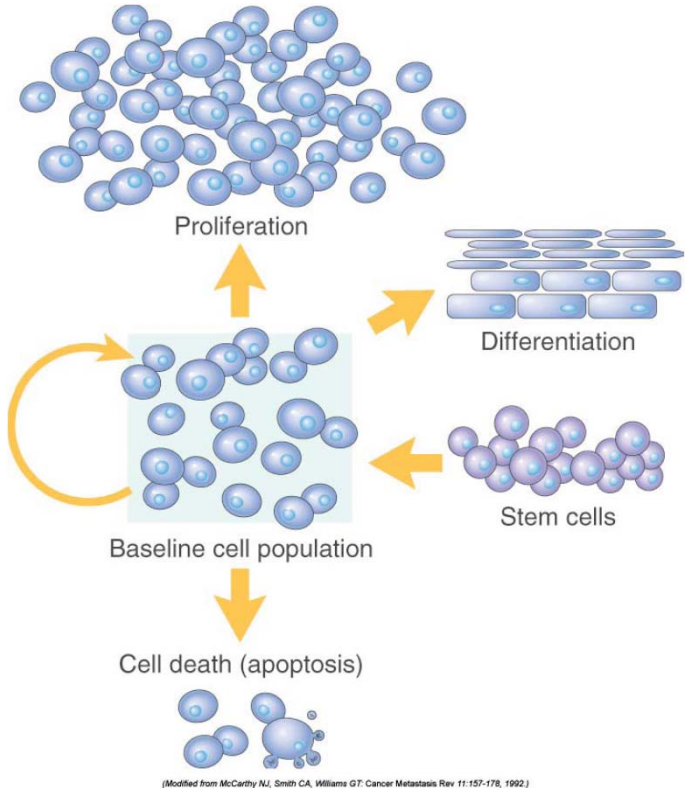
- The G2/M checkpoint monitors the completion of DNA replication and checks whether the cell can safely initiate mitosis and separate sister chromatids.
- This checkpoint is particularly important in cells exposed to ionizing radiation.
- Cells damaged by ionizing radiation activate theG2/M checkpoint and arrest in G2□□
- Defects in this checkpoint give rise to chromosomal abnormalities.

Checkpoint Components

- The **sensors** and **transducers** of DNA damage appear to be similar for the G1/S and G2/M checkpoints.
- Sensors - the RAD family and ataxia telangiectasia mutated (ATM)
- Transducers - the CHK kinase families
- The checkpoint **effector** molecules differ, depending on the cell-cycle stage at which they act.
- In the G1/S checkpoint, cell-cycle arrest is mostly mediated through p53, which induces the cell-cycle inhibitor p21.
- Arrest of the cell cycle by the G2/M checkpoint involves both p53- dependent and independent mechanisms.

  Defect in cell-cycle checkpoint components is a major cause of genetic instability in cancer cells.

Mechanisms regulating cell populations



Steps of Cell Proliferation under physiologic conditions

1. The binding of a **growth factor** to its specific receptor generally located on the cell membrane
2. Transient and limited activation of the **growth factor receptor**, which, in turn, activates several signal transducing proteins on the inner leaflet of the plasma membrane
3. Transmission of the transduced signal across the cytosol to the nucleus via second messengers or by **signal transduction** molecules that directly activate transcription
4. Induction and activation of **nuclear regulatory factors** that initiate **DNA transcription**
5. Entry and progression of the cell into the cell cycle, ultimately resulting in cell division

Self-Sufficiency in Growth Signals

- **Oncogenes -** genes that promote autonomous cell growth in cancer cells
- **Protooncogenes** - their normal cellular counterparts; genes in normal cells which encode proteins that have normal function in cell

Protooncogenes and Oncogenes

- Protooncogenes are physiologic regulators of cell proliferation and differentiation
- Oncogenes are characterized by the ability to promote cell growth in the absence of normal mitogenic

Protooncogenes and Oncogenes

- Oncogene products, called **oncoproteins**,resemble the normal products of protooncogenes with the exception that oncoproteins are devoid of important regulatory elements
- Their production in the transformed cells becomes constitutive, that is, not dependenton growth factors or other external signals
- Because oncoproteins are constitutivelyexpressed, they endow the cell with selfsufficiency in growth
- ‘Enemies with in’

Cellular Oncogenes (c-onc)

- MUTATED FORM
- V-onc
- V-FES,v-SIS
- Some cancer-causing RNA viruses (i.e.,leukemia virus) have no viral oncogenes
- Proviral DNA insertion near a protooncogene induces a structural change in the cellular gene, converting it into a cellular oncogene (conc, or onc) – **insertional mutagenesis**
- Also retroviral promoters inserted in the vicinity of the protooncogenes lead to dysregulated expression of the cellular gene

Where Do Oncogenes Come From?

Proto-oncogenes-- Oncogenes via:

- mutations causing altered properties of the protooncogene product, inhibiting its normal activity
- mutation of regulatory sequences leading to overexpression of the protooncogene
- incorporation of foreign DNA causing altered expression of altered protooncogene product
- some may arise from chromosomal translocations

Requirements for Altered Cell Growth

Oncogenes act dominantly, needing only one gene copy to generate the altered phenotype

Loss of cell growth control therefore requires:

Mutations in both copies of tumor-suppressor genes

– Mutation of one copy of the proto-oncogene

Functional Category of Oncogenes

- Growth Factors
- Growth Factor Receptors
- Proteins Involved in Signal Transduction
- Nuclear Regulatory Proteins
- Cell-Cycle Regulators

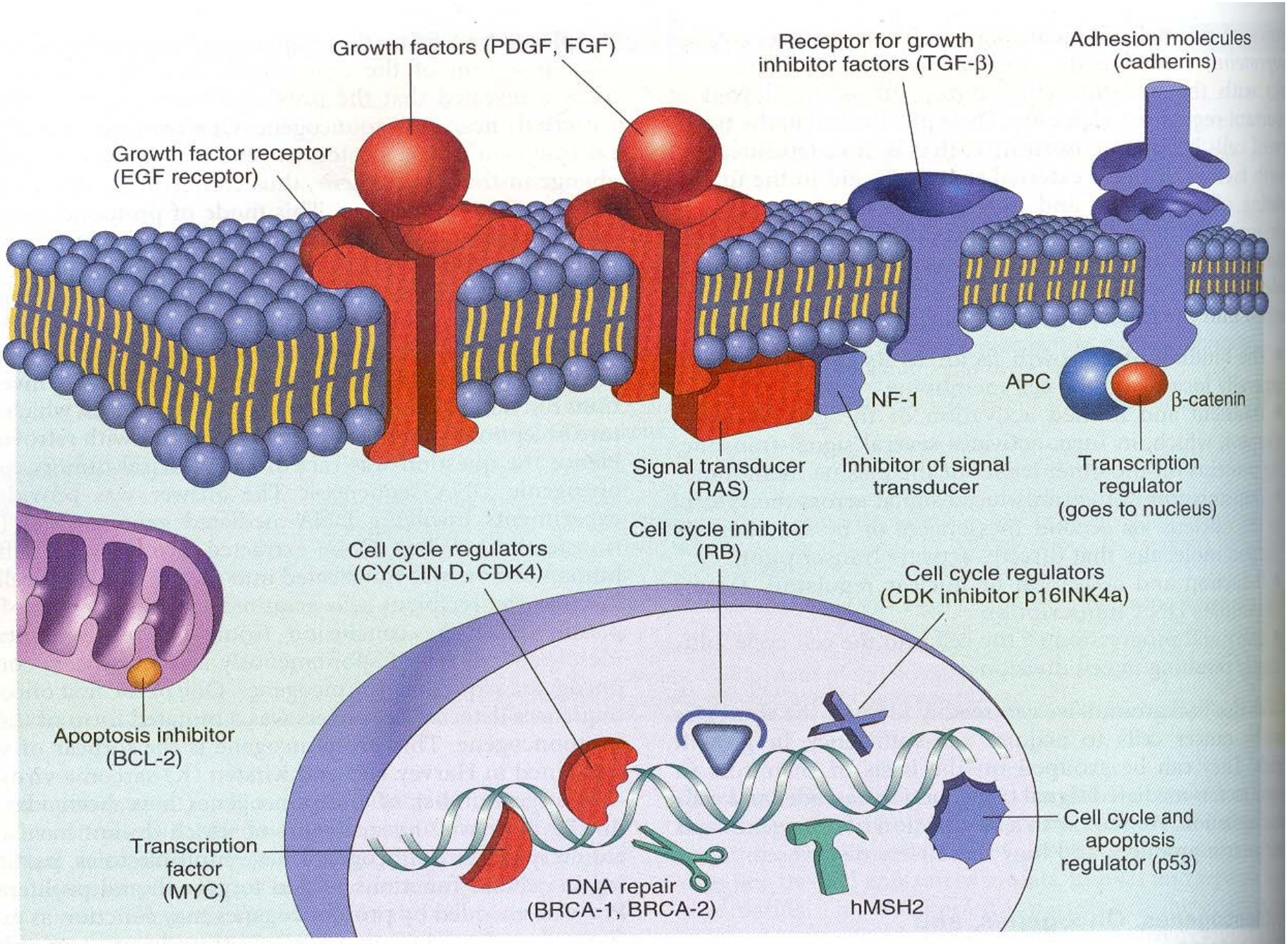
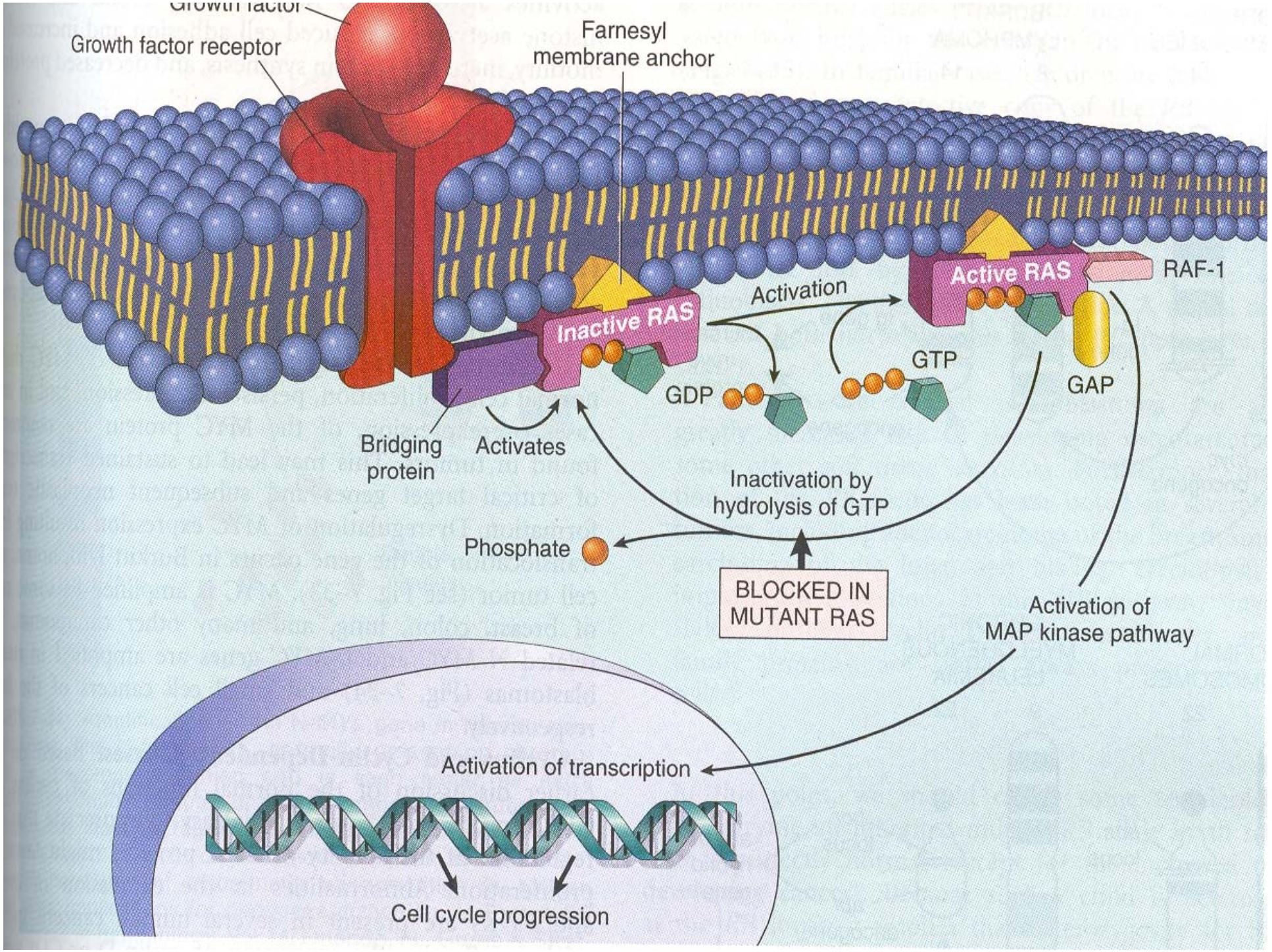


FIGURE 7–31 Subcellular localization and functions of major classes of cancer-associated genes. The protooncogenes are colored red, cancer suppressor genes blue, DNA repair genes green, and genes that regulate apoptosis purple.

TABLE 7–8 Selected Oncogenes, Their Mode of Activation, and Associated Human Tumors

Category	Protooncogene	Mode of Activation	Associated Human Tumor
Growth Factors			
PDGF-β chain	*SIS*	Overexpression	Astrocytoma Osteosarcoma
Fibroblast growth factors	*HST-1* *INT-2*	Overexpression Amplification	Stomach cancer Bladder cancer Breast cancer Melanoma
TGFα	TGFα	Overexpression	Astrocytomas Hepatocellular carcinomas
HGF	HGF	Overexpression	Thyroid cancer
Growth Factor Receptors			
EGF-receptor family	*ERB-B1 (ECFR)* *ERB-B2*	Overexpression Amplification	Squamous cell carcinomas of lung, gliomas Breast and ovarian cancers
CSF-1 receptor	*FMS*	Point mutation	Leukemia
Receptor for neurotrophic factors	*RET*	Point mutation	Multiple endocrine neoplasia 2A and B, familial medullary thyroid carcinomas
PDGF receptor	*PDGF-R*	Overexpression	Gliomas
Receptor for stem cell (steel) factor	*KIT*	Point mutation	Gastrointestinal stromal tumors and other soft tissue tumors
Proteins Involved in Signal Transduction			
GTP-binding	*K-RAS* *H-RAS* *N-RAS*	Point mutation Point mutation Point mutation	Colon, lung, and pancreatic tumors Bladder and kidney tumors Melanomas, hematologic malignancies
Nonreceptor tyrosine kinase	*ABL*	Translocation	Chronic myeloid leukemia Acute lymphoblastic leukemia
RAS signal transduction	*BRAF*	Point mutation	Melanomas
WNT signal transduction	β-*catenin*	Point mutation Overexpression	Hepatoblastomas, hepatocellular carcinoma
Nuclear Regulatory Proteins			
Transcriptional activators	*C-MYC* *N-MYC* *L-MYC*	Translocation Amplification Amplification	Burkitt lymphoma Neuroblastoma, small cell carcinoma of lung Small cell carcinoma of lung
Cell-Cycle Regulators			
Cyclins	*CYCLIN D* *CYCLIN E*	Translocation Amplification Overexpression	Mantle cell lymphoma Breast and esophageal cancers Breast cancer
Cyclin-dependent kinase	*CDK4*	Amplification or point mutation	Glioblastoma, melanoma, sarcoma


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

RAS Oncogene

- 15-20% of all human cancers have a RAS mutation
- Normally, RAS is activated by receptors to exchange GDP for GTP
- Activated RAS returns to ground state by its intrinsic GTPase activity
- GTPase activating proteins (GAPs) augment this process[1000 fold]
- •Mutant forms of RAS bind GAP but their GTPase activity is not augmented
- K-ras-colon, pancreatic,cholangioca
- H-ras-bladder ca
- N-ras –haematological tus
- Cell cycle regulation –cyclins
- Anti –ras therapy

Oncogenes, Oncoproteins: Nonreceptor tyrosine kinase

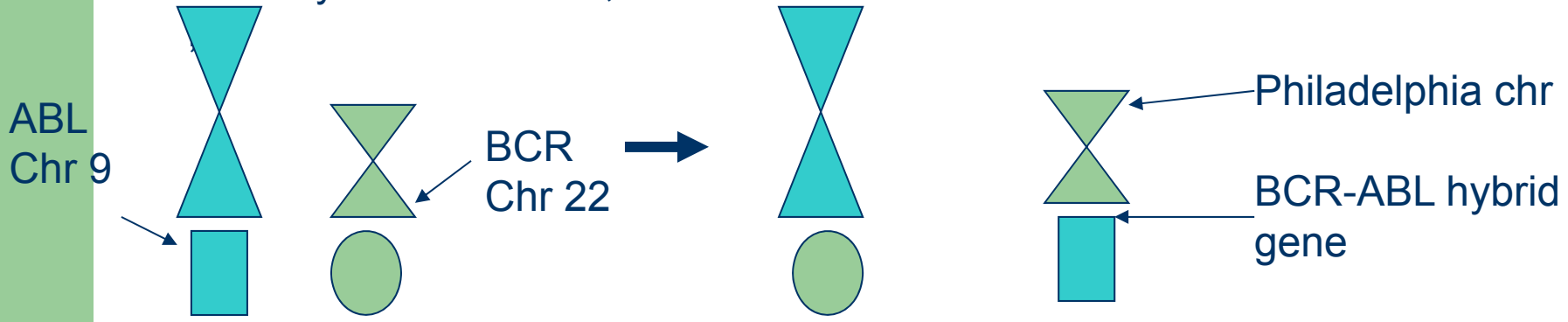
Tyrosine kinase in the signal transduction pathways regulating cell growth

ABL protooncogene product with TK action

Reciprocal translocation of Chr 9 (c-ABL) to chr 22 (BCR),

BCR-ABL protein with unrestrictive tyrosine kinase activity

Chronic myeloid leukemia,ALL



Oncogenes, Oncoproteins: Transcription factors

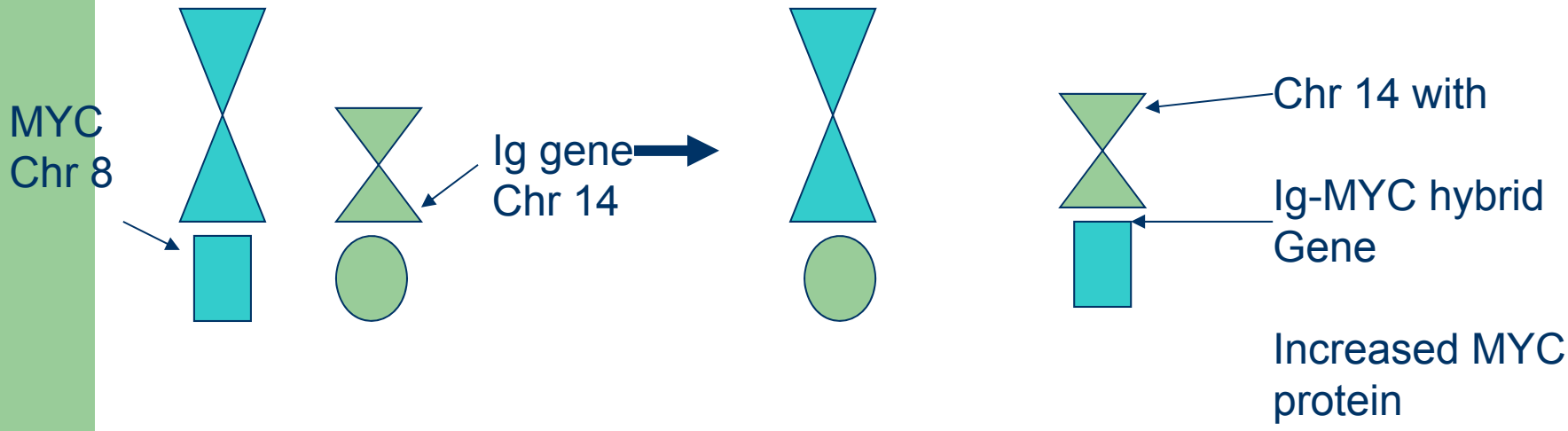
C-MYC, C-FOS, C-JUN

MYC is most common mutated

C-MYC (chr 8) translocated to chr 14 (Ig gene) increased MYC protein

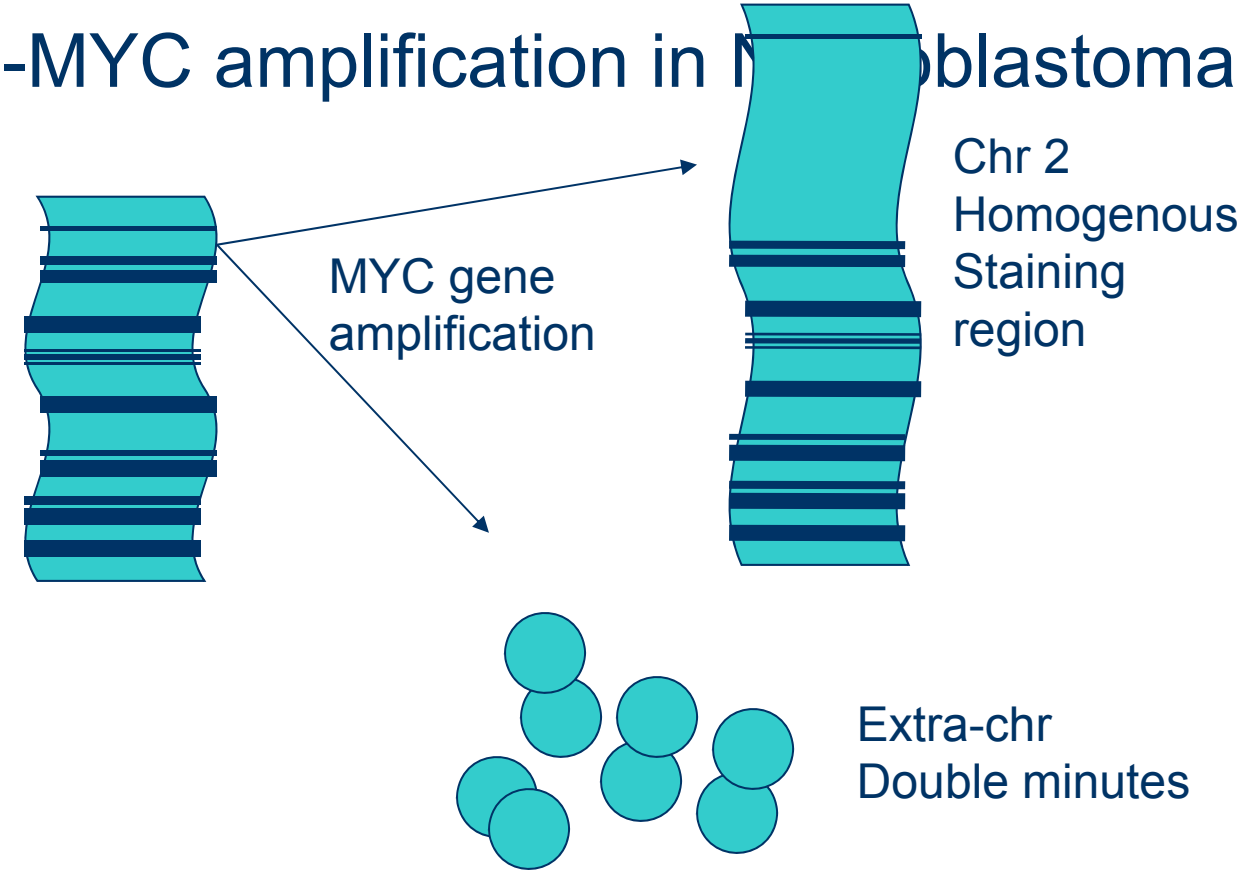
Burkitt's lymphoma

C-MYC amplified in colon, breast CA; L-MYC amplification small cell CA lung



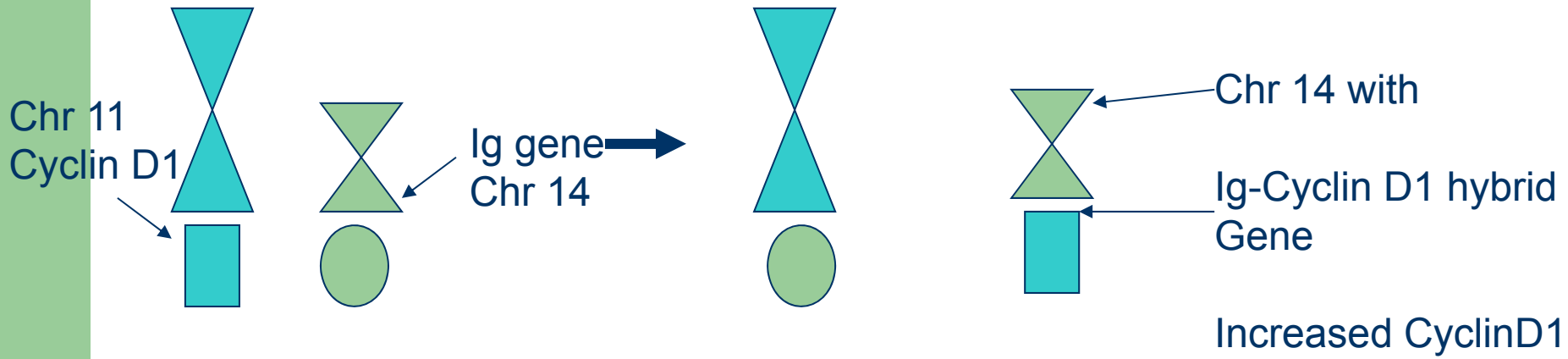
Oncogenes, Oncoproteins: Transcription factors

N-MYC amplification in N[illegible]blastoma



Oncogenes, Oncoproteins: cyclins, CDKs

Cyclin D gene overexpressed
Breast, esophagus & liver CA
Cyclin E gene overexpressed in breast CA
CDK4 gene amplification in GBM & sarcomas
Lymphomas
Mantle cell lymphoma



Insensitivity to Growth Inhibitory Signals:

Tumor Suppressor Genes

- Failure of growth inhibition is one of the fundamental alterations in the process of carcinogenesis.
- The proteins that apply brakes to cell proliferation are the products of tumor suppressor genes .
- Misnomer

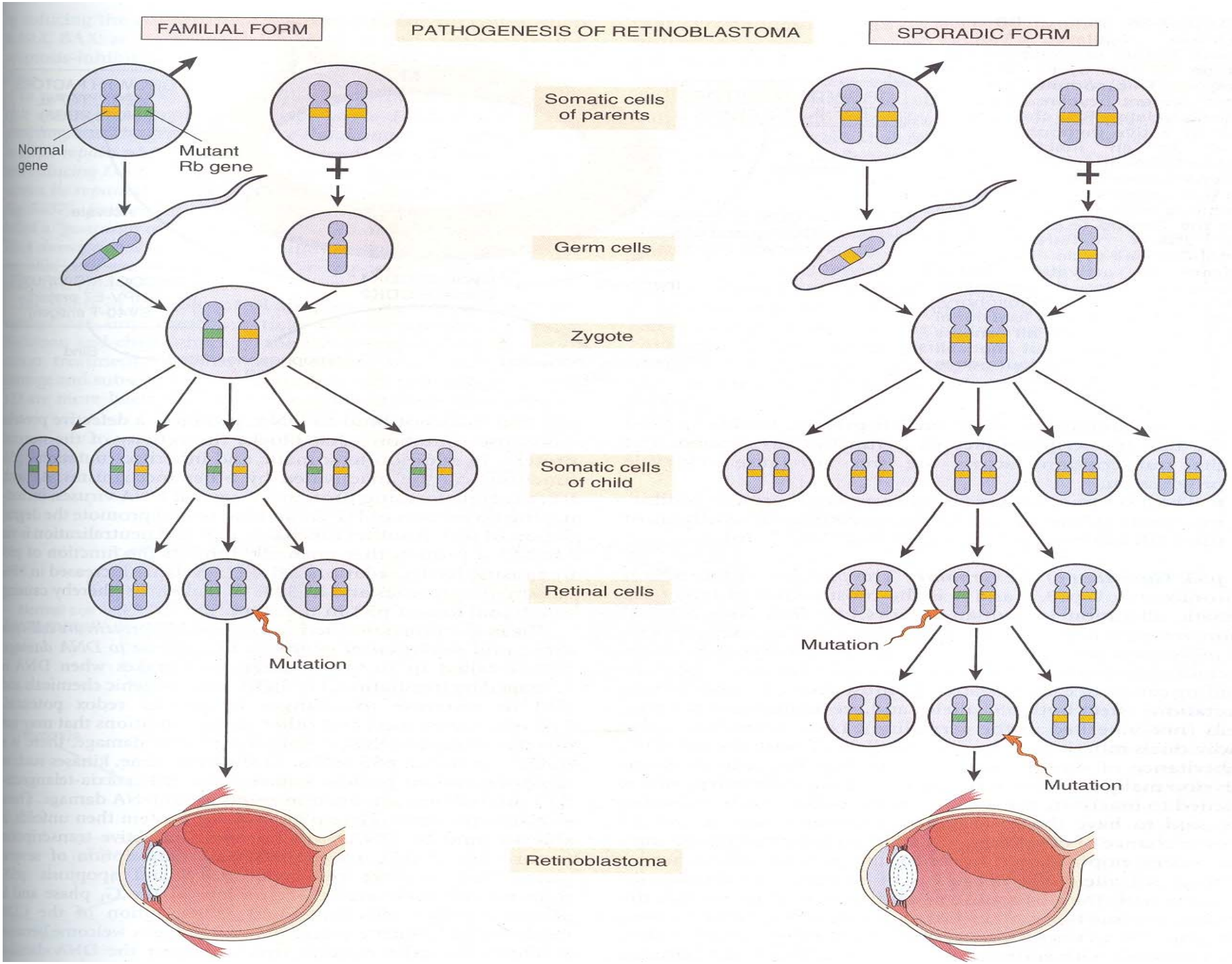
TABLE 7–9 Selected Tumor Suppressor Genes Involved in Human Neoplasms

Subcellular Location	Gene	Function	Tumors Associated with Somatic Mutations	Tumors Associated with Inherited Mutations
Cell surface	*TGF-β receptor*	Growth inhibition	Carcinomas of colon	Unknown
	E-cadherin	Cell adhesion	Carcinoma of stomach	Familial gastric cancer
Inner aspect of plasma membrane	*NF-1*	Inhibition of RAS signal transduction and of p21 cell-cycle inhibitor	Neuroblastomas	Neurofibromatosis type 1 and sarcomas
Cytoskeleton	*NF-2*	Cytoskeletal stability	Schwannomas and meningiomas	Neurofibromatosis type 2, acoustic schwannomas and meningiomas
Cytosol	*APC/β-catenin*	Inhibition of signal transduction	Carcinomas of stomach, colon, pancreas; melanoma	Familial adenomatous polyposis coli/colon cancer
	PTEN	PI-3 kinase signal transduction	Endometrial and prostate cancers	Unknown
	SMAD 2 and *SMAD 4*	TGF-β signal transduction	Colon, pancreas tumors	Unknown
Nucleus	*RB*	Regulation of cell cycle	Retinoblastoma; osteosarcoma carcinomas of breast, colon, lung	Retinoblastomas, osteosarcoma
	p53	Cell-cycle arrest and apoptosis in response to DNA damage	Most human cancers	Li-Fraumeni syndrome; multiple carcinomas and sarcomas
	WT-1	Nuclear transcription	Wilms tumor	Wilms tumor
	p16 (INK4a)	Regulation of cell cycle by inhibition of cyclin-dependent kinases	Pancreatic, breast, and esophageal cancers	Malignant melanoma
	BRCA-1 and *BRCA-2*	DNA repair	Unknown	Carcinomas of female breast and ovary; carcinomas of male breast
	KLF6	Transcription factor	Prostate	Unknown

Tumor suppressor genes

- Normally serve to inhibit cell proliferation
- First recognized in retinoblastoma, rare pediatric tumor of the eye
- RB ---tumor suppressor gene is a nuclear phosphoprotein that regulates cell cycle

- Knudson [Two-hit] Hypothesis of oncogenesis
- Loss of heterozygosity [LOH]
- Products of Tumor suppressor genes—cell cycle control,regulation of apotosis,growth and survival
- Functions-transcription factors, cell cycle inhibitors, signal transduction molecules, cell surface receptors, regulators of cell response to DNA damage


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

Tumor suppressor genes

- RB protein hypoPO4 binds E2F
- Mutation---RB absent or deficient binding E2F
- Unrestrained E2F function;
- Unchecked entry of cell from G1-S phase
- Retinoblastoma, osteosarcoma, Other tumors
- 40% familial (inherit AD one defective (mutated) copy of RB gene at chr13q14),LOH for this locus---both RB genes mutated & so lack of any functional RB protein---unrestrained E2F function
- 60% sporadic (both copies/ alleles of RB locus acquired mutation)
- Other tumors have mutation of genes controlling the RBPO4 & most of cancers have at least one of (cyclin, CDK, RB & p16INK4a) genes mutated
- DNA viruses-HPV

p53: Guardian of Genome

- Both copies of genes mutated--- acquried
- >50% cancers have p53 mutation
- One copy of mutated p53 gene may be inherited (Li-Fraumeni syndrome) & other mutation acquired. 25 fold increased risk by 50 yrs

  Sarcomas, breast CA, leukemia, brain tumor

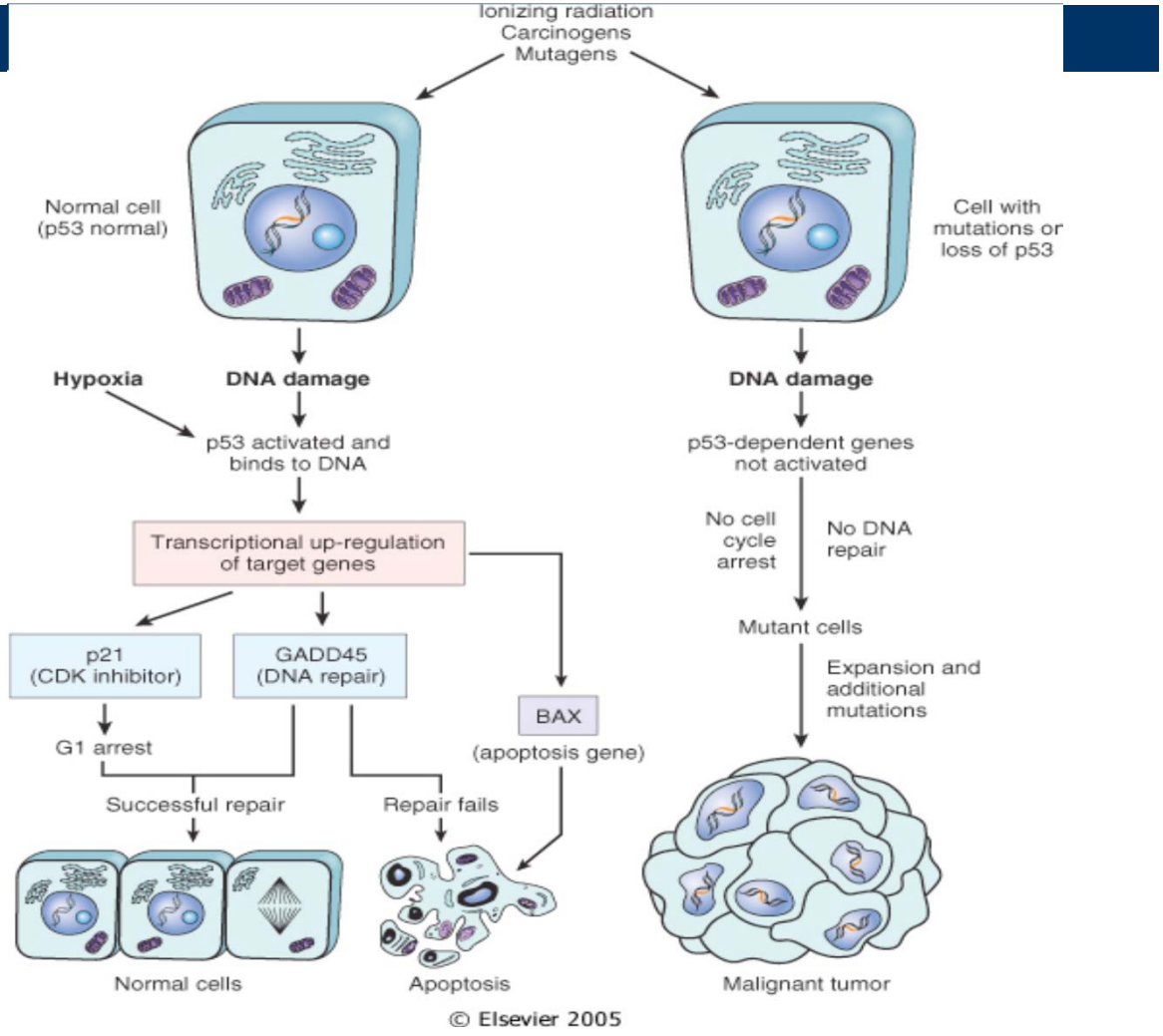
- Gatekeeper
- Molecular policeman

- Major function: Cell-cycle arrest and initiation of apoptosis in response to DNA damage.
- p53-induced cell-cycle arrest occurs late in the G1 phase and is caused by the p53-dependent transcription of the CDK inhibitor p21.
- If the DNA damage can not be successfully repaired, normal p53, as a last effort, sends the cell to the graveyard by inducing the activation of apoptosis-inducing genes, such as BAX
- Loss of p53 results in DNA damage unrepaired, mutations fixed in dividing cells, and eventually malignant transformation

Tumor suppressor genes: P53

- DNA damage---DNA dependent Kinases & Ataxia telangiectasia Mutated (ATM) proteins activated---PO4 to P53—unfolds---binds DNA---active transcription factor----p21(CDK inhibitor ---
- GADD45 (DNA repair)
- unrepairable damage ---BAX (apoptosis promotion by inhibition of the apoptosis inhibitor)
- Mutation---abnormal p53---no binding DNA---binding/blocking normal p53
- Homozygous loss of p53-- DNA damage unrepaired, mutations getting fixed, cell cycle goes unchecked—malignancy

Role of p53 in Maintaining the Integrity of Genome



Tumor suppressor genes:P53

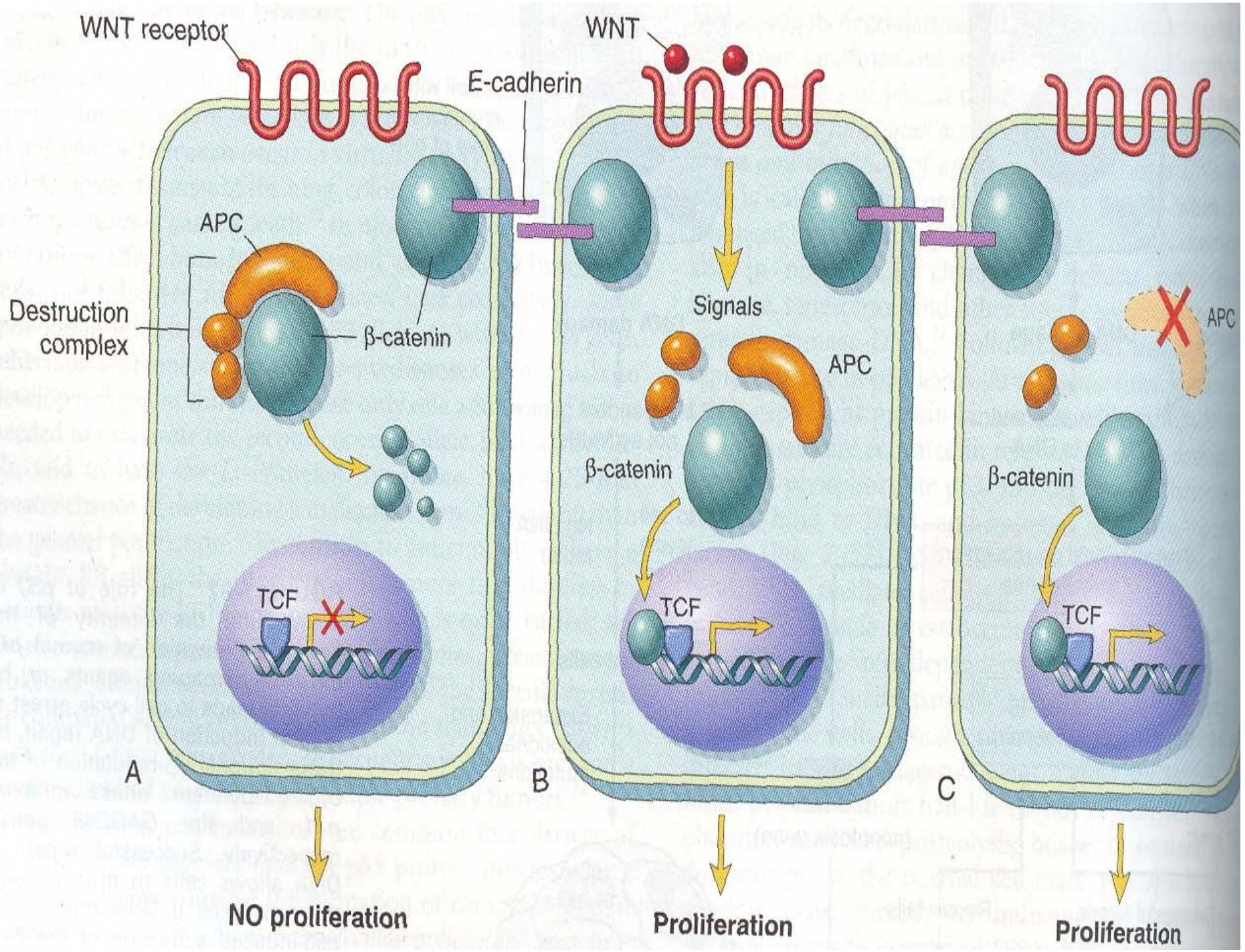
- E6 HPV protein of HPV binds degrades p53
- MDM2 levels (Degrades p53) increased in sarcomas & leukemias
- Radiotherapy & chemotherapy damage DNA induce apoptosis
- Tumor cells with defective p53 less likely respond
- Tumor cells with normal p53 likely respond
- Therapeutic enhancing p53 levels or killing p53 deficient tumor cells
- Partially homologous p63 & p73 proteins

Tumor suppressor genes

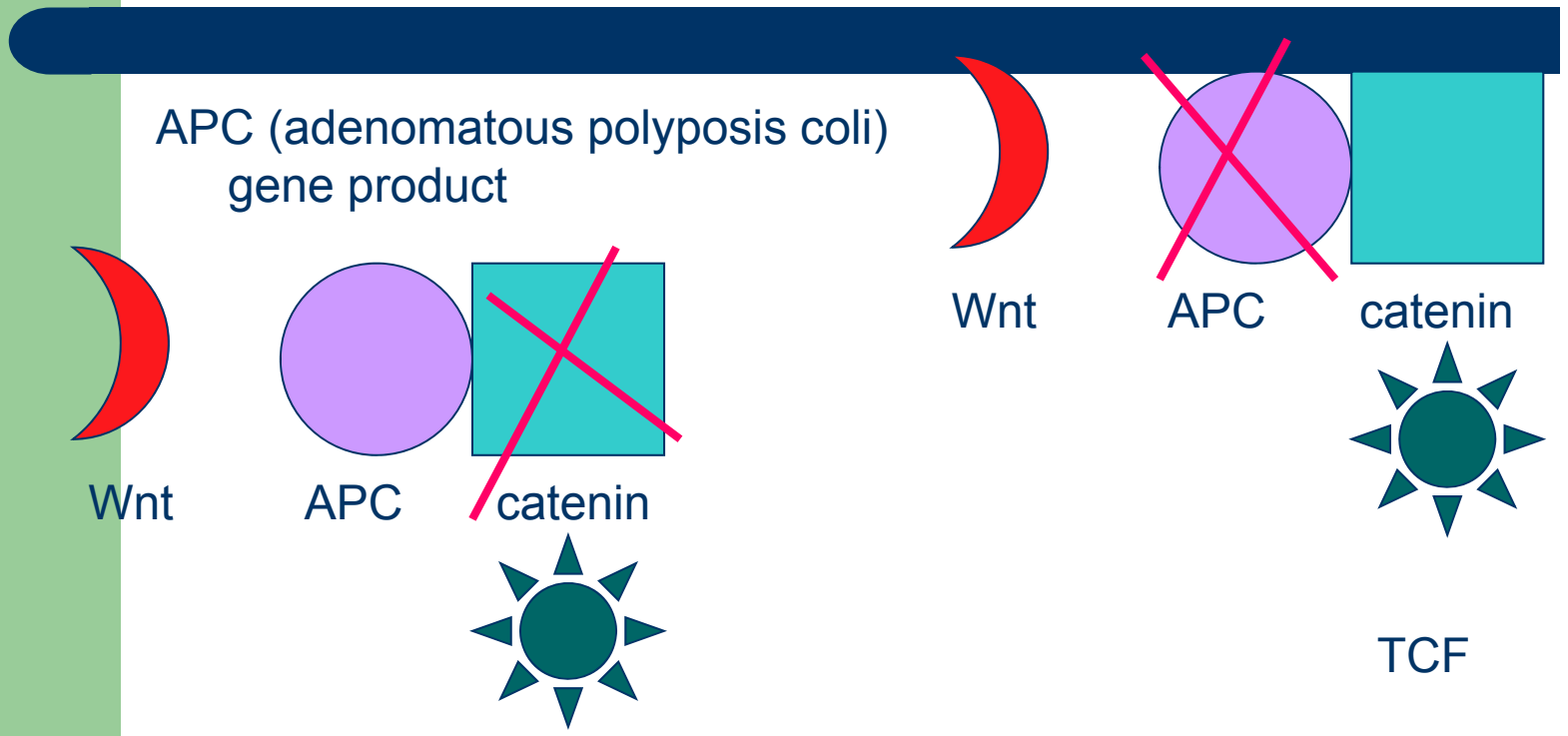
APC gene both copies inactivated for adenoma formation & in other colon tumors HNPCC

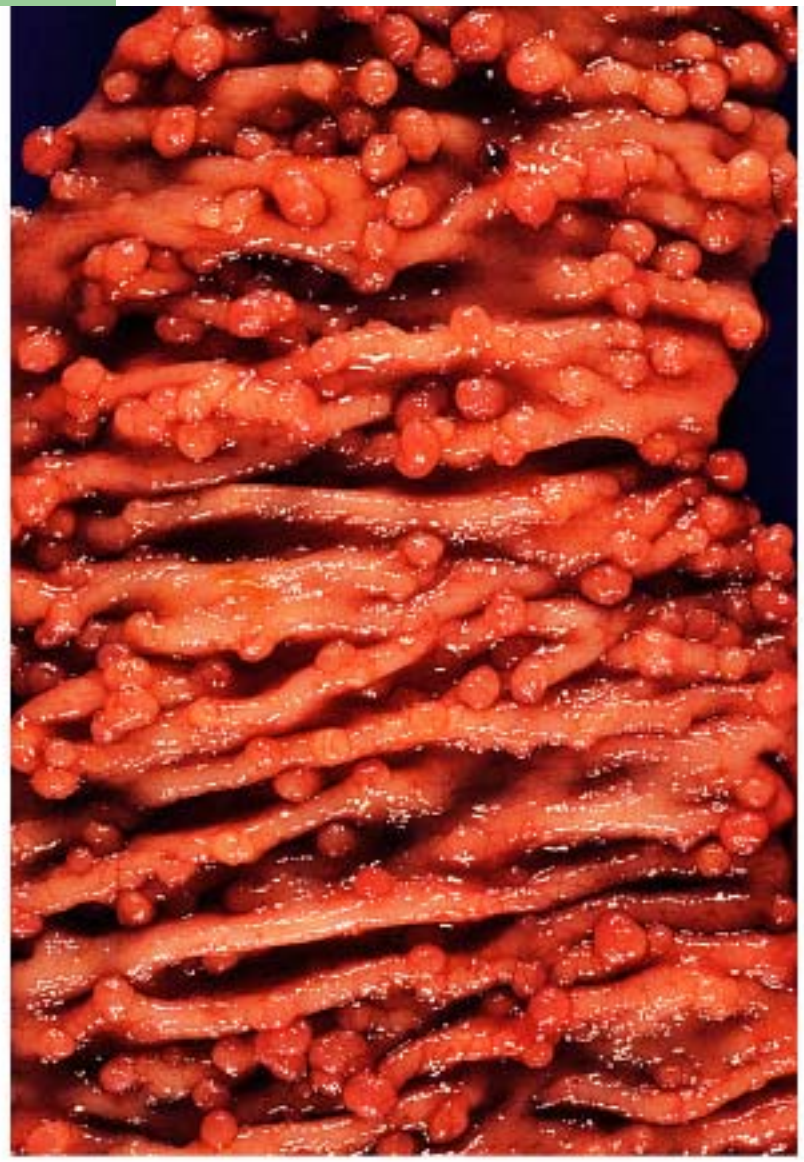
Thousands of adenomatous polyps late teens/20s (familial adenomatous polyposis-one mutation inherited); one or more malignant degeneration CA by additional mutations

β-Catenin: hepatoblastoma (50%)& HCC(20%)


WNT receptor
E-cadherin
WNT
APC
Destruction complex
β-catenin
Signals
APC
APC
β-catenin
β-catenin
TCF
TCF
TCF
A
B
C
NO proliferation
Proliferation
Proliferation

Tumor suppressor genes



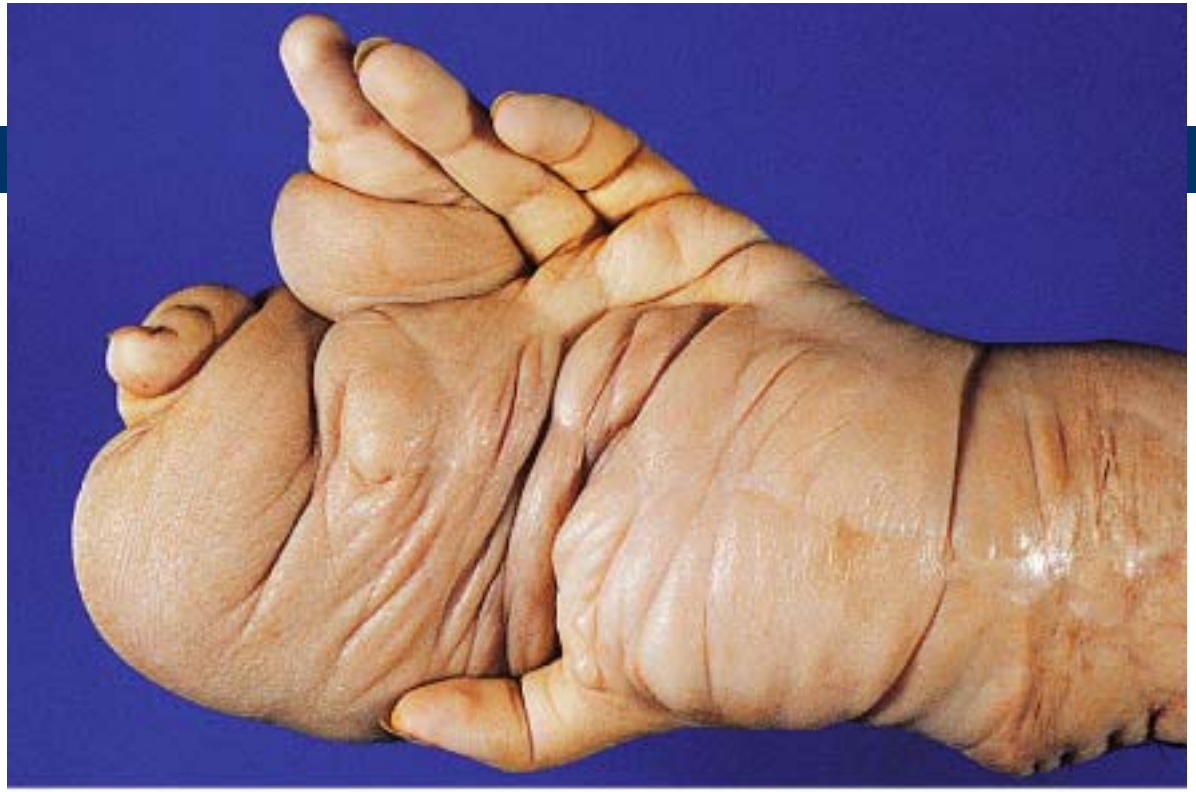


Tumor suppressor genes

TGF B:HNPCC-Ca colon Gastric ca, sporadic colon ca

NF1[17q]: benign neurofibromas (plexiform), MPNST
Neurofibromin-GTPase activating protein (GAP) for RAS deactivation

NF-2[22q]:Merlin—R.B.C. memb. Protein 4.1—actin, CD44
VHL[3p]: von hippel lindau protein (ubiquitin ligases)---acts on HIF—transcription of VEGF
Lack degradation of HIF, VEGF
RCC, Pheochromocytoma, Hemangioblastoma,Retinal angiomas,renal cysts



WT1[11p13]: involved in renal and gonadal genesis---- wilms tumor

PTEN[10q](Phophatase & Tensin homologue)-cell cycle arrest and apoptosis p27
Endometrial CA, GBM

INK4a/ARF: 20%melanomas, SCC, PANCREATIC Adenoca
cervical cancer--hypermethylation
KLF-6— T.F.—target genes-TGF &TGFR . INHIBITS PROLIFERATION by p21
Prostatic ca

PATCH[Patched] --Patched hedgehog family 20%Gorlin syndrome [naevoid basal cell ca]- TRF

CADHERINS

- PATCH[Patched] --Patched hedgehog family

  TGF-β,PDGF-R

  Gorlin syndrome [naevoid basal cell ca]- TRF

  - 20-50%SPORADIC basal cell ca
- CADHERINS
  - Ca oesophagus,breast,ovary,colon,prostate
  - Familial gastric ca

Apoptosis associated genes

BCL2 increased expression inhibits apoptosis

P53 decreased expression decreases BAX protein (BAX promotes apoptosis)

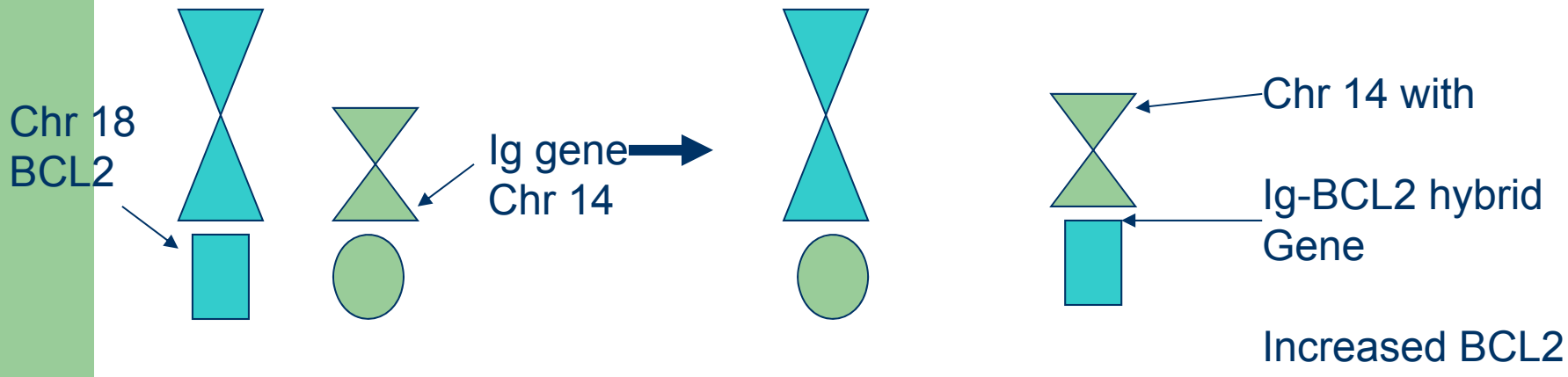
PTEN decreased expression decreases apoptosis.

1Apoptosis associated genes

Follicular lymphoma

BCL2--- decreased apoptosis--- reduced cell death--- B lymphocyte accumulation- lymphadenopathy

Increased cell life but not explosive cell proliferation.



DNA Repair genes

Mismatch repair genes

NER genes

Homologous recombination

Why the patients of Hereditary non polyposis colon carcinoma HNPCC syndrome develop early colon cancers

why genetic study of Microsatellites is significant in such patients.

DNA Repair genes

DNA replication mistakes (A—G, C---T),

Checked & corrected by Mismatch repair proteins

(MMR genes:MSH2, MLH1, PMS & PMS2 defective in HNPCC syndrome; one defective copy inherited other copy acquired)

Defective repair--- accumulation of DNA changes, mutations in the protooncogenes & tumor suppressor genes

DNA Repair genes

- Microsatellites are the tandem repeats of 1-6 nucleotides in the genome
- Due to accumulation of the DNA mistakes the microatellites vary in length markedly (microsatellite instability) which is marker for the defective mismatch repair genes
- Endometrial cancer, ovarian CA increased in the HNPCC
- TGF-β receptor, β-catenin pathway, BAX gene usually mutated in HNPCC
- Mismatch repair genes usually mutated in sporadic cancers(15% colon CA)

DNA Repair genes

NER genes

Why patients with xeroderma pigmentosum have increased predisposition of developing the skin cancers

DNA Repair genes

UV-A (320-400nm)

UV-B (280-320nm)

UV-C(200-280nm)

Radiation damage muation in p53 & RAS genes (skin CA)

Type of radiation: UV-C highly mutagenic but filtered out by ozone

Intensity of exposure (duration)

Quantity of light-absorbing melanin

DNA Repair genes

Pyrimidine dimers formation due to UV-B rays (280-320nm) repaired by the Nucleotide excision repair NER proteins

In XP NER genes are defective DNA changes accumulate

skin degenerative changes

cancers result from the accumulation of the mutated protooncogenes & tumor suppressor genes

DNA Repair genes

Homologus recombination repair

Why the patients with ataxia-telangiectasia, Bloom syndrome are prone to develop neoplasia

DNA Repair genes

- Proteins responsible for sensing & repairing the homologus recombination of DNA when it is damaged by the Ionizing radiations (x-rays, radioactive radiations/ partculate) or reactive oxygen species(ROS) are defective
- Ataxia telangiectasia (ATM-protein kinase---p53 stimulation does not occur & DNA damage/ changes accumulates---mutated oncogenes)
- ATM heterozygous 1% population at risk of radiation damage
- Bloom syndrome (BLM-helicase)

DNA Repair genes

BRCA-1, BRCA-2 genes defective & mutations in 80% familial breast CA & Ovarian CA

BRCA-1: breast & Ovarian CA,prostatic ca, colon ca

BRCA-2 male breast ca, melanomas ,pancreatic ca

Fanconi anemia FANCD1gene

Proteins usually involved in the repair of DNA damage (radiation/ ROS) by homologus recombination.

Limitless Replicative Potential:Telomerase

Telomerase enzyme is detected in 90% of tumors

explain the significance of this finding

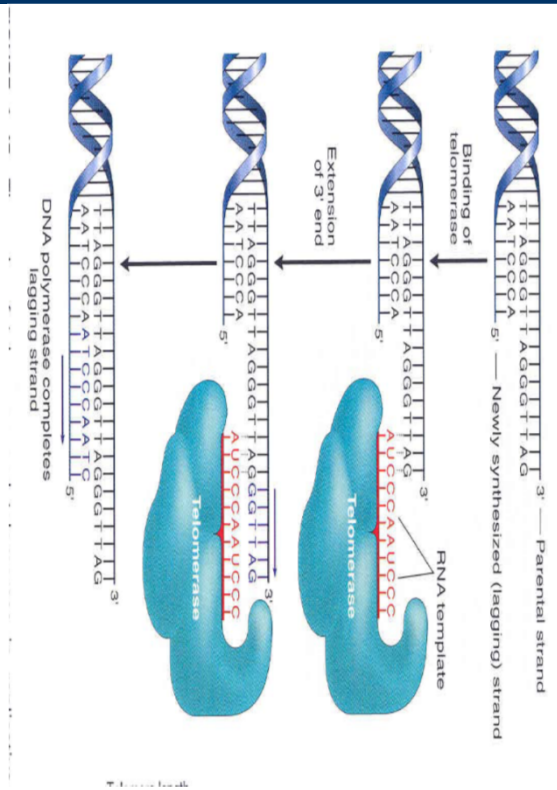
Replicative Senescence

- Normal cells, after a fixed number of divisions, become arrested in a terminally nondividing state known as replicative senescence.
- With each cell division there is some shortening of specialized structures, called telomeres, at the ends of chromosomes

Once the telomeres are shortened beyond a certain point, the loss of telomere function leads to activation of p53-dependent cell-cycle checkpoints, causing proliferative arrest or apoptosis. Thus, telomere shortening functions as a clock that counts cell divisions.

- Cancer cells must find a way to prevent telomere shortening

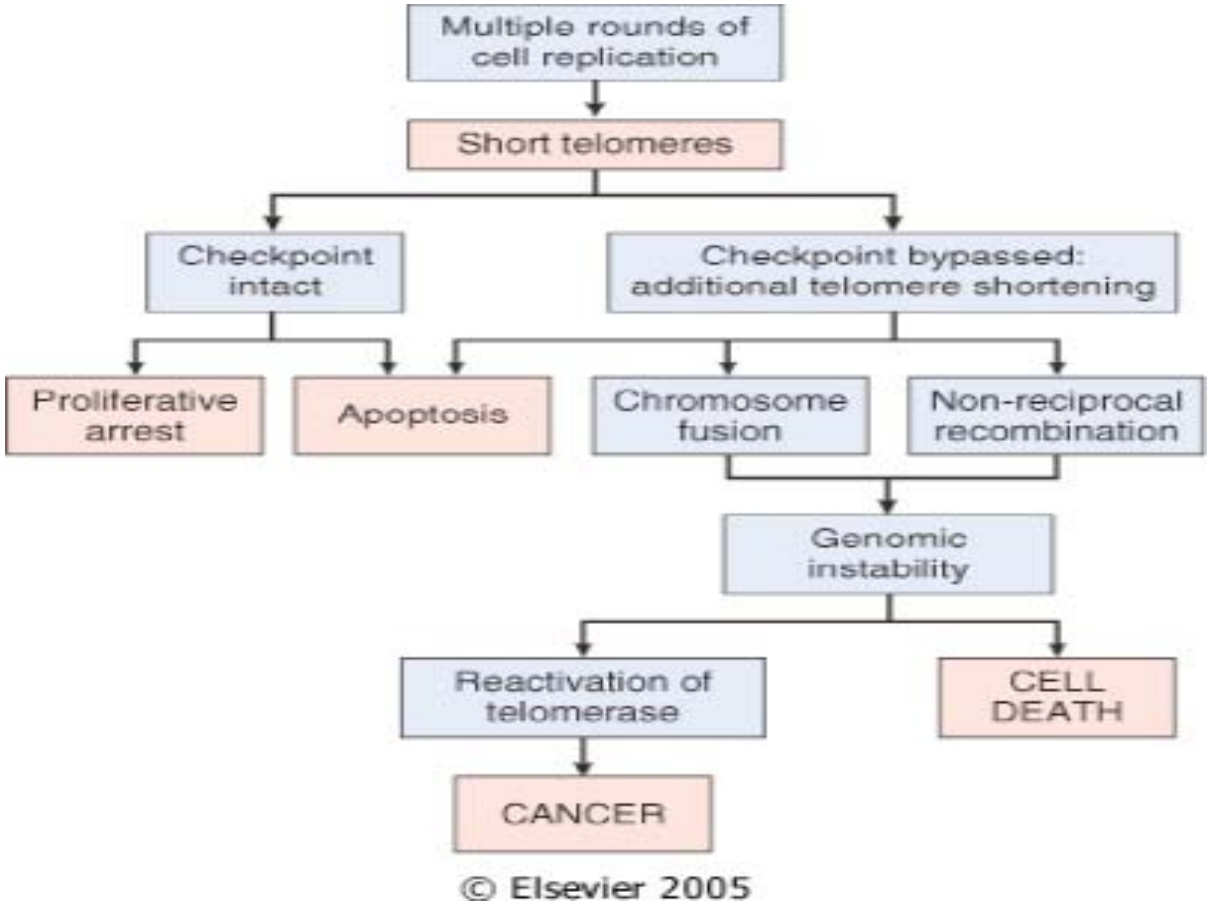
Replicative Senescence



Limitless Replicative Potential

- Telomerase activity and maintenance of telomere length are essential for the maintenance of replicative potential in cancer cells.
- Transformed cells may have defects in cell-cycle checkpoints,allowing for critical telomere shortening in dividing cells.. These cells may die by apoptosis or survive with chromosome defects that cause genomic instability

Replicative Senescence

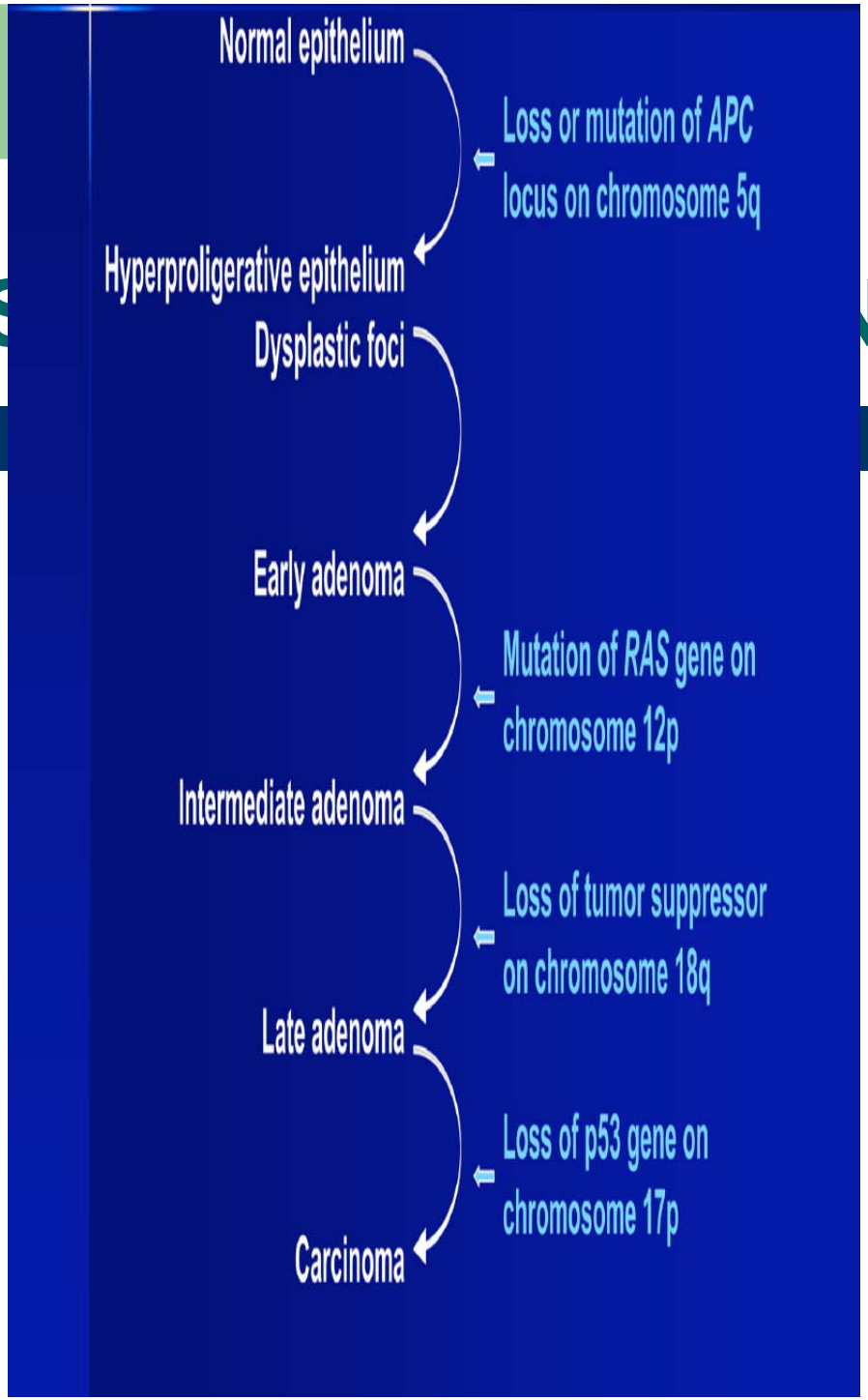


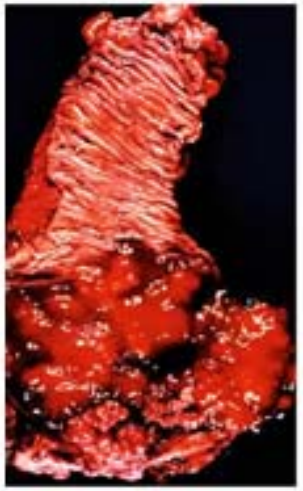
STEPWISE ACCUMULATION

- Cancer is associated with a progressive accumulation of genetic and epigenetic abnormalities.
- These defects lead to disruption of cell growth, cell death, apoptosis, differentiation, DNA repair, and other critical pathways.
- The molecular events in the development of familial adenomatous polyposis provide a good example of the genetic evolution that underlies progressive morphologic changes

- Multiple steps
- Sequence not sure in many cancers
- Step for Initiation of cancer may be different from the step of cancer progression
- Gatekeeper genes: directly regulate the cell growth—protooncogenes (MYC, RAS) & tumor suppressor genes p53 (related p14ARF, MDM2 genes)& RB (relatedINK4, cyclinD & kinases) the principal two pathways
- Caretaker genes: regulate the DNA repair
- Germline mutation of either predisposes to cancer
- More with gatekeeper genes
- Hypothesis: DNA repair defect is initial event in very early stage of cancer development

STEPWIS N


Normal epithelium
Loss or mutation of APC locus on chromosome 5q
Hyperproliferative epithelium
Dysplastic foci
Early adenoma
Mutation of RAS gene on chromosome 12p
Intermediate adenoma
Loss of tumor suppressor on chromosome 18q
Late adenoma
Loss of p53 gene on chromosome 17p
Carcinoma



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- Caretaker genes: regulate the DNA repair
- Germline mutation of either predisposes to cancer
- More with gatekeeper gene
- ---widespread mutation & genetic instability in neoplastic cells further susceptible to additional mutations (cancer cells with mutator profile)
- Tumor grows—aggressive—greater malignant potential (Tumor progression

MECHANISMS OF CARCINOGENESIS

- Chemical carcinogenesis
- Radiation carcinogenesis
- Viral oncogenesis

Chemical Carcinogenesis

Initiation
Promotion

Chemical carcinogens INITIATION

- Initiation results from exposure of cells to sufficient dose of a carcinogenic agent (initiator); an initiated cell is altered, making it potentially capable of giving rise to a tumor. Initiation alone, however, is not sufficient for tumor formation
- Initiation causes permanent DNA damage (mutations). It is therefore rapid, irreversible and has “memory”. Tumors are produced even if the application of the promoting agent is delayed for several months after a single application of the initiator

Chemical Carcinogens PROMOTION

- Promoters can induce tumors in initiated cells,but they are nontumorigenic by themselves
- Tumors do not result when the promoting agent is applied before, rather than after, the initiating agent
- in contrast to the effects of initiators, the cellular changes resulting from the application of promoters do not affect DNA directly & reversible

1. Initiation:

- Initiation involves a irreversible changes in DNA -a heritable change
- Initiated cells (altered cells) may reproduce faster,or fail to undergo apoptosis normally
- Initiation may involve more than one genetic alteration before a cell has the potential to become malignant
- Initiation itself is believed to involve at least 2 steps
- *Molecular lesion in a target cell*
- *The fixation of such lesions by a round of cell proliferation*

2. Promotion: Expansion of precursor populations

- The process by which an initiated tissue is induced to develop focal proliferative lesion
- Promotion alone does not lead to malignant transformation.
- Promotion must occur after initiation, or during stepwise initiation.
- Promotion is reversible.
- Promotion most likely does not involve genetic mutation. It can be viewed as an epigenetic change involving altered gene expression without a change in the DNA sequence

- Because malignant transformation results from mutations---most chemical carcinogens are mutagenic.
- Indeed, all direct and ultimate carcinogens contain highly reactive electrophile groups that form chemical adducts with DNA, as well as with proteins and RNA.

electrophile---reacts with DNA (nucleophile)---**Adduct**(addition formation)---DNA damage---Mutation

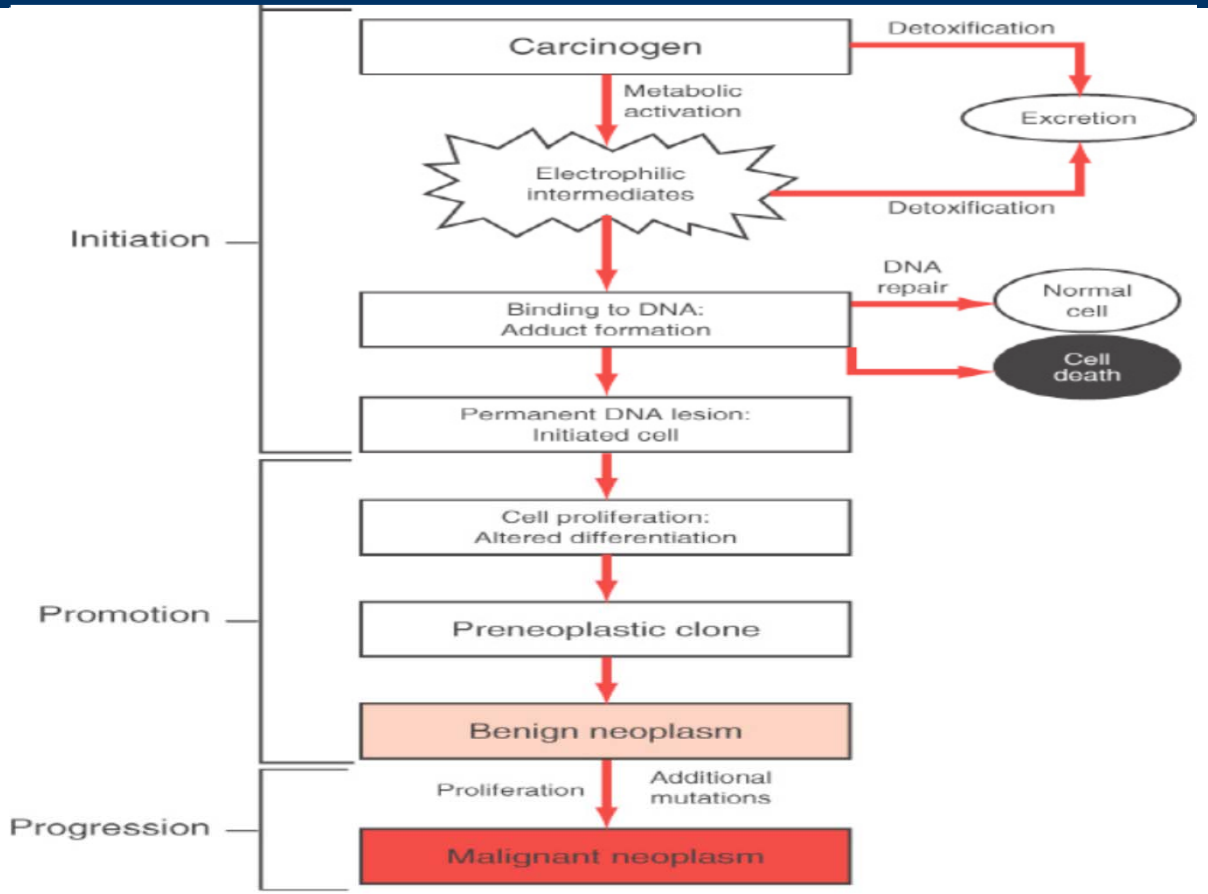
---?cell death? DNA repair ?**Tumor Initiation**

This initiated cell must divide once for the DNA change to get fixed (Irreversible) in the cell genome

Further proliferation of the initiated cell is augmented by acetaldehyde & phenol (Promoters) in the cigarette smoke (Tumor Promotion) also by the toxic damage & reactive proliferation

Proliferation of the Initiated cell with mutation is accompanied by further predisposition & accumulation of mutations **(Tumor Promotion**

Events in chemical carcinogenesis



(Modified from Kumar V, Abbas A, Fausto N: Robbins & Cotran pathologic basis of disease, ed 7, Philadelphia, 2005, Saunders.)

Chemical Carcinogens

- Carcinogen (Initiator) directly acting on DNA or metabolized first from procarcinogen to active form
- Most carcinogens are metabolic products & predisposition to cancer also depend upon the metabolizing enzyme activity
- 10% population highly inducible form of p-450 CYP1A1 (metabolizes benzopyrene) 7x increased risk of lung CA from light smoking
- 50% population have deleted gene for glutathione S transferase (enzyme for detoxifying benzopyrene) increased risk of lung CA
- Few of chemical carcinogens alkylating agents (cyclophosphamide, chlorombucil, Busulphan), & Acylating agents do not require metabolic activation

- Although any gene may be the target of chemical carcinogens, the commonly mutated oncogenes and tumor suppressors, such as RAS and p53, are important targets of chemical carcinogens.
- MOLECULAR FINGERPRINT
- Intiators usually attack the DNA at specific sites (aflatoxin b1 mutation at codon G:C—T:A 249Ser p53 gene)

- METABOLIC INACTIVATION
- Ames TEST—Mutagenic potential

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Chemical Carcinogens

- Direct-acting compounds – do not require chemical transformation for their carcinogenicity

- Indirect-acting compounds (procarcinogens) – require metabolic conversion in vivo to produce ultimate carcinogens capable of transforming cells

Chemical Carcinogens

Direct-Acting Carcinogens

Alkylating Agents

Diepoxybutane

Dimethyl sulfate

□-Propiolactone

Anticancer drugs(cyclophosphamide, chlorambucil, nitrosoureas, and others)

Acylating Agents

Dimethylcarbamyl chloride

1-Acetyl-imidazole

Chemical Carcinogens

Procarcinogens That Require Metabolic Activation

- ***Polycyclic and Heterocyclic Aromatic Hydrocarbons***
- Benz(a)anthracene
- 3-Methylcholanthrene
- Dibenz(a,h)anthracene
- Benzo(a)pyrene
- 7,12-Dimethylbenz(a)anthracene

Chemical Carcinogens

- ***Aromatic Amines, Amides, Azo Dyes***
- 2-Naphthylamine (□-naphthylamine)
  Benzidine
- 2-acetylaminofluorene
- Dimethylaminoazobenzene (butter yellow)

Chemical Carcinogens

- ***Natural Plant and Microbial Products***
- Griseofulvin
- Aflatoxin B
- Betel nuts
- ***Others***
- Insecticides, fungicides
- Vinyl chloride, nickel, chromium
- Nitrosamine and amides

- Some of the most potent indirect chemical carcinogens-the polycyclic hydrocarbons-are present in fossil fuels. For example, benzo[a]pyrene and other carcinogens are formed in the high-temperature combustion of tobacco in cigarette smoking. These products are implicated in the causation of lung cancer in cigarette smokers.
- Polycyclic hydrocarbons may also be produced from animal fats during the process of broiling meats and are present in smoked meats and fish..

- Few of chemical carcinogens alkylating agents (cyclophosphamide, chlorombucil, Busulphan), & Acylating agents do not require metabolic activation

Chemical Carcinogens

Other examples:

Polycyclic aromatic hydrocarbons in broiled & smoked animal meat/ fish GIT CA

Dye industry (amines /azo dyes-2-naphthylamine) bladder Ca

Aspergillus infection (certain strains) of stored food grains in China & south Africa Aflatoxin B1---hepatocellular carcinoma

Nitrosamines formed by gut bacteria from nitrates & nitrosable amines in food preservatives---Gastric CA

Asbestos---Mesothelioma & Bronchogenic CA

Vinyl chloride (PVC)---liver angiosarcoma

Arsenic---skin CA

Viral carcinogenesis

- HPV
- EBV
- KSHV
- HBV

HPV

- Among 70 genetic types of Human papilloma virus (HPV)
- 1,2,4,7 types are associated with the benign tumors (squamous papillomas of skin) atypes 16 & 18 are associated with the squamous cell carcinomas esp.

cervix

anogenital

Oral cavity

larynx

benign warts&low grade lesion—6&8

high grade lesion&invasive ca---16,18,31,33,35,51

- Benign tumors the viral DNA remains in episomal form in the cytoplasm
- Malignant tumors the viral DNA interrupted specifically at the E1/E2 of viral genome & is integrated with the host's DNA
- E2 normally represses transcription of E6 & E7 early viral protein; the E1/E2 disruption releases such repression & E6 & E7 proteins are formed in the host cells infected with HPV16 & 18

- E6 binds p53 & degrades it
- also activate Telomerase
- E7 binds RB protein & degrades it
- also inhibits p53 transcription
- also inhibits p21
- Cell cycle breaks released
- DNA damage is not repaired goes unchecked----- cancer

- HPV16, 18 & 31 E6 bind p53 with high affinity & degrade it
- HPV 6 & 11 bind p53 poorly & do not degrade it

- P53 polymorhic at aminoacid 72—arginine&proline

- HPV iinfection intiating event for Tumor initiation with more mutations---cancer
- Majority of HPV infections are cleared by the immune response only in few the infection causes the tumor intiation.
- (additional cofactors: smoking
  microbiological infections
  hormonal changes
  dietry factors

Epstein-Barr virus (EBV)

Epstein-Barr virus (EBV) infection is associated with B-cell lymphomas

Burkitt's lymphoma

B-cell NHL

Hodgkin's lymphoma

Nasophyrangeal CA

what mechanisms are involved in such causation?
What are the evidences of such association?

EBV—B lymphocytes (CD21)

Episomal infection,

Immortal B lymphocyte

Latent Membrane protein (LMP-1)---

---signaling pathway (NFkB & JAK/STAT)-----Promotes B cell proliferation & survival

EBNA-2

---Activates the LMP-1 expression & Cyclin D

--EBV ubiquitous infection

--Mostly asymptomatic

--Few Infectious mononucleosis (self limited)

Endemic Burkitt's lymphoma (central Africa/ New Guinea) 90 % of tumors contain EBV genome

100% pts have antibodies agst EBV

Such antibody titers are correlated with risk of BL.

- In the endemic areas cofactors (chronic malaria) favor sustained proliferation Immortal B-lymphocyte (EBV infected)---
- ---actively dividing cells----increased risk of mutation-----t (8;14)---c-myc activation---other mutations----release growth regulation----Burkitt's lymphoma

- Multiple CNS lymphomas
- Initially polyclonal population---Monoclonal population---tumors (lack of host immunity)

- Nasopharyngeal Ca
- 100% contain clonal EBV genome integration in tumor cells, China, Arctic, Africa
- EBV infection one step in the CA development other geographic factors ? Genetic, ?enviromental as cofactors in development of CA

HBV

- Hepatitis B virus strongly linked to hepatocellular carcinoma (China & Africa)
- -chronic tissue injury, regenerative Hepatic cells----- larger pool of dividing cells----prone to mutation (?spontaneous/?enviromental agents)
- HBx protein

  binds p53 (inhibits)

  Promotes transcription of Growth factors (ILGF)

Human T-cell leukemia virus type 1(HTLV-1)

- T-cell Lymphoma / Leukemia (Japan/ Caribbean)
- Infects T-lymphocytes & integrates with host's genome
- RNA virus (gag, pol, env & LTR regions +TAX gene)
- TAX protein promotes cell proliferation:

  -c-FOS gene
  -IL-2/ IL-2 receptor
  -myeloid CSF
  -inactivates p16INK4a
  -enhances cyclin D activation
  TAX protein leads to genomic instability:
  Interfere DNA repair, ATM checkpoints

Helicobacter pylori

- Helicobacter pylori infection—90%
- -Chronic gastritis, atrophy, metaplasia---- sustained epithelial proliferation (risk of mutation)

--Gastric ca ,Lymphoma(MALTOMA)

- -Hpylori protein immunogenic---T cells & B cells, lymphoid follicles in gastric mucosa
- Cag*A*,Vac*A*
- ----in few cases B cell Lymphoma (continuous proliferation t (11;18) MALT Lymphoma

effects of a tumor on host

- What are the local & hormonal effects of a tumor

Site specific mass effect (mechanical & functional compromise)

- GIT tumors: obstruction, rupture, Intussusception
- Respiratory tract tumors: obstruction, respiratory function loss,
- Oral cavity & upper aerodigestive tract tumors

--erosive destructive malignant growth/ pressure growth by benign tumor-----ulceration, secondary infection, bleeding

-Endocrine gland tumors

- Non-functional loss of endocrine function

Metastases

- functional endocrine tumors (usually well differentiated/ benign)

Acromegaly, hyperthyroidism, Hyperparathyroidism, hypoglycemia, Diabetes, Cushing syndrome

Cancer Cachexia

- *Many cancer patients suffer progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia, referred to as cachexia*.
- There is some correlation between the size and extent of spread of the cancer and the severity of the cachexia.

cachexia is not caused by the nutritional demands of the tumor.

current evidence indicates that cachexia results from the action of soluble factors such as cytokines produced by the tumor and the host rather than reduced food intake.

.

- In patients with cancer, calorie expenditure remains high, and basal metabolic rate is increased, despite reduced food intake. ----This is in contrast to the lower metabolic rate that occurs as an adaptational response in starvation.
- TNF produced by macrophages in response to tumor cells or by the tumor cells themselves mediates cachexia.
- TNF suppresses appetite

inhibits the action of lipoprotein lipase, inhibiting the release of free fatty acids from lipoproteins.

a protein-mobilizing factor called proteolysis-inducing factor, which causes breakdown of skeletal muscle proteins by the ubiquitin-proteosome pathway,

paraneoplastic syndrome

Symptom complex not attributable to local/ distant tumor spread or indigenous site hormone production

--10% of malignant tumors

-may be earliest tumor manifestation

-significant clinical problem & may be lethal

-mimic other disease (management problem)

Endocrinopathies

- Cushing syndrome

  ACTH or ACTH-like substance,P0MC

  Small-cell carcinoma of lung

  Pancreatic ca

  Neural tumors

- Syndrome of inappropriate antidiuretic hormone secretion

  Small-cell carcinoma of lung

  intracranial neoplasms

Antidiuretic hormone or atrial natriuretic hormone

- Hypercalcemia

` Parathyroid hormone-related protein, TGF-α, TNF, IL-1

Squamous cell carcinoma of lung

Breast carcinoma

Renal carcinoma

Adult T-cell leukemia/lymphoma

Ovarian carcinoma

- Hypoglycemia Fibrosarcoma Insulin or insulin-like substance

- Other mesenchymal sarcomas
- Hepatocellular carcinoma

- Hypoglycemia
  - Insulin or insulin-like substance
    - Fibrosarcoma
    - Other mesenchymal sarcomas
    - Hepatocellular carcinoma
-

- Carcinoid syndrome
- Serotonin, bradykin
- Bronchial adenoma (carcinoid)
- Pancreatic carcinoma
- Gastric carcinoma
- Polycythemia Erythropoietin
- Renal carcinoma
- Cerebellar hemangioma
- Hepatocellular carcinoma

Nerve and Muscle disorders

- Myasthenia
- Bronchogenic carcinoma --Immunological
- Disorders of the central and peripheral nervous systems Breast carcinoma

Dermatologic Disorder

- Acanthosis nigricans Gastric carcinoma Immunologic; secretion of epidermal growth fac
- Lung carcinoma
- Uterine carcinoma
- Dermatomyositis Bronchogenic, breast carcinoma Immunologic

- Osseous, Articular, and Soft-Tissue Changes

Hypertrophic osteoarthropathy and clubbing of the fingers

Bronchogenic carcinoma

- Vascular and Hematologic Changes

--Venous thrombosis (Trousseau phenomenon)

Pancreatic carcinoma

Bronchogenic carcinoma Tumor products (mucins that activate clotting

-- Nonbacterial thrombotic endocarditis --Advanced cancers ---Hypercoagulability

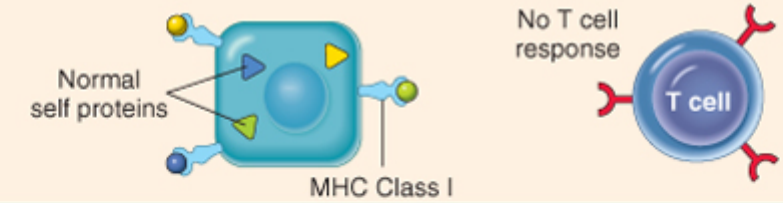
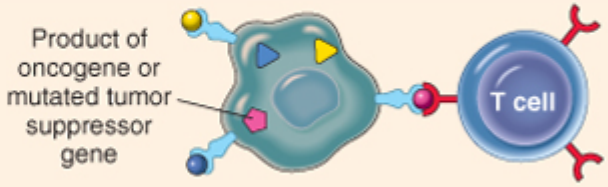
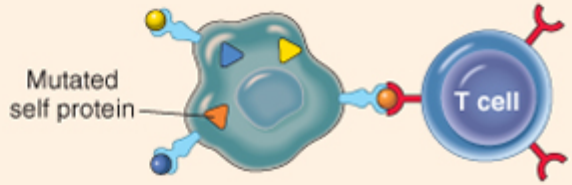
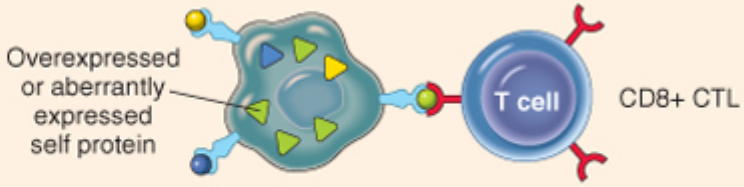
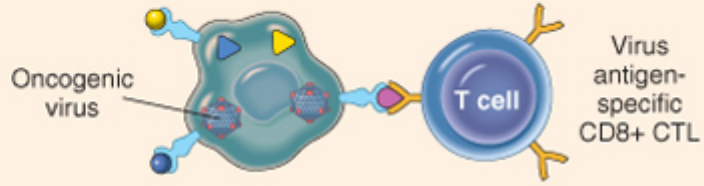
-- Anemia --Thymic neoplasms

- Nephrotic syndrome ----Tumor antigens, immune complex

Tumour immunity

TUMOUR Ags

Products of altered oncogene/ tumor suppressor gene
(altered p53, BCR-ABL, RAS proteins)
Products of other mutated genes (esp Radiation & Chemicals)
Overexpressed or aberrantly expressed proteins
(Tyrosinase in melanoma cells & cancer-testis family antigens-
MAGE in melanoma cells);GAGE,RAGE,BAGE
Proteins of oncogenic viruses (HPV & EBV)
Oncofetal antigens (AFP & CEA)
Altered cell surface glycolipids & **glycoproteins**
(Ganglioside GM2 GD2 GD3, CA125, CA 19.9, MUC-1)
Cell type specific differentiation antigens
(CD10, CD20, idiotypic determinants of surface immunoglobulin)

Normal host cell displaying multiple MHC-associated self antigens		EXAMPLES
Tumor cells expressing different types of tumor antigens		Oncogene products: mutated RAS, BCR/ABL fusion proteins Tumor suppressor gene products: mutated p53 protein
		Various mutant proteins in carcinogen or radiation, induced animal tumors; various mutated proteins in melanomas
		Overexpressed: tyrosinase, gp100, MART in melanomas Aberrantly expressed: cancer-testis antigens (MAGE, BAGE)
		Human papilloma virus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV-induced lymphoma

- What type of antitumor effector mechanisms exist

- **Cytotoxic lymphocytes** CD8+ T cells
  - MHC 1 antigen, wide variety Tumors
  - Esp. Viral induced Tumors (EBV & HPV)
  - Harvesting & expansion (in vitro) reinfusion
- **Natural killer lymphocytes** kill the tumor cells without prior sensitization, esp tumor cells with low MHC expression (In some tumors) IL2 activates; imunotherapy with in vitro expansion
- **Macrophages** activated by IFN γ from T cells & Natural killer cells
- **Antibodies** kill tumor cells by complement activation & antibody mediated cytotoxicity (by macrophages & NK cells)

- What is immune surveillance, what are the evidences that it exists, how tumor cells evade it

- Normal function of immune system is to survey the body for emerging malignant cells & to destroy them
- Increased cancer incidence in immunodeficient
- But mainly lymphoma (B cell immunoblastic)
- Lymphocytic infiltrate in the tumors
- Tumors mainly in immunocompetent
- (likely many must have been curbed & destroyed & the successful tumors develop ways to evade the immune system)

Mech. To evade immunity

- Selective outgrowth of antigenic negative Nonimmunogenic tumor cell variants
- Loss or reduced MHC molecule expression

  (evades killing by CTL but not by NK cells)
- Lack of costimulation

  MHC 1 with tumor antigen but no costmulatory molecule---t cells not stimulated or anergy or apoptosis

  (Autologous tumor cells with gene for costimulatory molecule---B7 or autologous APC wth tumor antigen expanded)

- Immunosuppression: chemicals, radiations, tumor products (TGFβ)
- Antigen masking by glycocalyx mucopolysacchrides
- Apoptosis of cytotoxic Lymphocytes

  (Fas ligand on tumor cells causes apoptosis of Fas receptor on T cells)

Lab. Diagnosis of cancer

1. What are the histologic methods used for the tumor diagnosis.

Incisional biopsy (Diagnosis of Tumor & Typing)

(part of tumor is cut & examined, before any definite tumor management planned)

- ✓ Skin biopsy, mucosal biopsy (Oronasal, genital)
- ✓ Laryngoscopic/ bronchoscopic biopsy for tumors of respiratory tract, transbronchial biopsy for tumors in lung parenchyma
- ✓ endoscopic biopsy GIT tumors
- ✓ Cystoscopic biopsy urinary bladder
- ✓ Trans uretheral resection of prostate (TURP)

Core Needle biopsy (Trucut needle biopsy)

Breast, prostate, liver, chest/ mediastinal, brain (burr hole), retroperitoneum

Excision specimen (biopsy) (Grading & Staging)

Skin & Soft tissue tumors

Appendicectomy

Cholecystectomy,

Colectomy

Mastectomy

Hysterectomy

Lobectomy

- Fixation 10 % foramalin (Formaldehyde sol.)
- Tissue Processing (Tissue treated with reagents for impregnation with paraffin wax)
- Paraffin wax block of tissue
- Thin sections (3-5um) Microtome--- on glass slides
- Stained with Dyes (Hematoxylin & Eosin)
- Microscopic evaluation
- Clinical correlation, Benign/Malignant criteria & tumor type differentiation & grading
- Histologic Sections & wax blocks can be stored for very long periods (many years—indefinitely)
- ~Two days (fixation, Processing & slide preparation)

Frozen sections :

Fresh tissue obtained from lesion during operation & sections prepared by freezing tissue at Cryostat, diagnosis in minutes conveyed to surgeon for intra-operative decision making

- Breast tumors
- intraabdominal tumors
- Brain tumors
- excision margins

2. What are the cytological methods of tumor diagnosis

Exfoliative cytology (Cancer cells loose adhesions)

- Urine cytology
- Sputum, bronchial washing, BAL, Ascitic fluid, pleural fluid, CSF cytology
- Vaginal, cervical cytology (Papanicolaou (PAP) smear test)

Most cost effective cancer reduction program

- ✓ **George N Papanicolaou**
- ✓ 70-80 % reduction of mortality from cervical Ca
- ✓ Early detection of precancer & treatable CA
- ✓ Reduction depends intensity of screening--- screening highest Scandinavian countries

- ✓ 1930 --USA Cervical CA most common cause of cancer death
- ✓ 2/3 rd mortality reduction to 8th position
- ✓ 89% women USA had screening
- ✓ In developing countries < 5% women screening , cervical CA leading cause of cancer mortality
- ✓ Evaluating microscopy: Nuclear atypia & Cytoplasmic, Architecture features

Fine Needle Aspiration Cytology

Fine Needle Aspiration Cytology (22G-25G)

- Cellular material aspirated by thin needle usage & smeared on glass slide---stained (MGG & H & E, PAP) & microscopically evaluated
- Tumors or other pathologies diagnosed, with experience High sensitivity & specificity
- -Superficial Palpable masses (Thyroid, breast, lymph nodes, salivary glands, soft tissue)
- Image guided (visceral --kidney, liver, lung, retroperitoneum, ovarian ; deep seated masses) CT scan, USG

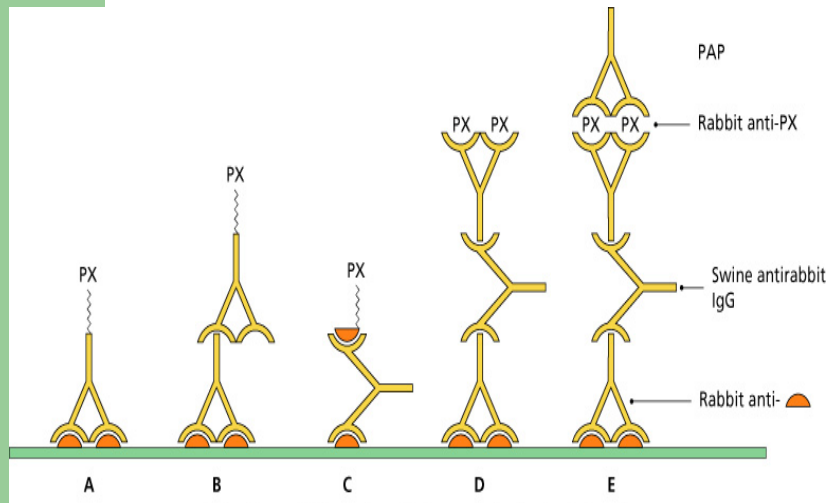
- ✓ OPD procedure, economical, no anasthesia, can be repeated
- ✓ Architecture not completely evaluated, Invasiveness evaluation not as specific as that of biopsy evaluation
- ✓ Blood cells & Lymphoid tissue tumors evaluated : Peripheral blood smear—stain, Bone marrow aspiration (Illiac crest)---smeared---stained; Bone marrow trephine biopsy
- ✓ Lymph node biopsy

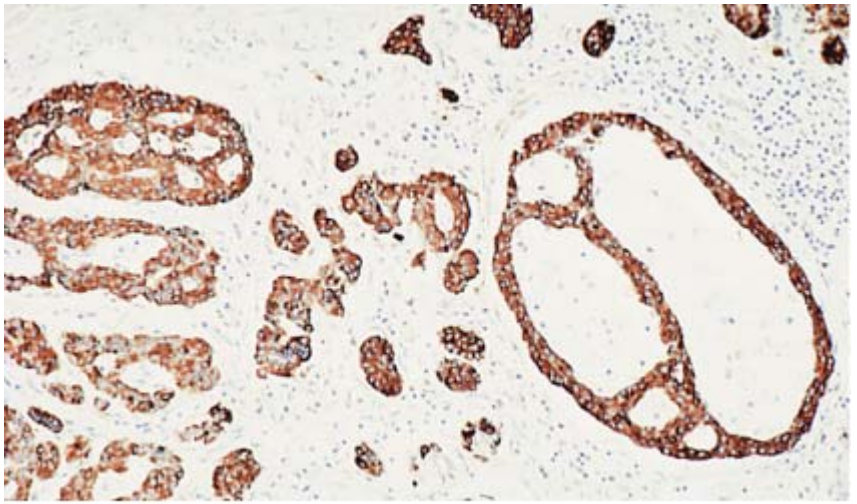
3. What is Immunohistochemistry, how it is applied to the tumor diagnosis?

--Monoclonal antibodies tag the type specific tumor antigens,

--such bound antibodies in sections are marked by anti globulins/ or Avidin biotin complex tagged with stain markers

Positivity in histology sections is seen as colored product with specific locations





Categorization of the poorly differentiated/ undifferentiated tumors

- Undiiferentiated Ca (Cytokeratin)
- Sarcoma (Desmin, vimenetin)
- Melanoma (HMB-45)
- Lymphoma (LCA, CD3/ CD19-20)

Categorization of Leukemia & Lymphoma

Specific lineage differentiation correlate with prognosis & tumor biology (T vs. B vs Myeloid)

Metastatic deposit origin PSA, Thyroglobulin

Prognostic Therapeutically significant molecules

ER/PR better prognosis breast CA Anti estrogen therapy

Her 2neu Poor prognosis but respond to Herceptin

4. How the molecular techniques are changing the ways of cancer patient's management

Diagnosis of neoplasms:

- Clonal arrangement of antigen receptor gene (T cell receptor/ immunoglobulin receptor rearrangement)
- Detection of specific translocation
- (routine cytogenetic analysis or Fluorescent in situ hybridization (FISH))
    - --Burkitt's lymphoma t 8; 14
    - --Follicular lymphoma t 14;18
    - --Mantle cell lymphoma t 11; 14
    - --Chronic myeloid leukemia t 9;22

- Detection of hybrid gene or specific DNA segment or its transcript by PCR Polymerase chain reaction

Sarcomas

- T ---Ewings sarcoma,
- t 12; 22 ---clear cell sarcoma
- , t 8; 22 ---epithelioid sarcoma,
- t x; 18--- synovial sarcoma,
- t 8; 11--- embroynal rhabdomyosarcoma
- t 3;12; ring (3) chromosome ----Atypical lipoma

Prognosis

- N-MYC amplification & 1p deletion bad prognosis for neuroblastoma
- T 9;22 in ALL bad prognosis
- t 15;17 in AML good prognosis

Minimum residual disease

Routine histology/ cytology/ radio-imaging mathods not senistive/reliable to pick residual neaplastic diasease after the anti-neoplastic treatment

PCR technique---amplify even minute DNA of tumor & specific sequences for the tumors can be identified by this method

BCR-ABL residual leukemia cells, K-RAS in stool samples colon cancer recurrence

- Hereditary predisposition to Cancer

BRCA 1/ BRCA2 RET oncogenes high association with Breast CA & MEN

5.Flowcytometery

Cell/ nuclear size

Cytoplasmic granules

DNA content of cells

Cell surface antigens markers

- (for diagnosis, typing of Hematolymphoid neoplasms)
- Aneuploidy bad prognosis

- What are tumor markers, how are they useful in diagnosis & monitoring of tumors

Support to the diagnosis in clinical context

Need to investigate

Prognosis Levels indicate tumor burden of tumor

Response to therapy (levels decline)

Residual disease (> 6 wks CEA high levels residual disease)

Relapse in the follow up period

(PSA, HCG, AFP, CEA, CA125, Calcitonin)

Tumor substances detectable in body fluids

- Human chorionic gonadotropin (HCG)----Trophoblastic tumors, NSeminomatous testicular T
- Calcitonin---Medullary CA thyroid
- Catecholamine/ metabolites---Pheochromocytoma
- α-Fetoprotein---HCC, NSGCTT (Yolk sac, fetal liver git) (liver injury, cirrhosis, fetal distress/ neural tube defect, pregnancy) CA colon, pancreas lung
- Carcinoembryonic antigen CEA (embroynic liver git pancreas) (IBD-CD/UC, alcoholic cirrhosis, hepatitis) colorectal CA 60-90%, pancreatic 50-80%, gastric/ breast CA 25-50%

- Prostate specific antigen PSA---Prostate CA (Prostatitis)
- Neuron specific enolase---neuroblastoma, small cell CA
- Immunoglobulins (M Protein)---Myeloma
- CA-125---Ovarian Ca
- CA19-9----Pancreatic colon Ca
- CA15-3----Breast Ca

Molecular Tumor markers

- P53, APC, RAS mutation in stool/ serum colon Ca

- p53 & RAS (stool & serum) --Pancreatic Ca
- p53 & RAS (sputum & serum) --- Lung Ca
- p53 (urine)--- Urinary bladder Ca