NEOPLASIA SHEET

Lectures 1 through 4

شيت يخص أول أربع محاضرات من مادة الدكتورة مها, يتضمن:
إعادة ترتيب السلايدات
الكلام المهم من المحاضرة
شرح الصور من كلام الدكتورة والكتاب
كويز بعد كل محاضرة
كويز نهاية الملف يشمل جميع المحاضرات

اتضح أن الملف رقم **5** ليس كمثل الملف الجديد والمحاضرة الجديدة.

يرجى اعتماد هذه النسخة

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Neoplasia sheet

(lectures 1-4)

❖ Neoplasia 1:

- Neoplasia is about tumors and their development process.
- Cancer is the second leading cause of death in the United States.

➢ Characteristics of cancers:

1. Cancer is a genetic disorder caused by DNA mutations.
    - **Most** pathogenic mutations are either:
        a) Induced by **exposure** to mutagens.
        b) Occur **spontaneously** as part of aging.
    - Cancers frequently show **epigenetic changes,** such as focal (focused) increases in DNA methylation and alterations in histone modifications which may themselves stem from acquired mutations in genes that regulate such modifications.

    ✓ These genetic and epigenetic changes alter the expression or function of key genes that regulate fundamental cellular processes such as growth, survival, and senescence (death).
2. Genetic alterations in cancer cells are heritable.
    - Cells bearing mutations that provide a growth or survival advantage outcompete their neighbors and thus come to dominate the population→ this is called progression of tumor cells.
3. Mutations and epigenetic alterations impart to cancer cells a set of properties that are referred to collectively as *cancer hallmarks.*

- Emergence of genetically distinct subclones with more aggressive characteristics is an important concept referred to as tumor **progression**.
- These properties produce the cellular phenotypes that dictate the natural history of cancers as well as their response to various therapies.

❖ NOMENCLATURE:

- Neoplasia literally means "new growth."
- Neoplastic cells are said to be transformed because they continue to replicate, apparently oblivious to the regulatory influences that control normal cells.
- Neoplasms enjoy a degree of autonomy (they don't need signals to support growth and survival) and tend to increase in size regardless of their local environment.

- Notes:
  - All neoplasms depend on the host for their nutrition and blood supply.
  - Neoplasms derived from hormone responsive tissues often also require endocrine support.
  - In common medical usage a neoplasm often is referred to as a tumor.
  - The study of tumors is called oncology (from oncos, "tumor," and logos, "study of")
  - Neoplasms are divided into (1)benign and (2)malignant **depending on a tumor's potential clinical behavior.**

❖ Types of neoplasms:

- All tumors, benign and malignant, have two basic components:
  1. The parenchyma made up of transformed or neoplastic cells
  2. The supporting stroma which host-derived, made up of connective tissue, blood vessels, and host derived inflammatory cells.

1. Benign:

- A tumor is said to be benign when its **microscopic** and gross characteristics are considered to be relatively innocent implying that it will remain **localized** and is amenable to local surgical removal.

- Nomenclature of benign tumors:
  - Benign tumors are designated by attaching the suffix **-oma** to the cell type from which the tumor arises.
    For example,
    - A benign tumor arising in fibrous tissue is a fibroma.
    - A benign cartilaginous tumor is a chondroma.
  - Adenoma is generally applied **not only** to benign epithelial neoplasms that **produce gland-like** structures but also to benign epithelial neoplasms that are derived from **glands** but lack a glandular growth pattern.
    For example,
    - Colonic adenoma.
    - Thyroid adenoma.

- Papillomas are benign epithelial neoplasms growing on any surface, that produce microscopic or macroscopic fingerlike fronds.
- Cystadenomas are hollow cystic masses that typically arise in the ovary.

2. Malignant:

- Lesion can invade and destroy adjacent structures and spread to distant sites (metastasize) to cause death.
- Malignant tumors are collectively referred to as cancers, derived from the Latin word for "crab"

- Nomenclature of malignant tumors:
  - Malignant neoplasms arising in "solid" **mesenchymal tissues** or its derivatives are called **sarcomas**.
  - Malignant neoplasms arising from the mesenchymal cells of the blood are called leukemias or lymphomas.

✓ Sarcomas are designated based on their cell-type composition presumably reflects their cell of origin.

Examples,

- Liposarcoma
- Chondrosarcoma
- Fibrosarcoma

  - Malignant neoplasms of epithelial cells are called carcinomas regardless of the tissue of origin.

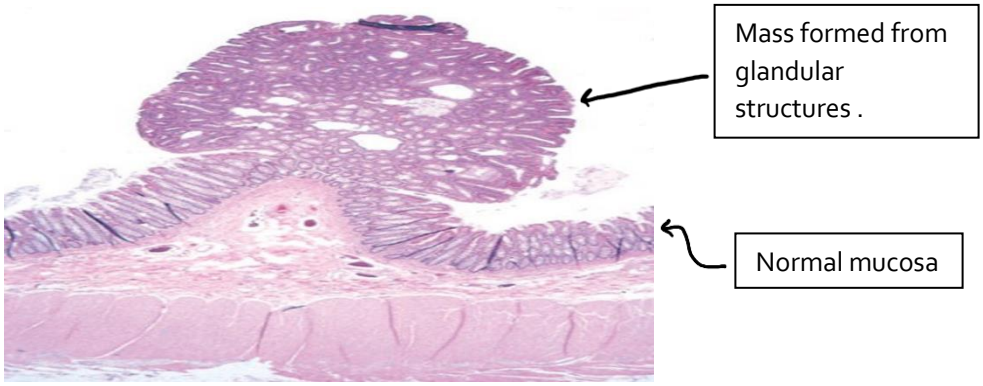
Examples,

- Carcinomas that grow in a glandular pattern are called adenocarcinomas.
- Carcinoma that produce squamous cells are called squamous cell carcinomas.
- Carcinomas arising from renal tubules Renal cell adenocarcinoma.

➢ A polyp is a mass that projects above a mucosal surface, as in the gut, to form a macroscopically visible structure

✓ Polyps can be: (1)Benign, (2)Malignant or (3)Non-neoplastic as inflammatory polyps.

Colonic polyp. This glandular tumor is seen projecting into the colonic lumen. The polyp is attached to the mucosa by a distinct stalk.



(Chronic polyp)

➢ Sometimes there would be Mixed tumors:

- Mixed tumors are still of **monoclonal origin** but the progenitor cell in such tumors has the **capacity to differentiate** down more than one lineage.

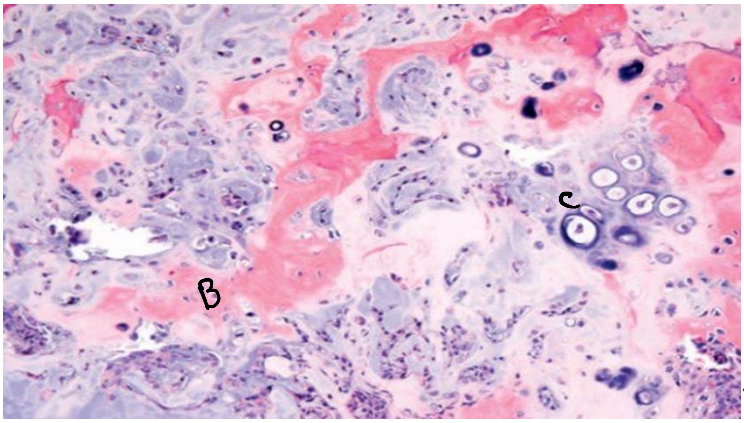
  - Examples,

1. mixed tumor of salivary gland (pleomorphic adenoma).
   - These tumors have obvious epithelial components dispersed throughout a fibromyxoid stroma with islands of cartilage or bone.
2. Fibroadenoma of the female breast Benign mixed tumor It consists of a mixture of proliferating ductal elements and fibrous tissue Only the fibrous component is neoplastic.

   Others,
   - Salivary glands : Pleomorphic adenoma (benign)

- Renal anlage : Wilms tumor (malignant)

Mixed tumor of the parotid gland. Small nests of epithelial cells and myxoid stroma forming cartilage and bone(an unusual feature) are present in thisfield.



(Pleomorphic adenoma of salivary gland)

➢ Special type of mixed tumors: Teratoma

- Teratoma is a special type of mixed tumor that contains **recognizable** mature or immature cells or tissues **derived from more than one germ cell layer** and sometimes all three.
- Teratomas originate from **totipotent** germ cells. (Totipotent cell is a single cell that can give rise to a new organism)
- Ovaries, testis, midline embryonic rests are common sites of tratoma.
  - ✓ Totipotential cells in gonads or in embryonic rests:
    - Mature teratoma.
    - Immature teratoma.
    - Teratocarcinoma.

← types of tumors that arise from totipotential cells

❖ Tumors classifications:

- One Parenchymal Cell Type:
  - Connective tissue and derivatives:
    - Fibroma - Fibrosarcoma
    - Lipoma - Liposarcoma
    - Chondroma -Chondrosarcoma
    - Osteoma - Osteogenic sarcoma
- Endothelium and related cell types:
  - Blood vessels: Hemangioma- Angiosarcoma
  - Lymph vessels: Lymphangioma - Lymphangiosarcoma
  - Mesothelium (usually malignant): X - Mesothelioma
  - Brain coverings: Meningioma - Invasive meningioma
- Blood cells and related cell types:

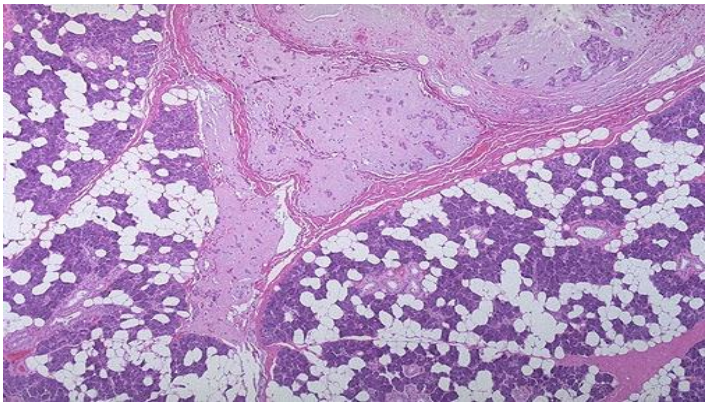
Those to the left are benign tumors, while the right are malignant.

- ✓ No benign tumors
    - Hematopoietic cells: Leukemias
    - Lymphoid tissue: Lymphomas
  - Muscle:
    - Smooth: Leiomyoma - Leiomyosarcoma
    - Striated: Rhabdomyoma – Rhabdomyosarcoma
  - Skin:
    - Stratified squamous: Squamous cell papilloma - Squamous cell or epidermoid carcinoma.
    - Basal cells of skin or adnexa: Basal cell carcinoma
    - Tumors of melanocytes: Nevus - Malignant melanoma
  - Epithelial lining of glands or ducts:
    - Adenoma - Adenocarcinoma
    - Papilloma - Papillary carcinomas
    - Cystadenoma – Cystadenocarcinoma

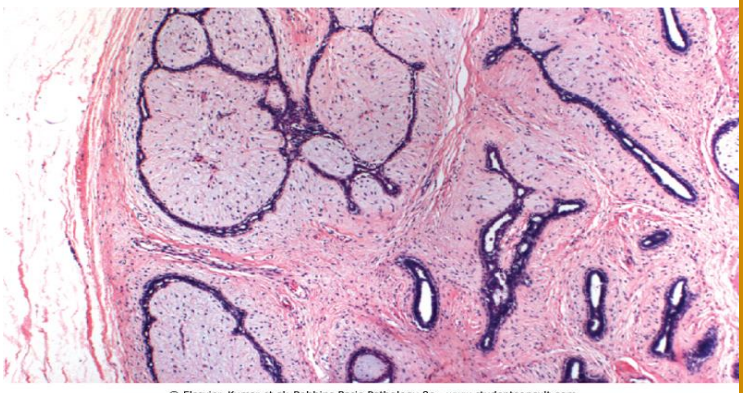
➢ Others:

- ✓ Lung: Bronchial adenoma - Bronchogenic carcinoma
- ✓ Kidney: Renal tubular adenoma - Renal cell carcinoma
- ✓ Liver: Liver cell adenoma - Hepatocellular carcinoma
- ✓ Bladder: Urothelial papilloma - Urothelial carcinoma
- ✓ Placenta: Hydatidiform mole - Choriocarcinoma
- ✓ Testicle: **No benign** - Seminoma, Embryonal carcinoma

* New pictures added:



Pleomorphic adenoma



Fibroadenoma

Here's a quiz on this lecture.

❖ Neoplasia 2:

➢ CHARACTERISTICS OF BENIGN AND MALIGNANT NEOPLASMS:

1. Differentiation and anaplasia.
2. Local Invasion.
3. Metastasis.

✓ Explanations of each:

1. Differentiation and anaplasia:

- Differentiation refers to the extent to which neoplasms resemble their parenchymal cells of origin, both morphologically and functionally.
- Lack of differentiation is called **Anaplasia.**
- Benign neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts.
- Malignant neoplasms exhibit a wide range of parenchymal cell differentiation most exhibit morphologic alterations.
- In well-differentiated benign tumors **mitoses** are usually **rare** and are of normal configuration.

a. For Malignant tumors, they can exhibit:
   i. Well differentiation
   ii. Intermediate differentiation
   iii. Poor differentiation
   iv. Anaplasia (dedifferentiation, or loss of the structural and functional differentiation of normal cells)

b. Also, they can display the following:
   i. Nuclear Pleomorphism (variation in size and shape)
   ii. Nuclear abnormalities (extreme hyperchromatism, variation in nuclear size & shape, or unusually prominent single or multiple nucleoli)
   iii. Increased nuclear-to-cytoplasmic ratio that approaches 1 : 1 instead of the normal 1 : 4 or 1 : 6.
   iv. Enlargement of the Nucleoli
   v. Increased mitotic activity
   vi. Atypical mitoses (tripolar or quadripolar)
   vii. Tumor giant cells
   viii. Loss of polarity of tumor cells
   ix. Alteration or loss of functional capacity (paraneoplastic syndrome)

✓ These are some characteristics of malignant tumors.

✦ Dysplasia and carcinoma in-situ:

- Dysplastic epithelium is recognized by a **loss in the uniformity** of individual cells and in their architectural orientation.
- Dysplasia is not synonymous with cancer.
- **Mild to moderate** dysplasias that do not involve the entire thickness of the epithelium sometimes regress completely, particularly if inciting causes are removed
- When dysplastic changes are **severe** and involve the entire thickness of the epithelium, the lesion is referred to as **carcinoma in situ**, which is a **preinvasive** stage of cancer.

2. Local Invasion:

- The growth of cancers is accompanied by progressive infiltration, invasion, and destruction of surrounding tissues. (definition)

○ For benign tumors:

- Most **benign** tumors grow as **cohesive expansile** masses that remain **localized** to their sites of origin.
- **Benign** tumors grow and expand **slowly**.
- Usually develop a rim of compressed fibrous tissue (**capsule**)
- This capsule consists largely of extracellular matrix that is deposited by stromal cells such as **fibroblasts** which are **activated** by **hypoxic damage** to parenchymal cells resulting from compression by the expanding tumor.
- Encapsulation creates a tissue plane that makes the tumor discrete, moveable (non-fixed), and readily excisable by surgical enucleation.
  - However, not all benign neoplasms are encapsulated
    For example,
    Leiomyoma of the **uterus** is discretely **demarcated** from the surrounding smooth muscle by a zone of compressed and attenuated normal myometrium **but lacks a capsule.**
- Encapsulation creates a tissue plane that makes the tumor **discrete, moveable** (non-fixed), and readily **excisable by surgical enucleation**.

✓ A few benign tumors are **neither** encapsulated nor discretely defined:

  - For example, **Benign** vascular neoplasms (**hemangiomas**) lack of **demarcation** makes them difficult to be excised

○ For malignant tumors:

- Malignant tumors lack well defined capsules
- Microscopic examination reveals **tiny crablike feet** penetrating the margin and infiltrating adjacent structures

- Malignant tumors are difficult to be removed totally; as they are not discrete and not demarcated.

3. Metastasis:
   - The spread of a tumor to sites that are physically discontinuous with the primary tumor. (definition)
   - It unequivocally marks a tumor as malignant.
   - Benign neoplasms do not metastasize.
   - 30% of patients with newly diagnosed solid tumors (excluding skin cancers other than melanomas) present with clinically evident metastases, while 20% have occult (hidden) metastases at the time of diagnosis.
   - **The more anaplastic and the larger the primary neoplasm, the more likely is metastatic spread.**
   - Exceptions Extremely small cancers have been known to metastasize while some large and ominous-looking lesions may not.
   - Basal cell carcinomas of the skin and most primary tumors of the central nervous system are **highly locally invasive but rarely metastasize**.
   - **Leukemias** and **lymphomas** are taken to be disseminated diseases at diagnosis and are always considered to be **malignant**.

➢ Pathways of metastasis:

1. Seeding within body cavities.
2. Lymphatic spread.
3. Hematogenous spread.

✓ Explanations:

1. Seeding:
   - Spread by seeding occurs when neoplasms invade a natural body cavity. For Example,
     - Cancers of the ovary which often cover the peritoneal surfaces widely.
     - Neoplasms of the central **CNS** such as a **medulloblastoma** or **ependymoma,** may penetrate the cerebral ventricles and be carried by the cerebrospinal fluid to **reimplant** on the meningeal surfaces either within the **brain or in the spinal cord**.
2. Lymphatic spread:
   - **Lymphatic** spread is more typical of **carcinomas** whereas [3]**hematogenous spread is favored by sarcomas**.
   - All forms of cancer may disseminate through either or both systems.

- The pattern of lymph node involvement **depends** principally on the **site of the primary neoplasm** and the **natural pathways of local lymphatic drainage.**

  For example,

  - **Lung** carcinomas arising in the respiratory passages **metastasize first** to the **regional bronchial** lymph nodes and **then** to the **tracheobronchial and hilar nodes**.
  - Upper outer quadrant breast lesions first spread to the axillary nodes.
  - Medial breast lesions may drain through the chest wall to the nodes along the internal mammary artery, then to supraclavicular and infraclavicular nodes.
- Cancer cells can travel in lymphatic channels within the immediately proximate nodes to be trapped in subsequent lymph nodes producing so-called "skip metastases"
- The cells may traverse all of the lymph nodes ultimately to reach the vascular compartment by way of the thoracic duct.
- A "sentinel lymph node" is the **first regional lymph** node that receives lymph flow from a **primary** tumor, it can be identified by injection of **blue dyes** or r**adiolabeled** tracers near the primary tumor.
  - Biopsy of sentinel lymph nodes allows determination of the **extent of spread** of tumor and can be used to **plan treatment**.

3. Hematogenous spread:
   - It is the favored pathway for **sarcomas,** Carcinomas use it as well.
   - Arteries are penetrated less readily than are veins.
   - With venous invasion the bloodborne cells follow the venous flow draining the site of the neoplasm.
   - Liver and lungs are the most frequently involved **secondary** sites in hematogenous dissemination;
     - Liver is the commonest secondary organ to be receive metastatic deposits from organs with portal venous drainage.
     - Lungs are the most common site to receive metastatic deposits from organs with caval venous drainage.
   - Cancers arising **near the vertebral column** often embolize through the **paravertebral plexus** as vertebral metastases of carcinomas of the thyroid and prostate glands.

- Certain carcinomas have a propensity to grow within veins.

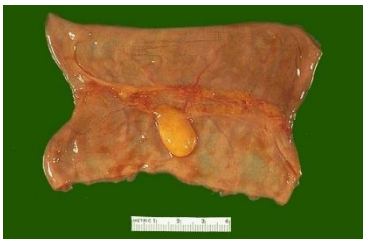
- Renal cell carcinoma often invades the **renal vein** to grow in a snakelike fashion up the **inferior vena cava** reaching the **right side** of the heart.
- **Hepatocellular** carcinomas often penetrate and **grow** within the **radicles of portal and hepatic veins** reaching the main venous channels.

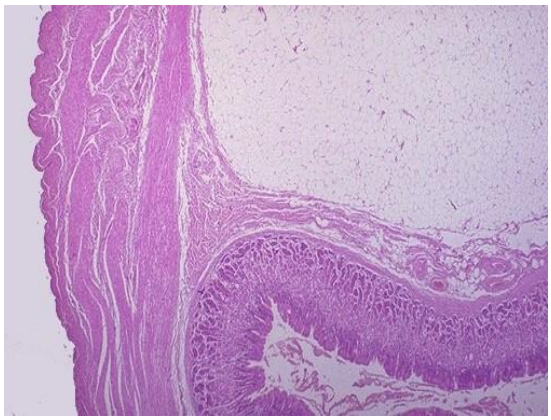
✓ The anatomic localization of a neoplasm and its venous drainage **cannot** explain the systemic distributions of metastases.

For example,

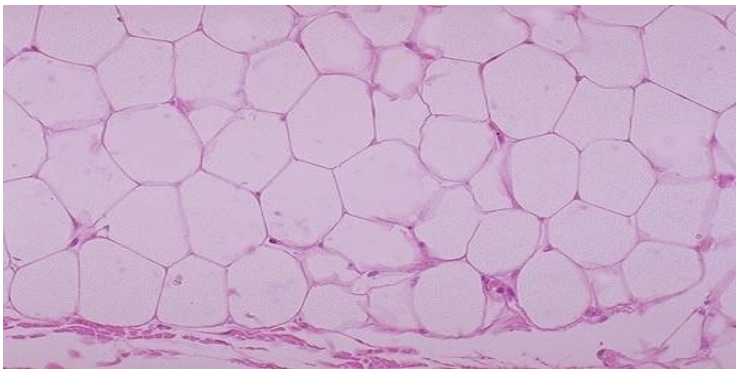
- **Prostatic carcinoma** preferentially spreads to **bone.**
- **Bronchogenic** carcinoma tends to involve the **adrenal glands.**
- **Neuroblastoma** spreads to the **liver** and **bones**.
- Skeletal muscles, although rich in capillaries, are rarely sites of tumor metastases

➢ Images in this lecture:



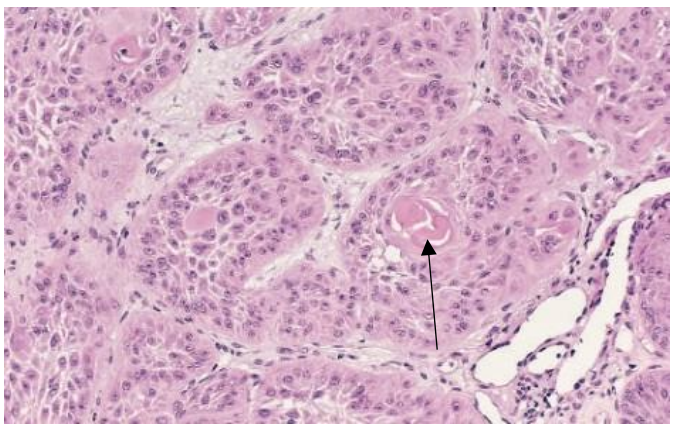


- A lipoma is made up of mature fat cells laden with cytoplasmic lipid vacuoles, and a chondroma is made up of mature cartilage cells that synthesize their usual cartilaginous matrix—evidence of morphologic and functional differentiation. **Benign**

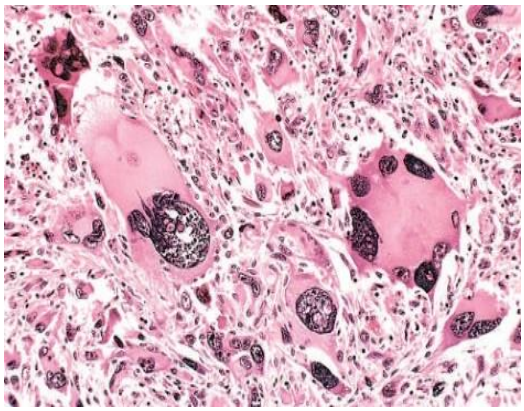


← Mature adipose tissue (lipoma).

Well differentiated – benign.



➢ Well differentiated (to do normal functions) squamous cell carcinoma; the tumor cells are strikingly similar to normal squamous epithelial cells, with intercellular bridges and nests of keratin (arrow)



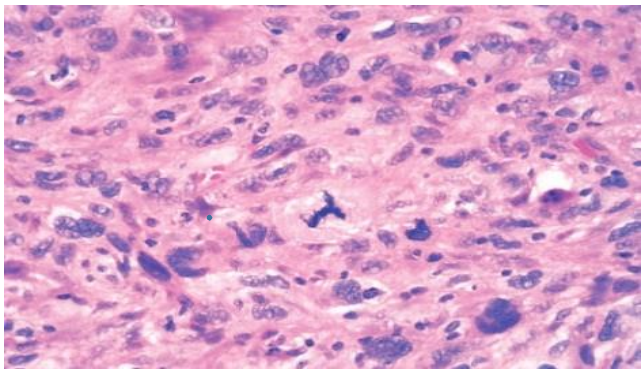
←Anaplasia;

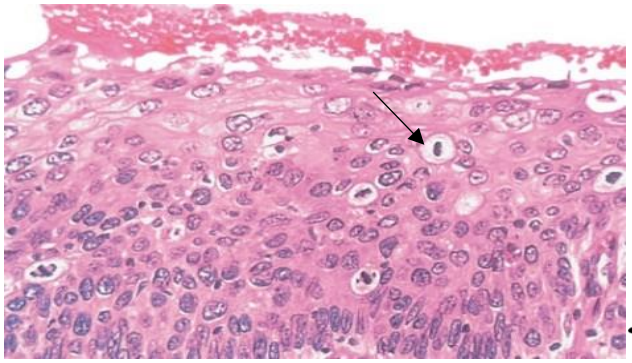
Pleomorphic malignant tumor (rhabdomyosarcoma). Note the marked variation in cell and nuclear sizes, the hyperchromatic nuclei, and the presence of tumor giant cells.

We can't decide the origin.

Abnormal mitosis→

High-power detailed view of anaplastic tumor cells shows cellular and nuclear variation in size and shape.The prominent cell in the center field has an abnormal tripolar spindle



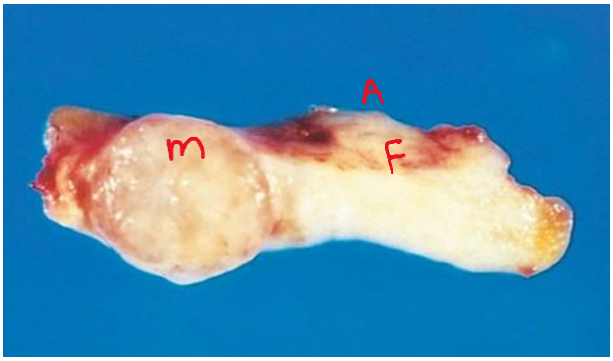


Dividing cells.

←High-power view of another region

shows failure of normal differentiation, marked nuclear and cellular pleomorphism, and numerous mitotic figures extending toward the surface.

- Dysplasia.



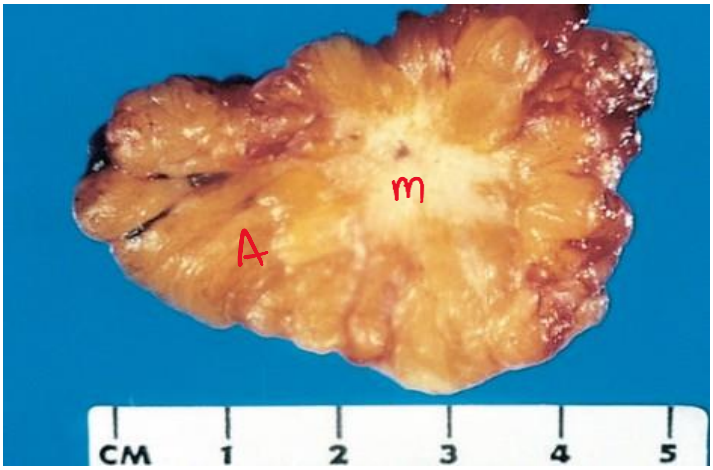
←Fibroadenoma of the breast.

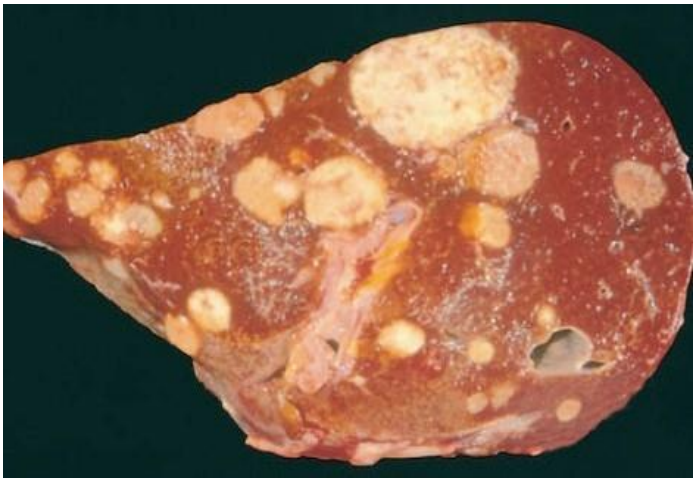
The tan-colored, encapsulated small tumor is sharply demarcated from the whiter breast tissue

m: mass
A: Adipose tissue
F: fibrous tissue

Cut section of invasive ductal carcinoma of the breast. The lesion is retracted infiltrating the surrounding breast substance.→

Not well demarcated.





←A liver with metastatic cancer.

Doesn't look normal.

Here's a quiz on this lecture

❖ Neoplasia 3:

➢ EPIDEMIOLOGY:

- Incidence of cancer is increasing.
- For the year 2012, the World Health Organization (WHO) estimated that there were about 14.1 million new cancer cases worldwide, leading to 8.2 million deaths (approximately 22,500 deaths per day).
- By the year 2035, the WHO expects that the numbers of cancer cases and deaths worldwide will increase to 24 million and 14.6 million, respectively (based on current mortality rates).

➢ Environmental Factors

- Environmental exposures appear to be the dominant risk factors for many common cancers, suggesting that a high fraction of cancers are potentially preventable.
- The geographic variation in death rates from specific forms of cancer is thought to stem mainly from differences in environmental exposures. For example:

        - Death rates from **breast cancer** are about four to five times **higher in the United States** and Europe than in Japan.
        - The death rate for **stomach carcinoma** in men and women is about seven times **higher in Japan** than in the United States.
    - Liver cell carcinoma is relatively infrequent in the United States but is the most lethal cancer among many African populations.

❖ **The most important environmental exposures linked to cancer include the following:**

1. **Diet.**
    - Certain features of diet have been implicated as predisposing influences.
    - Obesity is currently associated with a modestly increased risk for developing many different cancers.
2. **Smoking.**
    - Smoking, particularly of cigarettes, has been implicated in cancers of the mouth, pharynx, larynx, esophagus, pancreas, bladder, and, most significantly, the lung. Approximately 90% of lung cancer deaths are related to smoking.
3. **Alcohol consumption.**
    - Alcohol abuse is an independent risk factor for cancers of the oropharynx, larynx, esophagus, and liver.
    - Alcohol and tobacco smoking **synergistically** increase the risk for developing cancers of the upper airways and upper digestive tract.
4. Reproductive history.
    - There is strong evidence that lifelong cumulative exposure to estrogen stimulation, particularly if unopposed by progesterone, increases the risk for developing cancers of the endometrium and breast, both of which are estrogen-responsive tissues.
5. Infectious agents. (including viruses and bacterial microorganisms)
    - It is estimated that infectious agents cause approximately 15% of cancers worldwide.

Agents or Groups of Agents	Human Cancers for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Arsenic and arsenic compounds	Lung carcinoma, skin carcinoma	By-product of metal smelting; component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, esophageal, gastric, and colon carcinoma; mesothelioma	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), underlayment and roofing papers, and floor tiles
Benzene	Acute myeloid leukemia	Principal component of light oil; despite known risk, many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents; formerly widely used as solvent and fumigant
Beryllium and beryllium compounds	Lung carcinoma	Missile fuel and space vehicles; hardener for lightweight metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate carcinoma	Uses include yellow pigments and phosphors; found in solders; used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung carcinoma	Component of metal alloys, paints, pigments, and preservatives
Nickel compounds	Lung and oropharyngeal carcinoma	Nickel plating; component of ferrous alloys, ceramics, and batteries; by-product of stainless-steel arc welding
Radon and its decay products	Lung carcinoma	From decay of minerals containing uranium; potentially serious hazard in quarries and underground mines
Vinyl chloride	Hepatic angiosarcoma	Refrigerant; monomer for vinyl polymers; adhesive for plastics; formerly inert aerosol propellant in pressurized containers

➢ Age and Cancer:

- The frequency of **cancer increases with age**.
    - Most cancer deaths occur between 55 and 75 years of age.
    - The rate declines after 75 years of age.
- The rising incidence with age may be explained by:
    1. The accumulation of somatic mutations that drive the emergence of malignant neoplasms.
    2. The decline in immune competence that accompanies aging; preventing the immune system from taking care of developing abnormal cells, thus increasing risk of their survival.

✓ More than 10% of all deaths among children younger than 15 years of age is **due to cancer.**

✓ The major lethal cancers in children are:

a) Leukemias.
b) Tumors of the CNS.
c) Lymphomas.
d) Soft-tissue tumors.

➢ Familial Cancers:

- Virtually all the common types of cancers that occur sporadically have been reported to occur in familial forms.
- Examples:
    - Breast cancer.
    - Ovarian cancer.
    - Pancreatic cancer.

- Colon cancer.

❖ Features that characterize familial cancers include:

1. Early age at onset.
2. Tumors arising in two or more close relatives of the index case.
3. Multiple or bilateral tumors.

✓ Familial cancers **are not** associated with specific marker phenotypes.

- E.g., in contrast to the familial adenomatous polyposis syndrome, familial colonic cancers do not arise in preexisting benign polyps.

- In general, siblings have a relative risk between **2-3X**.
- The transmission pattern of familial cancers is not clear.
- Segregation analysis of large families usually reveals that **predisposition** to the tumors is **dominant**, but **multifactorial** **inheritance cannot be easily ruled out**.
- Certain familial cancers can be linked to the **inheritance of mutant genes**.

➢ Acquired Cancer Predisposing Conditions:

- Include:
  1. Disorders associated with chronic inflammation.
  2. Immunodeficiency states.
  3. Precursor lesions.
- Tumors arising in the context of **chronic inflammation are mostly carcinomas** but also include **mesothelioma or lymphoma**.
- **Immunodeficiency** states mainly **predispose to virus-induced cancers**, including specific types of lymphoma and carcinoma and **some** sarcoma-like lesions.
- Molecular analyses have shown that precursor lesions often possess some of the genetic lesions found in their associated cancers.

  Examples:

  - Squamous metaplasia and dysplasia of bronchial mucosa, seen in habitual smokers—a risk factor for lung carcinoma.
  - Endometrial hyperplasia and dysplasia, seen in women with unopposed estrogenic stimulation—a risk factor for endometrial carcinoma.
  - Leukoplakia of the oral cavity, vulva, and penis, which may progress to squamous cell carcinoma.
  - Villous adenoma of the colon, associated with a high risk for progression to colorectal carcinoma.

Table of Chronic inflammatory states and Cancer

Chronic inflammations with tissue loss increase the risk of related carcinomas.

Pathologic Condition	Associated Neoplasm(s)	Etiologic Agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibers, silica particles
Inflammatory bowel disease	Colorectal carcinoma	
Lichen sclerosis	Vulvar squamous cell carcinoma	
Pancreatitis	Pancreatic carcinoma	Alcoholism, germ line mutations (e.g., in the trypsinogen gene)
Chronic cholecystitis	Gallbladder cancer	Bile acids, bacteria, gallbladder stones
Reflux esophagitis, Barrett esophagus	Esophageal carcinoma	Gastric acid
Sjögren syndrome, Hashimoto thyroiditis	MALT lymphoma	
Opisthorchis, cholangitis	Cholangiocarcinoma, colon carcinoma	Liver flukes *(Opisthorchis viverrini)*
Gastritis/ulcers	Gastric adenocarcinoma, MALT lymphoma	*Helicobacter pylori*
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Osteomyelitis	Carcinoma in draining sinuses	Bacterial infection
Chronic cervicitis	Cervical carcinoma	Human papillomavirus
Chronic cystitis	Bladder carcinoma	Schistosomiasis

➢ Interactions Between Environmental and Genetic Factors:

- Inherited trait versus Acquired factors.

Table 6.4 Inherited Predisposition to Cancer

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

- ✓ **Retinoblastoma**: caused by a mutation in tumor suppressor gene, **R**etino**b**lastoma gene.
- ✓ **Li-Fraumeni syndrome** results from a mutation in **TP53** gene.
- ✓ **Melanomas** are associated with mutations in **cyclin-dependent kinases** genes (CDKN2A gene: Cyclin-dependent kinase inhibitor 2A, crucial tumor suppressor gene), which are a family of protein kinases that play crucial roles in regulating the cell cycle, transcription, and other cellular processes.
- ✓ **Hereditary nonpolyposis colon cancer** is associated with mutations in a group of genes related to **mismatch repair** genes, 2 and 6 (**MSH2** and **MSH6**).
- ❖ Inherited syndromes caused by mutations in **DNA repair genes** that increase the risk of developing cancer, such as **Xeroderma pigmentosum** which is associated with mutations in multiple DNA repair genes and increases the risk of developing **skin cancer**.

➢ CANCER GENES:

- **Are genes that are recurrently affected by genetic aberrations in cancers presumably because they contribute directly to the malignant behavior of cancer cells**

- **Causative mutations that give rise to cancer genes:**
    1. **may be acquired by the action of environmental agents as chemicals, radiation, or viruses.**
    2. **may occur spontaneously.**
    3. **may be inherited in the germ line.**

➢ Functional classes of cancer genes:

1. Oncogenes:
    - Are genes that induce a transformed phenotype when expressed in cells by promoting increased cell growth.
    - Oncogenes are mutated or overexpressed versions of normal cellular genes, which are called proto-oncogenes.
    - Most oncogenes encode transcription factors, factors that participate in pro-growth signaling pathways, or factors that enhance cell survival.
    - Oncogenes are considered dominant genes because a mutation involving a single allele is sufficient to produce a pro-oncogenic effect.
2. Tumor suppressor genes:
    - are genes that normally prevent uncontrolled growth and, when mutated or lost from a Cell allow the transformed phenotype to develop.
    - both normal alleles of tumor suppressor genes must be damaged for transformation to occur (recessive genes)
    - Tumor suppressor genes can be placed into two general groups:
        1. "Governors" that act as important brakes on cellular proliferation
        2. "Guardians" that are responsible for sensing genomic damage
            - Some **guardian** genes initiate "**damage control response**" that leads to the **cessation** of **proliferation** or, if the damage is too great to be repaired, or induce apoptosis.
3. Genes that regulate apoptosis:
    - They enhance cell survival of cells.
    - Genes of this class protect **against apoptosis** are often **overexpressed** in cancer cells.
    - Genes that **promote apoptosis** tend to be **underexpressed** or functionally **inactivated** by mutations in cancer cells.

➢ GENETIC LESIONS IN CANCER:

- The genetic changes found in cancers vary from point mutations involving single nucleotides to abnormalities large enough to produce gross changes in chromosome structure.

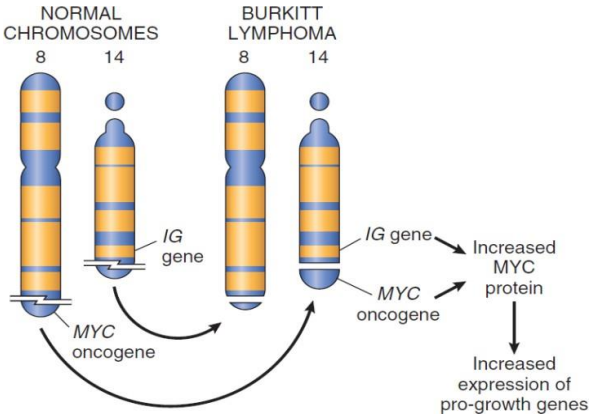
- In certain neoplasms**, genetic abnormalities are nonrandom and highly characteristic**.
- Specific chromosomal abnormalities have been identified in most leukemias and lymphomas and in an increasing number of nonhematopoietic tumors
- Other tumors are characterized by particular **point mutations**.

➢ Gene mutations in cancer:

1. Driver mutations
    - Driver mutations are mutations that alter the function of cancer genes and thereby directly contribute to the development or progression of a given cancer.
    - They are usually acquired but occasionally inherited.
    - Driver mutations tend to be tightly clustered within cancer genes.
2. Passenger mutations
    - Passenger mutations are acquired mutations.
    - Do **not** affect cellular behavior.
    - They occur at random.
    - Passenger mutations are sprinkled throughout the genome.
    - Passenger mutations related to cancers caused by carcinogen exposure**,** such as melanoma and smoking-related lung cancer.

➢ Types of gene mutations in cancer:

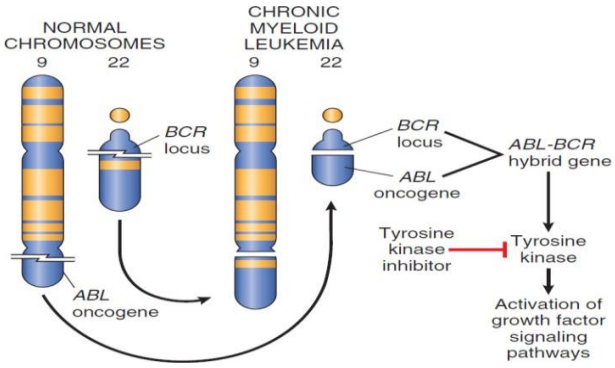
1. Point Mutations
    - Point mutations can either activate or inactivate the protein products of the affected genes
    - Point mutations that convert proto-oncogenes into oncogenes generally produce a gain of function.
    - A cardinal example is point mutations that convert the RAS gene into a cancer gene**,** one of the most comment events in human cancers.
    - The tumor suppressor gene that is most commonly affected by point mutations in cancer is TP53
2. Gene Rearrangements:
    - Gene rearrangements may be produced by chromosomal translocations or inversions.
    - Highly associated with Leukemias and sarcomas
    - Gene rearrangements can activate proto-oncogenes in two ways:



1. Some gene rearrangements result in **overexpression** of proto- oncogenes by **removing** them from their normal regulatory elements and placing them **under control of an inappropriate,** highly active **promoter** or **enhancer**.

Examples,

- Burkitt lymphoma: **Myc** gene translocation from **chr.8 to 14.**
- follicular lymphoma: a reciprocal translocation between **chr.14 and 18** leads to **overexpression** of the **anti-apoptotic gene** BCL2 on chr.18.



2. Oncogenic gene rearrangements create fusion genes encoding novel chimeric proteins.

Example,

- Philadelphia (Ph) chromosome in chronic myeloid leukemia, consists of balanced reciprocal translocation between **chr. 9** and **22** leading **to fusion of ABL oncogene(chr 9) with BCR locus.**
- ABL-BCR hybrid gene results in **activation of growth factor signaling pathways.**

3. Deletions:
    - Deletion of specific regions of chromosomes may result in the **loss** of particular **tumor suppressor genes**.

      Examples,
        1. RB gene deletions are associated with retinoblastoma
        2. Deletion of 17p is associated with loss of TP53.
4. Gene Amplifications:
    - Proto-oncogenes may be converted to oncogenes by gene amplification with consequent overexpression and hyperactivity of otherwise normal proteins.

      Examples,
        1. NMYC gene amplification in 20-35% of neuroblastoma
        2. HER2 (also known as ERBB2) amplification occurs in about 20% of breast cancers
5. Aneuploidy:
    - It is defined as a number of chromosomes that is **not a multiple of the haploid state** (i.e a chromosome number that is not a multiple of 23).
    - Aneuploidy is remarkably **common** in **carcinomas**.

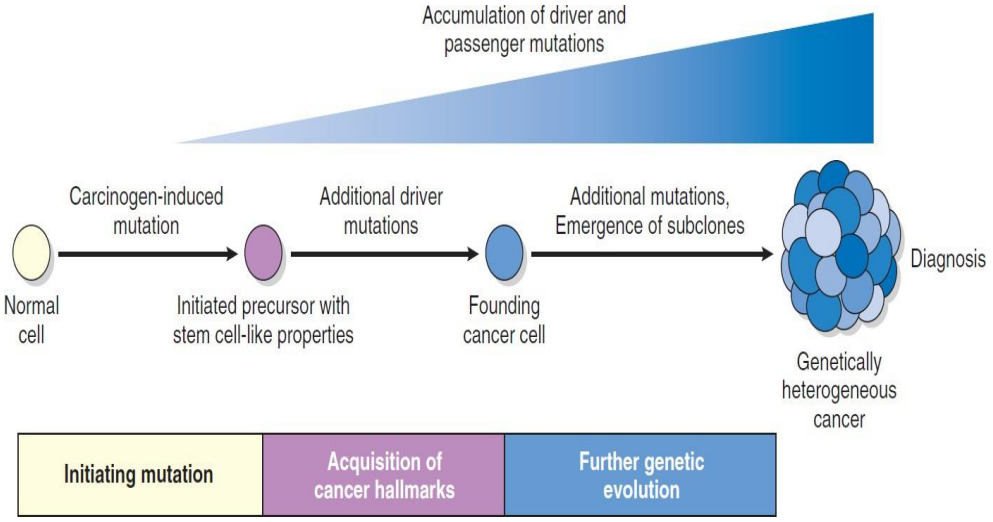
- Aneuploidy tends to **increase** the copy number of key **oncogenes** and **decrease** the copy number of **potent tumor suppressors**.
  Examples,
  1. Chr.8 carrying MYC oncogene is present in increased copies in tumor cells.
  2. Portions of chr.17 carrying TP53 gene are often lost in tumor cells.

Here's a quiz for this lecture.

❖ Neoplasia 4:

➢ Hall marks of cancer:

1- Self-sufficiency in growth signals
2- Insensitivity to growth-inhibitory signals
3- Altered cellular metabolism
4- Evasion of apoptosis
5- Limitless replicative potential (immortality)
6- Sustained angiogenesis
7- Invasion and metastasis
8- Evasion of immune surveillance



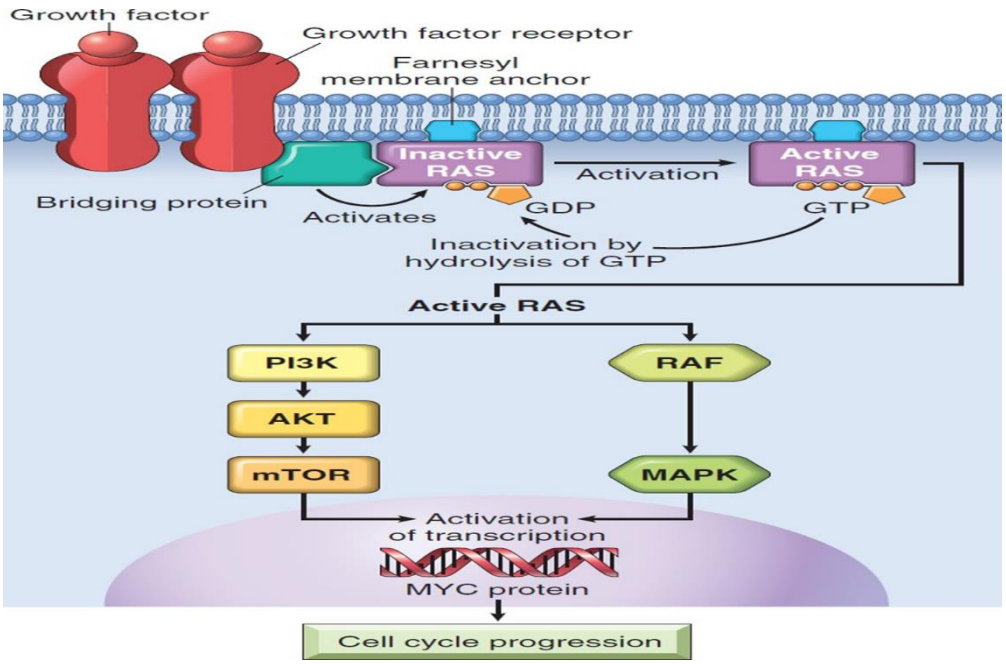
➢ Self-Sufficiency in Growth Signals:

- It stems from gain-of-function mutations that convert protooncogenes to oncogenes.
- Oncogenes encode proteins called oncoproteins that promote cell growth even in the absence of normal growth-promoting signals

➢ Steps of normal cell proliferation:

1. **Binding** of a growth factor to its specific receptor on the cell membrane.

2. Transient and limited **activation** of the growth factor **receptor,** which in turn **activates** several **signal transducing proteins** on the inner leaflet of the plasma membrane.
3. **Transmission** of the transduced signal across the cytosol **to the nucleus** by second messengers or a cascade of signal transduction molecules.
4. Induction and **activation** of **nuclear regulatory factors** that initiate and **regulate** DNA transcription and the biosynthesis of other **cellular components that are needed for cell division,** such as organelles, membrane components, and ribosomes.
5. Entry and progression of the cell into the cell cycle, resulting ultimately in cell division.



➢ Growth Factors:

- Cancers may secrete **their own** growth factors or **induce** stromal cells to **produce** growth factors in the tumor microenvironment.
- Most soluble growth factors are made by one cell type and act on a neighboring cell to stimulate proliferation (**paracrine action**).
- Some cancer cells acquire growth self-sufficiency by acquiring the ability to synthesize the same growth factors to which they are responsive.

  For example:
  - Many glioblastomas secrete platelet-derived growth factor (PDGF) and express the PDGF receptor
  - Many sarcomas make both transforming growth factor-α (TGF-α) and its receptor.

- In some cases, tumor cells send signals to activate normal cells in the supporting stroma to produce growth factors that promote tumor growth.

➢ Growth Factor Receptors

- Some growth factor receptors have an intrinsic tyrosine kinase activity that is activated by growth factor binding while others signal by stimulating the activity of downstream proteins.
- Many of the growth factor receptors function as oncoproteins when they are mutated or if they overexpressed.

  Examples:
  - Epidermal growth factor (EGF) receptor family.
  - ERBB1 is overexpressed in 80% of squamous cell carcinomas of the lung, 50% or more of glioblastomas, and 80-100% of epithelial tumors of the head and neck.
  - **HER2** (ERBB2) is **amplified** in approximately 20% of **breast cancers** and in a smaller fraction of adenocarcinomas of the lung, ovary, stomach, and salivary glands.
  - These tumors are exquisitely sensitive to the **mitogenic** effects of **small amounts** of growth factors.

✓ HER2 is significant in treatment.

✓ Tyrosine kinase activity is stimulated by **point mutations** or small indels that lead to subtle but functionally important changes in protein structure, or gene rearrangements that create fusion genes encoding chimeric receptors.

✓ Examples Leukemias, lymphomas, and certain forms of sarcoma.

➢ Downstream Signal-Transducing Proteins:

- The signaling proteins that couple growth factor receptors to their nuclear targets are activated by ligand binding to growth factor receptors.
- The signals are transmitted to the nucleus through various signal transduction molecules.

✦ Two important oncoproteins in the category of signaling molecules are Present:

1. RAS
2. ABL RAS

- RAS is the most commonly mutated oncogene in human tumors.
- Approximately 30% of all human tumors contain mutated RAS genes, and the frequency is **even higher in some specific cancers** (e.g., **pancreatic adenocarcinoma**)

- RAS is a member of a family of small G proteins that bind guanosine triphosphate [GTP] and guanosine diphosphate [GDP]).

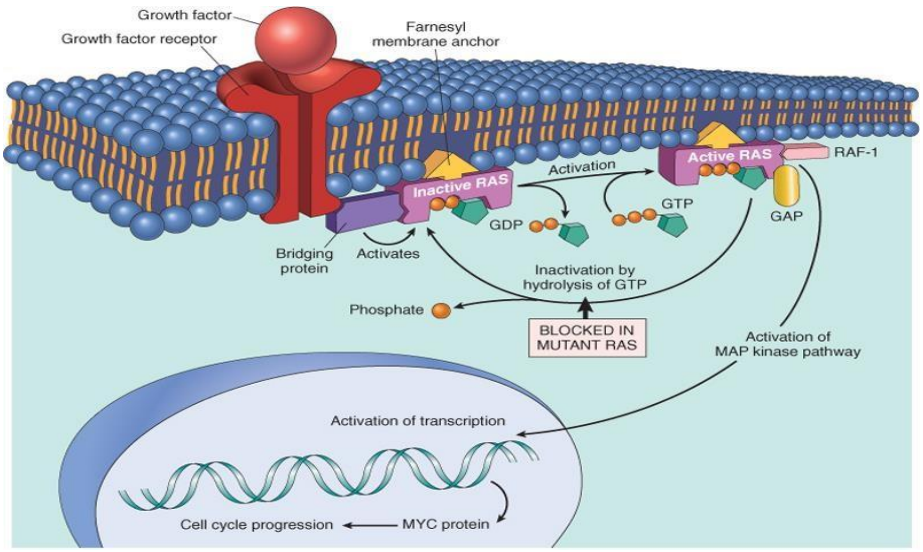
➢ Signaling by RAS involves the following sequential steps:

- Normally RAS flips back and forth between an excited signal transmitting state and a quiescent state.
- RAS is inactive when bound to GDP.
- Stimulation of cells by growth factors such as **EGF** and **PDGF** leads to exchange of GDP for GTP and subsequent conformational changes that **activate** RAS (RAS-GTP).
- Active RAS is short-lived because the activity of intrinsic guanosine triphosphatase (GTPase) activity.
- RAS hydrolyzes GTP to GDP releasing a phosphate group and returning the protein to its quiescent GDP bound state.
- The GTPase activity of activated RAS is magnified dramatically by a family of GTPase-activating proteins (GAPs)
- GAPs act as molecular brakes that prevent uncontrolled RAS activation by favoring hydrolysis of GTP to GDP.
- Activated RAS stimulates downstream regulators of proliferation by several interconnected pathways that converge on the nucleus and alter the expression of genes that regulate growth such as MYC.
- For example, BRAF, which lies in the so-called "RAF/ERK/MAP kinase pathway" is mutated in more than 60% of melanomas and is associated with unregulated cell proliferation

✓ **RAS** most commonly is **activated by point mutations** in amino acid residues that are either within the **GTP binding pocket** or in the **enzymatic region** that carries out GTP hydrolysis.

✓ Both kinds of mutations interfere with breakdown of GTP which is essential to inactivate RAS.

- ➢ RAS is thus trapped in its activated, GTP-bound form and the cell is forced into a continuously proliferating state.
- ➢ Activating mutations in RAS can be **mimicked** by loss-of function **GAPs** leading to a failure to simulate GTP hydrolysis and trapping RAS in active state.



Examples,

- Neurofibromatosis type 1 the GAP neurofibromin-1 (NF1) is mutated.
- A **tumor suppressor gene** called **PTEN** which is a negative inhibitor of PI3 kinase is frequently mutated in carcinomas and certain leukemias.

➢ ABL:

- ABL **proto-oncoprotein** has tyrosine kinase activity that is controlled by internal negative regulatory domains.
- In **chronic myeloid leukemia** and certain **acute leukemias** a part of the ABL gene is **translocated** from its normal site on chromosome 9 to chromosome 22 forming **Philadelphia** (Ph) chromosome.
- This fusion gene encodes as BCR-ABL **hybrid** protein that has a tyrosine kinase activity.
- The **BCR-ABL** protein **activates** all of the signals, is a potent stimulator of cell growth.
- **Imatinib mesylate** (also known as Gleevec) is BCR-ABL kinase **inhibitor** that has a dramatic clinical response in patients with chronic myeloid leukemia

➢ Nuclear Transcription Factors:

- Mutated RAS or ABL results in inappropriate and continuous stimulation of nuclear transcription factors that drive the expression of growth-promoting nuclear genes.
- **MYC, MYB, JUN, FOS,** and REL oncogenes, function as **transcription factors** that regulate the expression of growth-promoting genes, such as cyclins.
- MYC is involved most commonly in human tumors.

✓ **MYC activates several growth-promoting genes including cyclin-dependent kinases (CDKs).**

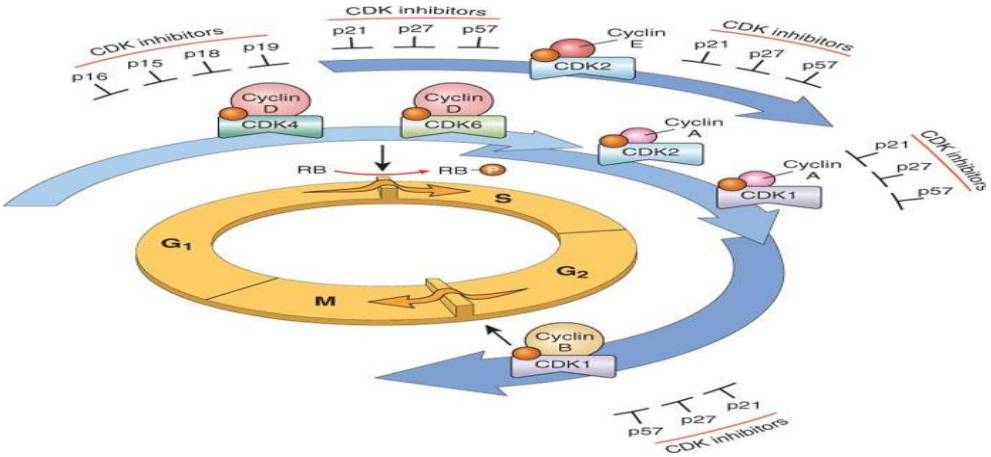
Examples:

- **MYC** translocation (8;14) (from chromosome 8 to 14) in **Burkitt lymphoma,** a highly aggressive **B-cell tumor.**

- **MYC** also is **amplified** in breast, colon, lung, and **many** other **cancers**.
- **NMYC** gene is amplified in **neuroblastoma**.
- **LMYC** gene is amplified in **small cell carcinoma of lung**.

➢ Cyclins and Cyclin-Dependent Kinases (CDKs):

- Progression of cells through the cell cycle is controlled by cyclin-dependent kinases (CDKs).
- CDKs are activated by binding to cyclins.
- Cyclins are characterized by **cyclic nature** of production and degradation, thus the name.



- CDK inhibitors (CDKIs) exert **negative** control over the cell cycle.
  - One family of CDKIs, composed of three proteins:
    1. p21 [CDKN1A]
    2. p27 [CDKN1B]
    3. p57 [CDKN1C]
  - inhibits the CDKs broadly.
  - The other family of CDKIs has selective effects on cyclin D/CDK4 and cyclin D/CDK6, the four members of this family:
    1. p15 [CDKN2B]
    2. p16 [CDKN2A]
    3. p18 [CDKN2C]
    4. p19 [CDKN2D]
  - are sometimes called **INK4 (A-D) proteins**.
- Expression of these inhibitors is **downregulated** by **mitogenic** signaling pathways promoting the progression of the cell cycle; inhibiting them causes hyperactivation of the cell cycle and proliferation of the cell.
  Examples,
  - p27 [CDKN1B], a CDKI that inhibits cyclin E, is expressed throughout **G1**.

    - Mitogenic signals inhibit p27, relieving inhibition of cyclin E-CDK2 and thus allowing the cell cycle to proceed.
- The CDK-cyclin complexes **phosphorylate** crucial target proteins that **drive** the cell through **the cell cycle**.
- On completion of this task, cyclin levels decline rapidly.
- More than 15 cyclins have been identified; cyclins **D, E, A, and B** appear sequentially during the cell cycle and bind to **one or more CDK**.
  • Mishaps affecting the expression of cyclin D or CDK4 seem to be a common event in neoplastic transformation.
  • The cyclin D genes are overexpressed in many cancers, including those affecting the breast, esophagus, liver, and a subset of lymphomas.
  •Amplification of the CDK4 gene occurs in melanomas, sarcomas, and glioblastomas.
  • Mutations affecting cyclin B and cyclin E and other CDKs also occur, but they are much less frequent than those affecting cyclin D/CDK4.
- **While cyclins arouse the CDKs,** CDK inhibitors (CDKIs) **silence** the CDKs and exert negative control over the cell cycle.
- The CDKIs are frequently mutated or otherwise silenced in many human malignancies.

  Examples,
    - **Germ-line mutations of p16**(CDKN2A) are associated with 25% of **melanoma**.
    - Acquired deletion or inactivation of p16(CDKN2A) is seen in:
        1. 75% of pancreatic carcinomas.
        2. 40% to 70% of glioblastomas.
        3. 50% of esophageal cancers.
        4. 20% of non-small-cell lung carcinomas, soft tissue sarcomas, and bladder cancers.

Here's a quiz on this lecture.

Overall quiz

Feedback

V1	تم ازالة محاضرة 5 من الملف. تم تغيير اللون الذهبي الفاتح إلى أغمق.
V2	تم اضافة المعلومات: ➢ Mixed tumors salivary glands : Pleomorphic adenoma (benign) Renal anlage : Wilms tumor (malignant) ➢ Totipotential cells in gonads or in embryonic rests Mature teratoma, Immature teratoma, teratocarcinoma على المحاضرة الأولى؛ بناءً على تغيير الملف على الموقع. (PAGES 4&5)
V3	ADDED NEW PICTURES P.6
V4	Added table p. 15 These were added to p. 13 … leading to 8.2 million deaths (approximately 22,500 deaths per day). … and 14.6 million, respectively (based on current mortality rates). Table p. 17 was altered (chronic cystitis)

THANK YOU