**Pathology of Neoplasia**

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**Learning objectives**

**Definition**

**-What is neoplasia ?**

**-What are the basic components of tumors?**

**-What is the basic classification of the tumors ?**

**How the tumors are designated (nomenclature and misnomers) ? -**

**Differences between Benign and Malignant tumors**

**-The characteristics of benign tumors**

**The characteristics of malignant tumors-**

**-What the tumor gradind system is**

**-What the tumor staging system is**

**Mechanisms of invasion & metastasis of malignant tumors**

**-What are the metastatic sub-clones**

**-The metastatic cascade**

**-What are the factors that determine the site of tumor secondaries (site specific homing) ?**

**Tumor angiogenesis**

**- How do growing tumors develop a blood supply?**

**-What are the angiogenic factors ?**

**-What are the angiogenesis inhibitors ?**

**Kinetic of tumor cell growth- factors that affect the rate of tumor growth**

**-What is the tumor growth fraction**

**Tumor immunity**

**-Host defense against tumor**

**-How the tumor cells be recognized by the immune system (tumor antigenes)**

**-What are the antitumor Effector Mechanisms**

**-Is immune surveillance exists ?**

**-How do cancers avoid the immune system in immunocompetent hosts?**

**Molecular basis of cancer**

**-What are the prinsiple targets of genetic dammage in cancer**

**-What is oncogene**

**-How do oncogenes promot the autonomous cell proliferation in cancer**

**-What is the role of tumor suppressor genes, apoptosis gens and DNA repairing genes ?**

**Causes of cancer – Carcinogenesis**

**-The steps of carcinogenesis**

**-The carcinogenic agents**

**-The mechanism of action of carcinogenic agents**

**Tumor effects on Host**

**-Local effects**

**-Hormonal effects**

**-Systemic effects**

References:

-Robbins Basic pathology 8th ed. 2007.

-Steven's Core pathology 3ed ed. 2oo9.

-Web sites

Defcinition

Neoplasm = New growth

Abnormal mass of tissue, the growth of which *exceeds* & is uncoordinated with that of normal tissue.

The growth *Persists* in the same excessive manner even after cessation of the stimuli which evoked the growth.

It is *Purposeless growth* , competes with the normal cells for energy & blood supply.

Tumor has two basic components:

1- Parenchyma = proliferating tumor cells

2- Supportive stroma =

a-Connective tissue

b- blood vessels.

Stroma :

- Scanty 🡪Soft tumor

- When stroma is abundant collagenous is called **Desmoplasia** 🡪Hard tumor

Basic classification of the tumors

Three categories

1- Benign tumors

2- Malignant tumors

- Primary

- Secondary ( metastatic)

3- Borderline tumors (potentially malignant tumors ) (Premalignant tumors)

**Nomenclature**

**Benign tumors**:

Aredesignated by adding the suffix ***oma*** to the cell of origin

**A**- **Mesenchymal tumors**

-Fibroblasts 🡪Fibroma

-Cartilage 🡪Chondroma

-Bone 🡪Osteoma

**B- Epithelial tumors**

**- Surface epithelial tumors are generally called  *"Papillomas*** "

-Squamous cell papilloma

-Transitional cell papilooma

**-Glandular epithelial tumors are generally called*****Adenomas"***

-Thyroid adenoma (like follicular adenoma)

-Salivary gland adenoma(like pleomorphic adenoma)

**Malignant tumors :**

1. **Malignant mesenchymal tumors**  are generally called **Sarcoma s**

-Fibroblasts Fibrosarcoma

-Adipose tissue liposarcoma

-Blood vessels Angiosarcoma

**2) Malignant epithelial tumors** are generally called **🡪Carcinoma** s

-Squamous cell carcinoma

-Transitional cell carcinoma

-Basal cell carcinoma of the skin

**Malignant glandular epithelial tumors are generally called Adenocarcinomas**

-Sweat gland adenocarcinoma

-Salivary gland adenocarcinoma

-Thyroid, breast, colon, pancreas 🡪adenocarcinoma

**Mixed tumors**

**-**Pleomorphic Salivary Adenoma (Benign mixed tumor of salivary glands)

**-**Carcinosarcoma (Carcinoma + Sarcoma)

**-**Teratoma: tumor composed of cells from more then one germ layer

**Tumors do not follow these bases of nomenclature** (misnomers)

Glioma = benign and malignant, tumor of glial cells in the CNS

Lymphoma = malignant tumor of lymphoreticular tissue

Plasmacytoma & M. myeloma = malignant tumor of plasma cells

Leukemia= malignant blood cells neoplasm

Melanoma =Malignant tumor of melanocytes

Hepatoma = liver cell carcinoma

Seminoma = malignant germ cell tumor of the testis

**Hamartoma**

Is a focal malformation ,composed of tissue elements normally found at the affected part. These tissue elements are growing in an abnormal proportion forming a disorganized mass.

Hmartoma grows at the same rate as the organ of origin

Hamartoma = abnormal formation of normal tissue

Examples

1-Nevus (common mole)

Normal intradermal melanocytes are present in an abnormaly high proportion

2- Pulmonary hamartoma (Adenochondroma)

composed of cartilage, smooth muscles & glandular epithelium

All are normal tissues in the lung but in abnormal proportion

**Teratoma**

Tumor of primitive *germ cell* origin

Consist of tissues from more than one embryologic germ layer

teratoma = a tumor composed of a mixture of tissues not normally found at that site

-Ovarian teratomas Usually benign & matur

-Testicular teratomas are almost always immature & malignant

**Differences between benign & malignant tumors**

**1- Mode of growth**

\*Benign tumors

-grow by expansion; Compress or displace the surrounding tissues

-do not infiltrate or invade the surrounding tissues

-remain localized to the site of origin

-no metastasis (can not metastasize to distant sites).

-Surrounded by fibrous capsule (compressed surrounding tissue)

\*Malignant tumors

-grow by local destructive *invasion-* progressively infiltrate and destroy

Surrounding tissues

-poorly demarcated from the surrounding normal tissues.

-*metastasize* to distant sites

Metastasis = the extremely important dangerous property of malignant tumors

The secondary tumors at distant sites are called *secondaries*or *or metastase,* which

are either similar to primary tumor or different from the primary tumor

Metastases (secondaries) are tumor implants **discontinuous** with the primary tumor.

All malignant tumors can metastasize

Metastasis = Malignancy

Few exceptions like CNS gliomas & skin basal cell carcinoma

1/3 of cancer patient present with metastases

Carcinomas prefer lymphatic spread

Sarcomas prefer hematogenous spread

With few exceptions; -choriocarcinoma prefers hematogenous spread

-Synovial sarcoma prefer lymphatic spread

**2-Rate of growth**

Malignant tumors have a faster rate of growth than benign tumors

**\***The tumor growth rate is related to the degree of *differentiation*

*.*

**3-Histological features**

A) Differentiation

Refers to the extent to which the tumor cells resemble comparable

normal cells both functionally& morphologically

*All Benign tumors*  are well differentiated (closely resemble normal)

*Malignant tumors* could be:

-well differentiated

-moderately differentiated

-poorly differentiated

-undifferentiated (Anaplastic tumor)

*Anaplasia* ***=*** *Lack of differentiation*

B) Cytological features

\*In benign tumors the nuclei are normal

\*Malignant tumors show the following Cytological features of malignancy:

**1-Pleomorphism****variation in size & shape**

**2-Nuclear hyperchromasia****dark staining** (**abundance of chromatin)**

**3-High nucleo/cytoplasmic (N/C) ratio**

normal N/C = **1:4 – 1:6**

in malignant tumor cells the N/C may approach **1:1**

**4-Overcrowding & loss of orientation**

**5-Mitotic activity**

Mitotic index refers to the number of mitotic figures per a given number

of cells each tumour has its own mitotic index, it is igher in malignant

tumors, but it dosen't necessarily indicate malignancy, howevere, *Abnormal*

*(Atypicai) mitotic figures* strong indication is a of malignancy

\*These cytological features of malignancy are grouped under a term **Atypia**

When cytological atypia is combined with disorganization of tissue structure

We use the term **Dysplasia**

Dysplasia is traditionally classified into **mild, moderate** and **severe dysplasia**

Or **Low grade** (mild + moderate) **dysplasia and high grade** (severe) **dysplasia**

**Intraepithelial neoplasia (Carcinoma in situ)** is aterm appliedwhen severe (high grade) dysplasia,involves the entire thickness of the epithelium, but still

within the normal confines of the epithelium , with intact basement membrane (no invasion to the basement membrane)

Allways there is evidence that intraepithelial neoplasia may progress to **Invasive** **carcinoma** (once the basement membrane is breached or invade)

**Tumor Grade**

refers to the extent of histological deviation from normal.

It is frequently correlates with degree of differentiation and the potential aggressiveness of the tumor

\*Grade I tumor is well differentiated and is leess aggressive

\*Grade II tumor is moderately differentiated and aggressive

\*Grade III tumor is poorly differentiated and more aggressive

\*Grade IV (anaplastic) tumor is undifferentiated and very aggressive

Each tumor has its own grading system (Some tumors have 2 gardes only; low grade and high grade, Other tumors have three grades: grade I, II and III. Other tumors have four or five grades)

**Tumor Stage**

Refers to the extent of the tumor spread, both clinically & histopathologically

TNM staging system is the most widly used

T = extent of the local infiltration by Tumor (related to the tumor size)

N = involvement of the local lymph Nodes

M = Presence (M1) or absence (MO) of distant Metastasis

\*N.B. each tumor has its own staging

**Mechanisms of invasion and metastasis**

Invasion and metastasis are the biological hallmarks of malignant tumors

-Not all tumor cells within a tumor have the ability to invade & metastasize

-Only certain subclones (metastatic subclones) that have the right combination of gene products (protiens) to complete all steps of invasion & metastasis

Metastatic cascade

Two main phases

1- Invasion of the extracellular matrix (ECM)

2- Vascular dissemination & homing of the tumor cells at the distant site

**1- Invasion of the extracellular matrix (ECM)** (basement membrane

and extracellular interstitium)

Occurs in 4 stepes:

a- Detachment (loosening up) of the tumor cells from the tumor mass

b- Attachment to the matrix components

c- Degradation of the ECM

d- Migration (locomotion) of tumor cells

**a- Detachment of metastatic cells from the tumor mass**

Normally cells are attached by adhesion molecule called Cadherin which is a trans membrane molecule

in cancer cells, there is deceased expression of cadherin

**b-Attachment of the metastatic cell to the matrix components**

-Laminin specific receptors

Increased expression of these receptors in malignant cells and are

distributed all around the cell membrane

-Integrins

Are cell surface receptors that interact with ECM in both outside-in &

inside-out with a rapid response of the cell to the environment

**c- Degradation of ECM**

To create passage ways for migration of the metastatic cells through the ECM

Degredation is an active enzymatic process achieved by proteolytic enzymes secreted by the tumor cells or host cells:

-Metalloprteinase is type IV collagenase

-cysteine proteinase & Serine proteinase : degrade fibronectin, laminin &

glycoproteins

**d-Migration (locomotion) of tumor cells through the degraded ECM**

By Autocrine motility factors expressed by the metastatic tumor cells

-degradation products of matrix components, have

\*growth promoting action

\*angiogenic action

\*chemotactic activity that promote migration

**2- Vascular dissemination & homing of the tumor cells**

1-Attachment to the vascular basement membrane

2-penetration of the vascular basement membrane

3-Intravasation: Within the circulation the metastatic tumor cells shoud be

able to protect themselves from the destruction by immune cells (NK cells)

The tumor cells adher to each other and to the platelets formin tumor cells

emboli that are transferred by the blood to distant sites.

4-Extravasation: Occurs at the distant site of metastasis. Starts by the dhesion of

the metastatic tumoe cells to the endothelial cells of the blood vesseles of the

target organ, followed by attachment to the vascular basement membrane,

degradation of ECM, then migration through the degraded matrix and homing

at the new site

**The site of secondary deposits (metastases or secondaries)**

Is related to the site of primary tumor & the natural pathway of vascular drainage:

Examples:

\*Breast carcinoma metastasizes to the axillay lymp nodes

\*Testicular tumor metastasizes to the para-oartic lymph nodes

This dose not always explain the distribution of the tumor secondaries

Examples:

\*Prostate carcinoma usuallu metastasize to the bone (spine)

\*Adrenal neuroblastoma usuallu metastasize to the liver & bone

\*Lung adenocarcinoma usuallu metastasize to the brain

This organ tropism (site-specific homing) may be related to factors other than

the primary tumor site & the natural pathway of vascular drainage. These factors include:

1- the first step in extravasasion is adhesion to endothelium. The tumor

cells may express adhesion molecules (Receptors) whose Ligands are

expressed on the endothelial cells of the capillaries of the target organ.

2- Target organs may liberate growth factors like insulin like growth factors

I & II, which have chemotactic activity for tumor cells.

3-After extravasation, tumor cells are dependent on the new receptive stroma

for growth. Thus, tumors may fail to metastasize to certain target tissues

because of the unfavorable environment for the growth of secondaries at the

new site. Eg. Protease inhibitor in the lung.

**Angiogenesis**

The most important factor that affect the rate of tumor growth.

and may also be a icritical key steps for tumor metastasis.

- tumors cannot enlarge beyond 1-2 mm unless they are vascularized.

Angiogenesis is a vital process in the progression of cancer from small, localized neoplasms to larger, growing, and potentially metastatic tumors.

**How do growing tumors develop a blood supply?**

Tumor angiogenesis is controlled by the balance between:

**angiogenic factors** & **angiogenesis inhibitors**

**Angiogenic factors**

**1-Vascular Endothelial Growth Factor (VEGF)**

Produced by the tumor cells or by the inflammatory cells

**2- Basic Fibroblastic Growth Factor (BFGF)** Produced by the cleavage of extracellular matrix by proteases

The angiogenesis is induced by several physiologic stimuli, such as hypoxia.

Whwn the tumor reach the critical size there will be relative lack of oxygen.

Hypoxia causes activation of hypoxia-induced factor-1α (HIF1α), an oxygen-sensitive transcription factor (Lack of O2 prevents recognition & destruction of HIF1α by von Hippel-Lindau protein (VHL))

HIF1α translocates to the nucleus and activates transcription of VEGF genes

Which encodes for the synthesis of VEGF by the tumor cells

**Anti-angiogenic factors (angiogenesis inhibitors)**

1-Thrombospondin-1,produced by the tumor cells

Is regulated by p53 gene which is frequently mutated in cancer cells

2-Angiostatin, produced by the cleavage of plasminogen

3-Endostatin, produced by the cleavage of collagen

4-Vasculostatin, produced by the cleavage of transthyretin

\*Early in their growth, most human tumors do not induce angiogenesis. They remain small or in situ for years until the angiogenesis starts.

\*In normal cells, *p53* can stimulate expression of anti-angiogenic molecules, such as thrombospondin-1, and repress expression of angiogenic molecules, such as VEGF.

with time some cells within the small tumor start to produce angiogenic factors, owing to the accumulation of mutations & with mutational inactivation of p53 the level of thrombospondin-1 decreases & angiogenesis starts.

**Kinetics of tumor cell growth**

**Growth fraction: i**s the proportion of tumor cells that are entering the cell cycle, i.e. in the *proliferative pool.*

The tumor growth rate depends on the Growth fraction which is determined by the

imbalance between cell loss & cell production

Some human cancers like Leukemia, lymphomas & lung small cell carcinoma have

high GF& grow at a faster rate with rapid clinical course

Most human cancers like breast & colon cancers haveLow GF (cell production exceeds cell loss by only 10% & grow at a slower rate)

**HOST DEFENSE AGAINST TUMORS: TUMOR IMMUNITY**

-How can the tumor cells be recognized by the immune system?

-What is the nature of tumor antigens?

-What host effecter systems may recognize & kill tumor cells?

-Is human immunity effective against neoplasm

-How do cancers avoid the immune system

**Tumor Antigens**

**1-*tumor-specific*** *antigens* present only on tumor cells

***2-tumor-associated antigens*** present on tumor cells and also on some normal cells

***Tumor-specific antigens***

In tumor cells many genes are mutated and encoding for altered proteins, these

alterd protiens are expressed on the surface of tumor cell in association with class

I MHC as non-self and are recognized by CTL (Immune response)

***Tumor-associated antigens (TAAs)***

-present on tumor cells and also on some normal cells

-They are normal self proteins

-Do not evoke an immune response

-Of a little significance in tumor rejection

-Of value in the diagnosis of some tumors (tumor markers) & in immunotherapy (Ab against them)

Tumor-associated antigens (TAAs) are of three types

1-Tumor associated Carbohydrate antigens (TACAs) -Abnormal form of glycoproteins & glycolipids.

Example mucin associated antigens detected in breast & pancreatic carcinoma.

2-Oncofetal antigens: Normally expressed in embryonic tissues but not in adult

tissues

Examples :

- Alfa-feto-protein (AFP) Liver cell carcinoma & germ cell tumors

- Carcinoembryonic antigen (CEA) colorectal ca, pancreatic ca, gastric ca

& breast ca.

3-Differentiation antigens: Are markers of differentiation state of the tumor

Example; prostate specific antigen (PSA) is expressed by normal prostatic tissue as well as by cracinoma of the prostate.

They are used for identifying the tissue of origin of tumor secondaries.

**Antitumor Effector Mechanisms**

**1-Cytotoxic T Lymphocytes (CTLs)**

Class-1MHC-restricted CD8+

they seem to play a protective role, chiefly against virus-associated neoplasms like EB virus &HPV

T- cell receptor (TCR) can recognize tumor antigen expressed on the surface of tumor cell in association with class-1 MHC

Then membrane to membrane contact (between T-cell and tumor cell) result in

release of **perforine** by T cell granules drill holes in the tumor cell membrane

causing osmotic lysis of tumor cells (most effective effector mechanism)

**2-Natural Killer Cells**

-can destroy tumor cells without prior sensitization

-provide the first line of defense

-After activation with IL-2, NK cells can lyse a wide range of human tumors.

- NK cells use a limited set of activating receptors(NKG2D) proteins to recognize stress-induced antigens that are expressed on the tumor cells and cells that have DNA damage (stress cells) (at risk for neoplastic transformation) and then kill these stress cells

**3-Macrophages**

Interferon-γ, (INF-Y) a cytokine secreted by T cells and NK cells, is a potent activator of macrophages

-Activated macrophages may kill tumor cells by secretion of tumor necrosis factor (TNF)

**4-Humoral Mechanisms (Ab)**

-No evidence for the protective effects of anti- tumor antibodies against tumors

-Can be therapeutically effective: A monoclonal antibody against CD20, a B cell surface antigen, is widely used for treatment of certain non-Hodgkin lymphomas

**Immune Surveillance**

Means there are immune cells that can recognize tumor cells & kill them.

Is such immune surveillance exists ?

The strong evidence is the increased frequency of cancers in immunodeficient hosts.

However, most cancers occur in individuals who do not suffer from any overt immunodeficiency (immunocompetent)

**Several escape mechanisms by which tumor cells can avoid the immune system**

**in immunocompetent hosts:**

*1-Selective outgrowth of antigen-negative cells*

strongly immunogenic tumor cells (cells express antigenes) may be eliminated

2*-Loss or reduced expression of MHC molecule*

*3-Lack of costimulation*

Sensitization of T cell requires 2 signals:

1) Foreign peptide with MHC (on tumor cell) + TCR (on T-cell) 🡪 signal 1

2) Costimulatory molecule B7-1(on tumor cell) + CD28 (on T-cell) 🡪 signal 2

\*Signal 1 + signal 2 result in CTL activation

\*Signal -1 without signal 2 (tumor cell dosen't express B7-1) result in

inactivation or apoptosis of CTL

*4-Immunosuppression*

-Many oncogenic agents (e.g. chemicals and ionizing radiation) suppress host

immune responses

-Tumors products also may be immunosuppressive Like TGF-β, secreted in

large quantities by many tumors, is a potent immunosuppressant.

**THE MOLECULAR BASIS OF CANCER**

principles

1- *Nonlethal DNA damage lies at the heart of carcinogenesis.*

*-* DNA damage is either *acquired* by chemicals, radiation, or viruses o*r iinherited*

2-*Four classes of normal regulatory genes are the principal targets of genetic damage:*

*-proto-oncogenes* *growth-promoting genes*

*-tumor suppressor genes**growth-inhibiting genes*

*-genes that regulate apoptosis*

*-genes involved in DNA repair*

3-*Carcinogenesis is a multistep process* resulting from the accumulation of multiple mutations.

**Oncogenes**

Are genes that promote autonomous (independent, self directed) cell growth in cancer

*They are derived by mutations in the normal proto-oncogenes*

*Characterized by the ability to promote cell growth in the absence of normal growth-promoting signals*

Convertion of proto-oncogenes to oncogenesis call "Oncogene Activation"

\*Oncogene present in the DNA of tumor cell is called Cellular oncogene (C-onc)

\*Gene sequences identical to cellular oncogene are present in the genome of rapidly oncogenic retroviruses is called Viral oncogen (V-onc)

Oncogenes activation results from:

-Mutation of the proto-oncogene caused by chemicals & radiations

-Oncoviruses which are of two types:

*-Slowly* tumorogenic retroviruses

*-Rapidly* tumorogenic retroviruses

Slowly tumorogenic retroviruses activate oncogene when the proviral DNA is integrated near a proto-oncogene causing structural changes in the cellular proto-oncogene and converting it to Oncogene

Rapidly tumorogenic retroviruses cary into the infected cell, their own activated oncogene

(V-onc)

The products of oncogenes are called **oncoproteins**

oncoproteins are devoid of important regulatory elements. Their production in the transformed cells does not depend on growth factors or other external signals.

All normal cells require stimulation by growth factors to undergo proliferation

Growth factor receptors are transmembrane molecules.

Binding of growth factor to the receptor leads to autophosphorylation of the receptor & binding of a bridging protein between the receptor & inactive RAS protein

RAS protein (encoded by RAS gene) is a membrane adherent protein, It regulates cell proliferation

-RAS protein cycles between inactive GDP binding form & active GTP binding form.

This cycling is regulated by GAP (GTPase Activating protein)

-GAP is responsible for inactivation of RAS protein by hydrolysis of GTP to GDP

-Mutations in RAS gene always affect the binding site of GTP, so inhibits GTPase even in the presence of GAP.

-Mutant RAS protein will be permanently fixed in the its active form with continuous stimulation of cell proliferation without any external stimuli. (No need for more growth factor)

-Activated RAS bind to & activates RAF

-Activated RAF bind to & activates MAP kinase (Mitogen activating protein kinase)

-Activated MAP kinase translocates to nucleus and activate transcription genes with

cell cycle pregress

-This results into autonomaous cell proliferation (No need for growth factor stimulation)

**Genes that regulate APOPTOSIS**

Three letters words beginning with ***b***

Some Inhibit apoptosis like ***bcl-2*** *&* ***bcl-xl***

Others Favor apoptosis like ***bax*** *&* ***bad***

**Tumor suppressor genes**

Are normal growth inhibitory genes.

-Their xpression prevent oncogenesis.

-Mutational inactivation predispose to cancer.

Examples:

1- Retinoblastoma (Rb) gene

Function regulation of cell cycle

Mutational inactivation predispose to Retinoblastoma in child and sarcoma in adults.

2. p53

Function → regulates cell cycle & apoptosis in response to DNA damage

Mutational inactivation → Most human cancers

3. WT1

Function → nuclear transcription

Mutational inactivation → Wilm’s tumor

4. BRCA1

Function → DNA repair

Mutational inactivation → Ca. of Female breast & ovary

5. BRCA2

Function → DNA repair

Mutational inactivation → Ca. of Female & Male breast

6- APC

Mutational inactivation Ca. of Colon, Stomach, pancreas ---

**Function of tumor suppressor genes**

**Rb gene**

The product of Rb gene is **PRb** (intra-nuclear, phosphoprotein)

-PRb protien regulates cell cycle. It controls the transition of the cell from G1 to

S phase

Quiescent cell (at G0 or early G1 phase) contains active hypophosphorylated PRb

which prevents cell replication by binding & sequestering E2F transcription factor.

When the cell is stimulated by growth factor, there will be syntehsis of cyclins E &

D that bind to in active cyclin dependent kinases ( CDK 4, 6 and 2) forming active complexes "cyclin D/CDK4", "cyclin D/CDK6" & "cyclin E/CDK2". Hyperphosphorylation of PRb results into release of the E2F transcription factor

wich binds to specific site in the DNA and activates the transcription genes of the S phase (transition of the cell from G1 to S phase)

Virtually all cancer cells show dysregulation of G1- S transition point, due to mutation in one of the genes that regulate the PRb phosphorylation, Rb, CDK4, Cyclin D & p16.

**p53** **gene**

Is one of the most commonly mutated genes in human cancers

p53 can be viewed as a central monitor of stress (DNA damage)

Whene there is DNA damage, P53 protein is activated and binds to DNA, stimulates transcription of the following genes:

\* CDK inhibitor (p21)

\* DNA repair genes (GADD45)

\*poptosis gene (bax)

-Activation of p21 gene, leads to arrest of cell cycle at G1

-Activation of GADD 45 leads to successful DNA repair and the cell proceeds with the

cell cycle without DNA damage

-If DNA repair fails: activated bax gene will activate Apoptosis of the stress cell.

**Chemical Carcinogenesis**

Multi-step process

Two stages

**1-Initiation**

Initiation results from exposure to an *appropriate* *dose* of a chemical carcinogenic agent called **Initiator**

**2-Promotion**

Results from exposure to another chemical agent call promotor. Promotors, by themselves are non-carcinogenic, they can induce tumor in inititated cells only

**Chemical Carcinogens**

1-Direct-Acting Agents

2-Indirect-Acting Agents

-Direct-Acting Agents

require no metabolic conversion to become carcinogenic (alkylating agents

are in general weak carcinogens

- Indirect-Acting Agents

require metabolic conversion to an *ultimate carcinogen* before they become active Examples:

-polycyclic hydrocarbons-are present in fuels & tobacco

-aromatic amines and azo dyes

-β-naphthylamine in the aniline dye and rubber industries urinary bladder Ca.

**Mechanisms of Action of Chemical Carcinogens**

Malignant transformation results from mutations

Most chemical carcinogens are mutagenic

**Initiators** cause a permanent DNA damage -(mutation) wich is rapid, permanent and has memory. So that tumor will be produced even if the application of promoter is delayed for a time.

**promoters** by themselves are nontumorigenic

To be effective, exposure to the promoter must follow the application of the initiator.

Promoters do not affect DNA directly and the cellular changes are reversible, and the

tumor fails to develop in initiated cell if the time between multiple applications of promoters is widely extended (because the effect of the promotor is reversible)

Most chemical carcinogens are mutagenic. All direct & ultimate carcinogens are highly reactive Electrophiles (Electron deficient atoms) that can react with the Nucleophilic (Electron – rich) sites in the cell (DNA, RNA, proteins)

Such interaction is usually lethal to the altered cell and no tumor will develop

But in In initiated cell this interaction should be "non-lethal"

DNA is the primary target for chemical carcinogens. Carcinogen –induced DNA changes do not necessarily lead to initiation because DNA damage can be repaired by cellular enzymes.

The essential first step in the process of initiation is "unrepairable" & "non-lethal" DNA damage, Then the carcinogen ultered cell must undergo at least one cycle of proliferation so that the DNA changes will be fixed & permanent.

The application of an initiator may cause the mutational activation of an oncogene (causes transformation of the normal cell into initiated cell) and subsequent application of promoters leads to proliferation & clonal expansion of the initiated (mutated) cells. These initiated cells have reduced growth factor demand

**Radiation Carcinogenesis**

Two types of radiation:

-UV rays

-Ionizing radiation

**UV rays**

-Derived from sun light

-Three types of UV:

1- UV-A, is harmless

2- UV-B, is Carcinogenic

3- UV-C, is a Potent mutagenic. It is filtered out by the ozone shell

**-UV ray h**as the ability to **damage DNA** by forming **pyrimidine dimers** in the DNA which lead to large transcription errors.

This type of DNA damage is repaired by the nucleotide excision repair pathway

With extensive exposure to UV light, the repair systems may be overwhelmed, and skin cancer results

There is increased risk of skin cancer in sun exposed parts of the body, in patients with *xeroderma pigmentosum, (inherited deficiency of one of the DNA repair enzymes)*

This provides the best evidence that DNA damage is important for the carcinogenic effect of UV.

**-Ionizing radiation**:

1-Electromagnatic; include X-rays & Gamma rays

2-Particulates; include Alfa, Beta, protons & neutrons

All Ionizing radiations are carcinogenic owing to their mutagenic effects

They cause either Single stranded DNA breaks or double-stranded DNA breaks (the most important)

-Attempts to repair Single-stranded DNA break result in to single base mutation.

- Attepts to repair double-stranded DNA breaks leed toTranslocation or Deletion with

major transcription errors

**Viral carcinogenesis**

Human oncogenic viruses are

1) Oncogenic RNA Viruses include HTLV-1

2) Oncogenic DNA Viruses; include; HPV, EBV, HBV & KSHV (Kaposi sarcoma herpes virus)

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

 The only retrovirus that has been demonstrated to cause cancer in humans.

 Is associated with T-cell leukemia/lymphoma

 Similar to the HIV, HTLV-1 has tropism for CD4+ T cells, which is the major target for neoplastic transformation

 The genome of HTLV-1 contains, in addition to the usual retroviral genes, a unique region called pX. This region encodes several genes, including one called TAX.

 TAX protein can bind to and activate cyclins and lead to progression of the cell cycle.

 TAX can repress the function of tumor suppressor gene p53 and this lead to suppression of bax (activate apoptosis) & this inhibit apoptosis.

So activation of cell cycle (cell proliferation) with inhibition of apoptosis will leed

To over growth of T-cells and lymphoma

Oncogenic DNA Viruses

Are strongly associated with human cancer

\*Human Papilloma viruses

are two groups:

-low-risk HPV types , like type 1, 2, 4, & 7. Cause squamous papillomas

-High-risk HPV types like;16 &18 cause squamous cell carcinoma

The oncogenic potential of HPV can be related to products of viral genes, E6 and E7. The E7 protein binds to an inactivate the retinoblastoma protein (PRB) and releases the E2F transcription factors that are normally sequestered by PRB, promoting progression through the cell cycle. E7 protein from high-risk HPV types has a higher affinity for PRB than does E7 protein from low-risk HPV types carcinoma

The E6 protein has complementary effects. It binds to and mediates the degradation of p53 and bax, so inhibits apoptosis. E6 protein from high-risk HPV types has a higher affinity for p53 than E6 protein from low-risk HPV types.

CONCLUSION: infection with high-risk HPV types inhibit tumor suppressor genes, inhibits apoptosis and activates cyclins leeding to Cell cycle progress

\*Epstein-Barr Virus

-Implicated in the pathogenesis of Burkitt lymphoma, B-cell lymphomas in cases of immunosuppression, some forms of Hodgkin lymphoma and nasopharyngeal carcinoma

EBV uses the complement receptor, CD21, to attach to and infect B- cells. One of the EBV-encoded genes, called LMP-1, acts as an oncogene stimulating the B-cell proliferation pathway. On the other hand, LMP-1 activates bcl2 & prevents apoptosis

\*Hepatitis B and Hepatitis C Viruses

Are involvbed in the pathogenesis of hepatocellular carcinoma (70% to 85%)

The oncogenic effects of HBV and HCV are multifactorial:

- chronic inflammation with hepatocyte death leading to regeneration, and genomic

damage

- mediators derived from the activated immune cells such as reactive oxygen species,

are genotoxic and mutagenic & can activate cell proliferation.

- the HBx protein of HBV and the HCV core protein can directly or indirectly activate

a variety of transcription factors

\*Helicobacter pylori (*H. pylori*)

Is the first bacterium classified as a carcinogen.

It is implicated in both gastric adenocarcinoma and gastric lymphoma .

The oncogenic effects of *H.pylori* are multifactorial & similar to those of HBV and HCV; Cell death & regeneration, genomic damage mediators derived from the activated immune cells, genotoxic.

**Effects of Tumor on Host**

Tumors cause problems by:

1) Local effects

2) Hormonal effects

3) Systemic effects

4) Additional effects of tumor secondaries

**1) Local effects**

a) Compression

b) Mechanical obetruction

c) Tissue destruction by malignant tumors that infiltrate and destroy vital structures

d) Infarction, ulceration and hemoorrhage

**a) Compression**

is critical in both benign and malignant tumors:

**\***A small (1-cm) pituitary adenoma can compress and destroy the surrounding normal

gland and give rise to hypopituitarism

**\*** Mediastinal tumor may compress superior vena cava producing SVC syndrome

\* Tumor of ampulla of vater causes biliary obstruction with obstructive jaundice

(severe itching) and liver cirrhosis (secondary biliary cirrhosis)

**b) Mechanical obstruction**

\*Esophageal tumor obstructing the lumen causing DYSPHAGIA

\*Intestinal tumor causes intestinal obstruction

\*A 0.5-cm leiomyoma in the wall of the renal artery may lead to renal ischemia and

serious hypertension.

**c) Tissue destruction** by malignant tumors that infiltrate and destroy vital structures

**d) Infarction, ulceration and hemorrhage**

\* Skin ulceration, mucus membran ulceration

\*Bleeding like melena, hematurea

\*The tumor may undergo necrosis and infection like severe UTI with severe dysurea

**2) Hormonal effects**

Common in benign tumors

-Adenoma of islets of langerhans may cause fatal hypoglycemia

-Thyroid adenoma causes hyperthyroidism

-Parathyroid adenoma causes hyperparathyroidism with osteoporosis and renal stones

**Systemic effects**

**Cancer Cachexia** (wasting syndrome)

*Kakos = bad*

*Hexia = condition*

Characterized by progressive loss of body mass, accompanied by profound weakness, anorexia, and anemia

-Is not caused by the nutritional demands of the tumor

In cancer patients the basal metabolic rate is increased, despite reduced food intake

(anorexia).

Pathogenesis of Cachexia

-Not clearly understood

-Related to cytokines produced by the tumor and host cells rather than reduced food

Intake

TNF alfa (produced by tumor cells & macrophages) mediate cachexia by:

- Increasing mobilization of fat from tissue stores

- Suppressing appetite

Other factors:

-Proteolysis inducing factors that increase the catabolism of muscles

-Lipid mobilizing factors that increase the catabolism of adipose tissue

Q - Define neoplasm, what is the basic classification of neoplasms,

Q – Enumerate the steps of invasion & metastasis of malignant tumors.

Q – What are the factors that determine the distrebution of tumor secondaries (metastases)?.

Q – Enumerate the factors that affect the rate of tumor gtrowth.

Q- How can the tumor cells escap the immune system in an immunocopetent hosts ?

Q- How can you explain that the intiated cells have a redudeced growth factor demand?

Q-What is the malignant counterpart of a benign tumor called

Leiomyoma ?

Q- What is the correlation between tumor grade and tumor aggressiveness.

Q- Explain why the initiated cells have reduced growth factor demand.

Q- Explain why DNA is the target of most of the chemical carcinogens