**LECTURE 7**

**CELL DISORDERS; *NEOPLASMS***

**NEOPLASIA**

Each cell has the ability to undergo mitosis, which is a tightly regulated and controlled process. Failure of these regulatory mechanisms causes the cell to become neoplastic. Whenever a normal cell passes through a cycle of cell division, the opportunity exists for it to become neoplastic. Neoplastic cells exhibit clonality and immortality.

***Terms***

Neoplasm: An abnormal mass of cells arising from abnormal cell division. May also be termed as a tumor. Neoplasms may be benign or malignant

Benign neoplasm. A neoplasm that does not metastasize or invade the surrounding tissue.

Malignant neoplasm. A neoplasm that metastasizes or invades the surrounding tissue. May be also be termed as cancer

Metastasis: Ability of a malignant tumor to establish a secondary tumor at a new location away from the primary tumor site

Invasion: Ability of a malignant tumor to spread to surrounding structures

**Normal Cell cycle control & Oncogenesis**

In cell division, Cells enter the mitotic cycle by progression from G0 to G1 in response

to growth factors and cytokines.

During G1, a commitment to enter the *S phase* of DNA replication is termed the restricted,

or *R point*.

This checkpoint allows the cell to confirm that its DNA is intactand exact copy before replication of nuclear DNA in the S phase.

The process is regulated by cyclins D & E, which in turn activate members of the cyclin-dependent protein kinases (Cdk) family.

Cdk 2, 4, and 6 phosphorylate retinoblastoma protein (Rb), which then unleashes transcription factors of the E2F family.

E2F has been identified as an important transcriptional activator playing a role in cell cycle control.

E2F drives the cell past the R point and allows synthesis of genes involved in DNA replication. Cdk inhibitors are regulated by the tumor suppressor protein p53.

However, Cancer cells often display **a loss of R point control** through mechanisms such as overexpression of cyclin D1, loss of Cdk inhibitors, or inactivation of the phosphorylated Rb (pRb) or p53 proteins.

Decreased levels of a Cdk inhibitor are associated with a poor prognosis

in adenocarcinoma of the colon and certain cancers of the lung. Conversely, a number of malignant tumors have been shown to overexpress several cyclins and Cdks.

*Bcl-2 and Apoptosis*

Apoptosis, or programmed cell death, is an important regulatory pathway in eliminating cells that are no longer useful, injured or that may be harmful to the body.

Two major mechanisms trigger activation of the caspase cascade leading to apoptosis:

• Release of cytochrome c from mitochondria

• Binding of specific ligands to cell surface ‘‘death’’ receptors such as Fas and tumor necrosis factor (TNF)

For tumor cells to acquire malignancy, they must escape apoptosis by dismantling the apoptotic mechanism.

One mechanism is to**(a) *cause overexpression of Bcl-2***, an antiapoptosis protein.

Bcl-2 prevents release of cytochrome c from mitochondria, thus suppressing apoptosis.

Bcl-2 is overexpressed in follicular B-cell lymphomas. *( bcl-2 gene expression has been observed in a variety of other human cancers).*

Many human cancers show other abnormalities in the apoptotic cascade, including the **(*b)overexpression of proteins that block caspase activation*** *and the inactivating mutations*

*of pro-apoptotic proteins.*

*(c)* ***mutations of p53 gene.*** The p53 molecule prevents cells from entering the S phase of the cell cycle if there is damage to DNA.

It also augments repair of damaged DNA. If the DNA damage cannot be repaired, *p53* increases transcription of a gene that induces

apoptosis of the cell with the damaged DNA.

Most human cancers display either inactivating mutations of *p53* or abnormalities in the proteins that regulate *p53* activity

(d) **Retinoblastoma gene(Rb).** Rb is the protein product of the tumor suppressor gene *Rb*. As

previously mentioned, when Rb is phosphorylated, it induces the

release of E2F transcription factor, thereby allowing progression

of the cell cycle from G1 to S. Inactivating mutations in *Rb* permit

unregulated cell proliferation.

Retinoblastoma is a rare childhood intraocular cancer attributed to the inactivation of the *Rb* gene.

BRCA1 & BRCA 2 genes acts in check point for breast tissue DNA repair genes for tumor suppression.

***Nomenclature***

Neoplasms are based on whether they are benign or malignant and on the cell type. Examples:

Carcinoma. Malignant growth originating in epithelial tissue.

Sarcoma. Malignant growth originating in connective tissue.

Leukemia and lymphoma. Malignant growth arising in the blood-forming cells of bone marrow and lymph nodes.

***Benign neoplasm****s*

**Benign tumors** do not penetrate adjacent tissue borders nor spread to distant sites. They have suffix ‘‘oma’’ preceded by reference to the cell or tissue of origin.

*Examples of benign tumors include:-*

* *Epithelioma:* Benign tumor of squamous epithelium
* *Papilloma:* A neoplasm that grows outward from epithelium
* *Adenoma:* Benign tumor arising from glandular epithelium
* *Polyp:* Mass of tissue that bulges outward from a surface
* *Teratoma*: Arises from all three germ cell layers; may contain a variety of structures; occurs mainly in gonads, and may be benign or malignant. They do not penetrate adjacent tissue borders.

*Characteristical features;-*

1. The cells are similar in structure to the original cells and to each other.
2. The cells are cohesive.
3. Undergo Slow even growth
4. Encapsulated with a well defined border
5. The capsule separates the tumor from surrounding tissue.
6. Requires minimal blood supply
7. Lacks the ability to metastasize or invade surrounding structures
8. Mainly has local manifestations, rarely causes systemic features
9. Rarely recurs, ulcerates, becomes necrotic, or causes systemic problems.

***Malignant neoplasms*** possess the following features.

1. Their cell structure is atypical.
2. They lose resemblance to the cells of origin and to each other
3. Cells are not cohesive.
4. Growth pattern is irregular.
5. There is no capsule formation.
6. Cells invade the adjacent cells. (metastasis)
7. Have the ability to metastasize
8. Growth rates vary with disorganized & random spatial arranged cells
9. Systemic manifestations are common
10. Blood supply is profuse.

**Causes of Neoplasia**

The exact cause of cancer is not known. However there are two theories that attempt to explain the causation of cancer, mutational and non mutational:

***Mutational theories***

These theories suggest that cancer genes can cause a genetic mutation or rearrangement that makes a cell become cancerous.

Numerous substances that are of a physical or chemical nature or oncogenic viruses have been identified as having cancer-causing abilities.

Activation is the first step in cancer-causing mutation, whereby certain individuals have enzymes that modify carcinogens to bind to nuclear DNA.

Initiation and promotion. Initial mutation increases the sensitivity of the cell to surrounding promoters. and a larger population of initiated cells is formed; this process continues for several cycles before a tumorous mass is formed.

***Non-Mutational theories***

These theories suggest that cancers arise from activation of genes normally repressed, resulting in

failure to respond to the process of differentiation.

Cells are embryonic in appearance. Frequency of malignancy increases during periods of alteration in growth and development

**Viruses in human cancers**.

One RNA retrovirus and five DNA viruses are associated with human cancers

*1. RNA Retrovirus*

1. Human T-Cell Leukemia Virus-1 (HTLV-1) is an RNA retrovirus that has been firmly associated with a rare adult T-cell leukemia endemic in southern Japan and the Caribbean basin.

Leukemia develops in less than 5% of infected persons and may have a latency of 40 years for its development.

HTLV-1 has a tropism for CD4\_ lymphocytes.

HTLV-1 genome contains no known oncogene, and does not integrate at a specific site in the host genome.

*2. DNA Viruses*

*A]. Human Papillomaviruses (HPVs)*

HPVs induce lesions in humans that progress to squamous cell carcinoma.

More than 80 distinct HPVs have been identified. Most are associated with benign lesions such as skin warts, genital warts, and laryngeal papillomas.

At least 20 HPV types are associated with cancer of the uterine cervix, *(esp HPV subtype 16 and 18)*

E6 and E7 are the major oncoproteins encoded by HPV. E6 targets p53 for degradation, and E7 inhibits Rb, thereby eliminating the tumor suppressing functions of these gene products.

*B]. Epstein-Barr Virus (EBV)*

EBV is a widely disseminated herpesvirus; 95% of adults worldwide have antibodies to it. EBV infects B lymphocytes and gives them the ability to proliferate indefinitely in vitro (immortalizes them).

EBV can cause infectious mononucleosis, a short-lived lymphoproliferative disease; however, it is also associated with the development of certain human cancers. EBV is also linked to the

following conditions:

(A) Burkitt lymphoma, a childhood cancer localized mainly to equatorial Africa: Prolonged stimulation of the immune system, such as occurs in malarial infections in equatorial Africa,may result in uncontrolled B-cell proliferation, which may, in turn, lead to deregulation of the c-*myc* oncogene and uncontrolled proliferation of a malignant clone of B cells.

(B) Nasopharyngeal cancer: This variant of squamous cell carcinoma is endemic in southern China and parts of Africa

*3. Hepatitis Viruses*

Epidemiological studies have established an association between chronic infection with hepatitis B virus (chronic hepatitis and cirrhosis) and primary hepatocellular carcinoma.

Chronic infection with a hepatotropic RNA virus (hepatitis C virus) also carries a high risk of hepatocellular carcinoma.

*4. Human Herpes Virus 8 (HHV 8)*

Kaposi sarcoma is a vascular neoplasm most commonly associated with AIDS, and the neoplastic cells contain sequences of the virus HHV 8.

Like other DNA viruses, the HHV 8 genome encodes proteins that interfere with*P53 & Rb tumor suppressor pathways.*

**Physical Carcinogenesis**

**a). Ultraviolet (UV) Radiation**

Cancers attributed to sun exposure, namely basal cell carcinoma,squamous carcinoma, and melanoma, occur predominantlyin fair-skinned people. The effects of UV radiation oncells include enzyme inactivation, inhibition of cell division,mutagenesis, cell death, and cancer.

- *Xeroderma pigmentosum*, a disease with a high incidence of skin cancers resulting from sensitivity to sunlight,

**b). Asbestos & Mesothelioma**

Mesothelioma, a cancer of the pleural and peritoneal cavities, occurs mainly in workers who have had heavy exposure to asbestos.

There is a strong correlation between lung cancer and asbestos exposed cigarette smokers.

**Chemical Carcinogenesis**

***Pathogenesis;-***There are four stages of chemical carcinogenesis:

1. **Initiation:** A mutation in a single cell occurs.

2. **Promotion**: Clonal expansion of the initiated cell occurs, but

the altered cells remain dependent on the promoting stimulus.

3. **Progression**: Growth is autonomous, and cells become immortalized.

4. **Cancer**: Cells acquire the capacity to invade and metastasize

*Common cancer markers*

* CA125🡪 ovarian carcinoma
* CALCITONIN🡪medullary carcinoma of thyroid
* PSA🡪prostatic cancer
* PLAP (placental alkaline phosphatase)🡪
* CEA(carcinoembryonic antigen)🡪gastrointestinal cancers
* AFP (a-Fetoprotein)
* CD99🡪Ewing sarcoma

**Cancer Invasion/Spread**

**Carcinoma in Situ**

Most carcinomas begin as localized growths confined to the epithelium

in which they arise. As long as they do not penetrate the

epithelial basement membrane, such tumors are termed carcinoma

in situ. At this stage they are asymptomatic and curable

*Hematogenous Metastases*

Capillaries and venules are more commonly invaded than are

thicker-walled arterioles and arteries. Because the liver receives

blood from the gastrointestinal (GI) tract, abdominal tumors can

lead to hepatic metastases. Other tumors penetrate systemic veins

that eventually drain into the vena cava and hence to the lungs.

Some tumor cells pass through the microcirculation to reach the

brain and the bones.

*Lymphatic Metastases*

Lymphatic capillaries lack a basement membrane; hence, tumor

cells can penetrate them more readily than capillaries. Tumors arising

in tissues that have a rich lymphatic network (e.g., the breast)

often spread by this route. Cells that penetrate lymphatics are carried

to the regional draining lymph nodes, where they lodge and

grow. Lymph nodes bearing metastatic deposits may be enlarged

many times their normal size, often becoming larger than the primary

lesion.

*Seeding of Body Cavities*

Malignant tumors arising in organs adjacent to the peritoneal and

pleural cavities may shed cells into these spaces. Tumors in these

sites produce large amounts of fluid (e.g., ascites, pleural

fluid).

Occasionally seeding into the pericardial cavity, joint space& brain spaces.

**Cancer Grading & Staging**

In an attempt to predict the behavior of a tumor, and to establish

criteria for therapy, many cancers are classified by grade and stage.

The choices of surgery and treatment are influenced by stage,

which reflects the extent of spread, and grade, which reflects cellular

characteristics.

***Grading***

Cytological and histological grading are based on the degree of anaplasia and on the number of proliferating cells.

Grading classify tumors into three or four grades.

Low-grade tumors are well differentiated, and high-grade ones are anaplastic.

***Staging***

Commonly used criteria include;-

*(a) tumor size*

*(b) extent of local growth*

*(c) presence of lymph node metastases*

*(d) presence* *of distant metastases*.

These criteria have been coded internationally as TNM cancer staging system:

 **T**: refers to size of primary tumor

 **N**: regional node metastases

 **M**: presence and extent of distant metastases