III. Oncogenic RNA Viruses

- HTLV-1 is associated with T cell Leukemia/lymphoma that is endemic in certain parts of Japan and the Caribbean
- HTLV-1 has tropism for CD4+ T cell and human infection requires transmission of infected T cells through sexual intercourse, blood products, or breastfeeding.
- Leukemia develops only in about 3-5% of infected persons after a long latent period of 20-50 years
- The HTLV-1 genome does not contain a viral oncogene with no consistent integration site next to a cellular oncogene has been discovered

Pathogenesis

- HTLV-1 genome contains PX region containing TAX gene

A. The *TAX* gene turns on several cytokine genes and their receptors (IL-2 , IL-2R and IL-15 and IL-15R), setting up an autocrine system that drives T cell proliferation

B. paracrine pathway is activated by increased production of granulocyte-macrophage colony-stimulating factor, which stimulates macrophages to produce other T cell mitogens

C. TAX activates cyclins and drive cell cycle progression

D. TAX can repress the function of *p16* and *TP53.*

IV. Oncogenic DNA Viruses

a. HPV has been associated with:

A- benign skin warts) (HPV 1,2,4) and .

B-genital warts(HPV6,11), Cervical cancer (HPV 16 & 18).

C- Oropharyngeal cancer.

Pathogenesis: The oncogenic potential of HPV can be related to products of two early viral genes, E6 and E7.

a. The E7 protein binds to the retinoblastoma protein and releases the E2F transcription factors that are sequestered by Rb, promoting progression through the cell cycle .

b. The E6 protein mediates the degradation of p53..

Note

- Infection with HPV itself is not sufficient for carcinogenesis and cotransfection with a mutated *RAS* results in malignant transformation.
- the primacy of HPV infection in the causation of cervical cancer is attested to by the near-complete protection from this cancer by anti-HPV vaccines

2. Epstein-Barr Virus is is implicated in the pathogenesis of

1-Burkitt lymphomas

2- lymphomas in immunosuppressed individuals with HIV infection or organ transplantation

3- Some forms of Hodgkin lymphoma

4- T cell lymphomas

5- NK cell lymphomas

6-Gastric carcinomas

7- Nasopharyngeal carcinoma

A. Burkitt lymphoma : is endemic in certain parts of Africa and is sporadic elsewhere.

- In endemic areas, tumor cells in virtually all affected patients carry the EBV genome.

1. One of the EBV-encoded genes, called *LMP1* (latent membrane protein 1) which :

a. Promotes B cell proliferation by activating signaling pathways, such as NF-κB and JAK/STAT,.

b. LMP1 prevents apoptosis by activating BCL2.,

2. Another EBV-encoded protein, EBNA2, transactivates several host genes, including cyclin D

.

Note: In immunologically normal persons, EBV-driven polyclonal B cell proliferation is controlled, and the affected patient either remains asymptomatic or develop a self-limited episode of infectious mononucleosis

- In regions of the world in which Burkitt lymphoma is endemic, concomitant (endemic) malaria impairs immune competence, allowing sustained B cell proliferation.
- although *LMP1* is the main transforming oncogene in the EBV genome, it is not expressed in Burkitt lymphoma, because it is one of the major viral antigens recognized by

the immune system; therefore Infected cells expressing

LMP-1 are kept in check by the immune system

- Lymphoma may emerge only when translocations activate the *MYC*, that allow the tumor to downregulate LMP1 and evade the immune system
- In patients with deficient T cell function, such as HIV patients and organ transplant recipients, EBV-infected B cells are B- lymphoblastoid-like cells which express LMP-1, that are recognized by T cells ;therefore, these proliferations can be subdued if T cell immunity can be restored, as may be achieved by withdrawal of immunosuppressive drugs in transplant recipients

3. Hepatitis B and Hepatitis C Viruses

- Account for 70% to 85% of hepatocellular carcinomas
- The mode of action of these viruses in neoplasia is not fully elucidated. because their genomes do not encode any viral oncoproteins,
- Their oncogenic effects multifactorial, but the dominant effect is immune- mediated chronic inflammation with hepatocyte death leading to regeneration and mutation.
- The activated immune cells also produce reactive oxygen . species, that are genotoxic and mutagenic

a. A key molecular step is activation of the nuclear factor-κB

pathway in hepatocytes and its activation blocks apoptosis, allowing the dividing hepatocytes to accumulate mutations

b. The HBV genome contains a gene *HBx,that* activates transcription factors and signal transduction pathways.

3. viral integration can cause multiple deletions that may harbor tumor suppressor genes

Note: HCV also is strongly linked to the pathogenesis of liver cancer by causing:

a. Chronic liver cell injury and compensatory regeneration,

b. HCV core protein, activatsing a variety of growth-promoting signal transduction pathways

- Helicobacter pylori :the first bacterium classified as a carcinogen and is implicated in the genesis of

a. Gastric adenocarcinomas

b. gastric Mucosa asssociated lymphoma(MALToma) that in early stages can be treated by irradication of H.pylori.

- The mechanism of H. pylori-induced gastric cancers is **multifactorial**, including Immunologically mediated chronic inflammation, stimulation of gastric cell proliferation, and production of reactive oxygen species that damage DNA.
- H.pylori pathogenicity genes, such as CagA, may also contribute by stimulating growth factor pathway.

Tumor Antigens

- Classified into 2 categories based on their patterns of expression:
- *1-tumor-specific antigens.:* which are present only on tumor cells and not on any normal cells.

2-t*umor-associated antigens.:* present on tumor cells and also on some normal cells.

- This classification, however, is imperfect, because many antigens thought to be tumor specific turned out to be expressed by some normal cells as well

- The modern classification of tumor antigens is based on their molecular structure and source.

1-Products of Mutated Oncogenes and Tumor Suppressor Genes : Antigens in this category are derived from mutant oncoproteins and cancer suppressor proteins.

- Unique tumor antigens arise from products of β-*catenin, RAS, p53,* and *CDK4* genes.
- The mutant proteins are present only in tumors, their peptides are expressed only in tumor cells.
- Since many tumors may carry the same mutation, such antigens are shared by different tumors.

2-Products of Other Mutated Genes

- Because of the genetic instability of tumor cells, many genes are mutated in these cells, including genes whose products are not related to the transformed phenotype and have no known function and products of these mutated genes are potential tumor antigens.
- These antigens are extremely diverse, because the carcinogens may randomly mutagenize virtually any gene.
- Mutated cellular proteins are found more frequently in chemical carcinogen- or radiation-induced animal tumors than in spontaneous human cancers.

3-Overexpressed or Aberrantly Expressed Cellular Proteins

- Tumor antigens may be normal cellular proteins that are abnormally expressed in tumor cells and elicit immune responses.
- Human melanomas tumor antigens are structurally normal proteins that are produced at low levels in normal cells and overexpressed in tumor cells

A. Tyrosinase, an enzyme involved in melanin biosynthesis that is expressed only in normal melanocytes and melanomas.

-T-cells from melanoma patients recognize peptides derived from tyrosinase, raising the possibility that tyrosinase

vaccines may stimulate such responses to melanomas

- It may be surprising that these patients are able to respond to a normal self-antigen.
- The probable explanation is that tyrosinase is normally produced in small amounts and in few cells that it is not recognized by the immune system and fails to induce tolerance.

B. "cancer-testis" antigens, are encoded by genes that are silent in all adult tissues except the testis .

- These antigens are tumor specific.
- Prototypic of this group is the MAGE family of genes.

- Although they are tumor specific, MAGE antigens are not unique for individual tumors.

MAGE-1 is expressed on :

1-37% of melanomas

2-lung, liver, stomach, and esophageal carcinomas.

4-Tumor Antigens Produced by Oncogenic Viruses

- The most potent of these antigens are proteins produced by latent DNA viruses such as HPV and EBV.
- vaccines against HPV antigens have been found effective in prevention of cervical cancers in young females.

5-Oncofetal Antigens

- Oncofetal antigens or embryonic antigens, such as carcinoembryonic antigen (CEA) and α-fetoprotein (αfp).

  expressed during embryogenesis but not in normal adult tissues.

- Derepression of the genes that encode these antigens causes their reexpression in colon and liver cancers.
- Used as serum markers for cancer.

6-Altered Cell Surface Glycolipids and Glycoproteins

These altered molecules include :

1-gangliosides.

2-blood group antigens.

3-mucins.

- Such antigens are not specifically expressed on tumors.
- They are present at higher levels on cancer cells than on normal cells.
- This class of antigens is a target for cancer therapy with specific antibodies.

<u>Examples include :</u>

1-CA-125 , expressed on ovarian carcinomas.

2-CA-19-9, expressed on ovarian carcinomas.

3-MUC-1, expressed on breast carcinomas.

7-Cell Type-Specific Differentiation Antigens

- Tumors express molecules that are normally present on the cells of origin.
- These antigens are called *differentiation antigens,* because they are specific for particular lineages or differentiation stages of various cell types.
- E.g lymphomas may be diagnosed as B-cell-derived tumors by the detection of surface markers characteristic of this lineage, such as CD10 and CD20.
- These differentiation antigens are typically normal self-antigens, and therefore they do not induce immune responses in tumor-bearing hosts.

CLINICAL ASPECTS OF NEOPLASIA

1.Effects of Tumor on Host: Location is crucial in both benign and malignant tumors.

a. A small (1-cm) pituitary adenoma can compress and destroy the normal gland and give rise to hypopituitarism.

b. A 0.5-cm leiomyoma in the wall of the renal artery may lead to renal ischemia and serious hypertension.

c. A small carcinoma within the common bile duct may induce fatal biliary tract obstruction.

d.Hormone production is seen with benign and malignantneoplasms arising in endocrine glands.

1. Adenomas and carcinomas of β-cells of the islets of the pancreas can produce hyperinsulinism, sometimes fatal.
2. some adenomas and carcinomas of the adrenal cortex elaborate aldosterone, which induces sodium retention, hypertension, and hypokalemia).

Such hormonal activity is more likely with benign tumors rather than with a corresponding carcinoma.

e. A tumor may ulcerate causing bleeding or infection.

f. Benign or malignant neoplasms that protrude into the gut lumen may become caught in the peristaltic pull of the gut, causing intussusception and intestinal obstruction or infarction.

- Progressive loss of body fat and lean body mass, with profound weakness, anorexia, and anemia.
- There is some correlation between the size and extent of spread of the cancer and the severity of the cachexia.
- Cachexia is not caused by the tumor nutritional demands .
- Although patients with cancer are often anorexic, current evidence indicates that cachexia results from the action of soluble factors such as cytokines produced by the tumor and the host rather than reduced food intake.
- In cancer patients basal metabolic rate is increased,

despite reduced food intake,This is in contrast to the lower metabolic rate that occurs inin starvation.

The basis of these metabolic abnormalities may be related to

1. TNF produced by macrophages in response to tumor cells or by the tumor cells themselves mediates cachexia.
2. TNF suppresses appetite and inhibits the action of lipoprotein lipase, inhibiting the release of free fatty acids from lipoproteins.
3. a protein-mobilizing factor called proteolysis-inducing factor, which causes breakdown of skeletal muscle proteins by the ubiquitin-proteosome pathway, has been detected in the serum of cancer patients.

- Symptom complexes that occur in patients with cancer and that cannot be readily explained by local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue of origin of the tumor.

- They appear in 10% to 15% of patients with cancer.

- It is important to recognize them for several reasons:

1.may represent the earliest manifestation of an occult neoplasm.

2-They may represent significant clinical problems and may even be lethal.

3- may mimic metastatic disease and confound treatment.

The most common syndromes are :

1-Hypercalcemia.: due to e synthesis of a parathyroid hormone-related protein (PTHrP) by squamous cell carcinoma of the lung .

Note: widespread osteolytic metastatic disease of bone can cause *hypercalcemia resulting from bone destruction but it is not a paraneoplastic syndrome*.

2-Cushing syndrome. is usually related to ectopic production of ACTH or ACTH-like polypeptides by small cell carcinoma a of the lung.

3-Nonbacterial thrombotic endocarditis: caused by adenocarcinoma.

4-Others as clubbing of the fingers and hypertrophic osteoarthropathy in patients with lung carcinomas.

5. hypercoagulability leading to venous thrombosis

- attempts to establish some estimate of its aggressiveness and It is based on :

1-the cytologic differentiation of tumor cells.

2-the number of mitoses within the tumor.

- The cancer may be classified as grade I, II, III, or IV, in order of increasing anaplasia.
- Criteria for the individual grades vary with each form of neoplasia
- Difficulties in establishing clear-cut criteria have led in some instances to descriptive characterizations as :

a.well-differentiated ,b.Moderately-differentiated.,c.Poorly-differentiated.d.Or highly anaplastic.

Staging of cancers is based on :

1-the size of the primary lesion.

2-its extent of spread to regional lymph nodes.

3-the presence or absence of metastases.

This assessment is usually based on clinical and radiographic examination (CTscan & MRI) and in some cases surgical exploration.