# TUMOR IMMUNOLOGY.

*Teaching Objectives:*

- Introduction to Cancer Immunology.
- Know the antigens expressed by cancer cells.
- Understand the nature of immune response to tumors.
- Study how cancers evade immune system.
- Describe the approaches used in Immunotherapy.

# Malignant Transformation:

- The proliferation of normal cells is carefully regulated.
- However, such cells when exposed to chemical carcinogens, irradiation and certain viruses may undergo mutations leading to their transformation into cells that are capable of uncontrolled growth, producing a tumor or neoplasm.

# Tumor immunology

* Pathological cell masses derived by abnormal and uncontrollable clonal expansion of single cell.

* Transformation of normal cells to malignant cells by:

a- Spontaneous mutation during daily cell division

b- It may be induced by
- chemical carcinogens
- physical carcinogens
- viruses

* Cells become antigenically different from normal cells

* They are recognized and destroyed by immune system

# Etiology Of Tumor.

1) Inherited :

Expression of inherited oncogene

e.g. viral gene incorporated into host gene

2) Viral:

- Human papilloma, herpes type 2, HBV, EBV (DNA)
- Human T-cell leukemia virus (RNA)

3) Chemical:

- Poly cyclic hydrocarbons cause sarcomas
- Aromatic amines cause mammary carcinoma
- Alkyl nitroso amines cause hepatoma

4) Radiological: Ultraviolet & ionizing irradiation

5) Spontaneous: failure in the cellular growth control

- **Cancer** cells are the progeny of a single transformed cell that undergo unregulated cell proliferation
- A tumor may be:

➢ Benign: If it is not capable of indefinite growth and the host survives.

➢ Malignant: If the tumor continues to grow indefinitely and metastasize, eventually killing the host.

- This uncontrolled growth may be due to up-regulation of oncogenes (cancer inducing genes) and/or down-regulation of tumor suppressor genes (that normally inhibit tumor growth often by inducing cell death).
- Solid tumors are collections of attached cancer cells which can **metastasize** (spread) from their original site.
- "Liquid" tumors are leukocyte tumors that circulate in the blood and may also form masses elsewhere in the body.

# Evidence for existence of an immune response against tumors.

The following criteria serve as evidence that tumors can elicit an immune response.

i. Tumors that have severe mononuclear cell infiltration have a better prognosis than those that lack it.

ii. Certain tumours regress spontaneously (e.g. melanomas, neuroblastomas).

iii. Some tumor metastases regress after removal of primary tumor.

iv. Although chemotherapy leads to death of a large number of tumor cells, the few that evade the action of the drugs can outgrow and kill the host. However, the immune system may be able to mount an attack against the few tumor cells that are spared by the chemotherapeutic agent.

v. There is an increased incidence of malignancies in immunodeficient patients such as AIDS patients who are susceptible to Kaposi sarcoma and transplant patients who are susceptible to Epstein Barr Virus (EBV)-induced lymphoma.

# Evidence for existence of an immune response against tumors (ctd).

vi. Tumor-specific antibodies and T lymphocytes (detected in cytotoxicity and proliferative response assays) have been observed in patients with tumors.

vii. The young and the old population have an increased incidence of tumors. These members of the population often have an immune system that is compromised.

viii. Hosts can be specifically immunized against various types of tumors.

# Tumor antigens.

- Tumorigenesis may lead to expression of new antigens or alteration in existing antigens that are found on normal cells.
- These antigens may include membrane receptors, regulators of cell cycle and apoptosis, or molecules involved in signal transduction pathways.

# Tumor Associated Antigens.

**1). Viral Antigen:**

a- Viral proteins and glycoproteins

b- New antigens produced by virally infected host cells under control of viral nucleic acid

**2). Tumor specific antigens:**

- Tumor cells develop new antigen specific to their carcinogens

**3). Tumor specific transplantation antigens:**

- Tumor cells express new MHC antigens due to alteration of normally present MHC antigens.

# Tumor Associated Antigens (ctd).

4). **Oncofetal antigens:**

a- Carcino-embryonic antigens (CEA)

- Normally expressed during fetal life on fetal gut
- Reappearance in adult life:

  GIT, pancreas, biliary system and cancer breast

b- Alpha fetoprotein:

- Normally expressed in fetal life
- Reappearance in adult life; hepatoma

- Although chemical-, UV- or virus-induced tumors express neo-antigens, majority of the tumors are often weakly immunogenic or non-immunogenic.
- In most cases, tumor-specific transplantation Ags cannot be identified easily.

# Virus-induced tumors:

Viruses that cause tumors include.

- DNA viruses:

1. Papova (papilloma, polyoma) viruses. Ex. Papilloma virus causes cervical cancer
2. Hepatitis virus: Hepatitis B virus causes hepatocellular cancer.
3. Adenoviruses

- RNA viruses:

Retroviruses: Human T-lymphotropic viruses (HTLV-I and HTLV-II) causes adult T cell leukemia.

Virus-induced tumors express tumor-associated viral Ags these are cell surface antigens that are distinct from antigens on the virion itself.

However, transplantation-associated viral Ags are shared by all tumors induced by the same virus, regardless of tissue origin of the tumor or normal animal in which the tumor exists.

# Chemically-induced tumors

- Chemically-induced tumors are different from virally-induced tumors in that they are extremely heterogeneous in their antigenic characteristics.
- Thus, any two tumors induced by the same chemical, even in the same animal, rarely share common tumor specific antigens. These unique antigens on chemically-induced tumors are referred to as tumor-specific transplantation antigens (TSTA).

# Immune Surveillance System

* During neoplastic transformation, new antigen develops

* The host recognize them as non-self antigens

* Cell mediated immune reactions attack these non-self tumor cells

* Immune response act as surveillance system to detect and eliminate newly arising neoplastic cells

# Immune Surveillance System

This system include :

1) Natural killer (NK) cells

They kill directly tumor cells, helped by interferon, IL-2

2) Cytotoxic T-cells

They also kill directly tumor cells

3) Cell mediated T-cells (effector T-cells)

They produce and release a variety of lymphokines :

a-Macrophage activation factor that activate macrophage

b-Gamma interferon and interleukin-2 that activate NK

c-Tumor necrosis factor (cachectine)

# Immune Surveillance System

## 4) B-cells :

- Tumor associated antigens stimulate production of specific antibodies by host B-cells

- These specific antibodies bind together on tumor cell surface leading to destruction of tumor through:

### a- Antibody mediated-cytotoxicity :

Cytotoxic T-cells —kill→ IgG-coated tumor cells

### b- Activation of macrophages

Sensitized T-cells —release→ macrophage activating factor

IgG-coated tumor cells ← macrophages

macrophages —activate→ macrophage activating factor

### c- Activation of classical pathway of complement leading to Lysis of tumor cells

# Tumor Escape

Mechanisms by which tumor escape immune defenses:

1) Reduced levels or absence of MHCI molecule on tumor so that they can not be recognized by CTLs

2) Some tumors stop expressing the antigens

These tumors are called “antigen loss variants”

3) Production of immunosuppressive factors by tumor e.g. transforming growth factor (TGF-β)

4) Tumor antigens may induce specific immunologic tolerance

# Tumor Escape (ctd)

5) Tumor cells have an inherent defect in antigen processing and presentation

6) Blocking of receptors on T-cells by specific antigen - antibodies complex (after shedding of tumor Ag) prevents them from recognizing and attacking tumor cells

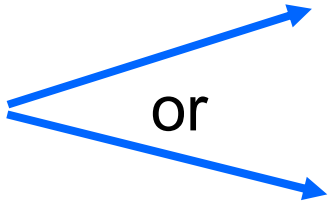
7) Antigens on the surface of tumors may be masked by sialic acid-containing mucopolysaccharides

8) Immune suppression of the host as in transplant patients who show a higher incidence of malignancy

# Tumor Markers

* Tumor markers :

* They are either



or

Tumor antigens

Tumor products
(enzymes and hormones)

* Tumor products are released in the serum of patients

* They are used to confirm diagnosis and follow up the response to therapy

# Tumor Antigens as tumor markers

1) Alpha fetoprotein antigen (AFP) in cases of hepatoma

2) Carcinoembryoinic antigen (CEA) in gastrointestinal tumors, tumors of biliary system and cancer breast

3) Cancer antigen 125 (CA 125) in ovarian carcinoma

4) Cancer antigen 15-3 (CA15-3) in breast cancer

5) Cancer antigen 19-9 in colon and pancreatic tumor

6) Prostatic specific antigen (PSA) in prostatic tumors

# Tumor Products

a) Hormones :

- Human chorionic gonadotrophins (HCG) are secreted in cases of choriocarcinoma
- Thyroxin (T3 & T4) is secreted in cases of cancer of thyroid gland

b) Enzymes :

- Acid phosphatase enzymes in cases of cancer of prostate
- Alkaline phosphatese, lipase and amylase enzymes in cases of cancer pancreas

# Immunotherapy.

- Immunotherapy has been used as a novel mode to treat cancer.
- Both active and passive means of stimulating the non-specific immune systems have been employed, in some cases with significant success.

1) **Active Immunotherapy:** Wherein the host actively participates in mounting an immune response

- a). **Nonspecific:**

i. Bacillus Calmette-Guerin (BCG)

ii. Corynebacterium parvum

- -These activate macrophages to be tumoricidal.

**b. Specific:**

i. Hepatitis B vaccine

ii. Human Papilloma virus (HPV) vaccine

2. **Passive Immunotherapy:** This involves transfer of preformed Abs, immune cells and other factors into the hosts.

a. **Specific:**

i. Antibodies against tumor Ags (e.g. Her2/Neu for treatment of breast cancer)

ii. Abs against IL-2R for Human T lymphotropic virus (HTLV-1)-induced adult T cell leukemia.

iii. Abs against CD20 expressed on non-Hodgkin's B cell lymphoma.

iv. Abs conjugated to toxins, radioisotopes and anti-cancer drugs have also been used. These enter the cells and inhibit protein synthesis. E.g. anti-CD20 conjugated to Pseudomonas toxin or ricin toxin.

**b. Nonspecific:**

i. Adoptive Transfer of lymphocytes:

1) Lymphokine-activated killer (LAK) cells which are IL-2 activated T and NK cells.

2) Tumor-infiltrating lymphocytes (TIL)

ii. Dendritic cells pulsed with tumor Ags may induce tumor-specific T cell responses. As tumor Ags are usually not known, tumor lysates are used.

iii. Cytokines

1) IL-2: Activates T cells/NK cells used in the treatment of renal cell carcinoma and melanoma

2) Interferon alpha (IFN-α): Induces MHC expression on tumors and used in the treatment of hairy B cell leukemias
3) Interferon gamma: Increases MHC expression; for treatment of ovarian cancers.
4) TNF-α: Kills tumor cells.

iv. Cytokine gene transfected tumor cells may also be used.