TUMOR IMMUNOLOGY.

Teaching Objectives:

- 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.

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

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 → activate

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
  - Tumor antigens
  - or
  - 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

Å a). **Nonspecific:**

i. Bacillus Calmette-Guerin (BCG)

ii. Corynebacterium parvum

Å -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.