

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

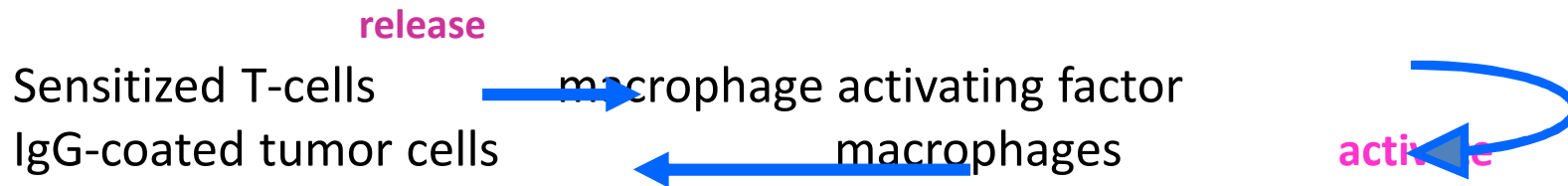
4) B-cells :

- 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 :



b- Activation of macrophages



c- Activation of classical pathway of complement

Lysis of tumor cells

leading to

Tumor Escape

Mechanisms by which tumor escape immune defenses:

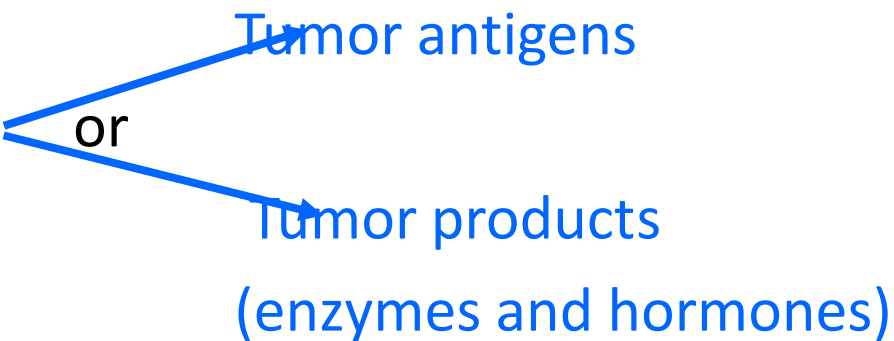
- 1) Reduced levels or absence of MHC I molecule on tumor so that they can not be recognized by CTLs
- 2) Some tumors stop expressing the antigens
These tumors are called “antigen loss variants”
- 3) Production of immunosuppressive factors by tumor e.g. transforming growth factor (TGF- β)
- 4) Tumor 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) Carcinoembryonic 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 phosphatase, 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.