

Tumor Immunology

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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**. A tumor may be

- 1) Benign, if it is not capable of indefinite growth and the host survives.
- 2) Malignant, if the tumor continues to grow indefinitely and spreads (metastasizes), eventually killing the host.

This uncontrolled growth may be due to upregulation of **oncogenes** (cancer-inducing genes) and/or downregulation of **tumor suppressor genes** (that normally inhibit tumor growth often by inducing cell death).

Evidence for existence of an immune response against tumors

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

1. Certain tumors regress spontaneously (*e.g.*, melanomas, neuroblastomas). suggesting an immunological response.
2. Tumors that have severe mononuclear cell infiltration have a better prognosis than those that lack it.
3. Some tumor metastases regress after removal of primary tumor which reduces the tumor load, thereby inducing the immune system to kill the residual tumor..
4. Although chemotherapy leads to rejection of a large number of tumor cells, the few tumor cells 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.
5. 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.
6. Tumor-specific antibodies and T lymphocytes (detected in cytotoxicity and proliferative response assays) have been observed in patients with tumors.
7. 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.
8. Hosts can be specifically immunized against various types of tumors demonstrating tumor Ags can elicit an immune response.

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. There are 2 main types of tumor antigens.

1. **Tumor-specific transplantation antigens** (TSTA) which are unique to tumor cells and not expressed on normal cells. They are responsible for rejection of the tumor.
2. **Tumor associated transplantation antigens** (TATA) that are expressed by tumor cells and normal cells.

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. Also, some of these antigens may be secreted while others include membrane-associated molecules.

Tumor associated transplantation antigens (TATA)

The majority of tumor Ags are the **tumor associated transplantation antigens (TATA)**. They may be expressed at higher levels on tumor cells when compared to normal cells. Alternatively, they may be expressed only during development of cells and lost during adult life but re-expressed in tumors. These include the **tumor-associated developmental Ags (TADA)** and **tumor-associated viral Ags (TAVA)**.

Tumor-associated developmental Ags (TADA) or Onco-fetal antigens

These include **alpha-fetoprotein (AFP)** and **carcino-embryonic antigen (CEA)** found secreted in the serum. AFP is found in patients with hepatocellular carcinoma whereas CEA is found in colon cancer. These are important in diagnosis.

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 (TAVA)**. These are cell surface antigens that are distinct from antigens on the virion itself. However, these transplantation-associated viral Ags are shared by all tumors induced by the same virus, regardless of tissue origin of the tumor or 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)**.

Syngeneic, Allogeneic and Xenogeneic Tumors:

A tumor that grows in an animal strain will also grow in another animal belonging to the same inbred strain obtained by repeated brother-sister matings. These animals express the same MHC molecules and are referred to as **syngeneic**. However, most normal animal populations are **allogeneic** and have various MHC haplotypes. Thus, a tumor transferred from one animal to another animal belonging to an outbred strain is rejected because of the allo-MHC rather than the TSTA. A tumor transferred from an animal belonging to one species to another animal belonging to a different species is rapidly rejected because the animals are **xenogeneic**.

Immune response to tumors:

Evidence for immunity against malignancy comes mostly from experimental studies, wherein mice were immunized by administering irradiated tumor cells or following removal of a primary tumor challenged with the same live tumor. These animals were found to be resistant to rechallenge with the same live tumor. While Abs may develop against few cancers, cell-mediated immunity plays a critical role in tumor rejection. Thus, immunity can be transferred, in most cases, from an animal, in which a tumor has regressed, to a naive syngeneic recipient by administration of T lymphocytes. The T helper (Th) cells recognize the tumor Ags that may be shed from tumors and internalized, processed and presented in association with class II MHC on antigen

presenting cells. These Th cells when activated will produce cytokines. Thus, the Th cells provide help to B cells in Ab production. The cytokines such as IFN- γ may also activate macrophages to become tumoricidal. Furthermore, the Th cells also provide help to tumor-specific cytotoxic T cells (CTL) by inducing their proliferation and differentiation. The CTL recognize tumor Ags in the context of class I MHC and mediate tumor cell lysis. In tumors that exhibit decreased MHC Ags, natural killer (NK) cells are important in mediating tumor rejection.

How tumors evade immune system:

According to the Immune Surveillance Theory, cancer cells that arise in the body are eliminated by the immune system. However, due to impaired immune reactivity, the cancer cells escape destruction.

Tumors evade immune recognition by several mechanisms. Some tumors may evade the immune system by secreting immunosuppressive molecules such as interleukin-10 (IL-10) or transforming growth factor-beta (TGF- β) and others may induce regulatory cells particularly the CD4⁺CD25⁺ FoxP3⁺ T regulatory cells or myeloid derived suppressor cells (MDSC) which have both granulocyte and macrophage markers (Gr-1⁺CD11b⁺). Also, some tumors may shed their antigens which in turn may interact and block antibodies and T cells from reacting with the tumor cells. Tumors may not express neo-antigens that are immunogenic or they may fail to express co-stimulatory molecules required for the activation of T cells. In addition, certain tumors are known to lack or be poor expressers of MHC antigen. Such tumors are however, susceptible to NK cell cytotoxicity. Another reason for failure of immune surveillance may be the fact that in the early development of a tumor, the amount of antigen may be too small to stimulate the immune system (low dose tolerance) or due to the rapid proliferation of malignant cells (high dose tolerance), the immune system is quickly overwhelmed. Tumor cells may express the death inducing ligand, FasL (CD95L) whereas the T cells express the death receptor, Fas (CD95), thereby leading to killing of the T cells. However, CTL have been shown to express FasL and some tumors may express Fas.

Immunotherapy

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

- 1) Active Immunotherapy: Wherein the host actively participates in mounting an immune response
 - a) Specific activation using vaccines:
 - i) Hepatitis B vaccine useful against development of hepatocellular cancer.
 - ii) Human Papilloma virus (HPV) vaccine (Gardasil) has been successfully used to prevent cervical cancers
 - b) Nonspecific activation which results in stimulation of generalized immune response is achieved by immunization with:
 - i) Bacillus Calmette-Guerin (BCG) mycobacteria.
 - ii) Corynebacterium parvumThese microbes lead to activation of macrophages which are tumoricidal.
- 2) Passive Immunotherapy: This involves transfer of preformed Abs, immune cells and other factors into the hosts.
 - a) Specific: Preformed Abs or CTL directed against tumor Ags are used in the treatment of tumors
 - i) Antibodies against tumor Ags (e.g. Abs against Her2/Neu for treatment of breast cancer)
 - ii) Abs against interleukin-2 receptor (IL-2R) are used in the treatment of Human T lymphotropic virus (HTLV-1)-induced adult T cell leukemia as this virus infects T cells and leads to production of IL-2 that binds to IL-2R and induces the T cell proliferation.
 - iii) Abs against CD20 expressed on all B cells are used in the treatment of non Hodgkin's B cell lymphoma.

These Abs bind to tumor Ags on the cell surface and activate complement (C') to mediate tumor cell lysis. In addition, Fc receptor bearing cells such as NK cells, macrophages and granulocytes may bind to the Ag-Ab complexes on tumor cell surface and mediate tumor cell killing through Ab-dependent cell-mediated cytotoxicity.

iv) Abs conjugated to toxins, radioisotopes and anti-cancer drugs have also been used. These enter the cells and inhibit protein synthesis because of the toxin. e.g. anti-CD20 conjugated to Pseudomonas toxin or ricin toxin has been used in the treatment of B cell tumors.

There are several problems with the use of Abs

(1) Abs are not efficient because the tumor Ags are associated with class I MHC Ags.

(2) The tumors may shed Ag or Ag-Ab complexes. Thus, immune cells cannot mediate tumor destruction.

(3) Some Abs may not be cytotoxic.

(4) Abs may bind nonspecifically to immune cells expressing the Fc receptors which include NK cells, B cells, macrophages and granulocytes without binding to tumor cells.

v) Dendritic cells pulsed with tumor Ags may be administered which can present tumor Ags in the context of class II MHC to tumor-specific Th cells. As tumor Ags are usually not known, tumor lysates are used. The Th cells may in turn produce cytokines which lead to development of CTL activity.

On the other hand, the dendritic cells may be transfected with the gene for tumor Ags, in which case, the Ags will associate with the Class I MHC and elicit a CTL response.

b) Nonspecific:

i) Adoptive Transfer of lymphocytes:

(1) Lymphokine-activated killer (LAK) cells which are IL-2 activated T cells and NK cells can be used in the treatment of melanoma and renal cell carcinoma

(2) Tumor-infiltrating lymphocytes (TIL) include T cells and NK cells. While the infiltrating NK cells will kill tumors nonspecifically, the CTL will be able to kill specific tumor targets.

ii) Cytokines

(1) Interleukin-2 (IL-2): Activates T cells/NK cells which express IL-2 receptors and leads to their proliferation. Used in the treatment of renal cell carcinoma and melanoma,

(2) Interferon-alfa (IFN α): Activates NK cell activity against tumors and also used in the treatment of Kaposi sarcoma, renal cell carcinoma and melanomas.

(3) IFN- γ : Increases class II MHC expression; used in the treatment of ovarian cancers.

(4) Tumor necrosis factor (TNF)- α : Kills tumor cells.

(5) Granulocyte-macrophage colony stimulating factor (GM-CSF): Useful in overcoming neutropenia due to chemo- or radiation therapy

iii) Cytokine gene transfected tumor cells may also be used which can activate T or LAK cells that can mediate anti-tumor immunity.

Reading: Immunology

By Male, Brostoff, Roth and Roitt

7th Edition

Pages 401-419