"The idea that a small group of tumor cells arises and expresses a new antigenic potential on membranes, induces an effective immune response followed by tumor regression without any visible clinical hint of its existence is unacceptable."

Macfarlane Burnet, immunologist 1957.

The tissue organization itself represents a kind of obstacle to the proliferation of tumor cells. For example, in normal epithelial cells that lose contact with the basement membrane, a special type of apoptosis called anoikis is activated. This mechanism limits the ability of epithelial cells to detach from normal tissue locations and grow at ectopic sites.

In addition to these cellular and tissue-specific mechanisms, mammals have developed another line of defense - the immune system. The immune system is very efficient in detecting and eliminating foreign infectious agents, sparing its own cells and tissues. Molecules appear on tumor cells that the tumor carrier's immune system could recognize as foreign and eliminate them with its effector mechanisms. This possible role of the immune system is called immune surveillance.

Evidence in support of this concept:

Histopathologically, it has been proven that there are lymphocytic infiltrates around the tumor - mononuclear cell infiltrates of T lymphocytes, NK cells, macrophages and PMN cells, and that activated lymphocytes and macrophages are found in the lymph glands that drain the region affected by the tumor.

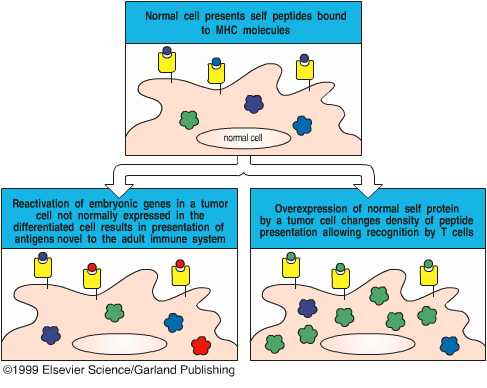
Sarcoma can be artificially induced on the skin of inbred mice by methyl-cholanthrene (MCA). When a tumor produced in this way is transplanted into a healthy, synergistic individual, it becomes ill because the tumor continues to grow. However, when the tumor tissue is transplanted back into the host, it rejects it. Moreover, T cells from an animal with a tumor can transfer protective immunity to other individuals that do not have a tumor. The immune response to tumors shows the characteristics of specific immunity: specificity, memory and the ability to mediation through lymphocytes.

The immune system fights tumor cells with effector mechanisms of both non-specific and specific immunity. However, due to the weak expression of tumor antigens or their weak immunogenicity, the immune system is powerless in the fight against tumors that continue to grow, which is also one of the mechanisms for avoiding the immune response. Another mechanism for avoiding the immune response is the rapid growth and spread of the tumor, but also the specialized mechanisms developed by the tumor in order to avoid the immune response.

**Tumor antigens**

The presence of molecules on tumor cells that are recognized by cells of specific immunity triggers an immune response. It has been proven both in experimental animals and in humans suffering from malignant diseases. The identification of tumor antigens is important because they can be used as components of antitumor vaccines and because the antibodies and effector T lymphocytes produced by them can be used in immunotherapy. Tumor antigens can be classified based on different criteria.

Tumor antigens can be mutated proteins of host cells. Tumors express genes necessary for malignant transformation. These genes are caused by point mutations, deletions, translocations or viral infections that attack oncogenic or tumor suppressor genes. The products of the altered genes are synthesized in the cytoplasm and, like all other cytosolic proteins, enter the process of processing and presentation as part of class I MHC molecules (Picture 1). As the altered genes are not present in normal cells, the proteins they encode induce a host T cell response (no tolerance). Specific immune responses can control tumors, and mutated host proteins can function as tumor antigens. Mutated cell proteins in the role of tumor antigens are more often found in tumors caused by carcinogenic substances or radiation than in "spontaneous" tumors.



Picture 1

Tumor antigens can also be encoded by oncogenic viruses. Products of oncogenic viruses function as tumor antigens and cause the response of specific T lymphocytes that tend to eliminate the tumor (DNA viruses, PAPOVA viruses, Simian virus 40-SV 40, adenoviruses, EBV virus and many others).

**Immune response to tumors**

The basic mechanism of the immune response to tumors is the killing of tumor cells via effector mechanisms of cell-mediated and humoral immunity, as well as by cells of non-specific immunity (macrophages and NK cells). CTLs may have a surveillance function by recognizing and killing potentially malignant cells. The function of CD4+T helper lymphocytes has not been sufficiently studied, but it is thought that they provide cytokines such as TNF-α and interferon-γ that can increase expression of type I MHC molecules on tumor cell and sensitivity to lysis by CTLs. The probable mechanism of activation of CD8+T and CD4+T lymphocytes is the so-called cross presentation. Tumor antigens are processed by professional antigen-presenting cells - APCs and presented as part of MHC class I molecules to be recognized by CD8+T lymphocytes. APCs express costimulators that provide the signals required for the differentiation of CD8+ T lymphocytes into antitumor CTLs, and also express a class of MHC class II molecules that can activate CD4+ helper T lymphocytes.

**Non-specific immune response to tumors**

**Macrophages**- activated macrophages successfully lyse tumor cells *in vitro*. Mechanisms of macrophage activation in the fight against tumor cells are insufficiently investigated. However, macrophages can be activated by recognition of some tumor cell surface antigens and by INF-γ from specific T lymphocytes. Macrophages kill tumor cells by releasing lysosomal enzymes, reactive oxygen radicals and nitric oxide-NO. Activated macrophages produce TNF that kills tumor cells through direct toxic effects or indirectly in blood vessels.

Virchow was the first to discover leukocytes in and at the border of tumor tissue in 1863. Today it is known that tumor-associated macrophages (TAMs) make up the major part of the leukocyte infiltrate around many tumors (both primary and metastases). TAMs have numerous functions, they affect tumor growth in two ways: progressive and regressive.

**NK cells** *in vitro* kill different types of tumor cells (especially hematopoietic tissue tumors), especially those that avoid lysis by CTLs by reducing expression of MHC class I molecules. By reducing the expression of class I MHC molecules, tumor cells become "easy" targets for NK cells. NK cells can bind to cells coated with IgG antibodies, via Fc receptors. The tumoricidal capacity of NK cells is increased by cytokines IL-2 and IL-12, through stimulation of activation (NK cells activated by LAK-lymphokines). *In vivo*, the role of NK cells has been insufficiently investigated, but it has been experimentally proven that mice with T cell deficiency do not have an increased incidence of spontaneous tumors because they have a normal number of NK cells. It has been found that patients with NK cell deficiency have an increased incidence of lymphoma.

**Specific immune response to tumors**

The activity of CD4+ T lymphocytes depends on antigen-presenting cells that take up, process and display tumor antigens as part of their MHC class II molecules. Upon recognition of the complex peptide + MHC molecule class II, CD4+ T lymphocytes are activated and produce cytokines that can directly (tumor necrosis factor, TNF-α) or indirectly (interferon γ- IFN-γ) stimulate other cells to kill malignant cells. They can also increase the expression of MHC class I molecules on tumor cells and the sensitivity to lysis by CTLs.

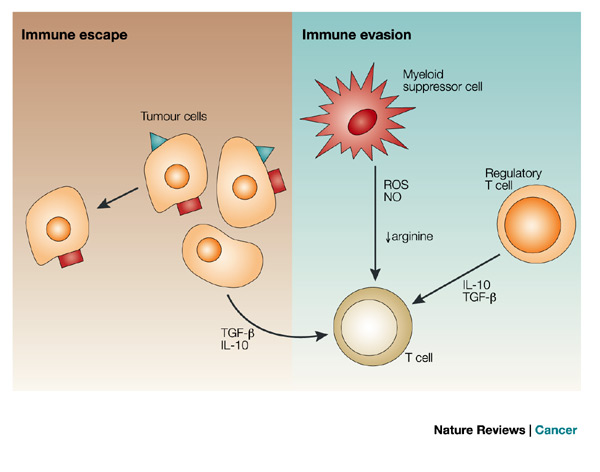
**CTLs** may have a surveillance function, by recognizing and killing potentially malignant cells. A likely mechanism of activation of tumor-specific CD8+ T lymphocytes is via cross-presentation. Most tumor cells are not derived from APCs, so they do not express the costimulatory molecules required for the induction of a T-cell response, nor do they express MHC class II molecules required for the activation of helper T-lymphocytes that stimulate the proliferation and differentiation of CD8+ T lymphocytes. Tumor cells and their antigens are processed in professional antigen-presenting cells - APCs (primarily in dendritic cells), where peptides originating from tumor antigens bind to MHC molecules and are presented to T lymphocytes. APCs express costimulators that provide signals for activation and differentiation of CD8+ T lymphocytes into antitumor CTLs. APCs also express MHC class II molecules that can activate CD4+ helper T lymphocytes (Picture 2). Cytotoxic CD8+ T lymphocytes (CTL) are crucial in killing tumor cells. These cells are not fully differentiated upon leaving the thymus. Although they carry a specific antigen receptor and can recognize the target cell, they are not yet capable of killing it. These are the so-called precytotoxic cells. Their further differentiation into functional CTLs requires two distinct types of signals. The first represents specific antigen recognition on the target cell, and the second depends on various cytokines or costimulators. The differentiation of pre-cytotoxic cells into CTL represents the process of acquiring molecules that are necessary for the lysis of the target cell. Killing of the target cell is strictly specific. A single CTL clone can kill only those target cells that carry the same complex of antigenic peptide and MHC molecules that initiated the differentiation of the pre-CTL cells. The killing process requires cell contact. It is achieved by the interaction of the TCR on the cytotoxic lymphocyte and the MHC class I antigen-molecule complex on the target cell, but also by additional interactions of various accessory molecules on both cells. There are two basic mechanisms by which cytotoxic lymphocytes kill target cells. One is based on the exocytosis of CTL granules and the action of perforin, and the other is realized by the interaction of the membrane molecules of the effector cell and the target cell (FasL and Fas interaction). Autologous tumor-specific CTLs can be isolated from the peripheral blood of tumor patients. The frequency of such tumor-specific CTL is significantly higher in the population of mononuclear cells that are isolated from solid tumor tissue, that is, in the population of so-called tumor-infiltrating lymphocytes (TIL).



picture 2

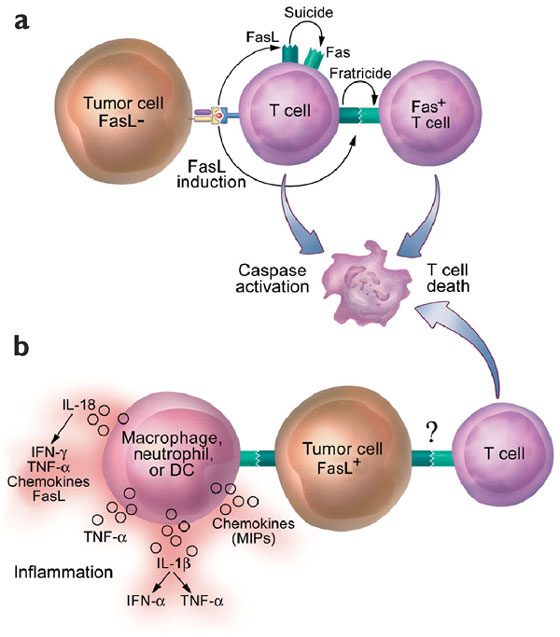
**Avoidance of immune responses**

* Tumors lose the expression of antigens that cause an immune response. This is one of the basic characteristics of fast-growing tumors. Tumor cells through immunoediting select only resistant clones, resulting in tumor cells that are resistant to immune responses or are not recognized by the components of the immune response.
* tumor cell products can "suppress" antitumor responses. An example of an immunosuppressive product is transforming growth factor β- **TGF-β**, which is secreted in large quantities by tumor cells and regulatory cells that are activated by tumor cells. TGF-β inhibits the proliferation and effector function of lymphocytes and macrophages (Picture 3).



picture 3

* Some tumor cells express Fas ligands that recognize Fas receptors on the surface of lymphocytes that try to destroy the tumor cell. The binding of Fas ligands to Fas receptors leads to the death of lymphocytes by the process of apoptosis (Figure 4).



picture 4

* Tumor antigens can induce specific immune tolerance. Tumor antigens can induce anergy of host T lymphocytes, which is the result of B7-CTLA-4 interaction.
* Antigens on the surface of tumor cells can be hidden from the immune system by glycocalyx molecules such as sialic acid. The process is called antigen masking. A tumor cell can protect itself by forming the so-called fibrin capsules.

Additional reading: Abul Abbas. Basic immunology. Immune response to tumors. p. 211-216.