Immunology Lecture – week 13

TUMOR IMMUNITY (Lippincott´s Immunology chapter 19)

A **tumor**, or **neoplasm**, is a collection of the clonal descendants of a cell whose growth has gone unchecked. When a tumor continues to grow and to invade healthy tissue, it is considered to be a **cancer**. **Malignant** tumors are distinguished from **benign** tumors by their progressive growth and invasiveness. **Metastasis** is a characteristic of many malignant tumors (cancers). Metastatic cells become dislodged from the main tumor, invade blood or lymphatic vessels, and travel to other tissues, where they continue to grow and to invade. In this way, tumors at one site can give rise to secondary tumors at other sites within the body. Classification of tumors is based on the embryonic origin of the tissue from which the malignant cells are derived. **Carcinomas** develop from endodermal or ectodermal tissues (e.g., skin, glands) and constitute the majority of malignant tumors, including cancers of the breast, colon, and lung. **Sarcomas** develop from bone and cartilage and have a much lower incidence than carcinomas. **Leukemias** are malignant cells of hematopoietic lineage that proliferate as individual cells, while **lymphomas** arise from malignant hematopoietic cells but grow as solid tumors.

Tumor immunity exists

- Proof of reactions of immunity to tumor
  - spontaneous regression of some tumors,
  - high incidence of tumors in immunodefficient patients.
  - antibodies and T lymfocytes reactins in some tumors
  - annimals ares successfully immunised against some tumors,
  - good prognosis in tumors with strong lymphoreticular infiltration

Bases of tumor immunity

- The reaction of immunity is based on reaction to foreign antigen
- Tumor must be recognised as foreign – endogennous antigen on the surface of self cells MHC I – Ts, Tc, NK
- *Alteration* of cell antigens during tumorgenesis (lack of MHC I – desactivation of KIR, new antgiens activation of KAR): activity of membrane molecules – new or supression of membrane proteins important for recognition and activation)
- Induced tumors – neo-antigens
- Spontanneous tumors – poor immunogens

The immune surveillance theory suggests that cancer cells frequently arise within the body but are normally eliminated before they multiply sufficiently to become clinically detectable. Accordingly, through the workings of an effective immune system that patrols the body and mounts responses against abnormal cells, most transformed cells never become true cancers. Tumors arise only if they are able to escape immune surveillance. Evidence supporting the immune surveillance theory comes from immunosuppressed and immunodeficient individuals who have increased tumor incidence.

NK cells have a limited ability to discriminate between tumor cells and normal cells. Recall that NK recognition of targets occurs via killer activation receptors (KARs) and killer inhibitory receptors (KIRs) (see Chapter 5). KIRs recognize human MHC class I molecules: HLA-B and HLA-C. Another inhibitory NK receptor, CD94, recognizes another class I molecule called HLAE. When a KAR is engaged by binding to its carbohydrate ligands on target cells, the “kill” signal to the NK cell is activated . However, if the KIR receptors are engaged by binding of ligands on the surface of a target cell, then the “do not kill” signal is received by the NK cell, and the target cell survives. Failure to engage the KIR will result in NK-induced lysis of the target cell. When expression of MHC I molecules on the cell surface is abnormally low, as is the case in some malignant cells, KIRs might not recognize ligands on the target (malignant) cell and might proceed to kill it. In some cases, Fc receptors on NK cells can bind to antibody present on tumor cells (produced as part of the adaptive response against the tumor cell), leading to antibody-dependent cellular cytotoxicity. NK cells that are induced to function attack malignant cells are sometimes referred to as **lymphokine-activated killer cells** (LAKs). These cells are generated in the presence of high concentrations of interleukin-2 and are able to kill fresh tumor cells.

Tumor-infiltrating lymphocytes (**TIL**) are T lymphocytes, often CD8+ CTLs. They may also include some CD4+ T cells and NKT cells. A therapeutic strategy against malignant melanoma involves obtaining tumor-specific TILs from tumor biopsies and expanding the cells by stimulating with interleukin-2. These cells are then injected back into the patient. In some cases, partial regression of the tumors has been observed.

Cytokines with antitumor activity are secreted by macrophages, which are often found in the vicinity of tumors.

Tumor necrosis factor (TNF) is one such antitumor cytokine. When injected into animals with tumors, TNF-α and TNF-β can stimulate necrosis of the tumor cells. TNF-α also inhibits angiogenesis, the growth of new blood vessels by decreasing blood flow to the tumor.

Interferons are another group of cytokines with antitumor activity. IFN-α, -β, and -γ have all been shown to increase MHC I expression on tumor cells (which often downregulate MHC I expression to evade the immune response). Increasing the MHC I expression can increase susceptibility of the tumor cells to CTLs. IFN-γ may also directly inhibit proliferation of tumor cells.

Specific antigen-dependent immune responses can develop to antigens that are present on tumor cells. Although they are not always effective in halting progression of a tumor, evidence exists that both humoral and cell-mediated immune responses can be induced in response to the presence of malignant cells.
Antibodies are known to be generated against certain tumor-specific antigens present on the surface of malignant cells.
CTLs can sometimes kill tumor cells by direct contact.
DTH reactions involve Th1 cells recruiting and activating macrophages, which attack and kill tumor cells.

Immunity against tumors

Nonspecific and specific, humoral and cellular – influence the growth and progression of tumors

Escape to immune mechanisms

Tumor
– does not present neoantigens that are immunogenic,
– does not express co-stimulating molecules, that activise T cells
– poor cooperation with MHC

Early stages – small amount of antigens., rapid growth – malignant growth – lack of apoptosis - rapid overload of immune system
Some tumors produce
- immunosuppresive substances or
- induce production of suppresor cells or
- antigens that bocks antibodies of T cells reactiong with tumor

Tumor antigens

TAA – tumor associated antigens
- oncofetal antigens – reemergence of embryonal proteins newly produced or present on membranes
AFP – alfafetoprotein,
CEA –carcinoembryonal antigen

TATA – tumor associated transplantation antigens
– neo antigens responssible for rejection
– on virus induced tumors – surface antigens on cells of tumors caused by oncogens from viruses

TSTA – tumor specific transplantation antigens
– na chemically induced tumors – heterogennous antigenic structure (two tumors induced by the same chemical substances or in the same individual have scarecely common specific antigens)

Tumor antigens include :

Tumor-specific transplantation antigens (TSTAs) that result from altered proteins expressed as a consequence of gene mutations within tumor cells. TSTAs are not found on normal somatic cells but result from mutations of genes and the resulting altered proteins that are expressed by the tumor cells. Identification of TSTAs on naturally occurring tumors has proved difficult, most likely because the immune response generally eliminates cells that TSTAs at levels great enough to be antigenic. However, TSTAs have been identified on tumors induced in culture by viral transformation or treatment with carcinogenic chemicals. When introduced into syngeneic mice, TSTAs cell-mediated immune responses that attack the tumor cells.

Tumor-associated transplantation antigens (TATAs) that are not unique to tumor cells but have unusual expression on tumor cells - Oncofetal antigens are expressed on tumors and on normal fetal cells. After the fetal stage of development, normal differentiated cells do not express these oncofetal antigens, except for germline cells of the testis. However, oncofetal antigens are also displayed on human melanomas, gliomas, and breast carcinomas. Another oncofetal antigen, alpha-fetoprotein, is found in fetal liver cells and liver carcinoma cells (and serum of individuals with liver cancer).

Imunotherapy of tumors

- Active and passive increase of nonspecific immunity

Active nonspecific – BCG, *Propionibacter acnes*
specific – killed tumor cells and extract, recombinant antigens, idiotypes, costimulationg molecules
Passive nonspecific – LAK cells, cytokines
pecific – antibodies alone or bound on drugs, T cells

- Immunopotentiating substances (modification of biological response)
– bacterial products (BCG – activation of macrophages and NK cells via cytokines),
- synthetic substances (pyran – induction of interferon production)
- cytokines (interferon, TNF – activation of macrophages)

- Substances activation macrophages and NK cells, stimuliting T lymfocytes and production of cytokines

Cancer immunotherapy is designed to increase the immune response against cancer cells. Cytokines and monoclonal antibodies have proven to have some limited effects in treating certain cancers. Vaccination, either to prevent development of a type of cancer or to inhibit recurrence of a tumor within a patient, continues to be explored.