

Tumor Immunology – Summary from Lecture 4/13/05 and Text Chapter 10

Cancer: A Multi-step process

- initial event that predisposes to transformation
- second event that causes the dysregulation of cell cycle

Oncogene – Genes where an alteration in genotype causes gain of function through over-expression of cell products.

Tumor Suppressor Genes – Control the normal lifespan. Loss of function results in cancer. Code for DNA repair proteins, cell cycle inhibitors, and apoptosis regulators.

Connection between Age and Cancer:

As we age, we lose the immune surveillance mechanisms to protect against cancer.

Immunosenescence – means immune function declines with age.

The thymus involutes with age and the rate of export of naïve T cells decreases. Over time, as memory and effector cells survive, but no new naïve cells are produced, the T cell population becomes skewed. In the elderly, its mostly CD8+ T cells that are clonally expanded against EBV and CMV viruses. They are deficient and don't produce enough INF- γ when they encounter virus, and they reduce the population of T cells available to respond to neoplasia. NK cells are also less active, which correlates with poor prognosis in gastric cancer patients.

Microbes Associated with Cancer:

Microbes are a contributing factor in 15% of all cancers.

Hep B or Hep C – Hepatocellular carcinoma

HPV – cervical cancer (E6, E7 proteins block cell cycle control pathways)

Helicobacter Pylori – Gastric cancer

HIV-1 – Kaposi's sarcoma

Immune Surveillance: A function of the immune system is to control growth of transformed (i.e. now cancerous) cells, and prevent their spread.

Evidence of this is that immuno-suppressed patients have an increased incidence of cancers. Immune surveillance is frequently overcome by tumors, as we know since many immuno-competent people still develop cancer.

Tumor Antigens:

Tumor antigens exist that the body's immune system can respond to. They may be mutated versions of a normal self protein, totally normal proteins being produced at the wrong place or in the wrong quantity, oncogene products, or related to an oncogenic virus. We learned about this from PND → An example of autoimmunity – where the body's response to tumor antigen also affects neurons that express the antigen and this causes an attack on neurons and severe neuro-degenerative disease.

TSA- Tumor specific antigen. It is UNIQUE to tumor cells.

TAA- Tumor associated antigen. Are expressed in both NORMAL and tumor cells, however they don't induce a response normally. Examples are alpha-feto protein and CEA.

Tumor Rejection:

Tumor antigens are usually cytosolic proteins expressed on MHCI. In order to get CD8+ CTLs and costimulation from CD4+ cells, we need MHCII presentation. This happens via Cross-Presentation. This is when tumor cells (with proteins on MHCI) are phagocytosed by professional APCs (dendritic cells) and then antigen is displayed on MHCII. This allows it to be seen by both CD4+ and CD8+ T cells.

So why do we still get cancer?

Tumors evade this host response in several ways.

1. Immune response is weak because tumor antigen is only weakly immunogenic.
2. Tumor cells may stop producing the antigen (antigen-loss variant)
3. Tumor cells may stop expressing MHC I altogether.
4. Tumor cells may produce other factors (TGF-B, IL-10, IDO, FasL) which suppress the immune response.
5. Down regulation of MICA and MICB impairs killing by NK cells

Strategies to Treat Cancer with Immunology:

Passive Immunization:

Inject monoclonal antibodies coupled with toxin into the body. The antibodies bind the tumor antigen, and activate host mechanisms (phagocytosis, complement) OR the toxin itself is delivered directly to the tumor cell (immunoconjugates). There are three types of immunoconjugates:

1. Radioimmunoconjugate – effector is an isotope
2. Immunotoxin conjugate – effector is a protein toxin
3. Antibody-drug conjugate – effector is a small drug

Ex. – Ab against HER2/neu for breast cancer

Ab against CD20 (a B cell protein) for B cell tumors

Adoptive Cellular Immunotherapy:

Experimental approach where they take out a person's tumor specific CTL cells and then grow them up, and then re-inject them into the person.

Stimulate Host Defenses Against Tumor:

Vaccinate the person against their own tumor cells using an adjuvant.

Give cytokines (IL-2) to stimulate their CTL response

Knock out normal inhibition of T cells via CTLA-4 (an inhibitory T cell receptor) which has a higher affinity for B7 than CD28.