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How Immune System Control Cancer Cells: An Overview

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IMMUNE SYSTEM

The immune system is classically considered to be comprised of the innate and adaptive arms, although this is a simplification since these arms have overlapping functions and are intimately related. The innate immune system includes dendritic cells, Natural Killer Cells (NK), macrophages, neutrophils, eosinophils, basophils, and mast cells. Innate immune cells do not require prior stimulation by antigens and act as the first line of defense against foreign antigens. The adaptive immune system includes B lymphocytes, CD4+ helper T lymphocytes, and CD8+ Cytotoxic T Lymphocytes (CTLs), and requires the formal presentation by Antigen-Presenting Cells (APCs) for its activation. The adaptive immune system generates antigen-specific T- and B-cell lymphocytes. The immune system is highly variable between individuals but relatively stable over time within a given person.

Each cell is estimated to experience over 20,000 DNA damaging events each day, which are normally repaired by specific DNA repair pathways with no lasting effects. Cells that are not repaired and which acquire malignant or potentially malignant changes are then usually recognized and killed by the tumor immune surveillance system. This involves predominantly cell-mediated mechanisms that can differentiate between self and non-self-antigens. Since a malignant cell can have more than 11,000 genomic mutations, many new Tumor-Associated Antigens (TAAs) may be expressed. TAAs include products of mutated proto-oncogenes, tumor suppressor genes, overexpressed or aberrantly expressed proteins, tumor antigens produced by oncogenic viruses, onco fetal antigens, altered glycolipids and glycoproteins, and cell type-specific differentiation antigens. These new TAAs, or fragments thereof, are presented on the cell surfaces with their Major Histocompatibility Complex (MHC) molecules. However, recognition of an antigen-MHC complex by a T-cell antigen receptor is insufficient for the initial activation of naive T-cells, requiring additional co-stimulatory signals that are provided by the engagement of the CD28 receptor on the T-cell surface with B7 ligand molecules (two of which are CD80 and CD86) on the APCs. This CD28 receptor/B7 ligand combination or "immunological synapse" stimulates the proliferation and function of the T-cells. Many other receptor/ligand combinations are possible between activated T-cells and other cells, including tumor cells, and some of these interactions are inhibitory, such as PD-1/PD-L1 and CTLA-4/B7, and are discussed later in this monograph.

Some malignant cells are able to evade the tumor immune surveillance system by manipulating their own characteristics as well as the cells in their microenvironment to become "successful" tumors; these evasive mechanisms represent the major area of interest in current Cancer Immunology (CI) research. The concept that the immune system is capable of detecting and killing nascent "non-self" malignant cells was first developed by Burnet and Thomas in their cancer immune surveillance hypothesis. The concept was not accepted initially but it is now considered a component of cancer immune-editing, whereby the surveillance system can determine or "shape" the immunogenicity of the tumor cells which are not eliminated initially. The immune-editing process has been formally divided into three main phases: elimination, equilibrium, and escape. The elimination phase refers to the initial damage and possible destruction of tumor cells by the innate immune system, followed by the presentation of the tumor antigens in the cellular debris to dendritic cells which then present them to T-cells and thereby create tumor-specific CD4+ and CD8+ T-cells. This helps destroys the remaining tumor cells if elimination is complete. The equilibrium phase occurs when any tumor cells survive the initial elimination attempt but are not able to progress, being maintained in a state of equilibrium with the immune cells. In the escape phase, cancer cells grow and metastasize due to loss of control by the immune system. The cancer cells which are not eliminated and which escape may do this by expressing fewer antigens on their surfaces or even by losing their MHC class I expression, They may also show the ability to protect themselves from T-cell attack by expressing Immune Checkpoint (IC) molecules on their surfaces like normal cells; these IC molecules are up-regulated by cytokines produced by activated T-cells and are part of a normal negative feedback loop to control excessive tissue damage from inflammation by down-regulating or suppressing T-cells.

The dynamic that exists between the immune system and tumor antigens is a phenomenon recognized relatively recently since it was only in 1991 that van der Bruggen and colleagues first reported the existence of a human tumor antigen recognized by T-cells.

They were able to clone the Melanoma Antigen-Encoding Gene (MAGE), which encodes an antigen recognized by cytotoxic T-cells. This provided not only proof that the immune system was capable of seeking and destroying tumor cells but also provided the first identification of a molecular target.

The ability of cancer cells to evade immune destruction has been proposed as the eighth hallmark of cancer. As noted above, a tumor is able to do this not only by modulating its own cellular characteristics but also by creating its own "tumor microenvironment" by recruiting apparently normal immune cells to help shield it from attack by the immune system. Through the production of various cytokines and chemokines, successful cancers and their metastatic derivatives are able to generate an immunosuppressive, protumorigenic, and prometastatic microenvironment by recruiting and "training" immune cells, including macrophages, regulatory T-cells, immature myeloid cells (which become "myeloid-derived suppressor cells"), T helper 17 cells, regulatory B- cells, and leukocytes. Even before they metastasize, tumors can influence the systemic environment by altering hematopoiesis as well as the tissue parenchyma of organs at distant sites, thereby forming "pre-metastatic niches". While some cancer immunotherapies have had marked successes in manipulating these tumor microenvironments, the loss of MHC class I expression by a tumor represents a major immunotherapy treatment challenge. The intrinsic immunological ability of an individual to combat cancer has been called the "cancer-immune set point", and is influenced by a complex set of factors involving the tumor, the host, and environmental factors.