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Cancer immunology- A breakthrough in carcinogenesis

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Abstract

The responsibility of the immune system is to detect and destroy the abnormal cells and unwanted elements along with the inhibition of development of various cancers. The immune system exerts a protective role, and under certain circumstances, it could be damaging in terms of modulating the oncogenic process. The failure in host's immunological responses against tumor growth and dissemination implicates that both immunologic and nonimmunologic factors may work together to affect tumorigenesis. Hence, understanding the aspects pertaining to tumor immunology which deals with the complex interactions between the host's immune system and neoplasm is essential. Tumor immunology mainly associated with three steps includes: Immuno surveillance, Immuno editing, Immune evasion. In this

review article, mainly these parameters are discussed to enlighten tumor immunology.

Keywords: Carcinogenesis, Immunoediting, Immuno surveillance, Immunity

Introduction

Cancer immunology is the study of interactions between immune system and cancer cells. This is a rapid growing field of research that aims to identify various investigations in cancer diagnosis and to develop innovative cancer therapeutic processes. Activation of the immune system for therapeutic benefit in cancer has long been a goal in immunology & oncology. [1]

Immunity refers to protection against infections, and the immune system is the collection of cells and molecules that are responsible for defending the body against the countless pathogenic microbes in the environment. Immunology is a branch of biology that covers the study of immune systems in all organisms. It charts, measures, and contextualizes the physiological functioning of the immune system in states of both health and diseases.[1,2]

Cancer is not a single disease but represents a wide spectrum of conditions caused by a failure of the controls that normally govern cell behaviour in a complex multicellular organism. The major differences between cancer types largely stem from the unique character of their tissue of origin. Thus, there are considerable differences between cancers that originate in the skin versus the liver, lung, gut, or blood.[3] Because each of these cell types have unique environments and gene expression signatures, the nature of the mutations that will enable each of them to disobey social controls on cell behaviour will also differ. [4]

Cancer development is characterized by an abnormal increase in a number of structural differences in cells spread throughout the body. Cells that undergo malignant transformation escape these controls, invade surrounding tissue, and may ultimately migrate to other sites in the body to establish secondary Tumors. [5,6]

Although earlier theories on the nature of cancer proposed that abnormal cellular growths were caused by infectious agents, such as viruses, these theories were gradually supplanted by the idea that cancer is caused primarily by mutagens – agents that provoke genetic mutation. [1,3,6]

It is now well accepted that most carcinogens (i.e., cancer-causing agents) act through provoking DNA damage either directly or indirectly. Such damage can be relatively subtle, resulting in point mutations that alter a single amino acid in the protein encoded by the affected gene, or more dramatic, provoking translocation of whole chromosomal segments from one chromosome to another.[2]

The role that the immune system plays in resisting or eradicating formation and progression of incipient neoplasia, late-stage Tumors, and micro metastases is largely under analysis of late. The long-standing theory of immune surveillance proposes that cells and tissues are constantly monitored by an ever-alert immune system, and that such immune surveillance is responsible for recognizing and eliminating most incipient cancer cells and thus nascent tumor. An increasing body of evidence, both from genetically engineered mice and from clinical epidemiology, suggests that the immune system operates as a significant barrier to tumor formation and progression, at least in some forms of non-virus-induced cancers. [2,4,5]

The immune system can respond to cancer cells in two ways by reacting against tumor specific antigens (molecules that are unique to cancer cells) or against tumor associated antigens.[6]

Cancer immunology is based on the concepts of immunosurveillance and immunoediting which act by

protecting the organism, against development of Tumors. Immune surveillance is ability of the immune system to identify and eliminate tumors.[7] Immuno editing is a dynamic process that consists of immuno surveillance and tumor progression. It describes the relation between the tumor cells and the immune system. It is made up of three phases: elimination, equilibrium, and escape.[6]

The main aim of cancer immunology is to understand and delineate the various ways of determining cancer specific antigens and how the immune system can respond to the threat and the genetic and molecular pathogenesis of cancer and develop a specific approach that is immunotherapy to enable the patient's immune system to target cancer cells and destroy them.[6,7]

Immuno therapy is one of the important options in the treatment of cancer as it can directly target the tumor and its micro environment. Thus, it is possible to have individualized therapy with less toxicity and less side effects.[4,5,6]

In light of these considerations and the still-ongoing demonstrations of antitumor immunity as a significant barrier to tumor formation and progression in humans, it is important to discuss the mechanism-based targeted therapies to treat human cancers which have been heralded as one of the fruits of three decades of remarkable progress of research into the mechanisms of cancer pathogenesis and its treatment.[2,4]

The field of cancer immunology, more than any other area of cancer research, remains in great flux, with basic concepts still a matter of great debate. Still, this is an area of cancer biology that is well worth our time and study, since it holds great promise for new insights into cancer pathogenesis and new ways of treating human tumors.[3,4] Keeping this background knowledge in mind, a thorough and detailed review has been compiled, documenting the present literature, on basics of 'Cancer Immunology'.

Review

The immune system reacts to cancer cell in two ways

1.By reacting against tumor specific antigen

2. By the tumor associated antigen.

The tumor associated antigen are mainly Carcinogen embryonic antigen, Muc, Oncofetal antigen. Some differential antigens are also present, which are elevated in patient with malignancy, such as prostate specific antigen, Carcinoembryonic antigen 125.[3,5]

Tumor specific antigens are found in malignant cell but absent in normal cell of the host, like mutation of proto-oncogene and tumor suppressors which lead to abnormal protein production as a result of formation of tumor and called as tumor specific antigen like abnormal form of RAS and P53.P53 is a protein whose main function is to repair DNA to prevent altered DNA.[6] When the damage in DNA is too extensive to be repaired, P53 proteins signal cells to undergo programmed cell death.[7,8]

The retinoblastoma (RB) protein is a tumor suppressor protein and one of its functions of Rb is to prevent excessive cell growth by in hibiting cell cycle progression until a cell is ready to divide.9

When the cell is ready to divide, Retinoblastoma is phosphorylated to pRb, leading to the inactivation of Rb. This process allows cells to enter the cell cycle state. It is also a recruiter of several enzymes such as methylases and acetylases.[9,10]

All Ras protein family members belong to a class of protein called small GTPase and are involved in transmitting signals within cells. Ras is the prototypical member of the Ras super families of proteins. The three Ras genes in humans HRAS, KRAS and NRAS are the most common oncogene in human cancers; mutations

that permanently activate Ras inhibitors are being studied as a treatment for cancer and other diseases with Ras overexpression.[11]

Immunosurveillance

Immunological surveillance is a complex relationship between the immunity and cancer. If the immunological surveillance is effective cancer will not arise. In some circumstances, when immunological surveillance cannot work properly, like when rate of proliferation of malignant cell is too high that escape immune response against it.[1,4,12]

Some tumor cells may be at low immunogenic state or emanates cytokines like transforming growth factor which suppress cell mediate immunity.[1]

Tumor cell can also express lower level of major histocompatibility complex I molecules and hence cannot be recognized by the CD8 and CTL for its destruction.[1]

Cancer immunoediting is the process, that comprises of three steps -

1) Elimination 2) Equilibrium 3) Escape.

Elimination phase

Elimination is the hallmark of the original concept in cancer immune surveillance for the successful eradication of developing tumor cells, working in concert with the intrinsic tumor suppressor mechanisms of the non-immunogenic surveillance process.[13] The process of elimination includes innate and adaptive immune responses to tumor cells. For the innate immune response, several effector cells such as Natural Killer, NKT, and T cells are activated by the inflammatory cytokines, which are released by the growing tumor cells, macrophages and stromal cells. The secreted cytokines recruit more immune cells, which produce other pro-inflammatory cytokines such as IL-12 and IFN-γ. Perforin-, FasL- and TRAIL-mediated killing of tumor cells by natural killer cells releases tumor antigens, which lead to produce adaptive immune responses.[14]

The following four phases have been proposed for the elimination process.[15]

1. To identify the tumor cells by innate immune response, when a solid tumor has grown to more than 2–3 mm, it requires a blood supply and stromal remodelling for tumor progression, which in turn induces pro-inflammatory signals leading to the recruitment of innate immune cells such as Natural Killer cell, NKT, T cells, macrophages and Dendritic Cells into the tumor site.
2. Maturation and migration of dendric cells and cross-priming for T cells: IFN-γ exerts a limited cytotoxicity via antiproliferative and anti-angiogenic effects and induces apoptosis.
3. Formation of Tumor Antigen-specific T cells: the recruited tumor-infiltrating Natural Killer and macrophages produce, IL-12 and IFN-γ, which kill more tumor cells by activating cytotoxic mechanisms such as perforin, TRAIL and reactive oxygen.
4. Tumor specific- T cells move to the tumor site and eliminate the tumor cells.

Equilibrium phase

The next step in cancer immunoediting is the equilibrium phase in which a continuous molding of tumor cells produces cells resistant to immune capable cells. This process leads to the immune selection of tumor cells with reduced immunogenicity. These cells are more capable of surviving in an immunocompetent host, which explains the apparent paradox of tumor formation in immunologically intact individuals.[1,6]

One experiment showing, the lymphomas formed in the pfp deficient mice were more immunogenic than those in IFN-γ-deficient mice, suggesting that pfp may be more

strongly involved in the immune selection of lymphoma cells than IFN-γ.

No connection was established, between this loss of immunogenicity and the loss of MHC class I expression. Furthermore, two important issues can be suggested--one is that perforin-mediated cytotoxicity in T cells contributes more to the elimination of lymphoma cells than epithelial tumor cells, whereas IFN-γ-mediated cytotoxicity is directed more to the removal of mesenchymal tumor cells such as sarcomas.[8]

Tumor microenvironments play a prime role in the growth of tumor. The equilibrium phase is responsible for the continuous elimination of tumor cells and the production of resistant tumor variants by immune selection pressure.[9]

Equilibrium is likely found to be the longest of the three processes in cancer immunoediting and may occur over a period of many years.[11]

In this process, lymphocytes and IFN-γ plays a crucial role in exerting immune selection pressure on tumor cells. During this time of Darwinian selection, many tumor variants from the original are killed but new variants emerge carrying different mutations that increase resistance to immune attack.[10,11]

Escape mechanism

The loss of CD3-£ is reported to be correlated with increased levels of IL-10 and TGF-β, and down-regulation of IFN-γ. The CD3-£ chain is located in the TCR that forms part of the TCR–CD3 complex, which functions as a single transducer upon antigen binding.[6] Since the TCR signal transduction through the formation of the CD3 complex is one of three important signals for initiating a successful immune response as well as the expression of tumor antigen and T helper 1 polarization, any alterations in the CD3-£ chain are associated with the absence of p56lck tyrosine kinase.[11]

The alterations of TCR-£ in several types of Tumors such as pancreatic malignancy, malignant melanoma, renal cell malignancy, ovarian cancer and oral cancer have been shown to be attributed to immune invasion that links to poor prognosis. In oral squamous cell carcinoma, a high proportion of T cells in the tumor undergo apoptosis.[11]

The following factors play an important role in escape phase

Interferon-gamma Endogenously produced interferon-γ protects the host against transplanted tumor and the formation of chemically induced and spontaneous tumors.[12]

Perforin and Fas/FasL system

Perforin and Fas/Fas ligand (FasL) are playing a crucial role, which is involved in immune surveillance. In general, cell-mediated cytotoxicity attributed to cytotoxic T lymphocytes (CTLs) and NK cells are derived from either the granule exocytosis pathway or the Fas pathway. The granule exocytosis pathway utilizes pfp to direct the granzymes to appropriate locations in target cells, where they cleave critical substrates that initiate apoptosis. Granzymes A and B induce death via alternate, non-overlapping pathways. The Fas/FasL system is responsible for activation-induced cell death but also plays an important role in lymphocyte-mediated killing under certain circumstances.[6,7,9]

Lymphocytes

Although some experience had accumulated that the immune surveillance of cancer was dependent on interferon γ and lymphocytes, the critical demonstration for the involvement of lymphocytes came from the use of gene-targeted mice which is lacking the recombination activating gene 1 (Rag1) or Rag2.[2,3] Homozygous mutants of Rag-2 are viable but fail to

produce mature B or T lymphocytes. Loss of the Recombinant activating gene 2 function in vivo results in a total inability to initiate Variable Diversity Joining segment rearrangement. Since nude mice do not completely lack functional T cells and the two components of the immune system, IFN-γ and pfp, to prevent tumor formation in mice, an graceful study using a Recombinant activating gene 2 and stat 1 mouse model showed for the first time that lymphocytes and IFN-γ collaborate to prevent the formation of carcinogen-induced sarcomas and spontaneous epithelial carcinomas.[4,8] In the collaboration between the lymphocyte- and IFN-γ/Stat1-dependent tumor suppressor mechanisms, mice which is lacking of both genes, showed increased susceptibility to MCA-induced tumors.[10]

Tumor-derived soluble factors

Tumors progress mechanisms escape immune control by a process called immune editing, which provides a selective pressure in the tumor microenvironment that can lead to malignant progression.[12]

Local and regional immunosuppressive networks, including vascular endothelial growth factor (VEGF), IL-10, TGF-b, prostaglandin E2, soluble Fas, soluble FasL and soluble MICA are deposited at the primary tumor site, can extend immunosuppressive effects into local lymph nodes and the spleen, so by this way promoting invasion and metastasis.[15]

Vascular Endothelial Growth Factor plays a critical role in recruiting immature myeloid cells from the bone marrow to enrich the microenvironment as tumor-associated immature Dendritic Cells and macrophages. Accumulation of Tumor associated immature Dendritic Cells may cause drifting Dendritic Cells and T cells to become suppressed through activation of indoleamine 2,3-dioxygenase and arginase I by tumor-derived growth factors. VEGF prevents DC differentiation and maturation by suppression.[3,6,10]

Conclusion

The immune system controls tumor promotion and the various modalities of immunotherapy that can induce strong immune responses against cancer. Such medical knowledge has stimulated the invention of novel immunotherapeutic modalities including therapeutic antibodies, vaccines, and cell-based treatments. Immunology of cancer will help in our modern medicine to produce new therapy that can fight against these dreaded diseases and overcome from this in future.

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