SIGNIFICANCE OF KNOWLEDGE OF IMMUNITY IN REFERENCE TO CANCER

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ABSTRACT

The developing tumor cells in the body are being detected and eliminated by the immune system via a process termed Cancer Immuno surveillance, which works as a defense mechanism against cancer. In the rapidly evolving field of immuno-oncology, activation of the immune system and cancer pathogenesis is a subject of great interest and debate for many decades due to provide a framework to mediate protection against development of cancer and its progression. In the rapidly evolving field of immuno-oncology, understanding the tumor-specific immune response enhances understanding of cancer resistance. In the tumor microenvironment (TME), the complex network of infiltrating immune cells and soluble factor can dictate migration and differentiation of tumor-infiltrating leukocytes and shift the antitumor immune response on tumour progression, which depends upon to the certain type of cancer.

Key words - Cancer, Immunity, pathogenesis, Tumor microenvironment

INTRODUCTION

Cancer is among the leading causes of death globally and, with an aging population, its annual toll of 8.2 million is only expected to increase. Inflammation associated with cancer at different stages of tumorigenesis, contributes to genomic instability, epigenetic modification, aggravate of cancer cell proliferation, enhancement of cancer anti-apoptotic mechanisms, activation of angiogenesis and cancer dissemination. Pre-cancerous and malignant cells may induce an immune response which results in destroying of these cells before they developed into detectable tumors., this process called as immune surveillance.

The interplay between the immune system and cancer is unquestionable. During tumorigenesis, the immune system identifies and eliminates the cancer cells including through antigen-specific
responses initiated against antigens demonstrated by these cells. The tumor microenvironment (TME) is the complex network of cells i.e. proliferating tumor cells, the tumor stroma, blood vessels, infiltrating inflammatory cells and a variety of associated tissue cells can dictate the differentiation of tumor-infiltrating leukocytes and alteration of the antitumor immune response into promoting neoplastic growth.

The immune system has the capacity to either eradicate the tumor growth and deteriorate persist tumors, or to enhances tumorigenesis and convert to metastatic states. Continuation of these conditions depends on the equilibrium between the pro- and anti-tumor mediators of innate and adaptive immunity. The specific T cell subsets including γ, δ T cells and CD4 α β lymphocytes include cells have anti-tumor activity against cancer phenomenon with spontaneous regulatory activity to diminish protective immunity.

Modulation of the existing patient immune system through influencing of immune checkpoint inhibitors (ICIs) such as anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4), anti-PD1 (anti-programmed cell death protein 1) and anti-PDL1 has resulted in dramatic remission of various tumor types. During antigen presentation CTLA-4 mediates immunosuppression by indirectly limiting signaling through the co-stimulatory receptor CD28 and promotes the activation threshold of T cells.

Two ligands of PD-1 such as PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) which can be found on the surface of antigen-presenting cells (like macrophages, and monocytes, dendritic cells). Interferon (IFN)-γ is the most responsible factor to cause PD-L1 and PD-L2 upregulation. During chronic immune activation PD-1 can be upregulated due to its signal transduction can only come into effect during TCR-dependent signalling and simultaneous T cell activation. These inhibitory receptor has been situated on both tumor-infiltrating lymphocytes and circulating tumor-specific T cells. Type I immune responses such as IFN-γ production and cytotoxic T cell functions, are associated with better responses to anti-CTLA-4 and anti-PD-1 antibodies and responsible for effective anti-tumor immune responses.

Correlation of immunity and cancer

Cancer is a systemic disease that develop several functional and compositional changes to the immune system. The relationship between cancer and immunity involves three basic principles in which how the immune system attack to antigen and protect an individual- a) it identifies “nonself” antigens from pathogens or tumor cells, b) it encompasses effector functions to specific targets and destruction cancer cells and protecting the host and c) it produces immunological memory through the adaptive immune responses for subsequent defense mechanisms against the attack of the host.

The immune system includes a wide variety of various types of soluble bioactive molecules, cytokines, proteins, and cells that collectively develop the multifaceted network of biochemical mechanisms that recognize and protect against “nonself” antigens. A plethora of mechanisms which are responsible for control of cellular growth and death, due to DNA mutations and the failure of these processes, that is the most causative factor for the development of aberrant cells and formation of malignant cells.

The important role of the immune system in preventing carcinogenic mechanisms is also mentioned by different studies associating with the presence of tumor-specific T cells in the blood and bone marrow. This multifaceted process has three primary sequences: elimination, equilibrium, and escape, that contribute to cancer development, elimination, and progression.
Firstly, the immune system protects the host from virus-induced tumors by destroying or suppressing the viral infections and the elimination of infected cells and prompt resolution of inflammatory mechanism can prevent tumorigenesis process environment. Finally, the immune system can recognize and destroy cancer cells in specific tissues on the basis of their presence of tumor-specific antigens (TSAs). This third process, known as cancer immunosurveillance, in which the immune system recognizes new transformed cells that have escaped cell-intrinsic tumor-suppressor process and eliminates before they can develop into malignant conditions. These effector immune cells employ especially different mechanisms to control tumor growth including the initiation of tumor cell death by mitochondrial and cell death receptor pathways, and so evasion of immunosurveillance is referred as the seventh hallmark of cancer. Tumor escape can resulting in changes of the tumor cells by directly inhibiting tumor recognition by immune effector cells.

In cancer patients, spontaneous anti-tumor T cell responses occur frequently and led to the molecular identification of tumour cells that are recognized by T cells. The presence of T cells within tumours, which is often associated with a more favourable clinical outcome, is probably a consequence of these spontaneous responses. The immunogenicity of a tumour depends on its antigenicity and other various immunomodulatory factors in the tumour microenvironment that are produced either by cancer cells or by host cells.

A plethora of immunosuppressive mechanisms early in tumour development, and when that immunosuppression suppress and resistant variants emerge such that antigen processing or the expression of dominant antigens are downregulated in the cancer cells. The secretion of immunosuppressive mediators, such as transforming growth factor-β (TGFβ) or natural killer (NK) cell receptor, and the expression of ligands of co-inhibitors like CTLA-4 and PDL1 are contribute of immune resistance in tumor cells. CD8+ T-cell memory is heterogeneous and distinguished by specific functions, phenotypes, and anatomic localization. The memory T-cell subsets originate in the tumor-bearing state with those existing during chronic infectious conditions. Impaired immune responses, enforced by Treg cells and variation of the cytokine environment, further discriminate both the tumor-bearing and chronic inflammatory states.

The cell-mediated innate immunity involve phagocytes (neutrophils, monocytes, and macrophages) and natural killer (NK cells) activate immune system by engulfing cells through presenting the non-self pathogens and destroying with lysosomal enzymes. The equilibrium stage, the influence of balance between effector and regulatory cells by favoring the infiltration and accumulation of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSC) within certain cancers through fade in the presence of epigenetic alterations significantly disturbing the biological process of tumor cells by suppressive pathway.

**Tumor progression and immunity**

Immune contexture can be strongly influenced by tumour-originating factors. During cancer immune editing, the immune system is capable to identifies and eliminates the most immunologically vulnerable antigen presenting tumor cells. The progressive formation of an immunosuppressive environment consequently within the tumor in which protective responses against transforming cancer cells can be generated when immune therapies are delivered prior to tumor challenge but unable against developed cancers. Simultaneous inhibition in development of antitumor immunity in different stages can be obtained through the secretion of immunosuppressive cytokines by cancer cells such as TGF-β secretion which leads to inhibition of DC activation, T cell and NK cell function.
Cancer progression ends in metastatic stage, which is the major cause of cancer death. For metastatic conditions to develop from solid malignancies, cancer cells need to undergo a phenomenon that is referred as the metastatic cascade. Throughout each step of the metastatic cascade, mutant and thus probably immunogenic cancer cells interact with the immune system, which can identifies them and hampering their growth.

In initial stage, cancer cells escape from the antitumour immune response and distantly prepare the environment of cancer progression (pre-metastatic niche). In this metastatic processes, tumour-infiltrating immune cells, specially myeloid cells such as macrophages, also actively participate and perform distinct functions in response to tumor environmental signals.

**Suppressing Function**

In the tumor microenvironment, Antigen presenting cells (APCs) that would normally active the rest of the immune system to the presence of malignant conditions are unable to mature into effector cells. Some chemical signals such as IL-8, IFNγ, and colony stimulating factor 1 (CSF-1) are prompt the suppression of limiting tumor cells by Tcells. Additionally, tumor cells recruit regulatory T cells (T-reg) into their microenvironment by producing C-C motif chemokine 22 (CCL22) and TGFβ. T-reg are suppressive immune cells that restrict the production and activity of other effector immune cells. TGFβ is also known to change CD4+ Th cells into regulatory cells to suppress function.

**FACTORS THAT TUMORS EXPLOIT TO AVOID IMMUNE RESPONSES**

Tumours develop various mechanisms to avoid detection and destruction by the immune system by modulating the recruitment, expansion and function of tumour-infiltrating leukocytes, such as immunoregulatory myeloid cells, regulatory T cells (TReg cells), T helper 17 cells (Th17 cells), and regulatory B cells (BReg cells). The impaired immune-mediated rejection of the primary tumour may promote the aggravation of metastatic conditions that will escape from the primary tumour and enhancement of the survival of cancer cells spreading to the metastatic site.

Similarly, some recent preclinical study indicates that inhibition of TReg cells and MDSCs by down regulation of p110δ isoform of phosphoinositide 3-kinase (PI3Kδ) initiate the immune-mediated rejection of different types of cancers.

**Regulatory cells**

IFN-γ, perforin and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) perform as effector molecules in immune surveillance for the inhibition of tumor formation. Activation or inhibition of T cells correlate with the presence or absence of cytokines in their immediate microenvironment. Because cancer cells produce various cytokines and chemokines that can hampering the maturation and function of immune cells such as Vascular endothelial growth factor (VEGF) cytokine is secreted by many tumors. An another cytokine proinflammatory factor prostaglandin E2 (PGE2) is expressed by multiple tumors as a result of enhanced expression of rate-limiting enzyme cyclooxygenase 2 for PGE2 synthesis. In cancer phenomenon, the IL-10-mediated down-regulation of TAP1 and TAP2 proteins may also be cause of loss of HLA class I expression.

Immune checkpoint is induced by both innate and adaptive components of the cellular immunity against tumor cells. The adaptive component mainly consists of CD8+ CTLs cells for identification of tumor antigens which are presented by MHC class I molecules on cancer cells.

**Natural killer (NK) cells**
In innate immunity, Natural killer (NK) cells mostly MHC class I-deficient variants have long been implicated in innate immunity against tumor cells. Some recent studies have mentioned regarding of a pivotal role of NK cells through natural process from primary tumor formation induced by secretion of chemical carcinogen methylcholanthrene (MCA). A unique small subpopulation of true T cells i.e. NKT cells, play a significant role in regulating immune responses through the innate and adaptive immune systems.

A pleiotropic cytokine i.e. IFN-γ that functions on both tumor cells and host immunity. Interferon gamma (IFN-γ) increases NK cell cytotoxicity by upregulating the presence of adhesion molecules and by enhancing the sensitivity of tumor cells to perforin- and Fas ligand (FasL)-mediated cytotoxicity. NK-induced programmed cell death (apoptosis) can occur by different processes like tumor-necrosis factor-alpha- (TNF-α) dependent secretion of cytoplasmic granules (perforin and granzymes) that develop pores in cell membranes, by antibody-dependent complement cytotoxicity due to the expression of antibody receptor (CD16) on Natural killer (NK) cell surface and by the release of cytokines like IFN-γ which mediates stimulation and maturation of antigen-presenting cells. Cells are resistant to NK-mediated lysis due to normal expression of MHC class I that stimulates inhibitor receptors on NK cells which prohibits NK cell induced programmed cell death.

T Cells

Regulatory T cells play a major role in maintaining T-cell tolerance to self-antigens. Regulatory T cells are thought to diminish T-cell immunity to tumour-associated antigens and to be the main complication tempering effective immunotherapy and active vaccination. In the tumor microenvironment regulatory T cells (Treg) are responsiblr for suppressing of proliferation of other T cells through contact-dependent methods or release of IL-10 and TGF-β mediators. CD4+ T_H1 cells and CD8+ cytotoxic T lymphocytes (CTLs) are utmost mediators of anti-tumor immunity. IL-13 has also direct acts on tumor growth, metastatic site and protect from apoptosis for specific types of cancer. The infiltration of T cells has a critical role in tumor microenvironment and extensively studied in primary tumors in multiple cancers. The anti-metastatic effect of T cell activation has been analyzed in bone metastasis from breast carcinoma indicates that cytotoxic CD8+ T cells play a primary role in anti-metastatic defense in an interferon-dependent sequence.

T helper cell-dependent and cell-independent mechanisms can be activated antibody-secreting effector functions for maturation and stimulation of B cells, resulting in a severe variety of antibodies are activated which are specific for the type of immune responses. These adaptive immune responses, are thought to eradicate the development of specific types of cancer through cell-extrinsic tumor suppressor processes, so which may never be distinguish clinically.

Innate Immunity and Cancer

Innate cells can control neoplastic growth by directly interacting with tumor cells, and enhancing the functions of other cells in the tumor microenvironment. During tumorigenesis various components of the innate immunity are activated in efforts to diminish cancer-mediated inflammation. This process also activates adaptive immune responses for targeting the cancer through many specific immune processes. CRP-mediated complement suppression may also result in insufficient activation and augmentation of B and T cells that can target the certain tumor cells. The induction of immune inhibition mechanisms is a complex mechanisms that includes the involvement of tumor and immune cells that act synergistically to reduce antitumor immune response.
Tumour-associated antigens (TAAs), primary triggers of the immune system, activate through major histocompatibility complex (MHC) and the T cell defense response against tumorigenesis. TAMs differentiate nearby from recruited peripheral blood monocytes in response to cytokines and growth factors released by stromal and tumor cells in the tumor microenvironment (TME).

The enormous genetic alterations characteristic of tumor cells release a wide range of tumor antigens that facilitate the immune system to differentiate neoplastic cells from normal cells. The variation in distribution of immune cells within tumour cells in different sites is thought to afflict the clinical outcome. The persistence of tumours against host immunity suggests that tumour cells progress immune avoidance. The positive prognostic association of high CD4 and CD8 T cell invading within a tumour implies a clinically appropriate anti-tumour immune responses.

Tumour-associated macrophages (TAMs) are a crucial component of inflammatory mechanisms that are initiated highly by monocyte chemotactic protein (MCP) chemokines and invades in neoplastic tissues. Cancers can also escape the immune response by up-regulating inhibitory molecules and activating a variety of self-tolerance. Both inhibitory receptors cytotoxic T-lymphocyte associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1) are participated in down-regulation of immune responses.

A complex tumour microenvironment consists of stromal cells, lymphoid and myeloid cells, vascular and lymphatic vessels, and the resultant cytokine and chemokine mediators. Several researches highlights that peripheral immune perturbations in cancer context has focused on its progression in immunosuppressive myeloid populations. Though the innate immunity plays a crucial role in controlling the cancer pathogenesis, other hand equally participate in cancer biology is the role of adaptive immunity.

Adaptive immunity

The concept of central dogma of cancer immunity involves the development of neoantigens, that are formed due to tumorigenesis process and phagocytosed by antigen-presenting cells (APCs) or dendritic cells for antigen processing. Within this phenomenon, there are many regulatory factors that act as immune checkpoints in the preference of adaptive immune responses to mediate either cancer aggravation or remission.

These processed tumor-associated antigens are presented on the antigen-presenting cells by MHC class II and MHC class I molecules to the antigen-specific T cell receptor on CD4+ T cells or CD8+ T cells. After that activation of CD4+ T cells on APC primes them by MHC class II for subsequent exposures to that particular antigenic peptide/MHC class II complex, for developing of memory T cells. Similarly, activation of CD8+ T cells by interplay of antigen-specific T cell receptors with MHC class I complexes leading to induction of cytolytic CD8+ T cell-mediated degradation of tumor cells. Under this scenario, Lack of an appropriate costimulatory signal resulting in degrade of T cell energy and a state of immune tolerance to cancer cell-associated antigens; ultimately adaptive immunity fail against cancer progression.

Similarly, immune tolerance is also induced by CTLA4 on T cells binding to the CD80/CD86 proteins on the antigen-presenting cells (APCs). Contrary, the binding of CD28 with these proteins and interaction of CTLA4 with CD80/CD86 resulting in T cell inhibition and mediates downregulation of immune responses in cancer patients.

Many cancers is also expressed CTLA4 and further interaction with immune tolerance phenomenon in cancer progression. Interestingly, a cell surface receptor molecule on the T cells
referred as programed cell death protein 1 (PD-1) which can bind to PD-L1, on the antigen-presenting cells (APCs) and mediates immunosuppression. Immune responses in tumor microenvironment can also be suppressed by Tregs cells. Several Recent studies suggest that cancer management have emerged from advanced immunotherapies targeting T-cell inhibitory receptors, including cytotoxic T-lymphocyte associated antigen (CTLA)-4 and programmed cell death (PD)-1.34

CONCLUSION
Cancer cells produce several heterogeneous tumours due to its high mutation rates and containing innumerable mutants. These mutant cells postulate a reservoir of drug-resistant cells that are able to prosper after the selective pressure of chemotherapy.14 A cancer-immunity complex is required for the development of an efficient anti-tumor immune response. Therefore, an advanced understanding of tumour immunology must evaluate the systemic immune landscape beyond the tumour microenvironment (TME). The peripheral immune system is required to activate the potent natural and therapeutically initiate antitumour immune responses.

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