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Immuno Defense Mechanism against Tumors

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Abstract

The hypothesis of immune responses is predicted on theory of immune system that is capable of eliminating foreign antigens including tumor specific antigens in the process, immunosurveillance. To defense against tumors immune system activates cell mediated and humoral immune responses, cell mediated immune system protects the body from itself by controlling cancerous cells, this includes activation of Cytotoxic T Lymphocytes, Natural Killer cells, Macrophages, Dendritic Cells, Lymphokines, etc., where as humoral immune system recognizes foreign particles. These cells play important role in defending as well as in diagnostic processes. Here I discussed about the cell mediated and humoral mediated immuno mechanisms involved in the defense mechanism against tumors.

Keywords: Immune System; Immune Responses; Tumors; Cytotoxic T Lymphocytes; Natural Killer Cells; Interleukins; Interferons; CD-cells; Antigen Presenting Cells; T- Cell Receptors; Humoral Immunity; Major Histocompatibility Complex; Antigens

Abbreviations: APC: Antigen Presenting Cells; CTL: Cytotoxic T Lymphocyte; DC: Dendritic Cell; MHC- Major Histocompatibility Complex; TCR: T Cell Receptors; IL: Interleukins; INF: Interferons; LAK: Lymphokine Activated Killer Cells; TNF: Tumor Necrosis Factor; TRAIL: TNF related Apoptosis – Inducing Ligand ; MDSC: Myeloid Derived Suppressor Cells; Ag: Antigen

Introduction

Immune responses are the complex group of defense responses produced by immune system in humans as well as other advanced vertebrates which helps to repel diseases and pathogens. These immune responses can also help to eliminate abnormal cells of the body that develops to cancer. Cancer is a major health problem worldwide and one of the most important causes of morbidity and mortality in children and adults [1,2]. Tumors arise from the uncontrolled proliferation and spread of clones of transformed cells [3,4]; they can even caused by DNA damage by oxidative reaction species [5]. Cancer cells are normal body cells that have been altered in a manner that allows them to divide relentlessly, ignoring normal signals of restraint. As a result, cancer cells form clusters of cells [6], called tumor that invade and colonize tissues, eventually undermining organ function and causing death. The genome regulatory network level(GRN), the cancer attractors hypothesis naturally explains tumorigenesis[7], but such a new network-based intellectual framework is still quite abstract and also remains incompletely understood what its evolutionary origin is and what causes normal somatic cells be entrapped in [8].

From an immunologic perspective, cancer cells can be viewed as altered self-cells that have escaped normal growth-regulating mechanisms [9]. The possibility that cancers can be eradicated by specific immune responses has been the impetus for a large body of work in the field of tumor immunology [10]. There are several requirements for tumor antigens to be recognized by T cells. Tumor antigens can be recognized by T cells as well as by antibodies [11]. There is a need for new therapies towards cancer which can prolong survival and decrease mortality [12].

Cellular Immunity

The immune system can identify and destroy nascent tumor cells in a process termed cancer immunosurveillance, which functions as an important defense against cancer [13]. The identification of tumor specific antigens has provided important advance in tumor immunology [14]. Most of the tumors are immunogenic but the immunity they evoke is either too weak to reject a rapidly growing tumor or the tumor induces a suppressor effect on the host immune system [15]. Several immunocyte populations are active in the natural cellular defense against tumors. These include macrophages, Natural Killer Cells, Cytotoxic cells, chemokines and lymphokines [16,17].

Cytotoxic T Lymphocytes

These belong to sub group of T lymphocytes which are capable of inducing death of somatic and tumor cells which were infected or damaged. Cytotoxic T cells recognize fragments of antigen producing CTL responses [18]. These CTL responses directs toward Major Histocompatability Complex - 1 molecule bounded to peptide antigens [19]. The pMHC-I complexes are expressed on infected cells where they are specifically recognized by αβ T cell receptors [20]. αβ T-cell receptors (TCRs), can engage a broad array of foreign peptide-laden major histocompatibility complex (pMHC) landscapes, plays an essential role in protective immunity[21,22]. Tumor associated antigens having T cell epitopes proven to play significant role in rejection of tumors. Stimulation of a potent and specific immune response against tumor cells most likely results in tumor clearance [23]. Antitumor responses are mediated by T cells and particularly by cytotoxic T lymphocytes (CTLs) [24]. The induction of a strong CTL effector and memory response was demonstrated to be dependent on the dose of antigen (Ag) and the number of Ag-presenting cells (APCs) presenting the Ag [25].

APC (B cells, monocyte/macrophages and dendritic cells) are potent stimulators of antigen-specific T-cell responses, through their

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ability to process and present antigens in the context of both MHC class I and class II molecules, and by providing the appropriate second signals to the naive T cell to stimulate cell activation and clonal expansion [26]. By fusing tumor cells with professional APC, hybrid cells with the antigen expression of the parent tumor cell and the antigen processing and immunostimulatory capacity of the parent APC are generated. The generation of such human APC/tumor cell hybrids, using an Epstein–Barr virus-transformed B-lymphoblastoid cell line (EBV B-LCL) as the APC partner, had shown APC/tumor cell hybrids stimulating strong allogeneic T-cell responses, express and present relevant tumor-associated antigens [27,28].

Natural Killer Cells

Natural killer cells are type of cytotoxic lymphocytes that constitute major compartment of innate immunity [29,30]. They kill foreign bodies by releasing small proteins called perforins and granzymes which makes the cells to die by apoptosis [31]. Natural killer cells have been initially identified as a lymphoid population representing the 10–20% of PBMC, able to lyse MHC class I (MHC-I) negative tumor and virus-infected cells and to orchestrate innate immunity of the organism. Upon cytokine stimulation, NK cells become lymphokine-activated killer (LAK) cells that proliferate, produce cytokines [32], and up-regulate effector molecules such as adhesion molecules, NKp44, perforin, granzymes, Fas ligand (FasL), and TNF related Apoptosis – Inducing Ligand (TRAIL) [33].

TRAIL or Apo-2 ligand, generates excitement because of its apparent unique ability to induce apoptosis in a wide range of transformed cell lines, but not in normal tissues [34]. To date, four homologous, but distinct, human TRAIL (hTRAIL) receptors have been identified as DR4- TRAIL-R1 and DR5/ TRAIL-R2, possess the ability to initiate the apoptosis signaling cascade after ligation, and the other two TRAIL-R3 and TRAIL-R4 lack this ability [35].

Macrophages

Macrophages are the cells produced by differentiation of monocytes in tissues. They function in both innate immunity as well as adaptive immunity [36]. Macrophages are believed to help cancer cells proliferate as well. They are attracted to oxygen-starved (hypoxic) tumor cells and promote chronic inflammation. Inflammatory compounds such as Tumor necrosis factor (TNF) released by the macrophage activates the gene switch nuclear factor-kappa B [37]. NF-κB then enters the nucleus of a tumor cell and turns on production of proteins that stop apoptosis and promote cell proliferation and inflammation [38,39]. The role of macrophages in relation to tumor growth has recently excited much interest. A number of reports have indicated an effector role for macrophages against tumor cells after both specific and non-specific sensitization of the host. The cytotoxic mechanism in most cases appears to depend on direct contact with the target cells as originally described against fibroblast and L cell monolayers [40].

The killing of tumor cell by macrophages is an immunologically specific reaction followed by non specific lethal reaction. A range of released products from macrophages can show cytostatic and cytotoxic [41] activities for tumor cells [42]. Tumor cytostatic effects are mediated by various cytokines (INFs, TNF-a, IL-6, IL-1 (a/b), reactive intermediates of oxygen or nitrogen, enzymes (e.g. arginase) metabolizing essential amino acids, prostanoid [43] metabolites (e.g. PGE2) and nucleotides (e.g. thymidine). Cytotoxic effects are mediated either by soluble factors (see above) or require close contact between the macrophage and the targeted tumor cells. TNF-a plays a crucial role in macrophage-mediated cytotoxicity. TNF-a mediated killing is believed to be via induction of apoptosis and has been described in many cell types in vitro [44]. Many of the biological effects of soluble TNF-a, including programmed cell death, can be mediated through the p55 TNF receptor I (TNFRI).However, the membrane bound form of TNF-a was also found to activate TNFR II and lead to apoptosis, even in cells resistant to the cytotoxic effects of soluble TNF-a [45]. Thus, membrane-bound TNF-a may be crucial for induction of apoptosis [46]. This is consistent with the observation that cell to cell contact appears essential in macrophage-mediated apoptosis [47].

Dendritic Cells

Dendritic cells are antigen-presenting cells (APCs) which play a critical role in the regulation of the adaptive immune response [48]. Dendritic cells (DCs) are unique APCs and have been referred to as "professional" APCs, since the principal function of DCs is to present antigens [49]. The function of DCs falls broadly into three categories, each of which involves antigen presentation. The first category of DCs function is antigen presentation and activation of T cells. The second category of DC function is not as well established, but it has been suggested that a different class of DCs exist with the function of inducing and maintaining immune tolerance [50]. The third categories of DCs, known as follicular DCs, appear to work to maintain immune memory in tandem with B cells.

DCs are being studied as adjuvants for vaccines or as a direct therapy to induce immunity against cancer. DCs loaded with tumor lysates, tumor antigen-derived peptides, MHC class I restricted peptides, or whole protein have been shown to generate anti-cancer immune responses and activity, including in some cases the ability to induce complete regression of existing tumor.

Lymphokines

Lymphokines are the subsets produced by T-lymphocytes, they include colony-stimulating factors (CSFs), Interferons (IFN -γ), Interleukins [51] (ILS 1-8, 10-13), Tumor Necrosis Factor (TNF-α, β) [52,53]. Activated T-lymphocytes, through the release of lymphokines, have the capacity to control inflammatory responses. Lymphokine production is associated with, but not limited to, helper T cells, and usually follows antigenic or mitogenic stimulation. Lymphokines have a unique capacity of killing NK-resistant fresh human tumor cells in short-term assays [54]. Lymphokine Activated Killer cells (LAK) appear to kill autologous tumors as well as TNP-modified self and allogeneic tumors with complete cross reactivity, both at the population and clonal level. Initial studies on the classification of LAK conclude that LAK are distinct from the classical NK and T-lymphocyte systems based on a number of criteria including surface phenotype, activation conditions, and spectrum of susceptible target cells. LAK kill rasoncogene-transfected fibroblasts in a manner similar to fresh tumors.

The systemic administration of lymphokine activated killer (LAK) cells and recombinant interleukin-2 (RIL-2) is effective in reducing the number of established pulmonary and hepatic metastasis [55,56] from multiple murine tumors and has recently been shown to be effective in mediating the regression of metastatic cancer in humans [57].

Regulatory T Cells

Regulatory T cells also called as suppressor T- cells are essential for maintaining immunologic self tolerance and homeostasis [58]. Regulatory T cells prevent auto immune diseases by suppressing self reactive T cells and may also suppress immune response against cancer.

Natural CD4+CD25+ T cells play an important role in the suppression of autoimmune responses via inhibition of self-reactive T cells [59]. T cells play a role in the suppression of responses to viral, bacterial, and protozoal infections. Additionally, CD4+CD25+ T cells were found to suppress protective antitumoral immunity. In turn, blocking Treg function with a neutralizing antibody against cytotoxic T lymphocyte-associated antigen 4 (CTLA- 4) induced an increase in protective immune responses [60].

Myeloid Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells that expand during cancer, inflammation and infection, and that have a remarkable ability to suppress T-cell responses [61]. These cells constitute a unique component of the immune system that regulates immune responses in healthy individuals and in the context of various diseases. MDSCs in the periphery of or within a tumor that suppresses the anti-tumor functions of T cells, are CD11b+, CD11c+, Gr-1+, IL-4R+, inflammatory monocytes. MDSCs within tumors also have a potent, immunosuppressive phenotype and produce reactive nitrogen compounds (peroxynitrites, among others) that have recently been shown to nitrosylate the CD8 and TCR molecules on T cells, thereby inhibiting T cell reactivity.

Humoral Immunity

The term humoral refers to the non-cellular components of the blood, such as plasma and lymphatic fluid. The humoral immune response denotes immunologic responses that are mediated by antibodies [62]. Humoral immunity includes the primary and secondary immune responses to antigen. During the primary immune response, an antigen is encountered by the host for the first time. Virgin B cells need to be activated and proliferate before an effective immune response can be generated. This primary response may be too slow to protect against many pathogens. Secondary antibody response, which results from the activation of a memory B cell, is faster and more effective in halting the progress of infection due to increased antibody binding affinities.

Humoral immune responses increase the recruitment and activation of innate immune cells in neoplastic microenvironments [63] where they regulate tissue remodeling, pro-angiogenic [64] and pro-survival pathways that together potentiate cancer development [65]. The humoral response is triggered by the interaction between the variable regions of an antibody with specific epitopes on cell-surface molecules. The cellular response involves recognition of antigens by T-cell receptors (TCRs) when they are presented by the cell in conjunction with the major histocompatibility complex (MHC) molecules [66]. Antibodies are not capable of detecting the small processed peptides on MHC molecules [67] on the cell surface, so the nature of the antigens that are recognized by the humoral and cellular arm is different.

Population-based studies examining individuals with chronic inflammatory disorders have revealed that states of suppressed cellular immunity, in combination with enhanced humoral immunity and humoral immunity-associated cytokines, cooperate and effectively suppress anti-tumor immune responses while simultaneously enhancing angiogenesis and presumably overall cancer risk in afflicted tissue [23,68]. Tumor-specific humoral immune responses directed against oncoproteins, mutated proteins such as p53 [69]. In many cancers humoral immune responses are induced by MUC 1. MUC1 is a membrane-tethered mucin expressed on the ductal cell surface of glandular epithelial cells. Loss of polarization, over expression and aberrant glycosylation of MUC1 in mucosal inflammation and in adenocarcinomas induces humoral immune responses to the mucin. MUC1 IgG responses have been associated with a benefit in survival in patients with breast [70], lung, pancreatic, ovarian [71] and gastric carcinomas [72]. Humoral immunity or development of auto immune antibodies against tumor associated proteins can be used as biomarkers in tumor diagnosis [73,74].

Conclusion

Our immune system plays an important role in provoking anti-tumor responses, Cytotoxic T Lymphocytes and Natural Killer cells induce the death of tumor cells by producing CTL responses against tumor cells adhered by MHC class I molecules mediated by Antigen Presenting Cells, where as Natural Killer cells become Lymphokine Activated Killer cells and up regulate effectors such as adhesion molecules, TRAIL, TNF. Macrophages activate TNF-αβ which induces apoptosis. Dendritic cells helps in activation of T-cells, maintain immuno tolerance and immuno memory in tandem B-cells. Dendritic cells are being studied as adjuvants for vaccines to induce tumor immunity. Systemic administration of LAK and recombinant IL-2 is effective in reducing metastasis. Vaccines were produced against Regulatory T-cells to induce protective immune response by blocking its regulatory function. Based on the above mechanisms vaccines were developed to provoke immune response against tumors.

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