



A Review on Immunity Against Tumor Cells

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Abstract

The immune response is a complex group of defense responses produced in both humans and advanced vertebrates that are involved in the elimination of abnormal somatic cells that develop into cancer. It occurs through the development of immunological memory through extensive effector functions to target and destroy pathogens, or through adaptive immune responses for subsequent defense mechanisms. This multifaceted mechanism consists of three main stages: elimination, equilibrium, and escape, each of which contributes to cancer elimination, quiescence, and progression. The purpose of this article is to review tumor immunotherapy. For this purpose, there are two forms of immune response. It is congenital, non-specific, fast-acting, first responder, and adaptable, characterized by specificity for target antigens, and acquires an immunological memory form. The former minimizes cancer-mediated inflammation, provokes an adaptive immune response, and attacks cancer through more specific immune mechanisms that can target antigens. The central doctrine behind the concept of cancer immunity is formation of neo antigens produced as a result of tumorigenesis/carcinogenesis that is phagocytosed by antigen-presenting cells (APCs) or pinocytosed by dendritic cells for antigen processing. Tumor growth can be controlled by antigen-specific or non-tumor-specific reactions. Tumor-specific immunity is predominantly mediated by both T cells and B cells, and non-specific tumor destruction is mediated by the innate immune system, independent of T cells, and is evoked by activating compounds that target pattern recognition receptors such as Toll-like receptors and Nod-like receptors. In summary, the immune system plays an important role in triggering an antitumor response and is changing rapidly, creating increasing excitement in human and veterinary medicine.

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Abbreviations: ADCC: Antibody Dependent Complement Cytotoxicity; APC: Antigen Presenting Cells; CDC: Complement Dependent Cytotoxicity; CTL: Cytotoxic T Lymphocyte; CTLA: Cytotoxic T Lymphocyte-Associated Antigen; DAMPs: Danger Associated Molecular Patterns; HIF-1 α : Hypoxia Inducible Factor-1 α ; LAK: Lymphokine Activated Killer Cells; MDSC: Myeloid Derived Suppressor Cells; MHC: Major Histocompatibility Complex; MT: Liposomal Muramyl Tripeptide; NF κ B: Nuclear Factor Kappa B; NLR: Nod-like receptors; PAMPs: Pathogen Associated Molecular Patterns; ROS: Reactive Oxygen Species; TCR: T Cell Receptors; TLR: Toll-Like Receptors; TNF: Tumor Necrosis Factor; TRAIL: TNF related Apoptosis Inducing Ligand.



Introduction

Cancer cells are self-cells that have undergone changes or have bypassed normal growth-control mechanisms [42]. They are regular bodily cells that have been changed in such a way that they can continue to divide despite typical signals of constraint. As a result, cancer cells develop tumors, which penetrate and colonize tissues, eventually impairing organ function and resulting in death [65]. Cancer is a major public health issue that affects people all over the world and is one of the leading causes of morbidity and mortality [9]. Tumors grow when clones of altered cells proliferate and spread uncontrollably [13].

Immune responses are a sophisticated set of defense reactions produced by the immune system in humans and other advanced vertebrates that aid in the prevention of disease and infections. These immune responses may also aid in the elimination of cancer-causing aberrant cells in the body. The connection between the immune system and cancer has been well recognized for over a century, and Rudolph Virchow was the first to point it out over 150 years ago [36].

The underlying basis of this cancer-immunity relationship involves three basic principles about how the immune system works to protect and defend an individual: It detects antigens that are not from pathogens or infected/malignant cells; it includes effector functions to specifically target and destroy pathogens or infected/malignant cells while protecting the host; and it develops immunological memory through adaptive immune responses for further defense mechanisms following injury or host attack [39].

Through this process, the immune system has acquired pattern-generating features known as immune editing, which provides a balance between immune surveillance and cancer progression in the field of oncology [54]. This multifaceted mechanism involves three main phases: clearance, balance, and exit, which contribute to clearance, dormancy and cancer progression, respectively [72]. Interestingly, cancer's ability to evade or escape this immune response is now recognized as one of the most prominent features of cancer, providing the basis for treatments in immunotherapy. Although the early use of immunotherapy to treat cancer dates back to the early 19th century, this points to the work of William B. Coley and colleagues [3,36].

It is the responsibility of veterinarians to notice the growth patterns of tumor cells and their control by the immune system in the animals they care for. As the cancer hide itself, it can be left unnoticed in farm animals because they are thought to be disease-free and it remains serious due to its proliferative problem. Therefore, this review aims to evaluate tumor (cancerous) cells and their immunity against them, and to elucidate how immunity controls these out-of-control body cells.

Literature review

Tumor cells

Cancer cells are normal body cells that have become abnormal and continue to divide uncontrollably, despite normal signals telling them to stop. As a result, Cancer cells form groups of cells [65], called tumors, that invade and colonize tissues, eventually leading to organ dysfunction and death. Tumors are caused by the uncontrolled growth and spread of clones of transformed cells [13]. Cancer cells are mutated self-cells that have evaded the usual growth-control mechanisms [42].

Cancers that remain limited to their origin site are referred to as "primary cancer," but cancers that spread to other parts of the body are referred to as "secondary cancer or metastatic cancer." Certain altered cells are able to separate themselves from the main cancer development (neoplasm) and spread through other areas via lymphatic flow or blood circulation, which is how metastasis develops [26]. While metastatic malignancies retain the altered cells from the main tumour, they develop specific characteristics throughout time that assist differentiate them from the parent malignancy [49].

It's vital to remember that the terms "cancer" and "tumor" are not interchangeable. Tumors are clumps of aberrant cell growth (neoplasms) that can be benign or cancerous (injurious). These benign tumors stay isolated at the place of origin, whereas malignant tumors spread to other organs and are referred to as cancerous [26].

The onset of cancer

Cancer is caused by a variety of spontaneous and induced genetic mutations, including changes in glycosylation patterns, chromosomal gain or loss, and translocation [78]. DNA methylation and other epigenetic changes play a role in cancer etiology [79]. Hyper methylation, for example, is a known strategy for silencing tumor suppressor genes [25]. DNA hypomethylation of mobile DNAs, on the other hand, triggers gene activation and has been reported in a variety of malignancies [25]. These epigenetic alterations can affect a wide spectrum of tissues and organs, leading to cancers including prostate cancer and breast cancer [51].

Macrophages are thought to aid cancer cell proliferation by attracting oxygen-depleted tumor cells (hypoxic) and promoting chronic inflammation. The gene-switch nuclear factor-kappa B is activated by inflammatory chemicals generated by macrophages, such as tumor necrosis factor (TNF) [88]. NF B then reaches a tumor cell's nucleus and activates the synthesis of proteins that prevent apoptosis and promote cell proliferation and inflammation [90].

Not all cancer cells in circulation survive, but those that do can attach to the endothelial cell lining of capillary venules or blood arteries and travel to secondary tissues or organs via complex signaling pathways [62]. Cancers' hypoxic environment causes the development of proteins like hypoxia inducible factor-1alpha (HIF-1), which can control the expression of angiogenic growth factors like vascular endothelial growth factor (VEGF) [33].

Though a range of other proteins, such as cytokines, interleukins, and other growth factors, also have a role in cancer proliferation through angiogenesis [61]. Cancer or tumors can arise from a variety of tissues, including epithelium, mesenchyme (connective tissue/bones), or glands, and are classified as carcinoma, sarcoma, or adenocarcinoma, depending on the site of origin [9]. Lymphomas are cancers that begin in the lymphatic system and impact the lymphoid organs, whereas myeloma and leukemia are tumors that develop in the bone marrow and influence the formation of plasma cells in myeloma and erythrocytes and leukocytes in leukemia, respectively [34].

Immune System

The immune system is made up of a variety of soluble bioactive molecules, cytokines, proteins, and cells that work together to build a complex web of biochemical processes that recognize

and protect against “non-self” proteins or antigens [39]. The immune system consists of two types of immune responses: innate and adaptive, which provide protection and preserve the host’s normal state of homeostasis [39].

Innate Immunity and Cancer: Several components of innate immunity are engaged during cancer pathogenesis in order to reduce cancer-related inflammation (Dunn, 2006). This process also triggers adaptive immune responses, which allow more specialized immune systems to target the tumour [91]. Changes in the makeup of cancer cells’ cell surface proteins correspond with changes in their pathogenesis, resulting in the expression of tumor related antigens that can be identified by complement proteins, predisposing cancer cells to complement-mediated death (Pio *et al.*, 2014).

Innate immunity recognizes unique danger or pathogen associated molecular patterns (DAMPs or PAMPs) and uses receptors like TLRs and others to discriminate between self and non-self cells [39]. TLR7, for example, is an intracellular receptor that can recognize single stranded RNA but also suppresses Treg production, which is beneficial in the tumor setting [50]. Modified cell surface indicators and patterns on the surface of cancer cells occur from genetic and epigenetic change. MHC class I is one such cell surface marker whose expression is changed or diminished in cancer cells (Waldhauer, 2008). This abnormal or decreased MHC class I expression activates NK cells through activating receptors on the NK cell surface, such as NKG2D, which bind to surface glycol proteins called MICA/B that may be present on tumors (Steinle, 2008).

TNF-dependent release of cytoplasmic granules (perforin and granzymes) that form pores in cell membranes; antibody-dependent complement cytotoxicity due to the presence of antibody receptor (CD16) on NK cell surface; and the release of cytokines such as IFN-, which mediates activation and maturation of antigen-presenting cells such as dendritic cells, are all examples of NK-induced programmed cell death (apoptosis) (Waldhauer and Steinle, 2008). Phospholysosomes, found in neutrophils, include enzymes such as NADPH oxidase, which oxidizes superoxide radicals and other reactive oxygen species (ROS). ROS have been shown to not only promote cancer through genetic alterations caused by DNA damage, but also to induce cytotoxicity by disrupting the cell membrane on tumors [1].

In addition, different cell types act as evolutionary linkers between innate and adaptive immunity. Dendritic cells, $\gamma\delta$ T cells, macrophages, and NK T cells are examples of these cells. Dendritic cells and macrophages, for example, which serve as phagocytes in innate immune responses, can also serve as antigen-presenting cells in adaptive immunological responses [40]. NKT cells contribute to immune responses against tumor cells by secreting IFN, which activates the effector capabilities of cells like NK cells and CD8+ T cells, allowing them to cause tumor destruction via granzymes or perforin [53].

Similar to NK and CD8+ T cells, the $\gamma\delta$ T cells express NKG2D which interacts with MICA/B on tumor cells and promotes secretion of perforin proteins and subsequent tumor lysis (Gogoi and Chiplunkar, 2013). Other mechanisms implemented by the $\gamma\delta$ T cells for regulating cancer progression involve secretion of IFN- γ that can activate NK or CD8+ T cells for tumor lysis, recognition of tumor-associated antigens by CD16 (Fc receptor) to mediate antibody-dependent complement cytotoxicity, and the ability of $\gamma\delta$ T cell receptors to bind to self-antigens such as heat shock proteins that are upregulated in the cancer microenvironment [1].

Similarly, $\gamma\delta$ T cells, like NK and CD8 T cells, express NKG2D, which binds to MICA/B on tumor cells and increases perforin protein release and tumor lysis (Gogoi and Chiplunkar, 2013). T cells also regulate cancer progression through the secretion of IFN- γ , which can activate NK or CD8 T cells for tumor lysis, recognition of tumor-associated antigens by CD16 (Fc receptor) to mediate antibody-dependent complement cytotoxicity and the ability of $\gamma\delta$ T-cell receptors to bind to autologous antigens, such as heat shock proteins, are well regulated in the microenvironment [1].

Adaptive immunity and cancer

By utilizing the effect or functions of antibodies, T cells, B cells, and antigen-presenting cells, this type of immune response is capable of targeting antigens unique to cancer cells [73]. MHC class II molecules present foreign tumor antigen peptides, whereas MHC class I molecules present endogenous cancer antigen peptides [73]. MHC class II on APC activates CD4+ T cells, priming them for subsequent antigenic peptide/MHC class II complex exposures, resulting in the formation of memory T cells [98].

Thymus independent (TI) processes, which involve antigens with highly repetitive motifs, can activate B cells [10]. Antibodies that can bind to the tumor-derived antigen are produced once TI B cells are activated. This might cause tumor cell lysis via antibody-dependent complement cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), as well as attaching [28] to Fc receptors on NK cells [31]. The binding of antigen-specific T cell receptors with MHC class I/tumor antigen complexes activates CD8+ T cells, resulting in the induction of cytolytic CD8+ T cell-mediated destruction of cancer cells [91].

T cells contain a cell surface receptor molecule called programmed cell death protein 1 (PD-1) that can attach to its ligand, PD-L1, on APCs and mediates immunosuppression. The PD-1 expression has also been reported in multiple other immune cells such as B cells, NK cells, monocytes, dendritic cells, and Tregs [35]. Similar to CTLA4, the PD-L1 protein is expressed by a variety of cancer cells, suggesting that it may be a method by which cancer cells evade immunity [19]. Tregs can also suppress immune responses in an oncogenic setting (Nishikawa and Sakaguchi, 2010).

Cellular immunity

In a process known as cancer immune surveillance, the immune system may detect and eliminate emerging tumor cells, which serve as a key cancer defense [54]. The discovery of tumor-specific antigens has resulted in significant advancements in tumor immunology [63]. The majority of cancers are immunogenic, but the immunity they elicit is either insufficient to reject a fast growing tumor or the tumor causes the host immune system to become suppressed [106]. In the normal cellular fight against malignancies, several immunocyte populations are active. Macrophages, Natural Killer Cells, Cytotoxic cells, Chemokines, and Lymphokines are among them [74].

Cytotoxic T lymphocytes

These T lymphocytes are part of a subgroup of T lymphocytes that can kill infected or injured somatic and tumor cells. CTL responses are triggered when cytotoxic T cells identify antigen fragments [102]. These CTL responses are directed against the MHC-1 (MHC-I) molecule, which is linked to peptide antigens [15]. The pMHC-I complexes are expressed on infected cells and

are recognized by $\alpha\beta$ T cell receptors specifically [14]. T-cell like $\alpha\beta$ T-cell receptors (TCRs) play an important role in protective immunity because they may engage a wide range of foreign peptide-laden major histocompatibility complex (pMHC) landscapes (Gras *et al.*, 2011). Tumor related antigens with T cell epitopes have been shown to play an important role in tumor rejection. Tumor clearance is most likely the outcome of activating a robust and targeted immune response against tumor cells (Balashova, Lkhov, 2010).

Natural killer cells

Natural killer cells are a type of cytotoxic lymphocyte that makes up a large part of the innate immune system [6]. They eliminate foreign substances by releasing tiny proteins known as perforins and granzymes, which cause cells to undergo apoptosis and perish [41].

Macrophages

Macrophages are the cells that result from monocyte differentiation in tissues. They play a role in both innate and adaptive immune responses [16]. Macrophages kill tumor cells in an immunologically specific reaction that is followed by a nonspecific deadly reaction. For tumor cells, a variety of macrophage-released chemicals can have cytostatic and cytotoxic [96] effects. Various cytokines (INFs, TNF- α , IL-6, IL-1 (a/b), reactive oxygen or nitrogen intermediates, enzymes (e.g., arginase) metabolizing essential amino acids, prostanoid [77] metabolites (e.g. PGE2), and nucleotides (e.g. thymidine) mediate tumor cytostatic actions. The cytotoxic effect is mediated either by soluble factors (see above) or requires close contact between macrophages and the targeted tumor cells. TNF α plays an important role in macrophage-mediated cytotoxicity. TNF α -mediated killing is thought to occur through apoptosis induction and has been described in many cell types in vitro [76].

Dendritic cells

Dendritic cells are antigen-presenting cells (APCs) that play an important role in the regulation of the adaptive immune response [24]. Dendritic cells (DCs) are unique APCs and are referred to as "professional" APCs because the primary function of DCs is antigen presentation [21].

Lymphokines

Colony-stimulating factors (CSFs), Interferons (IFN -), Interleukins [87] (ILS 1-8, 10-13), and Tumor Necrosis Factor (TNF- α) [86] are examples of lymphokines produced by T-lymphocytes. In short-term experiments, lymphokines show a unique ability to destroy NK-resistant fresh human tumor cells [18]. At the population and clonal level, Lymphokine Activated Killer cells (LAK) appear to destroy autologous malignancies as well as TNP-modified self and allogeneic tumors with perfect cross reactivity. The systemic infusion of lymphokine activated killer (LAK) cells and recombinant interleukin-2 (RIL-2) has recently been found to be beneficial in lowering the amount of established lung and hepatic metastases from different mouse malignancies [47] and regulating the regression of metastatic cancer in humans [84].

Regulatory T cells

Regulatory T cells, also known as suppressor T cells, are necessary for immune self-tolerance and homeostasis [82]. Regulatory T cells limit the immune response to malignancy and prevent auto immune disorders by reducing self-reactive T

cells. Natural CD4+CD25+ T cells play a key role in autoimmune response suppression by inhibiting self-reactive T cells [23]. T cells are involved in the inhibition of viral, bacterial, and protozoal infection responses. CD4+CD25+ T cells were also discovered to inhibit protective antitumoral responses. Blocking Treg function using a neutralizing antibody against CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) resulted in an increase in protective immunological responses [94].

Myeloid derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a diverse group of cells that grow during cancer, inflammation, and infection and have a remarkable ability to dampen T-cell responses [56]. These cells are a special type of immune cell that modulates immunological responses in healthy people as well as in the setting of various disorders.

Humoral immunity

The non-cellular components of the blood, such as plasma and lymphatic fluid, are referred to as humoral. Immunologic responses mediated by antibodies are known as humoral immune responses [44]. The primary and secondary immune responses to antigen are referred to as humoral immunity. The host encounters an antigen for the first time during the initial immunological response. Before an effective immune response can be created, naive B cells must be activated and proliferated. Many pathogens may be too fast for this main response to guard against. Due to enhanced antibody binding affinities, the secondary antibody response, which occurs from the activation of a memory B cell, is faster and more efficient in preventing the progression of infection.

In neoplastic microenvironments, where they regulate tissue remodeling, pro-angiogenic (Shimoyama, 2011), and pro-survival pathways [67], humoral immune responses boost the recruitment and activation of innate immune cells [105]. The contact of the variable portions of an antibody with specific epitopes on cell-surface molecules triggers the humoral response. Oncoproteins, altered proteins like p53, are targets of tumor-specific humoral immune responses [64].

Conclusion

In general, the immune system is a natural defense system that plays an important role through cellular and humoral immunity in inducing anti-tumor responses. Cytotoxic T lymphocytes and natural killer cells induce tumor cell death by inducing a CTL response against tumor cells that are adhered to by MHC class I molecules mediated of antigen-presenting cells, while natural killer cells become killer cells activated by lymphokines and upregulate agents such as adhesion molecules, TRAIL, and TNF. TNF $\alpha\beta$ - is activated by macrophages and induces apoptosis. Dendritic cells help activate T cells, maintain immune tolerance and immune memory in B cells in tandem.

Although immune cells fight against tumor cells, some are involved in the formation of tumor cells, for example macrophages which are believed to help cancer cells to proliferate, by being attracted to oxygen-starved tumor cells and promoting chronic inflammation. Epigenetic alterations such as DNA methylation also play a role in carcinogenesis. Many proteins such as cytokines, interleukins, and other growth factors also contribute to angiogenesis for carcinogenesis. Therefore, further studies are needed to obtain immune cells that eliminate only tumor cells and improve them further.

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