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Research Progress on the Regulation of Tumor Microenvironment in Immunotherapy

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Abstract: ***The tumor microenvironment (TME) is an important component of cancer. Cancer cells can secrete a variety of cytokines, chemokines, and other factors, which can reprogram the surrounding cells and play a decisive role in tumor survival and progression. Immune cells are an important part of the tumor stroma and play a crucial role in anti-tumor immunity. An increasing amount of evidence shows that when innate immune cells (macrophages, dendritic cells, natural killer cells, and myeloid-derived suppressor cells) and adaptive immune cells (T cells and B cells) are present in the TME, they will promote tumor progression. Current research has identified new targets in the TME that can guide and improve the efficacy of various cancer therapies. This article reviews the latest understanding of the impact of immune cells, cancer-associated fibroblasts, hypoxia, etc. in the microenvironment on tumor immunotherapy, and discusses existing and potential strategies.***

Keywords: Tumor microenvironment, Immune cells, Tumor fibroblasts, Hypoxia, Tumor immunotherapy.

1. Introduction

The continuous increase in the incidence and mortality of tumors poses a significant threat to human health. Finding safe and effective treatment methods is a formidable challenge for researchers worldwide. Traditional tumor treatment methods include surgical resection, radiotherapy, and chemotherapy, but their impact on patient survival rates is still controversial. With the development of disciplines such as oncology, immunology, and molecular biology, tumor immunotherapy has been developed based on the study of the mechanisms of tumor immune escape. Tumor immunotherapy can inhibit the pathways of tumor immune escape and reactivate the immune system to fight against tumors. The immune system plays an important role in the occurrence and development of tumors. As a promising, effective, and low-side-effect treatment approach, immunotherapy has received widespread attention, including antibodies, cancer vaccines, adoptive cell therapy, and immune checkpoint blockade therapy [1][2][3]. However, immunotherapy also faces many problems. For example, in some patients, it shows limited efficacy, adverse reactions, and a narrow anti-tumor spectrum, indicating the complexity of the regulatory factors of the tumor immune response. The components of the tumor microenvironment mainly include tumor cells, immune cells, cancer-associated fibroblasts, signaling molecules, and the extracellular matrix (EMC). Many studies have proven that the occurrence and development of tumors and tumor recurrence after treatment are affected by the TME. Recent studies have shown that the response of tumors to immunotherapy can be regulated by the TME. A profound understanding of the impact of the TME on the immune response will significantly improve the effectiveness of immunotherapy.

The composition of the TME is very complex, and it has only recently become the focus of tumor research. Currently, our understanding of the TME is not comprehensive. This review mainly elaborates on the latest research progress on the impact of immune cells, cancer-associated fibroblasts, hypoxia, and other physical factors in the tumor microenvironment on tumor immunotherapy, aiming to find breakthrough points for enhancing anti-tumor effects in these aspects.

2. Regulation of Tumor Immune Response by Immune Cells

The tumor microenvironment is infiltrated with many innate and adaptive immune cells. Currently, treatments targeting the TME mainly focus on T cells, such as immune checkpoint blockade and chimeric antigen receptor (CAR)-T cell therapy. With in-depth research, it has been found that innate immunity can not only indirectly affect the TME by controlling the fate of T cells but also critically shape the TME. These innate immune cells mainly include regulatory T cells (Tregs), macrophages, dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), natural killer cells (NKs), etc. To enhance the effectiveness of tumor immunotherapy, it is necessary to have a comprehensive understanding of innate immune cells and conduct further research to find treatment methods for dysfunctional cells in the TME.

2.1 Regulatory T Cells

Regulatory T cells play a bidirectional regulatory role in immunity. They can not only prevent the occurrence of autoimmune diseases caused by excessive immunity in the body but also inhibit the immune response under pathological conditions. The classic marker combination on the surface of Tregs is $CD4^+CD25^+Foxp3^+$. In the tumor microenvironment, $CD4^+CD25^+Foxp3^+$ can secrete immune inhibitory molecules such as IL-10, TGF-β, and IL-35, and induce the occurrence and development of tumors by inhibiting the maturation and function of DC cells, suppressing T cell metabolism, and promoting the lysis of NK cells and CD8+ T cells [4]. Removing Treg cells from the tumor microenvironment or inhibiting the function of Treg cells is a method for treating tumors. CD137 is an important molecular target for anti-tumor immunity [5], and hypoxia can significantly increase the expression of CD137 on activated T cells.

For naive T cells to effectively activate anti-tumor antigens, a

co-stimulatory signal provided by the binding of CD28 on the surface of T cells and the B7 molecule on the surface of antigen-presenting cells (usually DCs) is required. The activation of T cells will upregulate the surface expression of CTLA-4, so the activation of T cells is strictly regulated at the co-stimulatory level. CTLA-4 has a high degree of homology with CD28, and its ability to bind to the B7 molecule is stronger than that of CD28, resulting in CTLA-4 blocking the co-stimulation and ultimately inhibiting the function of T cells. Treg cells can also express a high level of CTLA-4. Therefore, anti-CTLA-4 antibody treatment can deplete these cells from the TME, thereby releasing the inhibition of anti-tumor CTL activity [6]. Treg cells secrete immune regulatory factors such as TGF-β, IL-10, and IL-35 [7]. Among them, TGF-β can promote tumor metastasis and the formation of the tumor stroma, inhibit NK cells and T cells, and further promote the generation and expansion of Tregs [8]. Some studies have proven that in several different types of tumors, the TME can induce the expression of the apoptosis inducer Fas ligand (FasL) on tumor vascular endothelial cells, which can effectively establish a selective immune barrier and promote tumor tolerance [9]. The expression of FasL enables endothelial cells to kill CTLs through Fas-mediated apoptosis, but not Tregs, because the increased surface expression of c-FLIP on Tregs confers resistance to FasL exposure. Therefore, the low infiltration of CTLs and the presence of Treg cells in tumors are advantageous for the expression of FasL. Downregulating the expression of FasL on endothelial cells by inhibiting VEGF-A or cyclooxygenase may become a target for enhancing cancer immunotherapy [9].

2.2 Tumor-Associated Macrophages

The regulation of immune homeostasis requires macrophages. Macrophages have the functions of phagocytosing pathogens and presenting antigens, and they also play a role in promoting wound healing and tissue repair [10]. Macrophages are tissue-specific and ubiquitous, and they play important roles in wound healing, tissue formation, coagulation, inflammation, and tissue remodeling [11]. Many studies have shown that macrophages play an important role in eliminating tumor cells. According to their functions and cytokine secretion, macrophages can be divided into two types: classically activated (M1) and (M2). In solid tumors, some immunosuppressive signals can impair the function of macrophages [12]. Macrophages in solid tumors are called tumor-associated macrophages (TAMs), which are a subset of infiltrating immune cells in tumors and can assist in tumor development and metastasis [13]. TAMs can express a variety of receptors or ligands of inhibitory receptors, such as B7-1, PD-L1, and PD-L2, to inhibit the function of immune cells. TAMs can release a large number of cytokines, chemokines, and enzymes to inhibit the functions of $CD4^+$ and $CD8^+$ T cells. The TME will secrete cytokines such as IL-4 to enhance the immunosuppressive effect of M2 macrophages. Macrophages account for 50% of the cells in tumors, which can promote tumor growth and development [14]. The poor prognosis of the vast majority of tumors is related to the massive infiltration of macrophages, including lung cancer, breast cancer, liver cancer, gastric cancer, and other malignant tumors, further demonstrating the role of macrophages in tumor progression [15][16][17].

TAMs account for 50% of the tumor volume in some hematological malignancies and most solid tumors, but the classification of TAMs is highly dynamic and heterogeneous [18][19][20][21][22]. TAMs can be divided into pro-inflammatory M1 and anti-inflammatory M2 according to different phenotypes, metabolisms, and functions. M1 macrophages are activated by interferon-γ (IFN-γ) secreted by Th1 cells, pathogen-associated molecular pattern (PAMP) signaling pathways, and interactions with toll-like receptors (TLRs). M1 macrophages produce pro-inflammatory mediators such as IL-1β, IL-6, IL-12, tumor necrosis factor-α (TNF-α), reactive oxygen species (ROS), and nitrogen. Conversely, M2 macrophages are stimulated by IL-3, IL-4, and IL-10 secreted by Th2 cells to produce another type of cytokine that helps to relieve inflammation [23][24]. However, this classification of macrophages has several limitations: (1) Macrophages cannot expand clonally like T cells, so there are differences between each macrophage [25][26][27]; (2) This classification reflects the response to in vitro stimulation, but these stimuli do not exist independently in tumor tissues. Macrophages are derived from the differentiation of monocytes, and the background and intensity of the stimuli they receive determine the activation and transcription of macrophages, often resulting in a mixed phenotype; (3) Macrophages can change their phenotypes through interactions with other immune cells, pathogens, or cancer cells, and they are highly plastic cells.

2.3 Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) include immature granulocytes, dendritic cells, and monocytes, and they have a significant inhibitory effect on T cells. They can not only prevent T cell-mediated adaptive immune responses but also prevent the innate immune system mediated by NK cells or TAMs, with the aim of killing tumor cells [28]. MDSCs can inhibit the function of effector T cells (Teff) from multiple aspects: first, they secrete IL-10 and TGF-β to induce the formation of Treg cells [29]; Second, MDSCs can promote the differentiation of TAMs through the CD45 dimer, which is beneficial to tumor proliferation [30];Third, MDSCs can express a large amount of nitric oxide synthase 2 to produce nitric oxide, which can inhibit the function of $CD8^+$ T cells; fourth, in xenograft mouse models, MDSCs can reduce the expression of IFN-γ and decrease the expression of the NKG2D molecule to inhibit the formation and cytotoxicity of NK cells [31]; fifth, MDSCs can consume some nutrients that are crucial for T cell activity, thereby affecting the function of Teff cells. For example, the lack of arginine leads to T cell exhaustion mediated by protein biosynthesis, resulting in the inactivation of Teff cells [32]. There are factors in the TME that can change the fatty acid oxidation metabolism of MDSCs and upregulate Arg1 and NOS2 [33]. MDSCs can promote the occurrence, growth, and metastasis of tumors, so it has been proven that depleting or blocking MDSCs can effectively prevent tumor development.

2.4 Natural Killer Cells

Natural killer cells (NKs) are divided into two subsets, CD16 and CD56, namely $CD56^{hi}$ $CD16^{\pm}$ and $CD56^{lo}$ $CD16^{hi}$ [34]. $CD56^{hi}$ $CD16^{\pm}$ NK cells secrete inflammatory factors, while $CD56^{lo}$ $CD16^{hi}$ NK cells have cytotoxic and killing functions.

NK cells can effectively limit tumor metastasis and eliminate malignant cells [35]. NK cells target tumor cells and inhibit tumor growth through perforin (granzyme)-mediated cytotoxicity and death receptor-mediated apoptosis [36]. Although NK cells have a killing and destructive effect on tumor cells, the killing effect of NK cells in the tumor microenvironment is greatly reduced. This is because tumors adopt various mechanisms to evade the killing of NK cells. For example, tumor cells use platelets as a shield, and NK cells cannot recognize tumor cells; tumor cells wrap themselves with collagen to contact inhibitory NK receptors [37]. In the tumor microenvironment, the inflammatory cytokines of both NK cell subsets will decrease, and their cytotoxicity will be reduced or absent. These two subsets of cells are called tumor-infiltrating natural killer cells (TINK). The cytokines in the TME will reduce the cytotoxicity of TINK cells and also inhibit the proliferation and expansion of T cells. Enhancing the cytotoxicity of NK cells or targeting tumor-infiltrating natural killer cells may be the direction of future tumor immunotherapy efforts. Therefore, it can also be inferred that NK cells may be a method for preventing cancer or metastasis. In the 1960s, it was reported that platelets have the ability to promote tumor metastasis [38]. Platelets can quickly bind to cancer cells that enter the bloodstream. Platelets can wrap cancer cells, directly inhibiting the killing of NK cells, and can also promote the epithelial-mesenchymal transition (EMT) of cancer cells [39][40].

2.5 Dendritic Cells

Dendritic cells (DCs) are a bridge between the adaptive immune system and the innate immune system. They can initiate pathogen-specific T cell responses and are important for enhancing protective immunity. It should be noted that B cells and macrophages can also present antigens, but their activity is lower than that of DCs. To effectively stimulate an adaptive immune response, DCs must recognize, capture, and present antigens, upregulate co-stimulatory molecules, produce inflammatory cytokines, and then travel to secondary lymphoid organs to present antigens to T cells. If DCs cannot perform these functions, it will greatly hinder the immune response to tumors, pathogens, and viruses. cDCs can be further divided into cDC1 and cDC2. In tumors, dendritic cells are widely known as tumor-infiltrating dendritic cells (TIDCs). TIDCs can be immunogenic or tolerogenic, depending on the environmental signals. To support the survival of DCs, tumor cells usually reprogram their microenvironment. By secreting cytokines, they upregulate the transcription of metabolic pathways and tolerogenic phenotypes, such as the IDO, Arg1, iNOS, and STAT3 pathways [41]. These pathways can trigger changes in DC metabolism, metabolite production, energy transfer, and chromatin accessibility [42]. Usually, when DCs patrol the TME, they will encounter immunosuppressive factors such as IL-10, VEGF, TGF-β, and prostaglandin E2 (PGE2) and other cytokines. These cytokines will inhibit the maturation of DCs into immunogenic cells and promote their development into a tolerogenic phenotype, not only hindering the initiation of Th1 but also promoting the ability of Th2 and T regulatory responses [43]. Once out of the TME, these DCs will regain the ability to process antigens and initiate T cells [44]. This indicates that stimulating the inflammatory function of DCs in the TME may be an effective treatment strategy.

3. Regulation of Tumor Immune Response by Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) are the main components of the tumor stroma, which highly express fibroblast activation protein α, platelet-derived growth factor receptor β, and prolyl-4-hydroxylase. CAFs are transformed during epithelial-mesenchymal transition, endothelial - mesenchymal transition, or during the differentiation of progenitor cells and stem cells, but the activation of CAFs mainly depends on adjacent quiescent fibroblasts. CAFs are prone to stable glycolysis and can secrete a large number of cytokines and chemokines to inhibit tumor immunity, such as IL-6, vascular endothelial growth factor (VEGF), CXCL12, CXCL8, CCL2, TGF-β, tumor necrosis factor (TNF), and co-regulatory molecules B7H1/B7DC [45][46]. CAFs can assist in tumor proliferation, invasion, and metastasis and have the function of wound healing. CAFs can promote the polarization of macrophages to the M2 phenotype, secrete immunosuppressive cytokines, and lead to the reduction and exhaustion of CD8+ T cells [47]. Some studies have shown that CAFs can increase the expression of PD-1 and Fas on the surface of T cells, leading to the depletion of CD8+ T cells in an antigen-dependent manner through PD-L2 and Fas ligand (FasL) [48][49]. The IL-6 secreted by CAFs can upregulate the expression of PD-L1 and recruit MDSCs to inhibit the tumor immune response, reducing the efficacy of anti-PD-L1 immunotherapy for hepatocellular carcinoma (HCC), but blocking IL-6 can enhance the efficacy of PD-L1 [50]. In general, the cytokines and chemokines produced by CAFs can regulate tumor immune escape and promote tumor growth and metastasis [51]. Targeting CAFs for treatment can enhance the effect of the tumor immune response. The SynCon FAP DNA vaccine can induce the activation of $CD8^+$ and $CD4^+$ T cells and inhibit tumor growth and metastasis by reducing the expression of FAP^+ CAFs [52][53].

4. Regulation of Tumor Immune Response by Hypoxia

Hypoxia is a common feature of solid tumors. Hypoxia can severely affect the immune recognition of tumor cells. To avoid being recognized and eliminated by immune cells [54], tumor cells will reduce the expression of tumor antigens and MHC. The expression of these two factors will affect the migration and maturation of tumor-specific T cells and dendritic cells (DCs). "Hot tumors" are tumors infiltrated by a high density of T cells. PD-L1 on tumor cells can target PD-1 on activated T cells, turn off the immune response of T cells, and protect tumor cells [55][56]. Hypoxia in the tumor microenvironment can inhibit the immune killing function and is beneficial for protecting cancer cells from immune attacks [57][58][59]. Hypoxia-inducible factor 1α (HIF-1α) is the main regulator of the hypoxic adaptive response, and its functions include regulating angiogenesis, cell proliferation, metastasis, invasion, and glucose metabolism [60]. HIF-1α can increase the expression of PD-L1 in tumor cells, thereby inhibiting the function of T cells. Liu et al. [61] found that using hyperbaric oxygen (HBO) can disrupt the immunosuppression caused by hypoxia, help immune checkpoint blockade antibodies (α-PD-1) to stimulate a strong cytotoxic T lymphocyte killing effect and long-lasting

immune memory, thereby enhancing the anti-tumor effect or inhibiting tumor.

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