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Role of tumor-associated Macrophages in Tumor Development

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Abstract: The role of tumor-associated macrophages (TAM) in tumor development cannot be ignored. The number of Tams is related to the malignant degree of tumors and poor prognosis. Tams with obvious heterogeneity and plasticity are the main components of solid tumor microenvironment and become a promising target for cancer immunotherapy. Targeted therapy for TAM, combined with traditional treatment methods, may bring a new dawn to the treatment of tumors. This review summarizes the origin, types, roles in tumor progression and treatment strategies of Tams, aiming to provide new ideas and methods for the research and treatment of Tams.

Keywords: Tumors; Macrophages; Mechanism.

1. Introduction

Tumor-associated macrophages (Tams) are important cellular components of tumor microenvironment (TME). Macrophages differentiate into tumor cells and tumor suppressor cells, two types of cells. TAMs are considered to be closer to tumor-promoting macrophages, also known as activated macrophages, and TAMs play an important role in the link between inflammation and cancer. At present, it is generally believed that TAMs affect many aspects of tumor tissue by releasing a variety of cytokines during the occurrence and development of tumors, including stem cells, metabolism, angiogenesis, lymphangiogenesis and metastasis. [1] Therefore, the study of TAMs is a new strategy for the treatment of cancer.

2. Formation of TAM

The current consensus is that they may be derived from early embryonic precursor progenitor cells, which seed into tissues to form independent populations during their development. It may also originate from circulating monocytes derived from adult hematopoietic stem cells.

Franklin recently proposed that there are two pathways for the development of TAM in tumor tissues: (1) during carcinogenesis, tissue-resident macrophages derived from embryonic or monocytic cells may undergo phenotypic/ activation changes, which are called tissue-resident TAM; (2) During tumor growth, monocytes undergo a distinct stage of differentiation and eventually become macrophages, which are called tumor-induced Tams. It is possible that both cell populations are present in a given tumor at the same time, or that tissue-resident Tams are predominant in the early stages of tumor growth, while tumor-induced Tams are prominent in the later stages. [2] In addition, monocytes entering the tumor tissue may produce phenotypic changes to TME other than macrophages. Such cells are called tumor-induced effector monocytes. [2] According to the activation type of Tams and their different roles in TME, Tams are often divided into two types: the classic activated M1 type and the alternate activated M2 type. M1-type TAM has antibacterial and immunostimulatory properties. However, M2-type TAM can inhibit T cell response and promote tumor cell growth, invasion and metastasis. CD163 is usually used as a specific marker for M2-type TAM cells. In the last decade, results have shown that tissue-resident Tams are not homogeneous subsets, but rather a functionally and phenotypically similar group of cells, many of which are non-terminally differentiated and cannot be classified as simple polarized types. [3] It has now been shown that the tissue environment itself is a major regulator of the TAM phenotype, affecting the expression of many genes regardless of their origin. [3] In tumor tissue, M1-and M2-polarized Tams represent two extremes in a continuum of functional status. At present, the M1 and M2 polarization models can be extended to lineage models with at least nine different TAM activation processes. [4] The dynamic changes of TAM phenotype occur in the process of tumor occurrence, progression and metastasis, and TAM subsets have promoting activities on different tumors. In different regions of tumor tissue, the distribution and function of TAM are also quite different. Large-scale transcriptome analysis showed that Tams had mixed phenotypic expression of M1-like and M2-like markers. [4]

3. The Role of TAM in TME

TME is mainly composed of immune cells, such as macrophages, T lymphocytes, natural killer cells (NK cells), dendritic cells, and neutrophils. TME, as a major immunosuppressive cell, has a wide range of effects on TME by synthesizing and secreting a variety of cytokines.

3.1. TAM has Immunosuppressive Effect

In normal tissues, macrophages have the ability to break down tumor cells, display tumor-related antigens to T cells, and enhance the anti-tumor activities of T cells and NK cells. However, TAM had no such activity and could not produce an effective anti-tumor immune response. The chemokines and cytokines released by Tams have the ability to impede the anti-tumor response of T cells and NK cells present within the tumor, while also collaborating with MDSCs, tumor-associated dendritic cells, and neutrophils derived from the bone marrow to facilitate the development of an immunosuppressive tumor microenvironment (TME). [5] TAMs have the ability to hinder T cell activity through the

release of specific enzymes, including nitric oxide synthase (NOS) and arginase (AR GI). Moreover, TAMs display PD-1 and CTLA-4 receptor ligands (such as PD-1 and B7-H1), which, upon activation, suppress the cytotoxic functions of T cells and NK cells.

3.2. TAM Promotes Angiogenesis and Lymphangiogenesis

Angiogenesis involves many factors, such as hypoxia, hypertonicity, and pro-angiogenic factors, such as VEGF, TGF-β, COX-2, PDGF, EGF, Ang, and chemokines. TAM has the ability to not only release pro-angiogenic factors, but also produce an antibody against Wnt protein family 7B (Wnt7b). This antibody specifically acts on vascular endothelial cells, promoting the production of vascular endothelial growth factor and triggering an angiogenic switch. [6] TME supplies a significant amount of pro-matrix metalloproteinase (proMMP-9), which serves as a crucial factor in tumor angiogenesis and metastasis. Additionally, TAMs express VEGF-C and VEGF-D, demonstrating their involvement in tumor-associated lymphangiogenesis. M2-polarized TAMs specifically contribute to lymphangiogenesis within lymph nodes, playing a role in promoting lymphangiogenesis by producing VEGF-C. [7]

3.3. TAMs Regulate the Phenotype and Function of Cancer Stem Cells

Cancer stem cells (CSCs) are a type of cells that possess the ability to self-renew and give rise to diverse tumor cells within the tumor. The plasticity and function of CSCs can be regulated by tumor-associated macrophages (TAMs). Recent experimental evidence has confirmed the interconnections between TAMs and CSCs. Specifically, TAMs can secrete a protein called milk fat globulin (EGF-VIII), which activates specific pathways in CSCs, including STAT3, Hedgehog, and Sonic. Activation of these pathways enhances drug resistance and tumorigenic properties in CSCs. Furthermore, TAMs also produce milk fat ball epidermal growth factor-8 (MFG-E8) and interleukin-6 (IL-6), both of which play a role in co-regulating the tumorigenicity and drug resistance of CSC subsets. Additionally, in the context of brain tumors, microglia and TAMs mediate the behavior of glioma stem cells by releasing high levels of transforming growth factor-β1 (TGF-β1). this, in turn, promotes increased aggressiveness in CD133-positive glioma stem cell-like cells. [8]

4. Effect of TAM on Tumor Progression

Tams, as the main immune cells in TME, have a significant impact on the progression of tumors. Some scholars used immunohistochemistry to analyze macrophages in 150 cases of colorectal cancer, using CD68 as a TAM lineage marker, CD80 as a pro-inflammatory TAM marker, and CD163 as an anti-inflammatory TAM marker. The results showed that CD163 positive Tams were mainly distributed in the front of tumor invasion. However, CD80-positive TAM were almost exclusively located in the adjacent normal mucosa. In stage III tumors, higher CD68 and lower CD80 / CD163 ratios were associated with decreased overall survival. This study proposes that Tams can undergo diverse polarization states in response to microenvironmental stimuli, thereby exerting varied influences on the advancement of tumors. [9] I In recent times, Nie has observed a correlation between the growth of TAM density and the aggressive advancement of phyllodes tumors in the breast. TAM induces the rapid growth and invasive behavior of phyllodes tumors by stimulating the transformation of myofibroblasts via the chemokine CCL-18. Furthermore, the presence of CCL-18 serves as an independent prognostic factor for phyllodes tumors. [10].

Currently, tumor-associated macrophages (TAM) have emerged as crucial contributors to the spread of tumors. They play a significant role in enhancing tumor progression and metastasis through the release of various chemokines, inflammatory factors, and growth factors. TAMs induce a crucial step in tumor cell growth and migration known as epithelial-mesenchymal transition (EMT), which involves the transformation of both epithelium and stroma. This process is facilitated by the expression of various factors by TAMs, including TGF-beta and IL-6, which prompt EMT initiation. Additionally, TAMs are capable of secreting EGF-like ligands/factors that activate the epidermal growth factor receptor (EGFR) pathway in cancer cells, thus further promoting EMT.

5. TAMs Targeted Therapy is Used in Combination with Other Therapies

Tams-targeted therapy has demonstrated effectiveness in cancer treatment, and researchers are currently exploring the potential of combining Tams-targeted therapy with other treatment modalities such as chemotherapy, radiotherapy, and immune checkpoint inhibitors. Tams-targeted therapy can improve the prognosis of patients, so it can be used as a complementary treatment for cancer treatment. [11] Nevertheless, immune checkpoint inhibition proves to be effective only for a subset of patients, with a significant number of cases exhibiting no response or even developing resistance to the treatment. [12]

Macrophages express ligands of PD-1 and CTLA4 (PD-L1, PD-L2, B7H4, B7-1 and B7-2), which contribute to the immunosuppressive function of macrophages. TAMs targeted therapy can complement the antitumor effects of immune checkpoint blockade therapy, which, when combined with CSF-1R antagonists, PI3Kγ inhibitors, class IIa HDAC inhibitors, or anti-CD47 antibodies, has shown enhanced tumoricidal effects or the ability to restore therapeutic responses in patients resistant to conventional therapies. [11] In addition, preclinical studies targeting prostate cancer have found that the CSF-1/ CSF-1R pathway is related to the limit of the efficacy of radiotherapy. The combination of radiotherapy and CSF-1R inhibitor was more effective than radiotherapy alone in inhibiting tumor growth. [13]

6. Conclusion

Currently, there is increasing evidence highlighting the impact of tumor microenvironment (TME) on tumor development. Comprising a diverse range of immune cells, TME is primarily composed of tumor-associated macrophages (TAMs), which exhibit notable heterogeneity and phenotypic plasticity. TAMs play a significant role in the progression of various tumor types, making them an intriguing target for cancer immunotherapy. The unique characteristics and heterogeneity of TAMs in tumors provide a foundation for the development of personalized treatment strategies centered around TAMs. Targeting and repolarizing TAMs has emerged as a promising approach in the field of cancer treatment, potentially offering a new avenue for

biological tumor therapy. Therefore, combining targeted TAM therapy with conventional treatment methods holds great promise in revolutionizing tumor treatment.

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