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Research Progress on the Role of Tumor Microenvironment in Glioma

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Abstract: ***As a malignant tumor of the nervous system, the pathogenesis of glioma is still unclear. Through treatment methods such as surgery, radiotherapy, chemotherapy, immunotherapy, and electric field therapy, gliomas can achieve certain therapeutic effects, but there are still problems such as large adverse reactions and toxic side effects, which cause serious economic and psychological burdens to patients. In recent years, the tumor microenvironment (TME) has played an important role in the progression and treatment of gliomas, as it can delay the progression of gliomas and achieve therapeutic effects. In recent years, there have been many research achievements related to this, but there is a lack of systematic organization. Therefore, this study aims to systematically summarize the relevant mechanisms of TME in glioma, in order to provide new ideas for the treatment of glioma.***

Keywords: Tumor microenvironment, Glioma, Molecular mechanism, Research progress**.**

1. Introduction

Gliomas originate from glial cells and are the most common and malignant primary tumors of the nervous system. Glioblastoma (GBM) belongs to grade IV glioma, with the highest degree of malignancy, accounting for about 60-70% of all glioma patients. The median overall survival of patients is approximately 15 months [1,2]. At present, the main treatment methods for glioma are surgical resection and postoperative synchronous radiotherapy and chemotherapy [3]. However, due to the difficulty of completely removing tumor tissue through surgery and the high incidence of adverse reactions to radiotherapy or chemotherapy in some patients, as well as the existence of immune resistance reactions [4,5], the survival period and quality of life of patients cannot be guaranteed. Therefore, exploring the mechanisms underlying the occurrence and progression of glioma is currently a top priority in treatment. The tumor microenvironment (TME) is mainly composed of tumor cells, tumor associated macrophages, fibroblasts, regulatory T cells, stromal cells, immune cells, and various signaling factors. TME is closely related to the rate of tumor progression [7,8].

Through reading a large number of literature, it has been found that there are many research results on the regulation of glioma by tumor microenvironment. However, this research field lacks systematic induction and sorting. Therefore, this article summarizes and sorts out the intrinsic mechanisms of tumor microenvironment regulation of glioma, in order to provide theoretical research for the development of drugs for the prevention and treatment of glioma.

2. Overview of Tumor Microenvironment

The tumor microenvironment is an important foundation for the growth, proliferation, and metastasis of tumor cells. It is composed of tumor cells, extracellular matrix, blood vessels, immune cells, fibroblasts, as well as various cytokines, chemokines, and other components. In gliomas, the tumor microenvironment has unique characteristics and is closely related to the occurrence, development, treatment resistance, and prognosis of gliomas.

3. The Relationship between Tumor Microenvironment and Glioma

3.1 Tumor Associated Macrophages

Tumor associated macrophages (TAMs) are positively correlated with poor prognosis and low overall survival rate of tumors [9]. The phenotype of macrophages in TME is mainly composed of classically activated M1 macrophages and alternatively activated M2 macrophages. M1 TAMs secrete pro-inflammatory cytokines, which inhibit tumor growth and promote immune responses, while M2 TAMs induce anti-inflammatory and immune suppression, stimulate tumor angiogenesis and lymphangiogenesis, and promote tumor invasion and metastasis [10]. In the early stage of tumor growth, TAM mainly polarizes from M1 type to M2 type; In the later stages, the number of M2 TAMs far exceeds that of M1 TAMs [11]. In the glioma microenvironment, M2 type TAM recruitment induces tumor promotion and immune suppression. In the hypoxic glioma microenvironment, extracellular vesicles induce M2 polarization of macrophages through IL-6/pSTAT3/miR-155-3p/autophagy/pSTAT3 positive feedback loop, promoting malignant progression of glioma [12]. The M2 polarization of macrophages affects the secretion of complement component C5, inducing DNA damage repair or IL-11 secretion to activate the STAT3 MYC signaling pathway in glioma cells, thereby inducing chemotherapy drug resistance in tumor cells [13, 14].

Existing studies have shown that CSF-1R inhibitors target M2 TAMs through the VEGF-DII4/Notch-VFR2 signaling pathway to reduce VRDF-A expression, restore normal vascular patterns and function, and improve the efficacy of chemotherapy drugs, thereby inhibiting glioma growth [15]. In addition, CSF-1R inhibitors can also block alternative activation pathways of microglia and macrophages to enhance radiotherapy efficacy [16].

TAMs play a crucial role in the occurrence, development, and metastasis of tumors. They interfere with the expression of P2X4 receptors in TAMs, reduce the levels of IL-1 β, IL-18,

and protein expression, and can affect the invasion and metastasis of gliomas [17]. KIM et al. [18] found that CD169 macrophages in gliomas have a promoting effect on inflammatory response, mediating the accumulation of T cells and NK cells and anti-tumor response, which will provide new targets for glioma immunotherapy.

3.2 Tumor Associated Fibroblasts

Tumor associated fibroblasts (CAFs) are a core component of tumor microenvironment (TME) and are closely associated with poor prognosis in glioma patients [19]. CAFs can promote tumor cell growth, inhibit tumor cell immune response, promote tumor angiogenesis, and enhance tumor invasion and metastasis ability during tumor progression [20]. Research has shown that CAFs directly promote tumor cell proliferation by secreting growth factors, and can also promote tumor cell invasion by inducing angiogenesis and reshaping the extracellular matrix. CAFs also accelerate tumor progression by promoting tumor cell immune escape and developing resistance to therapeutic drugs [21]. In addition, CAFs can promote polarization of TAMs towards M2 TAMs and induce immune suppression [22].

Targeting CAFs not only effectively inhibits tumor proliferation and invasion, but also induces the construction of a tumor suppressive microenvironment. The LI M team [23] found that oncolytic adenovirus targets the GBM stromal cell population marked by the co expression of fibroblast activation protein alpha and platelet-derived growth factor receptor beta, affecting immune cells and the tumor vasculature to kill tumor cells, while regulating the tumor microenvironment. This provides a new direction for GBM therapy.

ZHAO J et al. [24] used qRT PCR and Western blot to detect the gene and protein levels of DLEU1 and mRNAs. They found that activation of HSF1 protein by CAFs can increase the level of DLEU1 gene in GBM. The binding of DLEU1 gene to ZFP36 gene induces SLC7A11 protein expression, which significantly inhibits iron death in tumor cells. Therefore, iron death inducers can effectively reduce the vitality and invasion ability of GBM cells. Inducing iron death in glioma cells will bring hope for the treatment of GBM patients.

3.3 Tumor Infiltrating Lymphocytes

Tumor infiltrating lymphocytes (TILs) are one of the main types of immune cells in the tumor microenvironment, mainly composed of T cells, B cells, and natural killer cells (NK cells). They have the function of recognizing, killing tumor cells, and participating in anti-tumor immune responses [25]. Research has found that using methods such as Ficoll density gradient centrifugation to separate TIL from excised tumor tissue promotes the recruitment or consumption of CD8+T cells and Tregs cells to enhance the anti-tumor effect of TIL [26]; TILs, after being isolated, cultured, and amplified in vitro, are implanted into patients' bodies and have a specific killing effect on tumors, with relatively few adverse reactions [27].

Mathewson N D et al. [28] found that the application of dexamethasone is significantly associated with a decrease in the number of infiltrating T cells in GBM patients. PDCD1 or KLRB1 mRNA enhances the anti-tumor function of different T cell populations, especially CD8+T cells, by blocking the CLEC2D-CD161 pathway. Combined with PD-1 blockade therapy, it increases the immune therapeutic effect of diffuse glioma. Clinical studies have shown that CD161 is enriched in high-grade gliomas and IDH wild-type gliomas, and the high expression of CD161 is closely related to the pathology and molecular pathology of gliomas. Meanwhile, CD161 promotes the progression of glioma by inhibiting T cell function [29]. Therefore, CD161 is a potential new target for immunotherapy strategies in glioma treatment.

NK cells, as a key mediator in tumor immunotherapy, inhibit tumor cell proliferation and promote tumor cell apoptosis by releasing cytokines such as interferon-γ and tumor necrosis factor-α [30]. NK cells can also kill tumor cells through Fc γ RIIIA/CD16a mediated antibody dependent cytotoxicity (ADCC) [31]. Research has found that NK cells infiltrate extensively in GBM, and NK cells play an important role in the lysis of GBM and medulloblastoma [32]. BERGER et al. [33] found through experimental research that NK cells promote the activation of the STING pathway in GBM, which is highly expressed in tumor blood vessels and produces different levels of inflammatory cytokines, thereby regulating immune response. Therefore, STING agonists can become another potential target for tumor immunotherapy. CAR-NK cell therapy, as an emerging cancer treatment method, has been proven to have related targets such as EGFR, EGFRvIII, HER2, CD133, IL-13R α2, etc. It has entered the clinical development stage in GBM treatment and brings great hope for prolonging the survival of GBM patients [31]. In addition, the combination of TGF-β inhibitors and NK cells can enhance the anti-tumor activity of NK cells and improve the therapeutic effect of GBM. Shaim et al. [34] treated GSC transplanted mice with allogeneic NK cells combined with α v integrin/TGF-β inhibitor/TGFBR2, and found that GSC induced NK cell dysfunction was eliminated and tumor growth was inhibited. Overall, NK cells may play a role in GBM treatment by directly killing tumor cells, identifying and killing tumor cells, and promoting immune response. Further research on the accurate role and potential efficacy of NK cells in GBM treatment will help improve the prognosis of GBM patients.

3.4 Other Cells in the Tumor Microenvironment

Tumor associated dendritic cells (TADCs) are key antigen-presenting cells in the tumor immune system. TADCs engulf and process antigens, delivering them to immune cells such as T cells and B cells to activate immune responses against tumors [35]. The stimulation of T cell immune response by TADCs is key to enhancing tumor immunotherapy. Phospholipid (cPLs) adjuvants induce high expression of MHC II in TADCs, promote their maturation and initiate their presentation ability, and enhance anti-tumor immune response [36]. This indicates that cPLs adjuvants have strong immunostimulatory activity in vivo and can serve as a new target for immunotherapy. Clinical trials have shown that the combination of tumor cell lysate DC vaccine (DCVax-L) with standard radiotherapy and chemotherapy can induce effective immune responses in GBM patients, and has

good tolerability, which can prolong the survival of GBM patients [37,38].

Studies have shown that extracellular vesicles (EVs) play an extremely important role in the occurrence and progression of gliomas, including promoting glioma cell proliferation and invasion, promoting tumor angiogenesis, and developing drug resistance [39,40]. Through in situ tumor formation experiments in mice, the effects of glioma stem cell (GSC) and differentiated glioma cell (DGC) derived EVs on the proliferation and temozolomide resistance of U87 glioma cells were analyzed. It was found that compared with DGC derived EVs, GSC derived EVs significantly enhanced the proliferation, invasion, and temozolomide resistance of U87 cells [41]. This indicates that EV can significantly promote tumor growth and reduce the survival of glioma patients, providing a new exploration for studying the mechanisms of poor prognosis and resistance to temozolomide in glioma patients, and helping to reveal the molecular mechanisms of malignant progression of glioma. In addition, NIU W et al. [42] designed a biomimetic drug delivery system using EV functional characteristics combined with heparin nanoparticles (DN) loaded with doxorubicin. The biomimetic EV DNs can bypass the blood-brain barrier and penetrate into glioma tissue through receptor-mediated phagocytosis and membrane fusion, greatly promoting cell internalization and anti proliferative ability, prolonging drug circulation time, and providing a novel approach for future clinical treatment of glioma.

Immune escape and suppression of tumor cells are key factors in the malignant progression of tumors, and myeloid derived suppressor cells (MDSCs) play an important role in tumor mediated immune escape [43]. Research has found that cyclooxygenase-2 (COX-2), interleukin-6 (IL-6), prostaglandins, vascular endothelial growth factor (VEGF), and other factors promote the proliferation of MDSCs by activating the JAK2/STAT3 signaling pathway. MDSCs infiltrate extensively in the glioma microenvironment, activating immune suppressive cells and inhibiting effector immune cell responses such as T cells and NK cells to evade immune system surveillance [44,45]. Inhibition of MDSCs activity may bring new hope for clinical treatment of glioma, but the specific mechanism still needs further exploration.

3.5 Tumor Microenvironment Related Signaling Factors

Transforming growth factor beta (TGF-β) is abundant in the GBM microenvironment, and the widespread invasion and drug resistance of glioma cells are closely related to the abnormal expression of TGF-β [46]. Research has found that the expression rate of TGF-β in GBM exceeds 80%. TGF-β interacts with immune cells in tumor tissue in the hypoxic tumor microenvironment, forming an immunosuppressive tumor microenvironment that promotes tumor cell growth [47]. Yan et al. [48] found that TGF-β can promote the expression of CLDN4 and induce mesenchymal transition; Overexpression of CLDN4 significantly increases the expression of mesenchymal related genes in GBM cells, thereby enhancing their proliferation, migration, and invasion abilities. TGF-β can also activate the Smad signaling pathway through TSP1 to promote microtubule formation in GBM, leading to widespread invasion of GBM cells and resistance to chemotherapy [49]. Developing drugs targeting TGF-β protein for GBM can improve the tumor immune microenvironment and inhibit glioma cell proliferation [50].

VEGF is an important factor that promotes angiogenesis, stimulates the formation of new blood vessels, and provides sufficient blood supply for tumor growth and metastasis [51]. The characteristic of GBM is abnormal vascular proliferation, and VEGF is highly expressed in GBM, promoting abnormal proliferation of tumor blood vessels [52]. The VEGFR1 and VEGFR2 signaling pathways are considered key factors for the survival of GBM tumors [53]. Chen et al. [54] analyzed the effects of high expression and deficiency of ARL13B on the cerebral vascular system in intracranial glioma transplanted mice and found that ARL13B promotes angiogenesis and tumor growth by activating VEGFA-VVEGFR2 signaling. Therefore, targeting ARL13B may be a potential method for glioma immunotherapy. Research has found that the combination of amiodarone and VEGF inhibitors not only reshapes the GBM vascular system, but also promotes the infiltration and activation of CD8+and CD4+T cells, enhancing the autophagy ability of GBM cells [55]. Currently, anti angiogenic drugs have been studied as a potentially promising anti GBM therapy. Among anti VEGF drugs, Bevacizumab, as one of the first drugs approved by the FDA for the treatment of recurrent GBM, has good tolerance to patients with recurrent GBM and is significantly correlated with anti GBM activity, which can significantly prolong the survival of patients with recurrent GBM [56].

Interleukin-10 (IL-10) is an important immunosuppressive molecule, and its high expression in GBM is associated with the activity levels of various tumor associated immune cells, which is a key factor in the malignant progression of GBM [57]. Experimental results have shown that interleukin-8 (IL-8) can promote angiogenesis and enhance anti-tumor immune response. Meanwhile, IL-8 can recruit MDSCs, thereby promoting immune suppression of glioma TME. Therefore, utilizing the IL-8-CXCR1/CXCR2 signaling pathway can effectively inhibit the anti-tumor effect mediated by immune checkpoint blockade [58]. In addition, Zha C et al. [59] found that neutrophil extracellular traps (NETs) stimulate the NF-κ B signaling pathway, thereby promoting the secretion of IL-8 in glioblastoma. NETs promote the proliferation, migration, and invasion of glioma cells by regulating the HMGB1/RAGE/IL-8 axis. However, as a novel anti-cancer drug, interleukin-21 (IL-21) was used by Sun Y et al. [60] to treat a mouse GL261 glioma model using a new generation of oncolytic cowpox virus expressing IL-21. It was found that IL-21 can regulate the tumor microenvironment, enhance the body's immune response to tumors, and thus achieve the goal of inhibiting tumor growth and prolonging patient survival.

Tumor necrosis factor (TNF) is a signaling factor produced by macrophages, neutrophils, and other cells, which has a bidirectional regulatory effect in the glioma microenvironment. It has both anti-tumor and pro tumor growth effects [61]. In the treatment of glioblastoma, TNF has the ability to directly kill tumor cells, promote immune response, and increase chemotherapy sensitivity [62]. Tumor necrosis factor-α (TNF-α) has been shown to promote the formation and progression of the tumor inflammatory microenvironment. In recent years, it has been found that

TNF-α can also promote the high expression of TNFR1 and ANXA1 in glioma cells, thereby promoting glioma cell proliferation through the TNF-α/TNFR1/ANXA1 axis [63]. In addition, the C3a receptor expressed on astrocytes triggers astrocyte activation by activating the p38 MAPK pathway after interacting with PDGFR α, while promoting tumor cell production of TNF-α, thereby promoting proliferation of neuroblastoma cells [64]. Research has shown that high levels of TNIP1 in glioma tissue are significantly associated with low survival rates. TNIP1 reduces the phosphorylation and degradation of I κ B-α in glioma cells by mediating the TNF-α/NF-κ B signaling pathway, thereby promoting tumor cell proliferation [65]. In addition, CD70 is a typical representative of the TNF superfamily and is closely related to the prognosis of glioma [66]. Seyfrid et al. [67] found that high expression of CD70 in recurrent GBM can increase the invasiveness of GBM cells, knocking down CD70 reduces the tumorigenicity of GBM cells in vitro and in vivo, and animal experiments have shown that CD70 immunotherapy can significantly improve the survival rate of animal models. LIU C et al. [68] also found through their research that MAGED4B is widely distributed in the glioma microenvironment compared to other types of tumors, and is positively correlated with glioma grading, tumor diameter, Ki-67 levels, and patient age. High expression of MAGED4B promotes tumor cell proliferation, invasion, and migration, and reduces chemical sensitivity to cisplatin and temozolomide. It inhibits TRIM27 protein expression and suppresses TNF-α cell-mediated apoptosis through the TRIM27/USP7/RIP1 signaling pathway, thereby promoting glioma cell growth. Therefore, targeted therapy targeting TNF family related factors is highly likely to improve the prognosis of glioma patients.

4. Targeted Treatment Strategies for Glioma Targeting the Tumor Microenvironment

Multiple anti angiogenic drugs such as bevacizumab have been developed to address the mechanism by which glioma cells secrete VEGF to promote angiogenesis. These drugs can inhibit tumor angiogenesis, cut off the nutritional supply to the tumor, and thus suppress tumor growth. However, anti angiogenic therapy also has some limitations, such as the possibility of increased invasiveness of tumor cells after normalization of tumor blood vessels, and long-term use may induce drug resistance in tumor cells. Immunotherapy includes immune checkpoint inhibitor therapy, aimed at blocking immunosuppressive interactions between tumor cells and immune cells. For example, by inhibiting the interaction between programmed death receptor 1 (PD-1) and its ligand (PD-L1), T cells can enhance their immune killing activity against glioma cells. In addition, there are immunotherapy strategies such as tumor vaccines based on dendritic cells (DCs) that activate the body's own immune system to recognize and kill glioma cells. However, the efficacy of immunotherapy in gliomas still needs to be further improved, partly due to the strong immunosuppressive nature of the tumor microenvironment. Develop drugs targeting CAFs or inhibitors of specific signaling pathways in the tumor microenvironment, such as the PI3K/Akt pathway [69]. By interfering with these key factors in the tumor microenvironment, it is possible to alter the pro tumor properties of the tumor microenvironment and improve the therapeutic efficacy of glioma.

5. Conclusion and Prospect

In the field of glioma research, the tumor microenvironment has been proven to be a key factor affecting tumor occurrence, development, invasion, and treatment resistance. Previous studies have given us a preliminary understanding of the complex interactions between gliomas and the tumor microenvironment. Immune cells, endothelial cells, fibroblasts, and extracellular matrix components in the microenvironment all cooperate or antagonize with glioma cells, shaping the unique biological characteristics of tumors. However, there are still many issues that urgently need to be addressed. For example, how to precisely regulate the immune suppression network in the tumor microenvironment to enhance the effectiveness of immunotherapy, how to develop more effective combination therapies targeting tumor angiogenesis and microenvironment remodeling, and how to deeply analyze the core role of the tumor microenvironment in glioma recurrence and drug resistance mechanisms. In the future, with the continuous integration and innovation of multidisciplinary technologies, high-throughput sequencing, single-cell analysis, organoid models, and new imaging technologies will provide us with more refined research tools, which are expected to further reveal the mysteries of the relationship between glioma and the tumor microenvironment, laying a solid foundation for the development of revolutionary personalized treatment strategies, ultimately improving the prognosis of glioma patients, increasing their survival rate and quality of life, and bringing new hope to overcome this malignant tumor.

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