Review Article

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Tumor microenvironment in treatment of glioma

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Abstract: Glioma is one of the most malignant and fatal tumors in adults. Researchers and physicians endeavor to improve clinical efficacy towards it but made little achievement. In recent years, people have made advances in understanding characteristics and functions of tumor microenvironment and its role in different processes of tumor. In this paper, we describe the effects of tumor microenvironment on glioma proliferation, invasion and treatments. By explaining underlying mechanisms and enumerating new therapy strategies employing tumor microenvironment, we aim to provide novel ideas to improve clinical outcomes of glioma.

Keywords: Glioma; Tumor microenvironment; Treatment

1 Introduction

The occurrence, progress and invasion of tumor are closely related with the microenvironment surrounding the tumor, which is a network including various cell types, stroma, blood vessels, secreted factors, surrounding matrix and also inner environment of tumor cells. Tumor cells can change and maintain their ambience through autocrine and paracrine to promote their own proliferation and development. There exist mutual dependency, promotion, antagonism and fight between tumor and the environment. With recent achievements in oncocytology and molecular biology, we have got a deeper understanding on relationship of tumor and its microenvironment, which means a lot in study, diagnosis, treatment and prognosis of tumors. In immunotherapies for tumors, positive responds are usually depending on the interaction of tumor cells and immunoregulation in tumor microenvironment. Tumor microenvironment plays a crucial role in suppression or enhancement of immune response. A good understanding of tumor microenvironment and its mutual effects with tumor is important to more than reveal the mechanisms but also provide new strategies to improve efficacy of immunotherapies.

Glioma is one of the most common and aggressive primary tumors in adults. Despite improved insight into the underlying molecular mechanisms, it is still hard to be treated and the prognosis of patients remains poor due to fast progress and scarcity of effective treatment strategies. The highly heterogeneous tumor microenvironment plays a substantial role in tumor malignancy and treatment responses. It is also related with resistance of glioma cells to chemotherapy [1]. In this review, we summarized influences of tumor microenvironment on glioma cells behaviors, clinical efficacy and prognosis of glioma, revealed possible underlying mechanisms and shared some therapy strategies that utilizing characteristics of microenvironment to improve clinical outcomes [2-5].

2 Tumor microenvironment and glioma and related mechanisms

As the most abundant glial cells in glioma microenvironment, astrocytes significantly contribute to glioma pathogenesis. Activated astrocytes surround and infiltrate glioma cells and protect them from cytotoxic effects caused by various chemotherapeutic agents. As one of the major stromal cells in the brain, astrocytes are closely related to the malignant phenotype of gliomas, and they play important roles in chemo-resistance of gliomas. Recent studies showed that through direct contact with glioma cells and infiltrating around the tumor, astrocytes demonstrated

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protective effects for glioma against chemotherapeutic drugs, which might reveal the mechanism underlying the unsatisfactory clinical outcomes of chemotherapy [6, 7]. The gap junctional communication (GJC) between glioma cells and astrocytes has presented protective effect via expression levels regulation of various critical survival genes by astrocytes. That result indicated that the microenvironment may affect the behavior of tumor cells and might be related with resistance in glioma cells [8]. Astrocytes could increase the secretion of IL-6 and induce the expression of membrane type 1 matrix metalloproteinase (MMP14), and thus enhance the migration and invasion of gliomas, which is a proof of influence of microenvironment on tumor processes [9]. A syngeneic model of glioma resection and recurrence in mice was developed and influences of surgical resection on glioma biology and the local microenvironment were examined. Results demonstrated that resection-induced injury led to alterations in reactive astrocytes in the peritumoral microenvironment and astrocyte injury induced changes in transcriptome and secretome as well as promotion of tumor proliferation and migration. That indicates a necessity of further knowledge of the postsurgical tumor microenvironment for targeted anticancer agents development [10].

Myeloid-derived suppressor cells (MDSCs) constitute >40% of the infiltrating immune cells and can accumulate to induce immunosuppression in glioma. MDSCs can also secret many kinds of cytokines that are involved in antigen-specific T cell suppression. Researchers demonstrated that depletion or blockade of MDSCs augment the efficacy of immunotherapy, which presented promise for increasing the efficacy of immunotherapies for glioma [11]. Within the glioma microenvironment, macrophages and microglia could produce CCL2, which is critical for recruiting MDSCs and regulatory T cells (Treg). In clinical specimens of glioma, enhanced expression of CCL2 is related with reduced overall survival. This is another proof of how tumor microenvironment induces immunosuppression and drive glioma progression [12].

Heparanase (HPSE), which cleaves Heparan sulfate proteoglycans (HSPG), breaks down modified sugar chains on cell surfaces as well as in the extracellular space. Its level is positively correlated with tumor development in the brain. Tumor microenvironment, reactive astrocytes, microglia/monocytes and tumor angiogenesis are also influenced by HPSE. HPSE is highly expressed in glioma and inhibition of HPSE reduces glioma cell numbers. Furthermore, high levels of HPSE appeared to be related with shorter survival in patients with high-grade glioma. These data provide proof for anti-HPSE treatment of glioma [13].

B7-H4 (B7x/B7S1) is a B7 family member whose expression in tumors was associated with prognosis malignant grades of glioma. Silencing of B7-H4 expression in glioma and microenvironment supporting cells lead to increased microenvironment T-cell function and tumor inhibition, which made it an important immunosuppressive event holding back effective T-cell immune responses and a potential therapy target [14].

Tumor microenvironment can also drive resistance to inhibition of colony-stimulating factor-1 receptor (CSF-1R), which targets macrophages accumulate in glioma progression. Mechanisms of this effect conclude IGF-1 induced phosphatidylinositol 3-kinase (PI3K) pathway activity [15].

EGFR amplification and mutation, especially EGFRvIII are the mostly found signatures in glioma. Researchers demonstrated that hypoxia tumor microenvironment and ECM vitronectin could enhance tumor cell invasion and EGFRvIII activity through EGFRvIII and integrin β3 complex, emphasizing key roles of tumor microenvironment in tumor progression and metastasis [16].

Extracellular matrix tenascin-C (TNC) consist the brain tumor microenvironment. Studies show that decreased TNC leads to tumor invasion reduction and tumor proliferation increase, which means that tumor microenvironment, modulates stromal cells behaviors and influences tumor behavior as well [17].

Ca^{2+}-activated K^+ channel (KCa3.1) is expressed in both glioma and infiltrating microglia/macrophages (M/MΦ) and is involved in glioma progress promotion under mechanisms including FAK and PI3K/AKT. Inhibition of KCa3.1 would lead to a switch of M/MΦ cells toward a pro-inflammatory, antitumor phenotype and contribute to glioma development reduction, suggesting a possible role for KCa3.1 as a therapeutic target in glioma [18].

As an important gap junction protein in astrocytes, connexin43 (Cx43) is over-expressed in glioma-associated astrocytes at the peri-tumoral region. Cx43 increases malignancy in tumor cells through mediating intercellular communication. And expression of Cx43 is related with glioma cells dissemination from the tumor core by manipulating the microenvironment [19].

A study has proved that tumor microenvironment can facilitate malignant transformation of bone marrow stromal cells (BMSCs) into glioma cancer stem cells (CSCs) [20].

Exosomes are one type of extracellular vesicles (EVs), which mediate intercellular communication for normal and tumor cells as well. Exosomes secreted by tumor cells take parts in different tumor processes and modify tumor microenvironment for progression. The roles exosomes play in cross-talk within tumor microenvironment and

intercellular communication make them tumor biomarkers and a potential therapeutic target/delivery system [21].

3 New therapy strategies

3.1 Drug delivery system

Advances have been achieved in active targeting drug delivery system (DDS) in glioma diagnosis and therapy. Lack of sufficient targets on glioma cells and limited penetration capability of DDS significantly compromise the treatment efficacy. So it is important to explore effective receptor targets. Researchers constructed dual-decorated nanoparticulate DDS loaded with paclitaxel (PTX). By taking advantages of the tumor microenvironment dual-targeting and angiogenic blood vessels effect, this DDS extensively accumulated at glioma site and resulted in improved anti-glioma efficacy with enhanced penetration capability in vivo, which made it a promising drug delivery method in glioma treatment [22].

In another research, nanoparticles (NPs) were related with a substrate of large amino acid transporter 1 (LAT1) that is overexpressed in both blood-brain-barrier and glioma cells. And as levels of adenosine-5'-triphosphate (ATP) and glutathione (GSH) are remarkably diverse between extracellular and intracellular milieu, the doxorubicin (DOX)-conjungated NPs were designed to be targeting both ATP&GSH. Results showed that both enhanced NP accumulation and rapid DOX release in glioma were demonstrated, with more efficient therapeutic effects and no systemic toxicity observed. This study proved the feasibility of GSH & ATP dual-responsive utilizing microenvironment strategy to improve efficacy of chemotherapy for glioma [23].

Based on the cognition that the pH environment in gliomas is acidic, people constructed pH-sensitive liposomes with DOX encapsulated in them. Responding to the acidic pH in glioma, a specific targeting drug release was observed. Anti-tumor activity of the liposomes was also demonstrated in the in vivo experiment, which made those particles one of the drug delivery systems that are suitable for targeting anti-tumor therapy [24].

In a study, a delivery system based on gold nanoparticle was developed. The nanoparticles loading DOX were coated with PEG. Results showed that the release of DOX was pH-dependent and cellular uptake as well as glioma distribution were both at a higher intensity. Longer median survival time was also acquired in glioma-bearing mice, making these nanoparticles a feasible drug delivery system [25].

PEG-PLA nanoparticles were designed to target fibronectins (FNs), which is a prevailing component in the abundant extracellular matrix (ECM). ECM is abundant in the glioma microenvironment and play a critical role in different tumor progresses. This FN-targeting drug delivery system loaded with paclitaxel demonstrated favored penetration into glioma spheroids and significant proliferation inhibitive effects as well as prolonged survival time, proving that ECM could be a potential target for drug delivery in clinical applications [26].

3.2 Viroimmunotherapy

Vesicular stomatitis virus (VSV) expressing a complementary cDNA library is applicated in tumors treatments by vaccinating against tumor associated antigens (TAAs). This systemic viroimmunotherapy consisting of histological type-specific antigens and location-specific antigens against gliomas achieved satisfying immune responses, which could be enhanced by immune checkpoint inhibitors. That indicates that VSV-TAA therapy, combined with checkpoint inhibition, has got clinical values, as well as the importance of the tumor microenvironment in immunotherapy [27].

In an intratumoral virotherapy research, an oncolytic adenovirus was administrated intratumorally. Decreased tumor-infiltrating Tregs and increased IFNγ-producing CD8+ T cells was observed, even in highly immunosuppressive tumor microenvironment in late stage diseases. Additionally, this treatment could enhance systemically transferred tumor-antigen-specific T cell therapy and reprogram immunosuppressive Tregs to a stimulatory state [28].

In one study, adoptive immunotherapy with transferred antigen-specific T cells is adopted. Researchers combined systemic injection of bacterial lipoprotein (BLP), a TLR1/2 agonist, with that therapy. BLP could maintain T cell persistence, modify the tumor microenvironment and even induce systemic anti-tumor immunity and thus improve the adoptive T cell therapy, which might offer a strategy to overcome the obstacles for immunotherapy for glioma [29].

3.3 Antiangiogenic therapy

Antiangiogenic therapy added to immunotherapeutic approaches towards glioma has achieved clinical bene-

fits, among which the endogenous microenvironment or vaccine-induced inflammatory responses is importantly subsidiary to its effectiveness. An inhibitor of vascular endothelial growth factor, aflibercept, was applied in combination with an antitumor vaccine. Delayed tumor progression and survival extension were observed, which confirmed the efficacy of combining antiangiogenic and immunotherapy approaches as well as the value of delineating tumor microenvironment [30].

Sunitinib, a small molecule with known anti-angiogenic effect, was found to induce glioma cell death by targeting VEGFR2 while protecting neurons and astrocytes. Sunitinib could normalize the tumor-derived aberrant vasculature and reduce tumor vessel pathologies multitargeted receptor tyrosine kinase inhibitor, on constituents of the tumor microenvironment such as gliomas, astrocytes, endothelial cells, and neurons. Sunitinib has a. We found that sunitinib normalizes the aberrant tumor-derived vasculature, reduces tumor vessel pathologies, and alleviate tumor-induced neurodegeneration. Furthermore, when combined with temozolomide, sunitinib could amplify the effects of temozolomide on glioma cells, of which the researchers thought to be related with influences of sunitinib on the brain tumor microenvironment [31].

Anti-angiogenic molecules combined with autophagy inhibitor have been proved effective in treating gliomas in vivo. Hypoxia could augment this potency possibly through stimulation of autophagosome, which is prevalent in the glioma microenvironment and late stage autophagy inhibitor may act by drive cytotoxic autophagic vacuole accumulation that is cytotoxic towards glioma cells [32].

4 Conclusion

Tumor microenvironment is a double-edged sword in occurrence, treatment and prognosis of glioma. Tumor cells can adjust its neighborhood to facilitate its own progress and microenvironment can contribute to proliferation, invasion and drug-resistance of glioma. But on the other side, targeting tumor environment may improve infiltration and efficacy of chemical agents and assist immunotherapy to take effect. All above indicate importance to further explore mechanisms related with tumor environment and make these understanding helpful to clinical treatments.

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