

Research Progress of Brain Glioma Tumor Microenvironment

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Abstract: Glioma ranks among the most ubiquitous brain tumors, and the central nervous system displays unique attributes compared to other bodily organs. A physiological blood-brain barrier exists, as well as a specialized tissue environment, inextricably linked with the onset and progression of glioma. To amplify glioma treatment prospects, it is imperative to comprehend the interplay between glioma and its environmental context. This manuscript expounds upon how the glioma environment can facilitate tumor growth, providing putative clinical targets for impeding glioma development and novel avenues for treatment.

Keywords: Glioma; Microenvironment; Immune Cells.

1. Introduction

Glioma is a malignant neoplasm emanating from glial cells, with an annual incidence of approximately (3-6.4) per 100,000, comprising about 23.3% of central nervous system tumors. It constitutes roughly 78.3% of malignant tumors, with the peak annual incidence being glioblastoma (GBM) [1]. According to the Chinese Glioma Genome Atlas (CGGA), the median overall survival duration for low-grade (WHO Grade II) gliomas was 78.1 months, for medium-grade gliomas was 37.6 months, and for malignant gliomas was a mere 14.4 months. The 6-month, 1-year, 3-year, and 5-year overall survival rates are enumerated as follows: for low-grade gliomas, 99%, 94%, 79%, and 67%, respectively; for anaplastic gliomas, 88%, 75%, 51%, and 36%, respectively; for glioblastoma, 87%, 61%, 15%, and 9%, respectively[2]. Notwithstanding significant advancements in glioma research, treatment efficacy remains deficient, rendering glioma a pathology with a dismal prognosis.

The tumor microenvironment (TME) encompasses an assemblage of cellular constituents and an extracellular matrix modulated by tumor cells to sustain their viability. This incorporates not only the tumor tissue itself but also the adjacent structures, encompassing a plethora of immune cells, vascular endothelial cells within the tumor stroma, fibroblasts, the extracellular matrix, a multitude of cytokines, and cellular interactions. Previous research has underscored the crucial role of TME in tumor initiation, advancement, and distal metastasis. Specifically, the immune response orchestrated by selective TME-associated cells and the propensity for distal metastasis catalyzed by TME constituents indubitably contribute to tumor initiation and advancement. Therefore, this manuscript endeavors to provide a theoretical framework for glioma immunotherapy and targeted therapy by illuminating the composition of the glioma immune microenvironment.

2. Brain Glioma Tumor Microenvironment

2.1. Blood-brain Barrier (BBB)

The Blood-Brain Barrier (BBB) serves as a physiological

fortification within cerebral tissue, primarily constituted of capillary endothelial cells and the intercellular tight junctions between them, astrocyte foot processes, perivascular cells, and the basement membrane. In the physiological state, BBB safeguards central nervous system equilibrium by modulating permeability [3].

On one hand, BBB exerts potent protective effects upon cerebral tissue; on the other hand, it restricts the intrusion of preliminary treatment pharmaceuticals, impacting therapeutic responses. Neoplastic cells can manipulate substance secretion through a multitude of cytokines, engendering significant alterations in the microenvironment. For instance, tumor cells can secrete vascular endothelial growth factor, destabilizing tight junctions between endothelial cells, culminating in increased capillary permeability and, ultimately, noteworthy BBB degradation, disrupting central nervous system homeostasis, and yielding a poor prognosis[4]. Even if BBB is compromised to some extent and drug permeability potentially augments with neoplastic progression, by this juncture, the tumor has evolved to intermediate or advanced stages with increased invasiveness, still depriving patients of benefits[5].

In recent years, copious research has concentrated on enhancing BBB permeability through diverse methods, such as biological viruses, focused cerebral ultrasound, receptor-mediated targeted interventions, and traditional Chinese medicine "borneol." However, additional empirical investigation is imperative to optimize clinical efficacy.

2.2. Tumor-associated Macrophages (TAMs)

Tumor-Associated Macrophages (TAMs) constitute more than 30% of the infiltrative cells in GBM and are one of the principal contributors to immunosuppression. TAMs in gliomas comprise peripheral macrophages and resident microglia, which are recruited and differentiated by a plethora of cytokines in the TME, originating respectively from bone marrow hematopoietic stem cells and embryonic yolk sac progenitors[6]. TAMs can be expansively classified into two dissimilar phenotypes: M1 macrophages, distinguished by classical activation pathways, and M2 macrophages, characterized by alternative activation pathways. M1 macrophages, efficacious in responding to bacterial and viral

infections, generate numerous pro-inflammatory cytokines and also possess tumor-lytic capabilities. In contrast, M2 macrophages exhibit anti-inflammatory functions but lack the anti-tumoral effects observed in M1 cells; instead, they facilitate tumor initiation, progression, invigoration, and metastasis. Nevertheless, when stimulated by particular cytokines (such as IL-6, IL-10, and fibroblast growth factor), M1 macrophages can undergo transmutation into the M2 phenotype[7, 8].

Antecedent studies inclined towards characterizing TAMs in GBM as having an M2-like phenotype. Conversely, recent studies have ascertained that TAMs exhibit both M1 and M2 phenotypes in the GBM microenvironment[9]. Moreover, the number of infiltrative cells correlates with the proliferation index, pathological stratification, and unfavorable prognosis of glioma[10]. Macrophages infiltrate the TME through chemotactic agents like CSF-1, CCL2, and osteopontin (OPN), subsequently transitioning from M1 to M2 under the auspices of cytokines secreted by GBM cells, thus propelling tumor progression[11]. Furthermore, TAMs not only inhibit T cell-mediated tumor cytotoxicity but also directly fortify tumor growth and infiltration by excreting cytokines and growth factors[12]. Consequently, exploring the interactions between TAMs and tumors within the GBM microenvironment holds immense significance.

2.3. Dendritic Cells (DC)

Dendritic cells (DCs), originating from myeloid lineage, constitute the most efficacious antigen-presenting cells known. They surveil the surrounding environment and transmit captured information to T and B lymphocytes. Current studies have unveiled the intricate and incompletely elucidated interactions among various cells within the glioma TME. Within the TME, DCs can monitor and sequester tumor antigens from neoplastic cells and then present these antigens to T lymphocytes, inducing the generation of tumor antigen-specific cytotoxic T cells (CTLs), consequently abrogating neoplastic cells and fulfilling their anti-tumor role [13]. However, tumor cells themselves synthesize copious amounts of cytokines that are capable of attenuating DC activation and transmutating DCs into an inhibitory or regulatory phenotype, thereby suppressing killer T cell activation and obviating the anti-tumor immune response[14]. Research on DC-based therapies is flourishing, with preclinical studies demonstrating the successful induction of anti-tumor immune responses and prolonged overall survival in patients through DC vaccines[15]. In summary, while comprehension of DC function continually evolves, their roles and mechanisms within the glioma TME warrant further exploration, with additional clinical trials imperative to optimize DC vaccine immunotherapy.

2.4. Neutrophilic Granulocyte

Neutrophils, the most plentiful type of white blood cells, primarily fulfill roles in inflammation and defense against pathogens. Formerly considered to be mainly antimicrobial, emerging scholarship underscores their broader contributions to immune responses. Neutrophils, also known as tumor-associated neutrophils (TANs), are implicated in GBM progression. Infiltration and activation of neutrophils are correlated with poor prognosis in glioma. Elevated levels of neutrophils, increased expression of arg-1 impeding T cell function, augmented presentation of S100A4, and elevated levels of IL-12 correlate with gliomas[16, 17]. Several studies

have unveiled interactions between TANs and glioma cells, identifying tumor cell-secreted IL-6 and IL-8 as crucial activators of TANs[18]. Recent investigations suggest that neutrophils infiltrating tumors induce iron deficiency anemia, leading to enhanced tumor necrosis and accelerating GBM progression[19]. Concurrently, either neutrophil or monocyte is termed a "criminal partner" that collaborates to establish an effective immune response. For instance, when microbes infect, tissue macrophages release a repertoire of neutrophil-recruiting factors, including IL-1 α , CXCL1, and CXCL2, which promptly recruit neutrophils to the site of infection[20]. Nevertheless, the mechanisms by which neutrophils are recruited and interact with TAMs in GBM growth require further research.

3. Conclusion

In summary, the glioma tumor microenvironment exerts a profound influence on its development and treatment. Despite recent advancements in understanding the glioma tumor microenvironment, the importance of this milieu and its constituents in treatment remains an area rich for investigation. This manuscript reviews the unique structure and functions of prevalent immune cells in the tumor microenvironment and their roles in glioma progression and therapeutic interventions. However, the glioma tumor microenvironment comprises complex and multifaceted components. Discerning the significance and functionalities of these components in treatment warrants further investigation. Consequently, this treatise provides insights into the roles and mechanisms of key immune cells and related cytokines within the glioma tumor microenvironment. Continued investigation of their actions and interrelationships may provide new avenues for oncological treatment modalities.

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