Immunotherapy of Glioblastoma

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Glioblastoma is the most common brain malignant tumor in the adult population, and immuno-therapy is playing an increasingly central role in the treatment of many cancers. Nevertheless, the search for effective immunotherapeutic approaches for glioblastoma patients continues. The goal of immunotherapy is to promote tumor eradication, boost the patient's innate and adaptive im-mune responses, and overcome tumor immune resistance. A range of new, promising immuno-therapeutic strategies has been applied for glioblastoma, including vaccines, oncolytic viruses, immune checkpoint inhibitors, and adoptive cell transfer. However, the main challenges of im-munotherapy for glioblastoma are the intracranial location and heterogeneity of the tumor as well as the unique, immunosuppressive tumor microenvironment.

Keywords: glioblastoma ; immunotherapy ; tumor model ; stem cell ; organoid ; heterogeneity ; immunosuppression ; microenvironment

1. Introduction: Glioblastoma and Its Heterogeneity

The most aggressive and also most common primary brain tumor in adults is glioblastoma (Glioblastoma WHO grade IV). Glioblastoma is poorly responsive to therapy, which includes maximal surgical removal that is followed by chemotherapy and radiation therapy and has one of the shortest survival rates amongst all cancers [1]. For example, tumor treating fields treatment together with chemotherapy improved median overall survival of glioblastoma patients from 16 to 20.9 months [2]. Despite novel modalities in treatment, which rely on the Stupp protocol from 2005, the 5-year survival rate of patients is less than 5% [3][4][5]. Glioblastoma has distinct histological characteristics, including a pleomorphic cell composition, increased mitotic and cellular activity, and significant angiogenesis and necrosis [6]. The poor response of glioblastoma to treatment and its poor prognosis are associated with diffused invasion patterns within the central nervous system (CNS) [7]. Furthermore, the blood-brain barrier (BBB) presents both a physical and biochemical barrier to the CNS for large molecules [8][9]. Lymphatic vessels have been found in the meninges of humans and mice [10][11][12], causing the notion of the CNS as an immune-privileged system to be reconsidered. Brain-resident macrophages, i.e., microglia, are also now broadly recognized as antigen-presenting cells of the CNS. Although the brain is an immunologically distinct site, the brain microenvironment is capable of generating robust immune responses and offers adequate opportunities for the implementation of brain tumor immunotherapy [13]. In addition, the BBB can be disrupted in brain tumor patients, which increases the infiltration of immune cells into the tumor area. However, most GBM patients have variable regions of disrupted BBB, meaning that tumor regions with disrupted BBB and tumor regions with intact BBB exist [14].

The successful treatment of glioblastoma remains one of the most difficult challenges in brain cancer therapy. This is due to (1) the small population of therapy-resistant glioblastoma stem cells (GSCs) [15][16][17][18] and (2) inter- and intra-tumor heterogeneity that consists of a variety of different subtypes of glioblastoma [19] and stromal cells in the tumor microenvironment (TME) [20][21]. Glioblastomas have been genetically categorized by The Cancer Genome Atlas into three subtypes: proneural, classical, and mesenchymal. Each of these subtypes is characterized by mutations causing platelet-derived growth factor receptor alpha activation, epidermal growth factor receptor (EGFR) activation, and neurofibromin 1 deletions, respectively. Glioblastoma subtypes differ in their prognostic value, with mesenchymal and proneural subtypes exhibiting the shortest and longest overall survival rates, respectively [19]. Moreover, the composition of the TME is linked to the molecular subtypes of glioblastoma. Mesenchymal tumors contain abundant gene expression signatures for macrophages, $CD4^+$ T cells, and neutrophils [22]; this is also associated with a higher glioma grade [19]. An increase in macrophages and microglia cells occurs upon disease recurrence and is associated with shorter relapse time after therapy.

GSCs are largely responsible for glioblastoma recurrence and therapy resistance due to their DNA repair and multi-drug resistance mechanisms as well as their ability to evade the immune response [23][24]. GSCs are maintained in hypoxic and peri-arteriolar GSC niches [25][26] and are more abundant in more aggressive, high-grade tumors with worse prognoses [27][28]. The glioblastoma TME regulates and determines the cellular state and drives GSC plasticity [29], which leads to the therapeutic resistance of tumors [30].

The predominant immune cells in the brain are macrophages, more specifically, tissue-resident macrophages known as microglia [31]. In brain cancer or other brain inflammatory conditions, additional peripheral monocytes are recruited from bone marrow and are differentiated in the brain into macrophages that are phenotypically distinct from microglia [32][33]. Immune cells are recruited and phenotypically changed by glioblastoma cells; this supports tumor growth and an immunosuppressive TME [34] through the release of cytokines, extracellular vesicles, and connecting nanotubes [35]. Chemoattraction between cells is mediated by members of a large family of chemokines [36][37]. For example, in glioblastoma, the chemokine (C-C motif) ligand 5 (CCL5) and its receptor C-C chemokine receptor type 5 (CCR5) are involved in autocrine and paracrine cross-talk between glioblastoma cells and the TME, contributing to stromal and immune cell tumor infiltration and glioblastoma cell invasion[38][39]. The attraction between endothelial and glioblastoma cells in GSC niches is predominantly maintained by the binding of C-X-C motif chemokine 12 (CXCL12, also known as stromal cell-derived factor 1α (SDF-1α)) to the C-X-C chemokine receptor type 4 (CXCR4) in GSCs.

2. The Immunosuppressive Microenvironment of Glioblastoma

Multi-layered immunosuppression exists in glioblastoma, both at the systemic and local level [40]. Systemic immunosuppression in glioblastoma patients is, to a large extent, induced by standard treatment including radiotherapy, temozolomide, and corticosteroids, which weakens the adaptive and innate immune responses [41]. Moreover, defects in antitumor responses arise from defective T cell mobilization from the periphery due to T cell entrapment in the bone marrow, which is caused by the loss of the surface sphingosine-1-phosphate receptor 1 (S1P1) [42][43] that binds the lipid second messenger sphingosine-1-phosphate (S1P) [44]. The S1P-S1P1 axis plays a role in governing lymphocyte trafficking. Naïve T cell egress from bone marrow or secondary lymphoid organs cannot occur without functional S1P1 on the cell surface, as S1P1 is essential for lymphocyte recirculation [45].

The glioblastoma microenvironment is extremely immunosuppressive due to its low immunogenicity, the immunosuppressive properties of many cells (including cancer cells, cancer stem cells (CSCs), and tumor-infiltrating immunosuppressive immune cells, e.g., myeloid cells and T regulatory cells (Tregs)), and the lack of antigen-presenting potential and costimulatory antigens, leading to tumor resistance to immunotherapy.

Glioblastoma cells and GSCs employ several mechanisms to evade the immune response. These include their intrinsic resistance to the induction of cell death, modulation of tumor antigens and cell surface molecules (which are important for the recognition and destruction of immune effector and antigen-presenting cells), and secretion of extracellular vehicles, cytokines, and growth factors. For example, glioblastoma cells express the programmed cell death receptor 1 ligand (PD-L1) that inhibits the cytotoxicity of cytotoxic T cells and downregulates major histocompatibility complex (MHC) class I, resulting in deficient T cell cytotoxicity. Moreover, glioblastoma cells may increase the expression of natural killer (NK) cell inhibitory ligands and decrease the expression of NK cell-activating NK group 2 member D (NKG2D) ligands, leading to inhibited NK cell-mediated lysis [46].

Glioblastoma is immunologically a cold tumor with low NK and T cell infiltration compared to other solid tumors. In glioblastoma, T and NK cells become dysfunctional. T cells are senescent, tolerant, exhausted, and anergic due to the immunosuppressive glioblastoma TME [47]. NK cells are important as immune effectors of the first line of defense against tumor cells and have been shown to control metastasis by eliminating circulating cancer cells [48]. The proposed mechanisms for the functional inactivation of tumor-associated NK cells are the overexpression of Fas ligand, the loss of mRNA for granzyme B [49], and the decrease of CD16 and its associated zeta chain [50][51][52]. T and NK cell dysfunction is also caused by co-expression of multiple co-inhibitory receptors, including programmed cell death protein 1 (PD-1), T cell immunoglobulin and mucin-domain containing-3 (TIM3), lymphocyte activation gene 3 protein (LAG3), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) [53].

Glioblastoma immunosuppressive TME is driven by tumor-intrinsic factors and brain (host) tissue responses to tumor antigens, such as overexpression of the indoleamine 2,3-dioxygenase (IDO) enzyme [54][55] and oncogene transforming growth factor-beta (TGF-β), respectively. IDO is a tryptophan catabolic enzyme overexpressed in several tumor types that creates an immunosuppressive microenvironment via the suppression of cytotoxic ($CD8^+$) T cell proliferation and effector function [56] and the promotion of Treg generation via an aryl hydrocarbon receptor-dependent mechanism [56]. Cytokines, such as IL-10 and TGF-β, within the glioblastoma TME cause microglia to lose MHC expression [57][58]. TGF-β reduces NK and $CD8^+$ T cell activation through inhibiting NKG2D expression, which is responsible for inducing lysis of NKG2D ligand-bearing cells that express class I MHC-related proteins, MHC Class I Polypeptide-Related Sequence A (MICA) and B, and the UL16 binding protein (ULB) 1–4 protein family [59].

Glioblastoma cells in the TME hijack many different cells to support tumor growth through the recruitment and suppression of many cells of the innate and adaptive immune responses. For example, Tregs and myeloid-derived suppressive cells that inhibit the proliferation and activation of effector cells (i.e., T cells and NK cells) and antigen-presenting cells are recruited. Increased numbers of forkhead box P3 (FOXP3)$^{+}$ Tregs were found in glioblastoma [60][61]; however, their correlation with patient survival was modest [62][63]; Microglia and tumor-infiltrating macrophages influence immunosuppression by secreting the cytokine IL-10, TGF-β, and extracellular vesicles [64][65]. These complex interactions open new therapeutic windows for glioblastoma treatment. Colony-stimulating factor 1 (CSF-1) is a potent chemoattractant that regulates the differentiation of monocytes into tumor-associated macrophages (TAMs), and its overexpression correlates with increased TAM infiltration and poor clinical outcomes [66]. Inhibition of the CSF-1 receptor (CSF-1R) enhanced sensitivity to irradiation by altering both the recruitment and the phenotype of myeloid-derived cells recruited to the irradiated glioblastoma [67]. TAMs also express high levels of PD-L1 . Moreover, hypoxic conditions in the glioblastoma TME, through increased hypoxia-inducible factor (HIF) transcription factors and vascular endothelial growth factor (VEGF), increase TAM tumor infiltration.

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