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Emerging hallmark of gliomas microenvironment in evading immunity: a basic concept

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Abstract

Background Over the last decade, since clinical trials examining targeted therapeutics for gliomas have failed to demonstrate a meaningful increase in survival, the emphasis has recently been switched toward innovative techniques for modulating the immune response against tumors and their microenvironments (TME). Cancerous cells have eleven hallmarks which make it distinct from normal ones, among which is immune evasion. Immune evasion in glioblastoma helps it evade various treatment modalities.

Summary Glioblastoma's TME is composed of various array of cellular actors, ranging from peripherally derived immune cells to a variety of organ-resident specialized cell types. For example, the blood–brain barrier (BBB) serves as a selective barrier between the systemic circulation and the brain, which effectively separates it from other tissues. It is capable of blocking around 98% of molecules that transport different medications to the target tumor.

Objectives The purpose of this paper is to offer a concise overview of fundamental immunology and how 'clever' gliomas avoid the immune system despite the discovery of immunotherapy for glioma.

Conclusions Herein, we highlight the complex interplay of the tumor, the TME, and the nearby normal structures makes it difficult to grasp how to approach the tumor itself. Numerous researchers have found that the brain TME is a critical regulator of glioma growth and treatment efficacy.

Keywords Glioma, Glioblastoma, Microenvironment, Immune evasion, Immunotherapy

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Background

Gliomas are among the most prevalent primary central nervous system (CNS) cancers. A glioma is categorized according to its histogenesis into the standard WHO Grades I–IV [1, 2], with grades III–IV referred to as the high-grade glioma (HGG) [3]. Recently, the World Health Organization (WHO) added phenotypic and genotypic characteristics to the classification [2]. Glioblastoma multiforme (GBM), the most aggressive kind of glioma, has the worst prognosis. Despite the availability of modern multimodal therapy options, the median progression-free survival (PFS) is 7−8 months and a 5-year overall survival (OS) of 9.8% [4].

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Resistance to standard treatment in malignant gliomas has been frequently described [5–8]. Hanahan and Weinberg [9] postulated six hallmarks of cancer in 2000, including the capacity to foster proliferative signals, dodge growth suppressors, stimulate invasion and metastasis, enable replicative immortality, induce angiogenesis, and resist cell death. Years later, additional four hallmarks were proposed to strengthen the theory of cancer biology [10].

Among Hanahan and Weinberg's eleven traits, the most intriguing is arguably the capacity to prevent immunological breakdown [10]. This exceptional capacity is the result of interplay between the components of the tumor microenvironment (TME). The TME of gliomas is immunosuppressive and is equipped with a variety of survival mechanisms [11]. Understanding the function of TME in glioma immune evasion would benefit both scientists and clinicians, since it will allow for the advancement of contemporary therapies for the management of HGG.

Clinical presentation

Headache is the most common symptom of brain tumors, and in 1–2 in 1000 patients with headache are later diagnosed with a brain tumor [12, 13]. The characteristics vary based on its location, size, and growth rate. Exacerbated on waking up because of supine position, and also precipitated by coughing or Valsava manoeuvre. The likelihood on underlying brain tumor is increased if the headache is increasing in frequency and severity and the later development of other neurological symptoms or signs [12]. Ozawa et al. reported that headache accompanied with progressive weakness or cognitive dysfunction, especially in the frontal lobe, increases the likelihood of a brain tumour 44-fold or 59-fold, respectively [13]. Seizure are second most common presenting symptoms in approximately 20% of patients, followed by progressive weakness (1.5%), and confusion (1.4%) [13].

Prognosis

The typical survival time for adults under the age of 70 who do not receive therapy for high-grade glioma is roughly 3–4.5 months [14]. Then, a biopsy procedure followed by chemotherapy, with or without radiotherapy, boosts survival to approximately 8–10 months on average. Survival rates are 27–31% at 2 years and 7–10% at 5 years when maximal treatment involving debulking surgery and chemoradiotherapy is administered [15].

The median survival time for elderly individuals who receive only the best supportive care is less than 4 months [14, 15]. In patients over 65 years who have undergone a biopsy or resection, hypofractionated irradiation and chemotherapy result in a median survival time of 7–9 months, as opposed to radiation alone [16,

17]. Despite evidence of a survival benefit, the inclusion of adjuvant chemotherapy has no effect on the quality of life of this group [15, 17]. Due to the incurability of glioblastoma, patients should be appropriately advised about the potential impact of adverse effects of treatments on quality of life, in addition to potential survival benefits, particularly elderly patients and those with a poor performance status, who have a particularly poor prognosis [14, 16].

The tumor microenvironment
Cancer cells

A tumor is made up of various different types of cells, and even more so in cancer cells. Early in their development, cancer cells are initially homogeneous only to diversify later. The rise of cell heterogeneity is a result of genetic instability, which favors the formation of distinct cell subpopulations [10, 18].

Immune cells

Macrophages are the most commonly found immune cells in glioma [18], contributing to approximately 30% of tumor mass [19]. Macrophages in a brain tumor may be tissue-resident microglia or bone marrow macrophages (BMDM). Microglia are formed throughout the embryonic development process [20, 21], whereas BMDMs are present when the homeostasis of brain tissue is compromised by a particular pathological state [22]. In the presence of a brain tumor, a compromised blood–brain barrier (BBB) is hypothesized to assist the recruitment of peripherally circulating monocytes into the tumor mass [23]. The tumor-associated macrophages and microglia (TAMs) are composed of these two kinds of macrophages [19]. TAMs are pro-tumorigenic cells that grow in number as tumor grade increases [24, 25]. Despite their origins as macrophages, TAMs generate few pro-inflammatory cytokines and are largely ineffective in stimulating T cells [26].

Dendritic cell

Dendritic cells (DCs) are cells involved in the surveillance of pathogens and in the repair of microenvironmental tissue damage [27]. DCs trigger the immune response by engulfing tumor antigens and presenting them to T- and B-cells [28]. DCs are more prevalent in vascular-rich compartments such as the choroid plexus and meninges rather than in brain parenchyma. This suggests the possibility of peripheral DCs migrating into the CNS via vascular-rich compartments [29, 30]. DCs can gain entry to the brain and spinal cord through afferent lymphatics or venules in the presence of a pathological condition, such as cancers [31]. DCs may detect and present tumor antigens to T cells in the deep cervical lymph nodes to

activate coordinated T-cell-mediated responses [31]. DCs release exosomes which express tumor or stimulatory antigens to activate Cytotoxic T cell responses—a feature antagonized by tumor-cell-derived exosomes [32].

Blood–brain barrier (BBB)

Endothelial cells (EC), extracellular matrix (ECM), astrocytes, and pericytes comprise the BBB [33]. The EC is sealed with tight junctions and bordered by an ECM-based basal lamina. On the basal lamina's outer surface, astrocyte end-feet and pericytes complete the BBB [34]. The BBB's strict control over the passage of chemicals and cells into and out of the brain [35, 36] may be relaxed under pathologic condition to allow entry to certain immune cells [35, 37]. In gliomas, BBB integrity is weakened due to the tumor's high metabolic requirement. Such conditions accelerate vasculogenesis, which results in the formation of tortuous arteries [38, 39]. These impaired arteries would inevitably result in hypoxia and an acidic microenvironment. Interestingly, this ostensibly detrimental state promotes tumor development rather than destroying its cells [19, 40, 41]. In addition, the presence of a brain tumor disintegrates astrocytic end-feet and pericytes, resulting in a leaky BBB [42]. The tight junction of the endothelial cell (EC) is known to be compromised in GBM as a result of the activity of vascular endothelial growth factor (VEGF) [43, 44].

Immune evasion

Gliomas weaken the immune system through various means. Gliomas have the capacity to release immunosuppressive substances that have diverse consequences, including the modification of the major histocompatibility complex (MHC) expression, promotion of immature DCs as antigen-presenting cells (APCs) [45], and proliferation of regulatory T (Treg) cells [39, 40]. Using chemokines, glioma also induces T-cell anergy, inhibits natural killer (NK) cells, induces T-cell death, and recruits immunosuppressive T cells [46]. All of these pathways are frequently interconnected, resulting in a vicious cycle that promotes glioma survival.

Immunosuppressive factors

It is well established that gliomas release immunosuppressive substances to inhibit the immune response [45]. It is also known that the secretion of these substances promotes the proliferation of Treg cells. All of the alterations generated by the secreted immunosuppressive substances would later impair the function of cytotoxic T lymphocytes (CTLs) [38, 40, 41]. Interleukin-10 (IL-10), interleukin-6 (IL-6), transforming growth factor (TGF), and prostaglandin E-2 (PGE-2) are the most researched immunosuppressive factors in the glioma microenvironment. Although TAMs are the primary generators of these substances [49–51], it has been found that the glioma cells secrete these factors as well [52].

Glioma is also equipped with Glycoprotein A repetition predominant (GARP), a surface molecule known to activate Treg cells, as shown in a study on histopathological specimens of low-grade astrocytomas and glioblastomas. GARP exerts its immunoregulatory function by inducing Treg cells through the help of TGF-ß and also by inhibiting the proliferation of Cytotoxic T cells [53, 54].

Down-regulation of MHC

MHC is a molecule involved in antigen presentation; it is commonly classified into classes I and II, with the former being expressed mostly on nucleated cells and the latter on APCs. Class I MHC binds to internal antigenic peptides and transports them to the cell surface, where they are recognized by CTL [55]. Class I MHC expression was lost in nearly 50% of 47 GBM samples, according to one study [56]. There was a significant positive correlation between HLA class I antigen loss and tumor grade [57]; the analogy is shown in Fig. 1a, and b. Immunosuppressive cytokines such as TGF- and IL-10 are considered to suppress the expression of Class I MHC. These cytokines not only impair antigen presentation, but also induce the expression of the Programmed Death-1 (PD-1) receptor on invading T cells. This receptor would bind to tumor cell-expressed PD-1 ligands (PD-L1) and produce T-cell anergy [58]; an analogous is illustrated in Fig. 1c, and d. The effect of immunosuppressive cytokines and the interaction between PD-1 and its ligand will be discussed in greater detail later in this section. Class II MHC expression is also lowered in glioma-associated microglia (GAM) as a result of the cytokines' impact [59, 60].

Impaired DC function

DCs derived from myeloid cells are initially uncommitted to antigen presentation. Numerous stimuli would then classify DCs into two phenotypes: type-1 and type-2 polarized effector DCs (cDC1 and cDC2, respectively) [61]. The cDC1s can activate CTLs via Class I MHC, whereas the cDC2s can activate T helper cells via Class II MHC [62, 63]. Various chemokines such as CCL5 and XCL1 recruit cDC1s into the TME [64], where they use the tumor antigen to either stimulate naive CTL at a lymph node [65, 66], or release chemokine to directly recruit CTL into the tumor [67, 68]. However, the presence of TGF-β and PGE-2 in the GBM's TME converts DCs to a regulatory phenotype, which promotes Treg proliferation instead of CTLs [69]. In addition, it is hypothesized that IL-6 and IL-10 generated by microglia and TAMs [38, 39, 61] impede DC maturation and instead encourage immature DC to proliferate [45].
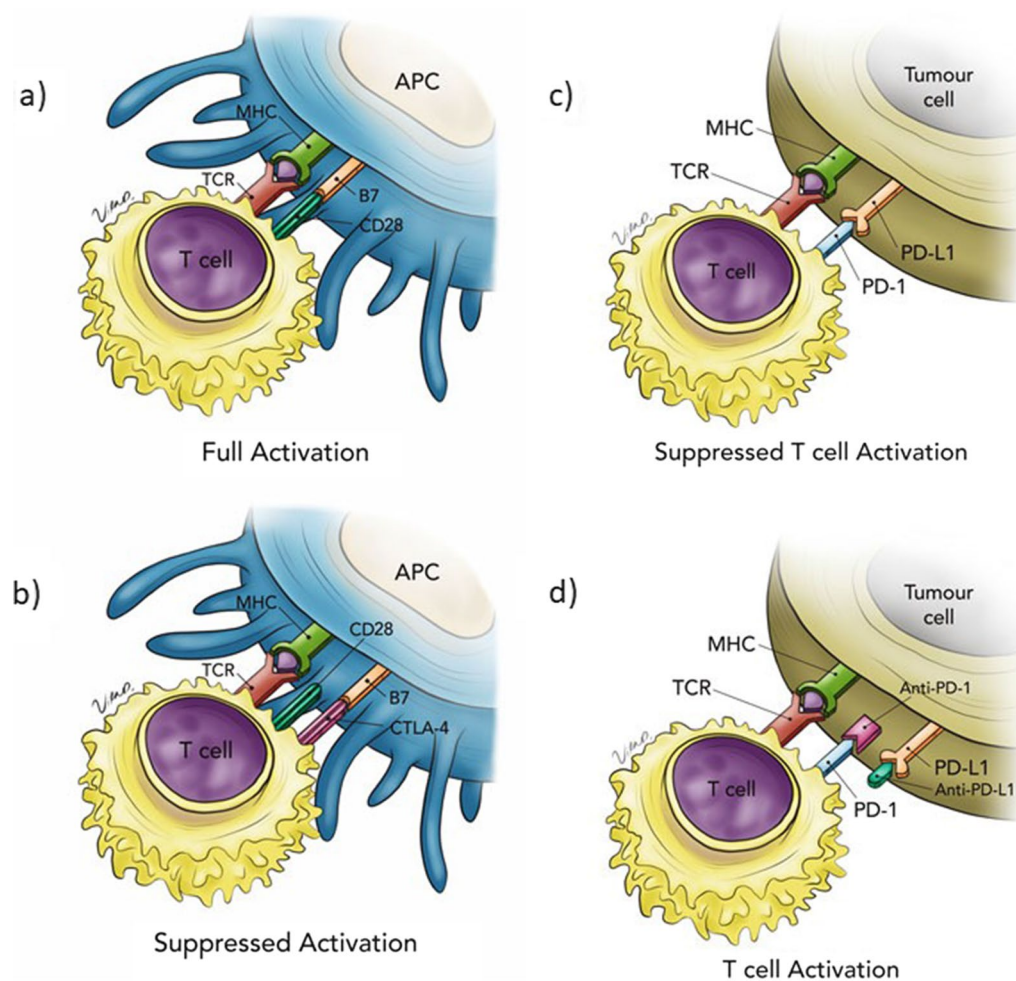
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Fig. 1 Schematic of CTLA-4 activate (**a**) and blockade (**b**); steps involved in generation of tumor-specific T cells. The figure shown is a schematic of an APC, with associated cell–cell interactions via CTLA-4/B7. Tumor-associated antigens or neo-antigens are presented by MHC on APCs or tumor cells to T cells with appropriate TCR. CD28 co-activating receptor on T cells binds B7 on APCs. Schematic of PD-1/PD-L1 blockade (**c**) and activate (**d**); steps involved in generation of tumor-specific T cells. Anti-PD-1 and PD-L1 antibodies are shown

Apart from their inability to deliver antigen to T cells [71], immature DC produce TGF-β, which contributes to an even more immunosuppressive condition inside the glioma microenvironment [45].

Immunosuppressive TAMs

TAMs as a non-inflammatory cell conforms to the conventional dichotomy of macrophage phenotypes, M1 and M2 [72]. According to this established notion, macrophages may acquire distinct characteristics in response to the stimuli they encounter. Interferon-γ (IFN-γ), lipopolysaccharides (LPS) [73] and granulocyte–macrophage colony stimulating factor (GM-CSF) [74], all induce macrophages to adopt the M1 phenotype, which is important in generating T helper type 1 (Th1) cells [73] and pro-inflammatory cytokines [75].

On the other hand, M2 macrophages promote Th2 lymphocytes, angiogenesis and tumor growth [76]. This trait is related to the low level of IL-12 and IL-23 and a high level of IL-10 and TGF-β. M2-phenotypes are also induced by Macrophage Colony-Stimulating Factor (M-CSF) [74], and IL-34 [75]. M-CSF and IL-34 both stimulate the mitogen-activated protein kinase (MAPK) signaling pathway via the CD115 receptor [75]. The MAPK pathways control a range of processes crucial for cell survival [77]. IL-10 [78] is one of the MAPK pathway's end products, since it drives Th cell differentiation into Th2 cells, hence increasing the production of anti-inflammatory cytokines [79]. Macrophages within the glioma TME are classified as M2, because they exhibit a high level of anti-inflammatory and pro-angiogenic factors (Fig. 2) [24].
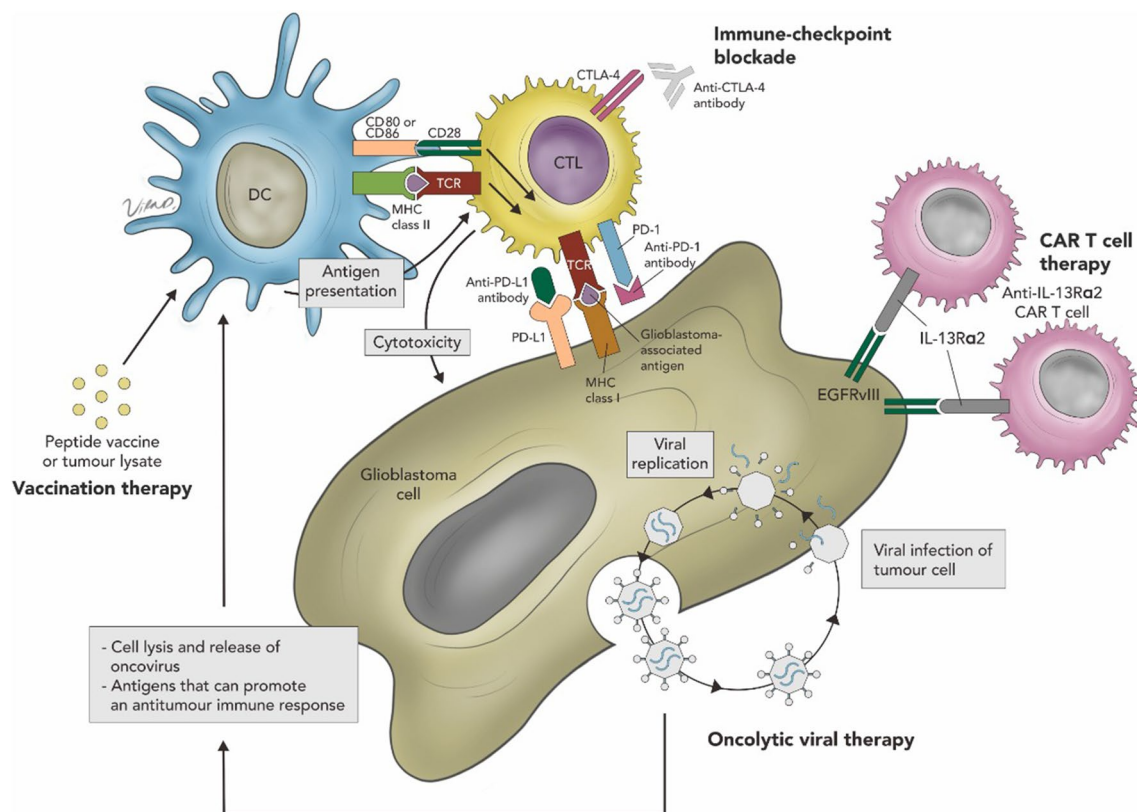
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Fig. 2 Mechanism of CAR T-cell therapy. The figure shows an illustration of combining CAR T-cell therapy with oncolytic viruses or immune checkpoint inhibitors resulted enhanced therapeutic outcomes for gliomas. (Original figure: created by co-author of this article for this article)

Natural killer (NK) cell inhibition

NK cells are huge granular lymphocytes that, in contrast to CTLs, eradicate virus-infected cells without prior antigen presentation (Fig. 2). NK cells are able to identify "stressed" cells which down-regulate Class I MHC to avoid identification by CTL. This ability is thus vital for anti-tumor immunity [80].

In vivo studies have reported that NK cells are scarce in the brains [81], but may increase in number when the BBB's integrity is impaired, such as in an autoimmune disease or infection [82–86]. In addition, the presence of CX3CL1, a chemokine generated by neurons, attracts NK cells [87]. The presence of NK cells in GBM revealed that this subgroup of lymphocytes plays a significant role in neoplasm surveillance [88]. TGF-β may inactivate NK cells by downregulating their activating receptors [89–91] and ligands, hence lowering their proliferation and convert them into the pro-tumor innate lymphoid cell (ILC)1-like cells [92]. TGF-β is known to suppress the production of the NKG2D receptor, an NK activating receptor [89], whose blockage has been shown to render NK cells incapable of cytotoxicity [93]. Due to its ability to actively release TGF-β, glioma is NKG2D deficient [89].

Under normal circumstances, NK cells express the NKp44 receptor, which can bind to the PDGF-D produced by the majority of GBM cells and generate cytokines that inhibit tumor growth [94]. NKp44 is an activating receptor for NK cells that—together with NKp30, NKp46, and CD16—belongs to the immunoreceptor tyrosine-based activation motif (ITAM) [95, 96]. On the other side, glioma has been shown to express a high level of Galectin [97], a protein family that has been shown to promote tumor angiogenesis [98], cancer cell migration [99], and tumor immune evasion [100]. Galectin-3 was discovered to bind selectively to NKp30 when released from tumor cells, thereby reducing NKp30-mediated cytotoxicity. Therefore, it was postulated that tumors secrete galectin-3 as a unique mechanism for evading NKp30-mediated NK cell immunosurveillance [101]. This hypothesis had previously been tested in vivo, by blocking Galectin-3 with N-acetyllactosamine or an anti-Galectin-3 antibody to restore production of IFN by CTLs [102].

T-cell anergy

GBM has been shown to deplete T cells and desensitize them to the tumor's presence [103]. This theory was

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based on findings in cases of chronic lymphocytic choriomeningitis virus (LCMV) infection [104, 105], but has now been demonstrated to occur in cancer as well [106]. Numerous inhibitory receptors were up-regulated following chronic antigen exposure [107]. Checkpoint inhibitors block inhibitory signals that regulate lymphocytes; among the up-regulated immune checkpoint inhibitory receptors are the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1, and PD-L1 (Fig. 2), which have been approved by the FDA as T-cell-based treatment for cancer [108].

PD-1 is a surface receptor which serves as an immunological checkpoint. This receptor is expressed on the surface of activated T cells, NK cells, B lymphocytes, macrophages, DCs, and monocytes [109]. PD-1 suppress immune cells' inflammatory activities when attached to its ligand, the PD-L1 [110]. Nduom and colleagues examined the expression of PD-L1 in 94 patients and discovered that it was a poor predictive factor for GBM [111]. However, Wang and colleagues used transcriptome data to evaluate 976 glioma samples and discovered that PD-L1 expression was positively linked with higher WHO glioma classification (Fig. 3) [112].

The phosphoinositide 3-kinase (PI3K), AKT [113], and mammalian target of rapamycin (mTOR) appear to influence PD-L1 expression (PI3K/AKT/mTOR pathway) [114]. In addition, this pathway is known to modulate various other characteristics of cancer to optimize tumor survival [115]. As indicated by a study on gastrointestinal stromal tumors, PD-1/PD-L1 is thought to promote CD8+apoptosis [116]. The MAPK signalling pathway is a signalling mechanism that contributes to glioma's immunosuppressive properties. Recent research has put more attention on the relationship between the PD-1/PD-L1 axis and the MAPK pathway. Stutvoet and colleagues demonstrated that inhibiting the MAPK pathway

reduced the induction of PD-L1 protein in lung cancer cells by epidermal growth factor (EGF) and interferon (IFN) [117]. Indeed, IFN-γ released by tumor infiltrating lymphocytes (TIL) is a powerful activator of PD-L1 expression in glioma [108].

Immunosuppresive T-cell recruitment using chemokines

CXCR2 and CXCL8 are two of the most prevalent chemokines in the glioma microenvironment [118]. The upregulation of both chemokine receptors was found to be associated with a bad outcome [118]. GBMs express high levels of CXCR2 which are known mostly for its role in angiogenesis [119]. CXCL8, on the other hand, leads to local and systemic immunosuppression [120] which enables GBM to evade host immunosurveillance. GBM-associated systemic immunosuppression is connected to the increase of immunosuppressive T cells, such as Tregs and myeloid-derived suppressor cells (MDSCs) [121, 122]. MDSCs exert their effect by suppressing T-cell proliferation and activation. MDSCs regulate inflammatory responses in the normal population, therefore, preventing autoimmune illness [123, 124]. CXCL8 expression by GBM has been shown to regulate the entry of MDSCs into the tumor environment via the CXCR2 receptor [125].

Regulatory T-cells (Tregs) and T-cell apoptosis

Numerous studies on many forms of cancer have established that Tregs are involved in immunosuppression [126, 127]. Tregs are a physiological fraction of CD4+ T cells that inhibit the function of T and B cells [128, 129], six different DCs [130–132], monocytes or macrophages [132], and NK cells [133, 134]. Functional Tregs express CD4+, CD25+, and Foxp3 [126]. Within the glioma microenvironment, both the number and function of
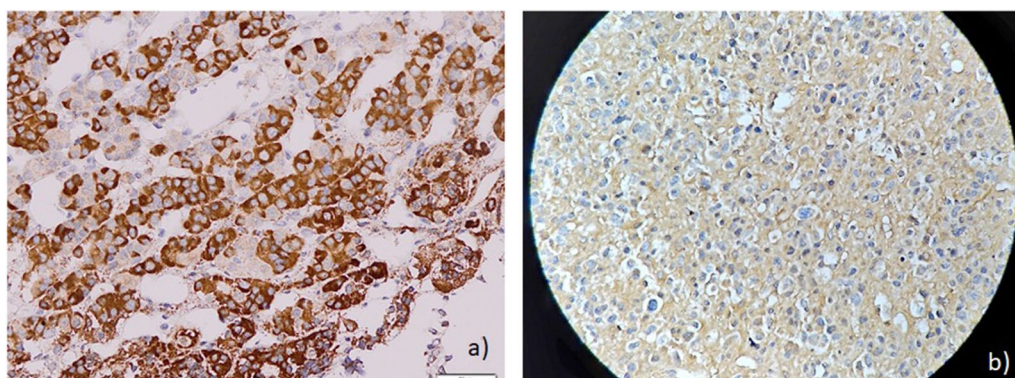

Fig. 3 Immunohistochemical detection of gliomas cells profile. This is representative image of a specimen that positively stained with PD-L1 both in glioma patient (**a**) and primary isolated cell line (**b**). Original magnification: × 200; scale bar: 50 µm. (Original figure: created by co-author of this article for this article)

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CD4$^+$ T cells are reduced, with an abnormally high proportion of Tregs [135].

A time-dependent increase of Tregs was seen in brain tumors in an in vivo research [136]. Hussain and colleagues isolated and labelled immune cells from human glioblastoma tissue to determine their phenotypes [26]. They discovered that glioma-specific CTL were phenotypically CD8$^+$ and CD25$^-$, indicating that they were inactive. The majority of T cells in a glioma were CD4$^+$, indicating Treg dominance, as demonstrated by positive intracellular staining for Foxp3 [26]. Another study compared GBM and normal brain tissue and discovered that CD4$^+$ CD25$^+$ Foxp3$^+$ Tregs were present only in GBM tissue [137]. The chemokine CXCR2 induces Treg migration into the glioma microenvironment [138].

Tregs have been shown to trigger T-cell death in vitro. T-cells were grown with Tregs for 72 h and apoptosis was demonstrated using transmission electron microscopy [139]. Numerous hypotheses have been advanced to explain how Tregs trigger T-cell death, including inappropriate T-cell activation [140–142] and depriving T cells of cytokines [139]. The former method favors aggressive apoptosis, whereas the latter favors quiet apoptosis. The cytokine deprivation-induced apoptosis was discovered preclinically, when pro-survival cytokines shielded T cells against apoptosis. In addition, it was shown that T cells die gradually over 3–4 days rather than instantly as in cytolysis. In addition, an in vitro investigation shown that the concentration of cytokines was lower in cultures containing Tregs than in cultures containing control T cells [139].

Another way for T cells to undergo apoptosis is via the Fas-mediated pathway. GBM expresses the Fas ligand (CD95L) on its surface, which induces T-cell death upon binding to Fas (CD95/APO-1) on T cells [143]. Fas-mediated apoptosis is a well-established concept of cell death. When Fas binds to its ligand, it recruits Fas-associated proteins to DD (FADD). This protein is responsible for the death of cells by recruiting caspase-8 and caspase-10 [144]. Another method of T-cell apoptosis occurs when CD70 on GBM cells interacts with CD27 on T cells. It has been demonstrated that inhibiting this connection partially protects T cells against GBM cell-induced death [145].

Extracellullar matrix

Numerous solid tumors contain abundant extracellular matrix (ECM) molecules, including fibrillar collagens, fibronectin, elastin, and laminins [146]. Up to 60% of the mass of many tumors is composed of extracellular matrix [146]. The tumor cells themselves, but to an even greater extent, cancer-associated fibroblasts (CAFs) are the source of these ECM molecules [147]. CAFs support tumor cells via paracrine stromal cell-derived factor-1 (SDF1) and transforming growth factor beta (TGF) signals, contributing not only to a more malignant tumor phenotype by driving epithelial-to-mesenchymal transition (EMT), but also inducing production of collagen and other ECM molecules [148].

The molecular expression profile can subdivide numerous cancers originating from the same tissue [148]. These molecular subtypes provide a great deal of information regarding the tumor's metabolism, dysregulation of survival and apoptosis pathways, and the presence or absence of specific proteins [148]. In many cancers, the expression profile of ECM-related genes is also a valuable prognostic factor [148]. In addition to immune suppression markers, high expression of Col3a1, Col4a1, and Col5a2 is associated with a poor prognosis in glioblastoma [148].

Inevitably, the occurrence of metastasis impacts treatment options and therapeutic outcome. EMT is associated with both increased metastasis and chemoresistance. EMT in cancer is associated with the development of stem-cell-like properties [149]. Loss of epithelial polarization, which is linked to anchorage of epithelial layers on a basement membrane, is characteristic of EMT [149]. On top of that, ECM had a role in glioma invasion. Glycosylated chondroitin sulfate proteoglycans (CSPGs), a major component of ECM in the brain contribute to induce glioma invasion.

Exosomes

Exosomes play a vital role in evading immunity and inducing tumor progression. Exosomes, released by DCs, express tumor or stimulatory antigens to activate cytotoxic T cell responses [32]. Previous studies have investigated the critical role of tumor-derived exosomes against immunity. Exosomes, released by impaired DCs, tend to have a greater impact under hypoxia. Exosomes released by hypoxic bone-marrow-derived mesenchymal stem cells (BMSCs) in TEM induce cancer cell invasion and epithelial mesenchymal transition [150]. Exosomes also contribute to the proliferation, invasion, and migration of human umbilical vein endothelial cells in esophageal squamous cell carcinoma under hypoxia [151]. In gliomas, recent study demonstrated that exosomal connexins 43 (Cx43) contributes to glioma angiogenesis mediated by exosomes under hypoxia [152]. Moreover, hypoxic glioblastoma-derived exosomes disrupt the permeability of blood–brain barrier (BBB) [153].

Discussion

In general, errors in a cell's genome are the cause of the development and formation of neoplastic cells. The tumor's microenvironment contains a number of

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factors that promote and sustain its growth. In addition, the resistance to applied therapies is also a result of tumor heterogeneity and its constant alterations [154, 155]. Nonetheless, cancer has developed a number of immune surveillance evasion mechanisms. These include the avoidance of recognition by the down-regulation of MHC, impaired DC function, immunosuppressive TAMs, Natural Killer (NK) cell inhibition, T-cell anergy, immunosuppressive T-Cell recruitment using chemokines, regulatory T-cells (Tregs), T-cell apoptosis and extracellullar matrix. Several of these mechanisms are conducive to progression, the creation of their own environment for cell development, and cell death in their own favorable environment [156–158]. Similar to other types of cancer, gliomas weaken the immune system through various pathways. Immunosuppressive ability of glioma plays a vital role for glioma survival. IL-10, IL-6, TGF, and PGE-2 were found to be immunosuppressive factors in the glioma microenvironment. In addition, the presence of GARP, a surface molecule, allows glioma to survive for a longer time by activating Treg cells [53, 112]. On top of that, glioma induced tumor progression by weakening BBB integrity. This will lead to accelerate vasculogenesis and impaired arteries which result in hypoxia and promote tumor development [153, 159]. Glioma also disrupted EC as a result of VEGF [43, 44]. All of these pathways are frequently interconnected, resulting in a vicious cycle that promotes glioma survival and progression. Understanding what occurs within the microenvironment of glioma and which mechanisms are responsible for glioma development and progression will reveal how glioma could protect itself from the immune system.

The concept of immunotherapy for GBM
Decreased MHC expression in GBM frequently correlates with worse prognosis. MHC-I downregulation has previously been attributed to epigenetic and transcriptional dysregulations involved in the stabilization of NFkB, interferon regulatory factors (IRFs), and NOD-like receptor family CARD domain containing protein 5 (NLRC5). These dysregulations are possibly reversible, implying the possibility of reversing MHC-I downregulation in cancer. In addition, STAT3 inhibition, STING activation, chemotherapy, and radiation can all stimulate MHC-I expression [160]. However, there are few trials targeting MHC-I in gliomas.

As previously stated, impaired DC proliferation will further impair CTL function [45]. DC vaccines (DCVs) are a type of immunotherapy that aims to enhance DC activities. DCVs comprised of immunostimulatory APCs created in vitro utilizing CD14 monocytes cultured with GM-CSF and IL-4. In short, DCVs are basically DCs loaded with tumor antigen and injected into the patient [161]. Autologous tumor lysate, cultured tumor cells from surgical specimens, irradiated autologous tumor cells, tumor RNA, or tumor related peptides were utilized as antigens. In a phase II GBM vaccine experiment, Wheeler and colleagues reported that 53% of GBM patients demonstrated a 1.5-fold increase in cytokine response following vaccination. Responders to vaccination have a longer median survival than non-responders (642 days and 430 days) [162]. A large phase III clinical trials is needed to confirm DCV's efficacy and safety in glioma, as results negating its benefits have also been published [162].

In gliomas, TAM infiltration is dominated by tumor-supportive M2 macrophages. Because TAMs require colony-stimulating factor (CSF) for differentiation and survival, BLZ945, a CSF-1 inhibitor, was utilized to target TAMs in mice GBM models. Inhibition of CSF-1 can decrease the quantity of M2 macrophages, resulting in tumor regression [163]. PLX3397 is a CSF-1 inhibitor that has the ability to cross the BBB and reduce TAMs, thus result in alleviation of tumor invasiveness in mice models of GBM [163]. TAMs-targeted immunotherapy may be useful in the treatment of GBM. However, at the moment this therapeutic modality is still limited to in vivo models [162].

NK cells have significant anti-tumor effects, particularly when CTL function is reduced. Although the number of NK cells in GBMs is deemed low, they retained cytotoxic activity [80]. Enhancing NK cells' oncolytic capacity might be achieved by counteracting their inhibition, that is through cutting the binding between MHC molecules and killer immunoglobin receptors (KIRs) [95]. Ishikawa and colleagues demonstrated tumor volume decrease using autologous NK cells. In addition, they suggested that this response could be enhanced by combining autologous NK cells with an IL-2 dosage or radiation therapy [164]. Another option is to use allogenic NK cells, which originate from an unrelated donor and are equipped with a KIR receptor that is incapable of recognizing MHC class I molecules. In allogenic NK cells, the KIR receptor does not recognize tumor MHC molecules, resulting in the absence of NK cells inhibition [95].

Anti-CTLA-4 and Anti-PD-1 therapies have primarily been studied in T cells for their direct immunological implications (Fig. 2). Due to their roles as immune checkpoint, therapies targeting CTLA-4 and PD-1 are hypothesized to be able to "free" T cells from inhibition to fight tumor cells. CTLA-4 (CD152) is an inhibitory receptor which downregulates T cell function [165, 166]. This receptor is mainly expressed on Tregs but might be upregulated on other subsets of T cells in pathologic

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condition, such as cancer. CTLA-4 suppresses the immune system indirectly by inhibiting signals via the co-stimulatory receptor CD28. CTLA-4 reduces immunological responses to weak antigens such as self- and tumor antigens by increasing the activation threshold of T cells [167]. PD-1 binding to PD-L1 is involved predominantly in inhibitory immune signaling. Although the majority of circulating T cells lack PD-1, its expression can be stimulated by exposure to cytokines, such as IL-2, IL-7, IL-15, IL-21, and TGF-β [167].

Neoantigens, which are formed from tumor-specific protein-coding mutations, are immune stimulatory and can operate as bona fide antigens that aid in tumor rejection. T-cell activation and subsequent tumor lysis driven by neoantigen vaccines offers an appealing precision medicine strategy. The process of developing a personalized neoantigen vaccination begins with a comparison of genetic data received from the patient's peripheral blood mononuclear cells (PBMCs) and excised tumor tissue [168]. Following administration of customized vaccinations, APCs come into contact with the neoantigens contained in the vaccine, thereby initiating the process of neoantigen MHC presentation [169]. Immune responses mediated by T cells are triggered when a certain T cell receptor recognizes a particular neoantigen. In addition, these neoantigen-specific T lymphocytes expand, move toward the tumor site, and subsequently enter the tumor. Immune responses can be found that are CD4 positive (which enhances the immune response) or CD8 positive (which has a cytotoxic effect). Tumor cells that have been eliminated create an adaptive immunological memory response by releasing neoantigens [170].

Adoptive T cell therapy, which entails the selection and development of antigen-specific T cell clones ex vivo, enables the enhancement of antigen-specific immunity without the in vivo restrictions associated with vaccine-based techniques. While some clinical responses have been found in vaccine trials, the amplitude of the induced T cell response has often been small or undetectable and has had a poor correlation with clinical responses. In comparison with vaccination methods, adoptive treatment procedures are capable of circumventing the in vivo restrictions that limit the amplitude and avidity of the targeted response. T cells with a given specificity, function, and affinity for a tumor can be selected in vitro and then expanded to achieve in vivo peripheral blood frequencies that are higher than those achieved by current immunization regimens and are consistent with the levels predicted to be required to mediate tumor elimination in murine tumor therapy models [171]. In DCs, due to their capability to acquire, process, and present antigens to T cells, they are a critical component of immunization. While immature DCs in peripheral tissues acquire antigens readily, antigen presentation typically results in immunological tolerance due to a lack of costimulatory molecules [172]. Immune tolerance is induced via a variety of methods, including T cell deletion and Treg cell growth [173]. DCs laden with antigens that have been activated (mature) induce the differentiation of antigen-specific T cells into effector T cells with distinct roles and cytokine profiles. DC maturation is associated with a variety of cellular changes, including (1) decreased antigen-capture activity, (2) increased expression of surface MHC class II molecules and costimulatory molecules, (3) acquisition of chemokine receptors such as CCR7 that direct their migration, and (4) the ability to secrete various cytokines that regulate T cell differentiation including IL-12 [174].

Current state of immunotherapy for glioma
DCVax-L® has shown a benign safety profile in Phase 3 study, as it has consistently done in prior early stage trials, and in a large group of patients. Study by Liau and colleagues, showed that only 7 of the 331 Intention-to-treat (ITT) patients experienced any grade 3 or 4 adverse events that were at least possibly related to the treatment. With such a safety profile, DCV looks promising and can potentially be combined with a range of other treatments, including immune checkpoint inhibitors and targeted therapies [175].

A review from Kennedy and colleagues shows that TAMs in glioma are a formidable foe, espousing an altered activation state within the local tumor microenvironment characterized by deficiencies in antitumor effector functions, upregulation of potent immunosuppressive mediators, and participation in tumorigenic loops of paracrine signaling [176]. Given the compelling evidence that TAMs contribute significantly to the creation and maintenance of immunosuppression and tumor progression, it is unlikely that clinically effective immunotherapy against malignant gliomas will be achieved until we gain a better understanding of how to influence TAM function in the local tumor microenvironment [176].

Golan and colleagues conclude that immunotherapy with NK cells seems to be a promising strategy for treating GBM patients. Furthermore, the use of techniques that increase direct cell-to-cell contact between GBM cells and NK cells could potentiate the antitumor effect [177].

Liu and colleagues concluded that there is an association between CTLA-4 expression with clinicopathological findings and IDH mutation status in gliomas. Moreover, CTLA-4 was positively correlated with other immune-related proteins in glioma. Additional studies are needed to further explore the molecular mechanisms

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mediating CTLA-4 expression in gliomas and responses to anti-CTLA-4 therapy [178].

CAR T-cell therapy has become a revolutionary approach for treating hematological malignancies and it has great potential for brain tumors. Land and colleagues discussed the various targets of CAR T-cell therapy, among which is the EGFRvIII [179]. The EGFRvIII is the most common EGFR mutation that occurs in about 45% of GBM patients [179]. In vivo study showed that CAR T-Cell targeting EGFRvIII improved survival of the subject animal, as well as reduced the tumor volume. The subject was mice implanted with EGFRvIII-positive glioblastoma cell line [180].

Limitations and future directions
Multiple therapeutic combination options must be confirmed through clinical research, which would make determining effective therapeutic combinations significantly more difficult and costly as the number of treatments targeting the various aspects of TME increases. To improve high-grade glioma prognosis, novel therapeutics that target multiple TME aspects could be administered alongside standard treatments.

Conclusion
Through a variety of mechanisms, high-grade gliomas are capable of evading immunosurveillance. This extraordinary ability may be one of the reasons behind glioma's poor prognosis despite regular treatments. Therefore, future efforts to develop novel therapeutics that simultaneously target multiple areas of high-grade glioma-TME interaction may yield better results than the current standard. Novel therapeutics that specifically target glioma's immune evasion mechanisms are among the most fascinating and promising areas of CNS oncology.

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