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Different T-cell subsets in glioblastoma multiforme and targeted immunotherapy

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ABSTRACT

Glioblastoma multiforme (GBM) is a brain tumor with a high mortality rate. Surgical resection combined with radiotherapy and chemotherapy is the standard treatment for GBM patients, but the 5-year survival rate of patients despite this treatment is low. Immunotherapy has attracted increasing attention in recent years. As the pioneer and the main effector cells of immunotherapy, T cells play a key role in tumor immunotherapy. However, the T cells in GBM microenvironment are inhibited by the highly immunosuppressive environment of GBM, posing huge challenges to T cell-based GBM immunotherapy. This review summarizes the effects of the GBM microenvironment on the infiltration and function of different T-cell subsets and the possible strategies to overcome immunosuppression, and thus enhance the effectiveness of GBM immunotherapy.

1. Introduction

Glioblastoma multiforme (GBM) is the most common and malignant brain tumor, accounting for 12%–15% of all brain tumors [1]. GBM tumor cells, which arise from stem cells or immature astrocytes due to genetic abnormalities, grow rapidly and disseminate in the brain [2]. In addition, GBM cells can invade the intracranial blood vessels to areas away from the tumor core [3]. This mechanism and the heterogeneity of GBM make this tumor difficult to treat. Besides the endogenous heterogeneity of GBM, the infiltration of immune cells also exhibits heterogeneity in different subtypes [4]. Traditional GBM treatment includes surgery, followed by radiotherapy and chemotherapy. However, the treatment outcome remains poor, with a median survival rate of only 12–18 months and a 5-year survival rate of 9.8% [5]. In recent years, immunotherapy has been widely used in the treatment of tumor diseases, including GBM [6]. Current strategies for tumor immunotherapy include dendritic cell (DC) vaccines [7], immune checkpoint inhibitors [8], and adoptive T cell therapy (ACT) [9]. However, the highly immunosuppressive microenvironment of GBM hinders the development of immunotherapy for its treatment.

GBM is a highly immunosuppressive tumor owing to its unique ability of immune escape. This ability may be ascribed to the fact that GBM is an intracranial tumor and lacks immune cells, thereby limiting the antitumor immune response [10]. Further, the severe inhibitory effect of GBM on cellular and humoral immunity is the major cause of the immunosuppressive environment and makes it difficult to treat this tumor [11]. The immunosuppressive environment of GBM is mainly caused by recruited immunosuppressive cells [12] tumor-derived immunosuppressive factors [13] overexpressed immune checkpoints [14] and GBM cell epigenetics to silence HLA molecules [15]. Activated T cells are crucial in initiating and promoting antitumor immune

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Abbreviations

GBM	Glioblastoma multiforme
DC	Dendritic cell
ACT	Adoptive T cell therapy
TCR	T cell receptor
NKT	Natural killer T cells
Tregs	Regulatory T cells
CCL	Chemokine C–C motif ligand
IL-10	Interleukin (IL)-10
TGF-β	Transforming growth factor β
MHC	Major histocompatibility complex
CNS	Central nervous system
VEGF	Vascular endothelial growth factor
MDSCs	Myeloid-derived suppressor cells
BBB	Blood brain barrier
BTIC	Brain tumor initiating cells
TNC	Tenascin-C
AHR	Aryl hydrocarbon receptor
TAMs	Tumor-associated macrophages
ICAM-1	Intercellular adhesion molecule 1
PD-1	Programmed cell death protein 1
Tim-3	T-cell immunoglobulin mucin-3
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
IDO-1	Pindoleamine-pyrrole 2,3-dioxygenase 1
PD-L1	Programmed cell death protein ligand 1
S1P1	Sphingosine-1-phosphate receptor 1
CMV	Cytomegalovirus
pp65	Phosphoprotein 65
G-MDSCs	Granulocytic MDSCs
LAG-3	Lymphocyte-activation gene-3
CAR T	Chimeric antigen receptor T cell
IL-13Rα2	Interleukin-13 receptor α2
HIF-1α	Hypoxia-inducible factor 1α
ICOSLG	Inducible T-cell co-stimulator ligand
LSP1	Lymphocyte-specific protein 1
PRF-P	Platelet-rich fibrin patch

responses [16]. However, GBM destroys the tumor immunity response by triggering qualitative and quantitative T cell dysfunction, leading to T cell aging, tolerance, inability, and exhaustion [17]. In addition, T cell receptor (TCR) ligation, activation, and intracellular signaling-related genes of peripheral T cells in GBM patients are downregulated compared with those in healthy controls [18].

T cells are lymphocytes that play an important role in the antitumor immune response [19]. These cells undergo "new recruit training" in the thymus to differentiate into different subtypes. Matured T cells then migrate to the surrounding lymphoid tissues and start functioning [20]. T cells are classified into different subtypes depending on the surface molecules they express and their functions. These subtypes include (i) adaptive T cells, including helper $CD4^+$, regulatory $CD4^+$, cytotoxic $CD8^+$, and memory T cells; and (ii) innate T cells, including natural killer T cells (NKT), mucosa-related invariant T cells, and γδ T cells [21]. As an important line of defense of the immune response, T cells determine the development and progression of tumor diseases [22]. Increased infiltration of T cells is associated with prolonged survival of GBM patients [23]. $CD4^+$ T cells coordinate antigen-specific immunity through their high plasticity and cytokine-producing ability. Increased Th1 cells can delay the progression of tumors, and a decreased Th1/Th2 ratio is related to the poor prognosis of GBM [24]. Regulatory T cells (Tregs) are immunosuppressive T cells that can be recruited by chemokine C–C motif ligand (CCL)2/CCL22 to the GBM tumor area to inhibit immune response and promote GBM progression [25]. The pro-tumorigenic effect of Tregs is exerted by the hallmark cytokines interleukin (IL)-10 and transforming growth factor β (TGF-β), which can inhibit the activity of antitumor effect T cells [26]. NKT cells are a special subset of T cells that have TCR and NK cell receptors on their surface. NKT cells secrete a large number of T-cell cytokines and chemokines, which play an important role in the immune regulation of tumor diseases [27]. These cells act as a bridge between innate and adaptive immunity. γδ T cells are a subset of innate T cells that critically contribute to antitumor and anti-infection immunity. γδ T cells can recognize and immediately respond to a variety of major histocompatibility complex (MHC)-like stress-induced autoantigens, many of which are also expressed in GBM [28]. Recently, a great number of experimental trials and clinical trials of γδ T cell-based GBM treatment have been conducted [29].

As important antitumor lymphocytes, T cells play an important role in the development and prognosis of GBM. Understanding the effect of the immunosuppressive environment of GBM on the tumor-infiltrating T cells is a key step in the use of T cells to fight tumors. This review summarizes this effect and will help understand and determine the direction in which T cell-based GBM treatment should be taken for developing better immunotherapeutic strategies.

2. Immunosuppressive microenvironment of GBM

GBM is the most common invasive and primary malignant tumor of the central nervous system (CNS) with a highly immunosuppressive environment, which complicates its treatment and causes poor prognosis. The immunosuppressive mechanism of GBM includes both endogenous and exogenous aspects. The former includes the down regulation of GBM tumor antigens [30]. GBM is a "cold tumor", characterized by low activated T cell infiltration caused by various factors such as lack of tumor antigens, inability of antigen-presenting cells (APCs) to effectively present 'non-self' tumor antigens to T cells, and failure of T cell activation. Exogenous mechanisms also lead to immunosuppression by GBM, such as the high expression of immune checkpoints on infiltrating lymphocytes and myeloid cells [14] and glioblastoma cell-derived suppressive factors and infiltration of a large number of immunosuppressive cells into the tumor microenvironment [31]. Immunosuppressive factors are the main inhibitors of T cell function. In the GBM microenvironment, the tumor cells can secrete a large amount of inhibitory factors, including gangliosides, kynurenine, TGF-β, and vascular endothelial growth factor (VEGF), which inhibit effector T cells and promote the tumor growth. In addition, the recruited immunosuppressive cells such as Tregs and myeloid-derived suppressor cells (MDSCs) also secrete a large number of immunosuppressive factors, including TGF-β and IL-10, which adds to the immunosuppressive environment. Unconventional lymphatic drainage and a relatively closed environment, antagonists of immune response triggers in the brain, are also external factors that contribute to the immunosuppression in GBM [32]. In general, the immunosuppressive environment of GBM is promoted by a variety of aspects, including the immune privilege of the CNS region due to the presence of the blood brain barrier (BBB), the concealment of GBM antigens, inability of a large number of tumor-killing cells to enter the tumor area and most importantly, the inhibitory factors of tumor-killing cells from multiple sources in the GBM microenvironment. This immunosuppressive microenvironment of GBM has been the biggest obstacle in developing effective GBM immunotherapy.

3. Effect of GBM microenvironment on T cells

In recent years, T cell-based tumor immunotherapy has made great

progress in a variety of tumors. Researchers have applied multiple immunotherapy approaches, such as DC vaccines, checkpoint inhibitors, and ACT to treat GBM [33]. Although some success has been achieved, the overall treatment outcome remains disappointing because the highly immunosuppressive environment of GBM causes the dysfunction of infiltrating T cells. T cells cannot exert their function on GBM because of the endogenous inhibition of T cells by GBM cells, upregulated immunosuppressive checkpoints, infiltration of a large number of immunosuppressive cells, and impaired migration of T cells [8,11,34].

3.1. GBM-derived factors mediate T-cell inhibition

Several studies have demonstrated that GBM cells generate some endogenous mediators that regulate the function and apoptosis of infiltrating T cells. Mahata et al. demonstrated that human GBM cells regulate T cell apoptosis by secreting gangliosides that increase ROS production and induce activated caspase-mediated T cell apoptosis. This leads to T cell exhaustion, greatly reducing the killing efficiency of T cells in GBM [35]. In addition, Reza et al. found that brain tumor initiating cells (BTIC) produces tenascin-C (TNC) that is deposited near tumor-infiltrating T cells in human GBM specimens. TNC inhibits T cell proliferation and activity by interacting with α5β1 and αvβ6 integrin on T cells, resulting in the blockade of T cell activation, which cannot effectively inhibit the occurrence and development of GBM [36] (**Table 1**). Another report proved that the GBM cell-derived kynurenine can suppress T cell immune response by activating the aryl hydrocarbon receptor (AHR) in tumor-associated macrophages (TAMs). In turn, AHR promotes the expression of the TAM exonuclease CD39, which can interact with CD73 to produce adenosine to promote T cell dysfunction. In human GBM, the expression levels of AHR and CD39 are the highest in grade IV GBM, and the expression level of AHR is associated with poor prognosis [37]. Jennifer et al. showed that the increased infiltration of T cells in the GBM microenvironment is related to the prolonged survival rate of GBM patients and that T cell infiltration is related to the expression of intercellular adhesion molecule 1 (ICAM-1) on the surface of blood vessels. However, they also proved that GBM-derived TGF-β1 and TGF-β2 downregulate the expression of ICAM-1, thereby inhibiting T cell infiltration [38]. Xuekai et al. showed that co-culture of GBM cells with T cells significantly increased the expression of the exhaustion marker CD57 on the surface of T cells. This result proves the status of GBM-infiltrated T cells from the side [39]. Since T cell dysfunction and decreased infiltration are regulated by endogenous factors secreted by GBM cells, targeting these factors can help improve the effectiveness of GBM immunotherapy.

T cell dysfunction and insufficiency in the GBM microenvironment are caused by other factors as well. The TCR diversity allows almost unlimited antigen recognition and response capabilities, ensuring an effective immune response in an ever changing environment [40]. However, the TCR repertoires in GBM patients are less diverse than those in healthy individuals, leading to inefficient recognition of tumor antigens and tumor clearance by T cells [41]. Moreover, GBM-infiltrated T cells express high levels of the Fas ligand FasL, which mediates T cells apoptosis [42] (**Fig. 1**). Understanding and overcoming the multiple strategies that GBM employs to suppress T cell immune responses are crucial to improve effectiveness of GBM immunotherapy.

Table 1
Tumor endogenous factors regulate the function of different T-cell subtypes.

Factor sources	Factors	Target cells	Effects	References
GBM	Gangliosides	T cells	Apoptosis↑	[35]
BTIC	TNC	T cells	Proliferation↓	[36]
GBM	Kynurenine	T cells	Dysfunction	[37]
/	ICAM-1	T cells	Infiltration↑	[39]
GBM	TGF-β	T cells	Infiltration↓	[42]
/	S1P1	T cells	Infiltration↓	[42]
Microglia	TLR2	$CD8^+$ T cells	Activation↑	[52]
GBM	VEGF	$CD8^+$ T cells	Activation↓	[54]
/	LAG-3	Th cells	Activation↓	[64]
/	HIF-1α	Tregs	Proliferation↑	[76]
GSCs	ICOSLG	Tregs	Proliferation↑	[77]
/	LSP1	Tregs	Infiltration↑	[78]
Macrophage	CCL2/22	Tregs	Infiltration↑	[83]

↑ Promote ↓ Inhibit/: Not mentioned.

3.2. Upregulated immune checkpoints mediate T-cell inhibition

Infiltrating T cells in GBM usually express one or more immunosuppressive checkpoints, such as programmed cell death protein 1 (PD-1), T-cell immunoglobulin mucin-3 (Tim-3), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), which inhibit T cell activation, proliferation, and immune responses [43]. Furthermore, GBM-infiltrated myeloid cells express high levels of programmed cell death protein ligand 1 (PD-L1), which is also upregulated by the tumor-killing activity of IFN-γ. The combination of PD-L1 and PD-1 causes the inhibition of T cell activation, eventually leading to an immunosuppressive microenvironment of GBM (**Fig. 1**). Immunosuppressive checkpoint inhibitors have been shown to alleviate GBM in the GL261 mice model. Further, immune checkpoints are a recognized component of immune autoregulation that keep immune response within control [44]. However, the malignant environment of GBM upregulates immune checkpoints on infiltrated T cell surface, resulting in T cell exhaustion. The up-regulated immune checkpoints on the surface of GBM-infiltrated T cells binding to their ligands can inhibit the activation of T cells and the implementation of anti-GBM tumor effects. The inhibition of classical immune checkpoints, CTLA-4 and PD-1, has been successfully implemented in the clinical treatment of many solid tumors, but its efficacy in GBM is still under clinical trials. High IDO-1 transcription levels are associated with poor prognosis in GBM patients and positively correlates with cell lysis and increased expression of Treg-related genes [45]. In addition, the co-expression of Tim-3 and PD-1 indicates T cell exhaustion. Jennifer et al. proved that blockade these two immune checkpoints followed by radiation could achieve a 100% survival rate in a GBM mouse model, with an improved activity of infiltrating immune cells and immune memory [46]. Blocking immune checkpoints as a therapeutic strategy is currently undergoing clinical trials. We believe that combining multiple immune checkpoint inhibitors and other therapy strategies is the key to restoring T cell function and treating GBM.

Immunosuppressive cells are the next important factor for the T cell suppression in GBM microenvironment. TAM and MDSCs that infiltrate in GBM can directly or indirectly inhibit T cell function. MDSCs increase in the circulation of GBM patients, causing reversible T cell dysfunction. Studies have shown that in the GBM microenvironment, where a large number of immunosuppressive cells exist, the proliferation and activation of T cells are blocked, resulting in the loss of GBM tumor killing effect. The inhibition of immunosuppressive cells leads to recovery of T cell function [47]. In addition, loss of sphingosine-1-phosphate receptor 1 (S1P1) from surface of T cells in GBM patients blocks the transport of the cells from the bone marrow to the blood and lymphoid organs, leading to low immune response [48].

4. Different T-cell subsets in GBM microenvironment

4.1. $CD8^+$ T cells

$CD8^+$ T cells, also known as cytotoxic T cells, are T cells that secrete various cytokines that participate in the immune response. They kill certain antigens, such as viruses and tumor cells, and are the main effector cells of tumor immune adoptive therapy [49]. The infiltration and activation of $CD8^+$ T cells critically affect the development and progression of a variety of tumors. However, the infiltrated $CD8^+$ T cells in most tumors are exhausted or their activation inhibited due to the influence of the tumor microenvironment [50]. Accordingly, strategies

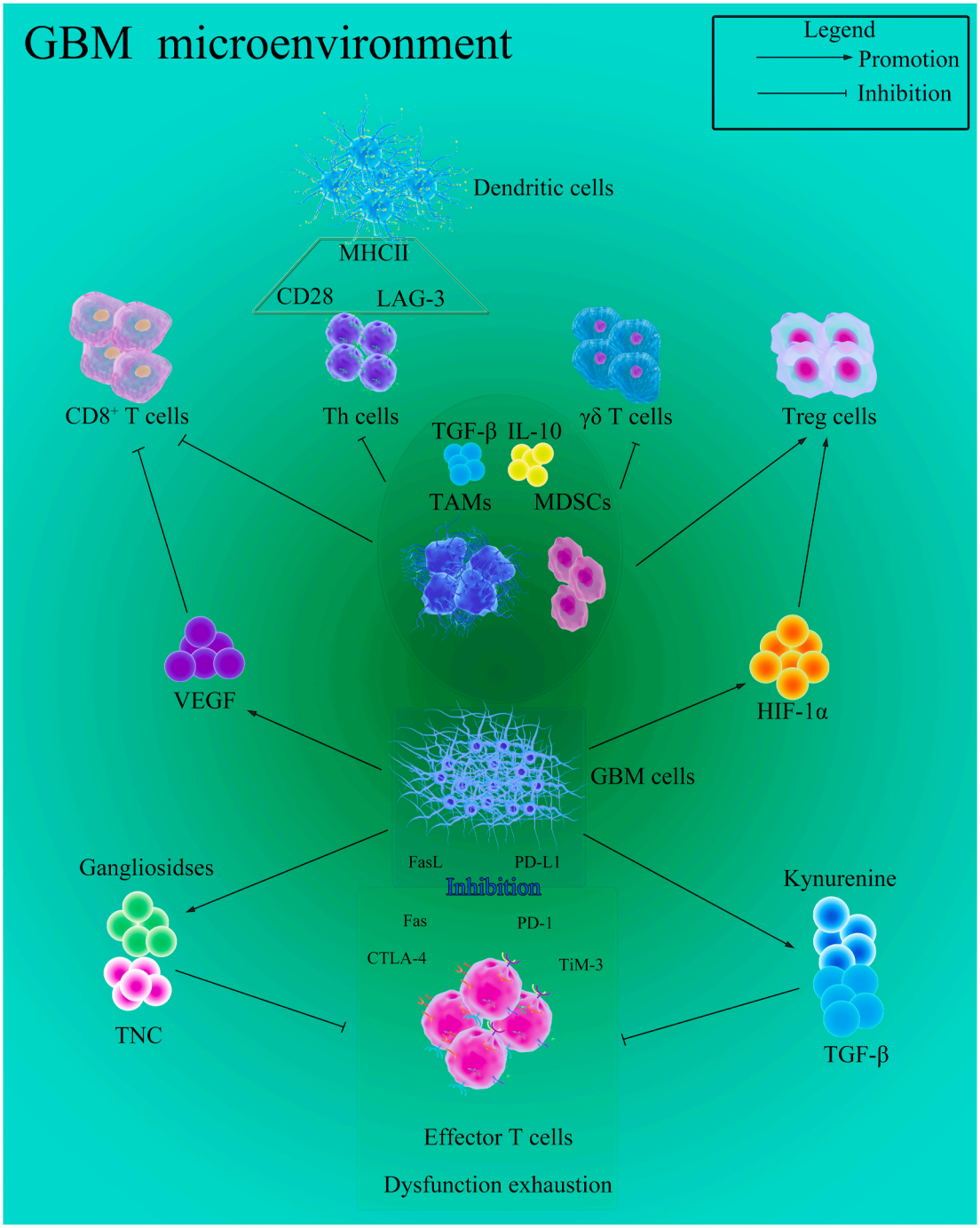

Fig. 1. Inhibition of different T-cell subsets in GBM microenvironment. In the GBM tumor microenvironment, GBM cells can inhibit the function of effector T cells by secreting inhibitory media such as VEGF, gangliosides, and kynurenine. In addition, GBM cells express a large number of immunosuppressive ligands on their surface, and their binding to effector T cell surface promotes the T cell dysfunction and exhaustion. GBM cell-derived HIF-1α can also suppress the T cell immune response by activating suppressor T cell Tregs. There are a large number of microglia and TAM in the GBM microenvironment, which can secrete a large number of immunosuppressive factors TGF and IL-10, which enhance the inhibitory effects on different subsets of effector T cells.

to facilitate tumor infiltration and overcome the functional inhibition of $CD8^+$ T cells are current research hotspots in GBM therapy.

Long-term survivors of GBM have more extensive infiltration of $CD8^+$ T cells in the tumor than in short-term survivors, proving that this infiltration correlates positively to the survival rate of GBM patients [51]. However, T cells exhaustion occurs due to various endogenous and exogenous factors in the GBM microenvironment, as discussed in detail above, that makes GBM difficult to treat. On the other hand, $CD8^+$ T cells infiltrating the GBM can be also activated by the endogenous microglia through the TLR2-MHC-I axis in the GBM microenvironment [52].

Currently, massive experimental studies have proven that the promotion of $CD8^+$ T cell activation is beneficial to alleviate the progress of GBM (**Table 2**). Sung et al. demonstrated that the excision of GBM tumor can substantially reduce MDSCs and increase the recruitment of $CD8^+$ T cells. Further, locally delivered IFN-β significantly enhanced the anti-GBM effect of the infiltrating $CD8^+$ T cells [53]. VEGF can promote the formation of tumor blood vessels and exacerbate tumor deterioration. It can also promote immunosuppression by inhibiting the function

Table 2
Therapeutic factors reverse the inhibitory status of different T-cell subtypes.

Therapeutic factors	Target cells	Effects	References
Anti-checkpoints	T cells	Activity↑	[44]
IFN-β	$CD8^+$ T cells	Anti-GBM↑	[53]
Anti-VEGF	$CD8^+$ T cells	Anti-GBM↑	[55].
TMZ	$CD8^+$ T cells	Proliferation↑	[57]
TK/Flt3L	$CD8^+$ T cells	Anti-GB↑	[59]
Ribosomal virus	$CD8^+$ T cells	Infiltration↑	[60]
IL-13Rα2	Th cells	Activity↑	[68]
anti-CD25	Tregs	knockout	[82]
PRF-P	Tregs	Infiltration↓	[83]
IL-21	γδ T cells	Activity↑	[90]
ZOL	γδ T cells	Activity↑	[91]
MDA	γδ T cells	Activity↑	[92]

↑ Promote ↓ Inhibit.

of DCs and the expression of inhibitory molecules on T cells to exacerbate tumor progression [54]. Malo et al. showed that the expression of costimulatory molecules B7-1, B7-2, and MHCII increased on DCs and the expression of PD-1 and Tim-3 on infiltrated $CD8^+$ T cells in the brain decreased after blocking VEGF in GBM mice. This observation indicates that anti-VEGF can upregulate DC function to promote the antitumor immunity of $CD8^+$ T cells, thereby inhibiting the growth of GBM [55]. A clinical trial for patients with recurrent GBM proved that specific adoptive transfer of cytomegalovirus (CMV) phosphoprotein 65 (pp65)-specific $CD8^+$ T cells has good clinical value, which prevents the recurrence of GBM and prolongs the survival time of patients. As a super potent antigen presenting cell, DCs have been widely used as antitumor vaccines. Elizabeth et al. demonstrated that the IFN-γ^+-, TNFα^+-, and CMV-specific $CD8^+$ T cells of patients with GBM receiving CMV-ATCT-DC vaccine significantly increased and was associated with the prolonged survival of GBM patients [56]. Serena et al. showed that intracranial injection of DC vaccine loaded with autologous GBM lysate, followed by temozolomide, promotes the proliferation of $CD8^+$ T cells but fails to generate a memory status. Thus, the failure to generate immune memory should be considered when developing improved treatments [57]. In the GBM microenvironment, myeloid-derived cells account for about 40% of tumor-infiltrated immune cells, which can express interleukin-4 receptor (IL-4R), inducible nitric oxide synthase (iNOS), arginase-1 (Arg-1), and PD-L1 to participate in the suppression of antigen-specific T cells [58]. Elimination of myeloid-derived cells strongly enhances the tumor-specific $CD8^+$ T cell response induced by TK/Flt3L gene therapy, thereby prolonging the survival rate of GBM patients [59]. Another studies also shown that injecting small ribosomal virus expressing an ovalbumin$_{257\text{-}264}$ antigen can enhance the ability of $CD8^+$ T cells to infiltrate in the brain and prolong the survival of GBM mice [60] **(Fig. 2).**

$CD8^+$ T cells, as the strongest antitumor T lymphoid cells, are often in a state of inhibition in tumor diseases, especially in GBM. Recent studies have shown that the activation of tumor-infiltrated $CD8^+$ T cells by DC vaccine or adoptive transfer of tumor antigen-specific $CD8^+$ T cells can alleviate tumor progression and prolong survival.

4.2. *Helper T (Th) cells*

Th cells, also known as $CD4^+$ T cells, express antigen receptors on

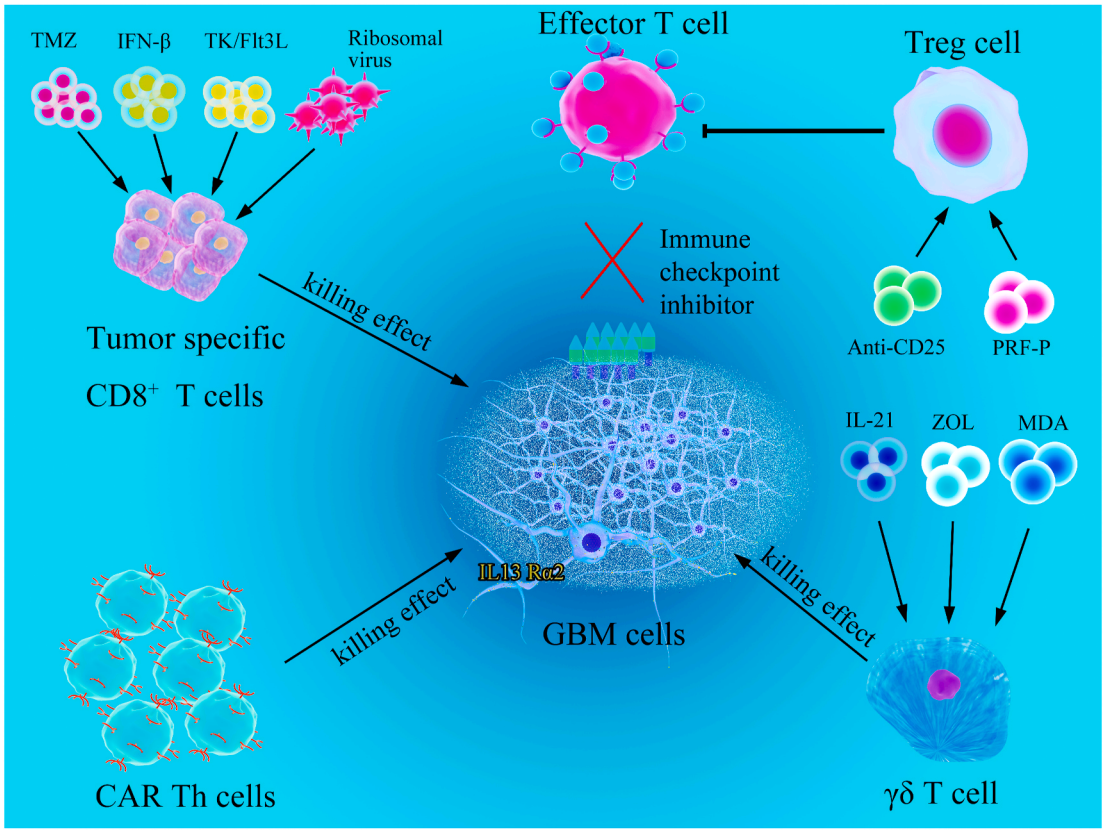

Fig. 2. Killing effects of different T-cell subsets to GBM. T cell-based GBM immunotherapy focuses on ways to restore the activity and function of the infiltrating T cells. Immune checkpoint inhibitors is currently the commonly used approach to restore the function of T cells in the tumor microenvironment and enhance antitumor immunity. Temozolomide, IFN-β, TK/Flt3, and ribosomal virus can promote the GBM tumor killing by activating potent antitumor $CD8^+$ T cells. IL-21, zoledronate, and minodronate act as powerful stimulants of γδ T cells, and greatly promote the anti-GBM effect of γδ T cells in the GBM microenvironment. In addition, CAR T cell therapy for IL-13Rα2 has achieved a good therapeutic effect in the treatment of GBM. Tregs, as an inhibitory T cell subset, play a significant role in suppressing the T cell immune response. Anti-CD25 and PRF-P blocking Tregs improve the activity of effector T cells in the GBM microenvironment.

their surface and can recognize the antigen fragments presented by MHC-II molecules. Once stimulated by antigen, Th cells proliferate and differentiate into active and memory Th cells. They are divided into Th1, Th2, Th17, and Thαβ helper cells [61]. In recent years, many studies have shown that Th cells play an important role in the occurrence and development of solid tumor diseases, including GBM.

In the GBM microenvironment, the dysfunction of Th cells and the imbalance of the Th1/Th2 ratio are important inducers of GBM progression. The expression of immunosuppressive molecules is one of the causes of Th cell dysfunction in the GBM microenvironment [62]. Brittany et al. showed that PD-1$^+$ Th cells are rich in tumors of GBM patients, which are unable to produce effector cytokines and proliferate, indicating the exhaustion of the Th cells infiltrating the GBM [63]. Daniel et al. also demonstrated that GBM-infiltrated granulocytic MDSCs (G-MDSCs) can inhibit the proliferation of Th cells and upregulate the expression of PD-1 on the affected Th cells to suppress immune response. In addition, lymphocyte-activation gene-3 (LAG-3), an inhibitory molecule expressed on the surface of Th cells, is homologous to the co-stimulatory molecules of Th cells and can compete to conjunct to MHC-II to promote the suppression of Th cells in the GBM microenvironment [64]. The balance between Th1 and Th2 cells is an important factor in tumor prognosis. In general, Th1 cells can kill tumors by secreting IFN-γ in the tumor microenvironment, and type 2 cytokines IL-4, IL-5, IL-10, and IL-13 derived from Th2 cells promote tumorigenesis [65]. There is a decrease in the levels of IL-12 and an increase in the levels of L-10 in the circulation of GBM patients, which reflects systematic immunosuppression [62]. Yasuo et al. also showed that the enrichment of Th1^{low} Th2^{low} and Th1^{high} Th2^{low} cells resulted in better prognosis than the increase in Th1^{high} Th2^{high} cells in GBM patients, suggesting that high levels of Th2 cells promote the development of GBM [66]. In addition, Shimato et al. demonstrated that Th cells have a significant Th1 bias in healthy people and a significant Th2 bias in GBM patients, especially in patients with recurrent GBM [67].

Currently, Th cell-based GBM treatment mainly includes chimeric antigen receptor T cell (CAR T) therapies and therapies that enhance the Th1 response. Interleukin-13 receptor α2 (IL-13Rα2) is highly expressed on tumor cells, but not so in normal cells, making IL-13Rα2-mediated fusion protein favorable for tumor-targeted therapy research [68]. Dongrui et al. proved that Th CAR T cell therapy against GBM IL-13Rα2 antigen has a long-lasting ability to fight GBM tumor cells. In addition, the maintenance of the CD4$^+$ T cell subpopulation is positively correlated with the recursive killing ability of CAR T cell products derived from GBM patients [69]. Steven et al. demonstrated that autologous DCs loaded with GBM tumor cell lysates can trigger a Th1 cell response against GBM tumor cells [70]. Th cell-based GBM treatment mainly reverses the imbalance status of Th1/Th2 cells. Recently, gene therapy has been widely used in tumor treatment [71]. Research to develop gene therapy vectors to deliver factors that promote Th1 cell induction should be pursued.

4.3. Tregs

Tregs are important in maintaining immune tolerance in the body. They are produced by the thymus and exported to the periphery. Tregs can inhibit the activation and proliferation of potential self-reactive T cells in a healthy body [72]. In tumors, Tregs, as immunosuppressive cells, promote tumor progression by suppressing antitumor immune responses, and are usually associated with poor tumor prognosis [73]. Recent studies have shown that a large number of Tregs infiltrate the GBM microenvironment, which promotes the immunosuppressive microenvironment of GBM [74].

GBM cells can promote the expression and expansion of Tregs through a variety of mechanisms. Studies have shown that the conditioned medium of GBM can promote the *in vitro* expansion of Tregs, suggesting a direct effect of GBM cell-related factors on Tregs [75]. Additionally, multiple indirect pathways promote the infiltration and expansion of Tregs in the GBM microenvironment. Hypoxia-inducible factor 1α (HIF-1α) is a metabolic converter for the glycolysis-driven migration and phosphorylation-driven immunosuppression of Tregs in GBM and promotes the migration of Tregs into the GBM microenvironment. HIF-1α deficiency has been shown to prevent the migration of Tregs, and significantly improve the survival rate of GBM model mice [76]. Inducible T-cell co-stimulator ligand (ICOSLG) is an immunomodulatory ligand of the B7 family, present in GBM. Bioinformatics analysis and GBM tissue microarray results indicated that upregulated ICOSLG expression is associated with poor prognosis of GBM patients. Knocking out ICOSLG significantly inhibits GBM growth with a reduction in IL-10 levels and Tregs, suggesting the inhibition of the ICOSLG-ICOS axis as a viable GBM immunotherapy strategy [77]. In addition, database analyses showed that the expression of lymphocyte-specific protein 1 (LSP1), an independent predictor of GBM progression, is upregulated in the GBM microenvironment. LSP1 expression is positively correlated with the infiltration of immunosuppressive cells, such as Tregs and MDSCs, in the GBM microenvironment [78]. Thus, LSP1 strengthens the GBM immunosuppressive environment by increasing the infiltration of Tregs. PD-L1, a ligand of the immunosuppressive molecule PD-1, is highly expressed in GBM cells. PD-L1 promotes the expansion of Tregs to maintain the immunosuppressive environment of GBM, and it is related to the decreased survival rate of GBM patients [75]. In addition, IDO-1$^+$ DCs can inhibit the antitumor immunity of effector T cells through the induction and recruitment of Tregs in draining lymph nodes [79]. CCL2, a chemokine of Tregs, is highly expressed in GBM the microenvironment, which could promote the infiltration of Tregs [80]. In addition to the traditional Foxp3$^+$ Tregs, Foxp3$^-$ type 1 Tregs (Tr1) also increase in the GBM microenvironment, and they have a strong ability to secrete IL-10 and TGF-β. GBM patients have high levels of Tr1 in peripheral blood compared with healthy controls, which is associated with the poor prognosis of GBM patients. Co-culture of Tr1 and CD4$^+$ T cells decreases the secretion of TGF-β-dependent IFN-γ and IL-10-dependent TNF-α, whereas co-culture of Tr1 with CD8$^+$ T cells reduces tumor-specific cytotoxicity [81].

Studies have shown that knocking out Tregs is beneficial for GBM relief, which makes the elimination of Tregs in GBM microenvironment the key to treating GBM. High-affinity IL-2R and CD25 are constitutively expressed on Tregs and thus, they have become the current therapeutic targets for knocking out Tregs. Anti-CD25 injection can prolong the survival rate of GBM mice [82]. In addition, Wojciech et al. proved that platelet-rich fibrin patch (PRF-P)-treated GL261 tumor-bearing mice could eliminate immunosuppressive Tregs. GL261 cells or CCL2/22 co-culture with PRF-P can eliminate the migration of Tregs, and CCL2/22 receptor pharmacological blockade can enhance the inhibition ability of PRF-P on Treg recruitment [83]. PRF-P can be used as a personalized Treg-selective inhibition platform to supplement and enhance the therapeutic effect of GBM (**Fig. 2**). In conclusion, Treg-based GBM treatment should follow the principle of reducing Treg induction and peripheral recruitment. This can be done by reducing the number of Tregs in the GBM microenvironment, which will relieve the inhibition of effector T cells, thereby increasing their antitumor ability.

4.4. γδ T cells

γδT cells are innate lymphocytes with the receptor TCRγδ expressed on their surface. TCRγδ can directly recognize and bind antigens without recognizing MHC molecules and the helper APCs. Moreover, the structure of γδ T cells is similar to that of immunoglobulin and antibody-TCR, and has the potential to recognize multiple antigens [84]. Thus, they play an important role in antitumor immunity. γδ T cells mainly participate in antitumor effects through cytotoxic effects [85]. Mice lacking γδ T cells are highly susceptible to skin cancer [86], and prostate cancer [87].

Recent studies have shown that γδ T cells, which increase in the tumor tissues and peripheral blood of GBM patients, regulate the

development of GBM [88]. Human allogeneic Vγ9Vδ2 T lymphocytes, the main subset of γδ T cells, have a cytotoxic effect on primary human GBM cells. This process is mediated by the γδ TCR and is regulated by the stress-related NKG2D pathway [89]. IL-21, a sensitizing factor of Vγ9Vδ2 T cells, can regulate the cytolytic response of Vγ9Vδ2 T cells. GBM cells are eliminated by allogeneic human γδ T cells through intracellular granzyme-mediated cytotoxicity, and the adoptive transfer of IL-21-sensitized γδ T cells can significantly eliminate GBM cells and prolong the survival rate of GBM mice [90]. In addition, zoledronate, an inhibitor of osteoclast activity, is thought to stimulate peripherally derived γδ T cells and sensitize tumors to γδ T cell-mediated killing. This has been demonstrated in GBM cells, where the enhanced killing effect could be blocked by anti-TCR [91]. Minodronate, a third-generation nitrogen-containing bisphosphonate, can cooperate with human γδ T cells to exert antitumor effects and play a direct and γδ T cell-mediated killing of many tumors, including GBM [92] **(Fig. 2).**

γδ T cells can widely recognize and immediately respond to a variety of MHC-like stressed autoantigens, many of which are expressed on GBM [93]. Due to the poor immunogenicity and high heterogeneity of GBM, common adaptive immune response effector T cells are difficult to recognize and kill GBM cells. Considering that γδ T cells do not need to recognize MHC molecules and rely on their unique TCRγδ, these cells can efficiently recognize some hidden antigens and kill the tumor cells [94]. Therefore, *in vitro* activation of γδ T cells and their transfer to GBM patients can be explored as a γδ T cell-based GBM therapy. In addition, development of drugs that can activate GBM-infiltrated γδ T cells and promote their function and expansion can be considered for targeting GBM cells. In short, increasing the number of γδ T cells and enhancing their function in the GBM microenvironment are key to γδ T cell-based GBM therapy.

5. Conclusions and future prospects

GBM is a malignant and highly lethal brain tumor. Traditional treatments have failed to effectively prolong the survival rate of GBM patients. The development of immunotherapy in recent years has ignited hope for the treatment of GBM [8]. However, the high heterogeneity and immunosuppressive microenvironment of GBM pose great challenges to immunotherapy. Therefore, understanding the role of different subsets of T cells in the GBM microenvironment is essential to improve the efficiency of GBM immunotherapy. A large number of immunosuppressive cells (such as Tregs, MDSCs, and TAM) infiltrating in the GBM microenvironment, upregulate multiple immune checkpoints (such as PD-1, Tim-3, CTLA-4, and IDO-1), and immunosuppressive ligands (such as PD-L1, on GBM cells and tumor-infiltrating myeloid cells) and conceal GBM tumor antigen. These factors contribute to the immunosuppressive environment of GBM and the dysfunction and proliferation inhibition of infiltrating T cells [23]. Therefore, eliminating or reducing the infiltration of immunosuppressive cells, and increasing the number and activity of effector T cells is the key to the success of GBM immunotherapy. Reintroducing GBM-specific antitumor effect T cells is indeed a good therapeutic strategy [95]. However, it is worth noting that the presence of BBB hinders the entry of tumor-killing cells into the GBM tumor area. Therefore, amplifying the infiltrated tumor-killing cells in the GBM microenvironment may be a promising method to improve GBM immunotherapy. Studies have shown that IL-12 delivered by viral vectors can effectively enhance the function of GBM-killing T cells in the GBM microenvironment [96]. Furthermore, Reversing the balance of M1/M2 and Th1/Th2 cells is another promising therapeutic strategy. GBM-infiltrated M2 and Th2 cells greatly promote the GBM immunosuppressive environment and are related to poor prognosis [97]. The use of gene therapy vectors to carry effective factors to transform M2 and Th2 cells into antitumor M1 and Th1 cells can hit two birds with one stone. Another challenge in development of GBM immunotherapy is its concealed tumor antigens. The release of GBM tumor antigens will activate the killing effect of tumor-killing T cells in the GBM environment, and that will greatly promote the effect of GBM immunotherapy. Oncolytic virus can destroy GBM tumors and release tumor antigens, and have been used in the treatment of GBM [96,98]. Further, considering the highly immunosuppressive microenvironment of GBM, T-cell-based GBM immunotherapy can be supplemented with a combination of immune checkpoints inhibitors with the delivery of cytokines that activate tumor-killing T cells. Studies have shown that the treatment effect of combination therapy is far better than monotherapy in the immunotherapy of GBM. In short, alleviating the immunosuppressive environment, activating tumor-killing cells in the tumor microenvironment, and releasing tumor antigens are the most promising immunotherapeutic strategies for GBM treatment, and combining the two or three strategies will inhibit the growth of GBM tumor and improve the treatment effect to the greatest extent.

Authors' contributions

HSW and HGZ wrote the manuscript. JNX, YPL, JXY, HC and JZ revised the manuscript. YZY, XCZ, SY and YQW draw the figures and modified the language. JW designed the study, drafted and wrote the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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