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REVIEW

The Immunosuppressive Microenvironment of Glioblastoma: Mechanisms, Clinical Challenges and Future Directions

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ABSTRACT

Glioblastoma (GBM) remains highly lethal due to intrinsic and extrinsic mechanisms, of which the immunosuppressive tumour microenvironment (TME) collectively limits treatment efficacy. This review synthesises recent advances in understanding how metabolic reprogramming, epigenetic remodelling and immune cell dysfunction converge to establish a stable immunosuppressive network dominated by tumour-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells and exhausted T cells. We further summarise emerging therapeutic strategies, including myeloid-targeting agents, epigenetic modulators, metabolic inhibitors and combination immunotherapy, and discuss their clinical potential in overcoming GBM immune resistance. These insights provide a mechanistic and translational framework for developing next-generation multimodal treatment approaches.

1 | Introduction

In the central nervous system (CNS), adult-type diffuse gliomas are categorised into three groups: astrocytoma (isocitrate dehydrogenase [IDH]-mutant, Grades 2–4), oligodendroglioma (IDH-mutant with 1p/19q co-deletion, Grades 2–3) and glioblastoma (GBM, IDH-wildtype, Grade 4) [1], of which GBM is characterised by rapid progression, genetic heterogeneity and resistance to conventional therapies. GBM accounts for approximately 46.6% of CNS malignancies, with an annual incidence of 3.19 per 100 000 population [2]. Intertumoral heterogeneity of GBM can be broadly classified into three major molecular subtypes: proneural, classical, and mesenchymal according to their distinct biological properties [3]. The proneural subtype is characterised by platelet-derived growth factor receptor-alpha (PDGFRA) alterations, isocitrate dehydrogenase (IDH) mutations in a subset and a more differentiated neural-like transcriptional programme. The classical subtype is characterised by epidermal growth factor receptor (EGFR) amplification and chromosome 7 gain/10 loss, displaying a highly proliferative phenotype. In contrast, the mesenchymal subtype is marked as neurofibromin 1 (NF1) loss, robust inflammatory and stromal signatures and the most immunosuppressive tumour microenvironment (TME) enriched in tumour-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs).

Standard treatment of GBM involves maximal surgical resection followed by chemoradiotherapy, such as the Stupp regimen, which combines temozolomide (TMZ) with radiotherapy. During the concurrent phase, TMZ is administered at 75 mg/m^2/day for 42 days, followed by a 4-week interval before transitioning to the adjuvant phase. In the adjuvant phase, TMZ

is given orally at 150–200 mg/m^2/day for 5 days per 28-day cycle, repeated for six cycles [4]. However, TMZ resistance is a major limitation, affecting approximately 50% of patients and significantly compromising therapeutic efficacy. Despite this multimodal approach, patient prognosis remains dismal, with a median survival of 12–15 months, a high recurrence rate (approximately 75% of patients relapse within 6.9 months), and only 25% surviving beyond 2 years [2].

GBM resistance to TMZ arises from a multilayered molecular regulatory network. In intrinsic GBM cells, recurrent studies have demonstrated that endoplasmic reticulum stress activates the PKR-like endoplasmic reticulum kinase (PERK)/PERK-eukaryotic translation initiation factor 2α (eIF2α)/activating transcription factor 4 (ATF4) signalling axis and increases sphingosine kinase 1 (SPHK1) expression to promote epithelial–mesenchymal transition and invasive phenotypes, resulting in TMZ resistance [5]. Inositol 1,4,5-triphosphate (IP3) kinase B (ITPKB) undergoes reduce TRIM25-mediated ubiquitination to suppress reactive oxygen species (ROS) generation and enhance drug resistance [6]. Additionally, eukaryotic translation initiation factor 4A3 (EIF4A3)-driven circular RNA circASAP1 exacerbates TMZ resistance by sponging miR-502-5p [7], thereby relieving its suppression of neuroblastoma Ras (NRAS), and silencing circASAP1 significantly enhances therapeutic efficacy in vivo. Another intrinsic mechanism relates to TMZ pharmacodynamics; TMZ has been shown to increase the protein expression of the drug efflux transporter ABCC1 and ABCA1 [8, 9]. Furthermore, polymerase I and transcript release factor (PTRF)/Cavin-1 accelerates TMZ clearance by promoting extracellular vesicle (EV)-mediated drug efflux [10].

Glioblastoma stem cells (GSCs), characterised by enhanced DNA damage tolerance, efficient activation of DNA repair pathways and a predominantly quiescent state, also represent a major driver of TMZ resistance and tumour relapse. GSCs exhibit metabolic and epigenetic plasticity, maintain high expression of stemness-associated transcription factors (e.g., SOX2, OCT4), and resist apoptosis through upregulation of anti-apoptotic signalling [9]. These properties enable GSCs to survive chemoradiation, repopulate the tumour mass, and contribute to the inevitable recurrence observed in GBM patients.

Besides, increasing studies have illustrated that a highly TME enriched with tumour-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs) and exhausted T cells is another vital factor in GBM resistance. For instance, immunosuppressive molecules in the TME prevent the activated T cells from crossing the blood–brain barrier (BBB). Therefore, this review specifically highlights two emerging and under-recognised themes: (i) the epigenetic–metabolic crosstalk that stabilises immunosuppressive transcriptional programmes across TAMs, MDSCs and Treg populations, and (ii) the spatial heterogeneity of immunosuppression shaped by uneven metabolic stress, differential vascular permeability and localised cytokine gradients within the tumour mass. These concepts, taken together, provide a more coherent explanation of how GBM maintains a highly resistant and self-reinforcing immune ecosystem, offering a refined lens for understanding therapeutic failure and guiding future treatment strategies.

2 | Immunosuppressive Mechanisms in the Glioblastoma TME: Metabolism–Epigenetic–Immune Network

The TME of GBM maintains an immunosuppressive state through multidimensional mechanisms including the following key aspects (Figure 1, Table 1).

2.1 | Molecular Subtype–Driven Immune Heterogeneity in GBM

Glioblastoma subtypes exhibit profoundly different immune landscapes, which have important implications for targeted immunotherapies. The seminal transcriptional classification by Verhaak et al. defined GBM as proneural, classical and mesenchymal, each displaying unique patterns of immune infiltration and cytokine signalling [3]. Subsequent work from Wang et al. and Mao et al. further demonstrated that the mesenchymal subtype is enriched in inflammatory and myeloid signatures, including high TAM/MDSC abundance and robust NF-κB–driven immune suppression [18, 19]. In contrast, the proneural subtype typically shows a more limited immune infiltrate and lower baseline inflammation, while the classical subtype exhibits intermediate immune activity dominated by EGFR-associated pathways.

These subtype-specific immune ecosystems critically affect therapeutic vulnerabilities. Mesenchymal tumours show the most significant resistance to immune checkpoint blockade due to myeloid suppression [20]. In contrast, proneural tumours may be more amenable to T-cell-based strategies in combination with microenvironmental modulation. Recognising and integrating these differences are essential for designing rational, subtype-tailored immunotherapies in GBM.

2.2 | Metabolic Reprogramming as the Driving Layer

TAMs, MDSCs and Tregs reprogramme their energy metabolism pathways within the TME—including glycolysis, lactate accumulation, and fatty acid metabolism—to adapt to hypoxic and nutrient-restricted conditions [21, 22]. For instance, accumulated lactate promotes the M2 polarisation of TAMs, results in enhanced secretion of IL-10 and TGF-β, and reinforces immunosuppressive phenotypes [11, 12]. MDSCs in IDH-mutant GBM enhance glycolysis and produce excessive IL1β, thereby reinforcing the inhibitory effects on M2-macrophages and myeloid-derived suppressor cells [13]. Moreover, Kloosterman et al. demonstrated that metabolically rewired TAMs, specialised as lipid-laden macrophages, directly transfered myelin-derived lipids to tumour cells and promoted GBM progression [23]. Specifically, Freitas-Cortez et al. revealed the fatty acid-binding protein 7 (Fabp7) reprogrammes lipid metabolism of CD8$^+$ T cells to promote immunotherapy resistance [16].

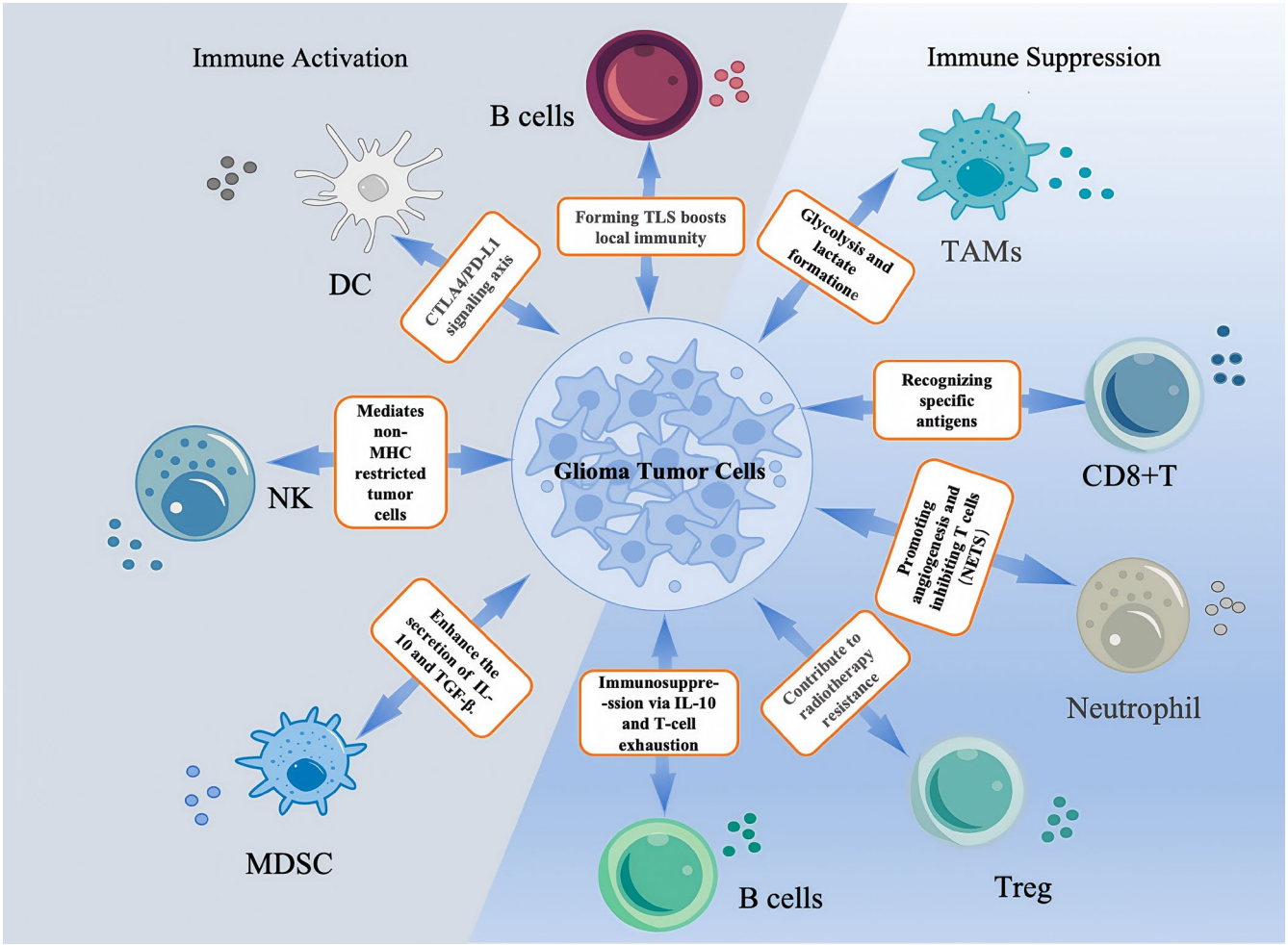

FIGURE 1 | Immune activation and suppression within the GBM microenvironment. Glioma tumour cells orchestrate a dynamic balance between immune activation and suppression. Interactions between glioma cells and immune populations—including TAMs, MDSCs, exhausted $CD8^+$ T cells, Tregs, DCs and natural killer (NK) cells—are bidirectional. On the activation side, dendritic cells (DCs) and neutrophils can promote antitumour responses through antigen presentation and the formation of neutrophil extracellular traps (NETs), while NK cells contribute to immune-mediated cytotoxicity. Conversely, glioma cells exploit multiple immunosuppressive mechanisms: TAMs undergo glycolytic reprogramming and secrete IL-10/TGF-β; MDSCs enhance PD-L1–mediated signalling; regulatory $CD4^+$ T cells suppress effector responses; $CD8^+$ T cells become exhausted despite recognising tumour-specific antigens and B cells can both boost local immunity and facilitate immune evasion through tertiary lymphoid structures (TLS).

2.3 | Epigenetic and Non-Coding RNA Regulation as the Amplification Layer

Epigenetic dysregulation represents a central driver of GBM evolution and the formation of an immunosuppressive niche. Histone deacetylases (HDAC) are profoundly deregulated across nearly all GBM subtypes, with multiple HDAC isoforms overexpressed, contributing to chromatin condensation, the repression of immune-stimulatory genes and the promotion of TAM/MDSC-supportive cytokine programmes. Wu et al. demonstrated that activation of the HDAC6/RBP/LINC00461 axis promoted GBM resistance [24]. Yang et al. further illustrated that HDAC1/2/6 promoted self-renewal of malignancy by regulating DNA repair transcription [25]. Similarly, Hanisch et al. revealed that HDAC1/2/3 enhanced the expression of the E3 ubiquitin ligase RAD18 to promote the bypass of O6-methylguanine DNA lesions [26]. Moreover, HDAC7 dysregulation in the H3K27ac-SOX8/JUN-LGALS3-ITGB1 axis facilitated the transformation of the mesenchymal phenotype of GBM and the M2 polarisation of monocyte-driven macrophages [27].

Beyond HDAC activity, DNA methylation, chromatin remodelling complexes, histone methylation and non-coding RNAs collectively orchestrate wide-ranging transcriptional reprogramming in glioma cells and infiltrating immune cells. These epigenetic alterations support stemness, enhance metabolic adaptability and promote immune evasion [28]. Dong et al. demonstrated that transcriptional condensation enhanced the activity of protein arginine methyltransferases (PRMT2) during GBM progression [29]. CircNEIL3 is transferred via exosomes to TAMs, where it stabilises IGF2BP3 protein and drives the expression of immunosuppressive genes [30]. Similarly, Yin et al. demonstrated the tumour-suppressor-like activity of microglia specialised by shifting cytosolic DNA sensing via the cGAS-STING-dependent pathway [31].

TABLE 1 | Key immune cells in the glioblastoma microenvironment.

Immune cell type	Main function	Immune mechanism
TAMs	Promote immunosuppression and angiogenesis	Secrete IL-10 and TGF-β to inhibit immune response; promote M2 polarisation to enhance tumour growth [11, 12]
MDSCs	Inhibit immune	Release IL-1β to reinforce the inhibitory effects on M2-macrophages and myeloid-derived suppressor cells [13]
Tregs	Suppress immune response and maintain immune tolerance	Release inhibitory cytokines (IL-10, TGF-β); directly suppress effector T cells; recruit other immunosuppressive cells [14]
Exhausted T cells	Reduce anti-tumour activity	Express inhibitory receptors (PD-1, CTLA-4); impaire cytokine production and cytotoxicity functions [15]
$CD8^+$ T lymphocytes	Eliminate cancer cells through the recognition and destruction of infected or malignant cells	Recognise tumour-specific antigens presented on MHC class I molecules, leading to the activation and cytotoxic response against cancer cells, though their function can be inhibited by immune checkpoints such as PD-1 within the tumour microenvironment [16]
Neutrophils	Tumour-promoting or tumour-suppressing roles depending on microenvironment signals	Release exosomes containing enzymes and cytokines; induce oxidative stress to suppress T-cell function [17]

Abbreviations: MDSCs, myeloid-derived suppressor cells; TAMs, tumour-associated macrophages; Tregs, regulatory T cells.

2.4 | Dynamic Crosstalk Among Immunosuppressive Cell Population

Except for TAMs, MDSCs and Tregs, other immune cell populations, including Dendritic cells (DCs), natural killer (NK) cells, and B cells, contribute to the immunological landscape of GBM.

DCs, specialised by antigens, exert the initiation and regulatory effects in GBM. DCs are commonly grouped into conventional DCs (cDCs) and plasmacytoid DCs (pDCs). cDCs generally prime neoantigen-specific $CD8^+$ T-cell responses against GBM [32], whereas pDCs often remain in an immature or tolerogenic state due to tumour-derived IL-10, CCL21, and metabolic suppression, resulting in suppressed $CD8^+$ T-cell priming ability [33]. NK cells can mediate cytotoxicity, which are frequently functionally inhibited in the GBM microenvironment through metabolic suppression, cytokine signalling (e.g., IL-10, TGF-β), and downregulation of activating ligands. However, Mathewson et al. demonstrated that NK cells exhibited context-dependent functions in GBM. Their study revealed that tumour-infiltrating T cells induced CD161 expression on NK cells, thereby suppressing T-cell-mediated killing of GBM cells [34].

Although neutrophil extracellular traps (NETs) are traditionally associated with antimicrobial immune activation and promote DCs recruitment or antigen exposure in inflammatory settings, their role in GBM is largely immunosuppressive. Jain et al. revealed that NETs released by intertumoral neutrophils enhance angiogenesis, remodeled the extracellular matrix and suppressed T-cell cytotoxicity through ROS production and protease release [17].

B cells exhibit double-edged-sword functions in GBM. Within tertiary lymphoid structures (TLS), B cells can participate in antigen presentation, antibody generation and local priming of T cells, thereby contributing to anti-tumour immune response (ATIR) surveillance [35, 36]. However, evidence suggests that TGF-β secreted from various cells in the TME mediates B-cell suppression of $CD8^+$ T-cell responses [37]. Thus, B cells in GBM should be understood as a heterogeneous compartment with both immunostimulatory and immunosuppressive effects, depending on local cytokine landscapes, metabolic restriction, and tumour-driven phenotypic reprogramming.

Within this metabolism–epigenetic framework, TAMs, MDSCs, and Tregs engage in continuous molecular and cellular interactions that maintain a highly suppressive milieu: metabolic signals serve not only as sources of inhibitory factors but also as signalling molecules that regulate immune cell fate, establishing a metabolism-driven foundation for immunosuppression. IL-10, TGF-β, and ROS can induce the overexpression of immune checkpoint molecules including PD-1 and CTLA-4 on T cells, leading to T-cell exhaustion and significantly weakening ATIR [14, 38–40]. Additionally, IL-8, secreted by tumour cells, MDSCs, and $CD8^+$ T cells, recruits MDSCs via the CXCR1/CXCR2 axis to induce angiogenesis and upregulate PD-1 and TIM-3 [41].

2.5 | Other Mechanisms

Stem cell-related mechanisms represent a critical layer of GBM resistance, in which glioblastoma stem cells (GSCs) undergo profound transcriptional and epigenetic reprogramming in response to inflammatory cues, hypoxia, therapeutic stress, and immune cells. This reprogrammed state—characterised by enhanced DNA repair, metabolic plasticity, and upregulation of immunomodulatory mediators—enables GSCs to resist cytotoxicity and shape an immune-tolerant niche [28, 42, 43]. Intrinsically, pathways including YBX1-SOX2, PRMT6-RCC1, and IGFBP5-ROR1-CREB induce GSCs proliferation and invasion [44–46]; VASN, CLOCK-BMAL1, and PHGDH promote self-renewal [47–49], while KAT5 and synapsin III accelerate the neural-like transdifferentiation of GSCs [50, 51]. Extrinsically, GSCs are well investigated for their interaction with TAMs, microglia, T cells, NK cells, and endothelial cells. On one hand, LGALS3 from GSCs and monocyte-derived macrophages mediated crosstalk among them to stimulate a mesenchymal-like state of GBM [27]. CXCL8, TNFAIP6, LOXL2, and TGF-β preferentially secreted by mesenchymal GSCs bound to the receptors, including CXCR2 and EGFR in TAMs to induce M2-like TAM phenotype [52–55]. Except for TAM, overexpression of ICAM1 in GSCs stimulated PD-L1/PD-1 interaction to induce cytotoxic $CD8^+$ T-cell population [56]. Secretion of GAL3 by GSCs bound to LAG3 to drive T-cell exhaustion [57]. Furthermore, Shaim et al. demonstrated that GSCs suppressed NK cell immune evasion through the αV integrin/TGF-β axis [58]. Chen et al. revealed that GSCs secreted histamine to activate endothelial cells [59]. While, Wang et al. and Pang et al. illustrated that POSTN and TFPI2 secreted by GSCs recruited microglia via CD70 or CD51 to induce an immunosuppressive tumour microenvironment [60, 61]. On the other hand, TGF-β, secreted by TAMs, promote the maintenance of GSCs via the αVβ5-Src-Stat3 axis [62]. TAM-secreted GPNMB interacted with CD44 on GSCs to promote their glycolytic and self-renewal abilities [63]. The literature supports the bidirectional interaction between GSCs and TME in GBM resistance (Figure 2).

Beyond GSCs, other stem cell populations also contribute to the IME. Haematopoietic stem cells (HSCs) can infiltrate the tumour bed and differentiate into immunoregulatory myeloid subsets, reinforcing TAM and MDSC dominance [64]. Mesenchymal stem/stromal cells (MSCs) recruited from peripheral tissues or the bone marrow induce PD-L1 upregulation in glioma cells and neovascularization to support tumour progression [65]. Together, these stem cell-driven processes amplify immune evasion by promoting a long-lived, therapy-resistant cellular reservoir and sustaining an immunosuppressive TME that limits effective antitumor immunity.

Recent transcriptomic analyses in immunocompetent mouse models have further expanded the understanding of immunosuppressive programmes active in GBM. Garcia-Vicente et al. identified robust upregulation of myeloid-associated suppressive genes (e.g., *Arg1*, *Il-10,* and *Tgfb1*), attenuation of interferon-response, enhanced expression of T-cell exhaustion markers (Pdcd1, Lag3, and Havcr2), and cytokine/chemokine circuits (CCL2, CXCL1, and IL-8) that amplify neutrophil recruitment and myeloid dominance [66]. Other studies have demonstrated that GBM cells can evade immune recognition by downregulating MHC molecule expression, thereby reducing antigen presentation and limiting T-cell activation [67]. Moreover, the gut microbiota may influence the immune status of TME through systemic immune modulation, though its role in GBM remains to be further explored [68]. Exosomes and extracellular vesicles may also contribute to immunosuppression by transferring immunosuppressive signalling molecules, such as PD-L1, to immune cells, thereby enhancing immune evasion within the TME [69]. Integrating this preclinical evidence with human GBM data helps refine target selection for immunotherapy development.

3 | Clinical Challenges in Treating Glioblastoma

Current GBM treatment strategies involve maximal safe surgical resection, followed by radiotherapy and TMZ chemotherapy. Despite aggressive treatment, the median survival remains only 12–15 months due to high recurrence rates and treatment resistance [70].

Immunotherapy approaches, including PD-1/PD-L1 inhibitors and CAR-T cell therapy, have shown limited efficacy due to multiple factors. On one hand, the BBB impedes immune cell infiltration, further hampering immunotherapy efforts [71, 72]. On the other hand, regulatory immune populations—particularly TAMs, MDSCs, and Tregs—collectively dominate the GBM microenvironment and suppress cytotoxic T-cell activity through cytokine-mediated inhibition, metabolic competition, and checkpoint ligand expression [73].

To overwhelm BBB, several approaches, including focused ultrasound combined with microbubbles, osmotic opening with mannitol, radiotherapy- or chemotherapy-induced endothelial modulation and vascular-targeted agents, are being explored to transiently increase BBB permeability and thereby enhance immune cell trafficking [74, 75]. These strategies can facilitate the entry of cytotoxic lymphocytes, monoclonal antibodies, and cellular therapies into the tumour bed. However, BBB disruption is a double-edged sword: excessive or prolonged opening may lead to vasogenic edema, intracranial haemorrhage, neurocognitive toxicity and treatment-related pseudoprogression, all of which complicate clinical management and response assessment. Therefore, emerging concepts emphasise controlled and reversible BBB modulation, coupled with real-time imaging, careful dosing schedules and the use of 'vascular normalisation' rather than indiscriminate barrier breakdown. Such balanced strategies aim to widen the therapeutic window—allowing sufficient immune and drug infiltration to achieve anti-tumour effects, while minimising neurological complications and preserving critical neurovascular function.

Furthermore, recent clinical trials targeting TAMs or immune checkpoints in GBM have shown promising results. The phase II/III NRG-BN007 trial compared radiotherapy with TMZ versus radiotherapy with immunotherapy in newly diagnosed MGMT-unmethylated GBM, aiming to determine whether dual immune checkpoint blockade could improve outcomes compared with standard therapy. Notably, NCT04396860 is evaluating whether the CSF-1R inhibitor could reprogramme TAMs, while NCT03493932 is investigating the combinational effect of PD-1 and LAG-3 blockade in recurrent GBM. These trials highlight a growing clinical shift towards modulating myeloid

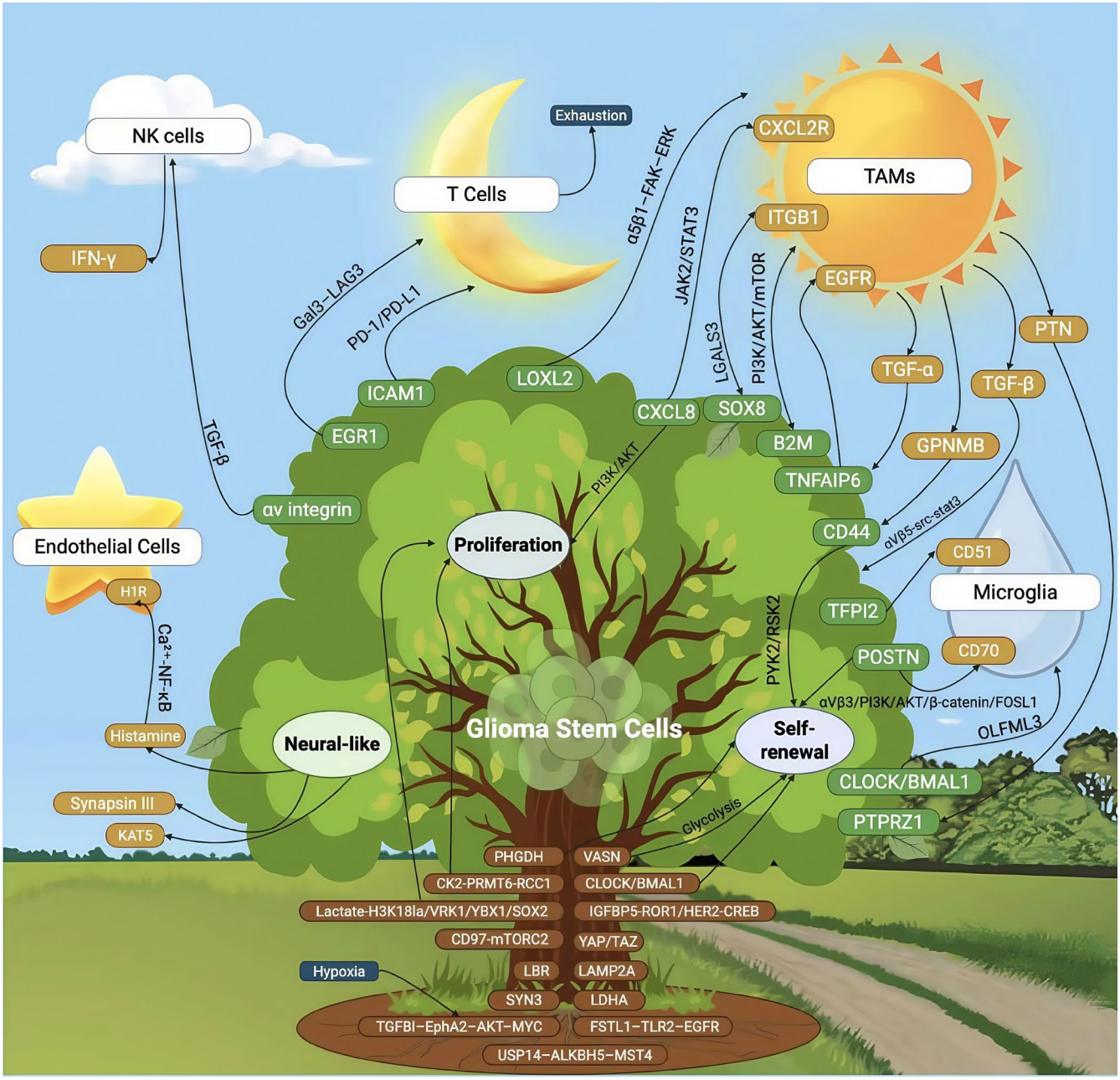

FIGURE 2 | Immune activation and suppression on glioblastoma stem cells (GSCs). GSCs undergo profound transcriptional and epigenetic reprogramming in response to inflammatory cues, hypoxia, therapeutic stress, and immune cells to resist cytotoxicity and shape an immune-tolerant niche.

and checkpoint pathways to overcome immune resistance. In addition, biomarker-guided treatment is becoming increasingly important in GBM. Established markers, such as MGMT promoter methylation, IDH mutation status, and emerging TME-based immune signatures, are applied to stratify patients and predict responsiveness to immunotherapy or myeloid-targeting approaches. Such stratification may enhance the translational impact of future GBM immunotherapies.

4 | Future Therapeutic Strategies

Future therapeutic strategies for GBM focus on overcoming the tumour's highly IME to improve treatment efficacy. Targeting key mechanisms such as immune checkpoint pathways, metabolic and epigenetic modulation, and cytokine signalling is a promising strategy to reprogramme the tumour microenvironment, enhance immune cell activation, and restore ATIR (Figure 3, Table 2) [82].

4.1 | Checkpoint Inhibitors for PD-1 and CTLA-4 on Exhausted T Cells

Checkpoint inhibitors targeting PD-1 and CTLA-4 on exhausted T cells offer a valuable tactic to reactivate immune responses in the GBM microenvironment. Anti-PD-1 antibodies, such as pembrolizumab and nivolumab, can restore T-cell activity and

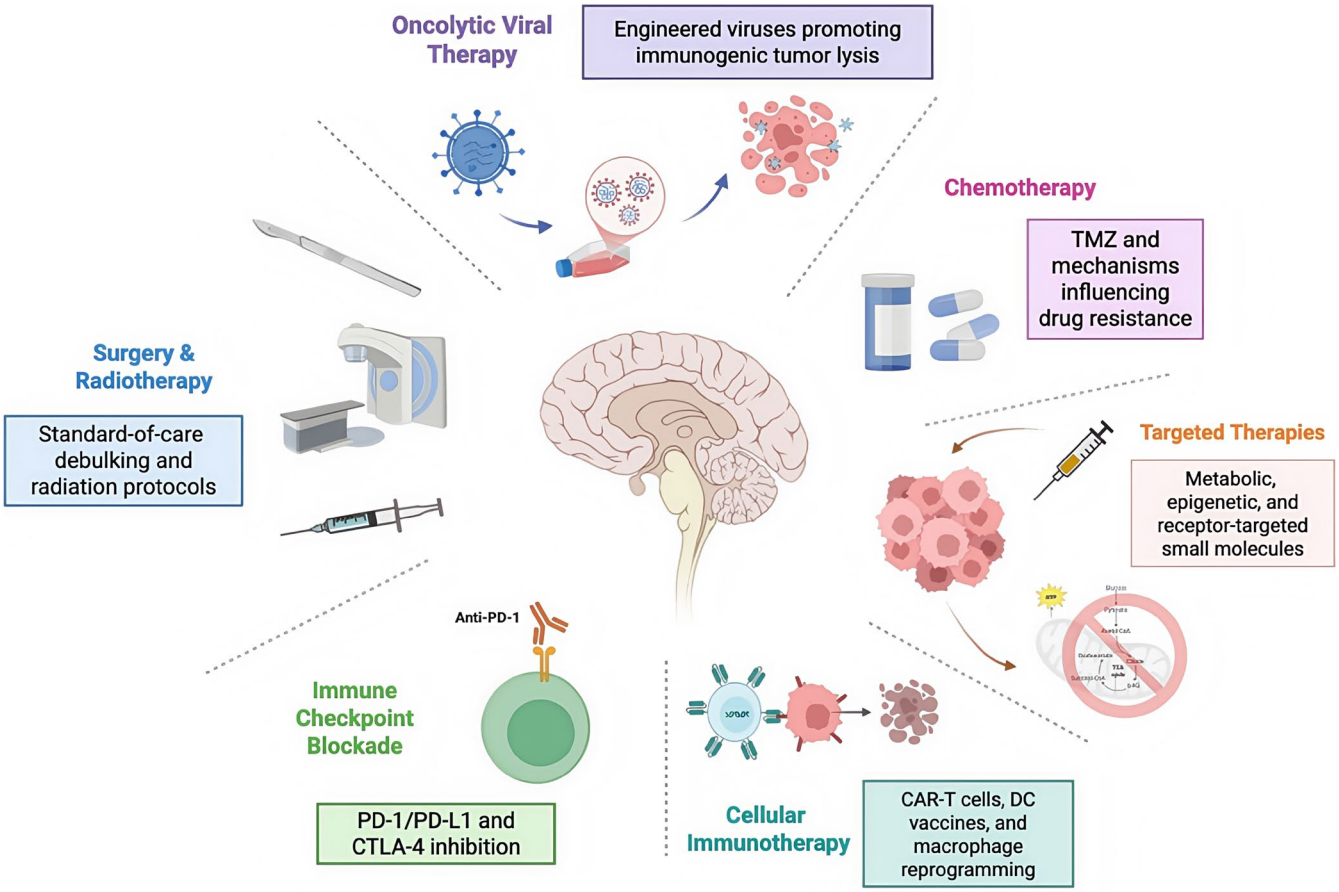

FIGURE 3 | Current therapeutic strategies for GBM. To overcome the tumour's highly IME is a potential strategy to improve treatment efficacy through targeting key mechanisms such as immune checkpoint pathways, metabolic and epigenetic modulation, and cytokine signalling. Those treatments include oncolytic viral therapy with engineered viruses, chemotherapy and immune checkpoint blockade.

enhance ATIR. Additionally, the combination of CTLA-4 (e.g., ipilimumab) and PD-1 inhibitors boosts immune activation by countering multiple immune suppression mechanisms within the TME [83, 84]. This dual-targeted strategy is possible for overcoming the immunosuppressive barriers in GBM and re-energising exhausted T cells.

4.2 | Targeting Glycolysis and Epigenetic Regulation in TAMs and MDSCs

In peripheral blood, granulocytic MDSCs directly suppress T-cell proliferation, whereas tumour-infiltrating MDSCs upregulate PD-L1, thereby inducing PD-1 expression on T cells and indirectly leading to T-cell exhaustion [85]. Additionally, glycolysis is a critical pathway supporting the immunosuppressive functions of TAMs and MDSCs. Therefore, targeting glycolysis in TAMs and MDSCs offers a potential approach to mitigate immunosuppression in the GBM microenvironment. As it is mentioned in Zarychta's study, applying glycolysis inhibitors like 2-deoxy-D-glucose (2-DG) to GBM therapy significantly decreased the ATP production and G0/G1 cell cycle arrest, thereby creating a more favourable environment for effective immune responses against tumour [86]. Similarly, histone deacetylase inhibitors (HDACi), including vorinostat and romidepsin, reduced ATP production and relieved immunosuppressive pressure [87].

4.3 | Targeting DNA Methylation in TAMs

Direct targeting of DNA methylation in TAMs is another strategy to reduce their immunosuppressive activities in the TME of GBM [88]. DNA methyltransferase inhibitors (DNMTi), such as decitabine, have been reported to inhibit immune responses. This reduction in TAM-mediated inhibition helps to restore T-cell activity and promote immune surveillance, creating a more favourable environment for ATIR within the TME [89].

4.4 | Targeting Cytokine-Receptor Pathway

IL-10 and TGF-β are the two key immunosuppressive cytokines that help counteract the immune suppression commonly observed in the GBM microenvironment [14, 40]. Monoclonal antibodies, such as anti-IL-10 and anti-TGF-β antibodies, neutralise these cytokines to block their suppressive effects on T-cell activity and promote a more favourable immune response against the tumour. Small molecule inhibitors, such as SB431542, specifically inhibit TGF-β signalling by blocking TGF-β receptor activity in immune cells. This could reverse immune suppression and enhance ATIR within the tumour microenvironment [90]. Additionally, IL-8, secreted by tumour cells, MDSCs and $CD8^+$ T cells, recruits MDSCs via the CXCR1/CXCR2 axis, induces angiogenesis, and upregulates PD-1 and TIM-3. Liu et al.

TABLE 2 | Potential therapeutic targets and mechanisms for immunosuppression in GBM.

Target cell/ pathway	Targeting mechanism	Potential therapy	Clinical trials	Status
TAMs	Inhibit survival or reprogramme to M1 phenotype	CSF-1R inhibitors; CD47 blockade	BLZ945 (NCT02829723) Cabiralizumab (NCT02526017) Magrolimab (NCT05169944)	Terminated (2024-01) Completed (2022-03) Completed (2025-07)
MDSCs	Block recruitment to the tumour site	CXCR2 inhibitors; arginine depletion	ADI-PEG (NCT04587830) BCT-100 (NCT03455140) [76]	Active (2025-08) Completed (2022-09)
Tregs	Block suppressive cytokine signalling	ALK5 (TGF-β inhibitors); TGF-β inhibitor + PD-L1 antibody	Galunisertib (NCT02423343) [77] Bintrafusp alfa (NCT02517398) [78][a]	Completed (2021-09) Completed (2022-05)
Checkpoint pathways (PD-L1/ PD-1)	Block immune checkpoint interaction	TGF-β inhibitor + PD-L1 antibody; CTLA-4 inhibitors	Bintrafusp alfa (NCT02517398) [78][a] Nivolumab ± ipilimumab ± bevacizumab (NCT02017717) [79] Tremelimumab ± durvalumab (NCT02794883)	Completed (2022-05) Completed (2024-06) Completed (2022-06)
CAR-T	Enhance T-cell infiltration and persistence in GBM	Combined with oncolytic viruses, cytokine modulation EGFRvIII CAR-T cells Combination with TGF-β inhibitors	EGFRvIII CAR-T (NCT01454596) [80] IL-8R-CD70- CAR-T (NCT05353530)	Completed (2019-01) Recruiting (2025-10)
Metabolic pathways	Target the increased dependency on glucose and glutamine, as well as the altered lipid metabolism observed in GBM cells	Caloric restriction ketogenic diet (KD-R), inhibition of glutaminase, cholesterol depletion, inhibition of fatty acid synthesis	Atorvastatin (NCT06327451) Ketogenic diet (NCT05708352) Telaglenastat (NCT03872427)	Recruiting (2024-03) Recruiting (2025-06) Active (2025-11)
Epigenetic targets	DNMTi; HDACi; EZH2; BET-BRD; H3K27M	5-Aza-CdR (DNMTi); Vorinostat, Romidepsin (HDACi); Tazemetostat (EZH2); JQ1, I-BET (BET-BRD)	Decitabine/vaccine (NCT02332889) Vorinostat (NCT00555399) Tazemetostat (NCT05023655) BMS-986158 or BMS-986378 (NCT03936465) ONC201 (NCT05580562)	Terminated (2016-07) Terminated (2024-08) Recruiting (2025-07) 2024-10 Completed 2025-08 Recruiting
Oncolytic viruses	Infect and kill tumour cells, releasing antigens to stimulate immunity Improve virus efficacy in TME through enhanced immune activation	Engineered oncolytic viruses Combination with checkpoint inhibitors	PVSRIPO (NCT01491893) [81] VBI-1901 (NCT03382977)	2023-09 Completed 2025-03 Recruiting

Abbreviations: BET-BRD: bromodomain and extra-terminal domain–bromodomain inhibitors; DNMTi, DNA methyltransferase inhibitors; EZH2, enhancer of zeste homologue 2; HDACi, histone deacetylases inhibitors.
[a]Bintrafusp alfa is a bifunctional fusion protein that targets PD-L1 and TGF.

revealed that neutralising IL-8 unlashed anti-PD-1-mediated antitumor immunity [41].

4.5 | Combination Strategies

Combination strategies that simultaneously target multiple immunosuppressive mechanisms hold great potential to enhance immune responses in the TME of GBM. Jiang et al. demonstrated that combining checkpoint inhibitor (anti-CD47) with glycolysis inhibitor (etomoxir) mitigated the suppressive metabolic effects imposed by TAMs and MDSCs [91]. Similarly, combining PD-1/CTLA-4 inhibitors helps to reduce the overall immunosuppressive environment, enhancing T-cell activation [92]. Additionally, CAR-T cell therapy combined with TGF-β inhibitors could improve CAR-T cell persistence and function by blocking TGF-β's suppressive effects, thereby enhancing CAR-T efficacy in the TME [93, 94]. These combination strategies leverage synergistic effects to counteract GBM's immune resistance, creating a more supportive setting for anti-tumour immunity. Besides, NK cells engineered to express IL-21 or HER2 enhanced anti-tumour efficacy against GBM [95, 96]. What is important is that the combination strategy needs to be well considered.

4.6 | Oncolytic Viral Therapy and Stimulation of Tertiary Lymphoid Structure in GBM

Oncolytic viral therapy has emerged as a promising approach for GBM by combining direct tumour cell lysis with secondary activation of ATIR. Engineered viruses can selectively replicate in glioma cells, induce immunogenic cell death and release tumour antigens that are subsequently taken up by DCs and convert an immunologically 'cold' tumour into a more inflamed microenvironment. However, several challenges currently limit the efficacy of oncolytic viruses in GBM, including restricted intratumoral spread, the physical and functional barriers imposed by the BBB, pre-existing or rapidly induced antiviral immunity and safety concerns such as neurotoxicity and treatment-related edema. To overcome these obstacles, multiple strategies are under investigation: optimising delivery routes (e.g., intratumoral injection or convection-enhanced delivery), combining oncolytic viruses with immune checkpoint blockade or myeloid-targeting agents to counteract the immunosuppressive TME and engineering viral backbones to express cytokines or costimulatory ligands that further enhance local T-cell and NK-cell activity [97]. Moreover, tertiary lymphoid structures formed with T-cell zones containing antigen-presenting dendritic cells and B-cell zones with germinal centres showed immune-permissive TME and improved overall survival [35].

5 | Conclusion

In summary, the immunosuppressive TME enriched with TAMs, MDSCs, Tregs, exhausted T cells, and stromal elements is particularly involved in GBM resistance. These TME show a dynamic interplay in a multilayered metabolism–epigenetic–immune network, which implicates the design of personalised, multimodal immunotherapeutic strategies to suppress GBM via reprogramming the immune microenvironment.

Author Contributions

Changming Pang: researched the literature, drafted the manuscript in detail, and drew figures. **Yan Wang:** critically revised the article for important intellectual content.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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