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REVIEW

Targeting immunosuppressive network in glioblastoma: Emerging strategies to overcome immunodeficiency and enhance therapeutic efficacy

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Abstract Glioblastoma (GBM), the most aggressive primary brain tumor, remains a formidable therapeutic challenge, with a median survival under 15 months. Despite the current standard of care-comprising maximal safe surgical resection, radiotherapy, and temozolomide chemotherapy-patient outcomes have seen minimal improvement over the past two decades. A key barrier to effective treatment is GBM's robust and multifaceted immunosuppressive network, which critically undermines antitumor immunity. While much of the research has focused on the local immunosuppressive tumor microenvironment, systemic immunosuppression represents an equally important yet often underappreciated obstacle, significantly impairing host immune competence. Effective immunotherapy relies on an intact and functional immune system capable of mounting durable T cell-mediated responses. However, GBM induces profound systemic immune dysfunction, manifested by severe lymphopenia and depletion of effector immune cells, which further limits immune-mediated tumor control. Therefore, a comprehensive

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understanding of both systemic and local immunosuppressive mechanisms is essential for the rational design of effective immunotherapeutic strategies. In this review, we examine the unique physiological features of the brain, dissect the immunosuppressive landscape of GBM at both local and systemic levels, and highlight recent insights into the underlying mechanisms. We also discuss current immunotherapeutic modalities, and emerging drug delivery strategies aimed at overcoming immunosuppression to improve therapeutic efficacy.

1. Introduction

Gliomas are the most common primary brain malignancies, accounting for approximately 80% of all malignant central nervous system (CNS) tumors[1]. These neoplasms are thought to originate from neuroglial progenitor cells, as suggested by their anatomical distribution and histological resemblance to differentiated neuroglial elements. Current classification systems categorize gliomas into distinct subtypes, including astrocytomas, oligodendrogliomas, and ependymomas, based on their presumed cellular origins[2]. Among these, glioblastoma (GBM), classified as a World Health Organization (WHO) grade IV glioma, is the most aggressive and prevalent primary brain tumor, comprising over 50% of all glioma cases[3]. Epidemiological data indicate an age-dependent incidence ranging from 0.59 to 3.69 per 100,000 individuals, peaking between 75 and 84 years, with a higher prevalence in males[1,2,4].

The current standard of care for GBM involves maximal safe surgical resection followed by adjuvant radiotherapy and temozolomide (TMZ) chemotherapy[5]. However, this multimodal approach provides only modest clinical benefit, with median survival remaining stagnant at 14−16 months[6]. Recent advancements, including tumor-treating fields therapy and molecularly targeted agents against receptor tyrosine kinase pathways, have shown limited success in significantly altering disease progression[7,8]. Despite extensive research efforts, treatment options that significantly improve long-term survival remain elusive, and patient outcomes have remained largely unchanged for over two decades[9]. The near-universal development of therapeutic resistance and inevitable tumor recurrence highlight the urgent need for novel treatment strategies.

Immunotherapy has revolutionized cancer treatment by leveraging the host immune system to establish durable antitumor responses through immunological memory formation[10]. While this approach has demonstrated remarkable success in hematological malignancies and melanoma, its application in GBM has been met with significant challenges. The unique pathophysiological features of GBM create an immunosuppressive network at both local and systemic levels through multifaceted mechanisms[11-13]. These biological adaptations lead to profound immunodeficiency, impairing the function of effector immune cells and diminishing antitumor immunity, thereby posing substantial barriers to effective immunotherapy. Although various immunotherapeutic strategies, immune checkpoint inhibitors (ICIs), vaccine-based approaches, oncolytic viruses (OVs), chimeric antigen receptor (CAR)-T cell therapies, and cytokine modulation, have been explored in preclinical and clinical settings, their success in GBM remains limited. In this review, we provide an overview of the physiological of the brain, and pathological characteristics of GBM, with a particular focus on its immunosuppressive network and its impact on current immunotherapies. We also summarize advances in clinical studies, and emerging therapeutic strategies aimed at overcoming immunosuppression and restoring immune function to enhance the therapeutic efficacy. Finally, we discuss the current challenges and future perspectives in the field, highlighting potential directions for improving immunotherapeutic interventions in GBM.

2. Distinct tumor microenvironment of GBM

GBM, located within the CNS, presents unique challenges for immune response activation compared to peripheral tumors, primarily due to the brain's distinct physiological features (Fig. 1). Historically, CNS was regarded as immune privileged because of the existence of blood−brain barrier (BBB), the absence of conventional lymphatic drainage, and the limited presence of specialized antigen-presenting cells in the brain parenchyma, which collectively restrict immune surveillance. However, recent evidence has reshaped this understanding, revealing that these interconnected elements instead tightly regulate a functional innate and adaptive immune system within the CNS. In this section, we introduce the physiological characteristics of the brain, discuss advancements in understanding CNS immunity, and analyze how GBM components contribute to local immunosuppression within the tumor microenvironment.

2.1. Physiological characteristics contribute to brain immune microenvironment

The immunological accessibility of the CNS to systemic immunity has been a subject of evolving scientific consensus. Contrary to the classical "immune privilege" doctrine that dominated neuroimmunology for decades—characterizing the brain as a sealed compartment protected by the BBB and lacking lymphatic connectivity—modern discoveries have revealed a more nuanced immunological landscape. Early experimental evidence from Medawar's seminal 1940s studies demonstrated that while primary intracerebral skin homografts evaded immune rejection, secondary grafts in pre-sensitized hosts underwent rapid elimination[14]. This paradox highlighted the CNS's capacity to sustain pre-existing immune responses but inability to initiate *de novo* adaptive immunity, a phenomenon originally ascribed to absent efferent lymphatic drainage[14]. Revolutionary findings in the past decade have identified functional meningeal lymphatic vessels along dural sinuses that connect to deep cervical lymph nodes, establishing a physical conduit for cerebrospinal fluid-derived antigen-presenting cells (APCs) and T lymphocytes to interact with peripheral immune compartments[15,16]. These anatomical revelations necessitate redefining the brain not as immunologically "privileged" but as "distinct"[17].

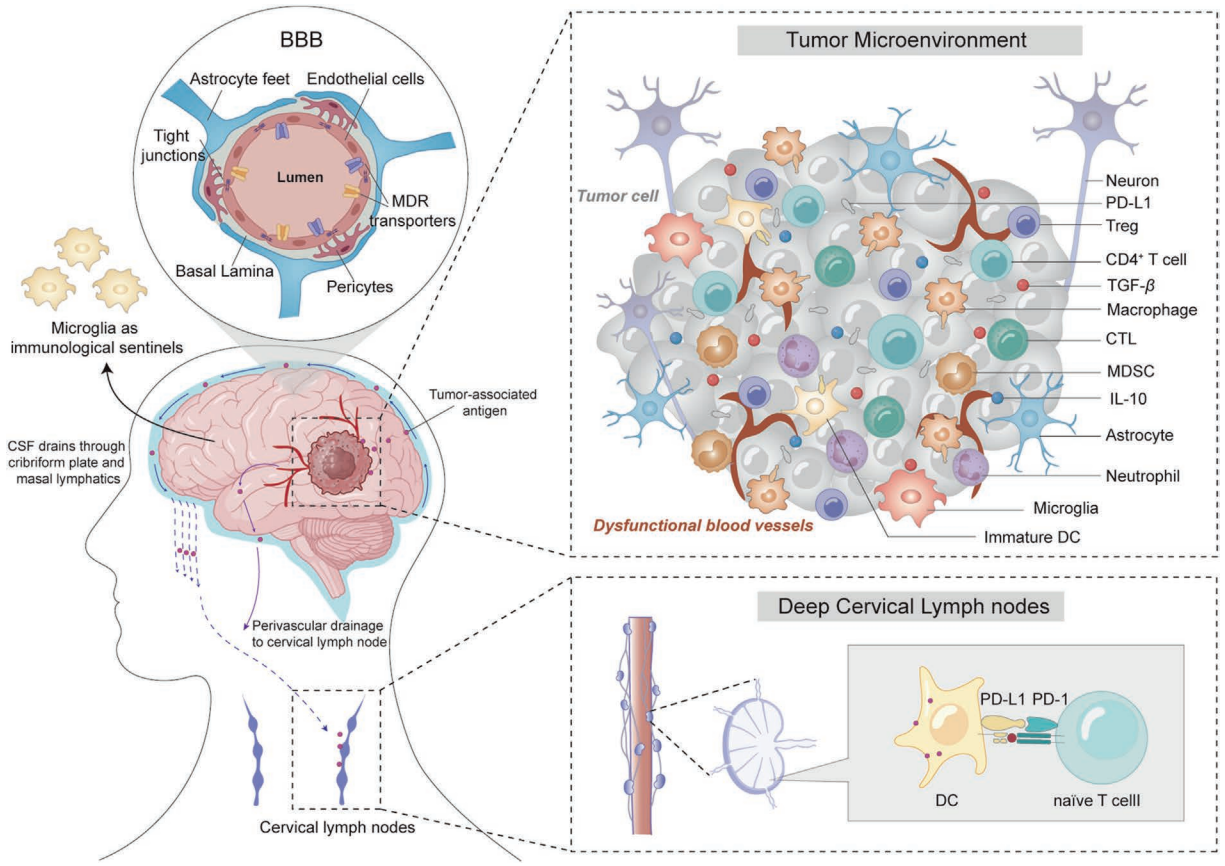

Figure 1 Brain physiology shapes the immunosuppressive microenvironment in GBM. Under normal physiological conditions, the BBB, maintained by endothelial tight junctions, limits the infiltration of peripheral immune cells and restricts therapeutic access to the brain parenchyma. In this immune-privileged environment, microglia function as the primary immune sentinels. In GBM, however, tumor-induced disruption of the BBB leads to the formation of perivascular niches that permit the entry of peripheral immune cells. Concurrently, the glymphatic system facilitates the drainage of cerebrospinal fluid—carrying immune cells and tumor-derived antigens—as well as interstitial fluid enriched with tumor antigens to the cervical lymph nodes. There, dendritic cells (DCs) present antigens to naïve T cells, initiating adaptive immune responses. Despite this immunological engagement, the GBM microenvironment is infiltrated by a heterogeneous population of immunosuppressive cells, including astrocytes, neurons, microglia, macrophages, neutrophils, myeloid-derived suppressor cells (MDSCs), immature DCs, and dysfunctional T cells. These cellular components, along with immunosuppressive cytokines such as transforming growth factor-β (TGF-β) and interleukin-10 (IL-10), collectively establish a profoundly immunosuppressive niche that impairs effective antitumor immunity.

The BBB constitutes the afferent regulatory arm of CNS immunity, comprising specialized endothelial cells with tight junctions, astrocytic endfeet, and pericytes[18]. This dynamic interface selectively permits ion/nutrient exchange while excluding >98% of small-molecule drugs, all macromolecular therapeutics and leukocytes under physiological conditions[19]. Parenchymal immune quiescence is maintained despite systemic antigen exposure, as demonstrated by attenuated leukocyte infiltration following direct CNS antigen challenge compared to peripheral administration[20]. However, emerging evidence indicates that pathological states induce BBB hyperpermeability, creating perivascular spaces that facilitate immune cell infiltration into the brain parenchyma. Notably, immune cells have been observed to transmigrate across the compromised BBB in neuroinflammatory disorders such as multiple sclerosis[18], cerebral abscesses[21,22], and brain tumors[23]. These clinical observations collectively suggest that BBB does not function as an absolute "hermetic seal" against immune cell trafficking, but rather operates as a dynamic interface with selective permeability modulated by local pathophysiological conditions.

Another unique characteristic of the brain immune environment is the CNS-resident myeloid populations, particularly microglia, which serve as principal immunological sentinels. Originating from yolk sac-derived progenitors during embryogenesis, these self-renewing cells perform continuous parenchymal surveillance through phagocytic clearance of apoptotic debris and synaptic pruning[24]. Upon activation, microglia upregulate pathogen recognition receptors and secrete pro-inflammatory cytokines/chemokines, yet paradoxically exhibit limited capacity to prime adaptive immunity[25,26]. These physiological characteristics collectively shape the brain's unique immune microenvironment, which inherently restricts immune activation to some extent, yet demonstrates that the CNS immunological barriers are surmountable, and that therapeutic immune responses can be effectively elicited in brain malignancies.

2.2. *Cellular and molecular constituents orchestrate the immunosuppressive tumor microenvironment of GBM*

The tumor microenvironment of GBM represents a complex ecosystem characterized by remarkable cellular and molecular heterogeneity. This multifaceted network encompasses neoplastic populations, diverse immune infiltrates, stromal components, and

bioactive mediators that collectively establish a pro-tumorigenic niche supporting malignant progression and therapeutic resistance. Notably, the very elements that constitute this specialized microenvironment directly orchestrate the characteristic "cold" immunological phenotype marked by T cell exclusion and dysfunctional antitumor immunity. Compelling evidence from single-cell technologies reveals that GBM progression is primarily driven by dynamic microenvironmental reorganization rather than molecular evolution of tumor cells, underscoring the pivotal role of microenvironmental remodeling in GBM pathogenesis[27]. This section systematically introduces these elements that cooperatively drive localized immune evasion in GBM.

2.2.1. Tumor-intrinsic factors promote local immunosuppression

GBM evolution is intrinsically linked to oncogenic reprogramming that shapes tumor cell plasticity, histopathological features, and immunosuppressive landscapes. Mounting evidence implicates tumor-intrinsic genetic and epigenetic alterations as central drivers of local immunosuppression[28]. One key factor contributing to this immunosuppression is GBM's inherently low tumor mutational burden (TMB). A high TMB is typically associated with increased neoantigen presentation, pre-existing antitumor adaptive immunity, and improved response to immunotherapy[29-31]. However, newly diagnosed GBM patients exhibit a median TMB of approximately 1.5 mutations per megabase, with fewer than 2% harboring more than 10 mutations per megabase[32]. This relatively low mutational landscape limits the repertoire of neoantigens available for T cell recognition, thereby restricting the diversity and efficacy of tumor-reactive T cell responses. In addition to a low TMB, GBM harbors a spectrum of genetic mutations, including alterations in EGFR amplification[33,34], TP53 mutations[35], PTEN deletions[36,37], and IDH variants[38], as well as dysregulation of the MAPK and Wnt/β-catenin signaling pathways[39]. These mutations significantly contribute to immune evasion. For instance, IDH1/2 mutations and activation of Wnt/β-catenin signaling (*via* CTNNB1) are associated with polarization of tumor-associated macrophages (TAMs) toward an immunosuppressive M2 phenotype and upregulation of immune checkpoint molecules[40]. Moreover, PTEN deficiency drives immunosuppressive adaptation GBM by activating PI3K-Akt signaling to upregulate programmed cell death 1-ligand 1 (PD-L1) expression, thereby establishing an immune-evasive microenvironment[37]. Beyond genetic drivers, GBM cells also orchestrate local immunosuppression through epigenetic change. Tumor cells upregulate immunosuppressive molecules such as PD-L1 and indolamine 2,3-dioxygenase (IDO) while downregulating histocompatibility complex-I (MHC-I) antigen presentation, effectively evading immune surveillance[13,41,42]. Collectively, these intrinsic tumor properties create a profoundly immunosuppressive niche that presents a major challenge for effective GBM immunotherapy.

2.2.2. Vascular abnormalities impede T-cell infiltration

The vasculature of GBM plays a crucial role in tumor progression by shaping the tumor microenvironment and contributing to both immunosuppression and therapeutic resistance. The aggressive proliferative capacity of GBM drives perpetual angiogenic signaling cascades, mediated through release of angiogenic factors including epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF)[43]. Pathologically remodeled vasculature in these tumors exhibits chaotic spatial distribution, defective pericyte coverage, and compromised BBB integrity[44]. These defects result in regions of hypoxia and nutrient deprivation within the tumor core, fueling malignant progression while simultaneously impairing the effectiveness of systemic therapies. The dysfunctional endothelial cells lining these vessels further exacerbate immunosuppression by forming a physical and biochemical barrier that limits T cells infiltration[45,46]. Moreover, the inflammatory and hypoxic conditions within the tumor microenvironment reinforce a pro-tumorigenic state, diminishing the efficacy of immune surveillance mechanisms[45]. Collectively, these factors create a formidable challenge for immunotherapy, underscoring the necessity of strategies that target vascular abnormalities to restore anti-tumor immunity and enhance therapeutic responses in GBM.

2.2.3. Reprogrammed astrocytes as architects of local immunosuppression

_under1Astrocytes, constituting about 50% of the cells in human brain, are traditionally recognized for their neurosupportive functions in maintaining BBB integrity, ion homeostasis, and metabolic coupling[47,48]. However, in the context of brain tumors, astrocytes undergo functional reprogramming to establish a multifaceted immunosuppressive network. Through direct secretory mechanisms, tumor-associated astrocytes release immunosuppressive cytokines including TGF-β, IL-10, granulocyte colony-stimulating factor (G-CSF), and growth differentiation factor-15 (GDF-15), creating an immune-evasive niche that impairs both innate and adaptive immune responses[49-51]. Additionally, astrocytes can upregulate PD-L1 to promote $CD8^+$ T cells exhaustion and apoptosis[52]. The immunosuppressive landscape is further reinforced through astrocyte-mediated recruitment and polarization of tumor-associated immune cells. Astrocyte-derived CCL2 and CSF1 facilitate the recruitment and pro-tumorigenic polarization of TAMs[53]. Simultaneously, STAT3 hyperactivation in astrocytes drives the accumulation of MDSCs and regulatory T cells (Tregs), mediated through IL-6 and VEGF secretion[54-56]. Furthermore, recent studies employing single-cell RNA sequencing and CRISPR-based technologies have identified STAT3-dependent expression of the death receptor ligand TRAIL in astrocytes, which limits tumor immunity by inducing T-cell apoptosis[57]. This immune cell modulation is complemented by extracellular matrix remodeling, where astrocyte-secreted tenascin-C creates a physical barrier that impedes T-cell infiltration and cytotoxic activity[58]. The convergence of these mechanisms, encompassing immune cell recruitment, effector cell suppression, and physical barrier formation, positions astrocytes as orchestrators of the GBM immunosuppressive microenvironment. This comprehensive understanding underscores the therapeutic imperative to develop strategies targeting astrocyte-mediated immunosuppression in GBM treatment.

2.2.4. Neuron-driven remodeling of the immunosuppressive tumor niche

The bidirectional crosstalk between neural and immune systems, where neurons respond to immune mediators and immune cells react to neurotransmitters, plays a profound role in shaping both neurological and immunological functions. Within the glioma tumor microenvironment, neurons exert non-canonical roles that extend beyond synaptic transmission to actively drive tumor progression and immunosuppression. Emerging evidence reveals that neuronal activity stimulates glioma proliferation through activity-dependent secretion of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neuroligin-3 (NLGN3), as well as neurotransmitters including glutamate and dopamine[59]. Notably, NLGN3 activates oncogenic PI3K signaling in tumor cells, fostering an

aggressive phenotype linked to poor clinical outcomes, with elevated NLGN3 expression inversely correlating with patient survival[60]. Reciprocally, gliomas amplify neuronal hyperexcitability *via* glutamate release and synaptogenesis, establishing a feedforward loop that sustains tumor growth[59]. Beyond fueling tumorigenesis, neuron-derived signals critically shape the immunosuppressive tumor microenvironment[50,61]. Neuronal hyperactivity enriches miR-200c-3p in exosomes, which polarize microglia toward an immunosuppressive M2 phenotype, thereby dampening antitumor immunity[62]. Furthermore, neurotransmitters such as γ-aminobutyric acid, released by neurons, act as oncometabolites that suppress immune cell infiltration and function, creating an immune-evasive niche[63]. Neuronal remodeling also extends to synaptic interactions: SEMA4F-mediated synaptic remodeling rewires neural circuits to modulate immune cell trafficking within the tumor microenvironment while maintaining chronic network hyperexcitability[64]. These mechanisms collectively hijack neural plasticity pathways to reinforce an immunosuppressive milieu characterized by impaired cytotoxic T-cell responses and enhanced regulatory immune cell recruitment. This intricate neuron−glioma−immune triad underscores the therapeutic potential of targeting neural signaling hubs to dismantle immunosuppression and restore antitumor immunity in GBM.

2.2.5. *Myeloid cells-driven immunosuppression*

The myeloid compartment constitutes over 95% of tumor-infiltrating immune populations in GBM, encompassing heterogeneous subsets including TAMs, MDSCs, neutrophils and DCs[65-67]. Central to this immunosuppressive network are TAMs, encompassing both brain-resident microglia and bone marrow-derived macrophages. These cells predominantly adopt an M2-like polarization state characterized by elevated secretion of chemokines including CCL20, IL-8, CXCL1 and CXCL2, which orchestrate and sustain immunosuppressive niches[67]. The immunosuppressive capacity of TAMs is further augmented by their upregulation of immune checkpoint molecules, including PD-L1 and Siglec-9, which directly impair T cell viability[68,69]. MDSCs, representing 4%−8% of $CD45^+$ infiltrates in GBM, disproportionately impair antitumor immunity through tumor-driven pathological activation[70]. These immature myeloid progenitors accumulate due to disrupted hematopoietic differentiation and develop diverse immunosuppressive functions. Key mechanisms include depleting nutrients essential for effector T cell responses, expanding Tregs, and generating oxidative stress that impairs T cell function[71,72]. Neutrophils are the predominant circulating myeloid population, which can form neutrophil extracellular traps (NETs) to establish a physical barrier that shields tumor cells from $CD8^+$ cytotoxic T lymphocytes (CTLs)-mediated destruction. Beyond their immunosuppressive functions, neutrophils undergo functional reprogramming to actively promote tumor progression. This is mediated through mechanisms such as ferroptosis-induced necrosis[73], and the maintenance of cancer stem cell populations[74], collectively driving GBM aggressiveness and treatment resistance. DCs, which are crucial for initiating anti-tumor immunity, exhibit a dysfunctional phenotype in GBM. Glioma-associated DCs remain in an immature state with impaired antigen presentation capacity, limiting their ability to activate T cells[75]. Consequently, myeloid cell-targeted strategies have garnered increasing attention as a means to reinvigorate anti-tumor immunity.

2.2.6. *Dysfunctional tumor-infiltrating lymphocytes (TILs)*

TILs, a heterogeneous population of immune cells within tumor microenvironment, exhibit dual roles, oscillating between antitumor activity and immunosuppression. Although CTLs are key mediators of tumor cell lysis, their presence in GBM is sparse (<1% of the tumor microenvironment) and functionally impaired[13,76]. These CTLs frequently display an exhausted phenotype, characterized by diminished cytotoxic granule secretion (*e.g.*, perforin, granzyme B), various inhibitory receptors including PD-1, CTLA-4, LAG-3 and TIM-3, and impaired tumor targeting ability, a state perpetuated by chronic antigen exposure and immunosuppressive signaling[77]. Meanwhile, $CD4^+$ T helper cells predominantly differentiate into Tregs, which suppress CTLs responses through IL-10 and TGF-β secretion and competitive cytokine receptor consumption, reinforcing an immunosuppressive niche[32,77]. This paradox, where TILs are both restricted in antitumor function and co-opted to sustain immune tolerance, underscores the challenge of leveraging adaptive immunity in GBM. Current therapeutic strategies aiming to reinvigorate exhausted CTLs or deplete Tregs have yielded limited clinical success, underscoring the need to address the multifactorial barriers that subvert TILs functionality within the tumor microenvironment.

2.2.7. *Soluble immunosuppressive mediators*

The GBM microenvironment is dominated by soluble immunosuppressive mediators, including cytokines, metabolic factors and extracellular vesicles (EVs), which collectively orchestrate profound antitumor immunity impairment. Key cytokines such as IL-10 and TGF-β directly inhibit CTLs activation while promoting the expansion of Tregs and TAMs[13]. Emerging evidence further implicates non-canonical cytokines in immune evasion, for example, Boeck et al. showed that IL-33 regulated chemokines to recruit and activate circulating and resident innate immune cells, fostering a protumorigenic environment[78]. Notably, cytokines exhibit pleiotropic immunosuppressive mechanisms, including immune checkpoint modulation. A prime example is IL-6: tumor-derived IL-6 activates the STAT3 pathway to upregulate PD-L1 expression on myeloid cells, effectively paralyzing antitumor immune responses[79].

Beyond cytokines, the metabolic byproducts of tumor reprogramming emerge as potent immunomodulators that critically reshape the tumor-immune interface. The glycolytic switch characteristic of GBM drives substantial lactate accumulation, which exerts multifaceted immunosuppressive effects ranging from inducing M2 phenotype macrophage polarization and impairing DCs function to suppressing cytotoxic lymphocyte activity and fostering regulatory T cell expansion[80,81]. Notably, lactate-mediated epigenetic reprogramming through histone lactylation has been shown to activate immunosuppressive transcriptional programs in tumor cells, including upregulation of the "don't eat me" signal CD47 to evade phagocytic clearance[82]. The metabolic landscape is further complicated by glutamine metabolism, where tumor cells actively compete for this essential nutrient through alanine-serine-cysteine transporter 2 (ASCT2) transporters, creating a metabolically hostile microenvironment that selectively starves effector T cells while fueling immunosuppressive populations[83,84]. Isocitrate dehydrogenase (IDH) mutations, prevalent in glioma, drive production of the oncometabolite *R*-2-hydroxyglutarate (2-HG), which accumulates in tumor microenvironment and induces immune dysfunction[38,85]. Additionally, tumor-derived kynurenine activates the aryl hydrocarbon receptor (AHR) axis in TAMs, skewing them toward an immunosuppressive phenotype while simultaneously suppressing $CD8^+$ T cell effector functions[86].

The spatial organization of this immunosuppressive network is further amplified by EVs that deliver immunosuppressive cargos,

including PD-L1, tenascin-C, and TGF-β, to both innate and adaptive immune cells. Mechanistically, EV-associated PD-L1 engages PD-1 on T cells to induce exhaustion, while tenascin-C disrupts T cell receptor clustering and immunological synapse formation, creating a multi-layered defense against antitumor immunity[87,88]. Together, these soluble mediators form an integrated defense system where cytokine signaling, metabolic competition, and vesicular communication synergistically establish an immunosuppressive niche that perpetuates tumor progression and therapeutic resistance.

3. Multifactorial drivers of systemic immunosuppression in GBM

Beyond the localized immunosuppressive effects within the tumor microenvironment, GBM exerts a significant systemic impact on immune function (Fig. 2). Even in the absence of distant metastases, patients with GBM commonly demonstrate marked systemic immunosuppression. Indeed, GBM represents a paradigm of cancer-associated systemic immunosuppression, characterized by multifaceted defects in both cellular immunity and lymphoid organ architecture[11,89,90]. Clinical observations reveal profound lymphopenia in GBM patients, with 73% demonstrating $CD4^+$ T cell counts below 300 cells/mm^3 during standard radio-chemotherapy[91]. Strikingly, some patients exhibit $CD4^+$ levels comparable to acquired immunodeficiency syndrome-defining thresholds (<200 cells/μL), accompanied by thymic involution and splenic atrophy-hallmarks of systemic immune collapse[11,92]. This immunosuppressive state also manifests functionally through impaired T-cell effector responses, including diminished IL-2 production and reduced IL-2Rα expression, along with attenuated delayed-type hypersensitivity reactions despite preserved tumor antigen recognition[93,94]. The precise mechanisms underlying this immunosuppressive state remain incompletely understood, but accumulating evidence suggests a multifactorial process driven by tumor, host, and treatment approaches.

3.1. Tumor-derived mediators driving systemic immunosuppression

Tumor-derived factors have been implicated as contributors to systemic immunosuppression. Previously researchers postulated

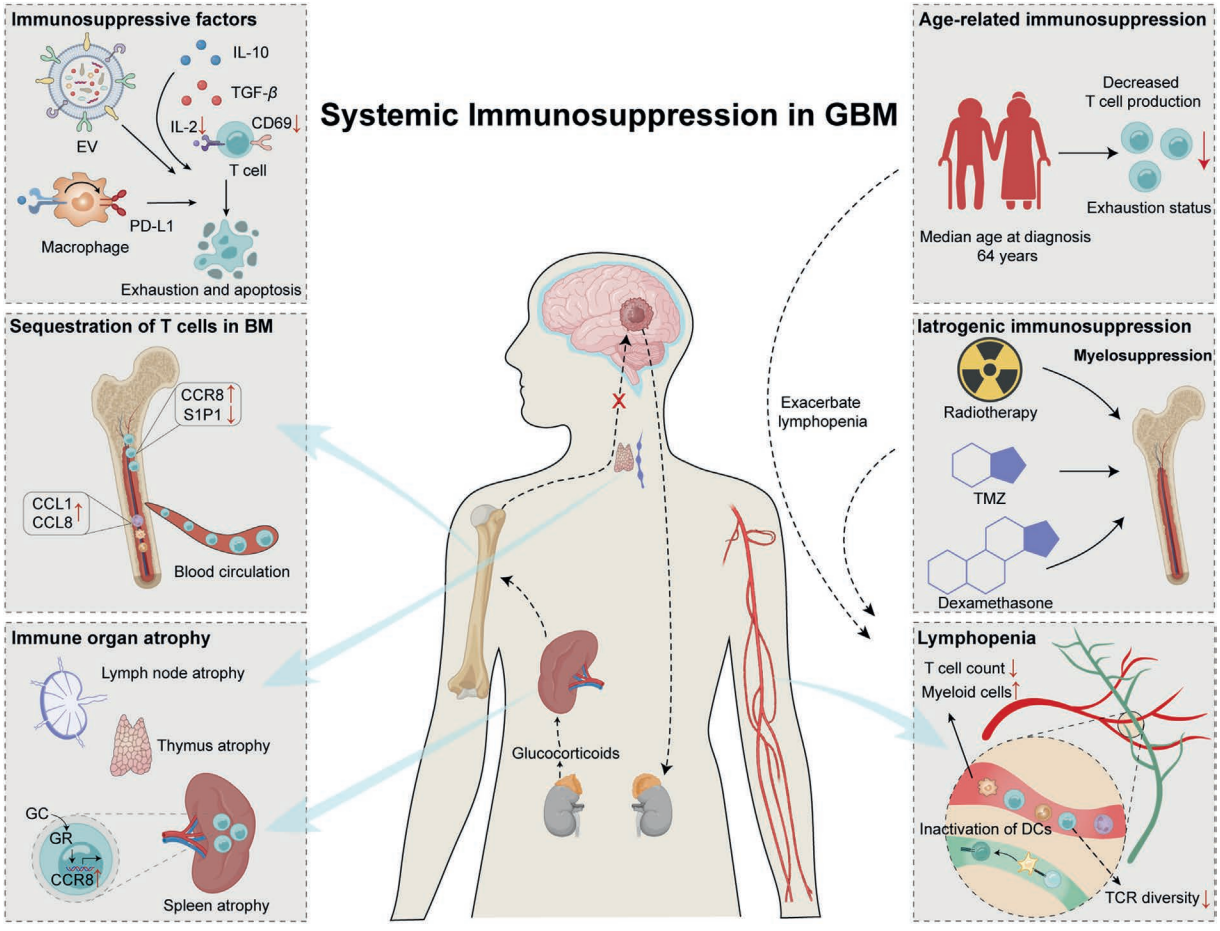

Figure 2 Overview of systemic immunosuppression in GBM. Systemic immunosuppression in GBM extends beyond the tumor microenvironment and manifests across multiple compartments of the immune system, including the bone marrow (BM), thymus, spleen, lymph nodes, and peripheral blood. GBM-driven alterations in the BM impair hematopoiesis and skew immune cell development. In the thymus, tumor-associated signals can disrupt T cell maturation and promote thymic involution. The spleen and lymph nodes exhibit reduced immune cell activation and altered antigen presentation, contributing to peripheral immune tolerance. Circulating immune cells in the blood display functional exhaustion, lymphopenia, and reduced effector responses. Specific mechanisms and representative immune alterations within each organ system are illustrated, highlighting the multifaceted nature of systemic immune dysfunction in GBM.

that circulating tumor-derived cytokines might account for this overt immunosuppression. However, while elevated levels of immunosuppressive cytokines such as TGF-β, IL-10, and IL-6 are characteristic of GBM, their direct correlation with immune dysfunction severity remains ambiguous[95,96]. In addition to cytokines, study found that peripheral blood macrophages from GBM patients exhibited upregulated PD-L1 expression, suppressing autologous T cell responses through PD-1 engagement[97]. Exosomes have also emerged as crucial mediators of tumor-induced systemic immunosuppression[98,99]. These EVs, secreted by tumor cells, facilitate intercellular communication by transferring bioactive molecules, including RNAs, proteins and cytokines, to distant immune cells[100]. Glioma-derived exosomes have been found to contain immunosuppressive factors such as epidermal growth factor receptor variant III (EGFRvIII) and TGF-β, which can modulate immune responses at systemic levels[101]. Notably, glioma-derived exosomes downregulated CD69 and IL-2Rα expression, impairing $CD4^+$ T cell activation and proliferation[102]. Moreover, studies have demonstrated that exosomes promoted the expansion of immunosuppressive MDSCs, further dampening systemic immune responses[103,104]. While some findings suggest that GBM-derived exosomes play a pivotal role in peripheral immune suppression, contradictory reports indicate that these exosomes alone may not be sufficient to drive systemic immunosuppression, suggesting the involvement of additional mechanisms[105].

Emerging evidence reveals more sophisticated mechanisms to elucidate the unique systemic immunosuppression for glioma: Brain tumors induced the loss of sphingosine-1-phosphate receptor 1 (S1P1) on the surface of naïve T cells, which led to the sequestration T cells in BM, contributing to systemic T cell depletion and lymphoid organ atrophy in GBM patients[11]. This process is exacerbated by tumor-induced glucocorticoid surges that promote CCR8-mediated T cell sequestration[106]. Importantly, while GBM patient-derived T cells maintain proliferative capacity *in vitro*, plasma-soluble factors potently inhibit their expansion and effector functions[12,107], demonstrating integrated cellular and humoral immunosuppressive pathways.

3.2. *Epidemiological features*

Beyond tumor-derived factors, host characteristics significantly influence the extent of systemic immunosuppression. Host immune competency is a crucial determinant of tumor progression, as evidenced by accelerated tumor development in immunodeficient mouse models and increased cancer susceptibility in immunosuppressed patients[108,109]. Various host-related factors, including age, sex, genetic background, infections, metabolic status, fitness, diet and microbiome composition, can modulate immune function[110,111]. Among these factors, aging is strongly associated with immunosenescence, characterized by diminished T cell output from the thymus and a decline in overall immune responsiveness[112-114]. Epidemiological studies indicate that the median age at GBM diagnosis is 64 years[115]. This population primarily consists of older adults, who experience age-related immunosuppression, further worsening their already compromised immune status[115]. This demographic characteristic suggests that GBM patients have weaker systemic immunity, likely due to their advanced age at diagnosis.

3.3. *Iatrogenic immunosuppression*

GBM treatment modalities, including radiotherapy and chemotherapy, also contribute to systemic immunosuppression. Although radiotherapy can enhance antigen presentation under certain conditions, it frequently results in immunosuppressive effect in GBM patients by depleting immune cells, particularly $CD4^+$ T cells, and altering DCs function[116]. TMZ is the first-line drug for the treatment of GBM, though it has demonstrated survival benefits, its major dose-limiting toxicity is myelosuppression, leading to prolonged systemic lymphopenia[117]. Combined radiation and TMZ therapy further deplete circulating lymphocytes, termed treatment-related lymphopenia (TRL)[116,118]. This lymphopenia is associated with reduced T cell receptor (TCR) diversity, impairing adaptive immune responses and compromising tumor control[119,120]. Dexamethasone, a potent glucocorticoid commonly used to manage cerebral edema in GBM patients, further exacerbates systemic immunosuppression[121]. While effective in reducing intracranial pressure, dexamethasone significantly impairs immune function by depleting circulating lymphocytes, particularly T cells, and increasing immunosuppressive myeloid cells[95]. It also exerts profound suppressive effects on DC subsets, impairing their ability to initiate anti-tumor immune responses[122]. Moreover, studies have proved that dexamethasone administration was associated with reduced efficacy of the present immunotherapy[123,124].

Taken together, systemic immunosuppression in GBM is a multifaceted phenomenon driven by tumor, host and treatment-associated effects. While significant progress has been made in elucidating the mechanisms underlying this immunosuppressive state, further research is still needed to develop effective strategies for restoring systemic immune function and enhancing the efficacy of immunotherapeutic interventions.

4. Current immunotherapeutic strategies explored in clinic studies

The field of GBM immunotherapy is rapidly evolving. Here, we review its clinical exploration, examine challenges related to the tumor's immune-cold status, and summarize emerging strategies designed to overcome immunosuppression and enhance therapeutic efficacy. Based on the characteristics of the cancer-immunity cycle, various immunotherapeutic approaches have been explored in clinical studies[125]. Recent advances include ICIs, vaccines, oncolytic viruses, CAR-T therapy and cytokine-based therapies, all of which have been investigated for GBM immunotherapy (Table 1). Despite these innovations, clinical translation remains slow, with fewer than 10% of immunotherapy trials advancing to Phase III. In the following subsections, we briefly introduce immunotherapeutic strategies explored in clinic studies for GBM and discuss the limitation of each approach.

4.1. *ICIs therapy*

ICIs work by disrupting inhibitory pathways—such as PD-1/PD-L1 and CTLA-4—that tumors exploit to suppress CTLs activity[126]. By blocking these interactions, ICIs aim to restore anti-tumor immune response against tumor cells. Clinical trials have explored agents like nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) for GBM therapy[127-129]. Early-phase studies report manageable safety profiles and modest survival improvements, with some regimens achieving 1-year survival rates exceeding historical benchmarks[129,130]. While ICIs demonstrate potential to enhance immune recognition, the clinical application faces several critical limitations in treating GBM, such as the existence of BBB, the complex immunosuppressive landscape-characterized by

Table 1 Representative clinical trials of immunotherapies for GBM.

Target	Intervention	Setting	Phase	NCT identifier
PD-1	Camrelizumab + Radiation + TMZ	Newly diagnosed	II	NCT04583020
PD-1	Retifanlimab + Radiation + TMZ	Newly diagnosed	I	NCT05083754
PD-1+CLTA-4	Nivolumab + Ipilimumab + Surgery	Recurrent	I	NCT04606316
PD-1+Tim-3	Spartalizumab + MBG453	Recurrent	I	NCT03961971
PD-1+LAG-3+CD137	Nivolumab + BMS-986016+BMS- 663513	Recurrent	I	NCT02658981
CLTA-4	Ipilimumab	Newly diagnosed	II	NCT05074992
Peptide vaccine	Cyclophosphamide + IMA950+GM-CSF	Newly diagnosed	I	NCT01403285
Peptide vaccine	SurVaxM + TMZ	Newly diagnosed	II	NCT02455557
Peptide vaccine	EO2401	Recurrent	I/II	NCT04116658
Peptide vaccine	PEP-CMV+TMZ	Newly diagnosed	I	NCT01854099
DC vaccine	Personalized cellular vaccine	Newly diagnosed	I	NCT02709616
DC vaccine	CMV pp65 RNA-pulsed DCs + GM-CSF	Newly diagnosed	I	NCT04963413
DC vaccine	Tumor lysate-pulsed DC vaccine + TMZ	Newly diagnosed	I	NCT01957956
DC vaccine	ICT-121 DC vaccine	Recurrent	I	NCT02049489
DC vaccine	Tumor lysate-pulsed autologous DC vaccine	Recurrent	I	NCT03360708
DC vaccine	DENDR1	Newly diagnosed	I/II	NCT04801147
Personalized neoantigen vaccine	Personalized neoantigen DNA vaccine	Newly diagnosed	I	NCT04015700
Personalized neoantigen vaccine	NeoVax + Pembrolizumab + Radiation	Newly diagnosed	I	NCT02287428
Adenovirus	DNX-2440	Recurrent	I	NCT03714334
Adenovirus	delta-24-RGD adenovirus	Recurrent	I/II	NCT01582516
Adenovirus	NRG-103	Recurrent	I	NCT06757153
Parvovirus	H-1PV	Primary or recurrent	I/II	NCT01301430
Polioviruses	Recombinant nonpathogenic polio-rhinovirus chimera (PVSRIPO)	Recurrent	I	NCT01491893
CAR-T	SNC-109 CAR-T cells	Recurrent	I	NCT05868083
CAR-T	CART-EGFR-IL13Ra2 cells	Recurrent	I	NCT05168423
CAR-T	Anti-EphA2/IL-13Ralpha2 CAR (E-SYNC) T cells	Newly diagnosed	I	NCT06186401
CAR-T	B7-H3 CAR-T + TMZ	Recurrent	I	NCT04385173
CAR-T	anti-EGFRvIII CAR T cells + Cyclophosphamide + Fludarabine	Recurrent	I	NCT02844062
CAR-T	IL13Ralpha2-CAR T cells + Ipilimumab + Nivolumab	Recurrent	I	NCT04003649
CAR-T	SNC109 CAR-T cells	Recurrent	I	NCT06616727
Cytokine	IL-2+CYNK-001	Recurrent	I/II	NCT05218408
Cytokine	Ad-RTS-hIL-12 +veledimex	Recurrent	I	NCT04006119
Cytokine	M032 expressing IL-12	Recurrent	I	NCT02062827
Cytokine	L19-mTNF	Primary or recurrent	I/II	NCT03779230 NCT04573192

redundant inhibitory pathways and immunosuppressive cell populations, and low T-cell infiltration. Furthermore, the non-selective mechanism of checkpoint blockade carries inherent risks of systemic immune-related adverse events (irAEs), particularly concerning in neurologically vulnerable patients[131]. Overall, while ICIs represent a groundbreaking approach to tumor treatment, ongoing research is essential to refine their efficacy and define optimal therapeutic combinations for GBM, ultimately enhancing outcomes for patients battling this challenging disease.

4.2. Vaccine therapy

Unlike traditional vaccines that prevent disease, tumor vaccines aim to stimulate a targeted immune response against tumor-specific antigens—molecules uniquely expressed by tumor cells, such as mutated proteins (*e.g.*, EGFRvIII) or personalized neoantigens derived from a patient's tumor[132]. The underlying theory posits that introducing these antigens, often combined with immune-boosting adjuvants, can activate DCs to prime CTLs, enabling them to infiltrate tumor microenvironment and eliminate tumor cells. In GBM, several vaccine strategies have been explored, including peptide-based vaccines targeting tumor-associated antigens, DC vaccines loaded with tumor lysates or RNA, and personalized neoantigen vaccines tailored to a patient's unique genetic tumor profile (Table 1). Early clinical trials, such as those evaluating the EGFRvIII-targeted vaccine rindopepimut, demonstrated initial promise with improved progression-free survival in subsets of patients, though later-phase studies highlighted challenges like tumor heterogeneity and immune evasion[133,134]. To overcome the limitations of low tumor mutational burden, two pioneering clinical trials have demonstrated that personalized neoantigen-based vaccines could safely induce sustained polyfunctional T-cell responses with evidence of intratumoral T cells infiltration[135,136]. While vaccine therapy offers advantages such as specificity and reduced off-target toxicity compared to conventional treatments, limitations persist, including variable patient responses, the complexity of antigen selection in highly heterogeneous tumors, and the need for timely, individualized manufacturing. Ongoing research seeks to refine antigen targets, optimize delivery platforms, and identify

biomarkers to better predict which patients may benefit most from this evolving frontier in GBM immunotherapy.

4.3. OVs therapy

OVs therapy utilizes engineered viruses to selectively target and destroy tumor cells while stimulating antitumor immunity[137]. These viruses are designed to exploit tumor-specific vulnerabilities, such as dysregulated signaling pathways or defective antiviral responses, enabling preferential replication within cancer cells. Early therapeutic strategies for OVs therapy prioritized non-replicating viral vectors to minimize neuroinflammatory risks such as encephalitis. In contrast, modern approaches increasingly employ replication-competent engineered platforms—including adenoviral, parvovirus, herpes simplex viruses (HSVs), measles viruses, retroviruses and polioviruses—designed to amplify tumor-specific cytotoxicity while maintaining attenuated neurovirulence through targeted genomic modifications[138]. A recent clinical study investigating the engineered HSV (CAN-3110) has demonstrated efficacy in targeting and infecting tumor cells without damaging normal neurons[139]. Similarly, PVSRIPO, a poliovirus chimera targeting tumor cells' receptor CD155, achieved prolonged survival in recurrent GBM patients, underscoring its tumor-selective tropism[140]. While these platforms demonstrate dual mechanisms of direct tumor lysis and immune activation, clinical translation faces hurdles including BBB restrictions, pre-existing antiviral immunity, and variable viral penetration into invasive tumor margins. Current research prioritizes optimizing delivery routes and combining OVs with immune modulators to enhance efficacy against GBM's aggressive and heterogeneous biology.

4.4. CAR-T cell therapy

CAR-T cell therapy represents a transformative approach in GBM immunotherapy, employing genetically engineered T cells to target tumor-associated/specific antigens with precision. By bypassing MHC restrictions, clinical targets include EGFRvIII, IL13Rα2, and HER2, which are selectively expressed on GBM cells. The recently developed CARv3-TEAM-E platform demonstrates significant therapeutic potential by combining EGFR/EGFRvIII targeting with T-cell-engaging antibody molecules (TEAM), achieving rapid tumor regression upon intraventricular administration, though transient responses highlight durability challenges[141]. Dual-targeting strategies are also explored to mitigate antigen escape: tandem CAR-T cells co-targeting HER2/IL13Rα2 demonstrate synergistic T cell activation[142], while bivalent CAR-T cells (CART—EGFR—IL13Rα2) induce tumor lysis correlating with cerebrospinal fluid cytokine responses in early-phase trials (NCT05168423)[143-145]. Next-generation strategies aim to address these hurdles through synNotch-CAR systems primed with tumor-specific neoantigens (*e.g.*, EGFRvIII) to activate secondary homogeneous glioma targets (EphA2/IL13Rα2), enhancing specificity and efficacy with acceptable safety[146]. Despite these advances, CAR-T therapy in GBM still faces critical limitations. Systemic delivery is hindered by the BBB, necessitating invasive intrathecal or intraventricular administration. Antigen loss/downregulation and on-target off-tumor toxicity, stemming from shared neural antigen expression, compromise long-term efficacy and safety. Furthermore, the immunosuppressive microenvironment impairs CAR-T activation and persistence. Immune-related toxicities such as cytokine release syndrome and neuroinflammation further necessitate stringent clinical monitoring.

4.5. Cytokine-based therapy

Cytokines are signaling proteins (<70 kDa) secreted by cells to regulate immune responses through local and systemic communication[147]. They are key mediators of cell-cell interactions within tumor microenvironment. Over the past four decades, cytokine-based therapies have transitioned from systemic administration of immunomodulators like interleukin-2 (IL-2) and interferon-α (IFN-α) to localized delivery strategies aimed at reducing systemic toxicity while targeting tumor[148-150]. Modern innovations employ engineered cytokines (*e.g.*, IL-12, IL-7) or gene-modified vectors to selectively activate antitumor immunity within tumor microenvironment. These agents promote antitumor effects by TAMs phenotypes, enhancing T-cell infiltration, and disrupting immunosuppressive networks mediated by TGF-β or IL-10. For example, L19-mTNF (NCT03779230, NCT04573192), an engineered antibody-cytokine fusion, demonstrates its high safety profile while promoting immune cell infiltration, inducing immunostimulatory pathways, and reducing immunosuppressive signaling[12,151]. Birocchi et al.[152] developed a lentiviral vector platform to engineer hematopoietic stem cells for spatiotemporally controlled release of IFN-γ or IL-12 at tumor sites. This approach reprogrammed tumor microenvironment toward a proinflammatory state and achieved robust GBM inhibition. Shanley et al. revealed that IL-21 enhances NK cell antitumor efficacy against GBM through C/EBP transcription factor-mediated epigenetic reprogramming[153]. Rimas V. Lukas' group initiated a clinical trial (NCT04006119) using a Veledimex (VDX)-regulated IL-12 gene therapy combined with nivolumab, showing synergistic GBM growth inhibition[154]. The similar study was also conducted by another group, Agliardi et al.[155] proposed a recombinant IL-12, which can reshape immunosuppressive tumor microenvironment and enhance the efficacy of EGFRvIII-specific CAR-T cell therapy. While cytokine-based immunotherapies exhibit therapeutic promise through immune activation, their clinical application remains hampered by pharmacological constraints including systemic toxicity (*e.g.*, cytokine release syndrome), short half-life, suboptimal neoplastic tissue biodistribution, functional pleiotropy, and a narrow therapeutic window[156].

5. Emerging strategies developed to overcome immunosuppressive network

While immunotherapeutic strategies for GBM have demonstrated preclinical promise, their clinical translation continues to face substantial barriers. GBM is highly effective at inducing a complex immunosuppressive network, both systemically and locally, which impairs the effector arm of antitumor immunity. This immunosuppressive landscape induces profound T-cell exhaustion characterized by functional impairment and numerical depletion, establishing a biological threshold that limits therapeutic susceptibility to conventional immune-based interventions. Overcoming these dual mechanisms of T-cell dysfunction represents a critical prerequisite for realizing the therapeutic potential of immunotherapy in GBM. The following section systematically examines emerging strategies to counteract local and systemic immunosuppression, thereby enabling more effective immunotherapeutic engagement against GBM.

5.1. *Therapeutic interventions against local immunosuppression*

The local tumor microenvironment is well characterized and serves as a key mechanism of immune evasion. Current therapeutic innovations focus on dismantling local immunosuppression through the following aspects: (1) tumor-intrinsic modulation, (2) vascular normalization to restore immune cell infiltration, (3) astrocyte reprogramming to disrupt immunosuppressive signaling networks, (4) neuronal activity regulation to decouple tumor-neural circuit interactions, (5) myeloid cell polarization toward immunostimulatory phenotypes, (6) T-cell reinvigoration *via* trafficking enhancement and functional reprogramming, and (7) targeting immunosuppressive factors (Fig. 3). This section synthesizes recent advances in precision-targeting these components, highlighting mechanistic breakthroughs and translational synergies that collectively redefine the paradigm of GBM immunotherapy.

5.1.1. *Modulating tumor-intrinsic factors to overcome immunosuppression*

The immunosuppressive tumor microenvironment in GBM is fundamentally shaped by tumor cell-intrinsic molecular features, providing critical therapeutic targets for tumor microenvironment reprogramming and immunotherapy potentiation. Emerging strategies targeting tumor-intrinsic mechanisms show particular promise in subverting immunosuppression: Ni et al.[157] showed that blocking the Gal-9/Tim-3 axis in PTEN-deficient GBM inhibited TAMs immunosuppressive functions, enhanced T-cell infiltration, and suppressed tumor growth. Similarly, Sang-Soo Kim et al. designed a tumor-targeting nanomedicine (SGT-53) capable of crossing BBB to introduce wild-type p53 gene, reshaping the tumor microenvironment and sensitizing GBM to anti-PD-1 antibody therapy[158]. A parallel approach involves triggering ICD through chemotherapy, radiotherapy, or targeted agents, which promotes the surface exposure of calreticulin and release of high mobility group box 1 and adenosine triphosphate. These damage-associated molecular patterns act as potent "eat-me" signals, enhancing DCs recruitment, antigen cross-presentation, and subsequent T cell priming[159,160]. In the future, further exploration is needed for precise combination strategies based on molecular typing, such as combining epigenetic drugs with ICIs, or developing multifunctional nanocarriers targeting tumor cells to interrupt tumor-intrinsic pathways to overcome the immunotherapeutic resistance.

5.1.2. *Vascular normalization to facilitate T-cell infiltration*

While antiangiogenic therapy initially emerged as a promising approach targeting the VEGF-driven hypervascularity of GBM, clinical outcomes with bevacizumab, a monoclonal anti-VEGF antibody, reveal limited survival benefits when combined with TMZ-based chemo-radiotherapy in newly diagnosed patients[161]. This clinical shortcoming prompts a strategic shift toward vascular normalization rather than indiscriminate vessel pruning. Emerging approaches now focus on correcting aberrant vasculature to alleviate hypoxia-driven immunosuppression and improve tumor

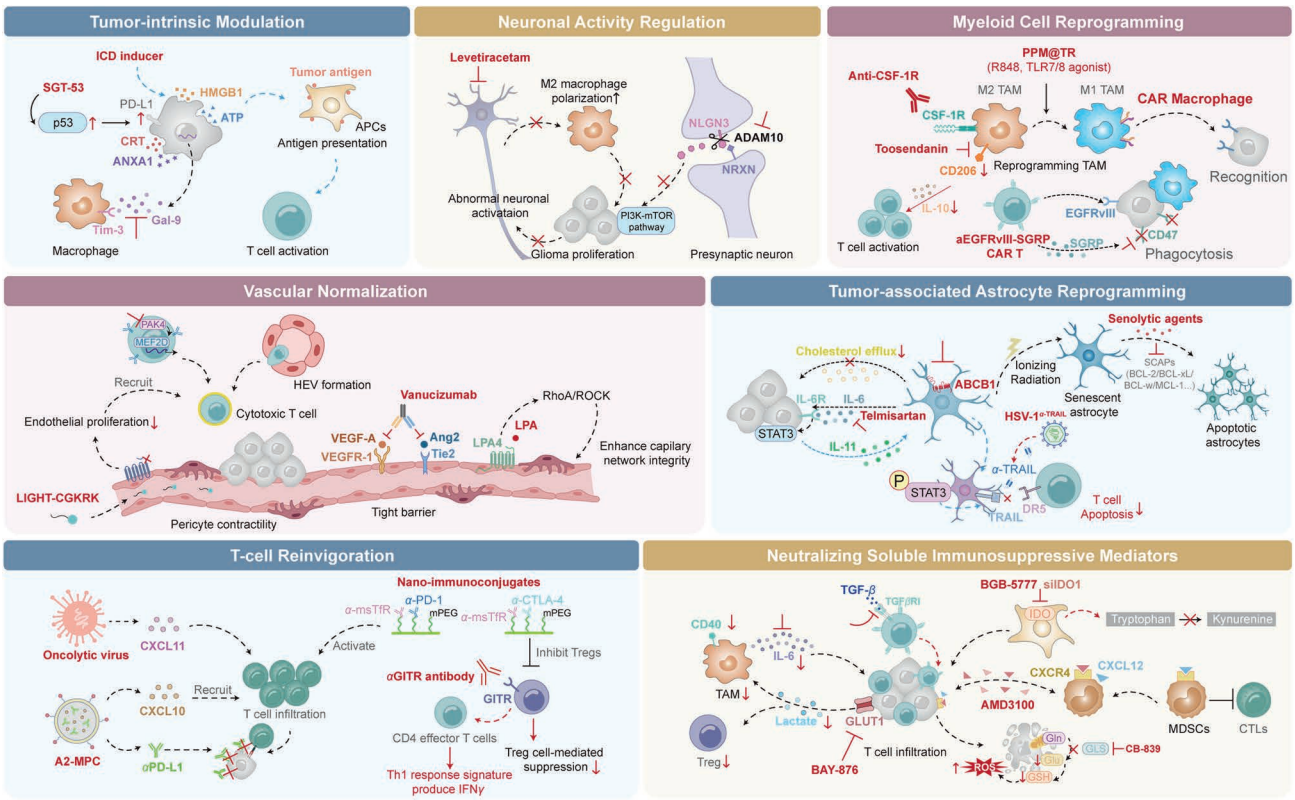

Figure 3 Representative therapeutic approaches to overcome local immunosuppression for GBM and their immunological targets. Schematic representation of key approaches to overcome immunosuppression in the GBM microenvironment, including tumor cells, abnormal vasculature, tumor-associated astrocytes and neurons, myeloid populations, tumor-infiltrating lymphocytes, and immunosuppressive soluble mediator. These strategies collectively target the major cellular and molecular components that contribute to the immunosuppressive tumor microenvironment in GBM.

vessels function to promote immune cell trafficking. Early clinical exploration of bispecific antibodies targeting VEGF and angiopoietin-2 (*e.g.*, vanucizumab) demonstrated dual-pathway inhibition could reduce vascular tortuosity while enhancing antitumor responses in solid tumors[162]. The following study combined VEGF, angiopoietin-2, and PD-1 blockade in a triple therapy approach, which also promoted global vascular normalization and increased CTLs levels, ultimately leading to extended survival[163]. Subsequent preclinical studies refined this concept: Dong et al.[164] revealed that anti-VEGF therapy (B20 antibody) synergizes with EGFRvIII-targeted CAR-T cells by normalizing tumor vasculature, thereby improving T-cell infiltration and prolonging survival in murine GBM models. Further mechanistic insights emerged from the Hanahan group, showing that VEGF pathway inhibitors combined with imipramine, a tricyclic antidepressant, remodeled tumor vasculature while reprogramming immunosuppressive myeloid populations. This dual-action strategy, when paired with PD-L1 blockade, achieved robust tumor control through coordinated T-cell activation in preclinical models[165]. Beyond VEGF-centric strategies, recent work identifies novel vascular targets. In 2022, Ma et al.[166] demonstrated that PAK4 inhibition restored endothelial adhesion proteins, normalizing tumor vasculature and sensitizing GBM to CAR-T cell therapy. Concurrently, Huang et al.[167] showed epidermal growth factor, latrophilin, and seven transmembrane domain-containing protein 1 (ELTD1) deletion reduced endothelial proliferation, promoting vascular normalization and T-cell recruitment to boost PD-1 blockade responses. Furthermore, researchers are investigating potential drug candidates to promote blood vessel normalization in GBM. For example, Eino et al.[168] reported that lysophosphatidic acid (LPA) signaling *via* LPA4 enhanced capillary network integrity by strengthening endothelial junctions, facilitating lymphocyte infiltration, and amplifying immunotherapy efficacy. He et al. utilized the peptide CGKRK to deliver the tumor necrosis factor superfamily member LIGHT to angiogenic tumor vessels, promoting vessel normalization and enhancing immunotherapy against GBM[169]. Although vascular normalization strategies have shown some success in preclinical studies, the therapeutic window remains narrow—excessive normalization may recreate hypoxic niches, while insufficient modulation sustains immune exclusion. Optimizing treatment sequencing (*e.g.*, vascular priming before immunotherapy) and biomarker-driven patient stratification are crucial for enhancing clinical translation.

5.1.3. Reprogramming tumor-associated astrocytes to alleviate immunosuppression

Malignant astrocytes critically shape the immunosuppressive microenvironment in GBM through multifaceted mechanisms, driving innovative therapeutic strategies to reprogram their activity and enhance immunotherapy. Kyle Malone et al. demonstrated that astrocyte-mediated protection of GBM cells diminished the efficacy of smac mimetic compounds (SMCs), suggesting astrocyte targeting as a viable approach to overcome treatment resistance[170]. Mechanistic insights into astrocytic regulation promote the development of potential therapeutic strategy. Perelroizen et al.[53] demonstrated that targeting astrocytic cholesterol efflux *via* ABCA1 reprogrammed the immunological properties of tumor microenvironment and inhibited tumor progression. Ji et al.[171] showed that radiotherapy-induced astrocyte senescence perpetuated immunosuppression, a process reversible by senolytic agents that remodeled tumor microenvironment and extent survival. Further studies revealed that telmisartan inhibits the IL-6/STAT3 signaling pathway between astrocytes and glioma, demonstrating potential for improving immunosuppressive tumor microenvironment[172]. Recent advances extended these findings by showing that genetic inactivation of the IL-11 receptor or TRAIL in astrocytes enhanced T-cell and macrophage responses and prolonged survival in GBM models[57]. Complementing this approach, researchers employed an oncolytic HSV-1 virus engineered to express a TRAIL-blocking single-chain antibody within the tumor microenvironment, which extended survival and enhanced tumor-specific immunity in preclinical models. These strategies collectively demonstrate therapeutic potential for astrocyte-mediated immunosuppressive networks. Continued innovation in precision targeting and combinatorial approaches remains pivotal to advancing astrocyte-centric therapies for GBM.

5.1.4. Regulating neuronal activity to normalize immune function

Emerging evidence highlights neurons as critical regulators of GBM progression and immunosuppressive microenvironment formation through activity-dependent mechanisms. Pioneering work by Venkatesh et al.[173] demonstrated that ADAM10 inhibitors reduced the release of NLGN3 from neurons and inhibited the growth of glioma. This strategy is being tested in clinical study (NCT04295759). Recent advances further reveal that neuronal hyperactivity modulates immune landscapes. Guo et al.[62] reported that the anti-seizure medication levetiracetam treatment impaired neuronal activation, subsequently reducing neuron-induced microglial M2 polarization in GBM. These findings collectively position neuronal signaling as a master regulator of tumor-immune crosstalk, where activity-dependent secretion of neurodevelopmental factors (*e.g.*, NLGN3) establish an immunosuppressive niche. While neuron-targeted immunomodulation remains underexplored, these mechanistic insights unveil dual therapeutic opportunities, directly disrupting neuron-glioma synaptic communication and indirectly normalizing neuron-driven immune dysfunction.

5.1.5. Reprogramming myeloid cell phenotype to exert antitumor activity

Recent advances in myeloid cell modulation strategies have emerged as pivotal approaches to overcome local immunosuppression and potentiate immunotherapy in GBM. While ICIs remain central to current therapeutic efforts, their efficacy appears contingent upon synergistic strategies targeting the myeloid compartment[13]. Foundational studies reveal CSF-1R inhibition's capacity to reprogram TAMs and impede tumor progression, a mechanism validated across multiple therapeutic contexts[174,175]. Building on these insights, contemporary research employs sophisticated delivery platforms to achieve precise myeloid cell modulation. pH-responsive nanoparticles enable targeted delivery of resiquimod (TLR7/8 agonist) to induce M1 macrophage polarization[176], while cathepsin B-responsive systems[177] and glycopolymer nanoparticles[178] demonstrate the capacity to remodel tumor microenvironment to polarize TAMs to pro-inflammatory phenotype. Parallel advancements in innate immune activation utilize STING agonists delivered *via* lipid nanoparticles and mesoporous silica carriers, effectively converting immunosuppressive myeloid populations into antitumor effectors and establishing durable T cell immune response[179,180].

Therapeutic innovation extends to enhancing myeloid phagocytic capacity through CD47/SIRPα axis disruption, with engineered CAR-T cells secreting signal regulatory protein gamma

(SIRPγ)-related protein (SGRP) demonstrating improved tumor clearance through TAMs-mediated phagocytosis[181]. This paradigm combines with emerging cellular therapies such as cavity-injectable nanoporter-hydrogel superstructure that induced CAR macrophages, which established locoregional immunity and prevented postoperative recurrence when paired with CD47 blockade strategy[182]. Complementary strategies employ natural compounds like toosendanin to reverse myeloid-mediated immunosuppression and sensitize GBM to CAR-T therapy[183]. Concurrently, myeloid depletion approaches also show promise to enhance PD-1 inhibition efficacy[184,185]. While myeloid-targeted strategies have significantly advanced GBM immunotherapy, clinical translation requires optimized delivery systems for CNS penetration and resolution of temporal coordination between combination therapies.

5.1.6. Reinvigorating T-cell to enhance immunotherapy efficacy

Overcoming T-cell exclusion remains pivotal for advancing GBM immunotherapy, driving innovative strategies to enhance T-cell infiltration and functionality. Early breakthroughs demonstrated chemokine modulation's potential, with CXCL11-armed oncolytic adenoviruses and hydrogel-encapsulated CXCL10 significantly improving T-cell trafficking and sustained antitumor immunity[186,187]. Emerging cellular engineering strategies, including CXCR1/2-modified CAR-T cells exploiting IL-8 gradients[188] and CXCL10−Nrf2−FTH-engineered mesenchymal stem cells to increase CXCL10 secretion[189], demonstrated enhanced T-cell infiltration. Subsequent refinements integrate nanotechnology to bypass BBB, exemplified by macrophage-membrane-camouflaged nanovesicles delivering CXCL10 and anti-PD-L1 antibody[190], and phosphorus dendrimer nanocomplexes restoring CTLs and NK cell activity[191]. Parallel advances in immune checkpoint modulation revealed CD161 blockade[192] and nano-immunoconjugates targeting CTLA-4/PD-1[193] as effective strategies to reinvigorate dysfunctional T cells, with recent microglia-mimetic platforms further enhancing BBB penetration and tumor-specific delivery of anti-PD-1 antibody[194]. Complementary approaches focus on reshaping immunosuppressive T-cell populations, where an agonistic antibody (αGITR)-mediated Treg-to-effector conversion synergized with PD-1 inhibition to alleviate immune suppression[195]. These multidimensional interventions addressing the challenge of T-cell recruitment, functional activation, and suppressive population modulation, can combined with the above-mentioned strategies to overcome the immunosuppression and enhance immunotherapy for GBM.

5.1.7. Neutralizing soluble immunosuppressive mediators to reverse immunosuppression

Targeting soluble immunosuppressive mediators has emerged as a cornerstone strategy to reverse the immunosuppressive milieu in GBM. Interventions focused on cytokine neutralization tend to be effective, exemplified by IL-6 targeting[196] and CAR-T cells engineered with dominant-negative TGF-β receptor II[197], which demonstrated enhanced T-cell functionality in tumor microenvironment. Disrupting the chemokine signaling strategy also achieve some advancements. For example, Alghamri et al.[198] developed nanoparticles loaded with AMD3100 to interfere with the CXCL12/CXCR4 pathway, which reduced MDSC infiltration and achieved durable remission when combined with radiotherapy.

The field has since evolved toward multimodal metabolic intervention strategies. Lactate generation inhibitors have shown dual benefits by simultaneously reprogramming cancer stem cell glucose metabolism and alleviating immunosuppression through reduction of tumor-infiltrating CAR-Treg cells, potentially enhancing CAR-T therapy efficacy in glioblastoma[199]. Building on this concept, Li et al.[200] developed an injectable thermogel (Gel@B-B) co-loaded with GLUT1 inhibitor BAY-876 and PD-1/PD-L1 blocker BMS-1, which demonstrated synergistic effects by inhibiting lactate excretion and reducing immunosuppressive TAMs and Tregs. Glutamine metabolism inhibition has emerged as another promising therapeutic avenue. Guo et al.[201] designed an injectable peptide gel incorporating glutaminase inhibitor CB-839 and copper peptide nanoparticles (Cu-His NPs), which fine-tunes glutamic acid production to enhance chemodynamic therapy efficacy while promoting ICD and improving the immune microenvironment, ultimately reducing tumor recurrence and extending survival in preclinical models. For IDH-mutant gliomas, vorasidenib, a brain-penetrant mutant IDH1/2 inhibitor, has shown clinical promise by reducing 2-HG levels and restoring CTLs activity, recently receiving FDA approval based on its ability to prolong progression-free survival in glioma patients (NCT04164901)[202]. Additional strategies targeting tryptophan metabolism have shown promise, including indoleamine 2,3-dioxygenase 1 (IDO1) silencing through siRNA-loaded nanoregulator[187] and small molecule inhibitors BGB-5777 synergizing with PD-1 blockade[203], both effectively alleviating kynurenine-mediated immunosuppression. Recent breakthroughs integrate epigenetic reprogramming with viral vector technologies, as evidenced by IRF8-delivering retroviral vectors that simultaneously boost DCs activation while suppressing myeloid-derived Arg1/IDO1 expression[204]. These multifaceted intervention approaches collectively work to rebalance the immune response, transforming "cold" immunosuppressive niches into immunoreactive environments conducive to T-cell effector functions. Future directions can prioritize smart nanoplatforms capable of dynamic cytokine sensing/neutralization and synthetic biology approaches for immune microenvironment regulation.

5.2. Therapeutic interventions against systemic immunosuppression

In contrast to tumor microenvironment, systemic immunosuppression in GBM remains poorly understood, but emerging therapeutic strategies are overcoming this immunotherapy barrier through multimodal interventions (Fig. 4). Pioneering approaches targeting host immune potentiation and lymphocyte trafficking modulation demonstrate capacity to reverse global lymphopenia and restore antitumor immunity. These strategies collectively recalibrate systemic immune competence, providing a critical foundation for enhancing immunotherapy efficacy against GBM.

The advances in cytokine-based therapies demonstrate promising strategies to counteract systemic immunosuppression in GBM. Interleukin-7 (IL-7), a pivotal regulator of T-cell homeostasis, has emerged as a cornerstone therapeutic for lymphopenia reversal[205]. Advancements in recombinant cytokines with prolonged *in vivo* activity have led to multiple clinical trials investigating IL-7 as a potential therapy for GBM. For instance, NT-I7, a long-acting recombinant human IL-7, has been shown to increase $CD8^+$ T cells in lymph nodes, spleen, thymus, and tumors in GBM-bearing mice, effectively mitigating radiation-induced lymphopenia and improving survival rates[206]. Similarly, the systemic administration of rhIL-7-hyFc, a modified form of recombinant human IL-7, effectively restored and sustained total lymphocyte counts in recurrent GBM patients undergoing various salvage chemotherapy regimens, without inducing significant

adverse events[207]. Multiple ongoing clinical trials are already evaluating the potential benefits of IL-7 in glioma patients (NCT03687957, NCT03619239, NCT04065087, NCT04289155, NCT02659800, NCT04600817, NCT05191784, and NCT05465954).

Strategies targeting the potential immunosuppressive mechanisms are also investigated to restore systemic T cell functionality in GBM. Clinical studies demonstrated that anti-CD25 monoclonal antibodies reduced circulating Tregs, thereby mitigating systemic immunosuppression and enhancing vaccine-induced humoral immunity[208]. However, research by Chongsathidkiet et al.[11] reveals limitations of granulocyte colony-stimulating factor (G-CSF) monotherapy, which, while capable of mobilizing bone marrow-sequestered T cells, fails to consistently improve survival outcomes in GBM models, suggesting that mere T cell release is insufficient for robust antitumor immunity. As the research deepens, recent studies have found that elevated glucocorticoid levels in GBM patients upregulated CCR8 on T cells, which bound to CCL1/CCL8 in BM, trapping T cells and preventing tumor infiltration. Pharmacological inhibition of glucocorticoid receptor (GR) (*e.g.*, mifepristone) or genetic ablation of GR/CCR8 restored T-cell circulation, increased intra-tumoral $CD8^+$ T-cell density, and synergized with anti-PD-1 therapy in preclinical models[106]. Given that GBM employs multiple immune evasion mechanisms, it remains uncertain whether current strategies can fully rectify the unique systemic deficiencies observed in clinical settings. Further research is needed to uncover the mechanisms behind GBM-induced systemic immunosuppression to advance immunotherapeutic approaches.

5.3. Therapeutic interventions against both systemic and local immunosuppression

While tumor immunotherapy has traditionally focused on reinvigorating cytotoxic effectors within the tumor microenvironment, emerging evidence underscores the fundamentally systemic nature of effective antitumor immunity. Recent work by Ravi et al.[209] employing single-cell and spatial omics technologies has provided compelling evidence that host environment plays an important role in reshaping the local tumor microenvironment. These findings reinforce the paradigm that both systemic and local immune function are indispensable for sustaining the cancer-immunity cycle and generating robust antitumor responses. Given the profound systemic and local immunosuppression characteristic of GBM, strategies simultaneously targeting both aspects have emerged to potentiate immunotherapy.

The preclinical investigations have highlighted the limitations of unilateral approaches targeting either systemic or local immunosuppression. Fecci et al. initially showed that while G-CSF could mobilize BM-sequestered T cells, this monotherapy failed to confer antitumor efficacy in GBM models[11]. This team subsequently developed a dual-target strategy combining 4-1BB agonism with S1P1 stabilization, achieving a 40% improvement in survival in orthotopic glioma models[11]. Although not explicitly

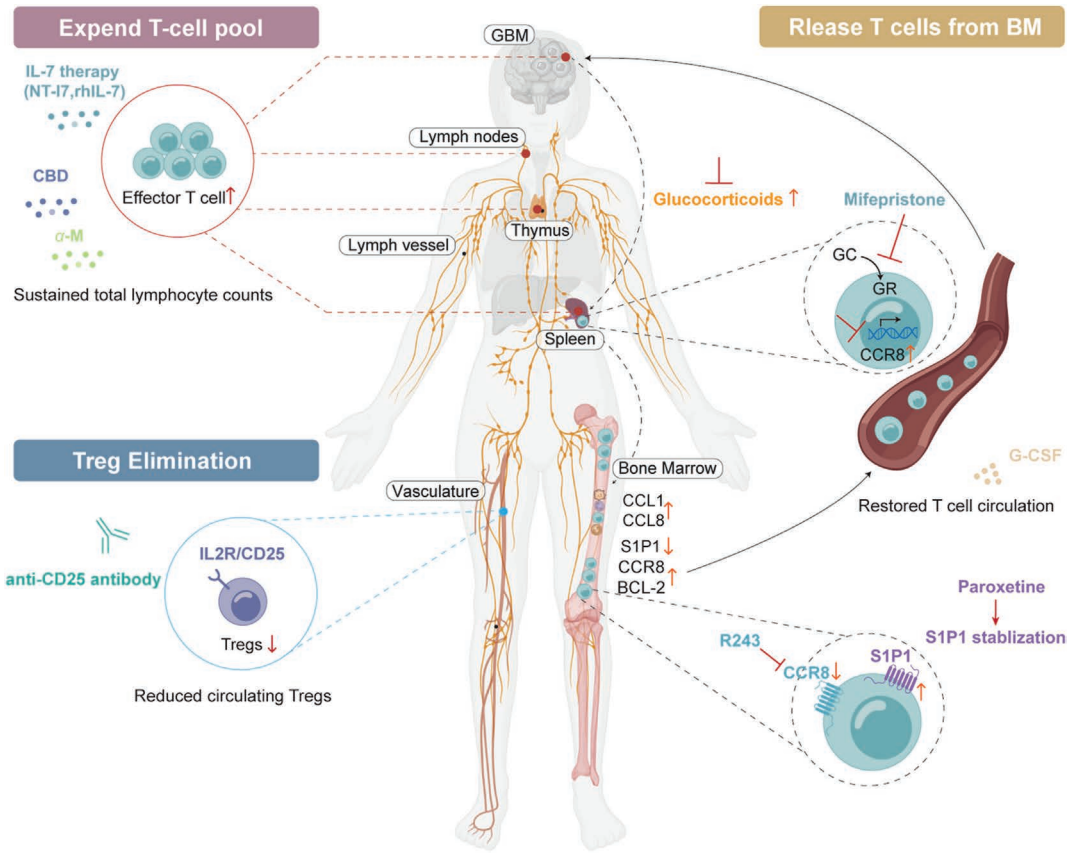

Figure 4 Systemic immunomodulation strategies for GBM treatment and their immunological targets. Schematic representation of key therapeutic approaches targeting systemic immunosuppression in GBM, including stabilization of S1P1 by paroxetine, blockade of GR *via* mifepristone, blockade of CCR8 *via* antagonist R243 to mobilize BM-sequestered T cells, depletion of circulating Tregs *via* anti-CD25 antibodies, and enhancement of T-cell production in lymphoid organs using natural products or modified cytokines.

framed as addressing both systemic and local immunosuppression, this work provided critical conceptual inspiration for combinatorial approaches. Building on these insights, our group has pioneered the concept of concurrently overcoming systemic and local immunosuppression to enhance GBM immunotherapy. Natural products with immunomodulatory potential show promise in cancer immunotherapy[210]. Through systematic investigation of natural product-derived immunomodulators, we identified cannabidiol (CBD), a main non-psychoactive cannabinoid component extracted from the plant *Cannabis sativa* L., efficiently expanding peripheral T-cell pools and reversing systemic immunosuppression (Fig. 4). Complementing this systemic approach, we incorporated LIGHT (TNFSF14), which reprograms the immunosuppressive tumor microenvironment in IDH-wild type GBM while inducing high endothelial venule (HEV) formation to facilitate T-cell infiltration[211]. The translational implementation of this dual-targeting concept was achieved through an engineered nanoparticle platform ("Nano-reshaper") capable of co-delivering CBD and LIGHT plasmid, which demonstrated synergistic efficacy in reprogramming both systemic and local immune function while significantly enhancing anti-PD-1 therapeutic outcomes[212]. Recognizing the distinct oxidative stress vulnerability of IDH-mutant glioma cells, we further developed an "Immuno-initiator" platform combining the natural product α-mangostin (α-M) with the photosensitizer indocyanine green (ICG). This system concurrently targeted both systemic and local immunosuppression in IDH-mutant gliomas, where α-M-mediated T-cell expansion reversed systemic immune dysfunction while ICG-induced ICD remodeled the local immunosuppressive microenvironment, synergistically enhancing the efficacy of anti-PD-1 therapy[213]. The proposed conceptual framework has been independently validated by another research group. Wang et al.[214] demonstrated that paroxetine (PX)-mediated inhibition of G protein-coupled receptor kinase 2 (GRK2) prevented S1P1 internalization, thereby preserving its surface expression on T cells. They also developed biomimetic nanoparticles loaded with JQ1 to reduce PD-1 and TIM-3 expression on T cells and PD-L1 expression on tumor cells. This combinatorial approach successfully mobilized functional bone marrow-sequestered T cells while improving their tumor infiltration capacity, significantly prolonging survival in GBM models[214].

The limited clinical progress in GBM immunotherapy may stem from the predominant focus on either local tumor microenvironment modulation or systemic immune enhancement alone. Our work establishes a paradigm shift by demonstrating that concurrent targeting of both systemic and local immunosuppression yields superior preclinical outcomes. As the understanding of GBM immunosuppression mechanisms deepens, we anticipate the development of more sophisticated strategies that integrate tumor-specific microenvironmental characteristics with systemic immune reprogramming. This requires careful consideration of GBM's local immune landscape, including its spatiotemporal heterogeneity and molecular subtypes. For instance, recurrent tumors exhibit distinct immunophenotypes versus primary GBM, characterized by increased tumor-infiltrating lymphocytes and macrophages, yet paradoxically elevated PD-L1 and PD-1 expression[27,215,216]. This evolving immunosuppressive architecture necessitates precision interventions tailored to disease phase, where successful dual-targeting strategies incorporate dynamic microenvironmental profiling and stage-specific therapeutic optimization. Furthermore, the relatively immune-cold microenvironment of IDH-mutant gliomas, with their diminished infiltration of macrophages, DCs, and T cells, demands innovative strategies to provoke immune cell infiltration and initiate antitumor responses[38,217]. Thus, future research should focus on understanding the specific mechanisms underlying systemic and local immunosuppression in GBM to develop tailored therapeutic approaches that restore immune function and enhance immunotherapy effectiveness.

6. Conclusions and perspectives

Despite significant advances in immunotherapy over the past decades, GBM remains an incurable malignancy with dismal patient outcomes. Progress in this field has expanded our understanding of the immune landscape of GBM and spurred the development of novel therapeutic strategies. Numerous approaches have been designed to counteract the dysfunctional local immune response, particularly the immunosuppressive tumor microenvironment. However, the immune system operates as a coordinated network, and GBM immunotherapy research has largely focused on local microenvironment-associated mechanisms while overlooking the critical impact of systemic immunosuppression. Few studies have investigated the role of systemic immune dysfunction or explored therapeutic strategies to mitigate it. More importantly, current evidence reveals a striking knowledge gap regarding mechanistic links between local tumor microenvironment factors and systemic immune dysfunction. Available data indicate that effective local immune responses rely on functional peripheral immune cells to initiate and sustain antitumor immunity. This is further supported by the observation that the tumor-burdened immune system operates differently from an unperturbed one, and *de novo* antitumor immune responses originating in the periphery are crucial for immunotherapeutic efficacy. Thus, the profound systemic immunosuppression observed in GBM patients-driven by tumor-derived, host-associated, and treatment-related factors-likely contributes to the limited clinical success of localized immune-modulating strategies. While the precise mechanisms underlying systemic immunosuppression in GBM remain incompletely understood, they represent a major barrier to effective immunotherapy. Future studies should aim to identify the potential molecular mediators to connecting local immunosuppression to systemic effects, characterize CNS-specific immune trafficking pathways, and develop improved models for studying local-systemic immune interactions in GBM. Such advances are essential for driving the development of more effective GBM immunotherapies.

Given these challenges, monotherapy targeting either systemic or local immunosuppression alone is unlikely to achieve durable therapeutic outcomes. A dual-pronged approach is essential: first, reversing systemic immunosuppression to restore peripheral immune function, and second, alleviating local immunosuppressive mechanisms within the tumor microenvironment to enhance the activity of effector immune cells against tumor cells. Overcoming both systemic and local immunosuppression is paramount for restoring robust antitumor immunity and improving the efficacy of immunotherapy in GBM. Further elucidation of the molecular and cellular mechanisms by which GBM establishes its immunosuppressive network and evades immune surveillance will be instrumental in guiding the development of next-generation immunotherapeutic strategies.

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The authors completed the first draft independently, and the authors used DeepSeek for language polishing and grammar checking to enhance the clarity of the manuscript. The authors assume full responsibility for the research content, data interpretation, and conclusions. The AI tool was used solely for linguistic refinement.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Schaff LR, Mellinghoff IK. Glioblastoma and other primary brain malignancies in adults: a review. *JAMA* 2023;**329**:574−87.
2. Delgado-Martín B, Medina MÁ. Advances in the knowledge of the molecular biology of glioblastoma and its impact in patient diagnosis, stratification, and treatment. *Adv Sci* 2020;**7**:1902971.
3. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS, Khasraw M. Management of glioblastoma: state of the art and future directions. *CA Cancer J Clin* 2020;**70**:299−312.
4. Liu H, Qiu W, Sun T, Wang L, Du C, Hu Y, et al. Therapeutic strategies of glioblastoma (GBM): the current advances in the molecular targets and bioactive small molecule compounds. *Acta Pharm Sin B* 2022;**12**:1781−804.
5. Pawlowski KD, Duffy JT, Babak MV, Balyasnikova IV. Modeling glioblastoma complexity with organoids for personalized treatments. *Trends Mol Med* 2023;**29**:282−96.
6. Pang L, Khan F, Dunterman M, Chen P. Pharmacological targeting of the tumor−immune symbiosis in glioblastoma. *Trends Pharmacol Sci* 2022;**43**:686−700.
7. Rominiyi O, Vanderlinden A, Clenton SJ, Bridgewater C, Al-Tamimi Y, Collis SJ. Tumour treating fields therapy for glioblastoma: current advances and future directions. *Br J Cancer* 2021;**124**:697−709.
8. De Witt Hamer PC. Small molecule kinase inhibitors in glioblastoma: a systematic review of clinical studies. *Neuro Oncol* 2010;**12**:304−16.
9. Stupp R, Taillibert S, Kanner A, Read W, Steinberg DM, Lhermitte B, et al. Effect of tumor-treating fields plus maintenance temozolomide *vs* maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA* 2017;**318**:2306−16.
10. Oliveira G, Wu CJ. Dynamics and specificities of T cells in cancer immunotherapy. *Nat Rev Cancer* 2023;**23**:295−316.
11. Chongsathidkiet P, Jackson C, Koyama S, Loebel F, Cui X, Farber SH, et al. Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors. *Nat Med* 2018;**24**:1459−68.
12. Ayasoufi K, Pfaller CK, Evgin L, Khadka RH, Tritz ZP, Goddery EN, et al. Brain cancer induces systemic immunosuppression through release of non-steroid soluble mediators. *Brain* 2020;**143**:3629−52.
13. Lim M, Xia Y, Bettegowda C, Weller M. Current state of immunotherapy for glioblastoma. *Nat Rev Clin Oncol* 2018;**15**:422−42.
14. Medawar PB. Immunity to homologous grafted skin; the fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. *Br J Exp Pathol* 1948;**29**:58−69.
15. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015;**523**:337−41.
16. Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med* 2015;**212**:991−9.
17. Kipnis J. Multifaceted interactions between adaptive immunity and the central nervous system. *Science* 2016;**353**:766−71.
18. Zierfuss B, Larochelle C, Prat A. Blood−brain barrier dysfunction in multiple sclerosis: causes, consequences, and potential effects of therapies. *Lancet Neurol* 2024;**23**:95−109.
19. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood−brain barrier: structure, regulation and drug delivery. *Signal Transduct Targeted Ther* 2023;**8**:217.
20. Andersson PB, Perry VH, Gordon S. The acute inflammatory response to lipopolysaccharide in CNS parenchyma differs from that in other body tissues. *Neuroscience* 1992;**48**:169−86.
21. Stollg G, Jander S. The role of microglia and macrophages in the pathophysiology of the CNS. *Prog Neurobiol* 1999;**58**:233−47.
22. Nichols JR, Aldrich AL, Mariani MM, Vidlak D, Esen N, Kielian T. TLR2 deficiency leads to increased Th17 infiltrates in experimental brain abscesses. *J Immunol* 2009;**182**:7119−30.
23. Arvanitis CD, Ferraro GB, Jain RK. The blood−brain barrier and blood−tumour barrier in brain tumours and metastases. *Nat Rev Cancer* 2020;**20**:26−41.
24. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* 2010;**330**:841−5.
25. Woodroofe MN, Bellamy AS, Feldmann M, Davison AN, Cuzner ML. Immunocytochemical characterisation of the immune reaction in the central nervous system in multiple sclerosis: possible role for microglia in lesion growth. *J Neurol Sci* 1986;**74**:135−52.
26. Schiffer D, Mellai M, Bovio E, Annovazzi L. The neuropathological basis to the functional role of microglia/macrophages in gliomas. *Neurol Sci* 2017;**38**:1571−7.
27. Hoogstrate Y, Draaisma K, Ghisai SA, van Hijfte L, Barin N, de Heer I, et al. Transcriptome analysis reveals tumor microenvironment changes in glioblastoma. *Cancer Cell* 2023;**41**:678−92.
28. Bikfalvi A, da Costa CA, Avril T, Barnier JV, Bauchet L, Brisson L, et al. Challenges in glioblastoma research: focus on the tumor microenvironment. *Trends Cancer* 2023;**9**:9−27.
29. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. *Science* 2015;**348**:69−74.

30. Hellmann MD, Ciuleanu T-E, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018;**378**: 2093−104.
31. Goodman AM, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Therapeut* 2017;**16**:2598−608.
32. Sampson JH, Gunn MD, Fecci PE, Ashley DM. Brain immunology and immunotherapy in brain tumours. *Nat Rev Cancer* 2020;**20**: 12−25.
33. Hu C, Leche CA, Kiyatkin A, Yu Z, Stayrook SE, Ferguson KM, et al. Glioblastoma mutations alter EGFR dimer structure to prevent ligand bias. *Nature* 2022;**602**:518−22.
34. Cui X, Zhao J, Li G, Yang C, Yang S, Zhan Q, et al. Blockage of EGFR/AKT and mevalonate pathways synergize the antitumor effect of temozolomide by reprogramming energy metabolism in glioblastoma. *Cancer Commun* 2023;**43**:1326−53.
35. Ham SW, Jeon HY, Jin X, Kim EJ, Kim JK, Shin YJ, et al. TP53 gain-of-function mutation promotes inflammation in glioblastoma. *Cell Death Differ* 2019;**26**:409−25.
36. Brennan CW, Verhaak RGW, McKenna A, Campos B, Noushmehr H, Salama SR, et al. The somatic genomic landscape of glioblastoma. *Cell* 2013;**155**:462−77.
37. Parsa AT, Waldron JS, Panner A, Crane CA, Parney IF, Barry JJ, et al. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. *Nat Med* 2007;**13**:84−8.
38. Bunse L, Pusch S, Bunse T, Sahm F, Sanghvi K, Friedrich M, et al. Suppression of antitumor T cell immunity by the oncometabolite (*R*)-2-hydroxyglutarate. *Nat Med* 2018;**24**:1192−203.
39. Tomaszewski W, Sanchez-Perez L, Gajewski TF, Sampson JH. Brain tumor microenvironment and host state: implications for immunotherapy. *Clin Cancer Res* 2019;**25**:4202−10.
40. Fan D, Yue Q, Chen J, Wang C, Yu R, Jin Z, et al. Reprogramming the immunosuppressive microenvironment of IDH1 wild-type glioblastoma by blocking Wnt signaling between microglia and cancer cells. *OncoImmunology* 2021;**10**:1932061.
41. Nduom EK, Wei J, Yaghi NK, Huang N, Kong LY, Gabrusiewicz K, et al. PD-L1 expression and prognostic impact in glioblastoma. *Neuro Oncol* 2015;**18**:195−205.
42. Zhai L, Bell A, Ladomersky E, Lauing KL, Bollu L, Nguyen B, et al. Tumor cell IDO enhances immune suppression and decreases survival independent of tryptophan metabolism in glioblastoma. *Clin Cancer Res* 2021;**27**:6514−28.
43. Broekman ML, Maas SLN, Abels ER, Mempel TR, Krichevsky AM, Breakefield XO. Multidimensional communication in the microenvirons of glioblastoma. *Nat Rev Neurol* 2018;**14**:482−95.
44. Brighi C, Puttick S, Rose S, Whittaker AK. The potential for remodelling the tumour vasculature in glioblastoma. *Adv Drug Deliv Rev* 2018;**136-137**:49−61.
45. Sattiraju A, Kang S, Giotti B, Chen Z, Marallano VJ, Brusco C, et al. Hypoxic niches attract and sequester tumor-associated macrophages and cytotoxic T cells and reprogram them for immunosuppression. *Immunity* 2023;**56**:1825−43.
46. Ramachandran M, Vaccaro A, van de Walle T, Georganaki M, Lugano R, Vemuri K, et al. Tailoring vascular phenotype through AAV therapy promotes anti-tumor immunity in glioma. *Cancer Cell* 2023;**41**:1134−51.
47. Hasel P, Liddelow SA. Astrocytes. *Curr Biol* 2021;**31**:R326−7.
48. Zhang H, Zhou Y, Cui B, Liu Z, Shen H. Novel insights into astrocyte-mediated signaling of proliferation, invasion and tumor immune microenvironment in glioblastoma. *Biomed Pharmacother* 2020;**126**:110086.
49. Heiland HD, Ravi VM, Behringer SP, Frenking JH, Wurm J, Joseph K, et al. Tumor-associated reactive astrocytes aid the evolution of immunosuppressive environment in glioblastoma. *Nat Commun* 2019;**10**:2541.
50. Laws MT, Walker EN, Cozzi FM, Ampie L, Jung MY, Burton EC, et al. Glioblastoma may evade immune surveillance through primary cilia-dependent signaling in an IL-6 dependent manner. *Front Oncol* 2023;**13**:1279923.
51. Zhou Z, Li W, Song Y, Wang L, Zhang K, Yang J, et al. Growth differentiation factor-15 suppresses maturation and function of dendritic cells and inhibits tumor-specific immune response. *PLoS One* 2013;**8**:e78618.
52. Schachtele SJ, Hu S, Sheng WS, Mutnal MB, Lokensgard JR. Glial cells suppress postencephalitic $CD8^+$ T lymphocytes through PD-L1. *Glia* 2014;**62**:1582−94.
53. Perelroizen R, Philosof B, Budick-Harmelin N, Chernobylsky T, Ron A, Katzir R, et al. Astrocyte immunometabolic regulation of the tumour microenvironment drives glioblastoma pathogenicity. *Brain* 2022;**145**:3288−307.
54. Chen Z, Yuan SJ, Li K, Zhang Q, Li TF, An HC, et al. Doxorubicin-polyglycerol-nanodiamond conjugates disrupt STAT3/IL-6-mediated reciprocal activation loop between glioblastoma cells and astrocytes. *J Control Release* 2020;**320**:469−83.
55. Cheng F, Wang H-W, Cuenca A, Huang M, Ghansah T, Brayer J, et al. A critical role for stat3 signaling in immune tolerance. *Immunity* 2003;**19**:425−36.
56. Bunt SK, Yang L, Sinha P, Clements VK, Leips J, Ostrand-Rosenberg S. Reduced inflammation in the tumor microenvironment delays the accumulation of myeloid-derived suppressor cells and limits tumor progression. *Cancer Res* 2007;**67**: 10019−26.
57. Faust Akl C, Andersen BM, Li Z, Giovannoni F, Diebold M, Sanmarco LM, et al. Glioblastoma-instructed astrocytes suppress tumour-specific T cell immunity. *Nature* 2025;**643**:219−29.
58. Huang JY, Cheng YJ, Lin YP, Lin HC, Su CC, Juliano R, et al. Extracellular matrix of glioblastoma inhibits polarization and transmigration of T cells: the role of tenascin-C in immune suppression. *J Immunol* 2010;**185**:1450−9.
59. Johung T, Monje M. Neuronal activity in the glioma microenvironment. *Curr Opin Neurobiol* 2017;**47**:156−61.
60. Venkatesh HS, Johung TB, Caretti V, Noll A, Tang Y, Nagaraja S, et al. Neuronal activity promotes glioma growth through neuroligin-3 secretion. *Cell* 2015;**161**:803−16.
61. Ye L, Xu Y, Hu P, Wang L, Yang JA, Yuan FE, et al. Development and verification of glutamatergic synapse-associated prognosis signature for lower-grade gliomas. *Front Mol Neurosci* 2021;**14**: 720899.
62. Guo X, Qiu W, Li B, Qi Y, Wang S, Zhao R, et al. Hypoxia-induced neuronal activity in glioma patients polarizes microglia by potentiating RNA m6A demethylation. *Clin Cancer Res* 2024;**30**: 1160−74.
63. Neman J, Termini J, Wilczynski S, Vaidehi N, Choy C, Kowolik CM, et al. Human breast cancer metastases to the brain display GABAergic properties in the neural niche. *Proc Natl Acad Sci U S A* 2014;**111**:984−9.
64. Huang-Hobbs E, Cheng YT, Ko Y, Luna-Figueroa E, Lozzi B, Taylor KR, et al. Remote neuronal activity drives glioma progression through SEMA4F. *Nature* 2023;**619**:844−50.
65. Zhang Y, Sloan Steven A, Clarke Laura E, Caneda C, Plaza Colton A, Blumenthal Paul D, et al. Purification and characterization of progenitor and mature human astrocytes reveals transcriptional and functional differences with mouse. *Neuron* 2016;**89**:37−53.
66. Darmanis S, Sloan SA, Croote D, Mignardi M, Chernikova S, Samghababi P, et al. Single-cell RNA-Seq analysis of infiltrating neoplastic cells at the migrating front of human glioblastoma. *Cell Rep* 2017;**21**:1399−410.
67. Miller TE, El Farran CA, Couturier CP, Chen Z, D'Antonio JP, Verga J, et al. Programs, origins and immunomodulatory functions of myeloid cells in glioma. *Nature* 2025;**640**:1072−82.
68. Mei Y, Wang X, Zhang J, Liu D, He J, Huang C, et al. Siglec-9 acts as an immune-checkpoint molecule on macrophages in glioblastoma,

restricting T-cell priming and immunotherapy response. *Nat Cancer* 2023;**4**:1273−91.
69. Wu M, Wu L, Wu W, Zhu M, Li J, Wang Z, et al. Phagocytosis of glioma cells enhances the immunosuppressive phenotype of bone marrow−derived macrophages. *Cancer Res* 2023;**83**:771−85.
70. Lin H, Liu C, Hu A, Zhang D, Yang H, Mao Y. Understanding the immunosuppressive microenvironment of glioma: mechanistic insights and clinical perspectives. *J Hematol Oncol* 2024;**17**:31.
71. Gieryng A, Pszczolkowska D, Walentynowicz KA, Rajan WD, Kaminska B. Immune microenvironment of gliomas. *Lab Invest* 2017;**97**:498−518.
72. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. *Nat Rev Immunol* 2012;**12**: 253−68.
73. Yee PP, Wei Y, Kim SY, Lu T, Chih SY, Lawson C, et al. Neutrophil-induced ferroptosis promotes tumor necrosis in glioblastoma progression. *Nat Commun* 2020;**11**:5424.
74. Jeon HY, Ham SW, Kim JK, Jin X, Lee SY, Shin YJ, et al. Ly6G$^+$ inflammatory cells enable the conversion of cancer cells to cancer stem cells in an irradiated glioblastoma model. *Cell Death Differ* 2019;**26**:2139−56.
75. Friedrich M, Hahn M, Michel J, Sankowski R, Kilian M, Kehl N, et al. Dysfunctional dendritic cells limit antigen-specific T cell response in glioma. *Neuro Oncol* 2022;**25**:263−76.
76. Han S, Ma E, Wang X, Yu C, Dong T, Zhan W, et al. Rescuing defective tumor-infiltrating T-cell proliferation in glioblastoma patients. *Oncol Lett* 2016;**12**:2924−9.
77. Woroniecka KI, Rhodin KE, Chongsathidkiet P, Keith KA, Fecci PE. T-cell dysfunction in glioblastoma: applying a new framework. *Clin Cancer Res* 2018;**24**:3792−802.
78. De Boeck A, Ahn BY, D'Mello C, Lun X, Menon SV, Alshehri MM, et al. Glioma-derived IL-33 orchestrates an inflammatory brain tumor microenvironment that accelerates glioma progression. *Nat Commun* 2020;**11**:4997.
79. Lamano JB, Lamano JB, Li YD, DiDomenico JD, Choy W, Veliceasa D, et al. Glioblastoma-derived IL6 induces immunosuppressive peripheral myeloid cell PD-L1 and promotes tumor growth. *Clin Cancer Res* 2019;**25**:3643−57.
80. Torrini C, Nguyen TTT, Shu C, Mela A, Humala N, Mahajan A, et al. Lactate is an epigenetic metabolite that drives survival in model systems of glioblastoma. *Mol Cell* 2022;**82**:3061−76.e6.
81. Certo M, Tsai CH, Pucino V, Ho PC, Mauro C. Lactate modulation of immune responses in inflammatory *versus* tumour microenvironments. *Nat Rev Immunol* 2021;**21**:151−61.
82. Wang S, Huang T, Wu Q, Yuan H, Wu X, Yuan F, et al. Lactate reprograms glioblastoma immunity through CBX3-regulated histone lactylation. *J Clin Investig* 2024;**134**:e176851.
83. Leone RD, Powell JD. Metabolism of immune cells in cancer. *Nat Rev Cancer* 2020;**20**:516−31.
84. Xia L, Oyang L, Lin J, Tan S, Han Y, Wu N, et al. The cancer metabolic reprogramming and immune response. *Mol Cancer* 2021; **20**:28.
85. Kohanbash G, Carrera DA, Shrivastav S, Ahn BJ, Jahan N, Mazor T, et al. Isocitrate dehydrogenase mutations suppress STAT1 and CD8$^+$ T cell accumulation in gliomas. *J Clin Investig* 2017;**127**:1425−37.
86. Takenaka MC, Gabriely G, Rothhammer V, Mascanfroni ID, Wheeler MA, Chao CC, et al. Control of tumor-associated macrophages and T cells in glioblastoma *via* AHR and CD39. *Nat Neurosci* 2019;**22**:729−40.
87. Ricklefs FL, Alayo Q, Krenzlin H, Mahmoud AB, Speranza MC, Nakashima H, et al. Immune evasion mediated by PD-L1 on glioblastoma-derived extracellular vesicles. *Sci Adv* 2018;**4**: eaar2766.
88. Mirzaei R, Sarkar S, Dzikowski L, Rawji KS, Khan L, Faissner A, et al. Brain tumor-initiating cells export tenascin-C associated with exosomes to suppress T cell activity. *OncoImmunology* 2018;**7**: e1478647.
89. Allen BM, Hiam KJ, Burnett CE, Venida A, DeBarge R, Tenvooren I, et al. Systemic dysfunction and plasticity of the immune macroenvironment in cancer models. *Nat Med* 2020;**26**:1125−34.
90. Hiam-Galvez KJ, Allen BM, Spitzer MH. Systemic immunity in cancer. *Nat Rev Cancer* 2021;**21**:345−59.
91. Grossman SA, Ye X, Lesser G, Sloan A, Carraway H, Desideri S, et al. Immunosuppression in patients with high-grade gliomas treated with radiation and temozolomide. *Clin Cancer Res* 2011;**17**: 5473−80.
92. Fecci PE, Mitchell DA, Whitesides JF, Xie W, Friedman AH, Archer GE, et al. Increased regulatory T-cell fraction amidst a diminished CD4 compartment explains cellular immune defects in patients with malignant glioma. *Cancer Res* 2006;**66**:3294−302.
93. Elliott LH, Brooks WH, Roszman TL. Cytokinetic basis for the impaired activation of lymphocytes from patients with primary intracranial tumors. *J Immunol* 1984;**132**:1208−15.
94. Elliott LH, Brooks WH, Roszman TL. Inability of mitogen-activated lymphocytes obtained from patients with malignant primary intracranial tumors to express high affinity interleukin 2 receptors. *J Clin Investig* 1990;**86**:80−6.
95. Gustafson MP, Lin Y, New KC, Bulur PA, O'Neill BP, Gastineau DA, et al. Systemic immune suppression in glioblastoma: the interplay between CD14+HLA-DRlo/neg monocytes, tumor factors, and dexamethasone. *Neuro Oncol* 2010;**12**:631−44.
96. Rodrigues JC, Gonzalez GC, Zhang L, Ibrahim G, Kelly JJ, Gustafson MP, et al. Normal human monocytes exposed to glioma cells acquire myeloid-derived suppressor cell-like properties. *Neuro Oncol* 2009;**12**:351−65.
97. Bloch O, Crane CA, Kaur R, Safaee M, Rutkowski MJ, Parsa AT. Gliomas promote immunosuppression through induction of B7-H1 expression in tumor-associated macrophages. *Clin Cancer Res* 2013; **19**:3165−75.
98. Mathieu M, Martin-Jaular L, Lavieu G, Théry C. Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. *Nat Cell Biol* 2019;**21**:9−17.
99. Chen G, Huang AC, Zhang W, Zhang G, Wu M, Xu W, et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. *Nature* 2018;**560**:382−6.
100. Buzas EI. The roles of extracellular vesicles in the immune system. *Nat Rev Immunol* 2023;**23**:236−50.
101. Graner MW, Alzate O, Dechkovskaia AM, Keene JD, Sampson JH, Mitchell DA, et al. Proteomic and immunologic analyses of brain tumor exosomes. *FASEB J* 2009;**23**:1541−57.
102. Domenis R, Cesselli D, Toffoletto B, Bourkoula E, Caponnetto F, Manini I, et al. Systemic T cells immunosuppression of glioma stem cell-derived exosomes is mediated by monocytic myeloid-derived suppressor cells. *PLoS One* 2017;**12**:e0169932.
103. Ludwig N, Rao A, Sandlesh P, Yerneni SS, Swain AD, Bullock KM, et al. Characterization of systemic immunosuppression by IDH mutant glioma small extracellular vesicles. *Neuro Oncol* 2021;**24**:197−209.
104. Harshyne LA, Nasca BJ, Kenyon LC, Andrews DW, Hooper DC. Serum exosomes and cytokines promote a T-helper cell type 2 environment in the peripheral blood of glioblastoma patients. *Neuro Oncol* 2015;**18**:206−15.
105. Iorgulescu JB, Ivan ME, Safaee M, Parsa AT. The limited capacity of malignant glioma-derived exosomes to suppress peripheral immune effectors. *J Neuroimmunol* 2016;**290**:103−8.
106. Zhang J, Shi Y, Xue X, Bu W, Li Y, Yang T, et al. Targeting the glucocorticoid receptor−CCR8 axis mediated bone marrow T cell sequestration enhances infiltration of anti-tumor T cells in intracranial cancers. *Cell Mol Immunol* 2024;**21**:1145−57.
107. Brooks WH, Netsky MG, Normansell DE, Horwitz DA. Depressed cell-mediated immunity in patients with primary intracranial tumors. Characterization of a humoral immunosuppressive factor. *J Exp Med* 1972;**136**:1631−47.
108. Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Investig* 2007;**117**:1137−46.

109. Rosenberg SA, Dudley ME, Restifo NP. Cancer immunotherapy. *N Engl J Med* 2008;**359**:1072.
110. Falcomatà C, Bärthel S, Schneider G, Rad R, Schmidt-Supprian M, Saur D. Context-specific determinants of the immunosuppressive tumor microenvironment in pancreatic cancer. *Cancer Discov* 2023; **13**:278−97.
111. Kurz E, Hirsch CA, Dalton T, Shadaloey SA, Khodadadi-Jamayran A, Miller G, et al. Exercise-induced engagement of the IL-15/IL-15Rα axis promotes anti-tumor immunity in pancreatic cancer. *Cancer Cell* 2022;**40**:720−37.e5.
112. Salih Z, Banyard A, Tweedy J, Galvani E, Middlehurst P, Mills S, et al. T cell immune awakening in response to immunotherapy is age-dependent. *Eur J Cancer* 2022;**162**:11−21.
113. Ladomersky E, Zhai L, Lauing KL, Bell A, Xu J, Kocherginsky M, et al. Advanced age increases immunosuppression in the brain and decreases immunotherapeutic efficacy in subjects with glioblastoma. *Clin Cancer Res* 2020;**26**:5232−45.
114. Montecino-Rodriguez E, Berent-Maoz B, Dorshkind K. Causes, consequences, and reversal of immune system aging. *J Clin Investig* 2013;**123**:958−65.
115. Preusser M, Lim M, Hafler DA, Reardon DA, Sampson JH. Prospects of immune checkpoint modulators in the treatment of glioblastoma. *Nat Rev Neurol* 2015;**11**:504−14.
116. Ghosh S, Huang J, Inkman M, Zhang J, Thotala S, Tikhonova E, et al. Radiation-induced circulating myeloid-derived suppressor cells induce systemic lymphopenia after chemoradiotherapy in patients with glioblastoma. *Sci Transl Med* 2023;**15**:eabn6758.
117. Le Rhun E, Oppong FB, Vanlancker M, Stupp R, Nabors B, Chinot O, et al. Prognostic significance of therapy-induced myelosuppression in newly diagnosed glioblastoma. *Neuro Oncol* 2022;**24**: 1533−45.
118. Lin AJ, Campian JL, Hui C, Rudra S, Rao YJ, Thotala D, et al. Impact of concurrent *versus* adjuvant chemotherapy on the severity and duration of lymphopenia in glioma patients treated with radiation therapy. *J Neuro Oncol* 2018;**136**:403−11.
119. Zhang JL, Zhong XS, Yang SB, Kang X, Li Y, Chen JX, et al. Features and therapeutic potential of T-cell receptors in high-grade glioma. *Chin Med J (Engl)* 2019;**132**:1435−40.
120. Cordell EC, Alghamri MS, Castro MG, Gutmann DH. T lymphocytes as dynamic regulators of glioma pathobiology. *Neuro Oncol* 2022;**24**: 1647−57.
121. Habashy KJ, Mansour R, Moussalem C, Sawaya R, Massaad MJ. Challenges in glioblastoma immunotherapy: mechanisms of resistance and therapeutic approaches to overcome them. *Br J Cancer* 2022;**127**:976−87.
122. Wong ET, Swanson KD. Dexamethasone—friend or foe for patients with glioblastoma? *JAMA Neurol* 2019;**76**:247−8.
123. Koch MS, Zdioruk M, Nowicki MO, Griffith AM, Aguilar E, Aguilar LK, et al. Systemic high-dose dexamethasone treatment may modulate the efficacy of intratumoral viral oncolytic immunotherapy in glioblastoma models. *J Immunother Cancer* 2022;**10**:e003368.
124. Iorgulescu JB, Gokhale PC, Speranza MC, Eschle BK, Poitras MJ, Wilkens MK, et al. Concurrent dexamethasone limits the clinical benefit of immune checkpoint blockade in glioblastoma. *Clin Cancer Res* 2021;**27**:276−87.
125. Mellman I, Chen DS, Powles T, Turley SJ. The cancer-immunity cycle: indication, genotype, and immunotype. *Immunity* 2023;**56**: 2188−205.
126. Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. *Lancet* 2021;**398**:1002−14.
127. Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, et al. Effect of nivolumab *vs* bevacizumab in patients with recurrent glioblastoma: the checkMate 143 phase 3 randomized clinical trial. *JAMA Oncol* 2020;**6**:1003−10.
128. Brown NF, Ng SM, Brooks C, Coutts T, Holmes J, Roberts C, et al. A phase II open label, randomised study of ipilimumab with temozolomide *versus* temozolomide alone after surgery and chemoradiotherapy in patients with recently diagnosed glioblastoma: the Ipi-Glio trial protocol. *BMC Cancer* 2020;**20**:198.
129. Duerinck J, Schwarze JK, Awada G, Tijtgat J, Vaeyens F, Bertels C, et al. Intracerebral administration of CTLA-4 and PD-1 immune checkpoint blocking monoclonal antibodies in patients with recurrent glioblastoma: a phase I clinical trial. *J Immunother Cancer* 2021;**9**: e002296.
130. Lyon JG, Mokarram N, Saxena T, Carroll SL, Bellamkonda RV. Engineering challenges for brain tumor immunotherapy. *Adv Drug Deliv Rev* 2017;**114**:19−32.
131. Yin Q, Wu L, Han L, Zheng X, Tong R, Li L, et al. Immune-related adverse events of immune checkpoint inhibitors: a review. *Front Immunol* 2023;**14**:1167975.
132. Liu J, Fu M, Wang M, Wan D, Wei Y, Wei X. Cancer vaccines as promising immuno-therapeutics: platforms and current progress. *J Hematol Oncol* 2022;**15**:28.
133. Schuster J, Lai RK, Recht LD, Reardon DA, Paleologos NA, Groves MD, et al. A phase II, multicenter trial of rindopepimut (CDX-110) in newly diagnosed glioblastoma: the ACT III study. *Neuro Oncol* 2015;**17**:854−61.
134. Weller M, Butowski N, Tran DD, Recht LD, Lim M, Hirte H, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. *Lancet Oncol* 2017;**18**: 1373−85.
135. Keskin DB, Anandappa AJ, Sun J, Tirosh I, Mathewson ND, Li S, et al. Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. *Nature* 2019;**565**:234−9.
136. Hilf N, Kuttruff-Coqui S, Frenzel K, Bukur V, Stevanović S, Gouttefangeas C, et al. Actively personalized vaccination trial for newly diagnosed glioblastoma. *Nature* 2019;**565**:240−5.
137. Ma R, Li Z, Chiocca EA, Caligiuri MA, Yu J. The emerging field of oncolytic virus-based cancer immunotherapy. *Trends Cancer* 2023;**9**: 122−39.
138. Carpenter AB, Carpenter AM, Aiken R, Hanft S. Oncolytic virus in gliomas: a review of human clinical investigations. *Ann Oncol* 2021; **32**:968−82.
139. Ling AL, Solomon IH, Landivar AM, Nakashima H, Woods JK, Santos A, et al. Clinical trial links oncolytic immunoactivation to survival in glioblastoma. *Nature* 2023;**623**:157−66.
140. Desjardins A, Sampson J, Peters K, Vlahovic G, Threatt S, Herndon II J, et al. AT-21:final results of a phase 1 trial of an oncolytic polio/rhinovirus recombinant (PVSRIPO) against recurrent glioblastoma (GBM). *Neuro Oncol* 2014;**16**:v13.
141. Choi BD, Gerstner ER, Frigault MJ, Leick MB, Mount CW, Balaj L, et al. Intraventricular CARv3-TEAM-E T cells in recurrent glioblastoma. *N Engl J Med* 2024;**390**:1290−8.
142. Hegde M, Mukherjee M, Grada Z, Pignata A, Landi D, Navai SA, et al. Tandem CAR T cells targeting HER2 and IL13Rα2 mitigate tumor antigen escape. *J Clin Investig* 2016;**126**:3036−52.
143. Bagley SJ, Logun M, Fraietta JA, Wang X, Desai AS, Bagley LJ, et al. Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: phase 1 trial interim results. *Nat Med* 2024;**30**:1320−9.
144. Logun M, Wang X, Sun Y, Bagley SJ, Li N, Desai A, et al. Patient-derived glioblastoma organoids as real-time avatars for assessing responses to clinical CAR-T cell therapy. *Cell Stem Cell* 2025;**32**: 181−90.
145. Park DH, Bhojnagarwala PS, Liaw K, Bordoloi D, Tursi NJ, Zhao S, et al. Novel tri-specific T-cell engager targeting IL-13Rα2 and EGFRvIII provides long-term survival in heterogeneous GBM challenge and promotes antitumor cytotoxicity with patient immune cells. *J Immunother Cancer* 2024;**12**:e009604.
146. Choe JH, Watchmaker PB, Simic MS, Gilbert RD, Li AW, Krasnow NA, et al. SynNotch-CAR T cells overcome challenges of specificity, heterogeneity, and persistence in treating glioblastoma. *Sci Transl Med* 2021;**13**:eabe7378.

147. Yi M, Li T, Niu M, Zhang H, Wu Y, Wu K, et al. Targeting cytokine and chemokine signaling pathways for cancer therapy. *Signal Transduct Targeted Ther* 2024;**9**:176.
148. Hsu W, Lesniak MS, Tyler B, Brem H. Local delivery of interleukin-2 and adriamycin is synergistic in the treatment of experimental malignant glioma. *J Neuro Oncol* 2005;**74**:135−40.
149. Merchant RE, McVicar DW, Merchant LH, Young HF. Treatment of recurrent malignant glioma by repeated intracerebral injections of human recombinant interleukin-2 alone or in combination with systemic interferon-α. results of a phase I clinical trial. *J Neuro Oncol* 1992;**12**:75−83.
150. Xiao Q, Li X, Li Y, Wu Z, Xu C, Chen Z, et al. Biological drug and drug delivery-mediated immunotherapy. *Acta Pharm Sin B* 2021;**11**: 941−60.
151. Weiss T, Puca E, Silginer M, Hemmerle T, Pazahr S, Bink A, et al. Immunocytokines are a promising immunotherapeutic approach against glioblastoma. *Sci Transl Med* 2020;**12**:eabb2311.
152. Birocchi F, Cusimano M, Rossari F, Beretta S, Rancoita PMV, Ranghetti A, et al. Targeted inducible delivery of immunoactivating cytokines reprograms glioblastoma microenvironment and inhibits growth in mouse models. *Sci Transl Med* 2022;**14**:eabl4106.
153. Shanley M, Daher M, Dou J, Li S, Basar R, Rafei H, et al. Interleukin-21 engineering enhances NK cell activity against glioblastoma *via* CEBPD. *Cancer Cell* 2024;**42**:1450−66.e11.
154. Chiocca EA, Gelb AB, Chen CC, Rao G, Reardon DA, Wen PY, et al. Combined immunotherapy with controlled interleukin-12 gene therapy and immune checkpoint blockade in recurrent glioblastoma: an open-label, multi-institutional phase I trial. *Neuro Oncol* 2021;**24**: 951−63.
155. Agliardi G, Liuzzi AR, Hotblack A, De Feo D, Núñez N, Stowe CL, et al. Intratumoral IL-12 delivery empowers CAR-T cell immunotherapy in a pre-clinical model of glioblastoma. *Nat Commun* 2021; **12**:444.
156. Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. *Nat Rev Clin Oncol* 2022;**19**:237−53.
157. Ni X, Wu W, Sun X, Ma J, Yu Z, He X, et al. Interrogating glioma-M2 macrophage interactions identifies Gal-9/Tim-3 as a viable target against PTEN-null glioblastoma. *Sci Adv* 2022;**8**:eabl5165.
158. Kim SS, Harford JB, Moghe M, Slaughter T, Doherty C, Chang EH. A tumor-targeting nanomedicine carrying the p53 gene crosses the blood−brain barrier and enhances anti-PD-1 immunotherapy in mouse models of glioblastoma. *Int J Cancer* 2019;**145**:2535−46.
159. Nie D, Ling Y, Lv W, Liu Q, Deng S, Shi J, et al. *In situ* attached photothermal immunomodulation-enhanced nanozyme for the inhibition of postoperative malignant glioma recurrence. *ACS Nano* 2023;**17**:13885−902.
160. Chen H, Li T, Liu Z, Tang S, Tong J, Tao Y, et al. A nitric-oxide driven chemotactic nanomotor for enhanced immunotherapy of glioblastoma. *Nat Commun* 2023;**14**:941.
161. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, et al. Bevacizumab plus radiotherapy−temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014;**370**:709−22.
162. Hidalgo M, Martinez-Garcia M, Le Tourneau C, Massard C, Garralda E, Boni V, et al. First-in-human phase I study of single-agent vanucizumab, a first-in-class bispecific anti-angiopoietin-2/anti-VEGF-A antibody, in adult patients with advanced solid tumors. *Clin Cancer Res* 2018;**24**:1536−45.
163. Di Tacchio M, Macas J, Weissenberger J, Sommer K, Bähr O, Steinbach JP, et al. Tumor vessel normalization, immunostimulatory reprogramming, and improved survival in glioblastoma with combined inhibition of PD-1, angiopoietin-2, and VEGF. *Cancer Immunol Res* 2019;**7**:1910−27.
164. Dong X, Ren J, Amoozgar Z, Lee S, Datta M, Roberge S, et al. Anti-VEGF therapy improves EGFR-vIII-CAR-T cell delivery and efficacy in syngeneic glioblastoma models in mice. *J Immunother Cancer* 2023;**11**:e005583.
165. Chryplewicz A, Scotton J, Tichet M, Zomer A, Shchors K, Joyce JA, et al. Cancer cell autophagy, reprogrammed macrophages, and remodeled vasculature in glioblastoma triggers tumor immunity. *Cancer Cell* 2022;**40**:1111−27.
166. Ma W, Wang Y, Zhang R, Yang F, Zhang D, Huang M, et al. Targeting PAK4 to reprogram the vascular microenvironment and improve CAR-T immunotherapy for glioblastoma. *Nat Cancer* 2021; **2**:83−97.
167. Huang H, Georganaki M, Conze LL, Laviña B, van Hooren L, Vemuri K, et al. ELTD1 deletion reduces vascular abnormality and improves T-cell recruitment after PD-1 blockade in glioma. *Neuro Oncol* 2021;**24**:398−411.
168. Eino D, Tsukada Y, Naito H, Kanemura Y, Iba T, Wakabayashi T, et al. LPA4-mediated vascular network formation increases the efficacy of anti-PD-1 therapy against brain tumors. *Cancer Res* 2018; **78**:6607−20.
169. He B, Jabouille A, Steri V, Johansson-Percival A, Michael IP, Kotamraju VR, et al. Vascular targeting of LIGHT normalizes blood vessels in primary brain cancer and induces intratumoural high endothelial venules. *J Pathol* 2018;**245**:209−21.
170. Malone K, Dugas M, Earl N, Alain T, LaCasse EC, Beug ST. Astrocytes and the tumor microenvironment inflammatory state dictate the killing of glioblastoma cells by Smac mimetic compounds. *Cell Death Dis* 2024;**15**:592.
171. Ji J, Ding K, Cheng B, Zhang X, Luo T, Huang B, et al. Radiotherapy-induced astrocyte senescence promotes an immunosuppressive microenvironment in glioblastoma to facilitate tumor regrowth. *Adv Sci* 2024;**11**:2304609.
172. Quan W, Xu CS, Ma C, Chen X, Yu DH, Li ZY, et al. Anti-tumor effects of telmisartan in glioma-astrocyte non-contact co-cultures: a critical role of astrocytic IL-6-mediated paracrine growth promotion. *Int Immunopharmacol* 2024;**139**:112707.
173. Venkatesh HS, Tam LT, Woo PJ, Lennon J, Nagaraja S, Gillespie SM, et al. Targeting neuronal activity-regulated neuroligin-3 dependency in high-grade glioma. *Nature* 2017;**549**:533−7.
174. Pyonteck SM, Akkari L, Schuhmacher AJ, Bowman RL, Sevenich L, Quail DF, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. *Nat Med* 2013;**19**: 1264−72.
175. Akkari L, Bowman RL, Tessier J, Klemm F, Handgraaf SM, de Groot M, et al. Dynamic changes in glioma macrophage populations after radiotherapy reveal CSF-1R inhibition as a strategy to overcome resistance. *Sci Transl Med* 2020;**12**:eaaw7843.
176. Li J, Yang J, Jiang S, Tian Y, Zhang Y, Xu L, et al. Targeted reprogramming of tumor-associated macrophages for overcoming glioblastoma resistance to chemotherapy and immunotherapy. *Biomaterials* 2024;**311**:122708.
177. Jiang S, Li W, Yang J, Zhang T, Zhang Y, Xu L, et al. Cathepsin B-responsive programmed brain targeted delivery system for chemo-immunotherapy combination therapy of glioblastoma. *ACS Nano* 2024;**18**:6445−62.
178. Hsu FT, Chen YT, Chin YC, Chang LC, Chiang SC, Yang LX, et al. Harnessing the power of sugar-based nanoparticles: a drug-free approach to enhance immune checkpoint inhibition against glioblastoma and pancreatic cancer. *ACS Nano* 2024;**18**:28764−81.
179. Zhang P, Rashidi A, Zhao J, Silvers C, Wang H, Castro B, et al. STING agonist-loaded, CD47/PD-L1-targeting nanoparticles potentiate antitumor immunity and radiotherapy for glioblastoma. *Nat Commun* 2023;**14**:1610.
180. Bielecki PA, Lorkowski ME, Becicka WM, Atukorale PU, Moon TJ, Zhang Y, et al. Immunostimulatory silica nanoparticle boosts innate immunity in brain tumors. *Nanoscale Horiz* 2021;**6**:156−67.
181. Martins TA, Kaymak D, Tatari N, Gerster F, Hogan S, Ritz M-F, et al. Enhancing anti-EGFRvIII CAR T cell therapy against glioblastoma with a paracrine SIRPγ-derived CD47 blocker. *Nat Commun* 2024;**15**: 9718.
182. Chen C, Jing W, Chen Y, Wang G, Abdalla M, Gao L, et al. Intracavity generation of glioma stem cell-specific CAR macrophages primes locoregional immunity for postoperative glioblastoma therapy. *Sci Transl Med* 2022;**14**:eabn1128.

183. Yang F, Zhang D, Jiang H, Ye J, Zhang L, Bagley SJ, et al. Small-molecule toosendanin reverses macrophage-mediated immunosuppression to overcome glioblastoma resistance to immunotherapy. *Sci Transl Med* 2023;**15**:eabq3558.
184. Zannikou M, Duffy JT, Levine RN, Seblani M, Liu Q, Presser A, et al. IL15 modification enables CAR T cells to act as a dual targeting agent against tumor cells and myeloid-derived suppressor cells in GBM. *J Immunother Cancer* 2023;**11**:e006239.
185. Wang PF, Zhang YX, Su J, Yao K, Li SW, Huang GR, et al. Neutrophil depletion enhances the therapeutic effect of PD-1 antibody on glioma. *Aging* 2020;**12**:15290.
186. Wang G, Zhang Z, Zhong K, Wang Z, Yang N, Tang X, et al. CXCL11-armed oncolytic adenoviruses enhance CAR-T cell therapeutic efficacy and reprogram tumor microenvironment in glioblastoma. *Mol Ther* 2023;**31**:134−53.
187. Zhang J, Chen C, Li A, Jing W, Sun P, Huang X, et al. Immunostimulant hydrogel for the inhibition of malignant glioma relapse post-resection. *Nat Nanotechnol* 2021;**16**:538−48.
188. Jin L, Tao H, Karachi A, Long Y, Hou AY, Na M, et al. CXCR1- or CXCR2-modified CAR T cells co-opt IL-8 for maximal antitumor efficacy in solid tumors. *Nat Commun* 2019;**10**:4016.
189. Mao J, Li J, Chen J, Wen Q, Cao M, Zhang F, et al. CXCL10 and Nrf2-upregulated mesenchymal stem cells reinvigorate T lymphocytes for combating glioblastoma. *J Immunother Cancer* 2023;**11**:e007481.
190. Xu X, Zhang Z, Du J, Xue Y, Chen X, Zhang J, et al. Recruiting T-cells toward the brain for enhanced glioblastoma immunotherapeutic efficacy by co-delivery of cytokines and immune checkpoint antibodies with macrophage-membrane-camouflaged nanovesicles. *Adv Mater* 2023;**35**:2209785.
191. Peng Y, Zhan M, Karpus A, Zou Y, Mignani S, Majoral JP, et al. Brain delivery of biomimetic phosphorus dendrimer/antibody nanocomplexes for enhanced glioma immunotherapy *via* immune modulation of T cells and natural killer cells. *ACS Nano* 2024;**18**:10142−55.
192. Mathewson ND, Ashenberg O, Tirosh I, Gritsch S, Perez EM, Marx S, et al. Inhibitory CD161 receptor identified in glioma-infiltrating T cells by single-cell analysis. *Cell* 2021;**184**:1281−98.
193. Galstyan A, Markman JL, Shatalova ES, Chiechi A, Korman AJ, Patil R, et al. Blood−brain barrier permeable nano immunoconjugates induce local immune responses for glioma therapy. *Nat Commun* 2019;**10**:3850.
194. Fan Q, Kuang L, Wang B, Yin Y, Dong Z, Tian N, et al. Multiple synergistic effects of the microglia membrane-bionic nanoplatform on mediate tumor microenvironment remodeling to amplify glioblastoma immunotherapy. *ACS Nano* 2024;**18**:14469−86.
195. Amoozgar Z, Kloepper J, Ren J, Tay RE, Kazer SW, Kiner E, et al. Targeting Treg cells with GITR activation alleviates resistance to immunotherapy in murine glioblastomas. *Nat Commun* 2021;**12**:2582.
196. Yang F, He Z, Duan H, Zhang D, Li J, Yang H, et al. Synergistic immunotherapy of glioblastoma by dual targeting of IL-6 and CD40. *Nat Commun* 2021;**12**:3424.
197. Li N, Rodriguez JL, Yin Y, Logun MT, Zhang L, Yu S, et al. Armored bicistronic CAR T cells with dominant-negative TGF-β receptor II to overcome resistance in glioblastoma. *Mol Ther* 2024;**32**:3522−38.
198. Alghamri MS, Banerjee K, Mujeeb AA, Mauser A, Taher A, Thalla R, et al. Systemic delivery of an adjuvant CXCR4−CXCL12 signaling inhibitor encapsulated in synthetic protein nanoparticles for glioma immunotherapy. *ACS Nano* 2022;**16**:8729−50.
199. Sun T, Liu B, Li Y, Wu J, Cao Y, Yang S, et al. Oxamate enhances the efficacy of CAR-T therapy against glioblastoma *via* suppressing ectonucleotidases and CCR8 lactylation. *J Exp Clin Cancer Res* 2023;**42**:253.
200. Li T, Xu D, Ruan Z, Zhou J, Sun W, Rao B, et al. Metabolism/immunity dual-regulation thermogels potentiating immunotherapy of glioblastoma through lactate-excretion inhibition and PD-1/PD-L1 blockade. *Adv Sci* 2024;**11**:2310163.
201. Guo Y, Jiang T, Liang S, Wang A, Li J, Jia Y, et al. Immunostimulatory hydrogel with synergistic blockage of glutamine metabolism and chemodynamic therapy for postoperative management of glioblastoma. *Adv Sci* 2025;**12**:2412507.
202. Mellinghoff IK, Bent MJvd, Blumenthal DT, Touat M, Peters KB, Clarke J, et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N Engl J Med* 2023;**389**:589−601.
203. Ladomersky E, Zhai L, Lenzen A, Lauing KL, Qian J, Scholtens DM, et al. IDO1 inhibition synergizes with radiation and PD-1 blockade to durably increase survival against advanced glioblastoma. *Clin Cancer Res* 2018;**24**:2559−73.
204. Montoya M, Collins SA, Chuntova P, Patel TS, Nejo T, Yamamichi A, et al. Interferon regulatory factor 8-driven reprogramming of the immune microenvironment enhances antitumor adaptive immunity and reduces immunosuppression in murine glioblastoma. *Neuro Oncol* 2024;**26**:2272−87.
205. Kim J, Choi H, Jeun S-S, Ahn S. From lymphopenia to restoration: IL-7 immunotherapy for lymphocyte recovery in glioblastoma. *Cancer Lett* 2024;**588**:216714.
206. Campian JL, Ghosh S, Kapoor V, Yan R, Thotala S, Jash A, et al. Long-acting recombinant human interleukin-7, NT-I7, increases cytotoxic CD8 T cells and enhances survival in mouse glioma models. *Clin Cancer Res* 2022;**28**:1229−39.
207. Ahn S, Park JS, Kim H, Heo M, Sung YC, Jeun SS. Compassionate use of recombinant human IL-7-hyFc as a salvage treatment for restoring lymphopenia in patients with recurrent glioblastoma. *Cancer Med* 2023;**12**:6778−87.
208. Sampson JH, Schmittling RJ, Archer GE, Congdon KL, Nair SK, Reap EA, et al. A pilot study of IL-2Rα blockade during lymphopenia depletes regulatory T-cells and correlates with enhanced immunity in patients with glioblastoma. *PLoS One* 2012;**7**:e31046.
209. Ravi VM, Will P, Kueckelhaus J, Sun N, Joseph K, Salié H, et al. Spatially resolved multi-omics deciphers bidirectional tumor-host interdependence in glioblastoma. *Cancer Cell* 2022;**40**:639−55.
210. Dong S, Guo X, Han F, He Z, Wang Y. Emerging role of natural products in cancer immunotherapy. *Acta Pharm Sin B* 2022;**12**:1163−85.
211. Tang H, Wang Y, Chlewicki Lukasz K, Zhang Y, Guo J, Liang W, et al. Facilitating T cell infiltration in tumor microenvironment overcomes resistance to PD-L1 blockade. *Cancer Cell* 2016;**29**:285−96.
212. Zhou S, Huang Y, Chen Y, Liu Y, Xie L, You Y, et al. Reprogramming systemic and local immune function to empower immunotherapy against glioblastoma. *Nat Commun* 2023;**14**:435.
213. Zhou S, Ma F, Gong J, Huang Y, Chen Y, Tong S, et al. Immunoinitiator rectifies immunodeficiency to restore immune function and potentiate immunotherapy against IDH mutant glioma. *ACS Nano* 2025;**19**:26980−7004.
214. Wang T, Zhang H, Han Y, Zheng Q, Liu H, Han M, et al. Reversing T cell dysfunction to boost glioblastoma immunotherapy by paroxetine-mediated GRK2 inhibition and blockade of multiple checkpoints through biomimetic nanoparticles. *Adv Sci* 2023;**10**:2204961.
215. Gupta P, Dang M, Oberai S, Migliozzi S, Trivedi R, Kumar G, et al. Immune landscape of isocitrate dehydrogenase-stratified primary and recurrent human gliomas. *Neuro Oncol* 2024;**26**:2239−55.
216. Wang F, Cathcart SJ, DiMaio DJ, Zhao N, Chen J, Aizenberg MR, et al. Comparison of tumor immune environment between newly diagnosed and recurrent glioblastoma including matched patients. *J Neuro Oncol* 2022;**159**:163−75.
217. Tang F, Wang DW, Xi C, Yang JZ, Liu ZY, Yu DH, et al. Local and systemic effects of IDH mutations on primary glioma patients. *Immunology* 2023;**169**:503−14.