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Unraveling the immunosuppressive microenvironment of glioblastoma and advancements in treatment

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Glioblastoma, the most common and aggressive primary brain tumor, remains a significant challenge in oncology due to its immunosuppressive tumor microenvironment (TME). This review summarizes the complex interplay of immune cells and cytokines within the TME, which contribute to immune evasion and tumor progression. We further emphasize the synergistic crosstalk among these components and how it shapes therapeutic vulnerability. Besides, we highlight recent advancements in immunotherapy, including immune checkpoint inhibitors, CAR-T cell therapy, NK cell therapy, oncolytic viruses, and vaccine-based strategies. Despite promising preclinical and clinical results, overcoming the immunosuppressive TME remains a critical hurdle. This review underscores the potential of targeting the TME to enhance therapeutic outcomes in glioblastoma.

KEYWORDS

glioblastoma, immune microenvironment, cytokines, immunotherapy, immune checkpoint inhibitor, tumor vaccine

1 Introduction

Glioblastoma, the most common primary malignant brain tumor in the central nervous system (CNS), accounts for 80% of adult primary malignant brain tumors (1) and is the leading cause of intracranial malignancy-related deaths (2). Traditional treatments like surgical resection, radiotherapy, and temozolomide chemotherapy shows limited efficacy in improving the long-term survival rates of patients with glioblastoma (3–5). Emerging immunotherapies face challenges due to the immunosuppressive tumor immune microenvironment, a dynamic ecosystem crucial for tumor survival (6). The TME, comprising tumor-secreted cytokines, immune cells, and extracellular matrix, plays a pivotal role in tumor initiation, growth, invasion, and metastasis (7). Immune cells and

cytokines in the TME not only facilitate immune evasion but also promote angiogenesis, proliferation, and invasiveness (8). This review focuses on the immune evasion mechanisms through immune cell infiltration and cytokines in the TME, and highlights the advancements in immunotherapy for glioblastoma.

2 Immune microenvironment of glioblastoma

2.1 Tumor-associated macrophages

Macrophages polarize into M1 (tumor-inhibiting) or M2 (tumor-promoting) phenotypes based on the microenvironment, with M1 TAMs enhancing Th1-mediated anti-tumor responses and counteracting immunosuppression (9). However, in advanced tumor stages, M2 TAMs dominate, suppressing adaptive immunity, promoting tumor growth, angiogenesis, and metastasis (10). Besides, hypoxia–driven lactate acts through GPR81-mediated signaling on TAMs to suppress NF-κB and YAP activation and cytokine production, thereby attenuating anti-tumor immunity (11, 12). In glioblastoma, M2 TAMs correlate with poor prognosis (13). Yu et al. (14) found TAM-derived CCL5 promotes glioblastoma cell migration and invasion, while Dong et al. (15) showed TAMs drive glioblastoma stem cell invasiveness via TREM1-mediated TGF-β2 secretion. These findings highlight TAMs' critical role in the TME and potential therapeutic targets.

2.2 Tumor-infiltrating T lymphocytes

T cells are essential to the adaptive immune system, responding to antigens presented by dendritic cells and macrophages. They are categorized into $CD4^+$ and $CD8^+$ subsets based on surface markers and functions. $CD4^+$ T cells recognize antigen-MHC class II complexes, initiating immune responses and activating other immune cells. Regulatory T cells (Tregs), a $CD4^+$ subset expressing FOXP3, suppress pathological immune responses and maintain immune balance (16). $CD8^+$ T cells, or cytotoxic T lymphocytes, directly kill infected cells via MHC class I interactions (17). In the TME, $CD4^+$ T cells activate $CD8^+$ T cells and NK cells, enhancing immune responses (18). They also secrete cytokines like IFN-γ and TNF-α, which have cytotoxic effects on tumors. Tregs maintain immune homeostasis by producing inhibitory cytokines (IL-10, IL-35, TGF-β), suppressing excessive immune activity, though their hyperactivity can impair anti-tumor immunity. $CD8^+$ T cells recognize tumor antigens via TCRs, releasing perforin and granzyme to kill cancer cells and secreting IFN-γ and TNF-α to inhibit tumor growth (19). Glioblastomas reprogram T cells into dysfunctional or pro-tumor states, recruiting Tregs that secrete immunosuppressive cytokines (IL-10, TGF-β), suppressing $CD8^+$ T cells and promoting glioblastoma survival (20). Loss of T cell anti-tumor function exacerbates immune evasion, aiding tumor progression.

2.3 Natural killer cells

NK cells, a lymphocyte subset in the innate immune system, exhibit cytotoxic capabilities crucial for tumor surveillance, with reduced activity linked to increased cancer risk. They target neoplastic cells via death receptor-mediated apoptosis and perforin/granzyme-mediated cytotoxicity, limiting primary tumor growth. However, glioblastomas show minimal NK cell infiltration. CRISPR-Cas9-mediated TIM3 knockout in NK cells enhances their cytotoxicity against glioblastoma cells (21). Additionally, NK cell-related genetic signatures predict glioblastoma malignancy and patient survival (22).

2.4 Dendritic cells

DCs are highly efficient antigen-presenting cells that play a central role in the immune system, linking innate and adaptive immune responses by activating other immune cells and promoting tumor-specific immunity (23). Upon exposure to pathogens, nucleic acids, or type I interferons, DCs undergo activation and maturation, acquiring the ability to effectively stimulate T cells (24). While the exact role of DCs in glioblastomas is still under investigation, current research highlights their interactions with tumor cells and the TME. Single cell RNA sequencing studies have identified conventional DC1 (cDC1), cDC2, and plasmacytoid DC subsets within glioblastoma specimens, each endowed with distinct transcriptional programs and functional potentials (25). Mature DCs up regulate co stimulatory molecules and secrete IL 12, fostering Th1 polarized anti-tumor responses (26). Conversely, glioblastoma-derived factors, like TGF β, IL-10, prostaglandin E_2, can lock DCs in a tolerogenic state characterized by PD-L1 expression and diminished IL-12 production, thereby dampening T cell activation (27). A study by Friedrich et al. (28) indicated that DCs might contribute to the enhancement of anti-tumor immunity in glioblastomas, with their function potentially modulated by isocitrate dehydrogenase (IDH) mutations. These mutations may influence glioblastoma immune responses by altering the function of DCs.

2.5 Tumor-associated neutrophils

Neutrophils are actively involved in various stages of tumorigenesis, tumor progression, and metastasis, exhibiting a more intricate function than previously thought. These cells display both tumor-suppressive and tumor-promoting characteristics within the TME (29). They can directly kill tumor cells via reactive oxygen species (ROS) (30) or cell-cell contact (31), yet also support tumor growth by secreting immunosuppressive molecules like TGF-β, IL-6, and IL-8 (32). Neutrophil infiltration correlates with glioblastoma pathological grading (33, 34), and neutrophil extracellular traps (NETs) facilitate tumor cell migration and immune evasion (35). In glioblastomas, NET formation is driven by HMGB1 and the RAGE/ERK/NF-κB axis, which induces IL-8 release, promoting NETs (36).

2.6 Myeloid-derived suppressor cells

MDSCs, comprising granulocytic (G/PMN-MDSCs), monocytic (M-MDSCs), and early-stage (e-MDSCs) subsets, are immunosuppressive cells originating in the bone marrow (37). They mediate immune suppression through nitric oxide and cytokines, inhibiting cytotoxic T cells, NK cells, macrophages, and dendritic cells, thereby facilitating immune evasion (38). MDSCs also recruit Tregs, B cells, and M2 macrophages, potentially promoting glioblastoma progression (38). Elevated MDSC levels in glioblastoma patients' peripheral blood correlate with tumor progression and survival, suggesting a disrupted immune environment and their potential as diagnostic and prognostic biomarkers (39).

2.7 B cells and microglia in glioblastoma

B cells constitute a minor proportion of immune cells within glioblastoma, yet they are pivotal in tumor progression and response to treatment (40). Within glioblastoma, the B cell population is predominantly composed of regulatory B cells, which exert immune-suppressive effects, and antigen-presenting B cells that facilitate T cell expansion (41, 42). These cells promote immune suppression and angiogenesis by secreting IL-10 and TGF-β, which inhibit T cell and NK cell activity, while also supporting brain development and tumor invasion (43). Furthermore, B cells release angiogenic factors, including VEGF, CXCL12, and CXCL13, which enhance neovascularization, ensuring the tumor's access to essential nutrients and oxygen (44). Microglia is the principal immune cells in the CNS that maintains a quiescent state and exhibit a distinctive branched morphology under normal physiological conditions (45). When exposed to pathological stimuli, these cells become rapidly activated and undergo significant morphological changes to perform immune surveillance and defensive functions (46). In the context of the TME, microglia are attracted to the tumor site, guided by chemotactic factors like CCL2. They secrete a range of cytokines and growth factors, such as IL-6, TGF-β, and VEGF, which contribute to tumor progression by promoting metastasis and invasion (47).

2.8 Cross-talk between immune cells within the glioblastoma TME

The aforementioned immune subsets do not operate in isolation but engage in a highly coordinated network that ultimately dictates glioblastoma progression or regression. For example, TAMs release TGF-β and IL-10, inhibiting effector T cells and promoting Treg expansion, fostering immunosuppression (48). TAMs also suppress T cell function via PD-L1, exacerbating exhaustion and impairing anti-tumor immunity (49). The programmed cell death protein 1 (PD-1) and its ligand PD-L1 constitute a critical immune checkpoint mechanism that facilitates tumor immune escape. Malignant cells frequently overexpress PD-L1, which binds to PD-1 receptors on T lymphocytes, leading to T cell exhaustion and functional impairment (18). This immunosuppressive pathway is further amplified by multiple components of the tumor microenvironment, including: Immunosuppressive cytokines, TAMs, and Tregs. Besides, emerging studies demonstrate that crosstalk between gliomas and immune cells (including macrophages, neutrophils, dendritic cells, MDSCs, and NK cells facilitate oncogenic progression (50).

3 Cytokines in the immune microenvironment of glioblastoma

3.1 IL-10

IL-10, a key anti-inflammatory cytokine, modulates immune responses and prevents excessive inflammation (51). It is secreted by tumor cells, microglia, and astrocytes, not T or B cells (52). IL-10 deficiency releases pro-inflammatory cytokines, suppressing anti-tumor immunity and promoting growth (53), while high IL-10 levels may enhance tumor-specific immunity (54). Blocking IL-10 boosts anti-tumor immunity (55), and IL-10 may upregulate KPNA2, promoting tumor growth; KPNA2 knockout impairs these processes (56). *In vitro*, IL-10 enhances proliferation and invasion, while its blockade activates T cells (57). In glioblastoma, IL-10 promotes tumor proliferation and migration, with elevated levels correlating with malignancy (50–52), however, recent evidence indicates that IL 10 can paradoxically augment anti-tumor immunity by activating $CD8^+$ T cells through the JAK1/STAT3 pathway, leading to enhanced granzyme B release and tumor lysis (58). Targeting TAMs to regulate IL-10 may enhance anti-tumor immunity, highlighting its therapeutic potential in glioblastoma.

3.2 IL-6

Research indicates IL-6 plays a critical role in tumorigenesis by promoting tumor cell proliferation, immune evasion, survival, angiogenesis, and metastasis (59). In glioblastoma, IL-6 is pivotal for immunosuppression, with elevated expression in tumor tissues correlating with disease progression and higher malignancy grades (60). Post-surgical reductions in IL-6 levels in serum and cerebrospinal fluid suggest its prognostic value for survival outcomes (61). Autocrine IL-6 secretion is linked to poor prognosis, driving tumor growth and invasion through: (1) direct stimulation of glioblastoma cell proliferation and survival; (2) STAT3 activation, which promotes tumor cell proliferation, inhibits apoptosis, and suppresses immune cell function; and (3) a cytokine feedback loop involving IL-6 and IL-10, sustaining tumor growth and impairing anti-tumor immunity (62), indicating IL-6 is a promising therapeutic target.

3.3 SDF-1

Chemokines regulate inflammation, immune responses, infection control, tissue damage, apoptosis, and cell migration. The SDF-1/CXCR4 axis, involving CXC chemokine ligand 12 (SDF-1) and receptor CXCR4, is critical for organ development (63). In glioblastomas, SDF-1 attracts stem cells to endothelial cells, where TGF-β induces pericyte differentiation, enhancing vascular activity and tumor growth (63, 64). Disrupting pericyte formation (e.g., ganciclovir) or inhibiting CXCR4 impairs tumor progression by limiting pericyte-endothelial integration (64). Elevated SDF-1 increases pericyte coverage, protecting vasculature and fostering resistance to anti-angiogenic therapies, contributing to recurrence (65).

3.4 TGF-β

TGF-β, a multifunctional regulatory polypeptide, is pivotal in cellular processes such as proliferation, apoptosis, differentiation, and immune surveillance (66). USP15 activates the TGF-β pathway, while its inhibition reduces TGF-β activity, suppressing Glioblastoma cell proliferation. TGF-β2 promotes autophagy via Smad-dependent and independent pathways, enhancing Glioblastoma invasion (67). pSMAD2, a key TGF-β signaling mediator, is found in the cytoplasm and nucleus, serving as a biomarker for pathway activation. Elevated pSMAD2 in glioblastoma correlates with increased invasiveness, therapy resistance, and poorer survival (68, 69). TGF-β2 overexpression is linked to higher tumor grades (70). Trabedersen, a TGF-β2 inhibitor, improved survival in a Phase II trial (71). Macromolecular TGF-β antagonists show greater selectivity and therapeutic potential than small molecules (72).

3.5 Colony-stimulating factors

CSFs are essential for macrophage development. High M-CSF in glioblastoma correlates with poor survival (73), promoting M2 polarization linked to higher tumor grade and worse prognosis (74). Inhibiting GM-CSFR slows tumor progression without reducing macrophages (75); without GM-CSFR, cytokines sustain macrophage survival but reduce immune suppression (76). CSF receptor inhibitors may modulate TAM phenotypes, improving prognosis, but resistance limits their efficacy (77, 78), requiring combination therapies.

3.6 Vascular endothelial growth factor

In glioblastoma progression, a critical aspect is neovascularization. VEGF plays a central role in this process, mediating paracrine and autocrine signals that activate receptor binding and subsequent signaling pathways, which foster the development of a new blood vessel network around the tumor. This promotes tumor growth and metastasis (79). Bevacizumab, a monoclonal antibody targeting VEGF-A, binds to circulating VEGF-A, thereby altering its interaction kinetics with endothelial cells and inhibiting angiogenesis (80). Clinical evidence indicates that bevacizumab therapy for glioblastoma can reduce tumor size, prolong progression-free survival, and diminish the reliance on corticosteroids to manage tumor-induced edema (81) (Figure 1).

4 Immunotherapy of glioblastoma

4.1 Immune checkpoint inhibitor therapy

Immune checkpoints regulate immune responses, preventing autoimmunity, but tumors exploit these mechanisms by expressing ligands, leading to T cell exhaustion and immune evasion (82–84). Immunotherapy utilizing immune checkpoint inhibitors (ICIs) has transformed solid tumor management by augmenting T cell-mediated antitumor responses. Among these, programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) blockade has demonstrated clinical benefits across various malignancies, including gastrointestinal cancers (85, 86). In neuro-oncology, six active clinical trials are currently evaluating PD-1/PD-L1 targeting agents for glioblastoma treatment. Preliminary results from a Phase II investigation (NCT02968940) revealed improved outcomes when combining PD-L1 blockade with radiation therapy in recurrent cases, while pembrolizumab single-agent therapy extended median survival duration (87, 88). Nevertheless, subsequent Phase III evaluations, such as those conducted by Filley et al. (89) and trial NCT02617589, failed to demonstrate statistically significant survival advantages with nivolumab treatment, potentially attributable to the profoundly immunosuppressive characteristics of glioblastoma. Emerging combination approaches, particularly dual PD-1 and CTLA-4 inhibition (NCT03233152), represent promising therapeutic avenues (90). Indoleamine 2,3-dioxygenase (IDO), upregulated in glioblastomas, suppresses T cell function and correlates with poor prognosis (91–94). Preclinical studies support IDO inhibition (95). TIM-3, highly expressed in glioblastoma, enhances $CD8^+$ T cell activity but correlates with aggressive tumors and worse prognoses (96, 97). These findings underscore the potential of targeting immune checkpoints in glioblastoma treatment.

4.2 CAR-T

Chimeric antigen receptors (CARs) are synthetic receptors designed to direct immune cells against tumor-associated antigens, enhancing anti-tumor responses (98). While CAR-T therapy has achieved FDA approval for $CD19^+$ B-cell malignancies (99), its success in glioblastoma remains limited. Recent studies, however, indicate progress. Ahmed et al. (100) reported that HER2-targeted CAR-T cells were safe and feasible in GBM, though tumor suppression was modest. O'Rourke et al. (101) conducted the first clinical trial (NCT02209376) targeting

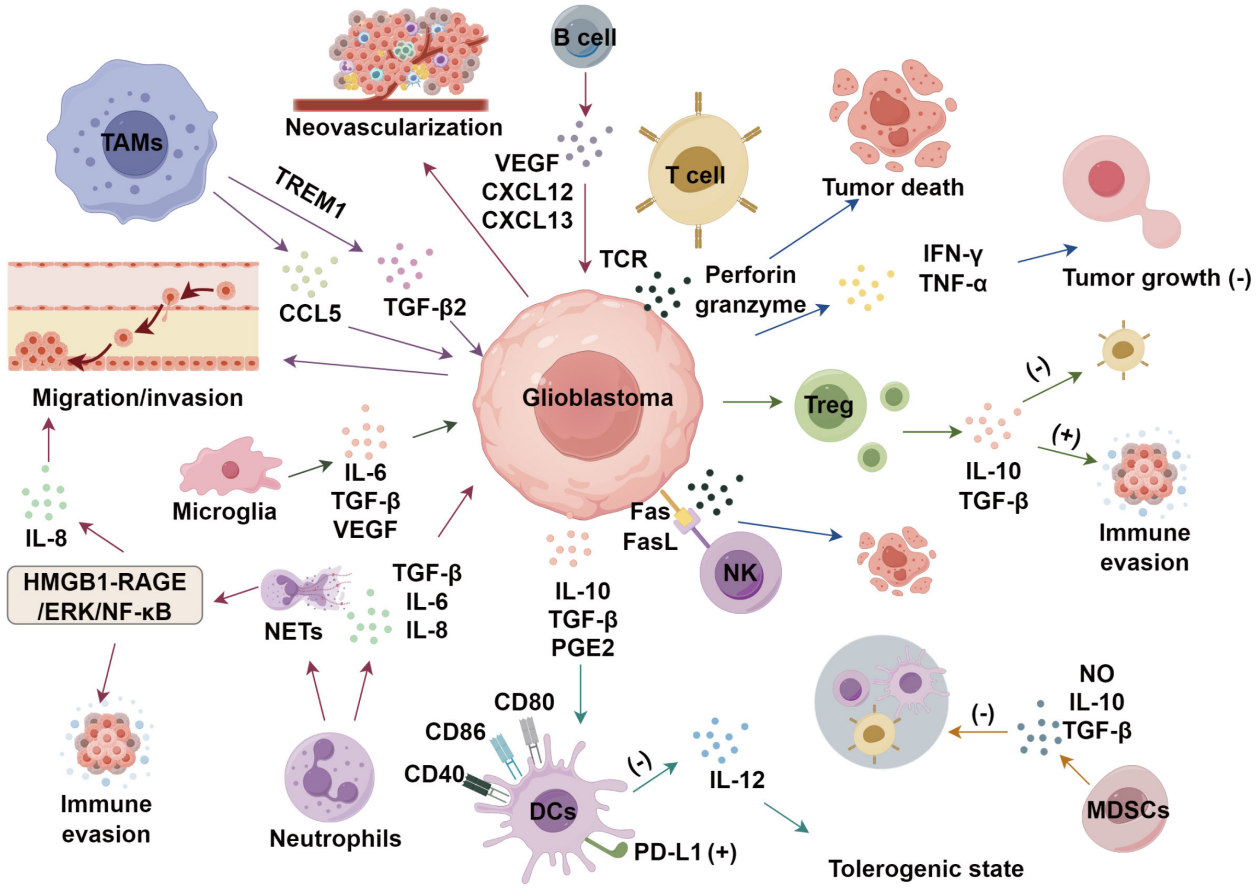

FIGURE 1
Immunosuppressive microenvironment of glioblastoma.

EGFRvIII in recurrent GBM, showing CAR-T infiltration, reduced EGFRvIII expression, and TME modulation, despite no significant regression. Earlier data suggested persistent EGFRvIII in recurrent GBM (102), but subsequent trials (NCT02208362, NCT03389230) (103) confirmed that EGFRvIII-targeted CAR-T suppresses tumor activity. Key challenges include antigen loss, TME immunosuppression, and toxicity (104). A novel TanCAR strategy, combining IL-13 and EphA2scFv, improves GBM targeting while minimizing off-tumor effects, presenting a potential solution (105).

4.3 NK cell therapy

NK cells, crucial components of the innate immune system, directly target and eliminate tumor cells by secreting interferons, perforins, and granzymes, and upregulating death receptors like Fas ligand and TRAIL. They induce apoptosis via the caspase cascade and mediate antibody-dependent cellular cytotoxicity through FcγRIIIA/CD16A. NK cells also enhance T-cell-mediated tumor immunity by sustaining DC populations and promoting tumor antigen presentation (106). Besides, NK cells infiltrate glioblastomas more than T-cells (107). Clinical trials, such as Lim et al. (108), demonstrated NK cell therapy's safety and efficacy in glioblastoma patients, with median OS of 22.5 months and PFS of 10 months. Shaim et al. (109) and Wang et al. (110) highlighted enhanced tumor suppression when NK cells were combined with integrin/TGF-β inhibitors or other therapies. However, challenges like *in vivo* NK cell persistence, limited cytokine support, and immunotherapy efficacy barriers must be addressed for broader clinical application (111).

4.4 Oncolytic virus

OVs, a promising immunotherapy, selectively target and replicate within tumor cells, destroying them while sparing healthy cells. Research includes adenovirus-based therapies and herpes simplex virus (HSV) variants, with notable preclinical success. In Japan, the modified HSV G47D is approved for glioblastoma treatment (112). Treatment with OV DNX-2401 in glioblastoma patients, tumor reduction, partial remission, and disease stabilization, with a median survival of 17.8 months were observed (113). Bernstock et al. (114) reported improved 2-year and 3-year survival rates with viral therapy. While preclinical studies confirm OV safety and efficacy, further clinical trials are needed to establish OVs as a standard glioblastoma treatment.

4.5 Tumor vaccine

Dendritic Cells (DCs) are pivotal in antitumor immunity, activating $CD8^+$ and $CD4^+$ T cells via MHC I/II presentation, driving lymphocyte proliferation and tumor antigen targeting (115). DC vaccines (DCVs) like Sipuleucel-T (116) demonstrate clinical potential. In glioblastoma, DCVax-L (NCT00045968) enhanced median survival without toxicity (117), while ICT-107 showed comparable efficacy (118). Limitations include suboptimal DC maturation, migration, complex manufacturing, antigen selection hurdles, and cost (119). Heat shock proteins (HSPs), ubiquitous molecular chaperones, augment antigen presentation and T-cell activation (120). Preclinical data reveal HSP vaccines with radiotherapy suppress glioblastoma growth (121). Clinical studies report improved survival post-surgery with autologous HSP vaccines (122), and HSPPC-96 (NCT02122822) extended survival in newly diagnosed patients (123). However, some trials associate HSP vaccines with worsened outcomes when combined with chemo/radiotherapy (124). IDH1 mutations define a glioblastoma subset. Murine studies demonstrate IDH1 R132H vaccines elicit IFN-γ-dependent T-cell responses, suppressing tumors (125). A study in glioma patients with IDH1 mutations found 93.3% developed immune responses, with 26/30 showing T-cell and 28/30 B-cell responses, confirming efficacy over 46.9 months median follow-up (126, 127). The NCT02454634 trial detected immune responses in IDH1 $R132H^+$ gliomas but no survival benefit with adjuvant therapy (128).

5 Conclusion

Glioblastoma's immunosuppressive TME, characterized by immune cell infiltration and cytokine-mediated immune evasion, plays a pivotal role in tumor progression and resistance to therapy. While traditional treatments have shown limited efficacy, emerging immunotherapies, such as immune checkpoint inhibitors, CAR-T cells, and oncolytic viruses, offer new hope. However, challenges like antigen escape, TME complexity, and treatment-related toxicity persist. Future research should focus on interdisciplinary collaboration and technological integration to elucidate glioblastoma regulatory networks, identify new targets, and refine personalized therapies. Combining cellular immunotherapy and molecular targeted therapy is a promising trend, offering hope for glioblastoma patients and insights for treating other solid tumors.

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