TREM2 in glioma: Reprogramming the immune microenvironment from mechanistic understanding to clinical translation (Review)

JUNQI FAN[1], HONGYAN SHEN[2], DAN LIU[3], SONGBAI LUO[3], QINGQING HUANG[3], YI WEN[4] and LIBANG YUAN[3]

[1]Department of Neurosurgery, The General Hospital of Western Theater Command, Chengdu, Sichuan 610083, P.R. China; [2]Department of Rheumatology and Immunology, The General Hospital of Western Theater Command, Chengdu, Sichuan 610083, P.R. China; [3]Department of Anesthesiology, The General Hospital of Western Theater Command, Chengdu, Sichuan 610083, P.R. China; [4]Department of General Surgery, The General Hospital of Western Theater Command, Chengdu, Sichuan 610083, P.R. China

Received March 12, 2026; Accepted June 12, 2026

DOI: 10.3892/mmr.2026.13952

Abstract. The poor prognosis of high-grade gliomas, such as glioblastoma, is largely driven by a notably immunosuppressive tumor microenvironment (TME), wherein microglia and tumor-associated macrophages play important roles. The present review summarizes the current evidence supporting triggering receptor expressed on myeloid cells 2 (TREM2) as a key immunoregulator in the glioma TME. The present review explores the context-dependent dual role of TREM2, which can either be hijacked to promote immunosuppression and tumor progression or inhibit tumor progression through its notable functions in phagocytosis and antigen presentation. The present review also examines the clinical association of TREM2 expression with glioma grade and patient prognosis, evaluating its potential as a diagnostic and prognostic biomarker. Furthermore, the present review discusses the current landscape of TREM2-targeted therapeutic strategies, from direct TREM2 inhibition and myeloid-targeted immunocytokines to nano-engineered drug delivery systems, and addresses the core translational challenges of these strategies. Looking forward, the importance of leveraging spatial multi-omics and artificial intelligence to decipher the functional heterogeneity of TREM2 and to guide precision immunotherapy is highlighted. In conclusion, the present review provides a comprehensive framework for understanding the role of TREM2 in glioma; this receptor serves not only as a biomarker for glioma, but as an important signaling hub in the glioma TME. Therefore, the present review aims to support the development of novel therapeutic strategies targeting the immune microenvironment in glioma.

Correspondence to: Dr Yi Wen, Department of General Surgery, The General Hospital of Western Theater Command, 270 Rongdu Avenue, Jinniu, Chengdu, Sichuan 610083, P.R. China
E-mail: 13980881194@163.com

Dr Libang Yuan, Department of Anesthesiology, The General Hospital of Western Theater Command, 270 Rongdu Avenue, Jinniu, Chengdu, Sichuan 610083, P.R. China
E-mail: lemonbang@126.com

Key words: triggering receptor expressed on myeloid cells 2, glioma, tumor microenvironment, microglia, macrophages, immunotherapy

Contents

1. Introduction

Glioma currently represents the most common and aggressive primary brain tumor in adults and has been associated with a poor prognosis (1). Despite the progress achieved by research on glioma treatments, the median survival time of patients with glioma remains <15 months (2,3). One of the primary drivers of therapeutic resistance in glioma is the markedly complex and immunosuppressive tumor microenvironment (TME), which has been shown to not only support tumor growth but also to actively subvert antitumor immunity (4-6).

Tumor-associated microglia and tumor-associated macrophages (collectively termed TAMs) constitute dominant components of the TME of glioma (4,7,8). Notably, TAMs can be manipulated by glioma cells to adopt an immunosuppressive phenotype that facilitates tumor progression, angiogenesis and treatment resistance (8-13). However, the simplistic binary

classification of TAMs into pro-inflammatory or anti-inflammatory phenotypes that was employed previously is no longer adequate; these cells have now been recognized to exhibit multifaceted and context-dependent roles in the TME (8-13).

Triggering receptor expressed on myeloid cells (TREM)2 is an important immunoregulatory receptor that governs key microglial functions, such as phagocytosis, lipid metabolism, viability and inflammatory responses (14,15). Although the protective effects of TREM2 in Alzheimer's disease (AD) remain well-documented (16,17), the dual function of TREM2 in glioma has been a notable source of research and debate. On one hand, notable evidence has positioned TREM2 as a promoter of glioma; the pro-tumor activity of TREM2 is primarily mediated by its ability to foster an immunosuppressive microenvironment and enhance angiogenesis, which in turn promotes glioma progression (18-20). However, emerging evidence has also suggested that, under specific conditions, TREM2 can play an immunoprotective role in glioma. Recently, a key study revealed that TREM2 deficiency in glioma models accelerates tumor progression, and this effect was linked to impaired myeloid-mediated phagocytosis of tumor cells and reduced major histocompatibility complex class II (MHCII) expression, which subsequently resulted in a loss of $CD4^+$ T cells (21). In addition, another recent study identified TREM2 as an immunoprotective factor in glioblastoma (GBM), and its deficiency has been shown to accelerate tumor progression, directly contrasting with its established immunosuppressive role in peripheral cancers (22-25). These findings illustrate the complex mechanistic role of TREM2 in glioma, reflecting the intricacy of the TME in the central nervous system (CNS) and highlighting the importance of further research into the role of this receptor in glioma.

Given the notable role of TAMs in the glioma microenvironment, these cells have become a central research focus within glioma oncology, with numerous studies aiming to understand their interactions with key pathological processes, such as tumor progression, recurrence and immunotherapy responses. Within the context of glioma, TREM2 has emerged as an important molecular regulator of tumor progression, exhibiting the dual capacity to both protect against and contribute to glioma pathology (22-25). This duality underscores the notable complexity of TREM2 activity in glioma, as well as the requirement for further in-depth investigations into the multifaceted roles of TREM2 in glioma pathogenesis within the CNS.

2. TREM2: A conserved regulator of CNS myeloid function

TREM2 is an important immunoregulatory receptor that is predominantly expressed on microglial cells, which are resident macrophages of the CNS (26,27). Notably, TREM2 has been shown to form a signaling complex with the adaptor protein TYRO protein tyrosine kinase-binding protein (DAP12), which is important for transducing signals that govern key myeloid functions, such as phagocytosis, cell survival, lipid metabolism and the modulation of inflammatory responses (28). As such, TREM2 is a central regulator of immune homeostasis in the CNS and has been shown to play an important, albeit context-dependent, role across a spectrum of pathological conditions, ranging from neurodegenerative diseases to cancer (16,29).

TREM2 activity is initiated by its interaction with a diverse array of ligands, such as lipids, apolipoproteins and amyloid-β (Aβ). These interactions trigger downstream signaling that is important for maintaining CNS integrity (30-32). Notably, TREM2 activity is important for a number of fundamental neural processes. For example, during development, TREM2 is required for synaptic pruning, and TREM2 deficiency has been shown to lead to impaired synapse elimination and altered neural connectivity (33). Another core function exhibited by TREM2 is the regulation of phagocytic clearance, enabling microglia to remove apoptotic neurons, myelin debris and protein aggregates, thereby supporting CNS tissue homeostasis and neuronal health (32,34-37). In AD, TREM2 has been shown to bind to Aβ oligomers, facilitating their clearance and modulating microglial responses to amyloid plaques. This interaction is important as it mitigates the progression of AD by influencing microglial activation and viability (38,39). However, TREM2 exhibits a dual role in inflammation in the CNS; although it can promote the resolution of inflammation, TREM2 signaling has also been shown to exacerbate neuropathic pain by driving the release of pro-inflammatory cytokines from microglia (40). Conversely, in models of ischemic stroke, TREM2 activity has been shown to partially attenuate neuroinflammation and CNS injury, highlighting its therapeutic potential in mitigating neural inflammation (41,42).

In summary, TREM2 is a conserved master regulator of myeloid-cell function (26,27) with notable implications for glioma therapy. The ability of TREM2 to modulate immune responses, promote the clearance of cellular debris and influence cell survival in the CNS positions this receptor at the crossroads of CNS homeostasis, neurodegeneration, cancer and systemic inflammation.

3. Context-dependent dual role of TREM2 signaling in the glioma microenvironment

In the TME of glioma, the TREM2 signaling pathway is activated in myeloid cells by numerous ligands. However, the functional outcome of this activation is notably context-dependent, embodying a dual role that can either promote tumor progression or support antitumor immunity. Although TREM2 signaling is frequently activated by glioma cells to foster an immunosuppressive niche and support tumor growth (18,19), the TREM2-regulated capacity of microglia for phagocytosis and antigen presentation is important for T-cell activation (21,22). This inherent duality makes TREM2 a central but complex signaling hub in glioma pathology. Hijacked TREM2 signaling has been shown to regulate the TME in glioma through the mechanisms discussed in this section (Fig. 1).

Shaping an immunosuppressive niche. In glioma, TREM2 knockdown in microglia has been shown to promote a pro-inflammatory microglial phenotype and suppress tumor progression by increasing the activity of the Janus kinase/STAT signaling pathway and suppressing the NF-κB pathway. Consequently, the transcriptional program that sustains an immunosuppressive niche in the glioma TME is suppressed (43-47). These findings indicate that TREM2 contributes to the development of an immunosuppressive

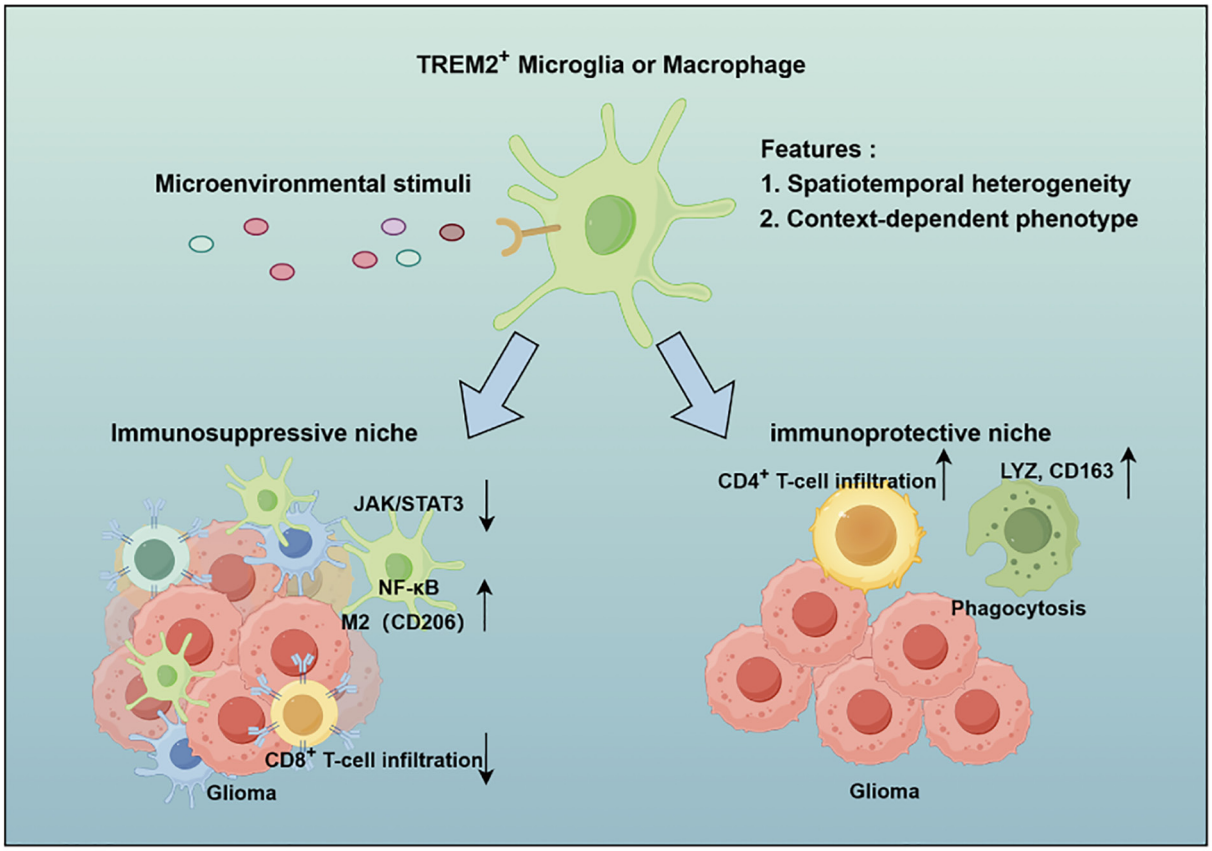

Figure 1. Functional heterogeneity and context-dependent roles of TREM2+ microglia and macrophages in the glioma microenvironment. Microenvironmental stimuli induce diverse signaling pathways, including: i) Immunosuppressive pathways, such as the JAK/STAT3 and NF-κB pathways; and ii) immunoprotective processes, for example those mediated by LYZ or CD163. These pathways shape CD4+ and CD8+ T-cell responses and influence tumor progression. Generated by Figdraw (https://www.figdraw.com/#/; copyright code: YTOUT656f1). LYZ, lysozyme; TREM2, triggering receptor expressed on myeloid cells 2; JAK, Janus kinase; M2, alternatively activated macrophages.

microenvironment, which is a characteristic feature of glioma pathology (7,48,49). TREM2 expression has also been strongly associated with the M2 polarization of microglia and macrophages, which has been linked to a higher glioma grade and a poorer prognosis for patients (18,19,50). Notably, inhibition of TREM2 signaling reprograms myeloid cells toward a pro-inflammatory phenotype, promoting CD8+ T-cell infiltration and activity in the TME. Furthermore, TREM2 inhibition has been shown to synergize with anti-programmed cell death protein 1 immunotherapy to improve patient survival in preclinical glioma models (20). Collectively, these findings underscore the concept that the TREM2-dependent immunosuppressive niche contributed to by TAMs is markedly involved in promoting tumor advancement and treatment failure in glioma.

Regulating phagocytosis and an immunoprotective niche. Studies have demonstrated that TREM2 signaling enhances the uptake of glioma cells by myeloid cells; this increase in phagocytic function has been associated with changes in the levels of canonical phagocytosis markers, for example, lysozyme and CD163. TREM2 has also been shown to trigger the phosphorylation of DAP12 and activate downstream spleen tyrosine kinase (Syk), which is an important event for the efficient phagocytosis of tumor cells, acting through cytoskeletal remodeling, calcium mobilization, and activation of PI3K-AKT and MAPK signaling pathways (51-54).

Notably, this TREM2-mediated regulation of phagocytosis extends beyond the clearance of tumor cells to influence the direct interactions of microglial cells with adaptive immunity. This functional link is important for regulating efficient antigen presentation. Notably, TREM2 deficiency impairs MHCII expression on TAMs, leading to a reduction in CD4+ T-cell tumor infiltration and diminished antitumor immune responses (21). By applying integrated single-cell and spatial transcriptomics, a recent study redefined the role of TREM2 in GBM. In contrast to its established role as a key immunosuppressive target in peripheral tumors, the aforementioned study reported that TREM2 appears to exert an immunoprotective function in GBM; its deficiency was shown to accelerate tumor progression and to associate with immunosuppressive signatures (22). Collectively, these findings underscore that TREM2 plays a central yet complex role in phagocytosis and immune reprogramming, challenging simplistic strategies for therapeutic inhibition of TREM2 and demanding context-specific strategies.

Microenvironmental and molecular determinants of TREM2 functional duality in glioma. A central dilemma to be elucidated concerns the mechanisms that prime TREM2-expressing myeloid cells toward a pro-tumor vs. an antitumor state. The determination of these phenotypes likely involves spatial, metabolic and temporal factors within the

glioma microenvironment. Regarding molecular triggers, TREM2-ligand identity represents an important determinant of myeloid phenotype. TREM2 has been shown to bind to a diverse range of molecules, including oxidized lipids, myelin debris and apolipoproteins (30-32), although the ligand repertoire for TREM2 likely varies across tumor models. Notably, redundant pathways, such as those mediated by T-cell immunoglobulin and mucin-domain containing-3 or AXL, may compensate for TREM2 loss. Competitive ligand binding further complicates TREM2 signaling (55,56).

Metabolic reprogramming of the glioma microenvironment also shapes TREM2-mediated immune responses. TREM2 expression is closely linked to enhanced lipid metabolism in TAMs, and the hypoxia-driven shift in lipid metabolism observed within the tumor core may enhance TREM2 signaling to foster an immunosuppressive TAM phenotype (57,58). At the invasive margin of glioma, damage-associated molecules, for example phosphatidylserine and gangliosides, are released from disrupted neuronal architecture and activate TREM2 signaling; this creates a functional gradient from pro-inflammatory signaling at the tumor-neuron interface to an increasingly immunosuppressive microenvironment toward the glioma core (59). Within this hypoxic core, $TREM2^+$ cells exhibit reduced antigen presentation (59). Temporally, TREM2 does not exert protective effects in the early stages of TAM differentiation; instead, its expression peaks at the terminal phase of monocyte-to-TAM differentiation, in parallel with immunosuppressive hallmarks such as arginase 1, CD274 and glycoprotein NMB (10).

Another overlooked layer of complexity regarding the function of TREM2 is the heterogeneity observed between preclinical glioma models themselves. The commonly used orthotopic glioma cell lines, namely the GL261, CT2A, NPA C54B and SB28 cell lines, harbor distinct genetic backgrounds and origins (60,61). Consequently, their responses to immune checkpoint blockade are notably different; for example, GL261 cells are immune checkpoint blockade-responsive, whereas SB28 cells demonstrate resistance to this treatment (60). These divergent responses may consequently influence the specific mechanisms underlying TREM2-mediated responses in these models. In the GL261 glioma model, TREM2 expression has been associated with a shift from a pro-inflammatory to an immunosuppressive immune microenvironment (10). The aforementioned factors, including glioma model immunogenicity, ligand availability, receptor redundancy, spatial niche and temporal stage of differentiation, converge in a context-dependent manner to influence the outcomes of TREM2 activity in glioma. Future studies using spatial transcriptomics, lineage tracing, metabolic profiling and glioma-model comparisons are required to identify therapeutically targetable switches.

The dual nature of TREM2 notably reflects the heterogeneity of high-grade glioma and the complex interplay of TREM2 with the TME (61). This interaction-based heterogeneity results in the marked context-dependency of the immune functions of TREM2; its intrinsic phagocytic and antigen-presenting capacity can, under specific conditions, support antitumor immunity (21), whereas hijacking TREM2 activity to induce its immunosuppressive function has been shown to promote immune evasion and tumor progression in glioma. Consequently, within this complex microenvironment, TREM2 emerges as a central, yet multilayered, immune-signaling hub. Therapeutic targeting of TREM2 therefore requires precise modulation to effectively block the activity of its pro-tumor pathways whilst preserving its residual or inducible protective functions, making it a compelling but challenging axis for TME reprogramming (15).

4. Potential of TREM2 as a biomarker in glioma diagnosis

Studies have indicated that TREM2 holds notable potential for the diagnosis and prognosis of glioma; its expression is markedly higher in tumor tissues from patients with GBM compared with that in normal tissues or low-grade glioma cases (19). Furthermore, this elevated expression has been shown to associate markedly with molecular features linked to the aggressive behavior of the tumor, including the mesenchymal subtype, isocitrate dehydrogenase (IDH) wild-type status and lack of 1p/19q codeletion (19). Supporting its functional role, TREM2 deficiency in mouse glioma models has been shown to result in a reduction in the proportion of M2-polarized microglia within tumors, underscoring the key role of TREM2 in remodeling the immunosuppressive TME (43). Notably, emerging single-cell resolution data have revealed that a TREM2-high lipid-metabolic macrophage subset is linked to poorer survival outcomes for patients with glioma (50). However, high TREM2 expression, specifically within tumor-infiltrating myeloid cells, has paradoxically been associated with improved survival outcomes and an antitumor immune signature in a study by Zhong *et al* (22). The expression profile of TREM receptors in the peripheral circulation also carries prognostic importance. Research has shown that a higher TREM1/TREM2 ratio on circulating $CD14^+$ monocytes is an independent predictor of reduced overall survival, whereas a higher percentage of $TREM2^+$ monocytes has been associated with improved patient outcomes specifically in the GBM subgroup (62). Furthermore, this relationship may be modulated by a number of factors, such as vitamin D levels, which are positively associated with the proportion of $TREM2^+$ monocytes in low-grade glioma (63). These results indicate that composite indicators incorporating TREM2 and other biological markers possess superior potential for guiding clinical prognosis assessment relative to single markers.

A study has demonstrated that soluble TREM2 (sTREM2) levels are markedly elevated in the cerebrospinal fluid (CSF) of patients with multiple sclerosis but return to normal following treatment. By extension, TREM2 shows promise as a diagnostic biomarker in the CSF of patients with glioma (64). Similarly, elevated sTREM2 levels observed in the CSF of patients with neuromyelitis optica spectrum disorder, which is also a type of neuroinflammatory condition, have been genetically and clinically associated with disease risk and severity. Notably, elevated sTREM2 levels have been shown to result in microglial dysfunction and NF-κB pathway activation. This pathological state is characterized by excessive activation, enhanced phagocytosis and metabolic reprogramming (65). In another study of 205 patients with GBM, AD-associated neuropathological changes were present in the tumor-adjacent cortex of 52% of patients, and the degree of this pathology was positively associated with microglial activation (66). However, the cross-disease robustness of sTREM2 levels as

a biomarker for CNS pathology presents a notable challenge for glioma-specific diagnosis. Therefore, sTREM2 alone is unlikely to reliably differentiate high-grade glioma from other neuroinflammatory or neurodegenerative conditions in a clinical setting.

To enhance its specificity as a biomarker, sTREM2 should be: i) Incorporated into a multi-analyte panel that includes multiple tumor-derived markers, such as glial fibrillary acidic protein, matrix metalloproteinases, IDH mutation status or O-6-methylguanine-DNA methyltransferase promoter methylation; or ii) combined with advanced imaging features. Furthermore, establishing disease-specific sTREM2 cut-off values and dynamically monitoring sTREM2 changes over time may improve its clinical utility as a biomarker of glioma. Future studies should directly compare CSF-derived sTREM2 levels between patients with glioma and well-matched control groups with other neurological diseases to define its specificity and diagnostic accuracy. Together, these findings suggest the potential of sTREM2 as a diagnostic and prognostic biomarker for brain tumors (67,68).

5. TREM2-targeted microglial therapy for glioma

Targeting the TREM2 signaling pathway represents a promising therapeutic strategy for reprogramming microglia within the glioma TME. Preclinical studies, primarily those using the murine GBM cell line GL261, have demonstrated that TREM2 deficiency or knockdown markedly inhibits tumor growth and angiogenesis (18,43). This antitumor effect is linked to the inhibition of key pro-survival and inflammatory pathways in the microglia, such as the Wnt/β-catenin and NF-κB pathways, which can in turn enhance antitumor immune responses (43,69). In AD research, targeting TREM2 on microglia has achieved notable therapeutic progress toward mitigating AD-associated pathological changes. For example, a phase I clinical trial using the TREM2-targeting antibody AL002 demonstrated target engagement and pharmacodynamic effects in the CNS of patients with AD (70). Although, to the best of our knowledge, clinical trials targeting TREM2 have not yet been launched in glioma, the progress made in the phase 2 trial of AL002 in AD (70) offers important preliminary evidence for pharmacologically modulating TREM2 in the human brain for glioma therapy.

Beyond direct receptor inhibition, a recent study has explored TREM2 as a target for precision drug delivery using an innovative strategy. This study designed TREM2-specific peptide-conjugated nanoliposomes to deliver doxorubicin specifically to glioma cells; this approach demonstrated enhanced drug accumulation in brain tumors and improved antitumor efficacy compared with untargeted PLD (non-modified PEGylated nanoliposomal doxorubicin) in preclinical models, validating the effectiveness of TREM2-targeting strategies in glioma therapy (71).

The findings of the aforementioned studies have offered valuable insights for future therapeutic directions in glioma research, including direct TREM2 inhibition or precision drug delivery leveraging the TREM2 signaling pathway. Examples of potential therapeutic strategies targeting TREM2 in neuro-oncology include the use of precision-targeted nanotechnology, antibody engineering and the development of novel inhibitor designs; these strategies may be combined with existing therapies to modulate the immunosuppressive glioma TME and improve immunotherapeutic outcomes. However, the role of TREM2 in glioma is marked by notable functional heterogeneity; this functional duality highlights the requirement for further research in order to elucidate the complex mechanisms of TREM2 in glioma, thereby providing a solid foundation for the development of future clinical therapeutic strategies.

6. Challenges and future directions for TREM2-targeted therapy

Preclinical studies have demonstrated that strategies targeting TREM2 show notable promise for glioma therapy, yet there remain numerous challenges to realizing the clinical potential of these strategies. A primary challenge lies in the complexity of the ligand-receptor interactions of TREM2. As a multiligand receptor, TREM2 binds to a diverse array of molecules (55), which in turn trigger multiple downstream effects, complicating its therapeutic targeting (22). This characteristic of TREM2 may be a contributing factor to the clinical failure of some ligand-dependent TREM2 inhibitors (56). Such clinical failure highlights the translational gap between promising preclinical data and clinical outcomes. The dynamic nature of ligand binding, along with the existence of multiple known and unknown ligands competing for the receptor in human biology, makes it difficult to achieve effective and specific TREM2 blockade with conventional approaches (56). To overcome this challenge, a shift in therapeutic development toward innovative ligand-independent inhibition strategies would enable the blockade of downstream signaling from a novel perspective, permitting TREM2 blockade irrespective of which ligand is bound. Such an approach could diminish the impact of competitive ligands and reduce the off-target effects of inhibitors, consequently allowing inhibitors to function more effectively (56,72,73).

Future research should focus on developing precision medicine and multidimensional strategies to effectively advance targeted drug development and immunotherapy (Fig. 2). The dual functionality of TREM2 is highly context-dependent within the glioma microenvironment. The integration of single-cell and spatial multi-omics technologies will enable future research to move beyond bulk analyses and to precisely assess the functional heterogeneity of TREM2-expressing microglia and macrophages across different tumor regions and disease stages (10,22,59). For example, single-cell RNA sequencing has revealed that myeloid cell states in glioma are driven more by microenvironmental signals than by cellular origin, identifying distinct immunosuppressive and inflammatory programs (8,48,74). Notably, spatial transcriptomic technologies are now enabling researchers to map these cellular states within the intact tissue architecture (75,76). As such, spatial transcriptomics has proven effective in resolving cellular heterogeneity and spatial organization within tumors. For example, a study in GBM employed spatial transcriptomic technologies to highlight the heterogeneous infiltration patterns of immune cells from the tumor core to the invasive margin (75). The application of single-cell and spatial transcriptomic technologies in future studies will help to elucidate

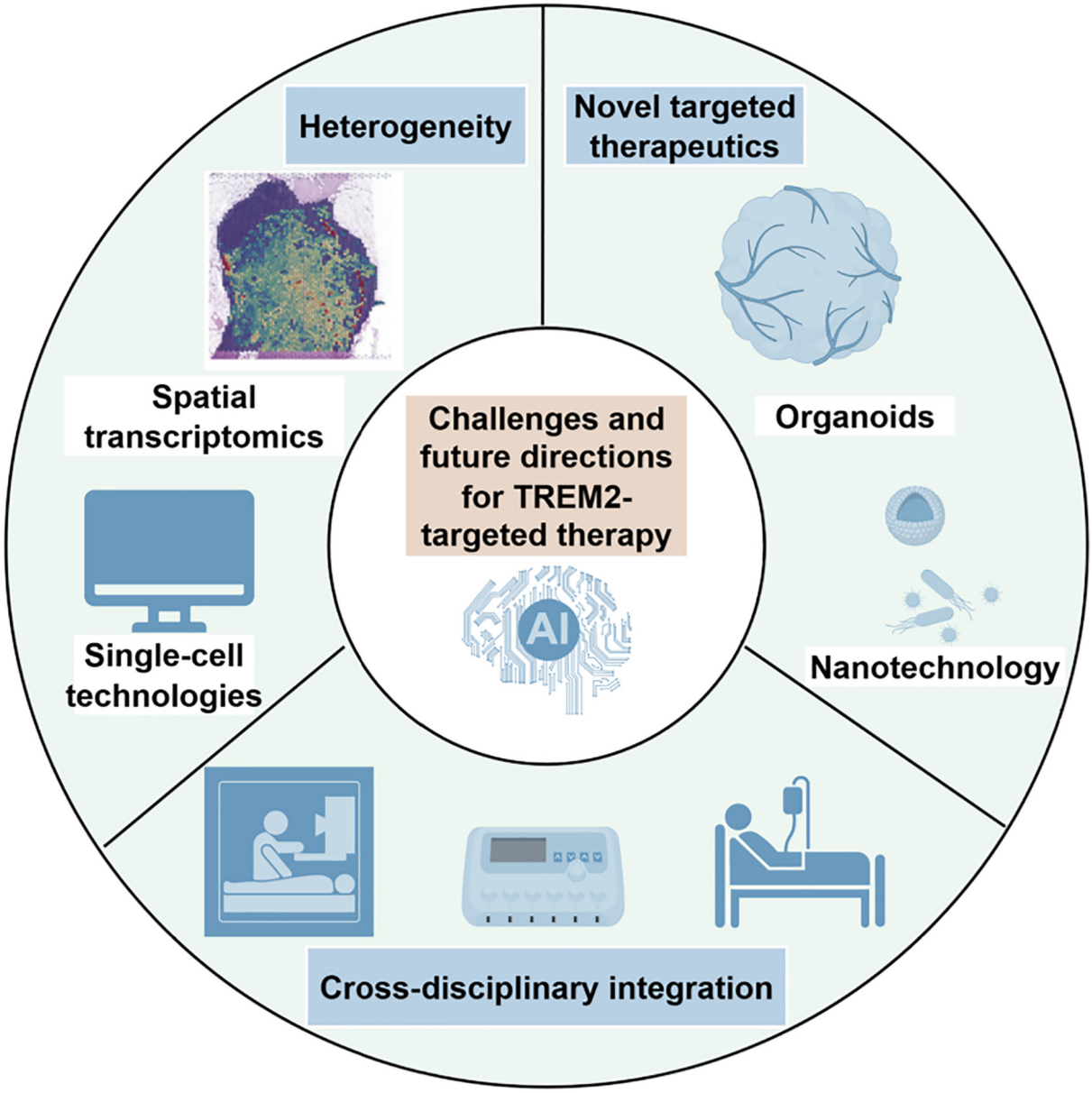

Figure 2. Strategic roadmap for advancing TREM2-targeted therapy in glioma. The diagram highlights three key directions: i) Decoding spatial and functional heterogeneity of TREM2 functions via single-cell and spatial transcriptomics; ii) developing novel preclinical and therapeutic strategies, including organoid models and nanotechnology; and iii) fostering cross-disciplinary integration of clinical data through AI-driven multi-omics and clinical translation. Generated by Figdraw (https://www.figdraw.com/#/; copyright code: SIYIT86e04). AI, artificial intelligence; TREM2, triggering receptor expressed on myeloid cells 2.

the spatial localization, temporal dynamics and specific interactions of TREM2$^+$ TAMs in glioma (10,21,22,59), including interactions with glioma cells, various immune cells and TME components, such as vascular endothelial cells.

Determining whether TREM2 inhibition or activation associates with an immunosuppressive or immunoprotective microenvironment in patients with specific genetic backgrounds is important for glioma therapy. Furthermore, understanding whether variations in these spatiotemporal interactions (TREM2$^+$ TAM interactions with glioma cells, various immune cells and TME components) enhance or undermine immunotherapeutic efficacy, or whether these interactions associate with therapeutic resistance, is important for designing optimal clinical interventions and achieving precision medicine goals; the elucidation of mechanisms responsible for these clinical features is also necessary for improving therapeutic outcomes. Notably, exploring the differential metabolic regulation of TREM2$^+$ TAMs at specific spatiotemporal nodes, including lipid metabolism pathways analogous to those in AD models, presents another promising option for deciphering the function of these cells and identifying novel therapeutic targets (69).

Nanotechnology has been shown to provide robust technical support for effective TREM2-targeted therapy, enabling the precise delivery of targeted drugs and supporting their regulation of the TME through highly specific and controlled drug release (77-79). One notable study investigated the therapeutic efficacy of a novel strategy integrating synthetic immunology and protein-engineering designed myeloid-targeted immunocytokines (MiTEs), which can bind

to TREM2 on immunosuppressive TAMs. After being cleaved by a specific protease present in TAMs, MiTEs released an IL-2 signal that activated cytotoxic T cells and natural killer cells, thereby initiating an antitumor immune response. This strategy achieved notable efficacy in preclinical models by orchestrating a multi-axis antitumor immune response while minimizing systemic toxicity, indicating the promising potential of TREM2-targeted immunotherapy (80).

Concurrently, a recent study developed PEGylated nanoliposomes conjugated with TREM2-targeting peptides for use in glioma therapy. Although this construct delivered a conventional chemotherapeutic agent, doxorubicin, rather than directly modulating immunity, this therapeutic strategy validated the effectiveness of TREM2-targeting nanocarriers. By leveraging localized TREM2 expression, these nanoparticles achieved specific targeting to glioma tissues and enhanced the accumulation of antitumor drugs in targeted brain tumors, promoting their notable tumor-killing effects. These findings demonstrate the potential of TREM2-targeted nanodrug delivery for future integration with immunotherapy or chemotherapy strategies in the treatment of glioma (71).

Notably, advanced and reliable preclinical models are important for discovering and validating the therapeutic effects of nanodrugs or advanced biologics, such as MiTEs. This highlights the advantages of optimized conditional-knockout mice and patient-derived organoid co-culture models (81-83); these models are valuable for studying the functions and mechanisms of TREM2-associated TAMs, conducting high-throughput drug screenings and investigating the dynamic interactions between $TREM2^+$ TAMs and other cells (81,84,85).

A notable and often underappreciated challenge to therapeutic drug delivery is the blood-brain barrier (BBB), which markedly restricts the delivery of systemically administered biologics and nanoparticles into the brain parenchyma. Although the BBB is locally disrupted at the GBM core, it remains largely intact at the infiltrating tumor margin, which is a primary site of recurrence (86,87). Therefore, even TREM2-targeted nanoliposomes (71) or MiTEs (80) that show robust efficacy in preclinical intracranial models are hindered in clinical settings by their large size, which limits passive diffusion across the intact or partially intact BBB. Strategies to overcome this size-limitation may include receptor-mediated transcytosis, for example via transferrin or low-density lipoprotein receptor-related protein 1 targeting, focused ultrasound-induced BBB disruption or alternative drug delivery routes, such as intranasal administration (88,89). Future TREM2-directed therapeutic designs should incorporate such BBB-crossing mechanisms from the outset for effective clinical translation.

The ultimate translation of TREM2-directed strategies into clinical application will also be guided by notable cross-disciplinary collaboration (Fig. 2). The convergence of neurosurgery, neuropathology and molecular diagnostics is important for obtaining and analyzing high-quality, spatially annotated tumor specimens (90). The data generated from these specimens can span genomics, transcriptomics, proteomics and digital pathology, collectively creating a complex and integrated big-data network; as such, artificial intelligence (AI) and big-data analytics may serve important roles in the clinical translation of TREM2-targeted therapies (91-95).

AI can accelerate the design of novel TREM2-targeting compounds at the drug discovery stage by modeling protein-protein interactions, enabling virtual drug screening and facilitating *de novo* molecular design to optimize drug efficacy and safety, thereby reducing the reliance of drug development on costly and resource-intensive traditional wet-lab experiments. Furthermore, AI can integrate multi-omics data with clinical imaging data to build predictive models that identify patients harboring TREM2-driven immunosuppressive tumor niches, thereby informing personalized therapy selection (96-100). In clinical development, AI can optimize trial design and patient stratification by analyzing real-world data, improving patient recruitment efficiency and predicting patient survival outcomes, which is important for efficiently testing the next generation of TREM2-directed therapies (101-103). Furthermore, machine-learning techniques such as federated learning can enable privacy-preserving institutional collaboration by allowing AI models to be trained on clinical data distributed across multiple institutions without the raw data ever leaving its source. This is important for building robust, generalizable models while adhering to strict data-security and patient-privacy regulations (94,104). Harnessing AI-driven clinical-data analysis in the future will be an important component for deciphering the context-specific roles of TREM2 and translating preclinical research findings into effective treatment methods for glioma.

7. Conclusions

TREM2-associated TAMs represent a notable regulatory node within the immune microenvironment of glioma. They are notable mediators of the glioma TME and possess promising therapeutic potential. Previous research has highlighted the dual role of TREM2 in glioma, encompassing both immunosuppressive and immunoprotective functions; this duality reflects the complex biology of the brain TME. Future research and therapeutic success will require the stratification of patients based on the microenvironmental features that determine whether the TREM2 signaling axis sustains tumor growth or supports antitumor immunity in specific spatial and temporal contexts. Subsequently, targeted precision medicine can be developed based on the heterogeneity of these features. This will require deeper investigation into TREM2 activity in glioma and the integration of these research findings with innovative clinical practices. Notably, interdisciplinary integration that incorporates AI offers a promising possibility for elucidating the complexity of TREM2 signaling and improving treatment outcomes for high-grade glioma.

Acknowledgements

Not applicable.

Funding

Funding was received from the Key Specialist Fund (grant no. 41C41B26), the Medical Research Project of Chengdu City (grant no. 2024097) and the Military Center of Neuroanesthesia.

Availability of data and materials

Not applicable.

Authors' contributions

JF conceptualized the study and contributed toward performing the literature investigation, generating the figures and writing the original draft of the manuscript. QH was responsible for editing and reviewing the manuscript. DL contributed to performing the literature investigation and reviewing and editing the manuscript. SL contributed toward performing the literature investigation and writing the original draft of the manuscript. HS contributed to writing the original draft of the manuscript and generating the figures. YW supervised the study and contributed to writing the original draft of the manuscript. LY supervised the study, conceptualized the study, reviewed and edited the manuscript and acquired the funding. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Price M, Ballard C, Benedetti J, Neff C, Cioffi G, Waite KA, Kruchko C, Barnholtz-Sloan JS and Ostrom QT: CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2017-2021. Neuro Oncol 26 (Suppl 6): vi1-vi85, 2024.
2. Schaff LR and Mellinghoff IK: Glioblastoma and other primary brain malignancies in adults: A review. JAMA 329: 574-587, 2023.
3. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS and Khasraw M: Management of glioblastoma: State of the art and future directions. CA Cancer J Clin 70: 299-312, 2020.
4. Klemm F, Maas RR, Bowman RL, Kornete M, Soukup K, Nassiri S, Brouland JP, Iacobuzio-Donahue CA, Brennan C, Tabar V, *et al*: Interrogation of the microenvironmental landscape in brain tumors reveals disease-specific alterations of immune cells. Cell 181: 1643-1660.e17, 2020.
5. Kloosterman DJ, Erbani J, Boon M, Farber M, Handgraaf SM, Ando-Kuri M, Sánchez-López E, Fontein B, Mertz M, Nieuwland M, *et al*: Macrophage-mediated myelin recycling fuels brain cancer malignancy. Cell 187: 5336-5356.e30, 2024.
6. White J, White MPJ, Wickremesekera A, Peng L and Gray C: The tumour microenvironment, treatment resistance and recurrence in glioblastoma. J Transl Med 22: 540, 2024.
7. Khan F, Pang L, Dunterman M, Lesniak MS, Heimberger AB and Chen P: Macrophages and microglia in glioblastoma: Heterogeneity, plasticity, and therapy. J Clin Invest 133: e163446, 2023.
8. Miller TE, El Farran CA, Couturier CP, Chen Z, D'Antonio JP, Verga J, Villanueva MA, Gonzalez Castro LN, Tong YE, Saadi TA, *et al*: Programs, origins and immunomodulatory functions of myeloid cells in glioma. Nature 640: 1072-1082, 2025.
9. Li J, Ross JL, Hambardzumyan D and Brat DJ: Immunopathology of glioblastoma. Annu Rev Pathol 21: 135-162, 2026.
10. Kirschenbaum D, Xie K, Ingelfinger F, Katzenelenbogen Y, Abadie K, Look T, Sheban F, Phan TS, Li B, Zwicky P, *et al*: Time-resolved single-cell transcriptomics defines immune trajectories in glioblastoma. Cell 187: 149-165.e23, 2024.
11. Pombo Antunes AR, Scheyltjens I, Lodi F, Messiaen J, Antoranz A, Duerinck J, Kancheva D, Martens L, De Vlaminck K, Van Hove H, *et al*: Single-cell profiling of myeloid cells in glioblastoma across species and disease stage reveals macrophage competition and specialization. Nat Neurosci 24: 595-610, 2021.
12. Wang W, Li T, Cheng Y, Li F, Qi S, Mao M, Wu J, Liu Q, Zhang X, Li X, *et al*: Identification of hypoxic macrophages in glioblastoma with therapeutic potential for vasculature normalization. Cancer Cell 42: 815-832.e12, 2024.
13. Waibl Polania J, Hoyt-Miggelbrink A, Tomaszewski WH, Wachsmuth LP, Lorrey SJ, Wilkinson DS, Lerner E, Woroniecka K, Finlay JB, Ayasoufi K and Fecci PE: Antigen presentation by tumor-associated macrophages drives T cells from a progenitor exhaustion state to terminal exhaustion. Immunity 58: 232-246.e6, 2025.
14. Pocock J, Vasilopoulou F, Svensson E and Cosker K: Microglia and TREM2. Neuropharmacology 257: 110020, 2024.
15. Molgora M, Liu YA, Colonna M and Cella M: TREM2: A new player in the tumor microenvironment. Semin Immunol 67: 101739, 2023.
16. Deczkowska A, Weiner A and Amit I: The physiology, pathology, and potential therapeutic applications of the TREM2 signaling pathway. Cell 181: 1207-1217, 2020.
17. Hou J, Chen Y, Grajales-Reyes G and Colonna M: TREM2 dependent and independent functions of microglia in Alzheimer's disease. Mol Neurodegener 17: 84, 2022.
18. Chen X, Zhao Y, Huang Y, Zhu K, Zeng F, Zhao J, Zhang H, Zhu X, Kettenmann H and Xiang X: TREM2 promotes glioma progression and angiogenesis mediated by microglia/brain macrophages. Glia 71: 2679-2695, 2023.
19. Yu M, Chang Y, Zhai Y, Pang B, Wang P, Li G, Jiang T and Zeng F: TREM2 is associated with tumor immunity and implies poor prognosis in glioma. Front Immunol 13: 1089266, 2023.
20. Sun R, Han R, McCornack C, Khan S, Tabor GT, Chen Y, Hou J, Jiang H, Schoch KM, Mao DD, *et al*: TREM2 inhibition triggers antitumor cell activity of myeloid cells in glioblastoma. Sci Adv 9: eade3559, 2023.
21. Zheng J, Wang L, Zhao S, Zhang W, Chang Y, Bosco DB, Huang T, Dheer A, Gao S, Xu S, *et al*: TREM2 mediates MHCII-associated CD4+ T-cell response against gliomas. Neuro Oncol 26: 811-825, 2024.
22. Zhong J, Xing X, Gao Y, Pei L, Lu C, Sun H, Lai Y, Du K, Xiao F, Yang Y, *et al*: Distinct roles of TREM2 in central nervous system cancers and peripheral cancers. Cancer Cell 42: 968-984.e9, 2024.
23. Park MD, Reyes-Torres I, LeBerichel J, Hamon P, LaMarche NM, Hegde S, Belabed M, Troncoso L, Grout JA, Magen A, *et al*: TREM2 macrophages drive NK cell paucity and dysfunction in lung cancer. Nat Immunol 24: 792-801, 2023.
24. Chu T, Zhu G, Tang Z, Qu W, Yang R, Pan H, Wang Y, Tian R, Chen L, Guan Z, *et al*: Metabolism archetype cancer cells induce protumor TREM2^{+} macrophages via oxLDL-mediated metabolic interplay in hepatocellular carcinoma. Nat Commun 16: 6770, 2025.
25. Sun R, Lei C, Xu Z, Gu X, Huang L, Chen L, Tan Y, Peng M, Yaddanapudi K, Siskind L, *et al*: Neutral ceramidase regulates breast cancer progression by metabolic programming of TREM2-associated macrophages. Nat Commun 15: 966, 2024.
26. Lin M, Yu JX, Zhang WX, Lao FX and Huang HC: Roles of TREM2 in the pathological mechanism and the therapeutic strategies of Alzheimer's disease. J Prev Alzheimers Dis 11: 1682-1695, 2024.
27. Yin P, Su Z, Shu X, Dong Z and Tian Y: Role of TREM2 in immune and neurological diseases: Structure, function, and implications. Int Immunopharmacol 143: 113286, 2024.
28. Zhao Y, Guo Q, Tian J, Liu W and Wang X: TREM2 bridges microglia and extracellular microenvironment: Mechanistic landscape and therapeutical prospects on Alzheimer's disease. Ageing Res Rev 103: 102596, 2025.
29. Painter MM, Atagi Y, Liu CC, Rademakers R, Xu H, Fryer JD and Bu G: TREM2 in CNS homeostasis and neurodegenerative disease. Mol Neurodegener 10: 43, 2015.
30. Vijayan N, Thanikachalam PV and Patel S: Decoding of the role of TREM2 in neuropathic pain: Molecular pathway and neuroinflammatory mechanism. Drug Dev Res 86: e70111, 2025.

31. Yang H, Kim D, Yang Y, Bagyinszky E and An SSA: TREM2 in neurodegenerative disorders: Mutation spectrum, pathophysiology, and therapeutic targeting. Int J Mol Sci 26: 7057, 2025.
32. Atagi Y, Liu CC, Painter MM, Chen XF, Verbeeck C, Zheng H, Li X, Rademakers R, Kang SS, Xu H, *et al*: Apolipoprotein E is a ligand for triggering receptor expressed on myeloid cells 2 (TREM2). J Biol Chem 290: 26043-26050, 2015.
33. Filipello F, Morini R, Corradini I, Zerbi V, Canzi A, Michalski B, Erreni M, Markicevic M, Starvaggi-Cucuzza C, Otero K, *et al*: The microglial innate immune receptor TREM2 is required for synapse elimination and normal brain connectivity. Immunity 48: 979-991.e8, 2018.
34. Konishi H and Kiyama H: Non-pathological roles of microglial TREM2/DAP12: TREM2/DAP12 regulates the physiological functions of microglia from development to aging. Neurochem Int 141: 104878, 2020.
35. Cignarella F, Filipello F, Bollman B, Cantoni C, Locca A, Mikesell R, Manis M, Ibrahim A, Deng L, Benitez BA, *et al*: TREM2 activation on microglia promotes myelin debris clearance and remyelination in a model of multiple sclerosis. Acta Neuropathol 140: 513-534, 2020.
36. McCray TJ, Bedford LM, Bissel SJ and Lamb BT: Trem2-deficiency aggravates and accelerates age-related myelin degeneration. Acta Neuropathol Commun 12: 154, 2024.
37. Xue T, Ji J, Sun Y, Huang X, Cai Z, Yang J, Guo W, Guo R, Cheng H and Sun X: Sphingosine-1-phosphate, a novel TREM2 ligand, promotes microglial phagocytosis to protect against ischemic brain injury. Acta Pharm Sin B 12: 1885-1898, 2022.
38. Zhao Y, Wu X, Li X, Jiang LL, Gui X, Liu Y, Sun Y, Zhu B, Piña-Crespo JC, Zhang M, *et al*: TREM2 is a receptor for β-amyloid that mediates microglial function. Neuron 97: 1023-1031.e7, 2018.
39. Zhong L, Wang Z, Wang D, Wang Z, Martens YA, Wu L, Xu Y, Wang K, Li J, Huang R, *et al*: Amyloid-beta modulates microglial responses by binding to the triggering receptor expressed on myeloid cells 2 (TREM2). Mol Neurodegener 13: 15, 2018.
40. Kobayashi M, Konishi H, Sayo A, Takai T and Kiyama H: TREM2/DAP12 signal elicits proinflammatory response in microglia and exacerbates neuropathic pain. J Neurosci 36: 11138-11150, 2016.
41. Wei W, Zhang L, Xin W, Pan Y, Tatenhorst L, Hao Z, Gerner ST, Huber S, Juenemann M, Butz M, *et al*: TREM2 regulates microglial lipid droplet formation and represses post-ischemic brain injury. Biomed Pharmacother 170: 115962, 2024.
42. Kawabori M, Kacimi R, Kauppinen T, Calosing C, Kim JY, Hsieh CL, Nakamura MC and Yenari MA: Triggering receptor expressed on myeloid cells 2 (TREM2) deficiency attenuates phagocytic activities of microglia and exacerbates ischemic damage in experimental stroke. J Neurosci 35: 3384-3396, 2015.
43. Yan Y, Bai S, Han H, Dai J, Niu L, Wang H, Dong Q, Yin H, Yuan G and Pan Y: Knockdown of trem2 promotes proinflammatory microglia and inhibits glioma progression via the JAK2/STAT3 and NF-κB pathways. Cell Commun Signal 22: 272, 2024.
44. Liu T, Gao H, Xi Z, Yu T, Gu Y, Mai H, Yuan H, Liu Y, Liu H, Zhang Q, *et al*: CAR-T triggers TAM reeducation and adaptive anti-tumor response via TREM2 deficiency or CD40 agonist. Cell Rep Med 7: 102539, 2026.
45. Ruganzu JB, Zheng Q, Wu X, He Y, Peng X, Jin H, Zhou J, Ma R, Ji S, Ma Y, *et al*: TREM2 overexpression rescues cognitive deficits in APP/PS1 transgenic mice by reducing neuroinflammation via the JAK/STAT/SOCS signaling pathway. Exp Neurol 336: 113506, 2021.
46. Wang M, Zhao R, Su Y, Zhai D, Liang H, Zhang L, Wang W, Wang Z, Qi M, Jiang X, *et al*: 4,4'-Dimethoxychalcone mitigates neuroinflammation following traumatic brain injury through modulation of the TREM2/PI3K/AKT/NF-κB signaling pathway. Inflammation 48: 3487-3505, 2025.
47. Yang D, Sun X, Wang H, Wistuba II, Wang H, Maitra A and Chen Y: TREM2 depletion in pancreatic cancer elicits pathogenic inflammation and accelerates tumor progression via enriching IL-1β^{+} macrophages. Gastroenterology 168: 1153-1169, 2025.
48. Lin H, Liu C, Hu A, Zhang D, Yang H and Mao Y: Understanding the immunosuppressive microenvironment of glioma: Mechanistic insights and clinical perspectives. J Hematol Oncol 17: 31, 2024.
49. Elguindy MM, Young JS, Ho WS and Lu RO: Co-evolution of glioma and immune microenvironment. J Immunother Cancer 12: e009175, 2024.
50. Li J, Yu X, Yang D, Chen S, Xu J, Ma X, Huang C, Xu B, Xue L and Wang Y: Lipid-metabolically active TREM2^{high} microglia-derived macrophages predict poor prognosis and represent an immunotherapeutic target in glioma. J Neuroimmune Pharmacol 20: 92, 2025.
51. Peshoff MM, Gupta P, Oberai S, Trivedi R, Katayama H, Chakrapani P, Dang M, Migliozzi S, Gumin J, Kadri DB, *et al*: Triggering receptor expressed on myeloid cells 2 (TREM2) regulates phagocytosis in glioblastoma. Neuro Oncol 26: 826-839, 2024.
52. Li P, Sun Z, Chen Y, Fang Z, Yu D, Wang L, Ren Y and Gong P: Role of eCIRP in mediating post-ischemia microglial phagocytosis via TREM-2 receptor: insights from porcine and mouse cellular models. Mol Neurobiol 63: 483, 2026.
53. Zhang Z, Yu K, Cao Y, Xie P, Wang L, Shen Z and Qin J: TREM2 facilitates gastric cancer progression and immune evasion via inhibiting TRIM21-mediated STAT1 degradation in tumor-associated macrophages. Cell Death Dis 16: 845, 2025.
54. Zhao Y, Hu H, Wang J, Hu Y, Yang L, Wu Z, Zhao S, Wang X, Mu Y, Zheng M, *et al*: SYK-dependent lipid handling in monocyte-derived macrophages governs functional recovery after spinal cord injury. Brain Res Bull 237: 111823, 2026.
55. Colonna M: The biology of TREM receptors. Nat Rev Immunol 23: 580-594, 2023.
56. Sigalov AB: TREM-1 and TREM-2 as therapeutic targets: Clinical challenges and perspectives. Front Immunol 15: 1498993, 2024.
57. Lu J, Chu S, Wang S, Wang S, Yu Z, Yan Z, Ji G, Zhou H, Wang J and Zhu C: Spatiotemporal and metabolic heterogeneity of tumor-associated macrophages in glioblastoma: From single-cell insights to therapeutic targeting. Front Cell Dev Biol 14: 1774215, 2026.
58. Cheng Y, Zhao W, Xie M, Zheng X, Ding F and Du J: Decoding myeloid heterogeneity in glioblastoma: Spatial insights from transcriptomics. J Transl Med 24: 432, 2026.
59. Villa G, Delev D and Heiland DH: Mapping myeloid cell function: Spatial diversity in tumor and neuronal microenvironment. Cancer Cell 42: 934-936, 2024.
60. Genoud V, Marinari E, Nikolaev SI, Castle JC, Bukur V, Dietrich PY, Okada H and Walker PR: Responsiveness to anti-PD-1 and anti-CTLA-4 immune checkpoint blockade in SB28 and GL261 mouse glioma models. Oncoimmunology 7: e1501137, 2018.
61. Ghosh S and Rothlin CV: TREM2 function in glioblastoma immune microenvironment: Can we distinguish reality from illusion? Neuro Oncol 26: 840-842, 2024.
62. Kluckova K, Kozak J, Szaboova K, Rychly B, Svajdler M, Suchankova M, Tibenska E, Filova B, Steno J, Matejcik V, *et al*: TREM-1 and TREM-2 expression on blood monocytes could help predict survival in high-grade glioma patients. Mediators Inflamm 2020: 1798147, 2020.
63. Kluckova K, Kozak J, Szaboova K, Suchankova M, Svajdler M, Blazickova S, Makohusova M, Steno J, Matejcik V and Bucova M: Low serum vitamin D levels are associated with a low percentage of TREM-2+ monocytes in low-grade gliomas and poorer overall survival in patients with high-grade gliomas. Bratisl Lek Listy 122: 172-178, 2021.
64. Ohrfelt A, Axelsson M, Malmestrom C, Novakova L, Heslegrave A, Blennow K, Lycke J and Zetterberg H: Soluble TREM-2 in cerebrospinal fluid from patients with multiple sclerosis treated with natalizumab or mitoxantrone. Mult Scler 22: 1587-1595, 2016.
65. Qin C, Chen M, Dong MH, Yang S, Zhang H, You YF, Zhou LQ, Chu YH, Tang Y, Pang XW, *et al*: Soluble TREM2 triggers microglial dysfunction in neuromyelitis optica spectrum disorders. Brain 147: 163-176, 2024.
66. Greutter L, Miller-Michlits Y, Klotz S, Reimann R, Nenning KH, Platzek S, Krause E, Kiesel B, Widhalm G, Langs G, *et al*: Frequent Alzheimer's disease neuropathological change in patients with glioblastoma. Neurooncol Adv 6: vdae118, 2024.
67. Zhong L, Chen XF, Wang T, Wang Z, Liao C, Wang Z, Huang R, Wang D, Li X, Wu L, *et al*: Soluble TREM2 induces inflammatory responses and enhances microglial survival. J Exp Med 214: 597-607, 2017.
68. Zhang L, Xiang X, Li Y, Bu G and Chen XF: TREM2 and sTREM2 in Alzheimer's disease: From mechanisms to therapies. Mol Neurodegener 20: 43, 2025.
69. Zheng H, Jia L, Liu CC, Rong Z, Zhong L, Yang L, Chen XF, Fryer JD, Wang X, Zhang YW, *et al*: TREM2 promotes microglial survival by activating Wnt/β-catenin pathway. J Neurosci 37: 1772-1784, 2017.

70. Ma YN, Hu X, Karako K, Song P, Tang W and Xia Y: The potential and challenges of TREM2-targeted therapy in Alzheimer's disease: Insights from the INVOKE-2 study. Front Aging Neurosci 17: 1576020, 2025.
71. Li H, Xu D, Cai W, Liu J, Bing Z and Zhang Q: PEGylated nanoliposomal doxorubicin conjugated with specific TREM2 peptides for glioma-targeting therapy. Adv Healthc Mater 14: e2403096, 2025.
72. Sigalov AB: Inhibition of TREM-2 markedly suppresses joint inflammation and damage in experimental arthritis. Int J Mol Sci 23: 8857, 2022.
73. Gallop D, Scanlon KM, Ardanuy J, Sigalov AB, Carbonetti NH and Skerry C: Triggering receptor expressed on myeloid cells-1 (TREM-1) contributes to bordetella pertussis inflammatory pathology. Infect Immun 89: e0012621, 2021.
74. Zhou F, Mukherjee P, Mu J and Chen P: Therapeutic potential of targeting macrophages and microglia in glioblastoma. Trends Pharmacol Sci 46: 848-862, 2025.
75. Harwood DSL, Artzi SB, Pedersen V, Locallo A, Lü MJS, Scheie D, Nørøxe DS, Hammouda NM, Lassen U, Weischenfeldt J and Kristensen BW: Genomic heterogeneity drives distinct infiltration patterns in glioblastoma. Acta Neuropathol Commun 14: 5, 2025.
76. Lemoine C, Da Veiga MA, Rogister B, Piette C and Neirinckx V: An integrated perspective on single-cell and spatial transcriptomic signatures in high-grade gliomas. NPJ Precis Oncol 9: 44, 2025.
77. Kim J, Zhu Y, Chen S, Wang D, Zhang S, Xia J, Li S, Qiu Q, Lee H and Wang J: Anti-glioma effect of ginseng-derived exosomes-like nanoparticles by active blood-brain-barrier penetration and tumor microenvironment modulation. J Nanobiotechnology 21: 253, 2023.
78. Wang C, Feng W, Li J, Wang J, Liu L, Ye SH, Zhang Y, Fu J, Zheng H, Chen E, *et al*: Enhanced nano-vaccine utilizing biomineralized virus-like particles for efficient glioblastoma immunotherapy via the nose-to-brain delivery pathway. ACS Nano 19: 21154-21168, 2025.
79. Kuang L, Han M, Wu X, Deng Z, Liu T, Yin Y, Tang Y, Dong Z, Hu X, Zhu S, *et al*: Starting the engine and releasing the brakes of T-cell responses: A biomimetic dendritic cell nanoplatform for improved glioblastoma immunotherapy. ACS Nano 19: 21365-21384, 2025.
80. von Locquenghien M, Zwicky P, Xie K, Jaitin DA, Sheban F, Yalin A, Uhlitz F, Gur C, Eshed RS, David E, *et al*: Macrophage-targeted immunocytokine leverages myeloid, T, and NK cell synergy for cancer immunotherapy. Cell 188: 7099-7117.e26, 2025.
81. Lago C, Gianesello M, Santomaso L, Leva G, Ballabio C, Anderle M, Antonica F and Tiberi L: Medulloblastoma and high-grade glioma organoids for drug screening, lineage tracing, co-culture and in vivo assay. Nat Protoc 18: 2143-2180, 2023.
82. Pasupuleti V, Vora L, Prasad R, Nandakumar DN and Khatri DK: Glioblastoma preclinical models: Strengths and weaknesses. Biochim Biophys Acta Rev Cancer 1879: 189059, 2024.
83. Correia CD, Calado SM, Matos A, Esteves F, De Sousa-Coelho AL, Campinho MA and Fernandes MT: Advancing glioblastoma research with innovative brain organoid-based models. Cells 14: 292, 2025.
84. Wen J, Liu F, Cheng Q, Weygant N, Liang X, Fan F, Li C, Zhang L and Liu Z: Applications of organoid technology to brain tumors. CNS Neurosci Ther 29: 2725-2743, 2023.
85. Zheng C, Wang P, Zhang D, Fang Z, Feng Y, Chen J, Chen J, Fu Y, Yang B, Yu S, *et al*: A novel organoid model retaining the glioma microenvironment for personalized drug screening and therapeutic evaluation. Bioact Mater 53: 205-217, 2025.
86. Schupper AJ and Hadjipanayis CG: Novel approaches to targeting gliomas at the leading/cutting edge. J Neurosurg 139: 760-768, 2023.
87. Gampa G, Vadlakonda R, Stefanich E, Kamath AV, Sadekar S and Shivva V: Bridging the blood-brain barrier: Strategies to improve delivery of biologics to tumors in the brain. Fluids Barriers CNS 23: 25, 2026.
88. Wang N, Qing Q, Xue Y, Cai S, Zheng M, Zhang D and Ismail M: Enhancing lipid nanoparticles-mediated RNA delivery to glioblastoma via targeted strategies. J Control Release 389: 114472, 2026.
89. Arjmand B, Mojavezi AR, Kamroo A, Yazdi RK, Rezaei-Tavirani M and Vahedi MS: Advances in intranasal delivery of exosomes for central nervous system disorders. Mol Neurobiol 63: 193, 2025.
90. Pai B, Ramos SI, Cheng WS, Joshi T, Özen E, Kulumani Mahadevan LS, Silva-Hurtado TJ, Price GA, Tome-Garcia J, Nudelman G, *et al*: Spatial multiomics defines a shared tumor infiltrative signature at the resection margin in high-grade gliomas. Cancer Res 85: 4233-4250, 2025.
91. Fan H, Luo Y, Gu F, Tian B, Xiong Y, Wu G, Nie X, Yu J, Tong J and Liao X: Artificial intelligence-based MRI radiomics and radiogenomics in glioma. Cancer Imaging 24: 36, 2024.
92. Luo J, Pan M, Mo K, Mao Y and Zou D: Emerging role of artificial intelligence in diagnosis, classification and clinical management of glioma. Semin Cancer Biol 91: 110-123, 2023.
93. Wang YRJ, Wang P, Yan Z, Zhou Q, Gunturkun F, Li P, Hu Y, Wu WE, Zhao K, Zhang M, *et al*: Advancing presurgical non-invasive molecular subgroup prediction in medulloblastoma using artificial intelligence and MRI signatures. Cancer Cell 42: 1239-1257.e7, 2024.
94. Morello G, La Cognata V, Guarnaccia M, Gentile G and Cavallaro S: Artificial intelligence-driven multi-omics approaches in glioblastoma. Int J Mol Sci 26: 9362, 2025.
95. Lin B, Tan Z, Mo Y, Yang X, Liu Y and Xu B: Intelligent oncology: The convergence of artificial intelligence and oncology. J Natl Cancer Cent 3: 83-91, 2022.
96. Li H, Nithin C, Kmiecik S and Huang SY: Computational methods for modeling protein-protein interactions in the AI era: Current status and future directions. Drug Discov Today 30: 104382, 2025.
97. Sarvepalli S and Vadarevu S: Role of artificial intelligence in cancer drug discovery and development. Cancer Lett 627: 217821, 2025.
98. Zhang K, Yang X, Wang Y, Yu Y, Huang N, Li G, Li X, Wu JC and Yang S: Artificial intelligence in drug development. Nat Med 31: 45-59, 2025.
99. Ocana A, Pandiella A, Privat C, Bravo I, Luengo-Oroz M, Amir E and Gyorffy B: Integrating artificial intelligence in drug discovery and early drug development: A transformative approach. Biomark Res 13: 45, 2025.
100. Vecchietti LF, Wijaya BN, Armanuly A, Hangeldiyev B, Jung H, Lee S, Cha M and Kim HM: Artificial intelligence-driven computational methods for antibody design and optimization. MAbs 17: 2528902, 2025.
101. Wang Z, Zhang RY, Ji C, Zhang JY, Yue BT and Wang F: Revolutionizing gastrointestinal cancer research with artificial intelligence: From precision patient stratification to real-world evidence. World J Gastrointest Oncol 17: 111339, 2025.
102. Jin D, Shmatko A, Patel A, Rutz S, Friedrich L, Banan R, Rahmanzade R, Sievers P, Hamelmann S, Schrimpf D, *et al*: Hetairos is a histology-based artificial intelligence model for predicting central nervous system tumor methylation subtypes. Nat Cancer: Jun 10, 2026 (Epub ahead of print).
103. Zapaishchykova A, Zielke J, Tak D, Climent Pardo JC, Mojahed-Yazdi R, Soto-Rivera CL, Liu KX, Saraf A, Ye Z, Wang W, *et al*: Artificial intelligence analysis of temporalis muscle thickness for monitoring sarcopenia and clinical outcomes in individuals with paediatric brain tumours: A retrospective cohort study. Lancet Digit Health: 100973, 2026 (Epub ahead of print).
104. Ning Y, Teixayavong S, Shang Y, Savulescu J, Nagaraj V, Miao D, Mertens M, Ting DSW, Ong JCL, Liu M, *et al*: Generative artificial intelligence and ethical considerations in health care: A scoping review and ethics checklist. Lancet Digit Health 6: e848-e856, 2024.