Role of matrix metalloproteinases in the invasion of glioblastoma and drug interventions (Review)

BOHAO ZHENG, YING HAN and HAIYING ZHANG

The First Clinical College of Liaoning University of Traditional Chinese Medicine, Shenyang, Liaoning 110000, P.R. China

Received June 19, 2025; Accepted November 18, 2025

DOI: 10.3892/ijmm.2025.5704

Abstract. Glioblastoma (GBM) is the most aggressive primary malignant brain tumor type in adults, and is characterized by high invasiveness, therapeutic resistance and recurrence. Current treatments, primarily surgery combined with radiotherapy and chemotherapy, offer limited efficacy, thus necessitating more effective interventions. Matrix metalloproteinases (MMPs) crucially contribute to GBM progression through extracellular matrix degradation, epithelial-mesenchymal transition and angiogenesis. MMP expression is intricately regulated by signaling pathways, non-coding RNAs and the tumor microenvironment. Recently, strategies targeting MMPs have gained attention, including natural active substances and small-molecule compounds with promising therapeutic potential. Nano-delivery systems have notably improved drug delivery efficiency to the brain by overcoming the blood-brain barrier, and combination therapies have demonstrated enhanced efficacy. However, chemotherapy resistance and functional heterogeneity remain critical challenges. The present review summarizes recent advances in understanding MMP regulatory mechanisms in GBM, highlighting the roles of signaling pathways and non-coding RNAs. Additionally, the therapeutic potential of natural products, small-molecule inhibitors, smart nanocarriers and combination treatments are discussed. Future research should focus on identifying novel inhibitors, and leveraging interdisciplinary approaches to facilitate precision-targeted drug development, thereby addressing current treatment bottlenecks in GBM.

Contents

Correspondence to: Dr Haiying Zhang, The First Clinical College of Liaoning University of Traditional Chinese Medicine, 33 Beiling Street, Huanggu, Shenyang, Liaoning 110000, P.R. China
E-mail: 86223187@163.com

Key words: matrix metalloproteinases, glioblastoma, drug intervention, tumor cell invasion

1. Introduction

Glioblastoma (GBM) stands as the most common malignant primary brain tumor type affecting the adult central nervous system (CNS), comprising 48% of all malignant CNS tumors and 57% of gliomas. The isocitrate dehydrogenase (IDH) wild-type subtype of GBM is designated as grade IV by the World Health Organization due to its aggressive behavior (1-3). Current GBM treatment typically involves a multifaceted approach, including surgery, radiotherapy and chemotherapy, supported by innovative physical therapies and targeted drugs. During surgical procedures, gross total resection (GTR) employs advanced techniques such as 5-aminolevulinic acid (5-ALA) fluorescence guidance and intraoperative desorption electrospray ionization mass spectrometry to precisely locate tumor boundaries (4-6). Notably, the biological traits of GBM profoundly impact surgical outcomes, with IDH-mutant tumors being more responsive to GTR due to their reduced aggressiveness (7). In radiotherapy, the addition of temozolomide (TMZ) to conventional radiation therapy notably increases patient survival compared with single-modality treatment (8). For elderly patients (>70 years old), hypofractionated radiotherapy is used to minimize toxicity (9). Chemotherapy, predominantly with TMZ, operates by inducing O^6-guanine methylation, thereby causing DNA damage. A phase III clinical trial combining TMZ with lomustine has shown potential for extending patient lifespan (10,11). Innovative physical therapies such as tumor-treating fields exhibit antitumor activity by causing neuronal depolarization and disrupting microtubule formation during cell division, specifically targeting rapidly proliferating tumor cells (12,13). Although their combination with TMZ can increase the median overall survival (mOS), these therapies are associated with a higher rate of systemic side effects (14). Targeted therapies, including bevacizumab (BEV), enhance progression-free survival (PFS), but do not improve OS and may increase adverse reactions (15,16).

The pathological hallmarks of GBM are manifested in three distinct aspects. Firstly, there is the widespread infiltrative growth of tumor cells, which spread along nerve fiber bundles and vascular spaces. Secondly, radially arranged

pseudopalisading structures develop around necrotic cores. Lastly, a triad of vascular abnormalities is observed, including pathological angiogenesis, abnormal endothelial cell proliferation and intravascular thrombosis (17,18). Clinical studies have shown that patients with GBM often exhibit a hypercoagulable state, which is strongly linked to the aggressiveness of the tumor (19-22). The matrix metalloproteinase (MMP) family plays a key role in this process (23). MMPs are zinc-dependent endopeptidases classified into subfamilies based on their substrate specificity and structural features, including collagenases (MMP-1, -8 and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3 and -10), and membrane-bound MMPs (MMP-14, -16 and -17) (24,25). These enzymes critically regulate tumor invasion and metastasis by mediating epithelial-mesenchymal transition (EMT), degrading extracellular matrix (ECM) components and promoting tumor angiogenesis (26-28). In GBM, the expression of several MMPs, particularly MMP-2 and MMP-9, is significantly increased, and their enhanced activity correlates with invasive tumor growth and blood-brain barrier (BBB) disruption, highlighting the crucial role of MMPs in disease progression (29,30).

In recent years, notable advancements have occurred in mechanistic studies on MMPs during the invasion process of GBM (31-33). However, two major obstacles must be addressed before their effective clinical targeting. Firstly, the BBB, with its complex interplay of active transport systems (including uptake and efflux proteins) and metabolic enzymes, poses a formidable biological barrier. This barrier effectively hinders small molecules from reaching the brain, thus considerably diminishing drug accumulation efficiency (34). Emerging drug delivery approaches, utilizing nano-drug delivery systems such as liposomes (35), nanoparticles (NPs) (36) and hydrogel carriers (37), offer promise for enhancing the targeted accumulation of antitumor agents in the brain. Additionally, the multifactorial mechanisms underlying TMZ resistance involve not only DNA damage repair mediated by O^6-methylguanine-DNA methyltransferase (MGMT) overexpression and drug efflux transporter activation (38,39), but also mismatch repair defects (40), glioma stem cell (GSC) self-renewal (41) and aberrant cell signaling pathways (42). Breakthroughs in synthesizing natural medicines and novel compounds have presented innovative strategies to tackle drug resistance (43,44), thereby expanding GBM treatment options and paving the way for targeted therapies.

The present review comprehensively examines the regulatory mechanisms of the MMP family in GBM invasion, focusing on recent developments. It further explores recent progress in therapeutic approaches, including natural bioactive compounds, small molecules and nanotechnology-driven combinations. The aim of the present study is to establish a theoretical foundation and guide treatment innovations for GBM.

2. Central role of MMPs in the invasion and metastasis of GBM

MMP-mediated degradation and remodeling of the ECM. The ECM is crucial in GBM malignant invasion, a process mediated by MMPs. In the brain, the ECM preserves the homeostasis of the neural microenvironment via specific structures and functions of the basilar membrane, interstitial matrix and perineuronal nets (PNNs) (45). However, GBM disrupts this balance by degrading the ECM and triggering pro-invasive signals such as EMT. This occurs through the abnormal overexpression of MMPs, including MMP-2, MMP-9 and MMP-14, which stimulate the development of invasive pseudopodia in tumor cells and aid in the spread of intercellular vesicles (46-49) (Fig. 1).

The ECM in the brain plays a dual role in GBM invasion. On one hand, GBM directly degrades ECM components by upregulating MMPs. On the other hand, it creates a microenvironment that promotes invasion by forming invasive pseudopodia and releasing extracellular vesicles carrying MMPs. Specifically, the ECM can be classified into three types based on location: i) The basement membrane, which is located around blood vessels (neurovascular unit), and consists of components such as collagen and laminin, which help maintain the stability of the blood vessel-neural interface; ii) the interstitial matrix, which is distributed in the interstitial space between neurons and glial cells, and forms a loose network with hyaluronic acid and proteoglycans to support intercellular material exchange; and iii) the PNN, which directly surrounds neuronal cell bodies and dendrites, and is composed of a hyaluronic acid scaffold and chondroitin sulfate proteoglycans (such as aggrecan), forming a dense structure whose formation relies on neuronal activity (45). In GBM, contrary to the widespread notion that most models involve membrane-type (MT)-MMPs activating progelatinase A, previous research has revealed that MT-MMPs are predominantly produced by GBM cells and play a direct role in their migration (46). Notably, MMP-17 and MMP-25 exhibit particularly pronounced effects in this process (46). During GBM invasion, a marked elevation in MMP-9 levels leads to the breakdown of the ECM. This degradation is accompanied by increased prolidase activity, which releases metabolites such as proline. Simultaneously, the production of proline within GBM cells serves to further augment their invasive capabilities (47). Additional research has shown that, from a cellular structural perspective, GBM cells have the ability to form invasive pseudopodia equipped with matrix-degrading functions. These cells also secrete small extracellular vesicles (sEVs) enriched in MMP-2. These sEVs not only exhibit a close association with pseudopod activity but can also be internalized by adjacent GBM cells. This internalization significantly enhances the invasive potential of the recipient cells by transferring highly invasive pseudopod activity (48). Furthermore, vesicles released by GBM cells can stimulate astrocytes to secrete MMP-9, thereby further facilitating the invasion of GBM (49).

In addition, the ECM modulates tumor angiogenesis via a dual mechanism. Firstly, it interacts with cell receptors, activating signaling pathways such as MAPK, and thereby enhancing endothelial cell proliferation, migration and survival (50,51). Secondly, ECM remodeling, facilitated by proteases such as MMPs and fibrinolytic enzymes, releases angiogenic factors, including vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β) and fibroblast growth factor-2, further influencing angiogenesis (52,53). In GBM, a distinctive pathological trait emerges where MMPs degrade the ECM, paving the way for new

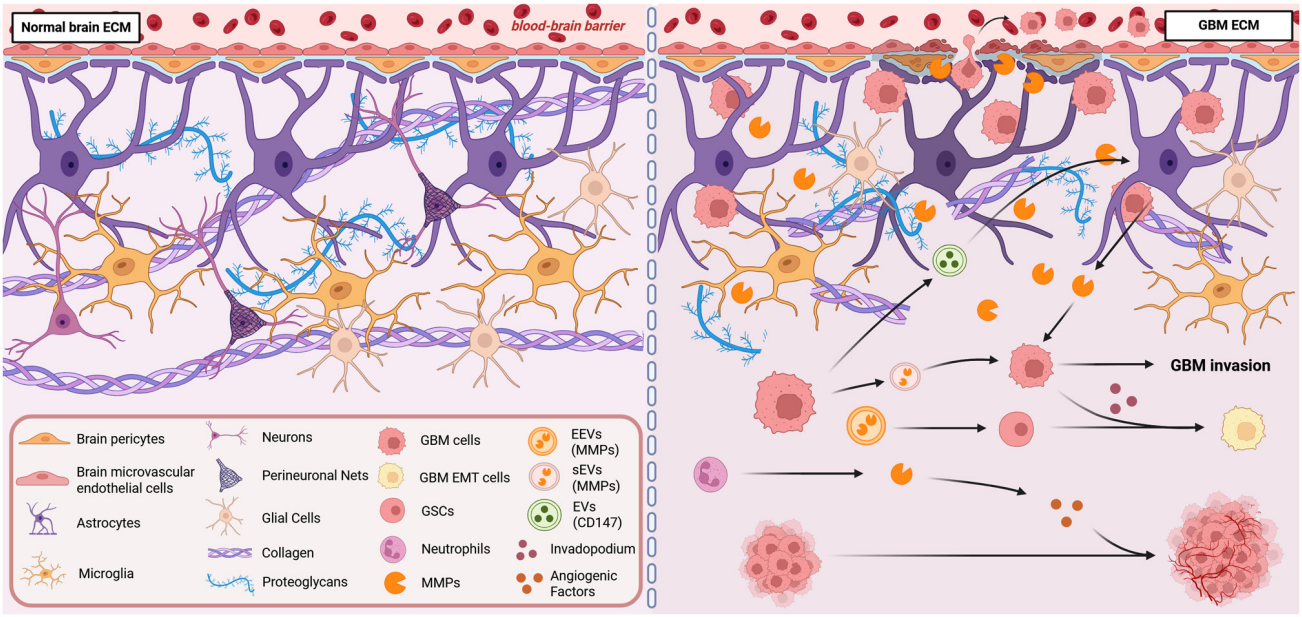

Figure 1. ECM in normal brain tissue vs. GBM. In normal state, the brain ECM is primarily composed of and maintained by brain microvascular endothelial cells, astrocytes, microglia, oligodendrocytes, neurons and the surrounding perineuronal nets. Components such as collagen and proteoglycans are interwoven within this structure, ensuring the structural and functional stability of the neurovascular unit. In GBM pathological state, MMPs accumulate in the BBB region, degrading the perivascular basement membrane, astrocytic end-feet structures and key ECM components such as collagen and proteoglycans, thereby disrupting ECM homeostasis and leading to BBB leakage. EVs released by GBM cells can induce astrocytes to secrete MMPs; these EVs are also taken up by neighboring GBM cells, promoting an invasive phenotype. EVs released by endothelial cells can induce epithelial-mesenchymal transition in GBM stem cells. Furthermore, MMPs released by neutrophils promote tumor angiogenesis by modulating the expression of angiogenesis-related factors, collectively driving GBM invasion. → indicates the direction of action; key factors contained within EVs are indicated in parentheses. ECM, extracellular matrix; GBM, glioblastoma; MMP, matrix metalloproteinase; BBB, blood-brain barrier; EVs, extracellular vesicles; EMT, epithelial-mesenchymal transition; GSCs, glioma stem cells; sEVs, small extracellular vesicles; EEVs, endothelial cell-derived extracellular vesicles. Created in BioRender. Zheng, B. (2025) https://BioRender.com/dxwgq2l.

tumor angiogenesis, while potentially altering the function and structure of preexisting blood vessels (23). Notably, tumor-infiltrating neutrophils elevate the expression of VEGFA through the secretion of MMP-9, introducing an additional layer of angiogenesis regulation (54). Furthermore, previous bioinformatics analysis has uncovered a significant association between elevated MMP-14 expression and several angiogenesis-related signaling pathways, such as Visfatin, VEGF and TGF-β, as well as the endothelial-mesenchymal transition process (55). Previous research has indicated that MMP-14 can stimulate angiogenesis in GBM (56).

EMT modulates the tumor microenvironment (TME) through multiple mechanisms, thereby enhancing the invasiveness of GBM. EMT augments the aggressiveness of tumor cells by inducing the formation of actin-rich invadopodia, which are dynamic adhesive structures capable of locally releasing MMP-mediated proteolytic enzymes at cell-ECM contact zones, thus facilitating cellular invasion (57). Within the TME, endothelial cell-derived vesicles activate the NF-κB signaling pathway within GBM stem cells (GSCs) by delivering MMPs, inducing the transformation of pro-neural cells into a mesenchymal phenotype and promoting the shift towards an invasive phenotype (58). Previous research has revealed an interaction between MMP-14 and TGF-β receptor signaling in GBM. These two factors induce the programmed activation of EMT through the stimulation of Snail transcription factors. This synergistic action of proteases and growth factors ultimately leads to a highly invasive tumor phenotype (59).

MMPs are core biomarkers of GBM invasiveness. MMPs are not only key molecules mediating ECM degradation and driving tumor invasion in GBM, but their expression and activity levels constitute critical biomarkers reflecting the invasive potential of GBM. In GBM tissues, particularly at the tumor invasion front and in neovascularization areas, MMP expression is significantly higher than in normal brain tissue. Concurrently, MMP-2 and MMP-9 expression levels have been found to be further elevated in recurrent GBM tissues, closely correlating with malignant biological behaviors such as tumor invasion, dissemination and recurrence (60). Furthermore, MMPs are important in bodily fluid tests. A prospective study showed that serum MMP-9 concentrations were significantly elevated in patients with GBM (n=66) and correlated with tumor activity status. Serum MMP-9 levels in patients without radiological lesions were significantly lower than in those with active disease (P=0.0002), suggesting its potential as a serum marker for disease monitoring, although MMP-9 showed no significant correlation with OS (61). However, a subsequent larger prospective study (n=192) challenged this view. That study, through systematic analysis of serum samples, found that, although MMP-9 is highly expressed in GBM tissue, its serum level did not correlate significantly with radiological disease status (P=0.33), indicating that circulating MMP-9 cannot reliably reflect local GBM progression. While a longitudinal increase in serum MMP-9 showed a weak correlation with shorter survival [hazard ratio (HR)=1.1 per doubling; P=0.04], multivariate analysis revealed that it was not an independent prognostic factor (P=0.11). These

results further suggest the limited clinical value of serum MMP-9 as a dynamic monitoring or independent prognostic biomarker for GBM (62). Notably, compared with serum, continuous monitoring in patients with recurrent GBM (n=4) undergoing a specific biochemotherapy regimen (irinotecan, thalidomide and doxycycline) revealed that MMP-9 levels in the cerebrospinal fluid (CSF) significantly and continuously increased over the treatment period (P=0.001), and this elevation preceded magnetic resonance imaging (MRI) detection of tumor progression signs, suggesting that CSF-derived MMP-9 could serve as an early biomarker for GBM recurrence or progression (63).

MMPs as biomarkers can also assess treatment response to GBM drugs. A previous prospective-retrospective dual-cohort analysis found that, in patients with recurrent GBM, the group with high baseline plasma MMP-2 levels, when subjected to the anti-angiogenic drug BEV, exhibited a significantly improved objective response rate (80 vs. 17.6%), median PFS (7.1 vs. 4.2 months) and mOS (12.8 vs. 5.9 months) compared with the low-level group. Crucially, this predictive value was only evident in the BEV treatment group and disappeared in the cytotoxic drug-only treatment group, suggesting MMP-2 is a predictive biomarker specific to BEV efficacy (64). In addition, a retrospective analysis of the large phase III AVAglio trial (NCT00943826) confirmed that baseline plasma MMP-9 levels could predict survival benefit from BEV in patients with newly diagnosed GBM. Patients in the low MMP-9 group had a significantly prolonged OS by 5.2 months (HR=0.51; P=0.0009), whereas the high MMP-9 group showed no significant benefit (54). Additionally, multi-cohort transcriptome analysis revealed that low tumor tissue MMP-9 mRNA expression was not only associated with longer OS (P=0.0012) and PFS (P=0.0066), but also significantly predicted the degree of survival benefit that patients received from standard TMZ chemoradiotherapy, whereas the high MMP-9 group had limited benefit, suggesting that tissue MMP-9 expression is a potential predictive biomarker of TMZ efficacy (65).

In summary, the localized expression of MMPs in tissues, their dynamic changes in bodily fluids and their value as predictors of treatment response provide crucial molecular basis for assessing GBM invasiveness, predicting patient prognosis, real-time monitoring of disease status and guiding individualized treatment strategies. Although the value of serum MMP-9 as an independent monitoring and prognostic biomarker has been questioned by large-sample studies, highlighting the need for careful consideration of source specificity in its clinical application, the overall central role of MMPs as core biomarkers in disease progression and treatment prediction remains solid. Given the core driving role of MMPs in the pathological process of GBM and their biomarker value, untangling their complex regulatory networks is an indispensable foundation for developing novel and effective targeted intervention strategies.

3. Regulatory mechanism of MMPs in GBM

Multiple signaling pathways, including PI3K/AKT, MAPK, TGF-β and Wnt/β-catenin, play a crucial role in regulating the expression and activity of MMP-2, MMP-9 and other MMPs (66-69). Non-coding RNAs also participate in the regulation of MMP expression (70,71). Additionally, epigenetic mechanisms contribute to the modulation of MMP expression (72). At the same time, metabolic reprogramming and alterations in the TME collectively form multiple factors influencing MMP function (33,73-75). This diverse range of mechanisms lays a theoretical groundwork for deciphering the invasive processes of GBM, and pinpoints prospective targets for therapeutic intervention (Table SI).

Signal transduction regulation. Aberrant expression of MMPs in GBM is controlled by several signaling pathways that considerably interact (Fig. 2). First, the PI3K/AKT signaling pathway is permanently activated and plays a critical role in GBM (76), significantly driving the upregulation of MMP-2 and MMP-9 expression. Aldehyde dehydrogenase (ALDH)1A1 activates this pathway by specifically enhancing the phosphorylation of the AKT protein at the Ser473 and Thr308 residues, thereby promoting the expression of MMP-2 and MMP-9, and driving the invasiveness of GBM cells (77). This effect can be synergistically amplified by small transmembrane glycoprotein (78). Notably, the micro-orchidism family CW-type zinc finger protein 2 (MORC2), which exhibits high expression in GBM cells, binds to and inhibits the transcription of N-Myc downstream regulated gene 1 (NDRG1), leading to the downregulation of phosphatase and tensin homolog (PTEN) expression. This subsequently relieves the inhibition of the PI3K/AKT signaling pathway, ultimately inducing the upregulation of MMP-2 and MMP-9, and enhancing tumor invasion and migration. Conversely, knocking down MORC2 or overexpressing NDRG1 can reverse this signaling pathway and inhibit tumor progression (66). It is noteworthy that GRB10 interacting GYF protein 2 and brain and muscle ARNT-like protein 1 inhibit AKT phosphorylation, thereby downregulating MMP-9 expression and impairing the invasive capacity of GBM cells, untangling the complexity of PI3K/AKT pathway regulation of MMPs (79,80). WD repeat domain 34 in GBM inhibits PTEN while activating both the PI3K/AKT and Wnt/β-catenin pathways, thus significantly increasing the levels of phosphorylated (p)-AKT, nuclear β-catenin and c-Myc, and consequently upregulating MMP-2 and MMP-9 expression and promoting cell invasion (81).

Regarding the Wnt/β-catenin pathway, DNA topoisomerase IIα directly binds to the β-catenin promoter to enhance its transcription, thus promoting β-catenin protein expression and its nuclear accumulation, alongside a significant increase in MMP-2 and MMP-9 mRNA levels and enzymatic activity (67,82). By contrast, Lin-7 homolog A inhibits the nuclear translocation of β-catenin, thereby suppressing the expression of MMP-2 and MMP-9 as well as their pro-invasive functions (83). The activation of this pathway is also associated with the sodium-potassium-chloride cotransporter 1 (NKCC1). High expression of NKCC1 in GBM (its expression level significantly correlates with tumor grade, P<0.05), when knocked down, leads to reduced protein levels of the key Wnt/β-catenin pathway effector β-catenin, which is accompanied by downregulation of MMP-2 and MMP-9, thus significantly impairing tumor cell invasion. This indicates that NKCC1 regulates MMP expression via the Wnt/β-catenin signaling pathway, thereby affecting cell invasion (84).

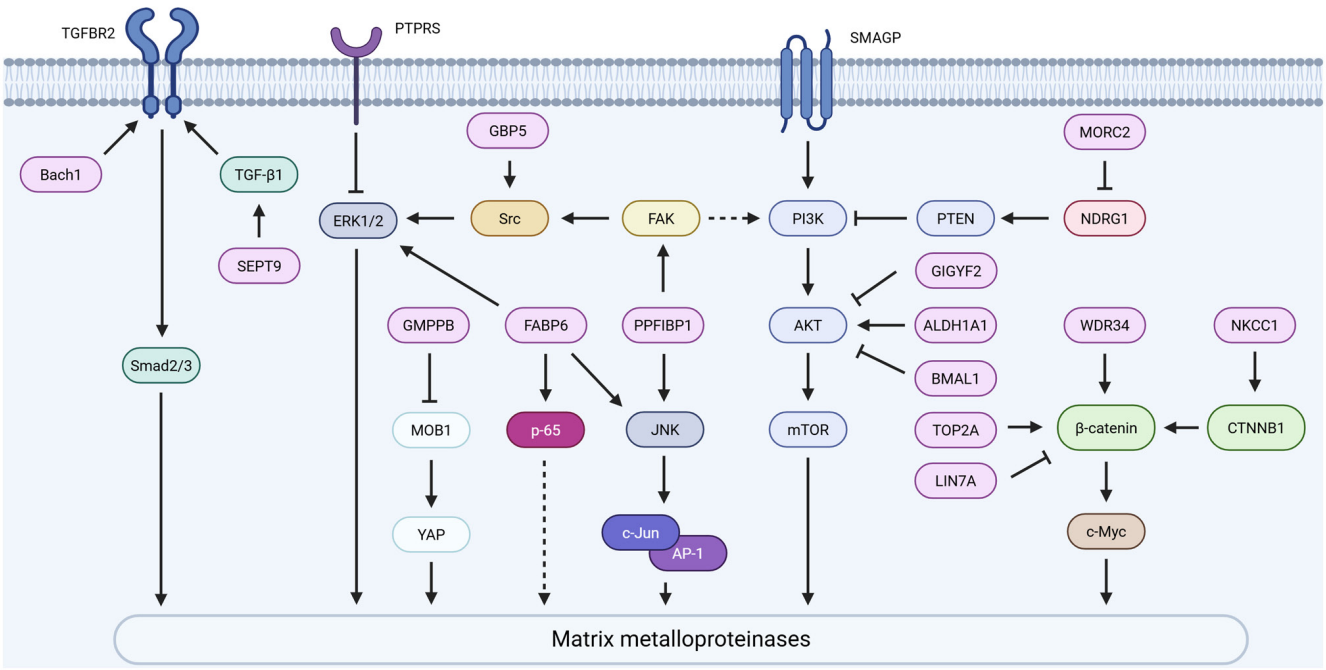

Figure 2. Key signaling pathway networks regulating matrix MMPs. The PI3K/AKT/mTOR, Wnt/β-catenin, MAPK, TGF-β and Hippo signaling pathways constitute the core network regulating the expression and activity of MMPs. Additionally, key signaling molecules such as FAK and Src are involved. Effector proteins such as GIGYF2 and TOP2A primarily influence MMPs by regulating AKT and β-catenin signaling. By contrast, FABP6 and PPFIBP1 indirectly modulate MMP activity by acting on multiple signaling pathways. → indicates promotion; --- indicates an inferred interaction based on literature evidence that has not been directly reported; ⊥ indicates inhibition. MMP, metalloproteinase. Created in BioRender. Zheng, B. (2025) https://BioRender.com/dxwgq2l.

The TGF-β signaling pathway is also an important mechanism for regulating MMPs. Overexpression of broad-complex, tramtrack, and Bric-à-brac domain and cap 'N' collar homolog 1 significantly upregulates TGF-β receptor 2 (TGFBR2) and its downstream mothers against decapentaplegic homolog (Smad)2/3 protein levels, and enhances MMP-2 protein expression and secretion activity (68). Further research revealed that Septin 9 (SEPT9) was highly expressed in GBM tissues, and positively correlated with TGF-β1. Knocking down SEPT9 led to a significant reduction in MMP-9 protein expression, thereby inhibiting GBM cell invasion. Previous *in vivo* experiments further confirmed that targeted inhibition of SEPT9 effectively reduced lung metastasis in GBM, thus highlighting the crucial role of SEPT9 in promoting GBM distant metastasis by upregulating MMP-9 (85).

In addition to the aforementioned key pathways, the MAPK (including the ERK and JNK branches) and NF-κB signaling pathways are also involved in the regulation of MMPs (69,86). Receptor-type tyrosine-protein phosphatase S expression is downregulated in GBM tissues, and its loss leads to increased phosphorylation levels of ERK1/2, subsequently upregulating the transcription and protein expression of MMP-2 and MMP-3, thus promoting cell invasion (87). Fatty acid-binding protein 6 (FABP6) was shown to be highly expressed in GBM tissues; its knockdown not only led to significant downregulation of MMP-2, but also reduced the activation levels of p-ERK, p-JNK and p-p65 (NF-κB), ultimately inhibiting tumor cell invasion. This suggests that FABP6 may influence MMP-2 and consequently GBM invasion by regulating the ERK/JNK/NF-κB signaling axis (69). PPFIA binding protein 1 expression was revealed to be positively associated with GBM progression. It enhanced the phosphorylation levels of FAK (Y397), Src (Y416), JNK and c-Jun, significantly upregulated MMP-2 expression, and enhanced tumor infiltration within the brain parenchyma (86,88-90). Human guanylate-binding protein 5 was demonstrated to enhance MMP-3 expression activity by promoting the phosphorylation of Src and ERK1/2 (91). Furthermore, GDP-mannose pyrophosphorylase B was shown to be highly expressed in GBM, and its knockdown activated the Hippo signaling pathway, and promoted the phosphorylation of Mps one binder kinase activator-like 1 and Yes-associated protein, thereby inhibiting MMP-3 expression and impairing cell invasion ability (32).

Regulation by non-coding RNAs. Non-coding RNAs modulate the invasive capacity of GBM cells by interactively regulating the expression levels of MMP-2 and MMP-9 (Fig. 3). Among them, an endogenous circular (circ) RNA derived from exons 11 to 14 of the CLSPN gene (*Homo sapiens*_circ_0011591, circCLSPN) was shown to function as a competitive endogenous RNA by sequestering microRNA (miRNA or miR)-370-3p, thus releasing ubiquitin-specific peptidase 39 from miRNA-mediated repression, and resulting in marked upregulation of MMP-2 and MMP-9 expression (70,92). Concurrently, circATXN1, mediated by serine/arginine-rich splicing factor 10, promoted MMP-2 expression, and enhanced the invasive potential of GBM cells by binding to miR-526b-3p and blocking its inhibitory effect on downstream target genes (93). Both miR-361-5p and miR-16, which are significantly downregulated in GBM, have been demonstrated to possess tumor invasion-suppressive potential. Overexpression of miR-361-5p was shown to directly target the ubiquitin protein ligase E3 component N-recognin 5 (UBR5), thus inhibiting the UBR5-mediated ubiquitination and degradation

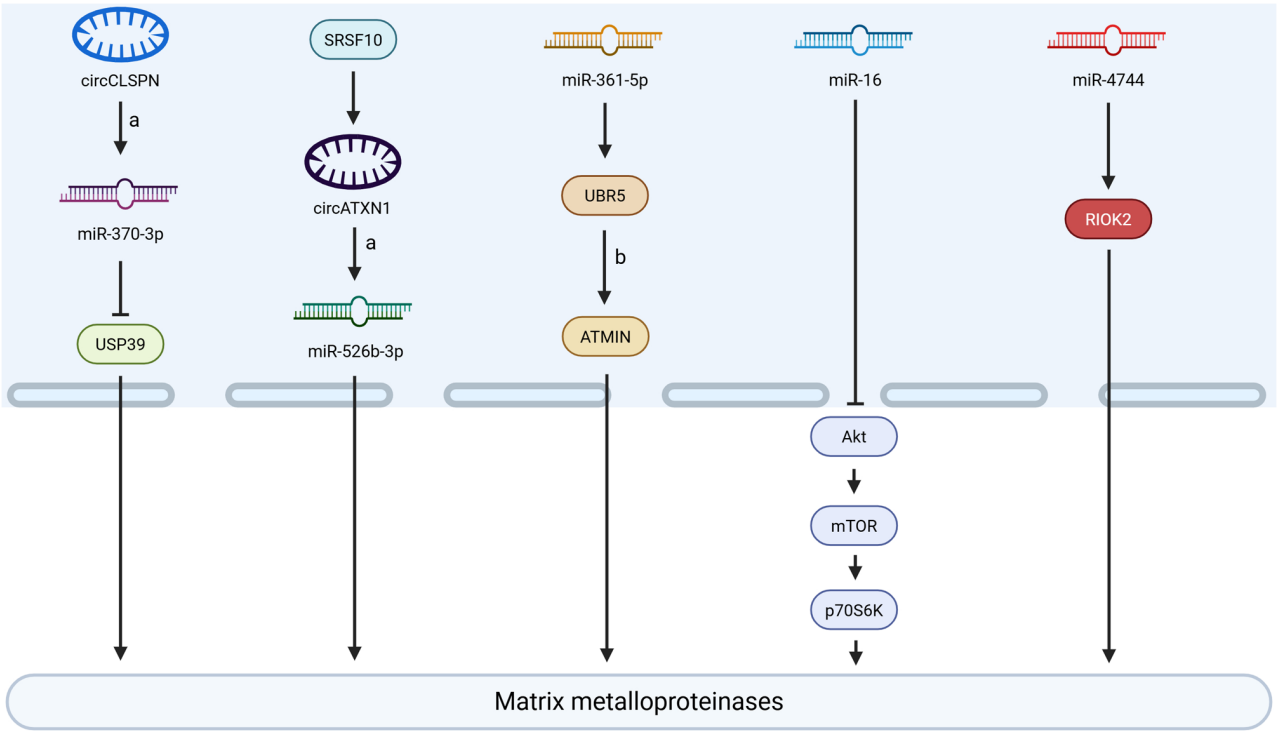

Figure 3. Mechanisms of non-coding RNA regulation of MMPs. Circular RNA primarily functions as a ceRNA, influencing the expression and function of MMPs by sponging miRNAs. Additionally, ubiquitination modifications and related kinases are involved in mediating miRNA-mediated regulation of MMPs. Furthermore, miRNAs can also affect MMPs by modulating the activity of the PI3K/AKT signaling pathway in the cytoplasm. → indicates promotion; ⊥ indicates inhibition; a denotes ceRNA function; b denotes the ubiquitination process. MMP, matrix metalloproteinase; ceRNA, competing endogenous RNA; miRNA or miR, microRNA. Created in BioRender. Zheng, B. (2025) https://BioRender.com/dxwgq2l.

of ATM-interacting protein (ATMIN), thereby stabilizing ATMIN protein and downregulating MMP-2 expression, ultimately blocking GBM cell migration and invasion (71). In addition, miR-16 overexpression was demonstrated to suppress the phosphorylation of key nodes in the PI3K/AKT/mTOR signaling pathway [namely, AKT (Ser473), mTOR (Ser2448) and p70S6K (Thr389)], leading to downregulation of MMP-2 and MMP-9 expression, and thereby inhibiting GBM cell migration and invasion (94). Additionally, right open reading frame kinase 2 (RIOK2), a member of the RIO kinase family that is highly expressed in GBM, was shown to enhance cell migration and invasion by upregulating MMP-2 and MMP-9. By contrast, miR-4744 could directly target and suppress RIOK2 expression, effectively reversing its pro-invasive effects (95).

Regulation of the TME. GBM invasion involves complex interactions within the TME that modulate the expression and activity of MMPs. This occurs through metabolic reprogramming, physical stimuli and immune modulation (Fig. 4). Metabolically, formate treatment was shown to significantly activate the expression of MMP-2 and MMP-9 in GBM cells, and enhanced their invasive capacity by reprogramming lipid metabolism. (U-^{13}C)glucose/glutamine stable isotope tracing and lipidomics analysis confirmed that formate drives fatty acid synthesis and cytosolic lipid accumulation. Fatty acid synthase inhibitor could block this metabolic reprogramming process, and effectively suppress formate-induced MMP-2 expression and invasion (73,96). Concurrently, serglycin enhanced the expression of MMP-9 and MMP-14 by activating the TGFBR1 and C-X-C motif chemokine receptor 2 (CXCR-2) signaling axes, contributing to the pro-invasive effect in GBM (97).

Physical environmental factors are also crucial. Mechanical stress stimuli such as high osmotic pressure (440 mOsmol/kg) or hydrostatic pressure (30 mmHg) can significantly upregulate the mRNA expression and secretion levels of MMP-2 and MMP-9 in GBM cells, as well as enhance their invasive ability (74). Previous research indicated that such pressure stimuli upregulated the expression of caveolin-1 (CAV1) and caveolae-associated protein 1 (CAVIN1), promote caveolae formation, and thereby induce MMP-2 and MMP-9 expression and invasion. This process may be related to CAV1/CAVIN1-mediated induction of aquaporin-1 (AQP1). The Cancer Genome Atlas analysis shows that co-high expression of CAV1/AQP1 predicts poor prognosis (98,99). Notably, AQP1 has been demonstrated to directly mediate pro-MMP-9 activation (100). Conversely, static magnetic field (1,000±100 Gs) treatment was shown to significantly downregulate MMP-2 protein expression in GBM cells. When combined with TGF-β1, the inhibitory effect on MMP-2 and the accompanying reduction in invasive capacity were more pronounced (101). A hypoxic microenvironment, which is a hallmark feature of GBM, influences MMP regulation. The high expression of MutS protein homolog 6 in GBM exacerbated the accumulation of hypoxia-inducible factor 1-α (HIF1α) protein induced by hypoxia, thereby significantly enhancing the invasive capacity mediated by MMP-2 and MMP-9 (102). Furthermore, twisted gastrulation BMP signaling modulator 1 was revealed

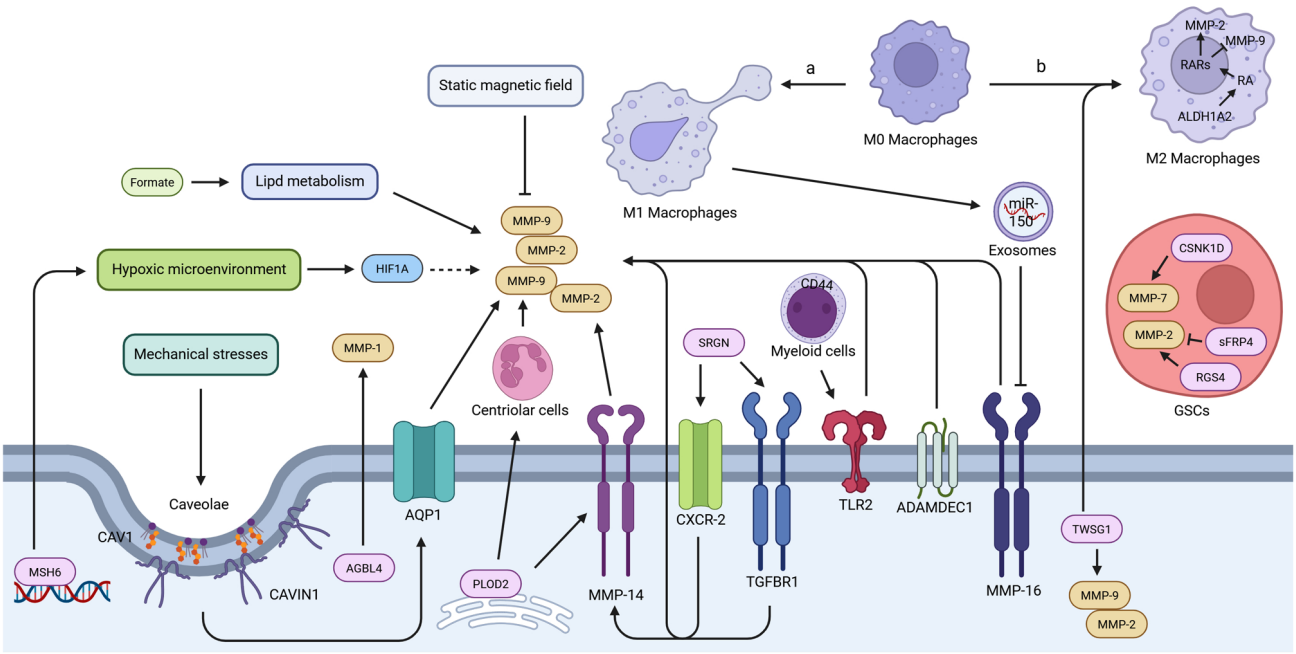

Figure 4. Mechanisms of MMP regulation in the TME. The expression of MMPs is regulated by metabolic reprogramming (lipid metabolism), physical factors (osmotic/hydrostatic pressure and static magnetic fields) and hypoxic conditions within the TME. Cell membrane-associated structures (caveolae), membrane proteins (AQP1 and TLR2) and membrane-type MMPs also participate in the regulation of MMP expression and activity. At the immune cell level, M1 macrophages, neutrophils and myeloid-derived suppressor cells significantly influence MMP expression levels. Notably, MMP levels in M2 macrophages and glioblastoma stem cells are regulated by specific proteins (RGS4 and ALDH1A2). → indicates promotion/stimulation; --- indicates an inferred interaction based on literature evidence but not directly reported; ⊥ indicates inhibition/suppression; a indicates M1 macrophage polarization; b indicates M2 macrophage polarization. TME, tumor microenvironment; MMP, matrix metalloproteinase. Created in BioRender. Zheng, B. (2025) https://BioRender.com/dxwgq2l.

to be highly expressed in GBM. Its knockdown not only significantly inhibited tumor cell migration and invasion, and downregulated MMP-2 and MMP-9, but also remodeled the phenotype of tumor-associated macrophages, reducing M2-type markers [such as CD206, arginase 1, interleukin (IL)-10 and TGF-β] and upregulating M1-type markers (such as inducible nitic oxide synthase and IL-1β) in co-cultured THP-1 cells (103-106).

Intrinsic factors within tumor cells are also important for regulating MMPs in the microenvironment. ATP/GTP binding protein like 4 (AGBL4), which is highly expressed in recurrent GBM tissues, has been shown to drive tumor migration by specifically upregulating MMP-1 expression; *in vivo* experiments further revealed that inhibiting AGBL4 delays intracranial tumor progression and prolongs the survival of tumor-bearing animals, an effect that can be partially reversed by high MMP-1 expression (31). ADAM-like Decysin 1 expression level in GBM was shown to be significantly associated with tumor malignancy and poor prognosis, and it promoted tumor cell invasion by upregulating MMP-2 expression (107).

Notably, the stemness and invasiveness of GSCs in the microenvironment are regulated by specific proteins and MMPs. Elevated expression of casein kinase 1D (CSNK1D) in GBM tissues was demonstrated to promote the upregulation of GSC stemness markers [CD133 and SRY-box transcription factor 2 (SOX2)] as well as MMP2 and MMP-7 expression upon its overexpression, enhancing cell invasion. By contrast, knockdown of CSNK1D inhibited stemness and invasion, and prolonged survival in model mice (75). Similarly, regulator of G protein signaling 4 knock out also significantly downregulated MMP2 expression in GSCs and inhibited invasion (108). Conversely, secreted frizzled related protein 4 utilized its N-terminal cysteine-rich domain and C-terminal cysteine-rich domain to effectively inhibit MMP-2 activity in GSCs, suggesting a potential negative regulatory mechanism (109).

The regulation of MMP expression by myeloid cells in the microenvironment also affects tumor invasion, with macrophages of different polarization states exhibiting distinct functions. M1 macrophages were shown to directly inhibit MMP-16 expression in tumor cells by releasing exosome-encapsulated miR-150 (33). Given that MMP-16 could upregulate MMP-2, this inhibition indirectly reduced MMP-2 expression levels (110). By contrast, M2 macrophages rely on retinoic acid (RA) produced by ALDH1A2 catalysis to selectively upregulate MMP-2 while downregulating MMP-9 expression, but this regulation does not directly affect the protease activity of the tumor cells themselves (111). It is noteworthy that the regulation of MMPs by myeloid cells is influenced by tumor cells. On one hand, lysyl hydroxylase 2 expressed by GBM cells not only promoted the release of active MMP-2 by tumor cells via upregulating MMP-14, but also regulated secreted factors to activate neutrophils to release MMP-9, thereby synergistically increasing microenvironmental MMP levels and enhancing invasion (112). On the other hand, GBM cells could induce wild-type myeloid cells to significantly upregulate MMP-9 mRNA expression upon Toll-like receptor 2 (TLR2) agonist stimulation. This response was shown to be markedly attenuated in CD44-deficient myeloid cells, which also lost their ability to promote GBM cell invasion in Boyden chamber co-culture models, confirming that CD44 is a key molecule mediating the pro-invasive function of myeloid cells, partly through MMP-9 (113).

4. Drug intervention strategies for MMPs

From natural products to small-molecule compounds, both can effectively regulate the expression and activity of MMP-2, MMP-9, MMP-1, MMP-3 and MMP-14 (114-118). Concurrently, the development of combination therapy strategies and nanomaterial-based drug delivery systems has provided new approaches for precise and controllable drug release, thereby further enhancing therapeutic efficacy (119-121). These diverse and multi-target intervention techniques collectively present expansive opportunities for halting the progression of GBM.

Therapeutic strategies of natural products. Natural active products modulate MMPs through multi-target mechanisms, presenting potential avenues for cancer treatment. Curcumin and its derivatives, as well as the structurally related natural sesquiterpene Zerumbone, have been demonstrated to effectively inhibit the invasion and migration of GBM cells by targeting and suppressing the expression and activity of MMP-2 and MMP-9. In an *ex vivo* stress model induced by norepinephrine (NE), curcumin significantly downregulated the expression and secretion of CD147 and its downstream effector molecules MMP-2 and MMP-9 by inhibiting ERK1/2 phosphorylation, thereby blocking NE-mediated GBM cell invasion (114). Concurrently, bisdemethoxycurcumin (BDMC) was shown to act synergistically on the PI3K/AKT, MAPK/ERK and NF-κB signaling pathways. After treating GBM cells with BDMC for 48 h, the protein levels of key molecules, including PI3K, p-AKT, MEK, p-ERK1/2, NF-κB, and the downstream MMP-2 and MMP-9, were significantly downregulated, which was accompanied by the inhibition of GBM cell migration and invasion (122). Notably, the natural compound Zerumbone also exhibited significant anti-invasive effects, inhibiting the migration and invasion of GBM cells in a concentration- and time-dependent manner. It downregulated the total protein levels of ERK1/2 and AKT, thereby cooperatively inhibiting the mRNA expression, protein content and enzymatic activity of MMP-2 and MMP-9, consequently blocking GBM cell invasion (123). Similarly, the turmeric extract Curzerene significantly reduced MMP-9 levels in glioma cells by inhibiting glutathione S-transferase A4 expression and the phosphorylation of molecules of the mTOR/p70S6K signaling axis, thus effectively suppressing GBM migration and invasion both *ex vivo* and in a nude mouse xenograft model (124). Furthermore, the photodynamic effect of curcumin provides a novel approach for inhibiting tumor invasion. Upon activation by 430-nm blue light irradiation for 5-10 min, curcumin induced a significant increase in intracellular reactive oxygen species (ROS) levels in GBM cells. Flow cytometry and immunofluorescence results confirmed that elevated ROS was accompanied by downregulation of MMP-2 and MMP-9 expression, indicating that blue light-activated curcumin could inhibit MMP-2 and MMP-9 via the ROS pathway, thereby attenuating the invasive potential of GBM cells (125).

Concurrently, various natural compounds effectively inhibit GBM invasion by influencing MMP expression or activity. Isocucurbitacin B inhibited GBM cell proliferation, migration and invasion in a concentration- and time-dependent manner. It reduced the mRNA and protein expression of MMP-2 and MMP-9 by downregulating the total protein levels and phosphorylation of PI3K, AKT and MAPK1/3, thereby blocking GBM invasiveness (126). Also acting on the MAPK signaling pathway, *Coriolus versicolor* and its active molecule, the methyl ester of 9-KODE (AM), significantly inhibited tumor necrosis factor (TNF)-α-induced p38 MAPK phosphorylation, and dose-dependently reduced MMP-3 mRNA and protein levels. Invasion assays further confirmed that AM directly impaired the invasive capacity of GBM cells (115). The myrrh resin extract Guggulsterone (GS) significantly reduced the expression of MMP-2 and MMP-9 in GBM cells by activating dual degradation pathways involving the proteasome and lysosome, thereby inhibiting their migration and invasion. This mechanism was experimentally verified. Both the proteasome inhibitor MG132 and the lysosome inhibitor NH_4Cl effectively reversed the GS-induced downregulation of MMP-2 and MMP-9 and the associated inhibition of invasion. An orthotopic xenograft model further demonstrated that GS reduced intratumoral MMP-2 levels and prolonged the survival of tumor-bearing mice (127). The natural sesquiterpene lactone compound Alantolactone, extracted from the roots of *Inula helenium*, specifically inhibited the activity of Lin-11, Isl-1, and Mec-3 kinase (LIMK), inducing the dephosphorylation and activation of its key substrate, cofilin. This subsequently increased the ratio of monomeric actin (G-actin) to filamentous actin (F-actin), ultimately leading to significant downregulation of MMP-2 and MMP-9 expression, thereby effectively inhibiting the migration and invasion of GBM cells (128). Targeting the secretion process of MMPs, the compound erythrose from rhubarb root extract inhibited the extracellular secretion of neuroleukin by blocking its binding to the gp78 receptor, thereby significantly downregulating the expression levels of MMP-1 and MMP-9 in GSCs and ultimately inhibiting their *ex vivo* invasive capacity (116). Furthermore, kaempferol extract and its biotransformation product (KPF-ABR) also exhibited significant anti-invasive effects. Both significantly downregulated MMP-9 expression and inhibited the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced activation of cell migration. Notably, KPF-ABR, enriched with kaempferol aglycone, was particularly effective, notably blocking the TPA-stimulated upregulation of MMP-9 and inhibiting neurosphere formation by GSCs (129). Other natural products have also been shown to exert anti-invasive effects by inhibiting MMPs, including Bacoside A and Diosgenin, which effectively inhibited the invasive ability of GBM cells by downregulating MMP-2 and MMP-9 (130,131).

Beyond plant-derived components, fungi, animals and metabolites also demonstrate potential for targeting MMPs to inhibit GBM invasion. The fungus-derived compound 10,11-dehydrocurvularin significantly downregulated MMP-2 levels by inhibiting PI3K-p85 expression and blocking AKT phosphorylation, thereby suppressing GBM invasion (43). *Antrodia camphorate*, also a fungus, and the quinone derivative coenzyme Q (CoQ)0 from its fermentation broth, inhibited the invasive ability of GBM cells by downregulating the expression levels of MMP-2 and MMP-9 (132). By contrast, the structurally similar CoQ10 exerted its anti-invasive effect by directly inhibiting the enzymatic activity of MMP-2 and MMP-9 (133). Additionally, the animal-derived component bee venom and the metabolite Urolithin B have been reported to

inhibit the enzymatic activity of MMP-2 and MMP-9, thereby reducing GBM invasiveness (134,135). Notably, melatonin, an important endogenous hormone, has also been confirmed to effectively inhibit the invasive capacity of GBM tumor spheroids by suppressing the mRNA and protein expression levels of MMP-9 (136).

In summary, this section systematically described how natural active ingredients, including curcuminoids, fungal and animal metabolites, significantly inhibit the invasive ability of GBM by targeting key signaling pathways and proteins such as PI3K/AKT, MAPK and NF-κB (Table SII), thereby regulating MMP gene expression, protein secretion and enzymatic activity. This provides a solid theoretical foundation and candidate strategies for developing innovative therapies against GBM metastasis.

Small molecule inhibitors. Various small molecule compounds regulate the expression and activity of MMPs through different molecular mechanisms, thus inhibiting the invasive behavior of GBM. Core signaling pathways serve as key regulatory points. For instance, Chrysomycin A downregulated the expression of β-catenin and its downstream target proteins c-Myc and cyclin D1 by inhibiting the phosphorylation levels of AKT and GSK-3β, thereby regulating and reducing MMP-2 protein expression, ultimately suppressing the migration and invasion capabilities of GBM cells (137). The cell-penetrating peptide trans-activator of transcription (Tat)-nuclear translocation signal (NTS) inhibited NF-κB phosphorylation by specifically blocking the nuclear translocation of annexin-A1, consequently downregulating the expression and activity of MMP-2 and MMP-9 (117). The farnesoid X receptor agonist GW4064 downregulated MMP-2 activity by inhibiting protein kinase C alpha (PKCα) phosphorylation, an effect reversible by the PKCα agonist phorbol 12-myristate 13-acetate (138). Concurrently, the specific p53-Snail binding inhibitor GN25 also affected the invasion process by reducing MMP-2 expression (139). Furthermore, metabolism regulation is involved; PPARγ agonists (such as pioglitazone and rosiglitazone) and the PPARα agonist WY-14643 were shown to inhibit MMP2 by upregulating the regulatory factor X1, effectively suppressing tumor invasion in *in vivo* models (140). Notably, ion channel function has also been demonstrated to be associated with MMP regulation; for example, the hERG channel agonist NS1643 reduced MMP-9 protein levels (141). In terms of epigenetic regulation, the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA) significantly inhibited MMP14 transcription in GBM cells by reducing histone H3 lysine 27 acetylation levels, and this downregulation has been demonstrated as a key mechanism for SAHA-mediated radiosensitization (118). Non-coding RNA networks are also crucial. The sevoflurane derivative Sev downregulated MMP-2 and MMP-9 through the circRELN/miR-1290/RORA and miR-27b/VEGF signaling pathways and by direct targeting by miR-34a-5p, with its anti-invasive effects confirmed in both cellular experiments and tumor-bearing mice (142-144). Similarly, propofol was shown to inhibit MMP-2 and MMP-9 activity via the circNCAPG/miR-200a-3p/RAB5A pathway (145). Viral vectors, such as the third-generation oncolytic adenovirus TS-2021 (with E1A regulated by Ki67/TGF-β2 UTR and carrying IL-15), was revealed to significantly downregulate MMP3 expression by inhibiting p-MKK4/p-JNK signaling, thereby effectively suppressing the invasive ability of GBM cells (146).

Notably, certain compounds demonstrate significant clinical translational potential. The novel compound NP16 (structural feature, 3,4,5-trimethoxymethyl on the N-phenyl ring) significantly downregulates MMP-9 levels by inhibiting COX-2 expression and blocking STAT3 phosphorylation and nuclear translocation. In a C6 orthotopic model, its tumor inhibition rate (66.01%) surpassed that of TMZ (54.83%). It also exhibited favorable BBB penetration capability (brain/blood concentration ratio, 0.38) and significantly prolonged the survival of tumor-bearing rats (147). A class of Pt(IV) complexes, designed to overcome challenges in GBM treatment, are based on a cisplatin core with axial ligands comprising the anthraquinone drug Rhein and a hydrophilic acetic acid ligand, achieving dual-drug synergistic effects via linkers of different lengths. These complexes exhibit superior synergistic effects compared with single agents in inhibiting MMP-2 and MMP-9 expression and cell migration, and remain active under hypoxic conditions. Computational simulations predict enhanced BBB penetration capability, offering a novel direction for combination therapy (148).

In summary, this section not only untangled the diverse molecular mechanisms by which small molecules target the regulation of MMPs to inhibit GBM invasion (involving key signaling pathways, metabolism, non-coding RNAs and ion channels), but also highlighted the considerable clinical translational potential of certain compounds [such as NP16 and novel Pt(IV) complexes] with excellent BBB penetration and *in vitro/in vivo* activity in overcoming GBM invasiveness (Table SIII).

Nanotechnology strategies. In recent years, various design strategies for nanomaterial-based drug delivery systems targeting MMPs have emerged in the field of GBM therapy. Researchers have developed intelligent delivery platforms that specifically respond to different MMP subtypes. For instance, dual-sensitive NPs rapidly dissociate in the TME with high MMP-9 expression, releasing the loaded doxorubicin while simultaneously forming nanogels. This process significantly enhanced drug penetration and retention within the tumor core, effectively inhibited GBM spheroids and tumor volume, and substantially prolonged the survival time of mice (119). Similarly, leveraging MMP subtype responsiveness, D@MLL nanocarriers can be transported across the BBB by monocytes driven by low-dose radiotherapy-induced high C-C motif chemokine ligand 2 expression. Subsequently, doxorubicin is rapidly released in areas of high MMP-2 activity, triggering immunogenic cell death, as evidenced by significantly upregulated calreticulin expression and high mobility group box 1 release. Concurrently, this promotes the polarization of tumor-associated macrophages towards the M1 phenotype and activates $CD8^+$ T cells, thereby synergistically inhibiting GBM progression and extending survival (149). Furthermore, nano-delivery systems can synergize with radiotherapy to enhance efficacy. For example, Au@DTDTPA(Gd) NPs combined with X-ray radiotherapy significantly inhibit the invasive capacity of escape cells from GBM spheroids, and attenuate their invasiveness and stem cell-like characteristics

(such as SOX2 downregulation) by reducing MMP-2 secretion and activity and inducing mitotic catastrophe (150). Additionally, fMbat NPs achieve BBB-crossing capability via transferrin receptor-mediated transport, effectively delivering batimastat to the GBM TME and potently inhibiting MMP-2 activity in GBM cells (151). Dual-targeting liposomes (co-loaded with daunorubicin and rofecoxib) and carboxymethyl-stevioside-modified magnetic NPs can simultaneously inhibit the expression and function of MMP-2 and MMP-9, effectively suppressing GBM invasion (35,152). Notably, CuO NPs not only significantly downregulate the expression of proteins such as MMP-9, EphA2 and YKL-40 in the hippocampus and cells of GBM model rats to restrict tumor invasion, but also demonstrate the potential to improve spatial recognition and memory abilities in model rats (36).

In summary, the aforementioned nanodrug delivery systems, by achieving specific responses to MMP-rich microenvironmental stimuli, controlled drug release and multiple mechanisms of action (such as enhancing the permeability and retention effect, triggering immune responses, synergizing with radiotherapy, inhibiting invasion and crossing the BBB), provide powerful novel strategies for precisely targeting and modulating MMP-related key pathological processes in GBM (Table SIV).

Combination therapy strategies. In pharmacological interventions targeting MMPs, combination therapy strategies have significantly enhanced antitumor efficacy through multi-target synergistic effects. Among these, the combination of chemotherapeutic agents with other treatment modalities has demonstrated substantial potential. TMZ, as a foundational chemotherapeutic drug, was shown to synergize with photodynamic therapy in downregulating the expression of MMP-2, HIF-1α and glucose transporter 1, thereby inhibiting glucose uptake and ATP production. This effectively blocked tumor invasion and energy supply, significantly suppressed tumor growth, and prolonged the survival of tumor-bearing mice, with effects superior to monotherapy (120). Natural products and their derivatives can also synergize with TMZ. The combination of TMZ and Chuanxiong essential oil (CEO) was demonstrated to reverse drug resistance and inhibit GBM cell invasion *ex vivo* by suppressing MMP-9 expression. Furthermore, the combination of ligustilide, a key component of CEO, with TMZ enhanced tumor suppression effects and TMZ sensitivity in animal models (153). The combination of TMZ with 4-methylumbelliferone was revealed to inhibit invasion by reducing MMP-2 activity and enhanced the drug sensitivity of cells resistant to TMZ and vincristine (154). The combined application of cordycepin and doxorubicin has also been confirmed to inhibit MMP-9-mediated invasion at the cellular level (155).

miRNA replacement therapy combined with chemotherapeutic drugs has also demonstrated significant synergistic potential. A previous study found that the combined application of overexpressed miR-181a and carmustine effectively curbs the invasive capacity of GBM cells by targeting and inhibiting MMP-2 expression (121). It is noteworthy that the proteasome inhibitor bortezomib alone can significantly downregulate MMP-2 and MMP-9 expression and inhibit invasion. When combined with the polo-like kinase 4 (PLK4) inhibitor CFI-400945, it synergistically enhanced the downregulation of MMP-2 and MMP-9 as well as the inhibition of invasion. Conversely, overexpression of PLK4 reversed this effect and attenuated the efficacy of bortezomib. The core mechanism involves the synergistic activation of PTEN expression and the inhibition of the phosphorylation and expression of proteins of the PI3K/AKT/mTOR pathway, ultimately leading to the downregulation of MMP-2 and MMP-9 expression (156). Combined therapy with TNF-related apoptosis-inducing ligand and celastrol inhibited GBM cell invasion by upregulating GSK-3β, reducing the transcription and protein levels of β-catenin and its downstream targets c-Myc, cyclin D1 and MMP-2 (157). Similarly, *ex vivo* experiments with aprepitant combined with 5-ALA demonstrated effective restriction of GBM cell invasion through inhibition of MMP-2 and MMP-9 activity (158).

In summary, the above section has systematically elaborated on strategies involving chemotherapy combined with physical/natural therapies, miRNA replacement therapy, targeted drug combinations and signaling pathway inhibitors (Table SV) to synergistically regulate MMPs and their associated signaling networks (such as the PI3K/AKT/mTOR and Wnt/β-catenin pathways). These strategies not only significantly inhibit tumor invasion and overcome drug resistance, but also effectively suppress tumor growth and prolong survival, thereby establishing a solid mechanistic foundation and providing direction for the development of more efficient, multi-targeted anti-GBM treatment plans.

Limitations of preclinical studies and translational challenges. Although intervention strategies targeting MMPs have demonstrated therapeutic potential in preclinical studies, their clinical translation faces important challenges. These challenges primarily stem from the inability of existing model systems to adequately recapitulate the complex pathobiology of GBM, resulting in a gap between preclinical data and outcomes from human trials.

The limitations of tumor models represent the primary obstacle. Long-term cultured GBM cell lines (such as U-251MG) undergo significant genomic drift. Characteristic chromosomal abnormalities (including deletions in 18q11-23 and amplifications in 4q12) emerge in subclones, leading to aberrant activation of key tyrosine kinase receptors such as PDGFRα. These genetic alterations drive cells to acquire enhanced proliferative, clonogenic and invasive capacities, causing their biological characteristics to deviate markedly from the original tumor features (159). More importantly, GBM exhibits heterogeneity at both histological and molecular levels. The TME harbors diverse cell populations (including GSCs, differentiated tumor cells, necrotic areas and aberrant vasculature), which display significant differences in proliferation kinetics, invasive properties and therapeutic sensitivity (160). Concurrently, complex genomic variations (including mutations, copy number alterations and epigenetic modifications) and distinct molecular subtypes (such as proneural, classical and mesenchymal) collectively result in differential signaling pathway activation states and varied responses to MMP-targeted therapies (161,162). Existing models struggle to replicate this complexity, introducing systematic bias into efficacy evaluations. The results may not encompass all tumor

cell subpopulations, and predictions of potential adverse effects are often inadequate. This has been corroborated by a phase II clinical trial, where the combination of TMZ with the broad-spectrum MMP inhibitor marimastat improved the 6-month PFS rate in patients with recurrent GBM; however, 47% of patients experienced dose-limiting joint toxicity (163), further underscoring the fundamental limitations of preclinical models in assessing toxicity risks.

The complex pathological structure of the BBB constitutes the second major obstacle. In the GBM microenvironment, aberrantly upregulated MMP activity and an imbalance with their natural inhibitor, tissue inhibitor of metalloproteinases-1, lead to degradation and loss of agrin, a key component of the perivascular basal lamina. This subsequently disrupts the structural integrity of astrocytic end-feet, causing BBB leakage in the tumor core (164). However, at the invasive front, the BBB structure remains relatively intact and harbors active efflux pump systems, such as P-glycoprotein and breast cancer resistance protein, creating a spatially heterogeneous drug delivery barrier (165,166). This unique pathological structure results in highly uneven intratumoral distribution of therapeutic agents, making it difficult for targeted drugs to reach effective concentrations in the invasive regions (167,168). Furthermore, the physicochemical properties of the drugs themselves (such as lipophilicity) are directly related to their ability to penetrate the intact BBB and resist efflux pumps. Highly lipophilic compounds tend to accumulate in peripheral tissues, potentially causing systemic toxicity, while polar molecules often fail to effectively reach central targets (169). However, existing *in vitro* BBB models cannot mimic these dynamic pathological changes and spatial heterogeneity, leading to fundamental limitations in predicting drug permeability and the therapeutic window.

5. Conclusions and future perspectives

MMPs occupy a central position in the invasion process of GBM, primarily through three mechanisms: i) Facilitating EMT via ECM degradation; ii) remodeling the vascular niche; and iii) thereby fueling tumor malignancy. The expression of MMPs is modulated by a network of signaling pathways, including PI3K/AKT, MAPK and TGF-β, as well as transcription factors such as Snail and activator protein 1, and non-coding RNAs. Notably, physicochemical factors within the tumor niche also exert a marked influence on the enzymatic activity of MMPs.

Therapeutic strategies targeting MMPs show considerable promise. Several reported small-molecule compounds exhibit excellent BBB penetration capability and superior *ex vivo* inhibitory efficacy compared with TMZ. Nanodelivery systems can synergistically address the dual challenges of BBB penetration and targeted delivery. By enabling drug release specifically in response to MMPs, these systems hold potential for circumventing the joint toxicity associated with the broad-spectrum inhibitor marimastat, which arises from the non-selective inhibition of MMPs involved in joint formation (170,171). Concurrently, in cell therapy, chlorotoxin-targeted chimeric antigen receptor (CAR) T cells (NCT04214392), administered via intracavitary tumor injection in patients with recurrent GBM, have shown promising preliminary clinical data. These cells demonstrated persistence within the tumor cavity and a favorable safety profile (absence of systemic inflammation or anti-CAR antibody responses, and no dose-limiting toxicities), and achieved transient disease stabilization in 3 out of 4 patients (172), providing initial evidence for MMP-targeted therapies.

Previous research on the side effects of MMP-related drug interventions have revealed that TMZ can upregulate MMP-9, enhancing tumor invasiveness (173). Although the combination of radiotherapy and TMZ reduces GBM cell viability, it enhances the invasive capacity of GBM cells by inducing the secretion of sEVs carrying MMP-2 and upregulating thrombospondin-1 in invasive pseudopodia (48,174). It is noteworthy that excessive fluoride accumulation can significantly enhance GBM invasiveness by activating the expression of MMP-2 and MMP-9 (175). Furthermore, physical therapies carry potential risks; surgical thermal injury markedly increases MMP-9 activity by activating astrocytes, thereby exacerbating the malignant progression of GBM (176). These phenomena reveal that single interventions may trigger compensatory invasive mechanisms, highlighting the complexity of precisely regulating the MMP network.

Due to the intricate MMP regulatory network and bottlenecks in clinical translation, interdisciplinary technological collaboration is essential. To mitigate issues of genetic drift in GBM cell lines, prioritizing the use of low-passage cells is crucial for ensuring experimental reproducibility. Artificial intelligence (AI) is increasingly becoming a key driver for overcoming clinical translation hurdles. AI algorithms, such as convolutional neural networks and vision transformers, can efficiently capture disease features from MRI images, significantly improving GBM classification accuracy and reducing scan times. Integrated with high-throughput omics data (genomics and transcriptomics), AI can more precisely delineate GBM molecular subtypes, laying the groundwork for targeted drug therapies (177-180). The application of AI has further expanded to surgical planning [including predicting interstitial thermal therapy ablation areas to optimize prognosis (181)], drug development [such as predicting drug responses and mechanisms (182)] and precision medicine [including developing personalized treatment plans or predicting therapeutic efficacy (183)]. Simultaneously, developing physiologically relevant *ex vivo* BBB models is a core component for translating preclinical research to the clinic. Microfluidic technology has successfully established three-dimensional co-culture BBB models incorporating human brain vascular pericytes, astrocytes and endothelial cells. These models exhibit physiologically relevant structure, selective permeability, reversibility, and effectively simulate GBM-induced vascular remodeling and drug delivery barriers (184). Three-dimensional (3D) printing technologies, such as two-photon lithography, have also been employed to construct controllable brain TME models, achieving tri-culture of endothelial cells, astrocytes and glioma spheroids to form a functional BBB (185). Notably, 3D gradient hydrogel models, by mimicking the dynamic changes in matrix stiffness within the GBM microenvironment, have revealed a dose-dependent association between mechanical stress stimulation and the regulation of MMP activity (186,187), offering novel

perspectives for understanding the mechanical mechanisms of BBB disruption.

In summary, although interventions targeting MMPs show potential in GBM treatment, their complex biological functions, potential pro-invasive effects and challenges in clinical translation remain core issues to be resolved. Future research, through multidisciplinary integration and the close combination of basic mechanistic exploration, innovative technology application and clinical translation studies, may transform strategies such as targeting MMPs into clinical regimens that improve survival outcomes for patients with GBM.

Acknowledgements

We express sincere gratitude to Dr Jinpeng Hu (Department of Neurosurgery, The First Hospital of China Medical University, Shenyang, P.R. China) for his expert guidance in manuscript revision, figure preparation, and table design.

Funding

The present research was supported by the Chen Xiao-Ping Foundation for the Development of Science and Technology of Hubei Province (grant no. CXPJJH123003-058) and the General Program of Joint Natural Science Foundation of Liaoning Provincial Science and Technology Plan (grant no. 2025-MSLH-480).

Availability of data and materials

Not applicable.

Authors' contributions

BZ conceived and designed the review, as well as wrote, reviewed, and edited the manuscript. YH performed data extraction and synthesis, provided original insights and interpretations, and critically revised the manuscript. HZ acquired funding, supervised the project, designed the review scope, and conducted expert analysis. All authors read and approved the final manuscript. Data authentication is not applicable.

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. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2016-2020. Neuro Oncol 25 (12 Suppl 2): iv1-iv99, 2023.
2. Xiao D, Yan C, Li D, Xi T, Liu X, Zhu D, Huang G, Xu J, He Z, Wu A, *et al*: National brain tumour registry of China (NBTRC) statistical report of primary brain tumours diagnosed in china in years 2019-2020. Lancet Reg Health West Pac 34: 100715, 2023.
3. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, *et al*: The 2021 WHO classification of tumors of the central nervous system: A summary. Neuro Oncol 23: 1231-1251, 2021.
4. Barone DG, Lawrie TA and Hart MG: Image guided surgery for the resection of brain tumours. Cochrane Database Syst Rev 2014: CD009685, 2014.
5. Pirro V, Alfaro CM, Jarmusch AK, Hattab EM, Cohen-Gadol AA and Cooks RG: Intraoperative assessment of tumor margins during glioma resection by desorption electrospray ionization-mass spectrometry. Proc Natl Acad Sci USA 114: 6700-6705, 2017.
6. De Boer E, Harlaar NJ, Taruttis A, Nagengast WB, Rosenthal EL, Ntziachristos V and Van Dam GM: Optical innovations in surgery. Br J Surg 102: e56-e72, 2015.
7. Hervey-Jumper SL and Berger MS: Maximizing safe resection of low- and high-grade glioma. J Neuro-Oncol 130: 269-282, 2016.
8. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, *et al*: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352: 987-996, 2005.
9. Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, Fay M, Nishikawa R, Cairncross JG, Roa W, *et al*: Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med 376: 1027-1037, 2017.
10. Rodríguez-Camacho A, Flores-Vázquez JG, Moscardini-Martelli J, Torres-Ríos JA, Olmos-Guzmán A, Ortiz-Arce CS, Cid-Sánchez DR, Pérez SR, Macías-González MDS, Hernández-Sánchez LC, *et al*: Glioblastoma treatment: State-of-the-art and future perspectives. Int J Mol Sci 23: 7207, 2022.
11. Weller M and Le Rhun E: How did lomustine become standard of care in recurrent glioblastoma? Cancer Treat Rev 87: 102029, 2020.
12. Kirson ED, Dbalý V, Tovaryš F, Vymazal J, Soustiel JF, Itzhaki A, Mordechovich D, Steinberg-Shapira S, Gurvich Z, Schneiderman R, *et al*: Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci USA 104: 10152-10157, 2007.
13. Giladi M, Schneiderman RS, Voloshin T, Porat Y, Munster M, Blat R, Sherbo S, Bomzon Z, Urman N, Itzhaki A, *et al*: Mitotic spindle disruption by alternating electric fields leads to improper chromosome segregation and mitotic catastrophe in cancer cells. Sci Rep 5: 18046, 2015.
14. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, Toms S, Idbaih A, Ahluwalia MS, Fink K, *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 318: 2306-2316, 2017.
15. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, *et al*: Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 370: 709-722, 2014.
16. Le Rhun E, Preusser M, Roth P, Reardon DA, van den Bent M, Wen P, Reifenberger G and Weller M: Molecular targeted therapy of glioblastoma. Cancer Treat Rev 80: 101896, 2019.
17. Navone SE, Guarnaccia L, Locatelli M, Rampini P, Caroli M, La Verde N, Gaudino C, Bettinardi N, Riboni L, Marfia G and Campanella R: Significance and prognostic value of the coagulation profile in patients with glioblastoma: Implications for personalized therapy. World Neurosurg 121: e621-e629, 2019.
18. Cuddapah VA, Robel S, Watkins S and Sontheimer H: A neurocentric perspective on glioma invasion. Nat Rev Neurosci 15: 455-465, 2014.
19. Streiff MB, Ye X, Kickler TS, Desideri S, Jani J, Fisher J and Grossman SA: A prospective multicenter study of venous thromboembolism in patients with newly-diagnosed high-grade glioma: Hazard rate and risk factors. J Neurooncol 124: 299-305, 2015.
20. Chen Y, Fei W, Shi Y, Ma W, Jiao W, Tao F, Zhu J, Wang Y and Feng X: Venous thromboembolism risk factors in pediatric patients with high-grade glioma: A multicenter retrospective study. Front Pediatr 13: 1595223, 2025.

21. Marras LC, Geerts WH and Perry JR: The risk of venous thromboembolism is increased throughout the course of malignant glioma: An evidence-based review. Cancer 89: 640-646, 2000.
22. Semrad TJ, O'Donnell R, Wun T, Chew H, Harvey D, Zhou H and White RH: Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. J Neurosurg 106: 601-608, 2007.
23. Brat DJ, Castellano-Sanchez AA, Hunter SB, Pecot M, Cohen C, Hammond EH, Devi SN, Kaur B and Van Meir EG: Pseudopalisades in glioblastoma are hypoxic, express extracellular matrix proteases, and are formed by an actively migrating cell population. Cancer Res 64: 920-927, 2004.
24. Gross J and Lapiere CM: Collagenolytic activity in amphibian tissues: A tissue culture assay. Proc Natl Acad Sci USA 48: 1014-1022, 1962.
25. Visse R and Nagase H: Matrix metalloproteinases and tissue inhibitors of metalloproteinases: Structure, function, and biochemistry. Circ Res 92: 827-839, 2003.
26. Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, Ramírez-Camacho MA and Alvarez-Sánchez ME: Role of matrix metalloproteinases in angiogenesis and cancer. Front Oncol 9: 1370, 2019.
27. Gialeli C, Theocharis AD and Karamanos NK: Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. FEBS J 278: 16-27, 2011.
28. Niland S, Riscanevo AX and Eble JA: Matrix metalloproteinases shape the tumor microenvironment in cancer progression. Int J Mol Sci 23: 146, 2021.
29. Dibdiakova K, Majercikova Z, Galanda T, Richterova R, Kolarovszki B, Racay P and Hatok J: Relationship between the expression of matrix metalloproteinases and their tissue inhibitors in patients with brain tumors. Int J Mol Sci 25: 2858, 2024.
30. Wolburg H, Noell S, Fallier-Becker P, Mack AF and Wolburg-Buchholz K: The disturbed blood-brain barrier in human glioblastoma. Mol Aspects Med 33: 579-589, 2012.
31. Zhang S, Cheng L, Su Y, Qian Z, Wang Z, Chen C, Li R, Zhang A, He J, Mao J, *et al*: AGBL4 promotes malignant progression of glioblastoma via modulation of MMP-1 and inflammatory pathways. Front Immunol 15: 1420182, 2024.
32. Huang ZL, Abdallah AS, Shen GX, Suarez M, Feng P, Yu YJ, Wang Y, Zheng SH, Hu YJ, Xiao X, *et al*: Silencing GMPPB inhibits the proliferation and invasion of GBM via hippo/MMP3 pathways. Int J Mol Sci 24: 14707, 2023.
33. Yan P, Wang J, Liu H, Liu X, Fu R and Feng J: M1 macrophage-derived exosomes containing miR-150 inhibit glioma progression by targeting MMP16. Cell Signal 108: 110731, 2023.
34. Hitchcock SA: Blood-brain barrier permeability considerations for CNS-targeted compound library design. Curr Opin Chem Biol 12: 318-323, 2008.
35. Xie HJ, Zhan-Dui N, Zhao J, Er-Bu AGA, Zhen P, ZhuoMa D and Sang T: Evaluation of nanoscaled dual targeting drug-loaded liposomes on inhibiting vasculogenic mimicry channels of brain glioma. Artif Cells Nanomed Biotechnol 49: 595-604, 2021.
36. Tian S, Xu J, Qiao X, Zhang X, Zhang S, Zhang Y, Xu C, Wang H and Fang C: CuO nanoparticles for glioma treatment in vitro and in vivo. Sci Rep 14: 23229, 2024.
37. Castro-Ribeiro ML, Castro VIB, Vieira De Castro J, Pires RA, Reis RL, Costa BM, Ferreira H and Neves NM: The potential of the fibronectin inhibitor arg-gly-asp-ser in the development of therapies for glioblastoma. Int J Mol Sci 25: 4910, 2024.
38. Yang WB, Chuang JY, Ko CY, Chang WC and Hsu TI: Dehydroepiandrosterone induces temozolomide resistance through modulating phosphorylation and acetylation of Sp1 in glioblastoma. Mol Neurobiol 56: 2301-2313, 2019.
39. Munoz JL, Bliss SA, Greco SJ, Ramkissoon SH, Ligon KL and Rameshwar P: Delivery of functional anti-miR-9 by mesenchymal stem cell-derived exosomes to glioblastoma multiforme cells conferred chemosensitivity. Mol Ther Nucleic Acids 2: e126, 2013.
40. McFaline-Figueroa JL, Braun CJ, Stanciu M, Nagel ZD, Mazzucato P, Sangaraju D, Cerniauskas E, Barford K, Vargas A, Chen Y, *et al*: Minor changes in expression of the mismatch repair protein MSH2 exert a major impact on glioblastoma response to temozolomide. Cancer Res 75: 3127-3138, 2015.
41. Song H and Park KH: Regulation and function of SOX9 during cartilage development and regeneration. Semin Cancer Biol 67 (Pt 1): 12-23, 2020.
42. Guo XR, Wu MY, Dai LJ, Huang Y, Shan MY, Ma SN, Wang J, Peng H, Ding Y, Zhang QF, *et al*: Nuclear FAM289-galectin-1 interaction controls FAM289-mediated tumor promotion in malignant glioma. J Exp Clin Cancer Res 38: 394, 2019.
43. Yan H, Fu Z, Lin P, Gu Y, Cao J and Li Y: Inhibition of human glioblastoma multiforme cells by 10,11-dehydrocurvularin through the MMP-2 and PI3K/AKT signaling pathways. Eur J Pharmacol 936: 175348, 2022.
44. Yuan Z, Yang Z, Li W, Wu A, Su Z, Jiang B and Ganesan S: Triphlorethol-a attenuates U251 human glioma cancer cell proliferation and ameliorates apoptosis through JAK2/STAT3 and p38 MAPK/ERK signaling pathways. J Biochem Mol Toxicol 36: e23138, 2022.
45. De Jong JM, Broekaart DWM, Bongaarts A, Mühlebner A, Mills JD, Van Vliet EA and Aronica E: Altered extracellular matrix as an alternative risk factor for epileptogenicity in brain tumors. Biomedicines 10: 2475, 2022.
46. Thome I, Lacle R, Voß A, Bortolussi G, Pantazis G, Schmidt A, Conrad C, Jacob R, Timmesfeld N, Bartsch JW and Pagenstecher A: Neoplastic cells are the major source of MT-MMPs in IDH1-mutant glioma, thus enhancing tumor-cell intrinsic brain infiltration. Cancers (Basel) 12: 2456, 2020.
47. Sawicka MM, Sawicki K, Jadeszko M, Bielawska K, Supruniuk E, Reszeć J, Prokop-Bielenia I, Polityńska B, Jadeszko M, Rybaczek M, *et al*: Proline metabolism in WHO G4 gliomas is altered as compared to unaffected brain tissue. Cancers (Basel) 16: 456, 2024.
48. Whitehead CA, Fang H, Su H, Morokoff AP, Kaye AH, Hanssen E, Nowell CJ, Drummond KJ, Greening DW, Vella LJ, *et al*: Small extracellular vesicles promote invadopodia activity in glioblastoma cells in a therapy-dependent manner. Cell Oncol (Dordr) 46: 909-931, 2023.
49. Colangelo NW and Azzam EI: Extracellular vesicles originating from glioblastoma cells increase metalloproteinase release by astrocytes: The role of CD147 (EMMPRIN) and ionizing radiation. Cell Commun Signaling 18: 21, 2020.
50. Perruzzi CA, De Fougerolles AR, Koteliansky VE, Whelan MC, Westlin WF and Senger DR: Functional overlap and cooperativity among αv and β1 integrin subfamilies during skin angiogenesis. J Invest Dermatol 120: 1100-1109, 2003.
51. Whelan MC and Senger DR: Collagen I initiates endothelial cell morphogenesis by inducing actin polymerization through suppression of cyclic AMP and protein kinase A. J Biol Chem 278: 327-334, 2003.
52. Davis S, Aldrich TH, Jones PF, Acheson A, Compton DL, Jain V, Ryan TE, Bruno J, Radziejewski C, Maisonpierre PC and Yancopoulos GD: Isolation of angiopoietin-1, a ligand for the TIE2 receptor, by secretion-trap expression cloning. Cell 87: 1161-1169, 1996.
53. Winer A, Adams S and Mignatti P: Matrix metalloproteinase inhibitors in cancer therapy: Turning past failures into future successes. Mol Cancer Ther 17: 1147-1155, 2018.
54. Jiguet-Jiglaire C, Boissonneau S, Denicolai E, Hein V, Lasseur R, Garcia J, Romain S, Appay R, Graillon T, Mason W, *et al*: Plasmatic MMP9 released from tumor-infiltrating neutrophils is predictive for bevacizumab efficacy in glioblastoma patients: An AVAglio ancillary study. Acta Neuropathol Commun 10: 1, 2022.
55. Luo W, Quan Q, Xu Z, Lei J and Peng R: Bioinformatics analysis of MMP14+ myeloid cells affecting endothelial-mesenchymal transformation and immune microenvironment in glioma. Heliyon 10: e26859, 2024.
56. Yi B, Li H, Cai H, Lou X, Yu M and Li Z: LOXL1-AS1 communicating with TIAR modulates vasculogenic mimicry in glioma via regulation of the miR-374b-5p/MMP14 axis. J Cell Mol Med 26: 475-490, 2022.
57. Kryczka J, Papiewska-Pajak I, Kowalska MA and Boncela J: Cathepsin B is upregulated and mediates ECM degradation in colon adenocarcinoma HT29 cells overexpressing snail. Cells 8: 203, 2019.
58. Adnani L, Kassouf J, Meehan B, Spinelli C, Tawil N, Nakano I and Rak J: Angiocrine extracellular vesicles impose mesenchymal reprogramming upon proneural glioma stem cells. Nat Commun 13: 5494, 2022.
59. Djediai S, Gonzalez Suarez N, El Cheikh-Hussein L, Rodriguez Torres S, Gresseau L, Dhayne S, Joly-Lopez Z and Annabi B: MT1-MMP cooperates with TGF-β receptor-mediated signaling to trigger SNAIL and induce epithelial-to-mesenchymal-like transition in U87 glioblastoma cells. Int J Mol Sci 22: 13006, 2021.

60. Komatsu K, Nakanishi Y, Nemoto N, Hori T, Sawada T and Kobayashi M: Expression and quantitative analysis of matrix metalloproteinase-2 and-9 in human gliomas. Brain Tumor Pathol 21: 105-112, 2004.
61. Hormigo A, Gu B, Karimi S, Riedel E, Panageas KS, Edgar MA, Tanwar MK, Rao JS, Fleisher M, DeAngelis LM and Holland EC: YKL-40 and matrix metalloproteinase-9 as potential serum biomarkers for patients with high-grade gliomas. Clin Cancer Res 12: 5698-5704, 2006.
62. Iwamoto FM, Hottinger AF, Karimi S, Riedel E, Dantis J, Jahdi M, Panageas KS, Lassman AB, Abrey LE, Fleisher M, *et al*: Longitudinal prospective study of matrix metalloproteinase-9 as a serum marker in gliomas. J Neuro-oncol 105: 607-612, 2011.
63. Wong ET, Alsop D, Lee D, Tam A, Barron L, Bloom J, Gautam S and Wu JK: Cerebrospinal fluid matrix metalloproteinase-9 increases during treatment of recurrent malignant gliomas. Cerebrospinal Fluid Res 5: 1, 2008.
64. Tabouret E, Boudouresque F, Barrie M, Matta M, Boucard C, Loundou A, Carpentier A, Sanson M, Metellus P, Figarella-Branger D, *et al*: Association of matrix metalloproteinase 2 plasma level with response and survival in patients treated with bevacizumab for recurrent high-grade glioma. Neuro Oncol 16: 392-399, 2014.
65. Li Q, Chen B, Cai J, Sun Y, Wang G, Li Y, Li R, Feng Y, Han B, Li J, *et al*: Comparative analysis of matrix metalloproteinase family members reveals that MMP9 predicts survival and response to temozolomide in patients with primary glioblastoma. PLoS One 11: e0151815, 2016.
66. Zhang J, Yang Y, Dong Y and Liu C: Microrchidia family CW-type zinc finger 2 promotes the proliferation, invasion, migration and epithelial-mesenchymal transition of glioma by regulating PTEN/PI3K/AKT signaling via binding to N-myc downstream regulated gene 1 promoter. Int J Mol Med 49: 16, 2022.
67. Liu Y, Ma J, Song JS, Zhou HY, Li JH, Luo C, Geng X and Zhao HX: DNA topoisomerase II alpha promotes the metastatic characteristics of glioma cells by transcriptionally activating β-catenin. Bioengineered 13: 2207-2216, 2022.
68. Cong Z, Yuan F, Wang H, Cai X, Zhu J, Tang T, Zhang L, Han Y and Ma C: BTB domain and CNC homolog 1 promotes glioma invasion mainly through regulating extracellular matrix and increases ferroptosis sensitivity. Biochim Biophys Acta Mol Basis Dis 1868: 166554, 2022.
69. Pai FC, Huang HW, Tsai YL, Tsai WC, Cheng YC, Chang HH and Chen Y: Inhibition of FABP6 reduces tumor cell invasion and angiogenesis through the decrease in MMP-2 and VEGF in human glioblastoma cells. Cells 10: 2782, 2021.
70. Hu T, Lei D, Zhou J and Zhang B: circRNA derived from CLSPN (circCLSPN) is an oncogene in human glioblastoma multiforme by regulating cell growth, migration and invasion via ceRNA pathway. J Biosci 46: 66, 2021.
71. Jia J, Ouyang Z, Wang M, Ma W, Liu M, Zhang M and Yu M: MicroRNA-361-5p slows down gliomas development through regulating UBR5 to elevate ATMIN protein expression. Cell Death Dis 12: 746, 2021.
72. Amini J, Zafarjafarzadeh N, Ghahramanlu S, Mohammadalizadeh O, Mozaffari E, Bibak B and Sanadgol N: Role of circular RNA MMP9 in glioblastoma progression: from interaction with hnRNPC and hnRNPA1 to affecting the expression of BIRC5 by sequestering miR -149. J Mol Recognit 38: e3109, 2025.
73. Delbrouck C, Kiweler N, Chen O, Pozdeev VI, Haase L, Neises L, Oudin A, Fouquier d'Hérouël A, Shen R, Schlicker L, *et al*: Formate promotes invasion and metastasis in reliance on lipid metabolism. Cell Rep 42: 113034, 2023.
74. Pu W, Qiu J, Riggins GJ and Parat MO: Matrix protease production, epithelial-to-mesenchymal transition marker expression and invasion of glioblastoma cells in response to osmotic or hydrostatic pressure. Sci Rep 10: 2634, 2020.
75. Liu Y, He W, Guo Y, Qu S, Yao F, Liu J, Chai J, Yang Y, Xu T, Liu Y, *et al*: CSNK1D is associated with stemness and invasiveness in glioblastoma. Pathol Res Pract 240: 154187, 2022.
76. Vivanco I and Sawyers CL: The phosphatidylinositol 3-kinase-AKT pathway in human cancer. Nat Rev Cancer 2: 489-501, 2002.
77. Huang YK, Wang TM, Chen CY, Li CY, Wang SC, Irshad K, Pan Y and Chang KC: The role of ALDH1A1 in glioblastoma proliferation and invasion. Chem Biol Interact 402: 111202, 2024.
78. Ni H, Ji D, Huang Z and Li J: SMAGP knockdown inhibits the malignant phenotypes of glioblastoma cells by inactivating the PI3K/akt pathway. Arch Biochem Biophys 695: 108628, 2020.
79. Yang W, Yuan Q, Zhang S, Zuo M, Li T, Li J, Zhou X, Li M, Feng W, Xia X, *et al*: Elevated GIGYF2 expression suppresses tumor migration and enhances sensitivity to temozolomide in malignant glioma. Cancer Gene Ther 29: 750-757, 2022.
80. Gwon DH, Lee WY, Shin N, Kim SI, Jeong K, Lee WH, Kim DW, Hong J and Lee SY: BMAL1 suppresses proliferation, migration, and invasion of U87MG cells by downregulating cyclin B1, phospho-AKT, and metalloproteinase-9. Int J Mol Sci 21: 2352, 2020.
81. Zuo J, Liu C, Ni H and Yu Z: WDR34 affects PI3K/akt and wnt/β-catenin pathways to regulates malignant biological behaviors of glioma cells. J Neurooncol 156: 281-293, 2022.
82. Sun L, Hui AM, Su Q, Vortmeyer A, Kotliarov Y, Pastorino S, Passaniti A, Menon J, Walling J, Bailey R, *et al*: Neuronal and glioma-derived stem cell factor induces angiogenesis within the brain. Cancer Cell 9: 287-300, 2006.
83. Lyu X, Shi Y, Wang D, Cao X, Guo J, Huang G, Zhou L, Zhang M and Dong Z: Impact of LIN7A silencing on U87 cell invasion and its clinical significance in glioblastoma. Sci Rep 15: 7212, 2025.
84. Sun H, Long S, Wu B, Liu J and Li G: NKCC1 involvement in the epithelial-to-mesenchymal transition is a prognostic biomarker in gliomas. PeerJ 8: e8787, 2020.
85. Zhang G, Feng W and Wu J: Down-regulation of SEPT9 inhibits glioma progression through suppressing TGF-β-induced epithelial-mesenchymal transition (EMT). Biomed Pharmacother 125: 109768, 2020.
86. Dong C, Li X, Yang J, Yuan D, Zhou Y, Zhang Y, Shi G, Zhang R, Liu J, Fu P, Sun M: PPFIBP1 induces glioma cell migration and invasion through FAK/src/JNK signaling pathway. Cell Death Dis 12: 827, 2021.
87. Zhang Y, Chang L, Huang P, Cao M, Hong R, Zhao X, He X and Xu L: Loss of PTPRS elicits potent metastatic capability and resistance to temozolomide in glioblastoma. Mol Carcinog 63: 1235-1247, 2024.
88. Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, Misra A, Nigro JM, Colman H, Soroceanu L, *et al*: Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. Cancer Cell 9: 157-173, 2006.
89. Costa BM, Smith JS, Chen Y, Chen J, Phillips HS, Aldape KD, Zardo G, Nigro J, James CD, Fridlyand J, *et al*: Reversing HOXA9 oncogene activation by PI3K inhibition: Epigenetic mechanism and prognostic significance in human glioblastoma. Cancer Res 70: 453-462, 2010.
90. Lin K, Taylor JR Jr, Wu TD, Gutierrez J, Elliott JM, Vernes JM, Koeppen H, Phillips HS, de Sauvage FJ and Meng YG: TMEFF2 is a PDGF-AA binding protein with methylation-associated gene silencing in multiple cancer types including glioma. PLoS One 6: e18608, 2011.
91. Yu X, Jin J, Zheng Y, Zhu H, Xu H, Ma J, Lan Q, Zhuang Z, Chen CC and Li M: GBP5 drives malignancy of glioblastoma via the src/ERK1/2/MMP3 pathway. Cell Death Dis 12: 203, 2021.
92. Wang R, Zhang S, Chen X, Li N, Li J, Jia R, Pan Y and Liang H: EIF4A3-induced circular RNA MMP9 (circMMP9) acts as a sponge of miR-124 and promotes glioblastoma multiforme cell tumorigenesis. Mol Cancer 17: 166, 2018.
93. Liu X, Shen S, Zhu L, Su R, Zheng J, Ruan X, Shao L, Wang D, Yang C and Liu Y: SRSF10 inhibits biogenesis of circ-ATXN1 to regulate glioma angiogenesis via miR-526b-3p/MMP2 pathway. J Exp Clin Cancer Res 39: 121, 2020.
94. Yang Y and Zhao F: MicroRNA-16 inhibits the growth and metastasis of human glioma cells via modulation of PI3K/AKT/mTOR signalling pathway. Arch Med Sci 20: 839-846, 2020.
95. Song Y, Li C, Jin L, Xing J, Sha Z, Zhang T, Ji D, Yu R and Gao S: RIOK2 is negatively regulated by miR-4744 and promotes glioma cell migration/invasion through epithelial-mesenchymal transition. J Cell Mol Med 24: 4494-4509, 2020.
96. Meiser J, Schuster A, Pietzke M, Vande Voorde J, Athineos D, Oizel K, Burgos-Barragan G, Wit N, Dhayade S, Morton JP, *et al*: Increased formate overflow is a hallmark of oxidative cancer. Nat Commun 9: 1368, 2018.
97. Manou D, Golfinopoulou MA, Alharbi SND, Alghamdi HA, Alzahrani FM and Theocharis AD: The expression of serglycin is required for active transforming growth factor β receptor I tumorigenic signaling in glioblastoma cells and paracrine activation of stromal fibroblasts via CXCR-2. Biomolecules 14: 461, 2024.

98. Pu W, Qiu J, Nassar ZD, Shaw PN, McMahon KA, Ferguson C, Parton RG, Riggins GJ, Harris JM and Parat MO: A role for caveola-forming proteins caveolin-1 and CAVIN1 in the pro-invasive response of glioblastoma to osmotic and hydrostatic pressure. J Cell Mol Med 24: 3724-3738, 2020.
99. Pu W, Nassar ZD, Khabbazi S, Xie N, McMahon KA, Parton RG, Riggins GJ, Harris JM and Parat MO: Correlation of the invasive potential of glioblastoma and expression of caveola-forming proteins caveolin-1 and CAVIN1. J Neurooncol 143: 207-220, 2019.
100. Oishi M, Munesue S, Harashima A, Nakada M, Yamamoto Y and Hayashi Y: Aquaporin 1 elicits cell motility and coordinates vascular bed formation by downregulating thrombospondin type-1 domain-containing 7A in glioblastoma. Cancer Med 9: 3904-3917, 2020.
101. Sun Z, Zhao W, Fei X, He B, Shi L, Zhang Z and Cai S: Static magnetic field inhibits epithelial mesenchymal transition and metastasis of glioma. Sci Rep 15: 12430, 2025.
102. Shi Y, Jiang J, Cui Y, Chen Y, Dong T, An H and Liu P: MSH6 aggravates the hypoxic microenvironment via regulating HIF1A to promote the metastasis of glioblastoma multiforme. DNA Cell Biol 40: 93-100, 2021.
103. Feng K, Ye G, Wang H, Li S, Wen X and Chen M: Research on the mechanism of TWSG1 in the malignant progression of glioma cells and tumor-associated macrophage infiltration. J Neuropathol Exp Neurol 83: 843-852, 2024.
104. Hodgson JG, Yeh RF, Ray A, Wang NJ, Smirnov I, Yu M, Hariono S, Silber J, Feiler HS, Gray JW, *et al*: Comparative analyses of gene copy number and mRNA expression in glioblastoma multiforme tumors and xenografts. Neuro Oncol 11: 477-487, 2009.
105. Korde LA, Lusa L, McShane L, Lebowitz PF, Lukes L, Camphausen K, Parker JS, Swain SM, Hunter K and Zujewski JA: Gene expression pathway analysis to predict response to neoadjuvant docetaxel and capecitabine for breast cancer. Breast Cancer Res Treat 119: 685-699, 2010.
106. Griesinger AM, Birks DK, Donson AM, Amani V, Hoffman LM, Waziri A, Wang M, Handler MH and Foreman NK: Characterization of distinct immunophenotypes across pediatric brain tumor types. J Immunol 191: 4880-4888, 2013.
107. Qi H, Wang P, Sun H, Li X, Hao X, Tian W, Yu L, Tang J, Dong J and Wang H: ADAMDEC1 accelerates GBM progression via activation of the MMP2-related pathway. Front Oncol 12: 945025, 2022.
108. Guda MR, Velpula KK, Asuthkar S, Cain CP and Tsung AJ: Targeting RGS4 ablates glioblastoma proliferation. Int J Mol Sci 21: 3300, 2020.
109. Yasmin IA, Mohana Sundaram S, Banerjee A, Varier L, Dharmarajan A and Warrier S: Netrin-like domain of sFRP4, a wnt antagonist inhibits stemness, metastatic and invasive properties by specifically blocking MMP-2 in cancer stem cells from human glioma cell line U87MG. Exp Cell Res 409: 112912, 2021.
110. Georgescu MM, Islam MZ, Li Y, Traylor J and Nanda A: Novel targetable FGFR2 and FGFR3 alterations in glioblastoma associate with aggressive phenotype and distinct gene expression programs. Acta Neuropathol Commun 9: 69, 2021.
111. Sanders S, Herpai DM, Rodriguez A, Huang Y, Chou J, Hsu FC, Seals D, Mott R, Miller LD and Debinski W: The presence and potential role of ALDH1A2 in the glioblastoma microenvironment. Cells 10: 2485, 2021.
112. Kreße N, Schröder H, Stein KP, Wilkens L, Mawrin C, Sandalcioglu IE and Dumitru CA: PLOD2 is a prognostic marker in glioblastoma that modulates the immune microenvironment and tumor progression. Int J Mol Sci 23: 6037, 2022.
113. Ivanova EL, Costa B, Eisemann T, Lohr S, Boskovic P, Eichwald V, Meckler J, Jugold M, Orian-Rousseau V, Peterziel H and Angel P: CD44 expressed by myeloid cells promotes glioma invasion. Front Oncol 12: 969787, 2022.
114. Wang P, Hao X, Li X, Yan Y, Tian W, Xiao L, Wang Z and Dong J: Curcumin inhibits adverse psychological stress-induced proliferation and invasion of glioma cells via down-regulating the ERK/MAPK pathway. J Cell Mol Med 25: 7190-7203, 2021.
115. Yang CL, Chik SC, Lau AS and Chan GC: Coriolus versicolor and its bioactive molecule are potential immunomodulators against cancer cell metastasis via inactivation of MAPK pathway. J Ethnopharmacol 301: 115790, 2023.
116. Gallardo-Pérez JC, Trejo-Solís MC, Robledo-Cadena DX, López-Marure R, Agredano-Moreno LT, Jimenez-García LF and Sánchez-Lozada LG: Erythrose inhibits the progression to invasiveness and reverts drug resistance of cancer stem cells of glioblastoma. Med Oncol 40: 104, 2023.
117. Luo Z, Liu L, Li X, Chen W and Lu Z: Tat-NTS suppresses the proliferation, migration and invasion of glioblastoma cells by inhibiting annexin-A1 nuclear translocation. Cell Mol Neurobiol 42: 2715-2725, 2022.
118. Zhou Y, Liu H, Zheng W, Chen Q, Hu S, Pan Y, Bai Y, Zhang J and Shao C: MMP14 contributes to HDAC inhibition-induced radiosensitization of glioblastoma. Int J Mol Sci 22: 10403, 2021.
119. Dosta P, Dion MZ, Prado M, Hurtado P, Riojas-Javelly CJ, Cryer AM, Soria Y, Andrews Interiano N, Muñoz-Taboada G and Artzi N: Matrix metalloproteinase- and pH-sensitive nanoparticle system enhances drug retention and penetration in glioblastoma. ACS Nano 18: 14145-14160, 2024.
120. Li Y, Wang D, Zhang Z, Wang Y, Zhang Z, Liang Z, Liu F and Chen L: Photodynamic therapy enhances the cytotoxicity of temozolomide against glioblastoma via reprogramming anaerobic glycolysis. Photodiagn Photodyn Ther 42: 103342, 2023.
121. Rezaei T, Hejazi M, Mansoori B, Mohammadi A, Amini M, Mosafer J, Rezaei S, Mokhtarzadeh A and Baradaran B: microRNA-181a mediates the chemo-sensitivity of glioblastoma to carmustine and regulates cell proliferation, migration, and apoptosis. Eur J Pharmacol 888: 173483, 2020.
122. Chen CJ, Shang HS, Huang YL, Tien N, Chen YL, Hsu SY, Wu RS, Tang CL, Lien JC, Lee MH, *et al*: Bisdemethoxycurcumin suppresses human brain glioblastoma multiforme GBM 8401 cell migration and invasion via affecting NF-κB and MMP-2 and MMP-9 signaling pathway in vitro. Environ Toxicol 37: 2388-2397, 2022.
123. Jalili-Nik M, Afshari AR, Sabri H, Bibak B, Mollazadeh H and Sahebkar A: Zerumbone, a ginger sesquiterpene, inhibits migration, invasion, and metastatic behavior of human malignant glioblastoma multiforme in vitro. BioFactors 47: 729-739, 2021.
124. Cheng B, Hong X, Wang L, Cao Y, Qin D, Zhou H and Gao D: Curzerene suppresses progression of human glioblastoma through inhibition of glutathione S-transferase A4. CNS Neurosci Ther 28: 690-702, 2022.
125. Alkahtani S, S AL-Johani N, Alarifi S and Afzal M: Cytotoxicity mechanisms of blue-light-activated curcumin in T98G cell line: Inducing apoptosis through ROS-dependent downregulation of MMP pathways. Int J Mol Sci 24: 3842, 2023.
126. Han M, An J, Li S, Fan H, Wang L, Du Q, Du J, Yang Y, Song Y and Peng F: Isocucurbitacin B inhibits glioma growth through PI3K/AKT pathways and increases glioma sensitivity to TMZ by inhibiting hsa-mir-1286a. Cancer Drug Resist 7: 16, 2024.
127. Yang JF, Chen TM, Chang HH, Tsai YL, Tsai WC, Huang WY, Lo CH, Lin CS, Shen PC and Chen Y: Guggulsterone inhibits migration and invasion through proteasomal and lysosomal degradation in human glioblastoma cells. Eur J Pharmacol 938: 175411, 2023.
128. Wang X, Zou S, Ren T, Zhao LJ, Yu LF, Li XY, Yan X and Zhang LJ: Alantolactone suppresses the metastatic phenotype and induces the apoptosis of glioblastoma cells by targeting LIMK kinase activity and activating the cofilin/G-actin signaling cascade. Int J Mol Med 47: 68, 2021.
129. Dos Santos JS, Suzan AJ, Bonafé GA, Fernandes AMAP, Longato GB, Antônio MA, Carvalho PO and Ortega MM: Kaempferol and biomodified kaempferol from sophora japonica extract as potential sources of anti-cancer polyphenolics against high grade glioma cell lines. Int J Mol Sci 24: 10716, 2023.
130. Khathayer F and Ray SK: Diosgenin as a novel alternative therapy for inhibition of growth, invasion, and angiogenesis abilities of different glioblastoma cell lines. Neurochem Res 45: 2336-2351, 2020.
131. Liu HY, Ji YL, Du H, Chen SH, Wang DP and Lv QL: Bacoside a inhibits the growth of glioma by promoting apoptosis and autophagy in U251 and U87 cells. Naunyn Schmiedebergs Arch Pharmacol 397: 2105-2120, 2024.
132. Yang HL, Chang YH, Pandey S, Bhat AA, Vadivalagan C, Lin KY and Hseu YC: Antrodia camphorataand coenzyme Q0, a novel quinone derivative of antrodia camphorata, impede HIF-1α and epithelial-mesenchymal transition/metastasis in human glioblastoma cells. Environ Toxicol 38: 1548-1564, 2023.

133. Frontiñán-Rubio J, Llanos-González E, García-Carpintero S, Peinado JR, Ballesteros-Yáñez I, Rayo MV, de la Fuente J, Pérez-García VM, Perez-Romasanta LA, Malumbres M, *et al*: CoQ10 reduces glioblastoma growth and infiltration through proteome remodeling and inhibition of angiogenesis and inflammation. Cell Oncol (Dordr) 46: 65-77, 2023.
134. Małek A, Strzemski M, Kapka-Skrzypczak L and Kurzepa J: Anticancer activity of melittin-containing bee venom fraction against glioblastoma cells in vitro. Int J Mol Sci 26: 2376, 2025.
135. Eidizade F, Soukhtanloo M, Zhiani R, Mehrzad J and Mirzavi F: Inhibition of glioblastoma proliferation, invasion, and migration by urolithin B through inducing G0/G1 arrest and targeting MMP-2/-9 expression and activity. BioFactors 49: 379-389, 2023.
136. Doğanlar O, Doğanlar ZB, Delen E and Doğan A: The role of melatonin in angio-miR-associated inhibition of tumorigenesis and invasion in human glioblastoma tumour spheroids. Tissue Cell 73: 101617, 2021.
137. Liu DN, Liu M, Zhang SS, Shang YF, Song FH, Zhang HW, Du GH and Wang YH: Chrysomycin a inhibits the proliferation, migration and invasion of U251 and U87-MG glioblastoma cells to exert its anti-cancer effects. Molecules 27: 6148, 2022.
138. Lin YH, Chen TM, Lai CR, Tsai YL, Tsai WC and Chen Y: GW4064 inhibits migration and invasion in human glioblastoma multiforme through the downregulation of PKCα. Eur J Pharmacol 991: 177329, 2025.
139. Wen ZH, Chang L, Yang SN, Yu CL, Tung FY, Kuo HM, Lu IC, Wu CY, Shih PC, Chen WF and Chen NF: The anti-angiogenic and anti-vasculogenic mimicry effects of GN25 in endothelial and glioma cells. Biochim Biophys Acta Mol Cell Res 1871: 119799, 2024.
140. Shan W, Zuo K and Zuo Z: Hypoglycemic agents increase regulatory factor X1 to inhibit cancer cell behaviour in human glioblastoma cells. J Cell Mol Med 28: e70260, 2024.
141. Benn KW, Yuan PH, Chong HK, Stylii SS, Luwor RB and French CR: hERG channel agonist NS1643 strongly inhibits invasive astrocytoma cell line SMA-560. PLoS One 19: e0309438, 2024.
142. Zhao H, Xing F, Yuan J, Li Z and Zhang W: Sevoflurane inhibits migration and invasion of glioma cells via regulating miR-34a-5p/MMP-2 axis. Life Sci 256: 117897, 2020.
143. Kang X, Li H and Zhang Z: Sevoflurane blocks glioma malignant development by upregulating circRELN through circRELN-mediated miR-1290/RORA axis. BMC Anesthesiol 21: 213, 2021.
144. Zhan X, Lei C and Yang L: Sevoflurane inhibits cell proliferation and migration of glioma by targeting the miR-27b/VEGF axis. Mol Med Rep 23: 408, 2021.
145. Zhang L, Chen H, Tian C and Zheng D: Propofol represses cell growth and metastasis by modulating the circular RNA non-SMC condensin I complex subunit G/MicroRNA-200a-3p/RAB5A axis in glioma. World Neurosurg 153: e46-e58, 2021.
146. Wang J, Zhang J, Zhang Q, Zhang W, Zhang Q, Jin G and Liu F: TS-2021, a third-generation oncolytic adenovirus that carried Ki67 promoter, TGF-β2 5'UTR, and IL–15 against experimental glioblastoma. J Med Virol 96: e29335, 2024.
147. Fan X, Li J, Long L, Shi T, Liu D, Tan W, Zhang H, Wu X, Lei X and Wang Z: Design, synthesis and biological evaluation of N-anthraniloyl tryptamine derivatives as pleiotropic molecules for the therapy of malignant glioma. Eur J Med Chem 222: 113564, 2021.
148. Gabano E, Gariboldi MB, Caron G, Ermondi G, Marras E, Vallaro M and Ravera M: Application of the anthraquinone drug rhein as an axial ligand in bifunctional pt(iv) complexes to obtain antiproliferative agents against human glioblastoma cells. Dalton Trans 51: 6014-6026, 2022.
149. Kuang J, Rao ZY, Zheng DW, Kuang D, Huang QX, Pan T, Li H, Zeng X and Zhang XZ: Nanoparticles hitchhike on monocytes for glioblastoma treatment after low-dose radiotherapy. ACS Nano 17: 13333-13347, 2023.
150. Durand M, Chateau A, Jubréaux J, Devy J, Paquot H, Laurent G, Bazzi R, Roux S, Richet N, Reinhard-Ruch A, *et al*: Radiosensitization with gadolinium chelate-coated gold nanoparticles prevents aggressiveness and invasiveness in glioblastoma. Int J Nanomedicine 18: 243-261, 2023.
151. Horta M, Soares P, Sarmento B, Leite Pereira C and Lima RT: Nanostructured lipid carriers for enhanced batimastat delivery across the blood-brain barrier: An in vitro study for glioblastoma treatment. Drug Deliv Transl Res 15: 2794-2813, 2025.
152. Gupta R and Sharma D: (carboxymethyl-stevioside)-coated magnetic dots for enhanced magnetic hyperthermia and improved glioblastoma treatment. Colloids Surf, B 205: 111870, 2021.
153. Ke G, Hu P, Xiong H, Zhang J, Xu H, Xiao C, Liu Y, Cao M and Zheng Q: Enhancing temozolomide efficacy in GBM: The synergistic role of chuanxiong rhizoma essential oil. Phytomedicine 140: 156575, 2025.
154. Pibuel MA, Poodts D, Sias SA, Byrne A, Hajos SE, Franco PG and Lompardía SL: 4-methylumbelliferone enhances the effects of chemotherapy on both temozolomide-sensitive and resistant glioblastoma cells. Sci Rep 13: 9356, 2023.
155. Chen J, Zhuang YD, Zhang Q, Liu S, Zhuang BB, Wang CH and Liang RS: Exploring the mechanism of cordycepin combined with doxorubicin in treating glioblastoma based on network pharmacology and biological verification. PeerJ 10: e12942, 2022.
156. Wang J, Ren D, Sun Y, Xu C, Wang C, Cheng R, Wang L, Jia G, Ren J, Ma J, *et al*: Inhibition of PLK4 might enhance the anti-tumour effect of bortezomib on glioblastoma via PTEN/PI3K/AKT/mTOR signalling pathway. J Cell Mol Med 24: 3931-3947, 2020.
157. Qin JJ, Niu MD, Cha Z, Geng QH, Li YL, Ren CG, Molloy DP and Yu HR: TRAIL and celastrol combinational treatment suppresses proliferation, migration, and invasion of human glioblastoma cells via targeting wnt/β-catenin signaling pathway. Chin J Integr Med 30: 322-329, 2024.
158. Ebrahimi S, Mirzavi F, Hashemy SI, Khaleghi Ghadiri M, Stummer W and Gorji A: The in vitro anti-cancer synergy of neurokinin-1 receptor antagonist, aprepitant, and 5-aminolevulinic acid in glioblastoma. Biofactors 49: 900-911, 2023.
159. Torsvik A, Stieber D, Enger PØ, Golebiewska A, Molven A, Svendsen A, Westermark B, Niclou SP, Olsen TK, Chekenya Enger M and Bjerkvig R: U-251 revisited: Genetic drift and phenotypic consequences of long-term cultures of glioblastoma cells. Cancer Med 3: 812-824, 2014.
160. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro Oncol 20 (suppl_4): iv1-iv86, 2018.
161. Gritsch S, Batchelor TT and Gonzalez Castro LN: Diagnostic, therapeutic, and prognostic implications of the 2021 world health organization classification of tumors of the central nervous system. Cancer 128: 47-58, 2022.
162. Satgunaseelan L, Sy J, Shivalingam B, Sim HW, Alexander KL and Buckland ME: Prognostic and predictive biomarkers in central nervous system tumours: The molecular state of play. Pathology 56: 158-169, 2024.
163. Groves MD, Puduvalli VK, Hess KR, Jaeckle KA, Peterson P, Yung WK and Levin VA: Phase II trial of temozolomide plus the matrix metalloproteinase inhibitor, marimastat, in recurrent and progressive glioblastoma multiforme. J Clin Oncol 20: 1383-1388, 2002.
164. Wolburg H, Wolburg-Buchholz K, Fallier-Becker P, Noell S and Mack AF: Structure and functions of aquaporin-4-based orthogonal arrays of particles. Int Rev Cell Mol Biol 287: 1-41, 2011.
165. Endicott JA and Ling V: The biochemistry of P-glycoprotein-mediated multidrug resistance. Annu Rev Biochem 58: 137-171, 1989.
166. Van Tellingen O, Yetkin-Arik B, De Gooijer MC, Wesseling P, Wurdinger T and De Vries HE: Overcoming the blood-brain tumor barrier for effective glioblastoma treatment. Drug Resist Updat 19: 1-12, 2015.
167. Parrish KE, Sarkaria JN and Elmquist WF: Improving drug delivery to primary and metastatic brain tumors: Strategies to overcome the blood-brain barrier. Clin Pharmacol Ther 97: 336-346, 2015.
168. Oberoi RK, Parrish KE, Sio TT, Mittapalli RK, Elmquist WF and Sarkaria JN: Strategies to improve delivery of anticancer drugs across the blood-brain barrier to treat glioblastoma. Neuro Oncol 18: 27-36, 2016.
169. Wu D, Chen Q, Chen X, Han F, Chen Z and Wang Y: The blood-brain barrier: Structure, regulation and drug delivery. Signal Transduct Target Ther 8: 217, 2023.
170. Holmbeck K, Bianco P, Caterina J, Yamada S, Kromer M, Kuznetsov SA, Mankani M, Robey PG, Poole AR, Pidoux I, *et al*: MT1-MMP-deficient mice develop dwarfism, osteopenia, arthritis, and connective tissue disease due to inadequate collagen turnover. Cell 99: 81-92, 1999.

171. Martignetti JA, Aqeel AA, Sewairi WA, Boumah CE, Kambouris M, Mayouf SA, Sheth KV, Eid WA, Dowling O, Harris J, *et al*: Mutation of the matrix metalloproteinase 2 gene (MMP2) causes a multicentric osteolysis and arthritis syndrome. Nat Genet 28: 261-265, 2001.
172. Barish ME, Aftabizadeh M, Hibbard J, Blanchard MS, Ostberg JR, Wagner JR, Manchanda M, Paul J, Stiller T, Aguilar B, *et al*: Chlorotoxin-directed CAR T cell therapy for recurrent glioblastoma: Interim clinical experience demonstrating feasibility and safety. Cell Rep Med 6: 102302, 2025.
173. Thanh HD, Lee S, Nguyen TT, Huu TN, Ahn EJ, Cho SH, Kim MS, Moon KS and Jung C: Temozolomide promotes matrix metalloproteinase 9 expression through p38 MAPK and JNK pathways in glioblastoma cells. Sci Rep 14: 14341, 2024.
174. Whitehead CA, Morokoff AP, Kaye AH, Drummond KJ, Mantamadiotis T and Stylli SS: Invadopodia associated thrombospondin-1 contributes to a post-therapy pro-invasive response in glioblastoma cells. Exp Cell Res 431: 113743, 2023.
175. Żwierełło W, Maruszewska A, Skórka-Majewicz M, Wszołek A and Gutowska I: Is fluoride blameless?-the influence of fluorine compounds on the invasiveness of the human glioma-like cell line U-87. Int J Mol Sci 25: 12773, 2024.
176. Huang W, Li J, Geng X, Li S, Zou Y, Li Y, Jing C and Yu H: The reactive astrocytes after surgical brain injury potentiates the migration, invasion, and angiogenesis of C6 glioma. World Neurosurg 168: e595-e606, 2022.
177. Ahmed MM, Hossain MM, Islam MR, Ali MS, Nafi AAN, Ahmed MF, Ahmed KM, Miah MS, Rahman MM, Niu M and Islam MK: Brain tumor detection and classification in MRI using hybrid ViT and GRU model with explainable AI in Southern Bangladesh. Sci Rep 14: 22797, 2024.
178. Rastogi A, Brugnara G, Foltyn-Dumitru M, Mahmutoglu MA, Preetha CJ, Kobler E, Pflüger I, Schell M, Deike-Hofmann K, Kessler T, *et al*: Deep-learning-based reconstruction of undersampled MRI to reduce scan times: A multicentre, retrospective, cohort study. Lancet Oncol 25: 400-410, 2024.
179. Lu CH, Wei ST, Liu JJ, Chang YJ, Lin YF, Yu CS and Chang SL: Recognition of a novel gene signature for human glioblastoma. Int J Mol Sci 23: 4157, 2022.
180. Shi J: Machine learning and bioinformatics approaches for classification and clinical detection of bevacizumab responsive glioblastoma subtypes based on miRNA expression. Sci Rep 12: 8685, 2022.
181. Rivera CA, Bhatia S, Uppalapati V, Berke CN, Merenzon MA, Daggubati LC, Levy AS, Shah AH, Komotar RJ and Ivan ME: Leveraging machine learning for preoperative prediction of supramaximal ablation in laser interstitial thermal therapy for brain tumors. Neurosurg Focus 57: E6, 2024.
182. Kuenzi BM, Park J, Fong SH, Sanchez KS, Lee J, Kreisberg JF, Ma J and Ideker T: Predicting drug response and synergy using a deep learning model of human cancer cells. Cancer Cell 38: 672-684.e6, 2020.
183. Marques L, Costa B, Pereira M, Silva A, Santos J, Saldanha L, Silva I, Magalhães P, Schmidt S and Vale N: Advancing precision medicine: A review of innovative in silico approaches for drug development, clinical pharmacology and personalized healthcare. Pharmaceutics 16: 332, 2024.
184. Seo S, Nah S, Lee K, Choi N and Kim HN: Triculture model of in vitro BBB and its application to study BBB-associated chemosensitivity and drug delivery in glioblastoma. Adv Funct Mater 32: 2106860, 2022.
185. Tricinci O, De Pasquale D, Marino A, Battaglini M, Pucci C and Ciofani G: A 3D biohybrid real-scale model of the brain cancer microenvironment for advanced in vitro testing. Adv Mater Technol 5: 2000540, 2020.
186. Zhu D, Trinh P, Li J, Grant GA and Yang F: Gradient hydrogels for screening stiffness effects on patient-derived glioblastoma xenograft cellfates in 3D. J Biomed Mater Res A 109: 1027-1035, 2021.
187. Wang C, Sinha S, Jiang X, Murphy L, Fitch S, Wilson C, Grant G and Yang F: Matrix stiffness modulates patient-derived glioblastoma cell fates in three-dimensional hydrogels. Tissue Eng Part A 27: 390-401, 2021.