

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

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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 micro-environment. 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.

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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 O⁶-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 anti-tumor agents in the brain. Additionally, the multifactorial mechanisms underlying TMZ resistance involve not only DNA damage repair mediated by O⁶-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 prolydase 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

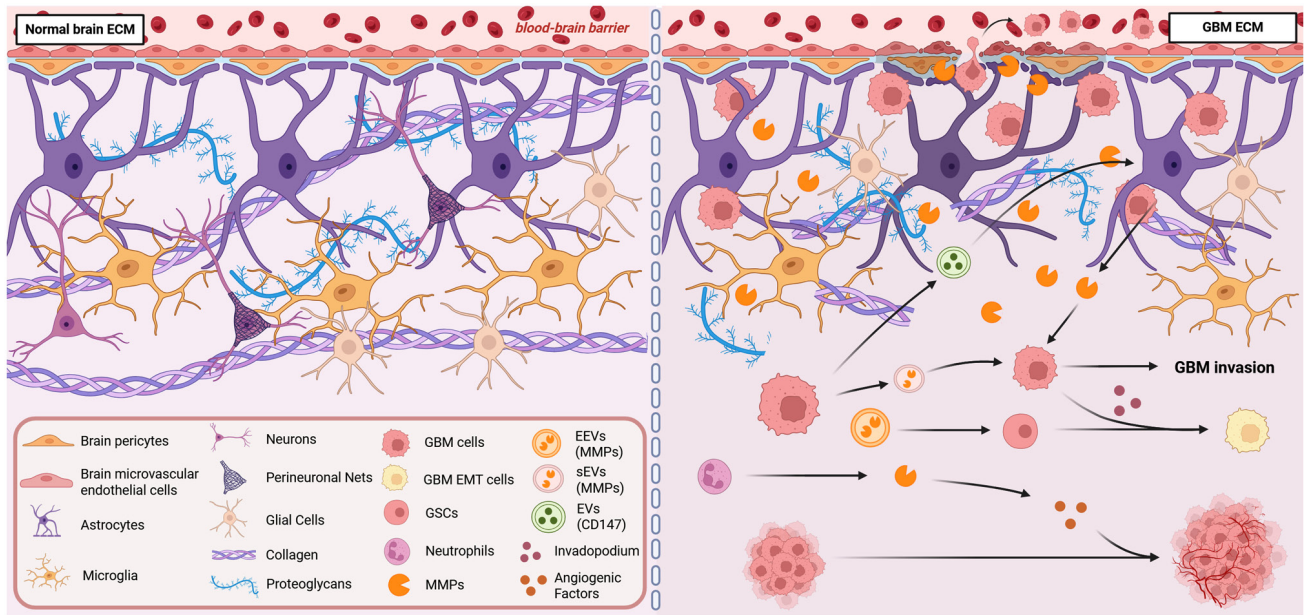


Figure 1. ECM in normal brain tissue vs. GBM. In normal state, the brain ECM is primarily composed of and maintained by brain microvascular endothelial cells, astrocytes, microglia, oligodendrocytes, neurons and the surrounding perineuronal nets. Components such as collagen and proteoglycans are interwoven 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/dxwqg2l>.

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- κ B 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 II α 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).

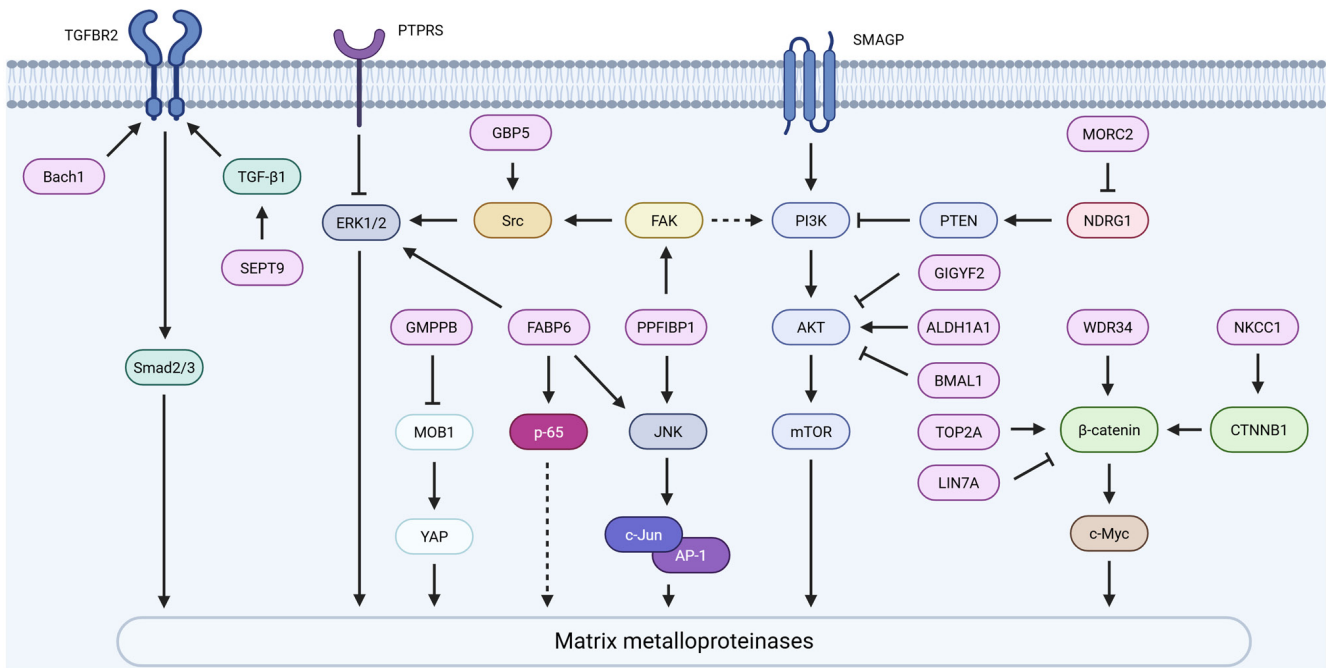


Figure 2. Key signaling pathway networks regulating matrix MMPs. The PI3K/AKT/mTOR, Wnt/ β -catenin, MAPK, TGF- β and Hippo signaling pathways constitute the core network regulating the expression and activity of MMPs. Additionally, key signaling molecules such as FAK and Src are involved. Effector proteins 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. \rightarrow indicates promotion; $---$ indicates an inferred interaction based on literature evidence that has not been directly reported; \perp indicates inhibition. MMP, metalloproteinase. Created in BioRender. Zheng, B. (2025) <https://BioRender.com/dxwqg2l>.

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- β 1. 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- κ B 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 down-regulation of MMP-2, but also reduced the activation levels of p-ERK, p-JNK and p-p65 (NF- κ B), ultimately inhibiting tumor cell invasion. This suggests that FABP6 may influence MMP-2 and consequently GBM invasion by regulating the ERK/JNK/NF- κ B 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

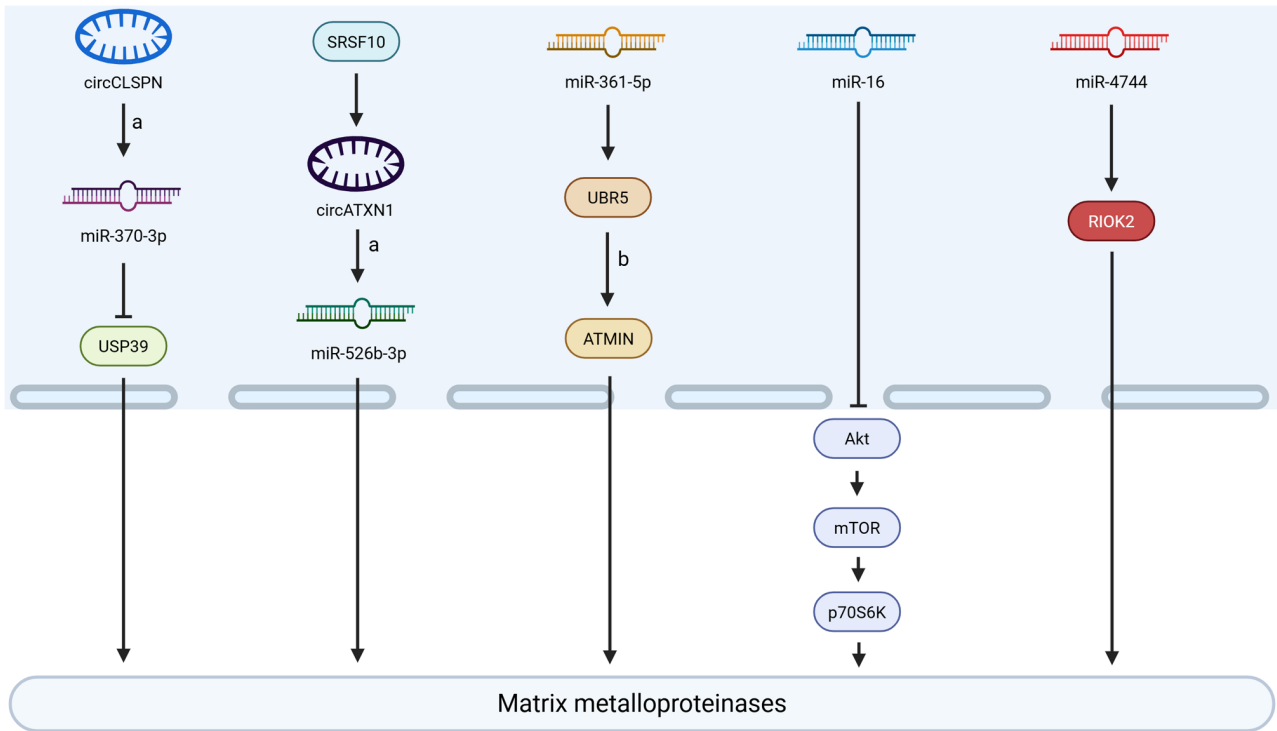


Figure 3. Mechanisms of non-coding RNA regulation of MMPs. Circular RNA primarily functions as a ceRNA, influencing the expression and function of MMPs by sponging miRNAs. Additionally, ubiquitination modifications and related kinases are involved in mediating miRNA-mediated regulation of MMPs. Furthermore, miRNAs can also affect MMPs by modulating the activity of the PI3K/AKT/mTOR 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/dxwqg2l>.

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. ($U\text{-}^{13}C$)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 ($1,000\pm 100$ Gs) treatment was shown to significantly downregulate MMP-2 protein expression in GBM cells. When combined with TGF- β 1, 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 (HIF1 α) 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

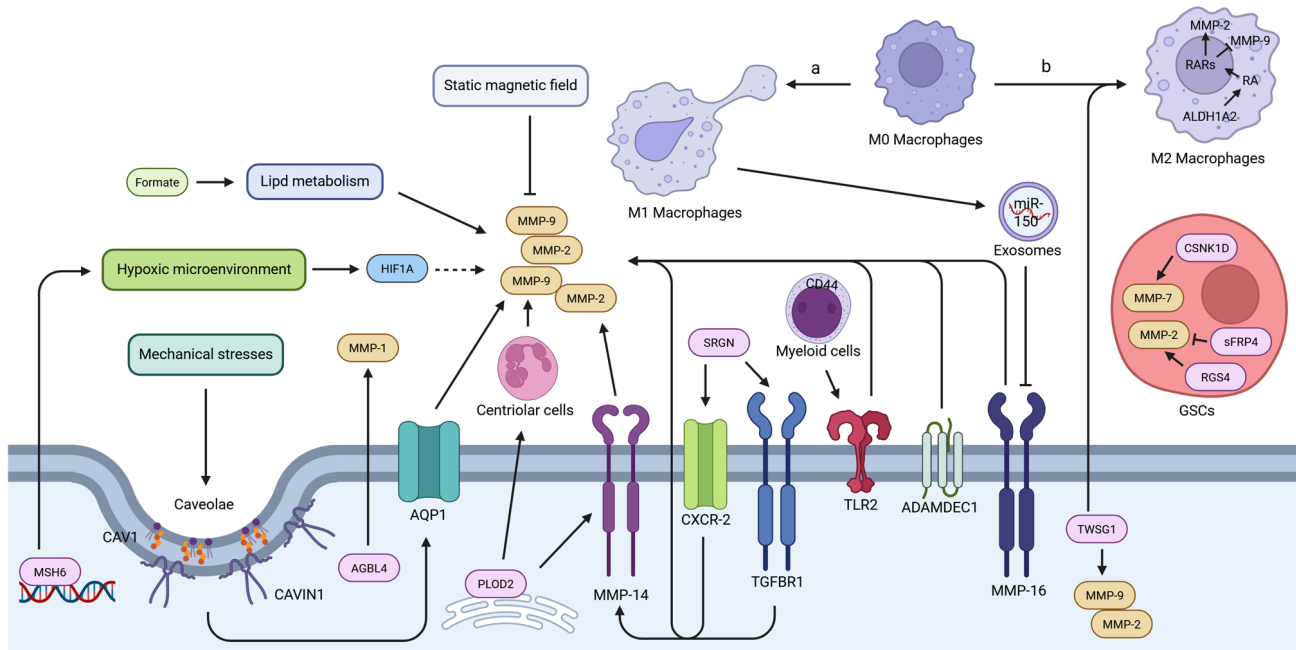


Figure 4. Mechanisms of MMP regulation in the TME. The expression of MMPs is regulated by metabolic reprogramming (lipid metabolism), physical factors (osmotic/hydrostatic pressure and static magnetic fields) and hypoxic conditions within the TME. Cell membrane-associated structures (caveolae), membrane 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/dxwqg21>.

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 nitric 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 AGLB4 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- κ B 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- κ B, 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 NH₄Cl 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- κ B (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, Chrysoerythrin 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-3 β , 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- κ B 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 (PKC α) phosphorylation, an effect reversible by the PKC α 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; PPAR γ agonists (such as pioglitazone and rosiglitazone) and the PPAR α 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- β 2 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 potentially 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 micro-environmental 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-1 α 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 celestrol inhibited GBM cell invasion by upregulating GSK-3 β , 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 PDGFR α . 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 micro-environment, 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.

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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

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Competing interests

The authors declare that they have no competing interests.

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