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Review

Glioma Pathogenesis and Treatment Modality: Novel Insights From Midkine Research

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Abstract

Gliomas, the most common and aggressive primary tumors in the central nervous system, are characterized by high invasiveness and resistance to therapy, making them a major focus of neuro-oncology research. Although substantial progress has been achieved in elucidating their molecular underpinnings in recent years, effective treatment modalities remain limited owing to their complex pathogenesis and tumor microenvironment. Midkine (MDK), a multifunctional growth factor, has increasingly been implicated in glioma pathogenesis and biology. MDK not only contributes to tumor cell proliferation, migration, and therapy resistance, but also plays a pivotal role in modulating the tumor microenvironment. Notably, MDK functions as both an intrinsic oncogenic driver and an extrinsic modulator of the tumor microenvironment, in to the molecular mechanisms underlying glioma pathogenesis that is critical to the formulation of effective treatments, have not comprehensively reviewed. This review summarizes the roles of MDK in various signaling pathways and summarizes recent advances in unraveling the expression patterns and functional roles of MDK and their therapeutic implications and potential as treatment targets for gliomas.

Keywords: midkine; glioma; pathogenesis; tumor microenvironment; therapeutic target

1. Introduction

Gliomas are primary tumors of the central nervous system and encompass various subtypes, such as diffuse astrocytoma, oligodendroglioma, and glioblastoma (GBM). Gliomas are characterized by pronounced heterogeneity, a strong infiltrative behavior, high recurrence rates, and poor prognosis. GBM is the most aggressive among all the subtypes and has an extremely dismal prognosis. The median overall survival of patients with GBM is approximately 15 months, and despite multimodal therapies comprising surgical resection, radiotherapy, and chemotherapy, the tumor remains refractory to cure, with high recurrence rates [1,2]. The marked invasiveness and heterogeneity of gliomas enable tumor cells to extensively infiltrate surrounding brain parenchyma, thereby increasing therapeutic difficulty and the risk of relapse [3]. In addition, complex processes within the tumor microenvironment (TME), including immune evasion, maintenance of glioma stem cells (GSCs), and metabolic reprogramming, further drive tumor progression and therapeutic resistance [4,5].

For newly diagnosed glioblastoma, standard treatment generally consists of maximal safe surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide (TMZ) [6,7]. However, therapeutic outcomes remain suboptimal because of tumor-cell heterogeneity and multiple biological processes that influence glioma progression and treatment responses, including immune modulation within the tumor microenvironment [8,9,10,11], the self-renewal and signaling activity of glioma stem cells [12,13,14], and metabolic reprogramming of tumor and immune cells [15,16,17]. For example, glioma cells can upregulate multiple oncogenic pathways, including Notch and phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR) signaling, to promote proliferation, migration, antiapoptotic capacity, and therapeutic resistance [18,19,20,21,22]. In parallel, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling has been implicated in inflammatory and chemokine-related programs in glioma-associated glial cells [23]. Meanwhile, tumor-associated macrophages (TAMs) contribute to glioma progression by promoting immune escape and neoangiogenesis [24,25].

Advances in molecular biology technologies, particularly single-cell sequencing, spatial transcriptomics, and integrative multi-omics, have provided powerful tools to elucidate glioma pathogenesis [26,27,28,29]. Studies have revealed the diversity of tumor-cell subpopulations, such as mesenchymal (MES)-like subgroups with high invasiveness that are closely associated with tumor recurrence [1], as well as the pivotal role of GSC populations in promoting recurrence and therapeutic resistance [30]. Moreover, metabolic reprogramming and the complex interplay within the TME have emerged as research hotspots [31,32]. However, reviews on the etiology, pathology, and physiological and therapeutic treatments (or lack of) for gliomas have not

paid sufficient attention to the role of midkine (MDK) in gliomas. They predominantly focused on canonical targets such as *isocitrate dehydrogenase* (*IDH*) mutations, *epidermal growth factor receptor* (*EGFR*) amplification, and the receptor tyrosine kinase (RTK)/PI3K/AKT signaling axis, and immune checkpoints, such as programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1). Although these studies have established a critical understanding of the etiological aspects of gliomas and the existing therapeutic modalities, the high recurrence rate suggests that upstream regulators that can bridge these distinct pathways may have been overlooked.

In this context, MDK, a highly conserved heparin-binding growth factor and cytokine, has attracted considerable attention in recent years because of its roles in embryonic development, tissue regeneration, and inflammatory responses [33,34]. MDK plays pro-tumorigenic functions in various solid tumors, participating in cell proliferation, migration, angiogenesis, and immune regulation [35,36]. Elevated MDK expression has been reported in various malignancies and is closely associated with poor prognosis [37]. Mechanistically, MDK promotes the maintenance of tumor cell stemness and TMZ resistance via the Notch1/phosphorylated Jun N-terminal kinase (p-JNK) signaling pathway [38]. Moreover, MDK modulates macrophage polarization within the TME, fostering an immunosuppressive state that facilitates tumor progression [24,39]. Therapeutic strategies targeting MDK and its related signaling pathways, such as the use of the small-molecule inhibitor ACT001, have shown promise in overcoming TMZ resistance and suppressing tumor growth [40]. Furthermore, the interactions of MDK with other signaling mediators offer new avenues for targeted therapy.

Given these factors, gliomas, as highly malignant brain tumors, possess complex pathogenesis and treatment resistance that merit an extensive investigation. Our understanding of tumor-cell subpopulations, signaling pathways, and TME continues to expand. Despite the potential of MDK as a therapeutic target and the increasing understanding about its physiological functions, to the best of our knowledge, no review has related its structure and function to the various aspects of the complex network of gliomas and their occurrence and progression. A systematic overview of the progress of research on MDK in gliomas is crucial for uncovering its oncogenic mechanisms and for the development of precision therapeutic strategies.

2. MDK-Relevant Glioma Milieu: Heterogeneity, Pathway Rewiring, and Immunosuppression

The molecular heterogeneity, pathway rewiring, and immunosuppressive microenvironment of gliomas provide an important framework for interpreting the context-dependent roles of MDK. Within this framework, MDK may function as an extracellular mediator linking tumor-cell-intrinsic signaling with microenvironmental regulation. Gliomas are defined by pronounced molecular and cellular heterogeneities spanning inter-patient, intratumoral, and spatiotemporal dimensions, which collectively determine disease trajectory, therapeutic sensitivity, and recurrence patterns [41,42] (the block shaded in light blue in Fig. 1).

At the molecular level, canonical genetic alterations, such as *IDH* mutations, *1p/19q* codeletion, O6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation, telomerase reverse transcriptase (*TERT*) promoter mutations, *EGFR* amplification, and cyclin-dependent kinase inhibitor 2A/2B (*CDKN2A/B*) deletions, define distinct molecular subgroups that exhibit unique clinical behaviors and therapeutic vulnerabilities [43,44]. Tumors harboring *IDH* mutations generally show favorable prognosis, whereas *IDH*-wildtype diffuse astrocytic gliomas, particularly those with molecular features of glioblastoma, are associated with aggressive biological behavior and poor clinical outcomes [45,46,47,48]. Genome-wide and epigenetic alterations, including copy-number changes, driver gene rearrangements, the glioma CpG island methylator phenotype, and remodeling of chromatin accessibility, collectively reprogram three major signaling axes, namely RTK/RAS/PI3K, tumor protein 53 (p53), and retinoblastoma (RB), thereby shaping parallel oncogenic routes and clonal evolutionary trajectories [49,50]. Single-cell multiomics maps highly plastic cellular-state lineages, with tumor cells dynamically traversing neurodevelopment-related coordinates (e.g., neural progenitor-like, oligodendrocyte progenitor-like, and astrocyte-like), while mesenchymal-axis GSCs become enriched under hypoxia, inflammation, and therapeutic stress and drive invasion, resistance, and immune escape [51]. The metabolic network is broadly rewired (glycolytic shift, enhanced purine/pyrimidine biosynthesis, and lipid and one-carbon metabolism remodeling) to support rapid proliferation and DNA repair, and metabolic by-products (e.g., 2-hydroxyglutarate (2-HG) arising from *IDH* mutations) alter DNA/histone methylation, forming a "metabolism–epigenetics–phenotype" feedback loop [52]. Spatial heterogeneity manifests as marked regional differences in gene expression, metabolic features, and immune infiltration within the same lesion, with juxtaposition of distinct molecular subtypes and even histological grades, complicating precise sampling, diagnostic stratification, and therapy design [53,54]. Overall, molecular heterogeneity underlies divergent treatment responses and recurrence, providing the foundation for multitarget combination and individualized intervention strategies. These heterogeneous molecular backgrounds may also influence the extent to which MDK contributes to glioma progression, immune remodeling, and therapeutic resistance.

At the level of signaling pathways and regulatory mechanisms, the oncogenic network in glioma cen-

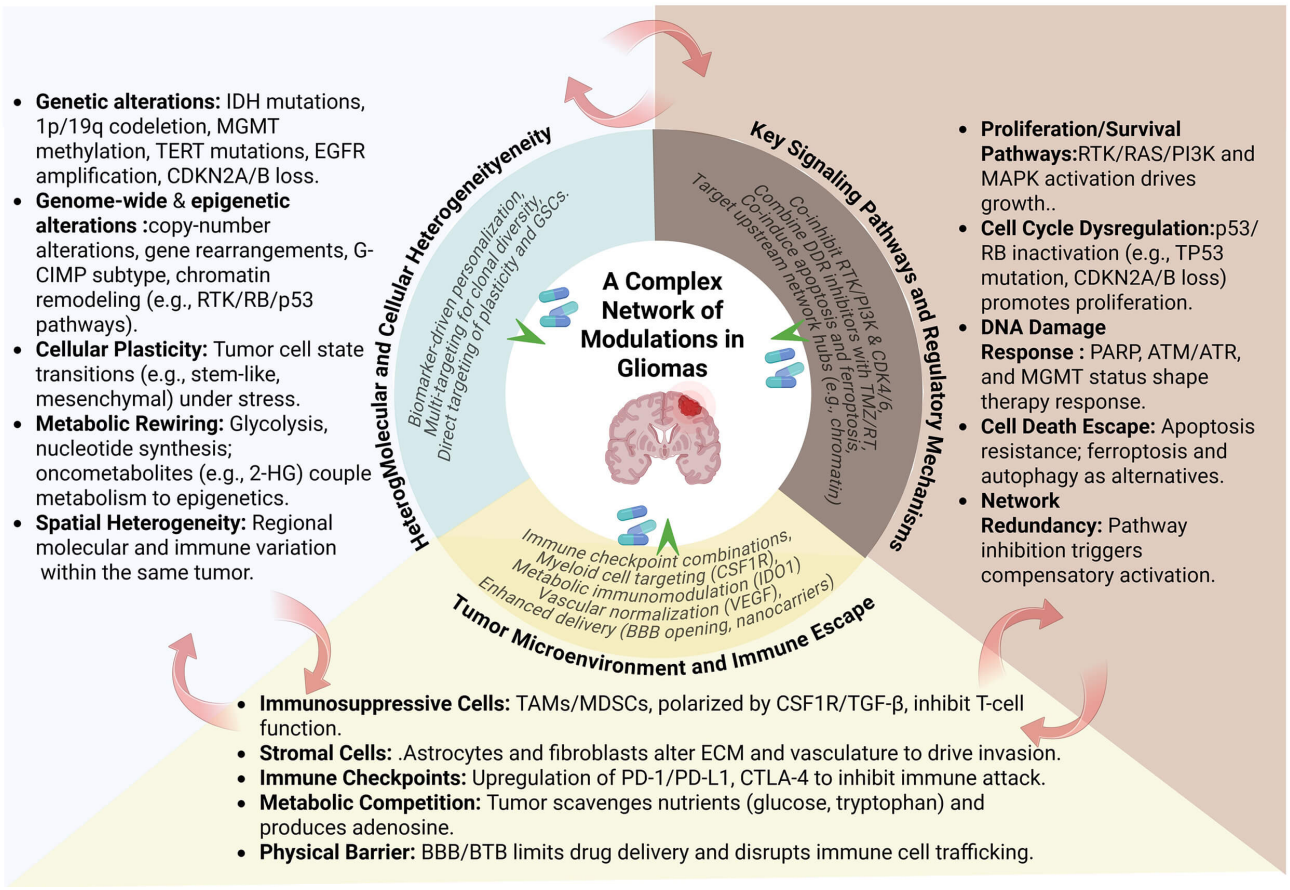

Fig. 1. Interconnected network driving glioma pathogenesis and therapeutic resistance. IDH, isocitrate dehydrogenase; MGMT, O6-methylguanine-DNA methyltransferase; TERT, telomerase reverse transcriptase; EGFR, epidermal growth factor receptor; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/2B; RTK, receptor tyrosine kinase; 2-HG, 2-hydroxyglutarate; TAMs, tumor-associated macrophages; MDSCs, myeloid-derived suppressor cells; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen-4; BBB, blood–brain barrier; BTB, blood–tumor barrier. Created in BioRender. 2026. (https://BioRender.com/4h4mhc4).

ters on proliferation, survival, cell-cycle control, programmed cell death, and DNA damage response (DDR), and is systematically sculpted by upstream RTKs and epigenetic programs (the block shaded in light brown in Fig. 1). The RTK/RAS/PI3K and mitogen-activated protein kinase axes are constitutively activated by amplifications/mutations of *EGFR*, platelet-derived growth factor receptor alpha (*PDGFRA*), mesenchymal-epithelial transition factor (*MET*), among others, driving growth, metabolic adaptation, and anti-apoptosis [55,56]. Dysregulation of the p53 and RB axes, mouse double minute 2/4 (*MDM2/4*) amplification, *CDKN2A/B* loss, and cyclin-dependent kinase 4/6 (*CDK4/6*) amplification, lifts constraints on the cell cycle and genomic stability barriers, promoting malignant progression [50]. The DNA damage response (DDR) network, including poly (ADP-ribose) polymerase (PARP), serine/threonine-protein kinase ATR (ATR), ATR/checkpoint kinase 1 (CHK1), serine-protein kinase ATM (ATM), and DNA repair protein RAD51 homolog 1 (RAD51) is dynamically modulated during TMZ and radiotherapy, and together with *MGMT* promoter methylation and mismatch repair status, determines chemoradiosensitivity and acquired resistance [57,58]. Within cell-death programs, the B-cell lymphoma 2 (BCL-2) family and the inhibitor of apoptosis proteins (IAPs) modulate the apoptotic threshold, and ferroptosis glutathione peroxidase 4 (GPX4), cystine/glutamate antiporter system Xc− (system Xc−), lipid peroxidation, and autophagy provide alternative survival routes, forming an elastic buffer against therapeutic stress [59,60]. Metabolic nodes, including mutant IDH, dihydroorotate dehydrogenase (DHODH) and glutaminase (GLS), serve as key interfaces among energy metabolism, biosynthetic demand, epigenetic remodeling, and therapeutic vulnerability in glioma [61,62,63]. Despite the large number of pathway targets, inhibition of a single pathway is frequently offset by cellular-state plasticity, network redundancy, and TME-mediated adaptive resistance. Hence, there is an urgent need to pinpoint upstream regulators with pathway-integrating functions (e.g., chromatin remodeling complexes, super-enhancer-driven tran-

scriptional programs, and stress-response transcription factors) and extracellular mediators (cytokines, chemokines, and exosomal cargo) to dismantle resistance via cross-pathway coupling. Derived strategies include parallel inhibition of RTK/PI3K and CDK4/6 to simultaneously suppress proliferative and cell-cycle drivers, combining DDR inhibitors with TMZ/radiotherapy to amplify lethality, co-targeting apoptotic and ferroptotic pathways to overcome death escape, and metabolism epigenetics co-interventions to sever malignant homeostatic loops. In this context, MDK is particularly relevant because it can interface with several glioma-associated programs, including Notch/p-JNK-mediated stemness, ALK-PI3K/AKT/mTORC1 signaling, p53-associated microenvironmental remodeling, and c-Myc/Wnt/β-catenin-related malignant progression.

TME and immune escape constitute another core dimension of glioma refractoriness [64] (Refer to the light yellow section of Fig. 1 for details). TME is profoundly immunosuppressive, dominated by TAMs and myeloid-derived suppressor cells (MDSCs), which are polarized through colony-stimulating factor 1 (CSF1)/colony-stimulating factor 1 receptor (CSF1R), thus transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and related axes to suppress effector T-cell function and antigen presentation [65,66]. Tumor-associated astrocytes, fibroblast-like cells, endothelial cells, and pericytes cooperatively change the extracellular matrix (ECM) and vascular ecology, promoting invasion and aberrant angiogenesis [67,68]. A bidirectional signaling network of cytokines, chemokines, and extracellular vesicles not only sustains GSCs and MES-like transdifferentiation but also orchestrates recruitment, polarization, and exhaustion of immune cells across compartments. Immune checkpoints,such as programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4), are induced by the inflammatory/therapeutic process, coupled with metabolic competition (glucose, tryptophan, and lipid substrates) and the hypoxia–adenosine axis. They collectively blunt antitumor immunity. Dynamic abnormalities of the blood–brain barrier (BBB)/blood–tumor barrier (BTB) permit the ingress of inflammatory factors and myeloid cells while restricting effective drug delivery to tumor cores and invasive margins, yielding heterogeneous drug distribution and dysregulated immune control. Accordingly, strategies are shifting from “point-wise inhibition” to “network-level” integrated interventions. This network-level view is consistent with the proposed role of MDK as a mediator linking tumor-cell signaling, macrophage/microglial polarization, immune suppression, and therapeutic resistance.

On the immune front, aside from PD-1/PD-L1 and CTLA-4, combination regimens targeting myeloid axes (CSF1R and TGF-β), metabolism–immunity interfaces (indoleamine 2,3-dioxygenase 1/tryptophan pathway, and adenosine axis), vascular normalization (vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) combinations), and exosome-mediated communication are under active exploration. In drug delivery, ultrasound-mediated BBB opening, engineered nanocarriers, and convection-enhanced delivery are being paired with pathway/immune interventions to enhance spatiotemporally precise intratumoral exposure and counter TME-dominated adaptive resistance.

With regard to major therapeutic targets, classical targets such as EGFR and VEGF serve as the entry points for early precision therapy, and *EGFR* amplification/mutations and VEGF-driven angiogenesis can yield radiographic responses and symptomatic relief in selected patients. However, acquired resistance and limited durability are common, and effective drug delivery is hindered by BBB [69]. Among emerging targets, *IDH* mutations drive tumor phenotypes and TME remodeling via dual metabolic and epigenetic routes, and have entered clinical evaluation with preliminary feasibility signals [70,71]. *TERT* promoter alterations and telomere-maintenance mechanisms represent important molecular features in glioma biology and may provide additional opportunities for risk stratification and therapeutic exploration [72]. Additional target classes span metabolic enzymes (DHODH and GLS), the cell-cycle axis (CDK4/6), the DDR network (PARP, ATR/CHK1, ATM), and cell-death programs (BCL-2 family, IAPs, and ferroptosis regulators), constituting a multilayered intervention landscape. In immunotherapy, PD-1/PD-L1 and CTLA-4 inhibitors show efficacy in selected populations but are broadly constrained by immunosuppressive TME and BBB barriers [73,74]. Combination strategies, including checkpoint blockade combined with tumor vaccination, oncolytic virotherapy, chimeric antigen receptor T-cell (CAR-T)/chimeric antigen receptor natural killer cell (CAR-NK) cell therapies, myeloid reprogramming, and metabolic and immune modulation, are gaining traction to reprogram the tumor immune microenvironment, improve therapeutic delivery, and sensitize tumors to treatment. Current translational evidence underscores that monotherapies rarely suppress multiaxis redundancy and cellular-state plasticity effectively. A promising path forward is biomarker-guided, multi-target combinations delivered concurrently, sequentially, or adaptively; examples include dual RTK/PI3K and CDK4/6 blockade to suppress proliferative drivers, DDR inhibition with TMZ, radiotherapy to potentiate cytotoxicity, parallel induction of apoptosis and ferroptosis to override intrinsic resistance mechanisms and combined metabolic and epigenetic therapy to disrupt malignant homeostasis. In parallel, enhancing BBB/BTB permeability and deploying localized delivery techniques should enable adequate exposure in tumor cores and infiltrative fronts.

Taken together, glioma heterogeneity, signaling redundancy, and TME-mediated resistance provide the biological framework in which MDK should be interpreted.

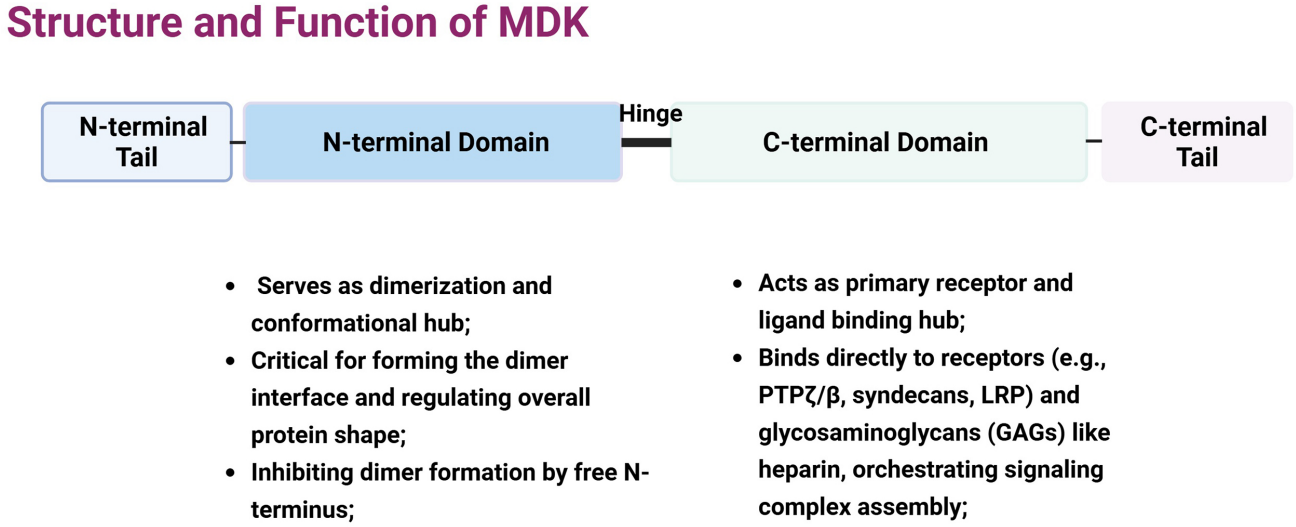

Fig. 2. Structure and functions of MDK. MDK, midkine. Created in BioRender. 2026. (https://BioRender.com/txrvoq7).

Rather than acting as a single universal driver, MDK may function as a context-dependent mediator linking tumor-cell-intrinsic signaling, stemness, immune suppression, and therapeutic resistance. This MDK-centered perspective provides the rationale for discussing its structure, expression patterns, functional roles, and therapeutic potential in the following sections.

3. Biological Characteristics of MDK

3.1 Structure and Function of MDK

MDK is a small, pleiotropic cytokine and a prototypical heparin/heparan sulfate-binding growth factor. It has a molecular mass of 15,585 Da and comprises 143 amino acids. As shown in Fig. 2, MDK consists of an N-terminal signal peptide that directs secretion and a mature polypeptide. The mature chain contains N- and C-terminal domains,connected by a hinge region; each domain consists of three antiparallel β-strands and is stabilized by disulfide bonds [75,76].

In terms of functions (Fig. 2), the N- and C-terminal domains cooperate in dimerization; Specifically, the N-terminus plays a critical role in the dimer interface and global conformational regulation. A free N-terminus can act as a dominant-negative fragment to suppress dimer formation. By contrast, the C-terminus serves as the principal hub for binding receptors and glycosaminoglycans (GAGs), such as heparin/chondroitin sulfate, thereby orchestrating the assembly of signaling complexes with protein tyrosine phosphatase zeta/beta (PTPζ/β), syndecans, and low-density lipoprotein receptor-related protein (LRP) and triggering downstream pathways that underlie neurite outgrowth, cell migration, and related activities. Truncation of either terminal tail markedly weakens neuritogenic activity; notably, an isolated C-terminal domain lacking its own C-tail can retain substantial activity, suggesting that the terminal tails primarily maintain the correct N/C domain orientation and thus exert indirect effects.

The C-terminal domain principally determines most of MDK's biological effects, including promotion of neuronal survival, regulation of cell migration and adhesion, fibrinolysis-/thrombosis-related activities, and chemotactic and immunomodulatory roles within inflammatory microenvironments. The conformational features of the C-terminal hairpin loop and C-tail can form "pocket/groove"-like surfaces that enhance selectivity for distinct sulfation patterns of GAGs and are linked to reported antimicrobial activity. The N-terminal domain functions largely as a structural and functional "synergist", that is, together with the C-terminus, it stabilizes the overall structural folding, may participate in low-affinity protein–protein contacts and spatial orientation, and improves the efficiency of C-terminus–mediated receptor complex assembly. Deletion- and mutation-based studies have indicated that preservation of the C-terminal domain is often sufficient to maintain major heparin binding and signal-transduction capacity.

Overall, MDK is ideally characterized as a C-terminus–dominated GAG-sensing, signaling-assembly module, with the N-terminus providing structural support and fine-tuning of interactions. The coordinated actions of both termini underpin MDK's pleiotropy across development, regeneration, cancer, and inflammation [34].

3.2 Spatiotemporal and Pathology Specific Expression Patterns of MDK

MDK expression is developmentally regulated. During embryogenesis, MDK is highly expressed in multiple developing tissues and contributes to cell proliferation, survival, migration, neurogenesis, and organogenesis [77,78]. Studies of the midkine family in vertebrate models further demonstrate its important roles in nervous system formation and development [79,80].

In healthy adult tissues, MDK expression declines to very low levels, and weak expression is maintained only in select sites (e.g., renal tubular epithelial cells, respiratory epithelium, endothelial cells, skin, and subsets of immune cells) Such low-level expression helps maintain the local tissue microenvironment, cellular homeostasis, and localized repair capacity. Within the CNS, MDK is primarily expressed by oligodendrocyte progenitor cells, embryonic astrocytes, neurons, and newly generated oligodendrocytes. In the human embryonic brain, astrocytes constitute a major source of MDK. *In vitro*, activated astrocytes and neurons express MDK, whereas microglia show minimal expression. Under stress and pathological conditions, such as trauma and inflammation, MDK expression is markedly induced, promoting cell repair, antiapoptotic signaling, and tissue regeneration.

In healthy populations, plasma MDK concentrations in children are approximately 116–483 pg/mL (median ≈ 205 pg/mL), and median levels in adult serum are around 154 pg/mL. A threshold of 500 pg/mL is often used as a reference cutoff to indicate abnormally elevated levels [81,82]. Multiple studies have indicated that MDK participates in the growth and differentiation of CNS tumors [83,84]. Broadly, MDK has been reported to be upregulated in multiple malignancies and is associated with tumor progression and poor prognosis [77]. High MDK expression promotes tumor cell proliferation, migration, resistance to apoptosis, angiogenesis, and immune evasion.

4. MDK Expressions and Roles in Gliomas

4.1 MDK Expression in Glioma Cells

MDK is a neurotrophic factor that exhibits aberrant overexpression across multiple cancers, with particularly high levels in GBM [40,85,86]. *MDK* is substantially overexpressed in gliomas according to analyses of two human cohorts from the Gene Expression Omnibus (GEO) (sample sizes of 100 and 180), and its expression increases with increasing World Health Organization (WHO) grades. Specifically, grade IV tumors exhibit a higher *MDK* expression level than grade II tumors (Bonferroni-corrected $p = 0.002$), and grade III and grade IV tumors show higher expression than non-tumor controls ($p = 0.044$ and $p < 0.001$, respectively). After adjusting for WHO grade and age, Kaplan–Meier analysis showed that high *MDK* expression is significantly associated with poorer overall survival (hazard ratio for death 2.38; 95% CI: 1.22–4.63) [85].

Ma et al. [87] reported that an elevated expression of *MDK* in gliomas independently predicts poor overall survival and early recurrence, and its co-overexpression with pleiotrophin confers strong prognostic value for unfavorable outcomes. Moreover, *MDK* expression is closely correlated with the WHO grade, Karnofsky performance status, and patient survival time. Array comparative genomic hybridization revealed frequent copy number gains in the 11p11.2–q13.2 region harboring the *MDK* gene in gliomas, a feature tightly linked to malignant progression. Notably, the gain frequency of *MDK* reaches 50% in low-grade gliomas and GBM [88].

Additional studies have shown that MDK expression in GBM cells is markedly higher than that in normal brain tissue and correlates with tumor aggressiveness and prognosis [38,85,89]. Patients with *MDK*-high gliomas are classified as high risk and have short overall survival. A risk index incorporating *MDK* predicts prognosis independently of known factors such as age, chemotherapy, radiotherapy, *IDH* mutation, and *1p/19q* codeletion, and has been validated in two independent datasets [90]. *MDK* overexpression is associated with stem-like tumor cell properties, enhancing self-renewal capacity and therapeutic resistance [84]. In GBM, *MDK* expression also presents an inverse relationship with its methylation status [91].

Collectively, *MDK* expression levels are closely associated with glioma progression and patient outcomes. *MDK* has also been included in methylation-driven prognostic models for GBM, although its utility for monitoring therapeutic response requires further validation [92,93]. This expression pattern underscores MDK's role in glioma progression and provides a rationale for its development as a candidate therapeutic target and an important prognostic biomarker in gliomas.

4.2 Interactions Between MDK and the Tumor Microenvironment

MDK plays a pivotal role in glioma TME. By modulating the release of cytokines and chemokines in TME, MDK enhances tumor cell survival and therapeutic resistance. Its interaction with various cellular components, including tumor cells and immune cells, further promotes immune evasion in gliomas [38].

A growing body of evidence indicates that MDK regulates immune cell polarization, notably promoting M2 polarization of macrophages. This polarization confers immunosuppressive properties on tumor-associated macrophages, thereby facilitating tumor growth and metastasis. Additional studies have shown that *MDK* is transcriptionally upregulated by p53, a central factor in the DDR pathway, which in turn drives microglia toward an M2-like phenotype, reshaping and reinforcing immunosuppressive TME in GBM [94]. In EGFRvIII positive GBM, MDK secretion is upregulated via the extracellular signal-regulated kinase (ERK)/c-Fos pathway. It then activates the macrophage receptor low-density lipoprotein receptor-related protein 1 (LRP1) to promote M2 polarization and induce C-X-C motif chemokine ligand 1 secretion, recruiting immunosuppressive cells, sculpting an immunosuppressive TME, and accelerating tumor progression [24] (cf. Fig. 1). Furthermore, MDK induces chemokines and immunosuppressive factors (e.g., C-C motif chemokine ligand 17, IL-10, granulocyte-macrophage colony-stimulating factor, and PD-L1), reprograms myeloid cells, and pro-

motes regulatory T cell (Treg) recruitment and aberrant angiogenesis, thereby establishing an "inflammation-immunosuppression-invasion" phenotype. Functional assays have revealed that recombinant MDK can directly induce macrophages to secrete multiple immunoregulatory factors and that a subset of these effects can be reversed by MDK neutralization [93].

Altogether, the aforementioned findings suggest that therapeutic strategies targeting MDK may help restore immune-cell function and enhance the efficacy of antitumor immunotherapies, particularly in tumor types with high MDK expression.

4.3 MDK-Mediated Additional Signaling Pathways

MDK is an important neurotrophic factor involved in diverse biological processes. In gliomas, MDK signals through multiple pathways (Fig. 3). Studies have demonstrated that MDK enhances the stem-like properties of glioma cells, including the expression of cluster of differentiation 133 and Nanog, through modulation of the Notch1/p-JNK signaling pathway, thereby promoting tumor growth, inhibiting apoptosis, increasing invasiveness, and conferring resistance on chemotherapeutic agents such as TMZ [38]. In addition, MDK activates the receptor tyrosine kinase anaplastic lymphoma kinase (ALK), integrates upstream growth factor signals, and augments PI3K/AKT/mechanistic target of rapamycin complex 1 (mTORC1) activity, thereby broadly suppressing autophagy and fostering malignant phenotypes. This signaling axis displays context-dependent functional diversity. First, MDK/ALK suppresses the endoplasmic reticulum stress p8/tribbles homolog 3 (TRB3) pathway and the initiation of autophagy, enabling tumor cells to tolerate cannabinoid tetrahydrocannabinol (THC)-induced autophagic cell death [95,96]. Second, in glioma initiating cells (GICs), MDK/ALK sustains stemness networks and tumorigenicity, and blockade of this axis relieves autophagy suppression, triggering autophagy–lysosome–mediated selective degradation of the key transcription factor SRY-box transcription factor 9 (SOX9), thereby reducing stemness markers and sphere-forming capacity [84]. Thus, MDK/ALK functions both as an upstream driver of drug resistance and as a central node for stemness maintenance. Pharmacologic inhibition (e.g., ALK inhibitors) can be combined with TMZ or cannabinoids to synergistically activate autophagy and enhance therapeutic efficacy against GICs and overall tumor burden (cf. Fig. 3).

MDK signaling is also linked to cell cycle regulation and apoptosis. Inhibition of MDK can reduce glioma cell viability by inducing cell cycle arrest and apoptosis driven by oxidative stress. It can also modulate ECM degradation and the expression of motility-associated proteins, thereby influencing cell migration [97]. MDK further serves as a critical connector within the DDR pathway. Acting as a molecular bridge between altered DNA repair and remodeling of glioma TME, MDK expression is directly regulated by p53, a core DDR transcription factor [94]. One of us has demonstrated that MDK directly interacts with cellular Myc (c-Myc), stabilizing it by modulating its ubiquitination and degradation, which in turn activates Wnt/β-catenin signaling, upregulates pro-survival and epithelial–mesenchymal transition (EMT) programs, and promotes malignant progression and TMZ resistance in gliomas [40]. Multiomics and single-cell studies have indicated that MDK drives proliferation, EMT, and ECM remodeling, accompanied with the activation of pathways, such as MYC, DNA repair, and oxidative phosphorylation [93]. Under extracellular acidic stress, MDK is upregulated as an acyl-CoA synthetase long-chain family member 5-dependent downstream effector to promote cell survival, thereby facilitating tumor adaptation and progression in a hostile microenvironment [98]. The transcription factor specificity protein 1 can also bind directly to the *MDK* promoter to regulate its expression and thereby influence glioma cell proliferation [86]. Moreover, hypomethylation of the *MDK* promoter may underlie the high expression of *MDK* observed in high-grade tumors [97]. Overall, the signaling processes orchestrated by MDK in glioma progression can be targeted in new therapeutic approaches.

5. Therapeutic Potential of MDK

5.1 Current Status of MDK Inhibition

As mentioned above, MDK plays an important role in the onset and progression of various cancers. In recent years, research on inhibitors targeting MDK has drastically accelerated, highlighting its potential as a therapeutic target in oncology [99,100]. For example, MDK modulates immune cell polarization within TME and promotes tumor immune evasion to negatively affect the therapeutic outcome [101].

Multiple preclinical studies on MDK targeting inhibitors are underway. MDK has emerged as a potential therapeutic target for drug development in malignant tumors and other diseases [102]. In addition, MDK signaling shows promising implications for other cancer types such as prostate and colorectal cancers [103,104]. The MDK inhibitor iMDK can induce cell cycle arrest and apoptosis in multiple myeloma cells and primary effusion lymphoma cells [105,106]. Moreover, iMDK can also suppress tumor growth and angiogenesis in oral squamous cell carcinoma [107]. Another study identified HBS-101 as the first orally available small-molecule MDK inhibitor; it inhibits the AKT/mTOR, the signal transducer and activator of transcription 3 (STAT3), and NF-κB pathways. HBS-101 also substantially reduces cell viability in triple-negative breast cancer and curbs the growth of brain metastases while exhibiting favorable BBB permeability [108]. ACT001 has been found to specifically disrupt the MDK/c-Myc complex, thereby reversing TMZ resistance and markedly enhancing therapeutic efficacy [40].

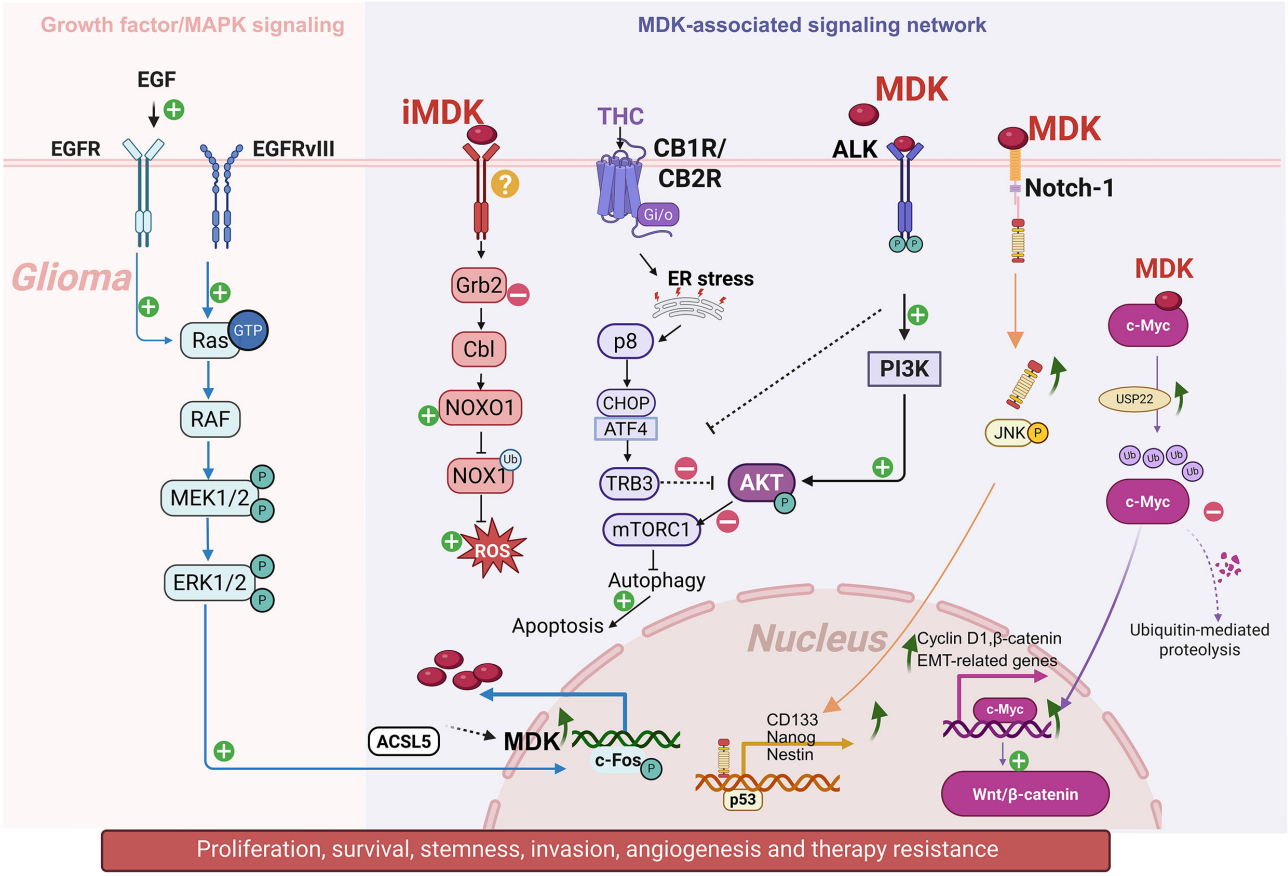

Fig. 3. MDK-associated signaling pathways in glioma cells. The figure illustrates two interconnected components: growth factor/MAPK signaling and the MDK-associated intracellular signaling network, which collectively regulate glioma cell proliferation, survival, stemness, invasion, angiogenesis, and therapy resistance."+" and "−" indicate positive and negative regulation, respectively; dashed lines indicate indirect or putative regulatory relationships; and "?" indicates an unidentified receptor or unclear intermediate mechanism. THC, tetrahydrocannabinol; ALK, anaplastic lymphoma kinase; iMDK, MDK inhibition; CHOP, C/EBP homologous protein; ATF4, activating transcription factor 4; ACSL5, Acyl-CoA Synthetase Long-Chain Family Member 5. Created in BioRender. 2026. (https://BioRender.com/2qy9a24).

Combining MDK inhibition with other therapeutic approaches has gained momentum. In hepatocellular carcinoma (HCC), iMDK, combined with lenvatinib, synergistically inhibits tumor angiogenesis and M2 macrophage infiltration while mitigating Lenvatinib-related adverse effects (e.g., pericardial effusion) [109]. Furthermore, studies in colorectal cancer show that inhibiting the CDK7/MDK axis can reverse irinotecan resistance, suggesting that MDK inhibitors may serve as chemosensitizers [110]. In melanoma, MDK suppresses dendritic cell (DC) function via the STAT3 pathway, leading to resistance to immune checkpoint inhibitors. Downregulating MDK can restore DC activity and enhance the efficacy of immunotherapy [39]. In neuroblastoma, multi-omics analyses identified both MIF and MDK as candidate immunosuppressive targets; however, functional enhancement of CAR-T-cell activity in that study was demonstrated primarily through MIF depletion or degradation, whereas the role of MDK remained context-dependent and unclear [111].

5.2 Prospects and Challenges of MDK in Clinical Applications

MDK shows broad prospects as a therapeutic target, but targeting it has faced several challenges in clinical studies. Many current inhibitors have undergone preliminary efficacy and toxicity evaluations. For example, HBS-101 achieves a tumor inhibition rate of over 50% in mouse models at a 5 mg/kg dose, with no observed organ toxicity or weight loss [108]. iMDK has likewise shown controllable effects on normal tissues in animal studies [109].

Despite the promising antitumor activity of MDK-targeted strategies in preclinical studies, glioma-specific clinical validation remains limited. Current evidence is mainly derived from glioma preclinical studies on ACT001-mediated disruption of the MDK/c-Myc complex and from nonglioma cancer models evaluating MDK inhibitors, such as iMDK and HBS-101 [40,107,108]. Therefore, no completed clinical trial has directly established the safety and efficacy of MDK inhibitors in glioma patients.

ACT001-based clinical regimens, including ACT001 combined with anti-PD-1 therapy in surgically accessible recurrent glioblastoma and ACT001 treatment for diffuse intrinsic pontine glioma (DIPG)- or H3K27-altered high-grade gliomas (ClinicalTrials.gov identifiers: NCT05053880 and NCT06838676), are currently being explored for brain tumors. However, these studies are not designed exclusively as MDK inhibitor trials. Future studies should clarify MDK target engagement, CNS pharmacokinetics, intratumoral exposure, safety, and combination efficacy in glioma patients.

Moreover, the expression and function of MDK may be heterogeneous across different tumor types, implying that the therapeutic efficacy of MDK inhibitors may depend on the cancer subtype and other patient-specific factors [110]. Given the diverse biological functions of MDK, its inhibition may lead to unforeseen side effects, which should be carefully considered in the process of drug development [100,104]. Furthermore, determining how to effectively combine MDK inhibitors with existing therapies (e.g., chemotherapy and immunotherapy) to improve outcomes is critically needed in future research.

5.3 Translational Potential of MDK Inhibition in Gliomas and Prospects for Combination Therapy

Although systematic studies directly targeting brain gliomas (especially GBM) remain scarce, multiple lines of evidence have exhibited feasibility and suggested prioritization for translational applications in gliomas based on the existing MDK inhibitors.Small-molecule MDK inhibitors, such as iMDK and the recently reported oral inhibitor HBS-101, have demonstrated antitumor activity in several non-glioma cancer models. iMDK has been shown to induce cell-cycle arrest and apoptosis and to suppress tumor growth and angiogenesis, whereas HBS-101 suppresses AKT/mTOR, STAT3, and NF-κB signaling and demonstrates BBB permeability [108,109,110,111]. These features closely align with the oncogenic axes mediated by MDK in gliomas, including PI3K/AKT, Notch/JNK, c-Myc, and Wnt/β-catenin pathways, suggesting their potential mechanistic portability. Moreover, functional studies have shown that blocking the MDK/ALK axis within glioma stem cell populations substantially reduces self-renewal, weakens TMZ resistance, and, when combined with TMZ, nearly eradicates GICs. On the basis of the finding that MDK drives M2 polarization in the immunosuppressive GBM microenvironment via receptors, such as LRP1, the multimodal combination approach on the basis of MDK inhibitors + chemotherapy/radiotherapy/immunotherapy may deliver dual benefits of sensitization and immune reprogramming.

Thus, immediate research priorities in the glioma field should include screening MDK inhibitor candidates with high BBB permeability (including optimizing delivery systems, such as liposomes, polymeric nanoparticles, and convection-enhanced delivery), validating effects on GIC suppression and TME remodeling in orthotopic and patient-derived xenograft models, and systematically evaluating synergy with TMZ, anti-PD-1/PD-L1 agents, and antiangiogenic drugs. In parallel, companion biomarkers centered on MDK expression/secretion levels, downstream signaling activation profiles, and immune infiltration features should be developed to enable patient stratification and response monitoring. These points are summarized in Table 1.

Overall, although glioma-specific clinical evidence is still lacking, the strong convergence between cross-cancer pharmacological findings and glioma mechanistic biology suggests that MDK inhibition may represent a highly plausible translational strategy constructed over a solid biological rationale and feasible implementation approaches, warranting further pharmacokinetic/pharmacodynamic investigation and early-phase clinical exploration in GBM.

6. Outlook

The preclinical results for MDK-targeted therapy in glioma are promising. However, clinical translation faces notable challenges. Future research must move beyond efficacy in xenograft models to address human physiological complexity. Key priorities include rigorous safety profiling, development of next-generation inhibitors, and overcoming CNS delivery barriers. Along this line, we anticipate that the field will put emphasis on and progress to the research of the following aspects.

(1) Safety profiling and off-target evaluation in human-relevant models.

A major translational challenge is to define the therapeutic window of MDK inhibition. A critical gap is the evaluation of MDK inhibition of normal tissue homeostasis. MDK expression is low in healthy adults but rises transiently during tissue repair, inflammation, or ischemia. In pathogen-free animal models, the demand for this repair is minimal; this potentially masks toxicity. By contrast, patients with glioma often face systemic stress from chemotherapy or surgery. In this context, systemic MDK inhibition might impair wound healing or aggravate renal and cardiac issues. Therefore, toxicology studies must define a precise therapeutic window. Intermittent dosing strategies could potentially balance antitumor efficacy with tissue maintenance. Furthermore, we must screen for off-target effects in human-relevant organoids, rather than relying solely on murine systems.

(2) Development of selective and BBB-penetrant MDK-targeted agents.

The development of selective and BBB-penetrant MDK-targeted agents is essential for the clinical translation of MDK-targeted therapy in glioma. Currently available or recently reported agents, such as iMDK and HBS-101, provide important proof-of-concept evidence, but further optimization is still required in terms of potency, specificity, pharmacokinetics, CNS exposure, and

Table 1. Mechanisms, indications, preclinical evidence, and translational prospects of MDK inhibitors relevant to glioma treatment.

Inhibitor name	Mechanism of action	Indications	Preclinical evidence and translational prospects
iMDK	Induces cell-cycle arrest and apoptosis; suppresses tumor growth and angiogenesis in preclinical models	Multiple myeloma, primary effusion lymphoma, and oral squamous cell carcinoma	Demonstrates antitumor activity in multiple preclinical tumor models
HBS-101	Oral small-molecule inhibitor that inhibits AKT/mTOR, STAT3, and NF-κB pathways and induces cell-cycle arrest and apoptosis	Triple-negative breast cancer	Shows promising BBB permeability, potential in gliomas
ACT001	Disrupts MDK/c-Myc complex and enhances TMZ efficacy	Glioma and other solid tumors	Preclinical studies show efficacy in gliomas, with promising results in animal models
MDK/ALK axis inhibition	Blocks MDK/ALK axis, reduces glioma stem cell self-renewal, and enhances TMZ sensitivity	Glioma stem cells	Effective in reducing self-renewal of glioma stem cells and overcoming TMZ resistance in mouse models

Note: MDK, midkine; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; BBB, blood-brain barrier; TMZ, temozolomide; ALK, anaplastic lymphoma kinase.

intratumoral accumulation. Future strategies may include structure-guided small-molecule design, inhibitors targeting MDK-associated receptor complexes, and degradation-based approaches directed at relevant intracellular mediators or receptor-dependent signaling components. In parallel, delivery platforms, such as liposomes, polymeric nanoparticles, exosomes, and convection-enhanced delivery, may help improve drug accumulation within glioma tissues while reducing systemic toxicity. Furthermore, given the redundancy of glioma signaling and the adaptive nature of TME, MDK-targeted therapy may need to be combined with other therapeutic modalities, such as anti-VEGF therapy, immune checkpoint blockade, TMZ, or radiotherapy, to prevent adaptive resistance and improve therapeutic efficacy.

(3) Overcoming BBB-related delivery barriers.

The BBB remains a formidable obstacle to effective drug delivery for brain diseases in general and glioma in particular. Inhibitors that are potent under physiological conditions may still fail if they cannot reach the tumor after oral administration or intravenous injection. Many small molecules act as substrates for efflux pumps on glioma endothelium, severely limiting intratumoral accumulation. Addressing this issue requires a multipronged approach. First, medicinal chemistry must optimize properties, such as lipophilicity, to reduce efflux affinity. Second, physical strategies, such as low-intensity focused ultrasound combined with microbubbles, can transiently open BBB, enabling drug delivery to the invasive edge. Third, biomimetic carriers, such as exosomes or neutrophil-mediated transport, offer a strategy to partially overcome these barriers.

In summary, MDK is a promising but still incompletely validated therapeutic target that links stemness, immune suppression, and drug resistance. The next decade of research must prioritize specific, BBB-penetrant degraders or inhibitors to achieve clinical readiness.This effort must be coupled with safety evaluations that respect the physiological role of MDK. Systematically addressing these bottlenecks will transform research on MDK into tangible survival benefits for patients. Given the pathway redundancy and microenvironmental plasticity of gliomas, MDK inhibition is unlikely to be sufficient as a stand-alone strategy. Rational combinations with TMZ, radiotherapy, immune checkpoint blockade, antiangiogenic therapy, or myeloid-reprogramming approaches should be evaluated using biomarker-defined models. Such studies should determine optimal sequencing, dosing, and patient-selection criteria to maximize therapeutic benefit while limiting toxicity. Moreover, pathway redundancy, intratumoral heterogeneity, and the lack of glioma-specific clinical validation for current MDK inhibitors remain major hurdles that may limit the efficacy of MDK-targeted monotherapy.

7. Conclusion

Glioblastoma and other high-grade gliomas remain highly challenging because of their molecular heterogeneity, immunosuppressive microenvironment, and intrinsic or acquired therapy resistance. This review summarizes the multifaceted roles of MDK in glioma pathogenesis and highlights its potential relevance as a prognostic biomarker and a therapeutic target.

MDK is overexpressed in gliomas and associated with high tumor grade and poor patient prognosis. Mechanistically, MDK promotes glioma-cell proliferation, stemness,

invasion, and TMZ resistance through multiple signaling pathways, including Notch1/p-JNK, PI3K/AKT/mTOR, c-Myc/Wnt/β-catenin, and the MDK/ALK–autophagy axis. Aside from its direct effects on tumor cells, MDK also contributes to TME remodeling by promoting M2-like polarization of macrophages or microglia, facilitating regulatory T-cell recruitment, and participating in immune-checkpoint regulation, including PD-L1. These findings suggest that MDK may act as a candidate mediator linking tumor aggressiveness with immune evasion and therapeutic resistance.

Preclinical evidence indicates that MDK-targeted strategies, including iMDK, HBS-101, ACT001-mediated disruption of the MDK/c-Myc complex, and blockade of the MDK/ALK axis, may suppress tumor growth, reduce glioma stem-like properties, and reverse chemoresistance. However, clinical translation remains limited by the lack of glioma-specific clinical validation, the need for BBB-penetrant inhibitors, potential toxicity related to the physiological roles of MDK, and pathway redundancy.

MDK represents a promising but still incompletely validated biomarker and therapeutic target in glioma. Future research should prioritize the development of selective CNS-penetrant agents; validation in patient-derived and clinically relevant models; rational combination strategies involving TMZ, radiotherapy, antiangiogenic therapy, and immunotherapy; and identification of predictive biomarkers for patient stratification and response monitoring.

Abbreviations

ALK, Anaplastic Lymphoma Kinase; ACSL5, Acyl-CoA Synthetase Long-Chain Family Member 5; array-CGH, Array Comparative Genomic Hybridization; AKT, Protein Kinase B; ATM, Serine-Protein Kinase ATM; ATR, Serine/Threonine-Protein Kinase ATR; BCL-2, B-cell Lymphoma 2; BBB, Blood-Brain Barrier; BTB, Blood-Tumor Barrier; c-Myc, Cellular Myc; CAR-NK, Chimeric Antigen Receptor Natural Killer Cell; CAR-T, Chimeric Antigen Receptor T-cell; CB1R, Cannabinoid Receptor Type 1; CB2R, Cannabinoid Receptor Type 2; CD133, Cluster of Differentiation 133; CSF1, Colony-Stimulating Factor 1; CSF1R, Colony-Stimulating Factor 1 Receptor; CXCL1, C-X-C Motif Chemokine Ligand 1; CHK1, Checkpoint Kinase 1; CI, Confidence Interval; CNS, Central Nervous System; CDK4/6, Cyclin-Dependent Kinase 4/6; CDK7, Cyclin-Dependent Kinase 7; CDKN2A/B, Cyclin-Dependent Kinase Inhibitor 2A/2B; system Xc−, Cystine/Glutamate Antiporter System Xc−; CTLA-4, Cytotoxic T-Lymphocyte Antigen-4; DC, Dendritic Cell; DHODH, Dihydroorotate Dehydrogenase; DDR, DNA Damage Response; DIPG, Diffuse Intrinsic Pontine Glioma; ERK, Extracellular Signal-Regulated Kinase;EGFR, Epidermal Growth Factor Receptor; EMT, Epithelial-Mesenchymal Transition; ECM, Extracellular Matrix; GEO, Gene Expression Omnibus; GBM, Glioblastoma; GSCs, Glioma Stem Cells; GICs, Glioma Initiating Cells; G-CIMP, Glioma-CpG Island Methylator Phenotype; GLS, Glutaminase; GPX4, Glutathione Peroxidase 4; GAGs, Glycosaminoglycans; HCC, Hepatocellular Carcinoma; IDO1, Indoleamine 2,3-Dioxygenase 1; IAPs, Inhibitor of Apoptosis Proteins; IL-10, Interleukin-10; LRP1, Low-Density Lipoprotein Receptor-Related Protein 1; IDH, Isocitrate Dehydrogenase; LRP, Low-Density Lipoprotein Receptor-Related Protein; MIF, Macrophage Migration Inhibitory Factor; mTOR, Mechanistic Target of Rapamycin; mTORC1, Mechanistic Target of Rapamycin Complex 1; MET, Mesenchymal-Epithelial Transition Factor; MES-like, Mesenchymal-like;MGMT, O-6-methylguanine-DNA methyltransferase; MDK, Midkine; MMR, Mismatch Repair; MAPK, Mitogen-Activated Protein Kinase; MDM2/4, Mouse Double Minute 2/4; MDSCs, Myeloid-Derived Suppressor Cells; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; OPCs, Oligodendrocyte Progenitor Cells; OXPHOS, Oxidative Phosphorylation; p-JNK, Phosphorylated Jun N-terminal Kinase; PI3K, Phosphatidylinositol 3-Kinase; PARP, Poly(ADP-ribose) Polymerase; PDGFRA, Platelet-Derived Growth Factor Receptor Alpha; PTN, Pleiotrophin; PD-1, Programmed Death 1; PD-L1, Programmed Death-Ligand 1; PTPζ/β, Protein Tyrosine Phosphatase Zeta/Beta; RAS, Rat Sarcoma; RAD51, DNA Repair Protein RAD51 Homolog 1; RTK, Receptor Tyrosine Kinase; RB, Retinoblastoma; STAT3, Signal Transducer and Activator of Transcription 3; SP1, Specificity Protein 1; SOX9, SRY-Box Transcription Factor 9; TERT, Telomerase Reverse Transcriptase; TMZ, Temozolomide; TGF-β, Transforming Growth Factor-β; THC, Tetrahydrocannabinol; Treg, Regulatory T Cell; TRB3, Tribbles Homolog 3; TNBC, Triple-Negative Breast Cancer; TME, Tumor Microenvironment; TP53/p53, Tumor Protein 53; TAMs, Tumor-Associated Macrophages; VEGF, Vascular Endothelial Growth Factor; VEGFR, Vascular Endothelial Growth Factor Receptor.

Author Contributions

TZ contributed to literature search, literature screening, data collection, and figure preparation. FZ and XP contributed to literature screening, analysis and interpretation of the collected information, and critically reviewed and revised the manuscript. XX conceived and designed the review and wrote the original draft. All authors contributed to editorial changes in the manuscript, read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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