Review

Dynamic Reorganization of Microtubule and Glioma Invasion

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Gliomas are characterized as highly diffuse infiltrating tumors, and currently available treatments such as surgery, radiation and chemotherapy are unfeasible or show limited efficacy against these tumors. Recent genetic and epigenetic analyses of glioma have revealed increasing evidence of the role of driver genetic alterations in glioma development and led to the identification of prognostic factors. Despite these findings, the survival rates of glioma patients remain low, and alternative treatments and novel targets are needed. Recent studies identified neural stem cells as the possible origin of gliomas, and some evidence has revealed shared functions and mechanisms between glioma cells and neurons, also supporting their similarity. The cytoskeleton plays important roles in the migration of normal cells as well as cancer cells. Recent reports have described a role for microtubules, a component of the cytoskeleton, in glioma invasion. Notably, several factors that regulate microtubule functions, such as microtubule-associated proteins, plus-end tracking proteins, or motor proteins, are upregulated in glioma tissues compared with normal tissue, and upregulation of these factors is associated with high invasiveness of glioma cells. In this review, we describe the mechanism of microtubules in glioma invasion and discuss the possibility of microtubule-targeted therapy to inhibit glioma invasion.

Key words: glioma, cytoskeletons, invasion, microtubules

G lioma is one of the most aggressive brain tumors with a poor prognosis compared with other brain cancers. The WHO classification categorizes gliomas into four grades based on pathological and genetic alterations [1]. Glioblastoma (GBM), grade IV, has the poorest prognosis among all gliomas, with a median overall survival time of less than 2 years despite the availability of aggressive treatments including surgery, chemotherapy, radiation therapy and tumor-treating fields [2,3]. Several new treatments have been explored, including immunotherapy [4] and molecular targeted therapy [5-7]; however, an improved survival benefit from these treatments has not been achieved. Even ana-

plastic astrocytoma (grade III) shows an overall 5-year survival of approximately 50-60% [8,9]. The poor prognoses of these brain tumors are caused by pathological and molecular features. Recent deep molecular analysis revealed the genetic heterogeneity of GBM [10,11], which contributes to the limited efficacy of molecular targeted therapy and subclonal selection [12]. Furthermore, the tumor hierarchy is also complicated in GBM [13]. Liau *et al.* reported the epigenetic regulation of glioma stem cells (GSCs), which contribute to resistance to chemotherapy and radiotherapy and exhibit tumorigenic properties, and the authors showed reversible phenotypic changes between GSCs and differentiated glioma cells [14]. GSCs are also involved in glioma invasiveness [15], which is another factor that

contributes to poor prognosis.

In pathological features, GBM shows prominent angiogenesis, diffuse invasion and high proliferation [16] (Fig. 1A and B). Microvascular proliferation is a histological hallmark of GBM and typically presents as so-called glomeruloid tufts of multilayered endothelial cells and pericytes. The tumor blood vessels are more dilated and tortuous with excessive branching; the vessels lack the normal artery-capillary-vein hierarchy and show increased cellular fenestration as well as widened intercellular junctions or gaps [17]. These abnormal structures result in high vascular permeability, hyperosmosis in stroma, and hypoxia and contribute to resistance to drug delivery. Diffuse invasion of tumor cells into normal brain is another characteristic feature of glioma, and the highly invasive nature of glioma cells makes complete surgical resection unfeasible and renders radiotherapy and local drug delivery ineffective. Matsukado reported that more than 50% of untreated brain tumors spread into the contralateral hemisphere [18], and therefore even radical surgical resection such as complete removal of the tumor-bearing hemisphere does not prevent tumor recurrence [19]. Conventional radiological imaging with computed tomography or magnetic resonance imaging is used for establishing treatment plans and evaluating the treatment response

[20], but both of these imaging techniques significantly underestimate the extent of infiltrative glioma growth, as tumor cells are present outside of low density areas of computed tomography [21] and hyperintensive regions on T2-weighted images [22].

GBM is characterized by prominent angiogenesis with overexpression of VEGF-A, a key molecule in regulating angiogenesis and the neovasculature [23]. Therefore, blockage of VEGF with bevacizumab, an anti-VEGF monoclonal antibody, has been used for GBM patients [6,7,24]. However, both AVAGlio and RTOG-0825 studies showed no survival benefit of bevacizumab for newly diagnosed GBM. One possible reason may be due to bevacizumab-induced glioma invasion. Our previous studies [25-27] and other reports [28-30] showed aggressive glioma invasion after bevacizumab treatment, and several factors such as proneural to mesenchymal transition [31,32], MET [33], or Wnt [30] signaling are known to be activated and promote invasion after bevacizumab treatment. Together these studies demonstrate that the highly invasive feature of glioma cells is an important factor that contributes to poor prognosis of glioma patients [34,35].

Cell migration is an important biological process for normal development and immune surveillance, and the
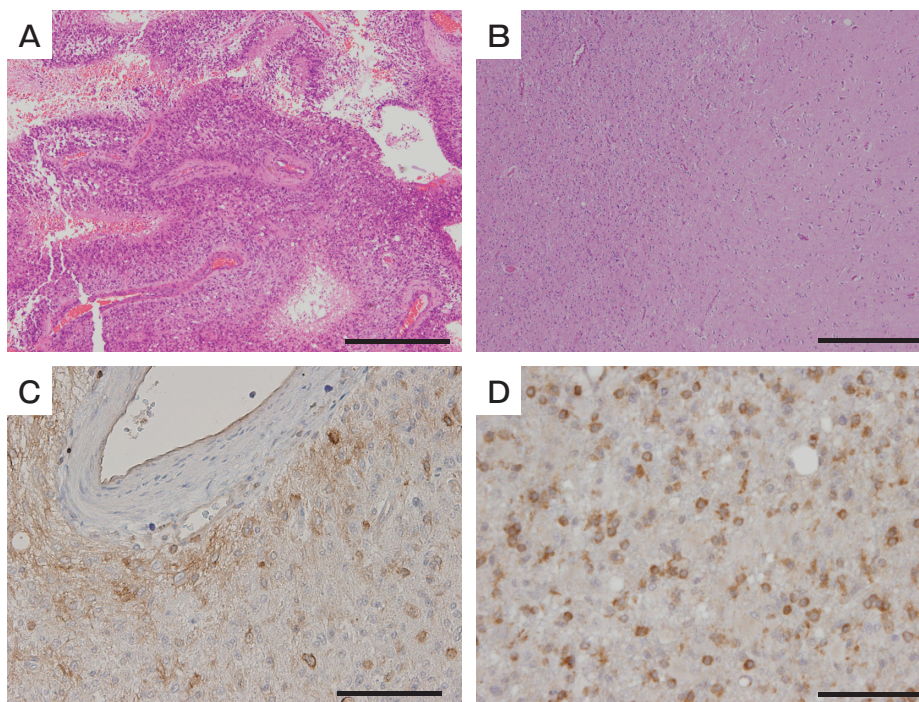
Fig. 1   Two distinct invasion patterns of glioma cells and molecular expression. The characteristic pathological features of glioma are prominent angiogenesis (**A**) and diffuse invasion (**B**). Our previous studies using 2 glioma models, J3T-1 and J3T-2, revealed two different invasion patterns and key molecular expressions: annexin A2 in perivascular invasion and fibroblast growth factor 13 (FGF13) in diffuse invasion to surrounding healthy parenchyma [26,55-57]. Immunohistochemistry of human glioblastoma specimens showed high annexin A2 expression in glioma cells located around vasculature (**C**), and FGF13 expression in the cytoplasm of glioma cells in diffuse infiltrating area (**D**). Scale bars, 500 μm (**A** and **B**) and 100 μm (**C** and **D**).

cytoskeleton is a critical regulator of cell migration. Numerous studies have also demonstrated the role of the cytoskeleton in tumor cell motility, including glioma [36-39]. Glioma was originally named due to its morphological similarity to glial cells, the presumed cell origin of glioma. However, recent evidence suggested the origin cells of gliomas are neural stem cells or precursor cells of the oligodendroglial lineage [40-42], as glioma cells show similar behaviors with these cells [41,43], including migration patterns [44]. In the mammalian brain, microtubules, one of the structural components of the cytoskeleton, make up approximately 20% of total protein compared with 3-4% of total protein in somatic tissues [45], and microtubules play an important role in neuronal migration. In this review, we focus on the role of the cytoskeleton, especially microtubules, in glioma invasion.

Patterns of Glioma Invasion

The morphological patterns of glioma invasion dependent on preexisting tissue elements was reported by Hans Joachim Scherer as 'secondary structures' [46], and today these secondary structures of Scherer are referred to as 1) perineuronal satellitosis, 2) perivascular satellitosis, 3) subpial spread, and 4) invasion along the white matter tract [47]. These invasion patterns are different from the spreading of brain tumor from the metastases of systemic cancer [48]. In the human brain, blood vessels represent hundreds of miles of linear tracks covered with extracellular matrix factors, such as collagen, laminin, and fibronectin [49-51], and function as an important scaffold for glioma invasion [52,53]. Watkins et al. reported that a vast majority of human glioma cells that travelled outside of the main tumor mass were associated with blood vessels and tumor cells inserted between the endfeet and the endothelial wall of the preexisting blood vessel, which leads to the loss of tight junction and a focal breach of the blood-brain barrier (BBB) [53]. Montana et al. showed that endothelial cell-derived bradykinin attracts glioma cells to the vasculature and promotes tumor invasion [54]. Zagzag et al. also demonstrated that stromal cell-derived factor-1α (SDF-1α) was highly expressed in vasculatures, neurons, white matter tract, and subpial regions, and glioma cells around these structures expressed high levels of CXCR4, the receptor for SDF-1α. This indicates a possible mechanism of

Scherer's secondary structures based on SDF-1α/CXCR4 expression at the invading edge of GBM [47].

We also identified annexin A2 as a candidate protein that may regulate glioma invasion along the vasculature using our two novel invasive glioma models: J3T-1 and J3T-2 [55-57] (Fig. 1C). Annexin A2 is a 36-kDa calcium-dependent phospholipid-binding protein [58-60] that is mainly distributed in the plasma membrane and cytoplasm, with slight expression in the nucleus [61,62]. Calcium, phospholipid and F-actin binding sites in the C-terminal are important for annexin A2 activities in the plasma membrane and cytoplasm, including extracellular degradation, angiogenesis, actin cytoskeleton regulation, and cell-cell adhesion [60,63-72]. A nuclear export signal and multiple phosphorylation sites such as Tyr23, Ser11 and Ser25 in the N-terminal of annexin A2 are important for its nuclear transport [73,74], and annexin A2 plays an important role in the nucleus in DNA synthesis and mRNA transport and translation [75]. We showed that overexpression of annexin A2 induced angiogenesis and co-opted glioma cells to vasculature, whereas silencing of annexin A2 suppressed this process [57]. Notably, Hirata et al. evaluated C6 glioma invasion pattern in vivo with 2-photon imaging and revealed two different invasion patterns [76], which indicated different glioma invasion patterns based on location. On blood vessel walls, glioma cells showed a spindle shaped morphology with a single pseudopodium and fast migration in a saltatory manner. In contrast, glioma cells invading into the brain parenchyma showed multiple pseudopodia.

A recent study was performed to elucidate the origin of GBM by Lee et al., and the authors revealed that neural stem cells in the human subventricular zone (SVZ) tissue are the origin cells of GBM [77]. The authors conducted deep sequencing of triple-matched tissues consisting of (i) normal SVZ tissue away from the tumor, (ii) tumor tissue, and (iii) normal cortical tissue (or blood). Normal SVZ tissue away from the tumor contained GBM driver mutations in 56.3% of patients with wild-type IDH GBM. The adult human SVZ tissue comprises three anatomically distinct layers: the ependymal layer, hypocellular gap, and astrocytic ribbon [78]. The astrocytic ribbon layer contains SVZ astrocytes that can function as neural stem cells [78-80]. Lee et al. identified significant enrichment of TERT promoter mutation in astrocyte-like stem cells from the astrocytic ribbon layer and suggested that the stem cells

harboring driver mutations clonally evolved to tumors away from the SVZ in patients with GBM [77]. As mentioned above, the pattern of glioma cell migration strongly resembles the glial progenitor cell migration pattern during normal brain development [36,44], and understanding the neurogenesis mechanism may help uncover the mechanism of glioma invasion.

Neurogenesis is observed in both the developing and adult brain, and most of these processes are regulated by similar mechanisms. In the course of brain developing, newborn neurons migrate tangentially or radially [81]. Excitatory pyramidal neurons migrate radially into the developing cortex and hippocampus, while inhibitory cells migrate tangentially to reach their position in the dorsal forebrain [82]. In the adult brain, newly generated neurons migrate through the rostral migratory stream to the olfactory bulb, where they mature and are integrated into the neuronal circuitry [83]. Neurons also migrate into injury sites such as in stroke and differentiate into functional neurons [84]. In both the developing and adult brain, neurons migrate in a saltatory manner that involves 1) leading-process extension, 2) swelling formation and centrosomal migration, and somal translocation, and the cytoskeleton, especially microtubules, play important roles in this migration pattern [85,86]. As mentioned above, Hirata *et al.* evaluated C6 glioma invasion patterns *in vivo* and found that glioma cells on vasculature migrated in a saltatory manner [76]. Monzo *et al.* also observed glioma migration in a saltatory manner with patient-derived glioma cells and C6 cells [87]. Glioma cells exhibited saltatory migration on microfabricated laminin tracks similar to their motion in the brain, and this movement had two phases. In the first phase, the cell extended leading processes with small lamellipodia and the cell body moved forward at a slow speed (cell elongation phase). In the second phase, the cell restored its original length by sudden retraction of the tail, rapid movement of the cell body forward, and constant leading-edge movement (tail retraction phase). Notably, nocodazole, a microtubule-depolymerizing drug, severely inhibited glioma cell motility by blocking polarization but not lamellipodial activity. Furthermore, Panopoulos *et al.* revealed GBM cell motility in the absence of actin polymer [88]. Strikingly, glioma cells exhibit no motility in the presence of microtubule inhibitors; however, cells displayed persistent motility in the presence of actin inhibitors at concentrations suf-

ficient to fully disassemble actin, which indicated the heavy involvement of microtubules in glioma invasion.

Cytoskeleton

The cytoskeleton is composed of 3 polymers, actin, intermediate filaments, and microtubules, which are structurally, morphologically, and functionally different from each other and have distinctive dynamic properties that are important for their individual functions. Each of the three polymers is associated with a large number of accessory proteins that can regulate the assembly properties of these polymers and mediate interactions among themselves and with other cellular structures, including various organelles, plasma membrane, and chromosomes. During cell movement, the cytoskeleton shows asymmetrical distribution of these polymers (Fig. 2A).

Actin.   Actin is the most abundant protein in most eukaryotic cells and the main globular protein that forms microfilaments. Actin exists either in monomeric (G-actin) or polymeric forms (F-actin) in cells, and actin filaments have polar structures with a plus-end and minus-end. Actin filaments are involved in cell migration and generate force through 2 different mechanisms: (i) ATP-dependent elongation of actin filaments at their barbed ends and shortening at the pointed ends, and (ii) through the involvement of myosin-family motor proteins. Actin-binding proteins also work together to organize the dynamics of actin filaments [89]. Rho GTPases are a family of 20 small G proteins that are divided into subfamilies, including Rho, Rac, Cdc42, Rnd, RhoD, RhoF, RhoH, and RhoBTB. Rho GTPases are important regulators of actin, and RhoA, Rac, and Cdc42 have shown key roles in cell motility [90]. Rho GTPases are upregulated in cancers including glioma, and their high expression is correlated with invasiveness [91-94]. In the mechanism of cell movement, the first step is actin-driven protrusions at the leading edge, followed by contractions at the cell body and rear. Actin-driven protrusions at the leading edge include lamellipodia and filopodia, and these protrusions are driven by Rac and Cdc42 activation, respectively [95,96]. Contractions at the cell body and rear are induced by Rho [97]. Recent studies revealed that Rho GTPases also regulate microtubule dynamics and, in turn, microtubules affect Rho GTPases activites [98].

Intermediate filaments. Intermediate filaments are ubiquitous cytoskeletal elements that function to support the cell membrane, serving as a structural scaffold to maintain cell shape. Unlike F-actin and microtubules, which are composed of highly conserved proteins, intermediate filaments are formed from 40 different subunit proteins and are subdivided into six classes, which include keratins, neurofilaments, desmin, lamin and vimentin [99, 100]. Multiple studies have demonstrated the roles of actin and microtubules in cell migration, however the function of intermediate filaments in migration is less known. Vimentin is in the type III class of intermediate filaments, and Rogel *et al.* reported that vimentin is sufficient and required for cell migration and wound repair closure [101]. Nestin, a type IV intermediate filament, is also involved in development processes, such as in the migration of neural progenitor cells [102]. Some studies have demonstrated an involvement of intermediate filament proteins in glioma invasion. Zhao *et al.* showed that withaferin-A, a chemical inhibitor of vimentin, inhibited the migration of U251 and U87 glioma cells *in vitro* [103]. Nestin is a glioma stem cell marker and associated with the malignant potential of glioma [104]. One study showed that knockdown of nestin reduced glioma invasion [105].

Microtubules. Microtubules are highly dynamic structures that have important roles in vesicular transport, mitosis, and motility. Microtubules are composed of α/β-tubulin heterodimers. There are 10 α- and 9 β-tubulin isotypes that display tissue- and developmental-specific expression [106]. Microtubules are polar structures, consisting of α-tubulin at the slow-growing minus-end and β-tubulin exposed at the fast-growing plus end [45]. Polymerized microtubules form a hollow fiber 25 nm in diameter. In mammalian cells, minus-ends are often stably anchored, whereas the plus-ends are highly dynamic and stochastically switch between phases of growth and shrinkage, a process that is powered by GTP hydrolysis [107]. This rapid growth and collapse is known as dynamic instability and is regulated by the local free tubulin, microtubule-associated proteins (MAPs), plus-end tracking proteins, post-translational modifications (PTMs), and motor proteins (Fig. 2B).

The Role of Microtubules in Glioma Motility

MAPs. MAPs include MAP1, MAP2, and MAP4 proteins and Tau proteins and mostly function to regulate microtubules. MAP2 and Tau are the major MAPs in the central nervous system and show a distinct sub-
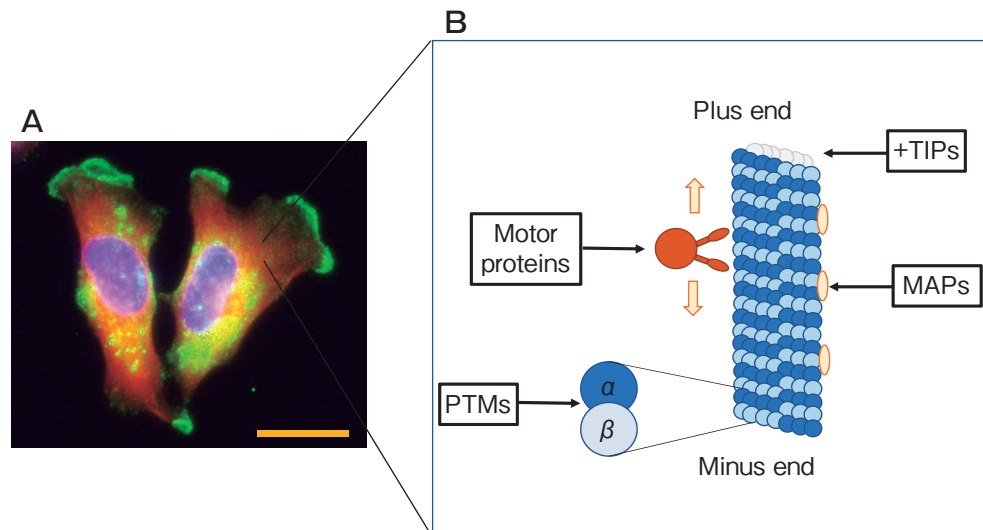
Fig. 2 Microtubule-binding proteins regulate glioma invasion. (**A**) Immunofluorescent staining of human glioma LN229 cells showed different distribution of F-actin (green) and microtubules (red). DAPI, 4',6-diamidino-2-phenylindole, was used for nuclear staining. Scale bar, 25μm. (**B**) Microtubules are composed of α β-tubulin heterodimers and extend at their plus-end. Microtubule plus-end tracking proteins (+TIPs) specifically accumulate at microtubule plus-ends and regulate microtubule dynamics. Microtubule-associated proteins (MAPs) also play a crucial role in microtubule dynamics. Motor proteins such as kinesins and dyneins move along microtubules and are involved in glioma invasion. Post-translational modifications (PTMs) also affect microtubule dynamics.

cellular localization [108]. MAP2 is the most abundant neuronal MAP and is mainly expressed in the dendrites and neuronal cell body. MAP2 has four different isoforms (MAP2a, b, c, and d), which show specific expression patterns: MAP2a, 2b, and 2d are expressed in the adult brain whereas MAP2c is expressed in the embryonic and neonatal brain [109]. Tohyama *et al.* evaluated MAP1b, MAP2b, and MAP2c expression in five glioma cell lines (U87MG, U138MG, U251MG, U373MG, and HS683) using northern blot and immunoblot analysis [110]. All glioma cell lines expressed MAP1b, and three cell lines expressed MAP2c; however, only U373MG cells expressed MAP2b. Zhou *et al.* reported that protein kinase A (PKA) activator treatment induced MAP2 expression via signal transducer and activator of transcription 3 (STAT3) in glioma cells, which resulted in the reduction of glioma invasion [111].

Doublecortin (DCX) is another MAP that promotes microtubule polymerization and stabilization [112]. During brain development, DCX is expressed by migrating neuronal precursor cells and post-migratory neurons [113,114], while in the adult brain, DCX is expressed by migrating neuroblasts [115]. DCX is mutated in lissencephaly, which is characterized by disorganized layers of the cerebral cortex [116]. Daou *et al.* showed that DCX is preferentially expressed in invasive brain tumors such as GBM, anaplastic astrocytoma, and oligoastrocytoma [117]. Ortensi *et al.* demonstrated reduced glioma invasiveness by knockdown of Rai (ShcC/N-Shc), a member of the Shc-like adaptor protein family, accompanied by a significant reduction in DCX [118]. DCX function is regulated by several serine-threonine kinases and phosphatases [15]. Cyclin-dependent kinase 5 (CDK5), a serine-threonine kinase that forms complexes with p35 and p39 and is indispensable for brain development [119], phosphorylates DCX at Ser297 and decreases its binding affinity to microtubules in neurons [120]. Liu *et al.* also showed that Cdk5 mediates migration and invasion of GBM cells [121]. In addition, the small molecule inhibitor AC1MMYR2 attenuated CDK5 activities by functionally targeting CDK5RAP1, resulting in inhibition of glioma invasion [122]. DCX is also regulated by PKA and MAP/MARK signaling, as well as the phosphatase and tensin homolog (PTEN) pathway. Both signal pathways are frequently dysregulated in GBM [10] and involved in glioma invasion [123,124], which indicates

a possible mechanistic involvement of DCX or microtubules in glioma invasion.

The Disrupted in Schizophrenia 1 (DISC1) gene was originally identified as a candidate gene for schizophrenia [125]. Later studies revealed its distribution in microtubule-associated cytoskeletons and mitochondria and its various functions, such as in neuronal migration, neurogenesis, and cAMP signaling. DISC1 interacts with MAP1A and MIPT3 proteins [126]. Gao *et al.* showed that silencing of DISC1 in U251 MG cells inhibited glioma migration and invasion *in vitro* [127].

Stathmin is a microtubule destabilizing protein [128] that functions in cell migration by assisting in new leading edge microtubule growth [129,130]. Stathmin is also involved in cancer cell migration and its expression is upregulated in several cancers including leukemia, lymphoma, Wilms tumor, ovarian cancer, prostate cancer, breast cancer, head and neck cancer, hepatocellular carcinoma, osteosarcoma, lung cancer and mesothelioma [131]. Some groups reported that downregulation of stathmin expression inhibited migration in multiple glioma cell lines [132,133].

Spastin is a microtubule-severing protein encoded by the SPG4 gene and a member of ATPases [134]. Spastin has 2 domains: a microtubule-interacting and endosomal trafficking (MIT) domain and an ATPases associated with various cellular activities (AAA) domain. Spastin exhibits functions in microtubule severing as well as microtubule bundling. A previous study showed that knockdown of spastin decreased glioma invasion [135].

Fibroblast growth factor 13 (FGF13) is another microtubule-stabilizing protein that regulates neuronal polarization and migration and was recently identified by Wu *et al.* [136-138]. FGF13 has 2 splicing isoforms, FGF13A and FGF13B, which are spatially differentially expressed in the nucleus and cytoplasm, respectively. In the developing brain, FGF13B is dominant and regulates microtubule dynamics and neuronal migration. Cerebral cortex-specific knockdown of FGF13 in mice resulted in disorganization of laminar development of the cerebral cortex. We previously identified dominant FGF13B expression compared with FGF13A in GBM specimens as well as established glioma cells and patient-derived GSCs and found that FGF13B colocalized with microtubules in the cytoplasm of these samples [26] (Fig. 1D). Moreover, knockdown of FGF13 reduced glioma invasion *in vitro* and *in vivo*. FGF13

expression level is regulated by SoxD in *Xenopus* [138] and Sox2 in glioma [139,140]. Notably, Wang *et al.* recently reported CD133⁺ GSCs that are preferentially located on and invaded along white matter tracts expressing NOTCH-induced SOX2 and SOX9, whereas the nerve fibers expressed JAG1, the NOTCH ligand [141]. In our study, FGF13 was highly expressed in the J3T-2 glioma model, which showed diffuse glioma invasion without angiogenesis. FGF13 was expressed at higher levels in the proneural group, in which NOTCH signaling is upregulated. These data indicate that FGF13 might be involved in angiogenesis-independent glioma invasion.

Plus-end tracking proteins. The plus-ends of microtubules are highly dynamic, and the microtubule plus-end tracking proteins (+TIPs) specifically accumulate at microtubule plus ends [142]. More than 20 +TIP families have been reported since the first +TIP cytoplasmic linker protein of 170 kDa (CLIP-170) was discovered [143]. End-binding 1 protein (EB1) is a member of the EB family in +TIPs and is located on the plus-ends of growing microtubules, where it controls microtubule dynamics and regulates linking to other cellular structures. EB1 overexpression correlates with poor prognosis in GBM [144] as well as in other cancers such as breast cancer [145], esophageal squamous cell carcinoma [146], gastric adenocarcinoma [147], colorectal cancer [148] and hepatocellular carcinoma [149]. Berges *et al.* showed that overexpression of EB1 in glioma cells promoted invasion and accelerated tumor growth *in vivo*, while downregulation of EB1 inhibited glioma invasion and proliferation. Furthermore, overexpression of EB1 sensitizes GBM cells to vinca-alkaloids.

PTMs. PTMs such as acetylation, deacetylation, phosphorylation, glutamylation, Δ2 modification, and glycylation also affect microtubule activity [150,151]. Acetylated tubulin is a hallmark of long-lived microtubules and stable tubulin [152]. Tubulin is acetylated on lysine 40 by the α-tubulin acetyltransferase 1 (αTAT1) [153] and its acetylation is reversed by histone deacetylase 6 (HDAC6) [154] and sirtuin 2 (SIRT2). Overexpression of HDAC6 significantly increases cell motility [154] and a previous study showed a significant association between metastatic breast cancer cell lines and high acetylation of α-tubulin [155]. Wu *et al.* revealed a role for HDAC6 in glioma invasion [156]. Overexpression of invasion inhibitory protein 45,

which is a binding partner of HDAC6, decreased HDAC6 activity and reduced glioma migration. Therefore, several HDAC6 inhibitors are being currently evaluated in clinical trials (as described later).

Motor proteins. Motor proteins such as dynein and kinesin are important for microtubule organization and carry organelles, mRNA, proteins, and signaling molecules along the microtubule [157]. Migrating cells exhibit a highly polarized shape along the anterior-posterior axis. In neurons, cytoplasmic dynein links to the nuclear envelope and pulls the nucleus forward along microtubules, whereas inhibition of dynein or its regulator Lissencephaly-1 (LIS1) attenuates nuclear migration [86]. High grade glioma shows high expression of dynein compared with low grade glioma [158], and expression of dynein cytoplasmic 2 heavy chain 1 (DHC2) has been associated with temozolomide resistance [159]. In contrast, Neubauer *et al.* reported a dramatic downregulation of DYNC1I1 in GBM specimens, in which lower expression correlated with poor prognosis [160]. Lis1, a dynein-binding protein, colocalized with CD133+ GSCs, and knockdown of Lis1 decreased U87 cell migration [161]. Kinesin is another target for glioma invasion. Venere *et al.* showed that kinesin family member 11 (KIF11), which enhances elongation of tubulin protofilaments at the plus-end, is upregulated in GBM, and knockdown of KIF11 reduced self-renewal and motility of glioma cells [162].

Microtubule-targeting Agents (MTAs) to Block Glioma Invasion

MTAs are classically divided into drugs that act as inhibitors and those that act as enhancers of tubulin polymerization. Both categories of MTAs alter microtubule dynamics defined by growth to shrinkage transitions (catastrophes) and reverse transitions (rescue) and inhibit not only invasion but also mitosis. While MTAs have showed efficacy in treatment of diverse cancers, the use of MTAs in GBM treatment has been restricted due to the BBB that blocks the crossing of most clinically relevant, natural product-derived MTAs [39,163]. Furthermore, microtubules are essential for central nervous system function, and a therapeutic dose of MTAs leads to neurotoxicity in the central nervous system, a common issue for the peripheral nerve system after systemic administration of MTAs [164]. Therefore, efforts are underway to develop new MTAs that can cross the BBB and identify MAPs or other microtu-

bule-regulating factors whose inhibition would block mitosis and migration without producing neurotoxicity [162].

Several MTAs have shown potential efficacy in inhibiting glioma invasion. BAL101553 is a prodrug of BAL27862 and can efficiently distribute into the brain and tumor. This MTA can inhibit GBM proliferation and migration in an EB1-dependent manner [39] and is currently in clinical trials for advanced cancers including GBM (NCT02490800, NCT02895360). Patupilone is another brain-penetrating microtubule-stabilizing agent and can overcome traditional taxane resistance mechanisms because of its efficacy against both wild-type and common mutated forms of β-tubulin and as it is a poor substrate for the P-glycoprotein efflux pump [165]. Clinical trials have confirmed its safety and drug accumulation in glioma (NCT00045708, NCT00715013) [165]. Pagano *et al.* reported that a non-cytotoxic concentration of patupilone reduced accumulation of EB1 and inhibited glioma cell movement [166]. Ispinesib is an anti-kinesin drug and the small molecule inhibitor of KiF11. Venere *et al.* showed significant reduction of glioma migration by ispinesib [162]. In a study by Berges *et al.* [167], the NFL-TBS.40-63 peptide (a tubulin-binding peptide) was shown to disrupt the microtubule network in glioma cells but not in normal astrocytes and neurons and thus demonstrated potential as a primary or supplementary glioma treatment modality. Vorinostat is a FDA-approved drug for the treatment of cutaneous T cell lymphoma that selectively inhibits HDAC6. Clinical trials with volinostat in glioma are also being conducted (NCT02420613) [168-170]. Zhang *et al.* showed the decrease of glioma migration and invasion *in vitro* with vorinostat [171]. Interestingly, the HDAC6 inhibitor could not only inhibit glioma invasion [156,171], but it also improved the efficacy of other treatments such as chemotherapy [172], radiation [173], and oncolytic virus therapy [174].

Future Directions and Conclusions

Glioma is a highly invasive brain tumor, and recent studies have demonstrated similar mechanisms between glioma and neural progenitor cells including in migration, which involves dynamic instability of microtubules. Developing novel treatments to target microtubules whose inhibition would block mitosis and

migration in glioma cells without toxicity in normal brain is extremely important, which can inhibit both aspects of 'go and grow' [162]. Recently, tumor-treating fields, an antimitotic treatment that selectively affects dividing GBM cells by delivering low-intensity, intermediate-frequency alternating electric fields via transducer and perturbs microtubules during mitosis, showed survival benefit in newly diagnosed GBM [3] and also inhibited glioma invasion [175]. Further discoveries of microtubule-targeted therapies may improve the clinical outcome of glioma patients.

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