5 Molecular Mechanisms of Glioma Cell Motility

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Abstract: Gliomas are the most common intracranial tumors in humans. The most malignant among these tumors is glioblastoma (GBM), with an incidence of 3–5 out of 100,000 persons in Western countries. GBM arises either *de novo* (primary GBM) or develops from a lower grade glioma (secondary GBM). The prognosis is poor. GBMs are lethal tumors and even optimal surgical resection, followed by chemotherapy and irradiation, results in a median survival of about 12–15 months. One characteristic that is responsible for GBM malignancy, and its worse prognosis, is the highly infiltrative growth of GBM cells into the healthy brain. GBM cell migration and invasion is a very complex process that is regulated by several factors, which include changes in the migrating cell itself as well as the tumor microenvironment. This chapter provides an overview of routes of invasion of glioma cells, the signaling pathways that drive glioma cell motility, and the processes through which glioma cells modulate their surrounding environment.

Key words: Glioma migration; Invasion; Molecular mechanisms

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Introduction

Glioblastoma (GBM), the most malignant brain tumor, has a complex biology, and despite decades of research, much is still unknown. GBM separates itself from lower grade gliomas by exhibiting central necrosis and microvascular proliferation. It is characterized by a rapid and highly infiltrative growth. In GBM, extracranial metastases are extremely rare; tumor cell invasion and migration are the main features of GBM spreading (1). The invasive nature of GBM leads to local destruction of healthy tissues, and is the main source of recurrence (2). Even with the best imaging methods available, it is difficult to detect cells that had migrated away from the primary tumor. Glioma cells are able to migrate far away from the original tumor and can even cross into the contralateral hemisphere making complete surgical resection of GBM impossible (3). Invasion of glioma cells into the healthy brain also leads to the escape of these cells from irradiation and chemotherapy. Therefore, understanding the biology of glioma cell motility is of great importance for developing novel therapeutic approaches to treat GBM patients.

Glioma cells mainly use two routes to invade the healthy brain: the perivascular space around blood vessels and axons (4). Whether glioma cells exclusively use one route over the other, or whether other roads are also utilized, is not fully understood. In addition, it is not known how glioma cells decide to choose one pathway over the other for invasion. There are several cellular and environmental requirements that set the stage for a glioma cell to move. For example, migrating cells show changes in energy metabolism that are often induced by hypoxic conditions (5, 6). Cytokines, chemokines, nutrition deprivation, and hypoxia lead to changes in the expression of transcription factors (TFs), and subsequently to altered protein expression (7). In this regard, differential expression of ion channels, neurotransmitters, proteases, chemokines, and cytokines has been described in moving versus resting glioma cells (2). Besides transcriptional changes, the cytoskeleton of the glioma cell has to be rearranged to allow cell movement, cell adhesion has to be reduced, and the tumor cell has to be shrunk to fit into the small perivascular space. Furthermore, the extracellular matrix (ECM) has to be remodeled or destroyed to allow glioma cell invasion (8). Even the interaction of glioma cells with adjacent nonneoplastic cells like astrocytes or endothelial cells is important for glioma cell migration (9, 10). This chapter gives an overview of different processes and mechanisms glioma cells use to migrate and invade, and the signaling cascades that regulate the motility of glioma cells.

Infiltration of Diffuse Glioma

PATTERNS OF GLIOMA CELL INFILTRATION

Glioma cells infiltrate into the healthy brain parenchyma using preexisting structures like blood vessels or myelinated nerve fibers of white matter tracts, both of which present high mechanical rigidity (11, 12). ECM stiffness is a major regulator of cell motility. The movement of cells toward a more rigid ECM area is called

mechanotaxis (13). A more rigid ECM, as in the perivascular space, promotes glioma cell migration (14). Stiffness varies with the grade of glioma. It is known that invasive GBM produces stiffness-promoting factors like collagen, fibronectin (FN), and laminin. Furthermore, glioma cells overexpress components of the basal membrane of the cerebral vasculature, for example, tenascin (TN)-C, which is associated with glioma progression (15). Glioma cells are recruited to the perivascular space around blood vessels by chemoattractants like bradykinin, which is produced by endothelial cells (16). Also, overexpression of chemokine receptors on glioma cells has been associated with perivascular invasion (17). Cell movement along white matter tracts, a second known route of glioma cell invasion, is mediated by a variety of proteins called axonal guidance molecules (see the section "Axonal Guidance Molecules"), which act as attracting or repelling factors.

HYPOXIA

The center of GBM is characterized by necrosis, surrounded by an area where tumor cells deal with hypoxia and nutrient starvation. Around the necrotic region, the population of "pseudopalisading" cells become prominent. These glioma cells activate migratory processes in an attempt to escape hypoxia and to reach oxygen-rich areas adjacent to blood vessels (18). Some of the pro-migratory and pro-invasive factors produced or activated in response to hypoxic conditions include: metalloproteases like MMP-9, A Disintegrin, and Metalloproteinase (ADAM)-17 (19, 20); galectins (21); epithelial to mesenchymal transition (EMT) transcriptional regulators like SLUG and SNAIL and the zinc-finger E-Box-binding homeobox proteins ZEB-1 and ZEB-2 (22, 23); and CXCR4 and CXCR7, the latter mediating glioma cell migration toward stromal-derived factor (SDF)-1α/CXCL12 (24, 25).

THE "GO OR GROW" OF TUMOR CELLS

Migration and proliferation of glioma cells are mutually exclusive. This phenomenon, called "Go or Grow," was first discovered in astrocytoma cells, where proliferation and migration are timely separated (26). The "Go or Grow" is modulated by changes in the microenvironment like hypoxia or nutrient depletion, which prompts a tumor cell to "Go" in order to reach a more favorable environment and re-settle there, or to "Grow" if the environment provides enough oxygen and nutrients. The pentose phosphate pathway (PPP) is mainly used during proliferation, and glycolysis is used as the energy source during migration (5). Other parameters that influence the "Go or Grow" of glioma cells are the cell volume, cytoskeleton dynamics, and the ECM composition (27). Differential activation of TFs has been reported: increased NF-κB activity in migrating cells, and c-myc in proliferating cells (28). Also, changes in miRNAs expression modulate the "Go or Grow": elevated miR-451 expression is associated with a shorter GBM patient survival and higher proliferation (29), whereas mir-9, being highly expressed in glioma cells, inhibits proliferation but promotes migration (30). Understanding the process of "Go or Grow" in glioma is of central importance since it is known that ionizing irradiation used for the treatment of GBM promotes the "Go" and thereby the invasive phenotype of glioma cells (31, 32).

Extracellular Matrix

ECM constitutes 10–20% of brain volume. It is produced by the surrounding cells. ECM not only has a structural function but also a major role in brain development, cell survival, migration, maturation, differentiation, and tissue homeostasis (33, 34). The main components of the brain ECM are proteoglycans, hyaluronan, link-proteins like TN-C, and others (Figure 1) (35). Another ECM type in the brain is the basement membrane that covers blood vessels and is part of the perivascular space. Deregulated ECM dynamics is a hallmark of cancer. The ECM of glioma differs from that of the healthy brain. Whereas universal ECM components are expressed uniformly in healthy brains (36), in high-grade glioma fibrous proteins and laminin are upregulated (15, 37). Besides, the interaction of the ECM component hyaluronan with its receptor CD44, both being overexpressed in glioma cells, is a major requirement for glioma invasion (38–40). For glioma cells to invade the healthy brain tissue, the intact ECM has to be destroyed and remodeled. ECM degrading and remodeling enzymes include several MMPs, A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS), the serine protease plasmin, 6-O-sulfatases, heparanases, cathepsins, and urokinase (uPa). These enzymes are not only regulated at the transcriptional and translational levels but also post-translationally by their functionally inhibitory pro-domains or by selective natural proteinase inhibitors (41).

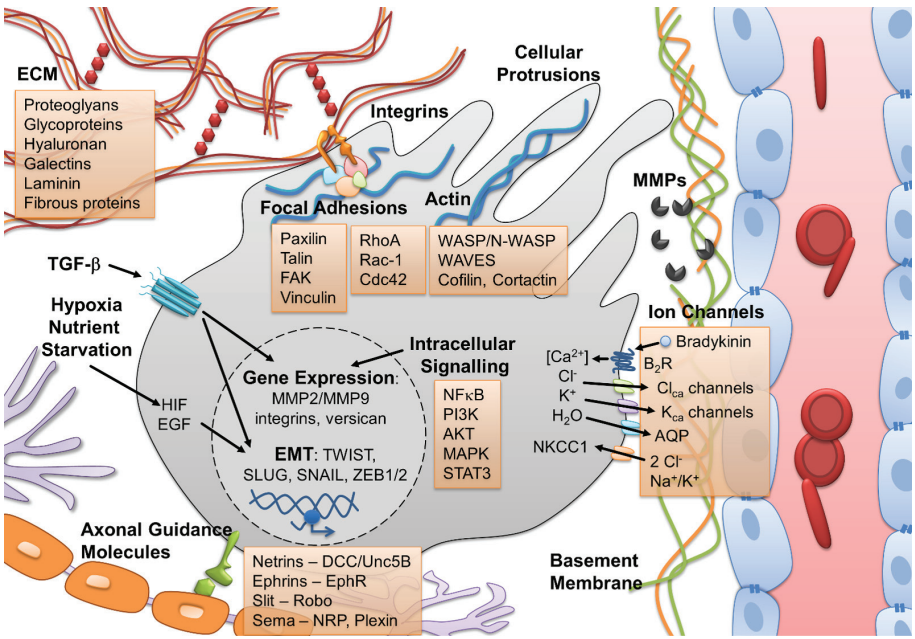

Figure 1 Mechanisms involved in the migration and invasion of glioblastoma (GBM). The migrational phenotype of GBM cells is regulated by a complex interplay of different factors, signaling cascades, as well as cellular and environmental features.

MATRIX-METALLOPROTEINASES

MMPs are a family of secreted or membrane-anchored endoproteinases (42). Their main function is the degradation and remodeling of the ECM. MMP expression in the normal brain is low. In glioma, MMPs are overexpressed or activated. MMP-2 and MMP-9 are of interest for invasive processes in gliomas as their expression correlates with tumor grade and progression (43, 44). MMP-2 and MMP-9 convert latent pro-migratory transforming growth factor (TGF)-β into its active form, which in turn induces MMP-2 in a feedback loop (see the section "The Role of TGF-β in Glioma Cell Motility" (45–47)). MMP-9 expression or activity can be regulated by: activation of signal transducer and activator of transcription (STAT)3; epidermal growth factor (EGF); FN; vitronectin (VN); interleukin (IL)-1β; tumor necrosis factor (TNF)-α; and TGF-β (47–52). Furthermore, glioma cells exploit MMP-14 that is expressed by surrounding microglia cells (53). MMP-14 activates MMP-2 by cleaving its pro-peptide (54, 55). Furthermore, MMP-3, -7, -12, -13, -16, -19, and -26 are also highly expressed and mostly associated with enhanced glioma invasion (56–63). MMPs are inhibited by the four tissue inhibitors of metalloproteinases (TIMP), TIMP-1–4. They inhibit all MMPs but also have other functions including MMP activation. TIMP-2 can form a ternary complex with pro-MMP-2 and MMP-14 that is necessary for efficient MMP-2 activation (55, 64). High TIMP-1 levels and TIMP-3 silencing are associated with a poor prognosis for glioma patients (65–68). Due to these paradoxical effects, the important role of TIMPs in glioma invasion remains elusive.

INTEGRINS—THE LINK BETWEEN THE ECM AND CELLS

Integrins are catalytic inactive heterodimeric transmembrane glycoproteins responsible for cell–ECM interactions. They are the link between the ECM and the cytoskeleton and important for signal transduction. To date, 24 integrins composed of different combinations of 18 α- and 8 β-subunits have been identified (69). The α/β combination determines ligand specificity. Typical ECM ligands for integrins are laminin, collagen, and FN, which are part of the basement membrane in the brain and are expressed by high-grade gliomas (70). Other integrin ligands are thrombospondin (TSP), osteopontin (OPN), VN, and TN-C, all being overexpressed in gliomas. Upon ligand binding, integrins form clusters, leading to activation of the focal adhesion kinase (FAK) and finally to enhanced migration (71). FAK is active and overexpressed in gliomas, and its expression correlates with the tumor grade (72–74). Upon integrin clustering, the cytoplasmic domain attaches to cytoskeletal components to form focal adhesion points at the leading edge of migrating cells (75). This adhesion points give cells a polarity which enable them to move forward. In GBM, integrin β1 is overexpressed and is associated with migration (76, 77). Integrin α9β1 expression correlates with glioma grade and influences MMP-9 expression (78, 79). Furthermore, integrin α5β1 can stimulate MMP-2 expression upon interaction with angiopoietin (80). In addition, integrin αvβ3 and αvβ5 expression is associated with disease progression. Both can bind to the latency-associated peptide (LAP) of the LAP-TGF-β complex and thereby release active TGF-β (81, 82). In summary, integrins are substantial for glioma cell migration, establishing the link between the brain ECM and the tumor cells (Figure 1).

CHONDROITIN SULFATE PROTEOGLYCANS, GLYCOPROTEINS, AND GALECTINS

One important class of proteoglycans are chondroitin sulfate proteoglycans (CSPG), which are overexpressed in glioma and associated with increased glioma invasion (83). A subgroup of CSPG, the lecticans, forms tertiary complexes with hyaluronan and TN-R. Three of them, versican, BEHAB/brevican, and neurocan, are overexpressed in glioma and enhance glioma motility (84–86).

Invasion-promoting ECM glycoproteins secreted in glioma are: Secreted Protein Acidic and Rich in Cysteine (SPARC); TN-C supporting cell adhesion through integrin binding; OPN and VN (87–90). In addition, TSP-1, a multifunctional matrix glycoprotein, is implicated in cell adhesion, migration, invasion, and activation of TGF-β (91; see the section "The Role of TGF-β in Glioma Cell Motility"). Galectins are soluble lectins with specificity for β-galactoside which allow them to bind to proteoglycans and glycoproteins in the brain ECM (92). In malignant gliomas, galectin-1, -3, and -8 are overexpressed and promote glioma cell migration and invasion by modulating the actin cytoskeleton (93–96).

Migration-Associated Changes of the Cytoskeleton

Cell migration is a multistep process initiated by binding of chemoattractants or pro-migratory factors to cell surface receptors, followed by the activation or inactivation of diverse small GTPases and cytoskeleton reorganization (97). The resulting structures are called filopodia, lamellipodia, and podosomes. Turnover of adhesion site formation at the cell front and disruption at the rear is essential for cell movement (98).

SMALL GTPASES

The most important and well-characterized small GTPases associated with cytoskeletal remodeling are: RhoA, which is responsible for coordination of contractility at the cell body and cell rear; RAC-1 that regulates protrusion formation at the leading edge; and CDC42 that modulates cell polarity (99). RAC-1 protein levels correlate with tumor grade in astrocytomas. In addition, RAC-1 is hyperactivated in GBM (100). Enhanced activity of CDC42 and RAC-1 has been reported in infiltrating glioma cells (101). Migration-associated small GTPase activity is regulated by a variety of factors and signals. Rho GTPase activity is mediated by several receptors and effectors. In GBM, two members of the TNF receptor superfamily act through RAC-1: TNF-like weak inducer of apoptosis (TWEAK) and TNF receptor superfamily member 19 (TROY) (99, 102). EGFRvIII, a truncated and constitutively active EGF receptor, and Platelet Growth Factor Receptor alpha (PDGFRα) activate RAC-1-mediated migration through tyrosine protein kinase SRC-dependent DOCK180 phosphorylation (103, 104). RAC-1 is also activated by the IQ-domain GTPase-Activating Protein (IQGAP)-1/ADP-Ribosylation Factor 6 (ARF6), neurotensin, and ephrinB3 signaling (105–107). RAC-1 activity is further modulated by CDC42 (104, 108) as well as by axonal guidance molecules (see the section "Axonal Guidance Molecules"). RhoA activity correlates with

increased glioma cell migration. Functional evidence for the role of RhoA has been demonstrated via inhibition of the RhoA effector ROCK, which leads to enhanced invasion due to the fact that ROCK, together with mDia, coordinates stress fiber formation and focal adhesion, thereby exacerbating migration. The activity of Rho and RAC GTPases is tightly regulated by three main proteins: guanine nucleotide exchange factors (GEFs), GTPase-activating proteins (GAPs), and guanine nucleotide dissociation inhibitors. Many GEFs (e.g., Ect2, ARHGEF7 [βPIX], SWAP, SGEF, Vav3, Trio, Dock180, and Dock9) have been correlated with glioma pathology, higher tumor grade, and glioma invasion, in particular when co-localized with small GTPases (99).

ACTIN REARRANGEMENT, ADHESION COMPLEXES, AND CELLULAR PROTRUSIONS

Nonmotile cells show nonpolarized cell morphology. In these cells, the machinery for actin filament and protrusions formation is inactive. Protrusion formation and actin polymerization requires, besides actin, at least six other proteins: the Arp2/3 complex; an Arp2/3 complex-activating nucleation promoting factor (NPF); a barbed-end capping protein; cofilin and profilin, the latter binding both ADP-bound and ATP-bound actin monomers (109). Lamellipodia are flat, branched, sheet-like actin membrane protrusions that drive cell migration by attaching to the substrate and generating force at the leading edge. Filopodia are thin, finger-like projections beyond the lamellipodial edge, composed of long, bundled, and unbranched actin filaments. No Arp2/3 complex or cofilin are present in filopodia. Invadopodia/podosomes are ventral membrane protrusions responsible for ECM degradation with a not yet well-characterized actin organization (98).

The Wiskott–Aldrich Syndrome (WASP) family consists of two principal classes of proteins: WASPs and SCAR/WAVEs. WASP/N-WASP induces invadopodia and podosome formation, while WAVEs are key regulators of lamellipodia. Cofilin, involved in de-polymerization and polymerization of actin filaments, is highly expressed in migrating GBM cells. It is phosphorylated and inactivated by LIM1/2 kinase. For proper migration and protrusion formation, cofilin and LIM kinase activity must be perfectly balanced. Invadopodia formation is dependent on the activity of cortactin, an actin-binding protein (98).

During cell movement, focal adhesion complexes (FACs) are formed to connect the rearranged actin cytoskeleton to the ECM. While integrin clustering is the first step for FAC formation, microtubule extension promotes FAC disruption. Several studies reported a transport of integrins from the rear to the front of the cell during migration, maintaining the focal adhesion turnover. The presence of large focal adhesions creates more links to actin stress fibers and makes cell movement more difficult (110). The molecular structure of FAC includes integrins, intracellularly bound to paxillin and talin, which subsequently recruit FAK and vinculin. FAK then phosphorylates alpha-actinin, leading to cross-links with actin filaments. The resulting structures lead to alterations of the cell morphology and the generation of traction force necessary to move the cell body. Recent reports indicate that focal adhesion protein expression, like talin and alpha-actinin, is related to the invasiveness of glioma cells (111).

Ion Channels and Their Contribution to Glioma Cell Migration

AUTOCRINE GLUTAMATE SIGNALING

Gliomas express glutamate receptors (GluRs) like α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptors (AMPAR), N-methyl-D-aspartate (NMDA) receptors, and metabotropic mGluRs. AMPARs are composed of four types of subunits: GluR1–4. Through autocrine glutamate signaling, they contribute to enhanced glioma cell invasion (112, 113). The subunits, especially GluR2, influence the cation permeability of AMPAR. In the presence of GluR2, the channel is Ca^{2+} impermeable, the situation in the mature and healthy brain (114, 115). In glioma, GluR2 is not expressed, leading to high Ca^{2+} permeability (116, 117). Artificial GluR2 overexpression in glioma cells inhibits migration (117, 118). Overexpression of GluR1 positively correlates with glioma cell adhesion to collagen, whereas stimulation of AMPAR leads to detachment from the ECM. In a mouse glioma model, overexpression of GluR1 results in enhanced invasion of glioma cells into the perivascular space similar to patterns described in human GBM.

HYDRODYNAMIC MODEL OF GLIOMA CELL MIGRATION

Glioma cells migrate through the extracellular space in the brain. To aid such migration, they reduce their volume by more than 30% by releasing cytoplasmic water (119). For this purpose, glioma cells exploit ion channels which normally function as membrane potential regulators (Figure 1). Unlike adult neurons, glioma cells have high intracellular Cl^- levels (120). This is due to the constitutive expression and prolonged activity of the $Na^+/K^+/Cl^-$ cotransporter 1 (NKCC1) that correlates with glioma grade and invasiveness (121). Upon opening of Cl^- channels, the outflow of Cl^- is accompanied by the efflux of water through aquaporins due to osmotic forces, leading to volume shrinkage. In glioma, the chloride channels ClC-2 and ClC-3 are functionally expressed, and blocking them reduces glioma migration (122–124).

The K^+ gradient, regulated by Na^+/K^+-ATPase, is essential for invasion (125). The KCa family of Ca^{2+}-activated K^+ channels, especially KCa3.1, is overexpressed in 32% of the glioma patients, and its expression correlates with patient survival (126). KCa3.1 is localized at the leading edge of migrating cells, and its inhibition results in reduced migration (127, 128). The bradykinin receptor B_2 (B_2R) is also expressed at the leading edge of migrating glioma cells. It is a critical attractor of glioma cells toward the vasculature, and an activator of ion channels (127, 129). Binding of bradykinin to B_2R leads to increases in intracellular Ca^{2+} which induces the opening of the KCa3.1 and ClC-3 channels, resulting in the efflux of Cl^-, K^+, and water (16, 127, 130). As a result, the glioma cells shrink which enable them to migrate through the narrow space of the brain.

Axonal Guidance Molecules

Glioma cell movement can also occur along myelinated neuronal axons of white matter tracts. A multitude of proteins act as axonal guidance molecules by either attracting or repelling axonal growth cones and modulating neural cell motility

during development (Figure 1). The most prominent axonal guidance molecules are: ephrins (Eph); netrins; Slits and their roundabout (Robo) receptors; semaphorins (Sema) and their receptors plexin and neuropilin (NRP) (131).

EPHRINS

Ephrins serve as ligands of ephrin receptors (EphRs), a family of proteins containing nine EphR class A and five EphR class B members. Interaction of Eph and EphR regulates cell–cell interaction by forward (Eph to EphR) or reverse (EphR to Eph) signaling. Eph regulates cell migration, adhesion, morphology, differentiation, proliferation, and survival through Jun-N-terminal kinase (JNK), STAT3, PKB/AKT, Rho GTPase, and paxillin pathways. Recent studies have detected an abnormal expression of EphB1 receptors in brain tumors (132). Eph proteins have a dual role in glioma cell migration: negative regulation that inhibits migration and positive regulation that promotes migration (133, 134). Therefore, it could be postulated that these proteins might serve as regulators of the "Go or Grow" behavior of GBM.

NETRINS AND SLIT/ROBO

Netrins are a family of laminin-related proteins. Netrin-1, the most prominent representative of the netrin family, is widely expressed in fetal and adult brain tissues. Its expression is associated with progression of various types of human cancers. Netrin-1 binds to UNC5-family dependence receptor (DR) deleted in colorectal cancer (DCC), or other UNC5 molecules. While the absence of netrin-1, DCC/UNC induces apoptosis, the absence of the DRs or enhanced netrin-1 expression is tumorigenic. Netrin expression is associated with poor patient prognosis in lower grade gliomas. In GBM cells, elevated netrin expression activates notch signaling, finally resulting in the gain of stemness and enhancement of invasiveness of these cells (135).

Slit (Slit 1–3) and the Robo receptor family proteins are evolutionarily conserved molecules. During normal development, secreted Slit proteins regulate axon guidance and neuronal precursor cell migration by mediating chemorepulsive signals on cells expressing Robo. In glioma, Slit2 and Robo1 provide different patterns. By hypermethylation of its promoter, the expression of Slit is low in most gliomas (136), whereas the expression of Robo1 is high. Slit2/Robo1 signaling inhibits glioma cell migration and invasion by inactivation of CDC42 signaling. *In vivo*, Slit-2 mitigates infiltration of glioma cells into the healthy brain (137), indicating that a chemo-repulsive signal transmitted by the interaction of Slit2/Robo1 participates in glioma cell migration or guidance (138).

SEMAPHORINS AND THEIR RECEPTORS

Semaphorins (Sema), originally identified as guidance molecules that navigate axon growth in the brain, fall into eight subclasses of secreted, membrane-anchored, and transmembrane proteins (139). Class 3 semaphorins (Sema3) transfer their function through a receptor complex consisting of plexins and neuropilin (NRP)-1 and -2 (140, 141). Downstream signaling of Sema involves RhoA,

RAC-1, and cofilin, leading to the reorganization of the cytoskeleton (142). In GBM cells, inactivation of RhoA by Sema3F leads to the collapse of the cytoskeleton, whereas inhibition of Sema3F promotes cell motility (143, 144). Similar effects have been observed for Sema3G (145), and higher expression of Sema3G in GBM patients has been associated with a better prognosis (146). While Sema3A, 3B, and 3F show antitumorigenic properties in many cancers, other Sema3 family members are associated with tumor progression. Overexpression of Sema3C promotes cell invasion of prostate cancer cell lines, whereas enhanced expression of Sema3E induces metastasis in lung cancer (147, 148). Regarding this dual function of semaphorins, it should be kept in mind that the signaling complexes of Semas and their Robo receptors as well as the downstream signaling cascades that are modulated by Semas are complex and interconnected, which then might finally determine whether they work in a pro- or anti-migratory fashion.

The Role of TGF-β in Glioma Cell Motility

The TGF-β superfamily of cytokines consists of TGF-β 1–3 which are master regulators of inflammation and cell differentiation. They play a key role in tumor progression and metastasis (149). After binding to the TGF-β receptor (TGFβ-R)-I, TGFβ-RII is phosphorylated. This in turn phosphorylates SMAD2/3, which then combines with SMAD4. This complex translocates to the nucleus and regulates gene expression (150). TGF-β is heavily secreted by glioma cells *in vitro* and *in vivo*. TGF-β promotes a mesenchymal phenotype in GBM cells, enhancing invasion and migration *in vitro*, and in an orthotopic mouse model (151). TGF-β also stimulates the production of reactive oxygen species (ROS), and activates ERK1/2, JNK, and NFκB. NFκB finally upregulates the expression of MMP-9 (152). Other mechanisms of TGF-β influencing the ECM and promoting migration include the upregulation of integrin αvβ3 and the versican isoforms V0/V1 (84, 153). Furthermore, TGF-β suppresses phosphatase and tensin homolog (PTEN) in glioma cells through enhanced miR10a/b expression (154). In patient samples, TGFB1I1 (TGF-β1-induced transcript 1) expression was found to be correlated with tumor grade, and activation of EMT pathways (152). In reaction to radiation treatment, the invasion capability of glioma cells is enhanced and TGF-β is upregulated. This suggests a role for TGF-β in treatment resistance (155).

EMT-Like Processes

EMT is a process by which epithelial cells lose their polarity and cell–cell adhesion, resulting in a mesenchymal phenotype characterized by enhanced motility, chemoresistance, and stem-like properties. EMT is involved in various biological functions such as wound healing, embryonic development, and fibrosis (156). In epithelial carcinoma, EMT is a well-established driver of invasion and metastasis (157), and even though gliomas are nonepithelial tumors, EMT-like processes have been described (158). Among the signals that have been shown to induce EMT in glioma are TGF-β, EGF, and Hypoxia-Inducible Factor (HIF; Figure 1) (159).

TWIST, SNAIL, SLUG, AND ZEB

TWIST1 and TWIST2 are helix-loop-helix TFs involved in EMT during development and cancer progression (160). In glioma, TWIST was found to be a possible prognostic marker, and its expression correlates with tumor grade (161, 162). TWIST overexpression promotes invasion of glioma cells *in vitro* and in orthotopic glioma xenotransplants *in vivo* by inducing the expression of EMT-associated genes like MMP-2 and FN-1. The SNAIL family of transcriptional repressors consisting of SNAIL/SNAI1 and SLUG/SNAI2 is known to drive invasion and metastasis in various carcinomas (163). SNAIL binds to E-box DNA sequences of genes related to an epithelial phenotype through carboxy-terminal zinc-finger domains, thereby suppressing their expression. Knockdown of SNAIL in glioma cells by siRNA diminished glioma migration and invasion (164, 165). In GBM, the Rho family GTPase (RND)-3 has been shown to promote the degradation of SNAIL *in vitro* and *in vivo*, while downregulation of RND3 strongly induces SNAIL expression and migration (166). SLUG expression was found to correlate with histologic grade and invasive phenotype in glioma, whereas knockdown of SLUG attenuated invasion and prolonged survival in an intracranial mouse model (167).

The TFs Zinc-finger E-box Binding homeobox proteins (ZEB)-1 and -2 also bind to E-boxes of DNA sequences, thereby repressing cell polarity-associated genes such as E-cadherin/CDH1, cell–adhesion molecules, and stemness-inhibiting miR-200 (168, 169). In GBM patients, ZEB-1 overexpression correlated with poor overall survival. Glioma cells implanted in mice brain were less invasive after knockdown of ZEB-1. ZEB-1 and PDGFRα were found to be co-expressed in tissue samples from GBM patients, while high expression of both ZEB-1 and activated PDGFRα was identified to significantly coincide with poor survival. The same study further established Protein Tyrosine Phosphatase/Nonreceptor type (PTPN)-1 as a regulator of ZEB-1-induced and PDGFR-induced EMT in glioma (170). EMT may also be directly promoted by the microenvironment of GBM. Both the hypoxic marker HIF1α and ZEB-1 were shown to colocalize in hypoxic areas of human GBM. In glioma cells, the suppression of HIF1α negatively affected the level of ZEB-1 (22). ZEB-2 was overexpressed in glioma tissue samples compared to healthy brain tissue, and higher expression of ZEB-2 correlated with glioma pathology grading. Knockdown of ZEB-2 showed an upregulation of E-cadherin, whereas N-cadherin and SNAIL were repressed (171).

CADHERINS

Cadherins are Ca^{2+}-dependent transmembrane molecules with an important role in cell to cell adhesion, recognition, and signaling (172). In epithelial cancers, the loss of E-cadherin and an increased expression of N-cadherin, the so-called "cadherin switch," is considered to be a hallmark of EMT (173). In tissues of GBM and healthy brain, the expression of E-cadherin is generally only marginal (174, 175). However, in a minor subset of GBM showing epithelial differentiation, high expression of E-cadherin is observed, correlating with poorer clinical outcome compared to GBM with low or no E-cadherin expression. Glioma cells with high E-cadherin expression show greater invasion when orthotopically implanted in mice (176). In contrast to its role in carcinoma, N-cadherin is frequently

downregulated in GBM compared to the healthy brain (177, 178). N-cadherin overexpression has been shown to decrease glioma invasion *in vitro* and *in vivo* (179). Interestingly, the role of N-cadherin in glioma is postulated not only to be determined by its expression level but also by its distribution in the cell membrane (180). ZEB-1 knockdown in GBM cells showed a loss of invasiveness and concentration of N-cadherin to the juxtaposed membranes between adjacent cells; the axon-guidance molecule Robo-1 mediated by ZEB-1 can reverse this process by severing the anchorage of N-cadherin to the cytoskeleton (181).

Conclusion

Migration and invasion of glioma cells in the brain follow different migratory routes. It is a complex process regulated by the surrounding environmental conditions, and interconnected by diverse signaling cascades. Understanding the process of migration and invasion of glioma cells is of central importance since these characteristics make GBM aggressive and complete resection impossible. Identifying the molecular mechanisms that govern the motility of GBM cells will help develop new therapeutic strategies to treat this deadly tumor.

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