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ORIGINAL PAPER

The Unwanted Cell Migration in the Brain: Glioma Metastasis

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Abstract Cell migration is identified as a highly orchestrated process. It is a fundamental and essential phenomenon underlying tissue morphogenesis, wound healing, and immune response. Under dysregulation, it contributes to cancer metastasis. Brain is considered to be the most complex organ in human body containing many types of neural cells with astrocytes playing crucial roles in monitoring both physiological and pathological functions. Astrocytoma originates from astrocytes and its most malignant type is glioblastoma multiforme (WHO Grade IV astrocytoma), which is capable to infiltrate widely into the neighboring brain tissues making a complete resection of tumors impossible. Very recently, we have reviewed the mechanisms for astrocytes in migration. Given the fact that astrocytoma shares many histological features with astrocytes, we therefore attempt to review the mechanisms for glioma cells in migration and compare them to normal astrocytes, hoping to obtain a better insight into the dysregulation of migratory mechanisms contributing to their metastasis in the brain.

Keywords Cell migration · Astrocyte · Glioma · Astrocytoma · Glioblastoma multiforme · Metastasis

Introduction

Cell migration is a highly orchestrated process which is known by now as a fundamental and essential phenomenon underlying tissue morphogenesis, wound healing and

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immune response. When its orchestration was disrupted, it would induce unwanted cell migration such as metastasis. Metastasis is one of the "Hallmarks of Cancer" and the leading cause of cancer mortality. When cancer has metastasized, the possibilities of curative treatment would greatly reduce. The latest data showed that there were 14 million new cases and 8.2 million cancer related deaths in 2012 [1]. The number is expected to rise by about 70% over the next two decades in the lowest-income countries.

Surgery is one of the main treatments for cancer. However, when Michael Baum asked the question "Does surgery accelerate or disseminate cancer cells?" [2], the effectiveness of surgery as a cancer treatment had already been questioned. There are reports on surgery significantly stimulating the malignant growth of tumor mass [3] and promoting micrometastases [4]. These suggestions chime perfectly with our previous findings that a physical scratch in culture or a stab wound in brain simulating surgery would induce the astrocytes along the wound to be reactivated into highly migratory cells [5, 6]. Some of these migratory cells also acquired many oncogenic properties [7]. These observations supported the potential of surgery in inducing unwanted cell reactivation, movement and migration, thus might result in metastasis after tumor removal.

Cancer in the brain is the most difficult among all cancers to deal with. Astrocytoma is the most common glioma arisen from astrocyte, and accounts for ~75% of all glioma [8]. World Health Organization (WHO) classified gliomas into four grades of ascending malignancy [9]. Glioblastoma multiforme (GBM) is grade IV that comprises 55% of all gliomas [10]. Their cells diffuse and infiltrate widely into brain tissues making a complete surgical resection impossible [11]. Migration and infiltration of astrocytes and glioma cells appear to be regulated by some very similar mechanisms [7]. This review addresses some interesting and promising mechanisms related to glioma cell migration, including metabolism, epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET), β-catenin, integrins, cell polarity, cytoskeleton, epidermal growth factor receptor (EGFR) signaling, aquaporins and so forth. Meanwhile, some of the similarities and differences between migration of injured astrocytes [12] and metastasis of glioma were compared (Table 1), with a hope to further delineate the multiple cues in GBM metastasis - the unwanted cell migration.

Glioma metabolism

In the adult mammalian brain, the primary energy substrate is glucose [120]. An increase in glucose metabolism was observed in the glioma periphery. It would up-regulate aquaporin 1 (AQP1), lactate dehydrogenase (LDH), and cathepsin B. These up-regulations would contribute to the acidification of the extracellular milieu to enhance invasiveness of the glioma cells [16]. Tumor growth is usually faster than angiogenesis, thus leading to many portions of the tumor under a hypoxic microenvironment. The hypoxic condition would stimulate Warburg anaerobic glycolysis of GMB in both aspects of glucose consumption and lactate production [121–123]. Warburg effect, hypothesized by Nobel Laureate Otto Heinrich Warburg in 1924, was believed to be the root cause of cancer [124]. It stated that cancer, malignant growth, and tumor growth were caused by the fact that tumor cells mainly generate energy by non-oxidative glycolysis with lactate secretion even in the presence of oxygen. The changes of glucose concentration in tumors would induce carbohydrate-response element (ChoRE) expression. The hypoxia would lead to an increase in production of hypoxia-inducible factor (HIF-1) that acts as a key regulatory transcription factor responsible for adaptive cellular changes. HIF-1 and ChoRE interact to induce changes with particularly notable in genes on metabolism. These genes are glucose transporter (GLUT1), hexokinase (HK), phosphoglucose isomerase (PGI), phosphofructokinase (PFKL), fructose-bisphosphate aldolase (ALDO), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), phosphoglycerate kinase (PGK), phosphoglycerate mutase (PGM), enolase 1 (ENOA), pyruvate kinase (PK), pyruvate dehydrogenase kinase (PDK1) and lactate dehydrogenase A (LDH-A) [125, 126]. Under stressful and pathological conditions, lactate and ketone bodies can be used as a substitute for glucose [127]. High concentration of lactate was known to induce glioma cell migration through its strong association with TGF-beta2-dependent regulation of MMP-2 and integrin $\alpha_v\beta_3$ receptors [17].

On the other hand, Professor Ursula Sonnewald has described that cultured astrocytes and glioblastoma C6 cells do not show any difference in lactate production in the presence and absence of glucose [14]. Instead, they are different in their ketone metabolism. Astrocyte utilizes ketone bodies to produce glutamine and glutathione. However, glioblastoma also utilizes ketone bodies, but could not perform anaplerosis. They could only produce an extremely small amount of glutamine, but a lot of glutamate and release them into the extracellular space. This glutamate would not only excitotoxically damage and kill many neurons in the tumor neighborhood via the activation of glutamate receptors and changes in the microenvironment [14], but also facilitate the invasiveness of the glioblastoma cells by stimulating cell proliferation and motility [128, 129]. Therefore, further studies on these specific characteristics and changes of metabolic pathways in tumor cells might lead us to identify some direct targets for the future development of metabolic therapy in blocking or manipulating glioma growth and metastasis.

Table 1 Molecular and cellular factors involved in astrocyte migration and glioma metastasis

Factors			Astrocyte migration	Glioma metastasis
Metabolism	Glutamate		Regulation of astrocyte synaptic cleft invasion via Cx30 [13]	Stimulation of proliferation and motility of glioblastoma cells via activation of glutamate receptors and enhancement of invasion of surrounding tissue by causing excitotoxic damage to normal brain and necrosis in glioblastoma [14]
	Glucose		Impact significantly on astrocyte proliferation, adhesion, and migration by increased production of inflammatory cytokines and oxidative stress [15]	Providing a scenario to the invasive potential of glioma cells in perivascular space [16]
	Lactate		Undetermined	Induction of glioma cell migration through TGF-β2 -dependent regulation of MMP-2 and integrin $\alpha_v\beta_3$ receptors [17]
Extracellular Environment	ECM	Fibronectin[§*]	Involvement in astrocyte adhesion and migration [18]	Promotion of glioma cell migration [19]
		Laminins	Laminins containing β2 and γ3 chains: indispensable for migration and spatial organization of astrocytes [20]	Prevention the invasion of the tumor spheroid into the target aggregate and inhibition of glioma cell migration [21]. Laminin-8: promotion the spread of glioma [22]
		TN-C*	Regulation of migration in cultured astrocytes [23]	High expression in glioma tissue and playing a crucial role in cell migration or invasion [24]
		Brevican	Undetermined	Consistent expression by human glioma and playing a role in glioma invasion [25]
		OPN[§]	Participation in astrocyte migration after focal ischemia [26]	Link with NECL1 in inhibiting migration and invasion of glioma cells [27]
		Collagens[*‡]	Collagen I and VIII: stimulation of astrocyte migration [28, 29]	Collagen I: suppression of malignant glioma invasion [30]. Collagen IV: mediation of MMP-9 depletion induced diminishment of migration speed and reduction of invasion in glioma cells [31]
		Versican[§]	Undetermined	Correlation with invasive phenotype of low-grade astrocytoma [32]
	IL-1β		Enhancement of astrocyte migration [33]	Induction of glioma cell invasion [34]
	IL-18		Undetermined	Enhancement of glioma cell migration through NO/cGMP pathway [35]
	5-HT		Undetermined	Positive modulation of glioma cell proliferation, migration, and invasion [36]
	MMPs[§*‖]		MMP-2: regulation of astrocyte motility through interplay with integrins and actin cytoskeleton [37] MMP-9: positive correlation with astrocyte migration [38]	MMP-2: promotion of glioma cell invasion [39] MMP-9: positive correlation with glioma cell adhesion, migration, and invasion through collagen IV [31]
Cell Membrane Proteins	Channels	AQPs	AQP4: enrichment in astrocyte endfoot membrane domains facing microvessels and pia [40]; with free mobility in plasma membrane and rapid diffusion into extending lamellipodial regions for astrocyte migration support [41] AQP5: promotion of astrocyte process elongation via its up-regulation and polarization to the migrating processes and plasma membrane in the leading edge of the scratch [6]	AQP1: enhancement of glioma cell growth, migration and invasion [42] AQP4: promoting glioma cell migration [43] AQP9: high expression in astrocytoma and positive correlation with the pathological grade of gliomas [44]
		ASIC-1	Undetermined	Regulation of glioma cell proliferation and migration through interactions with integrin-β1, mediated by α-actinin [45]
		TRPV1	Mediation of extracellular Ca^{2+} influx and cytoskeletal changes induced by mechanical stress in astrocyte mobilization [46]	Undetermined

Table 1 (continued)

Factors			Astrocyte migration		Glioma metastasis
		KCNH1	Undetermined		Low expression in brain metastasis including GBM patients [47]
		BK channels	Undetermined		Co-localization with ClC-3 chloride channel to the invading processes of glioma cells [48]
	Receptors	EGFR	Guidance of astrocyte migration [49]		Regulation of glioma growth control and metastasis [50]
		CXCR4/ CXCL12	Undetermined		Control of glioma invasion via autologous chemotaxis driven by their activation [51]
		uPAR	Undetermined		Promotion of glioblastoma cell migration and invasion [52]
		PDGFR	Association with MMP-9 expression induced by thrombin, IL-1β, and LTA in astrocyte migration [33, 53–55]		Overexpression in high-grade poorly differentiated gliomas [56] and promotion of medulloblastoma migration [57]
		NTR	Undetermined		Regulation of glioma invasion in a neurotrophin dependent way [58] and mediation of medulloblastoma invasion via NTR proteolytic processing [59]
		EBI2	Stimulation of ERK phosphorylation, Ca^{2+} signaling and induces astrocyte migration [60]		Undetermined
		$CysLT_1R$	Mediation of TGF-β1 induced astrocyte migration [61]		Undetermined
		S1PR	Mediation of phosphorylated FTY720 to promote astrocyte migration [62]		Enhancement of glioma invasion partially through uPA and CCN1 [63]
		P2YR[§]	Interaction with α integrin to mediate astrocyte migration [64]		Mediation of glioma cell mobility and migration [65]
	Others	Integrins[#]	β_1 integrin	Co-localization and interaction with MMP-2 at the leading edge of migrating astrocytes as a linker between pericellular proteolysis and the actin cytoskeleton [37]	Regulation of glioma metastasis in the process of cell–cell and cell–matrix contact sites [45]
			$\alpha_v\beta_3$ integrin	Induction of astrocyte migration [66]	High expression in glioma cells and contribution to the processes of glioma migration and invasion [67]
			$\alpha_5\beta_1$ integrin	Support of filopodial adhesion to the astrocytic migration template via interaction with fibronectin [68]	Undetermined
			$\alpha_9\beta_1$ integrin	Undetermined	Participation in the increase of diffusive properties of glioma cells [69]
		N-cadherin[§*#]	Promotion of a faster and less-directed migration in astrocyte under reduction of expression [70]		Impact on glioma cell polarity and promotion of a non-directed migration [70]
		E-cadherin*[#]	Contribution to the distinct EMT in reactive astrocytes concomitant with enhanced migration and invasion activity [71]		Inhibition of glioma metastatic behaviors while restoration of its expression [72]
		CD44[#]	Playing a pivotal role in cytoskeleton activation and astrocyte migration via interaction with Rac1-PKNγ [73]		Involvement in human glioma cell invasion *in vitro* through its role in cell interactions with extracellular matrix proteins [74]
		Cx30[#]	Regulation of astrocyte synaptic cleft invasion [13]		Undetermined
		Cx43[#]	Modulation of phenotypical changes in cell morphology, migratory activity including migration and process formation, and cell adhesion in astrocytes [75]		Regulation of p38-mediated cell migration and invasion induced selectively in glioma cells by low doses of γ-radiation in an ERK1/2-independent manner [76]
		Thy-1	Induction of astrocyte migration through the engagement of $\alpha_V\beta_3$ integrin and syndecan-4 via its mediated cell–cell contact [66]		Undetermined

Table 1 (continued)

Factors		Astrocyte migration	Glioma metastasis
Cytoskeletons	Arp2/3 complex	Undetermined	Regulation of glioma cell migration and invasion [77]
	APC	Requirement for the polarization of migrating astrocytes [78]	Undetermined
	GFAP	Regulation of astrocytic hypertrophy and migration occurring after astrocyte activation [79]	A marker for extracranial metastasis of astrocytoma [80]
	β-Tubulin	Undetermined	High expression in astrocytoma and its nitration level positive correlation with the grade of astrocytoma [81]
	SEPT7	Undetermined	Involvement in glioma cell migration with the assistance of cofilin phosphor-mediated cytoskeleton locomotion [82]
	Filamin-A	Undetermined	A specific and sensitive marker for high-grade astrocytoma patients [83]
	Nestin	Localization at the margins of the wound and the immediately adjacent region in astrocytes [7]	Dysregulation of its localization within astrocytoma [7]
	Vimentin*	Expression in proximal reactive astrocytes correlation with migration after focal brain injury [84]	Regulation of glioma progression and metastasis [85]
Signaling Pathways and Kinases	PI3K/Akt*	Activation in astrocyte migration [33, 53–55, 86]	Involvement in glioma metastasis [87]
	VEGF/VEGFR[§]	Strong impact on astrocyte proliferation and motility [88]	Requirement in glioma metastasis [89]
	Wnt/β-catenin*	Participation in Cdc42-dependent phosphorylation of GSK-3β occurring specifically at the leading edge of migrating astrocytes [90]	Regulation of glioma cell migration and invasion [71, 91]
	PLC-PKCα	Promotion of astrocyte migration upon its activation [92]	Undetermined
	PLC-PKCδ	Modulation of astrocyte migration through mediation of ERK1/2 phosphorylation [93]	Undetermined
	MEK-ERK	Initiation of astrocytes migration after injury partly upon its activation [94]	Participation in glial tumor metastasis [95]
	GSK-3α	Undetermined	Suppression of cell invasion induced by its down-regulation [96]
	GSK-3β	Promotion of astrocyte proliferation and migration following injury [96]	Requirement for cell polarity formation and glioma cell invasion [97]
	cGMP-protein kinase G	Enhancement of astrocyte migration induced by its stimulation [98]	Undetermined
	ROCK1	Involvement in increased mobility of astrocytes after injury [99]	Regulation of glioma cell proliferation and metastasis [100]
	mTOR	Attenuation of astrocyte migration upon its blockade [101]	Mediation of migration and invasion in glioma cells [87]
	PKCα	Regulation of ERK1/2 phosphorylation and migration of astrocytes [92]	Regulation of glioma cell metastasis via actin cytoskeleton rearrangements [102]
	PKCζ	Negative association with proper polarization, orientation, and migration of astrocytes [103]	Promotion of glioblastoma cell migration and invasion [104]
	PKCε	Undetermined	Participation in the suppression of glioma metastasis [102]
	CK2	Regulation of migratory ability in astrocytes through reorganization of cytoskeleton [105]	Overexpression in glioblastoma and regulation of glioblastoma metastasis [106]

Table 1 (continued)

Factors			Astrocyte migration	Glioma metastasis
Others	Rho GTPases	RhoA	Requirement in astrocyte migration [66]	Contribution to Netrin-1-promoted glioblastoma cell invasiveness and angiogenesis via its activation [107]
		Rac1	Requirement in cytoskeleton activation and astrocyte migration via interaction with CD44/hyaluronan [73]	Regulation of glioma cell migration and invasion [108, 109]
		Cdc42	Control of centrosome positioning in front of the nucleus and cell orientation toward the wound in migrating astrocytes [110]	Regulation of medulloblastoma cell migration and invasion via actin cytoskeleton disruption induced by Src [111]
	S100		Regulation of astrocyte migration [112] S100A4: reduction of the migratory capacity of reactive white matter astrocytes in the injured CNS [113] S100B: regulation of astrocyte shape and migration via interaction with Src kinase [86]	S100A4: stimulation of the migration rate of glioma cells by modifying the organization of their actin cytoskeleton [114] S100B: participation in invasive properties of glioma cells [86]
	TWIST1*		Undetermined	Expression in human gliomas and promotion of invasion [115]
	Nm23-R1/NDPKββ		Undetermined	Interaction with intermediate filaments in glioma metastasis [116]
	IDH1/2		Undetermined	Involvement in the metastasis of gliomas [117]
	Tiam1		Regulation of wound closure in confluent monolayers of primary astrocytes [118]	Undetermined
	PICK1		Undetermined	Negative regulation of neoplastic infiltration in astrocytic tumors [119]

*Epithelial-mesenchymal transition markers

§Molecules in tumor microenvironment

#Cell adhesion molecules

‡Collagen I and collagen III belong to epithelial-mesenchymal transition markers

‖MMP2, MMP3 and MMP9 belong to epithelial-mesenchymal transition markers

AP-1 activator protein 1, *APC* adenomatous polyposis coli, *AQPs* aquaporins, *ASIC-1* acid-sensing ion channel 1, *BK* big potassium, *bHLH* basic helix-loop-helix, *CCN1* CCN family member 1, *Cdc42* cell division control protein 42 homolog, *CK* creatine phosphokinase, *ClC-3* chloride channel 3, *Cx30* connexin 30, *Cx43* connexin 43, *CXCR4* chemokine (C-X-C motif) receptor 4, *CysLT$_1$R* cysteinyl leukotriene receptor 1, *EBI2* Epstein-Barr virus-induced G-protein coupled receptor 2, *EGFR* epidermal growth factor receptor, *ERK* extracellular signal-regulated kinases, *GBM* glioblastoma multiforme, *GFAP* glial fibrillary acidic protein, *GSK3α* glycogen synthase kinase 3 alpha, *GSK3β* glycogen synthase kinase 3β, *IDH1/2* isocitrate Dehydrogenase1/2, *IL-1β* Interleukin 1β, *IL-18* Interleukin 18, *KCNH1* Potassium voltage-gated channel subfamily H member 1, *5-LOX* 5-lipoxygenase, *LTA* lipoteichoic acid, *MEK* Mitogen-activated protein kinase kinase, *MMPs* matrix metalloproteinases, *mTOR* the mechanistic target of rapamycin, *NDPKβ* nucleoside diphosphate kinase β, *βNECL1* nectin-like molecule 1, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *NGF* nerve growth factor, *NTR* low-affinity nerve growth factor receptor, *OPN* osteopontin, *PDGFR* platelet-derived growth factor receptor, *PICK1* protein interacting with C Kinase-1, *PI3K* phosphatidylinositol-4,5-bisphosphate 3-kinase, *PLC* phospholipase C, *PKC* protein kinase C, *ROCK* Rho-associated protein kinase, *5-HT* serotonin/5-hydroxytryptamine, *SEPT7* septin 7, *SphK* sphingosine kinase, *S1PR* sphingosine-1-phosphate receptor, *Thy-1* CD90-cluster of differentiation 90, *Tiam1* T-cell lymphoma invasion and metastasis-inducing protein 1, *TIMP* tissue inhibitor of metalloproteinase, *TN-C* tenascin C, *TRPV1* transient receptor potential cation channel subfamily V member 1, *uPA* urokinase-type plasminogen activator, *uPAR* urokinase receptor, *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor

EMT and MET

EMT is a process through which epithelial cells differentiate into mesenchymal cells by losing their cell polarity, cell-cell adhesion, and obtaining migratory and invasive properties. EMT is also known to be essential in the initiation of cancer metastasis [130]. MET is the reverse process of EMT [130]. Relatively little is known about the role MET plays in cancer when compared to the extensive studies of EMT in tumor metastasis. MET is believed to participate in the establishment and stabilization of distant metastasis by allowing cancerous cells to regain epithelial properties and integrate into organs [131, 132]. EMT initiates metastasis by breaking the carcinoma cells adhesion and allows them to break through the basement membrane into the bloodstream through intravasation. Later, when these circulating tumor cells (CTCs) exit the bloodstream to form micrometastases, they undergo MET for clonal outgrowth at these metastatic sites. Thus, EMT and MET form the initiation and completion of the invasion-metastasis cascade.

In gliomas, cells would undergo EMT to obtain the capacity to initiate metastasis and invasion. Glioma tissues have a diverse phenotype which might be caused by various microenvironmental factors and intrinsic genetic alterations. The process of EMT is highly affected by glioma microenvironment such as hypoxia or the enrichment of myeloid cells, indicating epigenetic mechanisms might be more crucial than genetic changes in this process. Interestingly, EMT-inducing factors in gliomas are typically varied from those in other cancers [133]. For example, gliomas rarely expressed the most important cell-cell contact factor E-cadherin [133]. Moreover, Twist-related protein 1 (TWIST1), a bHLH transcription factor orchestrating cancer metastasis through EMT [134], is believed to be a great promising target as a cancer therapeutic [135]. In addition, migrating glioma cells underwent EMT may also undergo MET for metastatic tumor nodules establishment [133]. In recent years, researchers have begun to investigate MET as one of many potential therapeutic targets in the prevention of metastasis [136]. This approach for preventing metastasis is known as differentiation-based therapy or differentiation therapy.

β-Catenin

Catenins are a family of proteins to form complexes with cadherin in cell adhesion. Four catenins have been identified. They are α-catenin, β-catenin, γ-catenin and δ-catenin. Several types of catenins work with N-cadherins to play important roles in learning and memory [137, 138]. Among these subtypes, most studies were focused on α-catenin and β-catenin on their multiple roles in cell adhesion. They were identified in association with cadherins at cell-cell junctions linking their cytoplasmic tails to actin via α-catenin [139].

β-Catenin is a marker protein of EMT and has recently received a lot of attention. The dysregulation of β-catenin pathway inevitably affects cell growth, proliferation, and metastasis [140]. Our previous work has demonstrated that β-catenin was dissociated from the catenin-cadherin complex in cell membrane after astrocyte injury and the detached catenin was translocated into nucleus during astrocyte reactivation [7]. High level of β-catenin protein would lead to an enhancement in cell migration [141]. The high level is likely resulted from the inhibition of its degradation [142]. Inhibition of β-catenin reduces both the response of astrocytes to injury and the induction of the malignant phenotype of astrocytoma. In astrocytoma, catenin signaling pathways were also found to be activated and dysregulated [7]. Therefore, β-catenin is not only important in astrocytes migration after injury, but also essential in glioma metastasis [142–144].

β-Catenin is also regarded as a key signal transducer of the canonical Wnt signaling pathway in many central developmental and pathologic contexts [145]. The up-regulation of many key molecules in the Wnt/β-catenin signaling pathway has been identified in astrocytoma [7, 142, 146]. The Wnt/β-catenin pathway is involved in the regulation of glioma cell migration through promoting nuclear translocation of β-catenin [91]. The pathway was also shown to be up-regulated by FoxM1 which plays an important role in the development and progression of GBM by regulating factors involved in EMT and tumor cell invasion [91]. Wnt inhibitory factor 1 (WIF1) was found to be down-regulated in numerous cancers [147]. It is conceivable that WIF1 inhibits Wnt/β-catenin signal to induce the reversal of EMT, i.e., MET. Some recent basic and clinical research have provided promising results for treating various catenin-associated cancers [148]. Apparently, the Wnt/β-catenin pathway plays crucial roles in glioma metastasis and elicits a variety of actions and functions, some of which may possibly even prove to be anti-oncogenic. Before further elucidation of the pathway, its diversity would create lots of difficulties in finding precision cancer therapeutic targets related to catenin [148].

Integrins

When cancer cells undergo metastasis, invasion and migration to a new tissue, they will have to detach, penetrate and attach to the basal matrix of the target tissue. This process allows cancer cell to leave from their primary site and pull itself forward into the new tissue. Integrins are a large

family of cell-surface receptors mediating the attachment of tumor cells [149]. They are heterodimers with α and β subunits and with many variants [150]. Integrins interact with major plasma membrane components of the tumor cell and ion channels to play crucial roles in metastasis. Integrins are essential for cell migration and invasion, not only for their direct mediation of cell adhesion to the extracellular matrix (ECM) [150], but also for sending and receiving molecular signals for regulating cytoskeletal organization, force generation and survival.

Integrins express and distribute remarkably higher on the surface of malignant tumors as compared with the same type of pre-neoplastic tumors [151]. Its up-regulation in gliomas has been demonstrated to be closely correlated with tumor metastasis [28]. Tumor cells adhere and migrate along the ECM components in the brain via integrin receptors [152].

As mentioned above, integrin $\alpha_v\beta_3$ works closely with lactate in glioma metastasis. Now with more details, integrin $\alpha_v\beta_3$ is part of matrix metalloproteinase (MMP)-activating complex [153] which modulates glioma cell migration [154]. The up-regulation of integrin $\alpha_v\beta_3$ is a needed factor for transforming growth factors β (TGF-β) to promote glioma cell migration [155]. The interactions of integrins with ECM and the signaling pathways triggered could be negatively regulated by tumor suppressor PTEN through their direct dephosphorylation of two key tyrosine-phosphorylated proteins [156]. Moreover, integrin-β1 could interact with an amiloride-sensitive nonselective cation channel through α-actinin to regulate glioma cell migration and proliferation [45]. This ion channel complex composed of acid-sensing ion channel (ASIC)-1 and epithelial Na^+ channel (ENaC) α- and γ-subunits and has not been identified yet in normal astrocytes.

Integrins could indirectly contribute to tumor metastasis by activating other oncogenes/mitogens such as HIFs. In addition to the metabolic effects mentioned above, HIFs could contribute to the modulation of the tumor microenvironment through secretion of growth factors such as erythropoietin (EPO) and vascular endothelial growth factor (VEGF) [157, 158]. Paulus and Tonn identified that integrins are also involved in basement membrane invasion preceding meningeal dissemination and metastasis of glioma cells [159]. Taken together, integrins appear to play important roles in the penetrative growth, migration and invasion of glioma cells. Therefore, they have the potential to be attractive tumor therapeutic targets for GBM [160].

Cell Polarity

One important initial step for preparation of a cell in migration is the establishment of cell polarity, which is essential for directional cell translocation. Perturbation of cell polarity is a distinctive characteristic of cancer cells. Glioma cell polarization, migration and invasion are known to be affected by glycogen synthase kinase 3 (GSK-3), Arp2/3 complex, N-cadherin and Rho-mDia1 pathways [7, 77, 96, 161].

GSK-3 is encoded by GSK-3α and GSK-3β. The phosphorylation of GSK-3β at the Ser9 (pSer9-GSK-3β) was enriched and localized at the leading edge of scratched glioma cells [96]. The enrichment and polarized localization of pSer9-GSK-3β involved with PKC and MAPK pathways and were critical for glioma cell invasion [96]. On the other hand, the down-regulation of GSK-3α and 3β by specific small interfering RNAs inhibited glioma cell invasion [96]. Actin-related proteins (Arps) play a major role in the regulation of actin cytoskeleton. Two of its subunits, Arp2 and Arp3, closely resemble the structure of monomeric actin. Arp2/3 complex is a seven-subunit protein complex that binds to actin networks to rearrange actin cytoskeleton, an important process for cell locomotion, phagocytosis, and intracellular motility of lipid vesicles. Inhibition of Arp2/3 complex would demolish lamellipodia and cell polarity. This would seriously de-escalate the ability of glioma cell migration and invasion [77]. However, loss of N-cadherin in EMT would contribute to the loss of cell polarity and promote the invasive capacity with a faster but less-directed migration of astrocytoma [70]. Such effects were acquired through the modulation of focal adhesions and subsequent integrin dependent cell division cycle 42 (cdc42)-mediated polarity pathway [70]. mDial, a member of the formin protein family, is a Rho effector. Rho-mDia1 pathway works critically to direct cell migration in gliomas through regulating polarization and focal adhesion turnover by aligning cytoskeleton actin [161]. In addition, glioma cell polarization and directional cell migration were also found to be actively regulated by interstitial flow through a CXC chemokine receptor type 4 (CXCR4) dependent mechanism [51]. Although the above findings indicated an essential involvement of cell polarity in gliomas, the amount of data is still not enough to fully elucidate the underlying mechanism. Therefore, it is still too early to consider the translation of these polarity information into therapeutics in prevention of unwanted cell migration in cancer.

Cytoskeleton

Cytoskeleton is the network of filaments and tubules interconnecting filamentous bridges which give shape, structure and organization to the cytoplasm. Cytoskeletal filaments compose of microfilaments, intermediate filaments, and microtubules. Dysregulation of these filaments has been identified in various types of tumors and the locomotion

of these filaments is a crucial contributor of cancer cell spreading.

Microfilaments, also called actin filaments [162], are filamentous structures in the cytoplasm and form part of the cytoskeleton, which are involved in the movement of all mobile cells. The importance of actin regulation has been underscored by inhibition of Rho kinase. Among many regulators of actin filaments, we shall focus more in discussion of the Rho GTPases family. Rho GTPases have been shown to regulate many aspects of intracellular actin dynamics in cell adhesion, migration and invasion. Rho GTPases belong to the family of small signaling G proteins and also are a subfamily of the Ras superfamily. Rho GTPases members have been identified in astrocytoma and melanomas [163]. The Rho family contains 22 members, among which Cdc42, Rac1, and RhoA are being studied in detail [163].

Activation of Rho or Rac has been shown to associate with the proliferative and migratory phenotype of glioma cells [82, 164]. Abnormalities of Rho and Rho-associated coiled-coil-containing protein kinase (ROCK) enhance glioma cell migratory phenotype and induce the local spread of GBM [165]. Overexpression of Rac1N17 in glioma cells has been shown to promote cell migration [108]. Deletion of Rac1 inhibited the medulloblastoma cells migration and invasion through decreasing the cross-linked actin network and pseudopodia [109]. Inhibition of Rho kinase leads to the down-regulation of matrix metalloproteinases (MMPs) and VEGF expression in glioma cells. These down-regulations would also reduce the migration of adjacent endothelial cells and angiogenesis. Moreover, Src-induced disruption of actin network would lead to a decrease of cell migration and invasion [111]. Again, the Src effect is also known to be mediated by the inactivation of Rho-Rac-Cdc42. Thus, Rho kinase might end up playing a key role in establishing a tumor microenvironment [166]. The up-regulation of TWIST1, a great promising target as a cancer therapeutic [135], has been found to significantly promote actin cytoskeletal re-organization and enhance cell migration, adhesion and invasion in GBM [135, 167]. SEPT7 is documented as a cytoskeletal protein with GTPase activity and with markedly decrease level in various gliomas [82]. SEPT7 functions in gliomagenesis and in the suppression of glioma cell growth. Its expression is decreased in astrocytomas with different grades and plays a tumor suppressor role. It was found to reduce glioma cell migration by promoting the phosphorylation of cofilin, a widely distributed intracellular actin-modulating protein to cause actin depolymerization [82].

There are also other actin related regulators involved in glioma metastasis but without known relationship to Rho GTPases. For example, plasma filamin-A is an actin-binding protein crosslinking actin filaments to membrane glycoproteins, and was also determined to be a specific and sensitive marker for high-grade astrocytoma [83]. Extracellular S100 protein A4 interacts with both intracellular and extracellular signaling proteins to speed up astrocytic tumor cell migration through modification of actin cytoskeleton [114]. Blocking the PKC-mediated actin cytoskeleton rearrangements using co-treatment of As_2O_3 and berberine would significantly inhibit glioma cell metastasis [102].

Intermediate filaments GFAP and nestin expression in astrocytoma appeared to be dysregulated for their localizations in contrast to their organized pattern in normal reactive astrocytes [7]. Moreover, intermediate filaments interact with nucleoside diphosphate kinase β (Nm23-R1/NDPKβ), an enzyme functional in cell proliferation, differentiation, tumor progression and metastasis, in cAMP-induced differentiation of rat C6 glioma cells [116]. In glioblastomas, cells strongly express GFAP, vimentin and nestin. In subependymal giant-cell astrocytoma (SEGA), the majority of tumors were GFAP positive and cell processes were filled with intermediate filaments [168]. Furthermore, intermediate filaments were also abundant in gangliogliomas [169]. However, in oligodendrogliomas, intermediate filament proteins are barely observed [170]. Apparently, the direct involvement of intermediate filaments in glioma metastasis remains undefined.

Like in other tumors, glioma metastasis also requires a flexible adaptation of cell shape and cell plasticity. Microtubules associate with centrosome, and together they regulate cell structure and shape [171]. Microtubule β-tubulin shows elevated expression in astrocytoma, and the nitration of β-tubulin to form nitro-β-tubulin which functions in cytoskeleton and cell migration, is positively correlated to the grade of astrocytoma [81]. γ-Tubulin, a core centrosomal protein essential for microtubule nucleation, co-immunoprecipitated with tumor metastasis suppressor Nm23-R1, a constituent of the centrosome, indicating a possible role involved [172].

Although studies with consistent differences in cytoskeletal structure between gliomas and astrocytes have not been well identified so far, the presence of more subtle biochemical alterations in the cytoskeletal structure of glioma cells that contributes to metastasis indicates the important roles cytoskeletal network plays. Further work need to be directed at identifying the various alterations of cytoskeletons involved in glioma metastasis in a more systematic way.

EGFR Signaling

Epidermal growth factor receptor (EGFR) is a transmembrane receptor with intrinsic tyrosine kinase activity. It is a potent mitogen receptor but normally not detectable in the mature CNS. Astrocytes in the cerebral cortex of mouse

express a low level of EGFR [173, 174], but with completely undetectable amount in human brain [175–178]. However, EGFR level in astrocytes is substantially induced and enhanced under mechanical injury, ischemia and human glial tumors [175–178]. Ligand binding to these EGFR causes receptor phosphorylation and activates several important signaling pathways such as PI3K, Akt and mTOR. These subsequently result in changes of cell morphology, motility, and gene expression leading to cell migration [179].

EGFR signal dysregulation is a very common phenomenon in gliomas [180]. The gene encoding EGFR is frequently mutated, amplified, and/or rearranged in malignant astrocytoma. EGFRvIII is a constitutively active form of truncated EGFR. GBM cells expressing EGFRvIII release soluble urokinase receptor to promote glioblastoma cell migration and invasion via activation of ERK1/2 pathway [52]. Dysregulation of EGFR pathway by the deficient in endogenous inhibitory elements such as microRNA-7 eventually leads to the failure in control of glioma growth and causes tumor metastasis [50]. Nevertheless, EGF is an essential factor to maintain the self-renewal of glioma stem cells in vitro, indicating EGFR signals play a role in maintenance of the stem cell population in gliomas [179, 181]. It is now believed that targeting EGFR with microRNA-7 might be a promising plasmid-based antitumor and anti-metastasis gene therapy for human malignant glioma treatment [50].

Aquaporins

Cell preparation for migration in its confined 3D microenvironments requires cell volume regulation via water permeation. Aquaporins (AQPs), a family of water channels, constitute the principal pathway for water movement across the plasma membranes. AQPs were identified to play important roles in tumor cell migration, angiogenesis, cerebral edema and cell-cell adhesion in the brain [182–184].

AQPs on tumor cell membrane could create a net inflow of water and ions to the leading cell protrusions to affect their polarization, total number and size [43, 185, 186]; meanwhile they could allow a net outflow at the trailing edge leading to the cell displacement [187]. Modification of the expression and localization of different isoforms of AQPs correlate well with glioma cell migration [42]. AQP1 and AQP4 are detected in all biopsies from glioma patients with their expressions associated with histological subtype and tumor location [42, 182]. High levels of AQP1 and AQP4 are detected in astrocytoma [182]. AQP5 is also detected in some of the biopsy samples. Furthermore, the level of AQP9 in astrocytoma is significantly higher than in the normal brain tissues and its expression levels are positively correlated with the pathological grade of tumor [44].

The level of AQP1 was reported to be extremely high in GBM [42, 188]. The high level of AQP1 was found to enhance glioma cell growth, migration and invasion [42, 189]. Up-regulation of AQP1 contributes to acidification of the extracellular milieu and to the invasive potential of glioma cells in perivascular space [16]. The exact subcellular localization of AQP1 in the CNS is still not clear and its functions remain to be elucidated.

An increase of AQP4 expression was found in GBM. AQP4 is the most studied AQP in the brain. It was believed to be the major water channel in maintaining water and ion homeostasis in CNS [182]. AQP4 expression was shown to be slightly higher than AQP1 in astrocytoma, and it was involved in promoting cancer cell migration [182]. GBM cell migration and invasion was significantly impaired after AQP4 was deleted [43]. AQP4 was reported to undergo rapid rearrangements of their localization in glioma, leading to changes of the actin and the osmolality of the cytoplasm [43, 185, 186]. Therefore, AQP4 might mediate water flux, thus facilitates rapid modification of cell volume and shape in order to accelerate cell movement [190]. PKC activation could inhibit the AQP4 mediated water permeability and at the same time the rate of glioma invasion [191]. However, the underlying molecular mechanisms of these AQP4 effects are far from understood. Therefore, further research on AQPs is urgently required to provide more insight into how water influences the unwanted migration and infiltration of glioma cells.

Other Factors in Glioma Metastasis

Tumor metastasis is a very complex process. Up to today, we have acquired a great amount of knowledge on its mechanism and markers, but unfortunately it is still far from identifying precise metastatic factors and mechanisms for therapeutic purpose. Primary tumor would create a favorable microenvironment to promote tumor cell metastasis. Many mediators and cellular effectors were accumulated in the local microenvironment that would contribute to tumors metastasis. Some of these key mediators and effectors include primary tumor-derived factors VEGF, CD44, N-cadherin, versican and osteopontin (OPN), local stromal-derived components fibronectin, and tumor/stromal-derived factors CXCL12 and MMPs. Among these factors, VEGF, N-cadherin and MMPs have been addressed above. Some not described in details were summarized in Table 1.

In order to further understand this undiscovered life's mystery-unwanted cell migration, we have reviewed a variety of cellular and molecular components involved in glioma metastasis and compared them to normal astrocyte

migration. In Table 1, we classified them into six categories based on their migration/metastasis-mediating characteristics. Of course, not all of these factors were being researched thoroughly. We have selected 69 factors and addressed the most interesting and promising ones with known details. Table 1 has shown that about 60% (41 factors) of the reviewed factors participated in both normal astrocyte migration and glioma metastasis. Therefore, astrocyte migration and glioma cell infiltration in the brain might be regulated by many common mechanisms [7]. However, the 18 factors specifically participated in glioma metastasis but not in normal astrocyte migration might be better candidates for future development of metastatic therapies.

In this review, we did not describe possible contributions from other cell types in the CNS to tumor metastasis. For example, glioma-derived ECM activates microglia to secret IL-18 to enhance the migration of glioma cell through NO/cGMP pathway [35]. In addition, metastatic spreading of glioma could also be linked to their extracellular vesicles (EVs) released as exosomes to transfer tumor cell derived genetic materials and signaling proteins [192, 193]. The mechanistic environment caused by suspended and aligned nanofibers might also influence glioma cell migration and membrane blebbing dynamic, indicating the possible roles of biophysical components in glioma metastasis [194].

Furthermore, there must be many more unknown factors among cell and cell interactions waited to be discovered and identified. Moreover, cell drinking is known to be involved in glioma metastasis [193, 195, 196]; however, whether this drinking process a preparation of tumor cell to enter metastasis still requires future elucidation.

Conclusion

We have previously reported that physical scratch simulating surgery would result in astrocyte reactivation and a huge amount of cell migration along the scratch [5, 7, 12]. Among these reactive astrocytes, many of them acquired tumor cells characteristics through the dysregulation of β-catenin signaling pathway [7, 140]. These findings arouse our vigilance whether the well-established surgical removal of cancer as a choice of glioma and cancer treatment [7]. If this is valid, operation on tumor will well-induce a storm of cell reactivation and migration along the surgical wound - a perfect source of unwanted metastasis. The search for answers to the questions of why reactive astrocytes and glioma cells are highly migratory after injury, what factors lead to or facilitate metastasis, and what are the underlying migration mechanisms becomes urgently necessary so as for us to assess whether surgery is one of the causes of metastasis and still a proper treatment for cancer.

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References

1. McGuire S (2016) World cancer report 2014. Geneva, switzerland: world health organization, international agency for research on cancer, who press, 2015. Adv Nutr 7:418–419
2. Baum M (1996) Does surgery disseminate or accelerate cancer? Lancet 347:260
3. Bogden AE, Moreau JP, Eden PA (1997) Proliferative response of human and animal tumours to surgical wounding of normal tissues: Onset, duration and inhibition. Br J Cancer 75:1021–1027
4. Demicheli R, Valagussa P, Bonadonna G (2001) Does surgery modify growth kinetics of breast cancer micrometastases? Br J Cancer 85:490–492
5. Gao K, Wang CR, Jiang F, Wong AY, Su N, Jiang JH, Chai RC, Vatcher G, Teng J, Chen J, Jiang YW, Yu AC (2013) Traumatic scratch injury in astrocytes triggers calcium influx to activate the jnk/c-jun/ap-1 pathway and switch on gfap expression. Glia 61:2063–2077
6. Chai RC, Jiang JH, Wong AY, Jiang F, Gao K, Vatcher G, Hoi Yu AC (2013) AQP5 is differentially regulated in astrocytes during metabolic and traumatic injuries. Glia 61:1748–1765
7. Yang C, Iyer RR, Yu AC, Yong RL, Park DM, Weil RJ, Ikejiri B, Brady RO, Lonser RR, Zhuang Z (2012) Beta-catenin signaling initiates the activation of astrocytes and its dysregulation contributes to the pathogenesis of astrocytomas. Proc Natl Acad Sci USA 109:6963–6968
8. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS (2015) Cbtrus statistical report: primary brain and central nervous system tumors diagnosed in the united states in 2008–2012. Neuro Oncol 17(Suppl 4):iv1–iv62
9. Kleihues P, Burger PC, Scheithauer BW (1993) The new who classification of brain tumours. Brain Pathol 3:255–268
10. Goodenberger ML, Jenkins RB (2012) Genetics of adult glioma. Cancer Genet 205:613–621
11. Maher EA, Furnari FB, Bachoo RM, Rowitch DH, Louis DN, Cavenee WK, DePinho RA (2001) Malignant glioma: genetics and biology of a grave matter. Genes Dev 15:1311–1333
12. Zhan JS, Gao K, Chai RC, Jia XH, Luo DP, Ge G, Jiang YW, Fung YW, Li L, Yu AC (2017) Astrocytes in migration. Neurochem Res 42:272–282
13. Pannasch U, Freche D, Dallerac G, Ghezali G, Escartin C, Ezan P, Cohen-Salmon M, Benchenane K, Abudara V, Dufour A, Lubke JH, Deglon N, Knott G, Holcman D, Rouach N (2014) Connexin 30 sets synaptic strength by controlling astroglial synapse invasion. Nat Neurosci 17:549–558
14. Eloqayli H, Melo TM, Haukvik A, Sonnewald U (2011) [2,4-(13)c]beta-hydroxybutyrate metabolism in astrocytes and c6 glioblastoma cells. Neurochem Res 36:1566–1573
15. Shin ES, Huang Q, Gurel Z, Sorenson CM, Sheibani N (2014) High glucose alters retinal astrocytes phenotype through increased production of inflammatory cytokines and oxidative stress. PLoS ONE 9:e103148

16. Hayashi Y, Edwards NA, Proescholdt MA, Oldfield EH, Merrill MJ (2007) Regulation and function of aquaporin-1 in glioma cells. Neoplasia 9:777–787
17. Baumann F, Leukel P, Doerfelt A, Beier CP, Dettmer K, Oefner PJ, Kastenberger M, Kreutz M, Nickl-Jockschat T, Bogdahn U, Bosserhoff AK, Hau P (2009) Lactate promotes glioma migration by tgf-beta2-dependent regulation of matrix metalloproteinase-2. Neuro Oncol 11:368–380
18. van Strien ME, Breve JJ, Fratantoni S, Schreurs MW, Bol JG, Jongenelen CA, Drukarch B, van Dam AM (2011) Astrocyte-derived tissue transglutaminase interacts with fibronectin: A role in astrocyte adhesion and migration? PLoS ONE 6:e25037
19. Ohnishi T, Hiraga S, Izumoto S, Matsumura H, Kanemura Y, Arita N, Hayakawa T (1998) Role of fibronectin-stimulated tumor cell migration in glioma invasion in vivo: clinical significance of fibronectin and fibronectin receptor expressed in human glioma tissues. Clin Exp Metastasis 16:729–741
20. Gnanaguru G, Bachay G, Biswas S, Pinzon-Duarte G, Hunter DD, Brunken WJ (2013) Laminins containing the beta2 and gamma3 chains regulate astrocyte migration and angiogenesis in the retina. Development 140:2050–2060
21. Reith A, Bjerkvig R, Rucklidge GJ (1994) Laminin: a potential inhibitor of rat glioma cell invasion in vitro. Anticancer Res 14:1071–1076
22. Ljubimova JY, Fujita M, Khazenzon NM, Ljubimov AV, Black KL (2006) Changes in laminin isoforms associated with brain tumor invasion and angiogenesis. Front Biosci 11:81–88
23. Nishio T, Kawaguchi S, Yamamoto M, Iseda T, Kawasaki T, Hase T (2005) Tenascin-c regulates proliferation and migration of cultured astrocytes in a scratch wound assay. Neuroscience 132:87–102
24. Hirata E, Arakawa Y, Shirahata M, Yamaguchi M, Kishi Y, Okada T, Takahashi JA, Matsuda M, Hashimoto N (2009) Endogenous tenascin-c enhances glioblastoma invasion with reactive change of surrounding brain tissue. Cancer Sci 100:1451–1459
25. Zhang H, Kelly G, Zerillo C, Jaworski DM, Hockfield S (1998) Expression of a cleaved brain-specific extracellular matrix protein mediates glioma cell invasion in vivo. J Neurosci 18:2370–2376
26. Ellison JA, Barone FC, Feuerstein GZ (1999) Matrix remodeling after stroke. De novo expression of matrix proteins and integrin receptors. Ann N Y Acad Sci 890:204–222
27. Yin B, Li KH, An T, Chen T, Peng XZ (2010) Nectin-like molecule 1 inhibits the migration and invasion of u251 glioma cells by regulating the expression of an extracellular matrix protein osteopontin. Chin Med Sci J 25:100–104
28. Hirano S, Yonezawa T, Hasegawa H, Hattori S, Greenhill NS, Davis PF, Sage EH, Ninomiya Y (2004) Astrocytes express type viii collagen during the repair process of brain cold injury. Biochem Biophys Res Commun 317:437–443
29. Goldberg WJ, Levine KV, Tadvalkar G, Laws ER Jr, Bernstein JJ (1992) Mechanisms of c6 glioma cell and fetal astrocyte migration into hydrated collagen i gels. Brain Res 581:81–90
30. Honma K, Miyata T, Ochiya T (2007) Type i collagen gene suppresses tumor growth and invasion of malignant human glioma cells. Cancer Cell Int 7:12
31. Zhao Y, Xiao A, diPierro CG, Carpenter JE, Abdel-Fattah R, Redpath GT, Lopes MB, Hussaini IM (2010) An extensive invasive intracranial human glioblastoma xenograft model: role of high level matrix metalloproteinase 9. Am J Pathol 176:3032–3049
32. Varga I, Hutoczki G, Szemcsak CD, Zahuczky G, Toth J, Adamecz Z, Kenyeres A, Bognar L, Hanzely Z, Klekner A (2012) Brevican, neurocan, tenascin-c and versican are mainly responsible for the invasiveness of low-grade astrocytoma. Pathol Oncol Res 18:413–420
33. Yang CM, Hsieh HL, Yu PH, Lin CC, Liu SW (2015) Il-1beta induces mmp-9-dependent brain astrocytic migration via transactivation of pdgf receptor/nadph oxidase 2-derived reactive oxygen species signals. Mol Neurobiol 52:303–317
34. Huang HC, Huang CY, Lin-Shiau SY, Lin JK (2009) Ursolic acid inhibits il-1beta or tnf-alpha-induced c6 glioma invasion through suppressing the association zip/p62 with pkc-zeta and downregulating the mmp-9 expression. Mol Carcinog 48:517–531
35. Yeh WL, Lu DY, Liou HC, Fu WM (2012) A forward loop between glioma and microglia: glioma-derived extracellular matrix-activated microglia secrete il-18 to enhance the migration of glioma cells. J Cell Physiol 227:558–568
36. Merzak A, Koochekpour S, Fillion MP, Fillion G, Pilkington GJ (1996) Expression of serotonin receptors in human fetal astrocytes and glioma cell lines: a possible role in glioma cell proliferation and migration. Brain Res Mol Brain Res 41:1–7
37. Ogier C, Bernard A, Chollet AM, T LED, Hanessian S, Charton G, Khrestchatisky M, Rivera S (2006) Matrix metalloproteinase-2 (mmp-2) regulates astrocyte motility in connection with the actin cytoskeleton and integrins. Glia 54:272–284
38. Hsieh HL, Lin CC, Shih RH, Hsiao LD, Yang CM (2012) Nadph oxidase-mediated redox signal contributes to lipoteichoic acid-induced mmp-9 upregulation in brain astrocytes. J Neuroinflammation 9:110
39. Wick W, Platten M, Weller M (2001) Glioma cell invasion: regulation of metalloproteinase activity by tgf-beta. J Neurooncol 53:177–185
40. Nielsen S, Nagelhus EA, Amiry-Moghaddam M, Bourque C, Agre P, Ottersen OP (1997) Specialized membrane domains for water transport in glial cells: high-resolution immunogold cytochemistry of aquaporin-4 in rat brain. J Neurosci 17:171–180
41. Smith AJ, Jin BJ, Ratelade J, Verkman AS (2014) Aggregation state determines the localization and function of m1- and m23-aquaporin-4 in astrocytes. J Cell Biol 204:559–573
42. McCoy E, Sontheimer H (2007) Expression and function of water channels (aquaporins) in migrating malignant astrocytes. Glia 55:1034–1043
43. Ding T, Ma Y, Li W, Liu X, Ying G, Fu L, Gu F (2011) Role of aquaporin-4 in the regulation of migration and invasion of human glioma cells. Int J Oncol 38:1521–1531
44. Tan G, Sun SQ, Yuan DL (2008) Expression of the water channel protein aquaporin-9 in human astrocytic tumours: correlation with pathological grade. J Int Med Res 36:777–782
45. Rooj AK, Liu Z, McNicholas CM, Fuller CM (2015) Physical and functional interactions between a glioma cation channel and integrin-beta1 require alpha-actinin. Am J Physiol Cell Physiol 309:C308–C319
46. Ho KW, Lambert WS, Calkins DJ (2014) Activation of the trpv1 cation channel contributes to stress-induced astrocyte migration. Glia 62:1435–1451
47. Martinez R, Stuhmer W, Martin S, Schell J, Reichmann A, Rohde V, Pardo L (2015) Analysis of the expression of kv10.1 potassium channel in patients with brain metastases and glioblastoma multiforme: impact on survival. BMC Cancer 15:839
48. Sontheimer H (2008) An unexpected role for ion channels in brain tumor metastasis. Exp Biol Med 233:779–791
49. Liu B, Neufeld AH (2004) Activation of epidermal growth factor receptor causes astrocytes to form cribriform structures. Glia 46:153–168
50. Wang W, Dai LX, Zhang S, Yang Y, Yan N, Fan P, Dai L, Tian HW, Cheng L, Zhang XM, Li C, Zhang JF, Xu F, Shi G, Chen XL, Du T, Li YM, Wei YQ, Deng HX (2013) Regulation of epidermal growth factor receptor signaling by plasmid-based

microrna-7 inhibits human malignant gliomas growth and metastasis in vivo. Neoplasma 60:274–283
51. Munson JM, Bellamkonda RV, Swartz MA (2013) Interstitial flow in a 3d microenvironment increases glioma invasion by a cxcr4-dependent mechanism. Cancer Res 73:1536–1546
52. Gilder AS, Jones KA, Hu J, Wang L, Chen CC, Carter BS, Gonias SL (2015) Soluble urokinase receptor is released selectively by glioblastoma cells that express epidermal growth factor receptor variant iii and promotes tumor cell migration and invasion. J Biol Chem 290:14798–14809
53. Wang HH, Hsieh HL, Yang CM (2010) Calmodulin kinase ii-dependent transactivation of pdgf receptors mediates astrocytic mmp-9 expression and cell motility induced by lipoteichoic acid. J Neuroinflammation 7:84
54. Lin CC, Lee IT, Chi PL, Hsieh HL, Cheng SE, Hsiao LD, Liu CJ, Yang CM (2014) C-src/jak2/pdgfr/pkcdelta-dependent mmp-9 induction is required for thrombin-stimulated rat brain astrocytes migration. Mol Neurobiol 49:658–672
55. Hsieh HL, Wang HH, Wu CY, Tung WH, Yang CM (2010) Lipoteichoic acid induces matrix metalloproteinase-9 expression via transactivation of pdgf receptors and nf-kappab activation in rat brain astrocytes. Neurotox Res 17:344–359
56. Clarke ID, Dirks PB (2003) A human brain tumor-derived pdgfr-alpha deletion mutant is transforming. Oncogene 22:722–733
57. MacDonald TJ, Brown KM, LaFleur B, Peterson K, Lawlor C, Chen Y, Packer RJ, Cogen P, Stephan DA (2001) Expression profiling of medulloblastoma: Pdgfra and the ras/mapk pathway as therapeutic targets for metastatic disease. Nat Genet 29:143–152
58. Johnston AL, Lun X, Rahn JJ, Liacini A, Wang L, Hamilton MG, Parney IF, Hempstead BL, Robbins SM, Forsyth PA, Senger DL (2007) The p75 neurotrophin receptor is a central regulator of glioma invasion. PLoS Biol 5:e212
59. Wang X, Cui M, Wang L, Chen X, Xin P (2010) Inhibition of neurotrophin receptor p75 intramembran proteolysis by gamma-secretase inhibitor reduces medulloblastoma spinal metastasis. Biochem Biophys Res Commun 403:264–269
60. Rutkowska A, Preuss I, Gessier F, Sailer AW, Dev KK (2015) Ebi2 regulates intracellular signaling and migration in human astrocyte. Glia 63:341–351
61. Huang XQ, Zhang XY, Wang XR, Yu SY, Fang SH, Lu YB, Zhang WP, Wei EQ (2012) Transforming growth factor beta1-induced astrocyte migration is mediated in part by activating 5-lipoxygenase and cysteinyl leukotriene receptor 1. J Neuroinflamm 9:145
62. Mullershausen F, Craveiro LM, Shin Y, Cortes-Cros M, Bassilana F, Osinde M, Wishart WL, Guerini D, Thallmair M, Schwab ME, Sivasankaran R, Seuwen K, Dev KK (2007) Phosphorylated fty720 promotes astrocyte migration through sphingosine-1-phosphate receptors. J Neurochem 102:1151–1161
63. Young N, Pearl DK, Van Brocklyn JR (2009) Sphingosine-1-phosphate regulates glioblastoma cell invasiveness through the urokinase plasminogen activator system and ccn1/cyr61. Mol Cancer Res 7:23–32
64. Wang M, Kong Q, Gonzalez FA, Sun G, Erb L, Seye C, Weisman GA (2005) P2y nucleotide receptor interaction with alpha integrin mediates astrocyte migration. J Neurochem 95:630–640
65. Jantaratnotai N, McLarnon JG (2011) Calcium dependence of purinergic subtype p2y(1) receptor modulation of c6 glioma cell migration. Neurosci Lett 497:80–84
66. Kong M, Munoz N, Valdivia A, Alvarez A, Herrera-Molina R, Cardenas A, Schneider P, Burridge K, Quest AF, Leyton L (2013) Thy-1-mediated cell-cell contact induces astrocyte migration through the engagement of alphavbeta3 integrin and syndecan-4. Biochim Biophys Acta 1833:1409–1420
67. Kanamori M, Kawaguchi T, Berger MS, Pieper RO (2006) Intracranial microenvironment reveals independent opposing functions of host alphavbeta3 expression on glioma growth and angiogenesis. J Biol Chem 281:37256–37264
68. Stenzel D, Lundkvist A, Sauvaget D, Busse M, Graupera M, van der Flier A, Wijelath ES, Murray J, Sobel M, Costell M, Takahashi S, Fassler R, Yamaguchi Y, Gutmann DH, Hynes RO, Gerhardt H (2011) Integrin-dependent and -independent functions of astrocytic fibronectin in retinal angiogenesis. Development 138:4451–4463
69. Brown MC, Staniszewska I, Lazarovici P, Tuszynski GP, Del Valle L, Marcinkiewicz C (2008) Regulatory effect of nerve growth factor in alpha9beta1 integrin-dependent progression of glioblastoma. Neuro Oncol 10:968–980
70. Camand E, Peglion F, Osmani N, Sanson M, Etienne-Manneville S (2012) N-cadherin expression level modulates integrin-mediated polarity and strongly impacts on the speed and directionality of glial cell migration. J Cell Sci 125:844–857
71. Lu P, Wang Y, Liu X, Wang H, Zhang X, Wang K, Wang Q, Hu R (2016) Malignant gliomas induce and exploit astrocytic mesenchymal-like transition by activating canonical wnt/beta-catenin signaling. Med Oncol 33:66
72. Wang H, Zhou M, Shi B, Zhang Q, Jiang H, Sun Y, Liu J, Zhou K, Yao M, Gu J, Yang S, Mao Y, Li Z (2011) Identification of an exon 4-deletion variant of epidermal growth factor receptor with increased metastasis-promoting capacity. Neoplasia 13:461–471
73. Bourguignon LY, Gilad E, Peyrollier K, Brightman A, Swanson RA (2007) Hyaluronan-cd44 interaction stimulates rac1 signaling and pkn gamma kinase activation leading to cytoskeleton function and cell migration in astrocytes. J Neurochem 101:1002–1017
74. Merzak A, Koocheckpour S, Pilkington GJ (1994) Cd44 mediates human glioma cell adhesion and invasion in vitro. Cancer Res 54:3988–3992
75. Olk S, Turchinovich A, Grzendowski M, Stuhler K, Meyer HE, Zoidl G, Dermietzel R (2010) Proteomic analysis of astroglial connexin43 silencing uncovers a cytoskeletal platform involved in process formation and migration. Glia 58:494–505
76. Ghosh S, Kumar A, Tripathi RP, Chandna S (2014) Connexin-43 regulates p38-mediated cell migration and invasion induced selectively in tumour cells by low doses of gamma-radiation in an erk-1/2-independent manner. Carcinogenesis 35:383–395
77. Liu Z, Yang X, Chen C, Liu B, Ren B, Wang L, Zhao K, Yu S, Ming H (2013) Expression of the arp2/3 complex in human gliomas and its role in the migration and invasion of glioma cells. Oncol Rep 30:2127–2136
78. Etienne-Manneville S, Manneville JB, Nicholls S, Ferenczi MA, Hall A (2005) Cdc42 and par6-pkczeta regulate the spatially localized association of dlg1 and apc to control cell polarization. J Cell Biol 170:895–901
79. Yu AC, Lee YL, Eng LF (1993) Astrogliosis in culture: I. The model and the effect of antisense oligonucleotides on glial fibrillary acidic protein synthesis. J Neurosci Res 34:295–303
80. Gottschalk J, Martin H, Kretschmer B, Barz H, Janda J, Szymas J (1985) Significance of immunohistochemistry in neurooncology. I. Demonstration of glial fibrillary acid protein (gfap) in extracranial metastases from primary brain tumors. Zentralbl Allg Pathol 130:391–396
81. Peng F, Li J, Guo T, Yang H, Li M, Sang S, Li X, Desiderio DM, Zhan X (2015) Nitroproteins in human astrocytomas discovered by gel electrophoresis and tandem mass spectrometry. J Am Soc Mass Spectrom 26:2062–2076

82. Hou M, Liu X, Cao J, Chen B (2016) Sept7 overexpression inhibits glioma cell migration by targeting the actin cytoskeleton pathway. Oncol Rep 35:2003–2010
83. Alper O, Stetler-Stevenson WG, Harris LN, Leitner WW, Ozdemirli M, Hartmann D, Raffeld M, Abu-Asab M, Byers S, Zhuang Z, Oldfield EH, Tong Y, Bergmann-Leitner E, Criss WE, Nagasaki K, Mok SC, Cramer DW, Karaveli FS, Goldbach-Mansky R, Leo P, Stromberg K, Weil RJ (2009) Novel anti-filamin-a antibody detects a secreted variant of filamin-a in plasma from patients with breast carcinoma and high-grade astrocytoma. Cancer Sci 100:1748–1756
84. Wang K, Bekar LK, Furber K, Walz W (2004) Vimentin-expressing proximal reactive astrocytes correlate with migration rather than proliferation following focal brain injury. Brain Res 1024:193–202
85. Trog D, Fountoulakis M, Friedlein A, Golubnitschaja O (2006) Is current therapy of malignant gliomas beneficial for patients? Proteomics evidence of shifts in glioma cells expression patterns under clinically relevant treatment conditions. Proteomics 6:2924–2930
86. Brozzi F, Arcuri C, Giambanco I, Donato R (2009) S100b protein regulates astrocyte shape and migration via interaction with src kinase: implications for astrocyte development, activation, and tumor growth. J Biol Chem 284:8797–8811
87. Jiang Y, Zhang Q, Bao J, Du C, Wang J, Tong Q, Liu C (2015) Schisandrin b suppresses glioma cell metastasis mediated by inhibition of mtor/mmp-9 signal pathway. Biomed Pharmacother 74:77–82
88. Wuestefeld R, Chen J, Meller K, Brand-Saberi B, Theiss C (2012) Impact of vegf on astrocytes: analysis of gap junctional intercellular communication, proliferation, and motility. Glia 60:936–947
89. Goel S, Chen F, Hong H, Valdovinos HF, Hernandez R, Shi S, Barnhart TE, Cai W (2014) Vegf(1)(2)(1)-conjugated mesoporous silica nanoparticle: a tumor targeted drug delivery system. ACS Appl Mater Interfaces 6:21677–21685
90. Etienne-Manneville S, Hall A (2003) Cdc42 regulates gsk-3beta and adenomatous polyposis coli to control cell polarity. Nature 421:753–756
91. Wang Z, Zhang S, Siu TL, Huang S (2015) Glioblastoma multiforme formation and emt: Role of foxm1 transcription factor. Curr Pharm Des 21:1268–1271
92. Shu Q, Hu ZL, Huang C, Yu XW, Fan H, Yang JW, Fang P, Ni L, Chen JG, Wang F (2014) Orexin-a promotes cell migration in cultured rat astrocytes via ca2+-dependent pkcalpha and erk1/2 signals. PLoS ONE 9:e95259
93. Huang C, Wu J, Liao R, Zhang W (2012) Skf83959, an agonist of phosphatidylinositol-linked d(1)-like receptors, promotes erk1/2 activation and cell migration in cultured rat astrocytes. PLoS ONE 7:e49954
94. Lim JH, Gibbons HM, O'Carroll SJ, Narayan PJ, Faull RL, Dragunow M (2007) Extracellular signal-regulated kinase involvement in human astrocyte migration. Brain Res 1164:1–13
95. Cheng P, Alberts I, Li X (2013) The role of erk1/2 in the regulation of proliferation and differentiation of astrocytes in developing brain. Int J Dev Neurosci 31:783–789
96. Zou Q, Hou Y, Shen F, Wang Y (2013) Polarized regulation of glycogen synthase kinase-3beta is important for glioma cell invasion. PLoS ONE 8:e81814
97. Yin Y, Zhang X, Li Z, Deng L, Jiao G, Zhang B, Xie P, Mu H, Qiao W, Zou J (2013) Glucocorticoid receptor beta regulates injury-mediated astrocyte activation and contributes to glioma pathogenesis via modulation of beta-catenin/tcf transcriptional activity. Neurobiol Dis 59:165–176
98. Boran MS, Garcia A (2007) The cyclic gmp-protein kinase g pathway regulates cytoskeleton dynamics and motility in astrocytes. J Neurochem 102:216–230
99. Holtje M, Hoffmann A, Hofmann F, Mucke C, Grosse G, Van Rooijen N, Kettenmann H, Just I, Ahnert-Hilger G (2005) Role of rho gtpase in astrocyte morphology and migratory response during in vitro wound healing. J Neurochem 95:1237–1248
100. Zhang P, Lu Y, Liu XY, Zhou YH (2015) Knockdown of rho-associated protein kinase 1 suppresses proliferation and invasion of glioma cells. Tumour Biol 36:421–428
101. Li CY, Li X, Liu SF, Qu WS, Wang W, Tian DS (2015) Inhibition of mtor pathway restrains astrocyte proliferation, migration and production of inflammatory mediators after oxygen-glucose deprivation and reoxygenation. Neurochem Int 83–84:9–18
102. Lin TH, Kuo HC, Chou FP, Lu FJ (2008) Berberine enhances inhibition of glioma tumor cell migration and invasiveness mediated by arsenic trioxide. BMC Cancer 8:58
103. Narayanan AS, Reyes SB, Um K, McCarty JH, Tolias KF (2013) The rac-gap bcr is a novel regulator of the par complex that controls cell polarity. Mol Biol Cell 24:3857–3868
104. Guo H, Gu F, Li W, Zhang B, Niu R, Fu L, Zhang N, Ma Y (2009) Reduction of protein kinase c zeta inhibits migration and invasion of human glioblastoma cells. J Neurochem 109:203–213
105. Kramerov AA, Ahmed K, Ljubimov AV (2012) Cell rounding in cultured human astrocytes and vascular endothelial cells upon inhibition of ck2 is mediated by actomyosin cytoskeleton alterations. J Cell Biochem 113:2948–2956
106. Ji H, Lu Z (2013) The role of protein kinase ck2 in glioblastoma development. Clin Cancer Res 19:6335–6337
107. Shimizu A, Nakayama H, Wang P, Konig C, Akino T, Sandlund J, Coma S, Italiano JE Jr, Mammoto A, Bielenberg DR, Klagsbrun M (2013) Netrin-1 promotes glioblastoma cell invasiveness and angiogenesis by multiple pathways including activation of rhoa, cathepsin b, and camp-response element-binding protein. J Biol Chem 288:2210–2222
108. Hwang SY, Jung JW, Jeong JS, Kim YJ, Oh ES, Kim TH, Kim JY, Cho KH, Han IO (2006) Dominant-negative rac increases both inherent and ionizing radiation-induced cell migration in c6 rat glioma cells. Int J Cancer 118:2056–2063
109. Chen B, Gao Y, Jiang T, Ding J, Zeng Y, Xu R, Jiang X (2011) Inhibition of tumor cell migration and invasion through knockdown of rac1 expression in medulloblastoma cells. Cell Mol Neurobiol 31:251–257
110. Etienne-Manneville S, Hall A (2001) Integrin-mediated activation of cdc42 controls cell polarity in migrating astrocytes through pkczeta. Cell 106:489–498
111. Bhoopathi P, Gondi CS, Gujrati M, Dinh DH, Lakka SS (2011) Sparc mediates src-induced disruption of actin cytoskeleton via inactivation of small gtpases rho-rac-cdc42. Cell Signal 23:1978–1987
112. Donato R, Cannon BR, Sorci G, Riuzzi F, Hsu K, Weber DJ, Geczy CL (2013) Functions of s100 proteins. Curr Mol Med 13:24–57
113. Fang Z, Duthoit N, Wicher G, Kallskog O, Ambartsumian N, Lukanidin E, Takenaga K, Kozlova EN (2006) Intracellular calcium-binding protein s100a4 influences injury-induced migration of white matter astrocytes. Acta Neuropathol 111:213–219
114. Belot N, Pochet R, Heizmann CW, Kiss R, Decaestecker C (2002) Extracellular s100a4 stimulates the migration rate of astrocytic tumor cells by modifying the organization of their actin cytoskeleton. Biochim Biophys Acta 1600:74–83
115. Elias MC, Tozer KR, Silber JR, Mikheeva S, Deng M, Morrison RS, Manning TC, Silbergeld DL, Glackin CA, Reh TA, Rostomily RC (2005) Twist is expressed in human gliomas and promotes invasion. Neoplasia 7:824–837

116. Roymans D, Willems R, Vissenberg K, De Jonghe C, Grobben B, Claes P, Lascu I, Van Bockstaele D, Verbelen JP, Van Broeckhoven C, Slegers H (2000) Nucleoside diphosphate kinase beta (nm23-r1/ndpkbeta) is associated with intermediate filaments and becomes upregulated upon camp-induced differentiation of rat c6 glioma. Exp Cell Res 261:127–138
117. Rossetto M, Ciccarino P, Boisselier B, Labussiere M, Sanson M (2011) Metabolism of glioma and idh1/idh2 mutations. Rev Neurol (Paris) 167:699–703
118. Ellenbroek SI, Iden S, Collard JG (2012) The rac activator tiam1 is required for polarized protrusional outgrowth of primary astrocytes by affecting the organization of the microtubule network. Small GTPases 3:4–14
119. Cockbill LM, Murk K, Love S, Hanley JG (2015) Protein interacting with c kinase 1 suppresses invasion and anchorage-independent growth of astrocytic tumor cells. Mol Biol Cell 26:4552–4561
120. Peng S, Eidelberg D, Ma Y (2014) Brain network markers of abnormal cerebral glucose metabolism and blood flow in parkinson's disease. Neurosci Bull 30:823–837
121. Mangiardi JR, Yodice P (1990) Metabolism of the malignant astrocytoma. Neurosurgery 26:1–19
122. Rajendran JG, Mankoff DA, O'Sullivan F, Peterson LM, Schwartz DL, Conrad EU, Spence AM, Muzi M, Farwell DG, Krohn KA (2004) Hypoxia and glucose metabolism in malignant tumors: evaluation by [18f]fluoromisonidazole and [18f] fluorodeoxyglucose positron emission tomography imaging. Clin Cancer Res 10:2245–2252
123. Ziegler A, von Kienlin M, Decorps M, Remy C (2001) High glycolytic activity in rat glioma demonstrated in vivo by correlation peak 1h magnetic resonance imaging. Cancer Res 61:5595–5600
124. Warburg O, Posener K, Negelein E (1924) Ueber den stoffwechsel der tumoren[about the metabolism of tumors. Biochem Z 152:319–344
125. Kanehisa M, Goto S, Sato Y, Furumichi M, Tanabe M (2012) Kegg for integration and interpretation of large-scale molecular data sets. Nucleic Acids Res 40:D109–D114
126. Dang CV, Semenza GL (1999) Oncogenic alterations of metabolism. Trends Biochem Sci 24:68–72
127. Schurr A, Payne RS, Miller JJ, Rigor BM (1997) Brain lactate, not glucose, fuels the recovery of synaptic function from hypoxia upon reoxygenation: an in vitro study. Brain Res 744:105–111
128. Haas HS, Linecker A, Pfragner R, Sadjak A (2010) Peripheral glutamate signaling in head and neck areas. Head Neck 32:1554–1572
129. Ye ZC, Sontheimer H (1999) Glioma cells release excitotoxic concentrations of glutamate. Cancer Res 59:4383–4391
130. Thiery JP (2002) Epithelial-mesenchymal transitions in tumour progression. Nat Rev Cancer 2:442–454
131. Oskarsson T, Batlle E, Massague J (2014) Metastatic stem cells: sources, niches, and vital pathways. Cell Stem Cell 14:306–321
132. Xu F, Zhu JH (2007) Stem cells tropism for malignant gliomas. Neurosci Bull 23:363–369
133. Iwadate Y (2016) Epithelial-mesenchymal transition in glioblastoma progression. Oncol Lett 11:1615–1620
134. Yang J, Mani SA, Donaher JL, Ramaswamy S, Itzykson RA, Come C, Savagner P, Gitelman I, Richardson A, Weinberg RA (2004) Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis. Cell 117:927–939
135. Khan MA, Chen HC, Zhang D, Fu J (2013) Twist: a molecular target in cancer therapeutics. Tumour Biol 34:2497–2506
136. Varga J, De Oliveira T, Greten FR (2014) The architect who never sleeps: tumor-induced plasticity. FEBS Lett 588:2422–2427
137. Barco A, Brambilla R, Rosenblum K (2015) Neurobiology of learning and memory. Ed Neurobiol Learn Mem 124:1–2
138. Bozdagi O, Shan W, Tanaka H, Benson DL, Huntley GW (2000) Increasing numbers of synaptic puncta during late-phase ltp: N-cadherin is synthesized, recruited to synaptic sites, and required for potentiation. Neuron 28:245–259
139. McCrea PD, Gottardi CJ (2016) Beyond beta-catenin: prospects for a larger catenin network in the nucleus. Nat Rev Mol Cell Biol 17:55–64
140. Yang C, Rahimpour S, Yu AC, Lonser RR, Zhuang Z (2013) Regulation and dysregulation of astrocyte activation and implications in tumor formation. Cell Mol Life Sci 70:4201–4211
141. Qi S, Song Y, Peng Y, Wang H, Long H, Yu X, Li Z, Fang L, Wu A, Luo W, Zhen Y, Zhou Y, Chen Y, Mai C, Liu Z, Fang W (2012) Zeb2 mediates multiple pathways regulating cell proliferation, migration, invasion, and apoptosis in glioma. PLoS ONE 7:e38842
142. Pu P, Zhang Z, Kang C, Jiang R, Jia Z, Wang G, Jiang H (2009) Downregulation of wnt2 and beta-catenin by sirna suppresses malignant glioma cell growth. Cancer Gene Ther 16:351–361
143. Wang XH, Sun X, Meng XW, Lv ZW, Du YJ, Zhu Y, Chen J, Kong DX, Jin SZ (2010) Beta-catenin sirna regulation of apoptosis- and angiogenesis-related gene expression in hepatocellular carcinoma cells: potential uses for gene therapy. Oncol Rep 24:1093–1099
144. Gu X, Yao L, Ma G, Cui L, Li Y, Liang W, Zhao B, Li K (2014) Tctp promotes glioma cell proliferation in vitro and in vivo via enhanced beta-catenin/tcf-4 transcription. Neuro Oncol 16:217–227
145. Logan CY, Nusse R (2004) The wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol 20:781–810
146. Liu X, Wang L, Zhao S, Ji X, Luo Y, Ling F (2011) Beta-catenin overexpression in malignant glioma and its role in proliferation and apoptosis in glioblastma cells. Med Oncol 28:608–614
147. Wissmann C, Wild PJ, Kaiser S, Roepcke S, Stoehr R, Woenckhaus M, Kristiansen G, Hsieh JC, Hofstaedter F, Hartmann A, Knuechel R, Rosenthal A, Pilarsky C (2003) Wif1, a component of the wnt pathway, is down-regulated in prostate, breast, lung, and bladder cancer. J Pathol 201:204–212
148. Guardavaccaro D, Clevers H (2012) Wnt/beta-catenin and mapk signaling: allies and enemies in different battlefields. Sci Signal 5:pe15
149. Alphonso A, Alahari SK (2009) Stromal cells and integrins: conforming to the needs of the tumor microenvironment. Neoplasia 11:1264–1271
150. Hynes RO (1992) Integrins: versatility, modulation, and signaling in cell adhesion. Cell 69:11–25
151. Mizejewski GJ (1999) Role of integrins in cancer: survey of expression patterns. Proc Soc Exp Biol Med 222:124–138
152. Goldbrunner RH, Bernstein JJ, Tonn JC (1999) Cell-extracellular matrix interaction in glioma invasion. Acta Neurochir 141:295–305 (**discussion 304–295**)
153. Brooks PC, Stromblad S, Sanders LC, von Schalscha TL, Aimes RT, Stetler-Stevenson WG, Quigley JP, Cheresh DA (1996) Localization of matrix metalloproteinase mmp-2 to the surface of invasive cells by interaction with integrin alpha v beta 3. Cell 85:683–693
154. Deryugina EI, Bourdon MA, Luo GX, Reisfeld RA, Strongin A (1997) Matrix metalloproteinase-2 activation modulates glioma cell migration. J Cell Sci 110(Pt 19):2473–2482
155. Platten M, Wick W, Wild-Bode C, Aulwurm S, Dichgans J, Weller M (2000) Transforming growth factors beta(1) (tgf-beta(1)) and tgf-beta(2) promote glioma cell migration via up-regulation of alpha(v)beta(3) integrin expression. Biochem Biophys Res Commun 268:607–611

156. Tamura M, Gu J, Tran H, Yamada KM (1999) Pten gene and integrin signaling in cancer. J Natl Cancer Inst 91:1820–1828
157. Schmid-Brunclik N, Burgi-Taboada C, Antoniou X, Gassmann M, Ogunshola OO (2008) Astrocyte responses to injury: vegf simultaneously modulates cell death and proliferation. Am J Physiol Regul Integr Comp Physiol 295:R864–R873
158. Vangeison G, Carr D, Federoff HJ, Rempe DA (2008) The good, the bad, and the cell type-specific roles of hypoxia inducible factor-1 alpha in neurons and astrocytes. J Neurosci 28:1988–1993
159. Paulus W, Tonn JC (1994) Basement membrane invasion of glioma cells mediated by integrin receptors. J Neurosurg 80:515–519
160. Anton B, Leff P, Meissler JJ, Calva JC, Acevedo R, Salazar A, Matus M, Flores A, Martinez M, Adler MW, Gaughan JP, Eisenstein TK (2010) Nociceptin/orphanin fq suppresses adaptive immune responses in vivo and at picomolar levels in vitro. J Neuroimmune Pharmacol 5:143–154
161. Yamana N, Arakawa Y, Nishino T, Kurokawa K, Tanji M, Itoh RE, Monypenny J, Ishizaki T, Bito H, Nozaki K, Hashimoto N, Matsuda M, Narumiya S (2006) The rho-mdia1 pathway regulates cell polarity and focal adhesion turnover in migrating cells through mobilizing apc and c-src. Mol Cell Biol 26:6844–6858
162. Pollard TD, Borisy GG (2003) Cellular motility driven by assembly and disassembly of actin filaments. Cell 112:453–465
163. Benitah SA, Valeron PF, van Aelst L, Marshall CJ, Lacal JC (2004) Rho gtpases in human cancer: An unresolved link to upstream and downstream transcriptional regulation. Biochim Biophys Acta 1705:121–132
164. Fortin Ensign SP, Mathews IT, Symons MH, Berens ME, Tran NL (2013) Implications of rho gtpase signaling in glioma cell invasion and tumor progression. Front Oncol 3:241
165. Deng L, Li G, Li R, Liu Q, He Q, Zhang J (2010) Rho-kinase inhibitor, fasudil, suppresses glioblastoma cell line progression in vitro and in vivo. Cancer Biol Ther 9:875–884
166. Zhu F, Zhang Z, Wu G, Li Z, Zhang R, Ren J, Nong L (2011) Rho kinase inhibitor fasudil suppresses migration and invasion though down-regulating the expression of vegf in lung cancer cell line a549. Med Oncol 28:565–571
167. Mikheeva SA, Mikheev AM, Petit A, Beyer R, Oxford RG, Khorasani L, Maxwell JP, Glackin CA, Wakimoto H, Gonzalez-Herrero I, Sanchez-Garcia I, Silber JR, Horner PJ, Rostomily RC (2010) Twist1 promotes invasion through mesenchymal change in human glioblastoma. Mol Cancer 9:194
168. Buccoliero AM, Franchi A, Castiglione F, Gheri CF, Mussa F, Giordano F, Genitori L, Taddei GL (2009) Subependymal giant cell astrocytoma (sega): Is it an astrocytoma? Morphological, immunohistochemical and ultrastructural study. Neuropathology 29:25–30
169. Sikorska B, Papierz W, Zakrzewki K, Fiks T, Polis L, Liberski PP (2007) Ultrastructural heterogeneity of gangliogliomas. Ultrastruct Pathol 31:9–14
170. Colin C, Virard I, Baeza N, Tchoghandjian A, Fernandez C, Bouvier C, Calisti A, Tong S, Durbec P, Figarella-Branger D (2007) Relevance of combinatorial profiles of intermediate filaments and transcription factors for glioma histogenesis. Neuropathol Appl Neurobiol 33:431–439
171. Liu G, Dwyer T (2014) Microtubule dynamics in axon guidance. Neurosci Bull 30:569–583
172. Roymans D, Vissenberg K, De Jonghe C, Willems R, Engler G, Kimura N, Grobben B, Claes P, Verbelen JP, Van Broeckhoven C, Slegers H (2001) Identification of the tumor metastasis suppressor nm23-h1/nm23-r1 as a constituent of the centrosome. Exp Cell Res 262:145–153
173. Kornblum HI, Hussain R, Wiesen J, Miettinen P, Zurcher SD, Chow K, Derynck R, Werb Z (1998) Abnormal astrocyte development and neuronal death in mice lacking the epidermal growth factor receptor. J Neurosci Res 53:697–717
174. Sibilia M, Wagner EF (1995) Strain-dependent epithelial defects in mice lacking the egf receptor. Science 269:234–238
175. Duhem-Tonnelle V, Bieche I, Vacher S, Loyens A, Maurage CA, Collier F, Baroncini M, Blond S, Prevot V, Sharif A (2010) Differential distribution of erbb receptors in human glioblastoma multiforme: expression of erbb3 in cd133-positive putative cancer stem cells. J Neuropathol Exp Neurol 69:606–622
176. Hiesiger EM, Hayes RL, Pierz DM, Budzilovich GN (1993) Prognostic relevance of epidermal growth factor receptor (egfr) and c-neu/erbb2 expression in glioblastomas (gbms). J Neurooncol 16:93–104
177. Torp SH, Gulati S, Johannessen E, Dalen A (2007) Coexpression of c-erbb 1–4 receptor proteins in human glioblastomas. An immunohistochemical study. J Exp Clin Cancer Res 26:353–359
178. Torp SH, Helseth E, Dalen A, Unsgaard G (1991) Epidermal growth factor receptor expression in human gliomas. Cancer Immunol Immunother 33:61–64
179. Codeluppi S, Svensson CI, Hefferan MP, Valencia F, Silldorff MD, Oshiro M, Marsala M, Pasquale EB (2009) The rheb-mtor pathway is upregulated in reactive astrocytes of the injured spinal cord. J Neurosci 29:1093–1104
180. Libermann TA, Nusbaum HR, Razon N, Kris R, Lax I, Soreq H, Whittle N, Waterfield MD, Ullrich A, Schlessinger J (1985) Amplification, enhanced expression and possible rearrangement of egf receptor gene in primary human brain tumours of glial origin. Nature 313:144–147
181. Li ZW, Li JJ, Wang L, Zhang JP, Wu JJ, Mao XQ, Shi GF, Wang Q, Wang F, Zou J (2014) Epidermal growth factor receptor inhibitor ameliorates excessive astrogliosis and improves the regeneration microenvironment and functional recovery in adult rats following spinal cord injury. J Neuroinflamm 11:71
182. Wang D, Owler BK (2011) Expression of aqp1 and aqp4 in paediatric brain tumours. J Clin Neurosci 18:122–127
183. Shi WZ, Zhao CZ, Zhao B, Shi QJ, Zhang LH, Wang YF, Fang SH, Lu YB, Zhang WP, Wei EQ (2012) Aggravated inflammation and increased expression of cysteinyl leukotriene receptors in the brain after focal cerebral ischemia in aqp4-deficient mice. Neurosci Bull 28:680–692
184. Shi WZ, Zhao CZ, Zhao B, Zheng XL, Fang SH, Lu YB, Zhang WP, Chen Z, Wei EQ (2012) Aquaporin-4 deficiency attenuates acute lesions but aggravates delayed lesions and microgliosis after cryoinjury to mouse brain. Neurosci Bull 28:61–68
185. Ding T, Gu F, Fu L, Ma YJ (2010) Aquaporin-4 in glioma invasion and an analysis of molecular mechanisms. J Clin Neurosci 17:1359–1361
186. Ding T, Zhou Y, Sun K, Jiang W, Li W, Liu X, Tian C, Li Z, Ying G, Fu L, Gu F, Li W, Ma Y (2013) Knockdown a water channel protein, aquaporin-4, induced glioblastoma cell apoptosis. PLoS ONE 8:e66751
187. Stroka KM, Jiang H, Chen SH, Tong Z, Wirtz D, Sun SX, Konstantopoulos K (2014) Water permeation drives tumor cell migration in confined microenvironments. Cell 157:611–623
188. Oshio K, Watanabe H, Song Y, Verkman AS, Manley GT (2005) Reduced cerebrospinal fluid production and intracranial pressure in mice lacking choroid plexus water channel aquaporin-1. FASEB J 19:76–78
189. Fossdal G, Vik-Mo EO, Sandberg C, Varghese M, Kaarbo M, Telmo E, Langmoen IA, Murrell W (2012) Aqp 9 and brain tumour stem cells. Sci World J 2012:915176
190. Nicchia GP, Frigeri A, Liuzzi GM, Svelto M (2003) Inhibition of aquaporin-4 expression in astrocytes by rnai determines alteration in cell morphology, growth, and water transport

and induces changes in ischemia-related genes. FASEB J 17:1508–1510
191. McCoy ES, Haas BR, Sontheimer H (2010) Water permeability through aquaporin-4 is regulated by protein kinase c and becomes rate-limiting for glioma invasion. Neuroscience 168:971–981
192. Schiera G, Di Liegro CM, Di Liegro I (2015) Extracellular membrane vesicles as vehicles for brain cell-to-cell interactions in physiological as well as pathological conditions. Biomed Res Int 2015:152926
193. Svensson KJ, Christianson HC, Wittrup A, Bourseau-Guilmain E, Lindqvist E, Svensson LM, Morgelin M, Belting M (2013) Exosome uptake depends on erk1/2-heat shock protein 27 signaling and lipid raft-mediated endocytosis negatively regulated by caveolin-1. J Biol Chem 288:17713–17724
194. Sharma P, Sheets K, Elankumaran S, Nain AS (2013) The mechanistic influence of aligned nanofibers on cell shape, migration and blebbing dynamics of glioma cells. Integr Biol (Camb) 5:1036–1044
195. Wu X, Zheng T, Zhang B (2016) Exosomes in parkinson's disease. Neurosci Bull. doi:10.1007/s12264-016-0092-z
196. Zhang YB, Li SX, Chen XP, Yang L, Zhang YG, Liu R, Tao LY (2008) Autophagy is activated and might protect neurons from degeneration after traumatic brain injury. Neurosci Bull 24:143–149