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The Neural Extracellular Matrix, Cell Adhesion Molecules and Proteolysis in Glioma Invasion and Tumorigenicity

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1. Introduction

High-grade gliomas are the most prevalent and lethal form of primary intracranial tumors. Despite significant progress in surgical and adjuvant therapeutic treatments for gliomas, patient prognosis still remains dismal. The ability of gliomas to invade the normal surrounding brain tissue contributes to their capacity to evade therapeutic interventions, ultimately leading to tumor recurrence and subsequent disease progression (Rich & Bigner, 2004). Another major therapeutic obstacle comes from the high degree of intratumoral cellular heterogeneity. The tumor mass is comprised of both terminally differentiated cells, cells that exhibit finite capabilities of self-renewal and multipotency, and a smaller subpopulation of cells that exhibit stem cell-like qualities. These stem-like cells, termed Glioma Initiating Cells (GICs), exihibit pluripotency, self-renewal and, importantly, are capable of repopulating the original parental tumor. Therefore, more effective therapies may be derived from targeting both the infiltrative nature of gliomas and GICs (Louis, 2006; Park & Rich, 2009).

The ability of glioma tumor cells to infiltrate the normal surrounding brain tissue is a property that is restricted to intracranial tumors that are phenotypically glial within the central nervous system (CNS). As metastatic tumor cells that are highly invasive in the periphery fail to invade surrounding brain tissue once within the confines of the CNS, and invasive glioma tumors that originate in the brain rarely metastasize outside of the CNS. These findings suggest that the unique interaction between glioma tumor cells and the neural extracellular environment mediate glioma invasion (Bellail et al., 2004; Nutt et al., 2001a).

A defining attribute of the neural extracellular environment is the unique composition of the neural extracellular matrix (ECM), which unlike other peripheral matrices has low levels of fibrilliar proteins like collagens, fibronectin, and laminin (Ruoslahti, 1996). In both neural development and pathogenesis, the neural ECM regulates key biological processes including cellular migration, maturation, synapse formation, and plasticity. In the adult brain the composition of the neural ECM is largely inhibitory to cellular reorganization (Galtrey & Fawcett, 2007; Zimmermann & Dours-Zimmermann, 2008). Therefore, glioma tumor cell invasion into the normal surrounding brain tissue is derived from their ability to overcome this normally inhibitory extracellular environment. Decades of research has

demonstrated that glioma tumor cells are capable of remodeling the neural extracellular space by changing the expressions of proteins involved in intercellular and extracellular interactions. Glioma tumor cells also secrete proteases that cleave the adult neural ECM and temporary produced glioma ECM to create a permissive extracellular environment supportive of tumor cell invasion (Viapiano & Matthews, 2006). In addition, recent studies have determined that the expressions of several constituents of the neural ECM are enriched in the GIC subpopulation (Gunther et al., 2008; Phillips et al., 2006), suggesting that components of the neural ECM may facilitate the stem cell-like qualities of these cells by creating a permissive extracellular niche.

Targeting either the expression of proteins that mediate intercellular or extracellular interactions or the proteases responsible for the cleavage and turnover of these proteins represent potential therapeutic avenues that require further exploration. This chapter will focus on the role of the neural ECM, proteolytic cleavage, and alterations that occur in proteins that mediate intercellular interactions to facilitate glioma tumorigenicity and invasion and their therapeutic potential.

2. The neural extracellular matrix in normal and developing brain

2.1 The neural extracellular matrix

During both neurodevelopment and in several neuropathologies, the neural ECM and molecular determinants of cell-ECM and cell-cell interactions regulate key biological processes including cellular migration, maturation, differentiation, and synapse formation (Hartmann & Maurer, 2001). The composition of the neural ECM largely dictates the permissive or inhibitory properties of the neural extracellular environment, creating a permissive environment favoring cell migration and process outgrowth during development and a notoriously inhibitory environment in the mature CNS. The neural ECM is capable of undergoing dynamic remodeling resulting from alterations in both the expression levels of ECM components and alterations in proteolytic processing (Zimmermann & Dours-Zimmermann, 2008).

2.2 The composition of the neural extracellular matrix in normal brain

The composition of the neural ECM, while most similar to cartilage, is unique and distinguishes the neural extracellular environment from that of other tissues and organs. The neural ECM is chiefly comprised of Hyaluronic Acid (HA), a repeating sugar disaccharide, proteoglycans and glycoproteins, which through their interactions organize the extracellular space of the CNS (Delpech & Delpech, 1984). The neural ECM accounts for ten to twenty percent of the total volume of the mature brain and occupies an even larger percentage in the developing brain (Ruoslahti, 1996). Unlike peripheral matrices, the neural ECM has low levels of fibrillar proteins including laminin, collagens, and fibronectin with the majority of these proteins being localized to substructures of the CNS including basement membranes, the subpial space, blood vessels, and in white matter tracts (Liesi, 1984). Instead, the backbone of the neural ECM is HA, a non-sulfated glycosaminoglycan made up of alternating glucuronic acid and N-acetylglucosamine disaccharide subunits and devoid of a protein core (Ruoslahti, 1996; Toole, 2000, 2004). HA is produced and secreted by hyaluronan synthases located at the surface of the cellular plasma membrane, recent evidence suggests that HA synthases may also play a role in tethering HA to the cellular surface to facilitate its interactions with other components of the neural ECM (DeAngelis,

1999; Itano & Kimata, 2002; Weigel et al., 1997; Spicer & McDonald, 1998; Spicer & Tien, 2004).

Since HA forms the backbone of the neural matrix, proteins that organize and bind HA to the cell surface are particularly important for defining neural ECM structure and function. In many peripheral tissues the best studied HA receptor is CD44 but it is expressed at low levels in the adult CNS. Instead, the major HA binding proteins expressed in the CNS are the lectican family members of chondroitin sulfate proteoglycans (CSPGs), also called hyalectans, which include versican, aggrecan, and brain-specific neurocan, and Brain Enriched Hyaluronan Binding protein (BEHAB)/brevican (B/b) (Bandtlow & Zimmermann, 2000; Ruoslahti, 1996; Yamaguchi, 2000). Additionally, the HA Proteoglycan binding Link Proteins (HAPLNs) work in concert with lecticans to mediate HA binding (Spicer et al., 2003). CSPGs are glycosylated proteins that are decorated with chondroitin sulfate glycosaminoglycan (CS-GAG) chains. The number and sulfation of CS-GAG chains varies for individual proteoglycans and can modulate their functions and interactions with ligands (Maeda, 2010).

The structure and molecular interactions of lecticans in the normal brain has been reviewed thoroughly in previous publications and therefore is not included here, however, the model structure of the neural matrix and the position and interactions of lecticans in this matrix is shown in Figure 1 (Ruoslahti, 1996; Viapiano & Matthews, 2006; Yamaguchi, 2000). A complete understanding of the molecular interactions and functions of lecticans in the normal brain is, however, challenging. This is due in large part to the production of several protein isoforms resulting from alternative splicing, which causes a vast and microheterogeneous array of protein products (Viapiano et al., 2003, 2005; Dours-Zimmerman & Zimmerman, 1994). Adding to this complexity, different protein isoforms from the same gene are expressed in specific temporal and regional patterns (Milev et al., 1998; Seidenbecher et al., 1998). In addition, all lecticans are cleaved by A Disintegrin And Metalloproteinase with Thrombospondin Motifs (ADAMTS) and Matrix Metalloproteinase (MMPs) family members (Westling et al., 2004; Matthews et al., 2000). Finally the glycosylation of lecticans is extremely microheterogeneous and specific glycoforms can be expressed in a very anatomically distinct and precise manner in the normal CNS (Matthews et al., 2002). The molecular heterogeneity as well as the distinct spatial and temporal expression patterns of ECM components dictates the broad functional impact the neural ECM has over the CNS in both the physiological and pathophysiological state.

2.3 The function of the neural extracellular matrix

The neural ECM regulates a diverse array of functions in both the developing and mature CNS. During neurodevelopment the ECM has been shown to play a role in cell migration, process outgrowth, cell fate decisions, synaptogenesis and regulating cortical plasticity (Bandtlow & Zimmermann, 2000; Berardi et al., 2004; Frischknecht & Seidenbecher, 2008; Maeda et al., 2010). The composition of the ECM during neurodevelopment is largely permissive and favorable for cellular migration and process outgrowth (Zimmermann & Dours-Zimmermann, 2008). The expressions of certain lectican isoforms that aid in cellular movement and process outgrowth are also elevated and undergo increased proteolytic cleavage, which enables the turnover of ECM components to facilitate cellular migration. In fact, the proteolytic activities of certain proteases have been shown to be critical for normal development to proceed (Ethell & Ethell, 2007). As the mature synaptic circuitry is established the composition of the neural ECM changes to aid in stabilizing these
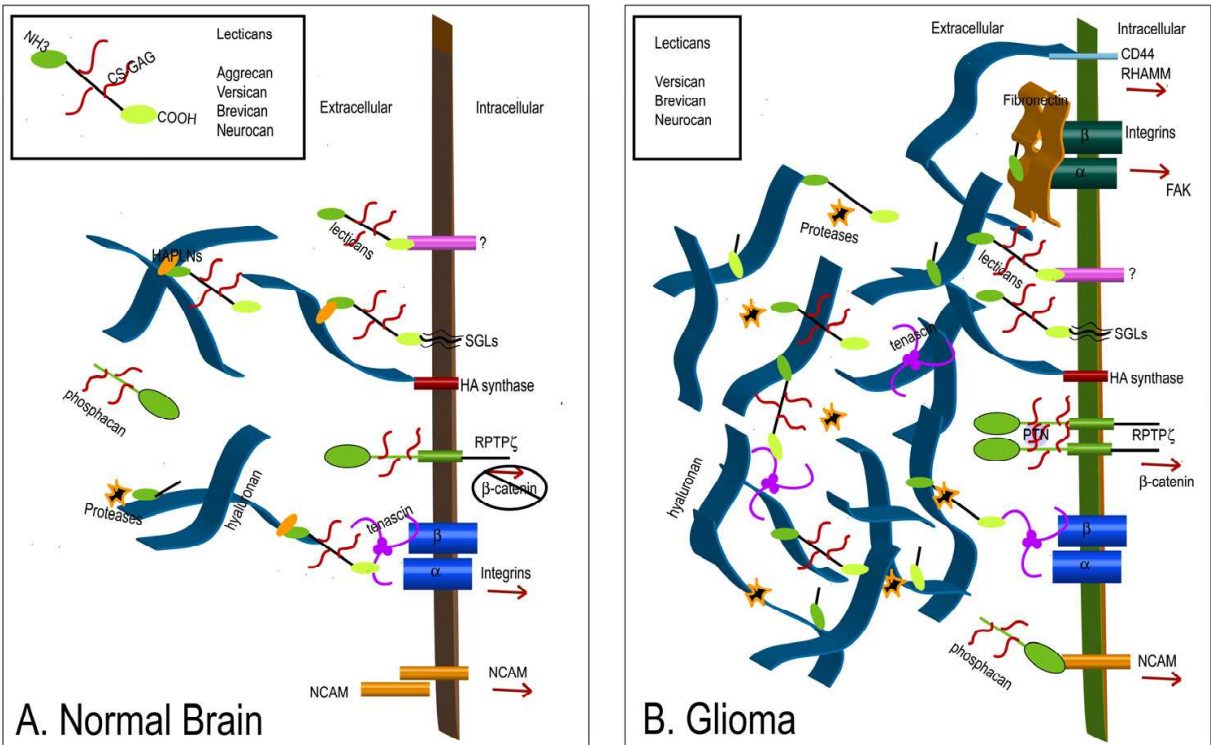
Fig. 1. Schematic Diagram of the Neural Extracellular Matrix. Diagram demonstrates the model composition of the ECM and cell-surface receptors in the normal adult brain (A) and the changes in the extracellular environment in gliomas (B). Arrows represent activation of signaling cascades.

connections, creating the notoriously inhibitory extracellular environment of the adult CNS (Galtrey & Fawcett, 2007). The expression of HA is substantially reduced and lectican family members and their specific isoforms that are inhibitory to extracellular reorganization appear (Frischknecht & Seidenbecher, 2008; Margolis et al., 1975). Often disorders and diseases that affect the CNS are accompanied by alterations in the composition of the neural ECM, which facilitates the pathophysiological condition by modifying the extracellular environment (Galtrey & Fawcett, 2007; Zimmermann & Dours-Zimmermann, 2008).

3. Extracellular matrix in brain tumors

3.1 The neural matrix facilitates glioma tumor cell invasion

While the extracellular environment of the mature CNS is notably resistant to plasticity and cellular dynamics that favor reorganization, glioma cells are capable of overcoming this inhibition to invade into the normal surrounding brain tissue. The invasive attributes of glioma cells leads to tumor cell dispersion and highly diffuse tumor-stromal boundaries, making complete surgical removal of tumor cells nearly impossible and tumor recurrence almost inevitable (Nakada et al., 2007). Brain tumor cell invasion into the normal surrounding brain tissue is a property that is restricted to tumors that are phenotypically glial and located within the CNS environment. Both non-glial tumors that originate in the CNS and tumors of non-neuroepithelial origin that metastasize to the CNS fail to invade the surrounding brain tissue, typically exhibiting well-defined brain-tumor boundaries (Bellail et al., 2004). Furthermore, gliomas rarely infiltrate the vasculature of the CNS and

disseminate outside of the nervous system environment (Kleihues et al., 1993, 2002; Bellail et al., 2004). The ability of glioma cells to invade the mature CNS strongly suggests that the unique interaction between these tumors and the extracellular neural environment is critical in this invasive process. The unique composition of the neural ECM defines the extracellular environment of the CNS and, therefore, the unique ability of glioma cells to interact with the neural ECM is a critical component of their invasiveness. Consistent with this hypothesis is work from a number of labs demonstrating that glioma tumor cells synthesize and secrete a specialized composition of ECM components and cell adhesion molecules that facilitate this interaction leading to tumor cell invasion (Bellail et al., 2004; Gladson, 1999).

The composition of the ECM produced by glioma cells closely resembles that during early neurodevelopment, as both the expression levels and presence of specific protein isoforms predominately expressed during neurodevelopment are overrepresented in the ECM of gliomas. As in several invasive and metastatic tumors, the synthesis of HA is dramatically increased in glioma along with HA receptors CD44 and RHAMM which mediate aspects of glioma invasion (Delpech et al., 1993; Kuppner et al., 1992; Merzak et al., 1994; Okada et al., 1996; Park et al., 2008; Radotra & McCormick, 1997). The expression of several lectican family members and their isoforms that are predominately expressed during early nervous system development and promote cellular reorganization are also upregulated in human glioma tumors. Exemplary to this are the elevated expressions of versican (Paulus et al., 1996), B/b (Jaworski et al., 1996), neurocan (Rauch, 2004), and Receptor Protein Tyrosine Phosphatase ζ (RPTPζ, also known as RPTPβ) (Norman et al., 1998; Peles et al., 1998). A specific model of a lectican isoform that is highly expressed during neurodevelopment and reappears in glioma tumors is a variant of B/b, B/bΔg. The B/bΔg form of brevican is expressed for a short developmental window in normal human brain spanning from 16 gestational weeks to one year of age. The expression of the B/bΔg isoform reemerges in human glioma tumors causing it to be expressed in a tumor-specific manner within the adult CNS (Viapiano et al., 2005). Additionally, unlike normal adult ECM, the tumoral ECM contains traditional fibrillar matrix proteins like laminin and fibronectin, which have been shown to bind to proteoglycans to enhance tumor cell motility (Hu et al., 2008; Zheng et al., 2004). While the expressions of typical fibrillar proteins are low in the extracellular milieu of the adult brain, these common matrix elements are expressed in localized regions of the developing brain (Rutka et al., 1988; Ruoslahti, 1996). Therefore, with respect to the neural ECM, oncology recapitulates ontogeny.

While the expression of unique ECM components in glioma cells is detailed above, glioma cells also modulate the expression of cell-surface receptors, which enhances their ability to interact within the neural environment. One class of surface receptors altered in glioma tumors are cell-cell adhesion molecules, which comprise several different molecular families of receptors (Barami et al., 2006). Cell-cell adhesion molecules play important roles in regulating cell motility through interactions with ECM components and other cell adhesion molecules. Several signal transduction pathways directly regulate the cellular repertoire of adhesion molecules to dictate both extracellular and intercellular interactions. The inverse is also true, as activated cell adhesion molecules are capable of modulating intracellular signaling to influence cellular processes like adhesion, motility and even cell fate (Cavallaro & Christofori, 2004). In terms of glioma tumor pathophysiology, the activation of cell adhesion molecules are equally as important as the activation of signal transduction cascades, as signaling from both modulate tumor cell behavior.

In glioma tumors, ECM receptors like tenascin, integrins and certain cell-cell adhesion molecules mediate interactions between the extracellular environment and surface of the cell to influence cell behavior by modulating intracellular signaling. Tenascins are large molecular weight cell-surface glycoproteins that can function as receptors for proteoglycans including the lectican family members. Importantly, tenascin family members are also overexpressed in glioma specimens and have been linked to tumor cell invasion and angiogenesis (Aspberg et al., 1995; 1997; Hirata et al., 2009; Leins et al., 2003; Zagzag et al., 2002). While tenascin can function as receptors for proteoglycans, they are also secreted proteins that depend in part on interactions with cell-adhesion molecules at the cellular plasma membrane to confer their functionality. Tenascin has been shown to interact with integrins, which are integral membrane cell surface receptors involved in cell-ECM interactions (Deryugina & Bourdon, 1996; Giese et al., 1996). In addition to binding tenascin, integrins also bind fibrillar proteins like laminin and fibronectin that are expressed in the tumoral extracellular environment (Knott et al., 1998; Ohnishi et al., 1998). The interaction of integrins with both tenascin and fibrillar matrix proteins in the tumor microenvironment have been shown to enhance the motility and invasive properties of glioma tumor cells (Deryugina & Bourdon, 1996; Hirata et al., 2009). Upon binding to ECM ligands, integrins effectively transduce changes in the ECM into alterations in cellular behavior by activating signal transduction cascades that reorganize components of the cellular cytoskeleton to facilitate cell movement (D'Abaco & Kaye, 2007).

Cell-cell and cell-ECM interactions of glioma tumor cells are also critically regulated by extracellular proteases. Tumor cell invasion is strongly influenced by the proteolytic cleavage of ECM components and certain cell adhesion molecules, as proteolysis creates an extracellular environment permissive to cellular migration by facilitating the turnover of ECM components (Rao, 2003 and section 2.2). The complex interplay between HA, proteoglycans and their receptors, integrins, cell-cell adhesion molecules, and proteases present within the tumor stroma facilitate glioma invasion through the normally inhibitory extracellular environment of the mature CNS.

The restricted invasive profile of gliomas suggests that nervous system-specific proteins expressed only by neoplastic cells that are phenotypically glial may be key mediators of glioma invasion. Thus, making components of the neural ECM and adhesion molecules with expressions that are restricted or specifically enriched within the CNS appealing avenues of research for future therapeutic targets. Proteins with CNS enriched or specific expression that are overexpressed in human glioma tumors include but are not limited to B/b (Jaworski et al., 1996), specific isoforms of versican (Dours-Zimmermann & Zimmermann, 1994; Paulus et al., 1996), and RPTPζ (Muller et al., 2003). Inhibiting molecular mechanisms leading to glioma tumor cell invasion is critical to effectively curing these deadly tumors. Furthermore, the identification of pro-invasive mediators that are both nervous system and tumor-specific would create molecular targets for novel therapies with reduced off-target effects, thus limiting the potential of inducing broad systemic toxicity.

3.2 Proteolytic degradation of the neural extracellular matrix is critically involved in tumor cell invasion

In order for glioma tumor cells to invade the normal surrounding brain tissue, tumor cells must both interact with the ECM of the adult CNS, which is accomplished through the synthesis of tumor-produced ECM, altered receptor expression, and proteolytic cleavage.

Several different families of proteases are overexpressed in gliomas including MMPs, ADAMTS, serine, cysteine, and asparate and play important roles in mediating glioma tumor invasion and progression (Levicar et al., 2003). Proteases expressed by glioma tumor cells degrade the mature inhibitory ECM of the adult CNS and the glioma-expressed matrix elements. Proteolytic activity allows for turnover of ECM components and facilitates invasion by dynamically remodeling the extracellular environment to become more permissive to cellular reorganization (Yamamoto et al., 2002). Therefore, glioma tumor cell invasion is dependent on both the overproduction and proteolytic cleavage of ECM components. The importance of ECM cleavage is highlighted by previous work on B/b that showed both its overexpression and proteolytic processing are required for increased glioma cell invasion, as a mutated non-cleavable form of B/b did not enhance cell invasion (Viapiano et al., 2008). In addition to mediating aspects of invasion, proteases belonging to these families have also been linked to increases in glioma tumor cell proliferation and angiogenesis (Lakka et al., 2005). The regulation of proteolytic activity in gliomas is complex with each level of regulation representing a facet for potential therapeutic intervention.

Proteolytic activity can be regulated at different levels resulting from either an increase in transcription or activation, as most proteases require cleavage of an inactive pro-peptide form for enzymatic activity. The proteolytic activity of both ADAMTS and MMP family members are naturally inhibited by endogenously occurring proteins belonging to the Tissue Inhibitor of Metalloproteinases (TIMP) family (Brew & Nagase, 2010). In several disease pathologies including gliomas, an imbalance between protease activity and TIMP expression accounts for elevated levels of proteolysis in the pathogenic state (Kachra et al., 1999). Therefore, both the overexpression and activation of ADAMTS and MMP proteases along with the TIMP family of endogenous protease inhibitors are attractive therapeutic targets for their role as molecular determinants of glioma tumor cell invasion.

The functional role of proteases in glioma tumor pathology is exemplified by the MMP family members, which have important roles in the progression of most neoplasms and happen to be the most well characterized protease family in glioma tumors (Levicar et al., 2003). The MMPs comprise a large family of matrix peptidases that are classified on the basis of their preferred substrate, for which there is considerable overlap between family members (Rao, 2003). MMPs are produced both by glioma tumor cells and endothelial cells that comprise the tumor vasculature (Raithatha et al., 2000). Two of the most well documented MMPs in glioma are MMP-2 and MMP-9, also known as gelatinase-A and gelatinase-B, respectively. Their expressions are increased in glioma tumors and have been correlated with increased glioma tumor cell invasiveness (Nakagawa et al., 1996; Wild-Bode et al., 2001; Levicar et al., 2003). Additionally, the expression of these proteases correlated with the degree of glioma tumor malignancy, as increased levels of MMP-2 and MMP-9 were observed in high-grade glioma tumors relative to low-grade (Wang et al., 2003). Knocking down the expression of MMP-9 in an invasive glioma cell line resulted in decreased tumor cell infiltration into the surrounding brain tissue and decreased cell motility and invasion in vitro (Zhao et al., 2010). Upstream signaling molecules that regulate the expressions of MMP-2 and MMP-9 are also potential therapeutic targets of interest. Previous studies have shown that JNK and ERK signaling positively regulate the expression of MMP-9, and interfering with either of these pathways reduced the invasiveness of a glioma cell line (Lakka et al., 2000).

Based on elevated MMP expression, activation, and function in glioma tumor invasion and progression, a considerable amount of investigation into using chemical inhibitors of MMPs

as therapeutic agents to reduce the pathogenesis of glioma tumors has ensued. Clinical trials using a broad MMP inhibitor failed to improve patient prognosis and caused systemic toxicity in patients, in the form of joint pain (Groves et al., 2006; Levin et al., 2006). The expression of MMPs in cartilage and their role in maintaining normal cartilage and joint physiology presumably accounted for these deleterious affects (Itoh et al., 2002). Findings from these studies suggest that the function of MMPs in both the pathogenesis of glioma tumors and its role in normal physiology are more complex than is currently understood. Additionally, these findings suggest that other proteases that play less of a role in maintaining normal physiology while still mediating aspects of glioma tumor invasion may be better candidates for therapeutic intervention.

Specific ADAMTS family members exemplify proteases that are attractive therapeutic candidates on the basis of their contribution to glioma tumor invasion and disease progression and seemingly less critical role in maintaining normal physiology (Majumdar et al., 2007; Nakada et al., 2005). Interestingly, the expression and activity of ADAMTS-4 and 5 are enriched in human glioma tumors relative to normal adult brain (Held-Feindt et al., 2006), with the expression of ADAMTS-5 being the most significantly upregulated in glioma (Nakada et al., 2005). Their expression has been shown to contribute significantly to glioma invasion and disease progression, which is mediated by their ability to cleave components of the extracellular matrix such as B/b (Matthews et al., 2000; Nakada et al., 2005) and versican (Sandy et al., 2001). Therefore, the preferred substrates of ADAMTS-4 and 5 in the CNS are presumably more restricted than other proteases, favoring extracellular matrix components that are enriched in glioma tumors with CNS-specific expression. Importantly, ADAMTS-4 and 5 are seemingly dispensable for normal physiology, as double knockout animals exhibited no deleterious affects and were indistinguishable from controls (Majumdar et al., 2007). Thus suggesting that targeting the systemic expression of ADAMTS-4 and 5 would have fewer off-target effects.

The pro-invasive contribution of ADAMTS-4 and 5 to proteolytic cleavage is further enhanced by recent work that described a novel molecular mechanism between these proteases and glioma produced ECM to facilitate glioma cell invasion. Importantly, the proteolytic cleavage of B/b by ADAMTS-4 and 5 was found to reveal cryptic binding sites on B/b to promote its motogenic effects (Hu et al., 2008). The proteolytic cleavage fragments of B/b were shown to effectively bind to fibronectin, which caused the polymerization of fibronectin microfibrils surrounding the surface of the cell and increased glioma tumor cell adhesion and motility. The interaction between B/b and fibronectin was only observed for the N-terminal proteolytic cleavage fragment of B/b and not for the full-length form of the protein. B/b mediated increases in cell adhesion and motility were found to be dependent on both its proteolytic processing and interaction with fibronectin, as a forced reduction in fibronectin expression attenuated the motogenic effects of B/b (Hu et al., 2008). In the adult brain the proposed mechanisms would be inconceivable given the lack of fibronectin expression, however the tumor-specific expression of it by glioma cells enables mechanisms of B/b-mediated cell motility to proceed in a nervous system specific manner that is critically dependent on proteolysis.

4. Tumoral cellular interactions within the extracellular space of the CNS

4.1 Extracellular interactions mediate tumor cell invasion

Dispersion of cells within the brain requires direct interactions of the tumor cells with the surrounding environment and ultimately activation of signaling pathways downstream of

these interactions. In gliomas, cellular interactions within the environment are mediated by a number of key receptor systems.

The most well-studied matrix receptors are the **Integrins**. Integrins are a family of cell surface receptors that communicate changes in the extracellular environment to intracellular mediators by activating several signal transduction cascades. Integrins are comprised of a large family of heterodimeric transmembrane glycoproteins, the dimerization of different integrin subunits dictates the specificity and preference of these receptors for particular ECM components (Akiyama, 1996). In gliomas the tumor-specific overexpression of integrins $\alpha V\beta 3$ and $\alpha V\beta 5$ have been described along with their localization along blood vessels and on the surface of glioma tumor cells, suggesting they play a role in angiogenesis and cell motility (Bello et al., 2001; D'Abaco & Kaye, 2007; Gladson, 1996; Schnell et al., 2008). Cilengitide, a synthetic RGD pentapeptide that acts as an inhibitor of integrins $\alpha V\beta 3$ and $\alpha V\beta 5$, has shown promising clinical results and is now being evaluated in Phase III clinical trials (Nabors et al., 2007, Tabatabai et al., 2010).

In addition to integrins, HA binding proteins like the lecticans mediate the interaction between the extracellular environment and glioma tumor cells. **BEHAB/ brevican (B/b),** a nervous-system specific lectican family member, is significantly upregulated in human glioma specimens relative to normal brain (Jaworski et al., 1996). The expression of B/b is limited to invasive tumors of glial phenotype within the intracranial environment, thus mirroring the restricted invasive profile of gliomas (Jaworski et al., 1996). Of importance, previous studies have shown that increased B/b expression led to elevated tumor cell invasion and tumor aggressiveness in animal models (Nutt et al., 2001b). Likewise, RNAi mediated knockdown of B/b decreased tumor cell invasion and reduces tumor aggressiveness leading to prolonged survival of animal models (RTM, unpublished findings). It has been determined that the upregulation of B/b expression in gliomas occurs at both the level of transcription and translation, suggesting that a glioma-specific signaling pathway is responsible for regulating increased B/b expression (Gary et al., 2000; Viapiano et al., 2005). These unknown regulatory mechanisms represent potentially valuable therapeutic candidates, as they presumably would be regulators of glioma cell motility with nervous system and tumor specific expression.

Understanding the function of B/b overexpression is challenging due to the presence of several post-translationally modified protein isoforms, all of which are present in glioma specimens at levels far greater than normal brain. These include the full-length secreted protein, proteolytic cleavage fragments, and tumor-specific isoforms B/bsia and B/bΔg (Viapiano et al., 2003, 2005). B/bsia is an over sialidated form of B/b, exhibiting typical post-translational increases in sialic acid modifications observed in many neoplasms (Viapiano et al., 2005). B/bΔg is a hypoglycosylated full-length protein isoform resulting from decreased decoration of the full-length core protein with O-linked oligosaccharides. Interestingly, B/bΔg is bound to the cellular plasma membrane by unknown mechansisms that are distinct from those tethering other B/b isoforms to the cellular surface. While the exact contribution of the B/bΔg isoform to B/b-mediated increases in cell motility and invasion is undetermined, B/bΔg is the most highly upregulated isoform of B/b present in human and rodent glioma tumor specimens and its localization to the cellular plasma membrane is suggestive of an important pathogenic function (Viapiano et al., 2003, 2005). Both the tumor-specific expression and cellular localization of B/bΔg make it an attractive therapeutic target for either its participation in B/b-mediated motogenic effects or for targeted drug delivery methods.

B/b also undergoes proteolytic processing by the ADAMTS-4 and 5 family members resulting in cleavage of the 150kDa full-length protein into a 50kDa and 100kDa N and C-terminal cleavage fragments, respectively (Matthews et al., 2000, Viapiano, 2005). The proteolytic processing of B/b is required for B/b-mediated increases in tumor cell motility as discussed previously (Viapiano et al., 2008; Hu et al., 2008). The overexpression and proteolytic processing of B/b was found to activate Epidermal Growth Factor Receptor (EGFR) signaling resulting in elevated levels of fibronectin expression which was assembled into microfibrils at the cells surface in a B/b-dependent manner. Increased expression of integrin β3 and N-cadherin were also observed in response to B/b overexpression and these affects were found to be specific to glioma cells cultured in the presence of fibronectin (Hu et al., 2008). The summation of findings on B/b expression and function in glioma suggests that targeting B/b at the levels of transcriptional regulation, post-translational modifications, and proteolytic processing all represent novel avenues that could potentially reduce glioma tumor cell invasion.

Versican, another member of the lectican family of CSPGs, is also highly expressed in glioma specimens along with other systemic cancer types like breast cancer. In human glioma specimens and cell lines many different spice variants of versican are overxpressed including both the nervous system-specific V2 isoform and the more broadly expressed V0/V1 isoforms (Arslan et al., 2007; Dours-Zimmerman & Zimmerman, 1994; Paulus et al., 1996). The expression of versican in glioma has been linked to increased tumor size, angiogenesis and glioma cell motility (Zheng et al., 2004). Protein isoforms containing the G3 domain of versican, which consists of the C-terminal domains common to lectican family members, has been shown to be abundantly expressed in glioma specimens and play a role in regulating tumor growth and angiogenesis. Overexpression of the versican G3 domain in glioma cells resulted in tumors of increased size and enhanced vasculature in animal xenographs compared to controls. Versican G3 conditioned media was found to enhance endothelial cell adhesion, proliferation and migration. Furthermore, the overexpression of versican G3 was found to increase the expression of fibronectin and Vascular Endothelial Growth Factor (VEGF). The elevated expression levels of fibronectin and VEGF formed a complex with versican G3 that could be co-immunoprecipitated, the additive effects of all three components of the complex – versican, fibronectin and VEGF to endothelial cells exacerbated the effect that either component alone or in pairs had on the adhesion, proliferation and migration of endothelial cells, substantially increasing it (Zheng et al., 2004). More recently, the ability of transforming growth factor β- 2 (TGFβ- 2) was shown to have an enhancing effect on the expression of versican V0/V1 isoforms. Furthermore, the addition of TGFβ- 2 exerted a motogenic effect on glioma cells that was partially mediated by increased V0/V1 expression (Arslan et al., 2007).

The overexpression of versican VI was found to induce neuronal differentiation of PC12 cells, an immortal cell line used to model neural precursor cells, through an integrin-dependent mechanism resulting from activation of EGFR and downstream signaling through ERK (Wu et al., 2004). While a versican-mediated affect on EGFR signaling in glioma tumor cells remains unexplored, mechanisms leading to B/b-mediated increases in cell invasion closely resemble those described for versican (Hu et al., 2008). Therefore it is interesting to speculate that overexpression of certain lecticans (B/b or versican or perhaps neurocan) by glioma tumor cells may be sufficient to mediate tumor cell motility by utilizing similar pathomechanisms stemming from increased fibronectin expression, EGFR activation, and integrin expression. Versican also undergoes proteolytic processing in glioma, however

the function of this cleavage in the pathogenesis of glioma remains unexplored (Westling et al., 2004). Versican represents an attractive therapeutic target for its functional role in glioma tumor growth, angiogenesis and cell motility.

The pro-invasive function of proteoglycans like B/b and versican may be, in-part, mediated by their interaction with cell-surface receptors, like **tenascins**. Tenascins are large secreted extracellular glycoproteins that bind to the cell surface through interactions with integrins (Bourdon & Ruoslahti, 1989). Tenascin-C and tenasin-R have been shown to bind to proteoglycans with high affinity to bridge the molecular gap between secreted proteoglycans in the extracellular space and the cellular plasma membrane (Aspberg et al., 1995, 1997; Barnea et al., 1994; Milev et al., 1997). Pioneering studies demonstrated that tenascin proteins are expressed by glioma cell lines in vitro and are present at higher levels in glioma specimens relative to normal brain tissue (Ventimiglia et al., 1992; Zagzag et al., 1995). Additionally, the use of tenascin as an immobilized protein substrate was found to enhance human glioma cell migration through an α2β1 integrin-dependent mechanism (Deryugina and Bourdon, 1996).

Subsequent to these studies, four tenascin family members were identified including tenascin-C, R, W, and X, all of which have been implemented in several physiological and pathophysiological functions including embryonic development, wound healing and are present in several solid tumor types. Tenascin-R expression is restricted to the CNS, while other tenascin family members are ubiquitously expressed (Hirata et al., 2009). The expressions of both tenascin-C and W have been identified surrounding tumor vasculature in glioma specimens, however tenascin-C is the best studied in glioma for its role in enhancing tumor cell invasion. In GBM patients, increased expression of tenascin-C is correlated with an adverse prognosis. Moreover, the endogenous expression of tenascin-C in GBM tumor cells was found to enhance cell invasion and correlated with reactive changes in the normal brain tissue surrounding GBM tumors in patients (Hirata et al., 2009). Like several ECM components, tenascin-C-mediated increases in glioma cell invasion are dependent on proteolytic processing. In glioma tumor cells tenascin-C is cleaved predominantly by MMP-12, and the inhibition of MMP-12 activity attenuated tenascin-C mediated glioma cell invasion (Sarkar et al., 2006). The tumor-specific upregulation of tenascin-C along with its pro-invasive function make it an attractive therapeutic target for anti-invasive therapies and it has shown some promise in clinical trials (Riva et al., 1999a ,b).

Another proteoglycan that has also been shown to interact with tenascins and is upregulated in glioma specimens is **(RPTPζ)/ Phosphacan** (Adamsky et al., 2001; Muller et al., 2003). RPTPζ is a transmembrane receptor tyrosine kinase phosphatase, which like the lecticans is also a CSPG bearing extensive decoration with CS-GAG chains. However unlike the lecticans, RPTPζ lacks an HA binding domain and does not interact directly with the HA scaffold of the neural extracellular space. The N-terminal protein domains of RPTPζ, are comprised of a carbonic anhydrase-like domain and a fibronectin type III-like domain. The central domain, which contains the transmembrane domain bears CS-GAG moieties that modulate the interaction of RPTPζ with several of its ligands, and the C-terminal protein domains are made up of two intracellular phosphatase domains (Peles et al., 1998).

While the protein structures of RPTPζ and lectican CSPGs are highly divergent, both RPTPζ, neurocan and versican have several common ligands including tenascins, NCAM, L1-CAM, contactin, and Transient Axonal Glycoprotein 1 (TAG-1/ axonin-1) (Peles et al., 1998; Rauch et al., 2001). RPTPζ is encoded from the PTPRZ1 gene and has four known isoforms resulting from alternative splicing. These include the full-length receptor form RPTPζ, a

short-receptor form, a secreted form, phosphacan, which lacks the transmembrane regions and intracellular phosphatase domains, and a truncated secreted form, PSI (Phosphacan Short Isoform) (Garwood et al., 2003). RPTPζ expression is enriched in the CNS and is upregulated in human glioma tumors along with its soluble ligand pleiotrophin (PTN)/ HB-GAM relative to normal brain (Muller et al., 2003). Upon binding to PTN, RPTPζ receptors cluster resulting in the inactivation of endogenous phosphatase activity, which leads to increased phosphorylation of downstream effector molecules like β-catenin. Phosphorylation of β-catenin stabilizes the protein and facilitates canonical β-catenin/cadherin and WNT pathway signaling, which have implications in cell motility, proliferation and cell fate decisions (Meng et al., 2000). In glioma tumor cells, RNAi mediated knockdown of RPTPζ in a human glioma cell line reduced the size of engrafted tumors in rodent models and decreased the proliferation rate of tumor cells in vitro. The reduction in RPTPζ expression also decreased PTN-mediated increases in cell proliferation and motility (Ulbricht et al., 2006). A similar study also found that RPTPζ knockdown cells had reduced motility on a PTN-immobilized substrate but did not see any affects on cell proliferation (Muller et al., 2003). Given that RPTPζ is upregulated in human glioma tumors, localized to the cellular surface and regulates complex cellular behaviors that contribute to glioma pathogenesis, RPTPζ is a prime candidate target for future glioma therapies. Both cell-ECM and cell-cell adhesion molecules play critical roles in translating changes in the extracellular environment to alterations in the cellular cytoskeleton

4.2 Intercellular interactions mediate tumor cell invasion

While interactions with the ECM mediate aspects of glioma invasion, this process also involves interactions between both adjacent tumor cells and tumor cells with normal cells within the CNS, which are typically mediated by cell adhesion molecules.

Cell-cell adhesion molecules typically exhibit homophilic binding to mediate intercellular interactions with adjacent cells expressing the same cell-adhesion molecule but have also been shown to interact with constituents of the ECM through heterophilic binding (Hinsby et al., 2004). In addition to mediating intercellular adhesion, molecules like the Immunoglobulin (Ig) superfamily of Cell Adhesion Molecules (CAMs) and cadherins also modulate signal transduction cascades to translate extracellular interactions into intracellular changes by impinging on the activation of receptor tyrosine kinases, molecular components of the WNT signaling cascade, and RhoGTPases (Cavallaro & Christofori, 2004). The functional roles of cell-cell adhesion molecules in glioma invasion are complex, as either their ability to enhance or inhibit glioma cell motility is dependent on both post-translational modifications and interactions with specific ligands. Neuronal- cadherin (N-cadherin) provides an exemplary model of this, as the degree of organization and maturation of N-cadherin cell-cell junctions impacts the migratory capacity of glioma cells, wherein more organized cell-cell junctions inhibit cell motility. However, the organization and maturation of cell-cell junctions depends critically on the presence or absence of specific ECM ligands (Perego et al., 2002). As a result of these complex biochemical underpinnings, the expressions and functions of specific cell-cell adhesion molecules have been differentially reported, most likely resulting from context-specific interactions that have yet to be fully understood.

The Ig-CAMs play important roles in cell migration and invasion in several physiological and pathophysiological functions including development, wound healing and cancer

metastasis. The Neural Cell Adhesion Molecule (NCAM) has a complex role in mediating aspects of glioma tumor cell adhesion, migration and invasion. The overexpression of NCAM was found to decrease glioma tumor cell motility through non-homophilic interactions by blocking binding of glioma tumor cells to extracellular substrates. Both the intracellular and extracellular portions of the NCAM receptor independently were found to block glioma cell motility, for which the extracellular Ig domains were determined to be critical. Therefore the attenuation of motility by the overexpression of the NCAM extracellular domain was believed to be due to the heterophilic interaction of the Ig domains with a constituent of the ECM thereby competing off endogenous motogenic receptors (Prag et al., 2002). More recently, a loss of NCAM expression in gliomas of increasing WHO grade was determined, suggesting that the negative regulation of NCAM is involved in glioma progression. The loss of NCAM expression was also correlated with more diffuse brain-tumor interfaces (Duenisch et al. 2011).

Interestingly, NCAM is the major substrate for Poly Sialic Acid (PSA) modifications resulting in PSA-NCAM. The overexpression of enzymes that attach the PSA moiety resulted in increased invasion of intracranial grafts compared to PSA negative NCAM alone. Furthermore, increased tumor cell invasion was observed for both PSA positive and negative NCAM glioma tumor cells in NCAM knockout mice, lacking NCAM expression in the nervous system environment, suggesting that the PSA modification serves to attenuate NCAM homophilic interactions to mediate increased glioma cell invasion (Suzuki et al., 2005). Furthermore, the expression of PSA-NCAM was found to correlate with an adverse progonisis for GBM patients (Amoureux et al. 2010). Therefore the negative regulation of NCAM homophilic binding resulting from either a decrease in NCAM expression or the glycosylation of NCAM to yield PSA-NCAM enhances glioma tumor cell motility and invasion.

The **cadherin** family members are calcium dependent cell-cell adhesion molecules that interact with catenins to signal changes in the actin cyctoskleton. Studies have demonstrated that N-cadherin is expressed by glioma cells, however conflicting evidence exists as to the function of this expression (Barami et al., 2006). Regardless of these conflicting reports, it has been determined that N-cadherin proteolytic cleavage by the ADAMTS-related protease ADAM-10 is a key mediator of GBM cell motility (Kohutek et al., 2009). Both epithelial-cadherin (E-cadherin) and N-cadherin have been found to play important roles in mediating glioma tumor cell motility with the CNS, but recent studies suggest that elevated E-cadherin levels at the expense of N-cadherin in glioma cell lines has been associated with increased tumor aggressiveness (Lewis-Tuffin et al. 2010). Further investigation into the complex pathomechanisms of cell-cell adhesion molecules and their heterophilic interactions with ligands of the ECM in the context of glioma cell dissemination is important to understanding the macroscopic contribution of the neural extracellular environment to glioma invasion and progression.

5. Glioma tumor initiating cells and the neural ECM

In addition to the ability of glioma tumor cells to invade the normal surrounding brain tissue, another major therapeutic obstacle is the presence of a tumor stem cell-like population of cells that reside within the solid tumor mass. This small cellular subpopulation is resistant to radiotherapy and capable of repopulating the original parental tumor leading to tumor recurrence and disease progression (Chalmers, 2007). Interestingly,

constituents of the neural ECM and cell-cell adhesion molecules are also implicated in the pathomechanisms of this small but lethal cellular subpopulation.

5.1 Cancer initiating cells are present in human glioma tumors

Cancer initiating cells (CICs) also called "cancer stem cells" were initially identified in human leukemia, and have since been described in several solid tumor types including gliomas (Galli et al., 2004; Singh et al., 2003, 2004). CICs were first isolated from human glioma tumors by culturing tumor cells in a media composition that closely resembles neural stem cell media, comprised of a serum-free base with Epidermal Growth Factor (EGF) and basic Fibroblast Growth Factor (bFGF). The resulting GIC population exhibited several distinct phenotypic characteristics from other glioma tumor cells, which serve as criterion to operationally define GICs and are: 1. the ability to self-renew, 2. multipotency – the ability to differentiate into every cellular subclass present within the CNS, and 3. the ability to phenotypically recapitulate the original parental tumor upon orthotopic transplantation (Galli et al., 2004; Singh et al., 2004). The presence of a GIC subpopulation within human glioma tumors suggests a complex intratumoral heterogeneity, wherein GICs are molecularly and phenotypically distinguishable from other glioma tumor cells. Recent evidence suggests that GICs are highly refractory to current adjuvant therapeutic treatments resulting from their slow progression through the cell cycle and upregulation of DNA repair mechanisms (Bao et al., 2006). According to the controversial "cancer stem cell hypothesis", CICs maintain stem-like characteristics that fuel the growth of the tumor by giving rise to all other tumor cell types through a process that closely resembles normal cellular differentiation and effective eradication of tumors requires the ablation of the CIC population.

While a significant amount of research supports the role of GICs in the pathophysiology of gliomas and the resemblance of GICs to their glial and neural stem cells counterparts, the utility of GICs as a model for primary glioma tumors is unparalleled. Initial evidence suggested that glioma tumor cells cultured in serum free media with EGF and bFGF more closely resembled original parental tumors both molecularly and phenotypically than serum cultured cell lines (Lee et al., 2006). These findings were seminal as they suggested, regardless of the controversy surrounding "cancer stem cells", that GICs are likely a more representative model of primary glioma tumors than traditional serum cultured cell lines.

GICs are highly tumorigenic and a significant amount of research has gone into identifying molecular markers of the most highly tumorigenic subpopulation. Although controversial, CD133 expression has been correlated to increased GIC tumorigenicity (Campos & Herold-Mende, 2011). While both CD133+ and CD133- GIC cells have been found to be highly tumorigenic, recent evidence suggests that two subpopulations of CD133- cells are present within glioma tumors; one which is tumorigenic and gives rise to CD133+ cells and another that is not (Chen et al., 2010). Thus offering a solution to the long-standing conundrum surrounding the correlation between CD133 expression and tumorigenicity.

5.2 Neural extracellular matrix expression denotes subtypes of gliomas and glioma initiating cells

High-grade gliomas, glioblastoma muliforme, were so named for the considerable intra as well as intertumoral heterogeneity observed across individual glioma tumors. In efforts to better characterize glioma subtypes and begin an investigation into the value of

individualized patient-tailored therapies, molecular subclasses of hundreds of primary glioma tumors were evaluated on the basis of their gene expression profile signatures. In this seminal study by Phillips and colleagues, three molecular subpopulations of glioma tumors were identified proneural, proliferative, and mesenchymal (Phillips et al., 2006). The identification of different molecular subclasses of glioma tumors set the stage for an investigation into the presence of distinct molecular subtypes of GICs. Gunther and colleagues created GIC cell lines from nine human GBM tumors and their molecular gene profile signatures determined (Gunther et al., 2008). Interestingly, two distinct molecular subpopulations of GICs emerged as separate clusters, cluster-1 and cluster-2. GIC cell-lines belonging to cluster-1 cells grew as spheres, had increased multipotency, expressed high levels of CD133, and created highly invasive intracranial tumors. In contrast, cluster-2 GICs grew as adherent or semi-adherent cultures, were restricted in cell fate, had little or no expression of CD133 expression, and exhibited low tumorigenicity and resulted in poorly invasive tumors in vivo (Gunther et al., 2008).

Lottaz and colleagues determined that cluster-1 GICs were most similar to proneural GBM tumors, while cluster-2 GICs were closely related to the mesenchymal GBM subtype (Lottaz et al., 2010). In accordance with these findings, the expression of BCAN was specifically enriched in the proneural GBM subtype and cluster-1 GICs which were found to be more highly tumorigenic than cluster-2 GICs and correlated with increased CD133 expression (Gunther et al., 2008). Work from our own lab has replicated these findings demonstrating that B/b is highly expressed by GICs with a phenotype similar to that described for cluster-1 cells. While the exact function of B/b expression by GICs is currently under investigation, the unique pathophysiological properties of GICs suggest that B/b may have broader functionality than observed in terminally differentiated glioma tumor cells. Likewise the restricted expression of CD44 was also identified in cluster-2 GICs along with integrins β1 and β5 (Gunther et al., 2008), again suggesting that differential expression of neural ECM components may contribute to differences in the pathophysiology of distinct molecular subclasses of GICs. The identification of neural ECM expression by GICs suggests that molecular constituents of the neural ECM could be employed as therapeutic targets that also impinge on the highly tumorigenic GIC subpopulation to reduce tumor recurrence and improve patient prognosis. Further research is needed to characterize the function of neural ECM components and cell adhesion molecules in the GIC population to fully evaluate the efficacy of targeting their expression to improve the prognosis of patients with GBM tumors.

5.3 The neural extracellular matrix and glioma initiating cells

While the function of neural ECM expression by GICs remains largely unknown, GICs are phenotypically and molecularly similar to normal neural stem cells (NSCs) (Rebetz et al., 2008). Suggesting that the microenvironment, or stem cell-like niche, surrounding GICs may share several parallels with the composition and function of the microenvironment surrounding NSCs during neurodevelopment and in the adult brain (Denysenko et al., 2010). In support of this hypothesis, the stem-cell niche that comprises the normal NSC microenvironment contains elevated levels of several ECM components whose expressions are enriched in GICs and gliomas including but not limited to laminin (Shen et al., 2008) and tenascin-C (Garcion et al., 2004). Moreover, NSCs themselves have been shown to express

the same neural ECM constituents expressed by GICs including the lectican family members (Kabos et al., 2004), phosphacan/ RPTPζ (Abaskharoun et al., 2010b, a), tenascin-C (Abaskharoun et al., 2010a), integrin α6β1 (Shen et al., 2008).

Of importance, both GICs and NSCs reside in highly vascularized niches and are often localized surrounding blood vessels (Gilbertson and Rich, 2007; Shen et al., 2008). Normal NSCs reside in the subventricular zone (SVZ) of the developing brain, which is inherently highly vascularized (Shen et al., 2008). In the adult SVZ, the association between endothelial cells comprising the vasculature of the stem cell microenvironment and NSCs are mediated by an interaction between laminin on endothelial cells and a major laminin binding integrin, α6β1. The inhibition of integrin α6 was found to disrupt the association between endothelial cells and NSCs and caused a significant decline in NSC proliferation. These findings highlight the functional significance of a close association between vascular endothelial cells and stem cells in maintaining their stem cell-like properties (Shen et al., 2008). Similar findings have also been reported for GICs, which further supports the hypothesis that the composition of the microenvironment surrounding GICs closely mirrors that for NSCs and as a result may have common functions in maintaining the stem cell-like state.

In gliomas the vasculature that comprises the GIC microenvironment typically arises de novo as part of tumorigenesis, or as recent evidence suggests from the differentiation of GICs into endothelial cells (Ricci-Vitiani et al., 2010). The close association between tumor vasculature endothelial cells and GICs was found to be imperative for maintaining the stem cell-like phenotype of this cellular population (Williams et al., 2010). Moreover, the expression of integrin α6 was identified as a marker of GICs residing within the perivascular niche. The inhibition of this cell adhesion molecule was found to block the interaction between laminin on vascular endothelial cells and GICs, which subsequently impeded GIC self-renewal, proliferation, and tumorigenic capacity (Lathia et al., 2010). These studies suggest that targeting the microenvironment, or stem cell-like niche, surrounding GICs may be a therapeutically advantageous approach to force the GIC subpopulation out of its stem cell-like state and to become subsequently more responsive to adjuvant therapies. Therefore, the components that comprise this unique stem cell-like microenvironment surrounding GICs represent attractive therapeutic candidates to inhibit tumor recurrence.

6. Conclusion

The ability of glioma cells to interact with and invade into the extracellular environment within the CNS is a critical contributor to the pathogenesis of these tumors and poor patient prognosis. Gliomas modulate their surrounding environment through the expression of unique matrix elements and cleavage of the normal matrix. In addition, they alter expression of cell surface receptors to mediate unique interactions within this neural environment. Recently, work suggests that GICs also employ a similar strategy to surround themselves with a neurogenic microenvironment. Therefore, therapeutic interventions that interfere with the expressions of neural ECM constituents, cell surface receptors, and cell adhesion molecules may represent ideal targets both to impede glioma invasion and also the tumorigenic qualities of GICs, thus targeting two major contributors to tumor recurrence and disease progression. Further work understanding the role of the ECM in glioma tumor pathogenesis is critical to develop better strategies for treatment of patients with gliomas.

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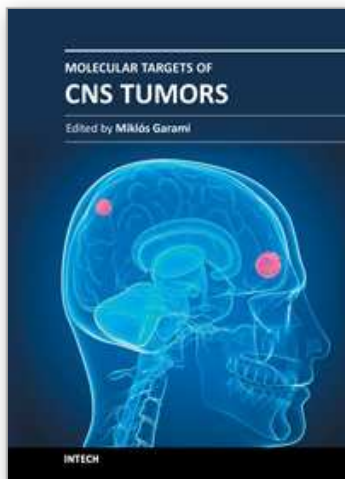
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