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Contributions of Chondroitin Sulfate Proteoglycans to Neurodevelopment, Injury, and Cancer

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Abstract

Chondroitin sulfate proteoglycans (CSPGs) are a diverse family of extracellular matrix (ECM) molecules that make significant contributions to the patterning and routing of migrating neural cells and extending axons. Three distinct modes of migration mediation have been observed, which result from the relative abundance and positioning of expressed CSPGs, the profile of CSPG receptors expressed by the motile cell types, and the overall way in which the CSPGs integrate into and stabilize the neural ECM. Here we discuss recent findings that help to clarify the molecular mechanisms that underlie these distinct migration-regulating properties as they pertain to neural development, CNS injury, and gliomagenesis.

Keywords

CSPG; Chondroitin Sulfate Proteoglycan; Cell Migration; Axon Guidance; Glial Scar; Brain Tumor; Glioma; Glioblastoma; Invasion; CSPG Receptor; LAR

Introduction

Chondroitin sulfate proteoglycans (CSPGs) are a large and diverse family of extracellular matrix (ECM) molecules. The central nervous system (CNS) enriched CSPGs, referred to collectively as the lectican subfamily, share three key features. The core protein structure of each lectican, which ranges from 97 to >262kD, begins and ends with a conserved N-terminal (G1) and C-terminal (G3) globular domain linked by a central, CS-GAG anchoring backbone, of variable length, bound to at least one, long-chain chondroitin sulfate

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glycosaminoglycan (CS-GAG) polysaccharide [1]. By binding hyaluronan and tenascin-R through their G1 and G3 domains, respectively, CSPGs provide one of three major components of the tripartite lattice that forms the CNS ECM [1,2]. While the contribution of CSPGs to the inhibitory nature of certain restricted territories within the embryo as well as the glial scar in the adult has been known for many years (see review by [3]), until recently, a mechanistic explanation of how CSPGs might redirect the advancement of cells or growth cones was lacking. This brief review will describe work that begins to elucidate how CSPGs provide varied biological effects during normal development and after trauma in the adult and, in addition, present some new ideas on how CSPGs orchestrate glioma invasion or the lack thereof.

Expression and the role of CSPGs During Development

During CNS development, glycosylated CSPGs are highly expressed in specific locations and were first thought to serve only as molecular barriers, blocking cells or axons from moving across the boundary between two adjacent, emerging structures (Fig. 1A). For example, CSPGs repel axons from extending across the roof plate of the spinal cord [4,5], the midline rhombencephalon and mesencephalon [6,7], the periphery of the developing retina [8,9], certain portions of the optic chiasm and distal optic tract [10,11] and the posterior somite [12]. A second mode of CSPG-mediated migration was then discovered within the sub-ventricular germinal centers of the embryonic and adult brain. This “addictive” growth constrained movement to pathways that were spatially defined by the uniform and robust expression of glycosylated CSPGs [13–16]. Unlike classic, chemo-attractive guidance, which involves forward movement up an increasing gradient of attractant, the addictive growth observed within the sub-plate of the developing forebrain [17] and the raphe [18], restricted cellular movement and process extension within specific, spatially-defined highways of CSPGs (Fig. 1B). Thus, two distinct cell migratory behaviors are associated with CSPGs during development: (1) turning away from a zone of CSPG production, and also (2) a type of “addictive” growth constrained within CSPG containing territories (Figure 1). What is the mechanism that allows for such diverse motile behaviors during interactions with the same family of molecules?

For years it was posited that CSPGs exert their effects through relatively nonspecific mechanisms such as substrate occlusion [19], or presentation of negative charge [20]. This view has evolved considerably with the discovery of several receptors that directly bind sulfated glycosaminoglycan moieties [21–23]. The receptor protein tyrosine phosphatase sigma (PTPRs, or PTPσ) was the first receptor identified with the ability to both bind CS-GAGs and convey a signal for growth inhibition [23]. PTPσ, together with PTPδ and LAR, are members of the class IIa/Leukocyte common antigen-related (LAR) family of receptor tyrosine phosphatases. Since all three LAR family receptors exhibit high sequence homology and contain a cluster of lysine residues that comprise a canonical glycosaminoglycan-binding domain [24,25], it was not unexpected when LAR was later shown to be another CS-GAG binding, CSPG receptor [22]. In addition to LAR family phosphatases, the NOGO receptors NgR1, NgR2, and NgR3 have been recently identified as receptors for CSPGs [21,26]. This discovery established a link between myelin derived inhibitors and proteoglycans, the two major classes of molecules that inhibit axon

regeneration and sprouting. Whether signaling by NgR1-3 and LAR family receptors converges on a common effector is an important and unanswered question (see review by [27]). Here, we will focus on LAR family receptors and discuss the implications of their differential expression mediating disparate CSPG-mediated migratory behaviors.

Turning versus addictive growth patterns may depend on a receptor competition mechanism

In vitro, neurons exhibit different growth patterns depending upon which substrate (CSPG containing or CSPG lacking) the neuron cell body first resides and the length of time upon which their axons remain on this surface [28,29]. For instance, neurons co-cultured with CSPG and laminin-expressing Schwann cells tend to preferentially extend their processes along the Schwann cell membranes over the laminin only coated background. Interestingly, chondroitinase ABC mediated CS-GAG removal mitigates this phenomenon and allows the axons to abandon the Schwann cell. [The bacterial enzyme chondroitinase ABC (Ch'ase ABC) catalyzes the degradation of CS-GAGs.] *In vitro* stripe assays have revealed similar addiction-like behaviors. Specifically, Ch'ase ABC digestion frees dorsal root ganglion (DRG) neurons from exclusive growth within tracts of purified CSPGs (combined with other ECM molecules, such as laminin or fibronectin). As mentioned above, during development it has been shown that in certain regions, migrating neuronal precursors or growing axons actually prefer the CSPG containing SVZ or sub-plate (Fig. 1B). Alternatively, the turning behaviors, observed at the roof plate [5], the developing mid and hindbrain [6,7], the retina [8], etc., occur when neurons arrive from a journey within a CSPG-free ECM and are suddenly presented with abundant CSPGs at a sharp interface (Fig. 1A). Thus, the abundance of CSPGs, especially the concentration of CS-GAGs, relative to other adhesive matrix molecules appears to predict turning versus additive migration behavior.

There is increasing evidence that neurons express different receptor profiles based upon which substrate molecules they encounter first and for how long. Further, cross talk between CSPGs and CS-GAG receptors and other ECM molecules and their receptors, such as laminin, fibronectin, and certain integrins is conceivable [30–33]. Thus, we hypothesize that neurons beginning on non-addictive, non-CSPG substrates, express high amounts of ECM adhesion receptors (i.e. integrins) and minute quantities of LAR family receptors. Cells or axons are therefore able to enter territories containing permissive molecules even when they contain relatively low amounts of CSPGs. Up-regulation of LAR family receptors may take some time, so short encounters with CSPGs are not enough to cause permanent addiction. However, if the neurite enters and grows within a CSPG and laminin or CSPG and fibronectin-containing ECM for extended periods, it will eventually also increase both integrin as well as LAR family receptors and will no longer leave without removing or interfering with the LAR/CS-GAG interaction [34].

A Novel Mechanism for Regeneration Failure: CSPG-Mediated Entrapment

While the contribution of CSPGs to the inhibitory nature of the glial scar has been known for many years (see review by [3]), a mechanistic explanation as to how CSPGs permanently

thwart advancing growth cones was lacking – until recently. Our laboratory has developed a simplified version of the injury site ECM, in which adult sensory neurons develop classic dystrophic endballs as they attempt to traverse an increasing gradient of CSPGs. Herein, adult DRG axons initially encounter a non-addictive ECM component, such as laminin or fibronectin, where they display dynamic filopodia with a highly motile growth cone that rarely collapses. However, when growth cones are exposed to a gradient of CSPGs they enter within the low end of the gradient and ascend until their initially elaborate growth cones convert into an immobilized state with slender tips and one or several extremely strong focal adhesions. The morphology of these dystrophic growth cones *in vitro* is remarkably similar to those described after spinal cord injury (SCI) by Ramon y Cajal in the early 20th century [35]. The molecular mechanism that leads to such strong bonds between neurons and CSPG-containing substrates is dependent upon the pro-synaptic LAR family receptors, which become highly concentrated in dystrophic growth cones. Using cell-permeable peptides that regulate the receptor and markedly reduce adhesion, we found that PTPσ in particular plays a critical role in converting growth cones into a dystrophic state by first mediating addiction, and eventually binding them so tightly to CSPG containing substrates that they can no longer advance [36] (Fig. 2).

Interestingly, *in vivo*, this injury-associated “extreme” addiction or entrapment within CSPGs may depend less on secreted lecticans and more on the membrane-anchored CSPG, NG2. NG2 is purportedly one of the more inhibitory CSPGs produced after SCI [37–39]. Upon SCI, severed axons dieback from the lesion core into the injury penumbra, where they closely associate with $NG2^+$ glial cells [40,41]. These polydendrocytes (for review see [42]) produce a complex ECM containing the membrane-bound CSPG as well as laminin and fibronectin. We investigated the role that membrane-bound CSPGs played in this tight cell-axon interaction and whether over-adhesion to these NG2-expressing cells might play a role in regeneration failure. Studies using CSPGs in combination with other adhesion molecules as well as adult cord-derived $NG2^+$ glia suggest that CSPGs are, indeed, involved in entrapping neurons. Once dystrophic axons become stabilized on polydendrocytes, they form synaptic-like connections *in vitro* and *in vivo*, which could potentially trap axons within the peri-lesional white matter for decades (Fig. 2). PTPσ knockouts exhibit increased axonal regeneration after optic nerve crush [43], dorsal column lesion [23], and corticospinal tract injury [44].

Expression of CSPGs within Diffusely Invasive Gliomas

There is potentially a third CSPG-mediated migration behavior that occurs in infiltrative glioma. High-grade astrocytoma is characterized by the diffuse infiltration of tumor cells throughout the brain. CSPGs have long been implicated in this diffusely invasive pathology [45,46], however the aforementioned turning and addiction mechanisms likely do not apply. Recall that both turning and addiction depend heavily on the relative abundance and positioning of CSPGs as well as the expression profile of CSPG receptors. On the receptor side, recent data suggests that LAR, NgR1, and NgR3-expression in invasive glioma are only minimally expressed and indistinguishable from the adult, non-tumor bearing brain [47]. Further, CSPG core protein levels [48] as well as glycosylated CSPGs [47] are also in low abundance and not significantly different between the glioma microenvironment and

healthy, non-malignant brain tissue. Thus, whereas the turning and addictive behaviors represent restrictions and constraints on the movement of cells, the widespread infiltration of glioma likely represents a separate biology.

If not turning or addiction, how can we reconcile the diffuse infiltration of tumor cells within a CSPG-containing ECM? Because CSPG-mediated migration is dependent on CS-GAGs, it is striking that more and more evidence suggests that the invasive glioma ECM is comprised of CSPGs that almost entirely lack CS-GAG side chains [46,47,49,50] (Fig. 3B). In this regard, it is worth exploring the possibility that the long-standing association between CSPGs and tumor infiltration might more accurately represent a lack of inhibition rather than the promotion of invasion. Multiple reports corroborate the scarcity of CS-GAGs from the glioma microenvironment and multiple splice variations and proteolytic cleavage reactions have been discovered in glioma cells that lead to the generation of non-glycosylated CSPGs [49–52].

The idea that CSPGs enable invasion extends from a series of reports published between the late 1990s and the early 2000s, in which a connection between brevican (BCAN) and invasive glioma was first described and then elaborated. Interestingly, while the structure and nomenclature of this BCAN molecule has been revised, investigators have held to the conclusion that glioma associated BCAN is an under-glycosylated or non-glycosylated species [45,46,50]. Inspired by these studies, investigators have expanded the scope of the analysis to additional lecticans as well as PCAN. For instance, Muller and colleagues demonstrated that the short (6.4kb), non-glycosylated, soluble splice variant of PCAN predominates the glioma ECM [49] and we have very recently demonstrated abundant, non-glycosylated BCAN, NCAN, PCAN, and VCAN species within patient-derived, infiltrative astrocytomas [47].

Functionally, multiple studies have demonstrated that CSPGs make important regulatory contributions to tumor cell invasion, however the molecular/mechanistic details of these regulations remain largely uncertain. CSPGs are known to bind adhesion [53] and motility [51] factors, which in turn, may act directly on invasive tumor cells. However, in terms of the CSPGs specifically, there is simply the indication, from multiple *in vitro* invasion assays as well as *in vivo* xenograft and allograft tumor models that CS-GAG side chain depletion is important in promoting glioma invasion. For instance, over-expression of the non-glycosylated hyaluronan-binding domain of BCAN [46] or the full-length molecule [52] from which this domain is readily generated, results in measurably increased tumor volumes.

Interestingly, in contrast it is clear that CS-GAG-rich, LAR-expressing tumors derived from the human glioma cell line U-87MG and the human grade II glioma cell line L7, grow expansively without microscopic infiltration and essentially mirror the CSPG-mediated addictive growth pattern displayed by developing and and regenerating neurons [47] (Fig. 3A). We have also observed an addictive form of growth from brain metastases generated by the CS-GAG-expressing human breast carcinoma line M4A4 (D. J. Silver, unpublished data). Importantly, we have demonstrated that enzymatic digestion of CS-GAGs away from

glioma-associated CSPGs can convert these non-invasive, U-87MG-derived tumors into diffusely infiltrating lesions [47].

One potential explanation for the role of CSPGs in diffuse glioma invasion was provided by the hyaluronan-lectican-tenascin-R (HLT) matrix model of the brain ECM [2]. The HLT model explains that the “tightness” of the brain ECM, or the degree to which the ECM resists the movement of cells, is dependent on abundant CS-GAGs. Thus, an invasion-permissive environment is established in glioma by destabilizing the otherwise inhibitory brain ECM with less inhibitory, CS-GAG deplete CSPGs. In total, these reports present CSPGs as important, albeit indirect facilitators or enablers of invasion. Further, these results hint that CS-GAGs could potentially oppose tumor cell infiltration (in accordance with their turning and addictive functions) but their absence or removal from the invasive glioma microenvironment instead serves to facilitate tumor cell infiltration.

Conclusion

This synthesis of classic and more recent studies presents a novel perspective into the biology of a family of molecules that has been studied in the nervous system for nearly 3 decades. It is clear that CSPGs, which were initially characterized as strictly inhibitory, actually mediate a diverse array of migratory behaviors that can both promote and inhibit the movement of cells and extending processes. Clinically, uncoupling entrapped axons from their constraints within the glial scar or peri-neuronal net has long been an attractive therapeutic possibility. The recent discoveries of the CS-GAG-binding, CSPG receptors LAR, PTPσ, NgR1, 2, and 3 offers the promise of currently unexplored therapeutic targets to leverage against this goal. On the tumor side, the picture may be more complicated. On one hand, the absence of CS-GAGs from the glioma microenvironment suggests that activation of one (or more) critical members of the CS-GAG post-translational modification machinery might be effective in a novel anti-invasive strategy. However, based on this new understanding of CSPGs, CS-GAGs, and CS-GAG receptors, could anti-invasive tumor therapies compromise the intrinsic plasticity of the CNS? What of the rare CNS injured patients with co-morbid CNS tumors or brain metastases? Could attempted regeneration through CSPG modification (especially if applied for long time periods) inadvertently exacerbate tumor infiltration? Seeking the foundational knowledge that clarifies this spectrum of cellular/environmental interactions has untold value. We offer this, more holistic view of matrix biology of the developing, injured, and tumor-bearing CNS as one attempt that may prove provocative and insightful.

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Highlights

1. CSPGs mediate three distinct modes of cellular migration.
2. CSPGs can redirect, confine, or amplify cell migration.
3. CSPG structure, time, location, and receptor profile determine migratory mode.

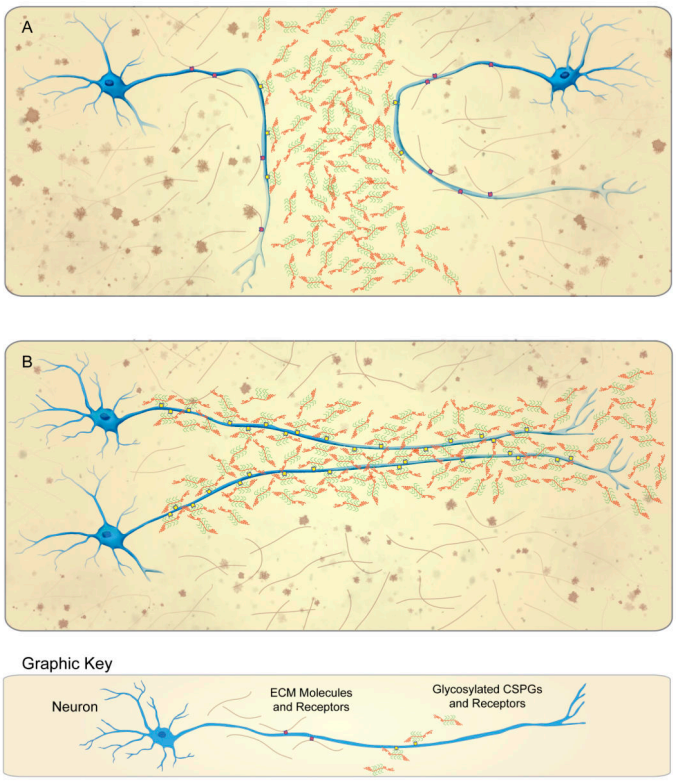

Figure 1.

CSPGs mediate the distinct migratory behaviors of turning and addiction. (A) Extending axons and migrating neuroblasts are re-directed, or “turned” away from developmentally-regulated proteoglycan boundaries when their receptor profiles favor adhesion to the non-addictive ECM molecules (i.e. laminin and fibronectin) adjacent to these CSPG-rich barriers. (B) In contrast, migrating neuroblasts and extending axons may become “addicted” to moving within CSPG-rich tracts through preferential expression of CSPG-receptors.

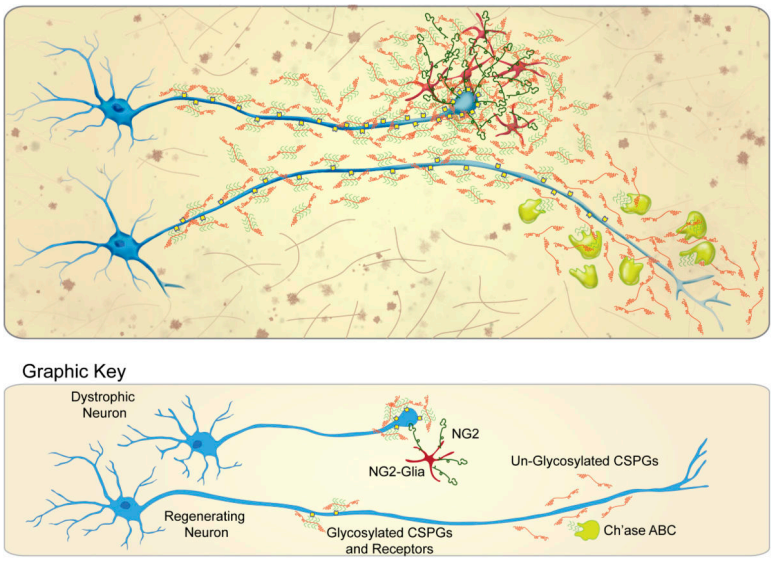

Figure 2.

Extreme "addiction," or entrapment occurs within the CSPG-rich glial scar that results from injury to the CNS. Overabundant expression of CSPG-receptors results in tight adhesion to injury-associated CSPGs, especially to the NG2 expressed by polydendrocytes within the lesion. Entrapped axons can escape and regenerate beyond the glial scar through treatments (i.e. Ch'ase ABC) that sever the CS-GAG/CSPG receptor connection.

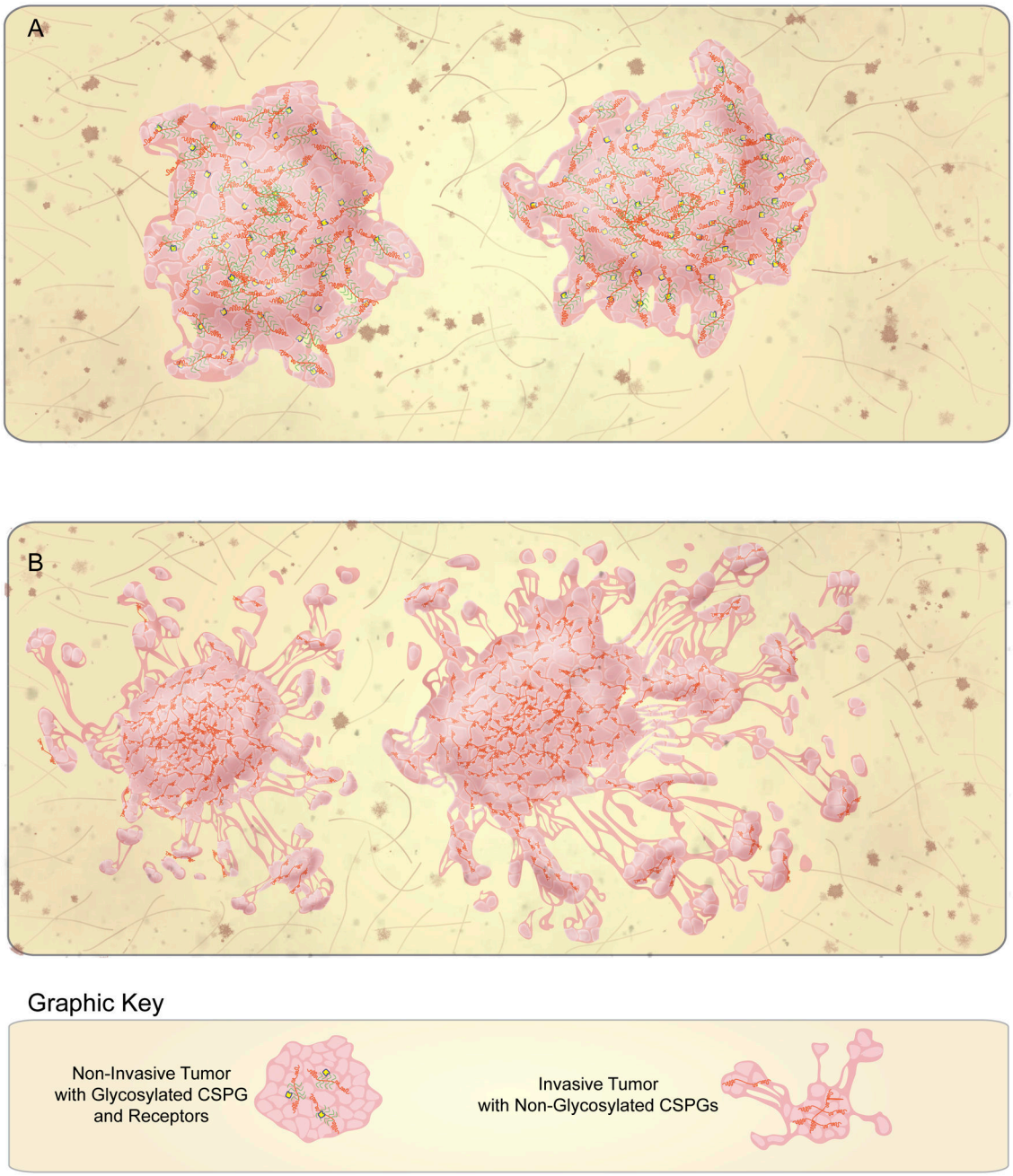

Figure 3.

CSPG addiction distinguishes non-invasive from invasive brain tumors. (A) Non-invasive brain tumors, such as non-neural brain metastases and certain low-grade gliomas express abundant CSPG receptors and glycosylated CSPGs, which mediate the self-containment of these tumors. (B) In contrast, invasive brain tumors, such as GBM, express various CSPG core proteins, but lack CS-glycosylation and CSPG receptors. The absence of addiction and the “loosening” of the brain ECM facilitates the diffuse infiltration of these tumors throughout the brain.