HHS Public Access

Author manuscript

J Neurosci Res. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

J Neurosci Res. 2018 April ; 96(4): 573–588. doi:10.1002/jnr.24151.

Extracellular Matrix and Traumatic Brain Injury

Naijil George and **Herbert M. Geller***

Laboratory of Developmental Neurobiology, Cell Biology and Physiology Center, NHLBI, NIH, Bethesda, MD 20892-1603, USA

Abstract

The Brain Extracellular Matrix (ECM) plays a crucial role in both the developing and adult brain by providing structural support and mediating cell-cell interactions. In this review, we focus on the major constituents of the ECM and how they function in both normal and injured brain, and summarize the changes in the composition of the ECM as well as how these changes either promote or inhibit recovery of function following Traumatic Brain Injury (TBI). Modulation of ECM composition to facilitates neuronal survival, regeneration and axonal outgrowth is a potential therapeutic target for TBI treatment.

Keywords

Proteoglycans; tenascin; hyaluronan; laminin; metalloprotease

1. Introduction

The extracellular matrix (ECM) of the brain is essential for the maintenance of proper brain function, providing both structural support and modulating intercellular communication (Frischknecht and Gundelfinger 2012). Following TBI, the breakdown of the blood brain barrier leads to infiltration of neutrophils, monocytes and other plasma components into the brain which then initiates an innate inflammatory response that involves activation of microglia and astrocytes (Lozano et al. 2015; Schnell et al. 1999). Subsequently, the release of inflammatory molecules by infiltrating immune cells, resident glial cells, cerebrovascular endothelial cells and neurons serves to amplify the immune response (Sordillo et al. 2016; Ziebell and Morganti-Kossmann 2010). Activation of both resident astrocytes and microglial cells in response to these mediators results in increased synthesis of extracellular matrix (ECM) molecules as well as the release of and activation of proteases which further remodel the ECM (Hemphill et al. 2015). These changes in the ECM can have both positive and negative consequences for recovery of function. The goal in this review is to discuss the normal constituents and functions of the ECM, how they are modified by TBI, and how

*Corresponding author: Herbert M. Geller, Ph.D., Laboratory of Developmental Neurobiology, Cell Biology and Physiology Center, NHLBI, Building 50 Room 4140, 50 South Dr, MSC 1754, Bethesda, MD 20892-1603, USA, Telephone 301-451-9440, geller@helix.nih.gov.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ROLE OF AUTHORS

Both authors contributed to the research for, writing of, and editing of the manuscript.

these modifications may affect recovery of function. This review is based on a literature search for each of the extracellular matrix molecules and proteases discussed in combination with the term “injury”.

Each of the cells within the brain is involved in neurovascular dysfunction following TBI, mainly through their altered secretion of cytokines which act both in an autocrine and paracrine manner to stimulate cytokine production as well as the synthesis of matrix molecules and matrix metalloproteases. A summary of the alterations in brain cell phenotypes and how they are altered by the interactions of the cytokine network is provided in Figure 1. In this scheme, the initial breach in the blood brain barrier allowing macrophage, monocyte and platelet entry initiates a cytokine cascade, altering resident astrocytes and microglia into a reactive phenotype and promoting the proliferation of oligodendrocyte progenitor cells (OPCs). These reactive cells then increase their secretion of other cytokines (Fig. 1B) and extracellular matrix. The released cytokines then promote further changes in each of the cell types (Fig. 1C). A list of the cytokines, their cellular sources and cells which respond is provided in Table 1.

The composition of the normal brain ECM is unique, comprised of a hyaluronan backbone to which are attached chondroitin sulfate proteoglycans of the lectican family, along with tenascins (Rutka et al. 1988) (Figure 1A, Inset). These molecules are produced by all the cell types found in the brain – neurons, astrocytes, oligodendrocytes and microglia. Other matrix molecules, such as heparan sulfate proteoglycans, laminins, collagen, and fibronectin, are produced by neurons and glia as well as endothelial cells and found in the basement membrane and maintain the blood brain barrier (Almutairi et al. 2016). Each of these classes of molecules is altered in response to TBI, both in terms of levels and distribution (Fig. 1C, Inset). A list of ECM molecules which are changed following TBI, their cellular sources, and how TBI alters their level or distribution, is provided in Table 2. The following sections discuss these ECM molecules and changes in their level in distribution, as well as their functional consequences, in more detail.

2. Proteoglycans

Proteoglycans are a heterogeneous class of glycoproteins characterized by a protein core with attached unbranched glycosaminoglycan (GAG) sugar chains (Fig. 2). These GAG chains are further modified by sulfation (Kjellen and Lindahl 1991). As major components of brain ECM, proteoglycans mediate cell-cell interactions and modulate growth factor and cytokine signaling during development as well as in response to various pathophysiological conditions in the adult (Cui et al. 2013). The signaling functions of proteoglycans in the brain are primarily due to their GAG chains (Miller and Hsieh-Wilson 2015), while the core proteins contain specific domains that determine localization and mediate interactions with cells and other matrix molecules. The major classification of proteoglycans is based on the composition of their associated GAG chains as either chondroitin sulfate proteoglycans (CSPGs), dermatan sulfate proteoglycans (DSPGs), heparan sulfate proteoglycans (HSPGs), or keratan sulfate proteoglycans (KSPGs), though some proteoglycans, such as aggrecan and agrin, can have GAG chains from more than one family (Iozzo and Schaefer 2015).

2.1 Chondroitin sulfate proteoglycans (CSPGs)

CSPGs are the most studied proteoglycan in the nervous system. CSPG core proteins are classified as lecticans, phosphacan, and NG2. Lecticans (neurocan, brevican, versican, and aggrecan) have a common structure including a hyaluronan-binding domain at amino terminal and a tenascin-R binding lectin domain at the carboxy-terminal. Versican has four different splice variants, three of which (V0–V2) are decorated by GAG chains (Wight 2002). Phosphacan is a splice variant of receptor protein tyrosine phosphatase-β (RPTP-β), which lacks its membrane spanning domain and is expressed by mature glial cells and neurons (Garwood et al. 1999; Hayashi et al. 2005). Unlike other CSPGs, NG2 (also known as CSPG4) has a transmembrane core protein with a large extracellular domain and a single GAG chain (Iozzo and Schaefer 2015). During development, the localized expression of CSPGs influences axonal pathfinding (Carulli et al. 2005; Wilson and Snow 2000). Once development is complete, CSPGs are mainly found in dense structures known as perineuronal nets, which serve to limit synaptic plasticity (Sorg et al. 2016).

Following experimental TBI, neurocan, aggrecan and NG2 are increased in glial scars around the injury core, while there is a simultaneous loss of CSPGs in the surrounding region, primarily a loss of PNNs (Harris et al. 2009; Yi et al. 2012). In rats, a unilateral knife cut in the cerebral cortex leads to increased versican-V2 immunoreactivity around the lesion at both 7 and 14 days post injury (dpi) (Asher et al. 2002). The loss of CSPGs from PNNs may help increase synaptic plasticity, while the increase found in the glial scar may serve to isolate the damaged region, much as it does in spinal cord injury (Anderson et al. 2016). In animals and humans, injury also causes a loss of mature oligodendrocytes, followed by proliferation of oligodendrocyte progenitor cells (OPCs) which produce the NG2 CSPG (Flygt et al. 2017; Levine 1994). NG2 is also found on melanoma cells, where it appears to promote migration (Burg et al. 1998), and it may have the same function for OPCs, which are highly migratory (Almad et al. 2011). NG2 may also be protective, as NG2-knockout mice had exacerbated damage as compared to wild-type mice (Huang et al. 2016)

In addition to increased expression of core proteins, there are also changes in the composition of CSPG GAG chains after TBI. Expression of chondroitin-4-sulfotransferase, chondroitin-6-sulfotransferase, and GalNAc4S-6 sulfotransferase are all upregulated at the injury site following cortical lesions in mice and rats (Bhattacharyya et al. 2015; Karumbaiah et al. 2011; Properzi et al. 2005). This results in an altered sulfation pattern of CSPGs that persists for months after injury (Harris et al. 2009; Jones et al. 2003; Yi et al. 2012). Immunolabeling studies from our laboratory showed that in the controlled cortical impact injury model, there is an increase in 4-sulfated GAG at the injury core and in a tight band surrounding the core. These changes were observed from 7 to 28 dpi (Yi et al. 2012). These changes in GAG chain levels and composition are proposed to have functional consequences. Both 4-sulfated (Wang et al. 2008) and 4,6 sulfated GAGs (Karumbaiah et al. 2011) inhibit axonal outgrowth in culture. Most recently, studies have demonstrated that the enzyme arylsulfatase-B, which regulates the 4-sulfation on the non-reducing end of the GAG chain (the end furthest from the protein core) can improve axonal growth in the spinal cord (Yoo et al. 2013). Studies directly investigating the role of chondroitin-4-sulfotransferases in brain injury are needed, but may be difficult because there are several different 4-

sulfotransferases in brain. While 4-sulfated GAGs are inhibitory to growing axons, 6-sulfated GAG is thought to be permissive (Lin et al. 2011). In vivo, chondroitin-6-sulfotransferase-1 KO mice have fewer regenerating TH-positive axons following a lesion to the nigrostriatal tract as compared to WT mice (Lin et al. 2011).

The exact mechanism by which CSPGs affect axonal guidance is not known. CSPGs may affect neuronal growth and regeneration by inactivating neuronal integrins (Tan et al. 2011). CSPGs also interact with several transmembrane receptors, including the Class IIA receptor protein tyrosine phosphatases, RPTPσ and the leukocyte common antigen-related receptor (LAR), and the Nogo receptors 1 and 3 (NgR1 and NgR3) (Dickendesher et al. 2012; Fisher et al. 2011; Shen et al. 2009). These interactions are dependent upon the sulfation pattern of the CS GAG chains, as only oversulfated GAGs and DS interact with these receptors (Dickendesher et al. 2012). Interestingly, 4-sulfated GAG chains, which are strongly upregulated following injury, do not interact with these receptors, suggesting that additional receptors remain to be revealed. In addition to binding to these neuronal receptors, CSPGs modulate FGF-2 (Sirko et al. 2010) and Semaphorin 5A signaling (Kantor et al. 2004).

2.2 Dermatan Sulfate Proteoglycans (DSPGs)

Dermatan sulfate (DS) GAG chains are derived from the epimerization of D-glucuronic acid in chondroitin sulfate to L-iduronic acid (Thelin et al. 2013). Although most of the functions of DS are related to the development and homeostasis of peripheral tissue, DS GAGs, especially oversulfated GAGs, stimulate neuritogenesis (Hikino et al. 2003; Nandini et al. 2005). In the rat brain, TBI-associated overexpression of DSPGs, including decorin and biglycan, is limited to the site of injury but lasts months (Stichel et al. 1995). DS was localized to fibrotic scar tissue following a stab-wound, and specific elimination with chondroitinase B promoted axonal growth across the scar (Li et al. 2013). Decorin is known to modulate the actions of TGF-β, and thus it may act to reduce scar formation (Logan et al. 1999). DSPGs also bind to FGF-2 and promote cell proliferation and astrocyte reactivity around the fibrotic scar (Penc et al. 1998).

2.3 Heparan Sulfate Proteoglycans (HSPGs)

HSPGs have important roles as modulators of cell signaling in brain, mainly by acting as co-receptors for many different cytokines and growth factors, such as FGFs (Qiao et al. 2003), GDNF (Barnett et al. 2002), sonic hedgehog (Rubin et al. 2002), semaphorin 5A (Kantor et al. 2004), and slit (Johnson et al. 2004). In addition, HSPGs bind to both the type IIA RPTPs and NgR1 and NgR3 receptors on neurons, again mediated through the HS GAG chains, rather than the core protein (Aricescu et al. 2002; Dickendesher et al. 2012). In contrast to the CSPGs, HSPGs binding to these receptors promotes axonal growth. To date, there is no clear explanation for this dichotomy of actions.

HSPG core proteins are classified into syndecans, glypicans, perlecan, and agrins (Fig. 2). Syndecan has four isoforms (1–4) that are transmembrane proteins consisting of an extracellular domain modified with HS chains, a single transmembrane domain and a short cytoplasmic domain (Afratis et al. 2017). Out of these isoforms, syndecan-3 is abundantly expressed in brain (Kim et al. 1994) and promotes neural migration (Hienola et al. 2006) and

neurite outgrowth (Raulo et al. 1994). Syndecan-2 is localized in synapses (Hsueh and Sheng 1999) and activates of protein kinase A and subsequent phosphorylation of Ena/VASP to promote filopodia and spine formation (Lin et al. 2007). Glypicans are GPI-anchored HSPGs with six isoforms (glypican1 to 6) all carrying two to five HS chains. Glypicans are expressed in early development (Luxardi et al. 2007), where they promote neuronal cell adhesion, neurite outgrowth and synapse formation (Allen et al. 2012; Kurosawa et al. 2001). Perlecan and agrins are HSPGs consisting of two or three HS chains attached to a multi-domain core protein. In brain, endothelial cells and astrocytes express perlecan, which is localized to the basement membrane and regulates growth factor signaling and blood brain barrier function (Roberts et al. 2012; Whitelock et al. 2008). Perlecan is a modular protein with 5 identified domains, each one interacting with different ECM proteins and growth factors (Gubbiotti et al. 2016; Whitelock et al. 2008). Agrin in basement membranes of the brain microvasculature plays a key role in maintaining blood brain barrier integrity (Steiner et al. 2014) while in neurons it promotes synaptogenesis and synaptic plasticity (Daniels 2012).

The expression of several HSPGs are increased in the region surrounding experimental injuries. Following a localized stab wound, both syndecan-1 and HS 2-O-sulfotransferase are increased, with a corresponding increase in 2-O-sulfation of associated HS GAGs (Properzi et al. 2008). TGF-α and TGF-β, cytokines associated with the CNS injury response, elicited the same changes in cultured astrocytes in vitro (Properzi et al. 2008). This leads to a positive feedback loop, as HS potentiates the activity of TGF-β1 (Lee et al. 2015a) and TGF-β increases the synthesis of both HSPGs and CSPGs (Dodge et al. 1990; Sugimoto et al. 2014). Cryoinjury produces an upregulation of glypican mRNA (Hagino et al. 2003b), suggesting a role for glypican in the neuroimmune response, but there is no direct demonstration of a role for glypicans in TBI.

Perlecan and agrin are also significantly increased after TBI (Falo et al. 2008; Garcia de Yebenes et al. 1999). After secretion, perlecan is cleaved by metalloproteases, releasing fragments with biological activity (Gonzalez et al. 2005). Amongst these, domain V, also called endorepellin, displays specific integrins which are masked in intact perlecan and that alter the physiology of endothelial cells and inhibit angiogenesis (Mongiat et al. 2003). Agrin is also increased in synaptic terminals and reactive astrocytes after TBI, in areas of active spouting, implicating a role in synaptogenesis and plasticity (Falo et al. 2008); additional experiments directly addressing the role of perlecan and agrin in TBI would be important.

2.4 Keratan Sulfate Proteoglycans (KSPGs)

KSPGs also show upregulation after CNS injury and inhibit neuronal outgrowth and regeneration (Geisert and Bidanset 1993; Geisert et al. 1996). Several CNS proteoglycans contain KS chains, the most prominent being claustrin (Cole and McCabe 1991), phosphacan (Takeda-Uchimura et al. 2015) and aggrecan (Virgintino et al. 2009). Injury-induced increased expression of KSPGs by infiltrating macrophages, microglia, and oligodendrocyte progenitor cells (OPCs) is partially responsible for the inhibition of neurite outgrowth and sprouting of neurons. KSPGs are also involved in glial scar formation by

activating microglia and OPCs (Jones and Tuszynski 2002). The effects of KSPGs are dependent on their GAG chains, as elimination of N-Acetylglucosamine 6-O-sulfotransferase-1, which eliminates 6-sulfation on KS GAGs, reduced scar-forming activity (Zhang et al. 2006) and degradation of keratan sulfate GAGs using keratanase promoted axonal regeneration and functional recovery (Ishikawa et al. 2015).

3. Other ECM components

TBI induces the expression of additional ECM components that are mainly expressed by developing or diseased brain. Out of these, hyaluronan, fibronectin, tenascin, laminins and osteopontin are known to have roles in TBI pathophysiology.

3.1 Hyaluronan

Hyaluronan (also called hyaluronic acid: HA) is a unique GAG which is not attached to a core protein and whose sugars are not modified by sulfation or epimerization. Many of hyaluronan's physiological properties, including providing biomechanical integrity, altering tissue hydration and facilitating tissue assembly, are dependent on its size, concentration, and localization. TBI is associated with the increased expression of the HA synthases (HAS1 and HAS2) (Xing et al. 2014).

TBI induced alterations in HA affect ECM integrity and signaling. HA is anchored to the ECM by forming highly stable complexes with hyaluronan-binding proteins (hyaladherins) which help to stabilizing the ECM. Hyaladherins can be either adhesion proteins or receptors, including CD44, RHAMM, Stabilin-2, TNFIP6, Brevican, SHAP, LYVE1, TLR-2 and TLR-4 (Jiang et al. 2011). Brain link protein, a hyaladherin predominantly expressed in brain, stabilizes the interaction between lecticans and HA and thus maintains ECM assembly (Cicanic et al. 2012; Hirakawa et al. 2000), especially of PNNs (Bekku et al. 2003). TBI also leads to the increased expression of other hyaladherins including CD44 (Xing et al. 2014), brevican (Jaworski et al. 1999), and TLR-2/TLR-4 on macrophages/microglia (Zhang et al. 2012), which further modulate the brain immune response. The increased expression of CD44 suggests a potential role in T-cell recruitment (DeGrendele et al. 1997) and astrocyte migration (Bourguignon et al. 2007) and may also help in the enhanced CD44-mediated internalization and degradation of HA fragments to inhibit the inflammatory response (Culty et al. 1992; Scheibner et al. 2006).

Another role of HA in TBI pathophysiology is through the degradation of HA into small fragments by injury-associated reactive oxygen species (Soltes et al. 2006) and activation of the HA degrading enzyme hyaluronidase (Xing et al. 2014). Hyaluronan fragments are biologically active, and can modulate the immune response and promote angiogenesis (Stern et al. 2006). Binding of HA fragments to TLR-2 activates proapoptotic signaling in neurons (Tang et al. 2007), increases astrocyte reactivity (Park et al. 2008), and promotes inflammatory cytokine release (Yu and Zha 2012). HA fragments may also have a positive effect on the neuroimmune response, as exogenous delivery of the tetrasaccharide HA4, a product of HA fragmentation, significantly improved functional recovery after spinal cord injury (Wakao et al. 2011). Additional experiments addressing this issue would be important.

3.2 Fibronectin

Fibronectin is a large multidomain glycoprotein expressed as an ECM protein or as a soluble plasma protein. In the adult CNS, fibronectin is restricted to the vasculature and is not expressed by neurons and glia (Paetau et al. 1980). Breakdown of the blood brain barrier during TBI leads to entry of plasma-derived fibronectin (Tate et al. 2007a) and macrophages (Giulian et al. 1989) into the brain parenchyma. In turn, the fibronectin activates both resident microglia and the invading macrophages (Milner and Campbell 2003), which serve to clear debris following injury. TBI in conditional plasma fibronectin knockout mice showed an increase in lesion volume and apoptotic cell death at the site of lesion (Tate et al. 2007a), suggesting that the TBI-associated increase in fibronectin has a protective role.

3.3 Tenascins

Tenascin-C and tenascin-R are oligomeric multi-domain anti-adhesive proteins expressed in the CNS and are known to have roles in cell adhesion, neuronal migration, migration and differentiation of oligodendrocytes and cellular responses to growth factors (Giblin and Midwood 2015; Pesheva and Probstmeier 2000). Tenascin-C is expressed by astrocytes, oligodendrocytes and some neuronal populations (Meiners et al. 1993; Zhang et al. 1995), while tenascin-R is expressed by oligodendrocytes and neurons (Pesheva and Probstmeier 2000). They are predominantly expressed during embryonic development and then again in response to nervous system injuries in both animals and humans (Brodkey et al. 1995; Laywell et al. 1992). Tenascin-C production in astrocytes is increased by several growth factors, including FGF-2 (Meiners et al. 1993) and TGF-β (Smith and Hale 1997). The increase in tenascin-C following experimental brain injury is eliminated by suramin, a polysulfonated napthylurea that has been shown to inhibit the binding of many different cytokines to their cell surface receptors (Di Prospero et al. 1998), suggesting that the increase is due to the actions of cytokines and growth factors. Tenascin-C has several splice variants, due to the inclusion or exclusion of fibronectin III domains, and injury appears to specifically upregulate a variant that contains a neurite promoting domain (Dobbertin et al. 2010). Tenascin-R is known to be growth repellant to axons (Becker et al. 2004), while tenascin-C has both growth-promoting (Meiners et al. 1999) and growth inhibiting (Probstmeier and Pesheva 1999) activities. How these activities affect the pathophysiology of TBI is an open question.

3.4 Laminins

Laminins are heterotrimeric glycoproteins composed of α-, β- and γ-subunits. To date, 14 different laminins have been identified (Plantman 2013), of which only Laminin 111 has been identified in the CNS, while multiple forms have been found in the peripheral nervous system (PNS). While laminin expression has been detected during pathway development (Letourneau et al. 1988), the major function of astrocyte-derived laminin in the adult is to maintain the blood brain barrier through actions on pericyte differentiation (Yao et al. 2014). In culture, laminins universally promote neurite outgrowth (Edgar et al. 1984), and an integrin-binding peptide (IKVAV) derived from laminin has similar actions and has been used to promote regeneration *in vivo* (Wei et al. 2007). Laminin levels are significantly increased in traumatic brain tissues, which may help in restoring the integrity of the blood

brain barrier after injury (Tao et al. 2015). Increased laminin in the brain is also considered as an indicator of neovascularization by formation of new glio-vascular connections and angiogenesis (Wappler et al. 2011).

3.5 Osteopontin

Osteopontin (OPN) is classified as a matrikine because it is both an adhesive protein present in the ECM as well as a soluble cytokine. Both astrocytes and microglia produce OPN (Choi et al. 2007). Injury is associated with a marked increase in the expression of OPN RNA (Cernak et al. 2011; Israelsson et al. 2008), and osteopontin (Plantman 2012). OPN undergoes post-translational modification by phosphorylation, glycosylation, sulfation that promotes diversity in its biological function by modulating interactions with many different integrins and the CD44 receptor (Sodek et al. 2000). OPN is cleaved by thrombin (Kubota et al. 1989) and MMP-9 (Takafuji et al. 2007) which produce active OPN fragments with novel integrin binding sites that promote glial mobilization, axonal clearance, synaptogenesis and cognitive recovery (Chan et al. 2014). In culture, neurite growth is promoted on an OPN substrate (Plantman 2012). *In vivo,* OPN treatment prevented neurological impairment, brain edema, and restored the blood brain barrier disruption after hemorrhage (Gliem et al. 2015; Suzuki et al. 2010). The role of OPN under various pathophysiological conditions suggests that it might have a role in the therapy of TBI as well.

4. Matrix Metalloproteinases (MMPs)

The role of MMPs in the brain and after TBI has been recently reviewed (Abdul-Muneer et al. 2016; Rempe et al. 2016), and thus we will address the most significant actions of MMPs on the ECM. The major secreted MMPs in the brain are MMP-3 (stromelysin), and MMP-2 and 9 (gelatinases) (Rempe et al. 2016). MMP-3 is at very low levels in the normal brain, but is increased 6h after contusion injury in the rat and reached the maximum at 5 days (Li et al. 2009). A rapid increase in MMP-3 activity has also been observed following TBI in humans (Sashindranath et al. 2012). MMP-9 is expressed in normal adult brain and is also elevated in response to TBI (Hadass et al. 2013; Hayashi et al. 2009). In humans, TBI is also associated with rapid increase of increased MMP-9 in brain parenchyma (Guilfoyle et al. 2015), cerebrospinal fluid (Liu et al. 2014), and plasma (Copin et al. 2012) and, which may be used for the prognosis of severity and outcome of injury (DeFazio et al. 2014; Vilalta et al. 2008).

The increase in MMP-9 activity promotes blood brain barrier hyperpermeability which leads to microhemorrhage, edema, neuroinflammation, and neurodegeneration (Hadass et al. 2013; Higashida et al. 2011). Furthermore, the ability of MMPs to proteolytically process inactive precursors of TNF-α (Gearing et al. 1994), IL-1β (Amantea et al. 2016) and OPN (Takafuji et al. 2007) into biologically active forms can further modulate neuroinflammation. In brain microvascular endothelial cells, TNF-α (Wiggins-Dohlvik et al. 2014) and IL-1β (Alluri et al. 2016) induced MMP-9 activation leads to the degradation of tight junctions and blood brain barrier hyperpermeability. Similarly, brain pericytes respond to TGF-β by increasing their production of MMP-9 (Takahashi et al. 2014). Pharmacological inhibition of MMP-9 attenuates the secondary phase of TBI through reduction of lesion volume, neuronal

loss, dendritic degeneration and glial activation along with improved neurobehavioral outcomes (Hadass et al. 2013; Lee et al. 2015b). Mice with a deletion of MMP-9 showed fewer motor deficits and a smaller lesion volume after TBI than wild type mice (Wang et al. 2000). Similarly, reduction of MMP-9 activity by inhibition of poly(ADP-ribose) polymerase with 3-aminobenzamide reduced disruption of the blood brain barrier and improved neurologic function as compared to untreated rats (Lescot et al. 2010).

MMPs also may have positive effects in promoting neuronal regeneration after TBI by degrading inhibitory CSPGs accumulated by reactive astrocytes. MMP-3 degrades CSPGs including brevican, NG2, neurocan, phosphacan, and versican-V1 and versican-V2 (Muir et al. 2002). In culture, treatment of astrocyte-derived ECM with MMP-3, -7 and -8 degrades the core proteins of CSPGs and reduce their inhibitory effect on neurite outgrowth (Cua et al. 2013). MMPs have also been reported to promote neuronal survival (Wetzel et al. 2003), neurite invasiveness (Nordstrom et al. 1995), nerve cell migration (Mao et al. 2016) and remyelination (Larsen et al. 2006). However, while MMP activity may help in promoting neural regeneration after TBI, inhibition of MMP activity has provided more functional improvement.

5. ECM modulation as a potential therapy for TBI

There is currently no FDA-approved therapeutic strategy to promote recovery of function following TBI. PNNs, comprised of CSPGs, are greatly reduced in the pericontusional area, probably through the action of MMPs (Yi et al. 2012). As PNNs are thought to restrict synaptic plasticity, the reduction in PNNs may be a pro-regenerative response to stimulate plasticity following TBI. Because this loss is very limited, one approach may be to further stimulate plasticity by reducing PNNs with the bacterial enzyme chondroitinase ABC (chABC), which degrades CS GAG side chains from core proteins (Harris et al. 2010; Pizzorusso et al. 2002). chABC has been shown to promote recovery of function from spinal cord injury (Bradbury et al. 2002), at least in part by increasing plasticity and sprouting (Barritt et al. 2006), but primarily by reducing CSPGs in the glial scar. Chondroitinase has also been reported to reduce brain edema following TBI (Finan et al. 2016), and improve the outcome in chronic stroke (Hill et al. 2012). However, the use of chondroitinase ABC *in vivo* is restricted by its lack of stability and potential immunogenicity. Because 4-S GAGs are increased following injury, ARSB, which is approved for use in the treatment of mucopolysaccharoidosis VI in humans, could be an alternative approach. Alternately, plasticity has been promoted by activation of the MMP ADAMTS-4 (type 4 disintegrin and metalloproteinase with thrombospondin motifs), which degrades CSPGs and promoted axonal regeneration/collateral sprouting (Lemarchant et al. 2014). Inhibition of MMPs has also shown to be effective in reducing the volume of a brain lesion (Lee et al. 2015b).

As discussed above, the ECM is a complex structure with many different components, each of which may have actions to either promote or inhibit regeneration. Several different biomaterials which incorporate ECM components demonstrate efficacy in injury models. Laminin, which provides a positive cue for both neuroblast migration and process outgrowth, has been incorporated into several different biomaterials that were used as implants. After a cryoinjury, a laminin-soaked sponge was inserted into the lesion cavity and

induced the migration of neuroblasts into the sponge(Ajioka et al. 2015). Others showed that a self-assembling peptide gel which contained the neurite-promoting IKVAV sequence from laminin could support the survival and differentiation of encapsulated neural stem cells after injection into a cerebral cortical wound Cheng (Cheng et al. 2013). Injection of the HSPG glypican improved recovery in a stroke model (Hill et al. 2012). A collagen-based scaffold that incorporated the soluble Nogo receptor improved recovery in a model of penetrating brain injury (Elias and Spector 2015). Based on these results, a promising area is the potential uses of ECM and ECM-derived peptides that improve neuronal regeneration and functional recovery (Estrada et al. 2014).

6. Summary

Alterations in the ECM following TBI play a significant role in TBI pathophysiology by controlling inflammation, blood brain barrier function and regeneration. Proteoglycans play a significant role in this response, as evidenced by their increased expression and alterations in their sulfation patterns. Brain injury also induces the expression of other developmentally restricted ECM components which contribute to the repair and regeneration of the damaged area, such as laminin and tenascins. MMPs actively participate in the dynamic modulation of brain ECM after injury by degrading matrix components. Efforts have been made to make a more permissive environment by manipulating the ECM composition around the lesion to minimize secondary damage and to promote axonal outgrowth and synaptic plasticity. Given the prominent role of the ECM in the pathophysiology of TBI, therapeutic interventions to target the ECM may enhance neuroregeneration and functional recovery after TBI.

References

Abdul-Muneer PM, Pfister BJ, Haorah J, Chandra N. Role of matrix metalloproteinases in the pathogenesis of traumatic brain injury. Mol Neurobiol. 2016; 53:6106–6123. [PubMed: 26541883]

Acarin L, Gonzalez B, Castellano B. Neuronal, astroglial and microglial cytokine expression after an excitotoxic lesion in the immature rat brain. Eur J Neurosci. 2000; 12:3505–3520. [PubMed: 11029620]

Afratis NA, Nikitovic D, Multhaupt HA, Theocharis AD, Couchman JR, Karamanos NK. Syndecans - key regulators of cell signaling and biological functions. The FEBS journal. 2017; 284:27–41. [PubMed: 27790852]

Ajioka I, Jinnou H, Okada K, Sawada M, Saitoh S, Sawamoto K. Enhancement of neuroblast migration into the injured cerebral cortex using laminin-containing porous sponge. Tissue engineering Part A. 2015; 21:193–201. [PubMed: 25010638]

Allen NJ, Bennett ML, Foo LC, Wang GX, Chakraborty C, Smith SJ, Barres BA. Astrocyte glypicans 4 and 6 promote formation of excitatory synapses via GluA1 AMPA receptors. Nature. 2012; 486:410–414. [PubMed: 22722203]

Alluri H, Wilson RL, Anasooya Shaji C, Wiggins-Dohlvik K, Patel S, Liu Y, Peng X, Beeram MR, Davis ML, Huang JH, Tharakan B. Melatonin preserves blood-brain barrier integrity and permeability via matrix metalloproteinase-9 inhibition. PLoS One. 2016; 11:e0154427. [PubMed: 27152411]

Almad A, Sahinkaya FR, McTigue DM. Oligodendrocyte fate after spinal cord injury. Neurotherapeutics. 2011; 8:262–273. [PubMed: 21404073]

Almutairi MM, Gong C, Xu YG, Chang Y, Shi H. Factors controlling permeability of the blood-brain barrier. Cell Mol Life Sci. 2016; 73:57–77. [PubMed: 26403789]

Amantea D, Russo R, Certo M, Rombola L, Adornetto A, Morrone LA, Corasaniti MT, Bagetta G. Caspase-1-independent maturation of IL-1β in ischemic brain injury: is there a role for gelatinases? Mini Rev Med Chem. 2016; 16:729–737. [PubMed: 26996625]

Anderson MA, Burda JE, Ren Y, Ao Y, O'Shea TM, Kawaguchi R, Coppola G, Khakh BS, Deming TJ, Sofroniew MV. Astrocyte scar formation aids central nervous system axon regeneration. Nature. 2016; 532:195–200. [PubMed: 27027288]

Aricescu AR, McKinnell IW, Halfter W, Stoker AW. Heparan sulfate proteoglycans are ligands for receptor protein tyrosine phosphatase σ. Mol Cell Biol. 2002; 22:1881–1892. [PubMed: 11865065]

Asher RA, Morgenstern DA, Fidler PS, Adcock KH, Oohira A, Braistead JE, Levine JM, Margolis RU, Rogers JH, Fawcett JW. Neurocan is upregulated in injured brain and in cytokine-treated astrocytes. J Neurosci. 2000; 20:2427–2438. [PubMed: 10729323]

Asher RA, Morgenstern DA, Shearer MC, Adcock KH, Pesheva P, Fawcett JW. Versican is upregulated in CNS injury and is a product of oligodendrocyte lineage cells. J Neurosci. 2002; 22:2225–2236. [PubMed: 11896162]

Barnett MW, Fisher CE, Perona-Wright G, Davies JA. Signalling by glial cell line-derived neurotrophic factor (GDNF) requires heparan sulphate glycosaminoglycan. J Cell Sci. 2002; 115:4495–4503. [PubMed: 12414995]

Barritt AW, Davies M, Marchand F, Hartley R, Grist J, Yip P, McMahon SB, Bradbury EJ. Chondroitinase ABC promotes sprouting of intact and injured spinal systems after spinal cord injury. J Neurosci. 2006; 26:10856–10867. [PubMed: 17050723]

Becker CG, Schweitzer J, Feldner J, Schachner M, Becker T. Tenascin-R as a repellent guidance molecule for newly growing and regenerating optic axons in adult zebrafish. Mol Cell Neurosci. 2004; 26:376–389. [PubMed: 15234343]

Beggah AT, Dours-Zimmermann MT, Barras FM, Brosius A, Zimmermann DR, Zurn AD. Lesion-induced differential expression and cell association of Neurocan, Brevican, Versican V1 and V2 in the mouse dorsal root entry zone. Neuroscience. 2005; 133:749–762. [PubMed: 15896911]

Bekku Y, Su WD, Hirakawa S, Fassler R, Ohtsuka A, Kang JS, Sanders J, Murakami T, Ninomiya Y, Oohashi T. Molecular cloning of Bral2, a novel brain-specific link protein, and immunohistochemical colocalization with brevican in perineuronal nets. Mol Cell Neurosci. 2003; 24:148–159. [PubMed: 14550776]

Bhattacharyya S, Zhang X, Feferman L, Johnson D, Tortella FC, Guizzetti M, Tobacman JK. Decline in arylsulfatase B and Increase in chondroitin 4-sulfotransferase combine to increase chondroitin 4-sulfate in traumatic brain injury. J Neurochem. 2015; 134:728–739. [PubMed: 25943740]

Bourguignon LY, Gilad E, Peyrollier K, Brightman A, Swanson RA. Hyaluronan-CD44 interaction stimulates Rac1 signaling and PKN γ kinase activation leading to cytoskeleton function and cell migration in astrocytes. J Neurochem. 2007; 101:1002–1017. [PubMed: 17403031]

Bradbury EJ, Moon LD, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB. Chondroitinase ABC promotes functional recovery after spinal cord injury. Nature. 2002; 416:636–640. [PubMed: 11948352]

Brodkey JA, Laywell ED, O'Brien TF, Faissner A, Stefansson K, Dorries HU, Schachner M, Steindler DA. Focal brain injury and upregulation of a developmentally regulated extracellular matrix protein. J Neurosurg. 1995; 82:106–112. [PubMed: 7529300]

Burg MA, Grako KA, Stallcup WB. Expression of the NG2 proteoglycan enhances the growth and metastatic properties of melanoma cells. J Cell Physiol. 1998; 177:299–312. [PubMed: 9766527]

Campbell SJ, Deacon RM, Jiang Y, Ferrari C, Pitossi FJ, Anthony DC. Overexpression of IL-1β by adenoviral-mediated gene transfer in the rat brain causes a prolonged hepatic chemokine response, axonal injury and the suppression of spontaneous behaviour. Neurobiol Dis. 2007; 27:151–163. [PubMed: 17580116]

Carulli D, Laabs T, Geller HM, Fawcett JW. Chondroitin sulfate proteoglycans in neural development and regeneration. Curr Opin Neurobiol. 2005; 15:116–120. [PubMed: 15721753]

Cernak I, Merkle AC, Koliatsos VE, Bilik JM, Luong QT, Mahota TM, Xu L, Slack N, Windle D, Ahmed FA. The pathobiology of blast injuries and blast-induced neurotrauma as identified using a

new experimental model of injury in mice. Neurobiol Dis. 2011; 41:538–551. [PubMed: 21074615]

Chan JL, Reeves TM, Phillips LL. Osteopontin expression in acute immune response mediates hippocampal synaptogenesis and adaptive outcome following cortical brain injury. Exp Neurol. 2014; 261:757–771. [PubMed: 25151457]

Cheng TY, Chen MH, Chang WH, Huang MY, Wang TW. Neural stem cells encapsulated in a functionalized self-assembling peptide hydrogel for brain tissue engineering. Biomaterials. 2013; 34:2005–2016. [PubMed: 23237515]

Choi JK, Park SY, Kim KH, Park SR, Lee SG, Choi BH. GM-CSF reduces expression of chondroitin sulfate proteoglycan (CSPG) core proteins in TGF-β-treated primary astrocytes. BMB reports. 2014a; 47:679–684. [PubMed: 24602609]

Choi JS, Kim HY, Cha JH, Choi JY, Lee MY. Transient microglial and prolonged astroglial upregulation of osteopontin following transient forebrain ischemia in rats. Brain Res. 2007; 1151:195–202. [PubMed: 17395166]

Choi SS, Lee HJ, Lim I, Satoh J, Kim SU. Human astrocytes: secretome profiles of cytokines and chemokines. PLoS One. 2014b; 9:e92325. [PubMed: 24691121]

Cicanic M, Sykova E, Vargova L. Bral1: “Superglue” for the extracellular matrix in the brain white matter. Int J Biochem Cell Biol. 2012; 44:596–599. [PubMed: 22300985]

Cohen NA, Kaufmann WE, Worley PF, Rupp F. Expression of agrin in the developing and adult rat brain. Neuroscience. 1997; 76:581–596. [PubMed: 9015340]

Cole GJ, McCabe CF. Identification of a developmentally regulated keratan sulfate proteoglycan that inhibits cell adhesion and neurite outgrowth. Neuron. 1991; 7:1007–1018. [PubMed: 1764241]

Copin JC, Rebetez MM, Turck N, Robin X, Sanchez JC, Schaller K, Gasche Y, Walder B. Matrix metalloproteinase 9 and cellular fibronectin plasma concentrations are predictors of the composite endpoint of length of stay and death in the intensive care unit after severe traumatic brain injury. Scand J Trauma Resusc Emerg Med. 2012; 20:83. [PubMed: 23249478]

Cua RC, Lau LW, Keough MB, Midha R, Apte SS, Yong VW. Overcoming neurite-inhibitory chondroitin sulfate proteoglycans in the astrocyte matrix. Glia. 2013; 61:972–984. [PubMed: 23554135]

Cui H, Freeman C, Jacobson GA, Small DH. Proteoglycans in the central nervous system: role in development, neural repair, and Alzheimer’s disease. IUBMB life. 2013; 65:108–120. [PubMed: 23297096]

Culty M, Nguyen HA, Underhill CB. The hyaluronan receptor (CD44) participates in the uptake and degradation of hyaluronan. J Cell Biol. 1992; 116:1055–1062. [PubMed: 1370836]

Daniels MP. The role of agrin in synaptic development, plasticity and signaling in the central nervous system. Neurochem Int. 2012; 61:848–853. [PubMed: 22414531]

Deckner M, Lindholm T, Cullheim S, Risling M. Differential expression of tenascin-C, tenascin-R, tenascin/J1, and tenascin-X in spinal cord scar tissue and in the olfactory system. Exp Neurol. 2000; 166:350–362. [PubMed: 11085900]

DeFazio MV, Rammo RA, Robles JR, Bramlett HM, Dietrich WD, Bullock MR. The potential utility of blood-derived biochemical markers as indicators of early clinical trends following severe traumatic brain injury. World Neurosurg. 2014; 81:151–158. [PubMed: 23313262]

DeGrendele HC, Estess P, Siegelman MH. Requirement for CD44 in activated T cell extravasation into an inflammatory site. Science. 1997; 278:672–675. [PubMed: 9381175]

Di Prospero NA, Zhou XR, Meiners S, McAuliffe WG, Ho SY, Geller HM. Suramin disrupts the gliotic response following a stab wound injury to the adult rat brain. J Neurocytol. 1998; 27:491–506. [PubMed: 11246489]

Dickendesher TL, Baldwin KT, Mironova YA, Koriyama Y, Raiker SJ, Askew KL, Wood A, Geoffroy CG, Zheng B, Liepmann CD, Katagiri Y, Benowitz LI, Geller HM, Giger RJ. NgR1 and NgR3 are receptors for chondroitin sulfate proteoglycans. Nat Neurosci. 2012; 15:703–712. [PubMed: 22406547]

DiProspero NA, Meiners S, Geller HM. Inflammatory cytokines interact to modulate extracellular matrix and astrocytic support of neurite outgrowth. Exp Neurol. 1997; 148:628–639. [PubMed: 9417838]

Dobbertin A, Czvitkovich S, Theocharidis U, Garwood J, Andrews MR, Properzi F, Lin R, Fawcett JW, Faissner A. Analysis of combinatorial variability reveals selective accumulation of the fibronectin type III domains B and D of tenascin-C in injured brain. Exp Neurol. 2010; 225:60–73. [PubMed: 20451518]

Dobbertin A, Rhodes KE, Garwood J, Properzi F, Heck N, Rogers JH, Fawcett JW, Faissner A. Regulation of RPTPβ/phosphacan expression and glycosaminoglycan epitopes in injured brain and cytokine-treated glia. Mol Cell Neurosci. 2003; 24:951–971. [PubMed: 14697661]

Dodge GR, Kovalszky I, Hassell JR, Iozzo RV. Transforming growth factor β alters the expression of heparan sulfate proteoglycan in human colon carcinoma cells. J Biol Chem. 1990; 265:18023–18029. [PubMed: 1698783]

Domowicz MS, Sanders TA, Ragsdale CW, Schwartz NB. Aggrecan is expressed by embryonic brain glia and regulates astrocyte development. Dev Biol. 2008; 315:114–124. [PubMed: 18207138]

Edgar D, Timpl R, Thoenen H. The heparin-binding domain of laminin is responsible for its effects on neurite outgrowth and neuronal survival. EMBO J. 1984; 3:1463–1468. [PubMed: 6745238]

Egan RA, Vijayan VK. Fibronectin immunoreactivity in neural trauma. Brain Res. 1991; 568:330–334. [PubMed: 1814578]

Elias PZ, Spector M. Treatment of penetrating brain injury in a rat model using collagen scaffolds incorporating soluble Nogo receptor. J Tissue Eng Regen Med. 2015; 9:137–150. [PubMed: 23038669]

Eriksson C, Van Dam AM, Lucassen PJ, Bol JG, Winblad B, Schultzberg M. Immunohistochemical localization of interleukin-1β, interleukin-1 receptor antagonist and interleukin-1β converting enzyme/caspase-1 in the rat brain after peripheral administration of kainic acid. Neuroscience. 1999; 93:915–930. [PubMed: 10473257]

Estrada V, Tekinay A, Muller HW. Neural ECM mimetics. Prog Brain Res. 2014; 214:391–413. [PubMed: 25410366]

Falo MC, Reeves TM, Phillips LL. Agrin expression during synaptogenesis induced by traumatic brain injury. J Neurotrauma. 2008; 25:769–783. [PubMed: 18627255]

Finan JD, Cho FS, Kernie SG, Morrison B 3rd. Intracerebroventricular administration of chondroitinase ABC reduces acute edema after traumatic brain injury in mice. BMC Res Notes. 2016; 9:160. [PubMed: 26969621]

Fisher D, Xing B, Dill J, Li H, Hoang HH, Zhao Z, Yang XL, Bachoo R, Cannon S, Longo FM, Sheng M, Silver J, Li S. Leukocyte common antigen-related phosphatase is a functional receptor for chondroitin sulfate proteoglycan axon growth inhibitors. J Neurosci. 2011; 31:14051–14066. [PubMed: 21976490]

Flygt J, Clausen F, Marklund N. Diffuse traumatic brain injury in the mouse induces a transient proliferation of oligodendrocyte progenitor cells in injured white matter tracts. Restor Neurol Neurosci. 2017; 35:251–263. [PubMed: 27768001]

Fok-Seang J, DiProspero NA, Meiners S, Muir E, Fawcett JW. Cytokine-induced changes in the ability of astrocytes to support migration of oligodendrocyte precursors and axon growth. Eur J Neurosci. 1998; 10:2400–2415. [PubMed: 9749768]

Frischknecht R, Gundelfinger ED. The brain's extracellular matrix and its role in synaptic plasticity. Adv Exp Med Biol. 2012; 970:153–171. [PubMed: 22351055]

Garcia de Yebenes E, Ho A, Damani T, Fillit H, Blum M. Regulation of the heparan sulfate proteoglycan, perlecan, by injury and interleukin-1α. J Neurochem. 1999; 73:812–820. [PubMed: 10428080]

Garwood J, Schnadelbach O, Clement A, Schutte K, Bach A, Faissner A. DSD-1-proteoglycan is the mouse homolog of phosphacan and displays opposing effects on neurite outgrowth dependent on neuronal lineage. J Neurosci. 1999; 19:3888–3899. [PubMed: 10234020]

Gautam J, Zhang X, Yao Y. The role of pericytic laminin in blood brain barrier integrity maintenance. Sci Rep. 2016; 6:36450. [PubMed: 27808256]

Gearing AJ, Beckett P, Christodoulou M, Churchill M, Clements J, Davidson AH, Drummond AH, Galloway WA, Gilbert R, Gordon JL, et al. Processing of tumour necrosis factor-α precursor by metalloproteinases. Nature. 1994; 370:555–557. [PubMed: 8052310]

Geisert EE Jr, Bidanset DJ. A central nervous system keratan sulfate proteoglycan: localization to boundaries in the neonatal rat brain. Brain Res Dev Brain Res. 1993; 75:163–173. [PubMed: 8261609]

Geisert EE Jr, Bidanset DJ, Del Mar N, Robson JA. Up-regulation of a keratan sulfate proteoglycan following cortical injury in neonatal rats. Int J Dev Neurosci. 1996; 14:257–267. [PubMed: 8842803]

Giblin SP, Midwood KS. Tenascin-C: Form versus function. Cell Adh Migr. 2015; 9:48–82. [PubMed: 25482829]

Giulian D, Chen J, Ingeman JE, George JK, Noponen M. The role of mononuclear phagocytes in wound healing after traumatic injury to adult mammalian brain. J Neurosci. 1989; 9:4416–4429. [PubMed: 2480402]

Gliem M, Krammes K, Liaw L, van Rooijen N, Hartung HP, Jander S. Macrophage-derived osteopontin induces reactive astrocyte polarization and promotes reestablishment of the blood brain barrier after ischemic stroke. Glia. 2015; 63:2198–2207. [PubMed: 26148976]

Gonzalez EM, Reed CC, Bix G, Fu J, Zhang Y, Gopalakrishnan B, Greenspan DS, Iozzo RV. BMP-1/Tolloid-like metalloproteases process endorepellin, the angiostatic C-terminal fragment of perlecan. J Biol Chem. 2005; 280:7080–7087. [PubMed: 15591058]

Gubbiotti MA, Neill T, Iozzo RV. A current view of perlecan in physiology and pathology: A mosaic of functions. Matrix Biol. 2016

Guilfoyle MR, Carpenter KL, Helmy A, Pickard JD, Menon DK, Hutchinson PJ. Matrix Metalloproteinase Expression in Contusional Traumatic Brain Injury: A Paired Microdialysis Study. J Neurotrauma. 2015; 32:1553–1559. [PubMed: 25858502]

Hadass O, Tomlinson BN, Gooyit M, Chen S, Purdy JJ, Walker JM, Zhang C, Giritharan AB, Purnell W, Robinson CR 2nd, Shin D, Schroeder VA, Suckow MA, Simonyi A, Sun GY, Mobashery S, Cui J, Chang M, Gu Z. Selective inhibition of matrix metalloproteinase-9 attenuates secondary damage resulting from severe traumatic brain injury. PLoS One. 2013; 8:e76904. [PubMed: 24194849]

Hagino S, Iseki K, Mori T, Zhang Y, Hikake T, Yokoya S, Takeuchi M, Hasimoto H, Kikuchi S, Wanaka A. Slit and glypican-1 mRNAs are coexpressed in the reactive astrocytes of the injured adult brain. Glia. 2003a; 42:130–138. [PubMed: 12655597]

Hagino S, Iseki K, Mori T, Zhang Y, Sakai N, Yokoya S, Hikake T, Kikuchi S, Wanaka A. Expression pattern of glypican-1 mRNA after brain injury in mice. Neurosci Lett. 2003b; 349:29–32. [PubMed: 12946579]

Hamel MG, Mayer J, Gottschall PE. Altered production and proteolytic processing of brevican by transforming growth factor β in cultured astrocytes. J Neurochem. 2005; 93:1533–1541. [PubMed: 15935069]

Haqqani AS, Hutchison JS, Ward R, Stanimirovic DB. Biomarkers and diagnosis; protein biomarkers in serum of pediatric patients with severe traumatic brain injury identified by ICAT-LC-MS/MS. J Neurotrauma. 2007; 24:54–74. [PubMed: 17263670]

Harris NG, Carmichael ST, Hovda DA, Sutton RL. Traumatic brain injury results in disparate regions of chondroitin sulfate proteoglycan expression that are temporally limited. J Neurosci Res. 2009; 87:2937–2950. [PubMed: 19437549]

Harris NG, Mironova YA, Hovda DA, Sutton RL. Chondroitinase ABC enhances pericontusion axonal sprouting but does not confer robust improvements in behavioral recovery. J Neurotrauma. 2010; 27:1971–1982. [PubMed: 20809786]

Hausmann R, Betz P. Course of glial immunoreactivity for vimentin, tenascin and alpha1-antichymotrypsin after traumatic injury to human brain. Int J Legal Med. 2001; 114:338–342. [PubMed: 11508799]

Hayashi N, Miyata S, Yamada M, Kamei K, Oohira A. Neuronal expression of the chondroitin sulfate proteoglycans receptor-type protein-tyrosine phosphatase β and phosphacan. Neuroscience. 2005; 131:331–348. [PubMed: 15708477]

Hayashi T, Kaneko Y, Yu S, Bae E, Stahl CE, Kawase T, van Loveren H, Sanberg PR, Borlongan CV. Quantitative analyses of matrix metalloproteinase activity after traumatic brain injury in adult rats. Brain Res. 2009; 1280:172–177. [PubMed: 19464272]

Hemphill MA, Dauth S, Yu CJ, Dabiri BE, Parker KK. Traumatic brain injury and the neuronal microenvironment: a potential role for neuropathological mechanotransduction. Neuron. 2015; 85:1177–1192. [PubMed: 25789754]

Hienola A, Tumova S, Kulesskiy E, Rauvala H. N-syndecan deficiency impairs neural migration in brain. J Cell Biol. 2006; 174:569–580. [PubMed: 16908672]

Higashida T, Kreipke CW, Rafols JA, Peng C, Schafer S, Schafer P, Ding JY, Dornbos D 3rd, Li X, Guthikonda M, Rossi NF, Ding Y. The role of hypoxia-inducible factor-1alpha, aquaporin-4, and matrix metalloproteinase-9 in blood-brain barrier disruption and brain edema after traumatic brain injury. J Neurosurg. 2011; 114:92–101. [PubMed: 20617879]

Hikino M, Mikami T, Faissner A, Vilela-Silva AC, Pavao MS, Sugahara K. Oversulfated dermatan sulfate exhibits neurite outgrowth-promoting activity toward embryonic mouse hippocampal neurons: implications of dermatan sulfate in neuritogenesis in the brain. J Biol Chem. 2003; 278:43744–43754. [PubMed: 12917413]

Hill JJ, Jin K, Mao XO, Xie L, Greenberg DA. Intracerebral chondroitinase ABC and heparan sulfate proteoglycan glypican improve outcome from chronic stroke in rats. Proc Natl Acad Sci U S A. 2012; 109:9155–9160. [PubMed: 22615373]

Hirakawa S, Oohashi T, Su WD, Yoshioka H, Murakami T, Arata J, Ninomiya Y. The brain link protein-1 (BRAL1): cDNA cloning, genomic structure, and characterization as a novel link protein expressed in adult brain. Biochem Biophys Res Commun. 2000; 276:982–989. [PubMed: 11027579]

Hsueh YP, Sheng M. Regulated expression and subcellular localization of syndecan heparan sulfate proteoglycans and the syndecan-binding protein CASK/LIN-2 during rat brain development. J Neurosci. 1999; 19:7415–7425. [PubMed: 10460248]

Huang C, Sakry D, Menzel L, Dangel L, Sebastiani A, Kramer T, Karram K, Engelhard K, Trotter J, Schafer MK. Lack of NG2 exacerbates neurological outcome and modulates glial responses after traumatic brain injury. Glia. 2016; 64:507–523. [PubMed: 26638112]

Huang X, Kim JM, Kong TH, Park SR, Ha Y, Kim MH, Park H, Yoon SH, Park HC, Park JO, Min BH, Choi BH. GM-CSF inhibits glial scar formation and shows long-term protective effect after spinal cord injury. J Neurol Sci. 2009; 277:87–97. [PubMed: 19033079]

Iozzo RV, Schaefer L. Proteoglycan form and function: A comprehensive nomenclature of proteoglycans. Matrix Biol. 2015; 42:11–55. [PubMed: 25701227]

Iseki K, Hagino S, Mori T, Zhang Y, Yokoya S, Takaki H, Tase C, Murakawa M, Wanaka A. Increased syndecan expression by pleiotrophin and FGF receptor-expressing astrocytes in injured brain tissue. Glia. 2002; 39:1–9. [PubMed: 12112370]

Ishikawa Y, Imagama S, Ohgomori T, Ishiguro N, Kadomatsu K. A combination of keratan sulfate digestion and rehabilitation promotes anatomical plasticity after rat spinal cord injury. Neurosci Lett. 2015; 593:13–18. [PubMed: 25770829]

Israelsson C, Bengtsson H, Kylberg A, Kullander K, Lewen A, Hillered L, Ebendal T. Distinct cellular patterns of upregulated chemokine expression supporting a prominent inflammatory role in traumatic brain injury. J Neurotrauma. 2008; 25:959–974. [PubMed: 18665806]

Jaworski DM, Kelly GM, Hockfield S. Intracranial injury acutely induces the expression of the secreted isoform of the CNS-specific hyaluronan-binding protein BEHAB/brevican. Exp Neurol. 1999; 157:327–337. [PubMed: 10364444]

Jiang D, Liang J, Noble PW. Hyaluronan as an immune regulator in human diseases. Physiol Rev. 2011; 91:221–264. [PubMed: 21248167]

Johnson KG, Ghose A, Epstein E, Lincecum J, O'Connor MB, Van Vactor D. Axonal heparan sulfate proteoglycans regulate the distribution and efficiency of the repellent slit during midline axon guidance. Curr Biol. 2004; 14:499–504. [PubMed: 15043815]

Jones LL, Margolis RU, Tuszynski MH. The chondroitin sulfate proteoglycans neurocan, brevican, phosphacan, and versican are differentially regulated following spinal cord injury. Exp Neurol. 2003; 182:399–411. [PubMed: 12895450]

Jones LL, Tuszynski MH. Spinal cord injury elicits expression of keratan sulfate proteoglycans by macrophages, reactive microglia, and oligodendrocyte progenitors. J Neurosci. 2002; 22:4611–4624. [PubMed: 12040068]

Joy A, Moffett J, Neary K, Mordechai E, Stachowiak EK, Coons S, Rankin-Shapiro J, Florkiewicz RZ, Stachowiak MK. Nuclear accumulation of FGF-2 is associated with proliferation of human astrocytes and glioma cells. Oncogene. 1997; 14:171–183. [PubMed: 9010219]

Kantor DB, Chivatakarn O, Peer KL, Oster SF, Inatani M, Hansen MJ, Flanagan JG, Yamaguchi Y, Sretavan DW, Giger RJ, Kolodkin AL. Semaphorin 5A is a bifunctional axon guidance cue regulated by heparan and chondroitin sulfate proteoglycans. Neuron. 2004; 44:961–975. [PubMed: 15603739]

Karumbaiah L, Anand S, Thazhath R, Zhong Y, McKeon RJ, Bellamkonda RV. Targeted downregulation of N-acetylgalactosamine 4-sulfate 6-O-sulfotransferase significantly mitigates chondroitin sulfate proteoglycan-mediated inhibition. Glia. 2011; 59:981–996. [PubMed: 21456043]

Kaur C, Sivakumar V, Yip GW, Ling EA. Expression of syndecan-2 in the amoeboid microglial cells and its involvement in inflammation in the hypoxic developing brain. Glia. 2009; 57:336–349. [PubMed: 18803305]

Kim CW, Goldberger OA, Gallo RL, Bernfield M. Members of the syndecan family of heparan sulfate proteoglycans are expressed in distinct cell-, tissue-, and development-specific patterns. Mol Biol Cell. 1994; 5:797–805. [PubMed: 7812048]

Kjellen L, Lindahl U. Proteoglycans: structures and interactions. Annu Rev Biochem. 1991; 60:443–475. [PubMed: 1883201]

Kubota T, Zhang Q, Wrana JL, Ber R, Aubin JE, Butler WT, Sodek J. Multiple forms of SppI (secreted phosphoprotein, osteopontin) synthesized by normal and transformed rat bone cell populations: regulation by TGF-β. Biochem Biophys Res Commun. 1989; 162:1453–1459. [PubMed: 2764941]

Kurosawa N, Chen GY, Kadomatsu K, Ikematsu S, Sakuma S, Muramatsu T. Glypican-2 binds to midkine: the role of glypican-2 in neuronal cell adhesion and neurite outgrowth. Glycoconj J. 2001; 18:499–507. [PubMed: 12084985]

Larsen PH, DaSilva AG, Conant K, Yong VW. Myelin formation during development of the CNS is delayed in matrix metalloproteinase-9 and -12 null mice. J Neurosci. 2006; 26:2207–2214. [PubMed: 16495447]

Lau LT, Yu AC. Astrocytes produce and release interleukin-1, interleukin-6, tumor necrosis factor alpha and interferon-γ following traumatic and metabolic injury. J Neurotrauma. 2001; 18:351–359. [PubMed: 11284554]

Laywell ED, Dorries U, Bartsch U, Faissner A, Schachner M, Steindler DA. Enhanced expression of the developmentally regulated extracellular matrix molecule tenascin following adult brain injury. Proc Natl Acad Sci U S A. 1992; 89:2634–2638. [PubMed: 1372985]

Lee J, Wee S, Gunaratne J, Chua RJ, Smith RA, Ling L, Fernig DG, Swaminathan K, Nurcombe V, Cool SM. Structural determinants of heparin-transforming growth factor-β1 interactions and their effects on signaling. Glycobiology. 2015a; 25:1491–1504. [PubMed: 26306634]

Lee M, Chen Z, Tomlinson BN, Gooyit M, Hesek D, Juarez MR, Nizam R, Boggess B, Lastochkin E, Schroeder VA, Wolter WR, Suckow MA, Cui J, Mobashery S, Gu Z, Chang M. Water-soluble MMP-9 inhibitor reduces lesion volume after severe traumatic brain injury. ACS Chem Neurosci. 2015b; 6:1658–1664. [PubMed: 26241578]

Lemarchant S, Pruvost M, Hebert M, Gauberti M, Hommet Y, Briens A, Maubert E, Gueye Y, Feron F, Petite D, Mersel M, do Rego JC, Vaudry H, Koistinaho J, Ali C, Agin V, Emery E, Vivien D. tPA promotes ADAMTS-4-induced CSPG degradation, thereby enhancing neuroplasticity following spinal cord injury. Neurobiol Dis. 2014; 66:28–42. [PubMed: 24576594]

Lescot T, Fulla-Oller L, Palmier B, Po C, Beziaud T, Puybasset L, Plotkine M, Gillet B, Meric P, Marchand-Leroux C. Effect of acute poly(ADP-ribose) polymerase inhibition by 3-AB on blood-brain barrier permeability and edema formation after focal traumatic brain injury in rats. J Neurotrauma. 2010; 27:1069–1079. [PubMed: 20380552]

Letourneau PC, Madsen AM, Palm SL, Furcht LT. Immunoreactivity for laminin in the developing ventral longitudinal pathway of the brain. Dev Biol. 1988; 125:135–144. [PubMed: 3334714]

Levine JM. Increased expression of the NG2 chondroitin-sulfate proteoglycan after brain injury. J Neurosci. 1994; 14:4716–4730. [PubMed: 8046446]

Levine JM, Stincone F, Lee YS. Development and differentiation of glial precursor cells in the rat cerebellum. Glia. 1993; 7:307–321. [PubMed: 8320001]

Li HP, Komuta Y, Kimura-Kuroda J, van Kuppevelt TH, Kawano H. Roles of chondroitin sulfate and dermatan sulfate in the formation of a lesion scar and axonal regeneration after traumatic injury of the mouse brain. J Neurotrauma. 2013; 30:413–425. [PubMed: 23438307]

Li RB, Guo XC, Liang HX, Wang FY, Zhu BL. Study on changes of MMP-3 expression after brain contusion in rats. Leg Med (Tokyo). 2009; 11(Suppl 1):S176–179. [PubMed: 19329348]

Liesi P, Kaakkola S, Dahl D, Vaheri A. Laminin is induced in astrocytes of adult brain by injury. EMBO J. 1984; 3:683–686. [PubMed: 6370690]

Lin R, Rosahl TW, Whiting PJ, Fawcett JW, Kwok JC. 6-Sulphated chondroitins have a positive influence on axonal regeneration. PLoS One. 2011; 6:e21499. [PubMed: 21747937]

Lin YL, Lei YT, Hong CJ, Hsueh YP. Syndecan-2 induces filopodia and dendritic spine formation via the neurofibromin-PKA-Ena/VASP pathway. J Cell Biol. 2007; 177:829–841. [PubMed: 17548511]

Lindholm D, Castren E, Kiefer R, Zafra F, Thoenen H. Transforming growth factor-β 1 in the rat brain: increase after injury and inhibition of astrocyte proliferation. J Cell Biol. 1992; 117:395–400. [PubMed: 1560032]

Litwack ED, Stipp CS, Kumbasar A, Lander AD. Neuronal expression of glypican, a cell-surface glycosylphosphatidylinositol-anchored heparan sulfate proteoglycan, in the adult rat nervous system. J Neurosci. 1994; 14:3713–3724. [PubMed: 8207484]

Liu CL, Chen CC, Lee HC, Cho DY. Matrix metalloproteinase-9 in the ventricular cerebrospinal fluid correlated with the prognosis of traumatic brain injury. Turk Neurosurg. 2014; 24:363–368. [PubMed: 24848175]

Logan A, Baird A, Berry M. Decorin attenuates gliotic scar formation in the rat cerebral hemisphere. Exp Neurol. 1999; 159:504–510. [PubMed: 10506521]

Lozano D, Gonzales-Portillo GS, Acosta S, de la Pena I, Tajiri N, Kaneko Y, Borlongan CV. Neuroinflammatory responses to traumatic brain injury: etiology, clinical consequences, and therapeutic opportunities. Neuropsychiatr Dis Treat. 2015; 11:97–106. [PubMed: 25657582]

Lu KT, Wang YW, Yang JT, Yang YL, Chen HI. Effect of interleukin-1 on traumatic brain injury-induced damage to hippocampal neurons. J Neurotrauma. 2005; 22:885–895. [PubMed: 16083355]

Luxardi G, Galli A, Forlani S, Lawson K, Maina F, Dono R. Glypicans are differentially expressed during patterning and neurogenesis of early mouse brain. Biochem Biophys Res Commun. 2007; 352:55–60. [PubMed: 17107664]

Mandarino LJ, Sundarraj N, Finlayson J, Hassell HR. Regulation of fibronectin and laminin synthesis by retinal capillary endothelial cells and pericytes in vitro. Exp Eye Res. 1993; 57:609–621. [PubMed: 8282048]

Mao W, Yi X, Qin J, Tian M, Jin G. CXCL12/CXCR4 axis improves migration of neuroblasts along corpus callosum by stimulating MMP-2 Secretion after traumatic brain injury in rats. Neurochem Res. 2016; 41:1315–1322. [PubMed: 26801174]

Margolis RU, Margolis RK. Distribution and metabolism of mucopolysaccharides and glycoproteins in neuronal perikarya, astrocytes, and oligodendroglia. Biochemistry. 1974; 13:2849–2852. [PubMed: 4276340]

Matthews RT, Kelly GM, Zerillo CA, Gray G, Tiemeyer M, Hockfield S. Aggrecan glycoforms contribute to the molecular heterogeneity of perineuronal nets. J Neurosci. 2002; 22:7536–7547. [PubMed: 12196577]

McKeon RJ, Jurynec MJ, Buck CR. The chondroitin sulfate proteoglycans neurocan and phosphacan are expressed by reactive astrocytes in the chronic CNS glial scar. J Neurosci. 1999; 19:10778–10788. [PubMed: 10594061]

Meiners S, Marone M, Rittenhouse JL, Geller HM. Regulation of astrocytic tenascin by basic fibroblast growth factor. Dev Biol. 1993; 160:480–493. [PubMed: 7504635]

Meiners S, Powell EM, Geller HM. Neurite outgrowth promotion by the alternatively spliced region of tenascin-C is influenced by cell-type specific binding. Matrix Biol. 1999; 18:75–87. [PubMed: 10367733]

Miller GM, Hsieh-Wilson LC. Sugar-dependent modulation of neuronal development, regeneration, and plasticity by chondroitin sulfate proteoglycans. Exp Neurol. 2015; 274:115–125. [PubMed: 26315937]

Milner R, Campbell IL. The extracellular matrix and cytokines regulate microglial integrin expression and activation. J Immunol. 2003; 170:3850–3858. [PubMed: 12646653]

Mongiat M, Sweeney SM, San Antonio JD, Fu J, Iozzo RV. Endorepellin, a novel inhibitor of angiogenesis derived from the C terminus of perlecan. J Biol Chem. 2003; 278:4238–4249. [PubMed: 12435733]

Morgenstern DA, Asher RA, Fawcett JW. Chondroitin sulphate proteoglycans in the CNS injury response. Prog Brain Res. 2002; 137:313–332. [PubMed: 12440375]

Muir EM, Adcock KH, Morgenstern DA, Clayton R, von Stillfried N, Rhodes K, Ellis C, Fawcett JW, Rogers JH. Matrix metalloproteases and their inhibitors are produced by overlapping populations of activated astrocytes. Brain Res Mol Brain Res. 2002; 100:103–117. [PubMed: 12008026]

Nandini CD, Itoh N, Sugahara K. Novel 70-kDa chondroitin sulfate/dermatan sulfate hybrid chains with a unique heterogeneous sulfation pattern from shark skin, which exhibit neuritogenic activity and binding activities for growth factors and neurotrophic factors. J Biol Chem. 2005; 280:4058–4069. [PubMed: 15557276]

Nordstrom LA, Lochner J, Yeung W, Ciment G. The metalloproteinase stromelysin-1 (transin) mediates PC12 cell growth cone invasiveness through basal laminae. Mol Cell Neurosci. 1995; 6:56–68. [PubMed: 7599958]

Ozerdem U, Monosov E, Stallcup WB. NG2 proteoglycan expression by pericytes in pathological microvasculature. Microvasc Res. 2002; 63:129–134. [PubMed: 11749079]

Paetau A, Mellstrom K, Vaheri A, Haltia M. Distribution of a major connective tissue protein, fibronectin, in normal and neoplastic human nervous tissue. Acta Neuropathol. 1980; 51:47–51. [PubMed: 7435140]

Park C, Cho IH, Kim D, Jo EK, Choi SY, Oh SB, Park K, Kim JS, Lee SJ. Toll-like receptor 2 contributes to glial cell activation and heme oxygenase-1 expression in traumatic brain injury. Neurosci Lett. 2008; 431:123–128. [PubMed: 18164130]

Pei D, Liu N, Li D, Yan H, Wang QB, Fang Y, Xie L, Li HP. Inhibition of platelet-derived growth factor receptor β reduces reactive glia and scar formation after traumatic brain injury in mice. Brain Res Bull. 2017

Penc SF, Pomahac B, Winkler T, Dorschner RA, Eriksson E, Herndon M, Gallo RL. Dermatan sulfate released after injury is a potent promoter of fibroblast growth factor-2 function. J Biol Chem. 1998; 273:28116–28121. [PubMed: 9774430]

Pesheva P, Probstmeier R. The yin and yang of tenascin-R in CNS development and pathology. Prog Neurobiol. 2000; 61:465–493. [PubMed: 10748320]

Pesheva P, Spiess E, Schachner M. J1–160 and J1–180 are oligodendrocyte-secreted nonpermissive substrates for cell adhesion. J Cell Biol. 1989; 109:1765–1778. [PubMed: 2477380]

Pizzorusso T, Medini P, Berardi N, Chierzi S, Fawcett JW, Maffei L. Reactivation of ocular dominance plasticity in the adult visual cortex. Science. 2002; 298:1248–1251. [PubMed: 12424383]

Plantman S. Osteopontin is upregulated after mechanical brain injury and stimulates neurite growth from hippocampal neurons through β1 integrin and CD44. Neuroreport. 2012; 23:647–652. [PubMed: 22692550]

Plantman S. Proregenerative properties of ECM molecules. BioMed research international. 2013; 2013:981695. [PubMed: 24195084]

Probstmeier R, Pesheva P. Tenascin-C inhibits β1 integrin-dependent cell adhesion and neurite outgrowth on fibronectin by a disialoganglioside-mediated signaling mechanism. Glycobiology. 1999; 9:101–114. [PubMed: 9949188]

Probstmeier R, Stichel CC, Muller HW, Asou H, Pesheva P. Chondroitin sulfates expressed on oligodendrocyte-derived tenascin-R are involved in neural cell recognition. Functional implications during CNS development and regeneration. J Neurosci Res. 2000; 60:21–36. [PubMed: 10723065]

Properzi F, Carulli D, Asher RA, Muir E, Camargo LM, van Kuppevelt TH, ten Dam GB, Furukawa Y, Mikami T, Sugahara K, Toida T, Geller HM, Fawcett JW. Chondroitin 6-sulphate synthesis is up-

regulated in injured CNS, induced by injury-related cytokines and enhanced in axon-growth inhibitory glia. Eur J Neurosci. 2005; 21:378–390. [PubMed: 15673437]

Properzi F, Lin R, Kwok J, Naidu M, van Kuppevelt TH, Ten Dam GB, Camargo LM, Raha-Chowdhury R, Furukawa Y, Mikami T, Sugahara K, Fawcett JW. Heparan sulphate proteoglycans in glia and in the normal and injured CNS: expression of sulphotransferases and changes in sulphation. Eur J Neurosci. 2008; 27:593–604. [PubMed: 18279312]

Qiao D, Meyer K, Mundhenke C, Drew SA, Friedl A. Heparan sulfate proteoglycans as regulators of fibroblast growth factor-2 signaling in brain endothelial cells. Specific role for glypican-1 in glioma angiogenesis. J Biol Chem. 2003; 278:16045–16053. [PubMed: 12591930]

Raulo E, Chernousov MA, Carey DJ, Nolo R, Rauvala H. Isolation of a neuronal cell surface receptor of heparin binding growth-associated molecule (HB-GAM). Identification as N-syndecan (syndecan-3). J Biol Chem. 1994; 269:12999–13004. [PubMed: 8175719]

Rempe RG, Hartz AM, Bauer B. Matrix metalloproteinases in the brain and blood-brain barrier: Versatile breakers and makers. J Cereb Blood Flow Metab. 2016; 36:1481–1507. [PubMed: 27323783]

Rhodes KE, Raivich G, Fawcett JW. The injury response of oligodendrocyte precursor cells is induced by platelets, macrophages and inflammation-associated cytokines. Neuroscience. 2006; 140:87–100. [PubMed: 16631314]

Roberts J, Kahle MP, Bix GJ. Perlecan and the blood-brain barrier: beneficial proteolysis? Front Pharmacol. 2012; 3:155. [PubMed: 22936915]

Rubin JB, Choi Y, Segal RA. Cerebellar proteoglycans regulate sonic hedgehog responses during development. Development. 2002; 129:2223–2232. [PubMed: 11959830]

Rutka JT, Apodaca G, Stern R, Rosenblum M. The extracellular matrix of the central and peripheral nervous systems: structure and function. J Neurosurg. 1988; 69:155–170. [PubMed: 3292716]

Saku T, Furthmayr H. Characterization of the major heparan sulfate proteoglycan secreted by bovine aortic endothelial cells in culture. Homology to the large molecular weight molecule of basement membranes. J Biol Chem. 1989; 264:3514–3523. [PubMed: 2521637]

Sashindranath M, Sales E, Daglas M, Freeman R, Samson AL, Cops EJ, Beckham S, Galle A, McLean C, Morganti-Kossmann C, Rosenfeld JV, Madani R, Vassalli JD, Su EJ, Lawrence DA, Medcalf RL. The tissue-type plasminogen activator-plasminogen activator inhibitor 1 complex promotes neurovascular injury in brain trauma: evidence from mice and humans. Brain. 2012; 135:3251–3264. [PubMed: 22822039]

Scheibner KA, Lutz MA, Boodoo S, Fenton MJ, Powell JD, Horton MR. Hyaluronan fragments act as an endogenous danger signal by engaging TLR2. J Immunol. 2006; 177:1272–1281. [PubMed: 16818787]

Schnell L, Fearn S, Klassen H, Schwab ME, Perry VH. Acute inflammatory responses to mechanical lesions in the CNS: differences between brain and spinal cord. Eur J Neurosci. 1999; 11:3648–3658. [PubMed: 10564372]

Seidenbecher CI, Gundelfinger ED, Bockers TM, Trotter J, Kreutz MR. Transcripts for secreted and GPI-anchored brevican are differentially distributed in rat brain. Eur J Neurosci. 1998; 10:1621–1630. [PubMed: 9751135]

Shen Y, Tenney AP, Busch SA, Horn KP, Cuascut FX, Liu K, He Z, Silver J, Flanagan JG. PTPσ is a receptor for chondroitin sulfate proteoglycan, an inhibitor of neural regeneration. Science. 2009; 326:592–596. [PubMed: 19833921]

Sirko S, von Holst A, Weber A, Wizenmann A, Theocharidis U, Gotz M, Faissner A. Chondroitin sulfates are required for fibroblast growth factor-2-dependent proliferation and maintenance in neural stem cells and for epidermal growth factor-dependent migration of their progeny. Stem Cells. 2010; 28:775–787. [PubMed: 20087964]

Smith GM, Hale JH. Macrophage/Microglia regulation of astrocytic tenascin: synergistic action of transforming growth factor-β and basic fibroblast growth factor. J Neurosci. 1997; 17:9624–9633. [PubMed: 9391017]

Smith GM, Strunz C. Growth factor and cytokine regulation of chondroitin sulfate proteoglycans by astrocytes. Glia. 2005; 52:209–218. [PubMed: 15968632]

Sodek J, Ganss B, McKee MD. Osteopontin. Crit Rev Oral Biol Med. 2000; 11:279–303. [PubMed: 11021631]

Soltes L, Mendichi R, Kogan G, Schiller J, Stankovska M, Arnhold J. Degradative action of reactive oxygen species on hyaluronan. Biomacromolecules. 2006; 7:659–668. [PubMed: 16529395]

Sordillo PP, Sordillo LA, Helson L. Bifunctional role of pro-inflammatory cytokines after traumatic brain injury. Brain Inj. 2016; 30:1043–1053. [PubMed: 27261102]

Sorg BA, Berretta S, Blacktop JM, Fawcett JW, Kitagawa H, Kwok JC, Miquel M. Casting a Wide Net: Role of Perineuronal Nets in Neural Plasticity. J Neurosci. 2016; 36:11459–11468. [PubMed: 27911749]

Steiner E, Enzmann GU, Lyck R, Lin S, Ruegg MA, Kroger S, Engelhardt B. The heparan sulfate proteoglycan agrin contributes to barrier properties of mouse brain endothelial cells by stabilizing adherens junctions. Cell Tissue Res. 2014; 358:465–479. [PubMed: 25107608]

Stern R, Asari AA, Sugahara KN. Hyaluronan fragments: an information-rich system. Eur J Cell Biol. 2006; 85:699–715. [PubMed: 16822580]

Stichel CC, Kappler J, Junghans U, Koops A, Kresse H, Muller HW. Differential expression of the small chondroitin/dermatan sulfate proteoglycans decorin and biglycan after injury of the adult rat brain. Brain Res. 1995; 704:263–274. [PubMed: 8788923]

Sticozzi C, Belmonte G, Meini A, Carbotti P, Grasso G, Palmi M. IL-1β induces GFAP expression in vitro and in vivo and protects neurons from traumatic injury-associated apoptosis in rat brain striatum via NFκB/Ca2+-calmodulin/ERK mitogen-activated protein kinase signaling pathway. Neuroscience. 2013; 252:367–383. [PubMed: 23928073]

Sugimoto K, Nishioka R, Ikeda A, Mise A, Takahashi H, Yano H, Kumon Y, Ohnishi T, Tanaka J. Activated microglia in a rat stroke model express NG2 proteoglycan in peri-infarct tissue through the involvement of TGF-β1. Glia. 2014; 62:185–198. [PubMed: 24311432]

Suzuki H, Ayer R, Sugawara T, Chen W, Sozen T, Hasegawa Y, Kanamaru K, Zhang JH. Protective effects of recombinant osteopontin on early brain injury after subarachnoid hemorrhage in rats. Crit Care Med. 2010; 38:612–618. [PubMed: 19851092]

Takafuji V, Forgues M, Unsworth E, Goldsmith P, Wang XW. An osteopontin fragment is essential for tumor cell invasion in hepatocellular carcinoma. Oncogene. 2007; 26:6361–6371. [PubMed: 17452979]

Takahashi Y, Maki T, Liang AC, Itoh K, Lok J, Osumi N, Arai K. p38 MAP kinase mediates transforming-growth factor-β1-induced upregulation of matrix metalloproteinase-9 but not -2 in human brain pericytes. Brain Res. 2014; 1593:1–8. [PubMed: 25451097]

Takeda-Uchimura Y, Uchimura K, Sugimura T, Yanagawa Y, Kawasaki T, Komatsu Y, Kadomatsu K. Requirement of keratan sulfate proteoglycan phosphacan with a specific sulfation pattern for critical period plasticity in the visual cortex. Exp Neurol. 2015; 274:145–155. [PubMed: 26277687]

Tan CL, Kwok JC, Patani R, Ffrench-Constant C, Chandran S, Fawcett JW. Integrin activation promotes axon growth on inhibitory chondroitin sulfate proteoglycans by enhancing integrin signaling. J Neurosci. 2011; 31:6289–6295. [PubMed: 21525268]

Tang SC, Arumugam TV, Xu X, Cheng A, Mughal MR, Jo DG, Lathia JD, Siler DA, Chigurupati S, Ouyang X, Magnus T, Camandola S, Mattson MP. Pivotal role for neuronal Toll-like receptors in ischemic brain injury and functional deficits. Proc Natl Acad Sci U S A. 2007; 104:13798–13803. [PubMed: 17693552]

Tao X, Chen X, Hao S, Hou Z, Lu T, Sun M, Liu B. Protective actions of PJ34, a poly(ADP-ribose)polymerase inhibitor, on the blood-brain barrier after traumatic brain injury in mice. Neuroscience. 2015; 291:26–36. [PubMed: 25668593]

Tate CC, Garcia AJ, LaPlaca MC. Plasma fibronectin is neuroprotective following traumatic brain injury. Exp Neurol. 2007a; 207:13–22. [PubMed: 17599836]

Tate CC, Tate MC, LaPlaca MC. Fibronectin and laminin increase in the mouse brain after controlled cortical impact injury. J Neurotrauma. 2007b; 24:226–230. [PubMed: 17263686]

Thelin MA, Bartolini B, Axelsson J, Gustafsson R, Tykesson E, Pera E, Oldberg A, Maccarana M, Malmstrom A. Biological functions of iduronic acid in chondroitin/dermatan sulfate. The FEBS journal. 2013; 280:2431–2446. [PubMed: 23441919]

van Dam AM, Poole S, Schultzberg M, Zavala F, Tilders FJ. Effects of peripheral administration of LPS on the expression of immunoreactive interleukin-1 α, β, and receptor antagonist in rat brain. Ann N Y Acad Sci. 1998; 840:128–138. [PubMed: 9629245]

Vilalta A, Sahuquillo J, Rosell A, Poca MA, Riveiro M, Montaner J. Moderate and severe traumatic brain injury induce early overexpression of systemic and brain gelatinases. Intensive Care Med. 2008; 34:1384–1392. [PubMed: 18350273]

Virgintino D, Perissinotto D, Girolamo F, Mucignat MT, Montanini L, Errede M, Kaneiwa T, Yamada S, Sugahara K, Roncali L, Perris R. Differential distribution of aggrecan isoforms in perineuronal nets of the human cerebral cortex. J Cell Mol Med. 2009; 13:3151–3173. [PubMed: 19220578]

Wakao N, Imagama S, Zhang H, Tauchi R, Muramoto A, Natori T, Takeshita S, Ishiguro N, Matsuyama Y, Kadomatsu K. Hyaluronan oligosaccharides promote functional recovery after spinal cord injury in rats. Neurosci Lett. 2011; 488:299–304. [PubMed: 21111028]

Wang H, Katagiri Y, McCann TE, Unsworth E, Goldsmith P, Yu ZX, Tan F, Santiago L, Mills EM, Wang Y, Symes AJ, Geller HM. Chondroitin-4-sulfation negatively regulates axonal guidance and growth. J Cell Sci. 2008; 121:3083–3091. [PubMed: 18768934]

Wang X, Jung J, Asahi M, Chwang W, Russo L, Moskowitz MA, Dixon CE, Fini ME, Lo EH. Effects of matrix metalloproteinase-9 gene knock-out on morphological and motor outcomes after traumatic brain injury. J Neurosci. 2000; 20:7037–7042. [PubMed: 10995849]

Wappler EA, Adorjan I, Gal A, Galgoczy P, Bindics K, Nagy Z. Dynamics of dystroglycan complex proteins and laminin changes due to angiogenesis in rat cerebral hypoperfusion. Microvasc Res. 2011; 81:153–159. [PubMed: 21192954]

Wei YT, Tian WM, Yu X, Cui FZ, Hou SP, Xu QY, Lee IS. Hyaluronic acid hydrogels with IKVAV peptides for tissue repair and axonal regeneration in an injured rat brain. Biomedical materials (Bristol, England). 2007; 2:S142–146.

Wetzel M, Rosenberg GA, Cunningham LA. Tissue inhibitor of metalloproteinases-3 and matrix metalloproteinase-3 regulate neuronal sensitivity to doxorubicin-induced apoptosis. Eur J Neurosci. 2003; 18:1050–1060. [PubMed: 12956705]

Whitelock JM, Melrose J, Iozzo RV. Diverse cell signaling events modulated by perlecan. Biochemistry. 2008; 47:11174–11183. [PubMed: 18826258]

Wiggins-Dohlvik K, Merriman M, Shaji CA, Alluri H, Grimsley M, Davis ML, Smith RW, Tharakan B. Tumor necrosis factor-α disruption of brain endothelial cell barrier is mediated through matrix metalloproteinase-9. Am J Surg. 2014; 208:954–960. discussion 960. [PubMed: 25312844]

Wight TN. Versican: a versatile extracellular matrix proteoglycan in cell biology. Curr Opin Cell Biol. 2002; 14:617–623. [PubMed: 12231358]

Wilson MT, Snow DM. Chondroitin sulfate proteoglycan expression pattern in hippocampal development: potential regulation of axon tract formation. J Comp Neurol. 2000; 424:532–546. [PubMed: 10906718]

Winkler S, Stahl RC, Carey DJ, Bansal R. Syndecan-3 and perlecan are differentially expressed by progenitors and mature oligodendrocytes and accumulate in the extracellular matrix. J Neurosci Res. 2002; 69:477–487. [PubMed: 12210841]

Xing G, Ren M, Verma A. Divergent temporal expression of hyaluronan metabolizing enzymes and receptors with craniotomy vs. Controlled-cortical impact injury in rat brain: a pilot study. Front Neurol. 2014; 5:173. [PubMed: 25309501]

Yamada H, Fredette B, Shitara K, Hagihara K, Miura R, Ranscht B, Stallcup WB, Yamaguchi Y. The brain chondroitin sulfate proteoglycan brevican associates with astrocytes ensheathing cerebellar glomeruli and inhibits neurite outgrowth from granule neurons. J Neurosci. 1997; 17:7784–7795. [PubMed: 9315899]

Yao Y, Chen ZL, Norris EH, Strickland S. Astrocytic laminin regulates pericyte differentiation and maintains blood brain barrier integrity. Nature communications. 2014; 5:3413.

Yi JH, Katagiri Y, Susarla B, Figge D, Symes AJ, Geller HM. Alterations in sulfated chondroitin glycosaminoglycans following controlled cortical impact injury in mice. J Comp Neurol. 2012; 520:3295–3313. [PubMed: 22628090]

Yin J, Sakamoto K, Zhang H, Ito Z, Imagama S, Kishida S, Natori T, Sawada M, Matsuyama Y, Kadomatsu K. Transforming growth factor-β1 upregulates keratan sulfate and chondroitin sulfate biosynthesis in microglias after brain injury. Brain Res. 2009; 1263:10–22. [PubMed: 19368826]

Yoo M, Khaled M, Gibbs KM, Kim J, Kowalewski B, Dierks T, Schachner M. Arylsulfatase B improves locomotor function after mouse spinal cord injury. PLoS One. 2013; 8:e57415. [PubMed: 23520469]

Yu ZQ, Zha JH. Genetic ablation of toll-like receptor 2 reduces secondary brain injury caused by cortical contusion in mice. Ann Clin Lab Sci. 2012; 42:26–33. [PubMed: 22371907]

Zhang H, Muramatsu T, Murase A, Yuasa S, Uchimura K, Kadomatsu K. N-Acetylglucosamine 6-O-sulfotransferase-1 is required for brain keratan sulfate biosynthesis and glial scar formation after brain injury. Glycobiology. 2006; 16:702–710. [PubMed: 16624895]

Zhang Y, Anderson PN, Campbell G, Mohajeri H, Schachner M, Lieberman AR. Tenascin-C expression by neurons and glial cells in the rat spinal cord: changes during postnatal development and after dorsal root or sciatic nerve injury. J Neurocytol. 1995; 24:585–601. [PubMed: 7595667]

Zhang Z, Zhang ZY, Wu Y, Schluesener HJ. Immunolocalization of Toll-like receptors 2 and 4 as well as their endogenous ligand, heat shock protein 70, in rat traumatic brain injury. Neuroimmunomodulation. 2012; 19:10–19. [PubMed: 22067617]

Ziebell JM, Morganti-Kossmann MC. Involvement of pro- and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. Neurotherapeutics. 2010; 7:22–30. [PubMed: 20129494]

Significance Statement

Traumatic brain injuries are a leading cause of death and are associated with long-term consequences for physical health and cognition. Despite the prevalence and associated complications, there is no effective treatment for TBI. Brain ECM plays a major role in TBI pathophysiology by modulating the inflammatory response, cell signaling and post-traumatic circuit remodeling. ECM components also limit functional recovery by inhibiting neuronal regeneration through the damaged region. Strategies to modulate brain ECM to reduce inflammation and facilitate neuroregeneration have therapeutic potential.

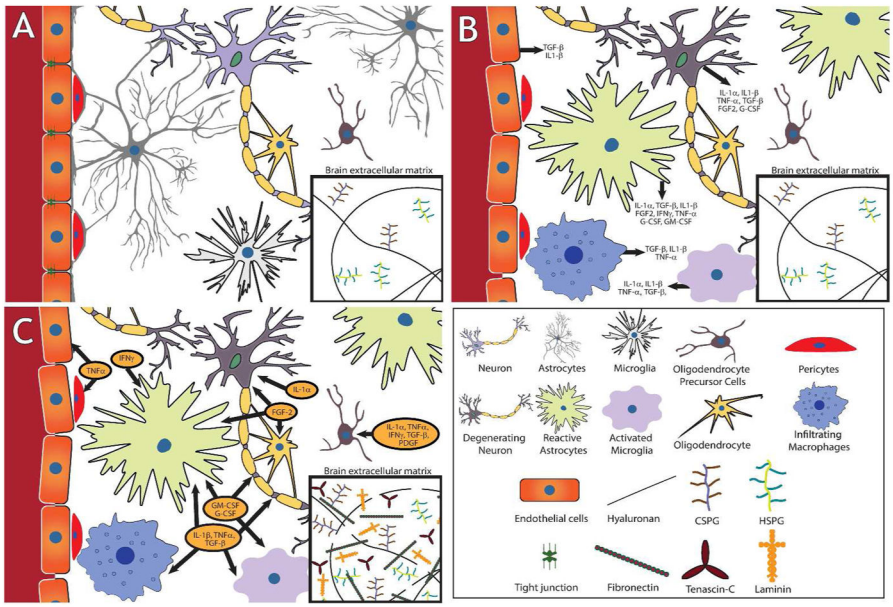

Figure 1.

Neurovascular unit changes following traumatic brain injury. A. Normal brain. Tight junctions between endothelial cells along with pericytes astrocytic end feet constitute the blood brain barrier. Processes of resting astrocytes and myelinating oligodendrocytes promote synaptic stability and neurotransmission. Inset: The extracellular matrix of normal brain contains CSPGs, HSPG and hyaluronan. Fibrous proteins, which are the major component of ECM in most tissues, are limited to the brain vasculature. B and C) Alterations in cellular activation soon after TBI. Injury leads to disruption of the blood brain barrier, followed by infiltration of blood components and macrophages into the brain, leading to the activation of resident glial cells. Reactive astrocytes and microglia as well as damaged neurons show morphological changes, increased metabolism, hypertrophy and release an array of cytokines. C. TBI-induced response. Cytokines released by resident and infiltrating cells affect brain inflammation and ECM remodulation. Inset: TBI leads to the degradation of hyaluronan along with the increased expression of CSPGs and HSPGs, as well as fibrous ECM proteins including fibronectin, tenascin-C and laminin.

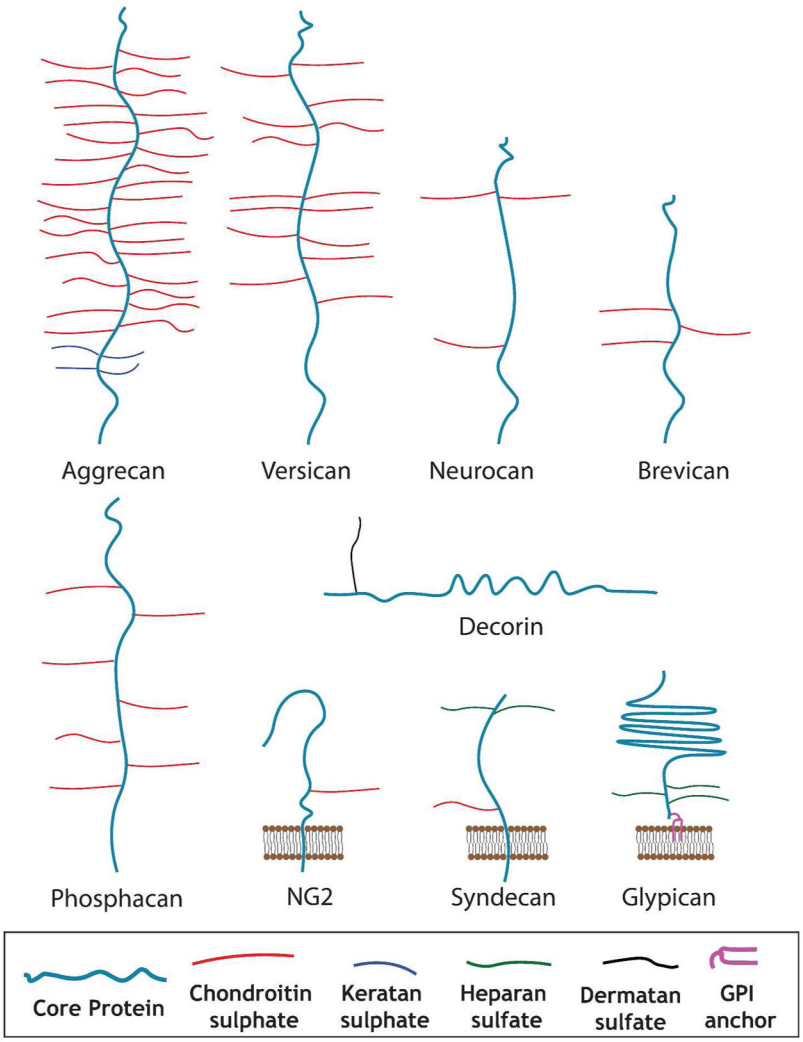

Figure 2.

Major brain proteoglycans. Proteoglycans consists of a protein core decorated with unbranched sulfated glycosaminoglycan sugar chains. CSPG core proteins are decorated with one or more chondroitin sulfate sugar chains. Based on the core protein they are classified into lecticans (which includes neurocan, brevican, versican, and aggrecan), phosphacan, and NG2. HSPGs are decorated with HS chains. Syndecans are transmembrane proteins, while glypicans are anchored to the cell membrane with a GPI linkage. Decorin is a secreted proteoglycan with dermatan sulfate side chains.

Table 1

Cytokines involved in ECM remodeling in the response to TBI

Cytokine	Cellular Source & Target		Role in brain extracellular matrix remodeling	Reference
IL-1α	**Source**	Astrocytes, Microglia, Neurons		Lau and Yu 2001; Lu et al. 2005; van Dam et al. 1998
	Target	OPCs	Increase NG2 immunoreactivity	Rhodes et al. 2006
IL-1β	**Source**	Astrocytes, Endothelial cells, Macrophages, Microglia,	Down-regulates CSPG expression Increased laminin	Acarin et al. 2000; Campbell et al. 2007; Eriksson et al. 1999; Lu et al. 2005; Sticozzi et al. 2013
	Target	Astrocytes	Induce MMP-9 expression	Lee et al. 2015
		Oligodendrocyte lineage cells	Increase versican-V2 expression	Asher et al. 2000
TNF-α	**Source**	Astrocytes, Macrophages, Microglia, Neurons		Acarin et al. 2000; Lau and Yu 2001
	Target	OPCs	Increase NG2 immunoreactivity	Rhodes et al. 2006
IFN- γ	**Source**	Astrocytes	Reduced CSPG expression	Lau and Yu 2001; Smith and Strunz 2005
	Target	Astrocytes	Reduced tenascin, laminin, and fibronectin	DiProspero et al. 1997
		OPCs	IFN-γ increase NG2	Rhodes et al. 2006
GM-CSF	**Source**	Astrocyte	Reduced expression of neurocan and NG2	Choi et al. 2014a; Huang et al. 2009
	Target	Astrocytes	Reduced expression of NG2, neurocan and phosphacan	Choi et al. 2014a
TGF-β	**Source**	Astrocytes, Macrophages, Microglia, Neurons		Acarin et al. 2000; Lindholm et al. 1992
	Target	Astrocytes	Increased production of tenascin and fibronectin	Fok-Seang et al. 1998
			Increased brevican	Hamel et al. 2005
			Increased neurocan and phosphacan	Choi et al. 2014a
		Oligodendrocytes	Increased versican-V2	Asher et al. 2000
		OPCs	Increased NG2	Rhodes et al. 2006
		Microglia	Induced KS and CS biosynthesis in cultured microglia	Yin et al. 2009
		Pericytes	Upregulation of MMP-2/9	Takahashi et al. 2014
FGF2	**Source**	Astrocytes		Joy et al. 1997
	Target	Astrocytes	Upregulate tenascin	DiProspero et al. 1997
G-CSF	**Source**	Astrocyte, Neurons		Choi et al. 2014b
	Target	Astrocytes	Increase the expression of NG2, neurocan, and phosphacan	Choi et al. 2014a
PDGF	**Source**	Platelets		
	Target	OPCs, Pericytes	Increased NG2	Pei et al. 2017

J Neurosci Res. Author manuscript; available in PMC 2018 October 01.

Table 2

Sources of ECM and changes after TBI

Matrix protein	Cellular source	Changes after TBI	Reference
CSPG			
• Lecticans			
○ Aggrecan	Neurons, astrocytes	Decreased in injury core	Domowicz et al. 2008; Harris et al. 2009; Matthews et al. 2002; Yi et al. 2012
○ Brevican	Neurons, astrocytes, oligodendrocytes	Secreted isoform is up-regulated; GPI-anchored isoform unchanged.	Beggah et al. 2005; Jaworski et al. 1999; Seidenbecher et al. 1998; Yamada et al. 1997
○ Neurocan	Neurons, astrocytes	Increased neurocan in a tight band surrounding the injury core	Asher et al. 2000; Dobbertin et al. 2003; McKeon et al. 1999; Yi et al. 2012
○ Versican-V2	Oligodendrocytes	Increased in the injury core	Asher et al. 2002; Beggah et al. 2005; Harris et al. 2009; Morgenstern et al. 2002; Yi et al. 2012
○ Phosphacan	Neurons, astrocytes, oligodendrocytes	Reduced in the glial scar	Dobbertin et al. 2003; Harris et al. 2009; Hayashi et al. 2005; McKeon et al. 1999
• NG2	Oligodendrocyte precursor cells, pericytes, microglia	Increased expression	Flygt et al. 2017; Levine et al. 1993; Ozerdem et al. 2002; Sugimoto et al. 2014
HSPG			
• Syndecans	Neuron, astrocytes, oligodendrocyte, oligodendrocyte precursors, microglia	Increased immunoreactivity	Iseki et al. 2002; Kaur et al. 2009; Properzi et al. 2008; Raulo et al. 1994; Winkler et al. 2002
• Glypicans	Neurons, astrocytes, oligodendrocyte, oligodendrocyte precursors	increased immunoreactivity	Hagino et al. 2003; Litwack et al. 1994; Winkler et al. 2002
• Perlecan	Endothelial cells, astrocytes, oligodendrocytes, oligodendrocyte progenitor cells, microglia	Increased immunoreactivity	Garcia de Yebenes et al. 1999; Saku and Furthmayr 1989; Winkler et al. 2002
• Agrins	Neurons, astrocytes	Increased in reactive astrocytes	Cohen et al. 1997; Falo et al. 2008
KSPG	Neurons and microglia	Increased immunoreactivity	Geisert et al. 1996; Yin et al. 2009; Zhang et al. 2006
Hyaluronan	Astrocytes, oligodendrocytes, neurons	Altered dynamics in synthesis and degradation.	Haqqani et al. 2007; Margolis and Margolis 1974; Xing et al. 2014
Fibronectin	Endothelial cells, pericytes, macrophages	Increased levels	Egan and Vijayan 1991; Tate et al. 2007a
Tenascin-C	Astrocytes, oligodendrocytes and neurons	Increased expression in animal and humans	Brodkey et al. 1995; Hausmann and Betz 2001; Laywell et al. 1992
Tenascin-R	Oligodendrocytes	Increased	Deckner et al. 2000; Pesheva et al. 1989; Probstmeier et al. 2000
Laminin	Astrocytes, endothelial cells, pericytes	Immunoreactivity increased	Gautam et al. 2016; Liesi et al. 1984; Mandarino et al. 1993; Tao et al. 2015; Tate et al. 2007b
Osteopontin	Astrocytes, microglia	Increased expression	Choi et al. 2007; Plantman 2012