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Extracellular matrix regulation of inflammation in the healthy and injured spinal cord

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Abstract

Throughout the body, the extracellular matrix (ECM) provides structure and organization to tissues and also helps regulate cell migration and intercellular communication. In the injured spinal cord (or brain), changes in the composition and structure of the ECM undoubtedly contribute to regeneration failure. Less appreciated is how the native and injured ECM influences intraspinal inflammation and, conversely, how neuroinflammation affects the synthesis and deposition of ECM after CNS injury. In all tissues, inflammation can be initiated and propagated by ECM disruption. Molecules of ECM newly liberated by injury or inflammation include hyaluronan fragments, tenascins, and sulfated proteoglycans. These act as “damage-associated molecular patterns” or “alarmins”, i.e., endogenous proteins that trigger and subsequently amplify inflammation. Activated inflammatory cells, in turn, further damage the ECM by releasing degradative enzymes including matrix metalloproteinases (MMPs). After spinal cord injury (SCI), destabilization or alteration of the structural and chemical composition of the ECM affects migration, communication, and survival of all cells – neural and non-neural – that are critical for spinal cord repair. By stabilizing ECM structure or modifying their ability to trigger the degradative effects of inflammation, it may be possible to create an environment that is more conducive to tissue repair and axon plasticity after SCI.

Keywords

Neuroinflammation; immune; DAMP; toll-like receptors; TLR; hyaluronan; tenascin; proteoglycan

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Introduction

Tissue damage triggers inflammation and degradation of the extracellular matrix (ECM)[1]. The ECM is an intricately arranged scaffold comprised of secreted proteins and complex sugars that together support cell function and survival. After injury, the ECM is degraded and the composition changes. Some ECM molecules become aberrantly expressed, whereas others are cleaved into bioactive fragments known as damage-associated molecular patterns (DAMPs) or "alarmins". Through their ability to bind to different types of pattern recognition receptors (PRRs), these ECM molecules can influence the phenotype and magnitude of inflammation (Bianchi, 2007; Piccinini and Midwood, 2010; Kigerl et al., this issue) but see (Erridge, 2010). Moreover, the enzymes and inflammatory mediators released by immune cells further degrade or alter the composition of the ECM.

Remarkably little is known regarding the relationship between ECM and neuroinflammation, especially in the context of SCI (Fig. 1). Intentionally altering the composition of the lesion ECM could influence inflammatory cell signaling and subsequent release of cytokines or growth factors that affect mechanisms of CNS repair. Conversely, targeting inflammatory cells directly could "improve" the composition of the ECM, favoring a mixture of molecules that permit axon growth or that suppress the harmful effects of inflammation.

In this review, interactions between the ECM and the immune system are highlighted. First, a brief overview of SCI-induced inflammation is provided followed by a detailed discussion of the ECM in the healthy CNS and the potential implications for enhanced ECM:immune cell interactions in the inflamed CNS. Several key ECM molecules are considered, with a focus on how they affect inflammation. Finally, potential strategies for manipulating ECM:immune cell interactions are discussed in the context of improving recovery after SCI.

SCI-induced inflammation: an overview

Injury to the spinal cord elicits an inflammatory response that, at least in its early stages, is remarkably similar to that initiated by injury elsewhere in the body (Popovich and Longbrake, 2008). Blood-spinal cord barrier breakdown occurs soon after injury leading to progressive hemorrhagic necrosis at the lesion epicenter (Noble and Wrathall, 1989; Popovich et al., 1996; Schnell et al., 1999; Simard et al., 2007; Simard et al., 2010). Blood-derived immune cells (leukocytes) invade the spinal cord in waves, regulated in part by newly-formed ECM molecules that act as chemoattractants. Neutrophils accumulate within 24 hpi, reaching maximal levels 3–14 dpi (Fleming et al., 2006; Kigerl et al., 2006; Stirling and Yong, 2008). Monocytes infiltrate 1–2 dpi with peak accumulation occurring ~7–14 dpi.

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[1]**Abbreviations:** ADAM: a disintegrin and metalloproteinase; ADAM-TS: a disintegrin and metalloproteinase with thrombospondin motif; CCL: CC chemokine ligand; chABC: chondroitinase ABC; CNS: central nervous system; CS: chondroitin sulfate; CS-A: chondroitin sulfate-A; CSPG-DS: disaccharide CSPG product; CXCL: CXC chemokine ligand; DAMP: damage-associated molecular pattern; dpi: days post-injury; DS: dermatan sulfate; EAE: experimental autoimmune encephalomyelitis; ECM: extracellular matrix; GAG: glycosaminoglycan; GPI: glycophosphatidylinositol; HA: hyaluronan; HMW-HA: high molecular weight hyaluronan; hpi: hours post-injury; HS: heparan sulfate; IL-: interleukin-; KO: knockout; KS: keratan sulfate; LMW-HA: low molecular weight hyaluronan; MMP: matrix metalloproteinase; MT-MMPs: membrane-bound metalloproteinases; PG: proteoglycan; PNS: peripheral nervous system; PRR: pattern recognition receptor; SLRP: small leucine-rich repeat protein; TGF: trasforming growth factor; TIMP: tissue inhibitors of metalloproteinases; TLR: toll-like receptor; TNF: tumor necrosis factor; TSP: thrombospondin

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Monocytes differentiate into macrophages that persist indefinitely at the lesion site (Kigerl et al., 2009; Kigerl et al., 2006; Popovich et al., 1997). In the pathological spinal cord, both neutrophils and macrophages adopt an inflammatory phenotype and release soluble factors, including cytokines, proteolytic enzymes and oxidative metabolites, that exacerbate injury. A unique feature of inflammation in the injured spinal cord (or brain) is that this response persists indefinitely, i.e., there is no resolution phase of inflammation in injured spinal cord and chronic waves of leukocyte recruitment occur (Beck et al., 2010; Kigerl et al., 2009; Kigerl et al., 2006; Pajoohesh-Ganji and Byrnes, 2011; Pruss et al., 2011). Chronic inflammation has adverse consequences, including fibrosis (the deposition of excess connective tissue) and impaired tissue healing (Diegelmann and Evans, 2004; Nathan and Ding, 2010). Accordingly, controlling inflammation holds promise for improving CNS repair. How to accomplish this is less obvious. On the one hand, methods to deplete or inhibit leukocyte functions can be neuroprotective and improve recovery, especially if the intervention is started early after trauma (Beril et al., 2007; Blight, 1994; Busch et al., 2009; Eng and Lee, 2003; Giulian and Robertson, 1990; Gris et al., 2004; Noble et al., 2002; Popovich et al., 1999). However, these same cells can enhance repair and disrupting the normal composition or dynamics of acute inflammation could have unwanted long-term consequences (Rapalino et al., 1998; Shechter and Schwartz, 2013; Stirling et al., 2009).

Cells intrinsic to the spinal cord also contribute to SCI-induced inflammation. Microglia and astrocytes near the lesion become activated, proliferate, and release inflammatory cytokines (Bartholdi and Schwab, 1997; Brambilla et al., 2005; Pineau et al., 2010; Popovich et al., 1997). In addition, astrocytes adjacent to the lesion form a matrix-rich glial scar, which limits the extent of hemorrhagic damage and leukocyte migration but also restricts axon plasticity (Alilain et al., 2011; Bradbury et al., 2002; Faulkner et al., 2004; McKeon et al., 1991; Wanner et al., 2013).

A novel approach for controlling inflammation might be to manipulate the ECM. The ECM can regulate inflammation by: (1) releasing DAMPS or alarmins that influence inflammatory cell activation via PRRs (also see Kigerl et al., this issue for a detailed review of PRR-mediated regulation of innate immunity in the injured CNS); (2) sequestering or presenting growth factors, cytokines, and chemokines (chemoattractant cytokines); and (3) affecting inflammatory cell migration (Gill et al., 2010). Altering the ECM in a manner that promotes an anti-inflammatory or immune modulatory response and decreases glial scar formation could improve tissue preservation and increase axon sprouting.

Composition and functions of ECM in the healthy and inflamed CNS

About 20% of the total volume of the adult CNS is extracellular space (Bignami et al., 1993) that contains highly organized ECM (see Hynes and Naba, 2012). As in peripheral tissues, the ECM is composed of interstitial and basement membrane ECM; however, in the CNS the ECM composition is remarkably different. Whereas interstitial ECM of most tissues is enriched in collagen, laminin, and fibronectin, the ECM of adult CNS is primarily a loose meshwork of hyaluronan (HA), sulfated proteogycans (PGs), and tenascin-R (Lau et al., 2013; Rauch, 2007). Unique high-density ECM aggregates called perineuronal nets (PNNs) also form around neuronal soma and dendrites. PNNs assemble during development and act

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to restrict synaptic plasticity and aberrant axon sprouting (Galtrey et al., 2008; Garcia-Alias and Fawcett, 2012). The significance of the PNN after SCI has been considered in recent reviews (Dityatev et al., 2010; Wang and Fawcett, 2012) and is beyond the scope of the current review. Instead, this review will focus on SCI-induced changes to the interstitial ECM and the inflammatory consequences of those changes.

The major components of the interstitial ECM in healthy CNS are HA, sulfated PGs, and tenascin-R. The interactions between fibronectin domains on tenascin and lectin domains on hyalectans, combined with hyalectan binding to hyaluronan, create massive, stable ECM complexes (Fig. 2). HA, the most prevalent ECM component, is a unique glycosaminoglycan (GAG) (Laurent and Fraser, 1992); GAGs are long unbranched chains of repeating disaccharides. Unlike other GAGs, HA is unsulfated and is not generally associated with a core protein. HA polymers are unusually large (MW>1000 kDa) and because they displace large volumes of water, they absorb forces well and are excellent lubricants (Tammi et al., 2002). In healthy tissue, this high molecular weight (HMW-) HA constitutes the framework for the structure of the CNS, as other ECM components like sulfated PGs can bind and cross-link HMW-HA (Hardingham and Fosang, 1992; Hardingham and Muir, 1972; Knudson and Knudson, 1993).

Sulfated PGs consist of a protein core that is covalently linked to one or more sulfated GAG chains. PGs can be categorized based on distinct properties of their core proteins, sulfation patterns, location, size, or modular composition. In general, there are three major categories of sulfated PGs: modular, cell-surface, and small leucine-rich repeat PGs (Schaefer and Schaefer, 2010). Modular PGs have multiple protein domains and are often elongated and highly glycosylated. Modular PGs are major constituents of the healthy CNS ECM, and can be further divided into HA-binding (hyalectans) and non-HA binding (mainly basement membrane PGs). The hyalectan aggrecan is particularly enriched in the CNS and forms large aggregates with HA (Rauch, 2004). Cell-surface PGs can be transmembrane or glycophosphatidylinositol-linked and are involved in cell signaling. Examples include NG2, RPTP-ρ, syndecan, and glypican (also see Shen; this issue for a detailed review of how PGs and other regeneration associated molecules influence intraspinal inflammation). Small leucine-rich repeat PGs (SLRPs), including decorin and biglycan, participate mainly in protein-protein interactions and have diverse functions (Moreth et al., 2012).

Another CNS ECM component is tenascin-R, a protein that forms homodimers or –trimers (Norenberg et al., 1996). Tenascin-R binds to lectin-like domains on hyalectans (Aspberg et al., 1997). In this manner, HA-hyalectan aggregates can be cross-linked to form a super-structure that provides a contiguous, stable substrate for cells and extracellular molecules (Fig. 2).

After SCI, key components of the intact ECM are degraded (e.g., HA), while other components are newly expressed (e.g., tenascin-C) (Fig. 2b). These latter molecules act as DAMPs that propagate inflammation, which subsequently causes further ECM degradation and remodelling. This feed-forward loop could be responsible for propagating chronic inflammation after SCI (Fig. 3).

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In all tissues, matrix metalloproteinases (MMPs) comprise a key intermediary between inflammation and the degradation or remodeling of ECM (Yong, 2005). MMPs are zinc-dependent endopeptidases that modify the ECM and other proteins including cytokines and cell surface receptors (Malemud, 2006). During inflammation, MMP activity is increased by fragmented HA (Sugahara et al., 2003; Yong and Guoping, 2008). In turn, increased MMP activity liberates ECM-derived DAMPs, including sulfated PGs (Brule et al., 2006) and tenascin fragments (Siri et al., 1995). MMP-evoked inflammation is likely detrimental to SCI repair; both MMP-9 and MMP-12 have been shown to limit recovery (Hansen et al., 2013; Hsu et al., 2008; Noble et al., 2002; Wells et al., 2003). The role of MMPs in tissue pathology and recovery after SCI has been reviewed elsewhere (Agrawal et al., 2008; Yong, 2005; Yong et al., 2007; Zhang et al., 2011). The remainder of this review focuses on the three major interstitial ECM components in the CNS: hyaluronan, sulfated PGs, and tenascins.

Hyaluronan: from scaffolding champ to damaging DAMP

Though its structure is simple, HA has remarkable properties. HA's viscosity and its ability to retain water underlie its critical functions in homeostasis and tissue integrity: HA acts as a scaffold that creates and maintains multivalent extracellular interactions between ECM molecules. HA is produced intracellularly by HA synthases (HAS1–3) and is released through plasma membrane pores into the ECM (Watanabe and Yamaguchi, 1996; Weigel et al., 1997). Extracellular HA interacts with several membrane receptors/proteins, including CD44, HA synthase, TLR-2 and -4, ICAM-1, and receptor for HA-mediated mobility (RHAMM) (Aruffo et al., 1990; Hardwick et al., 1992; Jiang et al., 2005; Jiang et al., 2007; McCourt et al., 1994; Turley et al., 2002).

Hyaluronan in healthy spinal cord

In the healthy spinal cord, HMW-HA (MW >1000 kDa) is the major HA form (Struve et al., 2005). HA is released into the extracellular space, mainly by astrocytes, then becomes localized around astrocytes, myelinated axons, and neuron cell bodies (Bignami and Asher, 1992; Eggli et al., 1992; Struve et al., 2005). HMW-HA decreases inflammatory signaling in cultured microglia, likely by blocking the ability of extracellular ligands to bind innate immune receptors (Austin et al., 2012). For example, because CD44 and TLR-4 exist in a receptor cluster, HMW-HA binding to CD44 could block LPS/TLR-4 interactions on the surface of microglia. In cultured astrocytes, HMW-HA reduces proliferation and CSPG deposition (Khaing et al., 2011). Given that various TLR-stimulating DAMPs are released after SCI, exogenous HMW-HA could be introduced into the lesion to restrict inflammation and reduce glial scarring.

HA and inflammation: implications for SCI repair

As a result of injury, HMW-HA becomes fragmented, creating a pool of low-molecular weight (LMW)-HA (<200 kDa) that can amplify inflammatory responses (Jiang et al., 2007). Inflammation-induced fragmentation, mediated in part through the release of enzymes including hyaluronidases and MMPs or reactive oxygen species also destabilizes the ECM (Esser et al., 2012; Hrabarova et al., 2011) (Fig. 2). In contrast to the immune inert

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HMW-HA, LMW-HA is a DAMP that initiates inflammatory signaling in macrophages or microglia culminating in elevated expression of inflammatory cytokines (e.g., MIP-1α, CCL-2, IL-12, and TNF-α), iNOS, and matrix-modifying enzymes (Collins et al., 2011). LMW-HA is also a potent macrophage and neutrophil chemoattractant (Jiang et al., 2005). LMW-HA elicits responses from inflammatory, but not unstimulated macrophages or monocytes (Brown et al., 2001; Levesque and Haynes, 1997; McKee et al., 1996), supporting a role for LMW-HA in propagating active inflammatory cascades.

Using macrophages obtained from TLR2 knockout (KO), TLR4 KO, or MyD88 KO mice, Jiang et al. (2005) found that LMW-HA stimulates inflammatory cytokine production through TLR-2 and TLR-4 via a signaling pathway that requires the adaptor protein MyD88 (see Kigerl et al; this issue). After SCI in mice, both TLR-2 and TLR-4 are increased, and are expressed in macrophages/microglia and astrocytes (Kigerl et al., 2007). At 7 days post-SCI, TLR-2 is expressed at similar levels by CD11b+ macrophages and GFAP+ astrocytes, whereas TLR-4 is preferentially expressed by macrophages. Given that SCI causes LMW-HA production and accumulation of TLR-2/4+ cells, LMW-HA represents a DAMP that is readily available in the lesion site with the potential to amplify select inflammatory cascades.

LMW-HA can also regulate inflammation by binding to CD44 expressed on microglia, macrophages, and astrocytes. Treatment of alveolar macrophages with function-blocking CD44 antibody prevented LMW-HA binding and restricted CD44-dependent increases in inflammatory cytokines (McKee et al., 1996). Also, CD44-HA interactions are required for normal neutrophil chemotaxis in response to MIP-2 *in vivo* (Khan et al., 2004). CD44 can inhibit inflammation by sequestering LMW-HA, thereby limiting its ability to bind TLRs or other PRRs (Kawana et al., 2008; Liang et al., 2007). Also, leukocyte CD44 facilitates LMW-HA internalization and degradation: in CD44 KO mice, bleomycin-induced lung inflammation causes HA to accumulate in the lung, an effect that is abrogated in CD44 KO mice reconstituted with wild-type macrophages (Hollingsworth et al., 2007). Interestingly, LMW-HA injection reduces cytokine release and the sickness behavior caused by injecting LPS into mice; this protective effect was abolished in CD44 KO mice (Muto et al., 2009). These results suggest a potential anti-inflammatory role for LMW-HA-CD44 interactions under specific conditions. Therefore, CD44 has important, yet conflicting roles in regulating inflammatory responses to HA.

The relationship between HA stability/degradation and inflammation could dramatically affect endogenous spinal cord repair. SCI increases CD44 expression (Moon et al., 2004) and LMW-HA formation (Struve et al., 2005). Although the functional significance of these changes is unknown, they could amplify or propagate post-injury neuroinflammation (see above) and gliosis. Indeed, astrocytes respond to LMW-HA by proliferating and releasing growth-inhibitory CSPGs (Struve et al., 2005). HMW-HA inhibits proliferation of cultured astrocytes, whereas hyaluronidase induces astrocyte cell division.

Decreasing DAMPs: Hyaluronan modulation as a potential SCI treatment

Since HMW-HA is a key CNS structural component and is immune inert, stabilizing the GAG or increasing its expression could improve CNS repair (though if simply

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overexpressed, HMW-HA could be degraded by endogenous inflammatory factors). HMW-HA can be used in bioengineered matrices (e.g., Austin et al., 2012; Gupta et al., 2006; Mothe et al., 2013) and may improve SCI repair, especially when combined with immune regulatory molecules or soluble factors that promote axon growth.

Two studies have reported that application of HA in gel matrices improves recovery in rat SCI models. Implantating a degradation-resistant HMW-HA hydrogel into a rat dorsal hemisection lesion reduced macrophage/microglial density, gliosis, and CSPG deposition within the first week post-injury (Khaing et al., 2011). In a separate study, Austin et al. (2012) injected hydrogel containing HMW-HA/methyl cellulose intrathecally 24h after a spinal compression injury. This treatment decreased lesion size, reactive gliosis, and IL-1α levels, and improved locomotor recovery.

Sulfated proteoglycans

Whereas HA is the only exclusively non-sulfated GAG, there are four types of sulfated GAGs: chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate (KS), and heparan sulfate (HS). Sulfated PGs are present throughout the body, but are notably enriched in the CNS (Haddock et al., 2007; Kwok et al., 2008; Sugahara and Mikami, 2007). Different PG core proteins can bind different numbers and combinations of GAG chains (Schaefer and Schaefer, 2010). For example, the SLRP decorin binds a single GAG chain while the hyalectan aggrecan includes up to 100 CS and 30 KS GAG chains. Functional domains on the core protein also vary and partly define PG function. Most PGs function in the extracellular space or are attached to the plasma membrane (Fig. 2).

Sulfated proteoglycans in the healthy spinal cord

The hyalectans versican (CS/DSPG), aggrecan (CS/KSPG), neurocan (CSPG), and brevican (CSPG) are expressed in the spinal cord (Jones et al., 2003; Lemons et al., 2003; Tang et al., 2003) (Fig. 2). The hyalectan core proteins have a characteristic three-domain structure, consisting of a central GAG-binding domain, surrounded by an HA-binding N-terminal domain and a lectin-like C-terminal domain (Schaefer and Schaefer, 2010). Through these domains, the sulfated proteoglycans interact with various membrane-bound and ECM ligands. The length of the central protein domain varies between PGs and defines the number of GAG attachment sites (Iozzo, 1998; Wu et al., 2005). Aggrecan, in particular, is enriched in healthy CNS tissue and forms enormous aggrecan-HA aggregates.

Several cell surface PGs are expressed in the healthy CNS, including members of the syndecan and glypican families (both HSPGs) (Ding et al., 2006; Hagino et al., 2003; Properzi et al., 2008). Also, the CSPG NG2 is expressed on oligodendrocyte progenitor cells and macrophages (Jones et al., 2002) (Fig. 2). These sulfated PGs can regulate diverse cellular functions, including adhesion/migration, proliferation, and differentiation.

Sulfated proteoglycans and inflammation: implications for SCI repair

Tissue injury frees GAGs from their PG backbone (Taylor and Gallo, 2006). Sulfated PGs and liberated GAGs regulate inflammatory cell responses by directly activating PRRs, by presenting or sequestering cytokines and extracellular proteins, and by modulating

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inflammatory cell migration (Gill et al., 2010). PGs and PG fragments liberated by inflammation can bind TLRs or other PRRs. During pulmonary inflammation, HS fragments bind to TLR-4 and augment inflammation (Johnson et al., 2004). Biglycan (CS/DSPG), an SLRP and TLR ligand can be released from the ECM and from activated macrophages to bind TLR-2/-4 (Schaefer et al., 2005; Schaefer and Iozzo, 2008). The hyalectan versican (CSPG) can bind TLR-2/TLR-6 and increase TNF-α expression (Kim et al., 2009). Inflammatory mediators that are elevated or newly expressed can bind intact sulfated PG components to amplify inflammation. In a model of rheumatoid arthritis, binding of complement family members to the lectin domain of aggrecan (intact or fragmented) can sustain inflammation (Melin et al., 2013).

Sulfated PGs can sequester or present chemokines, cytokines, growth factors, and MMPs. Biglycan, decorin (CS/DSPG), and fibromodulin (KSPG) bind transforming growth factor (TGF)-β with low affinity (Hildebrand et al., 1994). Decorin-TGF-β interactions can alter TGF-β intracellular signaling or cause TGF-β to become inactivated or sequestered in the ECM (Kolb et al., 2001); all of these scenarios would limit TGF-β-mediated glial scar formation and neutrophil chemotaxis. Conversely, the DS chain on decorin can enhance interferon-γ and TNF-α signaling (Bocian et al., 2013). Sulfated PGs also can control MMP localization and the ability of the enzyme to activate precursor proteins. For example, PGs can conceal MMP cleavage sites on cytokines, chemokines, and growth factors (Gill et al., 2010; Parks et al., 2004). Therefore, sulfated PGs can fine-tune activity of key bioactive molecules, and inflammation-induced dysregulation of sulfated PG composition or structure can have long-lasting impact on local cellular dynamics.

Sulfated PGs regulate migration and localization of leukocytes during inflammation (Gotte, 2003; Parish, 2006). GAG-bound chemokines immobilized on the surface of endothelia can be presented to leukocytes in the blood, promoting their transmigration into the inflammatory site. Chemokine-GAG interactions are highly specific, providing exquisite control over the location, extent, and duration of an inflammatory response. In the lung, CS and HS GAGs bind the neutrophil chemokine CXCL8 (IL-8), controlling its localization and promoting its retention and dimerization (Frevert et al., 2002; Frevert et al., 2003). This interaction favors neutrophil infiltration to sites of injury or inflammation. CD44v3 – a CD44 variant with an HS side chain – is expressed on endothelial cell surfaces, and interacts with CD11b/CD18 integrins on leukocytes to enhance their transmigration into inflamed tissue (Barbour et al., 2003; Zen et al., 2009). Therefore, PG-mediated chemokine presentation and PG binding to leukocyte adhesion receptors promotes accumulation of immune cells at inflammatory foci. After SCI, sulfated PG expression is altered around the lesion. Expression of aggrecan is decreased and its degradation products are detected (Andrews et al., 2012; Lemons et al., 2001). In contrast, neurocan, brevican, and versican increase at the lesion border, beginning at 1 dpi for up to two months post-injury (Jones et al., 2003). PGs phosphacan and NG2 also are upregulated by injury (Jones et al., 2002; Levine, 1994; McKeon et al., 1999). The SLRPs decorin and biglycan are strongly upregulated after brain injury and remain elevated for at least six months (Stichel et al., 1995), suggesting they could regulate chronic inflammation after CNS injury.

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During inflammation, the types and amounts of specific PG degradation components likely affect progression of the inflammatory response. Chondroitinase-ABC (chABC), a bacterial enzyme that specifically cleaves CS and DS GAG chains from their PG core protein (Prabhakar et al., 2006), limits the biological effects of CS/DSPGs. ChABC can degrade the endogenous chondroitin sulfate CS-A to a disaccharide CSPG product (CSPG-DS), which can modulate inflammation. In a mouse model of experimental autoimmune enchephalomyelitis (EAE), intravenous delivery of CSPG-DS led to improved EAE outcomes. Improved recovery was associated with decreased T-cell infiltration and activation (Rolls et al., 2006). In contrast, intravenous administration of intact CS-A prior to EAE symptom onset was detrimental for EAE progression, possibly by driving activation of T-cells towards EAE-propagating Th1 and Th17 cells (Zhou et al., 2010). Therefore, in EAE models, the balance between intact CS-A and its degradation product CSPG-DS have crucial implications for the intensity and duration of inflammation (for review, see (Haylock-Jacobs et al., 2011).

It is clear that many PGs restrict axon plasticity after SCI (see below); however, whether these PGs impact SCI-induced inflammation remains largely unexplored. Given the diverse functions for PGs, their altered expression/distribution, and their ability to act as DAMPs, PGs likely represent pivotal endogenous mediators of intraspinal inflammation – a function that may ultimately affect the efficiency of axon plasticity and tissue repair.

Plasticity unleashed: sulfated proteoglycan modulation as a potential SCI treatment

SCI-induced PG deposition is partially controlled by activation of the transcription factor NFκB in astrocytes. Inhibition of NFκB-mediated signaling in SCI mice, specifically in astrocytes, reduced lesion size and attenuated post-injury elevations of phosphacan and neurocan (Brambilla et al., 2005). Expression of TGF-β2, which drives fibrotic scar formation and neutrophil infiltration, also was decreased in these mice. These data illustrate how the ECM composition can be affected by manipulating inflammatory signaling after SCI.

Sulfated PG regulation of TGF-β availability could also impact cellular dynamics and tissue repair after SCI. In the injured spinal cord, TGF-β1 and TGF-β2 are highly expressed by leukocytes and astrocytes (Lagord et al., 2002; McTigue et al., 2000; O'Brien et al., 1994). Treatment of rat brain injury with multiple daily injections of antibodies that bind TGF-β1/β2 decreased astrogliosis (Moon and Fawcett, 2001). In another study, blockade of endogenous TGF-β2 (but not TGF-β1) using a bioengineered scaffold impregnated with anti-β2 antibodies, limited scar formation after SCI (King et al., 2004). By altering sulfated PG expression, it might be possible to limit availability or activity of TGF-β and limit formation of the inhibitory glial scar.

Most work on sulfated PGs after SCI has documented their potent inhibitory effects on axon growth. Bradbury et al. (2002) documented the therapeutic potential of chABC after SCI, showing that the enzyme enhances sensory and corticospinal tract axon regeneration, and improves functional sensory and locomotor recovery. As one of the most effective known treatments in experimental SCI models, chABC is often combined with other promising therapies to synergistically enhance SCI repair (reviewed by Zhao and Fawcett, 2013).

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Future clinical studies could establish whether chABC is effective after human SCI. Other sulfated PGs can also restrict (Iseki et al., 2002; Ramer et al., 2005) or promote (Davies et al., 2004) axon plasticity. Even intact sulfated PGs can modulate inflammation: macrophages cultured on aggrecan substrate induce axon dieback, an effect that is abolished by chABC-mediated aggrecan digestion (Busch et al., 2009). In addition, in an animal model of demyelination, xyloside-mediated inhibition of CSPG synthesis increased oligodendrocyte number and axon remyelination, suggesting this could be another mechanism that underlies the efficacy of CSPG-targeting therapies (Lau et al., 2012).

Few studies have addressed how sulfated PGs influence the SCI-induced inflammatory response. Sulfated PGs could have different effects on SCI-induced inflammation and repair over time. When added immediately after injury, xyloside-mediated inhibition of sulfated PG synthesis impaired locomotor recovery; in contrast, delaying xyloside addition until 2 dpi improved functional outcomes, possibly by modifying the inflammatory response (Rolls et al., 2008). In general, sulfated PGs potently elicit peripheral inflammation, so a similar role is expected in the injured CNS. Interactions between sulfated PGs and inflammatory cells in the injured CNS could enhance leukocyte migration and activation, promote glial scar formation, or influence axon plasticity. Future SCI studies should examine inflammation in transgenic mouse models in which specific sulfated PGs are removed (e.g., mice lacking aggrecan, biglycan, or syndecan-4 exist (Echtermeyer et al., 2001; Giamanco et al., 2010; Young et al., 2002)). Since sulfated PGs (and their modifications) can have vastly different effects after SCI, carefully defining the effects of specific sulfated PG variants will be instrumental in designing potential treatments. Conversely, the complexity involved in defining roles of specific PGs could be bypassed altogether by further studying the effects of molecules that inhibit expression of sulfated PGs in the first place (e.g., xyloside).

Tenascins: promiscuous proteins weave a complex narrative

The tenascin family of proteins is another key component of the CNS ECM. The mammalian tenascins include tenascin-C, -R, -W, and -X. Each tenascin subunit is composed of an N-terminal assembly domain, variable numbers of EGF and fibronectin type III repeats, and a C-terminal fibrinogen globe (Jones and Jones, 2000). The assembly domain allows for formation of tenascin oligomers (e.g., tenascin-C: hexamer; tenascin-R: dimer or trimer) (Erickson and Inglesias, 1984; Jones and Jones, 2000; Norenberg et al., 1996; Pesheva et al., 1989). The fibronectin repeats endow tenascins with the ability to interact with various extracellular molecules and cell surface receptors. For instance, specific tenascin-C fibronectin repeats bind to hyalectans, integrins, HSPGs, or TLR-4 (Midwood and Orend, 2009). Also, tenascins are highly elastic, allowing them to stretch over long distances and bind with multiple ligands (Oberhauser et al., 1998). These flexible tenascin oligomers can anchor and cross-link ECM molecules and cell surface receptors.

Tenascins in the healthy spinal cord

Of all the tenascins, only tenascin-R and tenascin-C have defined roles in the CNS: whereas tenascin-R is expressed throughout the healthy adult CNS, tenascin-C isoforms are expressed during development then become downregulated in adults, except in neuro- and

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gliogenic regions of the brain (Bartsch et al., 1992; Gotz et al., 1997; Joester and Faissner, 1999; Mitrovic et al., 1994). In the healthy adult spinal cord, tenascin-C expression is restricted to motor neurons, ependymal cells, and the pial surface (Zhang et al., 1995).

Tenascin-R has various roles in the healthy CNS. Tenascin-R is expressed by oligodendrocytes and motor neurons and also in perineuronal nets (Galtrey et al., 2008; Pesheva and Probstmeier, 2000). Its binding partners include CSPGs, contactin-1, RPTP-β/ζ, and myelin-associated glycoprotein (Milev et al., 1998; Yang et al., 1999; Zacharias and Rauch, 2006). Through these interactions, tenascin-R has been implicated in axon growth and guidance (Becker et al., 2004; Becker et al., 2000), neuron and oligodendrocyte differentiation (Pesheva et al., 1997), PNN formation/maintenance (Galtrey et al., 2008), and modulation of voltage-gated sodium channels in myelinated axons (Srinivasan et al., 1998).

Tenascins and inflammation: implications for SCI repair

Tenascin-C acts as a DAMP, eliciting activation of innate immune cells via by binding to TLR-4 (Goh et al., 2010). This was first demonstrated in a model of arthritis where inflammatory disease symptoms in tenascin-C KO mice resolved rapidly; conversely, tenascin-C injection elicited joint inflammation (Midwood et al., 2009). In macrophages isolated from patients with rheumatoid arthritis, tenascin-C triggers release of inflammatory cytokines in a TLR-4-dependent manner. Tenascin-C:TLR-4 binding can transform macrophages into potentially damaging foam cells (Liu et al., 2012) and can increase MMP-9 expression and transmigration of neutrophils (Kuriyama et al., 2011). TLR-4 stimuli upregulate tenascin-C in macrophages so tenascin-C can act in an autocrine loop to amplify acute inflammation (Goh et al., 2010). Although acute tenascin-C expression is required for proper wound healing (Sumioka et al., 2013), persistent expression can be detrimental; tenascin-C is upregulated in mice with Alzheimer's disease, and its deletion reduces neuropathology and inflammation (Xie et al., 2013). Tenascin-C is an important factor in propagating chronic inflammation and could act in a similar manner after SCI.

In addition to TLR-4, tenascin-C binds to various integrins (Jones et al., 1997; Schnapp et al., 1995; Sriramarao et al., 1993; Yokosaki et al., 1998). On inflammatory cells, these interactions regulate cell adhesion, migration, and activation. Tenascin-C interaction with α5β1 integrin restricts migration of human monocytes and neutrophils (Loike et al., 2001). Likewise, α9 integrin activation by tenascin-C triggers macrophage and neutrophil transmigration and cytokine production (Kanayama et al., 2009). Tenascin-C:integrin interactions also promote neurite outgrowth. Cultured chick motor and sensory neurons extend neurites on tenascin-C substrate; this growth is dependent on α8β1 integrin (Varnum-Finney et al., 1995). Similarly, whereas untreated rat dorsal root ganglion neurons do not extend neurites when plated onto a tenascin-C substrate, neurons engineered to overexpress α9 integrin exhibit extensive neurite outgrowth in vitro and in vivo (Andrews et al., 2009).

After SCI, *de novo* synthesis of tenascin-C occurs around the lesion by 3 dpi and its expression persists for at least 30 dpi (Zhang et al., 1997). Tenascin-C is expressed by astrocytes in the lesion border, within the dorsal columns and within the lesion epicenter. Interestingly, astrocytes cultured on tenascin-C express fewer scar-related markers and

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proliferate less than astrocytes grown on control substrates (Holley et al., 2005), implying that tenascin-C may restrict astrogliosis and scar formation after SCI.

The role of tenascin-R in inflammation has not been studied extensively, likely because tenascin-R expression is restricted to the healthy CNS in adult mammals (Pesheva and Probstmeier, 2000). After SCI, tenascin-R is upregulated around the lesion. Tenascin-R prevents adhesion of activated microglia *in vitro* and *in vivo* (Angelov et al., 1998). Also, tenascin-R elicits secretion of cytokines (e.g., TNF-α) and growth factors (e.g., brain-derived neurotrophic factor) from cultured microglia (Liao et al., 2005). Further studies must be performed to establish whether the effects of tenascin-R on microglia improve repair, and whether the ECM protein affects other immune cells or astrocytes after SCI.

Tailored tenascin targeting: potential as an SCI treatment

Data from different pre-clinical disease models indicate that tenascin-C exacerbates CNS inflammation (Jakovcevski et al., 2013), so tenascin-C might be predicted to propagate inflammation and impair recovery after SCI. However, tenascin-C KO mice show reduced recovery of locomotor function after SCI – an effect attributed to greater corticospinal tract axon dieback and reduced axon sprouting compared to wild-type mice (Chen et al., 2010). In a follow-up study using a model of lumbar spinal cord hemisection injury, global deletion of tenascin-C was associated with enhanced axonal plasticity and growth into the lesion site (Schreiber et al., 2013). The authors concluded that deleting tenascin-C conferred this benefit because of changes in the kinetics and composition of the inflammatory reaction and ECM.

Although global tenascin-C deletion impairs locomotor recovery, the precise mechanisms responsible for these changes have not been determined. Performing complementary gain-of-function experiments in wild-type mice and focused analyses of specific cellular and molecular pathways (e.g., inflammation) in KO mice are still needed. Clearly, the consistent upregulation of tenascin-C after injury and its ability to bind/activate TLRs suggest it is a candidate for controlling inflammation after SCI. If chronic tenascin-C upregulation after SCI is beneficial for axon growth but activates damaging inflammatory cascades, future experiments could differentially target these processes in space and time, or in specific cell types (e.g., conditional deletion). Moreover, the diverse functional domains of tenascin-C could have cell-specific effects. Delivery of engineered tenascin-C constructs to the site of injury might preserve the beneficial effects of tenascin-C while minimizing those effects that limit recovery after SCI.

Conclusions & implications

The intimate link between ECM structure and inflammatory activation is exemplified by the enormous changes elicited by SCI. SCI-induced ECM breakdown causes catastrophic destruction of structural meshwork that enables cell survival and functional communication (Fig.2b). ECM peptides are liberated that influence the subsequent inflammatory response. These peptides alert and provide information to glia and immune cells about the nature and intensity of damage, often through specialized PRRs. Unfortunately, in the injured CNS, many of these ECM alterations serve to amplify inflammatory responses beyond a threshold

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that leads to a chronic inflammatory state (Fig. 3). Major DAMPs released or expressed after SCI include LMW-HA, tenascin-C, and specific sulfated PG fragments. These drive expression of inflammatory cytokines and matrix modifiers, such as MMPs, which further degrade the ECM and propagate the destructive inflammatory cycle.

By restricting SCI-induced ECM degradation or expression of inflammatory ECM molecules, we may limit secondary damage and provide substrates for axon plasticity. This could involve using treatments that: 1) protect endogenous ECM structural components; 2) degrade components that elicit inflammation into less harmful (or protective) (e.g., chABC-mediated CS-A breakdown to CSPG-DS); 3)provide physical structure for tissue repair (e.g., addition of immune inert biomaterials); or 4) limit expression of potentially damaging intact ECM molecules (e.g., xyloside). Conversely, treatments that restrict inflammatory reactions after SCI could preserve remaining ECM structure. A more restrained inflammatory response may actually enhance tissue repair. Through targeting these cascades individually or in parallel, we may reduce tissue pathology, increase axon plasticity, and improve functional recovery.

Research on the relationship between ECM and inflammation after SCI is in its infancy. By examining existing data from other disease models, SCI (and CNS) researchers can gain valuable insight that could guide future research efforts. Given the consequences of the ECM-inflammation inter-relationship after SCI, discovering new treatments that alter these interactions could improve SCI repair.

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Highlights

SCI causes sustained inflammation and ECM degradation

Inflammation-induced ECM degradation liberates bioactive molecules

ECM-derived molecules activate the innate immune response

Disrupting ECM-inflammation cycle could improve repair

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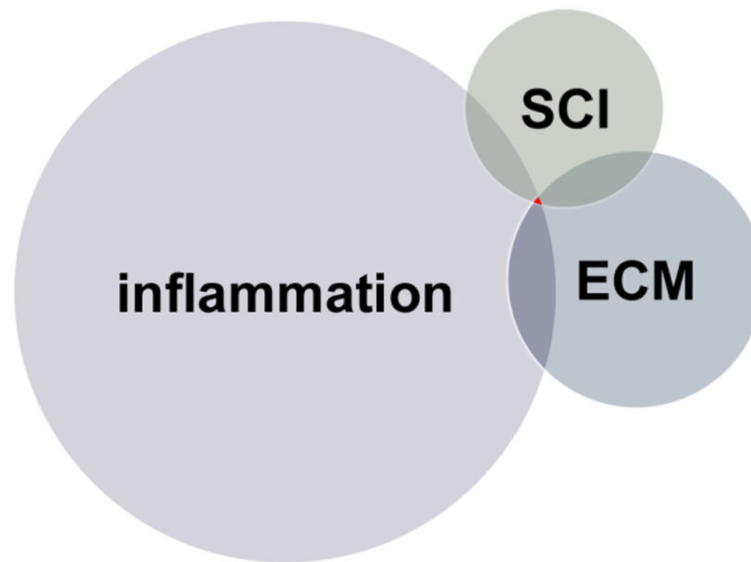

Figure 1.

Limited research publications exist with a focus on understanding the interactions between inflammation, the SCI, and ECM (red area). Searches were performed on PubMed for the words “inflammation”, “spinal cord injury”, and “extracellular matrix”, alone and in combination (as of September 2013). “Inflammation” returned ~418 000 results; “spinal cord injury” ~50 000, and “extracellular matrix” ~80 000. However, when a search combined all three terms, only 19 results were returned. Sizes of circles and overlaps are proportional to the total number of citations returned for each search (Venn diagram constructed using eulerAPE). In the context of SCI and its relationship to inflammation and the ECM, vast expanses of knowledge remain to be discovered.

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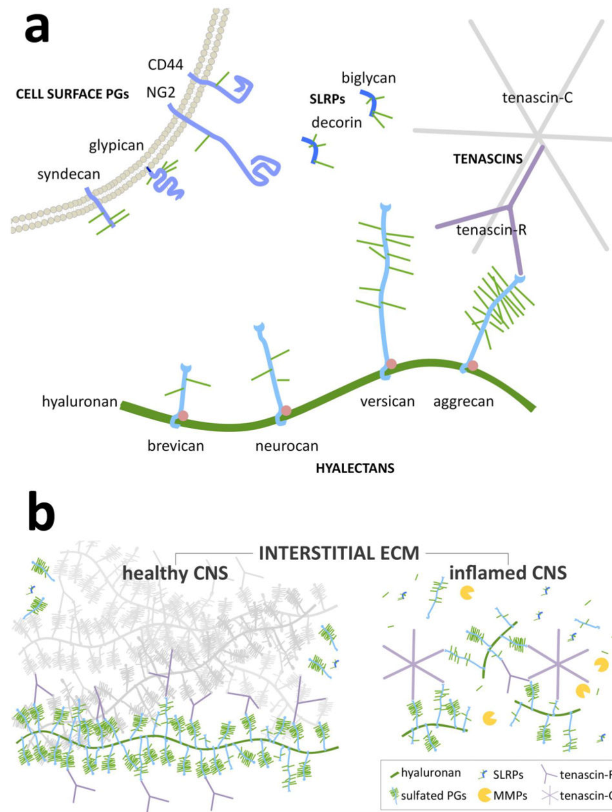

Figure 2.

(a) Major interstitial ECM components in the healthy CNS. The massive non-sulfated GAG hyaluronan (HA) is the most prominent structural component of CNS ECM. Aggrecan (CS/KSPG) and tenascin-R are also enriched in healthy ECM. The three types of PGs are hyaluronan-binding hyalectans, small leucine-rich repeat proteins (SLRPs), and cell surface PGs. GAGs (including HA) are green and are shown attached to thicker core proteins (shades of blue). The N-terminal of the hyalectans aggrecan, versican, neurocan, and brevican bind to HA with assistance from link proteins (pink circles). Small leucine-rich repeat proteins (SLRPs) exist in the extracellular space and participate in important protein-protein interactions. Cell surface PGs contain transmembrane domains or can be GPI-linked to the membrane. Some cell-surface PGs can also be released extracellularly by proteolytic processing (not shown). CD44 containing the v3 domain can bind HS or CS GAG (shown). The ECM protein tenascin-R, which exists as a dimer or trimer, can bind a lectin-like domain on the C-terminal of hyalectans. The HA-hyalectan-tenascin interactions likely underlie ECM scaffold development and maintenance in CNS ECM. Size of molecules in image approximates actual relative size (except HA, which is much longer than depicted) and GAG chain composition. Schematic is not representative of the relative abundance of these molecules in healthy CNS. Tenascin-C (grey) is not highly expressed in the healthy CNS; however, it is important after SCI. Small grey lines on cell surface PGs represent intramolecular disulfide bonds. **(b)** Model of ECM molecular interactions that contribute to scaffolding and structure adult CNS, before injury (left) and after injury (right). Massive HMW-HA GAG chains fill space and provide binding sites for hyalectans. The CS/DSPG

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aggrecan is particularly enriched in the healthy CNS, and forms large aggregates on HA GAGs. Tenascin-R interaction with lectin-like domains on hyalectans could link neighboring HA-based aggregates, creating defined 3D structure and organization of the CNS interstitial ECM. Hyalectans can also exist unbound to HA. After SCI, CNS ECM composition is changed, and its meshwork structure is fragmented. HMW-HA, which is normally ~2000 kDa, is degraded into LMW-HA (<200 kDa). As the most critical structural CNS ECM component, HA degradation causes catastrophic ECM breakdown. Aggrecan is downregulated/degraded after injury; the other hyalectans (brevican, versican, neurocan) are strongly upregulated for weeks after SCI. Hexameric tenascin-C is aberrantly expressed after SCI and could create new or different molecular interactions, and change steric configurations. SLRPs and the matrix-modifying MMPs are upregulated during inflammation. Size of molecules approximates actual scale.

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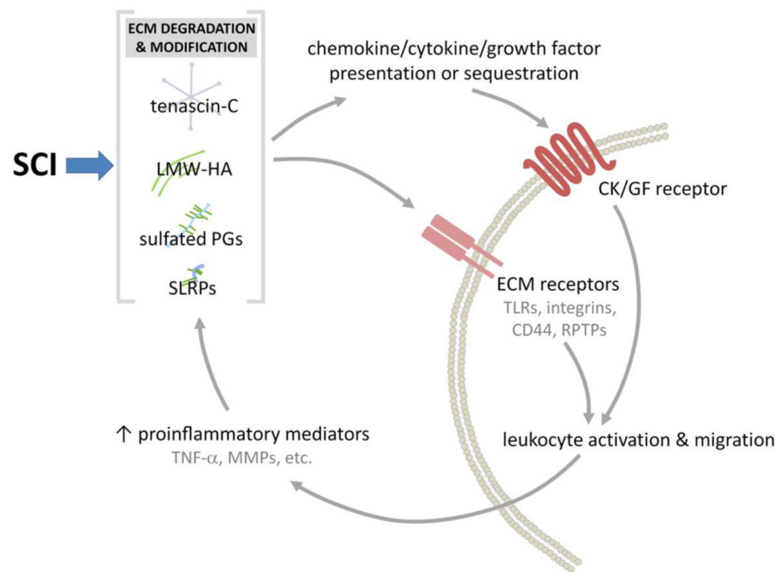

Figure 3.

SCI-induced changes in ECM composition and release of proinflammatory mediators contribute to a viscous feed-forward cycle exacerbates ECM degradation and inflammation. SCI causes degradation or nascent expression of various ECM molecules. Some of these newly-created ECM molecules act as DAMPs and can activate ECM receptors (including TLRs, integrins, CD44, and RPTPs); others can bind cytokines, chemokines, or growth factors to modulate their presentation to inflammatory cells. Activation of ECM receptors or chemokine/cytokine/growth factor receptors on leukocytes (or astrocytes and microglia) can elicit pro-inflammatory mediator secretion and migration of these cells. Accumulation of activated inflammatory cells contributes to secretion of pro-inflammatory mediators (which are also increased by other SCI-induced mechanisms, like primary trauma and hemorrhagic necrosis). Secreted pro-inflammatory mediators further modify and degrade ECM molecules.