Experimental Neurology 258 (2014) 24–34

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review

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

Andrew D. Gaudet *, Phillip G. Popovich **

Center for Brain and Spinal Cord Repair, Department of Neuroscience, College of Medicine, The Ohio State University, 670 Biomedical Research Tower, 460 West 12th Ave., Columbus, OH 43210, USA

ARTICLE INFO

Article history:
Received 18 October 2013
Revised 18 November 2013
Accepted 19 November 2013

Keywords:
Neuroinflammation
Immune
DAMP
Toll-like receptors
TLR
Hyaluronan
Tenascin
Proteoglycan

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 compositions 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.

Contents

* Correspondence to: A.D. Gaudet, Center for Brain and Spinal Cord Repair, Department of Neuroscience, The Ohio State University, 670 Biomedical Research Tower, 460 W. 12th Ave., Columbus, OH 43210, USA.
** Corresponding author.
E-mail addresses: andrew.gaudet@osumc.edu (A.D. Gaudet), phillip.popovich@osumc.edu (P.G. Popovich).

0014-4886/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.expneurol.2013.11.020

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., 2014-in 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.

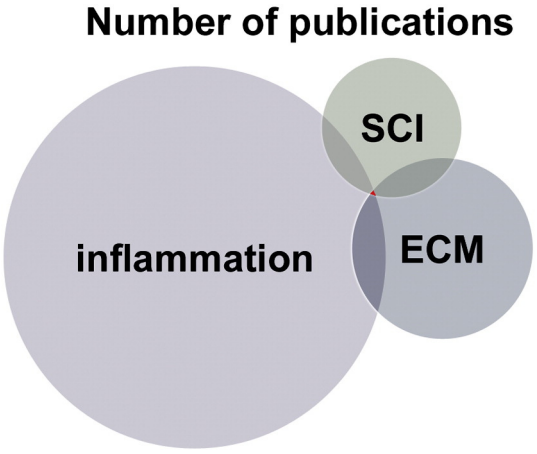

Fig. 1. Limited research publications exist with a focus on understanding the interactions between inflammation, SCI, and ECM (red area). Searches were performed on PubMed for the words "inflammation", "spinal cord injury", and "extracellular matrix", alone and in combination (as of September 2013). "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 ECM, vast expanses of knowledge remain to be discovered.

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, 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. Monocytes differentiate into macrophages that persist indefinitely at the lesion site (Kigerl et al., 2006, 2009; 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., 2006, 2009; 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., 2014-in 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.

[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: transforming growth factor; TIMP: tissue inhibitors of metalloproteinases; TLR: Toll-like receptor; TNF: tumor necrosis factor; TSP: thrombospondin.