Experimental Neurology 269 (2015) 169–187

Contents lists available at ScienceDirect

Experimental Neurology

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

Review

Chondroitin sulfate proteoglycans: Key modulators in the developing and pathologic central nervous system

Scott M. Dyck, Soheila Karimi-Abdolrezaee *

Regenerative Medicine Program, Department of Physiology and the Spinal Cord Research Centre, University of Manitoba, Winnipeg, Manitoba, Canada

ARTICLE INFO

Article history:
Received 16 December 2014
Revised 11 April 2015
Accepted 14 April 2015
Available online 18 April 2015

Keywords:
Chondroitin sulfate proteoglycans
Development
Glial scar
Extracellular matrix
Central
Nervous system
Spinal cord injury
Multiple sclerosis
Axonal regeneration
LAR
PTPσ
Plasticity
Intacellular mechanisms

ABSTRACT

Chondroitin Sulfate Proteoglycans (CSPGs) are a major component of the extracellular matrix in the central nervous system (CNS) and play critical role in the development and pathophysiology of the brain and spinal cord. Developmentally, CSPGs provide guidance cues for growth cones and contribute to the formation of neuronal boundaries in the developing CNS. Their presence in perineuronal nets plays a crucial role in the maturation of synapses and closure of critical periods by limiting synaptic plasticity. Following injury to the CNS, CSPGs are dramatically upregulated by reactive glia which form a glial scar around the lesion site. Increased level of CSPGs is a hallmark of all CNS injuries and has been shown to limit axonal plasticity, regeneration, remyelination, and conduction after injury. Additionally, CSPGs create a non-permissive milieu for cell replacement activities by limiting cell migration, survival and differentiation. Mounting evidence is currently shedding light on the potential benefits of manipulating CSPGs in combination with other therapeutic strategies to promote spinal cord repair and regeneration. Moreover, the recent discovery of multiple receptors for CSPGs provides new therapeutic targets for targeted interventions in blocking the inhibitory properties of CSPGs following injury. Here, we will provide an in depth discussion on the impact of CSPGs in normal and pathological CNS. We will also review the recent preclinical therapies that have been developed to target CSPGs in the injured CNS.

Contents

* Corresponding author at: Regenerative Medicine Program, Faculty of Medicine, University of Manitoba, 629-Basic Medical Sciences Building, 745 Bannatyne Avenue, Winnipeg, MB R3E 0J9 Canada.
E-mail address: karimis@cc.umanitoba.ca (S. Karimi-Abdolrezaee).

http://dx.doi.org/10.1016/j.expneurol.2015.04.006
0014-4886/

Introduction

The extracellular matrix (ECM) of the central nervous system (CNS) serves as supportive structure for cells which can influence cell proliferation, survival, migration, and differentiation through an abundance of signaling molecules. The neural ECM is mainly composed of hyaluronans, glycoproteins, and proteoglycans (Yamaguchi, 2000). Proteoglycans contribute to a large portion of the ECM in the CNS. These molecules contain a core protein which is bound covalently to repeating disaccharide units called glycosaminoglycans (GAG) (Sherman and Back, 2008). Proteoglycans include membrane associated heparin sulfate proteoglycans (HSPGs) and chondroitin sulfate proteoglycans (CSPGs) which are found in the pericellular space (Bandtlow and Zimmermann, 2000). Multiple studies have shown the importance of CSPGs in the organization of the ECM in the CNS, having critical roles in both its development, normal maintenance and pathology (Bandtlow and Zimmermann, 2000).

CSPGs are secreted by all cell types in the CNS and provide guidance cues for developing growth cones contributing to the formation of neuronal boundaries in the developing CNS (Brittis et al., 1992; Kurazono et al., 2001; Snow et al., 1990b). These extracellular glycoproteins are found in perineuronal nets (PNNs) which play a crucial role in the maturation of synapses and establishment and maintenance of stable connections by limiting synaptic plasticity (Matthews et al., 2002; Rhodes and Fawcett, 2004). Degradation of CSPGs in the PNN regions with chondroitinase ABC (ChABC), an enzyme known to degrade CSPGs, has been shown to reopen critical periods and synaptic plasticity in rodent models (Gogolla et al., 2009; Pizzorusso et al., 2002, 2006).

Following injury to the CNS, CSPGs expression is markedly upregulated (Pindzola et al., 1993). Injury-induced activation of astrocytes is the main source of increased deposition of CSPGs around the lesion site that results in the formation of a glial scar (Herrmann et al., 2008; Li et al., 2011; McKeon et al., 1991; Rabchevsky et al., 1998). Although initially beneficial in containing the lesion and limiting the extent of tissue damage, glial scar formation inhibits CNS repair in subacute and chronic stages of injury (for review see Karimi-Abdolrezaee and Billakanti, 2012; Sofroniew, 2009). CSPGs are considered the main inhibitory components of the glial scar (Buss et al., 2009; Cafferty et al., 2007; Grimpe and Silver, 2004) and thereby an attractive target for CNS repair. CSPGs are well studied in the context of spinal cord injury (SCI); upregulation of CSPGs following SCI is well known to limit axonal sprouting (Alilain et al., 2011; Barritt et al., 2006; Chen et al., 2002; Massey et al., 2006), regeneration (Bradbury et al., 2002; Cafferty et al., 2007; Fournier et al., 2003; Galtrey and Fawcett, 2007; Massey et al., 2008; Tom et al., 2009b) and conduction (Arvantan et al., 2009; Hunanyan et al., 2010; Petrosyan et al., 2013). Additionally, recent evidence indicates that CSPGs restrict oligodendrocyte replacement by limiting oligodendrocyte precursor cell (OPC) maturation *in vitro* (Pendleton et al., 2013) and driving the fate of neural precursor cells (NPCs) to an astrocytic lineage at the expense of oligodendrocyte differentiation following SCI (Karimi-Abdolrezaee et al., 2010, 2012). Studies on demyelination lesions also shows a negative correlation between the presence of CSPGs deposits around the lesion and success of remyelination (Lau et al., 2012, 2013). Several strategies have been utilized to manipulate CSPGs in SCI. Current treatment with chondroitinase ABC (ChABC) that cleaves inhibitory GAG chains from CSPGs has shown promising results in promoting axonal sprouting (Barritt et al., 2006; Cafferty et al., 2008; Wang et al., 2011a), regeneration (Bradbury et al., 2002; Houle et al., 2006; Moon et al., 2001; Tom et al., 2009b) and enhancing the outcomes of cell replacement strategies (Karimi-Abdolrezaee et al., 2010, 2012) following SCI. Recent studies also indicate that therapeutic approaches to inhibit CSPGs receptors can promote recovery from SCI (Fisher et al., 2011; Fry et al., 2010; Lang et al., 2015).

In this review, we will highlight the functional impact of CSPGs in development and pathology of the CNS and discuss its role in modulating neural differentiation, plasticity, neuroinflammation, regeneration, and cell replacement. Additionally, we will review the current known mechanisms of CSPGs including the recent discovery of four CSPGs receptors (Dickendesher et al., 2012; Fisher et al., 2011; Shen et al., 2009). Based on the emerging evidence from preclinical studies, manipulations of CSPGs holds promise as a therapeutic target for repairing the pathologic CNS.

CSPGs: an overview

CSPGs are a critical component of the ECM. Major components of the ECM in humans include adhesive glycoproteins (e.g., fibronectin, laminin, and tenascin), fibrous proteins (e.g., collagens and elastin), GAGs (e.g., hyaluronan, CSPGs, and HSPGs), as well as a wide variety of secreted growth factors and other molecules (for review see Galtrey and Fawcett, 2007). The ECM of the CNS is unique in that it contains a small amount of fibrous proteins and high amounts of GAGs. Major components include hyaluronan, CSPGs, link proteins, and tenascins (Deepa et al., 2006; Yamaguchi, 2000). CSPGs contain a core protein attached to one or more chondroitin sulfate glycosaminoglycans (CS-GAGs) (Sherman and Back, 2008). CSPGs have been shown to interact with hyaluronan, via the N terminal domain, and to tenascin, via the C terminal domain (Yamaguchi, 2000). The interaction between hyaluronan and CSPGs is stabilized by link proteins (Binette et al., 1994). CSPGs core proteins contribute minimally to their biological activity and the GAGs attached to the core proteins of CSPGs are the main functional component of these proteoglycans (Sherman and Back, 2008).

Structure of CSPGs

CSPGs represent a structurally diverse group. Their GAG carbohydrate chain consists of a long repeating disaccharide units containing