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Inhibitors of myelination: ECM changes, CSPGs and PTPs

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Abstract

After inflammation-induced demyelination, such as in the disease multiple sclerosis, endogenous remyelination often fails. However, in animal models of demyelination induced with toxins, remyelination can be quite robust. A significant difference between inflammation-induced and toxin-induced demyelination is the response of local cells within the lesion, including astrocytes, oligodendrocytes, microglia/macrophages, and NG2+ cells, which respond to inflammatory stimuli with increased extracellular matrix (ECM) protein and chondroitin sulfate proteoglycan (CSPG) production and deposition. Here, we summarize current knowledge of ECM changes in demyelinating lesions, as well as oligodendrocyte responses to aberrant ECM proteins and CSPGs after various types of demyelinating insults. The discovery that CSPGs act through the receptor protein tyrosine phosphatase sigma (PTPσ) and the Rho-ROCK pathway to inhibit oligodendrocyte process extension and myelination, but not oligodendrocyte differentiation (Pendleton et al., Experimental Neurology (2013) vol. 247, pp. 113-121), highlights the need to better understand the ECM changes that accompany demyelination and their influence on oligodendrocytes and effective remyelination.

Introduction

A hallmark of central nervous system (CNS) injury is the activation and proliferation of local glial cells, including microglia, astrocytes, and oligodendrocytes. Reactive glial cells, in particular astrocytes and microglia, contribute to formation of the so-called ‘glial scar’, by depositing extracellular matrix proteins and upregulating molecules that are often inhibitory to regeneration (Fitch and Silver, 2008; Galtrey et al., 2008; Morgenstern et al., 2002; Rhodes and Fawcett, 2004; Sherman and Back, 2008). High levels of chondroitin sulfate proteoglycans (CSPGs) are present in the scar after many types of CNS insults including spinal cord injury (SCI; Jones et al., 2003; Lemons et al., 1999; McTigue et al., 2001; Tang et al., 2003), epilepsy (Kurazono et al., 2001; Okamoto et al., 2003), Alzheimer's disease (DeWitt et al., 1993; Snow et al., 1988; 1990), Parkinson's disease (DeWitt et al., 1994), stroke (Carmichael et al., 2005; Deguchi et al., 2005) and multiple sclerosis (MS; Mohan et al., 2010; Sobel, 2001; Sobel and Ahmed, 2001). Deposition of CSPGs post-injury may be a

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protective CNS response that contains the damage and spares intact tissue from further injury (Galtrey and Fawcett, 2007; Silver and Miller, 2004; Yiu and He, 2006). However, that CSPG response often inhibits both regeneration of axons and remyelination by oligodendrocytes (Davies et al., 1999; Fitch and Silver, 2008; Jones et al., 2003; Lau et al., 2012; Sandvig et al., 2004; Schmalfeldt et al., 2000; Sherman and Back, 2008; Siebert and Osterhout, 2011; Siebert et al., 2011; and others).

In the September issue of Experimental Neurology (2013, vol. 247, pp. 113-121), Pendleton et al. shed light on why remyelination after CNS damage is often incomplete, despite the generation of new oligodendroglia at injury sites. They investigated the effects of several CSPGs (aggrecan, neurocan, and NG2) on oligodendrocyte differentiation, process outgrowth, and myelination. CSPGs inhibited both oligodendrocyte progenitor cells (OPCs) process outgrowth and myelination of DRG neurons in co-culture, without altering OPC differentiation when cultured alone. The inhibition was mediated, at least partially, through the receptor protein tyrosine phosphatase sigma (PTPσ) and the Rho-ROCK pathway. Strategies that target PTPσ to promote remyelination may prove to be beneficial in demyelinating disease such as MS.

CSPGs, the extracellular matrix, and myelination

CSPGs consist of a protein core and a varying number of long sulfated unbranched negatively charged glycosaminoglycan (GAG) chains made up of repeating disaccharide units. For discussions of CSPG structure and function see the many excellent CSPG reviews (Bandtlow and Zimmermann, 2000; Bradbury and Carter, 2011; Busch and Silver, 2007; Fitch and Silver, 2008; Galtrey and Fawcett, 2007; Kwok et al., 2012; Morgenstern et al., 2002; Properzi et al., 2003; Schaefer and Schaefer, 2010; Sharma et al., 2012; Sherman and Back, 2008; Zimmermann and Dours-Zimmermann, 2008). Protein cores with chondroitin sulfate GAGs include the hyalectans (aggrecan, brevican, neurocan, versican), NG2, phosphacan, appican, decorin, biglycan and neuroglycan C. In general, CSPGs have an inhibitory impact on cells (Carbonetto et al., 1983; Iaci et al., 2007; Inatani et al., 2001; Siebert and Osterhout, 2011; Turner et al., 1989 and others; Verna et al., 1989; and others). The sulfation pattern of the GAG chains influences CSPG inhibition, although the core proteins themselves also contribute to proteoglycan function (Castillo et al., 1998; Gama et al., 2006; Garwood et al., 1999; Inatani et al., 2001; Laabs et al., 2007; Nakanishi et al., 2006; Schmalfeldt et al., 2000; Sherman and Back, 2008; Snow et al., 1990). CSPGs bind to cell surface receptors to activate growth-inhibitory pathways, but also interact directly with growth factors, cytokines, and guidance molecules to control their availability to differentiating neurons and glia (Bandtlow and Zimmermann, 2000; Fitch and Silver, 1997; Sanes, 1989; Schaefer and Schaefer, 2010; Schwartz and Domowicz, 2004; Sirko et al., 2010; Yamaguchi, 2000; Zimmermann and Dours-Zimmermann, 2008). Hyalectans, particularly neurocan and brevican, are the predominant CNS CSPGs, while versican and aggrecan are throughout the body. The proteoglycan NG2 is also highly expressed in the CNS, primarily by OPCs and pericytes of the vasculature (Chang et al., 2000; Nishiyama et al., 1999; Ozerdem et al., 2001).

It is difficult to discuss the role of CSPGs in development or after injury without discussing the overall ECM environment. The CNS ECM provides critical structural support, but is also an important signaling scaffold that controls distribution and presentation of soluble molecules in the ECM (Bandtlow and Zimmermann, 2000 and others; Fitch and Silver, 1997; Sanes, 1989; Schaefer and Schaefer, 2010; Schwartz and Domowicz, 2004; Sirko et al., 2010; Yamaguchi, 2000; Zimmermann and Dours-Zimmermann, 2008) and others). It is enriched in proteoglycans and glycoproteins, particularly CSPGs, tenascins, and link proteins that bind hyalectans to hyaluronan, stabilizing ECM structure (Lundell et al., 2004; Yamaguchi, 2000). Collagen I and the small, leucine-rich proteoglycan, decorin, are widespread throughout the ECM, while collagen IV and laminin are expressed in basal laminae (Gordon and Hahn, 2010; Hanemann et al., 1993; Kappler et al., 1998; Villanova et al., 1997; Yurchenco et al., 1992). Fibronectin is expressed in neuroepithelial cells of the ventricular zone and radial glial cells during development, as well as the vasculature (Jones et al., 1982; Pearlman and Sheppard, 1996). During development, the ECM regulates neuronal and glial migration and process outgrowth, with early matrix being loose and allowing extensive cell migration (Carbonetto, 1984; Franco and Müller, 2011; Rutka et al., 1988; Liu et al., 2006; Pearlman and Sheppard, 1996; Sanes, 1989; Schwartz and Domowicz, 2004; and many others). With CNS maturation, the ECM composition changes to form a firmer matrix (Zimmermann and Dours-Zimmermann, 2008).

Besides being critical for CNS architecture and structure, CSPGs play important roles in CNS myelination. In developing white matter tracts, versican and brevican are most abundant (Ogawa et al., 2001; Schmalfeldt et al., 1998), along with the ECM glycoprotein tenascin-R, which is deposited by developing oligodendrocytes (Pesheva and Probstmeier, 2000; Pesheva et al., 1989). During myelination, brevican expression peaks as oligodendrocytes extend membrane processes to ensheath axons (Ogawa et al., 2001). Brevican and tenascin-R are also present at the nodes of Ranvier on large diameter myelinated axons, and the association of tenascin-R with nodes is dependent on brevican expression (Bekku et al., 2009). Thus, node of Ranvier formation is dependent on proper CSPG expression. Oligodendrocytes initially express brevican, but after myelination is complete, brevican is expressed by astrocytes rather than oligodendrocytes in white matter tracts (Ogawa et al., 2001); astrocytes also express numerous other proteins and proteoglycans that influence myelination (Barnett and Linington, 2012; Buttery and ffrench-Constant, 1999; Nash et al., 2010; Watkins et al., 2008; Williams et al., 2007).

CNS injury and CSPG production by astrocytes and oligodendrocytes

After CNS injury, the glial scar contains both reactive astrocytes and recruited OPCs. Astrocytes secrete many ECM molecules during this time, including laminin, fibronectin, and tenascin-C (Liesi et al., 1984; Stoffels et al., 2013; Tang et al., 2003; Zhao et al., 2009). Astrocytes and OPCs both upregulate inhibitory CSPGs, including brevican, neurocan, phosphacan, and versican (Jones et al., 2003; Massey et al., 2008; Rhodes and Fawcett, 2004; Tang et al., 2003), and OPCs also upregulate NG2 (Jones et al., 2002; Rhodes et al., 2006; Tan et al., 2005). Although reactive gliosis becomes a barrier to axon regeneration, it is an important protective response. If dividing astrocytes are ablated after SCI, the blood brain barrier (BBB) fails to reform, neuronal and oligodendroglial cell death increases, the

immune response is intensified, the lesion volume is greater, and motor defects worsen (Faulkner et al., 2004). Glial scar formation also initiates revascularization of the injured area, which supplies the surrounding tissue with much needed nutritional, metabolic, and trophic support (Liberto et al., 2004). In contrast to the reactive responses of microglia and astrocytes, OPCs respond to injury with increased NG2 proteoglycan expression only if there is an opening in the BBB, and this response is mediated by entering platelets and macrophages (McTigue et al., 2001; 2006; Rhodes et al., 2006; Tripathi and McTigue, 2007). The role of NG2 expression by OPCs after injury is less clear than that of CSPG expression by astrocytes. NG2 has been reported to inhibit axonal growth (Chen et al., 2002; Jones et al., 2003); however other reports suggest that NG2 may be inhibitory only to specific subpopulations of neurons, and it may actually support neuronal outgrowth in some contexts (Hossain-Ibrahim et al., 2007; Niehaus et al., 1999; Schneider et al., 2001; Yang et al., 2006).

ECM changes and demyelination

In contrast to the dearth of neuronal regeneration after injury, oligodendrocytes have a remarkable ability to regenerate damaged myelin sheaths that surround axons. In MS, repair does occur, and remyelination is seen in shadow plaques (Chang et al., 2012; Raine and Wu, 1993; and others). As the disease progresses, however, remyelination becomes less efficient, resulting in chronic demyelination, progressive neurodegeneration and increased clinical disability (Chang et al., 2002; Franklin, 2002). It is unlikely that this inability to remyelinate results from an absence of OPCs in the adult CNS, as OPCs are present in elderly patients even after decades of disease (Chang et al., 2012; 2002). Thus, it appears that this remyelination failure results from changes in the neurons themselves or in the extracellular environment of the CNS, and understanding these differences may yield valuable insights into the remyelination patterns seen in MS.

ECM changes and demyelination: in vivo animal models

Animal models of demyelination are studied for insight into the demyelination/remyelination processes in MS (Back et al., 2005; Bannerman et al., 2006; Fancy et al., 2011; Franklin et al., 1996; 1991; Harrington et al., 2010; Kawczak et al., 1998; Kotter et al., 2001; Lock et al., 2002; Mann et al., 2012; Nait-Oumesmar et al., 1999; Schonberg et al., 2007; Shields et al., 2000; Skihar et al., 2009; Sloane et al., 2010; Talbott et al., 2005; Ulrich and Bornstein, 1973; Zhao et al., 2009). Toxin-induced demyelination following lysolecithin injection into the spinal cord or corpus callosum, or ethidium bromide injection into the cerebellar peduncles results in minimal immune response and robust remyelination (Back et al., 2005; Franklin et al., 1996; 1991; Harrington et al., 2010; Kotter et al., 2001; Nait-Oumesmar et al., 1999; Schonberg et al., 2007; Shields et al., 2000; Skihar et al., 2009; Sloane et al., 2010; Talbott et al., 2005; Zhao et al., 2009). By contrast, immune-mediated demyelination models including experimental allergic encephalomyelitis (EAE) and Theiler's murine encephalomyelitis (TME) often have insufficient remyelination of demyelinated areas (Bannerman et al., 2006; Haist et al., 2012; Kawczak et al., 1998; Lock et al., 2002; Mann et al., 2012; Massa et al., 2002; Ulrich and Bornstein, 1973). Toxin-induced models create precise focal lesions and are used to study remyelination per se, but immune-mediated models more closely resemble the lesions seen in MS. Although none of

the animal models recapitulates MS completely, EAE has been effective at identifying several MS therapies, including glatiramer acetate, mitoxantrone, and natalizumab (for review see Denic et al., 2011). After demyelination in either type of model, the composition of the ECM changes, and each model has important spatiotemporal differences in the specific ECM changes. These differences may underlie the relative rates of remyelination success seen across demyelination models.

After injection of ethidium bromide into the cerebellar peduncles, rapid demyelination occurs, quickly followed by robust remyelination (Zhao et al., 2009). Following demyelination, OPCs upregulate αV integrin and migrate into the lesion. In early lesions, invading macrophages also express αV integrin, although at lower levels (Zhao et al., 2009). Once OPC proliferation is complete and OPCs begin to differentiate, αV integrin expression decreases. During early repair, many ECM proteins are upregulated in the lesion, including those that bind αV integrins, such as osteopontin, vitronectin, and fibronectin, which has the potential to impact OPC responses significantly (Zhao et al., 2009; 2008). Fibronectin leaks in from the vasculature, which may initially be permissive for OPC survival and migration (Hu et al., 2009; Stoffels et al., 2013). In early lesions, upregulation of tenascin-C by astrocytes and of vitronectin by microglia/macrophages may be supportive of OPC migration into lesions (Milner et al., 1996). At later time points, increased expression of tenascin-R and laminin-2 (merosin) correlates with OPC differentiation and axonal contact.

In immune-mediated demyelination models, there are also ECM protein and CSPG changes (Haist et al., 2012; Haylock-Jacobs et al., 2011; Sajad et al., 2011). Normally, meninges and blood vessels express collagen IV, entactin, and laminin, while meningeal connective tissues express collagen I, decorin, and fibronectin. Tenascin-C is expressed diffusely though both the grey and white matter and weakly in the meninges. After demyelination, in contrast to toxin-induced lesions, there is prolonged activation of astrocytes, and the basement membrane molecules collagen IV and laminin deposit perivascularly and accumulate in the lesions (Haist et al., 2012). Non-basement membrane molecules only accumulate in nonvascular patterns in demyelinated areas; tenascin-C is deposited first, followed by collagen, decorin and neurocan (Haist et al., 2012). Phosphacan progressively decreases over the course of TME. Fibronectin only increases in the lesion at late stages and is sometimes seen in the cytoplasm of macrophages

A significant difference between toxin- and immune-induced demyelination is astrocyte ECM deposition. In the absence of inflammation, astrocytes secrete ECM proteins that are supportive to OPC migration, survival, and proliferation. Neurons then respond with increased merosin secretion, which supports continued oligodendrocyte survival, maturation and myelination (Buttery and ffrench-Constant, 1999). In contrast, in the face of prolonged inflammation in EAE and TME, astrocytes change their ECM molecule secretion to create a barrier that could halt the immune assault (Haylock-Jacobs et al., 2011; Zhou et al., 2010). A consequence of this altered ECM deposition and increased CSPG level is inhibition of oligodendrocyte process outgrowth, differentiation, and myelination, which could underlie the decreased remyelination (Lau et al., 2012; Pendleton et al., 2013; Siebert and Osterhout, 2011).

Developing effective remyelination therapies will require understanding astrocyte responses to inflammation in demyelinated lesions. Since current MS therapies dampen the inflammatory response in patients, reducing the immune barrier function of the astrocyte-secreted ECM molecules could be an option. Thus, new repair therapies will require strategies to decrease inhibitory CSPG production by astrocytes and increase the deposition of ECM molecules that promote oligodendrocyte migration, maturation, survival and ultimately the myelination of neurons, as seen in non-immune mediated demyelination paradigms.

ECM changes and demyelination: multiple sclerosis

In MS patients, ECM composition changes occur in both active and chronic lesions, as well as in the normal appearing white matter (Gutowski et al., 1999; Mohan et al., 2010; Sobel, 2001; 1998; Sobel and Ahmed, 2001). ECM molecules that normally contribute to basement membranes, including laminin, collagen type IV, as well as heparan sulfate proteoglycans (HSPGs) and fibronectin, are abnormally expressed and form dense networks in active, but not pre-active or chronic MS lesions (Kurazono et al., 2001; Okamoto et al., 2003; van Horssen et al., 2006). In active MS lesions, both extracellular fibronectin and fibronectin deposited on vessel walls increases and the amount of fibronectin correlates with the degree of inflammation (Sobel and Mitchell, 1989). Macrophages express fibronectin receptors, as well as fibronectin mRNA, so fibronectin may be important for macrophage migration into the CNS. Astrocytes also synthesize fibronectin, which may be part of the gliosis in MS lesions. Fibronectin does not appear to impede remyelination unless it forms aggregates, which occurs in MS lesions but not in toxin-induced demyelination (Stoffels et al., 2013; Zhao et al., 2009). In active, but not chronic, demyelinated MS lesions, dystrophic, demyelinated axons, astrocytes and the microvasculature also express vitronectin (DeWitt et al., 1994; Sobel et al., 1995).

Besides adding to ECM structural stability, tenascins influence oligodendrocyte survival, proliferation, migration, differentiation and morphological maturation (Czopka et al., 2009; Garcion et al., 2001; Garwood et al., 2004; Kiernan et al., 1996). In acute MS lesions, tenascin-C and tenascin-R glycoproteins are lost, and the loss extends into the normal appearing white matter (Gutowski et al., 1999). The loss of tenascin-R and tenascin-C in demyelinated lesions coincides with the greatest density of macrophages (Gutowski et al., 1999). In subacute lesions, tenascin-C and tenascin-R immunoreactive astrocytes are present, particularly in the center of the lesion, while in chronic lesions, tenascin-C and tenascin-R are expressed at levels comparable to the adjacent white matter. Tenascins influence the reactivity of astrocytes, which are a major source of CSPGs after injury (Galtrey and Fawcett, 2007; Holley et al., 2005; Silver and Miller, 2004; Yiu and He, 2006), suggesting that the spatiotemporal expression of tenascin-C and tenascin-R in lesions may be important determinants of remyelination.

CSPGs themselves are also upregulated in demyelinated MS lesions (Haist et al., 2012; Haylock-Jacobs et al., 2011; Lau et al., 2012; Sobel and Ahmed, 2001; van Horssen et al., 2006). Specifically, astrocytes at the edge of active MS lesions upregulate versican, aggrecan, and neurocan. These CSPGs are decreased in the lesion center, and mostly absent

from inactive lesions, while phosphacan is unaltered (Crespo et al., 2007; Galtrey and Fawcett, 2007; Rhodes and Fawcett, 2004; Sobel and Ahmed, 2001; van Horssen et al., 2006). It is intriguing to note that several of these same CSPGs, namely neurocan, aggrecan and NG2, impair oligodendrocyte process outgrowth and myelination (Lau et al., 2012; Pendleton et al., 2013; Siebert and Osterhout, 2011).

Aberrant deposition of ECM matrix molecules occurs by leakage from the damaged vasculature and BBB disruption, and by altered secretion from reactive astrocytes. The aberrant deposition of ECM molecules then creates a lesion environment that is inhibitory to oligodendrocyte process extension and remyelination of axons, which in turn leads to increasing neuronal damage as the disease progresses. These are dynamic processes and the level of each ECM molecule changes as lesions progress and recover. The degree of remyelination likely results from the net ratios of supportive (unaggregated fibronectin, merosin) and inhibitory (CSPGs, tenascins, fibronectin aggregates) ECM molecules within and around the lesion.

These ECM changes raise the question of whether ECM deposition impacts leukocyte migration. In active lesions, the integrin receptors for vitronectin ($\alpha V\beta 1$) are increased on macrophages and glial cells, as well as on platelets and endothelial cells (Sobel et al., 1995; Zhao et al., 2009; 2008). Vitronectin or fibronectin deposition promotes B cell migration and activation in vitro (Salcedo and Patarroyo, 1995; Shibayama et al., 1995). Thus, ECM changes may allow immune cells to enter and invade lesions, and may even aid early OPC migration into demyelinated areas, while inhibiting later neuronal and oligodendroglia regeneration responses. The data suggest that leukocyte and macrophage invasion results in the destruction of the normal ECM in CNS white and grey matter.

Oligodendrocyte responses to demyelination and CSPGs

After injury, reactive astrocytes and macrophages upregulate CSPGs, and OPCs themselves become reactive, change morphologically, and increase expression of CSPGs, such as NG2 and versican (Chen et al., 2002; Tan et al., 2006). Thus, oligodendrocytes are exposed to very high levels of CSPGs after CNS damage. Following lysolecithin- or SCI-induced demyelination, CSPGs negatively influence oligodendrocyte remyelination of spared axons (Lau et al., 2012; Pendleton et al., 2013; Siebert et al., 2011). Oligodendrocytes share with neurons many of the inhibitory effects, receptors, and downstream signaling events in response to CSPGs. Thus, extensive information can be gleaned from the effects of CSPGs on neurons. Neurons can bind CSPGs via several recently identified receptors, such as the Nogo receptor family members, NgR1 and NgR2, and the leukocyte common antigen-related subfamily of receptor protein tyrosine phosphatases, LAR and PTPσ (Dickendesher et al., 2012; Fisher et al., 2011; Shen et al., 2009). PTPσ was originally identified as a neuronal receptor for heparan sulfate proteoglycans (HSPGs; Aricescu et al., 2002). PTPσ-HSPG binding plays a positive role in axon guidance promoting outgrowth and synapse formation (Aricescu et al., 2002; Coles et al., 2011; Horn et al., 2012), while PTPσ-CSPG binding mediates inhibition of axonal growth and neural regeneration (Coles et al., 2011; Shen et al., 2009). When bound to HSPGs, PTPσ oligomers expressed by neurons sequester in microdomains containing high phosphotyrosine-modified protein, which promotes

neuronal outgrowth. On the other hand, when bound to CSPGs, PTPσ is not tightly oligomerized and increased phosphatase activity reduces phosphorylation and inhibits axon growth (Coles et al., 2011). Whether or not PTPσ exhibits contrasting effects on oligodendrocyte process outgrowth and myelination when bound to HSPGs, as seen in neurons, remains to be determined.

Although it has been known that oligodendrocytes express PTPσ (Chesini et al., 2011; Harroch et al., 2002; Kuboyama et al., 2012; Lamprianou et al., 2011; Lamprianou and Harroch, 2006), the role of PTPσ in oligodendrocyte development was not reported until the current study by Pendleton et al. (2013). In this study, they show that CSPGs bound to PTPσ inhibit oligodendroglial process outgrowth. Oligodendrocytes cultured alone on mixtures of laminin and either aggrecan, neurocan, or NG2 had reduced process outgrowth. CSPG digestion with chondroitinase ABC (chABC), which cleaves the GAG side chains from the core protein (Bradbury et al., 2002; Huang et al., 2006), reduced the inhibition on process extension. Knockdown of PTPσ also reversed the inhibition of process outgrowth on CSPGs. PTPσ-CSPG binding also regulated DRG axon myelination in co-culture. Thus, pretreatment of wild type oligodendrocytes with the CSPG aggrecan reduced myelination of DRG axons, but aggrecan did not reduce axon myelination by PTPσ-/- oligodendrocytes. Intriguingly, OPCs cultured on aggregan did not reduce their expression of differentiation markers. Thus, PTPσ activation by CSPGs likely impedes myelination by interfering with process extension towards axons, rather than by inhibiting oligodendrocyte differentiation directly. As PTPσ has also been shown to be an important neuronal receptor for mediating the inhibitory actions of CSPGs on neuronal regeneration (Fry et al., 2010; Shen et al., 2009), these results suggest that strategies targeting PTPσ to promote axonal regeneration may have the added benefit of promoting remyelination. In addition, PTPσ may prove to be a viable new therapeutic target for demyelinating disease such as MS.

OPCs express low levels of PTPs, which increase as they mature into oligodendrocytes (Ranjan and Hudson, 1996). Each PTP has a unique impact on oligodendrocyte development. Early OPCs express PTPα, which is dramatically upregulated as the cells mature. PTPβ/ζ and PTPγ also increase in differentiated oligodendrocytes. Alternative splicing of PTPβ/ζ generates a secreted extracellular domain product, also known as phosphacan (Maurel et al., 1994). Only mature oligodendrocytes express PTPε, which is closely related to PTPα. PTP-specific knockout studies demonstrate that each PTP exerts control over a distinct set of oligodendrocyte activities. PTPα has a negative effect on proliferation and a positive effect on differentiation. Cultures of PTPα-/- OPCs have enhanced proliferation and survival and reduced growth factor dependence. PTPα-/- mice have increased oligodendrocyte lineage cells in the embryonic forebrain and delayed OPC development, with fewer mature oligodendrocytes in the early postnatal corpus callosum (Wang et al., 2012). In contrast, PTPβ/ζ negatively regulates proliferation as well as oligodendrocyte differentiation. PTPβ/ζ-deficient mice have increased proliferation and early differentiation of OPCs in both the brain and optic nerve. At P10, PTPβ/ζ- /- mice have more myelinated axons in the corpus callosum, though normal levels by 3 months of age (Kuboyama et al., 2012; Wang et al., 2012). PTPε, on the other hand, appears to promote oligodendrocyte differentiation and myelination. While most CNS myelin tracts are normal in mice expressing an inactive form of PTPε, there are lower numbers of differentiated

oligodendrocytes and delayed myelination of the optic nerve (Muja et al., 2004). However, since transgene expression also occurs in the retinal ganglion cells whose axons were abnormally myelinated, disruption of PTPε signaling occurred in both cell types, complicating interpretation. PTPβ/ζ is important for remyelination by oligodendrocytes following demyelination in EAE. However, there are conflicting reports about whether the suppression of PTPβ/ζ is beneficial and promotes oligodendrocyte survival (Kuboyama et al., 2012), or detrimental and increases apoptosis of mature oligodendrocytes (Harroch et al., 2002). In culture of human cells, PTPβ/ζ suppression maintains the self-renewal capacity of OPCs through activation of the β-catenin/TCF transcription (McClain et al., 2012).

Many of the downstream pathways regulated by PTPs in oligodendrocytes are known to influence oligodendrocyte proliferation, survival, differentiation, and myelination, in particular signaling through Rho, Rac, Cdc42 and the Rho-associated protein kinase (ROCK). For example, major substrates of PTPα are the Src family kinases (Pallen, 2003). In primary OPCs, PTPα acts through the Src kinase Fyn to negatively regulate the activity of Rho, Rac1, and Cdc42, thereby limiting proliferation and promoting differentiation (Pallen, 2003; Wang et al., 2012). In contrast, in differentiating oligodendrocytes, PTPα positively regulates Rac1 and Cdc42, while negatively regulating Rho signaling, which promotes cytoskeletal rearrangements necessary for process extension and maturation (Wang et al., 2012; 2009). Thus, the effect of PTPα on downstream GTPase activity varies in proliferating versus differentiating oligodendroglial cells. These changes in PTP responses could result from extracellular activation of other transmembrane receptors, such as growth factor receptor receptors, or integrins, as PTPs can be activated or inactivated by both of these receptor types (Mattila et al., 2005; Schlessinger et al., 1995; Wang et al., 2009). CSPG-mediated inhibition of oligodendrocyte process outgrowth acts through ROCK, and in vitro studies show that inhibition of ROCK can reverse the inhibitory effects of CSPGs on oligodendrocyte process outgrowth and differentiation (Pendleton et al., 2013; Siebert and Osterhout, 2011). Since OPCs express only low levels of CSPG receptors, they are able to migrate into active lesion sites, despite the high CSPG concentration. As OPCs mature and increase PTPσ expression, they would become more responsive to CSPGs present in the lesion that inhibit oligodendrocyte process extension and maturation. If PTPσ also has distinct roles at different phases of oligodendrocyte development, as the results of Pendleton et al. (2013) suggest, it will be important to determine these differences prior to considering PTPσ in oligodendrocytes as a therapeutic target.

Clinical implications

Multiple studies have demonstrated the benefit of reduced CSPG accumulation and signaling for both axonal regeneration and remyelination (Bradbury et al., 2002; Davies et al., 2004; Huang et al., 2006; Karimi-Abdolrezaee et al., 2012; Siebert et al., 2011; Soleman et al., 2012; Starkey et al., 2012; Tester and Howland, 2008). After injury, chABC-induced removal of the GAG side chains from the core CSPG protein reverses the inhibited axonal regeneration and improves functional outcomes in SCI (Barritt et al., 2006; Bradbury et al., 2002; Huang et al., 2006; Karimi-Abdolrezaee et al., 2012; Siebert et al., 2011; Soleman et al., 2012; Starkey et al., 2012; Tester and Howland, 2008; and others). As noted above, in injury paradigms, CSPGs also inhibit oligodendrocyte differentiation and remyelination.

Thus, reducing CSPG deposition can be beneficial for remyelination by enhancing OPC migration into the injury site and promoting endogenous OPC differentiation and maturation (Karimi-Abdolrezaee et al., 2012; Lau et al., 2012; Pendleton et al., 2013; Siebert et al., 2011; Siebert and Osterhout, 2011). Following spinal contusion injury, an immediate local injection of chABC at the site of SCI results in CSPG degradation and increases the number of migratory OPCs near the injury site, particularly at the lesion periphery (Siebert et al., 2011). Intrathecal application of chABC four days after SCI, along with growth factor treatment, increases the proliferation of neural stem cells in the cord, and promotes their differentiation into oligodendrocytes rather than astrocytes (Karimi-Abdolrezaee et al., 2012). In a study that specifically examined remyelination after lysolecithin-induced demyelination, CSPGs accumulated in astrocytes at the lesion edge and microglia in the lesion center at 7 days post injection (DPI, (Lau et al., 2012). At 14 DPI, CSPGs were reduced and they were cleared by the time of remyelination at 21 DPI. If the mice were systemically treated with xyloside, a glycoside that prevents the attachment of GAG side chains on to the CSPG protein cores, the level of CSPGs was reduced and the number of OPCs was increased at 7 DPI. At 21 DPI, the number of mature oligodendrocytes increased and the area of the dorsal columns that became remyelinated also increased.

These studies demonstrate that reducing CSPG levels in demyelinated lesions can promote axonal remyelination. Although removal of CSPGs with chABC has successfully improved recovery in various injury models, it would be difficult to translate this approach to the clinic. The bacterial enzyme requires continuous application or repeated injections into the site of injury to be effective and this could lead to an immune response directed against chABC. In MS, where lesions are diffuse and often hard to identify or access, a systemic treatment such as xyloside could be more beneficial but equally broad-acting. However, the study by Pendleton et al. (2013) suggests that targeting the downstream signaling pathway from the CSPG receptor PTPσ might be a more amenable approach to reducing CSPG inhibition of remyelination. Furthermore, a recent study identified small molecule inhibitors that are selective for PTPσ (Martin et al., 2012), which raises the intriguing possibility that such a tailored therapy may be on the horizon.

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