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Traffic lights for axon growth: proteoglycans and their neuronal receptors

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Abstract

Axon growth is a central event in the development and post-injury plasticity of the nervous system. Growing axons encounter a wide variety of environmental instructions. Much like traffic lights in controlling the migrating axons, chondroitin sulfate proteoglycans (CSPGs) and heparan sulfate proteoglycans (HSPGs) often lead to "stop" and "go" growth responses in the axons, respectively. Recently, the LAR family and NgR family molecules were identified as neuronal receptors for CSPGs and HSPGs. These discoveries provided molecular tools for further study of mechanisms underlying axon growth regulation. More importantly, the identification of these proteoglycan receptors offered potential therapeutic targets for promoting post-injury axon regeneration.

Key Words: axonal regeneration; chondroitin sulfate and heparan sulfate proteoglycans

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Chondroitin sulfate proteoglycans (CSPGs) and heparan sulfate proteoglycans (HSPGs)

Proteoglycans are proteins glycosylated with sulfated glycosaminoglycan (GAG) side chains. The diversity of proteoglycans arises from their core protein sequences, the degree of glycosylation, and the length and composition of the GAGs. Based on the types of associated GAGs, proteoglycans are classified into four families: chondroitin sulfate proteoglycans, heparan sulfate proteoglycans, dermatan sulfate proteoglycans, and keratan sulfate proteoglycans. CSPGs and HSPGs carry chondroitin sulfate (CS) and heparan sulfate (HS) GAGs, respectively. The CS and HS share similar polysaccharide structures, but differ in their sulfation patterns along the sugar chains. Many of these proteoglycans are secreted into the intercellular space, yet others are either transmembrane proteins or tethered to the cell membrane through a glycosylphosphatidylinositol (GPI) anchor. CSPGs and HSPGs are produced by many cell types and found in all vertebrate tissues and organs.

Expression patterns and functional significance in the nervous system

In the nervous system, CSPGs and HSPGs are synthesized by neurons and glia, and their spatiotemporal expression is dynamically regulated throughout the course of development (Brittis et al., 1992; Pindzola et al., 1993; Oohira et al., 1994; Stipp et al., 1994; Ivins et al., 1997; Milev et al., 1998; Hsueh and Sheng, 1999; Bovolenta and Fernaud-Espinosa, 2000). For example, Glypican-2, a nervous system specific HSPG, is expressed only transiently when axons are actively growing, but not after cell migration has completed and axons have reached their targets (Stipp et al., 1994; Ivins et al., 1997). Many CSPGs are highly expressed in the developing central nervous system (CNS). They appear around the critical period in the perineuronal nets and in boundary regions where axon growth is normally restricted (Brittis et al., 1992; Wang and Fawcett, 2012). As the CNS matures, the expression of CSPGs gradually declines (Oohira et al., 1994; Milev et al., 1998). In rat embryonic retina, regression of CSPG level closely correlates with the onset of ganglion cell differentiation (Brittis et al., 1992).

Although attenuated in the mature nervous system, the expression of CSPGs and HSPGs may resurrect upon injuries (Garcia de Yebenes et al., 1999; Asher et al., 2000; Iseki et al., 2002; Jones et al., 2003; Bloechlinger et al., 2004; Properzi et al., 2008; Yi et al., 2012). Spinal cord and brain lesions in adult rodents induce waves of post-injury CSPG expression near the injury epicenters (Asher et al., 2000; Jones et al., 2003; Yi et al., 2012). CSPGs are also upregulated in the perineuronal nets of deafferented neurons distal to spinal cord lesion sites (Massey et al., 2006; Alilain et al., 2011). Glypican-1, an HSPG, is upregulated in adult rat dorsal root ganglion (DRG) neurons after sciatic nerve injury, and the elevated Glypican-1 expression persists until the injured axons reinnervated their peripheral targets (Bloechlinger et al., 2004).

The dynamic expression patterns of these proteoglycans during development and injuries are consistent with their functional roles in these processes, as HSPGs and CSPGs are found to be crucial players in regulating embryonic axon pathfinding and post-injury axonal plasticity (Brittis et al., 1992; Pindzola et al., 1993; Bandtlow and Zimmermann, 2000; Bovolenta and Fernaud-Espinosa, 2000; Wilson and Snow, 2000; Alilain et al., 2011; Maeda et al., 2011). Interestingly, HSPGs and CSPGs often have opposite effects on

axonal behavior. In the developing nervous system, CSPGs function as repulsive guidance molecules, whereas HSPGs often present attractive signals to axons (Brittis et al., 1992; Kantor et al., 2004; Wang et al., 2012). Likewise, CSPGs inhibit, while HSPGs promote, neurite outgrowth in cultured neurons (Snow et al., 1990; Snow et al., 1991; Coles et al., 2011). After injuries in the CNS, CSPGs deposited at the lesion sites form a potent inhibitory barrier that prevents the regeneration of severed axons (McKeon et al., 1991; Davies et al., 1997; Busch and Silver, 2007; Bartus et al., 2012; Garcia-Alias and Fawcett, 2012). On the contrary, treatment with Glypican, an HSPG that promotes axon growth, improves anatomical regeneration and functional recovery after cerebral ischemia (Hill et al., 2012).

Although the functional significance of these proteoglycans in axon growth has been documented for decades, the underlying mechanisms remained poorly understood, mainly because no molecular signaling was identified. Fortunately, a number of neuronal receptors for CSPGs and HSPGs have recently been discovered, allowing further research to decode the signaling mechanisms underlying proteoglycan regulation of axon growth.

Neuronal receptors of CSPGs and HSPGs

The LAR family RPTPs

Three transmembrane receptor protein tyrosine phosphatases (RPTPs), PTPsigma, PTPdelta, and leukocyte antigen-related (LAR), form a family that is often referred to as the LAR family RPTPs. These RPTPs have long been implicated in synaptogenesis and axon pathfinding during development (Garrity et al., 1999; Ledig et al., 1999; Johnson and Holt, 2000; Chagnon et al., 2004; Dunah et al., 2005; Fox and Zinn, 2005; Johnson et al., 2006; Kwon et al., 2010; Horn et al., 2012; Hendriks et al., 2013; Takahashi and Craig, 2013), and are now increasingly recognized as key regulators of post-injury axonal plasticity (Xie et al., 2001; McLean et al., 2002; Thompson, 2003; Van der Zee et al., 2003; Sapieha et al., 2005; Shen et al., 2009; Fry et al., 2010; Fisher et al., 2011; Takahashi et al., 2012; Gardner and Habecker, 2013).

In the nervous system, the LAR family RPTPs are expressed by both neurons and glia. In neurons, they are localized in soma, axons, and growth cones (Zhang et al., 1998; Mueller et al., 2000; McLean et al., 2002; Thompson, 2003; Fisher et al., 2011; Takahashi et al., 2012). The LAR family RPTPs are highly expressed in the developing nervous system of the vertebrates, with certain splicing isoforms of PTPsigma and PTPdelta exclusively confined to the CNS (Yan et al., 1993; Pulido et al., 1995). As the animal matures, expression levels of these RPTPs significantly decline in most areas of the CNS, except some brain regions such as the hippocampus, where PTPsigma and PTPdelta expression remains substantial (Yan et al., 1993; Wang et al., 1995; Schaapveld et al., 1998).

In the adult nervous system, injuries may also play a role in regulating the expression of the LAR family RPTPs. There have been a number of reports on injury-induced changes of LAR and PTPsigma expression; however, the results were not always consistent between studies, possibly due to the different analytical methods used (Haworth et al., 1998; Xie et al., 2001; McLean et al., 2002; Thompson, 2003; Sapieha et al., 2005; Fry et al., 2010). Nonetheless, a growing number of studies have shown consistent results on the functional roles of PTPsigma and LAR in nervous system injuries. Despite opposite findings on post-injury LAR expression, different research groups showed similar results that genetic depletion of LAR hampers axon regeneration after sciatic nerve injuries (Xie et al., 2001; Van der Zee et al., 2003). On the other hand, many research groups, using various injuries models of both central and peripheral nervous systems, showed unanimously that PTPsigma deficiency improves axon regeneration (McLean et al., 2002; Thompson, 2003; Sapieha et al., 2005; Shen et al., 2009; Fry et al., 2010; Gardner and Habecker, 2013).

Receptors of CSPGs and HSPGs

For many years, despite growing implications of the LAR RPTPs in axon pathfinding and regeneration, little was know about the underlying molecular mechanisms. Although these RPTPs are transmembrane proteins with structures that resemble cell surface receptors, no functional ligands had been identified until recently.

The initial evidence of the LAR family RPTPs serving as proteoglycan receptors emerged from the finding that in chick embryos, PTPsigma, a retinal axon protein, binds with high affinity to HSPGs in retinal basal lamina (Aricescu et al., 2002). Heparinase treatment, which digests the HS epitopes from the retinal basal lamina, effectively removes PTPsigma binding. Mutations in the first N-terminal Ig-like domain of PTPsigma eliminate its binding to the HSPG ligands. These data suggest that the receptor-ligand binding is mediated by the N-terminal domain of PTPsigma and the GAG moieties of HSPGs. In addition, PTPsigma was recently shown to be a neuronal receptor for CSPGs (Shen et al., 2009). Through the same N-terminal domain, PTPsigma binds to CSPGs secreted by reactive astrocytes in spinal cord lesion sites. The same binding site mutations that abrogate PTPsigma-HSPG binding also eliminate PTPsigma-CSPG binding. Chondroitinase treatment, which degrades CS GAGs, abolishes PTPsigma binding to CSPGs. Therefore, PTPsigma serves as a common GAG receptor for both CSPGs and HSPGs. Furthermore, PTPsigma has similar affinity towards HSPGs and CSPGs. The fact that both CS and HS GAGs interact with PTPsigma through the same binding site and with comparable affinities suggests a competition between these ligands (Shen et al., 2009; Coles et al., 2011).

In neurons, PTPsigma mediates intracellular signaling from both classes of proteoglycans. The biological effects of HSPG and CSPG signaling through this same receptor, however, can be counteracting. In cultured neurons, PTPsigma-CSPG interaction inhibits neurite extension, and genetic depletion of PTPsigma desensitizes neurons to CSPG-inhibition. In injured spinal cord, deficiency of PTPsigma enhances axon extension into CSPG-enriched glial scar (Shen et al., 2009; Fry et al., 2010). On the other hand, HSPGs, such as Glypican-2, induce robust neurite outgrowth in

cultured neurons, and this effect is abolished in PTPsigma deficient neurons (Coles et al., 2011). In the presence of both CS and HS proteoglycans, the outcome of neurite outgrowth depends on the relative abundance of these competing PTPsigma ligands (Coles et al., 2011). PTPsigma therefore plays a role as a bifunctional receptor in the regulation of neurite extension by mediating "stop" and "go" signals from CSPGs and HSPGs, respectively.

Within the LAR family, the first N-terminal Ig-like domain, through which PTPsigma binds to the GAGs, is highly conserved (Coles et al., 2011). Thus it is conceivable that the other two members of the family, LAR and PTPdelta, may also function as receptors of CSPGs and HSPGs. In fact, all three LAR RPTPs, through their first N-terminal domains, bind to heparin, a structural analog of HS (Coles et al., 2011). Drosophila LAR, a remote homologue of the vertebrate LAR family RPTPs, functions as an axonal receptor of Syndecan, an HSPG, and mediates its positive regulatory signals in motor axon guidance and synaptic development (Fox and Zinn, 2005; Johnson et al., 2006). In zebrafish, LAR isoforms steer somatosensory innervation into the skin, presumably through a receptor-ligand interaction with HSPGs. Deleting the first N-terminal domain of LAR or removing the HS GAGs from the skin tissue disrupts innervation (Wang et al., 2012). Although yet to be verified, mammalian LAR may as well be an HSPG receptor, given that the N-terminal ligand-binding domain is highly conserved across species (Coles et al., 2011).

Moreover, LAR was recently found to be an additional receptor of CSPGs. Like PTPsigma, LAR binds to CSPGs through CS GAGs. Deficiency of LAR eliminates CSPG signaling and mitigates CSPGs-inhibition of neurite outgrowth in cultured neuron, suggesting a functional role of LAR-CSPG interaction in neurite extension (Fisher et al., 2011). It is therefore reasonable to expect that LAR deficiency would promote post-injury axon regeneration in a lesion environment rich of CSPGs, in a similar fashion as PTPsigma deficiency. However, after sciatic nerve injuries, axon regeneration is hampered by LAR deficiency, but enhanced by PTPsigma deficiency (Xie et al., 2001; McLean et al., 2002; Van der Zee et al., 2003). It is not clear what results in the discrepancy between the *in vitro* and *in vivo* effects of LAR deficiency.

Opposite axon growth signals by CSPGs and HSPGs

As discussed above, it seems that HSPGs and CSPGs signal opposite instructions to the axons, through the same neuronal receptor PTPsigma, much like turning on and off a molecular switch. What are the underlying mechanisms of such bimodal signaling? To decode this paradox, a recent study showed that CSPGs and HSPGs induce differential molecular configuration of the LAR family RPTPs (Coles et al., 2011). When bound to these RPTPs, HS GAGs and their analogs cluster the receptors into oligomers, whereas CS GAGs maintain them in monomers. In the presence of both HS and CS, the degree of receptor clustering appears to depend on the relative abundance of these competitive ligands. As suggested by previous studies, oligomerization of these receptor tyrosine phosphatases may lead to the inhibition of their enzyme activity (Bilwes et al., 1996; Wallace et al., 1998). If so, the binding of CS and HS to the RPTPs would switch their phosphatase activity "on" and "off", respectively. In a migrating growth cone, suppressed tyrosine phosphatase activity can be translated into a local increase of phosphotyrosine residues on many signaling molecules, thereby activating pathways leading to axon growth. In fact, Glypican-2, which possesses HS chains that cluster PTPsigma, stimulates robust neurite outgrowth in cultured neurons (Coles et al., 2011). Conversely, while CSPGs are notorious inhibitors of neurite extension, their CS GAGs, which dissociate the receptors in monomers, enhance LAR phosphatase activity in cultured cells (Fisher et al., 2011). Treatment with peptides that inhibit LAR phosphatase activity improves axon regeneration into CSPG-enriched glial scar after spinal cord injury, suggesting that CSPG-inhibition of axon growth is mediated by LAR enzyme activity (Fisher et al., 2011). In a similar vein, a very recent study showed that a PTPsigma inhibitory peptide significantly enhances axonal plasticity and promotes robust functional recovery following severe spinal cord injury (B. T. Lang, 2012).

Because of the counteracting functions of CSPGs and HSPGs in regulating axon growth, it is critical to maintain a homeostatic balance of these proteoglycans in the perineuronal environment. Pathological conditions of the nervous system, such as traumatic injuries, disrupt such balance and often lead to a CSPG-dominant lesion environment surrounding the injured neurons. As a consequence, this may deviate neuronal signaling through the LAR family RPTPs, which could result in downstream cellular events such as intense adhesion and low motility of the dystrophic axon tips, and eventual long-term entrapment of injured axons at the glial scar barriers or within the perineuronal nets (Busch et al., 2010; B. T. Lang, 2012).

The Nogo receptors (NgRs)

The Nogo receptor (NgR) family consists of three GPI-anchored receptors: NgR1, the bona fide "Nogo receptor", and its two homologues, NgR2 and NgR3. The NgRs are predominantly expressed by neurons throughout development and remain highly expressed in the adult nervous system (Lauren et al., 2003). Subcellular localization analysis showed that NgR1 and NgR2 are expressed on axons, and in particular on growth cones (Wang et al., 2002b; Venkatesh et al., 2005). Earlier studies have identified NgR1 as a receptor of the myelin-associated inhibitors (MAIs), including Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp). NgR1 was shown to mediate MAI-inhibition of axon regeneration in injured adult CNS (Kim et al., 2004; McGee et al., 2005; Cafferty and Strittmatter, 2006), although results were sometimes inconsistent between different research groups (Zheng et al., 2005). While denoted as Nogo receptors, neither NgR2 nor NgR3 binds to Nogo-A. NgR2 was instead found to be a receptor of MAG, and NgR3 does not interact with any of the MAIs (Venkatesh et al., 2005; Lauren et al., 2007).

Receptors of CSPGs (and HSPGs?)

A recent study showed that NgR1 and NgR3 are also functional receptors of CSPGs (Dickendesher et al., 2012). NgR1 and NgR3 each bind with high affinity to purified CS GAGs, and to CSPGs in developing brains and injured optic nerves. The binding of CSPGs and MAIs to NgR1 appears to be mediated by distinct domains, suggesting independent receptor engagement and possible synergistic signaling by these ligands through this common receptor. Interestingly, binding of CSPGs induces the formation of a receptor complex that comprises NgR1 and NgR3, along with p75, an NgR1 co-receptor in MAI signaling (Wang et al., 2002a). These findings therefore revealed a molecular platform shared by the MAIs and CSPGs, which involves multiple receptors and serves as a signal converging point for these axon growth inhibitors.

Although loss of Ngr1 or Ngr3 alone is not sufficient to overcome CSPG-inhibition, combined loss of Ngr1 and Ngr3 renders resistance to CSPG-inhibition in cultured neurons and promotes axon regeneration in injured optic nerves. A further enhancement of axon regeneration was observed with triple depletions of Ngr1, Ngr3, and PTPsigma, suggesting a functional redundancy among these receptors (Dickendesher et al., 2012).

The study also showed a robust binding of NgR1 to the HS GAGs in developing brains. The interactions of CS and HS with Ngr1 are mediated by the same motif on Ngr1, suggesting a competition between these GAG ligands for this common receptor. The biological relevance of HS-Ngr1 interaction, however, has not been characterized, leaving an interesting topic for future studies as this would reveal whether the NgRs behave as bifunctional receptors to mediate opposite axon growth instructions from CSPGs and HSPGs.

Semaphorin 5A

In addition to the LAR family and NgR family receptors, Semaphorin 5A, an axon guidance molecule, binds through its thrombospondin repeats to the GAGs of both CSPGs and HSPGs and thereby presents itself to the developing axons as a bifunctional guidance molecule (Kantor et al., 2004). Whereas HSPGs are required for axon attraction by Semaphorin 5A, CSPGs convert Semaphorin 5A into an inhibitory guidance cue.

Given the abundance of proteoglycans in the intercellular space, it would not be surprising that future studies may identify more receptors of CSPGs and HSPGs, and perhaps also receptors of other proteoglycans such as the dermatan sulfate proteoglycans and keratan sulfate proteoglycans.

Discussion

The functional significance of HSPGs and CSPGs in axon growth is known for decades; however, the underlying molecular mechanisms remain poorly understood. These recent discoveries of CSPG and HSPG receptors provided us with molecule tools to further dissect the mechanisms of axon growth regulation. More importantly, these proteoglycan receptors are likely potential therapeutic targets for promoting post-injury axon regeneration. The studies aforementioned in this review also give a few take-home messages regarding the treatment strategies that target these axon growth regulators.

Functional redundancy among CSPG receptors

The fact that CSPGs interact with multiple receptors in the LAR and NgR family suggests a functional redundancy among these receptors. Removing an individual CSPG receptor, or even a combined loss of NgR1 and NgR3 only results in a partial relief of CSPG-inhibition (Shen et al., 2009; Fisher et al., 2011; Dickendesher et al., 2012). Hence, a combinational targeting strategy that simultaneously interferes with multiple CSPG receptors may be necessary to achieve an optimal result in promoting post-injury axon regeneration. Nonetheless, in some occasions the injured axons may possess a predominant CSPG receptor. For example, in cardiac sympathetic neurons, where PTPsigma appears to be the major CSPG receptor, targeting PTPsigma alone is sufficient for a full reinnervation of the scar after ischemia-reperfusion injury (Gardner and Habecker, 2013). Therefore, the strategy to combat CSPG inhibition should be tailored based on the local distribution of the CSPG receptors.

Targeting a bifunctional receptor

For a bifunctional receptor such as PTPsigma, blocking ligand access to its binding domain will eliminate the inhibitory signals of CSPGs; however, this will also deprive the growth promoting signals of HSPGs. Such an approach therefore may not provide the best outcome in promoting axon growth. Instead, supplying HSPGs to the CSPG-enriched lesion environment is a simple strategy that eliminates CSPG-inhibition and stimulated axon growth simultaneously. Alternatively, inhibiting PTPsigma phosphatase activity can be another strategy to switch downstream signaling in favor of axon growth. Compared with the genetic deletion of PTPsigma, a PTPsigma inhibitory peptide evidently has much stronger effects in promoting axonal plasticity, presumably because the blockade of the phosphatase activity assimilates not only the removal of CS but also the addition of HS (as discussed above) (B. T. Lang, 2012).

Locations of treatment

In injured spinal cords, CSPGs are heavily deposited in the lesion areas, forming a barrier that halts the severed axons. It is therefore rational to apply CSPG-combatting treatments to the area of dystrophic axon tips. In fact, lesion site injection of Chondroitinase ABC, an enzyme that digests CS GAGs, effectively enhances axonal plasticity and functional recovery after spinal cord injuries (Bradbury et al., 2002; Garcia-Alias et al., 2009; Alilain et al., 2011).

However, the lesion sites are not the only location where CSPGs contact the injured neurons, and often neglected is the somatodendritic region where the proteoglycan receptors are surrounded by perineuronal CSPGs. Upon spinal cord injuries, CSPGs are upregulated in the perineuronal nets of deafferented neurons distal to the lesion sites (Massey et al., 2006; Alilain et al., 2011). In a recent study, systemic application of a PTPsigma inhibitory peptide achieved robust functional restoration, which appears to mostly result from sprouting fibers that presumably have broken through the perineuronal nets (B. T. Lang, 2012). These findings therefore suggest that the cell bodies of deafferented neurons distal

from the lesion site are additional locations where CSPG-receptor interaction plays a role in curtailing plasticity. Therefore, an optimal treatment regime should take into account both the axons and cell bodies of the injured neurons so as to maximize the opportunity for functional recovery.

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