

## Review Article

Diverse functions of protein tyrosine phosphatase  $\sigma$  in the nervous and immune systemsYosuke Ohtake<sup>a</sup>, Atsushi Saito<sup>b</sup>, Shuxin Li<sup>c,\*</sup><sup>a</sup> Department of Biochemistry, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima 734-8553, Japan<sup>b</sup> Department of Stress Protein Processing, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima 734-8553, Japan<sup>c</sup> Shriners Hospitals Pediatric Research Center, Department of Anatomy and Cell Biology, Lewis Katz School of Medicine at Temple University, Philadelphia, PA 19140, USA

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## ABSTRACT

Tyrosine phosphorylation is a common means of regulating protein functions and signal transduction in multiple cells. Protein tyrosine phosphatases (PTPs) are a large family of signaling enzymes that remove phosphate groups from tyrosine residues of target proteins and change their functions. Among them, receptor-type PTPs (RPTPs) exhibit a distinct spatial pattern of expression and play essential roles in regulating neurite outgrowth, axon guidance, and synaptic organization in developmental nervous system. Some RPTPs function as essential receptors for chondroitin sulfate proteoglycans that inhibit axon regeneration following CNS injury. Interestingly, certain RPTPs are also important to regulate functions of immune cells and development of autoimmune diseases. PTP $\sigma$ , a RPTP in the LAR subfamily, is expressed in various immune cells and regulates their differentiation, production of various cytokines and immune responses. In this review, we highlight the physiological and pathological significance of PTP $\sigma$  and related molecules in both nervous and immune systems.

## 1. Introduction

Protein tyrosine kinases and protein tyrosine phosphatases (PTPs) play essential roles in regulating signal transduction in multiple cell types by tyrosine phosphorylation and dephosphorylation, respectively. PTPs include non-receptor-type PTPs and receptor-type PTPs (RPTPs), which are vital cell surface proteins that have intracellular tyrosine phosphatase activity and extracellular domains with sequence homology to cell adhesion molecules. In contrast to the well-studied protein tyrosine kinases, the properties of most RPTPs remain less clear, including their specific substrates, regulation, biological functions and possible roles in human disorders (Han et al., 2016; Takahashi and Craig, 2013). The RPTP family includes eight sub-families based on their extracellular domain structures. Among them, type IIA RPTPs include three members in vertebrates, the leukocyte common antigen-related (LAR), PTP $\sigma$ , and PTP $\delta$ . These RPTPs contain typical cell adhesion Ig and fibronectin III domains, which contribute to their interactions with the extracellular matrix (ECM) molecules. Structurally, RPTPs have two cytoplasmic tandem regions, the membrane-proximal PTP domain (D1, catalytically active) and the membrane-distal PTP domain (D2, inactive) (Takahashi and Craig, 2013). Additional splicing of small exon segments contributes to the structural diversity of the

ectodomain (Pulido et al., 1995).

During development, LAR and PTP $\sigma$  are widely expressed by multiple tissues including the nervous system, lung, kidney and thymus, while PTP $\delta$  is more restricted in the nervous system (Schaapveld et al., 1998; Shishikura et al., 2016; Sommer et al., 1997; Wang et al., 1995; Zhang et al., 1998). In mammalian nervous system, type IIA RPTPs (LAR, PTP $\sigma$ , and PTP $\delta$ ) are important for regulating synaptogenesis (Takahashi and Craig, 2013; Um and Ko, 2013), especially formation of excitatory synapses by interacting with postsynaptic netrin-G ligand-3 (NGL-3) (Kwon et al., 2010). The type IIA RPTPs are also expressed in adult nervous system, but their functional significance is not known completely. Deleting each of these RPTPs shows distinctive morphological and functional phenotypes in the nervous system of adult mice (Kolkman et al., 2004; Meathrel et al., 2002; Uetani et al., 2006; Uetani et al., 2000; Yeo et al., 1997). Among these three RPTPs, LAR and PTP $\sigma$  have been shown to be important functional receptors that bind chondroitin sulfate proteoglycans (CSPGs) with high affinity and mediate their inhibitory effects through the convergent and divergent signaling pathway (Fisher et al., 2011; Ohtake and Li, 2015; Ohtake et al., 2016; Shen et al., 2009). Following CNS injury, severed axons fail to regenerate in adult mammals partly due to upregulation of various inhibitory ECM molecules around the lesion, especially the potent

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axon growth inhibitors of CSPGs. Whether PTP $\delta$  functions as a receptor of CSPGs remains to be determined.

Multiple PTPs are expressed preferentially in the haematopoietic system and some of them have been implicated in regulating development and functions in the immune system (Pike and Tremblay, 2013). Altered PTP activities may induce inappropriate proliferation, survival and activation of immune cells, and contribute to pathophysiology of inflammation and autoimmunity diseases. Thus, PTPs have the complex and diverse functions in the immune system and may become molecular targets for treating immune related disorders. Out of the three type-IIa RPTPs, LAR is expressed on immature thymocytes although its phosphatase activity appears unnecessary for T cell development and function (Kondo et al., 2010; Terszowski et al., 2001). LAR and PTP $\sigma$  are specifically co-expressed in murine plasmacytoid dendritic cells (pDCs) and deletion of both simultaneously increases interferon production by pDCs (Bunin et al., 2015). Recently, we demonstrate that PTP $\sigma$  is expressed in multiple immune cells, including DCs, and is critical for regulating their activation, cytokine production and immune-mediated inflammation (Ohtake et al., 2017). Because PTP $\sigma$  is highly expressed in both nervous and immune systems and has crucial functions in both systems, this review will focus on the diverse functions of PTP $\sigma$  and its related genes, and their significance in mediating neurological and autoimmune disorders.

## 2. RPTPs regulates neuronal growth and synapse formation during development

Three type-IIa RPTPs show divergent distribution patterns in the developmental nervous system. PTP $\sigma$  is widely expressed throughout the central and peripheral nervous system during embryonic development. The high levels of its mRNA are especially detected in several structures, including ventricular and subventricular zones, cortex, dorsal root ganglia (DRG), cranial nerve ganglia, olfactory epithelium, and retina (Wang et al., 1995). During postnatal development, its expression levels decrease in most brain regions, although certain areas still exhibit high levels, such as hippocampus. In contrast, LAR mRNA is expressed in neural and non-neural tissues with different patterns from PTP $\sigma$ . High levels of LAR mRNA are detected in epithelial layer of various embryonic tissues and in neuroepithelium and DRGs during embryogenesis. LAR expression shows developmental regulation during neural cell growth and differentiation (Longo et al., 1993). During embryonic development, PTP $\delta$  expression is relatively low and limited to differentiated cells of several structures, including olfactory bulb, cortical plate, thalamic nuclei, and olivary nucleus (Schaapveld et al., 1998; Sommer et al., 1997).

RPTPs are localized to the growth cone at axonal tip of immature neurons, while they are largely localized to the dendritic spines and excitatory synapse of mature neurons (Wyszynski et al., 2002). RPTPs are localized to distinct types of synapses. In culture hippocampal neurons, PTP $\sigma$ -immunostained puncta overlapped with the axonal vesicular glutamate transport protein 1, indicating its localization to CNS axons (Takahashi et al., 2011). LAR is concentrated in mature synapses in hippocampal neuronal cultures, and is vital for development and maintenance of excitatory synapses. LAR knockdown causes loss of excitatory synapses and dendritic spines, decrease of surface AMPA receptors, impaired dendritic targeting of cadherin-beta-catenin complex and dysfunction in excitatory synapses (Dunah et al., 2005; Woo et al., 2009). In contrast, in addition to expression in excitatory synapses, PTP $\delta$  accumulates in inhibitory presynapses and regulates their genesis by interacting with postsynaptic adhesion molecule Slit and Trk-like family proteins 3 (Slitrk3) (Takahashi et al., 2012). Thus, individual RPTPs appear to target different synapse types probably by binding to diverse ligands in distinct types of synapses.

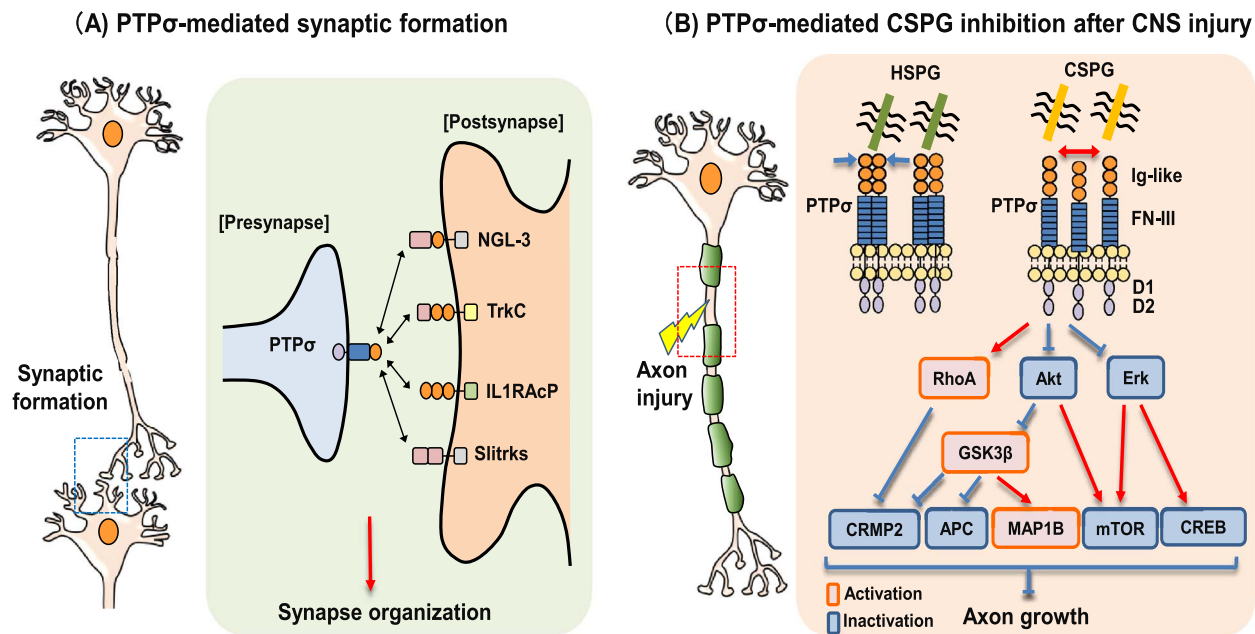
RPTPs, including PTP $\sigma$  and LAR, mediate various cell-ECM adhesions by binding some extracellular ligands, such as heparan sulfate proteoglycans (HSPGs) and CSPGs (Aricescu et al., 2002; Coles et al.,

2011; Johnson et al., 2006). HSPGs are the cell-surface and ECM glycoproteins usually containing one or more covalently attached heparan sulfate (HS) chains, a type of glycosaminoglycan (GAG). CSPGs are a diverse family of ECM molecules characterized by containing chondroitin sulfate (CS) chains. Each of the HSPGs and CSPGs comprises of a core protein and a variable number of highly sulfated GAG side chains frequently with negative charge. GAGs are long unbranched polysaccharides with repeating disaccharides, which comprise an amino sugar (*N*-acetylglucosamine or *N*-acetylgalactosamine) along with a uronic sugar (glucuronic acid or iduronic acid) or galactose. GAGs are classified into CS, HS, hyaluronic acid, dermatan sulfate, and keratan sulfate based on their component sugars. CS chains contain *N*-acetylgalactosamine and glucuronic acid in contrast to *N*-acetylglucosamine and glucuronic acid in HS chains. RPTPs interact with ECM molecules by binding the GAG chains of proteoglycans (Dickendesher et al., 2012; Fisher et al., 2011; Shen et al., 2009). PTP $\sigma$  binds to CS-D, CS-E, and DS, but not to CS-A or CS-C (Dickendesher et al., 2012). Recently, Geller's group demonstrated that the main binding sites for PTP $\sigma$  are located to neurons in adult mouse brain, but are not to GAG chains of proteoglycans (Yi et al., 2014). Further studies are required to clarify these discrepancies.

The highly-controlled sulfation patterns on CS chains are important for mediating CSPG functions (Miller and Hsieh-Wilson, 2015; Yu et al., 2018) although various studies revealed inconsistent results on the roles of different CS chains. CS-E, not CS-A, could suppress outgrowth of both cerebral cortical and DRG neurons (Brown et al., 2012; Butterfield et al., 2010; Karumbaiah et al., 2011; Verna et al., 1989), but CS-E was also reported to promote neurite growth of hippocampal and cortical neurons (Pulsipher et al., 2014; Tully et al., 2004). CS-C was either inhibitory or non-inhibitory to neurite growth reported by different groups (Brown et al., 2012; Butterfield et al., 2010). In contrast, CS-A, not CS-C, was found inhibitory to neurite growth of cerebellar granule cells (Wang et al., 2008). Therefore, it will be important to further elucidate the spatiotemporal regulation and precise functions of various CS chains, their specific molecular interactions and downstream signaling pathways.

CS and HS chains share common uronic sugar residues (glucuronic acid and iduronic acid) and a linkage region of xylose–galactose, but they consist of different amino sugar disaccharides, the *N*-acetylgalactosamine for CS and the *N*-acetylglucosamine for HS added by distinct enzymes (Lindahl et al., 2015; Yu et al., 2018). CSPGs and HSPGs regulate growth, guidance, and connections of CNS neurons, but these two subclasses of sulfated proteoglycans have distinct functions on neuronal growth, typically with suppression by the former and promotion by the latter on axonal elongation (Bandtlow and Zimmermann, 2000; Coles et al., 2011; Silver and Miller, 2004). Presence of CSPGs remarkably attenuated neurite outgrowth of cultured DRG neurons (Dill et al., 2008; Snow et al., 1990; Snow and Letourneau, 1992). In contrast, treatment with HSPGs, including glypican-2, strongly promoted elongation of cultured neurons *in vitro* (Coles et al., 2011; Hantaz-Ambroise et al., 1987; Lander et al., 1982).

HSPGs and CSPGs regulate axon growth during development through their HS or CS chains. HS treatment induced axon defasciculation and growth in incorrect directions in cultured cockroach embryos, while CS treatment had no effect. Enzymatic degradation of HS by heparitinase resulted in axon perturbation, whereas degradation of CS had no effect (Wang and Denburg, 1992). Similarly, heparin, a glycosaminoglycan containing heparan sulfate, resulted in abnormal axon behavior in retinal ganglion cells from *Xenopus laevis* embryos (Walz et al., 1997). CSPGs also play a remarkable role in guiding axons by forming inhibitory areas during development. CSPG expression shows precise spatial and temporal pattern in developing retina. CSPG was detected during retinal development of rat at embryonic day 12.5 (E12.5), gradually decreased from the central area to the periphery, and no longer detectable at E17 (Abbott et al., 2007). Treatment of cultured embryonic retina with chondroitinase ABC (ChABC) to remove CS GAG



**Fig. 1.** PTP $\sigma$  is important to regulate synapse formation by interacting with several postsynaptic proteins (A) and to mediate CSPG inhibition of neuronal growth as a receptor through multiple intracellular pathways (B). (A) PTP $\sigma$  is localized to the growth cone at axonal tip in immature neurons during development and serves as a presynaptic hub by interacting with diverse postsynaptic partners, including NGL-3, TrkC, IL1RacP and Slitrks, thus regulating the synapse formation in developmental neuron. (B) PTP $\sigma$  can bind both HSPGs and CSPGs. Binding with the former induces PTP $\sigma$  clustering and inactivation, promoting axon growth. In contrast, binding with CSPGs prevents PTP $\sigma$  dimerization and activates this receptor and its downstream signaling pathways, inhibiting axon growth after CNS injury. Intracellularly, activation of PTP $\sigma$  by CSPGs activate RhoA-Rock signaling and inactivate Akt and Erk pathways. Activation and/or inactivation of these signaling pathways mediate CSPG inhibition by other downstream signaling molecules, including GSK3 $\beta$ , CRMP2, APC, MAP1B, mTOR and CREB. Ig-like: immunoglobulin-like domains; FN-III: fibronectin type III domain; D1: D1 catalytic domain; D2: D2 non-catalytic domain.

chains induced abnormal retinal axon projections into the region where normal axons could not enter (Snow et al., 1991). Therefore, proteoglycans regulate axon guidance and extension during development probably by interacting with RPTPs, including PTP $\sigma$ .

RPTPs play an important role in mediating synapse formation during development. Based on the expression patterns and phenotypes in transgenic animals, PTP $\sigma$  and PTP $\delta$  appear to play more important roles than LAR for synapse organization during development. Functional interactions of RPTPs with a number of postsynaptic binding partners generate a complicated synaptic network and control synapse formation. Presynaptic RPTPs form trans-synaptic adhesion complexes with multiple postsynaptic adhesion molecules (Fig. 1A), including NGL-3 (Kwon et al., 2010; Woo et al., 2009), neurotrophin receptor TrkC (Takahashi et al., 2011), interleukin-1 (IL1) receptor accessory protein-like 1 (IL1RAPL1) (Valnegri et al., 2011; Yoshida et al., 2011), its paralog IL1RAPL2 (Pavlovsky et al., 2010; Valnegri et al., 2011; Yoshida et al., 2011), IL-1 receptor accessory protein (IL-1RacP) (Yoshida et al., 2012), and Slitrks (Takahashi et al., 2012; Yim et al., 2013). Though all three type-IIa RPTPs can bind to NGL-3 through their first two FNIII domains and also to IL-1RacP, Slitrks bind to PTP $\sigma$  and PTP $\delta$  selectively through the Ig domains. In contrast, TrkC binds to PTP $\sigma$  and IL1RAPL1 binds to PTP $\delta$  only.

Axonal RPTPs accumulate NGL-3 on dendrites and appear to promote excitatory postsynaptic development by interactions with NGL-3 and postsynaptic density protein (PSD-95). NGL-3 mainly induced excitatory presynaptic differentiation of contacting axons in co-cultured system and this effect is suppressed by treatment with soluble LAR ectodomain (Woo et al., 2009). Induced aggregation of NGL-3 on dendrites resulted in dendritic clustering of excitatory, but not inhibitory, postsynaptic proteins, including the scaffold protein PSD-95. Accordingly, the C-terminus of NGL-3 has been shown to bind the PDZ domains of PSD-95 (Kim et al., 2006). Although all three type IIa RPTPs can bind and interact with NGL-3, PTP $\sigma$  appears to be the main presynaptic component based on their exclusive excitatory synaptic localization, affinity for NGL-3 and expression pattern in the brain.

Presynaptic PTP $\sigma$  interacts with postsynaptic TrkC and seems to regulate development of excitatory synapses transduced by the intracellular domain of PTP $\sigma$ . Trks, a family of tyrosine kinases, are well characterized as the receptors of neurotrophic factors that control neural survival, differentiation, proliferation, the fate of neural precursors, axon and dendrite growth and patterning. With unbiased expression screen in co-culture system, PTP $\sigma$ , but not PTP $\delta$  and LAR, was identified as a TrkC binding partner (Takahashi et al., 2011). Moreover, TrkC induced excitatory, but not inhibitory, presynaptic differentiation and this effect is abolished by axonal expression of mutated PTP $\sigma$  lacking the intracellular region.

RPTPs promote excitatory synapse development also by interacting with members in the IL-1/Toll receptor family (IL1RAPL1, IL1RAPL2 and IL1RacP) and activating PSD-95 and Jun-N-terminal kinase (JNK) signaling pathways. IL1-RacP interacts with all three type IIa RPTPs, although IL1RAPL1 binds PTP $\delta$ , but not PTP $\sigma$  and LAR. IL1RAPL1-PTP $\delta$  interactions recruited GTPase-activating protein to regulate excitatory synapse formation, as well as dendritic synapse number and morphogenesis (Valnegri et al., 2011; Yoshida et al., 2011). IL-1RacP includes two isoforms, the ubiquitously-expressed IL-1RacP and the CNS-specific IL-1RacPb (Smith et al., 2009). Both isoforms regulate differentiation of excitatory presynapses, while IL-1RacPb also contributes to formation of dendritic spines. Because IL-1RacP interacted with PTP $\delta$  through the extracellular domain and the IL-1RacP-mediated formation of presynapses is partly abolished in cortical neurons derived from PTP $\delta$ -deficient mice (Yoshida et al., 2012), the interactions of IL-1RacP with other RPTPs, such as PTP $\sigma$  and/or LAR, may also play a significant role in this action. Given that IL1RAPL1-deficient neurons have reduced levels of phosphorylated PSD-95 and JNK proteins, these signaling pathways appear to mediate the RPTP-IL1RAPL1 interactions (Pavlovsky et al., 2010).

Slitrks play important roles in regulating synapse development by forming protein complex with RPTPs (Yim et al., 2013). Slitrks are a family of transmembrane receptors that contain six leucine-rich repeat domains. All six members (Slitrk1–6) are able to induce presynaptic

differentiation in neuronal co-cultures. Five Slitrks, except for Slitrk3, could interact with PTP $\sigma$  and contribute to excitatory synaptogenic activities. Only Slitrk3 can induce inhibitory, but not excitatory, pre-synaptic differentiation *in vitro* and *in vivo* by interact with presynaptic PTP $\delta$  (Takahashi et al., 2012). Of note, because CSPG plays an important role in restricting neuronal plasticity following injury, interactions of RPTPs with postsynaptic adhesion molecules during development may also be regulated by competing with CSPGs in a spatiotemporal manner.

### 3. PTP $\sigma$ mediates neuroplasticity in mature neurons

Although a number of brain regions show obvious mRNA distribution of PTP $\sigma$ , LAR and PTP $\delta$  in the adult mice, their expression patterns are very diverse (Schaapveld et al., 1998; Shishikura et al., 2016; Wang et al., 1995). During postnatal development, the expression level of PTP $\sigma$  decrease dramatically in most brain regions, but high levels continue to be detected in hippocampus, especially the pyramidal cell layer (Kwon et al., 2010). Strong signals for PTP $\sigma$  are also detected in several other areas of adult mammals, including the internal granule layer of olfactory bulb, piriform cortex, tenia tecta, septal area and cerebellum. Strong LAR signals are found in the internal granule layer of olfactory bulb, subventricular zone of caudate putamen and cerebellum, but are less abundantly in layer IV of cortex and septal area. In contrast, PTP $\delta$  protein or mRNA is expressed in the hippocampus (particularly the CA2 and CA3 regions), layer IV of cortex, granule cell layer of cerebellum, thalamic nuclei, and mitral and granular cell layers of the olfactory bulb, but it is undetectable in septal area. Therefore, three type IIa RPTPs exhibit overlapping, but differential distribution patterns in the developed brain.

PTP $\sigma$  modulates the neuronal plasticity in mature neurons. PTP $\sigma$ -deficient mice exhibit severe growth retardation, high neonatal mortality and neurological deficiencies, including thinning of the corpus callosum and cerebral cortex, hippocampal dysgenesis, abnormal pituitary development, motor dysfunction and defective proprioception (Meathrel et al., 2002; Uetani et al., 2006). PTP $\sigma$  null mice also have increased hippocampal mossy fibers and axon sprouting during aging, consistent with PTP $\sigma$  limiting synapse formation. PTP $\sigma$  deficiency increases the frequency of miniature post-synaptic currents mediated by  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, accompanied by an increase in synapse density, but decreases synaptic efficiency. Moreover, the role of PTP $\sigma$  in CNS plasticity has been demonstrated in learning and memory. PTP $\sigma$  null mice show reduced long-term potentiation (LTP, an activity-dependent synaptic plasticity) in hippocampal Schaffer collateral-CA1 synapses and enhanced performance in a novel object recognition memory test (Horn et al., 2012).

LAR deficient mice have smaller basal forebrain cholinergic neurons and reduced cholinergic innervation of their target neurons in the dentate gyrus (Yeo et al., 1997). Mice lacking the phosphatase domains of LAR have spatial learning deficiency and hyperactivity (Kolkman et al., 2004). PTP $\delta$  knockout mice also exhibit marked motor dysfunction, impaired visuospatial processing with low survival rates (Uetani et al., 2006; Uetani et al., 2000), and impaired learning and memory tasks and enhanced LTP (Uetani et al., 2000). The phenotype differences in deficiency of three RPTPs may result from diverse ligands, subcellular distribution or downstream signaling pathways.

PTP $\sigma$  regulates synaptic plasticity, learning and memory in adult CNS, but it is unclear whether its function is associated with the interactions with perineuronal nets (PNN) molecules, especially CSPGs. PNNs are composed of ECM macromolecules (including hyaluronan, CSPGs, tenascin-R, link proteins and other components) and organize these molecules into specific structures (Busch and Silver, 2007; Hagihara et al., 1999; Kwok et al., 2011; Massey et al., 2006). In extracellular space, CSPGs interact with HA polymer on cell surface and induce a stable connections with HA polymer chains and other linked

proteins. The C-terminal domains of CSPG core proteins bind tenascin-R to form highly organized constructions of PNNs. PNNs wrap the neuronal cell body, proximal dendrites and synapses of various neuronal populations. CNS starts to form PNNs in the late stage of development, especially during critical periods of synaptic maturation (Kwok et al., 2011). PTP $\sigma$  is one of the two identified RPTP receptors for CSPGs, the major components of PNN (Shen et al., 2009), but Geller's group did not detect PTP $\sigma$  binding to PNN in the mouse brain (Yi et al., 2014). Further studies are required to illustrate the molecular mechanisms for PTP $\sigma$ -mediated neuronal plasticity.

PNNs may play critical roles in the mature CNS, including synapse stabilization, neuroprotection, ionic buffering and neuronal plasticity. PNNs have been implicated to maintain and modify cognition, learning and memory functions. PNN formation in amygdala of mice affects developmental shift in the ability to erase fear memories by extinction (Gogolla et al., 2009). Organization of CSPGs in PNNs mediates formation of erasure-resistant fear memories because local treatment of amygdala with ChABC to digest CSPGs in adult mice re-enabled the subsequent erasure of fear memories by extinction. PNNs also play critical roles in controlling neuronal plasticity in hippocampus. Deficiency of PNN structures in transgenic mice shows reduced LTP by theta-burst stimulation in CA1 region of hippocampus. Pretreatment of cultured hippocampal slices with ChABC induces similar reduction of LTP *in vitro* (Bukalo et al., 2001). Deletion of brevican, one of brain-specific CSPGs, in mutant mice, or treatment of wild-type mice with anti-brevican antibody resulted in impaired LTP, although they exhibited normal behavior and spatial memory (Brakebusch et al., 2002).

### 4. PTP $\sigma$ functions as a CSPG receptor to mediate axon regeneration in the CNS

After CNS injuries, reactive astrocytes generate extremely high levels of CSPGs, which potentially suppress axon growth into and beyond the lesion area (Bradbury et al., 2002; Busch and Silver, 2007; Jones et al., 2003). The major CSPGs expressed in the CNS include lecticans (neurocan, versican, aggrecan, and brevican), phosphacan and NG2. Lecticans share many similar domains at both N- and C-termini of the core proteins and their core proteins are linked by a central CS-GAG anchoring backbone bound one or numerous long chain CS-GAG polysaccharide (Yamaguchi, 2000). Lecticans function as linkers of the ECM molecules. Phosphacan is the extracellular domain of transmembrane RPTP $\beta$ . NG2 is a transmembrane CSPG and has no significant homologies to other CSPGs. Because removing GAGs or preventing their sulfation neutralizes most suppression of axon growth by CSPGs *in vitro* (Gilbert et al., 2005; Sherman and Back, 2008; Wang et al., 2008), the sulfated GAG chains play crucial roles for CSPG function. CSPGs has been known to impede axon elongation for almost three decades, but the detailed mechanisms are not well known. The general mechanisms identified include binding functional CSPG receptors on neuronal membrane, formation of non-permissive PNNs that causes steric hindrance of growth-promoting adhesion molecules such as laminin and integrins, and facilitating functions of chemo-repulsive molecules, such as Sema 3A and 5A (Condic et al., 1999; Kantor et al., 2004; Tan et al., 2011). Transmembrane receptors appear important in conveying CSPG inhibition, including PTP $\sigma$ , LAR, and Nogo receptors 1 and 3 (Dickendesher et al., 2012; Fisher et al., 2011; Lang et al., 2015; Shen et al., 2009; Xu et al., 2015). Especially, PTP $\sigma$  and LAR bind CSPGs with high affinity and convey their inhibitions of axon extension after CNS injury.

CSPG neurocan can bind and interact with PTP $\sigma$  through the CSPG GAG chains and a few positively-charged residues in the first Ig-like domain of PTP $\sigma$  (Shen et al., 2009). DRGs derived from PTP $\sigma$  deficient mice increased neurite growth on CSPG and this effect was specific to CSPG because PTP $\sigma$  deletion does not overcome suppression of myelin-associated glycoprotein. PTP $\sigma$  knockout mice showed regeneration of lesioned ascending sensory neurons into the CSPG-rich lesion area

although regenerating axons failed to pass injured area (Shen et al., 2009). Corticospinal tract (CST) axons regrew into and beyond the lesion area in adult PTP $\sigma$  knockout mice after spinal cord injury (SCI) (Fry et al., 2010). Consistently, PTP $\sigma$  knockout mice exhibited enhanced regeneration of optic nerve and peripheral nerve after injury (McLean et al., 2002; Sapieha et al., 2005; Thompson et al., 2003). Moreover, PTP $\sigma$  plays a crucial role in converting growth cones into a dystrophic state by tightly stabilizing them within CSPG substrates. Systemic treatment with a membrane permeable peptide mimetic of the PTP $\sigma$  wedge domain, which regulates a variety of downstream signaling, restored extensive serotonergic innervation to the spinal cord caudal to lesion and promoted recovery of locomotor and urinary functions in adult rats with contusive SCI (Lang et al., 2015).

Similarly, CSPGs bind LAR dose-dependently also through CSPG GAG chains and the first Ig-like domain of LAR. LAR inhibition by transgenic deletion or pharmacological blockade with sequence-targeting blocking small peptides stimulated regrowth of serotonergic and CST axons, and functional recovery after transection SCI (Fisher et al., 2011; Xu et al., 2015). As another member of type IIa RPTPs, whether PTP $\delta$  also mediates CSPG suppression as a transmembrane receptor is unknown. However, PTP $\delta$  has recently been reported to contribute to Semaphorin-3A mediated growth cone collapse response in neuronal cultures probably by dephosphorylating tyrosine residues at the C-terminus of Fyn and activating this kinase (Nakamura et al., 2017). Notably, Semaphorin-3A is a component of PNN together with CSPGs and is able to bind the sugar chains of CSPGs with high affinity (Carulli et al., 2013).

Both CSPGs and HSPGs are the ligands of PTP $\sigma$  in nervous system with a similar binding affinity. Crystallographic analysis suggests that CSPGs can prevent PTP $\sigma$  dimerization (Fig. 1B), while HSPGs induce PTP $\sigma$  clustering (Coles et al., 2014; Coles et al., 2011). CSPGs and HSPGs share the same binding site of PTP $\sigma$  in the first Ig-like domain and they compete for PTP $\sigma$  binding, resulting in opposite effects on axon elongation. CSPGs inhibit axon outgrowth in neurons derived from wild-type mice, but this effect is diminished in PTP $\sigma$ -deficient neurons (Fry et al., 2010; Sapieha et al., 2005; Shen et al., 2009; Thompson et al., 2003). In contrast, HSPGs dramatically promote axon outgrowth in wild-type, but not PTP $\sigma$ -deficient neurons. Therefore, the CSPGs/HSPGs ratio is critical for determining PTP $\sigma$  dimerization status in regulating axon growth. However, some issues remain regarding the interactions between proteoglycans and RPTPs. The CS-C GAG chain used in previous study (Coles et al., 2011) did not bind to PTP $\sigma$  (Dickendeshner et al., 2012). Recently, Geller's group found that the fourth FNIII-containing domain of PTP $\sigma$  alone could bind to HSPG heparin independently of three Ig domains, but not to CS-E or dermatan sulfate (Katagiri et al., 2017). It will be interesting to further study detailed mechanisms for interactions between CSPGs/HSPGs and PTP $\sigma$  and potential role of the newly-identified binding domain of PTP $\sigma$  for heparin.

Several other studies further support that PTP $\sigma$  and LAR are important functional receptors for CSPGs. Newly-formed neurons from neuronal restricted precursors are intrinsically insensitive to CSPGs because low level expression of PTP $\sigma$  and LAR. Several factors secreted by cultured neuronal and glial restricted precursors decrease CSPG inhibition and stimulate axon growth *in vitro* (Ketschek et al., 2012). Both PTP $\sigma$  and LAR are expressed selectively in bad-regenerating neurons and have overlapping cellular distributions in Lamprey, a type of jawless fish (G. Zhang et al., 2014), indicating that PTP $\sigma$  and LAR mediate poor intrinsic regenerative capacity of bad-regenerating neurons and also serve as functional receptors for CSPGs in non-mammals.

PTP $\sigma$  and LAR mediate CSPG inhibitions through both convergent and divergent downstream pathways in neurons. Recently, we compared effects of PTP $\sigma$  and LAR on the activities of multiple signaling molecules using cultures of a neuronal cell line (Neuro-2A) to over-express these receptors and primary cultures of postnatal cerebellar neurons derived from knockout mice (Fisher et al., 2011; Ohtake et al.,

2016). PTP $\sigma$  and LAR employ a few signaling pathways commonly, including RhoA, Akt, extracellular signal-regulated kinase (Erk) and microtubule-associated protein 1B (MAP1B). Their actions in transmitting CSPG effects to inhibit axon growth also involve distinct signal molecules, including the use by PTP $\sigma$  of collapsing response mediator protein 2 (CRMP2, Fig. 1B), adenomatous polyposis coli (APC), S6 ribosomal protein (S6) and cAMP response element-binding protein (CREB), whereas the use by LAR of cofilin, protein kinase C $\zeta$  (PKC $\zeta$ ) and liver kinase B1 (LKB1). Consistent with these results, deletion of both PTP $\sigma$  and LAR showed additive effects in enhancement of axon growth in adult neurons *in vitro*. Thus, several intracellular signaling pathways are known to mediate CSPG actions through the RPTP receptors.

Previous reports also suggest that CSPGs use diverse pathways to suppress neuronal growth, including glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) and PKC (Dill et al., 2008; Powell et al., 2001). Cultured axons contain transcripts encoding RhoA and applying CSPGs to axon compartment enhanced axonal RhoA synthesis (Walker et al., 2012). Inhibition of RhoA transcripts in axons increased their growth in the presence of CSPGs. Treatment of neurons with LAR inhibitory peptides or deletion of PTP $\sigma$  elevated both Erk and Akt activities (Sapieha et al., 2005; Xie et al., 2001). In spite of recent progress in understanding intracellular signals of CSPGs, further studies are required to clarify some issues remained. For examples, Rho/Rock pathways inhibit both cofilin and CRMP2, but only PTP $\sigma$  inhibits CRMP2 whereas only LAR inhibits cofilin (Ohtake et al., 2016). Likewise, mTOR/S6 and CREB are activated by Akt and Erk, but only PTP $\sigma$  inhibits S6 and CREB signaling pathways.

## 5. PTP $\sigma$ regulates functions of immune cells and development of autoimmune diseases

PTP $\sigma$  is expressed by immune cells and has important functions in the immune system (Fig. 2). PTP $\sigma$ , but not LAR and PTP $\delta$ , is expressed in human pDCs controlled by transcription factor E2-2 (Bunin et al., 2015). PTP $\sigma$  is rapidly downregulated by pDC activation and its deficiency induces production of interferon  $\alpha$  (IFN $\alpha$ ) in pDCs. Antibody-mediated forced PTP $\sigma$  activation inhibited Toll-like receptor 9-mediated pDC activation. pDCs can secrete type I IFN (IFN $\alpha$  or  $\beta$ ) rapidly and abundantly in response to various stimuli and regulate viral infections through virus-specific T-cell responses. Accordingly, hyperactivation of pDCs is implicated in several autoimmune diseases, including inflammatory bowel disease (Cervantes-Barragan et al., 2012; Ganguly et al., 2013; Swiecki et al., 2010). DC-specific deletion of PTP $\sigma$  in mice with a LAR null background leads to IFN production by pDCs, leukocyte infiltration and mild spontaneous colitis (Bunin et al., 2015). Consistently, three single nucleotide polymorphisms (SNPs) in human PTPRS (PTP $\sigma$ ) gene have been linked to ulcerative colitis, an inflammatory bowel disease characterized by dysregulation of autoimmune responses (Muisse et al., 2007). PTP $\sigma$  normally functions as a positive regulator of intestinal epithelial barrier by orchestrating epithelial cell adhesion through targeting of adherens junction proteins, including E-cadherin,  $\beta$ -catenin and ezrin (Murchie et al., 2014). Together, PTP $\sigma$  is essential to balance DC tyrosine phosphorylation mediated by various kinases (Fujita et al., 2013) and to inhibit tyrosine phosphorylation-dependent pDC activation, spontaneous IFN production and immune-mediated intestinal inflammation.

We recently identified critical role of PTP $\sigma$  in regulating autoimmune disorders in the nervous system and extended the function of PTP $\sigma$  in immune system (Ohtake et al., 2017). We demonstrate that transgenic deletion or pharmacological inhibition of PTP $\sigma$  significantly exacerbates clinical symptoms and axon/myelin damages in the spinal cord of mice with experimental autoimmune encephalomyelitis (EAE), a widely-used model for multiple sclerosis (MS). Following immunization with myelin oligodendrocyte glycoprotein (MOG) peptide, PTP $\sigma$  knockout mice showed pro-inflammatory responses in the spinal cord and lymphoid organs by changing expression levels of various

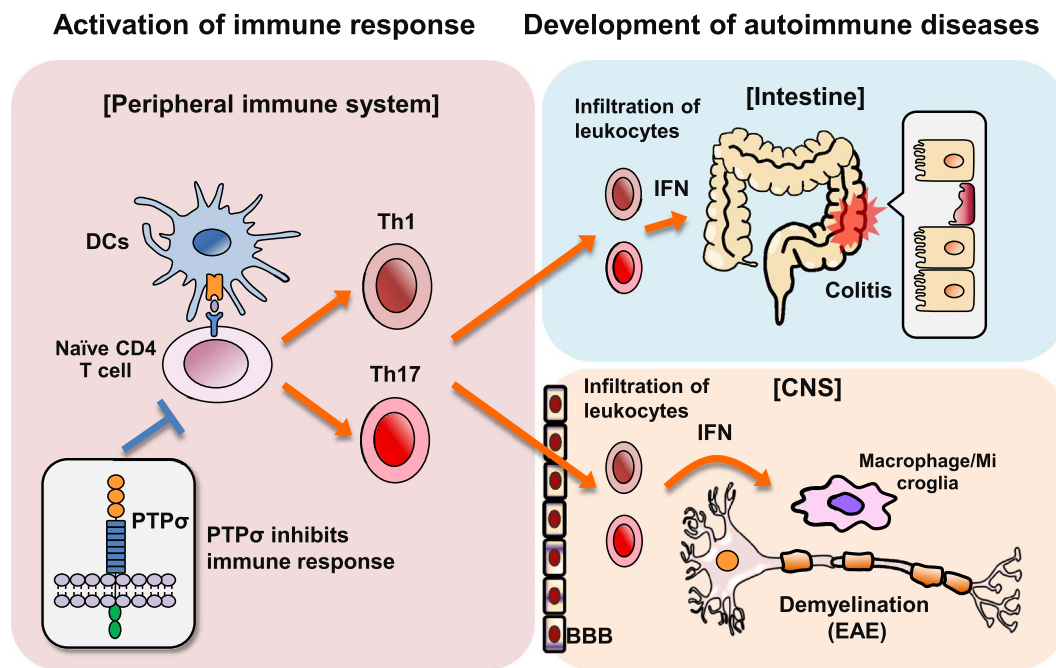


Fig. 2. PTP $\sigma$  inhibits activation of immune cells and development of autoimmune diseases, including colitis and EAE. PTP $\sigma$  deficiency induces activation of DCs (cDC and pDC), differentiation of CD4 $^{+}$  T cells into specific Th1 and Th17 cells, infiltration of leukocytes and generation of pro-inflammatory related cytokines including IFN. Thus, PTP $\sigma$  inhibition facilitates development of autoimmune diseases, such as colitis and CNS autoimmune demyelinating disease EAE.

inflammatory-related genes, including specific cytokines (*Ifng* and *Il17a*) and chemokines (*Ccl2*, *Ccl5* and *Cxcl10*) (Ohtake et al., 2017). Interestingly, PTP $\sigma$  deficiency stimulated activation of conventional DCs (cDCs), affected differentiation of CD4 $^{+}$  T lymphocytes directly, reduced number of regulatory T (Treg) cells, and facilitated infiltration of T cells and activation of macrophages and microglia in the CNS (Fig. 2). Moreover, adoptive transfer of PTP $\sigma$ -deficient cDCs stimulated with lipopolysaccharide to wild-type mice augmented EAE clinical symptoms following pulsed MOG<sub>35–55</sub> peptide immunization. PTP $\sigma$  deletion also enhanced expression of genes mediating immune responses, including *Tbx21* in Th1 and *Rorc* in Th17 cells (Ohtake et al., 2017). Consistently, PTP $\sigma$  deficiency has been reported to reduce expression level of *Foxp3*, a lineage-specific marker for Treg (Fontenot et al., 2005; Ziegler, 2006), which delay the onset of spontaneous EAE (Lowther et al., 2013). Therefore, PTP $\sigma$  is an important negative regulator for activation of pro-inflammatory responses of cDCs, differentiation of CD4 $^{+}$  T cells into Th1 and Th17 cells, and development of a CNS autoimmune disease. Notable, it is interesting to determine whether PTP $\sigma$  directly regulates function of myelinating glia. PTP $\zeta$  (PTPRZ), a member in the RPTP family, plays a negative role in oligodendrocyte differentiation during CNS development and remyelination in demyelinating CNS diseases by increasing apoptosis of mature oligodendrocytes (Harroch et al., 2002; Kuboyama et al., 2012).

PTP $\sigma$  appears to regulate immune responses as a receptor of various immune cells by mediating constitutive signaling derived from the ECM ligands. The upstream signaling and physiological ligands that modulate PTP $\sigma$  activity in immune cells or other cell types remain to be defined. HSPGs, the known ligands of RPTPs, have been reported to inhibit IFN production by macrophages in atherosclerosis mouse model (Gordts et al., 2014). Syndecan-1, a HSPG, could suppress various inflammatory responses and EAE development in mice and its deficiency exacerbated disease symptoms and impaired recovery in EAE mice (X. Zhang et al., 2013). In contrast, inhibition of CSPGs (also recognized ligands for RPTPs, but distinct type of proteoglycans from HSPGs) may become a therapeutic approach for autoimmune disease of MS. CSPGs are upregulated around the edge of MS lesions, whereas reduced in the center of active and chronic inactive plaques (Sobel and Ahmed, 2001).

Treatment with disaccharidic degradation product of CSPGs significantly alleviated clinical symptoms in EAE mice through reducing IFN $\gamma$  and TNF $\alpha$  production by splenocytes (Rolls et al., 2006; Zhou et al., 2010). Moreover, some cytokines, such as IFN $\gamma$  and TGF $\beta$ 1, could alter the expression level of CSPGs (Fujiyoshi et al., 2010; Smith and Strunz, 2005).

Also as a member of type IIa RPTPs, LAR is expressed during a certain stage of thymocyte development, but not in B cells. The physiological function of LAR in immune system remains controversial. One study indicates that the phosphatase activity of LAR is not required for T-cell development, repertoire selection and function (Terszowski et al., 2001), but the other group reported that LAR deficiency affected differentiation and expansion of immature thymocytes as well as negative and positive selection (Kondo et al., 2010). Moreover, T-cell receptor stimulation in response to calcium was significantly lower in thymocytes from LAR knockout mice, suggesting that LAR modulates T-cell receptor signaling for thymocyte differentiation.

## 6. PTP $\sigma$ is a therapeutic molecular target for CNS injury and autoimmune disorders

Surmounting potent inhibition by CSPG-rich scar and its receptor-mediated downstream signaling is an important therapeutic target for achieving successful axon regeneration and functional recovery after CNS injuries. So far, the main *in vivo* therapeutic approach to overcome inhibition of CSPGs is enzymatic digestion with local application of ChABC. However, several disadvantages may prevent using this enzyme as a therapeutic choice for patients. ChABC cannot completely digest GAG chains from core glycoproteins and may leave undigested carbohydrate side chains on the molecules, which though less potent are still inhibitory (Lemons et al., 2003). ChABC loses its enzymatic activity rapidly at body temperature and cannot cross the blood brain barrier. A group attempted to generate the thermostabilized ChABC (Lee et al., 2010). A single local application could not be sufficient to overcome the inhibition due to continuous generation of CSPGs after injury. Bacterial ChABC may also induce autoimmune reactions after pulsed injections. Therefore, new strategies to overcome inhibitory effects by CSPGs are

required to facilitate CNS axon regeneration and functional recovery. An alternative approach to overcome scar-sourced inhibition is to design novel compounds that block functions of CSPGs or their receptors, including PTP $\sigma$ .

In contrast to invasive approach of applying ChABC locally, systemic administration of peptides, antibodies and chemicals could block CSPG inhibition efficiently. A peptide (called intracellular PTP $\sigma$  peptide, ISP) mimetic of the catalytic domain of PTP $\sigma$  could overcome CSPG inhibition efficiently. Systemic treatment with ISP enhanced serotonergic axon regrowth and facilitated functional recovery of locomotor and urinary systems in rat with contusive SCI (Lang et al., 2015). Previously, we demonstrated that peptide antagonists for LAR reduced CSPG inhibition *in vitro* and increased descending serotonergic axon growth and promoted sustained locomotor recovery in SCI mice after systemic administration (Fisher et al., 2011). Consistently, silencing PTP $\sigma$  with lentivirus-mediated RNA interference promoted axon regeneration, synapse formation, and recovery of motor and sensory functions without affecting scar formation in rats with contusion SCI (Zhou et al., 2014). Because PTP $\sigma$  dimerization suppresses its phosphatase activity and CSPGs activate PTP $\sigma$  by preventing it from dimerizing after binding as ligands, the approach to induce and stabilize PTP $\sigma$  dimerization could be effective for blocking its function. Indeed, a new PTP $\sigma$  IgG monoclonal antibody could induce PTP $\sigma$  dimerization and promote neurite outgrowth in SH-SY5Y cells, a neuroblastoma cell line (Wu et al., 2017). Recently, a novel CSPG inhibitor, fluorosamine (peracetylated 4-fluorinated analog of glucosamine) has been shown to reduce CSPG contents and to promote process outgrowth and differentiation in oligodendrocyte precursor cells, thus accelerating remyelination after focal CNS demyelination in mice (Keough et al., 2016). Therefore, blocking CSPGs, their receptors, or CSPG-receptor interactions could overcome scar-mediated growth inhibitions and promote functional recovery after CNS injury. Given that multiple factors contribute to the repair failure after CNS injury, combing CSPG signaling blockade with other strategies, such as cell transplantation, is likely to be more effective.

Suppressing DC activation mediated by PTP $\sigma$  may become an attractive immunotherapy for several immune diseases. PTP $\sigma$  act as an inhibitory receptor on DCs that prevents DC hyperactivation, subsequent IFN production, and autoimmune related inflammation. pDC hyperactivation occurred in inflammatory bowel disease (Baumgart et al., 2011) and in colitis associated with Wiskott-Aldrich syndrome (Prete et al., 2013). Increased numbers of cDCs and pDCs accumulated in the cerebrospinal fluid and white matter of MS patients (Lande et al., 2008; Prete et al., 2013) and abnormalities in DCs have been associated with several stages of MS related disorders. Because PTP $\sigma$  is important for suppressing immune and autoimmune responses mediated by pDCs, cDCs, CD4+ T lymphocytes and other cells, and its suppression contributes to various immune-related diseases, such as EAE and spontaneous mild colitis (Bunin et al., 2015; Ohtake et al., 2017), selective activation of this signaling protein may become an effective strategy for treating autoimmune related disorders.

Both PTP $\sigma$  and its ligands, such as CSPGs, may become molecular targets for treating MS related disorders and other immune diseases. Any approaches that block PTP $\sigma$  dimerization might activate this phosphatase and reduce overactivation of immune cells. Treatment with the disaccharide degradation product of CSPG (CSPG-DS), a CSPG derivative, significantly decreases production of IFN $\gamma$  by brain-infiltrating lymphocytes in EAE mice (Rolls et al., 2006; Zhou et al., 2010). CSPG-DS treatment also markedly alleviated the clinical symptoms of EAE by reducing infiltrating T cells and activated microglia. In contrast, treatment with CS-A, a complete CS GAG chain unattached to proteoglycans, exacerbated EAE symptoms and increased infiltrated T cells in the CNS and their differentiation into pathogenic types of Th1 and Th17 (Zhou et al., 2010). It is interesting to dissect the precise mechanisms for CSPG-DS and CS-A to regulate EAE development and whether PTP $\sigma$  mediates these effects although CS-A does not bind PTP $\sigma$

(Dickendesher et al., 2012).

## 7. Prospective

PTP $\sigma$  plays important physiological and pathological roles in the nervous system of mammals during development and in adults. PTP $\sigma$  and other type IIa RPTPs are expressed in presynaptic terminals and make trans-synaptic adhesion complexes with post-synaptic adhesion molecules to organize synapse development and to modulate plasticity of mature neurons, including learning and memory. Importantly, PTP $\sigma$ , as well as LAR, functions as important receptors for CSPG inhibitors generated by reactive scar tissues. On the other hand, PTP $\sigma$  is expressed by various immune cells, especially pDCs, cDCs and CD4+ T cells, and plays crucial roles for regulating immune responses and development of autoimmune diseases, including EAE. The tremendous advances in our understanding of PTP $\sigma$  functions provide opportunity for developing effective therapeutic strategies for the disorders associated with dysfunctions of PTP $\sigma$  and its related genes. Because of the diverse regulatory roles of PTP $\sigma$  in different tissue systems, this phosphatase may become an important target for treating a number of human diseases, such as CNS injuries, MS and other autoimmune diseases. However, it seems important to develop effective approaches to target PTP $\sigma$  and its signaling pathway selectively. For example, PTP $\sigma$  suppression may have beneficial effects in the nervous system by promoting axon regeneration and neural repair, but it may also result in damaging roles in the other systems, such as inducing DC hyperactivation and autoimmune responses. Moreover, it is very important to further characterize functions of PTP $\sigma$  and related molecules, and their detailed cellular and molecular mechanisms in various cell types. Better understanding physiology and pathophysiology of PTP $\sigma$ -associated genes is likely to facilitate development of highly effective therapies for various neurological and autoimmune diseases.

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## References

- Abbott, A.P., Harris, R.C., Ryder, K.S., 2007. Application of hole theory to define ionic liquids by their transport properties. *J. Phys. Chem. B* 111, 4910–4913.
- Aricescu, A.R., McKinnell, I.W., Halfter, W., Stoker, A.W., 2002. Heparan sulfate proteoglycans are ligands for receptor protein tyrosine phosphatase sigma. *Mol. Cell. Biol.* 22, 1881–1892.
- Bandtlow, C.E., Zimmermann, D.R., 2000. Proteoglycans in the developing brain: new conceptual insights for old proteins. *Physiol. Rev.* 80, 1267–1290.
- Baumgart, D.C., Metzke, D., Guckelberger, O., Pascher, A., Grotzinger, C., Przesdzing, I., Dorffel, Y., Schmitz, J., Thomas, S., 2011. Aberrant plasmacytoid dendritic cell distribution and function in patients with Crohn's disease and ulcerative colitis. *Clin. Exp. Immunol.* 166, 46–54.
- Bradbury, E.J., Moon, L.D., Popat, R.J., King, V.R., Bennett, G.S., Patel, P.N., Fawcett, J.W., McMahon, S.B., 2002. Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature* 416, 636–640.
- Brakebusch, C., Seidenbecher, C.I., Asztely, F., Rauch, U., Matthies, H., Meyer, H., Krug, M., Bockers, T.M., Zhou, X., Kreutz, M.R., Montag, D., Gundelfinger, E.D., Fassler, R., 2002. Brevican-deficient mice display impaired hippocampal CA1 long-term potentiation but show no obvious deficits in learning and memory. *Mol. Cell. Biol.* 22, 7417–7427.
- Brown, J.M., Xia, J., Zhuang, B., Cho, K.S., Rogers, C.J., Gama, C.I., Rawat, M., Tully, S.E., Uetani, N., Mason, D.E., Tremblay, M.L., Peters, E.C., Habuchi, O., Chen, D.F., Hsieh-Wilson, L.C., 2012. A sulfated carbohydrate epitope inhibits axon regeneration after injury. *Proc. Natl. Acad. Sci. U. S. A.* 109, 4768–4773.
- Bukalo, O., Schachner, M., Dityatev, A., 2001. Modification of extracellular matrix by enzymatic removal of chondroitin sulfate and by lack of tenascin-R differentially affects several forms of synaptic plasticity in the hippocampus. *Neuroscience* 104, 359–369.
- Bunin, A., Sisirak, V., Ghosh, H.S., Grajkowska, L.T., Hou, Z.E., Miron, M., Yang, C., Ceribelli, M., Uetani, N., Chaperot, L., Plumas, J., Hendriks, W., Tremblay, M.L., Hacker, H., Staudt, L.M., Green, P.H., Bhagat, G., Reizis, B., 2015. Protein tyrosine phosphatase PTPRS is an inhibitory receptor on human and murine plasmacytoid dendritic cells. *Immunity* 43, 277–288.
- Busch, S.A., Silver, J., 2007. The role of extracellular matrix in CNS regeneration. *Curr. Opin. Neurobiol.* 17, 120–127.

- Butterfield, K.C., Conovaloff, A., Caplan, M., Panitch, A., 2010. Chondroitin sulfate-binding peptides block chondroitin 6-sulfate inhibition of cortical neurite growth. *Neurosci. Lett.* 478, 82–87.
- Carulli, D., Foscarin, S., Faralli, A., Pajaj, E., Rossi, F., 2013. Modulation of semaphorin3A in perineuronal nets during structural plasticity in the adult cerebellum. *Mol. Cell. Neurosci.* 57, 10–22.
- Cervantes-Barragan, L., Lewis, K.L., Firner, S., Thiel, V., Hugues, S., Reith, W., Ludewig, B., Reizis, B., 2012. Plasmacytoid dendritic cells control T-cell response to chronic viral infection. *Proc. Natl. Acad. Sci. U. S. A.* 109, 3012–3017.
- Coles, C.H., Shen, Y., Tenney, A.P., Siebold, C., Sutton, G.C., Lu, W., Gallagher, J.T., Jones, E.Y., Flanagan, J.G., Aricescu, A.R., 2011. Proteoglycan-specific molecular switch for RPTPsigma clustering and neuronal extension. *Science* (New York, N.Y.) 332, 484–488.
- Coles, C.H., Mitakidis, N., Zhang, P., Elegheert, J., Lu, W., Stoker, A.W., Nakagawa, T., Craig, A.M., Jones, E.Y., Aricescu, A.R., 2014. Structural basis for extracellular cis and trans RPTPsigma signal competition in synaptogenesis. *Nat. Commun.* 5, 5209.
- Condic, M.L., Snow, D.M., Letourneau, P.C., 1999. Embryonic neurons adapt to the inhibitory proteoglycan aggrecan by increasing integrin expression. *J. Neurosci.* 19, 10036–10043.
- Dickendesh, T.L., Baldwin, K.T., Mironova, Y.A., Koriyama, Y., Raiker, S.J., Askew, K.L., Wood, A., Geoffroy, C.G., Zheng, B., Liepmann, C.D., Katagiri, Y., Benowitz, L.I., Geller, H.M., Giger, R.J., 2012. Ngr1 and Ngr3 are receptors for chondroitin sulfate proteoglycans. *Nat. Neurosci.* 15, 703–712.
- Dill, J., Wang, H., Zhou, F.Q., Li, S., 2008. Inactivation of glycogen synthase kinase-3 promotes axonal growth and recovery in the CNS. *J. Neurosci.* 28, 8914–8928.
- Dunah, A.W., Hueske, E., Wyszynski, M., Hoogenraad, C.C., Jaworski, J., Pak, D.T., Simonetta, A., Liu, G., Sheng, M., 2005. LAR receptor protein tyrosine phosphatases in the development and maintenance of excitatory synapses. *Nat. Neurosci.* 8, 458–467.
- Fisher, D., Xing, B., Dill, J., Li, H., Hoang, H.H., Zhao, Z., Yang, X.L., Bachoo, R., Cannon, S., Longo, F.M., Sheng, M., Silver, J., Li, S., 2011. Leukocyte common antigen-related phosphatase is a functional receptor for chondroitin sulfate proteoglycan axon growth inhibitors. *J. Neurosci.* 31, 14051–14066.
- Fontenot, J.D., Rasmussen, J.P., Williams, L.M., Dooley, J.L., Farr, A.G., Rudenski, A.Y., 2005. Regulatory T cell lineage specification by the forkhead transcription factor foxp3. *Immunity* 22, 329–341.
- Fry, E.J., Chagnon, M.J., Lopez-Vales, R., Tremblay, M.L., David, S., 2010. Corticospinal tract regeneration after spinal cord injury in receptor protein tyrosine phosphatase sigma deficient mice. *Glia* 58, 423–433.
- Fujita, H., Kitawaki, T., Sato, T., Maeda, T., Kamihira, S., Takaori-Kondo, A., Kadowaki, N., 2013. The tyrosine kinase inhibitor dasatinib suppresses cytokine production by plasmacytoid dendritic cells by targeting endosomal transport of CpG DNA. *Eur. J. Immunol.* 43, 93–103.
- Fujiyoshi, T., Kubo, T., Chan, C.C., Koda, M., Okawa, A., Takahashi, K., Yamazaki, M., 2010. Interferon-gamma decreases chondroitin sulfate proteoglycan expression and enhances hindlimb function after spinal cord injury in mice. *J. Neurotrauma* 27, 2283–2294.
- Ganguly, D., Haak, S., Sisirak, V., Reizis, B., 2013. The role of dendritic cells in autoimmunity. *Nat. Rev.* 13, 566–577.
- Gilbert, R.J., McKeon, R.J., Darr, A., Calabro, A., Hascall, V.C., Bellamkonda, R.V., 2005. CS-4.6 is differentially upregulated in glial scar and is a potent inhibitor of neurite extension. *Mol. Cell. Neurosci.* 29, 545–558.
- Gogolla, N., Caroni, P., Luthi, A., Herry, C., 2009. Perineuronal nets protect fear memories from erasure. *Science* (New York, N.Y.) 325, 1258–1261.
- Gordts, P.L., Foley, E.M., Lawrence, R., Sinha, R., Lameda-Diaz, C., Deng, L., Nock, R., Glass, C.K., Erbilgin, A., Lusic, A.J., Witztum, J.L., Esko, J.D., 2014. Reducing macrophage proteoglycan sulfation increases atherosclerosis and obesity through enhanced type I interferon signaling. *Cell Metab.* 20, 813–826.
- Hagihara, K., Miura, R., Kosaki, R., Berglund, E., Ranscht, B., Yamaguchi, Y., 1999. Immunohistochemical evidence for the brevican-tenascin-R interaction: colocalization in perineuronal nets suggests a physiological role for the interaction in the adult rat brain. *J. Comp. Neurol.* 410, 256–264.
- Han, K.A., Jeon, S., Um, J.W., Ko, J., 2016. Emergent synapse organizers: LAR-RPTPs and their companions. *Int. Rev. Cell Mol. Biol.* 324, 39–65.
- Hantaz-Ambroise, D., Vigny, M., Koenig, J., 1987. Heparan sulfate proteoglycan and laminin mediate two different types of neurite outgrowth. *J. Neurosci.* 7, 2293–2304.
- Harroch, S., Furtado, G.C., Brueck, W., Rosenbluth, J., Lafaille, J., Chao, M., Buxbaum, J.D., Schlessinger, J., 2002. A critical role for the protein tyrosine phosphatase receptor type Z in functional recovery from demyelinating lesions. *Nat. Genet.* 32, 411–414.
- Horn, K.E., Xu, B., Gobert, D., Hamam, B.N., Thompson, K.M., Wu, C.L., Bouchard, J.F., Uetani, N., Racine, R.J., Tremblay, M.L., Ruthazer, E.S., Chapman, C.A., Kennedy, T.E., 2012. Receptor protein tyrosine phosphatase sigma regulates synapse structure, function and plasticity. *J. Neurochem.* 122, 147–161.
- Johnson, K.G., Tenney, A.P., Ghose, A., Duckworth, A.M., Higashi, M.E., Parfitt, K., Marcu, O., Heslip, T.R., Marsh, J.L., Schwarz, T.L., Flanagan, J.G., Van Vactor, D., 2006. The HSPGs Syndecan and Dallylike bind the receptor phosphatase LAR and exert distinct effects on synaptic development. *Neuron* 49, 517–531.
- Jones, L.L., Margolis, R.U., Tuszyński, M.H., 2003. The chondroitin sulfate proteoglycans neurocan, brevican, phosphacan, and versican are differentially regulated following spinal cord injury. *Exp. Neurol.* 182, 399–411.
- Kantor, D.B., Chivatarkam, O., Peer, K.L., Oster, S.F., Inatani, M., Hansen, M.J., Flanagan, J.G., Yamaguchi, Y., Sretavan, D.W., Giger, R.J., Kolodkin, A.L., 2004. Semaphorin 5A is a bifunctional axon guidance cue regulated by Heparan and chondroitin sulfate proteoglycans. *Neuron* 44, 961–975.
- Karumbaiah, L., Anand, S., Thazhath, R., Zhong, Y., McKeon, R.J., Bellamkonda, R.V., 2011. Targeted downregulation of N-acetylgalactosamine 4-sulfate 6-O-sulfotransferase significantly mitigates chondroitin sulfate proteoglycan-mediated inhibition. *Glia* 59, 981–996.
- Katagiri, H., Higashi, S., Morgan, A.A., Bangayan, N.J., Junka, R., Yu, P., Geller, H.M., 2017. Identification of a novel binding domain for heparin in RPTPσ, but not LAR or RPTPδ: implications for proteoglycan signaling. In: Neuroscience Meeting Planner: Society for Neuroscience Program No. 308.17/BB6.
- Keough, M.B., Rogers, J.A., Zhang, P., Jensen, S.K., Stephenson, E.L., Chen, T., Hurlbert, M.G., Lau, L.W., Rawji, K.S., Plemel, J.R., Koch, M., Ling, C.C., Yong, V.W., 2016. An inhibitor of chondroitin sulfate proteoglycan synthesis promotes central nervous system remyelination. *Nat. Commun.* 7, 11312.
- Ketschek, A.R., Haas, C., Gallo, G., Fischer, I., 2012. The roles of neuronal and glial precursors in overcoming chondroitin sulfate proteoglycan inhibition. *Exp. Neurol.* 235, 627–637.
- Kim, S., Burette, A., Chung, H.S., Kwon, S.K., Woo, J., Lee, H.W., Kim, K., Kim, H., Weinberg, R.J., Kim, E., 2006. NGL family PSD-95-interacting adhesion molecules regulate excitatory synapse formation. *Nat. Neurosci.* 9, 1294–1301.
- Kolkman, M.J., Streijger, F., Linkels, M., Bloemen, M., Heeren, D.J., Hendriks, W.J., Van der Zee, C.E., 2004. Mice lacking leukocyte common antigen-related (LAR) protein tyrosine phosphatase domains demonstrate spatial learning impairment in the two-trial water maze and hyperactivity in multiple behavioural tests. *Behav. Brain Res.* 154, 171–182.
- Kondo, S., Kishi, H., Muraguchi, A., 2010. Regulatory role of leukocyte-common-antigen-related molecule (LAR) in thymocyte differentiation. *Eur. J. Immunol.* 40, 1296–1302.
- Kuboyama, K., Fujikawa, A., Masumura, M., Suzuki, R., Matsumoto, M., Noda, M., 2012. Protein tyrosine phosphatase receptor type z negatively regulates oligodendrocyte differentiation and myelination. *PLoS One* 7, e48797.
- Kwok, J.C., Dick, G., Wang, D., Fawcett, J.W., 2011. Extracellular matrix and perineuronal nets in CNS repair. *Dev. Neurobiol.* 71, 1073–1089.
- Kwon, S.K., Woo, J., Kim, S.Y., Kim, H., Kim, E., 2010. Trans-synaptic adhesions between netrin-G ligand-3 (NGL-3) and receptor tyrosine phosphatases LAR, protein-tyrosine phosphatase delta (PTPdelta), and PTPsigma via specific domains regulate excitatory synapse formation. *J. Biol. Chem.* 285, 13966–13978.
- Lande, R., Gafa, V., Serafini, B., Giacomini, E., Visconti, A., Remoli, M.E., Severa, M., Parenterini, M., Ristori, G., Salvetti, M., Aloisi, F., Cocchia, E.M., 2008. Plasmacytoid dendritic cells in multiple sclerosis: intracerebral recruitment and impaired maturation in response to interferon-beta. *J. Neuropathol. Exp. Neurol.* 67, 388–401.
- Lander, A.D., Fujii, D.K., Gospodarowicz, D., Reichardt, L.F., 1982. Characterization of a factor that promotes neurite outgrowth: evidence linking activity to a heparan sulfate proteoglycan. *J. Cell Biol.* 94, 574–585.
- Lang, B.T., Cregg, J.M., DePaul, M.A., Tran, A.P., Xu, K., Dyck, S.M., Madalena, K.M., Brown, B.P., Weng, Y.L., Li, S., Karimi-Abdolrezaee, S., Busch, S.A., Shen, Y., Silver, J., 2015. Modulation of the proteoglycan receptor PTPsigma promotes recovery after spinal cord injury. *Nature* 518, 404–408.
- Lee, H., McKeon, R.J., Bellamkonda, R.V., 2010. Sustained delivery of thermostabilized chABC enhances axonal sprouting and functional recovery after spinal cord injury. *Proc. Natl. Acad. Sci. U. S. A.* 107, 3340–3345.
- Lemons, M.L., Sandy, J.D., Anderson, D.K., Howland, D.R., 2003. Intact aggrecan and chondroitin sulfate-depleted aggrecan core glycoprotein inhibit axon growth in the adult rat spinal cord. *Exp. Neurol.* 184, 981–990.
- Lindahl, U., Couchman, J., Kimata, K., Esko, J.D., 2015. Proteoglycans and Sulfated Glycosaminoglycans. In: Varki, A., Cummings, R.D., Esko, J.D., Stanley, P., Hart, G.W., Aebi, M., Darvill, A.G., Kinoshita, T., Packer, N.H., Prestegard, J.H., Schnaar, R.L., Seeberger, P.H. (Eds.), *Essentials of Glycobiology*, Cold Spring Harbor (NY), pp. 207–221.
- Longo, F.M., Martignetti, J.A., Le Beau, J.M., Zhang, J.S., Barnes, J.P., Brosius, J., 1993. Leukocyte common antigen-related receptor-linked tyrosine phosphatase. Regulation of mRNA expression. *J. Biol. Chem.* 268, 26503–26511.
- Lowther, D.E., Chong, D.L., Ascough, S., Ertorre, A., Ingram, R.J., Boyton, R.J., Altmann, D.M., 2013. Th1 not Th17 cells drive spontaneous MS-like disease despite a functional regulatory T cell response. *Acta Neuropathol.* 126, 501–515.
- Massey, J.M., Hubscher, C.H., Wagoner, M.R., Decker, J.A., Amps, J., Silver, J., Onifer, S.M., 2006. Chondroitinase ABC digestion of the perineuronal net promotes functional collateral sprouting in the cuneate nucleus after cervical spinal cord injury. *J. Neurosci.* 26, 4406–4414.
- McLean, J., Batt, J., Doering, L.C., Rotin, D., Bain, J.R., 2002. Enhanced rate of nerve regeneration and directional returns after sciatic nerve injury in receptor protein tyrosine phosphatase sigma knock-out mice. *J. Neurosci.* 22, 5481–5491.
- Meathrel, K., Adamek, T., Batt, J., Rotin, D., Doering, L.C., 2002. Protein tyrosine phosphatase sigma-deficient mice show aberrant cytoarchitecture and structural abnormalities in the central nervous system. *J. Neurosci. Res.* 70, 24–35.
- Miller, G.M., Hsieh-Wilson, L.C., 2015. Sugar-dependent modulation of neuronal development, regeneration, and plasticity by chondroitin sulfate proteoglycans. *Exp. Neurol.* 274, 115–125.
- Muise, A.M., Walters, T., Wine, E., Griffiths, A.M., Turner, D., Duerr, R.H., Regueiro, M.D., Ngan, B.Y., Xu, W., Sherman, P.M., Silverberg, M.S., Rotin, D., 2007. Protein tyrosine phosphatase sigma is associated with ulcerative colitis. *Curr. Biol.* 17, 1212–1218.
- Murchie, R., Guo, C.H., Persaud, A., Muise, A., Rotin, D., 2014. Protein tyrosine phosphatase sigma targets apical junction complex proteins in the intestine and regulates epithelial permeability. *Proc. Natl. Acad. Sci. U. S. A.* 111, 693–698.
- Nakamura, F., Okada, T., Shishikura, M., Uetani, N., Taniguchi, M., Yagi, T., Iwakura, Y., Ohshima, T., Goshima, Y., Strittmatter, S.M., 2017. Protein tyrosine phosphatase delta mediates the Sema3A-induced cortical basal dendritic Arborization through the activation of Fyn tyrosine kinase. *J. Neurosci.* 37, 7125–7139.
- Ohtake, Y., Li, S., 2015. Molecular mechanisms of scar-sourced axon growth inhibitors. *Brain Res.* 1619, 22–35.
- Ohtake, Y., Wong, D., Abdul-Muneer, P.M., Selzer, M.E., Li, S., 2016. Two PTP receptors mediate CSPG inhibition by convergent and divergent signaling pathways in neurons. *Sci. Rep.* 6, 37152.
- Ohtake, Y., Kong, W., Hussain, R., Horiuchi, M., Tremblay, M.L., Ganea, D., Li, S., 2017. Protein tyrosine phosphatase sigma regulates autoimmune encephalomyelitis development. *Brain Behav. Immun.* 65, 111–124.



- Pawlowsky, A., Gianfelice, A., Pallotto, M., Zanchi, A., Vara, H., Khelfaoui, M., Valnegri, P., Rezaei, X., Bassani, S., Brambilla, D., Kumpost, J., Blahos, J., Roux, M.J., Humeau, Y., Chelly, J., Passafaro, M., Giustetto, M., Billuart, P., Sala, C., 2010. A postsynaptic signaling pathway that may account for the cognitive defect due to IL1RAPL1 mutation. *Curr. Biol.* 20, 103–115.
- Pike, K.A., Tremblay, M.L., 2013. Regulating naive and memory CD8 T cell homeostasis—a role for protein tyrosine phosphatases. *FEBS J.* 280, 432–444.
- Powell, E.M., Mercado, M.L., Calle-Patino, Y., Geller, H.M., 2001. Protein kinase C mediates neurite guidance at an astrocyte boundary. *Glia* 33, 288–297.
- Prete, F., Catucci, M., Labrada, M., Gobessi, S., Castiello, M.C., Bonomi, E., Aiuti, A., Vermi, W., Cancrini, C., Metin, A., Hambleton, S., Bredius, R., Notarangelo, L.D., van der Burg, M., Kalinke, U., Villa, A., Benvenuti, F., 2013. Wiskott-Aldrich syndrome protein-mediated actin dynamics control type-I interferon production in plasmacytoid dendritic cells. *J. Exp. Med.* 210, 355–374.
- Pulido, R., Serra-Pages, C., Tang, M., Streuli, M., 1995. The LAR/PTP delta/PTP sigma subfamily of transmembrane protein-tyrosine-phosphatases: multiple human LAR, PTP delta, and PTP sigma isoforms are expressed in a tissue-specific manner and associate with the LAR-interacting protein LIP.1. *Proc. Natl. Acad. Sci. U. S. A.* 92, 11686–11690.
- Pulsipher, A., Griffin, M.E., Stone, S.E., Brown, J.M., Hsieh-Wilson, L.C., 2014. Directing neuronal signaling through cell-surface glycan engineering. *J. Am. Chem. Soc.* 136, 6794–6797.
- Rolls, A., Cahalon, L., Bakalash, S., Avidan, H., Lider, O., Schwartz, M., 2006. A sulfated disaccharide derived from chondroitin sulfate proteoglycan protects against inflammation-associated neurodegeneration. *FASEB J.* 20, 547–549.
- Sapieha, P.S., Duplan, L., Uetani, N., Joly, S., Tremblay, M.L., Kennedy, T.E., Di Polo, A., 2005. Receptor protein tyrosine phosphatase sigma inhibits axon regrowth in the adult injured CNS. *Mol. Cell. Neurosci.* 28, 625–635.
- Schaapveld, R.Q., Schepens, J.T., Bachner, D., Attema, J., Wieringa, B., Jap, P.H., Hendriks, W.J., 1998. Developmental expression of the cell adhesion molecule-like protein tyrosine phosphatases LAR, RPTPdelta and RPTPsigma in the mouse. *Mech. Dev.* 77, 59–62.
- Shen, Y., Tenney, A.P., Busch, S.A., Horn, K.P., Cuascut, F.X., Liu, K., He, Z., Silver, J., Flanagan, J.G., 2009. PTPsigma is a receptor for chondroitin sulfate proteoglycan, an inhibitor of neural regeneration. *Science (New York, N.Y.)* 326, 592–596.
- Sherman, L.S., Back, S.A., 2008. A 'GAG' reflex prevents repair of the damaged CNS. *Trends Neurosci.* 31, 44–52.
- Shishikura, M., Nakamura, F., Yamashita, N., Uetani, N., Iwakura, Y., Goshima, Y., 2016. Expression of receptor protein tyrosine phosphatase delta, PTPdelta, in mouse central nervous system. *Brain Res.* 1642, 244–254.
- Silver, J., Miller, J.H., 2004. Regeneration beyond the glial scar. *Nat. Rev. Neurosci.* 5, 146–156.
- Smith, G.M., Strunz, C., 2005. Growth factor and cytokine regulation of chondroitin sulfate proteoglycans by astrocytes. *Glia* 52, 209–218.
- Smith, D.E., Lipsky, B.P., Russell, C., Ketchem, R.R., Kirchner, J., Hensley, K., Huang, Y., Friedman, W.J., Boissoneault, V., Plante, M.M., Rivest, S., Sims, J.E., 2009. A central nervous system-restricted isoform of the interleukin-1 receptor accessory protein modulates neuronal responses to interleukin-1. *Immunity* 30, 817–831.
- Snow, D.M., Letourneau, P.C., 1992. Neurite outgrowth on a step gradient of chondroitin sulfate proteoglycan (CS-PG). *J. Neurobiol.* 23, 322–336.
- Snow, D.M., Lemmon, V., Carrino, D.A., Caplan, A.L., Silver, J., 1990. Sulfated proteoglycans in astroglial barriers inhibit neurite outgrowth in vitro. *Exp. Neurol.* 109, 111–130.
- Snow, D.M., Watanabe, M., Letourneau, P.C., Silver, J., 1991. A chondroitin sulfate proteoglycan may influence the direction of retinal ganglion cell outgrowth. *Development (Cambridge, England)* 113, 1473–1485.
- Sobel, R.A., Ahmed, A.S., 2001. White matter extracellular matrix chondroitin sulfate/dermatan sulfate proteoglycans in multiple sclerosis. *J. Neuropathol. Exp. Neurol.* 60, 1198–1207.
- Sommer, L., Rao, M., Anderson, D.J., 1997. RPTP delta and the novel protein tyrosine phosphatase RPTP psi are expressed in restricted regions of the developing central nervous system. *Dev. Dyn.* 208, 48–61.
- Swiecki, M., Gilfillan, S., Vermi, W., Wang, Y., Colonna, M., 2010. Plasmacytoid dendritic cell ablation impacts early interferon responses and antiviral NK and CD8(+) T cell accrual. *Immunity* 33, 955–966.
- Takahashi, H., Craig, A.M., 2013. Protein tyrosine phosphatases PTPdelta, PTPsigma, and LAR: presynaptic hubs for synapse organization. *Trends Neurosci.* 36, 522–534.
- Takahashi, H., Arstikaitis, P., Prasad, T., Bartlett, T.E., Wang, Y.T., Murphy, T.H., Craig, A.M., 2011. Postsynaptic TrkC and presynaptic PTPsigma function as a bidirectional excitatory synaptic organizing complex. *Neuron* 69, 287–303.
- Takahashi, H., Katayama, K., Sohya, K., Miyamoto, H., Prasad, T., Matsumoto, Y., Ota, M., Yasuda, H., Tsumoto, T., Aruga, J., Craig, A.M., 2012. Selective control of inhibitory synapse development by Slitrk3-PTPdelta trans-synaptic interaction. *Nat. Neurosci.* 15 (389–398), S381–382.
- Tan, C.L., Kwok, J.C., Patani, R., Ffrench-Constant, C., Chandran, S., Fawcett, J.W., 2011. Integrin activation promotes axon growth on inhibitory chondroitin sulfate proteoglycans by enhancing integrin signaling. *J. Neurosci.* 31, 6289–6295.
- Terszowski, G., Jankowski, A., Hendriks, W.J., Rolink, A.G., Kisielow, P., 2001. Within the hemopoietic system, LAR phosphatase is a T cell lineage-specific adhesion receptor-like protein whose phosphatase activity appears dispensable for T cell development, repertoire selection and function. *Eur. J. Immunol.* 31, 832–840.
- Thompson, K.M., Uetani, N., Manitt, C., Elchebly, M., Tremblay, M.L., Kennedy, T.E., 2003. Receptor protein tyrosine phosphatase sigma inhibits axonal regeneration and the rate of axon extension. *Mol. Cell. Neurosci.* 23, 681–692.
- Tully, S.E., Mabon, R., Gama, C.I., Tsai, S.M., Liu, X., Hsieh-Wilson, L.C., 2004. A chondroitin sulfate small molecule that stimulates neuronal growth. *J. Am. Chem. Soc.* 126, 7736–7737.
- Uetani, N., Kato, K., Ogura, H., Mizuno, K., Kawano, K., Mikoshiba, K., Yakura, H., Asano, M., Iwakura, Y., 2000. Impaired learning with enhanced hippocampal long-term potentiation in PTPdelta-deficient mice. *EMBO J.* 19, 2775–2785.
- Uetani, N., Chagnon, M.J., Kennedy, T.E., Iwakura, Y., Tremblay, M.L., 2006. Mammalian motoneuron axon targeting requires receptor protein tyrosine phosphatases sigma and delta. *J. Neurosci.* 26, 5872–5880.
- Um, J.W., Ko, J., 2013. LAR-RPTPs: synaptic adhesion molecules that shape synapse development. *Trends Cell Biol.* 23, 465–475.
- Valnegri, P., Montrasio, C., Brambilla, D., Ko, J., Passafaro, M., Sala, C., 2011. The X-linked intellectual disability protein IL1RAPL1 regulates excitatory synapse formation by binding PTPdelta and RhoGAP2. *Hum. Mol. Genet.* 20, 4797–4809.
- Verna, J.M., Fichard, A., Saxod, R., 1989. Influence of glycosaminoglycans on neurite morphology and outgrowth patterns in vitro. *Int. J. Dev. Neurosci.* 7, 389–399.
- Walker, B.A., Ji, S.J., Jaffrey, S.R., 2012. Intra-axonal translation of RhoA promotes axon growth inhibition by CSPG. *J. Neurosci.* 32, 14442–14447.
- Walz, A., McFarlane, S., Brickman, Y.G., Nurcombe, V., Bartlett, P.F., Holt, C.E., 1997. Essential role of heparan sulfates in axon navigation and targeting in the developing visual system. *Development (Cambridge, England)* 124, 2421–2430.
- Wang, L., Denburg, J.L., 1992. A role for proteoglycans in the guidance of a subset of pioneer axons in cultured embryos of the cockroach. *Neuron* 8, 701–714.
- Wang, H., Yan, H., Canoll, P.D., Silvennoinen, O., Schlessinger, J., Musacchio, J.M., 1995. Expression of receptor protein tyrosine phosphatase-sigma (RPTP-sigma) in the nervous system of the developing and adult rat. *J. Neurosci. Res.* 41, 297–310.
- Wang, H., Katagiri, Y., McCann, T.E., Unsworth, E., Goldsmith, P., Yu, Z.X., Tan, F., Santiago, L., Mills, E.M., Wang, Y., Symes, A.J., Geller, H.M., 2008. Chondroitin-4-sulfation negatively regulates axonal guidance and growth. *J. Cell Sci.* 121, 3083–3091.
- Woo, J., Kwon, S.K., Choi, S., Kim, S., Lee, J.R., Dunah, A.W., Sheng, M., Kim, E., 2009. Trans-synaptic adhesion between NGL-3 and LAR regulates the formation of excitatory synapses. *Nat. Neurosci.* 12, 428–437.
- Wu, C.L., Hardy, S., Aubry, I., Landry, M., Haggarty, A., Saragovi, H.U., Tremblay, M.L., 2017. Identification of function-regulating antibodies targeting the receptor protein tyrosine phosphatase sigma ectodomain. *PLoS One* 12, e0178489.
- Wyszynski, M., Kim, E., Dunah, A.W., Passafaro, M., Valtchanoff, J.G., Serra-Pages, C., Streuli, M., Weinberg, R.J., Sheng, M., 2002. Interaction between GRIP and liprin-alpha/SYD2 is required for AMPA receptor targeting. *Neuron* 34, 39–52.
- Xie, Y., Yeo, T.T., Zhang, C., Yang, T., Tisi, M.A., Massa, S.M., Longo, F.M., 2001. The leukocyte common antigen-related protein tyrosine phosphatase receptor regulates regenerative neurite outgrowth in vivo. *J. Neurosci.* 21, 5130–5138.
- Xu, B., Park, D., Ohtake, Y., Li, H., Hayat, U., Liu, J., Selzer, M.E., Longo, F.M., Li, S., 2015. Role of CSPG receptor LAR phosphatase in restricting axon regeneration after CNS injury. *Neurobiol. Dis.* 73, 36–48.
- Yamaguchi, Y., 2000. Lecticans: organizers of the brain extracellular matrix. *Cell. Mol. Life Sci.* 57, 276–289.
- Yeo, T.T., Yang, T., Massa, S.M., Zhang, J.S., Honkaniemi, J., Butcher, L.L., Longo, F.M., 1997. Deficient LAR expression decreases basal forebrain cholinergic neuronal size and hippocampal cholinergic innervation. *J. Neurosci. Res.* 47, 348–360.
- Yi, J.H., Katagiri, Y., Yu, P., Lourie, J., Bangayan, N.J., Symes, A.J., Geller, H.M., 2014. Receptor protein tyrosine phosphatase sigma binds to neurons in the adult mouse brain. *Exp. Neurol.* 255, 12–18.
- Yim, Y.S., Kwon, Y., Nam, J., Yoon, H.I., Lee, K., Kim, D.G., Kim, E., Kim, C.H., Ko, J., 2013. Slitrks control excitatory and inhibitory synapse formation with LAR receptor protein tyrosine phosphatases. *Proc. Natl. Acad. Sci. U. S. A.* 110, 4057–4062.
- Yoshida, T., Yasumura, M., Uemura, T., Lee, S.J., Ra, M., Taguchi, R., Iwakura, Y., Mishina, M., 2011. IL-1 receptor accessory protein-like 1 associated with mental retardation and autism mediates synapse formation by trans-synaptic interaction with protein tyrosine phosphatase delta. *J. Neurosci.* 31, 13485–13499.
- Yoshida, T., Shiroshima, T., Lee, S.J., Yasumura, M., Uemura, T., Chen, X., Iwakura, Y., Mishina, M., 2012. Interleukin-1 receptor accessory protein organizes neuronal synaptogenesis as a cell adhesion molecule. *J. Neurosci.* 32, 2588–2600.
- Yu, P., Pearson, C.S., Geller, H.M., 2018. Flexible roles for proteoglycan sulfation and receptor signaling. *Trends Neurosci.* 41, 47–61.
- Zhang, J.S., Honkaniemi, J., Yang, T., Yeo, T.T., Longo, F.M., 1998. LAR tyrosine phosphatase receptor: a developmental isoform is present in neurites and growth cones and its expression is regional- and cell-specific. *Mol. Cell. Neurosci.* 10, 271–286.
- Zhang, X., Wu, C., Song, J., Gotte, M., Sorokin, L., 2013. Syndecan-1, a cell surface proteoglycan, negatively regulates initial leukocyte recruitment to the brain across the choroid plexus in murine experimental autoimmune encephalomyelitis. *J. Immunol.* 191, 4551–4561.
- Zhang, G., Hu, J., Li, S., Huang, L., Selzer, M.E., 2014. Selective expression of CSPG receptors PTPsigma and LAR in poorly regenerating reticulospinal neurons of lampry. *J. Comp. Neurol.* 522, 2209–2229.
- Zhou, J., Nagarkatti, P., Zhong, Y., Nagarkatti, M., 2010. Immune modulation by chondroitin sulfate and its degraded disaccharide product in the development of an experimental model of multiple sclerosis. *J. Neuroimmunol.* 223, 55–64.
- Zhou, H.X., Li, X.Y., Li, F.Y., Liu, C., Liang, Z.P., Liu, S., Zhang, B., Wang, T.Y., Chu, T.C., Lu, L., Ning, G.Z., Kong, X.H., Feng, S.Q., 2014. Targeting RPTPsigma with lentiviral shRNA promotes neurites outgrowth of cortical neurons and improves functional recovery in a rat spinal cord contusion model. *Brain Res.* 1586, 46–63.
- Ziegler, S.F., 2006. FOXP3: of mice and men. *Annu. Rev. Immunol.* 24, 209–226.