ACS Chemical Neuroscience

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Targeting Chondroitin Sulfate Proteoglycans: An Emerging Therapeutic Strategy to Treat CNS Injury

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Cite This: *ACS Chem. Neurosci.* 2020, 11, 231−232 Read Online

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ABSTRACT: Chondroitin sulfate proteoglycans (CSPGs) are the most abundant components of glial scar formed after severe traumatic brain injury as well as spinal cord injury and play a crucial inhibitory role in axonal regeneration by selective contraction of filopodia of the growth cone of sprouting neurites. Healing of central nervous system (CNS) injury requires degradation of the glycosamine glycan backbone of CSPGs in order to reduce the inhibitory effect of the CSPG layer. The key focus of this Viewpoint is to address a few important regenerative approaches useful for overcoming the inhibitory barrier caused by chondroitin sulfate proteoglycans.

KEYWORDS: *Central nervous system injury, axonal regeneration, glial scar, chondroitin sulfate proteoglycan, heparan sulfate proteoglycan, chondroitinase ABC enzyme*

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Central nervous system (CNS) injury results in the formation of severe glial scar circumnavigating the zone of injury. Glial scar is composed of highly proliferating and migrating glial cells, and the majority of them are reactive astrocytes along with microglia and oligodendrocyte precursors. The formation of glial scar reduces the chance of spreading inflammatory responses throughout the brain by precluding the injured zone from other parts. Along with these glial cells, upregulated expression of other extracellular matrix (ECM) molecules like GAG (glycosaminoglycan) proteoglycans, e.g., chondroitin sulfate proteoglycans (CSPGs), heparan sulfate proteoglycans (HSPGs), dermatan sulfate proteoglycans (DSPGs), and keratin sulfate proteoglycans (KSPGs) is also well documented. Depending upon the native protein chain structure, types of polysaccharide units, and number of sulfate substitutions, these proteoglycans have various developmental and regulatory roles in the central nervous system. Glial scar composed of these proteoglycans creates a thick protective sheet surrounding the injury site in order to seal the disrupted blood-brain barrier rapidly, but this apparently protective glial scar and its ECM associated proteoglycans, mainly CSPGs, are some of the major inhibitory factors which lead to dilapidated axon regeneration of severed neurons. Thus, treatment of CNS injury becomes complicated due to these two contrasting factors. It has been observed that the disrupted blood-brain barrier remains permeable until after 10−14 days of injury and CSPGs are secreted rapidly (within 24 h) at the site of injury and can persist for many months. Proteoglycan homeostasis plays a crucial role throughout the development of the brain and regulates the growth and direction of newly generated neurons. It has been found that CSPGs are upregulated in embryonic rat brain and impart repulsive guidance to the growing axons contrary to the attractive guidance mediated by HSPGs. The CSPG level gradually decreases throughout the brain development phase and exacerbates only after major CNS injury. These altogether indicate that proper balance of CSPGs and other proteoglycans is the key to neuronal development. Chondroitin sulfate (CSPG) consists of a glycosaminoglycan (GAG) moiety which is basically a disaccharide unit containing glucuronic acid and *N*-acetyl galactosamine. Aggrecan, brevican, phosphacan, and versican all are various members of the CSPG family. These GAG residues are attached to the oxygen atom of the serine residues of the main protein chain via O-xylose linkage to form CSPG proteoglycans. Snow et al.[1] first observed that CSPG proteoglycans specifically inhibit neurite outgrowth of developing neurons in vitro as well as in vivo and its inhibitory effect creates major regeneration barrier after severe TBI and spinal cord injury.[1] Further studies reveal that the glycosaminoglycan residues of chondroitin sulfate proteoglycan interact with several neuronal developments inhibiting receptors like Nogo receptor1 and 3,[2] protein tyrosine phosphatase (RPTP),[3] and leukocyte common antigen-related phosphatase (LAR) and thereby restrain regeneration of axons. In various in vitro experiments, it is concluded that the neurite growth is severely jeopardized on the interface of growth-inducing laminin and aggrecan proteoglycan, resulting in a dystrophic end bulb of the growth cone. CSPGs not only perturb the growth of injured neurons, but they also impart massive barriers in cell transplantation therapy too. CSPGs also

Received: January 2, 2020
Accepted: January 3, 2020
Published: January 15, 2020

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https://dx.doi.org/10.1021/acschemneuro.0c00004
ACS Chem. Neurosci. 2020, 11, 231−232

stall the neural stem cell migration and do not allow them to enter into the injury site. Enzymatic degradation of glycosaminoglycan (GAG) chains of chondroitin sulfate with chondroitinase-ABC (ChABC) promotes both axonal regeneration and behavioral improvement in various CNS injury models (Figure 1).[4] Experimentally, it is observed that single

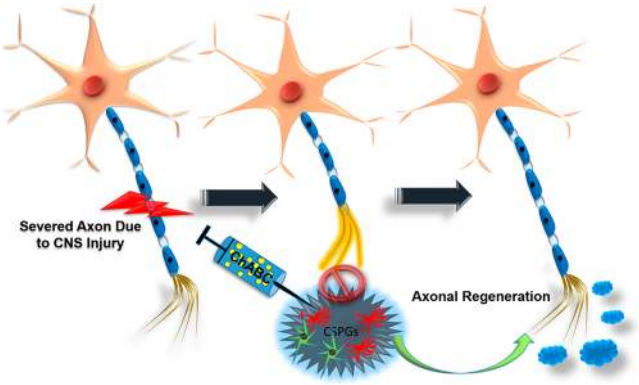

Figure 1. Cartoon representing regeneration of a severed axon after ChABC treatment.

administration of ChABC is capable of digesting the majority of GAG units of CSPGs, thereby decreasing its inhibition in axon regeneration. Being a highly temperature-sensitive bacterial enzyme, ChABC rapidly loses its enzymatic activity after few days of incorporation and thus requires a consistent supply which is currenlty achieved by intrathecal injection for almost 2−6 weeks after the event of CNS injury. The major challenges of this enzyme-mediated degradation of CSPGs treatment are thermal instability and lack of persistent in vivo release of ChABC in the site of injury. To enhance the efficacy of this treatment, designing efficient and multifunctionalized biomaterials or scaffolds such as liposome-, nanoparticle-, and hydrogel-based ones can lead to the major strategic advancement in this area. Apart from enzymatic degradation therapeutic strategy, a recent hydrogel induced axonal regeneration approach also seems to be promising. Several ECM mimetic biodegradable hydrogels made of self-assembled peptides containing growth-inducing laminin motifs, functionalized hyaluronan, chitosan, and alginate scaffolds were found to be quite effective in overcoming the regeneration barrier caused by CSPGs. Unlike CSPGs, HSPGs are found to exhibit a growth-enhancing effect on sprouting neurons and help in neurite outgrowth. It has been found that the administration of ChABC and heparan sulfate proteoglycan-like glypicans can successfully attenuate the growth inhibitory effect of CSPGs after ischemic stroke in rats. Xylosyltransferase-1 is the key enzyme responsible for the synthesis of GAG units present in core proteins. Targeting the mRNA of xylosyltransferase-1 by designing a unique DNA enzyme is another novel approach recently studied by Grimpe and Silver et al.,[5] who found substantial axonal regeneration in spinal cord injury in rats. Currently, gene therapies also exhibit promising therapeutic ways for treating inhibitory effects caused by CSPGs.

In summary, though CSPGs are the major ECM component of the central nervous system after CNS injury, their excessive upregulation has a detrimental effect on healing and regeneration procedures, and thus, they should be the major therapeutic target in developing future regenerative medicines for the CNS injury treatment.

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Funding

N. Mukherjee, S. Nandi, S. Garg, Satyajit Ghosh, Surojit Ghosh, and R. Samat thank MHRD and IIT Jodhpur for their fellowships, respectively. Surajit Ghosh kindly acknowledges IIT Jodhpur for SEED grant and infrastructural support.

Notes

The authors declare no competing financial interest.

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ACS Chem. Neurosci. 2020, 11, 231−232