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Review

Molecular mechanisms of scar-sourced axon growth inhibitors

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ABSTRACT

Astrogliosis is a defense response of the CNS to minimize primary damage and to repair injured tissues, but it ultimately generates harmful effects by upregulating inhibitory molecules to suppress neuronal elongation and forming potent barriers to axon regeneration. Chondroitin sulfate proteoglycans (CSPGs) are highly expressed by reactive scars and are potent contributors to the non-permissive environment in mature CNS. Surmounting strong inhibition by CSPG-rich scar is an important therapeutic goal for achieving functional recovery after CNS injuries. Currently, enzymatic digestion of CSPGs with locally applied chondroitinase ABC is the main *in vivo* approach to overcome scar inhibition, but several disadvantages may prevent using this bacterial enzyme as a therapeutic option for patients. A better understanding of molecular mechanisms underlying CSPG function may facilitate development of new effective therapies to overcome scar-mediated inhibition. Previous studies support that CSPGs act by non-specifically hindering the binding of matrix molecules to their cell surface receptors through steric interactions, but two members of the leukocyte common antigen related (LAR) phosphatase subfamily, protein tyrosine phosphatase σ and LAR, are functional receptors that bind CSPGs with high affinity and mediate CSPG inhibition. CSPGs may also act by binding two receptors for myelin-associated growth inhibitors, Nogo receptors 1 and 3. Thus, CSPGs inhibit axon growth through multiple mechanisms, making them especially potent and difficult therapeutic targets. Identification of CSPG receptors is not only important for understanding the scar-mediated growth suppression, but also for developing novel and selective therapies to promote axon sprouting and/or regeneration after CNS injuries.

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1. Introduction

Reactive astrogliosis occurs in response to CNS injuries and is characterized by proliferation of astrocytes, glial precursors, microglia and fibroblasts. Lesioned CNS usually induces formation of marked hypertrophy and proliferation of astrocytes along with significant overlap of astrocytic domains (Karimi-Abdolrezaee and Billakanti, 2012). Pronounced astrocytic proliferation occurs with overlapped and densely-packed astrocytic processes and overlapping astrocytes usually intertwine with fibromeningeal cells and NG2 positive glia to form dense scar tissues. In addition to the featured hypertrophic astrocytes in penumbra, the lesion core consists of NG2-expressing glia, including oligodendrocyte precursor cells (OPCs), meningeal and/or vascular derived fibroblasts, pericytes, ependymal cells and phagocytic macrophages (Cregg et al., 2014). Unlike other glia, fibroblasts invade the lesion site from adjacent meningeal and perivascular cells. After CNS injury with intact dura mater, perivascular collagen1α1 cells appear the main source of fibrotic scar (Soderblom et al., 2013). Reactive astrocytes express high levels of a great number of molecules, including intermediate filaments glial fibrillary acidic proteins (GFAP), nestin and vimentin (Ridet et al., 1997; Sofroniew, 2009). Astrogliosis is a defense response of CNS to minimize and repair primary damage, including isolation of intact tissue from secondary lesion, maintenance of favorable environment for surviving neurons, preservation of the blood brain barrier (BBB), generation of permissive substrates for neurite elongation and other protective effects (Karimi-Abdolrezaee and Billakanti, 2012; Sofroniew, 2009). However, reactive glial scar eventually generates harmful effects due to forming both physical and chemical barriers to axon regeneration, including producing high levels of inhibitory molecules to suppress neuronal elongation. An important class of molecules in the scar extracellular matrix (ECM) is chondroitin sulfate proteoglycans (CSPGs), which are highly upregulated after CNS injury and predominantly responsible for the non-permissive nature of glial scar. In this review, we will focus on recent progress in scar-rich axonal growth inhibitors and their molecular mechanisms.

2. Functions of reactive scar tissue after CNS injury

Astrocytes are actively involved in synthesis and maintenance of ECM molecules in intact CNS. Following CNS injury, reactive astrocytes remarkably change the ECM composition by highly expressing some ECM components, including CSPGs and tenascins (Carulli et al., 2005; Galtrey and Fawcett, 2007; Kwok et al., 2011). Numerous transgenic studies demonstrate that ablation of reactive astrocytes or interfering with their activation exacerbates tissue damage after spinal cord injury (SCI) by increasing tissue degeneration and failure to reconstruct BBB (Faulkner et al., 2004; Sofroniew, 2009). Astrocyte reactivity has beneficial effects in the early stage by limiting tissue damage to certain areas and preventing extension of injury into adjacent domains. Scar tissues produce a number of ECM components with growth-promoting properties, such as fibronectin and laminin, indicating possible repairing role of astrogliosis after CNS damage (Silver and Miller, 2004). However, migration of a large number of astrocytes into and around the lesion areas and formation of glial scar tissues also constitute physical barrier of axon regeneration. More importantly, upregulation of suppressing substances, particularly CSPGs, potently impedes neural repair and regeneration and the inhibitory properties of reactive astrocytes evolve with time after injury.

2.1. *Positive roles of reactive glial scar*

Glial scar is well known as an important impediment to axonal regeneration, but it is a defense mechanism of the CNS to injury and has multiple protective and repair functions. Many *in vivo* genetic studies strongly supported the protective roles of glial scar (Burda and Sofroniew, 2014). Conditional ablation of reactive astrocytes in transgenic mice increased vasogenic edema, tissue destruction, inflammation response, demyelination, oligodendrocyte death and worsen functional outcome following CNS injury (Faulkner et al., 2004; Sofroniew, 2009). Lack of scar formation in the suppressor of cytokine signaling 3 (SOCS3) or signal transducers and activators of transcription 3 (STAT3) deletion mice has similar effects by inducing widespread lesion and increasing neuronal and oligodendroglial cell death and locomotor deficits after SCI (Herrmann et al., 2008; Okada et al.,