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Review

Pleiotropic molecules in axon regeneration and neuroinflammation

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ABSTRACT

Neuroinflammation is the foremost defense reaction of the nervous system to most if not all insults. Injuries to the central and peripheral nervous system (CNS and PNS) are followed by immediate activation of innate immune cells and infiltration of peripheral immune cells, amid waves of upregulation of numerous inflammatory mediators. Prolonged inflammation can lead to secondary tissue damage and prohibit regeneration of the injured nervous system. The regulation of inflammation and neuroregeneration are orchestrated through a complex network of signal transduction. Interestingly, many molecules play pleiotropic roles in both processes. Growing evidence implicates a handful of axon regeneration regulators in the processes of neuroinflammation, among which are the myelin and glial scar associated axon growth inhibitors and their axonal receptors. In this article, we will review the roles of these canonical axon regeneration regulators in neuroinflammation.

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Introduction

Traumatic injuries of the nervous system lead to acute inflammation, as well as axonal damage and cell death that result in broken neural circuits. At lesion sites, a variety of molecules are released into the extracellular space that are known as axon regeneration inhibitors. Among these, the most intensively studied are the chondroitin sulfate proteoglycans (CSPGs) secreted mainly by the reactive glial cells, and the myelin associated inhibitors (MAIs), including myelin-associated glycoprotein (MAG), Nogo-A, and oligodendrocyte-myelin glycoprotein (OMgp). Receptors for these extracellular inhibitors are found on the surface of neurons and their ligand interactions lead to the formation of dystrophic growth cones and abortion of axon extension. To name a few, these include the Nogo receptor (NgR), p75 neurotrophin receptor (p75NTR), paired immunoglobulin-like receptor B (PirB), protein tyrosine phosphatase sigma (PTPRS), and leukocyte antigen related (LAR/PTPRF) (Akbik et al., 2012; Atwal et al., 2008; Dickendesher et al., 2012; Domeniconi et al., 2002; Fournier et al., 2001; Liu et al., 2002; Sharma et al., 2012; Shen et al., 2009; Wang et al., 2002a, 2002b; Yiu and He, 2006). Interestingly, the axon growth inhibitors also interact with the residential and infiltrating immune cells, as some of their receptors are as well expressed in these immune cells. Although these molecules have been intensively studied in axon regeneration, their roles in immune responses are less appreciated. In this

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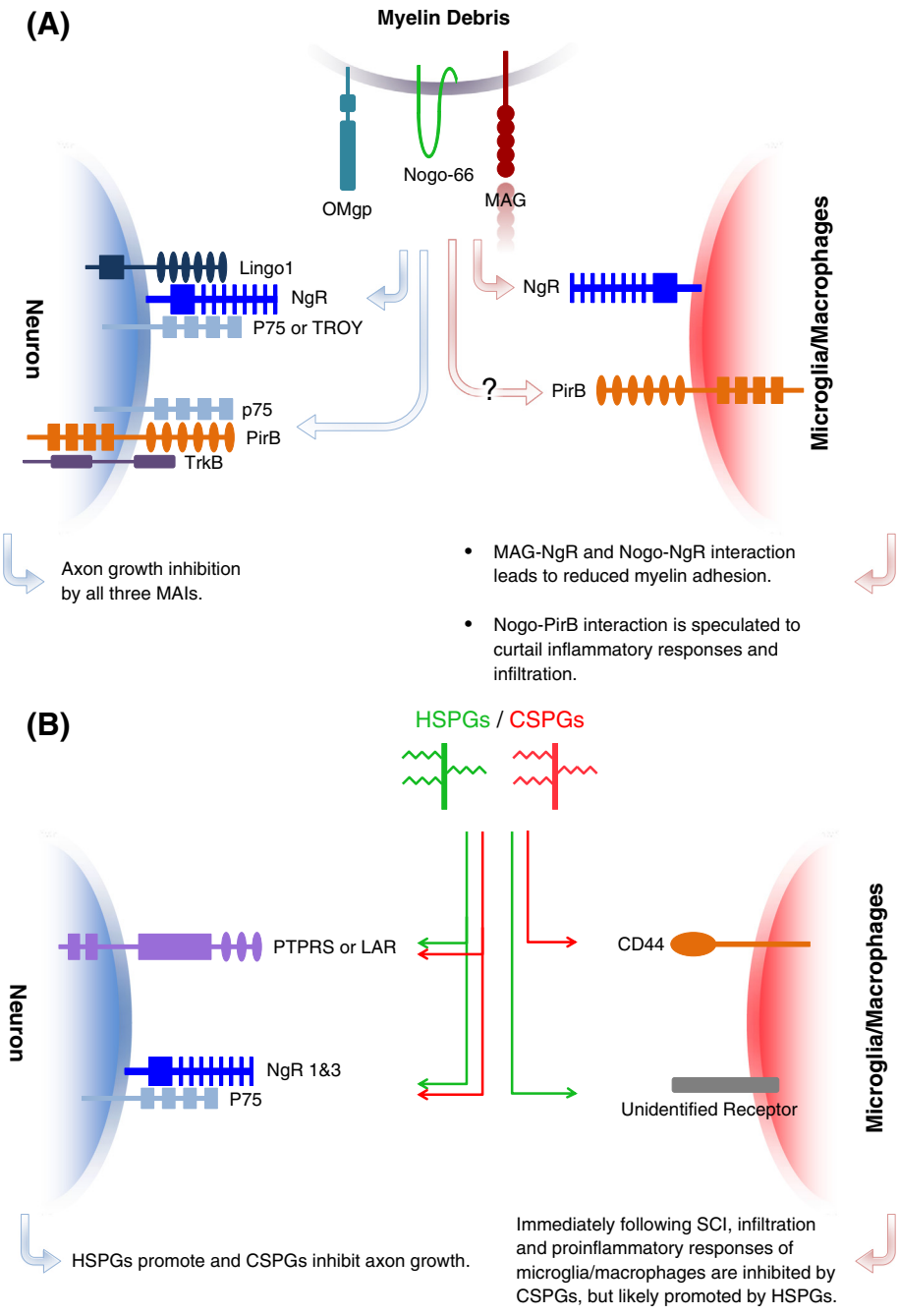

Fig. 1. Pleiotropic molecules in axon regeneration and neuroinflammation. MAIs (A) and proteoglycans (B) signal through receptors in neurons and microglia/macrophages. The same molecules can have both beneficial and detrimental impacts on the injured nervous system.

article, we will review emerging data on the involvement of these canonical axon regeneration regulators in neuroinflammation. Promoting axon regeneration and curtailing neuroinflammation are both crucial for post-injury recovery. A better understanding of their intertwined molecular mechanisms is important for the design of effective therapies (Fig. 1).

Nogo receptors (NgRs)

The Nogo receptor (NgR) family consists of three glycosylphosphatidylinositol (GPI)-anchored receptors: NgR1, the bona fide "Nogo receptor", and its two homologues, NgR2 and NgR3 (Borrie et al., 2012). The NgRs are predominantly expressed by neurons throughout development and remain highly expressed in the adult nervous system (Lauren et al., 2003). NgR1 is identified as a receptor of the MAIs, including Nogo-A, MAG, and OMgp (Domeniconi et al., 2002; Fournier et al., 2001; Liu et al., 2002; Wang et al., 2002b). In injured adult CNS, some studies showed that NgR1 mediates MAI-inhibition of axon regeneration (Cafferty and Strittmatter, 2006; Kim et al., 2004; McGee et al., 2005), although there are controversies between research groups (Zheng et al., 2005). While denoted as Nogo receptors, neither NgR2 nor NgR3 binds to Nogo. NgR2 was instead found to be a receptor of MAG, and NgR3 does not interact with any of the MAIs (Lauren et al., 2007; Venkatesh et al., 2005). Recently, NgR1 and NgR3 were also identified as receptors for CSPGs (Dickendesher et al., 2012).

Anchored to the cell membrane via GPI, the NgRs rely on co-receptors to mediate intracellular signaling. In neurons, NgR1 engages