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Review Article

Extracellular cues influencing oligodendrocyte differentiation and (re)myelination

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ABSTRACT

There is an increasing number of neurologic disorders found to be associated with loss and/or dysfunction of the CNS myelin sheath, ranging from the classic demyelinating disease, multiple sclerosis, through CNS injury, to neuropsychiatric diseases. The disabling burden of these diseases has sparked a growing interest in gaining a better understanding of the molecular mechanisms regulating the differentiation of the myelinating cells of the CNS, oligodendrocytes (OLGs), and the process of (re)myelination. In this context, the importance of the extracellular milieu is becoming increasingly recognized. Under pathological conditions, changes in inhibitory as well as permissive/promotional cues are thought to lead to an overall extracellular environment that is obstructive for the regeneration of the myelin sheath. Given the general view that remyelination is, even though limited in human, a natural response to demyelination, targeting pathologically 'dysregulated' extracellular cues and their downstream pathways is regarded as a promising approach toward the enhancement of remyelination by endogenous (or if necessary transplanted) OLG progenitor cells. In this review, we will introduce the extracellular cues that have been implicated in the modulation of (re)myelination. These cues can be soluble, part of the extracellular matrix (ECM) or mediators of cell–cell interactions. Their inhibitory and permissive/promotional roles with regard to remyelination as well as their potential for therapeutic intervention will be discussed.

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1. Introduction

Myelination in the central nervous system (CNS) is carried out by specialized glia cells, oligodendrocytes (OLGs), to enable rapid saltatory conduction of action potentials and to maintain axonal integrity and function (Hirrlinger and Nave, 2014; Saab et al., 2013; Simons and Nave, 2015; Trapp and Nave, 2008). The critical importance of the myelin sheath becomes evident in diseases in which this structure is damaged or its growth or maintenance is impaired. Classic examples for such pathological conditions are the major human demyelinating disease, multiple sclerosis (MS), and the dysmyelinating genetic disorders grouped under the term leukodystrophies (Griffin and Lassman, 2004). More recently, myelin dysfunction and/or damage has also been associated with ischemic and traumatic brain injury (Armstrong et al., 2016; Back and Rosenberg, 2014; Rosenzweig and Carmichael, 2015), perinatal white matter injury/periventricular leukomalacia (Back, 2015; Folkerth, 2006; Haynes et al., 2003; Volpe, 2009), as well as neuropsychiatric diseases (Haroutunian et al., 2014; Miguel-Hidalgo, 2013; Nave and Ehrenreich, 2014). In light of the disabling burden of all of the above mentioned neurologic disorders, there is the hope that our progressive biological understanding of the OLG and the regulation of CNS myelination will lead to therapeutic approaches aimed at the regeneration of the myelin sheath as a critical step toward curative treatments.

It has been well-recognized that re-establishment of the myelin sheath can occur in response to CNS injury and demyelination (Blakemore and Franklin, 2008; Patani et al., 2007; Patrikios et al., 2006; Powers et al., 2013), and that remyelination, at least in animal models, can restore function and provide axonal protection (Duncan et al., 2009; Irvine and Blakemore, 2006; Jeffery and Blakemore, 1997; Liebetanz and Merkler, 2006; Smith et al., 1979). However, this regenerative process is, in particular with progression of disease and/or age, often limited and only partially able to fully restore axonal conduction velocity and the neuroprotective functions of the myelin sheath (Franklin and Gallo, 2014; Goldschmidt et al., 2009; Piaton et al., 2009). Thus, enhancing remyelination is considered a promising strategy toward the regenerative/protective treatment of diseases in which the myelin sheath is lost (Franklin and Goldman, 2015; Hagemeier et al., 2012; Lubetzki and Stankoff, 2014).

Remyelination at large requires the activation, recruitment and maturation of adult OLG progenitor cells (OPCs) present throughout the CNS and/or derived from stem/progenitor cells located within the subventricular zone (SVZ) (Brousse et al., 2015; Chari and Blakemore, 2002; Hesp et al., 2015; Mecha et al., 2013; Moyon et al., 2015a; Reynolds et al., 2002; Sullivan et al., 2013; Xing et al., 2014). Impairment of myelin regeneration under pathological conditions has been attributed to a decrease in both OPC recruitment and differentiation, whereby the latter is currently considered to play a more prominent role in determining the rate of remyelination (Franklin and Goldman, 2015). While the exact reasons for impaired remyelination are not fully understood, there is increasing evidence for a critical role of the extracellular environment (Berezin et al., 2014; Hinks and Franklin, 2000; Satoh et al., 2009; van Horssen et al., 2006), which likely acts upstream of transcriptional and epigenetic mechanisms regulating OLG differentiation (Emery and Lu, 2015; Hernandez and Casaccia, 2015; Moyon et al., 2015b; Svaren, 2014). Importantly, OLG lineage cells, even in the aged CNS, retain their competence for efficient repair (Ruckh et al., 2012), thus supporting enhancement of endogenous processes as a viable strategy toward myelin regeneration.

Extracellular cues are increasingly recognized to mediate communication between cells in the CNS. Such extracellular cues can be soluble factors, such as growth factors and chemokines, cell–cell adhesion molecules or represent extracellular matrix (ECM) molecules, whereby the latter become progressively known to function as important molecular signals not only outside of, but also within the CNS. In this context, it is of note that in the CNS, ECM organized in a traditional basal lamina is only found lining endothelial cells and the pial surface; in the parenchyma, ECM components are found primarily in the form of dense networks (Rauch, 2007). During development, as well as under pathological conditions, this extracellular milieu undergoes dynamic changes and thereby influences the behavior and function of CNS cells, including OLGs (Colognato and Tzvetanova, 2011). In the following, we will focus on the review of extracellular signals that are known to influence OLGs and their progenitors at stages beyond their initial specification and that have been implicated in the regulation of CNS remyelination by functioning as inhibitory and/or permissive/promotional cues (for a schematic diagram see Fig. 1).

2. Secreted signaling molecules

2.1. Inhibitory effects on OLG differentiation and (re)myelination

2.1.1. Bone morphogenetic proteins (BMPs)

BMPs are secreted ECM-associated proteins of the TGFβ family of signaling molecules that have been recognized as key players in regulating a variety of developmental processes including OLG differentiation and myelination (Grinspan, 2015). To date, 22 members of the BMP family have been identified to activate, in the form of mature dimers, a signaling pathway that is initiated by binding to two copies of BMP type I (BMPR1) and type II (BMPR2) receptors (Brazil et al., 2015). Activation of this complex leads to downstream phosphorylation of a set of Smad proteins (R-Smad1/5/8), which, in turn, bind to the nuclear Smad4 protein and thereby mediate BMP-dependent gene expression. At each step, this pathway is tightly regulated, such as intracellularly by the inhibitory Smads Smad6 and Smad7 and extracellularly by antagonists such as Noggin and the Follistatin–Activin complex.

The first experiments demonstrating the inhibitory effect of an excess of BMPs on OLG differentiation were done in culture where treatment of OPCs with BMP2 or BMP4 inhibited the generation of mature OLGs and, at the same time, promoted the appearance of astrocyte-like cells (Grinspan et al., 2000; Mabie et al., 1997). This effect was found to be restricted to very early stages of the OLG lineage as treatment of immature OLGs with BMPs inhibited myelin gene expression without significantly affecting cell fate (See et al., 2004). Both inhibitory

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