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Review

Regenerative medicine in multiple sclerosis: Identifying pharmacological targets of adult neural stem cell differentiation

Jeffrey K. Huang *, Robin J.M. Franklin **

MRC Centre for Stem Cell Biology and Regenerative Medicine and Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge CB3 0ES, UK

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ABSTRACT

Progressive axonal loss from chronic demyelination in multiple sclerosis (MS) is the key contributor to clinical decline. Failure to regenerate myelin by adult oligodendrocyte precursor cells (OPCs), a widely distributed neural stem cell population in the adult brain, is one of the major causes of axonal degeneration. In order to develop successful therapies to protect the integrity of axons in MS, it is important to identify and understand the key molecular pathways involved in myelin regeneration (remyelination) by adult OPCs. This review highlights recent findings on the critical signaling pathways associated with OPC differentiation following CNS demyelination. We discuss the role of LINGO-1, Notch, Wnt, and retinoid X receptor (RXR) signaling, and how they might be useful pharmacological targets to overcoming remyelination failure in MS.

1. Introduction

Multiple sclerosis (MS) is one of the commonest neurological disorders among young adults and is characterized by the destruction of CNS myelin due to persistent inflammation in the brain and spinal cord (Lassmann et al., 2007). In the early stages of MS, a typical patient may undergo episodes of functional deficit (relapse) from inflammation driven demyelination in the CNS, followed by functional recovery periods (remission) without significant clinical symptoms. During the relapse stage of MS, myelin loss impairs axonal conduction, contributing to symptoms such as sensory deficits, impaired vision, and paresis. However, as the disease progresses to the chronic stages, episodes of functional deficits are prolonged with worsening symptoms and very little recovery, ultimately leading to irreversible clinical decline and permanent disability. It is becoming evident that the major contributor of clinical decline in chronic MS is the significant degeneration of demyelinated axons, suggesting that intact CNS myelin is necessary to maintain axonal integrity and for neuroprotection (Nave and Trapp, 2008; Stadelmann and Brück, 2008). Demyelination is thought to cause mitochondrial dysfunction in axons, leading to their degeneration (Kiryu-Seo et al., 2010). Indeed, cytosolic retention of the epigenetic modifier, HDAC1 in damaged axons has recently been shown to impair axonal mitochondrial transport (Kim et al., 2010). Therefore, in order to prevent axonal loss in MS, it is crucial that pharmacological therapeutics are tailored to (i) attenuating inflammatory attacks in the CNS and (ii) restoring CNS myelin (remyelination). Immunomodulatory drugs are currently available and some are showing significant promise in attenuating inflammation in MS (Coles et al., 2008; Giovannoni et al., 2010; Racke et al., 2010). However, no proven regenerative therapeutics are available to encourage CNS remyelination, but this would no doubt be a highly effective complement to immuno-modulatories in the treatment of MS.

2. Myelin replacement by adult stem/precursor cells

To regenerate myelin in demyelinating disorders such as MS, there are at least two possible strategies: remyelination by (i) exogenous cell transplantation, or (ii) stimulation of endogenous stem/precursor cells. Although previous studies have shown that myelin replacement by cell transplantation can be achieved in animal models of demyelination (Windrem et al., 2008; Mothe and Tator, 2008; Kondo et al., 2005; Barnett et al., 2000), this approach may not be beneficial in the treatment of MS due to the disseminate nature of lesions in the brain. Moreover, the route and timing of delivery, as well as cell survival and differentiation are major safety issues that would need to be resolved before any chance that cell transplantation should be considered as a feasible strategy to replace myelin. A more realistic strategy to replace myelin in MS is to encourage the differentiation of endogenous adult stem/precursor cells into mature oligodendrocytes in the lesions (Franklin and ffrench-Constant, 2008).

* Corresponding author. Tel.: +44 1223 765859.
** Corresponding author. Tel: +44 1223 337642.
E-mail addresses: jh424@cam.ac.uk (J.K. Huang), rjf1000@cam.ac.uk (R.J.M. Franklin).

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Unlike neuronal regeneration, which cannot be achieved efficiently, the mammalian adult CNS is highly competent in myelin regeneration (Franklin and ffrench-Constant, 2008). CNS remyelination is performed by a population of adult neural stem/precursor cells called adult oligodendrocyte precursor cells (OPCs). These cells are widely distributed, making up more than 5% of all cells in the adult CNS, and are capable of giving rise to mature oligodendrocytes, Schwann cells, and neurons (Fancy et al., 2004; Rivers et al., 2008; Zawadzka et al., 2010). Following CNS demyelination, neighboring adult OPCs can be recruited to lesions where they can differentiate into mature oligodendrocytes for myelin replacement. In the early stages of MS, remyelination can be achieved efficiently (Goldschmidt et al., 2009; Patani et al., 2007; Patrikios et al., 2006; Raine and Wu, 1993) – the success of repair may contribute to improved functional recovery reflected during the remission phase of the disease. However, in the progressive stages of MS, remyelination, for unclear reasons, is less efficient, which results in increased functional decline and axonal degeneration (Goldschmidt et al., 2009; Stadelmann and Brück, 2008). Although OPCs can still be recruited to lesions in chronic MS, they appear to be prevented from differentiating into oligodendrocytes for remyelination (Kuhlmann et al., 2008; Chang et al., 2002; Wolswijk, 1998). To overcome the OPC differentiation block and thus improve remyelination in MS, the identification of signaling pathways and pharmacological agents that stimulate endogenous adult OPC differentiation is therefore urgently needed. Moreover, by improving myelin regeneration, the integrity of CNS axons will likely be maintained, thus slowing down or preventing disease progression.

3. Critical regulators of adult OPC differentiation in the injured CNS

Several regulators of OPC differentiation have recently been identified using different experimental approaches. The timing and expression of these genes may regulate the efficiency of CNS remyelination. For example, epigenetic regulation of gene expression are thought to be important regulators of remyelination efficiency (Copray et al., 2009; Shen et al., 2008). We will focus on the role of LINGO-1, Notch1, Wnt, and retinoid X receptors (RXRs) signaling in CNS remyelination. These signaling pathways are of particular interest because they appear to play active roles in CNS remyelination. Moreover, pharmacological agonists or antagonists against these pathways are available or currently being developed for treatment against other diseases, such as cancer. LINGO-1, Notch and Wnt signaling in OPCs are negative regulators of differentiation, whereas RXRs are positive regulators of OPC differentiation. By targeting these pathways, it might be possible to pharmacologically encourage remyelination from endogenous OPCs in MS.

3.1. LINGO-1

LINGO-1 was identified in a search for CNS-specific leucine rich repeat (LRR) proteins (Mi et al., 2004). It has been shown to regulate axon outgrowth by interaction with the Nogo-66 receptor (NgR1) complex. More recently LINGO-1 has also been found to be a negative regulator of oligodendrocyte differentiation (Mi et al., 2005). Treatment of cultured OPCs with siRNAs generated against LINGO-1, dominant negative LINGO-1 or LINGO-Fc resulted in increased morphological differentiation of oligodendrocytes as characterized by the abundance of terminal membrane sheets. Mice deficient in LINGO-1 or treated with an antibody antagonist against LINGO-1 exhibited increased remyelination and functional recovery from experimental autoimmune encephalomyelitis (EAE), a model of immune-mediated demyelination (Mi et al., 2007). Moreover, the LINGO-1 antagonist is able to promote CNS remyelination by directly stimulating OPC differentiation in non-immune, toxin-induced models of demyelination in rats (Mi et al., 2009). These findings reveal the importance of LINGO-1 signaling in regulating OPC differentiation in the injured CNS. The restricted expression of LINGO-1 in the CNS makes therapeutic targeting of LINGO-1 potentially advantageous for improving myelin repair without affecting non-neural tissues.

3.2. Wnt signaling

A recent expression screen for genes encoding transcription factors that are induced during CNS remyelination in experimentally demyelinated mice has led to the identification of genes associated with the Wnt pathway (Fancy et al., 2009). Wnt signaling controls the temporal and spatial regulation of cell proliferation, migration and survival. During remyelination, Wnt activation negatively regulates OPC differentiation. A key gene, which functions to relay Wnt signaling to the nucleus of OPCs is the transcription factor, Tcf4, also called Tcf7l2 (Fancy et al., 2009; Ye et al., 2009). Tcf4 is expressed in the mouse white matter immediately after birth, but is barely detectable in the adult (Fancy et al., 2009; Ye et al., 2009; Fu et al., 2009). However, following demyelinating injury, Tcf4 is re-expressed and upregulated in OPCs recruited to the lesion (Fancy et al., 2009). Moreover, Tcf4 is highly expressed in active MS lesions, suggesting a role in remyelination. In response to Wnt activation, Tcf4 interacts with phosphorylated β-catenin in the cell nucleus to regulate transcription of Wnt-β-catenin pathway target genes (Nelson and Nusse, 2004). Constitutive induction of Wnt signaling in oligodendrocyte lineage cells by using transgenic mice that actively express a dominant active β-catenin gene results in mice displaying severe tremor and ataxia within one week after birth due to delayed oligodendrocyte differentiation and hypomyelination (Fancy et al., 2009). However, this effect is transient as CNS myelination ultimately catches up and appears normal in adult mice. Experimental demyelination performed on these transgenic mice results in a similar delay in oligodendrocyte differentiation and remyelination, without affecting OPC recruitment. These findings have opened up a new area of research to dissect the mechanism of Wnt signaling in OPC differentiation (Ye et al., 2009). But more importantly, given the growing interest to develop pharmacological inhibitors against the Wnt pathway in cancer therapy (Barker and Clevers, 2006), it might be possible in the near future to use Wnt inhibitors to stimulate OPC differentiation and improve CNS remyelination in MS.

3.3. Notch signaling

One of the potential contributors of remyelination inefficiency in MS is thought to be reactive astrocytosis in lesions (John et al., 2005). In an effort to identify putative astrocytic inhibitors of remyelination, a microarray analysis was performed on purified human astrocytes treated with cytokines that are known to be significantly upregulated in the brains of MS patients (John et al., 2002). This led to the identification of the Notch ligand, Jagged in astrocytes which is upregulated in response to the cytokine TGF-β. Notch1 and its effector Hes5 were detected in immature oligodendrocytes of MS lesions and following demyelination in mice (John et al., 2002; Stidworthy et al., 2004). When cultured human OPCs were exposed to Jagged, the OPCs failed to mature (John et al., 2002). While the role of Notch1 signaling on OPC differentiation during remyelination *in vivo* has remained inconclusive (Stidworthy et al., 2004), a recent study using a mouse mutant lacking Notch1 in oligodendrocyte lineage cells found that oligodendrocyte differentiation appeared to have accelerated in