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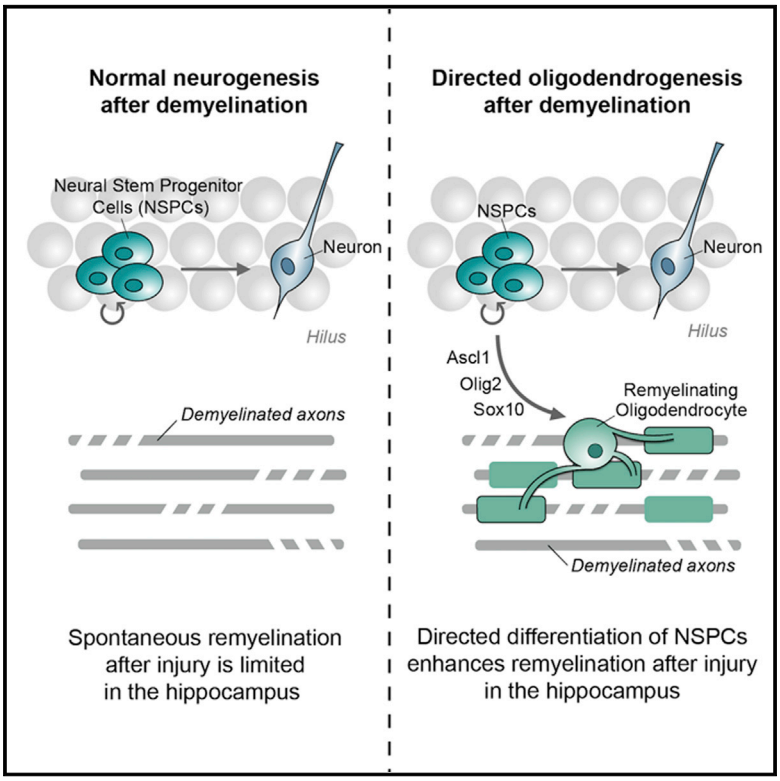
Report

Programming Hippocampal Neural Stem/Progenitor Cells into Oligodendrocytes Enhances Remyelination in the Adult Brain after Injury

Graphical Abstract



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In Brief

Regenerative approaches for replacing lost oligodendrocytes in demyelinating disease are scant. Braun et al. show that programming adult hippocampal neural stem/progenitor cells (NSPCs) into oligodendrocytes enhances remyelination in a genetic model of demyelination, highlighting the potential of targeting hippocampal NSPCs for the treatment of demyelinated lesions.

Highlights

- Programming hippocampal NSPCs into oligodendrocytes follows developmental programs
- Programming NSPCs into oligodendrocytes enhances remyelination after injury
- Induced oligodendrocytes mature and myelinate, as shown at a single-cell level
- Proof of concept for targeting hippocampal NSPCs for glial brain repair is provided

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Programming Hippocampal Neural Stem/Progenitor Cells into Oligodendrocytes Enhances Remyelination in the Adult Brain after Injury

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SUMMARY

Demyelinating diseases are characterized by a loss of oligodendrocytes leading to axonal degeneration and impaired brain function. Current strategies used for the treatment of demyelinating disease such as multiple sclerosis largely rely on modulation of the immune system. Only limited treatment options are available for treating the later stages of the disease, and these treatments require regenerative therapies to ameliorate the consequences of oligodendrocyte loss and axonal impairment. Directed differentiation of adult hippocampal neural stem/progenitor cells (NSPCs) into oligodendrocytes may represent an endogenous source of glial cells for cell-replacement strategies aiming to treat demyelinating disease. Here, we show that Ascl1-mediated conversion of hippocampal NSPCs into mature oligodendrocytes enhances remyelination in a diphtheria-toxin (DT)-inducible, genetic model for demyelination. These findings highlight the potential of targeting hippocampal NSPCs for the treatment of demyelinated lesions in the adult brain.

INTRODUCTION

Neural stem/progenitor cells (NSPCs) reside in two distinct regions of the adult mammalian brain: the subventricular zone (SVZ) and the hippocampal dentate gyrus (DG) (Gage, 2000). Harnessing the regenerative capacity of endogenous adult NSPCs can contribute to brain repair (Lindvall and Kokaia, 2006). Previous reports have suggested the remyelination potential of NSPC-derived oligodendrocytes in areas neighboring the adult SVZ (Menn et al., 2006; Nakatani et al., 2013; Rafalski et al., 2013). However, in striking contrast to the SVZ, NSPCs in the DG do not spontaneously differentiate into oligodendrocytes and remyelination is limited after injury in the hippocampal formation. The hippocampus plays a pivotal role in certain forms of learning and memory and is commonly affected in demyelinating diseases such as multiple sclerosis as well as other brain disorders, including traumatic brain injury, epilepsy, Alzheimer's disease, and schizophrenia (Chambers and Perrone-Bizzozero, 2004; Hemanth Kumar et al., 2014; Meier et al., 2004; Noble, 2004; Yang et al., 2009; Chiaravalloti and DeLuca, 2008; Geurts et al., 2007), underlining the need for therapies that promote remyelination within this brain region (Franklin and Ffrench-Constant, 2008). Overexpression of the transcription factor (TF) Ascl1 converts hippocampal NSPCs into oligodendrocytic cells in vivo (Jessberger et al., 2008), but their potential for remyelination remains unknown (Goldman and Natesan, 2008; Jessberger and Gage, 2009). Thus, we here evaluate the remyelination capacity of hippocampal NSPCs by in vivo reprogramming of hippocampal NSPCs into oligodendrocytes in a mouse model of demyelinating disease.

RESULTS

Overexpression of Ascl1, Olig2, or Sox10 TFs Directs Hippocampal NSPC Differentiation toward the Oligodendrocyte Lineage In Vivo

To identify novel TFs that direct NSPC progeny toward the oligodendrocyte lineage, we focused on a developmental pathway that plays an important role in oligodendrogenesis during brain development (Nakatani et al., 2013). Ascl1 is required for oligodendrogenesis through a genetic interaction with Olig2, an essential transcriptional regulator of oligodendrocyte fate (Petryniak et al., 2007; Zhou and Anderson, 2002). Furthermore, Olig2 binds regulatory elements to induce the expression of Sox10, a TF that is required for expression of myelin genes (Küspert et al., 2011; Stolt et al., 2002). First, we transduced adult hippocampal NSPCs in vitro using retroviruses overexpressing Ascl1, Olig2, or Sox10 and analyzed cell fates under differentiating conditions. We found that overexpression of either of these TFs increased oligodendrocyte differentiation of adult NSPCs when compared to cells infected with control retroviruses (Figures