

CAN THE DAMAGE IN MS BE REPAIRED? YES

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Multiple sclerosis (MS) is the most frequent demyelinating disease of the human CNS. The multifocal lesions are histologically characterized by demyelination and axonal damage initiated by inflammatory infiltrates. However, besides these destructive mechanisms also endogenous repair processes exist, such as remyelination.

Remyelination is relatively frequently observed in early lesion stages, but becomes less prominent with disease chronicity. In patients suffering from long-time disease only about 20 % of the lesions are completely remyelinated. The extent of remyelination depends apparently on lesion localization; however a subset of patients shows a more homogenous distribution in the extent of remyelination, suggesting that genetic factors might also influence remyelination. Myelinated axons are less prone to injury; animal studies demonstrated that the lack of single myelin proteins induces axonal damage and that prevention of remyelination increases axonal loss. Similar, remyelinated MS lesions have a higher axonal density than demyelinated lesion areas. Experimental animal studies have demonstrated an association between remyelination and clinical improvement, demonstrating that remyelination not only increases morphological integrity but also supports functional recovery.

Multiple factors contribute to limited remyelination in chronic MS disease stages. Axons and oligodendroglial progenitor cells (OPCs), prerequisite for successful remyelination, are present, even in chronic MS lesions. However, remyelination is not initiated, indicating that the differentiation of OPCs is impaired. This might be due to the lack of remyelination promoting factors and/or caused by the activation of inhibitory pathways.

During recent years a number of potentially inhibitory signaling cascades and molecules have been identified, e.g. the Wnt- β -catenin pathway or the receptor Lingo1. Binding of Wnt to its receptors results in the stabilization of β -catenin and its accumulation in the nucleus, where it together with additional transcription factors the transcription of target genes induces. Activation of Wnt signaling prevents oligodendroglial differentiation from OPCs to immature oligodendrocytes. Furthermore, blocking of Wnt signaling promotes oligodendroglial differentiation in vitro and in different demyelinating animal models. LINGO1 is a CNS specific highly evolutionary conserved transmembrane protein that is part of a tripartite receptor. In OPCs downregulation of LINGO-1 leads to reduced RhoA activity associated with oligodendroglial differentiation and increased myelination. Oligodendrocytes cultured from LINGO-1 KO mice differentiate more rapidly and show premature myelination compared to wild type cells. LINGO-1 antagonists increase (re-)myelination significantly in vitro and in vivo and phase-1 studies are currently under way. Mesenchymal stem cells (MSC) are able to prime neural progenitors towards an oligodendroglial fate. Intravenous infusions of MSC improve the clinical course in EAE, an animal model of MS. However, MSC have not only neuroprotective but also immunomodulatory properties. A first phase-2a study demonstrated safety of treatment and suggested some neuroprotective effects in MS patients with secondary progressive MS.

Endogenous repair processes in MS had been neglected for many years and only during recent times first attempts have been made to determine the cells, pathways and factors regulating remyelination. Despite this relative short time period already a number of remyelination promoting strategies have been identified and first clinical studies have been initiated supporting the hope that in MS functional damage can be repaired and clinical progression can be stopped.