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Editorials

Remyelination in multiple sclerosis: realizing a long-standing challenge



multiple sclerosis (M	1S)	experimental autoimmune encephalomyelitis (EAE)	demyelination	remyelination
oligodendrocytes	neur	oprotection			

The myelin sheath is essential for optimizing the nerve impulse conduction, as well as for axonal survival and regenerative capacity. In multiple sclerosis (MS), inflammatory autoimmune attack on the myelin in the central nervous system (CNS) leads to myelin destruction and formation of demyelinated lesions (plaques) in the white matter.[1] Diffuse changes in normal-appearing white matter and cortical demyelination have also been recognized as components of MS pathology. The widespread demyelination results in subsequent neuroaxonal damages, which comprise the degenerative aspect of the disease. The fundamental role of inflammation in MS pathology provided the rationale for immunomodulatory disease-modifying therapies that shift the immune system from pro-inflammatory to anti-inflammatory pathways, thus effectively reducing relapse rate and new lesions appearance in relapsing-remitting (RR) MS.[2] However, as yet, no treatment strategy has proven to significantly repair the CNS tissue damage and affect the progressive disease phase. The essential challenge for MS therapy is therefore to promote neuroprotective repair mechanisms, in particular remyelination.

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Remyeli		ning and
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synthesize myelin, extending processes to neighboring axons and enwrapping short axonal segments with several myelin layers.[5] Oligodendrocytes also provide trophic support and maintain the myelin sheaths. Importantly, myelin-producing oligodendrocytes are terminally differentiated cells with a limited capacity to respond to injury. In active demyelinating lesions they are destroyed, though to an extent that varies among patients.[1] Accordingly, remyelination requires proliferation of oligodendrocyte precursor cells (OPCs), their migration/recruitment into demyelinating sites and differentiation to mature myelinating oligodendrocytes. CNS injury in itself is a potent inducer of repair, [6] so subsequent to the demyelination, remyelination is triggered. Indeed, at the early stages of MS in newly evolved lesions, OPCs recruitment to demyelination sites frequently results in remyelination. However, at later disease stages, in particular in chronic lesions, remyelination is either absent or confined to a small rim at the lesion border.[1] Oligodendrocyte recruitment failure and maturation defects involving several signaling pathways are implicated in the poor remyelination occurring in chronic MS.[1,7] It is clear that factors that direct myelination during normal development are inhibited or absent in the MS lesions.

In view of the limited extent of endogenous remyelination, there is a great need for

therapeutic approaches that will improve myelin repair. To a certain ext	ent any
intervention that arrests disease progression is expected to reduce den	nyelination, at
least through secondary indirect mechanisms. However, anti-inflammat	tory treatments
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are attributed to increased OPCs proliferation and differentiation along the oligodendroglial maturation cascade.[9,13] GA induces elevation in brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), which are known to promote myelination, suggesting that its mode of action is linked to neurotrophic effects.[13,14] Another immunomodulatory treatment, fingolimod, was shown to modulate process outgrowth in immature oligodendrocytes and to enhance remyelination following lysolecithin-induced demyelination via sphingosine 1-phosphate receptors on astrocytes and oligodendrocytes.[15] However, conflicting results regarding the remyelination potency of FTY720 have been recently reported.[16] An additional immunomodulator, laquinimod, applied at the chronic EAE stage reduced myelin damages and induced neurotropic effect.[17] These combined findings support the notion that immunomodulation can support neuroprotection and remyelination within the CNS. Whether these effects result from genuine repair mechanisms or from anti-inflammatory consequences remain to be established. Regardless, the feasibility of repairing the extensive myelin damages in MS by immunomodulatory treatments is doubted, particularly in the progressive phase. Intensive efforts are thus devoted to develop "genuine" remyelination strategies that will be used as add-ons to the immunomodulatory therapeutics.

Stimulation of remyelination can be achieved by inhibiting	factors that hinder myelin
repair and/or by up-regulating growth factors that support	oliaodendrocytes
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Several novel therapeutic candidates that have shown promising effects on the oligodendrocyte population and/or myelin synthesis in animal models are currently or soon to be tested in clinical trials.[3,21,22] These include: rHIgM22 a recombinant autoantibody; the GNbAC1 antibody directed against the envelope protein of MS-associated retrovirus; quetiapine fumarate (chemically similar to the MS approved drug dimethyl fumarate); histamine receptor antagonists; VX15/2503, an antibody interfering with semaphorin 4D interaction with its receptor; an agonist for the retinoic acid receptor gamma (RXR- γ) and olesoxime, a cholesterol-like small-molecule compound. A number of small molecules targeting signaling cascades (such as the Notch pathway) that inhibit OPCs differentiation and remyelination in MS lesions are also under study.

Cell transplantation is also a promising strategy. Introducing exogenous pluripotent cells with differentiation and proliferation potential may replace the affected oligodendrocytes and induce myelin repair. Various cell types (e.g., neuronal progenitor cells, OPCs, oligodendrocytes, Schwann cells, mesenchimal stem cells, etc.) are potential candidates for this purpose. Indeed, in EAE mice, neuronal progenitor cells, administered by either intracerebral transplantation or systemic injection, were detected in CNS inflammatory sites, and their occurrence has been associated with remyelination and reduced disease severity.[22,23] Clinical trials testing the effect of these cells in MS patient are ongoing. Notably, accumulated evidence implies that the beneficia nodulatory X 11 effect ar administ e due to the multifoc nted stem cells to Importa are the the astro micro hatrix.[<u>1,4]</u> Further useful insights peutic targets. or goal for Myelin r MS thera hat is also a significant remyelination is not the only chanenge. Neuroaxonal pathology

constitute of this disease, occurring either secondary to the demyelination or independently as primary degeneration.[<u>1,3</u>] This could limit the effect of remyelination-stimulating treatments, at least in the subset of patients suffering from extensive axonal injury, particularly in the progressive stage. Currently, there is no treatment for which myelin repair, as such, has been proved to be effective and beneficial for MS patients. However, progress made in understanding the different pathologies associated with MS together with biotechnological advances will hopefully produce promising regeneration strategies. Tools to detect remyelinated lesions in the MS brain had been rather limited, but a growing number of clinical studies have incorporated novel imaging techniques to assess neuroprotective treatment outcomes. The ultimate goal is to provide a combination of effective immunomodulation together with regenerative modalities that will offer disease control and substantial reduction in the risk for disease progression.

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