Expert Review of Neurotherapeutics ›
Volume 15, 2015 - Issue 12

Free access

Editorials

Remyelination in multiple sclerosis: realizing a long-standing challenge

Rina Aharoni

Pages 1369-1372 | Published online: 11 Nov 2015

Cite this article https://doi.org/10.1586/14737175.2015.1112740 Check for updates

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Multiple autoimmune attack o e demyeli apy is to combine approaches that pro eous extent. Cumu e neur ses. Growing ances has resulted ntibodies and cell n the oligoden urrently or soon to

Keywords: multiple sclerosis (MS) experimental autoimmune encephalomyelitis (EAE) demyelination remyelination oligodendrocytes neuroprotection

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.

A prerequisite for developing new treatments is to understand the cellular and molecula cient endoger estigating the princ arious forms of exper on occurs on an inflar cuprizone which ex tional instrume lopmental myel ntribution of these in ingle system. e needed for more ac

Remyeli ning and coordina acroglia synthesi ng 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 extent any intervention that arrests disease progression is expected to reduce demyelination, at least through secondary indirect mechanisms. However, anti-inflammatory treatments might also block the beneficial aspects of inflammation such as neurotrophins secretion. Questions have therefore been raised whether immune-based treatments that den
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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 oligodendrocytes development and function. Putative targets for inhibition are myelin-associated components that negatively regulate oligodendroglial differentiation, such as the myelin-a dy to Nogo receptor trials.[18] Some gr beneficial effects i results by enhanci in EAE were reported blast growth f endrocyte linea ce a benefici lts emphasi this approac es, delivery problem

Several the oligoden urrently 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 beneficial effect of the transplanted cells may be attributed to an immunomodulatory effect and trophic support, rather than to oligodendrocytes replacement. Cell administration (systemic or intracerebral) to the damage sites is a challenge due to the multifoc nted stem cells to g

Importan are the astrocyt the microgli atrix.[1,4] Further e useful insigh peutic targe

Myelin re r goal for MS thera hat remyelin nificant constitut or indepen 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.

Financial & competing interest disclosure

The author has received a research grant from Teva Pharmaceutical Industries (Israel). The author has no other affiliations or financial involvement with any organization or entity with financial interests in or financial conflicts with the subject matter or materials discussed in the article.

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Notes

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