MD CONFERENCE EXPRESS

Can the Damage in MS be Repaired?

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YES

Multiple sclerosis (MS) is the most common demyelinating disease of the human central nervous system (CNS). The multifocal lesions of MS are characterized by demyelination and axonal damage initiated by inflammatory infiltrates. Endogenous repair processes, such as remyelination, occur relatively frequently in early lesion stages, but only about 20% of lesions in chronic MS are completely remyelinated. Tanja Kuhlman, MD, University Hospital, Muenster, Germany, presented evidence that the damage caused by MS can be repaired.

Remyelination is essential for axonal function and protection. Central remyelination has been shown to restore conduction of action potentials [Smith KJ. *Nature* 2008] and is associated with clinical recovery in experimental animal studies [Duncan ID. *Proc Natl Acad Sci* 2009]. Axons and oligodendroglial progenitor cells (OPCs) are present in chronic MS lesions. However, OPC differentiation appears to be impaired, contributing to the failure of remyelination. The impaired differentiation may be due to lack of remyelination-promoting factors and/or activation of inhibitory pathways.

Two potential methods to stimulate remyelination have been identified: stem cell transplantation and modulation of OPC differentiation inhibitor pathways. Mesenchymal stem cells (MSCs) secrete bioactive factors that promote remyelination by endogenous OPCs and have immunomodulatory effects. MSC infusions have been shown to improve experimental autoimmune encephalomyelitis (EAE), in an animal model of MS. Initial results of a Phase 2a study of MSC infusions in MS demonstrate the safety of treatment and are suggestive of neuroprotective effects in patients with secondary progressive MS [Connick P. *Lancet Neurol* 2012].

Activation of the Wnt/beta-catenin signaling pathway prevents oligodendroglial differentiation from OPCs to immature oligodendrocytes. Inhibition of the Wnt/beta-catenin signaling pathway promotes oligodendroglial differentiation *in vitro* and in animal models of demyelination.

Another potential path to remyelination is via the Lingo-1 receptor, which has a negative influence on remyelination. Oligodendroglial differentiation and myelination are inhibited by overexpression of Lingo-1. Down-regulation of Lingo-1 leads to reduced RhoA activity, which is associated with oligodendroglial differentiation and increased myelination. Blocking of Lingo-1 has been shown to promote remyelination in EAE and in the cuprizone model.

Remyelination reduces axonal damage, and restores clinical function. Endogenous remyelination is a frequent phenomenon in early MS. It is limited in chronic MS due to inhibition of oligodendrocyte differentiation. Endogenous remyelination can be successfully promoted by modulating inhibitory pathways or transplantation of stem/precursor cells. The first clinical trials of new remyelination-promoting strategies are under way.

NO

The pathology of MS is well understood, involving both demyelination and axon degradation. The late clinical course is characterized by a continuous decline in function. This progression of the disease implies that endogenous, functionally significant repair does not occur in a meaningful way. Eric J. Buenz, PhD, Mayo Clinic, Rochester, Minnesota, USA, argued that the neuronal damage caused by MS cannot be repaired.

Recent work in animal models of MS have identified pathways that can be manipulated to enhance the repair progress in damaged neurons. However, the differences between demyelination and axonal degradation and the relative importance of each must be considered in light of MS and the pathogenesis of the animal models on which these observations are based. The EAE and Theiler's virus animal models of MS are appropriate for studying the pathologic processes leading to demyelination but are largely inappropriate for clinically meaningful study of remyelination because mouse axons spontaneously remyelinate. Additionally, the shiverer mouse model with relatively denuded axons that have been used to test remyelinating agents lack an underlying inflammatory disease process.

Repair of the damage in MS would result in improvement in the disability scale and not simply stabilization. The remyelination that does occur in MS is structurally abnormal. Neuronal damage extends outside of the immediate lesion into white matter that is normal in appearance. Recently, axon integrity has been recognized as the critical factor in disease progression. Without intact axons, remyelination is irrelevant and, currently, robust regeneration of functionally meaningful axons is not possible.

MS causes damage to the oligodendrocytes and neurons. Successful remyelination in animal models is a poor predictor of success in humans. For repair to occur, scarring must be cleared, appropriate neuronal connections re-established, and axon fibers remyelinated.