Can the damage in MS be repaired? No
Eric J Buenz

The late clinical course of multiple sclerosis is characterized by a continuous functional decline.[1, 2] Superficially, the clinical observation of progression implies that endogenous, functionally-significant, repair does not occur in a meaningful way in multiple sclerosis. However, recent work in model systems has identified pathways that can be manipulated to enhance this apparently inadequate repair progress, to result in functionally-significant repair. To assess the potential clinical utility of these observations, it is necessary to further dissect the pathogenesis of these model systems in the context of multiple sclerosis. Specifically, the differences between and relative importance of demyelination and axonal degradation need to be considered in light of multiple sclerosis and the pathogenesis of the animal model on which these observations are based.

Until recently, the pathogenic model for both multiple sclerosis and the presumed analogs induced through cuprizone,[3] lysolecithin,[4] experimental autoimmune encephalomyelitis[5] or Theiler's virus[5] were dominated by demyelination as the precipitating pathogenic event resulting in disability. The use of the experimental autoimmune encephalomyelitis and Theiler's virus animal models were likely appropriate to assess the pathologic processes that resulted in demyelination;[5] however, these models were largely inappropriate to study clinically meaningful remyelination since mice spontaneously remyelinate.[6, 7] While remyelination occurs in multiple sclerosis, it is structurally abnormal.[8] On the other hand, shiverer mice with relatively denuded axons[9] served as vehicles to test remyelinating agents, but this model system lacked an underlying inflammatory disease process. In short, the model systems used to evaluate an intervention for remyelination ability were inappropriate predictors for the relevance of an intervention in multiple sclerosis. This assertion has proven true since a majority of interventions successful in an animal model have failed in the clinic.[10]

Recently it has become clear that axon integrity is actually the critical factor in disease progression.[1, 11] During early stages of the disease, there is a redundant reserve of axons that when injured, do not result in a functional impairment. However once that reserve is depleted, there is a consequential functional loss.[12] Obviously, without intact axons, remyelination is irrelevant. Unfortunately, there is currently no way to robustly regenerate functionally meaningful axons.[2]

Combining these demyelinating and axonal integrity understandings of multiple sclerosis reveals a bleak prospect for repairing the damage resulting from multiple sclerosis. In the case of a fulminant lesion, for example, it would be necessary to first remove the astrogliosis,[13] re-establish meaningful and appropriate axonal connections, and finally remyelinate the axonal fibers. Since none of these three steps are currently possible in humans, there is no realistic chance for the damage induced by multiple sclerosis to be repaired.

References

1. Lassmann, H. & van Horssen, J. The molecular basis of neurodegeneration in multiple sclerosis. *FEBS Lett* **585**, 3715-23 (2011).
2. Ferguson, T.A. & Son, Y.J. Extrinsic and intrinsic determinants of nerve regeneration. *J Tissue Eng* **2**, 2041731411418392 (2011).
3. Matsushima, G.K. & Morell, P. The neurotoxicant, cuprizone, as a model to study demyelination and remyelination in the central nervous system. *Brain Pathol* **11**, 107-16 (2001).
4. Pavelko, K.D., van Engelen, B.G. & Rodriguez, M. Acceleration in the rate of CNS remyelination in lysolecithin-induced demyelination. *J Neurosci* **18**, 2498-505 (1998).
5. Dal Canto, M.C., Melvold, R.W., Kim, B.S. & Miller, S.D. Two models of multiple sclerosis: experimental allergic encephalomyelitis (EAE) and Theiler's murine encephalomyelitis virus (TMEV) infection. A pathological and immunological comparison. *Microsc Res Tech* **32**, 215-29 (1995).
6. Murray, P.D., McGavern, D.B., Sathornsumetee, S. & Rodriguez, M. Spontaneous remyelination following extensive demyelination is associated with improved neurological function in a viral model of multiple sclerosis. *Brain* **124**, 1403-16 (2001).
7. Miller, D.J., Asakura, K. & Rodriguez, M. Central nervous system remyelination clinical application of basic neuroscience principles. *Brain Pathol* **6**, 331-44 (1996).
8. Prineas, J.W. & Connell, F. Remyelination in multiple sclerosis. *Ann Neurol* **5**, 22-31 (1979).
9. Kirschner, D.A. & Ganser, A.L. Compact myelin exists in the absence of basic protein in the shiverer mutant mouse. *Nature* **283**, 207-10 (1980).
10. Friese, M.A. et al. The value of animal models for drug development in multiple sclerosis. *Brain* **129**, 1940-52 (2006).
11. Bjartmar, C. & Trapp, B.D. Axonal and neuronal degeneration in multiple sclerosis: mechanisms and functional consequences. *Curr Opin Neurol* **14**, 271-8 (2001).
12. Neumann, H. Molecular mechanisms of axonal damage in inflammatory central nervous system diseases. *Curr Opin Neurol* **16**, 267-73 (2003).
13. Yiu, G. & He, Z. Glial inhibition of CNS axon regeneration. *Nat Rev Neurosci* **7**, 617-27 (2006).