

## A New Therapeutic Target for the Treatment of Multiple Sclerosis

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This commentary is the first of what I hope will be a regular column that will highlight important discoveries in the basic neurosciences. Specifically, my intent is to inform those in the clinical neurosciences who usually do not have the time to read and/or access high impact neuroscience journals about breakthroughs that have the potential to be transformative in our understanding and treatment of neurological disorders.

In this first installment, I highlight a recent report published in *Nature Neuroscience* showing a novel therapeutic target that may show great promise in the treatment of Multiple Sclerosis (MS)<sup>1</sup>. It is common knowledge that MS is characterized by the inflammation and subsequent loss of myelin in the central nervous system. The understanding of how this occurs is not completely known, limiting treatment options. It is known that certain immune mediators such as T helper cell 17 (T<sub>H</sub>17), in a mouse model of MS, is important for the induction and maintenance of encephalomyelitis (EAE). Indeed, in humans T<sub>H</sub>17 cells have been found in the MS lesions. How these cells are activated and controlled is not clear but their priming by various antigen presenting cells is known to be required. In particular it is known that viral nucleic acids may be an important co-factor in this activation. This activation is also known to be mediated by a Toll-like receptors (TLRs) and a family of helicases known as the Retinoic acid-inducible gene 1-like helicases (RLH) that include retinoic acid inducible gene I (RIG-1) and melanoma differentiation associated gene 5 (MDA5). What the authors have found is that RLHs are negative regulators of sterile inflammation thereby opening up new therapeutic opportunities for the treatment of MS.

The authors showed that in wild type mice, when challenged with myelin oligodendrocyte glycoprotein peptide 35-55 (MOG<sub>35-55</sub>), 100 % developed EAE.<sup>1</sup> However in mice lacking the adapter protein interferon promoter stimulator (IPS-1), which is essential for mediating the effects of RIG-I and MDA5, both the clinical score and macrophage infiltration were decreased. There was also reduced demyelination as well as an increase in anti-inflammatory cytokine production. Using activators of RLHs, such as 3phospho- RNA (3pRNA) or poly

I:C (viral nucleic analogues), showed the disease severity was reduced after onset of the MS symptoms. Again concomitant decreases in myelin damage and increases in anti-inflammatory cytokines were induced.

Finally the authors showed that the reduction of MS symptoms is mediated by type I Interferon receptor (IFNAR) signalling since mice lacking the IFNAR showed no benefit from RLH agonist treatment.<sup>1</sup> Most importantly, in the last set of experiments it was clearly demonstrated that dendritic cells were the key cell type involved in RLH-mediated activation IFN-β that resulted in the suppression of the expansion of auto-antigen specific T<sub>H</sub>17 cells. In their discussion Dann et al point out that these findings have the potential to radically alter the treatment of MS and overcome the current limitation associated with IFN-β MS therapy.<sup>1</sup> Current therapies using IFN-β fail in about one third patients, largely due to the appearance of IFN-β neutralizing antibodies. Presumably, the induction of endogenous interferon activity will circumvent this problem. As well, the rapid onset (< 6 hours) of the effect of RHLH ligands is also important to note as flare ups of MS may be effectively treated by these compounds. In summary, the results of this study demonstrate great promise in developing new and more effective treatments for MS sufferers.

### REFERENCE

1. Dann A, Poeck H, Croxford AL, et al. Cytosolic RIG-I-like helicases act as negative regulators of sterile inflammation in the CNS. *Nat Neurosci*. 2011;15:98-106.

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