NEUROLOGICAL DISORDERS

A second wave

In multiple sclerosis (MS), T cells attack the myelin sheath of axons, resulting in demyelination. However, the aetiology of MS and other demyelinating diseases remains unclear. Now, Traka *et al.* provide evidence that, in mice, primary demyelination resulting from ablation of oligodendrocytes (ODGs) can initiate the generation of myelin ODG glycoprotein (MOG)-specific T cells and a secondary degeneration of the myelin sheath at around 30 weeks after ODG ablation.

Previously, the authors had generated mice with Cre recombinase activity-dependent expression of diphtheria toxin fragment A specifically in ODGs (DTA mice); injection of 5–7-week-old DTA mice with tamoxifen results in an extensive loss of ODGs, demyelination and neurological symptoms such as ataxia. In this study, tamoxifen-treated DTA mice (DTA^{Tx} mice) seemed to recover from symptoms and replenish ODG numbers by ~10 weeks post-injection (w.p.i.); however, at around 40 w.p.i., these animals again exhibited neurological symptoms and demyelination, and about one-half of these mice died by 52 w.p.i. Control mice (tamoxifen-treated mice carrying the diphtheria toxin-encoding

gene but lacking Cre recombinase) showed no such neurological deficits, implying that these symptoms were due to the initial ODG ablation.

Histological analysis of the CNS showed that the late-onset neurological symptoms in DTA^{Tx} mice were associated with widespread demyelination and axonal loss. Flow cytometry at 10 and 40 w.p.i. revealed more infiltration of activated CD4⁺ T cells to the CNS in DTA^{Tx} mice than in controls. Splenic CD4⁺ T cells isolated from DTA^{Tx} mice at 40 w.p.i. showed increased proliferation in response to stimulation with the MOG_{35–55} epitope than did cells isolated from control mice. Together, these results indicate that ODG ablation may trigger an adaptive autoimmune response, resulting in infiltration of MOG-specific autoreactive CD4⁺ T cells to the CNS.

Inoculation of *Rag*^{-/-} mice — which lack functional B or T cells — with MOG_{35–55}-stimulated splenocytes isolated from DTA^{Tx} mice induced a mild autoimmune encephalomyelitis phenotype, with hindlimb weakness and mild ataxia, CNS infiltration of immune cells and mild demyelination. Thus, MOG-specific T cells are sufficient to induce CNS inflammation and myelin loss.

Next, the authors examined whether the development of MOG-specific immune tolerance could ameliorate the secondary neurological symptoms in DTA^{Tx} mice. They infused MOG_{35–55}-coupled nanoparticles into DTA^{Tx} mice at 32 w.p.i. Splenocytes that were taken from these mice and stimulated with MOG_{35–55} showed reduced proliferation and production of inflammatory cytokines (suggesting immune tolerance) compared with splenocytes from DTA^{Tx} mice treated with ovalbumin_{323–339}-coupled nanoparticles. Importantly, treatment with the MOG_{35–55}-coupled nanoparticles inhibited T cell infiltration to the CNS and limited the progression of motor impairment in these animals.

These results raise the possibility that cytotoxic insults to ODGs may be an underlying triggering event for the autoimmune response in MS. The DTA^{Tx} model of the secondary loss of myelin may prove to be useful for investigating the mechanisms underlying adult-onset demyelinating diseases.

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“MOG_{35–55}-coupled nanoparticles inhibited T cell infiltration to the CNS and limited the progression of motor impairment”

ORIGINAL ARTICLE Traka, M. *et al.* Oligodendrocyte death results in immune-mediated CNS demyelination. *Nat. Neurosci.* **19**, 65–74 (2016)