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AUTOIMMUNITY

Interfering with brain inflammation

Interferon-β (IFNβ) is a first-line therapy for patients with relapsing–remitting multiple sclerosis. This study provides insight into the pathways by which type I IFNs can suppress inflammation in the central nervous system (CNS) and suggests a new mechanism by which these pathways could be targeted therapeutically.

The authors looked at the role of the RNA helicases RIG-I and MDA5 — stimulation of which is known to induce type I IFN production — in the context of experimental autoimmune encephalomyelitis (EAE) in mice. Similarly to human multiple sclerosis, EAE is thought to be mediated by T helper 1 (T_H1) and T_H17 cells. In mice lacking the RIG-I and MDA5 adaptor protein MAVS (also known as IPS1, VISA and CARDIF) that were immunized with a myelin-associated antigen, the peak clinical EAE disease score was markedly increased compared with that of wild-type mice. This correlated with increased numbers of macrophages and T cells in the CNS and increased demyelination. The encephalitogenic T cell response in *Mavs*$^{-/-}$ mice was shifted further towards T_H1 and T_H17 cell responses compared with that of wild-type mice, as shown by the increased expression of cytokines and transcription factors associated with these subsets.

These results indicate that the RNA helicases might have a protective role in EAE, and this was confirmed by the administration of ligands for RIG-I and MDA5 to wild-type mice at the peak of disease. Treated mice had markedly decreased disease severity and greatly increased serum levels of IFNβ. The transcripts of T_H1 and T_H17 cell-associated factors were decreased in number in the CNS of mice treated with RIG-I and MDA5 ligands.

The authors went on to show that this protective effect requires signalling through the type I IFN receptor (IFNAR). IFNAR-deficient mice, which have previously been shown to have more severe EAE than wild-type mice, had no improvement of clinical disease after treatment with RIG-I or MDA5 ligands. Fluorescently labelled ligands for RIG-I or MDA5 injected into mice with EAE mainly reached the spleen — where they were largely taken up by $CD11b^+CD11c^+$ dendritic cells (DCs) — and could not be detected in the CNS. The importance of DCs for protection was confirmed by the conditional deletion of *Ifnar* in DCs; these mice did not have any improvement of disease severity after the administration of RIG-I or MDA5 ligands.

So what is the effect of IFNAR stimulation on DCs? Lymph node cells taken from mice with EAE after RNA helicase stimulation were exposed to a myelin-associated antigen *in vitro*; T cell proliferation and IFNγ and interleukin-17 production were markedly decreased compared with the levels in cells taken from non-treated mice, and this was dependent on the presence of IFNAR on DCs.

Overall, the data indicate that the stimulation of RIG-I and MDA5 in peripheral DCs can inhibit encephalitogenic T_H1 and T_H17 cells through a type I IFN response that engages IFNAR on DCs. Stimulating the endogenous production of type I IFNs in this manner could be used therapeutically to bypass the formation of neutralizing antibodies specific for exogenous IFNβ, an issue that currently limits the clinical efficacy of IFN therapy.

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ORIGINAL RESEARCH PAPER Dann, A. *et al.* Cytosolic RIG-I-like helicases act as negative regulators of sterile inflammation in the CNS. *Nature Neurosci.* 4 Dec 2011 (doi:10.1038/nn.2964)