Cytosolic RIG-I-like helicases act as negative regulators of sterile inflammation in the CNS.

The action of cytosolic RIG-I-like helicases (RLHs) in the CNS during autoimmunity is largely unknown. Using a mouse model of multiple sclerosis, we found that mice lacking the RLH adaptor IPS-1 developed exacerbated disease that was accompanied by markedly higher inflammation, increased axonal damage and elevated demyelination with increased encephalitogenic immune responses. Furthermore, activation of RLH ligands such as 5'-triphosphate RNA oligonucleotides decreased CNS inflammation and improved clinical signs of disease. RLH stimulation repressed the maintenance and expansion of committed T(H)1 and T(H)17 cells, whereas T-cell differentiation was not altered. Notably, T(H)1 and T(H)17 suppression required type I interferon receptor engagement on dendritic cells, but not on macrophages or microglia. These results identify RLHs as negative regulators of T(H)1 and T(H)17 responses in the CNS, demonstrate a protective role of the RLH pathway for brain inflammation, and establish oligonucleotide ligands of RLHs as potential therapeutics for the treatment of multiple sclerosis.