AUTOIMMUNE DISEASE

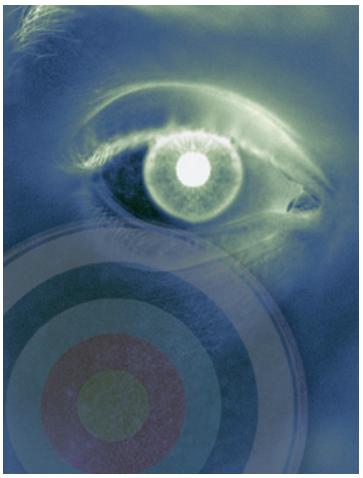
New drug target for MS?

Multiple sclerosis (MS) is an autoimmune inflammatory disease caused by myelin-specific T cells that induce an immune response against the white matter of the brain and spinal cord. The current therapeutic options are limited. Reporting in *Nature Medicine*, Yamashita and colleagues now show that repulsive guidance molecule A (RGMa), a membrane-bound axon guidance molecule, constitutes a promising new target for the treatment of MS.

RGMa was originally identified in the visual system, and is known to have a crucial role in the nervous system. The authors carried out an expression analysis in mice that revealed the presence of RGMa in dendritic cells, which prompted an investigation of its role in the immune system. *In vitro* experiments showed that RGMa expression can be induced by stimulating dendritic cells with lipopolysaccharide. RGMa was found to bind to neogenin, an immunoglobulin superfamily receptor that is expressed on $CD4^+$ T cells. Stimulation of $CD4^+$ T cells with RGMa results in the activation of RAP1, a small GTPase that promotes T cell adhesion by activating the integrin LFA1.

The relevance of these interactions to the development of MS was demonstrated in mice with experimental autoimmune encephalitis (EAE) — a model system for MS. Here, it was found that induction of the disease by vaccination with MOG, a myelin-derived antigen, was paralleled by an increase in RGMa expression on $CD11c^+$ dendritic cells. Immunohistochemical analysis showed neogenin expression on $CD4^+$ T cells, and elevated RAP1 activation in the cervical spinal cords of mice with EAE, but not in control mice. In humans, RGMa expression on dendritic cells was detected in samples of brain and spinal cord from patients with MS, but not in control samples.

To test whether RGMa can be therapeutically targeted, EAE mice were treated with RGMa-specific antibodies by intraperitoneal injection. This reduced the invasion of inflammatory cells to the central nervous system (CNS) and attenuated clinical signs of disease.



Adoptive transfer experiments in mice in which the disease was induced with MOG-pulsed bone marrow-derived dendritic cells (BMDCs) confirmed the critical role of RGMa on dendritic cells for disease induction; BMDCs in which RGMa was silenced with small interfering RNA had a reduced capacity to induce EAE. Further experiments indicated that RGMa expressed on dendritic cells activates T cells in peripheral tissues and the CNS, and that RGMa-specific treatment reduces T cell proliferation and cytokine responses. Importantly, the anti-RGMa antibody also showed effectiveness in a model of relapsing–remitting MS, in which administration of the antibody at the late stage of the first paralytic incident reduced the clinical severity of relapses.

In humans, it was shown that the RGMa-specific antibody can modulate T cell proliferative responses and cytokine expression in peripheral blood mononuclear cells isolated from patients with relapsing–remitting MS. Interestingly, RGMa polymorphisms have been associated with MS in humans. These findings suggest that RGMa is a promising new target for the treatment of MS.

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ORIGINAL RESEARCH PAPER Muramatsu, R. *et al.* RGMa modulates T cell responses and is involved in autoimmune encephalomyelitis. *Nature Med.* **17**, 488–494 (2011)