NEUROLOGICAL DISEASE

Br(e)aking the disease

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Multiple sclerosis (MS) is thought to be an autoimmune disease which results in the demyelination of CNS neurons. αB-crystallin (CRYAB) is a protein that is not expressed under normal conditions, but is highly expressed during the early phase of MS episodes. However, the role of CRYAB in MS is unknown. In a recent *Nature* publication, Ousman *et al.* show that, in a mouse model of MS, the pathology is more severe if the mice lack CRYAB, and they also show that CRYAB itself is targeted by the immune system in MS.

Mouse models of MS are based on immunization with myelin oligodendrocyte glycoprotein (MOG), which causes experimental autoimmune encephalomyelitis (EAE). To investigate the role of CRYAB in MS, Ousman *et al.* induced EAE in mice lacking CRYAB (*Cryab*$^{-/-}$ mice).

EAE induction caused more severe inflammation and demyelination in *Cryab*$^{-/-}$ mice than in control mice. This correlated with increased cell death: the CNS of the *Cryab*$^{-/-}$ mice contained increased levels of caspase-3, which mediates apoptosis, and more apoptotic or necrotic glia, as demonstrated by terminal deoxynucleotidyl transferase labelling (TUNEL).

Next, the authors investigated the immune response to EAE induction and showed that CD3^{+} T cells, macrophages and dendritic cells were hyper-responsive in *Cryab*$^{-/-}$ mice. These cells had a higher rate of proliferation and secreted more pro-inflammatory cytokines than cells from wild-type mice. These findings suggest that CRYAB reduces the immune cell response during EAE. However, because EAE can be induced in wild-type mice, this is not sufficient to halt disease progression.

Astrocytes are known to modulate inflammation in EAE. Astrocytes derived from *Cryab*$^{-/-}$ mice overproduced interleukin (IL)-6 and had higher levels of caspase-3 and TUNEL. Therefore, CRYAB might protect astrocytes from cell death by inhibiting caspase-3 activation.

The authors used an array of different myelin proteins and CRYAB to detect auto-antibodies in mice with EAE, and found that several epitopes of CRYAB were antibody targets. They also found auto-antibodies recognizing three different epitopes of CRYAB in the cerebrospinal fluid of MS patients, suggesting that antibody-mediated neutralization of CRYAB might contribute to disease progression.

In order to assess whether boosting CRYAB could counter the disease, the authors treated EAE-induced, wild-type mice with recombinant human CRYAB. This not only reduced the severity of the disease, but also lowered CNS immune-cell infiltration, suppressed immune-cell response and reduced cell death.

This study therefore suggests that CRYAB acts as a brake to slow down a runaway immune system in MS. Studies which investigate recombinant CRYAB as a viable therapy might lead to more efficient treatment of MS in the future.

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ORIGINAL RESEARCH PAPER
Ousman, S. S. *et al.* Protective and therapeutic role of αB-crystallin in autoimmune demyelination. *Nature* 13 June 2007 (doi:10.1038/nature05935)