RHEUMATOID ARTHRITIS

Halting disease in its tracks

Roughly 1% of the population suffer from rheumatoid arthritis (RA), a debilitating disease characterized by chronic inflammation of peripheral joints, cartilage destruction and bone erosion. A range of treatments, with varying side effects, currently exist for the management of RA, but none are able to halt advancement of the disease. Writing in *Nature Medicine*, Seo *et al.* now report experiments in mice showing that a monoclonal antibody targeting a receptor on T cells can block disease progression — the first treatment able to do so.

The target of the antibody is a T-cell costimulatory molecule receptor called CD137 (4-1BB), which has previously been targeted in mouse models of systemic lupus erythematosus (SLE), which, like RA, is an autoimmune disease. In these studies, anti-CD137 treatment protected mice genetically susceptible to SLE and conferred a normal lifespan on mice with established SLE. The current study builds on earlier demonstrations of the potential utility of targeting CD137 in autoimmune disease by providing hints as to the molecular mechanisms underlying the beneficial effects of anti-CD137 treatments.

Seo *et al.* studied collagen-induced arthritis (CIA) in mice, a commonly used model of human RA. The administration of anti-CD137 antibodies after the induction of CIA prevented the destruction of joints, and histological examination of treated mice indicated that they were free of disease. In another experiment, CIA was induced in mice, and, once disease was established, anti-CD137 treatment was administered. This had the effect of reversing arthritis and almost completely cleared antibodies against collagen from the serum.

So how does triggering CD137 work in combating arthritis? On the basis of previous studies, Seo *et al.* proposed that the effect of anti-CD137 would depend on the induction of interferon-γ and the enzyme indoleamine-2,3-dioxygenase (IDO). IDO is known to suppress immune rejection of foreign tissue in mice, and inhibition of IDO prevents this immune rejection. Similarly, the inhibition of IDO in the current experiments abolished the protective effects of anti-CD137 treatment. The authors suggest that IDO, a tryptophan-metabolizing enzyme, is required to produce tryptophan metabolites that might cause the selective deletion of helper T cells specific for collagen and which contribute to CIA.

It is far too early to say what prospects targeting CD137 might have in human RA, but the impressive results from these mouse studies certainly flag up the approach as one worthy of further investigation, if not to develop specific anti-CD137 therapies then to better elucidate the pathways that result in RA.

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References and links

ORIGINAL RESEARCH PAPER Seo, S. K. *et al.* 4-1BB-mediated immunotherapy of rheumatoid arthritis. *Nature Med.* **10**, 1088–1094 (2004)