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AUTOIMMUNITY

Troublemaker T cells target ribosomal protein

> RPL23A as a self antigen that is recognized by arthritogenic T cells

Characterizing the self antigens that are targeted in systemic autoimmune diseases has proven technically difficult; however, a new study in *Science* has identified a ubiquitously expressed ribosomal protein that is recognized by arthritogenic T cells from mice, and by T cells and autoantibodies from patients with rheumatoid arthritis.

The authors cloned single T cell receptors (TCRs) from arthritogenic $CD4^+$ effector T cells that were isolated from SKG mice; these mice spontaneously develop a disease that resembles human rheumatoid arthritis as a result of a genetic mutation that reduces the stringency of thymic negative selection. The ability of the cloned TCRs to cause disease was investigated in mice engineered to express the TCRs in developing T cells. The authors then sought to identify the epitope recognized by the TCR that caused the highest incidence of spontaneous rheumatoid arthritis-like disease, the so-called 7-39 TCR.

The serum from mice expressing the 7-39 TCR was found to react with an 18 kDa protein that was identified as the 60S ribosomal protein L23A (RPL23A) by mass spectrometry. Recombinant RPL23A protein induced dose-dependent interleukin-2 production by a 7-39 TCR-expressing T cell hybridoma, and also stimulated inflammatory cytokine production by $CD4^+$ T cells from the draining lymph nodes of the arthritic joints of 7-39 TCR-expressing mice.

Following the identification of RPL23A as a target of pathogenic T cells in genetically engineered mice, the authors sought to investigate whether these data translated into the setting of human disease. *RPL23A* mRNA was shown to be ubiquitously expressed in a range of healthy human tissues. Relative to healthy controls, a significantly greater proportion of patients with rheumatoid arthritis were shown to have IgG antibodies specific for RPL23A, whereas serum samples from patients with other systemic autoimmune conditions — such as systemic lupus erythematosus and osteoarthritis — were all negative. Furthermore, $CD4^+$ T cells from the synovial fluid of a subset of patients with rheumatoid arthritis were shown to produce interferon-γ in response to stimulation with RPL23A, suggesting that at least in a subset of patients with rheumatoid arthritis, immune responses targeting this ubiquitous ribosomal protein may contribute to pathology.

In summary, this study identifies RPL23A as a self antigen that is recognized by arthritogenic T cells and demonstrates that characterizing the antigen specificity of pathogenic T cells in mice with dampened thymic negative selection can reveal mechanisms that are relevant to autoimmunity in humans.

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ORIGINAL RESEARCH PAPER Ito, Y. *et al.* Detection of T cell responses to a ubiquitous cellular protein in autoimmune disease. *Science* **346**, 363–368 (2014)