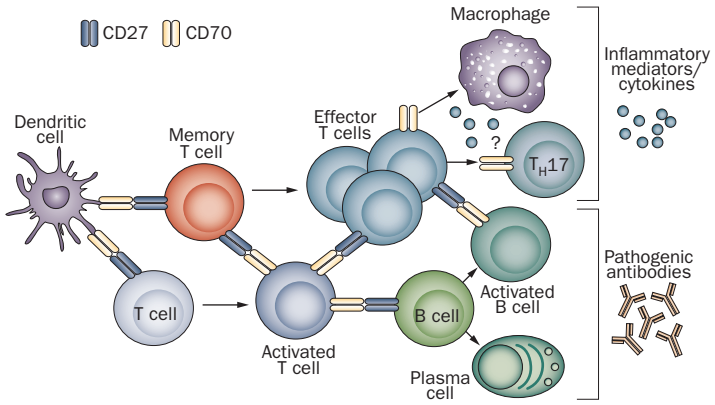
EXPERIMENTAL ARTHRITIS

Is CD70 a new therapeutic target?



The tumor necrosis factor (TNF) superfamily member CD70 (also known as TNFSF7) has previously been identified as a biomarker and potential target for the treatment of certain malignancies. Research by Oflazoglu and colleagues now suggests that CD27–CD70 blockade could be a promising therapeutic strategy for autoimmune and autoinflammatory disorders. In addition, because the expression of CD70 is restricted to the effector cells of the immune system, this could herald the development of more-targeted therapies with a lower risk of adverse effects than are associated with current, generalized immunotherapeutic agents.

CD70 is expressed on activated B cells, T cells and dendritic cells, and has an established role in the effector and memory functions of lymphocytes. Increased levels of CD70 have been observed in T cells from the synovium of patients with rheumatoid arthritis and psoriatic arthritis, as well as in the circulating T cells of patients with systemic lupus erythematosus where they correlated with disease severity. Additionally, treatment with an anti-CD70 antibody ameliorated T-cell-induced secretion of immunoglobulin by B cells *in vitro*, where T cells were harvested from patients with systemic lupus erythematosus.

The potential role of CD70 in autoimmunity and inflammation led researchers from Seattle Genetics Inc., WA, USA to investigate the effects of CD70 blockade on the pathogenesis and progression of disease in a collagen-induced mouse model of arthritis. The investigators developed a hamster anti-mouse CD70 monoclonal antibody that exerted its effect either by inhibiting interactions between CD70 and its receptor CD27, or by depleting CD70-positive lymphocytes using Fc-mediated effector functions.

They found that treatment with the anti-mouse antibody before disease onset prevented the development of collagen-induced arthritis. More importantly, however, treatment halted the progression of established arthritis, "providing direct evidence for the therapeutic potential of CD70 targeting in arthritis treatment," says Iqbal Grewal, one of the study's investigators. Furthermore, CD70 blockade was associated with significant reductions in autoantibody production, joint inflammation, and bone and cartilage destruction. "These results establish an *in vivo* role for CD70 in the inflammatory process leading to the development of arthritis," says Grewal. "Current arthritis treatment options include TNF blockers, the anti-IL-6 receptor antibody tocilizumab, the IL-1 blocker anakinra, and the CD28 costimulation blocker abatacept. An anti-CD70 antibody could be a novel therapeutic approach that would complement these existing regimens."

Although the current biologic therapies are undoubtedly effective, the number of reported adverse effects and lack of long-term clinical efficacy could point to a need for more specific and better tolerated therapies. Targeted therapy against CD70 via the depletion of CD70-positive activated lymphocytes or blockade of CD70–CD27 interactions could offer a means to selectively target effector lymphocytes without inducing generalized immunosuppression.

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Original article Oflazoglu, E. *et al.* Blocking of CD27–CD70 pathway by anti-CD70 antibody ameliorates joint disease in murine collagen-induced arthritis. *J. Immunol.* **183**, 3770–3777 (2009).