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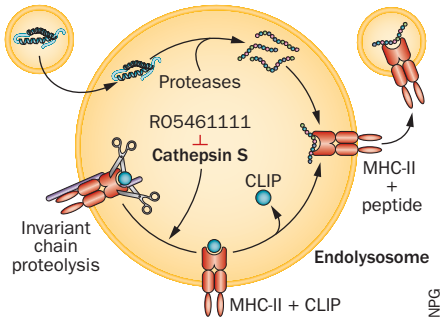
CONNECTIVE TISSUE DISEASES

Inhibiting cathepsin S to treat SLE and lupus nephritis

"Cathepsin S blockade specifically improves SLE by inhibiting autoantigen presentation" says Professor Hans-Joachim Anders, corresponding author of a study published in the *Annals of the Rheumatic Diseases*. His team used a newly developed antagonist of the cysteine protease cathepsin S, a papain family member that is vital for the endolysosomal assembly of MHC II–antigen complexes (see figure). The novel cathepsin S inhibitor, RO5461111 (Roche), works in humans and mice, allowing the researchers to test it in a mouse model of systemic lupus erythematosus (SLE). The drug inhibited humoral autoimmune responses "including hypergammaglobulinaemia and autoantibody production," says Anders, leading to an "improvement in the immune complex-related disease manifestations such as lupus nephritis."

The active-site competitive inhibitor, RO5461111, potently and specifically inhibited human (IC_{50} 0.4 nM) and mouse (IC_{50} 0.5 nM) cathepsin S. Oral administration of the inhibitor



(approximately 1.31 mg/day, stable plasma concentration of 400–600 ng/ml) protected MRL-*Fas*^{lpr} mice ($n = 15$), which spontaneously develop SLE and lupus nephritis, from severe disease. The researchers found significantly less IL-10 and TNF in plasma, a reduced percentage of activated dendritic cells and CD4$^+$ T cells in the spleen, and disrupted spatial organisation of germinal centre formation in treated mice compared with control mice. The RO5461111-treated mice also developed fewer glomerular IgG deposits and had fewer circulating anti-dsDNA IgG antibodies than control mice.

Cathepsin S is not involved in antigen loading MHC I molecules, therefore, inhibition had no effect on CD8$^+$ T cell numbers or activation. MHC II-restricted autoantigen presentation is thought to be important for the pathogenesis of a number of autoimmune diseases. The vital role of cathepsin S in the assembly of this machinery positions it as a potential therapeutic target for the treatment of autoimmune diseases other than SLE and lupus nephritis. Unlike commonly used broad spectrum immunosuppresants such as steroids, which can leave patients susceptible to infections, Anders says the inhibitor of "cathepsin S could be a more selective immunoregulatory agent," that will "...be further evaluated and eventually tested in a clinical trial."

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Original article Rupanagudi K. V. *et al.* Cathepsin S inhibition suppresses systemic lupus erythematosus and lupus nephritis because cathepsin S is essential for MHC II-mediated CD4 T cell and B cell priming. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2013-203717