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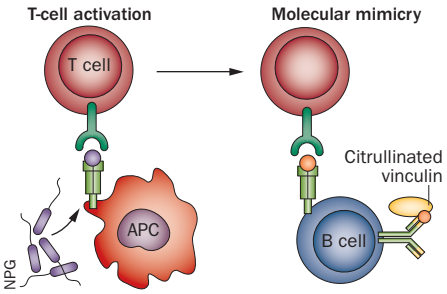
RHEUMATOID ARTHRITIS

Clues to the HLA–RA connection from T-cell crossreactivity to vinculin and microorganisms

The HLA class II locus has long been implicated as a risk factor for rheumatoid arthritis (RA), particularly anti-citrullinated protein antibody (ACPA)-positive disease, but the molecular basis for the effects of HLA molecules has remained unclear. New research by Rene Toes and colleagues suggests an important clue could lie in the T-cell response to an epitope that is found in microorganisms, the self-protein vinculin and the protective HLA molecule HLA-DRB1*13.

The epitope in question contains the core amino acid sequence DERAA. "We showed the presence of T cells with crossreactivity to microbes and the DERAA-containing self-protein vinculin," explains Toes. Presentation to these T cells was found to be restricted to HLA-DQ molecules encoded by HLA haplotypes that are associated with susceptibility to ACPA-positive RA. The researchers demonstrated that these HLA-DQ molecules, which are genetically linked



to HLA shared epitope (HLA-SE) alleles, are able to efficiently present DERAA epitopes derived from microorganisms as well as from vinculin.

The study also established that citrullinated vinculin is a novel autoantigen that is recognized by ACPAs, and that DERAA-directed T cells can provide help to B cells, ultimately leading to ACPA production. Importantly, the presence of these T cells was greatly reduced in carriers of the *HLA-DRB1*13:01* allele in comparison with non-carriers, presumably because presentation of HLA-DRB1*13-derived DERAA peptide in the thymus of carriers leads to negative selection of DERAA-directed T cells. "These results offer an explanation both for the protective effects of HLA-DR13-carriership as well as for the predisposing contribution of the HLA-SE-haplotypes on the development of ACPA-positive RA," says Toes.

Future studies could address the possibility of targeting T cells that recognize the DERAA epitope. "We are most interested in the protective effects associated with HLA-DR13 as these might open the way for pre-emptive strategies aiming to prevent development of RA in at-risk individuals," Toes concludes.

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Original article van Heemst, J. *et al.* Crossreactivity to vinculin and microbes provides a molecular basis for HLA-based protection against rheumatoid arthritis. *Nat. Commun.* doi:10.1038/ncomms7681