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Therapeutic targeting of a novel bone-destroying pathway in Rheumatoid arthritis

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Rheumatoid arthritis (RA) is characterized by chronic joint inflammation and bone damage in which IL-17-producing T helper (Th17) and osteoclast (OC) cells play important roles. Although the etiology of RA is not well understood, it has been long observed that the vast majority of RA patients carry *HLA-DRB1* alleles that code a five amino acid sequence motif called the 'shared epitope' (SE). The SE not only confers a higher risk for RA, but also increases the likelihood of developing a more erosive disease. The underlying mechanisms by which the SE affects susceptibility to - and severity of - RA are unknown. It has been recently demonstrated that the SE is a signal transduction ligand that binds specifically to the innate immune system receptor calreticulin, and activates a signaling pathway that facilitates differentiation of Th17 cells and OCs. When administered *in vivo* to mice with collagen-induced arthritis, the SE increased joint swelling, synovial tissue OC abundance and erosive bone damage. Thus, the SE contributes directly to arthritis severity by facilitating Th17 differentiation and activating OC-mediated bone destruction. In this talk, the new pathway will be described and a proposed therapeutic strategy that specifically targets it will be discussed. To illustrate the potential utility of the proposed therapeutic strategy, recent experiments with small chemical compounds that specifically and potently inhibit the SE-activated pathway and ameliorate inflammatory arthritis in mice will be presented.

Biography

Joseph Holoshitz received his MD from The Hebrew University in Jerusalem, and completed his basic research training at the Weizmann Institute and Stanford University. He is Professor of Internal Medicine at the University of Michigan, focusing his bench research effort on the pathogenesis of RA. His research has been recognized for its innovation by the Searle Scholar Award, NIH-EUREKA Award, the Carol Nachman International Prize for Rheumatology Research, and many other distinctions. His published work has been cited in over 3000 scientific articles.

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