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Interleukin-6-mediated signal transduction in autoimmune disorders

Interleukin-6 (IL-6) is one of several pro-inflammatory cytokines found at elevated levels in various autoimmune disorders such as rheumatoid arthritis (RA). In that regard, IL-6 was shown to play a prominent role in the pathogenesis and progression of RA. However, in order to establish how IL-6 could be involved in the progression of RA through its capacity to alter the function(s) of articular chondrocytes, we explored several relevant mechanisms by which IL-6 affected human chondrocytes *in vitro*. We found that incubating the C28/I2 line of immortalized human chondrocytes with recombinant human IL-6 (rhIL-6), the IL-6-like cytokine, rh-oncostatin M or the adipokine, rh-adiponectin caused phosphorylation (i.e. activation) of ERK1/2, p38α MAPK and JNK1/2. We also reported that rhIL-6 activated STAT-1, STAT-3 and STAT-5 without altering total STAT-1, -3 and -5, although STAT-1 was constitutively phosphorylated in another human chondrocyte line, T/C28a2. Matrix metalloproteinase-9 (MMP-9) plays a key role in RA by degrading cartilage extracellular matrix proteins. We found that rhIL-6 increased the synthesis of MMP-9 in the human chondrocyte lines. Of note, production of MMP-9 was inhibited by tocilizumab, a fully humanized monoclonal antibody which neutralizes the interaction of IL-6 with the membrane-bound IL-6 receptor-α/gp130 complex, membrane IL-6R or soluble IL-6 receptor (sIL-6R). Whereas the combination of rhIL-6 and sIL-6R significantly increased MMP-9 compared to sIL-6R, sIL-6R alone inhibited MMP-9 production by C28/I2 chondrocytes when compared to rhIL-6. This latter finding may be germane in the design of a future biological therapy for RA..

Biography

Charles J Malemud has received his PhD from George Washington University in 1973, and completed postdoctoral studies at the State University of New York at Stony Brook in 1977. Since 1977, he has been a Member of the Faculty at Case Western Reserve University School of Medicine where he is presently Professor of Medicine and Anatomy in the Division of Rheumatic Diseases and Senior Investigator in the Arthritis Research Laboratory. He has published more than 235 peer-reviewed papers, reviews and book chapters primarily in the fields of chondrocyte biology, extracellular matrix and signal transduction pathways. He is on the editorial board of several rheumatology, immunology and musculoskeletal journals and is Editor-in-Chief of the *Journal of Clinical & Cellular Immunology and Global Vaccines and Immunology*.

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