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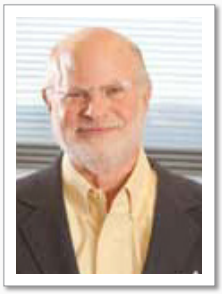

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Studies on signal transduction and apoptosis with the immortalized human Juvenile chondrocyte cell lines, T/C28a2 and C28/I2

T/C28a2 and C28/I2 are immortalized juvenile human chondrocytes that transcribe the cartilage-specific transcription factor, SOX9. We employed T/C28a and C28/I2 to examine the extent to which recombinant human tumor necrosis factor-α (rhTNF-α), rhIL-6, oncostatin M (rhOSM) and adiponectin (rhAPN)-induced activation of the SAPK/MAPK and JAK/STAT signaling pathways and whether these signaling pathways influenced induction of apoptosis. STAT1, STAT3 and STAT5 were constitutively phosphorylated in T/C28a2. Constitutive phosphorylation of these STAT proteins was JAK-dependent since the JAK inhibitors, ruxolitinib and WHIP-131, reduced STAT phosphorylation. By contrast, in C28/I2, STAT3 was the most abundant STAT protein and phosphorylation of STAT3 (i.e. P-STAT3) was induced by rhIL-6, rhOSM and rhAPN. Of note, treatment of C28/I2 suspension cultures with rhIL-6, soluble IL-6 receptor (sIL-6r), IgG4, tocilizumab, an IgG1κ monoclonal antibody which neutralizes IL-6/IL-6 receptor binding, or the combination of rhIL-6 and tocilizumab increased U-STAT1A and U-STAT1B. rhOSM and rhAPN, but not rhIL-6, increased P-ERK by 57% and 35%, respectively and U0126, an upstream inhibitor of ERK1/2 activation through inhibition of MEK1/2, reduced P-ERK to control levels. None of the IL-6-type cytokines increased P-JNK or P-p38α. rhTNF-α induced apoptosis measured by the TUNEL assay in C28/I2 with the frequency of TUNEL-positive C28/I2 chondrocytes further increased by the combination of rhTNF-α and U0126. Apoptosis was also increased by rhIL-6 but not by rhIL-6 and U0126, nor by rhOSM. (Support provided by Genentech/Roche Group and 5P30EY11373 from the National Eye Institute).

Biography

Charles J. Malemud received his Ph.D. 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 & Anatomy in the Division of Rheumatic Diseases and Senior Investigator in the Arthritis Research Laboratory. He has published more than 190 papers, chapters and reviews primarily in the field of chondrocyte biology. He is on the editorial board of several rheumatology, immunology and musculoskeletal journals and is Editor-in-Chief of the Journal of Clinical and Cellular Immunology.

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