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Charles J Malemud
Case Western Reserve University School of Medicine, USA

Blockade of recombinant human IL-6 with tocilizumab inhibits matrix metallo-proteinase-9 in the C 28/I2 cell line of immortalized human chondrocytes

In this study, we employed the immortalized human juvenile chondrocyte lines, T/C28a2 and C28/I2, to determine whether recombinant human (RH)-IL-6 caused STAT3 to be phosphorylated (p-STAT3). WHI-P131, a JAK3-selective small molecule inhibitor was used to validate the JAK/STAT response to rhIL-6 since WHI-P131 should decrease p-STAT3 without altering total STAT3 (STAT3). Tocilizumab (TCZ), a monoclonal antibody which neutralizes the interaction between IL-6 and its receptor(s) was also employed to determine if matrix metalloproteinase-9 (MMP-9) production was coupled to the predicted rhIL-6-mediated JAK/STAT response. Western blots revealed that the T/C28a2 and C28/I2 chondrocyte lines produced STAT3 protein. However, constitutive p-STAT3 was detected only in T/C28a2. C28/I2 chondrocytes incubated with rhIL-6 (50 ng/ml) for 30 min increased p-STAT3 which was inhibited by WHI-P131. Furthermore C28/I2 chondrocytes incubated with rhIL-6 increased MMP-9 synthesis. Importantly, the combination of rhIL-6 and TCZ (200 ng/ml) significantly decreased MMP-9 production after 60 min which was sustained after 4 hrs and rhIL-6 plus TCZ significantly reduced the number of MMP-9-positive C28/I2 chondrocytes. Of note, sIL-6R also significantly reduced the number of MMP-9-positive cells compared to rhIL-6 alone. In contrast the combination of rhIL-6 and sIL-6R significantly increased MMP-9 cell positivity. These results indicated that rhIL-6-mediated STAT3 phosphorylation was coupled to MMP-9 production in C28/I2 chondrocytes where MMP-9 production was significantly reduced by TCZ or sIL-6R. These findings also support the view that TCZ likely inhibits rhIL-6-mediated MMP-9 production in C28/I2 chondrocytes by neutralizing all 3 IL-6-mediated-signaling pathways.

Biography

Charles J Malemud received PhD from George Washington University in 1973 and completed Post-doctoral 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 over 200 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 for the journals of clinical and cellular immunology.

cjm4@case.edu

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