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Monosodium urate and tumor necrosis factor-α increase apoptosis in human chondrocyte cultures

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Increased levels of monosodium urate (MSU) or tumor necrosis factor- α (TNF- α) were previously shown to reduce chondrocyte function in several forms of arthritis and may even be responsible for the loss of chondrocyte vitality via apoptosis. We employed four sources of human chondrocytes to investigate whether MSU or recombinant human TNF-a (rhTNF-a) induced chondrocyte apoptosis measured either by the generation of intranucleosomal DNA fragments or the TUNEL assay. We also studied whether activation of the JAK/STAT pathway and/or stimulation of xanthine oxidase (XO) contributed to the induction of chondrocyte apoptosis because activation of JAK/STAT and XO were shown to contribute to apoptosis in other cell types. RhTNF- α induced apoptosis in human chondrocyte cultures initiated from osteoarthritic cartilage while at the same time increasing the activity of XO. MSU and rhTNF- α also increased the number of apoptotic normal human chondrocytes. Febuxostat, a specific inhibitor of XO, attenuated the activity of normal chondrocyte XO but did not blunt the rhTNF-a-mediated increase in apoptotic nuclei in normal chondrocytes. Treatment with MSU or rhTNF- α increased phosphorylation of STAT3 in macroaggregate pellet cultures initiated from either juvenile human chondrocytes or bone marrow-derived mesenchymal stem cells, but MSU or rhTNF-a increased the frequency of apoptosis only in the juvenile chondrocyte pellet cultures. These results indicated that MSU or rhTNF-a increased the number of apoptotic human chondrocytes in vitro. However, increased apoptosis did not appear to be dependent on either the activation of STAT3 nor full activity of XO. (Support provided by Takeda Pharmaceuticals North America, Inc.)

Biography

Charles J. Malemud received the 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, Dr. Malemud 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 185 papers and reviews primarily in the field of chondrocyte biology. Professor Malemud is on the editorial board of several rheumatology, immunology and musculoskeletal journals.