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Charles J Malemud

Case Western Reserve University School of Medicine, USA

How do Janus Kinase (JAK) inhibitors really work

The Janus Kinase/Signal Transducers and Activators of Transcription (JAK-STAT) signaling pathway plays a prominent role in several autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus, psoriasis/psoriatic arthritis, and, inflammatory bowel disease. Thus, the continuous activation of JAK-STAT signaling mediated by the substantially elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-17, IL-12/IL-23 and interferon- γ , to name just a few in these diseases, disrupts many of the downstream cellular events regulated by JAK-STAT signaling. This often results in the aberrant survival of immune cells and accessory cells thus perpetuating chronic inflammation. The extent to which JAK-STAT signaling is involved in these autoimmune diseases led to the pre-clinical development and clinical trials evaluation of JAK small molecule inhibitors (SMIs), now referred to as “Jak inhibitors.” These include tofacitinib, ruxolitinib, and baricitinib which were FDA-approved for the medical management of RA, psoriasis and myeloproliferative disease. In a pre-clinical analysis, tofacitinib demonstrated a relative selectivity for JAK1/JAK3 compared to JAK1/JAK2. At the cellular level, ruxolitinib, a JAK1/JAK2-selective SMI was shown to reduce the plasma levels of IL-6 and CD-40 as well as the phosphorylation of STAT3 *ex vivo* using blood cells from RA patients. Conversely, in cell-free assays, baricitinib is relatively selective for JAK1/JAK2 ($IC_{50}=5.9/5.7$ nM, respectively) compared to JAK3 and Tyk2 and exhibits no inhibitory activity towards either the tyrosine-protein kinase Met or checkpoint kinase-2. Baricitinib was also shown to inhibit IL-6-stimulated or IL-23-stimulated phosphorylation of STAT3 as well as the downstream synthesis of the chemokine, monocyte chemoattractant protein-1. At present, studies are being conducted by our research group to determine the extent to which tofacitinib inhibits matrix metalloproteinase gene expression by cultured human chondrocytes.

Biography

Charles J Malemud received the 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 & Anatomy in the Division of Rheumatic Diseases and Senior Investigator of the Arthritis Research Group. He has published over 230 papers, chapters and reviews primarily in the field of chondrocyte biology. He is on the editorial board of rheumatology, immunology, and musculoskeletal journals and is Editor-in-Chief of the Journal of Clinical and Cellular Immunology and Global Vaccines and Immunology.

cjm4@case.edu

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