The JAK/STAT Pathway In Waldenström Macroglobulinemia

Stephen M. Ansell, Lucy S. Hodge, Deanna Grote, Steven C. Ziesmer, Anne J. Novak.

Division of Hematology, Mayo Clinic, Rochester, MN

Waldenstrom macroglobulinemia (WM), a B-cell malignancy defined by a lymphoplasmacytic infiltrate in the bone marrow and also by the hyperproduction of monoclonal IgM protein. Cytokines such as B-lymphocyte stimulator (BLyS) and interleukin-6 (IL-6) are highly expressed in WM and play an important role in promoting IgM secretion. IL-6 signaling via the JAK/STAT pathway has been found to be critical for IgM secretion and inhibition of the pathway using a JAK inhibitor significantly suppresses IgM production.

Members of the signal transducers and activators of transcription (STATs) family of proteins function as secondary messengers mediating cellular responses to various cytokines and growth factors. Aberrant activation of STATs has frequently been implicated in the pathogenesis of hematologic malignancies due to the ability of these proteins to regulate the expression of genes involved in cell differentiation, proliferation, and survival. While IL-6 signals predominantly through STAT3, it is also able to activate STAT5. Both STAT3 and STAT5 have been found to be highly expressed in WM cells,

Because cytokines are highly expressed in WM and the JAK/STAT pathway is clearly activated, targeting this pathway provides a novel therapeutic approach to treating WM patients.