Session III: Genetic Basis and Pathogenesis

of WM and IgM Related Disorders

Abstract 116

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Role of CCL5 and Interleukin-6 in the Biology of Waldenström's macroglobulinemia. Stephen M. Ansell, Division of Hematology, Mayo Clinic, Rochester, MN, USA.

Recent gene array studies have suggested an important role for interleukin-6 (IL-6) in Waldenström's macroglobulinemia (WM), however, the precise role played by IL-6 in WM is largely unknown. Using a multiplex ELISA, we confirmed that IL-6 was significantly elevated in WM patients compared to controls, and also found that serum levels of CCL5 (Rantes) were elevated in WM. CCL5 has been shown to regulate IL-6 secretion, and we therefore determined whether CCL5 influenced IL-6 expression and the subsequent effect of IL-6 signaling in WM cells. To define the source of IL-6 in the tumor microenvironment, we used stromal cells from bone marrows of WM patients and healthy donors, malignant cells from WM patients, and the BCWM.1 cell line, and tested their ability to secrete IL-6 by ELISA. All cell types secreted IL-6, with stromal cells secreting the most. We then tested the ability of CCL5 to induce IL-6 secretion and found that CCL5 significantly increased IL-6 secretion by stromal cells as well as malignant B-cells. Using patient-derived WM cells and the BCWM.1 cell line, we determined the effect of IL-6 on growth of WM cells and found that IL-6 had a modest effect on cell proliferation but had no effect on cell viability. In contrast, when we addressed the role of IL-6 on IgM secretion, we found that IL-6 increased IgM secretion by WM cells in a dose-dependent manner. When we analyzed the downstream signaling events activated by IL-6 in WM cells we found that IL-6 stimulation resulted in phosphorylation of Stat1, Stat3 and Erk1/2, but not Akt. In summary, we have found that IL-6 upregulates IgM secretion by WM cells and that IL-6 secretion is regulated in part by CCL5. Therapies targeting CCL5, IL-6 secretion or the IL-6 signaling pathways may therefore provide clinical benefit to patients with WM.