Comprehensive Assessment of Cytokines and Chemokines in patients with Waldenstrom's Macroglobulinemia reveals a distinct profile with pathophysiological and clinical relevance.

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Waldenstrom's macroglobulinemia (WM) is a B-cell lymphoplasmacytic disorder characterized by elevated clonal IgM secretion and bone marrow infiltration. Dysregulation of plasma cytokines and chemokines have been described in related malignancies, though large scale comparative efforts to WM have been limited. We therefore evaluated the levels of 20 cytokines, 27 chemokines, and soluble CD27 (sCD27) given the putative memory B-cell origin of WM in peripheral blood derived plasma obtained from 54 patients with WM, 31 patients with Multiple Myeloma (MM), and 37 patients with monoclonal gammopathy of unknown significance (MGUS) using the Bio-Plex Pro Human Cytokine 27-plex Assay and the Bender instant soluble CD27 ELISA. Twenty-six age-matched normal donors (ND) were used as controls. Among WM patients, we detected significantly higher levels of the cytokines IL-1Rα ($p<0.001$), IL-5 ($p=0.009$), IL-6 ($p=0.017$), IL-8 ($p<0.001$), IL-10 ($p<0.001$), IL-17 ($p<0.001$), INFγ ($p=0.022$) and GM-CSF ($p<0.001$), as well as the chemokines CCL2 ($p<0.001$), CCL3 ($p<0.001$), and CXCL8 ($p<0.001$). IL-2 ($p<0.001$), IL-9 ($p< 0.001$), IL-15 ($p < 0.001$), FGF2 ($p<0.001$), and sCD27 ($p<0.001$) levels were also significantly increased, while IL-7 levels were decreased ($p<0.001$). The same pattern of up and down-regulation was also detected in MM and MGUS, suggesting these diseases share some pathophysiological characteristics. In distinction, we observed decreased levels of CCL11 ($p\leq0.02$) and RANTES ≤0.02) only among WM patients in comparison to MM, MGUS, and NDs. Taken together, these data highlight similarities and differences in cytokine and chemokine profile for WM patients, which may be relevant to WM pathogenesis (Figure 1). In addition, sCD27 was associated with several clinical markers, notably correlating negatively with B_2M (rho = -0.42, p = 0.016) and positively with CD8+ T-cell percentage (rho = 0.44, $p < 0.001$). sCD27 was also increased 1.9 fold in WM patients with a familial history of psoriasis (p = 0.021, n = 6). Among the cytokines and chemokines, GM-CSF was decreased 1.7 fold in the presence of lymphadenopathy (p = 0.003, n = 15), and IL-7 and CXCL10 were both increased in the four previously treated patients (fold = 5.5, p = 0.005; fold = 3.4, p = 0.003). In conclusion, there is significant cytokine, chemokine, and soluble CD27 dysregulation in WM, MM, and MGUS corresponding to important clinical correlations in WM. In addition to B-cell regulation, several of these dysregulations are also involved in T-cell regulation, signifying a need for further understanding of T-cell involvement in WM. These data demonstrate that further investigation of cytokine involvement in the pathogenesis and prognosis of these diseases is warranted.

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Table 1.