[ABSTRACT WM3.6]

The functional role of CD27-CD70 interactions in Waldenstrom's Macroglobulinemia

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Introduction: Waldenström's macroglobulinemia (WM) is a B-cell malignancy characterized by an IgM monoclonal gammopathy and bone marrow (BM) infiltration with lymphoplasmacytic cells (LPC). In support of these characteristics, mast cells (MC) are commonly present in excess and provide a proliferative advantage to the tumor through several TNF-family ligands (CD40L, APRIL, BLYS). In this study, we investigated the interaction between CD27 and CD70, another pair of TNF-receptor/ligand family members, in the pathogenesis of WM. Methods & Results: To this end, we first examined the serum levels of soluble CD27 (sCD27) by ELISA in patients with WM (n=66), Multiple Myeloma (MM)(n=25) and healthy donors (HD) (n=16). We found that sCD27 attains significantly higher levels in WM (median=120 U/mL) versus both MM (median=54U/mL) and HD (median=46U/mL)[$p<0.0001$]. We also demonstrated, via RT-PCR and flow cytometric (FACS) analysis, that CD27 and CD70 are constitutively expressed on WM LPC, MC and the WM cell lines. To then further elucidate the functional role of sCD27-CD70 interactions in WM, we incubated BM MC and LPC with recombinant-sCD27 [0.1-50 ìg/mL] for 24 hours and, using FACS analysis, observed an increase in the cell-surface expression of both CD40L and APRIL in MC alone. We next tested the SGN-70 (anti-CD70) humanized antibody to block sCD27-CD70 signaling; BM MC and LPC were incubated with SGN-70 [1 ìg/mL], which inhibited the previously-noted, sCD27-induced upregulation of CD40L and APRIL. The ability of SGN-70 [0.01-20 g/ml] to mediate the direct induction of apoptosis, complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) was also determined; as a result, significant ADCC activity against the BCWM1 cell line was observed. Lastly, SGN-70 [1 mg/kg, i.p., qOD] was tested in a WM SCID-hu mouse model; using ELISA, tumor engraftment and disease progression were monitored by measuring both serum human IgM and sCD27 levels in 12 mice. The results show that SGN-70 inhibited tumor growth in all treated mice. Conclusion: The results of these studies demonstrate a functional role for sCD27 in WM pathogenesis, along with its utility as a surrogate marker of disease and a target in the treatment of WM.