Mast Cells and sCD27 in Waldenström's Macroglobulinemia

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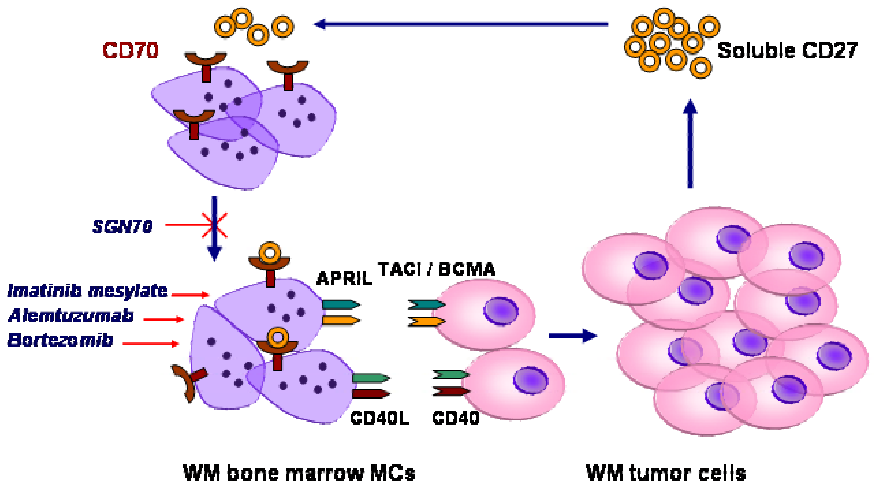
Waldenström's macroglobulinemia (WM) is a B-cell malignancy characterized by an increased presence of monoclonal IgM in serum and bone marrow infiltration with WM cells. Excess mast cells (MC) are commonly found in association with WM cells in the bone marrow of patients with Waldenström's macroglobulinemia. Recent studies in our center indicated that these mast cells provide growth and survival signals to WM cells. Co-culture of WM cells along with bone marrow MCs from the same WM patients resulted in MC dose-dependent tumor expansion. This tumor cell expansion supporting effect of MC was demonstrated through 2 principal tumor necrosis factor (TNF) family members [CD40 ligand (CD40L) and a proliferation-inducing ligand (APRIL)]. Further, we discovered that WM cells secrete a TNF-family member, soluble CD27 (sCD27), which is elevated in patients with WM. Importantly, we found that sCD27 interacted with CD70 (the receptor-ligand partner of CD27) on MCs and stimulated expression of CD40L (on 10 of 10 WM bone marrow MC samples) and APRIL (on 4 of 10 WM bone marrow MC samples). Based on these discoveries, we established a novel regulatory signaling pathway among bone marrow WM cells and MCs in WM (Figure 1).



Signals among WM cells and MCs in Waldenstrom's Macroglobulinemia

Moreover, the SGN-70 humanized antibody, which binds to CD70, abrogated sCD27 mediated up-regulation of CD40L and APRIL on WM MCs. Treatment of severe combined immunodeficiency-human (SCID-hu) mice with established WM using the SGN-70 antibody blocked disease progression in 12 of 12 mice, whereas disease progressed in all 5 untreated mice. These studies therefore support the investigation of SGN-70 as a novel therapy in WM patients. In addition to the functional role of sCD27, our studies also suggested that sCD27 may serve as a faithful marker of disease burden in patients with WM, even among patients experiencing a rituximab mediated IgM flare (an upsurge in serum IgM level) or plasmapheresis. Unlike IgM levels increased, sCD27 levels declined in 8 patients who experienced a rituximab mediated IgM flare; among 3 patients undergoing plasmapheresis, unlike IgM levels declined, sCD27 levels remained without significant change. Our studies reveal a tumor cell expansion supporting role for MC in WM and demonstrate a regulatory function for sCD27 in WM pathogenesis, along with its utility as a surrogate marker of disease; therefore provide the framework for therapeutic targeting of MCs and sCD27 in the treatment of WM.