Abstract

Update on Genetic and Pathogenesis Studies in Waldenstrom's Macroglobulinemia

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Numerous reports of familiar disease, including multigenerational clustering of WM and other B-cell lymphoproliferative disorders prompted us to evaluate the incidence of familial WM. We observed that 20% of patients in a cohort of 257 consecutive patients with the consensus diagnosis of WM had a first degree relative with either WM or another B-cell disorder including NHL, CLL, MM and MGUS. Importantly, patients with familial WM were diagnosed at a younger age, and had greater bone marrow involvement and serum IgM levels than those patients with non-familial disease. Frequent familiar association with other immunological disorders in healthy relatives, including hypogammaglobulinemia and hypergammaglobulinemia (particularly polyclonal IgM), has also been observed by us and others among WM patient family members. Intriguing has also been the observation that while IgM levels are often elevated in WM, IgA and IgG levels are subnormal in most patients with WM. Moreover, despite therapeutic responses including complete remissions, IgA and IgG hypogammaglobulinemia does not resolve in these patients even with long term follow-up suggesting that their deficiency may be a constitutional feature in WM with impairment of either plasmacytic differentiation, heavy chain class switching or both. These findings prompted us to investigate expression of the APRIL/BLYS-TACI-TRAF signaling system since defects in the TACI receptor have been reported amongst patients with Common Variable Immunodeficiency Disorder (CVID) who akin to WM patients demonstrate impaired IgA and IgG production. We observed mutations in APRIL and TACI in 20% and 25% of WM patients, respectively, as well as decreased expression of TRAF2 in half of patients with WM. Importantly, significantly lower levels of IgA and IgG expression were observed for those patients with aberrancies in TACI and TRAF2. These findings may have particular relevance for the pathogenesis of WM since TACI knockout mice are predisposed to lymphoma development, and CVID patients have up to a 300 fold increased risk of developing lymphomas. An interesting feature of the disease is the finding of increased number of mast cells in the BM of patients with WM, most typically in association with LPC. We and others have demonstrated that BM mast cells provide important growth and survival cues to WM lymphoplasmacytic cells through multiple TNF-family ligands including CD40L, A Proliferation Inducing Ligand (APRIL), and B-lymphocyte stimulator factor (BLYS). Importantly, WM cells provide cues to mast cells for the induction of CD40L and APRIL by secretion of soluble CD27 (sCD27), a TNF-family member whose levels are significantly elevated in patients with WM and which parallel disease burden. Moreover, the SGN-70 humanized monoclonal antibody which binds to CD70 (the receptor-ligand partner of CD27), abrogated sCD27 mediated upregulation of CD40L and APRIL on WM mast cells and blocked disease progression in SCID-hu WM mice. The results of these studies provide important clues into the genetic basis and pathogenesis of WM, and provide the framework for targeting WM and MC interactions in the treatment of WM.