Abstract

The Characterization and Modeling of MYD88L265P Mutation and Chromosome 6q Deletion in Murine B-cells

Waldenström macroglobulinemia (WM) is a B-cell malignancy characterized by the accumulation of clonal lymphoplasmacytic cells in the bone marrow (BM), excessive secretion of immunoglobulin M (IgM) paraprotein, and elevated levels of macroglobulins in the blood. These changes can lead to symptoms of hyperviscosity syndrome, including weakness, fatigue, bleeding disorders, and visual disturbances. Despite recent treatment advances, WM remains incurable, and most patients succumb to disease progression. This highlights the urgent need to better understand the genetic lesions driving WM pathogenesis and to develop a reliable preclinical murine model of WM.

Such a model would be a valuable resource for in vivo analysis of WM-related signaling pathways, genetic validation of potential drug targets, and testing novel therapeutic approaches to improve diagnosis and treatment. Whole-genome sequencing studies have identified recurrent somatic mutations and copy-number alterations (CNAs) in BM cells of WM patients, suggesting new oncogenic mechanisms. The most common genetic alteration is a gain-of-function mutation in the MYD88 gene (MYD88L265P). While we have shown that overexpression of mutant MYD88L265P in activated B-cells alone is insufficient to induce WM, it does lead to a pre-malignant polyclonal B-cell lymphoproliferative disorder with features reminiscent of WM.

In human B-cells, MYD88L265P triggers activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which in turn activates feedback mechanisms mediated by genes on chromosome 6q. Notably, chromosome 6q deletions, which are syntenic to mouse chromosome 10q, occur in nearly 50% of WM patients, suggesting that MYD88L265P mutation and 6q deletions may cooperate in WM development.

We hypothesize that generating engineered mice with a conditional deletion of chromosome 10q will enable the functional study of this recurring genetic event and facilitate the development of a preclinical mouse model that mimics the clinicopathologic features of human WM. In this study, we present the generation and biochemical and functional characterization of engineered mice bearing a conditional deletion of chromosome 10q in B-cells, designed to elucidate the role of 6q deletion in human lymphomagenesis. Mice carrying both the MYD88L265P mutation and the 10q deletion have been crossed, and the offspring are being evaluated for WM development over time. The results of these ongoing studies will be presented and discussed.