What regulates IgM secretion in WM?

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Waldenstrom's macroglobulinemia (WM) is a lymphoproliferative malignancy that by definition comprises a lymphoplasmacytic lymphoma involving the bone marrow, lymph nodes or spleen and a monoclonal IgM detectable in the serum. A comprehensive understanding of the mechanisms that result in the increased serum levels of IgM may provide therapeutic opportunities to suppress the function of the malignant clone.

We have found that B-lymphocyte stimulator (BLyS) and interleukin-6 (IL-6) are highly expressed in WM and play an important role in promoting IgM secretion. We have also found that BLyS and other cytokines, including IL-6 and IL-21, collectively promote increased IgM secretion. We have found that IL-6 secretion is regulated in part by CCL5 (also called RANTES) through GLI2, a member of the Hedgehog pathway. We have shown that IL-6 signaling via the JAK/STAT pathway is critical for IgM secretion. While IL-6 signals predominantly through STAT3, it is also able to activate STAT5. Similarly, IL-21 signals through STAT3 but directly activates STAT5 and we found STAT5 to be highly expressed in WM cells.

Taken together, our work has shown that cytokine signaling is important in WM and collectively promotes IgM secretion.