What are the key findings from genome and transcriptome profiling in WM?

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Whole genome sequencing (WGS) of Waldenström'sMacroglobulinemia (WM) lymphoplasmacytic cells has identified recurrent somatic mutations in MYD88, CXCR4, ARID1A, CD79B, TP53, MLL2, and MYBBP1A. Activating mutations in MYD88 are the most frequently observed somatic event WM, occurring in over 90% of patients.MYD88 mutations nearly always manifest as NM_002468:c.978T>C, resulting in aleucine to proline substitution at position 265 at the protein level.Other MYD88 mutations have been observed at frequencies of <1% and are consistent with the MYD88 mutations found in related diseases such as chronic lymphocytic leukemia and diffuse large B-cell lymphoma. Copy number alterations (CNA) or acquired uniparentaldisomies can result in increased mutant allele fraction or homozygous mutant MYD88 signaling, though the impact of these events remain to be clarified. Frameshift or nonsense mutations in the carboxyl-terminal tail region of CXCR4 are the second most common event, seen in 30-40% of WM patients.These mutations lead to constitutive signaling due to impaired internalization of the protein. These CXCR4 mutations are often subclonal and occur nearly exclusively in the context of MYD88 mutations leading to three major genomic groups in WM based on MYD88 and CXCR4 mutation status. Mutations in these genes can impact disease presentation, prognosis and response to therapy.

WGS also identified somatic CNAs in PRDM2 (93%), BTG1 (87%), HIVEP2 (77%), MKLN1 (77%), PLEKHG1 (70%), LYN (60%), ARID1B (50%), and FOXP1 (37%). These deletions are frequently subclonal in nature. Chromosome 6q deletions are the most common cytogenetic finding in WM. The most frequent gene losses in this region from WGS analysis were PLEKHG1, HIVEP2, ARID1B, and BCLAF1.

Next generation transcriptional profiling of 57 WM patients, as well as memory ($CD19^{+}CD27^{+}$) and non-memory ($CD19^{+}CD27^{-}$) B-cells from 9 healthy donors generated a distinct transcriptional profile for WM that included strong expressionof BCL2 and the VDJ recombination genes DNTT, RAG1 and RAG2, but not AICDA. CXCR4 signaling genes were up regulated regardless of mutation status and included CXCR4, CXCL12 and VCAM1. The profile associated with activating mutations in CXCR4 corresponded to impaired B-cell differentiation and diminished expression of tumor suppressors up regulated by MYD88 mutations. Pathway analysis indicated these changes wereassociated with the suppression of lipopolysaccharide signaling relative to patients mutated for MYD88 alone. Accordingly, TLR4 and NOD2 were down regulated in CXCR4 mutated patients while the IRAK4/1 inhibitor, IRAK3, was up regulated. CXCR4 and MYD88 transcription were negatively correlated and demonstrated allele specific transcription bias.Along with CXCL13 expression, both MYD88 and CXCR4 transcriptionwere associated with bone marrow disease involvement. These findings have provided insights into the molecular pathogenesis and created opportunities for additional targeted therapeutic strategies for WM.