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What are the important genomic findings 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. Somatic activating mutations in MYD88 are the most frequently observed event WM, occurring in approximately 95% of patients. MYD88 mutations nearly always manifest as NM_002468:c.978T>C, resulting in a p.Leu265Pro substitution 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 uniparental disomies can result in increased mutant allele fraction or homozygous mutant MYD88 signaling, though the impact of these events remains 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 receptor internalization. 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. Whole exome analysis of 18 $MYD88^{WT}$ patients identified somatic mutations that are predicted to trigger NFKB (TBL1XR1, PTPN13, MALT1, BCL10, NFKB2, NFKBIB, NFKBIZ, and UDRL1F), impart epigenomic dysregulation (KMT2D, KMT2C, KDM6A), or impair DNA damage repair (TP53, ATM and TRRAP). TBL1XR1 was the most commonly affected gene observed in 5 (28%) of patients $MYD88^{WT}$ patients yet was not observed in the 51 MYD88 mutant WGS samples. Overall 12/18 (66.7%) of $MYD88^{WT}$ study patients were found to harbor mutations on NFKB modulating genes that were downstream of BTK which may explain the lack of response of the BTK inhibitor ibrutinib in this patient population.

Next generation transcriptional profiling of 78 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 expression of 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. With the exception of CXCR4 and BCL2, this gene list was largely the same for $MYD88^{WT}$ WM which may explain many of the uniform characteristics shared among WM patients, regardless of their underlying MYD88 mutation status. $MYD88^{WT}$ patients also presented with a distinct patter of dysregulation relative to their MYD88 mutant counterparts which included significant enrichment for the upregulation of E2F, MYC, PIK3-AKT-MTOR, and G2M checkpoint signaling targets ($p \leq 0.009$ for all) as well as the downregulation of inflammatory response genes ($p=0.023$) and TNFA signaling through NFKB ($p<0.001$). 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 were associated 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. These findings have provided insights into the molecular pathogenesis and created opportunities for additional targeted therapeutic strategies for WM.