Comparative genomics analysis of Waldenström's Macroglobulinemia (WM) and low-grade B-cell malignancies identified common and disease-specific abnormalities

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Lymphoplasmacytic lymphomas (LPL) and marginal zone lymphomas of nodal (NMZL), extra-nodal (MALT lymphomas) and splenic (SMZL) types account for 10% of non-Hodgkin lymphomas. They are similar at the cell differentiation level. We used an array-based comparative genomic hybridization (aCGH) approach to better characterize the recurrent genomic aberrations associated with WM pathogenesis. We performed aCGH in 55 lymphoplasmacytic lymphomas (comprising 42 WM cases and 13 non-WM LPL), 101 marginal zone lymphomas (46 MALT lymphomas, 35 SMZL and 20 NMZL) and 50 B cell CLL. Overall, 90% of cases exhibited copy-number abnormalities (CNA). Non-WM LPL demonstrated the most genomic complexity (median of 7 CNA), followed by WM (5 CNA), MALT lymphomas (4 CNA), NMZL (3.5 CNA), SMZL and CLL (3 CNA each).

The most frequent abnormality in WM was the whole or partial deletion of 6q in 41% of cases. Two minimal deleted regions were defined on 6q21 (PRDM1) and 6q23.3–q24.1 (TNFAIP3). Partial or whole gains on chromosome 18 and 6p arm were the most common gains (17%, each), followed by gains of 4q13.1-q35.2 (12%), 3q13.3-q28 (10%), 8q (10%), and Xq27-q28 (10%). A minimal deleted region, including MIRN15A and MIRN16-1, was delineated on 13q14 in 10% of WM. There was a significant co-occurrence of gains on chromosomes 3 and 18 ($P = 0.002$). Of interest, we reported biallelic deletions and/or inactivating mutations with uniparental disomy in TRAF3 and TNFAIP3, two negative regulators of the nuclear factor-KB (NF-KB) signaling pathway. Furthermore, we confirmed the association between TRAF3 inactivation and increased transcriptional activity of NF-KB target genes.

A comparative analysis showed that most of the recurrent genomic aberrations observed in WM are shared with other low-grade B-cell neoplasms. Thus, trisomies 3, 12 and 18 and loss of 6q23-q24 were common to all entities. Losses of 13q14.3 and 17p13.3-p12 (TP53) were found in SMZL and CLL; loss of 11q21-q22 (ATM) in CLL, SMZL and NMZL; and loss of 7q32.1-q33 in MALT lymphomas and SMZL. Conversely, trisomy 4 seems to be unique in WM across low-grade B-cell neoplasias. Moreover, trisomy 4 has occasionally been found to be the sole genetic abnormality within a patient. Further analyses have not been able to identify a minimal gained region of chromosome 4, even using high-resolution approaches.

Overall, abnormalities affecting the NF-kB pathway were observed in 70% of MALT and LPL/WM and 30% of SMZL and NMZL, suggesting distinct roles of this pathway in the pathogenesis/progression of these subtypes. Recent data obtained from whole genome sequencing have shown the presence of *MYD88* mutation in 90% of WM cases, thus supporting the key role of the NF-kB pathway in the pathogenesis of WM. Furthermore, mutational activation of the NF-kB pathway highlights its biological importance, and suggests a therapeutic role for inhibitors of NF-KB pathway activation in the treatment of WM. Further elucidation of the genetic alterations contributing to the pathogenesis of these lymphomas is needed to design specific therapeutic approaches.