261 A Somatic Variant in MYD88 (L265P) Revealed by Whole Genome Sequencing Differentiates Lymphoplasmacytic Lymphoma From Marginal Zone Lymphomas

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Lymphoplasmacytic (LPL) and marginal zone lymphoma (MZL) are distinct clinicopathological entities under the WHO classification system for B-cell lymphomas. Differentiation of LPL from MZL has been difficult due to overlapping clinical, morphological, histopathological, immunophenotypic, and cytogenetic features. We therefore sought to identify a molecular marker by which LPL could be differentiated from MZL. Using paired normal/tumor tissues from 10 LPL patients, whole genome sequencing was utilized to identify somatic variants. These studies identified a somatic variant at position 38182641 in chromosome 3p22.2 with a single C in the myeloid differentiation primary response→nucleotide change from T (MYD88) gene, and a predicted non-synonymous change at amino acid position 265 from leucine to proline (L265P) in 10 of 10 LPL patients. MYD88 L265P is an oncogenically active mutation in DLBCL ABC cell lines via activation of IRAK1/4/TRAF-6/NF-κβ signaling, and is present in tumors from 29% of patients with ABC subtype of DLBCL, and 6% of patients with MALT lymphomas (Ngo et al, Nature 2011, 470:115-119). Further to these efforts, we performed Sanger sequencing of MYD88 in malignant cells obtained from 51 patients with LPL, 49 of whom had an IgM monoclonal protein and were therefore classified as Waldenstrom's Macroglobulinemia (WM), and 2 with an IgG monoclonal protein, along with 46 patients with MZL, which included 21 Splenic (SMZL), 20 Extranodal (EMZL), and 5 Nodal (NMZL) Subtypes, as well as B-cells from 15 healthy donors. Among LPL patients, the MYD88 L265P variant was found in malignant cells from 46/51 (90.1%) cases, which included 44 patients with WM, and 2 patients with IgG LPL. Expression of the MYD88 L265P variant was heterozygous in 42, and homozygous in 4 LPL patients. By comparison, only 3/46 (6.5%) patients with MZL (1 SMZL; 1 EMZL; 1 NMZL) exhibited the MYD88 L265P variant which was heterozygous ($p<0.0001$), and included 2 patients (1 SMZL, 1 NMZL) with extensive bone marrow involvement, a monoclonal IgM protein, and whose clinicopathological characteristics overlapped with LPL. By comparison, the MYD88 L265P variant was absent in $CD19^+$ cells from all 15 healthy donors. The results of this study demonstrate that the MYD88 L265P mutation is widely expressed in patients with LPL, and can be used to differentiate LPL from MZL.

Disclosures: Treon: *Millennium:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Celgene:* Membership on an entity's Board of Directors or advisory committees.