What genomic changes accompany transition of IgM MGUS to WM?

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In other hematological malignancies that, similarly to Waldenström's Macroglobulinemia (WM), have well-defined pre-malignant and malignant stages (e.g. non-IgM MGUS and multiple myeloma, or monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia), there is growing body of evidence suggesting that most of the genetic alterations found in patients with active disease, are present in tumor (yet benign) cells at pre-malignant stages. Does the same paradigm apply to the transformation of IgM MGUS or smoldering WM into symptomatic WM?

The pivotal study by Treon et al showing that MYD88 was recurrently mutated in WM patients but less frequently in IgM MGUS, suggested that the MYD88 mutation could represent a critical event for progression of IgM MGUS to WM. However, while subsequent studies using sensitive ASO-PCR confirmed the high prevalence of MYD88L265P in WM, they also unraveled that the MYD88 mutation is present in a much higher fraction (at least half) of IgM MGUS patients. These results indicate that although MYD88L265P may be considered as a unifying event in the pathogenesis of WM, by itself is insufficient to explain the malignant transformation of IgM MGUS to WM. From a phenotypic standpoint, we reported that the presence of light-chain restricted clonal B-cells could be detected in a few IgM MGUS, and progressively accumulate in smoldering and symptomatic WM. Such progressive accumulation of clonal B-cells was accompanied by the emergence of a characteristic Waldenström's phenotype (CD22+lowCD25+CD27+IgM+); however, because at the time we were limited by conventional 4-color flow cytometry, it was not possible to determine whether the emergence of a characteristic Waldenström's phenotype from IgM MGUS to WM was due to progressive accumulation of clonal B-cells, or to the phenotypic transformation of clonal, yet benign, B-cells, into full malignant tumor B-cells. More recently, we used multidimensional flow cytometry for sensitive detection and phenotypic characterization of clonal B-cells in IgM MGUS, smoldering and symptomatic WM. Subsequently, we performed FACS-sorting to investigate and compare the molecular signature and genomic landscape of clonal B-cells in the benign versus malignant stages of the disease. Our results show that IgM MGUS and WM patients share clonal B-cells with similar phenotypic and molecular signatures. Furthermore, the overall comparison of the gene expression profiles of clonal B-cells vs. distinct subsets of normal B-cells suggests that CD25+CD22+low activated B-cells could represent the normal counterpart of the Waldenstrom's clone.

Although phenotypic and molecular data support the hypothesis that the normal counterpart of WM is a memory B cell with a CD25+CD22+low phenotype, the question regarding the origin of cells with MYD88L265P remains unanswered. Recently, while investigating the role of B-cell selection in determining the MYD88 mutation status in WM, it was interesting to observe that in 6 patients it was only detected in unselected (CD19-) cells. These findings were highly unexpected and were attributed to the persistence of clonal PCs after treatment; however, according to our previous observations clonal PCs in WM are mostly CD19+ and it could be that other than PCs are accounting for the presence of MYD88 mutations in CD19- BM cells. Thus, we hypothesize that by integrating next-generation flow and sequencing technologies it could be possible to unravel the pathogenesis of WM through the identification of the most immature cell carrying the first genetic hit (e.g.: MYD88L265P), as well as secondary genetic hits present in the WM clone and that are absent in more immature cells. We will try to provide new insights about this hypothesis at the IWWM10 and 5th International Patient and Physician Summit on WM.