What phenotypic and genomic changes define transformation from IgM MGUS to symptomatic WM?

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Although information about the molecular pathogenesis of Waldenström's Macroglobulinemia (WM) has significantly advanced, the precise cell of origin and the mechanisms behind WM transformation from IgM MGUS remained mostly undetermined. Although conventional diagnosis of IgM MGUS requires the absence of BM infiltration in a trephine biopsy, the presence of MYD88 mutations indicate that a small B-cell clone may already be present. In line with this hypothesis, we have recently observed the presence of clonal B-cells in IgM MGUS (12% of patients), that 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. Accordingly, we most recently undertook an integrative phenotypic, molecular and genomic approach to study clonal B-cells from newly-diagnosed patients with IgM MGUS (n=22), smoldering (n=16), and symptomatic WM (n=11). Through principal-component-analysis of multidimensional flow cytometry data, we demonstrated highly overlapping phenotypic profiles for clonal B-cells from IgM MGUS, smoldering and symptomatic WM patients. Similarly, virtually no genes were significantly deregulated between FACS-sorted clonal B-cells from the three disease groups. Interestingly, the transcriptome of the Waldenström's B-cell clone was highly different than that of normal CD25-CD22+ B-cells, whereas significantly less genes were differentially expressed and specific WM pathways normalized once the transcriptome of the Waldenström's B-cell clone was compared with its normal phenotypic (CD25+CD22+low) B-cell counterpart. This suggests that CD25+CD22+low activated B-cells could represent the cellular origin of the Waldenstrom's clone. The frequency of specific copy number abnormalities [+4, del(6q23.3-6q25.3), +12, and +18q11-18q23] progressively increased from IgM MGUS and smoldering WM vs. symptomatic WM (18% vs. 20% and 73%, respectively; P=.008), suggesting a multistep transformation of clonal B-cells that albeit benign (i.e.: IgM MGUS and smoldering WM), already harbor the phenotypic and molecular signatures of the malignant Waldenström's clone.