Origins of WM: Implications from Genetic Analysis

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The malignant clone in Waldenstrom macroglobulinemia is dynamic, undergoing apparently continuous differentiation over time, providing phenotypic evidence of extensive WM clonal evolution. This dynamic evolution, in the face of treatment, has potentially profound implications for the clinic since WM may be a “moving target”. In addition, WM frequently harbors more than one clone each with its own unique IgH-VDJ molecular signature, with different clones in different anatomic locations in blood or bone marrow. The origins of intra-clonal and inter-clonal heterogeneity in WM may involve heterogeneity among cancer stem cell populations and potentially frequent transformation events. Aberrant mRNA splicing creates a family of HAS1 intronic splice variants with oncogenic potential. Inherited single nucleotide polymorphisms (SNPs) in the hyaluronan synthase 1 gene (HAS1) appear to predispose to WM, as well as to multiple myeloma (MM) and chronic lymphocytic leukemia (CLL). In addition, SNPs and recurrent HAS1 splicing mutations are shared by WM and MM patients. HAS1 SNPs and recurrent mutations alter HAS1 splicing patterns. Since predisposing SNPs are inherited, by definition they are present prior to transformative events. The resulting predisposition towards aberrant HAS1 splicing is known to generate oncogenic variants. HAS1 SNPs may be significant contributors to transforming events in systemic B-cell malignancies. A close relationship between WM, MM and CLL indicates that these malignancies share at least some genetic predispositions and perhaps a common first progenitor. Later oncogenic events may generate the cancer stem cells from which each malignancy subsequently arises. We speculate that the expression of aberrant HAS1 splice variants leads to ongoing transformation events, from which the primary WM clone emerges and becomes dominant. Other transformants may remain in a submissive and operationally dormant state imposed by the primary WM clone until e.g. clonal evolution or treatment compromise its dominance and allow submissive clones to emerge. The aberrant pre-mRNA splicing that leads to aberrant HAS1 splice variants may explain the observed risk of WM conferred by intronic HAS1 SNPs. There is thus a high probability that HAS1 is clinically important as a predisposing gene imposing risk for WM as well as being a contributor to oncogenesis and to progression of WM.