

[Abstract 01]

ORIGIN OF THE MALIGNANT CLONE IN WM

Linda M. Pilarski, Jitra Kriangkum, Tony Reiman, Michael J. Mant, Andrew R. Belch, Departments of Oncology and Medicine, University of Alberta and Cross Cancer Institute, Edmonton, Alberta, CANADA.

Clonotypic B cells of WM are CD20⁺IgM⁺IgD⁺ cells that lack ongoing somatic hypermutation (SHM) and class switch recombination (CSR). To understand the mechanisms that may contribute to the lack of CSR, activation-induced cytidine deaminase (AID) was analyzed in WM. Out of 14 WM patients analyzed, two expressed AID. Full-length AID transcripts of WM had a fully conserved sequence, thus ruling out the possibility of functional defects due to point mutations. Detection of AID in an unmutated VH clone suggested that lack of SHM is not as a result of an inability to produce AID. Three AID splice variants were identified in both patients. Single cell analysis indicated that only a small compartment (10% or less) of clonotypic B cells expressed AID, with multiple isoforms detectable in individual cells. *In vitro* activation of clonotypic WM B cells by CD40L/IL-4 did not yield detectable clonotypic isotypes. However sequencing of clonotypic-S μ switch regions in IgM MGUS and WM indicated that the mutation of switch regions essential for CSR were present in IgM MGUS but absent from WM B cells, suggesting that IgM MGUS may not be a precursor to WM, and further strengthening our hypothesis that the target cell in transformation to WM is an unusual type of B cell.