

[Abstract 02]

EVALUATING CLONAL ORIGINS IN WALDENSTROM'S MACROGLOBULINEMIA

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In probing the cell of origin and its clonal history in B-cell malignancy, multiple approaches will be required to fully elucidate disease evolution. In this regard, Ig variable (V) region analysis can provide critical insights into the stage of neoplastic arrest and clonal tumor evolution. To further track the origins of Waldenstrom's macroglobulinemia (WM), a tumor characterised by IgM expression and its secretion, we have coupled V_H gene analysis with key observations from global gene expression profiles (GEP). V_H gene analysis was determined in cDNA amplified for GEP, which increases initial transcript levels in tumor cells several-fold. Tumor-derived V_H genes were identified in 7/7 cases, and utilised V_H3 (4/7), and V_H1,4 and 7 (1 each). V_H genes revealed the expected feature of somatic mutations with no intraclonal variation in 6/7 cases, but in one case a low degree of variation was observed, indicative of localized events. Mutational status indicates on-going differences in disease behaviour. The incidence of glycosylation sites generated by mutations, which can be a distinctive niche-associated feature of lymphoma cells, was not increased, suggesting non-specific interactions with stroma via surface Ig may not be important. Additional WM associated features have been assessed by GEP and immunogenetic analyses, and these will be reported. In summary, V_H gene analysis and GEP have proved synergistic in characterizing clonal origins in WM.