[ABSTRACT WM3.3]

Gene expression profiling of waldenstrom's macroglobulinemia reveals genes that may be related to disease pathogenesis

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Introduction: To determine the molecular events linked to the pathogenesis, progression and clinical outcome of Waldenstrom's Macroglobulinemia (WM), we performed gene expression profiling (GEP) of the bone marrow (BM) WM tumor compartment. This tumor compartment includes two immunophenotypically distinguishable tumor populations: B-lymphocytes (CD19+) and plasma cells (CD138+). Material and Methods: BM aspirates were obtained from untreated patients with the consensus panel diagnosis of WM (Semin Oncol. 2003; 196-200). BM WM B-cells (WMBCs) and plasma cells (WMPCs) from 28 WM patients and 9 healthy controls were sequentially isolated using CD19 and CD138 microbeads, respectively. Using Affymetrix microarrays (U133 Plus2.0), we analyzed the GEP of WMBCs and WMPCs, and compared with their normal counterparts. Hierarchical cluster and significant analysis of microarray (SAM) test were used for the data analysis. Results: Unsupervised hierarchical cluster analysis demonstrated a distinct gene expression pattern between WMBC and WMPC versus their normal controls. By performing SAM test with 0.1% FDR, a set of 2463 (1533 and 903 up- and down-regulated, respectively) and 693 genes (563 and 130 up- and down-regulated, respectively) were differentially expressed in WMBC and WMPC, compared to their normal counterparts, respectively. A supervised hierarchic cluster analysis clearly demonstrated significant differences in WMBC and WMPC compared to controls. Particular genes of interest to lymphoplasmacytic cells growth and survival included BCL2, a key arbiter of the commitment to programmed cell death at the mitochondria that expressed in many cancers, was upregulated in tumor cells. Among other transcripts overexpressed in WMPCs were genes involved in transcription (ZKSCAN1, ZMYM1, ZNF189, ZNF19, and ZNF559) and interferon response (IFI16 and IFIH1). Of the under-expressed genes, the AP1 family genes JUND and FOSB were the most significant downregulated genes. Of the most significantly dysregulated genes in WMBC, IGLL1, has been shown to be involved in BCL-6 rearrangment and may contribute to dysregulation of BCL-6 in lymphoma. Upregulation of CCR2 expression may contribute to the marrow homing properties of the WM clone in responses to MCP ligands. Data comparing and contrasting WMPC and myeloma PC will be presented. These data begin to provide new molecular insights into the pathogenesis of WM.