Gene Expression Profiling of CD19, CD20, and CD138-Enriched Cells from Waldenstrom's Macroglobulinemia (WM) Reveals Distinct Classes and Novel WM-Specific Genes

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Waldenstrom macroglobulinemia (WM) is a rare plasma cell dyscrasia characterized by a monoclonal IgM paraproteinemia. The median survival of 5 years has not improved considerably since the introduction of purine analogues and complete response with any drug regimen is still uncommon. To afford a better understanding of molecular mechanisms, identify potential new molecular targets, and to develop a molecular based risk stratification of WM, we have performed comparative gene expression profiling of WM, multiple myeloma, as well as normal cell counterparts. Bone marrow aspirates were drawn from patients with WM and CD19-enriched (>90%) B-cells (WaldBC; n=11) and/or CD138-enriched (>90%) plasma cells (WaldPC; n=10) obtained. The expression profiles of ~12,000 genes were compared with those from CD19-enriched peripheral blood BC (PB-BC; n=7), and tonsil BC (TonBC; n=7), as well as CD138-enriched tonsil PC (TonPC; n=9), bone marrow PC (BonePC; n=15) from normal donors, or CD138-enriched PC from multiple myeloma (MMPC; n=30). Hierarchical cluster analysis of the B-cell populations using 6,504 genes clearly segregated WaldBC from TonBC and PB-BC. Cluster analysis of the plasma cell populations with 7,342 genes showed that TonPC, BonePC and MMPC were located on distinct branches with the WPC either dispersed within the TonPC cluster (n=5), within the MMPC cluster (n=1) or on a distinct sub-branch of the MM cluster (n=4). Comparisons across all samples identified 16 genes, to be over-expressed in the majority of WaldBC and/or WaldPC, but expressed at low or undetectable levels in the other cell types analyzed. Three genes mapping to chromosome 6, a frequent target of deletions in WM (Wong et al., 2001; Rafeal Fonseca, personal communication) were identified, and represented the largest group of genes mapping to one chromosome. Importantly, this included MYB (6q22), overexpression of which induces the rapid development of plasmacytoid lymphosarcomas in mice and B-cell lymphomas in chickens (Mushinski et al., 1983, Shen-Ong et al., 1984, Kanter et al., 1988). The receptor tyrosine kinase, PDGFRA, and target for STI-571 was also in this list and was observed to be expressed at very high levels (Affymetrix signal >10,000) in 9 of 21 patients. Thirteen genes with significant similarities between WM and MM were also detected. Finally, 20 "spike" genes, demonstrating highly elevated expression in subsets of WM, were recognized. Thus, gene expression profiling has identified genes whose altered expression is specific to WM and whose activation may be critical to WM development and/or progression and used as potential molecular targets of new therapeutics.