[Abstract 05]

GENE EXPRESSION PROFILING OF WALDENSTRÖM'SMACROGLOBULINEMIA: BIOLOGIC AND THERAPEUTIC IMPLICATIONS

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Waldenström's Macroglobulinemia (WM) is a lymphoproliferative disorder with IgM gammopathy and marrow infiltration with lymphoplasmacytoid cells. Using Affymetrix microarrays, we analyzed the expression of 12625 genes in purified malignant B and /or plasma cells from the bone marrow of 19 patients with WM, and compared them to gene expression profiles (GEP) of normal blood or tonsillar B cells, and plasma cells from normal marrow, tonsils, or myeloma patients. Using hierarchical cluster analysis, both B and plasma cells from WM marrow could be readily distinguished from their normal counterparts. A set of 55 and 47 genes were differentially up or down regulated in WM B or plasma cells, compared to their normal counterparts, respectively. Bone marrow derived CD-138 selected plasma cells appear to have an immature phenotype as they tend to express high levels of CD19 and CD20. A subset of WM cells were also identified to aberrantly express T cell associated genes, which was confirmed by immunohistochemistry. We have previously shown that myeloma plasma cells have gene expression patterns that allow classification based on similarities to distinct stages of late stages of B-cell differentiation (Zhan et al., Blood,101:1128-1140, 2003). In comparative hierarchical clustering, WM plasma cells were found to have either a tonsillar plasma cell- or myeloma plasma cell-like signature, with none being similar to plasma cells derived from normal healthy donors. Taken together these data support the concept that Waldenström's macroglobulinemia and possibly myeloma may be derived from either terminally differentiated cells with various degrees of plasticity or from cells transformed at distinct stages of late stage B-cell differentiation with the ability to self renew and to produce partially-differentiated (WM) or terminally-differentiated (myeloma) progeny. This analysis also identified a subset of 15 genes that were uniquely dysregulated in WM samples. Most importantly the data point to a possible deregulated autocrine IL-6 signaling loop in WM. Thus, it is possible that anti-IL-6 signaling therapy currently in clinical trials for Casteleman's disease may also be a therapeutic strategy in this disease. Data also point to deregulation of cytokines, chemokine and growth factor receptors, oncogenes, and signaling pathways not previously implicated in WM or other human plasma cell dyscrasias. These data therefore provide new molecular insights into the pathogenesis and suggest novel therapeutic targets for intervention in WM.