Microarray Analysis of the Peripheral Monocytes From Waldenstrom's Macroglobulinemia Patients Reveals a Distinct Gene Expression Profile

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Background: Waldenstrom's Macroglobulinemia (WM) is a B-cell malignancy characterized by the accumulation, predominantly in the bone marrow, of clonally related IgM-secreting lymphoplasmacytic cells. Macrophage derived inflammatory factors are elevated in WM suggesting a possible contribution by monocytes to the growth and survival of WM cells. **Patients and Methods:** Monocytes ($CD14^+$) from the peripheral blood of 8 untreated WM patients, and 6 healthy donors (HDs) were isolated by immuno-magnetic bead sorting. Gene expression profiling was then performed using Human Genome U133 Plus 2.0 chips, and data obtained from microarray was analyzed by dChip software with fold change >=2 and p<=0.05 as cut off points. Validation was performed by real time PCR. **Results:** Using Panther classification, 284 transcripts were identified as significantly different in monocytes derived from WM patients versus HDs. The resulted transcripts are involved in many critical signaling pathways, such as Toll-like immune receptor pathway (i.e. TLR1, TLR4, TLR8, TICAM); inflammatory response (i.e. CD40, PTAFR, FPR2), integrin binding (i.e. RAC2, ILK), chemokinesis (i.e. CCR2, CX3CR1), apoptosis (i.e. TNFSF10), p53 signaling (i.e. GADD45A, 1433F) and G-protein coupled receptors (i.e. CX3CR1). Fifteen of 21 genes were validated by real-time PCR, and were over-expressed in peripheral blood monocytes from WM patients in comparison to healthy age matched donors:

Gene	Mean Fold Change	Mann-Whitney Test
CD40	1.644057	0.02857
IL2RG	1.962768	0.02857
CKLF	1.983921	0.1143
TLR8	2.573933	0.02857
CD32	3.026544	0.02857
CD64	3.144555	0.02857
UBE2D1	3.19568	0.02857
FCGR2C	3.832584	0.02857
TLR1	3.888254	0.02857
CX3CR1	4.301427	0.05714
TNFSF10	5.365451	0.02857
TLR4	5.984486	0.02857
TICAM	7.324513	0.02857
CLU	15.10627	0.02857
CCR2	17.15738	0.02857

Conclusions: Peripheral monocytes from WM patients demonstrate a distinct gene expression profile characterized by up-regulation of genes affecting Toll-like innate immunity, inflammation, and apoptosis. These studies define a distinct micro-environmental signature, and provide a framework for the exploration of novel targets for prognosis and therapy in WM.