Aberrant expression of regulatory miRNAs and transcripts for IRS-PI3K growth and survival signaling in Waldenstrom's Macroglobulinemia.

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Background: Waldenstrom's Macroglobulinemia (WM) is a rare low grade non-Hodgkin's lymphoma characterized by the accumulation of IgM secreting lymphoplasmacytic cells in (LPC) the bone marrow, an elevated serum IgM, and frequently accompanied with hyperviscosity syndrome. The insulin receptor substrates (IRS) are important mediators of the insulin like receptor family and PI3K signaling leading to PKC and AKT activation.

Methods: TaqMan low density arrays were used to evaluate the relative levels of 667 miRNAs in 11 WM patient and 5 age matched healthy donor (HD) CD19+ bone marrow cells. The results of this screen were validated using individual stem loop RT-PCR assays. Additional mRNA targets were identified using an existing gene expression profiling (GEP) data set of 22 WM patients and 8 HD using the Affymetrix U133 plus 2 platform. GEP findings were validated using an independent cohort of 18 WM patients and 7 HD.

Results: Aberrant miRNAs identified were miR-21 (+3.27 fold $p=0.035$), miR-29c (+3.17 fold; $p=0.003$), miR-155 (+5.53 fold; $p=0.082$), miR-9* (-3.94 fold; $p=0.001$), miR-27b (-4.94 fold; $p=0.001$), miR-126 (-21.52 fold; $p=0.006$), miR-126* (-25.55 fold; $p=0.039$), miR-145 (-34.27 fold; $p<0.001$), miR-223 (-24.25 fold; $p=0.041$), and miR-886-5p (-3.01 fold; $p=0.004$). Importantly, 5 of these 10 miRNAs targeted members of the IRS-PI3K signaling pathway, a pathway important for growth and survival of WM cells: miR-29c (PIK3R1); R-155 (SHIP1); miR-21 (PTEN); miR-145 (IRS1); miR-126 (IRS1 and PIK3R2), and predict for increased protein levels for PIK3R2 and IRS1 with lower protein levels for PIK3R1, PTEN and SHIP1. Moreover, GEP and confirmatory RT-PCR revealed down-regulation of the IRS-PI3K pathway members IRS2 (-2.0 fold; $p=0.004$) and PIK3R1 (-2.0 fold; $p=0.04$).

Conclusions: The results of this demonstrate aberrant expression of regulatory miRNAs and transcripts for IRS-PI3K growth and survival signaling in WM, and provide support for the development of IRS/PI3K targeted therapeutics in WM.