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Do genomics impact cytokine related signaling in WM?

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Cytokines are secreted protein mediators of the immune system, chemokines are small cytokines with the ability to induce chemotaxis, regulating migration and homing. Cytokines and chemokines have an important role in the biology of malignant lymphoma, including WM, and influence cell growth, survival and migration. They can be produced by the malignant lymphoid cell, by stromal cells, as well as by cells that are part of the host immune system. Angiogenic cytokines are elevated in WM, suggesting a role of neovascularization[1]. Inflammatory cytokines are also elevated in WM compared to healthy donors possibly contributing to a tumor-enhancing microenvironment[2].

In recent years, three molecular subgroups of WM have been identified: $MYD88^{mut}$ $CXCR4^{wt}$, $MYD88^{mut}$ $CXCR4^{whim}$,and $MYD88^{wt}CXCR4^{wt}$. Over 90% of WM patients carry the somatic MYD88 L265P mutation; approximately 30-40% of these patients carry an additional CXCR4 WHIM-like mutation. CXCR4 is the receptor for CXCL12, a chemokine with a strong chemoattractive effect on lymphocytes. The WHIM-like gain-of-function mutations are only found in $MYD88^{mut}$ patients and are often subclonal. Interestingly, in a recent transcriptome study, genes related to CXCR4 signaling were upregulated regardless of CXCR4 mutation status, indicating a role for CXCR4 related pathways in all WM patients[3].

Several differences in serum cytokines and chemokines were found to correlate with molecular subtype[4]. Compared to healthy donors. IL6 was elevated in $MYD88^{mut}$ $CXCR4^{wt}$ patients only. IL2RA, IL1RA, CXCL10 and sCD27 plasma levels were higher in $CXCR4^{wt}$ versus $CXCR4^{whim}$ patients. These findings are in line with recent transcriptome data[3] showing normalized TLR4 signaling-associated gene expression in $MYD88^{mut}$ $CXCR4^{whim}$ compared to $MYD88^{mut}$ $CXCR4^{wt}$. They suggest that the lower levels of inflammatory cytokines in the serum of $MYD88^{mut}$ $CXCR4^{whim}$ patients may relate to the suppression of MYD88 L265P induced inflammatory pathways in the setting of CXCR4 mutations.

$MYD88^{wt}CXCR4^{wt}$ patients have a diverse and highly heterogenous transcriptional profile, including a downregulation of genes associated with NFkB-sigaling[3]. Together with the poorer clinical response to BTK-inhibition, this suggests that $MYD88^{wt}CXCR4^{wt}$ WM disease is less dependent on pro-inflammatory signals .

Mutations in ARID1A are third most common somatic mutations in WM, occurring in about 20% of patients . ARID1A mutations were associated with higher bone marrow tumor load

and increased transcription of CXCL13. In AITL CXCL13 is a possible mediator of the excess of mast cells in the tumor microenvironment. Interestingly, mast cell excess is also a known feature of WM.

1. Anagnostopoulos, A. *et al.* Serum concentrations of angiogenic cytokines in Waldenstrom macroglobulinaemia: the ration of angiopoietin-1 to angiopoietin-2 and angiogenin correlate with disease severity. *Br. J. Haematol.* **137,** 560–8 (2007).

2. Elsawa, S. F. *et al.* Comprehensive analysis of tumor microenvironment cytokines in Waldenstrom macroglobulinemia identifies CCL5 as a novel modulator of IL-6 activity. *Blood* **118,** 5540–9 (2011).

3. Hunter, Z. R. *et al.* Transcriptome sequencing reveals a profile that corresponds to genomic variants in Waldenstrom macroglobulinemia. *Blood* **128,** 827–838 (2016).

4. Vos, J. M. *et al.* CXCL13 levels are elevated in patients with waldenström macroglobulinemia, and are predictive of major response to ibrutinib. *Haematologica* (2017). doi:10.3324/haematol.2017.172627