Abstract: P1266

Title: MULTI-OMIC ANALYSIS OF CXCR4 AND CHROMOSOME 6Q DELETIONS IN CONTEXT OF WM SUBTYPE AND DISEASE EVOLUTION REVEAL KEY INSIGHTS INTO THE BIOLOGY OF WALDENSTROM'S MACROGLOBULINEMIA.

Abstract Type: Poster Presentation

Topic: Lymphoma biology & translational research

Background:

Following mutated MYD88 (MYD88Mut; 95-97%), the incidence of mutated CXCR4 (CXCR4Mut; 30-40%) and deletions in chromosome 6q (del6q; 40%) constitute the next most common abnormalities in Waldenstrom's macroglobulinemia (WM) (Hunter et al, Blood 2014). CXCR4Mut or del6q are subclonal to MYD88Mut and may facilitate WM disease progression. We recently described two distinct subtypes of MYD88Mut WM: B-cell like (BCL) and Plasma cell like (PCL), both of which evolve from an unsubtyped clone that is prevalent in early/smoldering WM. Using RNASeq from 249 untreated WM patients, we performed a diffusion pseudo-time (DPT) analysis that revealed a shared evolutionary track from smoldering WM to symptomatic disease, regardless of subtype. DPT values significantly correlated with time to first therapy, mutation burden, bone marrow (BM) infiltration, and symptomatic disease. This analysis was replicated with non-negative matrix factorization of the data which confirmed that subtype and DPT are independent factors that explain much of the heterogeneity in clinical presentation and RNA expression observed in WM (Hunter et al, ASH 2023).

Aims:

To characterize the clinical and transcriptional impact of recurrent somatic events including CXCR4Mut and del6q in WM while accounting for DPT and WM subtype to better understand how these events contribute to the pathology of WM.

Methods:

RNASeq was performed on CD19-selected BM samples from 249 untreated MYD88Mut WM patients. For 215 of these patients, whole exome sequencing (WES) was performed on samples from CD19-selected BM and CD19-depleted peripheral blood to identify somatic variants.

Results:

CXCR4Mut were identified in 73/87 (84%), 21/64 (33%), and 4/64 (6%) of BCL, unsubtyped, and PCL patients, respectively ($p<0.001$). Consistent with prior reports by us and others, CXCR4Mut patients showed higher levels of serum IgM (4,188 vs. 2,620 mg/dL; $p<0.001$), as well as decreased incidence of adenopathy 14% vs. 39%; $p<0.001$) versus wild-type CXCR4 (CXCR4WT). Multivariate analysis using linear/logistic regression with the covariates subtype, DPT, gender and age confirmed these associations with CXCR4. Multivariate studies also demonstrated that CXCR4Mut is associated with increased BM infiltration ($p=0.005$) and decreased incidence of splenomegaly ($p=0.03$), both of which were significantly confounded by DPT. Gene expression analysis included a significant upregulation of genes that were highly correlated with IGHM expression including CCR10, GAS6, CHAC1 and KDELR3 ($r>0.73$; $p<0.001$ for all comparisons). IgM transcription only correlated well with serum IgM in samples expressing more plasmacytic differentiation such as high levels of CD138. A trend for increased prevalence of Del6q in PCL was noted with 23/81 (28%), 19/59 (32%), and 29/62 (47%; $p=0.07$) of BCL, unsubtyped, and PCL exhibiting del6q, respectively. Differential gene expression revealed distinct signatures in BCL and PCL likely driven by deletions spanning from chr6q27 to chr6q14 in PCL while deletions in BCL were typically restricted between Chr6q25 and Chr6q16 ($p<0.001$). Among patients with del6q, BM involvement was higher (60% vs. 40%; $p<0.001$) versus 6q intact patients. This was true in the multivariate analysis with the inclusion of CXCR4 mutation status ($p=0.019$).

Summary/Conclusion:

This is the first study identify del6q span differences between distinct WM populations and to demonstrate the relation between IgM transcription and serum IgM. Accounting for DPT and WM subtype allows for insights into the underlying pathology of the of WM and provides are roadmap for future therapeutic strategies.

Keywords: CXCR4, Waldenstrom's macroglobulinemia, RNA-seq, Mutation analysis