

Proteogenomic Integration Reveals Predictive Signatures of Ibrutinib Response in Waldenström Macroglobulinemia

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Over a decade ago, the BTK inhibitor ibrutinib (IBR) became the first approved agent for the treatment of patients Waldenström Macroglobulinemia(WM). Despite the high response rates and durable remissions, about a third of patients fail to respond to therapy while there is notable heterogeneity in the depth and timing of response. Clonal characteristics are important in elucidating the reasons for this heterogeneity, but peripheral blood biomarkers could be able to capture clonal and microenvironmental heterogeneity of the disease, providing new insights and prognostic tools.

We conducted high-throughput plasma proteomic profiling using the Olink® Explore HT library. We profiled 84 peripheral blood plasma samples from 35 patients before (T1) and after (T2) IBR therapy, consisting of 21 responding (R) and 14 non-responding (NR) patients. Proteomic data were also integrated with single-cell RNA sequencing data from matched bone marrow (BM) samples to disentangle the relationship between BM gene expression and circulating plasma proteins.

Differential Protein Expression (NPX) analysis between T1 and T2 in both groups identified over 350 proteins up-regulated at T1 primarily enriched by chemokines such as CXCL13, CXCL5 and CCL17. Feature selection using elastic net regression combined with principal component analysis identified key genes enriched in NR, including AKT2, PPP2R5A, and RICTOR, mainly involved in AKT/mTOR signaling pathway. Integration analysis identified a cell–cell adhesion gene signature, comprising PCDH9, NEB, and CNTN5, that was driven by BM B cells and associated with increased plasma protein levels in R at T1 also associated with longer progression-free survival (PFS; $p < 0.05$). By applying linear models, we were able to infer the cell type of origin for key plasma proteins. Specifically, LTB, TNF, and PCDH9 were predominantly associated with malignant B cells, whereas LAG3, TIGIT, and CTLA4 were primarily derived from T cells. Furthermore, by incorporating IBR response as an interaction term in the linear models, we were able to identify the response group-specific cellular origin of these plasma proteins. Specifically, PCDH9 was predominantly derived from malignant B cells in the R group, whereas TNF and TIGIT originated primarily from malignant B cells and T cells in the NR group. To identify factors underlying shared variance between the two assays, we applied the MOFA-FLEX tool. We identified a latent factor (LF4) that differed significantly between the two response groups at diagnosis characterized by elevated protein expression of EIF4E and IRAK4 in the NR and increased gene expression of CD9, XBP1, and CHST15 in B cells of the R group; a signature also associated with shorter PFS ($p < 0.05$).

In conclusion, our results highlight the identification of plasma biomarkers for WM and demonstrate shared programs between the two compartments that can be used to elucidate response status and predict progression.

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