Comprehensive Characterization of Inflammatory Cytokines in Chronic Lymphocytic Leukemia Highlight Immune Dysregulation and Associates with MRD

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Background

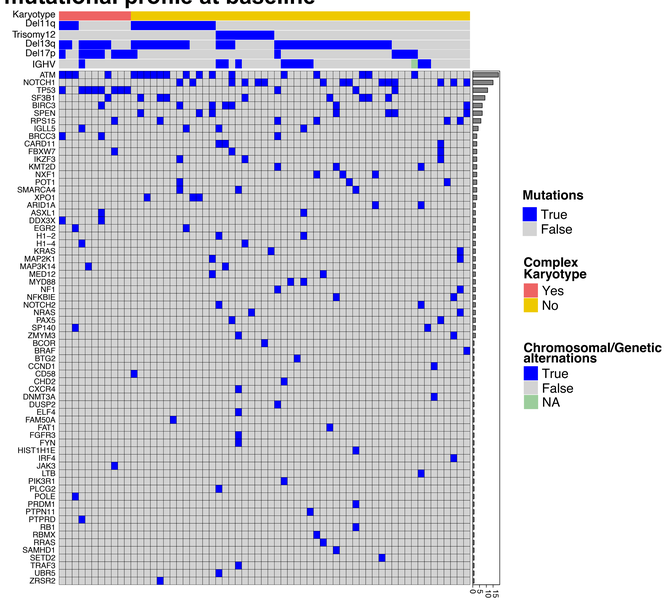
Chronic lymphocytic leukemia (CLL) is characterized by immune dysfunction and dysregulation resulting in increased risk for infection and second cancers. Prior studies indicated that chronic inflammation may contribute to worse clinical course in CLL. Comprehensive assessment of the inflammatory mediators and in context of response to treatment, particularly measurable residual disease (MRD), remains unexplored. We aimed to leverage a novel proteomic profiling of >250 inflammatory proteins with high sensitivity assay to assess serum inflammatory profiles at baseline and post-treatment and associations with MRD status

Sample and Methods

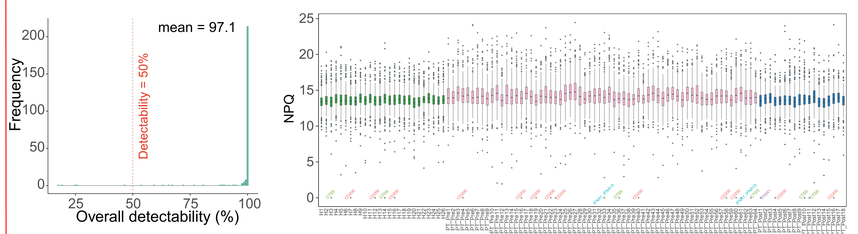
-- Baseline samples of 64 CLL patients treated first-line therapy on the randomized trial of acalabrutinib (ACA) + venetoclax (VEN) +/- early obinutuzumab (OBIN) (NCT04169737)
-- 18 patients with a paired end of treatment (EOC26) sample with bone marrow (BM) undetectable MRD status (uMRD4; 10^{-4} sensitivity)
-- 26 healthy donor plasma samples as control
-- Inflammatory proteome was evaluated through blood-based proteomic profiling of 251 soluble inflammatory proteins using NUcleic acid Linked Immuno-Sandwich Assay (NULISA), a proximity-ligation assay based on NGS or PCR allowing attomolar (10^{-18}) detection
-- Comparative analysis to identify differentially expressed cytokines at baseline or EOC26 compared to healthy to define dysregulated inflammatory protein networks
-- Logistic regression to assess cytokines prognostic for early uMRD4 at EOC9

Results

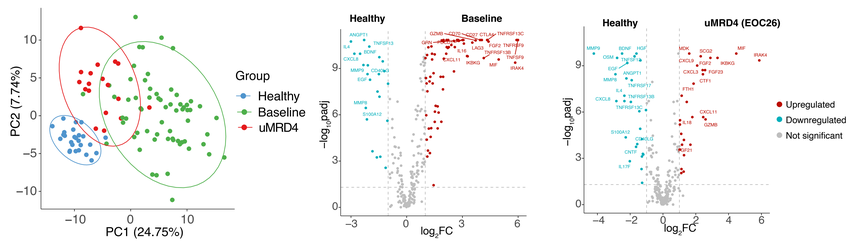
Cohort mutational profile at baseline



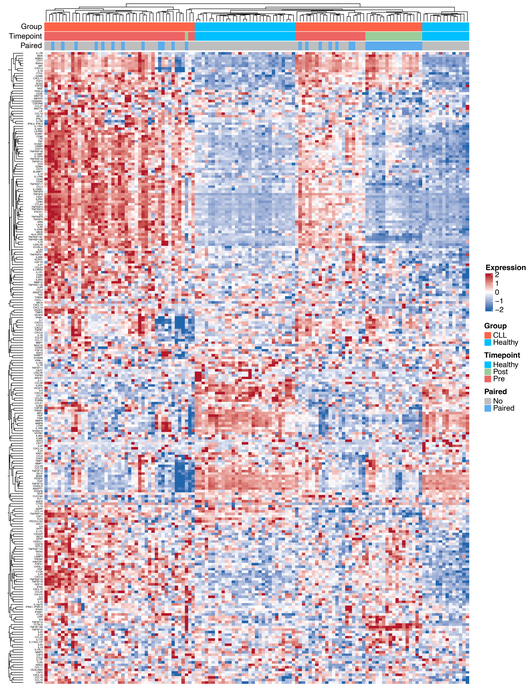
NULISAseq Platform Allows Highly Sensitive Inflammatory Protein Detec-



Inflammatory Protein Patterns Distinguish pre-, post- and healthy samples

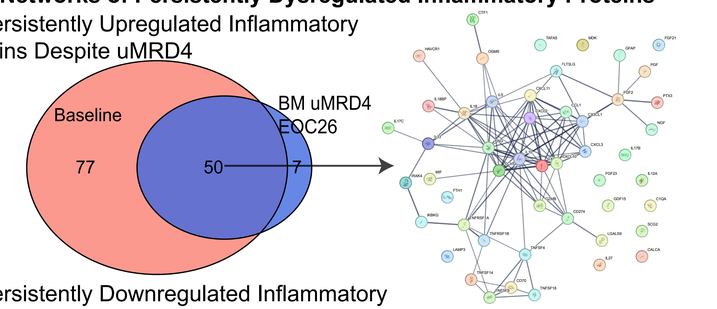


Distinct inflammatory profile between healthy, patients at time of therapy initiation, and at EOC26 with BM uMRD4 status

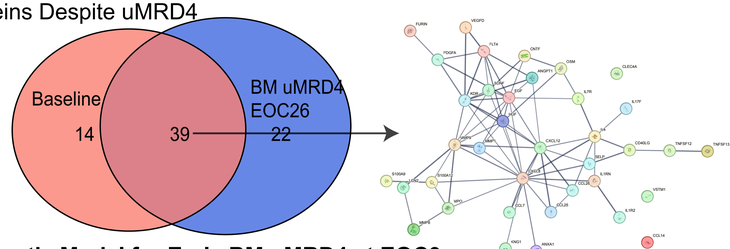


Protein Networks of Persistently Dysregulated Inflammatory Proteins

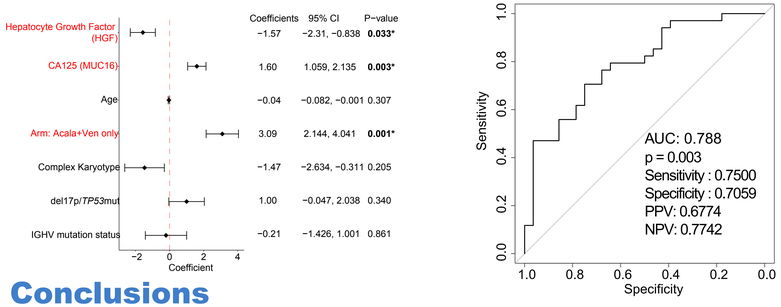
50 Persistently Upregulated Inflammatory Proteins Despite uMRD4



39 Persistently Downregulated Inflammatory Proteins Despite uMRD4



Prognostic Model for Early BM uMRD4 at EOC9



Conclusions

Through highly multiplexed proteomic profiling, we identified an integrated profile of coordinately expressed inflammatory proteins in patients with CLL versus normal healthy donors and which may be associated with immune dysfunction and dysregulation in the disease. MUC16 and HGF were associated with achieving early BM uMRD4 status in patients treated with ACA+VEN+/-OBIN. These findings demonstrated the value of high throughput cytokine profiling and may indicate therapeutic targets in CLL.

References

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2. Feng W.; Beer JC.; Hao Q. NULISA: a novel proteomic liquid biopsy platform with attomolar sensitivity and high multiplexing. Nat Commun. 2023, 9(14): 7238.

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