MULTI-OMICS INTEGRATION REVEALS THERAPEUTIC VULNERABILITIES AND IMMUNE MICROENVIRONMENT SUBTYPES IN ACUTE MYELOID LEUKEMIA

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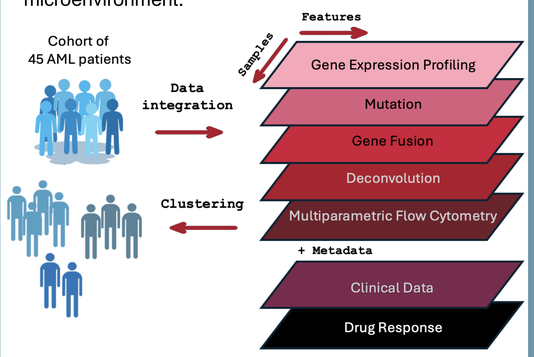
INTRODUCTION

Acute myeloid leukemia is a complex disease marked by a multitude of genetic mutations and dysregulated gene expression profiles stemming from genetic and epigenetic alterations. The molecular profiles of gene mutations and chromosomal anomalies within AML considerably impacts disease progression, therapeutic response, and survival prognosis. Several predictive and prognostic models are used but present inaccuracy at individual level. **Integrating multiple layers of biological data**, including transcriptomic analyses (**gene expression**, **mutational profiling**, **gene fusion identification**) and population-level characterization through **deconvolution** and **multiparametric flow cytometry**, offers a powerful approach to **better understand the complexity of AML and improve prognostic prediction and guide treatment strategies**.

METHOD

From primary AML samples, and patient data, we used a **multi-omics data integration approach**, including bulk **RNAseq-based gene expression** (n=45), **single nucleotide variant** and **gene fusion data** from bulk RNA sequencing (n=45), **deconvolution of tumor microenvironment immune subtypes** (n=45), **immune subtype identification and blast characterization using multiparametric flow cytometry** (MFC) (n=36), ***in vitro* drug response** (Venetoclax, n=23; 5-Azacytidine, n=23; Midostaurin, n=21, Gilteritinib, n=22), and relevant clinical metadata. This allowed us to thoroughly characterize tumor and its tumor microenvironment.



RESULTS

Figure 1: Multiomics Factor Analysis (MOFA) identified 9 principal factors capturing the diversity of the disease.

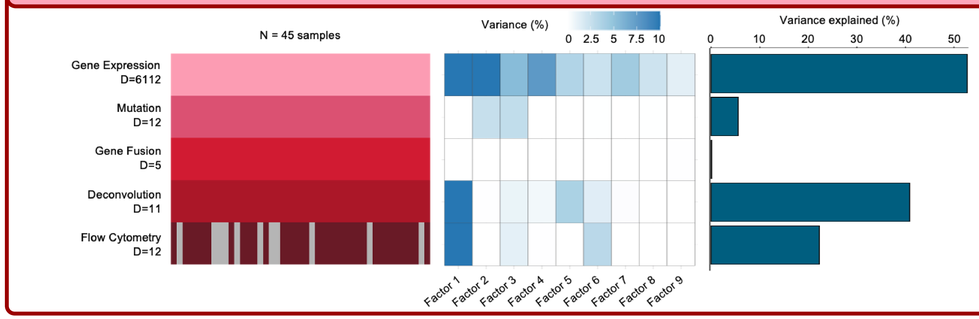


Figure 2: Association analysis with covariates demonstrated that Factor 1 is associated with AML subtypes and Venetoclax response, Factors 2 and 3 are associated with NPM1 and DNMT3A mutations, Factor 4 is related to AML progression, and Factor 8 is associated with undifferentiated AML and 5-Azacytidine response.

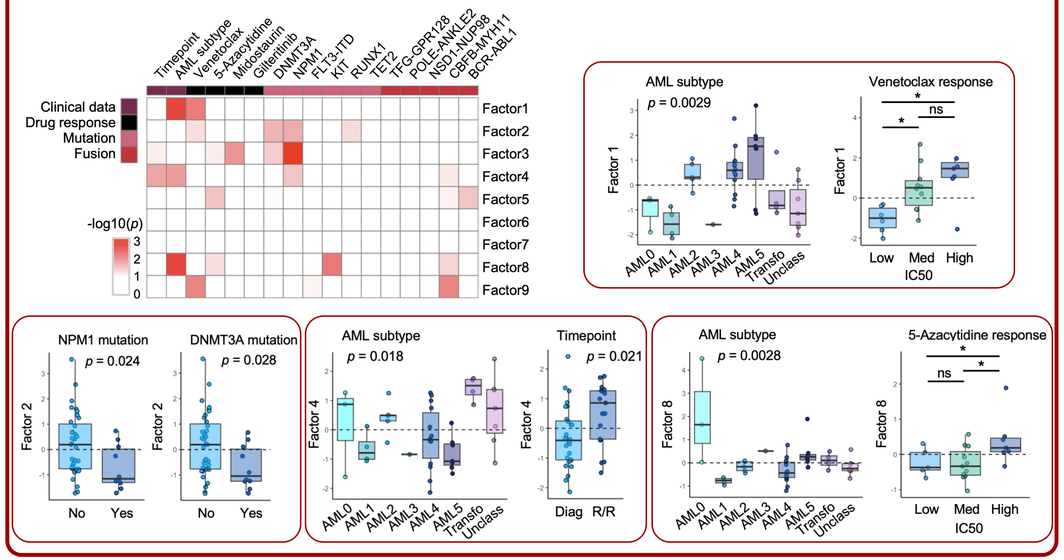


Figure 3: Unsupervised clustering using the latent MOFA factors identified four distinct clusters characterized by specific gene expression profiling, mutation profiling and tumor-microenvironment.

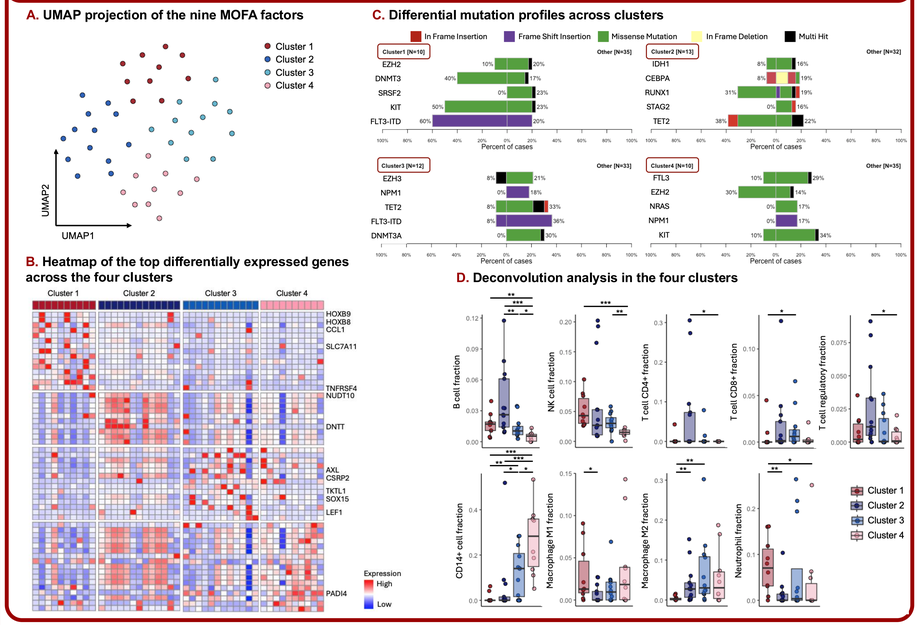
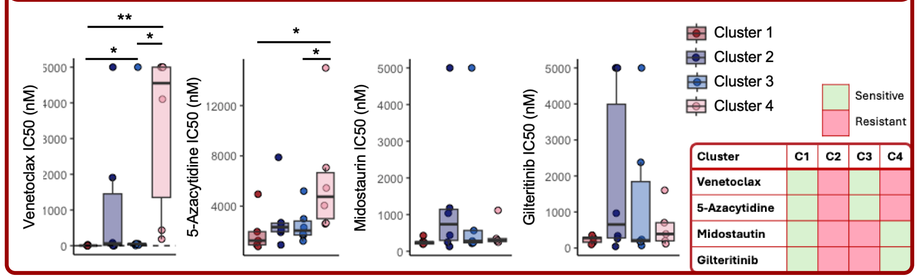


Figure 4: Therapeutic response profiling across molecular clusters revealed distinct patterns of drug sensitivity. Cluster 1 appeared sensitive, whereas Cluster 2 seemed resistant to all treatments. Cluster 3 showed sensitivity to Venetoclax and 5-Azacytidine but resistance to FLT3 inhibitors, with the opposite pattern observed for Cluster 4.



CONCLUSIONS

Our comprehensive multi-omics MOFA framework identified four clinically distinct AML subtypes with distinct therapeutic vulnerabilities, immune microenvironment characteristics, and mutational profile. Our approach demonstrates the potential of multi-omics integration for advancing personalized medicine in AML and provides a framework that will benefit from validation with larger cohorts to improve risk stratification and personalized treatment strategies.

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