Co-Mutational Patterns and Transcriptomic Heterogeneity Within *NPM1*-Mutated Acute Myeloid Leukemia: An Integrative Analysis Using the ASH HematOmics Program

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INTRODUCTION

NPM1-mutated AML, the largest molecular AML subgroup (~30% of AML), exhibits significant outcome heterogeneity driven by co-occurring mutations. Two menin inhibitors, revumenib and ziftomenib, were recently FDA-approved and work by blocking the HOX/MEIS1 pathway that drives *NPM1*-mutated AML. Understanding how different co-mutations affect gene expression patterns may help identify new treatment targets and guide therapy in these patients.

AIM

-Characterize the co-mutation landscape of NPM1-mutated AML

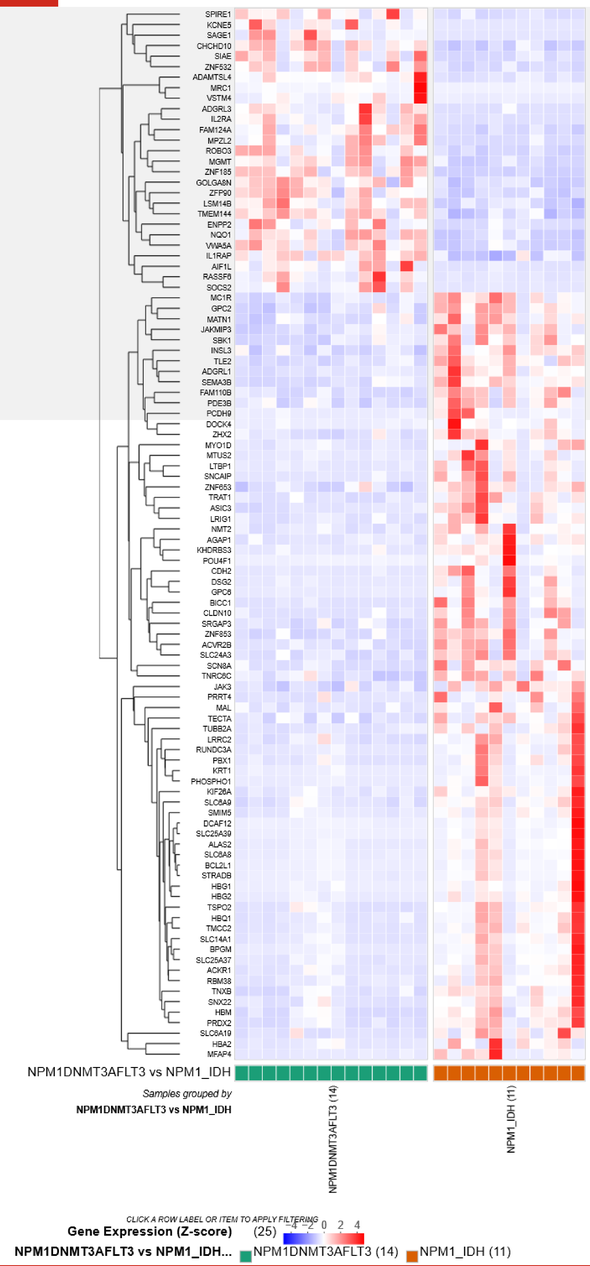
-Determine whether co-occurring mutations produce distinct transcriptomic signatures

-Identify subgroup-specific dysregulated pathways

-Explore potential therapeutic targets

METHOD

We used the ASH HematOmics Program (ASHOP), an open-access platform integrating genomic, transcriptomic, and clinical data from hematologic malignancies, to perform an integrated analysis of *NPM1*-mutated AML. *NPM1*-mutated AML patients were identified from the ASHOP database. Co-mutation landscapes were characterized using matrix and lollipop plots. Patients were stratified into co-mutation subgroups: *NPM1*/*FLT3*/*DNMT3A*, *NPM1*/*DNMT3A*, *NPM1*/*IDH1*-2, *NPM1*/*TET2*, and *NPM1* with (MRG) mutations, which are *ASXL1*, *SRSF2*, *BCOR*, *EZH2*, *U2AF1*, *STAG2*, *ZRSR2*, and *SF3B1*. Unsupervised UMAP clustering of RNA sequencing data identified transcriptomic subclusters. Differential expression analysis performed by edgeR focused on the above-mentioned subgroup comparisons. Pathway enrichment analysis was performed. Clinical outcomes, such as survival data, were not available for this subgroup.



RESULTS

Among 302 AML patients, 62 (20.5%) had *NPM1* mutation, with a median age of 76 years (range, 33–88). Co-mutation subgroups were *NPM1*/*FLT3*/*DNMT3A* (n=11), *NPM1*/*DNMT3A* with *FLT3* wild-type (n=7), *NPM1*/*IDH1*-2 (n=7), *NPM1*/*TET2* (n=9), and *NPM1*/MRG (n=6). DGE analysis identified 263 significantly differentially expressed genes between the *NPM1*/*FLT3*/*DNMT3A* and *NPM1*/IDH subgroups and 179 differentially expressed genes between the *NPM1*/*TET2* and *NPM1*/MRG subgroups (adjusted $P<0.05$; $|\log_2 FC|>1.0$). Hierarchical clustering of the top 100 differentially expressed genes demonstrated distinct transcriptomic profiles across subgroups. Pathway enrichment analysis revealed upregulation of Hallmark Heme Metabolism in the *NPM1*/IDH subgroup, while Interferon Gamma Response, IL6-JAK-STAT3 signaling, and TNF-α via NF-κB pathways were enriched in the *NPM1*/*FLT3*/*DNMT3A* subgroup.

CONCLUSIONS

NPM1 co-mutation subgroups exhibit distinct transcriptomic profiles and pathway enrichment patterns, suggesting biologically meaningful heterogeneity beyond mutational classification alone. The enrichment of inflammatory signaling pathways in the *NPM1*/*FLT3*/*DNMT3A* subgroup and heme metabolism in the *NPM1*/IDH subgroup may have implications for therapeutic targeting. Prospective validation with clinical outcome data is needed to determine whether these transcriptomic differences carry prognostic or predictive significance and can inform trial stratification or treatment selection.

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