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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Unbiased Subtyping of AML: Unraveling Genomic and Transcriptomic Features for Precision Medicine and Targeted Therapies Using Beat-AML and TCGA Data

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Background:
Acute Myeloid Leukemia (AML) is a heterogeneous hematological malignancy with variable clinical outcomes. Identifying patient subsets with relevant prognostic outcomes and understanding their molecular characteristics is crucial for developing targeted therapies. This study aimed to characterize molecular subtypes in AML patients using unsupervised clustering analysis, and investigate the relationship between transcriptomic features, signaling/immune pathways, recurrent DNA variants, and prognostic potential. Here, we show the potential of applying an integrative multi-omics approach to define the disease biology of a unique poor prognostic subtype of AML to uncover potential targeted therapeutic strategies.
Methods:
An unsupervised dimensionality reducing approach (non-negative matrix factorization) followed by consensus clustering was performed on the Beat-AML (discovery dataset, N=462) and TCGA-AML (validation dataset, N=173) RNAseq data from patient samples to identify transcriptomic-based molecular subtypes. The top 1000 most variable genes were used to reduce noise. The biological significance of gene expression in the identified subtypes was analyzed using GSVA on Hallmark, KEGG and Reactome databases. Immune cell type abundance scores were calculated by xCell method. The presence of recurrent DNA variants was evaluated in each subtype. The association between subtypes and clinical outcome was tested using Kaplan Meier method and a log-rank test. The findings were then reproduced in the TCGA AML cohort.
Results:
Analysis in the Beat-AML cohort revealed 5 clusters, including cluster 3 (n=86; comprising 20% of the AML cases) which showed worse overall survival (OS) compared to the other subtypes (HR (95% CI) = 1.41 (1.03, 1.92, P=0.03). A co-mutation in the genes *FLT3*, *NPM1* and *DNMT3A* was enriched in this subtype. Gene sets analysis showed enrichment of several pathways key to the mechanism of action of therapeutic antibodies, including enhanced enrichment of the complement pathway, NK cell-mediated cytotoxicity, and FCGR-mediated phagocytosis in this subgroup. Additionally, activation of oncogenic signaling (PI3K/AKT/MTOR, TGFβ, NOTCH), and metabolic pathways (fatty acid and oxidative phosphorylation) were enriched in this subgroup. Immune cell signatures showed elevated expression levels of M2 macrophages. The results were successfully reproduced in the TCGA AML cohort, validating the findings.
Conclusion:
This study identifies a distinct poor prognostic patient subpopulation in AML characterized by activation of immune and cancer related pathways, and enrichment of a specific co-mutation genotype. While co-mutation of *NPM1/FLT3*-ITD has been identified as an intermediate-risk genotype and *DNMT3A* mutation alone is associated with poor prognosis (Ley et al., 2010, *N Engl J Med*), the triple co-mutation enriched in cluster 3 of our analysis may itself lead to poor prognosis (Loghavi et al., 2014, *J Hematol Oncol*) but the biological features of this subtype have yet to be described.
The transcriptome data revealed patients in cluster 3, which may include nearly 20% of AML, exhibited activation of oncogenic signaling pathways, metabolic stress, and an immunosuppressed tumor microenvironment - all characteristics of aggressive disease; there is also enrichment of genes driving NK cell-mediated cytotoxicity, FCGR-mediated phagocytosis, and complement cascade, highlighting a potential opportunity for antibody-based immune effector function-dependent interventions. Replication of the results in an independent cohort strengthens the robustness of the findings. This study enhances our understanding of AML heterogeneity and may have implications for developing targeted antibody-based strategies to treat high-risk subtypes, such as this specific molecular subgroup, ultimately improving patient outcomes in AML.

Disclosures Karagoz: *Genmab:* Current Employment, Current equity holder in publicly-traded company. **Brady:** *Genmab:* Current Employment, Current equity holder in publicly-traded company. **Higgs:** *Genmab:* Current Employment, Current equity holder in publicly-traded company. **Si:** *Genmab:* Current Employment, Current equity holder in publicly-traded company.

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