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Acute Leukemias

AML ACROSS AGES: METABOLIC REWIRING AND GENOMIC HOTSPOTS IN ADULT AND PEDIATRIC THERAPY RESISTANCE

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Introduction: Acute myeloid leukemia (AML) in pediatric patients is a biologically heterogeneous malignancy, with particularly poor prognosis in relapsed or refractory cases. Evidence from adult AML suggests that metabolic rewiring and dependence on oxidative phosphorylation (OXPHOS) contribute to disease progression and therapeutic resistance. In contrast, the metabolic and genomic landscape of pediatric AML remains largely uncharacterized. This study aims to explore metabolic heterogeneity and genomic alterations in pediatric AML and to compare these preliminary findings with adult data, ultimately improving diagnostic and prognostic precision.

Methods: We employed two complementary approaches: real-time bioenergetic profiling using the Seahorse XF Analyzer to assess OXPHOS and glycolytic activity in AML blasts, and Oxford Nanopore long-read sequencing for comprehensive genomic characterization. Nanopore sequencing enables simultaneous detection of single nucleotide variants, structural rearrangements, copy number alterations, and methylation profiles. Samples were collected at diagnosis and at relapse or from non-responder patients. Although pediatric sample numbers were limited, this approach allows initial comparison of metabolic and genetic features between pediatric and adult AML.

Results: Preliminary analysis revealed distinct metabolic patterns associated with therapeutic resistance in the few pediatric cases studied, showing trends similar to adult AML, with higher OXPHOS activity correlating with adverse outcomes. Nanopore sequencing accurately reconstructed both the conventional mutational panel and karyotype of these patients. Furthermore, novel genomic “hotspots” were identified, including an expanded region within the FLT3 promoter in a representative case, potentially contributing to an “FLT3--like” phenotype and intrinsic therapy resistance. These findings illustrate the potential of long-read sequencing to uncover cryptic structural variants not detected by conventional diagnostics.

Conclusions: This study provides an initial integrated metabolic–genomic overview of pediatric AML and suggests functional links between OXPHOS activity and specific genomic features, consistent with adult AML observations. The combined use of Seahorse profiling and Nanopore sequencing establishes a framework for high-resolution, unified diagnostics. Future work will expand pediatric sample numbers and integrate RNA sequencing and metabolomics to refine molecular classification, identify predictive biomarkers, and develop metabolism-informed therapeutic strategies.