(PB2672) METABOLOMIC SIGNATURES IN UNTREATED AML SERUM ASSOCIATED WITH IN VITRO SENSITIVITY TO SYK INHIBITION

Topic: 03. Acute myeloid leukemia - Biology & translational research

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Background

Acute myeloid leukemia (AML) remains challenging due to high relapse rates and treatment resistance driven by genetic and phenotypic heterogeneity. Spleen tyrosine kinase (SYK) promotes leukemic cell survival and proliferation, making it an emerging therapeutic target. However, patient responses to SYK inhibition vary considerably, and predictive biomarkers are lacking. Metabolomic profiling of patient serum may offer a non-invasive approach to identify baseline signatures predictive of in vitro drug sensitivity.

Aims

To determine whether baseline serum metabolic profiles distinguish AML patients with high versus low in vitro sensitivity to SYK-targeted inhibitors.

Methods

Untreated serum from primary AML patients (n=49, median age 71 years, 36% FLT3-mutated) underwent untargeted metabolomics using the Metabolon platform with Liquid Chromatography-Mass Spectrometry (LC-MS). In vitro sensitivity to SYK-selective (Entospletinib, RO9021) and dual SYK/FLT3 inhibitors (Fostamatinib, TAK-659) was assessed by thymidine incorporation assay. Hierarchical clustering identified three sensitivity groups (high, intermediate, low); subsequent analyses compared the high (n=21) and low (n=15) response groups for SYK-selective inhibitors, and high (n=18) and low (n=8) for dual SYK/FLT3 inhibitors. Differentially abundant metabolites were identified using the limma package in R. Pathway and enrichment analyses were performed using MetaboAnalyst. Exploratory Random Forest (RF) classification in R, incorporating limma-based feature selection and SMOTE resampling, was applied to evaluate predictive accuarcy.

Results

No significant association was found between FLT3 or NPM1 mutation status and drug sensitivity (Mann-Whitney U and Fisher's exact tests). Untargeted metabolomics identified 1,204 metabolites across major pathways. Pathway and enrichment analyses revealed consistent alterations in amino acid, lipid, and xenobiotic metabolism between sensitivity groups for both inhibitor classes. Among top-ranked RF features, lipid metabolites dominated for dual SYK/FLT3 inhibitors, particularly acylcarnitines and fatty acid derivatives. For SYK-selective inhibitors, the metabolic signature was more diverse, with lipids, carotenoid/antioxidant compounds, and proline-related amino acids among the most discriminating features. Following feature selection and SMOTE resampling, RF classification improved sensitivity for the low-response group from 36% to 75.6% (AUC=0.833) for SYK-selective inhibitors, and from 0% to 41.7% (AUC=0.590) for dual SYK/FLT3 inhibitors, likely reflecting the limited sample size (n=8) in the low-response group.

Summary/Conclusion

Baseline serum metabolic signatures may inform in vitro sensitivity to SYK-targeted therapy in AML, though the metabolic features associated with response appeared to differ between inhibitor classes. Serum metabolomics, being both non-invasive and accessible, may offer valuable insights that help inform individualized therapeutic approaches. These findings are hypothesis-generating and require validation in larger, independent cohorts.