Global Metabolomic and Lipidomic Plasma Profiling Reveals Unique Biomarkers that Predict the Risk of Developing Pancreatitis with Asparaginase

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Background: Asparaginase is a cornerstone therapy for leukemia, but about 10% of users develop the complication of pancreatitis. In this study, we used a non-targeted metabolomic and lipidomic platform to determine whether there are unique biomarker signatures that will predict the development of asparaginase-associated pancreatitis (AAP).
Methods: We analyzed plasma samples, collected prior to asparaginase exposure, from 26 patients who went on to develop AAP, and compared them to 26 matched control patients who failed to develop pancreatitis (after a two-year follow-up from first asparaginase use). The plasma metabolites from extracted, separated by HPLC, and then run through a mass spectrometer to identify metabolites against an established library. Data were normalized and log-transformed. Statistical analysis was performed using Welch's 2-sample t-test, random forest analysis, principal component analysis (PCA), and pathway analysis.
Results: There was a total of 844 metabolites detected using the metabolomics platforms (HD4) and 979 metabolites detected using the lipidomics platform (CLP). Using a cut-off of $p<0.05$ for significance, only 42 metabolites in the HD4 and 49 in the CLP were differentially expressed between the experimental and control group, suggesting precise metabolic changes between the two groups. Four methods of statistical validation, including principal component analysis, filtering of imputed values, co-variate adjustment, and paired analysis, confirmed similar findings. The findings were differentially expressed pathways of polyamine, branched chain amino acid, purine/pyrimidine, and phosphatidylinositol and phosphatidylcholine metabolism.
Conclusion: In this pilot study, we identified several metabolic pathways that were altered at baseline in patients who went on to develop AAP, compared to control patients. While additional time point analysis, secondary validation, and mechanistic testing are required to confirm these novel findings, they point to the potential for identifying biomarkers that will predict AAP and, importantly, devising preventive or rescue therapies.

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