Untargeted Metabolomics links alterations of host tyrosine metabolism with susceptibility to Schistosoma mansoni infection

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Abstract:

Background: Hepatosplenic schistosomiasis caused by *Schistosoma mansoni* (Sm) remains a significant public health concern, particularly in endemic regions like Cameroon. Understanding the metabolic changes induced by Sm infection is crucial for uncovering unprecedented host signatures of the infection and markers of disease pathogenesis.
Methods: In this study, we employed LC-MS untargeted metabolomic profiling on plasma samples obtained from school-aged children in areas of low and moderate endemicity for Sm in Cameroon, strong holds of parasite persistent transmission that withstand elimination. Diagnosis of Sm infection was conducted using the Kato Katz (KK) method and complemented by an up-converting phosphor-lateral flow circulating anodic antigen (UCP-LF CAA) assay. Liver morbidity was assessed by ultrasonography (US). Children were stratified into four groups based on infection and liver fibrosis status: Group 1 - Infected without liver fibrosis (KK+US-); Group 2 - Infected with liver fibrosis (KK+US+); Group 3 - Not infected with liver fibrosis (KK-US+); and Group 4 - Not infected without liver fibrosis (KK-US-). From each group, three successive batches of patients were screened by untargeted metabolomics probing of isolated plasma to uncover differentially abundant metabolites and associated pathways during Sm infection and/or associated liver fibrosis. Every hit was searched for robust occurrence in the list of differential metabolites through a first 'discovery' metabolomics run, a 'validation' run and then a 'stability in front of polyparasitism' run (for the latter, studied groups included individuals coinfected with malaria or hepatitis). Comparative analyses were performed in each run using various statistical methods, including fold change analysis, t-tests, sPLSDA, VIP score, heatmap visualization, and ROC curve analysis.
Results: Our metabolomic profiling identified significant alterations in multiple metabolic pathways associated with Sm infection and liver fibrosis susceptibility. Strikingly, alteration of Tyrosine metabolism unprecedentedly emerged as a robustly perturbed pathway across the discovery and the validation runs during Sm infection, suggesting its potential as a candidate biomarker for Sm infection. Moreover, in the polyparasitism run, which examined the host plasma metabolome under conditions of concurrent infections, the persistence of alterations in tyrosine metabolism in Sm infected hosts highlighted the resilience of this pathway as a biomarker of Sm infection in the field (where coinfected sites are usually the norm).
Conclusion: This study highlights the consistent perturbation of tyrosine metabolism in the plasma of Sm infected hosts and its potential as a harnessable pathognomonic characteristic of Schistosomiasis to inform adjunct diagnostic, monitoring or therapeutic tools.

Keywords: Metabolomics, Schistosoma mansoni, liver fibrosis, tyrosine metabolism.