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Title:

Identification, Quantification, and Characterization of Microbiota Metabolites in Murine Gut using In Silico Analysis and Targeted Metabolomics

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Abstract:

Increasing evidence suggest that the metabolites produced by the gastrointestinal (GI) tract microbiota are important modulators of human health and disease. However, only a handful of bioactive microbiota metabolites in the GI tract have been identified. The microbiota has the potential to carry out a diverse range of biotransformation reactions that are unavailable to the mammalian host, and to produce a broad spectrum of metabolites nonnative to the host. Isolating and characterizing individual bacteria to identify metabolites is intractable, as many species present in the GI tract cannot be cultured under standard laboratory conditions. Untargeted metabolomics approaches have been useful in profiling bodily fluids and samples directly connected to GI tract, but are not well suited to resolving the origin of a metabolite as either bacterial or host metabolism. We present here a novel metabolomics strategy that integrates *in silico* analysis with targeted metabolomics to facilitate identification and quantification microbiota metabolites. We model the microbiota as an integrated metabolic system comprising 46 different species reported to be abundant in the gut microbiota, and represent this system with a metabolic reaction network. Of the 1,886 distinct reactions in the microbiota network, approximately 50% are strictly bacterial, i.e. absent in the murine host, with the largest number of reactions involved in amino acid metabolism. Focusing on tryptophan (TRP) as a representative, diet-derive amino acid, we utilize a probabilistic pathway construction algorithm to predict potential metabolic derivatives present in the murine GI tract, while also discriminating between microbiota- and host-specific derivatives. We validate the model-based predictions using multiple reaction monitoring (MRM), a quantitative mass spectrometry technique, on cecum and fecal samples from mice treated with antibiotic, dextran sodium sulfate (DSS), and vehicle. We find that both antibiotic and DSS treatment significantly alters the levels of the predicted TRP metabolites. To demonstrate the potential for the predicted and confirmed TRP derivatives to play a physiological role, we characterize these metabolites as ligands for the aryl hydrocarbon receptor (AhR).