

## Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites.

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Although it has long been recognized that the enteric community of bacteria that inhabit the human distal intestinal track broadly impacts human health, the biochemical details that underlie these effects remain largely undefined. Here, we report a broad MS-based metabolomics study that demonstrates a surprisingly large effect of the gut "microbiome" on mammalian blood metabolites. Plasma extracts from germ-free mice were compared with samples from conventional (conv) animals by using various MS-based methods. Hundreds of features were detected in only 1 sample set, with the majority of these being unique to the conv animals, whereas approximately 10% of all features observed in both sample sets showed significant changes in their relative signal intensity. Amino acid metabolites were particularly affected. For example, the bacterial-mediated production of bioactive indole-containing metabolites derived from tryptophan such as indoxyl sulfate and the antioxidant indole-3-propionic acid (IPA) was impacted. Production of IPA was shown to be completely dependent on the presence of gut microflora and could be established by colonization with the bacterium *Clostridium sporogenes*. Multiple organic acids containing phenyl groups were also greatly increased in the presence of gut microbes. A broad, drug-like phase II metabolic response of the host to metabolites generated by the microbiome was observed, suggesting that the gut microflora has a direct impact on the drug metabolism capacity of the host. Together, these results suggest a significant interplay between bacterial and mammalian metabolism.

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