Using targeted mass spectrometry-based metabolomics to dissect metabolic flux in health and disease

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Recent years have brought forth a marked expansion in the use of metabolic profiling tools aimed at developing metabolite signatures corresponding with both normal and pathophysiologic states. The human metabolome has an estimated 6,500 small molecule metabolites representing key biochemical pathways (see the Human Metabolome Database http://www.hmdb.ca). Assessment of these molecules allows an integrated view of metabolism encompassing other "-omics" such as genomics, transcriptomics, and proteomics since metabolism represents the end product of how genes, proteins, and the environment interact. The field of metabolomics has its genesis in the diagnosis of inborn errors but the technology has since been adapted by our groups and others to apply the use of these tools to study more subtle changes in metabolism as they relate to physiologic states. Using targeted mass spectrometry-based metabolic profiling approaches, we have shown that both genetic and diet-induced forms of insulin resistance are characterized by high rates of incomplete fat oxidation, atypical carnitine and branched-chain amino acid metabolism and production of mitochondrial acylcarnitine species (Koves *et al.*, 2005,2008; Noland *et al.*, 2009; Newgard *et al.*, 2009). This metabolic signature is also associated with impaired substrate switching from fatty acid to carbohydrate fuel during the fasted to fed transition thus imposing a chronic lipid oxidative burden on mitochondria. These perturbations and the accompanying glucose intolerance are alleviated by strategies that increase energy demand and reduce mitochondrial carbon load. We have employed a multi-faceted approach using various model systems such as isolated mitochondria, cell culture, transgenic animals, and humans to gain an insight into the biochemical relevance underlying our findings. Current challenges to the field involve the development of integrated "-omics" bioinformatics platforms that will allow researchers to store, catalog and explore the relationships between metabolite, gene, and protein data from various health and disease states to better understand how metabolic signatures are correlated with physiologic states. Once these signatures are uncovered, further efforts will be necessary to translate and retro-translate these findings to the clinics and back to the bench to better discern their significance.

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