Metabolic disease signatures translated to underlying mechanisms

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We seek to apply metabolomics and other 'omics' tools for understanding of mechanisms contributing to pandemic metabolic diseases of our era: diabetes, obesity, and cardiovascular disease. We have used these tools to define mechanisms underlying development of peripheral insulin resistance and glucose intolerance in animals and humans. For example, we have identified perturbations of branched chain amino acid (BCAA) catabolism in multiple cohorts of insulin resistant humans compared to normally insulin sensitive controls. Our studies and those of others have demonstrated the prognostic power of this signature to predict incident diabetes and intervention outcomes. These metabolites are also uniquely sensitive to the most efficacious interventions for obesity and diabetes. We have translated these findings to rodent models to demonstrate a contribution of BCAA to abnormalities in mitochondrial metabolism that contribute to the insulin resistant state, as well as to behavioral abnormalities associated with obesity. In hyperphagic Zucker obese rats, feeding of a standard chow diet partially restricted in BCAA content results in improved insulin sensitivity, with attendant changes in tissue metabolic profiles that suggest a relief of mitochondrial fuel overload as a contributing mechanism. Moreover, activation of BCAA catabolism by activation of the branched-chain ketoacid dehydrogenase complex by small molecule or genetic interventions improves glucose homeostasis. Finally, our studies provide evidence that the gut microbiome contributes to dysregulated BCAA homeostasis in obese humans. This work demonstrates the potential of metabolic profiling for defining novel metabolic disease mechanisms and new therapeutic strategies.