Final Report

Project Title: Monomethyl branched chain fatty acids (mmBCFAs) as potential biomarkers for risk of obesity-associated metabolic disease

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ABSTRACT:

Monomethyl branched chain fatty acids (mmBCFAs) are commonly found in many organisms and recent studies suggest that they play critical roles in regulating specific lipid metabolism and cellular signaling pathways. However, their physiological role and metabolic regulation are unknown. mmBCFAs are *de novo* synthesized from branched chain acyl CoA precursors derived from branched chain amino acids (BCAAs). Our study demonstrated that mmBCFAs are present in human adipose tissues and their levels are significantly lower in tissues from obese subjects with insulin resistance as compared to lean subjects. Moreover, our study explored potential mechanisms leading to the regulation of mmBCFA synthesis in obesity and its contribution to human insulin resistance. Collectively, our results suggest that mmBCFAs and the more complex lipid species containing those FAs may represent novel and more integrative biomarkers for predicting risk of obesity-associated metabolic dysfunction.

LAY SUMMARY:

Obesity is an important risk factor for developing type 2 diabetes (T2DM), which is caused by insulin resistance in conjunction with inadequate pancreatic function. It is also associated with a constellation of health complications, including inflammation, heart disease and cancer. Thus, it is important to identify specific biomarkers which predict risk and progression of obesity-associated metabolic pathology. The ideal biomarkers should be able to inform on activities of multiple metabolic pathways. Our data suggest that monomethyl branched chain fatty acids are such potential candidates. We performed detailed lipid analysis in human adipose to explore the obesity-related changes of these little-studied fatty acids. We believe our study will provide important information to identify novel and more integrative biomarkers which predict risk of obesity-associated metabolic disease.

INTRODUCTION:

FAs play important physiological roles in energy storage, membrane structure and various signaling pathways. The unique functions of various FAs are determined by their chemical structure and physical properties. The most abundant and also most studied FAs in mammalian cells are long chain even-numbered saturated and unsaturated FAs. However, recent studies uncovered intriguing functions of minor FA species which include hydroxylated FAs and branched chain FAs. Recent studies from several groups support a potential role of protein and AA metabolism in the development of metabolic disease and suggest potential synergies between this group of metabolites and lipids in the development of metabolic dysfunction. mmBCFAs are present in a wide variety of organisms from

bacteria to mammals, indicating a conservation of the related metabolic enzymes and unique functions of those molecules. These little-studied mmBCFAs are *de novo* synthesized with branched chain acyl CoA primers which are derived from branched chain amino acids (AA). Thus, BCAA catabolic enzymes are key regulators for both degradation of BCAA and synthesis of mmBCFA. Interestingly, the activity of key BCAA catabolic enzymes in adipose tissue is strongly influenced by obesity. However, the metabolic consequence of such changes is not clear. Our study aims to study the regulation of adipose mmBCFA synthesis in obesity and its correlation with insulin resisance in human subjects.

Methods:

FA methyl esters were prepared from human adipose tissues and analyzed by GC/MS as described (*Pediatr Res* 64: 605–609, 2008).

Results:

Our analysis of abdominal adipose tissues from lean and obese subjects revealed significant decrease of C17ISO and C17anteISO in obesity. This decrease of mmBCFAs is accompanied with decrease of FAS levels. We also examined adipose mmBCFA levels in subjects undergoing gastric bypass surgery and found that the decrease of mmBCFAs in obese subjects could be reversed by weight loss. Further analysis demonstrated that adipose mmBCFA levels correlate with tissue insulin sensitivity. Moreover, levels of enzymes involved in mmBCFA synthesis, but not plasma BCAA are determinants of mmBCFA levels.

Discussion:

Our study explored mechanisms leading to regulation of a class of little-studied FA species, mmBCFAs, in the well characterized lean, obese human subjects and obese subjects after weight loss. These results support a novel function of mmBCFA synthesis in regulating insulin sensitivity and suggest that mmBCFAs could be novel and more integrative predictors of the progression of metabolic disease, since they would inform on both BCAA catabolism and FA metabolism. Future study will aim to explore the physiological significance of mmBCFAs and their metabolic regulation in humans.

Future plans including planned grant submissions:

The results obtained from current grant period could allow us to submit an RO1 application to explore the physiological significance of mmBCFAs and the metabolic regulation of their levels under disease states.