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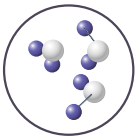

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Editorial

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New Insight into Obesity and Metabolic Disease through Metabolite Profiling

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The incidence of obesity has increased dramatically in the last 30 years, to the point where obesity now represents one of the major global health challenges. Obese individuals are characterized by abnormal or excessive fat accumulation and in many Western nations more than 60% of the adult population is overweight or obese [1]. The rise in the prevalence of obesity has been linked with the increased incidence of a number of serious disease states, including insulin resistance, type 2 diabetes, cardiovascular disease (CVD) and some cancers. The role of obesity in promoting metabolic disease is thought to be related to both an excessive accumulation of fatty acid metabolites in non-adipose tissue and over-activation of inflammatory and stress-related pathways [2,3]. Therefore it is essential that the pathways that lead to excessive lipid accumulation within the body are better understood in order to reduce the health burden resulting from the obesity epidemic.

Obesity results from a chronic imbalance between energy intake and energy expenditure. The oxidation and storage of nutrients involves integrated networks of many metabolic pathways in different organs, and abnormal flux through one or more of these pathways can lead to a deregulated metabolic state. While genetic abnormalities in metabolic enzymes and signaling pathways may be the underlying cause of some obesity [4], environmental factors, particularly excess dietary calories and reduced physical activity are also important contributors to the obesity epidemic. Given the complex interactions between different organs and the large array of factors that may promote obesity and metabolic disease, studies that employ broad approaches examining the entire metabolic landscape likely represent the most effective way to discover new insight into the pathogenesis of these conditions.

Global profiling or "omics" technologies (e.g. genomics, transcriptomics and proteomics) have been widely employed as tools for mechanistic investigations of many diseases. Metabolomics, which refers to the comprehensive profiling of small-molecule metabolites in a biological sample, is a relatively new bioanalytical technique in this field. The metabolite profile of tissues and body fluids can be thought of as a net output of changes in the biological activity of different pathways and in this respect represents an integrated profile of variability in genomic, transcriptomic and proteomic status. To date, the profiling of alterations in metabolite concentrations has shown great potential for gaining new insight into a number of different disease states [5-8].

In the field of obesity and metabolic disease, recent studies employing targeted metabolomics, have identified a number of novel metabolites and pathways that may be involved in disease pathogenesis [9-12]. Chronic lipid oversupply is well known to cause obesity and the accompanying insulin resistance is often associated with excessive accumulation of toxic lipid intermediates (e.g. diacylglycerols and ceramides) in insulin-sensitive tissues [2]. In a series of elegant studies using mass spectrometry-based metabolite profiling in rodents and cells, it has been recently shown that lipid oversupply can also lead to accumulation of fatty acylcarnitines within skeletal muscle [13-15]. This acylcarnitine signature, which is thought be the result of mitochondrial fatty acid overload, has also been observed in humans with obesity and type 2 diabetes [16,17]. To date a direct role for acylcarnitines in promoting metabolic defects in muscle has not been demonstrated, however recent work suggests that accumulation of these metabolites may serve as a marker for disturbances in the ability of mitochondria to efficiently transition between fuel substrates [18].

Metabolic profiling has also identified a critical role for gut flora-dependent metabolism of dietary phosphatidylcholine in the pathogenesis of CVD. Using an unbiased screen, Wang et al. [19] discovered that three metabolites of phosphatidylcholine (choline, trimethylamine *N*-oxide (TMAO) and betaine) were predictive of increased risk for CVD. Studies in mice, confirmed that these metabolites could directly promote atherosclerosis when included in the diet. Furthermore, through the use of germ-free mice and broad-spectrum antibiotics treatments, it was shown that intestinal microflora play an essential role in this pathogenic process. In addition to CVD, metabolomics analyses have also implicated an active role for the intestinal microbial community in determining the susceptibility to insulin resistance and non-alcoholic fatty liver disease [20].

A final example of how metabolomics has provided new insight into human metabolic disease states comes from studies that have identified a novel association between branched chain amino acids (BCAA) and insulin resistance. The metabolite profile of plasma from obese (BMI 37) and lean (BMI 23) individuals was examined and the component of the plasma that most strongly correlated with insulin resistance (HOMA score) was the BCAA concentration [21]. Studies in rats provided with high-fat diets with or without supplemented BCAA, suggested that BCAA may play a direct role in causing metabolic dysfunction [21]. Several subsequent reports have confirmed a strong association between the BCAA metabolite cluster and metabolic disease [22-24], sparking new interest in investigating the complex interplay between lipids and protein in the development of metabolic dysfunction.

The above are just a few examples illustrating the novel insight into factors contributing to obesity and metabolic disease provided by metabolite profiling. As the analytical tools and experimental platforms for metabolomics continue to develop, there will be an expanded scope for identifying novel disease mechanisms and

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biomarkers using this approach. Furthermore, the integration of metabolite profiles with genomic, transcriptomic and proteomic data will provide crucial new knowledge about the importance of different metabolic regulatory networks as potential therapeutic targets to treat obesity and metabolic disease.

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