Western Diet Causes Metabolic Disorder in Mouse Heart

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Authors
Stephen A. Whelan; Jean L. Spencer; Chunxiang Yao; Jessica B. Behring; Christian Heckendorf; Deborah A. Siwick; Wilson S. Colucci; Richard A. Cohen; Markus M. Bachschmid; Catherine E. Costello; Mark E. Mccomb

Institutes
Boston University School of Medicine, Boston, Ma

Introduction
Modern Western diet high in fat and sucrose has led to unfavorable metabolic conditions associated with obesity, type 2 diabetes and hyperlipidemia, all major causes for cardiovascular disease. The early detection and monitoring of the adverse effects of metabolic disease on the heart is now within reach with the accumulation of late disease-specific protein and post-translational modifications (PTM) changes. Our hypothesis is that changes which occur in the heart proteins may not only act as evidence of systemic metabolic disease but will also provide us with potential biomarkers to target in plasma. Here we apply label-free proteomics using a Western diet mouse model to elucidate potential biomarkers of CVD including changes in both proteins and observable PTMs.

Methods
Heart tissue was from control mice and mice fed a high fat / high sucrose diet (HFHS). Proteins were obtained via precipitation and digested with trypsin. LC-MS/MS analysis was carried out on a Q Exactive mass spectrometer coupled with a Waters NanoAcquity HPLC. MS feature identification was enabled by analyzing the MS/MS data using Proteome Discoverer (Thermo-Fisher) and Mascot (Matrix Science) software, searching custom protein databases using both variable-modification and error-tolerant search modes. Label-free quantification was conducted using both Scaffold (Proteome Software) and Progenesis LCMS (Nonlinear Dynamics). Collation and meta-analysis were conducted using the Trans Proteomic Pipeline (ISB), Scaffold and STRAP PTM (in-house) software.

Preliminary Results/Abstract

After 8 months on a Western diet the HFHS mouse model's left ventricle heart tissue was examined for protein and oxidative stress post-translational modification changes. Label-free LC-MS/MS analysis identified >800 proteins, >21,000 unique peptides from >600, 000 MS/MS spectra. There were 150 proteins up-regulated and over 250 proteins down-regulated in the HFHS mouse model due to diet. Between the two groups we observed differential changes in more than 18 distinct PTMs; these were mapped on over 1200 PTM sites. The PTM changes distinguished not only in up-regulated/down-regulated proteins, but diverged on proteins similarly regulated across both groups. Some of the most interesting diet-induced changes included cysteine oxidation, (mono-, di-, tri-oxidation), polyunsaturated fatty acid (PUFA) modifications (4-hydroxynonenal (HNE) and 4-oxo-2-nonenal (4-ONE)), nitration, nitrosylation, acetylation and hydroxyfarnesyl modification. These PTM changes were observed across protein classes and were indicative of modifications associated with oxidative stress pathways and direct modification through redox mechanisms. Ingenuity pathway analysis (IPA) of protein/PTM changes revealed their involvement in mitochondrial dysfunction, citric acid cycle, fatty acid metabolism, cardiac hypertrophy, inflammation, fibrosis and necrosis/cell death. They were also significantly represented in all 5 complexes of the electron transport chain. The Western diet induced significant PTM changes on a number of key metabolic and cardiovascular specific proteins including ATP synthase, aconitate hydratase, citrate synthase, sarcoplasm/ER Ca2+ ATPase2 (SERCA2A), cyclooxygenase (COX; PTGS), sodium-dependent phosphate transport protein 2B, myosin and actin. These changes in proteins and PTMs support the use of our HFHS mouse model and the potential for determination of circulating protein biomarkers in serum/plasma. Definition of a metabolic disorder/CVD-specific protein panel obtained from these mouse models will afford the first step in development of a biomarker panel that will enable disease diagnosis and change to be performed directly at the molecular level.
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Novel Aspect
Label-free proteomics analysis of mouse hypertrophied left ventricle heart tissue identifies biomarkers and PTMs associated with metabolic disorder and CVD.