Biomarkers of Cardiovascular Disease related to Metabolic Syndrome and the American Diet

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Abstract

Unfavorable metabolic conditions (metabolic disorders) associated with obesity and diabetes are major causes for cardiovascular disease. One major cause may be attributed to poor diet, aka the American diet model. Early detection of the adverse effects of metabolic disease remain elusive. We believe that nonspecific changes which occur in plasma proteins, indicators of inflammation and oxidants, may act as evidence of systemic metabolic disease. Here we use an American diet mouse model to elucidate potential biomarkers of CVD including both protein changes and changes in post-translational modifications (PTMs). Label-free mass spectrometry-based proteomics was used to interrogate changes in differential protein and PTM expression in our model. Plasma was from control mice and mice fed a high fat high sucrose diet. LC-MS/MS was performed on LTQ-Orbitrap or Q Exactive mass spectrometers, coupled with Waters NanoAcquity HPLCs. Proteome Discoverer (Thermo-Fisher), Mascot (Matrix Science) and Progenesis LCMS (Nonlinear Dynamics) were used for analysis. Meta-analysis was conducted using the Trans Proteomic Pipeline (ISB), Scaffold (Proteome Software), and STRAP, STRAP-PTM (in-house) software. Label-free LCMS/MS yielded more than 700 features ($p<0.05$, >2fold). A number of cardiovascular disease related proteins were observed. Up regulated proteins were: haptoglobin, a known biomarker related to inflammation, low mannose binding protein associated with inflammation and CVD in type 2 diabetes, superoxide dismutase and extracellular matrix protein both implicated in type 2 diabetes. We also observed different PTMs associated with oxidative stress including lipid peroxidation products such as hydroxynonenal and multiple forms of oxidation such as cysteine sulfonic acid. Development of a metabolic disorder/CVD-specific protein panel will afford the first step in biomarker panel development such that disease diagnosis and progression may be performed directly at the molecular level. This project was funded by NIH-NCRR grants P41 RR010888/ GM104603, S10 RR015942, S10 RR020946, S10 RR025082 and NIH-NHLBI contract N01 HV00239.