McComb, M. E; Bhatia, V. N; Siwik, D. A; Leymarie, N. M; Perlman, D. H; Bachschmid, M.; Ji, Y.; Lin, C.; Cohen, R. A; Colucci, W.; Costello, C. E. Oxidative Modifications Related to Metabolic Disorders as Early Markers of CVD. Abstracts of the Annual Conference of the Canadian National Proteomics Network, Toronto, ONT, April 2012.

Oxidative Modifications Related to Metabolic Disorders as Early Markers of CVD

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Systemic metabolic disorders, (obesity, diabetes, hyperlipidemia) often precede cardiovascular disease (CVD). These conditions involve oxidative stress and inflammation; PTMs related to metabolic irregularities could be early CVD markers. We are analyzing the plasma proteomes of mice on normal *vs*. high-fat, high-sucrose diets ±resveratrol. Mouse models should enable development of a CVD biomarker candidate list. Thus, we also analyze plasma and tissue samples from controls and patients with metabolic disorders underlying their CVD. Both stable-isotope labeling and label-free proteomics approaches are used to detect up- and down-regulated proteins/peptides with UPLC/MS/MS on Thermo-Fisher LTQ-Orbitrap and Q-Exactive and Bruker SolariX 12-T FTMS systems, emphasizing the detection of oxidative PTMs. Abundant protein removal is followed by analysis of both high- and low-abundance protein fractions. Isolation of abundant proteins yields ample quantities of well-defined proteins; these may bear informative makers that could serve as early indicators of CVD. Low-abundance fractions are analyzed to search for components exhibiting +/- regulation and for PTMs that may be disease markers. We are developing software to aid in the assignment and quantitative profiling of post-translationally modified proteins/peptides. Hierarchical clustering has yielded five distinct quantitative profiles. Some are diet-related; not all are resveratrol-responsive.

MS/MS identified > 200 relevant proteins. Proteins with a molecular function GO term which increased with the diet decreased with resveratrol treatment, *e.g.*, Troponin I. Troponin peptides in plasma had abundant OPTMs. Cysteine acylation of key proteins may be a regulatory mechanism.

Acknowledgements: NIH grants P41 RR010888, S10 RR015942, S10 RR020946, S10 RR025082; NIH contract N01 HV-00239.