Yale SCHOOL OF PUBLIC HEALTH

Environmental Health Sciences

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GLUTATHIONE HOMEOSTASIS IN ENVIRONMENTAL HEALTH AND DISEASE.

The goal of this project is to identify novel targets involved in protection against fatty liver disease (**FLD**) by elucidating novel functions of the antioxidant glutathione (**GSH**) as a master-signaling molecule that modulates pathways involved in the pathogenesis and progression of FLD. Over the past few years, remarkable progress has been made in our understanding of the pathophysiology of FLD. However, there is still pressing need for further clarification of the molecular events, signaling pathways and regulatory networks that are intimately involved in the pathogenesis of FLD. The management of FLD in humans remains a challenging prospect, with no effective early diagnostic tools and no significant advancements in the development of drugs for treatment. Oxidative stress plays a central role in many pathways involved in initiation and progression of FLD. A major factor contributing to the development of oxidative stress is depletion of hepatic GSH, the most abundant non-protein thiol antioxidant in the liver. We have developed transgenic mouse models in which hepatic GSH synthesis is repressed by preventing the expression of the catalytic (**GCLC**) or the modifier (**GCLM**) subunit of glutamate-cysteine ligase, the rate-limiting enzyme in GSH biosynthesis. Our preliminary studies have revealed a differential hepatic response to distinct profiles of hepatic cellular GSH concentration. Specifically, these mice exhibit resistance to nonalcoholic and alcoholic FLD ($Gclm^{-/-}$) or develop spontaneous hepatic damage characteristic of an advanced stage of FLD ($Gclc^{h/h}$). The proposed research project will utilize these animal models to expand upon these provocative findings and investigate our novel hypothesis that **GSH plays a central redox regulatory role in the pathogenesis of fatty liver disease by modulating key metabolic and stress response pathways.** Utilizing systems biology approaches in the liver, we propose to: *delineate target proteins of GSH-mediated redox modification by sub-cellular proteomic profiling (SA1), identify cellular metabolic pathways of GSH-mediated modulation by high resolution metabolic profiling (SA2), and decipher and prioritize novel redox-regulatory molecules/pathways that are essential for FLD development through synergizing analysis of molecular data derived from SA1-2 (SA3)*. Findings from these investigations will elucidate novel mechanisms by which GSH modulates cellular metabolic and stress responses to inducers of FLD. We strongly believe that completion of the project will greatly expand our understanding of the mechanisms by which the liver protects itself from oxidative damage. Further, it will provide profound translational information that will serve as a foundation for future development of novel diagnostic and therapeutic targets to improve the treatment of FLD.

Monday, April 21, 2014

12:00 PM LEPH 216, 60 College St.

Lunch Provided