Genomic and Metabolomic Responses to Alcohol-Induced Liver (ALD) Damage

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Alcohol consumption contributes to 4% of the global disease burden, and in the United States is the third leading lifestyle-related cause of death due in part to complications arising from alcohol-induced liver disease (ALD). In addition to obesity, chronic alcohol consumption leads to excessive hepatic free fatty acid (FFA) levels that inhibit β-oxidation pathways and ultimately cause liver disease (steatosis, inflammation, hepatomegaly, fibrosis, and cirrhosis). Interestingly, the adverse effects of alcohol on the liver, in humans and in mouse models, appear to be caused, in part, by attenuation of the peroxisome-proliferator activated receptor α (PPARα). The nuclear transcriptional factor PPARα serves a fundamental role in mammals by acting as a central modulator of signaling molecules that mediate changes in gene expression to maintain lipid homeostasis. The alcohol-fed *Ppara*-null mouse serves as an excellent model for ALD observed in humans and underscores the importance of PPARα in protecting against ALD. Additionally, this mouse model has been cited in over 750 publications supporting its significant utility in understanding the role of PPARα. Therefore, we will determine the mechanism of the influence of this receptor for potential therapeutic intervention strategies on ALD and develop biomarkers for early detection of this disease. To this end, we have developed the following specific aims: 1) to correlate alcohol-induced liver damage with gene expression and metabolomic biomarkers identified in alcohol-fed *Ppara*-null mice for the purpose of developing specific ALD biomarkers; 2) to identify potential epigenetic and post-transcriptional changes associated with decreased PPARα expression in mouse models following alcohol consumption; and 3) to develop toxicogenomic and toxicometabolomic signatures for types of alcohol-induced injury using primary hepatocyte cultures. **These aims seek to understand and integrate the histopathological, genomic, and metabolomic alterations associated with ALD for the purpose of developing early biomarkers associated with ALD pathogenesis.** This proposal combines the unique expertise and experience of Dr. Frank J. Gonzalez's laboratory (National Cancer Institute) and Dr. Albert J. Fornace's laboratory (Georgetown University) to support the discovery of ALD biomarkers and to define the PPARα regulatory and stress inducing mechanisms associated with alcohol consumption.