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SUMMARY

Alcoholic liver disease (ALD) is a serious public health problem in the US, and throughout the entire world. ALD results from chronic alcohol consumption and starts as simple steatosis, characterized by an over accumulation of lipid, primarily triglycerides (TG), in hepatocytes. A subset of subjects with simple steatosis progress to alcoholic steatohepatitis (ASH), which can further progress to fibrosis, eventually leading to cirrhosis and hepatoculluar carcinoma. The underlying general hypothesis for our studies is that the difference in susceptibility to ALD disease reflects individual variation in hepatic lipid metabolism. Since there are no direct treatments available for ALD, understanding better the mechanisms underlying alcoholic fatty liver development is crucial for developing effective interventions for blocking ALD. The overall goal of this application is to gain new understanding of the early events in ALD development.

The specific hypothesis that will be addressed experimentally in this proposal is that dysregulated hepatic TG hydrolysis and dysregulated TG synthesis have important contributory roles in the development of alcoholic steatosis. Since a fatty liver by definition implies excessive hepatic TG accumulation, we are proposing to investigate the 2 most proximal metabolic steps associated with TG accumulation, TG synthesis and degradation. All of our studies will be carried out in mice and will involve chronic feeding, for 4 weeks, of either the alcohol-containing or the isocaloric alcohol-free control Leiber-DeCarli diet formulations. These studies will also make use of adenoviral expression or knockdown constructs for a number of hepatic lipases and TG synthesizing enzymes, as well as other experimental protocols and expertise gained in our earlier published studies of the role of lipases in diet-induced (high fat diet) hepatic steatosis. In Specific Aim 1, we propose to evaluate the roles that several different hepatic lipases may have in the development/prevention of alcohol-induced fatty liver. Although the great majority of experimental protocols needed for undertaking this Aim are well established in the PI's laboratory, there is an exploratory element to this Specific Aim since the normal physiological role of one of the four lipases proposed for study in Specific Aim 1 is not well established. Specific Aim 2 will explore the specific roles that diacylglycerol acyltransferase 1 and 2 (DGAT1 and DGAT2), the two genetically distinct hepatic enzymes that catalyze the final step of TG synthesis, have in the development of alcoholic fatty liver. Our preliminary data establish that both DGAT1 and DGAT2 expression are elevated, by approximately 2-fold, in livers of alcohol-fed mice. Investigations proposed in Specific Aim 2 will define the specific actions of DGAT1 and DGAT 2 in the early stages of ALD development.