LAY ABSTRACT

Alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) are the most common liver diseases in the US. Alcoholic liver disease occurs in the 5% of the U.S. population who are chronically addicted to alcohol, while NASH affects about 3% of the normal weight population and 19% of the obese population. These two diseases have different clinical etiologies, but have almost identical liver pathological features and share similar risks of progression to cirrhosis. Our hypothesis is that aberrant hepatic methionine metabolism is present and integral to the pathogenesis of each of these liver diseases. The long term objective is to define similarities and differences in methionine metabolism, histopathology, and expressions of genes relevant to liver injury in a novel experimental mouse model of each disease. The approach is to study the effects of ethanol or high-calorie diet with or without betaine supplementation, a commercially available methyl donor, on the pathogenesis and prevention of ASH and NASH in the CbS deficient mouse, the best-characterized genetic deletion mouse model of aberrant methionine metabolism. We will use ethanol or high-calories feeding to induce ASH and NASH in sequential experiments, and will study and compare the effects of each diet, both with and without betaine, on liver methionine metabolites and on liver lipid accumulation, oxidative injury, and cell death and their molecular pathways. Demonstration of the graded effects of each treatment in each mouse genotype on liver methionine metabolites and injury and their prevention by betaine, will constitute proof of the central role of aberrant methionine metabolism in the pathogenesis of ASH and NASH.

The results will provide rationale for further epigenetic studies on the relationship of aberrant methionine metabolism to regulation of gene methylation in ASH and NASH. Based on outcomes of the present study, we plan to investigate the effects of ethanol and high calorie diets with and without the methyl donor betaine on epigenomic profiling of DNA methylation in regulation of genes relevant to pathogenesis of ASH and NASH.