LAY ABSTRACT

Alcoholic liver disease (ALD) is a major health problem in the US, and is characterized by excessive fat in the liver, fibrosis and potentially liver cancer. Chronic ethanol feeding induces abnormal liver methionine metabolism, which may play a role in the pathogenesis of ALD. The objective of the proposed research is to define epigenetic mechanisms for the causative relationship of abnormal liver methionine metabolism to the pathogenesis of ALD. Epigenetics is defined as reversible changes occurring in gene expression, without actual changes in the primary sequence of DNA. Two major areas of epigenetics- methylation of DNA and modifications of histone proteins- are known to have significant effects on controlling gene expression and they can be modulated by environmental factors including dietary factors. DNA hypo- or hypermethylation is now known to be as important as coding region mutations for loss or gain of function of key disease genes. Methionine is the precursor of S-adenosylmethionine (SAM), which is the universal methyl donor in regulation of gene expression. S-adenosylhomocysteine (SAH) is the product of methylation reactions and is both the product and precursor of homocysteine. Decreased liver SAM and increased liver SAH and homocysteine are associated with alcoholic liver injury. Since SAM is the universal methyl donor and SAH is an inhibitor of methylation reactions, a decrease in the SAM/SAH ratio may cause aberrant gene methylation. My research program focuses on the effects of ethanol-induced altered methionine metabolism on DNA and histone methylation and gene expression in the pathogenesis of ALD. The cystathionine beta synthase (CβS) deficient heterozygous (+/-) mouse is selected as an animal model for abnormal methionine metabolism. Combining genetic CβS deficiency with ethanol feeding will permit study of the graded effects of elevated liver homocysteine on the induction of ALD. The addition of betaine, a compound that corrects abnormal methionine metabolism, will confirm the causal association of aberrant methionine metabolism on the pathogenesis of ALD by correcting both liver methionine metabolism and liver injury. Other studies will be performed using clinical liver biopsies from ALD patients before and after treatment with SAM. The first specific aim of the study is to demonstrate the relationships between methylation status and gene expression in these experimental models by correlating the genome-wide gene expression profile with the DNA methylation profile using bioinformatic techniques. The second specific aim is to show functional relationships between histone protein modifications and gene expressions and their alterations in the three experimental models by defining histone modifications of genes that are found to be regulated by DNA methylation status from aim 1. I will use DNA and protein immunoprecipitation combined with DNA microarray technology to profile and quantify gene expression and acquire information on DNA and histine modifications.