

ALCOHOL INDUCED HISTONE ACETYLATION MEDIATED BY HISTONE ACETYL TRANSFERASE GCN5 IN LIVER

Mahua Choudhury

Dr. Shivendra D. Shukla, Dissertation Supervisor

ABSTRACT

Although several mechanisms have identified for alcoholic liver disease, at present there are no precise mechanisms for liver injury. We have observed that surrogate alcohols increases histone H3 acetylation selectively at Lys 9 (H3AcK9) via metabolites in primary rat hepatocytes. Alcohols and metabolites both increased the HAT activity. However, propionate and butyrate also decreased HDAC activity. In addition, oxidative stress also mediates ethanol induced histone acetylation and ADH1 gene expression. It is likely that both NADPH oxidase and mitochondria derived ROS are involved. The study presented here also identifies for the first time the specific HAT, GCN5, responsible for ethanol induced H3AcK9 in human hepatoma cell overexpressing ADH1 (VA-13). siRNA knock down of GCN5 decreased both ethanol induced H3AcK9 and HAT activity. In summery, we conclude that ethanol increases H3AcK9 via modulation of GCN5 in the liver. These original findings may contribute to a better understanding of the mechanism underlying the pathogenesis of alcoholic liver disease.