

Public Abstract

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

Alcoholism affects approximately 14 million Americans. Alcohol (especially ethanol) is used by around 75% of the population of the United States, with a 7% incidence of alcoholism. Alcohol abuse through the world is associated with social and medical implications. Especially, it enhances the risk of liver diseases. Alcoholic liver disease develops in 20% of alcoholics. In addition, alcohol accounts for approximately one million deaths in the USA each year, with 20% of those deaths attributable to liver cirrhosis. Liver cirrhosis resulting from alcohol abuse is one of the ten leading causes of death in USA.

Although several mechanisms and factors have been proposed to be responsible for alcoholic liver disease, at present there are no precise mechanisms for liver injury. Drinking ethanol as well as higher chain alcohols (called surrogate alcohol) causes severe liver problems including death. Emerging evidence highlight the importance of histone modifications, transcriptional regulators and gene expressions in liver disease. Histone acetylation plays an imperative role in transcription and within this process important class of transcriptional regulators are histone acetyl transferase (HAT) and histone deacetylase (HDAC). We have observed that surrogate alcohols increases histone H3 acetylation selectively at Lys 9 (H3AcK9) but not at Lys 14, 18, 23 or 27 in primary cultures of rat hepatocytes. The alcohol effect was inhibited by alcohol metabolizing enzyme inhibitors, and the metabolites showed a similar effect as the alcohols, suggesting the involvement of metabolism in histone acetylation. Alcohols and metabolites both increased the HAT activity. Propionate and butyrate also decreased HDAC activity.

There is also increasing evidence that oxidative stress plays an important etiologic role in the development of alcoholic liver disease. Alcohol administration has been found to cause accumulation of reactive oxygen species, including superoxide, hydroxyl radical, and hydrogen peroxide. Reactive oxygen species, in turn, cause lipid peroxidation of cellular membranes, and protein and DNA oxidation, which results in hepatocyte injury. Antioxidants are likely potential pharmaceutical agents for the treatment of alcoholic liver disease. However, relationship between ethanol induced oxidative stress and histone acetylation is unknown. A series of experiments to manipulate oxidative stress were carried out and the results demonstrate for the first time that oxidative stress mediates ethanol induced histone acetylation and ADH1 gene expression

The study presented here also identifies for the first time the specific HAT, GCN5, responsible for ethanol induced histone H3 acetylation of lysine 9 in human hepatoma cell overexpressing ADH1 (VA-13 cells). siRNA knock down of GCN5 in VA-13 cells decreased both ethanol induced H3AcK9 and HAT activity. In summery, we conclude that ethanol increases histone H3 acetylation at lysine 9 via modulation of histone acetyl transferase GCN5 in the liver. These original findings may contribute to a better understanding of the mechanism underlying the pathogenesis of alcoholic liver disease and also contribute towards development of potential therapeutic target at the nucleosomal level.

Although important progress has been made in understanding the pathogenesis of alcoholic liver disease, current therapies for this disease are not effective. Novel therapeutic approaches such as utilizing agents that successfully correct the fundamental cellular disturbances resulting from excessive alcohol consumption are attractive. This study will make a valuable contribution to the humanity.

