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EDITORIAL

Targeting Epigenetic Mechanisms to Alleviate Alcoholic Steatosis

Alcohol-related liver disease (ALD) is a major health concern and recent studies have reported nearly 1 million alcohol-related deaths from 1999 to 2017 in the United States.[1] ALD is a spectrum of conditions that ranges from early steatosis or fatty liver to inflammation or alcoholic steatohepatitis progressing to fibrosis and cirrhosis. Approximately 8%–20% of alcoholic steatohepatitis patients develop cirrhosis and, in some, alcoholic steatohepatitis can present in the form of acute-on-chronic liver failure, termed *alcoholic hepatitis*, owing to excessive drinking episodes. Corticosteroids are the first line of therapy for ALD, however, only marginal short-term survival benefit in patients with severe alcoholic hepatitis has been reported.[2] Studies from the National Institute on Alcohol Abuse and Alcoholism consortia have focused on preclinical or early clinical testing of drugs classified on the basis of pathogenic mechanisms such as targeting the gut–liver axis, anti-inflammatory agents, antioxidants, and drugs that promotes liver regeneration.[3] Despite several efforts, the treatment for alcoholic hepatitis remains suboptimal and there is an urgent need to develop new, safe, and effective therapies. Uncovering new targets directly involved in regulatory processes that influence gene expression and cellular phenotype could be an attractive strategy.

Epigenetic regulatory mechanisms are essential for orchestrating gene expression and cellular function. Increasing evidence has shown that acute and chronic alcohol exposure in vitro and in vivo regulate epigenetic mechanisms in the liver, brain, and gut, likely contributing to ALD.[4] Multiple modifications including acetylation, methylation, and phosphorylation of histones influence transcriptional activation or repression of target genes in alcoholic liver. Alcohol can alter histone acetyl transferases and histone deacetyl transferase (HDAC) activity to modify histone lysine residues and regulate histone–DNA interactions resulting in an open or closed chromatin state to induce or repress target genes respectively, in the liver. Livers from alcoholic hepatitis patients show alterations in DNA methylation and chromatin remodeling owing to defective hepatocyte nuclear factor-4α–dependent gene expression.[5] Overall previous reports and recent findings emphasized that alcohol alters epigenetic mechanisms contributing to ALD.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, building on their own group's earlier reports, Donde et al[6] present novel findings that chronic alcohol induces histone H3K9 deacetylation in the promoter region of the fatty acid oxidation gene, carnitine palmitoyltransferase-1 (CPT-1A), indicating a closed or repressive chromatin state and hence reduced CPT-1A gene expression in alcoholic steatotic livers. Their results showed that alcohol facilitated HDAC1 binding to CPT-1A promoter regions I (proximal) and II (distal), causing histone H3K9 deacetylation. Interestingly, transcriptional factors SP1 and hepatocyte nuclear factor-4α interacted directly with HDAC1 in the CPT-1A gene proximal and distal promoters to mediate transcriptional repression. Previous studies by this group reported that acute alcohol-induced down-regulation of CPT-1A also involved transcriptionally repressive histone de-acetylation mediated by the N-CoR-HDAC3 nuclear receptor corepressor complex, binding only to the distal CPT-1A promoter region.[7] It is noteworthy that chronic alcohol-mediated HDAC1-induced deacetylation occurs in the distal and proximal promoter, without any role for the N-CoR-HDAC3 complex. These studies point to distinct regulation of the CPT-1A promoter by acute and chronic alcohol and yet similar outcomes of reduced CPT-1A gene expression. Previous studies have shown that alcohol administration in vivo regulates peroxisome proliferator receptor α in hepatocytes and prevents induction of CPT-1A expression, affecting fatty acid oxidation.[8] Future studies to investigate whether HDACs and peroxisome proliferator receptor α act in concert to repress CPT-1A during ALD will provide important mechanistic insights.

Gut dysbiosis and intestinal permeability are important triggers in ALD and considerable evidence supports the premise that the "gut–liver axis" plays a crucial role.[9] Undigested dietary polysaccharides can be converted by microbial fermentation to short-chain fatty acids, including butyrate, which is the primary energy source in the colon and contributes to normal colonic health. In fact, butyrate is a HDAC inhibitor and can repress target gene expression. Ethanol consumption decreases short-chain fatty acids, particularly butyrate, likely owing to the alterations in the microbiome.[10] The use of tributyrin, a butyrate prodrug that when administered orally is hydrolyzed to butyrate, increases its concentration in circulation/plasma. Donde et al[6] administered tributyrin by oral gavage, resulting in increased butyrate in portal blood and liver, preventing steatosis and injury. Tributyrin induced transcriptional activation of CPT-1A promoter likely owing to decreased histone H3K9 deacetylation in the liver. Mechanistic in vitro experiments using chromatin immunoprecipitation analysis have shown that sodium butyrate inhibits alcohol-induced HDAC1 recruitment to the CPT-1A promoter, preventing histone deacetylation. Concomitantly, butyrate treatment facilitated recruitment of p300-histone acetyltransferase to the CPT-1A distal and proximal promoter, leading to promoter histone acetylation, Pol II recruitment, and CPT-1A transcription. Previous studies have reported that tributyrin treatment during alcohol feeding decreased liver Toll-like receptor and tumor

necrosis factor α expression and also prevented ethanol-induced disruption of intestinal tight junction proteins and intestinal permeability.[11] The current study extends the beneficial effect of tributyrin to alcoholic steatosis in ALD.

In summary, Donde et al[6] presented novel findings on ethanol-mediated inhibition of CPT-1A promoter via HDAC1 activity and histone deacetylation in hepatocytes contributing to alcoholic steatosis and liver injury. Furthermore, the beneficial effect of tributyrin on alcoholic steatosis by inhibition of HDAC1 activity and increased recruitment of p300 promoting CPT-1A gene expression also has been reported. These studies point to the potential of targeting HDAC1 using drugs/inhibitors in ALD. Furthermore, the clinical relevance of restoring intestinal and circulating butyrate levels as a therapeutic strategy also may be an attractive option for alcoholic hepatitis treatment.

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