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EDITORIAL

Obesity and Binge Drinking: Two Hits Driving Liver Fibrosis Progression?

Alcoholic fatty liver disease and nonalcoholic fatty liver disease frequently are associated with alcohol consumption and obesity. Both diseases start with steatosis/steatohepatitis, and some patients can develop advanced liver injuries and subsequent permanent liver damage, including fibrosis, cirrhosis, hepatocellular carcinoma, and liver failure. Epidemiologic evidence has shown that drinking alcohol synergistically increases the prevalence and severity of liver injury in obese individuals. Likewise, liver damage in alcohol abusers is greatly exacerbated by obesity. Obesity and alcohol consumption often co-exist and synergistically drive the detrimental progression of liver diseases. Despite epidemiology, the current knowledge on underlying mechanisms is insufficient because of the difficulties in developing proper laboratory rodent models mimicking the liver pathologic events induced by obesity and alcohol drinking.

There have been several studies on steatohepatitis in rodent models of obesity-alcohol synergism. In 2003, Carmiel-Haggai et al[1] reported that alcohol binges increased liver injury in obese rats. Xu et al[2] also investigated steatohepatitis in a mouse model with intragastric co-feeding of a high-fat diet (HFD) and alcohol in 2011. Our group in 2013 showed that chronic ethanol administration to genetically obese (ob/ob) mice exacerbated fatty liver injury.[3] Mechanistic studies have shown that multiple defective signaling routes governed by sirtuin 1 (Sirt1), a nicotinamide adenine dinucleotide^{+}-dependent protein deacetylase, occurred in the exacerbated liver damage in obese mice after ethanol administration. Interestingly, our group subsequently discovered in 2014 that liver-specific Sirt1-deficiency mice progressed partially from fatty liver to fibrotic liver in response to a chronic-binge ethanol challenge.[4] Our findings suggest that Sirt1 may be a central signaling molecule in controlling the severity of liver injury and progress of liver fibrosis induced by obesity and alcohol drinking.

In 2015, Chang et al[5] reported a clinically relevant HFD-plus-1 binge ethanol feeding rodent model that recapitulated the synergistic detrimental effects of alcohol drinking and obesity on mouse livers, including enhanced neutrophilic inflammation, exacerbated steatohepatitis, and an augmented increase of serum liver enzyme levels. However, whether the combined challenges of HFD and binge ethanol feeding promote liver fibrosis in this rodent model remained unknown at the time.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, building on their group's previous findings, Zhou et al[6] showed that significant liver fibrosis resulted from adding a single or multiple binges of ethanol to HFD feeding in mice. They reported substantial collagen deposition in the liver after HFD-plus-1 or multiple binges of ethanol feeding. They showed that the most up-regulated pathway upon HFD-plus-binge ethanol feeding was related to liver fibrosis and hepatic stellate cell (HSC) activation, and HFD-plus-multiple binges of ethanol feeding led to much more severe fibrosis compared with HFD-plus-1 binge ethanol feeding.

Their group's previous works have shown that hepatic neutrophil infiltration was vital to the liver damage in the HFD-plus-1 binge ethanol model.[5] In the present study, they examined the roles of neutrophils in liver fibrosis on the synergistic effects of alcohol and obesity. They showed that genetic ablation of (C-X-C motif) ligand 1 or intercellular adhesion molecule 1, 2 crucial mediators for neutrophil infiltration, greatly attenuated liver fibrosis in mice upon HFD-plus-1 binge ethanol challenge. Their results showed that neutrophil infiltration not only induced hepatocellular damage but also promoted liver fibrosis in the HFD-plus-1 binge ethanol feeding rodent model.

By using in vitro co-culture, they further analyzed reciprocal interactions between neutrophils and HSCs. They found that activated HSCs or conditioned medium of activated HSCs attenuated spontaneous apoptosis of neutrophils and increased neutrophil survival accompanied by increased levels of granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin 15 (IL15), 2 growth factors/cytokines produced by activated HSCs and known to prolong neutrophil survival. Furthermore, neutralizing GM-CSF and IL15 by incubation with anti–GM-CSF or anti-IL15 antibodies abolished the ability of activated HSCs to prolong neutrophil survival, indicating the causal effects of GM-CSF and IL15 on the survival of neutrophils.

One notable limitation of the present study was that the HFD-plus-multiple binges of ethanol feeding model was technically a challenge owing to a high rate of mouse mortality. To better define the pathogenesis of liver fibrosis induced by ethanol and obesity, this rodent model will need to be improved further.

In summary, the present study by Zhou et al[6] provided novel findings on liver fibrosis progression initiated by the combination of HFD and binge consumption of ethanol in mice. Of particular interest is the clairvoyant demonstration that GM-CSF and IL15 produced by the activated HSCs prolonged the survival of neutrophils, which may serve as a positive forward loop to promote liver fibrosis in the clinically relevant HFD-plus-binge ethanol rodent models (see graphic abstract in Zhou et al[6]). These findings shed light on the pathogenic mechanism by which obesity and alcohol synergistically interact to drive liver fibrosis progression. It will be of great interest to explore the role of Sirt1 and to integrate Sirt1 signaling into the proposed paradigm in the future (see graphical abstract in Zhou et al[6]).

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References

1. Carmiel-Haggai M, Cederbaum AI, Nieto N. Binge ethanol exposure increases liver injury in obese rats. Gastroenterology 2003;125:1818–1833.
2. Xu J, Lai KKY, Verlinsky A, Lugea A, French SW, Cooper MP, Ji C, Tsukamoto H. Synergistic steatohepatitis by moderate obesity and alcohol in mice despite increased adiponectin and p-AMPK. J Hepatol 2011; 55:673–682.
3. Everitt H, Hu M, Ajmo JM, Rogers CQ, Liang X, Zhang R, Yin H, Choi A, Bennett ES, You M. Ethanol administration exacerbates the abnormalities in hepatic lipid oxidation in genetically obese mice. Am J Physiol Gastrointest Liver Physiol 2013;304:G38–G47.
4. Yin H, Hu M, Liang X, Ajmo JM, Li X, Bataller R, Odena G, Stevens SM Jr, You M. Deletion of SIRT1 from hepatocytes in mice disrupts lipin-1 signaling and aggravates alcoholic fatty liver. Gastroenterology 2014;146:801–811.
5. Chang B, Xu MJ, Zhou Z, Cai Y, Li M, Wang W, Feng D, Bertola A, Wang H, Kunos G, Gao B. Short-or long-term high-fat diet feeding plus acute ethanol binge synergistically induce acute liver injury in mice: an important role for CXCL1. Hepatology 2015; 62:1070–1085.
6. Zhou Z, Xu M-J, Cai Y, Wang W, Jiang JX, Varga ZV, Feng D, Pacher P, Kunos G, Torok NJ, Gao B. Neutrophil–hepatic stellate cell interactions promote fibrosis in experimental steatohepatitis. Cell Mol Gastroenterol Hepatol 2018;5:399–413.

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