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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

S100A11 Overexpression Promotes Fatty Liver Diseases via Increased Autophagy?

Nonalcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis that may progress to nonalcoholic steatohepatitis, the more severe form of NAFLD, which is the most common chronic liver disease globally. Hepatic steatosis is developed because of an imbalance between the lipid input (intake and biosynthesis of triglycerides) and output (export and catabolism of triglycerides) resulting in NAFLD, which can further progress to nonalcoholic steatohepatitis.[1] Despite extensive research efforts, the molecular basis of the development and progression of NAFLD are still poorly understood. Therefore, there is a clear unmet need for research on the mechanisms of how NAFLD is developed.

Autophagy is a catabolic process whereby cellular contents are delivered to lysosomes via the formation of double membrane autophagosomes. Lipophagy, a selective form of autophagy for lipid droplets (LD), has been widely accepted as an important mechanism for regulating LD breakdown, which is impaired in NAFLD and alcoholic fatty liver diseases.[2-4] Moreover, pharmacologic activation of autophagy has also been shown to be protective against experimental NAFLD and alcoholic fatty liver diseases.[3,5-7] Although the evidence supporting the beneficial role of autophagy against NAFLD and alcoholic fatty liver diseases seems compelling, the opposite role of autophagy in promoting the biogenesis of LD and hepatic lipid accumulation has also been reported. On starvation, the number of LD increases because of increased autophagic degradation of intracellular membranes, which generates free fatty acids as fuels for de nova LD biogenesis.[8] Increased LD formation most likely serves as an adaptive protective mechanism against free fatty acids accumulation from autophagic breakdown, because free fatty acids are toxic and can induce lipotoxicity.[8] Mice with genetic deletion of essential autophagy genes in the liver are resistant to starvation or high fat diet–induced steatosis.[9-11] However, autophagy-deficient livers have increased liver injury and inflammation that is associated with many altered adaptive lipid metabolism pathways, including decreased liver X receptor α-mediated lipogenesis and peroxisome proliferator-activated receptor α-mediated lipid oxidation, whereas increased p62-mediated nuclear factor erythroid 2-related factor 2 activation.[9,10,12] Therefore, the role of autophagy in the development of NAFLD remains elusive.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Zhang et al[13] established a tree shrew model of NAFLD. Tree shews fed with a high-fat low-cholesterol diet developed simple steatosis but developed more advanced liver injury with fibrosis when they were fed with a high-fat high-cholesterol (HFHC) diet. Using an unbiased comparative proteomic analysis of the normal and different stages of NAFLD tree shrew livers, the authors identified S100A11, a Ca^{2+}-binding small protein with 2 EF-hands that is frequently upregulated in several human cancers, markedly induced in NAFLD. Follow-up studies confirmed the mRNA and protein levels of S100A11 significantly increased in high-fat low-cholesterol and HFHC-fed tree shew livers, and its expression levels were much higher in the high-grade damaged liver induced by HFHC. Overexpression of S100A11 exacerbated HFHC diet-induced hepatic steatosis in mice and increased lipid accumulation in several cultured hepatoma cells lines. These data imply that S100A11 may promote the progression from NAFLD to more severe nonalcoholic steatohepatitis.

How does S100A11 promote the progression of NAFLD? RNAseq analysis revealed a variety of autophagy-related genes were upregulated in HFHC-fed tree shrew livers that had hepatic overexpression of S100A11. The authors further found that overexpression of S100A11 increased the levels of acetylated forkhead box O1 (FOXO1), a transcription factor that is critical for regulating gene expression of gluconeogenesis and glycogenolysis. Furthermore, S100A11, FOXO1, and histone deacetylase 6 (HDAC6) physically interacted with each other. Pharmacologic inhibition of HDAC6 increased the levels of acetylated FOXO1 and autophagy proteins Atg7 and LC3-II accompanied by increased lipid accumulation in Hepa 1-6 cells, a murine hepatoma cell line. In contrast, pharmacologic inhibition of FOXO1 led to decreased Atg7 and LC3-II levels and lipogenic-related protein diacylglycerol O-Acyltransferase 2 and cell death inducing DFFA like effector C (CIDEC) resulting in decreased lipid accumulation in S100A11-overexpressed hepatoma cells. Collectively, these data seemed to support a S100A1-HDAC6-FOXO1 axis in enhancing autophagy that leads to hepatic lipid accumulation.

Although this study has largely extended the understanding of NAFLD development in the tree shew, and seemed to be supportive for a detrimental role of autophagy mediated by S100A11 in this model, caution needs to be taken for this conclusion because there are several limitations in this study. The authors only presented the change of steady state autophagy proteins in HFHC-fed tree shew livers, which often does not accurately reflect autophagic flux/activity. Moreover, most data mainly relied on the pharmacologic approaches to manipulate HDAC6 and FOXO1, which are not specific and may have additional effects beyond targeting autophagy. In addition, the in vivo data were not robust because only 3–4 animals were included in each experimental condition, although most findings were supportive by the complementary cell culture

studies. Notably, in addition to increasing autophagy markers, S100A11 overexpression also increased lipogenesis. Future work to further differentiate the contributions of autophagy and lipogenesis in the pathogenesis of NAFLD under S100A11 overexpression conditions is needed to provide better insights into whether targeting S100A11 is a potential NAFLD treatment strategy.

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Conflicts of interest
The authors disclose no conflicts.

Funding
Supported by R37 AA020518, R01 DK102142, U01 AA024733, R21 AA027250, and R01 AG072895.

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2352-345X
https://doi.org/10.1016/j.jcmgh.2020.11.013