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Commentary

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ChREBP refines the hepatic response to fructose to protect the liver from injury

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Overconsumption of fructose and other sugars has been linked to nonalcoholic fatty liver disease (NAFLD); however, the sugar-associated effects that lead to disease are poorly defined. In this issue of the *JCI*, Zhang and colleagues show that the carbohydrate response element-binding protein (ChREBP) coordinates an adaptive response to a high-fructose diet in mice and that loss of this transcription factor leads to hepatic inflammation and early signs of fibrosis. Intriguingly, ChREBP-dependent effects were due to an exaggerated activation of the proapoptotic arms of the endoplasmic reticulum stress response that is probably secondary to inappropriate derepression of cholesterol biosynthesis. These findings suggest that a previously unknown link exists between ChREBP and the regulation of cholesterol synthesis that affects liver injury.

Hepatic steatosis

Nonalcoholic fatty liver disease (NAFLD) is the ectopic accumulation of lipid in the liver parenchyma in the absence of alcohol overconsumption. Only recently defined as a distinct clinical entity, NAFLD has become the most common liver disease in many parts of the world (1, 2). Though the accumulation of intrahepatic triglycerides by itself may be relatively benign, hepatic steatosis can progress to nonalcoholic steatohepatitis (NASH), which is characterized by marked inflammation, hepatocyte death, and replacement with collagen matrix (fibrosis). Moreover, NAFLD and NASH are also associated with an increased risk of developing cirrhosis and hepatocellular carcinoma (3). Although NAFLD and NASH have become exceedingly common, there are currently no FDA-approved therapies for this spectrum of diseases, and, thus, treatments for NAFLD and NASH represent a significant unmet medical need.

Mouse models of NAFLD have been developed to study this disorder in genetically tractable organisms. In general, mice fed a fatty acid-enriched diet develop

hepatic steatosis without coincident fibrosis or other signs of NASH (4). Diets enriched with fructose also produce intrahepatic lipid accumulation in rodents (5), and some epidemiologic studies support the notion that overconsumption of sugar-sweetened beverages containing high-fructose corn syrup can be connected to the development of NAFLD in humans as well (6). In mouse models, supplementation of high-fat or fructose diets with 1% to 2% cholesterol produces liver injury reminiscent of human NASH (7), but the relevance of such high levels of cholesterol in the diet can be questioned.

In order for fructose and other sugars supplemented in the diet to contribute to complex lipids deposited in the liver, they must first be converted to fatty acids via de novo lipogenesis (DNL) (Figure 1). The carbon contained in fructose must be converted to acetyl-CoA and then citrate in the mitochondrion before entering into the process of DNL in the cytosol. This complex process is mediated by a number of metabolic enzymes and regulated at both the transcriptional and posttranslational levels. Transcriptionally, the

genes encoding these myriad enzymes are regulated by the basic helix-loop-helix transcription factors sterol response element-binding protein 1 (SREBP1c) and carbohydrate response element-binding protein (ChREBP), which are activated by insulin (8) and intermediates of carbohydrate metabolism (9), respectively.

Originally described as a glucose-responsive transcription factor, ChREBP has also been shown to be highly responsive to fructose in recent studies conducted in both rodents and humans (10). Indeed, in response to fructose feeding or an acute bolus of fructose, a ChREBP-dependent expression of the program of genes encoding various lipogenic enzymes is induced in the liver (11, 12). Many of the genes in this pathway, including fatty acid synthase (*Fasn*), sterol-CoA desaturase (*Scd1*), and acetyl CoA carboxylase 1 (*Acc1*) (13), are not induced in response to fructose in mice lacking ChREBP. Moreover, knockdown or knockout of *Chrebp* prevents the development of hepatic steatosis in models of fructose administration and in genetic models of obesity-related NAFLD (11, 12). However, there are also data suggesting that the induction of this gene program may play a protective role in liver, as mice lacking ChREBP fail to thrive or even die when placed on extremely high-carbohydrate diets (13). Other studies have suggested that ChREBP-mediated induction of the hepatokine FGF21 in response to fructose (10) communicates with the CNS to reduce fructose consumption (14, 15). Moreover, it has been suggested that while activation of ChREBP promotes fat storage, it also mitigates the development of insulin resistance that is associated with NAFLD (16). Indeed, many obese human subjects remain metabolically healthy, and it has been suggested that the capacity for lipogenesis may actually be increased in these obese, metabolically normal subjects compared with metabolically unhealthy individuals (17). The contribution of ChREBP to this phenomenon, especially in liver, remains unclear.

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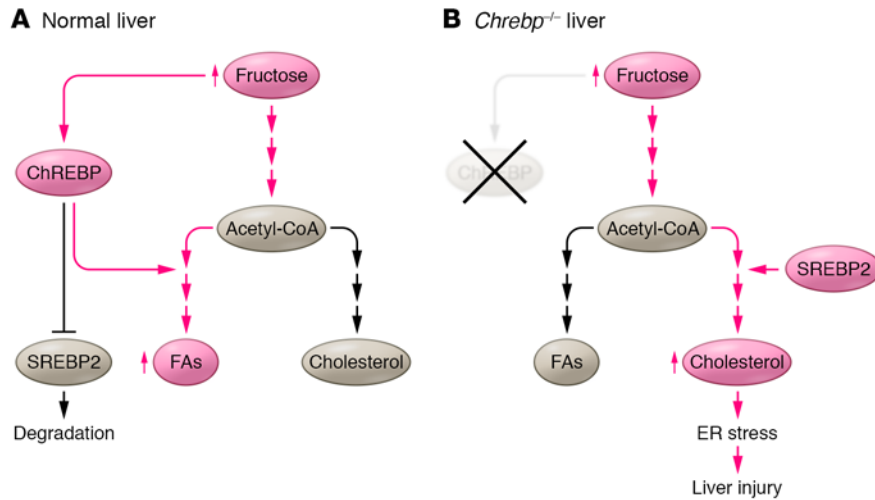


Figure 1. ChREBP senses fructose to coordinate a protective response in the liver. (A) Zhang et al. show that fructose-mediated activation of ChREBP in a normal liver results in increased DNL and promotes the degradation of SREBP2. This response is hepatoprotective, ultimately leading to an increase in hepatic triglyceride but no change in cholesterol levels. (B) On the other hand, mice lacking ChREBP do not accumulate excess triglycerides in their liver when fed a high-fructose diet. Because fatty acids and cholesterol share a common precursor, acetyl-CoA, carbon in fructose may flux toward cholesterol synthesis. Moreover, SREBP2 is activated in ChREBP-deficient hepatocytes to yield elevated hepatic cholesterol levels that predispose to maladaptive ER stress signaling, apoptosis, and hepatic injury.

ChREBP and the response to a high-fructose diet

In this issue, Zhang and colleagues (18) have demonstrated that mice fed a high-fructose diet exhibit selective induction of ChREBP, but not SREBP1c, in the liver. Moreover, as previously described, mice lacking ChREBP were protected from high-fructose diet-induced increases in FASN, SCD1, and ACC1 expression in the liver and the development of hepatic steatosis, suggesting that SREBP1c is not sufficient to mediate the adverse effects associated with a high-fructose diet. Despite being protected from liver triglyceride accumulation in response to fructose feeding, *ChREBP*^{-/-} mice had unexpected increases in liver injury and hepatocyte apoptosis. ChREBP-deficient mice showed signs of early stages of fibrosis and NASH in response to fructose, while WT mice did not.

Apoptosis and inflammation are key features of progressive NASH and are both linked to the endoplasmic reticulum (ER) stress response (19). Under conditions of severe distress, ER stress signaling activates the apoptotic signaling cascade (20). However, other components of this coordinated response actually represent adaptive responses to alleviate ER stress and are pro-survival. Zhang and colleagues found that a high-fructose diet failed to induce the adaptive arms of the ER stress response but heightened activation of the proapoptotic signaling mediators of the ER stress pathway in *ChREBP*^{-/-} mice. Notably, expression of GRP78 was reduced in fructose-fed *ChREBP*^{-/-} mice compared with expression

in WT mice fed the same diet. GRP78 is a chaperone protein that helps attenuate ER stress (21) and has not previously been linked to ChREBP signaling. On the other hand, *ChREBP*^{-/-} mice had increased activation of the protein kinase R-like endoplasmic reticulum kinase/activating transcription factor 4/C-EBP homology protein (PERK/ATF4/CHOP) pathway and induction of CHOP-mediated apoptosis on a high-fructose diet. Liver injury in fructose-fed *ChREBP*^{-/-} mice could be counteracted by adenovirus-mediated overexpression of GRP78, knockdown of CHOP, or administration of a chemical chaperone to attenuate ER stress. Together, these findings suggest that ChREBP is a fructose-responsive transcription factor that also fine-tunes the ER stress response and may promote activation of the adaptive arms in response to high-fructose concentrations, which can be a noxious stimulus.

Many lipid species are elevated in the livers of patients with NAFLD and have been implicated in the progression to NASH. Comparisons of plasma and hepatic lipid levels have revealed an increase in triglycerides, diglycerides, ceramides, other complex lipids, free fatty acids, and cholesterol in patients with NASH compared with those without NASH (22). Admittedly, many of these lipids have been linked to metabolic abnormalities and NAFLD-associated liver injury; therefore, a case can be made or argued for many of these lipids as mediators of disease. Nonetheless, studies conducted in animal models and human studies have correlated high intrahepatic free cholesterol levels with hepat-

ic inflammation, development of fibrosis, and NASH (19, 23), and the addition of high levels of cholesterol to diets fed to rodents is particularly associated with the development of hepatic fibrosis (7). Unexpectedly, Zhang et al. also determined that, while hepatic triglyceride content was reduced in *ChREBP*^{-/-} mice in response to high-fructose feeding, hepatic cholesterol content was markedly increased, coincident with increased cholesterol biosynthesis. In the livers of WT mice fed a high-fructose diet, the expression of enzymes involved in cholesterol biosynthesis was actually decreased compared with expression in those fed a control diet. In contrast, *ChREBP*^{-/-} mice failed to suppress hepatic cholesterol biosynthesis in response to a high-fructose diet; however, restoration of ChREBP expression in the livers of *ChREBP*^{-/-} mice suppressed the induction of many genes involved in cholesterol biosynthesis and reduced free cholesterol levels. In addition, suppression of cholesterol synthesis with atorvastatin attenuated liver injury in *ChREBP*^{-/-} mice. Thus, ChREBP may protect against fructose-induced liver injury, in part, by repressing cholesterol biosynthesis and cholesterol accumulation. By using a model system without high amounts of added dietary cholesterol, Zhang and colleagues provide strong new evidence that cholesterol aggregation in the liver is a trigger for liver injury and progression to NASH.

Zhang and colleagues also demonstrated that ChREBP directly interacts with SREBP2, which is the major transcriptional regulator of genes involved in hepatic

cholesterol biosynthesis, uptake, secretion, and transport. Their data suggest that ChREBP directly interacts with SREBP2 and that this interaction may promote the ubiquitination and subsequent degradation of SREBP2. This work, while quite preliminary and requiring repetition and validation without overexpression, suggests the existence of a new mechanism for regulating SREBP2 activity. The teleological or physiological reasons why this carbohydrate-responsive transcription factor would negatively regulate SREBP2 at this level remain unclear, but could represent a new mechanism of nutrient crosstalk. As both cholesterol and fatty acid synthesis require a common precursor (acetyl-CoA), it is possible that in the absence of ChREBP, some of the carbon that would have fluxed into the synthesis of new fatty acids is instead directed to flux toward cholesterol synthesis (Figure 1). This possibility will also need to be explored in future studies.

Concluding remarks

Taken with previous work, this study by Zhang et al. suggests that ChREBP plays an important protective role in the response to fructose overload. Many mechanistic questions remain unanswered in this initial report. For example, does ChREBP enhance SREBP2 ubiquitination by tethering a ubiquitin ligase to SREBP2 or by some other mechanism? Can ChREBP also regulate ubiquitination of other proteins that regulate fat metabolism, including SREBP1c, or is this effect specific to SREBP2? It also remains to be determined whether genetic variations in ChREBP may influence the response to fructose in humans or provide a potential mechanism to explain why some individuals are more likely to progress from steatosis to NASH when consuming diets rich in fructose. Identification of such a nutrient-gene interaction could provide

important insight into an individual's predisposition to develop NAFLD/NASH in a given dietary context and allow for individualized nutritional guidance.

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