HHS Public Access

Author manuscript

Hepatology. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Hepatology. 2015 October ; 62(4): 994–996. doi:10.1002/hep.27926.

ChREBP, SIRT1 and ethanol metabolism– a complicated network in alcohol-induced hepatic steatosis

Suthat Liangpunsakul, MD, MPH

Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine and Roudebush Veterans Administration Medical Center, Indianapolis, Indiana

Alcoholic liver disease (ALD) is characterized by the spectrum of liver injury ranging from steatosis, inflammation, fibrosis, and eventually cirrhosis[1]. The pathogenesis of ALD is complex involving many specific intracellular signaling pathways, transcription factors, innate immunity, and epigenetic alterations (reviewed by Gao et al[1]). The effect on these pathways could be directly from alcohol or indirectly from acetaldehyde, its metabolite, via alcohol dehydrogenase (ADH) and CYP2E1[1]. The transcription factor, sterol regulatory element-binding protein 1c (SREBP-1c), regulates lipogenic genes to control intrahepatic fatty acid synthesis[2]. Alcohol consumption increases SREBP-1c transcription via its metabolite acetaldehyde or down-regulates its suppressors, such as Sirtuin1 (SIRT1)[3, 4].

In addition to SREBP-1c, carbohydrate-responsive element-binding protein (ChREBP) is another transcription factor with a key role in glucose and lipid metabolism. ChREBP contains two nuclear export signals and one nuclear localization signal near the N-terminal, proline-rich domains, a basic helix-loop-helix leucine-zipper (b/HLH/Zip), and a leucine-zipper-like domain[5]. Transcriptional targets of ChREBP include L-pyruvate kinase (L-PK) and fatty acid synthase (FAS) which are important enzymes for the regulation of glucose and lipid metabolism respectively[5]. Activity of ChREBP can be regulated through post-translational modifications (as shown in Table 1). The importance of ChREBP in the pathophysiology of hepatic steatosis in non-alcoholic fatty liver disease has been described[5]; however, its role in the pathogenesis of ALD is not yet clear.

In this issue of HEPATOLOGY, Marmier et al. report a novel finding of the ChREBP/SIRT1/ADH axis in the control of alcohol metabolism and pathobiology of alcohol-induced hepatic steatosis in mice using a ‘binge drinking’ model[6]. In contrast to chronic alcohol drinking, which induces ChREBP activity through dephosphorylation[7], binge drinking induces ChREBP through acetylation[6]. Acetylated ChREBP binds to the SIRT1 promoter and suppresses its transcription; this represents a unique mechanism by which alcohol can inhibit SIRT1. The involvement of ChREBP in alcohol-induced hepatic steatosis was confirmed by Marmier et al. with ‘loss of function’ experiments, wherein silencing ChREBP prevents intrahepatic triglyceride accumulation. They also found that acetaldehyde is the

Corresponding Author: Suthat Liangpunsakul, MD MPH, Associate Professor of Medicine and Public Health, Division of Gastroenterology and Hepatology, 550 N. University Blvd, UH 4100, Indianapolis, IN 46202. Phone: (317) 278-1630; Fax: (317) 988-3180; sliangpu@iupui.edu.

Conflict of interest: The author did not have anything to disclose regarding the conflict of interest with respect to this manuscript

precursor for acetate and acetyl-CoA, the source of the acetyl group incorporated on ChREBP[6]. When alcohol-mediated induction of ADH activity is blocked by 4-methylpyrazole, ChREBP acetylation and the expression of its downstream lipogenic genes are reduced.

While the findings of Marmier et al. suggest that CHREBP might be an attractive therapeutic target for ALD, the authors observed a high mortality rate in mice lacking ChREBP during multiple gavages of alcohol due to hypothermia and hypoglycemia. These mice had high blood alcohol levels, but reduced hepatic concentrations of alcohol metabolites, acetaldehyde, acetate and acetyl-CoA, suggesting that alcohol metabolism was inhibited in ChREBP-silenced mice. To further elucidate the mechanism, the authors found that ADH can be regulated by SIRT1 through deacetylation[6]. Silencing ChREBP decreased ADH acetylation and its enzymatic activity through the activation of SIRT1[6]. Their discovery helps to explain the phenotype of alcohol intoxication in ChREBP-silenced mice following binge alcohol drinking.

A few observations from this study deserve further discussion. First, the blood alcohol kinetics after alcohol gavage are different from a previous report[8]. After gavage (at a dose of alcohol ~3–6 g/kg), alcohol is rapidly absorbed and blood alcohol concentration (BAC) peaks within 1–2 hr(s) and reduces to almost undetectable levels by 8–10 hrs[8]. Marmier et al. observed the peak of BAC at ~8–10 hrs, a peculiarly delayed BAC kinetics, with no clear explanation. Second, alcohol intoxication, especially in an undernourished or fasting person, can cause hypoglycemia; presumably from the inhibitory effects of alcohol on hepatic gluconeogenesis, when hepatic glycogen is depleted[9]. In such a situation, the liver simply cannot handle the reducing equivalents ($NADH^+$) provided by alcohol metabolism, through ADH, fast enough to prevent metabolic derangements. The excess in $NADH^+$ blocks the conversion of lactate to glucose, leading to hypoglycemia[9]. Paradoxically, Marmier et al. instead found profound hypoglycemia in mice lacking ChREBP[6], while ADH was inactivated; thus reducing alcohol metabolism and lowering the level of $NADH^+$. Previous metabolite and enzyme activity analyses revealed that the hepatic pyruvate level, the substrate for gluconeogenesis, in ChREBP-silenced mice is significantly lower compared to the wild-type counterparts because of the decreased hepatic glycolysis in response to an 80% reduction in L-PK activity[10]. The status of hepatic pyruvate and glycogen, which were not examined, may therefore contribute to the hypoglycemia in this study.

Previous studies have shown that ADH genes are primarily regulated through transcription factors (such as C/EBPα, HNF-1) binding to the proximal promoters at cis-acting elements[11]. Marmier et al. are first to demonstrate that ADH can be regulated through deacetylation by SIRT1[6]. The finding provides additional mechanistic insight into the role of SIRT1 on alcohol metabolism and in the pathogenesis of ALD. It also provides us a new perspective when considering SIRT1 as a therapeutic target for ALD. You et al. have shown that chronic alcohol exposure inhibits SIRT1, through miR-217/lipin 1, which leads to an increase in the acetylated form of SREBP-1c and activation of lipogenic genes[3, 4, 12]. Decreasing SIRT1 may also activate ADH through acetylation and increase the levels of acetylated ChREBP[6]. This, by itself, could directly activate lipogenesis or further inhibit SIRT1, leading to a vicious cycle which eventually aggravates the progression of ALD

(Figure 1). The connection among SIRT1, ADH acetylation associated with its kinetics/activity, and alcohol metabolism should therefore be further dissected in SIRT1 knockout mice treated with alcohol.

Activating SIRT1 can de-acetylate ADH and increase the risk of alcohol intoxication through the inhibition of alcohol metabolism[6]. This is the 'yin and yang' dilemma of using SIRT1 activators, such as resveratrol, in ALD treatment, as it may have differential effects depending on the patterns of alcohol consumption. In chronic drinkers, resveratrol might provide the benefit in the reduction of hepatic steatosis, as previously shown in mice chronically fed alcohol for 4 weeks[12]. In this scenario, BAC is likely not exceedingly high, and alcohol can still be metabolized due to the low Km of ADH enzymes for alcohol (particularly in Caucasian populations)[13], even when ADH activity is partially inhibited by resveratrol. However, in those with chronic plus binge drinking, resveratrol might lead to alcohol intoxication, because the reduction in ADH activity may be insufficient to metabolize a surge in blood alcohol levels during a binge episode. Clearly, future experiments are needed to test these assumptions. Lastly, this study raises some concerns in targeting acetaldehyde for the treatment of ALD. While previous report suggests that increased acetaldehyde clearance by activation of its catalytic enzyme aldehyde dehydrogenase2 (ALDH2) attenuates hepatic steatosis[14], paradoxical increase in hepatic lipogenesis may be observed, particularly in binge drinkers, if acetaldehyde metabolites feed forward to activate ChREBP (Fig 1).

In summary, Marmier et al[6] described the novel role of the ChREBP/SIRT1/ADH pathway in the control of alcohol and lipid metabolism. However, further detailed studies are needed to identify the location of the acetylated lysine residues on ADH and to confirm whether ADH activity is regulated by acetylation. Finally, the effect of SIRT1 activator on ADH activity, alcohol pharmacokinetics, ChREBP, and hepatic lipogenesis in vivo using different alcohol feeding models should be carefully determined. This may provide profound insights into the roles of this intricate pathway in the pathogenesis of ALD.

List of Abbreviations

ALD	alcoholic liver disease
ADH	alcohol dehydrogenase
ALDH	aldehyde dehydrogenase
BAC	blood alcohol concentration
C/EBP	CCAAT-enhancer-binding proteins
ChREBP	Carbohydrate-responsive element-binding protein
CYP2E1	cytochrome P450 2E1 enzyme
FAS	fatty acid synthase
HAT	histone acetyl-transferase
HNF1	hepatocyte nuclear factor1

Km	Michaelis constant
L-PK	L-pyruvate kinase
SREBP-1c	sterol regulatory element-binding protein 1c
SIRT1	silent mating type information regulation 2 homolog 1

Reference List

1. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011; 141(5):1572–1585. [PubMed: 21920463]
2. You M, Fischer M, Deeg MA, Crabb DW. Ethanol induces fatty acid synthesis pathways by activation of sterol regulatory element-binding protein (SREBP). J Biol Chem. 2002; 277(32): 29342–29347. [PubMed: 12036955]
3. Yin H, Hu M, Zhang R, Shen Z, Flatow L, You M. MicroRNA-217 promotes ethanol-induced fat accumulation in hepatocytes by down-regulating SIRT1. J Biol Chem. 2012; 287(13):9817–9826. [PubMed: 22308024]
4. Yin H, Hu M, Liang X, et al. Deletion of SIRT1 from hepatocytes in mice disrupts lipin-1 signaling and aggravates alcoholic fatty liver. Gastroenterology. 2014; 146(3):801–811. [PubMed: 24262277]
5. Xu X, So JS, Park JG, Lee AH. Transcriptional control of hepatic lipid metabolism by SREBP and ChREBP. Semin Liver Dis. 2013; 33(4):301–311. [PubMed: 24222088]
6. Marmier S, Dentin R, Daujat-Chavanieu M, et al. Novel role for ChREBP in the control of ethanol metabolism and susceptibility to binge drinking. Hepatology. 2015
7. Liangpunsakul S, Ross RA, Crabb DW. Activation of carbohydrate response element-binding protein by ethanol. J Investig Med. 2013; 61(2):270–277.
8. Carson EJ, Pruett SB. Development and characterization of a binge drinking model in mice for evaluation of the immunological effects of ethanol. Alcohol Clin Exp Res. 1996; 20(1):132–138. [PubMed: 8651442]
9. Harris, RA. Carbohydrate metabolism. In: Devlin, T., editor. Textbook of Biochemistry with Clinical Correlations. 6th. 2006. p. 581-635.
10. Burgess SC, Iizuka K, Jeoung NH, et al. Carbohydrate-response element-binding protein deletion alters substrate utilization producing an energy-deficient liver. J Biol Chem. 2008; 283(3):1670–1678. [PubMed: 18042547]
11. Edenberg HJ. Regulation of the mammalian alcohol dehydrogenase genes. Prog Nucleic Acid Res Mol Biol. 2000; 64:295–341. [PubMed: 10697413]
12. Ajmo JM, Liang X, Rogers CQ, Pennock B, You M. Resveratrol alleviates alcoholic fatty liver in mice. Am J Physiol Gastrointest Liver Physiol. 2008; 295(4):G833–G842. [PubMed: 18755807]
13. Crabb DW, Matsumoto M, Chang D, You M. Overview of the role of alcohol dehydrogenase and aldehyde dehydrogenase and their variants in the genesis of alcohol-related pathology. Proc Nutr Soc. 2004; 63(1):49–63. [PubMed: 15099407]
14. Zhong W, Zhang W, Li Q, et al. Pharmacological activation of aldehyde dehydrogenase 2 by Alda-1 reverses alcohol-induced hepatic steatosis and cell death in mice. J Hepatol. 2014
15. Kabashima T, Kawaguchi T, Wadzinski BE, Uyeda K. Xylulose 5-phosphate mediates glucose-induced lipogenesis by xylulose 5-phosphate-activated protein phosphatase in rat liver. Proc Natl Acad Sci U S A. 2003; 100(9):5107–5112. [PubMed: 12684532]
16. Bricambert J, Miranda J, Benhamed F, Girard J, Postic C, Dentin R. Salt-inducible kinase 2 links transcriptional coactivator p300 phosphorylation to the prevention of ChREBP-dependent hepatic steatosis in mice. J Clin Invest. 2010; 120(12):4316–4331. [PubMed: 21084751]
17. Guinez C, Filhoulaud G, Rayah-Benhamed F, et al. O-GlcNAcylation increases ChREBP protein content and transcriptional activity in the liver. Diabetes. 2011; 60(5):1399–1413. [PubMed: 21471514]

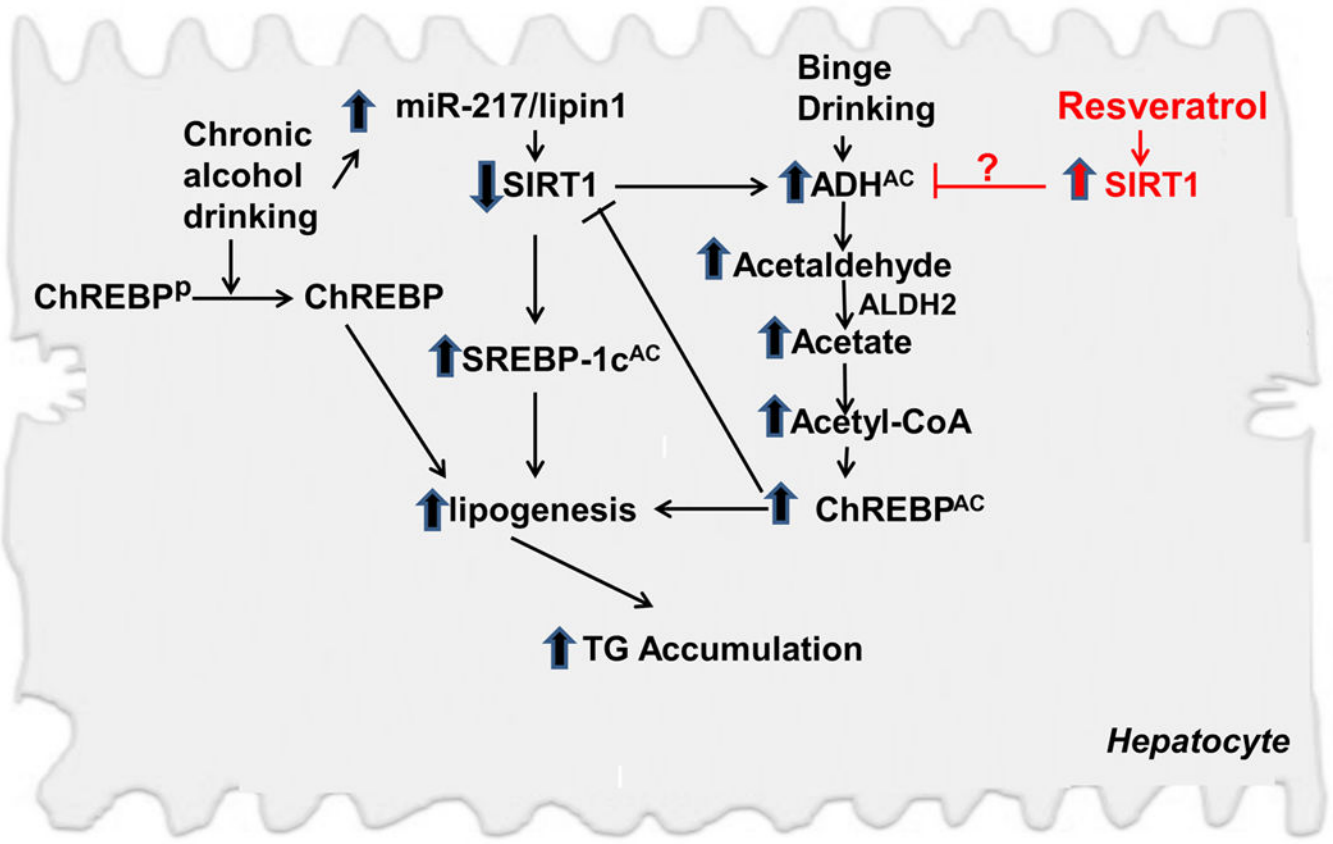

Fig 1. Complex mechanisms and the interplay of ChREBP, SIRT1, and ADH in the regulation of alcohol and lipid metabolism in hepatocytes

The regulation of SIRT1 and ChREBP by alcohol depends on the drinking pattern. Chronic alcohol drinking inhibits SIRT1, through miR-217/lipin 1, which leads to an increase in the acetylated form of SREBP-1c and activation of lipogenic genes[3, 4, 12]. In contrast to chronic alcohol drinking, which induces ChREBP activity through dephosphorylation[7], binge drinking induces ChREBP through acetylation[6]. Acetylated-ChREBP (ChREBP^{AC}) binds to the SIRT1 promoter and inhibits its activity. A decrease in SIRT1 activity is proposed to activate ADH activity through increased acetylation. This results in the acceleration of alcohol metabolism, increasing intrahepatic acetaldehyde, and ChREBP^{AC}. ChREBP^{AC} can directly activate lipogenic genes or further inhibit SIRT1, leading to a vicious cycles which eventually aggravate the progression of ALD in binge drinkers. Activating SIRT1 with compound such as resveratrol can de-acetylate ADH and increase the risk of alcohol intoxication through the inhibition of alcohol metabolism, as shown in red[6]. This leads to the therapeutic dilemma of using SIRT1 activators as the therapeutic potential for the treatment of ALD, especially in binge drinkers.

Table 1

Post-translational modifications regulating the activity of ChREBP

Enzyme	Mechanism	Activity	Outcomes
cAMP-dependent protein kinase (protein kinase A)[15]	Phosphorylation at Ser-196 and Thr-666 of ChREBP protein	Decrease	Inactivation of nuclear translocation and DNA binding activity
Protein phosphatase 2A[15]	Dephosphorylation at Ser-196 and Thr-666 of ChREBP protein	Increase	Activation of nuclear translocation and DNA binding activity of its target genes
histone acetyltransfer-ase (HAT) coactivator p300[16]	Acetylation of ChREBP at Lys672	Increase	Enhancing the recruitment of ChREBP to its target gene promoters
O-GlcNAc transferase[17]	O-GlcNAcylation at serine/threonine residues of ChREBP protein	Increase	Stabilizing the ChREBP protein and increasing its transcriptional activity