Review Article

Sirtuin 1 signaling and alcoholic fatty liver disease

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Abstract: Alcoholic fatty liver disease (AFLD) is one of the most prevalent forms of liver disease worldwide and can progress to inflammation (hepatitis), fibrosis/cirrhosis, and ultimately lead to end stage liver injury. The mechanisms, by which ethanol consumption leads to AFLD, are complicated and multiple, and remain incompletely understood. Nevertheless, understanding its pathogenesis will facilitate the development of effective pharmacological or nutritional therapies for treating human AFLD. Chronic ethanol consumption causes steatosis and inflammation in rodents or humans by disturbing several important hepatic transcriptional regulators, including AMP-activated kinase (AMPK), lipin-1, sterol regulatory element binding protein 1 (SREBP-1), PPARγ co-activator-1α (PGC-1α), and nuclear transcription factor-κB (NF-κB). Remarkably, the effects of ethanol on these regulators are mediated in whole or in part by inhibition of a central signaling molecule, sirtuin 1 (SIRT1), which is a nicotinamide adenine dinucleotide (NAD^+, NADH)-dependent class III protein deacetylase. In recent years, SIRT1 has emerged as a pivotal molecule controlling the pathways of hepatic lipid metabolism, inflammatory responses and in the development of AFLD in rodents and in humans. Ethanol-mediated SIRT1 inhibition suppresses or stimulates the activities of above described transcriptional regulators and co-regulators, thereby deregulating diverse lipid metabolism and inflammatory response pathways including lipogenesis, fatty acid β-oxidation, lipoprotein uptake and secretion and expression of pro-inflammatory cytokines in the liver. This review aims to highlight our current understanding of SIRT1 regulatory mechanisms and its response to ethanol-induced toxicity, thus, affirming significant role of SIRT1 signaling in the development of AFLD.

Keywords: Sirtuin 1 (SIRT1); alcoholic fatty liver; lipid metabolism; inflammation; transcriptional regulators; signal transduction

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Role of sirtuin 1 (SIRT1) in alcoholic fatty liver disease (AFLD)

SIRT1 is a nicotinamide adenine dinucleotide (NAD^+, NADH)-dependent class III histone deacetylase and acts as part of the deacetylation reaction, producing nicotinamide (NAM, vitamin B3) and acetyl-ADP-ribose (1-5). Liver is one of the key organs where SIRT1 plays a pivotal role in the regulation of lipid metabolism and inflammation by modifying the acetylation status of various target molecules, including histones, transcriptional regulators, and its co-regulators (1-5).

In human, chronic or acute alcohol intoxication is commonly associated with several forms of liver injuries, including excess accumulation of fat within the liver (steatosis), inflammation (hepatitis), fibrosis/cirrhosis, cancer, and can eventually cause liver failure (6). Considerable evidences from rodent and human studies demonstrate that disruption of the hepatic SIRT1 signaling by ethanol plays a central role in the development of AFLD (7-21). Ethanol down-regulates SIRT1 in hepatic cells and in animal liver. The ethanol-mediated disruption of SIRT1 signaling leads to excess fat accumulation and inflammatory responses in the liver of animals and humans. Treatment with resveratrol, a known SIRT1 agonist, can alleviate liver steatosis and normalize elevated levels of serum alanine

aminotransferase (ALT), which is a marker of liver injury, in chronically ethanol-fed mice (10,22). Stimulating SIRT1 activity by SIRT1wt overexpression in hepatocytes prevents fat accumulation in a cellular model of alcoholic steatosis (20). Genetic specific ablation of liver SIRT1 [liver specific knockout (Sirt1LKO) mice] is associated with rapid onset and progression of steatosis and inflammation in response to chronic-binge ethanol challenge (20). Strikingly, ethanol-administrated Sirt1LKO mice partially progressed from fatty liver to mild fibrotic liver (20). These findings suggest an essential role of SIRT1 signaling in AFLD.

Nutritional or pharmacological modification of SIRT1 prevents AFLD in animals

Growing evidence has demonstrated that stimulation of hepatic SIRT1 signaling by nutritional or pharmacological intervention protects against the development of AFLD in rodents. Treatment with resveratrol, a dietary polyphenol found in grapes, red wines and berries, stimulated SIRT1 signaling and alleviated alcoholic liver steatosis in mice (10). Consumption of high dietary content of saturated fatty acids, via up-regulation of SIRT1, protected against the development of liver steatosis in mice fed with ethanol (9,14). Supplementation of ethanol-containing diets with a peroxisome proliferator-activated receptor γ (PPARγ) agonist, rosiglitazone, attenuated hepatic lipid accumulation in mice by turning on SIRT1 signaling via inducing adiponectin, which is one of the adipocyte-derived hormones (13). Supplement of salvianolic acid B, an antioxidant isolated from the traditional Chinese medical herb Salvia miltiorrhiza, ameliorated acute alcohol-induced liver injury through modulating SIRT1-p53 axis in rats (21). These findings suggest that novel strategies to stimulate hepatic SIRT1 activity may serve as potential therapies for treating human AFLD.

Ethanol disrupts hepatic SIRT1 signaling

The molecular mechanisms of ethanol-mediated disruption of SIRT1 signaling and subsequent development of liver steatosis, inflammation, and mild fibrosis are still not fully understood. However, accumulating evidence demonstrates that ethanol-mediated SIRT1 inhibition leads to development of AFLD largely through disruption of a signaling network mediated by various transcriptional regulators and co-regulators, including AMP-activated kinase (AMPK), sterol regulatory element-binding protein 1 (SREBP-1), peroxisome proliferator-activated receptor α (PPARα), PPARγ co-activator-1α (PGC-1α), lipin-1, forkhead transcription factor O1 (FoxO1), β-catenin, nuclear transcription factor-κB (NF-κB), and nuclear factor activated T cells c4 (NFATc4) (*Figure 1*). Disruption of this signaling network by ethanol via SIRT1 inhibition ultimately leads to steatosis and over production of inflammatory cytokines in liver (7-21).

SIRT1-AMPK signaling system and AFLD

Ethanol-mediated dysregulation of hepatic AMPK, a vital lipid regulator, is one of the major mechanisms for AFLD (10,13,19,23-31). Hepatic AMPK inhibition induced by ethanol exposure leads to stimulated acetyl-CoA carboxylase (ACC), resulting in an induction of malonyl-CoA, which is a precursor for biosynthesis of fatty acids, and suppression of carnitine palmitoytransferase I (CPT-I), the enzyme that controls the transfer of long-chain fatty acyl-CoA into mitochondria. Ethanol-mediated impairment of AMPK signaling promotes lipid accumulation and halts lipid catabolism, which ultimately causes the development of AFLD in animals.

Accumulating evidences suggest that SIRT1 and AMPK regulate each other, share similar signaling pathways, and modulate many common targets (32). Studies in cultured hepatic cells and in animal liver have provided evidence that SIRT1 is able to stimulate AMPK activity via modulation of liver kinase B1 (LKB1), an upstream AMPK kinase (33,34). On the other hand, activation of AMPK via LKB-1 leads to increased cellular NAD^+ levels, which subsequently activates SIRT1 signaling (35,36). Thus, this unique SIRT1-AMPK axis participates in regulating various lipid metabolism and inflammation pathways (32-36).

Resveratrol, a known agonist of both SIRT1 and AMPK, exerts its protective action against AFLD by turning on the hepatic SIRT1-AMPK axis in mice (10). An adipocyte-derived hormone, adiponectin, alleviates steatohepatitis largely by stimulating hepatic SIRT1-AMPK axis in both cellular and animal models of AFLD (13,25). Thus, deregulation of SIRT1-AMPK axis by ethanol represents an attractive hypothesis of impaired central upstream signaling system for AFLD.

SIRT1-SREBP-1 axis and AFLD

Activation of SREBP-1 by ethanol is pivotal to pathogenesis of AFLD. Increase in hepatic SREBP-1c activity has been found in various alcoholic steatosis models including

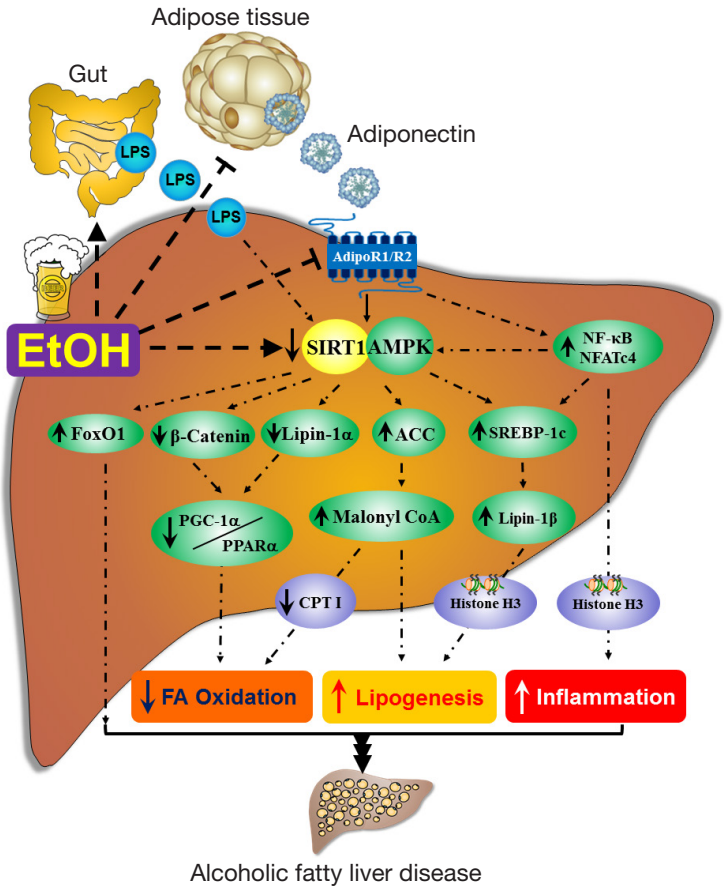

Figure 1 Proposed role of SIRT1 in the pathogenesis of alcoholic fatty liver. Ethanol-mediated SIRT1 inhibition and SIRT1 dysfunction may cause hyperacetylation of a set of molecules including histone H3, AMPK, SREBP-1, lipin-1, PGC-1α, PPARα, FoxO1, β-catenin, NF-κB or NFATc4 in the liver. The net effects of ethanol subsequently activate lipogenic pathways, inhibit fatty acid oxidation pathways, reduce fat mobilization, and induce inflammatory response and cause development of AFLD. AdipoR, adiponectin receptor; AMPK, AMP-activated kinase; ACC, acetyl-coenzyme A carboxylase; CPTI, carnitine palmitoyltransferase I; FoxO1, forkhead transcription factor O1; LPS, lipopolysaccharide; NF-κB, nuclear transcription factor-κB; NFATc4, nuclear factor activated T cells c4; SREBP-1c, sterol regulatory element-binding protein 1c; PGC-1α, peroxisome proliferator-activated receptor γ co-activator-alpha; PPARα, peroxisome proliferator-activated receptor alpha; SIRT1, sirtuin 1.

cultured hepatocytes, zebrafish, mice or micropig (9,10,25,27,37-44). Both acute and chronic ethanol exposure stimulated SREBP-1 activity and increased the gene and protein expression of a panel of SREBP-1-regulated enzymes including fatty acid synthase (FAS), stearoyl-CoA desaturase (SCD), mitochondrial glycerol-3-phosphate acyltransferase 1 (GPAT1), malic enzyme (ME), ATP citrate lyase (ACL), and ACC, and led to hepatic excessive lipid accumulation. More importantly, SREBP-1 knockout mice were completely protected from AFLD, indicating a causal involvement of SREBP-1 in AFLD (41). On the contrary, the development of alcoholic liver steatosis was also observed in the model of suppressed SREBP-1c signaling in rats, implying that the effects of ethanol on SREBP-1 might vary with species (45,46).

Several line of evidence demonstrates the interplay between SIRT1 and SREBP-1 (7,47,48). SREBP-1c protein stability and activity were dynamically regulated by reversible acetylation via histone acetyltransferase (HAT), CBP/p300, and SIRT1. SIRT1 regulates SREBP-1c activity by deacetylating SREBP-1c and by inhibiting its transcriptional activity, resulting in transcriptional repression of the SREBP-1c-targeted lipogenic enzymes such as FAS, SCD, GPAT1, ME, ACL, and ACC in

cultured hepatocytes and mouse liver (7,47,48). The acetylation level of SREBP-1 was highly elevated in hepatic cells exposed to ethanol or ethanol-fed mice. Inhibition of SIRT1 activity by ethanol feeding was associated with an increase in the acetylated active nuclear form of SREBP-1c, and consequently leads to the development of steatosis (7). More importantly, overexpression of SIRT1wt or treatment with resveratrol alleviated AFLD by reducing the ethanol-induced increases in SREBP-1c hyperacetylation levels and SREBP-1 activity (7,10). Therefore, the ability of ethanol to modulate SIRT1-SREBP-1c axis has been proposed as one of the underlying mechanisms linking ethanol exposure with hepatic lipogenic gene expression and AFLD development. Interestingly, ethanol-mediated SREBP-1 activation is partially mediated via AMPK inhibition, suggesting the regulation of SREBP-1 activity by SIRT1 either via AMPK dependent- or independent-mechanisms in the development of AFLD (23).

SIRT1-PGC-1α/PPARα axis and AFLD

PGC-1α is a prominent transcriptional regulator of lipid metabolism. SIRT1 directly interacts with, and deacetylates PGC-1α, which subsequently modulates PGC-1α activity (49-51). SIRT1 has been identified as a functional regulator of PGC-1α that activates a metabolic gene transcription program of mitochondrial fatty acid oxidation. Interestingly, the acetylation status of PGC-1α is generally considered as an *in vivo* marker of SIRT1 activity (50,51).

The role of PGC-1α in the development of AFLD in rodents has been unequivocally established (7,9,10,13,14,19,20,52,53). Severely reduced hepatic *PGC-1α* gene and protein expression occurred consistently in ethanol-fed mice. Moreover, ethanol administration to mice significantly increased the ratio of acetylated PGC-1α to total PGC-1α protein in mouse livers (7,9,10). We have recently found that removal of hepatic lipin-1 from mice augmented the ethanol-induced impairment of hepatic fatty acid oxidation and lipoprotein production, largely by deactivating hepatic PGC-1α (53).

PGC-1α co-activates with PPARα to induce expression of mitochondrial fatty acid oxidation enzymes (50). SIRT1 regulates lipid homeostasis by positively regulating PPARα (1,50). Hepatocyte-specific deletion of SIRT1 disturbs PPARα signaling, reduces fatty acid oxidation, and causes aggravated liver steatosis and inflammation. Impairments of both PGC-1α and PPARα have been implicated in the development of AFLD in animals (13,19,45,52-61). Therefore, it is likely that disruption of SIRT1-PGC-1α/PPARα axis by ethanol may act as one of the main triggers of AFLD.

SIRT1-lipin-1 axis and AFLD

Lipin-1, a mammalian Mg^{2+}-dependent phosphatidate phosphatase (PAP), is a protein that has dual functions as a PAP in the triglyceride synthesis pathway and as a transcriptional co-activator to promote fat oxidation and suppress *de novo* lipogenesis (62). The gene encoding lipin-1 (*LPIN1*) was originally identified though positional cloning of the mutant gene underlying lipodystrophy in the fatty liver dystrophy (*fld*) mouse (63). In the liver, two major lipin-1 protein isoforms (both containing a putative nuclear localization signal) are generated through alternative mRNA splicing of an internal exon within the *LPIN1*, namely, lipin-1α (891 amino acids), and lipin-1β (924 amino acids) (64).

In cultured hepatocytes, lipin-1α is predominantly located in the nucleus, whereas lipin-1β is primarily located in the cytoplasm (64). In the cytoplasm, lipin-1β-mediated PAP enzyme converts phosphatidate (PA) to diacylglycerol (DAG). The resulting DAG serves as substrate for the synthesis of TG as well as phosphatidylcholine (PC) and phosphatidylethanolamine (PE) (64). The lipin-1β is also associated with increased expression of lipogenic genes, and excessive hepatic fat accumulation in animals (64). In the nucleus, lipin-1α protein directly interacts with several nuclear receptors such as PGC-1α, PPARα and SREBP-1 and functions as a transcriptional co-activator to either stimulate the expression of mitochondrial genes involved in fatty acid oxidation or suppress the expression of lipogenic genes involved in lipogenesis (65-67). A splicing factor, namely, SFRS10 (official gene name, TRA2B), emerges as an important modulator of alternative splicing of *LPIN1* (68,69). The effects of reduced SFRS10 on *LPIN1* splicing, thereby favoring the *LPIN1β* isoform, have been shown to be sufficient to increase expression of lipogenic genes, activate lipogenesis, and cause excessive fat accumulation in the livers of high-fat-fed mice and in obese humans (68).

Ethanol-mediated dysregulation of hepatic lipin-1 function contributes to the abnormalities in hepatic lipid metabolism associated with AFLD (13,17,19,20,27,54,65,66,70). The development of AFLD in rodents and in humans is associated with significantly increased total hepatic lipin-1 gene expression and lipin-1-mediated PAP activity (27,65,66,70). More importantly, while ethanol induces the cytoplasmic pro-lipogenic activity of lipin-1, lipin-1 nuclear entry is

attenuated by ethanol exposure in cultured hepatocytes and in mouse livers (27). The net consequence of these ethanol-mediated effects on lipin-1 can enhance *de novo* lipogenesis and inhibit fatty acid, ultimately leading to development of liver steatosis.

Intriguingly, the AMPK-SREBP axis is found to be involved in the regulation of total lipin-1 gene expression induced by ethanol (27,71). Additionally, ethanol feeding to mice significantly increased acetylation level of hepatic lipin-1, while at the same time markedly increased its SUMOylation levels (27). The SUMOylation of lipin-1α is needed for its nuclear localization and co-regulator activity toward PGC-1α (72). Attenuated lipin-1 nuclear entry in response to ethanol challenge may be mediated through disturbing the interplay between acetylation/SUMOylation modifications of lipin-1 that eventually disrupts lipin-1 signaling.

Interestingly, ethanol exposure also markedly elevated the ratio of hepatic *Lpin1β/α* via SFRS10 suppression in cultured hepatocytes and in mice (17,19,20). Consistently, hepatic SIRT1 deficiency significantly augmented the ethanol-mediated increase of *Lpin1β/α* via SFRS10, implying that ethanol-mediated SIRT1 inhibition might reduce hepatic SFRS10 in mice (20). Indeed, while incubation of AML-12 hepatocytes with ethanol increased intracellular lipid accumulation, this fat accumulation was largely reversed when AML-12 cells were transfected with SIRT1wt or SFRS10wt, via blocking the ability of ethanol to increase the ratio of *Lpin1β/α* (20). These findings clearly suggest a causal role of SIRT1-SFRS10-lipin-1 axis in the development of alcoholic steatosis in mice. Paralleling these findings in mice, similar changes in mRNA levels of SIRT1, lipin-1α or SFRS10 were all found in liver samples from patients with alcoholic hepatitis (20). The precise mechanism by which SIRT1 regulates *SFRS10* gene and protein expression in the livers of ethanol-fed mice remains to be elucidated.

SIRT1-FoxO1 signaling and AFLD

FoxO1 has been established as a key player in the regulation of various pathways involved in lipid metabolism and oxidative stress response (73). FoxO1 activity is regulated by changes in its subcellular localization in association with its post-translational modifications, including acetylation/deacetylation (73,74). SIRT1 deacetylates the lysine residues within the FoxO1 DNA binding domain, and promotes nuclear retention of FoxO1 by either increasing or decreasing its transcriptional activity (73). Ethanol administration increases the acetylation of FoxO1, and subsequently downregulates nuclear FoxO1 protein in the livers of ethanol-fed mice (14,75). These observations clearly link an impaired liver SIRT1-FoxO1 axis with AFLD in mice.

Acute ethanol induces autophagy and partly reduces ethanol-induced liver injury (76). FoxO3a, another member of the FoxO family of transcription factors, is a vital molecule in regulating alcohol-induced autophagy and cell survival (76). Resveratrol-mediated SIRT1 activation further enhances ethanol-induced expression of autophagy-related genes, most likely by increasing deacetylation of FoxO3a, thus suggesting an involvement of SIRT1-FoxO3 axis in the ethanol action (76).

SIRT1-mediated histone H3 deacetylation and AFLD

SIRT1 can regulate gene expression by directly regulating histones. Although substrate specificity of SIRT1 has not been rigorously defined, mouse SIRT1 has been demonstrated to deacetylate histones with a preference for histone H3 at lysine 9 (Lys 9) and histone H4 at lysine 16 (Lys16) (77,78).

Chronic ethanol exposure has been shown to drastically and selectively increase acetylation of histone H3-Lys9 both *in vitro* and in animal liver (9,13,27,79-83). Conceivably, Histone H3-Lys9 deacetylation may occur at a significantly slower rate as a result of SIRT1 inhibition, thereby causing hyperacetylation of histone H3-Lys9 in the liver of ethanol-challenged animals. Intriguingly, activation of hepatic SREBP-1-lipin-1 axis by ethanol is also accompanied by its association with dramatically increased acetylated histone H3-lys9, suggesting that the SIRT1-histone H3 axis may regulate the expression of genes encoding lipogenic enzymes via SREBP-1-lipin-1 axis (72). Moreover, the protective effects of a diet high in saturated fatty acids against AFLD occur partially via the hepatic SIRT1-SREBP-1-histone H3-Lys9 axis, suppressing the expression of genes encoding lipogenic enzymes and slowing the synthesis of hepatic fatty acids (9).

It is worthwhile to note that SIRT1 directly deacetylates and represses the activity of acetyltransferase p300/CBP (84). Therefore, it is logical to speculate that ethanol may indirectly activate CBP/p300 through its inhibition on SIRT1, causing further hyperacetylation of various hepatic target proteins.

SIRT1-Wnt/β-catenin signaling and AFLD

Aberrant Wnt/β-catenin is a critical contributor to several

forms of liver injury, including liver degeneration, liver cancer and alcoholic liver disease (16,85). The livers of acute ethanol-challenged β-catenin-deficient (β-catenin KO) mice displayed redox imbalance, impaired PPARα-mediated mitochondrial fatty acid oxidation and severe liver steatosis (16). Further mechanistic studies revealed, in the absence of β-catenin, there were significant decreases in SIRT1 mRNA and protein levels in the livers of β-catenin KO mice following ethanol administration (16). As discussed above, SIRT1 is an established regulator of PPARα function and mitochondrial fatty acid oxidation. Therefore, hepatic Wnt/β-catenin signaling is likely associated with AFLD via modifying the SIRT1-PPARα signaling axis.

SIRT1-NF-κB axis and ethanol-mediated hepatic inflammation

SIRT1 exerts anti-inflammatory effects by deacetylation of the lysine residues on NF-κB, which is a master transcription factor involved in regulation of pro-inflammatory cytokines (1,55,86). Ethanol-mediated hepatic inflammatory response has been linked to elevated levels of gut-derived lipopolysaccharide (LPS), a major component of bacterial cell walls, and generation of major ethanol metabolites such as acetaldehyde and acetate (6). LPS or ethanol metabolites-induced overproduction of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), is a major contributor to the pathogenesis of alcoholic liver disease (6). Interestingly, LPS, acetaldehyde, or acetate significantly inhibited SIRT1 in cultured rat Kupffer cells and murine RAW 264.7 macrophages (11). Inhibition of SIRT1 by three putative agents of ALD resulted in a significant increase in the TNF-α generation, largely through disrupting SIRT1-mediated deacetylation of NF-κB in cultured macrophages (11). Consistently, ethanol administration exacerbated the inflammatory response in the livers of Sirt1LKO mice, as indicated by substantially enhanced levels of $F4/80^{+}$ staining accompanied by elevated mRNA expression levels of pro-inflammatory cytokines, including TNF-α and monocyte chemoattractant protein 1 (20).

NFATc4 is a non-nuclear receptor transcription factor involved in the regulation of pro-inflammatory cytokines such as TNF-α or IL-6 (20,53,87). NFATc4 nuclear localization and activity is generally regulated by calcineurin-mediated phosphorylation/de-phosphorylation. Ethanol administration to Sirt1LKO robustly promotes nuclear accumulation and activation of NFATc4, suggesting that SIRT1 acts as a repressor of NFATc4 activity (20). However, it remains unknown whether NFATc4 activity can be regulated by SIRT1 via acetylation/de-acetylation.

Recent evidence demonstrates that lipin-1 has potent anti-inflammatory properties (20,53,87). Lipin-1 suppressed expression of pro-inflammatory cytokines such as TNF-α by directly interaction with NFATc4 to inhibit its activity in adipocytes (87). Interestingly, liver lipin-1 ablation markedly increased the expression of pro-inflammatory cytokines via activation of both NFATc4 and NF-κB in mice fed with or without ethanol, implying a considerable interplay among NFATc4, NF-κB, and lipin-1 (53). Taken together, our laboratory has focused our attention in investigating the relationship among SIRT1, NF-κB, or NFATc4 and how SIRT1-NF-κB/NFATc4 axis is regulated by ethanol in Kupffer cells.

Adiponectin-SIRT1 axis and AFLD

Hypoadiponectinemia and altered hepatic adiponectin signaling are associated with steatosis and inflammation in several animal ALFD models such as mice, rats and micropigs (55). Stimulation of adipocytes adiponectin and hepatic adiponectin receptor (AdipoR)-mediated signaling by dietary or pharmacological manipulation largely alleviates development of AFLD in animals (55). Despite the exact mechanisms whereby ethanol affects the expression, production and secretion of adiponectin in adipose tissue remain to be elucidated, hepatic SIRT1 has emerged as one of the major mediators for adiponectin's beneficial effects on AFLD. Adipose adiponectin gene and protein expression are up-regulated by PPARγ, of which rosiglitazone is a potent agonist (13,54). Co-administration of rosiglitazone and ethanol to mice significantly increased the gene expression and circulating levels of total adiponectin and its high-molecular-weight (HMW) form (13). More importantly, these increases correlated closely with the activation of hepatic SIRT1 signaling and prevention of fatty liver in mice (13). Similarly, the resveratrol-mediated elevation of circulating adiponectin levels was associated with robust enhancement of hepatic SIRT1 protein expression and attenuation of hepatic lipid accumulation in chronically ethanol-fed mice (10). Those findings suggest that stimulated hepatic adiponectin-SIRT1 signaling partially contributed to the protective action of both rosiglitazone and resveratrol against AFLD in mice. It is important to point out that it is unlikely that the effects of ethanol on SIRT1 are mediated entirely via disrupting adiponectin signaling, as inhibitory effects of ethanol on

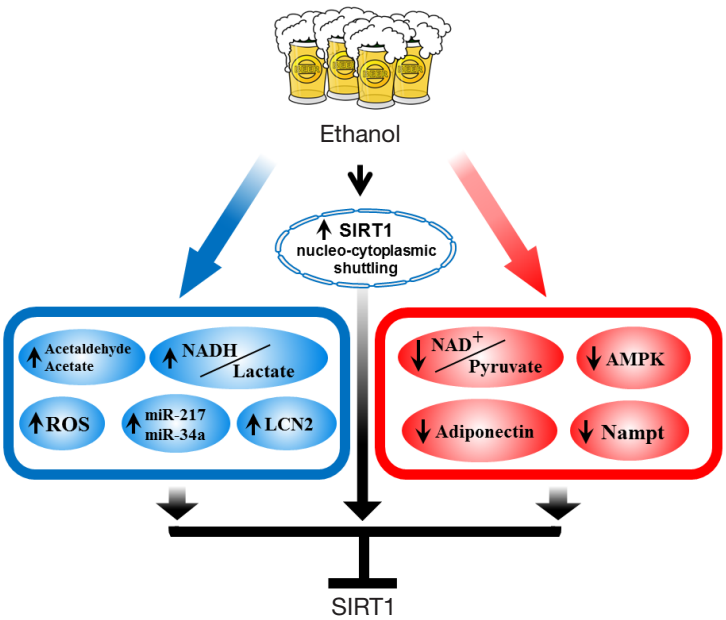

Figure 2 Proposed regulatory mechanisms of hepatic SIRT1 expression and activity in response to ethanol challenge. AMPK, AMP-activated kinase; LCN2, lipocalin 2; NAD^+ (or NADH), nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; ROS, reactive oxygen species.

SIRT1 are also observed in cultured hepatocytes, which would not be expected to be influenced by adiponectin.

Ethanol down-regulates hepatic SIRT1

Ethanol exposure (chronic, acute or chronic-binge) reduces SIRT1 gene and protein expression levels, induces SIRT1 nucleocytoplasmic shuttling, and ultimately inhibits SIRT1 deacetylase activity in the liver (7-21) (*Figure 2*). As we have discussed above, while the role of SIRT1 signaling in the development of AFLD is firmly established, yet the regulatory mechanisms of hepatic SIRT1 expression and activity in response to ethanol challenge needs to be fully elucidated.

Ethanol metabolism

Ethanol is mainly metabolized in the liver by class I (low Km) alcohol dehydrogenase (ADH) and aldehyde dehydrogenase 2 (ALDH2) enzymes, which in turn shifts the redox state, resulting in accumulation of NADH, reduction of NAD^+, a significant shift in (NAD^+)/(NADH), and elevation of the lactate/pyruvate ratio (6). Cellular redox status regulates SIRT1 expression and activity (5). Logically, ethanol metabolism-mediated redox shift favoring NADH could inhibit SIRT1 activity in liver. Moreover, in cultured macrophage cell lines, two major ethanol metabolites, acetaldehyde and acetate, also significant inhibit SIRT1 expression and activity (11).

Nicotinamide phosphoribosyltransferase (NAMPT) is a key enzyme in the salvaging pathway for the synthesis of NAD^+ (88). The enzymatic activity of NAMPT also directly reduces cellular NAM levels (89). Both of these actions of NAMPT can alter SIRT1 activity. The aberrant NAMPT signaling in the development of NAFLD has been demonstrated (90-92). Ethanol exposure may also compromise the NAMPT-mediated NAD^+ biosynthesis, leading to SIRT1 inhibition. Nevertheless, the mechanism of ethanol disruption of the NAMPT-mediated NAD^+ salvage pathway and subsequent inhibition of SIRT1 deacetylase activity will need to be further investigated.

Reactive oxygen species (ROS)

ROS inhibit SIRT1 activity and disrupt SIRT1 signaling (1,5). Overwhelming evidences indicate that oxidative stress contributes to alcoholic liver injury (6,91). Ethanol metabolism-generated oxidative stress has been proposed as a crucial contributor to the "second hit" that turned a simple liver steatosis into advanced stage liver injuries.

ROS are generated via multiple pathways in the hepatic ethanol metabolism, particularly the CYP2E1 microsomal ethanol oxidizing pathway. Ethanol metabolism-induced ROS production could be an important causative factor for the inhibition of SIRT1 by ethanol. It is also tempting to postulate that ethanol-mediated ROS production may also prolong the suppression of SIRT1 activity in the liver as the rodents adapted to chronic ethanol exposure.

Hepatic SIRT1 ablation induces oxidative stress, as demonstrated by an increase in hepatic malondialdehyde, a lipid peroxidation end product, in mice (20). The oxidative stress is further drastically exacerbated in response to ethanol administration in Sirt1LKO mice, suggesting that ethanol-mediated down regulation of SIRT1 may serve as a feedback loop to further inhibit SIRT1 via ROS generation and diminish the protective capacity of liver against oxidative stress, increasing the sensitivity of liver to stress damage (20).

The ability of LPS, acetaldehyde, or acetate to induce ROS has been demonstrated in cultured hepatic cells (11). Thus, the putative agents of AFLD may alter signaling cascades such as oxidative stress signaling that ultimately impinge on hepatic SIRT1 (11). Moreover, ethanol metabolism-induced reduction of SIRT1 activity may increase the vulnerability of liver to insults (second "hit") such as portal vein LPS or TNF-α, leading to the development of severe liver injuries.

miRNAs

A growing body of evidence suggests that aberrant expression of hepatic microRNAs (miRNAs) contributes to the development of alcoholic liver injury (92). Thus, miRNAs have been suggested as potential novel therapeutic targets for AFLD.

Recently, we have discovered that ethanol exposure drastically and specifically induced a known endogenous SIRT1 inhibitor, namely, miR-217, in AML-12 hepatocytes and in mouse livers (17). Overexpression of miR-217 in AML-12 hepatocytes promoted ethanol-mediated impairments of SIRT1 activity and SIRT1-regulated genes encoding lipogenic and fatty acid oxidation enzymes, and exacerbated alcoholic steatosis (17). Aberrant expression of miR-34a, one of known SIRT1 inhibitors, occurs in the processes that contribute to ALD progression. miR-34a is significantly elevated in ethanol-exposed hepatobiliary cell lines and in the livers of mice fed with ethanol, largely via SIRT1 inhibition (93).

There are other miRs known to regulate SIRT1 in addition to miR-217 and miR-34a (94). Their involvement in the development of AFLD will need to be further investigated. Moreover, the *in vivo* causal evidence of these miRs awaits confirmation utilizing the gain and/or loss of function approaches in mice.

Ethanol induces SIRT1 nucleocytoplasmic shuttling

SIRT1 is predominately located in the nucleus. SIRT1 activity is regulated by nucleocytoplasmic shuttling (95,96). A number of stimuli such as ROS lead to the translocation of SIRT1 from the nucleus, and disturbs SIRT1 activity (95-97). Ethanol exposure induced transport of SIRT1 from the nucleus to the cytoplasm in either cultured hepatocytes or in animal liver (14,17,19). Pre-treatment with an antioxidant, N-acetylcystine, largely prevented the ethanol-induced shuttling of SIRT1 to the cytoplasm, suggesting that ethanol-induced shuttling of SIRT1 is likely redox dependent (14).

Adiponectin

Adiponectin directly up-regulates SIRT1 in cultured hepatic cells. In cultured macrophages, treatment with mammalian globular adiponectin significantly increased SIRT1 protein levels in a dose-dependent manner (11). Although SIRT1 protein levels were significantly reduced by treatment with LPS or acetate, pre-incubation with globular adiponectin largely relieved LPS- or acetate-induced SIRT1 inhibition in cultured macrophages or Kupffer cells.

Consistently, in rat H4IIEC3 cells, full-length adiponectin significantly increased SIRT1 protein levels in a dose dependent manner (13). Knocking down both AdipoRs 1 and 2 (AdipoR1/2) completely abolished the elevation of SIRT1 by adiponectin, indicating direct involvement of adiponectin in the process (13). Moreover, the inhibition of SIRT1 by ethanol in H4IIEC3 cells was largely alleviated by treatment of adiponectin (13).

Lipocalin 2 (Lcn2)

Lcn2 [also named as SIP24/24p3 in mouse and neutrophil gelatinase-associated lipocalin (NGAL) in human], is a 25-kDa secretory small glycoprotein (98). We have recently discovered that ethanol administration elicited *Lcn2* gene up-regulation and its protein expression in the liver, which led to elevated circulating Lcn2 levels and development of AFLD in mice. Interestingly, adenovirus-mediated

overexpression of Lcn2 in the hepatocytes or mouse liver deteriorated to AFLD in correlation with inhibited SIRT1 protein expression (99).

Summary and conclusions

In recent years, SIRT1 has been gaining recognition as a central regulator signaling molecule in the pathogenesis of AFLD (7-21). Ethanol-caused SIRT1 dysfunction in the liver leads to development of steatosis and inflammation via disrupting multiple regulatory pathways of lipid metabolism and hepatocellular inflammatory processes through impairment of a signaling network involved by various vital transcriptional regulators and co-regulators as well as histones in rodents and humans (*Figures 1*,*2*).

Ample evidence demonstrates that ethanol has inhibitory effects on SIRT1 expression and on SIRT-mediated deacetylase activity (7-21). However, the precise regulatory mechanism by which ethanol inhibits SIRT1 activity and compromises SIRT1 signaling will require further elucidation. Given that SIRT1 can be regulated at multiple levels including NAD^+ levels and posttranslational modifications, it will be of great importance to examine whether and how ethanol affects acetylation, phosphorylation and SUMOylation of SIRT1, which can eventually impair SIRT1 activity. Moreover, SIRT1 activity can be modified by its interaction with other proteins. For example, DBC1 (deleted in breast cancer 1) has been identified as a negative regulator of SIRT1 (100). It would be interesting to explore the effects of ethanol on the interaction of SIRT1 and DBC1, and its relationship with AFLD. Additionally, deregulation of the intracellular localization of SIRT1 by ethanol warrants additional investigations. Exactly how ethanol interferences with the diverse regulatory mechanisms that fine-tune the activity of hepatic SIRT1 will needs to be further studied.

Further studies will be necessary to clarify the effects of ethanol or its relationship with other crucial machineries in the liver on the dynamics of the SIRT1-driven signaling regulatory networks, which ultimately cause AFLD. SIRT1 plays a pivotal role in regulating several newly emerged machineries such as circadian rhythms and autophagy (1-3). Impaired circadian rhythms and disturbed autophagy are associated with alcoholic liver injury (76,101). Therefore, it will be important to determine whether and how ethanol-mediated SIRT1 inhibition links to impairment of hepatocellular processes such as circadian rhythms or autophagy and subsequently contributes to pathogenesis of AFLD. Considerable evidences indicate mammalian target of rapamycin complex 1 (mTORC1) as a vital and central upstream regulator of SIRT1 (1-3). Ethanol activates hepatic mTORC1 activity in animal liver (19). It will be worthwhile to further characterize the functional role of mTORC1 in the development of AFLD.

In addition to SIRT1, other sirtuin family members (e.g., SIRT2-7) also play important roles in the development of AFLD (4). For example, the functions of mitochondrial sirtuins (e.g., SIRT3-5) may be compromised by ethanol, potentially resulting in the mitochondrial dysfunction observed in AFLD (6,102,103). It will be importance to investigate the interplay between SIRT1 and SIRT2-7 in the liver and how the coordination of sirtuin family member's network is disrupted by ethanol.

Finally, studies on clinical patients with AFLD are needed to translate our knowledge on SIRT1 in AFLD to human health. Undoubtedly, continued search for effective pharmacological and/or nutritional reagents for promoting hepatic SIRT1 activity or optimizing SIRT1 signaling will ultimately provide novel and effective remedies for human AFLD.

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