MINIREVIEW

Adiponectin: A Key Adipokine in Alcoholic Fatty Liver

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Alcoholic fatty liver is a major risk factor for advanced liver injuries such as steatohepatitis, fibrosis, and cirrhosis. While the underlying mechanisms are multiple, the development of alcoholic fatty liver has been attributed to a combined increase in the rate of de novo lipogenesis and a decrease in the rate of fatty acid oxidation in animal liver. Among various transcriptional regulators, the hepatic SIRT1 (sirtuin 1)-AMPK (AMPK-activated kinase) signaling system represents a central target for the action of ethanol in the liver. Adiponectin is one of the adipocyte-derived adipokines with potent lipid-lowering properties. Growing evidence has demonstrated that the development of alcoholic fatty liver is associated with reduced circulating adiponectin levels, decreased hepatic adiponectin receptor expression, and impaired hepatic adiponectin signaling. Adiponectin confers protection against alcoholic fatty liver via modulation of complex hepatic signaling pathways largely controlled by the central regulatory system, SIRT1-AMPK axis. This review aims to integrate the current research findings of ethanol-mediated dysregulation of adiponectin and its receptors and to provide a comprehensive point of view for understanding the role of adiponectin signaling in the development of alcoholic fatty liver. Exp Biol Med 234:850–859, 2009

Key words: adiponectin; adiponectin receptors; alcoholic fatty liver; lipid metabolism; transcriptional regulators; signal transduction

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Introduction

Adipokines are bioactive proteins secreted exclusively from adipocytes in response to various metabolic signals (1). Adiponectin (30 kDa) is the most abundant adipokine in circulation and is associated with a wide range of physiological benefits. At approximately 250 amino acids in length, it is comprised of an N-terminal signal-sequence, followed by a variable region, a collagen-like region, and, finally, a C-terminal globular domain. Adiponectin exists either as a full-length protein or as a fragment comprised of the C-terminal globular domain. Full-length adiponectin circulates in the serum in homomeric complexes, ranging from a low molecular weight trimeric form (LMW), to a medium molecular weight hexameric form (MMW) and a high molecular weight multimeric form (HMW). These various architectures have been shown to regulate distinct signaling pathways and mediate tissue-specific effects (2). Dysregulation of adiponectin production can lead to a wide array of liver problems, including steatosis, which is an early stage of liver injury (3–5). The critical role of adiponectin in liver steatosis has been further supported by a recent study demonstrating spontaneous hepatic steatosis in adiponectin knockout mice (6).

Clinically, alcoholic fatty liver occurs in those who consume excess amounts of alcohol and can be characterized by increased accumulation of fat in the liver. Alcoholic fatty liver can progress to more severe forms of liver injury, including steatohepatitis, fibrosis, and cirrhosis (7, 8). Over the past several years, there has been considerable progress toward understanding the molecular mechanisms that contribute to alcoholic fatty liver. Chronic ethanol exposure impairs lipid metabolism pathways mediated by crucial transcriptional regulators, including sirtuin 1 (SIRT1), AMP-activated kinase (AMPK), peroxisome proliferator-activated receptor (PPAR)-gamma coac-

tivator alpha (PGC-1alpha), PPARα, and sterol regulatory element-binding protein 1 (SREBP-1), leading to excessive accumulation of fat in liver (5, 7, 8).

Ample experimental evidence has suggested a pivotal role for adiponectin in the development of alcoholic fatty liver. Several rodent models of alcoholic liver steatosis have displayed significant decreases in concentrations of circulating adiponectin, which correlate closely with the accumulation of hepatic lipid (9–15). Replenishment of full-length, recombinant, mouse adiponectin to ethanol-fed mice depleted hepatic fat accumulation and normalized elevated levels of serum alanine aminotransferase (ALT), a marker of liver injury (9). Moreover, a number of independent studies have demonstrated that induction of adiponectin by dietary or pharmacological manipulation prevents development of alcoholic liver steatosis in several animal models (10, 13–15).

In this review, we will summarize the current knowledge of the effects of ethanol on adiponectin and its hepatic receptors and discuss the signal transduction mechanisms underlying the protective action of adiponectin against the development of alcoholic fatty liver. We will also assess the potential strategies for treating alcoholic fatty liver disease, including nutritional and pharmacological modulation of adiponectin and its receptors.

Ethanol Inhibits Adiponectin Expression and Secretion

Ethanol inhibits adiponectin gene expression and secretion in cultured adipocytes and in rodents. Ethanol treatment decreased activity of a mouse adiponectin promoter and reduced adiponectin secretion in differentiated 3T3-L1 adipocytes (10). In several rodent models, including mice, rats, and micropigs, chronic ethanol administration significantly reduced the mRNA and protein expression of adiponectin in adipose tissues (13–15). In addition, chronic ethanol administration to rats suppressed adiponectin secretion from subcutaneous adipocytes by impairing adiponectin intracellular trafficking (12). Together, these studies demonstrate that circulating adiponectin levels are significantly decreased in chronically ethanol-fed animals. The cellular and molecular mechanisms whereby ethanol affects the expression and production of adiponectin in adipose tissue are still not fully understood. However, it has been suggested that tumor necrosis factor alpha (TNFα), homocysteine, SIRT1, and PPARγ may be involved.

TNFα

Adiponectin and TNFα suppress each other's gene expression, protein synthesis, and production in adipocytes (16). Following chronic ethanol administration, there is an inverse relationship between adiponectin and TNFα levels in several rodent models (10, 13, 15). TNFα production in adipose tissue is increased at the early stage of alcoholic liver injury (17). Conceivably, ethanol's inhibitory effect on adiponectin may be mediated through enhancing TNFα production that, in turn, could suppress adiponectin expression in adipose tissue through paracrine or endocrine mechanisms. On the other hand, it is possible that a priori inhibition of adiponectin by ethanol may lead to the observed increases in TNFα levels. Moreover, in humans, moderate alcohol consumption significantly enhanced serum adiponectin concentrations without affecting circulating TNFα levels, suggesting that ethanol's regulation of adiponectin could also be mediated through separate, TNFα-independent mechanisms (18).

Homocysteine

The role of homocysteine in the regulation of adiponectin gene expression and secretion has been demonstrated both in vitro and in vivo (14). Addition of exogenous homocysteine to cultured rat primary adipocytes resulted in decreased gene expression, protein levels, and secretion of adiponectin. Similarly, in mice fed a high-methionine diet, hyperhomocysteinemia was associated with decreased adiponectin levels in both adipose tissue and serum.

Chronic ethanol exposure disturbs methionine metabolism in liver and in adipose tissue causing endoplasmic reticulum (ER) stress and elevated homocysteine levels (13, 14). Supplementation of betaine or S-adenosylmethionine (SAM) to mice or micropigs reduced homocysteine levels by normalizing methionine-homocysteine metabolism and subsequently increased circulating adiponectin concentrations. These findings suggest that ethanol-induced hyperhomocysteinemia contributes, at least in part, to decreased adiponectin production in adipose tissue.

SIRT1

SIRT1, a NAD^+-dependent protein deacetylase, regulates gene expression by deacetylation of histones and various transcriptional regulators (19). Resveratrol (trans-3,5,4′-trihydroxystilbene), a naturally occurring phytoalexin, present in a wide variety of plant species, including grapes, berries, and peanuts, has been identified as a strong activator of SIRT1 (20).

SIRT1 has recently been shown to be involved in the regulation of adiponectin expression both in vitro and in vivo. In cultured, differentiated 3T3-L1 adipocytes, genetic or pharmacological activation of SIRT1 induced adiponectin transcription and production (21, 22). In SIRT1 transgenic mice fed a high-fat diet, adiponectin transcript and protein levels significantly increased compared to wild-type mice (23). It is important to note that plasma TNFα levels were unchanged in these mice, suggesting that up-regulation of adiponectin by SIRT1 may be mediated by TNFα-independent mechanisms (23).

Although the exact mechanisms have not yet been resolved, several studies have suggested that SIRT1 acts through forkhead transcription factor O1 (FoxO1) to

increase adiponectin transcription and production (21–23). However, it also has been demonstrated that SIRT1 inhibited the secretion of adiponectin from 3T3-L1 adipocytes through its inhibition of PPARγ activity (24). These conflicting findings suggest that up- or down-regulation of adiponectin by SIRT1 may be mediated through distinct signaling pathways.

The role of SIRT1 in regulating ethanol's effect on adiponectin has recently been examined by our group (15). In chronically ethanol-fed mice, treatment with resveratrol markedly increased mRNA and serum adiponectin concentrations. The up-regulation of adiponectin was associated with increased mRNA levels of SIRT1 and FoxO1 in adipose tissues, suggesting that resveratrol may up-regulate adiponectin secretion in ethanol-fed mice by activating the SIRT1-FoxO1 axis.

PPARγ

The mouse adiponectin promoter contains a binding site for PPARγ and its cofactor, retinoid X receptor (RXR) (25). Hence, PPARγ is known to play a key role in the regulation of adiponectin gene expression in adipose tissue. The thiazolidinediones (TZDs) (e.g., rosiglitazone and pioglitazone) are potent ligands for PPARγ. These drugs increase the adiponectin mRNA, protein and secretion through inducing PPARγ activity in adipocytes (26). Pioglitazone prevented alcohol-induced liver injury in rats, suggesting that up-regulation of adiponectin by pioglitazone via activation of PPARγ may contribute to its hepatic protective effects (27–29). Recently, we also observed that administration of rosiglitazone to chronically ethanol-fed mice significantly increased adiponectin gene expression and serum adiponectin levels and attenuated hepatic lipid accumulation (Z. Shen and M. You, unpublished observation). Studies have also shown that ethanol inhibited PPARγ transcriptional activity in cultured hepatic cells, and ethanol feeding reduced hepatic RXRα expression levels in mice (30, 31). Therefore, ethanol may inhibit adiponectin gene expression through directly impairing PPARγ function despite the fact that adipose mRNA of PPARγ was not altered by ethanol consumption (13, 15).

Ethanol Down-Regulates Hepatic Adiponectin Receptors

Two major adiponectin receptors have been identified, namely, adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2). Each subtype displays a unique affinity profile for its endogenous ligands. AdipoR1 binds globular adiponectin with high affinity and full-length adiponectin with low affinity, while AdipoR2 possesses intermediate binding affinity for both forms. In terms of tissue distribution, AdipoR1 is abundantly expressed in skeletal muscle and various other tissues, while AdipoR2 is the predominate subtype in the liver (32, 33).

In liver, circulating adiponectin signals through binding and interacting with both AdipoR1 and R2. Currently, limited data exist on the effect of ethanol on hepatic AdipoR1/R2. Our group has recently shown that hepatic AdipoR2 was selectively down-regulated by chronic ethanol feeding in mice (15). We also found that hepatic AdipoR1 expression levels had a tendency to decrease in the ethanol-fed mice, but the change did not reach statistical significance (15). In Yucatan micropigs, chronic ethanol feeding selectively suppressed hepatic AdipoR1 mRNA expression (13). It has not yet been determined whether decreased expression levels of AdipoR1/R2 by ethanol are correlated with decreased binding of circulating adiponectin with hepatic AdipoR1/R2. Logically, an ethanol-caused reduction of AdipoR1/R2 expression levels should lead to a similar decrease in adiponectin binding and a net reduction in adiponectin signaling in the liver.

The intracellular signaling events triggered by ethanol to alter hepatic AdipoR1/R2 expression are largely unknown. Several recent studies have provided evidence that SIRT1 signaling is involved in regulating hepatic AdipoR1/R2 expression. The hepatic AdipoR2 mRNA levels were significantly higher in SIRT1 transgenic mice compared with wild-type mice (23). Consistently, administration of resveratrol or SRT1720 (a potent synthetic activator of SIRT1) to mice increased hepatic AdipoR1/R2 gene expression (15, 34).

Hepatic SIRT1 mRNA, protein, and activity were significantly reduced in response to chronic ethanol exposure in mice and rats (15, 35–38). Moreover, in chronically ethanol-fed mice, supplementation of resveratrol restored hepatic AdipoR1 and AdipoR2 to higher levels than in control or ethanol-fed mice, suggesting that ethanol may inhibit AdipoR1/R2 through down-regulating hepatic SIRT1 activity in animals (15). FoxO1 is known to positively regulate AdipoR1/R2 expression (39). SIRT1 promotes the nuclear retention of FoxO1 and increases FoxO1 transcriptional activity (39, 40). It is tempting to postulate that ethanol may inhibit AdipoR1/R2 by impairing SIRT1-FoxO1 signaling in liver.

Signal Transduction Mechanisms Underlying the Protective Action of Adiponectin Against Alcoholic Fatty Liver

While the precise cellular and molecular mechanisms underlying the protective effects of adiponectin against alcoholic fatty liver are still largely unknown, accumulating evidence suggests that adiponectin exerts its protective actions against alcoholic fatty liver through coordination of a complicated signaling network mediated by various transcriptional regulators, including SIRT1, AMPK, SREBP-1, PGC-1α/PPARα, uncoupling protein-2 (UCP2), and fatty-acid translocase (CD36) that ultimately leads to reduced lipid accumulation in liver (9, 15, 42–46).

Adiponectin-AMPK Signaling and Ethanol

AMPK, a pivotal lipid regulator, is a mediator of adiponectin signaling in liver. Stimulation of AMPK activity by adiponectin leads to the inhibition of acetyl-CoA carboxylase (ACC) activity. By inhibiting ACC, AMPK increases fatty acid oxidation via down-regulation of malonyl-CoA, which is a precursor for biosynthesis of fatty acids and a potent inhibitor of carnitine palmitoyltransferase I (CPT-I), the enzyme that controls the transfer of long-chain fatty acyl-CoA into the mitochondria. Therefore, adiponectin-AMPK signaling promotes lipid catabolism and opposes triglyceride formation in liver (47, 48).

Dysregulation of hepatic AMPK signaling in response to chronic ethanol exposure represents a crucial mechanism for development of alcoholic fatty liver. Chronic ethanol exposure of cultured hepatic cells and of animals inhibited AMPK activity and stimulated ACC, leading to an induction of malonyl-CoA, suppression of CPT1, and concomitant accumulation of hepatic lipid (49–52). Rescue of this effect was demonstrated by administering full-length adiponectin to ethanol-fed mice, which corrected alterations in AMPK signaling and prevented hepatic steatosis (9). It was further demonstrated that an indirect elevation in the levels of circulating adiponectin through consumption of a high saturated fat diet, resveratrol, SAM, or betaine likewise restored hepatic AMPK activity and alleviated ethanol-induced steatosis in mice or micropigs (10, 13–15).

The adapter molecule APPL1 has been shown to link adiponectin receptors to downstream AMPK signaling (53). It will be of great importance to determine whether ethanol's inhibition of AMPK is mediated through APPL1. If it is, then activation of adiponectin-APPL1-AMPK signaling might serve as a prophylaxis against alcoholic liver steatosis.

Adiponectin-SIRT1 Signaling and Ethanol

SIRT1 has emerged as an important molecule controlling the pathways of hepatic lipid metabolism (19). An association between SIRT1 and AMPK signaling has been established. In cultured hepatic cells or animal liver, SIRT1 regulates AMPK activity via modulation of LKB1, an upstream AMPK kinase (54–57). In skeletal muscle cells, AMPK activates SIRT1 signaling through regulation of the intracellular [NAD^+]:[NADH] ratio (57–59). These studies suggest that SIRT1-AMPK signaling serves as a central mechanism in regulating lipid metabolism.

Recently, SIRT1 has been gaining recognition as one of the critical components in mediating adiponectin signaling. In primary human myotubes, treatment with globular adiponectin significantly increased SIRT1 protein expression levels (42). More importantly, knocking-down AdipoR1/R2 blocked adiponectin's effects, indicating that adiponectin can directly up-regulate SIRT1 (42). Similarly, we too found that treatment of rat Kupffer cells with globular adiponectin increased SIRT1 protein levels (43).

As discussed above, hepatic SIRT1 is down-regulated in animals that chronically consume ethanol (15, 42–46). Impairment of SIRT1 signaling by ethanol exposure is, in whole or in part, responsible for development of alcoholic liver steatosis in those animals. Conceivably, activation of adiponectin-SIRT1 signaling would prevent accumulation of fat in ethanol-fed animals. Indeed, resveratrol-mediated increased circulating adiponectin levels were associated with robustly enhanced hepatic SIRT1 protein expression and attenuated hepatic lipid accumulation in chronically ethanol-fed mice (15). Nevertheless, it should be noted that the definitive role of adiponectin in regulating hepatic SIRT1 needs to be further confirmed, potentially by using tissue specific knockouts of either adipose adiponectin or hepatic adiponectin receptors.

Adiponectin-SREBP-1 Signaling and Ethanol

SREBPs are transcription factors regulating fatty acid, triglyceride, and cholesterol synthesis (60). Usually, SREBPs are embedded in endoplasmic reticulum (ER) membrane as inactive precursors. Upon activation, SREBPs are cleaved by a complex mechanism involving specific proteases to yield transcriptionally active forms. The activated SREBPs are then translocated to the nucleus, where they interact with promoters of genes that are involved in lipid metabolism. Among three members of the SREBP family (SREBP-1a, –1c and –2) identified, SREBP-1c is predominately expressed in liver and largely responsible for regulating hepatic lipid synthesis. Adiponectin-SREBP-1 signaling is associated with inhibited lipogenesis and reduced hepatic lipid accumulation in rodents (15, 44–46).

Ethanol-induced hepatic fat accumulation depends upon an increase of hepatic SREBP-1c signaling in several animal models. Both acute and chronic ethanol feeding stimulates hepatic SREBP-1 activity and increases the mRNAs of SREBP-1 regulated enzymes—including fatty acid synthase (FAS), steroyl-CoA desaturase (SCD), mitochondrial glycerol-3-phosphate acyltransferase 1 (GPAT1), malic enzyme (ME), ATP citrate lyase (ACL), and ACC—and leads to hepatic lipid accumulation (15, 35, 36, 61–64). Accordingly, SREBP-1 knockout mice are protected from acquiring ethanol-induced fatty liver (60). Interestingly, a recent study has demonstrated that development of liver steatosis in zebrafish in response to acute alcohol exposure requires activation of SREBP signaling (65).

It is important to point out that the effects of ethanol on SREBP-1c may vary with species. In rats, the development of alcoholic liver steatosis occurred in the presence of suppressed SREBP-1c signaling (66, 67). It is also worthwhile to note that there is some cross-talk between cascades of fatty acid synthesis and fatty acid oxidation. For instance, SCD1 and GPAT1, two known SREBP-1 regulated lipogenic enzymes, not only play key roles in

lipid synthesis, but are also involved in regulating fatty acid oxidation in hepatocytes and mouse liver (68, 69). Therefore, ethanol mediated activation of SREBP-1c and genes encoding lipogenic enzymes may also inhibit fatty acid oxidation.

While the precise mechanisms by which ethanol stimulates SREBP-1c activity remain incompletely understood, ethanol-mediated impairment of SIRT1-AMPK signaling system and ethanol-induced ER stress have each been suggested to contribute to the activation of SREBP-1c signaling in animal liver (15, 35, 49, 63). To date, it is still uncertain whether or not adiponectin can directly block the ethanol stimulated activation of SREBP-1c. Given that SIRT1-AMPK signaling is upstream of SREBP-1c, stimulation of SIRT1-AMPK signaling by adiponectin should blunt ethanol-mediated SREBP-1c activation and reduce hepatic lipid triglyceride synthesis.

Adiponectin-PGC-1α/PPARα Signaling and Ethanol

PPARα is a key transcription factor of genes involved in mitochondrial and peroxisomal β-fatty acid oxidation (70). Though PPARγ coactivator-1α (PGC-1α) was initially identified as a coactivator for PPARγ, it has subsequently been shown to serve as a cofactor for several other transcriptional factors including PPARα (71, 72). In the liver, the interaction of PGC-1α and PPARα induces fatty acid oxidation enzymes, including long-chain acyl-CoA dehydrogenase, medium-chain acyl-CoA dehydrogenase, acyl-CoA oxidase, and very-long-chain acyl-CoA synthetase, CPT-I, and fatty acid binding protein (70–72). In both cell culture and animal models, adiponectin stimulates PGC-1α/PPARα transcriptional activity and induces several hepatic fatty acid oxidation enzymes, which, in turn, increase the fatty acid catabolism (10, 44–46).

Accumulating evidence suggests that inhibition of the transcriptional dyad, and incomplete stimulation of its target genes during ethanol consumption partially contribute to the development of alcoholic fatty liver in several animal models (31, 73–76). The role of PGC-1α/PPARα signaling in alcoholic fatty liver has been further supported by studies showing that supplementation of PPARα activators (e.g., WY14 643 or clofibrate) prevented hepatic fat deposition by up-regulating PGC-1α/PPARα regulated enzymes and increasing the rate of fatty acid oxidation (31, 75). Not surprisingly then, PPARα knockout mice chronically fed ethanol developed more extensive liver injuries (e.g. hepatomegaly and steatohepatitis) than wild-type controls (76).

Treatment with adiponectin restored the ethanol-inhibited PGC-1α/PPARα activity in cultured hepatic cells and in animal liver, suggesting that stimulation of adiponectin-SIRT1 signaling may serve as an effective therapeutic strategy for treating or preventing human alcoholic fatty liver (44–46). However, it is important to note that decreased expression levels of PPARα in human versus rodent liver, may limit clinical applications of adiponectin or its activators that depend on adiponectin-PPARα signaling (70).

Adiponectin-CD36 Signaling and Ethanol

CD36 has been identified as a putative membrane protein responsible for the transport of fatty acids into cells (77). Specific induction of CD36 and subsequent increased fatty acid uptake in liver contribute to hepatic fat accumulation in rodents and humans (77–79).

It is not clear whether hepatic fatty acid uptake is induced by ethanol via up-regulated hepatic CD36 activity, however, CD36 is one of the lipogenic genes targeted by PPARγ (79). We recently found that ethanol feeding to mice increased hepatic PPARγ expression, suggesting that ethanol may either regulate CD36 directly or through its stimulation of PPARγ activity contributing to development of steatosis (15).

Administration of full-length, recombinant adiponectin to chronically ethanol-fed mice markedly suppressed the mRNA expression of hepatic CD36 and prevented fatty liver (9). This may partly explain the protective role of adiponectin against alcoholic fatty liver.

Adiponectin-UCP2 Signaling and Ethanol

UCP2 is a mitochondrial membrane transporter expressed in various organs, including liver (80), and has emerged as a major modulator in mediating the hepatoprotective effects of adiponectin (81). In both dietary obese mice and genetically obese mice, targeted disruption of the adiponectin gene led to decreased UCP2 gene and protein expression, severely impaired mitochondrial functions, and substantial lipid accumulation in the liver. Adenovirus-mediated adiponectin replenishment to these adiponectin knockout mice dramatically increased both the gene and protein levels of UCP2, restored the mitochondrial functions and prevented the lipid accumulation in liver (81). Moreover, the hepatoprotective effects of adiponectin against endotoxin-induced liver injuries were blocked in UCP2 knockout mice (81). These findings suggest that up-regulation of hepatic UCP2 by adiponectin might play a critical role in mediating its protective effects against liver injuries.

The detailed signaling mechanisms underlying adiponectin-stimulated hepatic UCP2 expression are not fully understood. Studies have shown a major role for PPARα in the up-regulation of UCP2 expression in the liver, suggesting that adiponectin may up-regulate hepatic UCP2 through stimulation of PPARα signaling (82). A recent study has demonstrated that exposure of endothelial cells or mice to either AICAR or metformin (two known activators of AMPK) caused AMPK-dependent up-regulation of UCP2, leading to attenuated oxidative stress in diabetes (83). These studies suggest that UCP2 may lie downstream of AMPK and PPARα.

Mitochondrial dysfunction plays a vital role in various

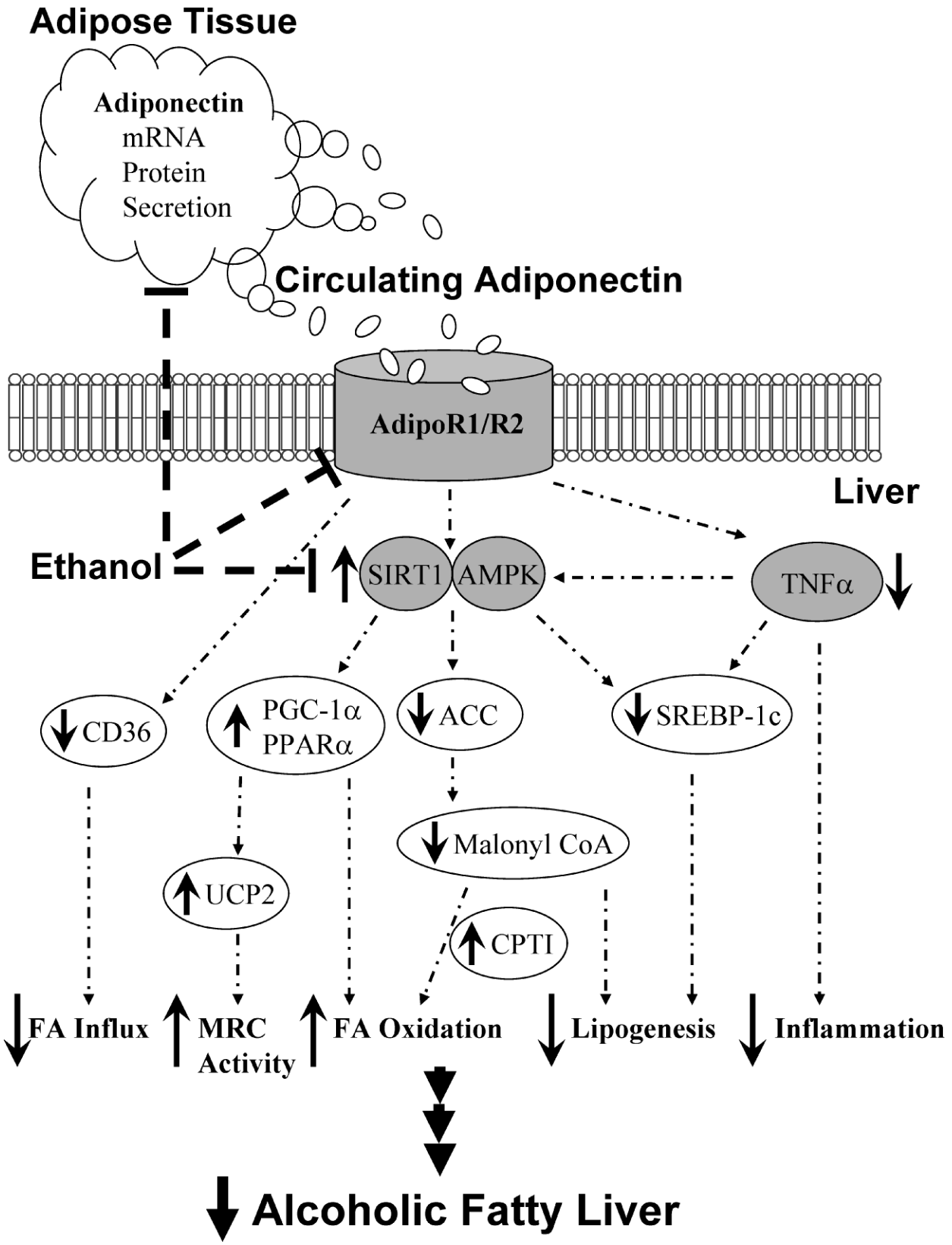

Figure 1. Proposed mechanisms that underlie the protective action of adiponectin against alcoholic fatty liver. Adiponectin protects against development of alcoholic fatty liver through coordination of multiple signaling pathways mediated by various transcriptional regulators including SIRT1, AMPK, SREBP-1, PGC-1α/PPARα, CD36, and UCP2. Abbreviations: AdipoR, adiponectin receptor; AMPK, AMP-activated kinase; ACC, acetyl-coenzyme A carboxylase; CD36, fatty-acid translocase; FA, free fatty acids; MRC, mitochondrial respiratory chain; SIRT1, sirtuin 1; SREBP-1c, sterol regulatory element-binding protein 1c; PGC-1α, peroxisome proliferator-activated receptor γ co-activator-alpha; PPARα, peroxisome proliferator-activated receptor alpha; TNFα, tumor necrosis factor alpha; UCP2, uncoupling protein-2.

forms of liver injury (84). Ultrastructural abnormalities in mitochondria have been shown at the fatty liver stage in chronically ethanol-fed animals as well as in alcoholics (85). It is reasonable to speculate that impairment of adiponectin-UCP2 signaling may contribute to mitochondrial abnormality and liver steatosis associated with chronic ethanol consumption. However, it is important to note the potentially contradictory role of UCP2 in development of liver injuries. There is evidence that a significant increase in hepatic UCP2 gene expression facilitates liver injury (86, 87). Moreover, one earlier study reported that chronic ethanol administration to mice significantly increased hepatic UCP2 mRNA expression levels (88). Since UCP2 activity is induced by reactive oxygen species (ROS) (80), it is possible that, in the ethanol-exposed liver, UCP2 is up-regulated to ensure a rapid, cellular response to elevated ROS generated by ethanol metabolism. The role of adiponectin-UCP2 signaling in alcoholic fatty liver warrants further investigation.

Adiponectin Signaling Antagonizes TNFα Activity in Liver

In addition to suppressing TNFα production in adipocytes, adiponectin directly opposes the damaging effects of TNFα within the liver tissue (16). Dysregulation of TNFα is profoundly involved in the pathogenesis of alcoholic liver injury (88–90). TNFα alters lipid metabolism by interfering with several crucial transcriptional regulators such as AMPK and SREBP-1 (91–94). A recent study has further demonstrated that TNFα provokes processing of SREBP-1 in ethanol-exposed hepatoma cell lines, resulting in the inappropriate induction of lipogenic enzymes (95). Thus, adiponectin may counter hepatic liver accumulation through antagonism of TNF-α. Furthermore, several lines of evidence have shown that globular adiponectin attenuates production of TNFα as well as ROS in liver Kupffer cells exposed to ethanol, suggesting that the anti-inflammatory activity of adiponectin contributes to its protective effects against alcoholic liver injury (88).

In contrast, one study, utilizing adiponectin knockout mice, demonstrated spontaneous development of hepatic steatosis in 3-week-old animals, despite equivalent measurements of hepatic TNFα as compared with the wild-type controls (80). Several mouse models of early alcoholic fatty liver have shown that ethanol feeding inhibited adiponectin levels without affecting hepatic TNFα content (10, 13, 95). These studies suggest that adiponectin (perhaps due to age-specific gene expression) may exert its protective effects through either TNFα-dependent or -independent mechanisms.

Dietary or Pharmacological Modulation of Adiponectin or Its Hepatic Receptors Prevents Alcoholic Fatty Liver

Growing evidence has suggested that modulation of adiponectin and its hepatic receptors by dietary or pharmacological intervention may prevent development of alcoholic fatty liver. In ethanol-fed mice, treatment with resveratrol, a dietary polyphenol, increased expression levels of adiponectin and hepatic AdipoR1/R2 and alleviated liver steatosis (15). Mice fed a diet high in saturated fatty acids and ethanol displayed elevated adiponectin levels and increased hepatic AdipoR2 expression and showed no sign of hepatic steatosis (10, 96). Supplementation of ethanol-containing diets with SAM or betaine normalized expression levels of adiponectin and hepatic AdipoR1 and attenuated hepatic lipid accumulation in animals (13, 14). As discussed above, a PPARγ agonist, pioglitazone, prevented development of alcoholic fatty liver in animals (27–29). All these studies imply that strategies to up-regulate or enhance the activity of adiponectin might serve as potential therapies for combating human alcoholic fatty liver disease.

Conclusion

Over the past several years, adiponectin, one of the adipocyte-derived adipokines, has emerged as an important regulator for the development of alcoholic fatty liver. Several animal models of alcoholic fatty liver have displayed reduced circulating adiponectin levels, decreased hepatic adiponectin receptors expression, and impaired hepatic adiponectin-mediated signaling. Adiponectin exerts its protective effects against alcoholic liver steatosis through interacting with hepatic AdipoR1/R2 and mediating multiple signaling pathways, which eventually lowers lipid accumulation in liver (Fig. 1).

The precise regulatory molecular mechanisms by which ethanol impairs adiponectin and its hepatic receptors will need to be further elucidated. In this respect, particular attention should be given to newly emerged candidates such as SIRT1 and FoxO1. It will also be of great importance to determine the regulation of individual adiponectin oligomeric forms by ethanol. Undoubtedly, a better knowledge of ethanol's effects on adiponectin, individual adiponectin oligomeric forms, and hepatic AdipoR1/R2 will help the development of potential therapeutic approaches for preventing and treating human alcoholic fatty liver disease.

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