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Invited Review

Endocrine Adiponectin–FGF15/19 Axis in Ethanol-Induced Inflammation and Alcoholic Liver Injury

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Alcoholic liver disease (ALD) is the most prevalent form of liver disease, encompassing a spectrum of progressive pathological changes from steatosis to steatohepatitis to fibrosis/cirrhosis and hepatocellular carcinoma. Alcoholic steatosis/steatohepatitis is the initial stage of ALD and a major risk factor for advanced liver injuries. Adiponectin is a hormone secreted from adipocytes. Fibroblast growth factor (FGF) 15 (human homolog, FGF19) is an ileum-derived hormone. Adipocyte-derived adiponectin and gut-derived FGF15/19 regulate each other, share common signaling cascades, and exert similar beneficial functions. Emerging evidence has revealed that dysregulated adiponectin–FGF15/19 axis and impaired hepatic adiponectin–FGF15/19 signaling are associated with alcoholic liver damage in rodents and humans. More importantly, endocrine adiponectin–FGF15/19 signaling confers protection against ethanol-induced liver damage via fine tuning the adipose–intestine–liver crosstalk, leading to limited hepatic inflammatory responses, and ameliorated alcoholic liver injury. This review is focused on the recently discovered endocrine adiponectin–FGF15/19 axis that is emerging as an essential adipose–gut–liver coordinator involved in the development and progression of alcoholic steatohepatitis.

Key words: Alcoholic steatohepatitis; Adiponectin; Inflammation; Iron; Mitochondria; Bile acids; Organ crosstalk; FGF15/19

INTRODUCTION

Clinically, alcoholic liver disease (ALD) occurs in patients who chronically drink and/or binge excessive alcohol, which can lead to life-threatening complications[1,2]. Alcoholic steatosis/steatohepatitis is the initial stage of ALD, which can progress to hepatitis, fibrosis/cirrhosis, liver cancer, and liver failure[1,2]. The underlying cellular and molecular mechanisms from alcohol consumption to liver injury are complex and still not fully understood. Because of limited understanding, currently there are few effective clinical treatment strategies to prevent or reverse severe forms of ALD.

Adiponectin, one of the most abundant adipokines expressed and secreted from adipocytes, circulates in the serum either as a full-length protein or as a fragment composed of the C-terminal globular domain. Adiponectin is also present in the serum as homomeric complexes: low- (LMW), middle- (MMW), and high-molecular weight (HMW), which is the most active form[3]. Two major adiponectin receptors (AdipoR1 and -R2) serve as transducers of multiple adiponectin-mediated signaling pathways in various organs, such as the liver[4] and intestine[5].

Fibroblast growth factor (FGF) 15, along with its human homolog (FGF19), is a terminal small intestine (ileum)-derived hormone that regulates bile acid and lipid metabolism, and inflammation[6]. Circulating FGF15/19 signals through binding and activating a receptor complex composed of fibroblast growth factor receptor 4 (FGFR4) and β-Klotho[7]. After reaching the liver through portal circulation, FGF15/19 binds and stimulates hepatic FGFR4/β-Klotho, leading to the inhibition of cholesterol 7α-hydroxylase 1 (CYP7A1), the rate-limiting step for bile acid synthesis[8]. In addition to serving as a negative regulator of bile acid synthesis, the binding of FGF15/19 to FGFR4/β-Klotho also activates multiple signaling cascades, such as mitogen-activated protein kinase[9,10] and

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peroxisome proliferator-activated receptor γ coactivator 1-α[11].

Growing evidence suggests that adiponectin and FGF15/19 regulate each other, modulate common signaling cascades, and share similar functions. This unique endocrine adiponectin–FGF15/19 axis is a pivotal regulator of the inflammation process, bile acid homeostasis, and lipid metabolism in liver[5,12,13].

Emerging evidence demonstrates that ethanol compromises the endocrine adiponectin–FGF15/19 axis and its signaling. The concurrent elevation of circulating adiponectin and FGF15/19 protects against the development of experimental alcoholic steatohepatitis in rodents. This review summarizes the current knowledge of the concerted protective actions of adiponectin and FGF15/19 as adipose–gut–liver coordinators in the development of alcoholic steatohepatitis, and integrates recent research findings of ethanol-mediated dysregulation of the endocrine adiponectin–FGF15/19 axis.

ENDOCRINE ADIPONECTIN–FGF15/19 AXIS

Several lines of evidence demonstrate an association and crosstalk between the adipocyte-derived adiponectin and gut-derived FGF15/19 in mice. Injection of an adeno-associated virus-expressing FGF15 markedly increased adipose adiponectin synthesis in mice[5]. When mice were treated with recombinant FGF19, adipose adiponectin mRNA levels were significantly increased, while hepatic mRNA of CYP7A1, an indicator of FGF15/19 signaling, was decreased[12]. Mice treated with recombinant globular adiponectin had significantly higher ileum FGF15 mRNA levels but, unexpectedly, increased levels of hepatic CYP7A1 mRNA[12]. These results suggested a potential regulatory link between adiponectin and CYP7A1. Additionally, FGF15 null mice demonstrated significantly lower adipose adiponectin mRNA levels and higher hepatic Cyp7a1 mRNA levels[12]. In FGFR4 knockout mice, FGF15/19 was concurrently elevated with adiponectin, leading to increased insulin sensitivity, improved glucose metabolism, and body weight reduction while on a high-fat diet[5]. These results demonstrated that adiponectin and FGF15/19 reciprocally regulate each other in mice and that the adiponectin–FGF15/19 axis participates in various signaling cascades, including inflammation and lipid metabolism pathways. Nonetheless, exactly how adiponectin and FGF15/19 regulate each other and the underlying mechanisms of their concerted actions in the liver are presently unknown.

ETHANOL DYSREGULATES ADIPONECTIN–FGF15/19 AXIS

Ethanol dysregulates adiponectin production, reduces hepatic adiponectin receptors, and disrupts adiponectin signaling. Several rodent models of alcoholic steatosis/steatohepatitis have displayed significant decreases in adipose adiponectin synthesis and production, and concentrations of serum adiponectin, which correlate closely with liver dysfunction[14,15]. On the contrary, some studies have demonstrated that ethanol consumption increases serum adiponectin levels in rodents and humans[16–18]. Nevertheless, existing evidence unequivocally demonstrates that ethanol-mediated disruption of hepatic adiponectin signaling leads to the development and progression of inflammation and liver injury in mice, rats, and pigs[14,19,20]. Genetic ablation of adiponectin in mice exacerbated onset and progression of steatosis and liver injury in response to ethanol challenge. Restoring adiponectin levels using recombinant adiponectin ameliorated the ethanol-induced steatohepatitis in mice with adiponectin deficiency[21]. Furthermore, elevation of adiponectin or stimulation of hepatic adiponectin signaling in ethanol-administrated animals by dietary (e.g., saturated fatty acids[22], resveratrol[23], and S-adenosylmethionine[19]) and pharmacological manipulation (e.g., rosiglitazone[14]) alleviated liver damage.

Although limited data exist on the effect of ethanol on ileum FGF15/19, ileum FGF15 was downregulated by chronic-binge or chronic ethanol feeding in mice[12,13]. Accordingly, the serum level of FGF15 was reduced in these mice after ethanol administration[12,13]. The lower expression of ileum FGF15 in the ethanol-fed mice could potentially be mediated via an increased absorption of bile acids into the portal circulation[24]. As discussed above, signaling of FGF15/19 requires FGFR4/β-Klotho in the liver[25,26]. FGFR4 gene and protein expression levels were significantly reduced in livers of the ethanol-fed mice[12]. More importantly, in comparison with healthy human livers, alcoholic fatty liver disease samples had significantly lower β-Klotho mRNA abundances, indicating clinical relevance of hepatic FGF15/19 signaling in the pathogenesis of ALD[27].

We recently identified a compelling link between adiponectin and FGF15/19 synthesis in their regulations by ethanol. Chronic-binge or chronic ethanol feeding with mice decreased serum adiponectin levels and decreased gene expression levels of ileum FGF15[12,13]. More importantly, ethanol administration concurrently increased levels of adiponectin and FGF15 in two knockout (global mitoNEET or myeloid cell-specific lipin-1) mice[12,13]. Nevertheless, it remains unknown whether ethanol's inhibitory effects on adipose adiponectin and on ileum FGF15 synthesis in mice are sequential or parallel, and if sequential, the order of cause and effect. The interplay between adipose adiponectin and ileum FGF15/19 and how the adiponectin–FGF15/19 axis is regulated by ethanol warrant future investigation.

ADIPONECTIN–FGF15/19 SIGNALING AMELIORATES ETHANOL-INDUCED HEPATIC INFLAMMATION AND ALLEVIATES ALCOHOLIC LIVER INJURY

Emerging evidence suggests that endocrine adiponectin–FGF15/19 signaling confers protection against ethanol-induced inflammation and liver injury via fine tuning the adipose–intestine–liver crosstalk[5,12,13]. Concomitantly, elevation of circulating adiponectin and FGF15 protects two knockout (global mitoNEET and myeloid cell-specific lipin-1) mice from inflammation and liver damage after ethanol administration[12,13].

MitoNEET [also named CDGSH iron sulfur domain 1 (CISD1)], an iron–sulfur (2Fe-2S) cluster-containing outer mitochondrial membrane protein[28,29], is widely expressed in various organs such as the liver[30], adipose[31], and intestine[13]. MitoNEET plays a vital role in regulating iron homeostasis due to its 2Fe-2S cluster[29,32]. Thiazolidinediones (TZDs), such as pioglitazone, are capable of binding and stabilizing the mitoNEET protein against 2Fe-2S cluster release and thus protecting tissue from mitochondrial injury[32]. Functionally, mitoNEET is an important regulator of diverse biological processes, including mitochondrial function, iron metabolism, reactive oxygen species (ROS) homeostasis[29], lipid metabolism[30], and inflammation[13].

Utilizing a global mitoNEET knockout mouse model, we uncovered an intriguing role of adiponectin–FGF15 signaling in the development of alcoholic steatohepatitis in mice. Chronic ethanol administration to mitoNEET knockout mice concurrently increased serum total and HMW adiponectin and ileum FGF15 synthesis in response to ethanol challenge. In concordance with an elevation of adiponectin and FGF15, mitoNEET knockout mice fed with ethanol were completely resistant to ethanol-induced steatohepatitis as revealed by dramatically reduced hepatic triglycerides, decreased hepatic cholesterol levels, and attenuated serum alanine aminotransferase levels[13].

Lipin-1 is a phosphatidate phosphohydrolase required for the generation of diacylglycerol during glycerolipid synthesis and exhibits dual functions in the regulation of lipid metabolism and inflammation process[33]. Lipin-1 has been implicated in the pathogenesis of alcoholic steatohepatitis[34]. Genetic removal of lipin-1 in myeloid cells ameliorated liver injury that would normally occur following the chronic-binge ethanol feeding protocol. Interestingly, the circulating levels of adiponectin and FGF15 were concomitantly elevated in myeloid cell-specific lipin-1 knockout mice after ethanol administration[12].

Taken together, these results have demonstrated that mitoNEET or myeloid cell-specific lipin-1 deficiency alleviates experimental alcoholic steatohepatitis in mice by stimulating the adiponectin–FGF15 axis[12,13].

Inflammation, such as neutrophilic inflammation, contributes to ethanol-induced hepatic dysfunction and injury[35]. Chronic or chronic-binge ethanol administration provoked inflammatory responses as revealed by increased myeloperoxidase staining, F4/80$^+$ staining, and elevated gene expression of inflammatory markers and generation of proinflammatory cytokines in livers of wild-type control mice. However, ethanol administration to the mitoNEET or myeloid cell-specific lipin-1 knockout mice drastically diminished hepatic inflammation by suppressing those inflammation markers. These findings suggest that the adiponectin–FGF15/19 axis participates in controlling ethanol-induced inflammation in mouse liver[12,13].

MECHANISMS UNDERLYING THE PROTECTIVE ACTION OF ENDOCRINE ADIPONECTIN–FGF15/19 AXIS AGAINST ALCOHOLIC LIVER INJURY

While the consequences of abrogating endocrine adiponecitn–FGF15/19 signaling during ethanol exposure are still incompletely understood, growing evidence suggests that adiponectin–FGF15/19 signaling exerts its protective actions against alcoholic liver injury through coordinating several crucial signaling cascades (Fig. 1).

Adiponectin–FGF15/19–Lipocalin-2 Signaling and Ethanol

Lipocalin-2 (LCN2) (also termed neutrophil gelatinase-associated lipocalin) is an important innate immune protein of the lipocalin family[36]. Although initially discovered in neutrophils and used as a marker of kidney disease, LCN2 is also expressed in the liver[37]. LCN2 protein is abundantly present in the circulation. One of the LCN2 receptors, LCN2R (24p3R in mouse or NGALR2/SLC22A17 in humans), can transduce LCN2-mediated signaling. For instance, 24p3R-expressing mammalian cells are sensitive to LCN2-mediated signals, such as apoptosis, through modulating iron metabolism[38]. In addition to critically involving innate immune responses, LCN2 is an important regulator of iron metabolism. Unlike other members of the lipocalin family, LCN2 protects against infections with certain Gram-negative bacteria by sequestrating iron from bacteria[36].

LCN2 has recently been identified as a detrimental player in driving inflammation and promoting the development and progression of alcoholic steatohepatitis in rodents and humans[12,27,34,39–41]. In cultured AML-12 hepatocytes, ethanol exposure significantly increased LCN2 gene expression. The activation of nuclear factor-κB (NF-κB), nuclear factor of activated T-cells c4, and miR-127–sirtuin 1 (SIRT1) axis may be responsible for

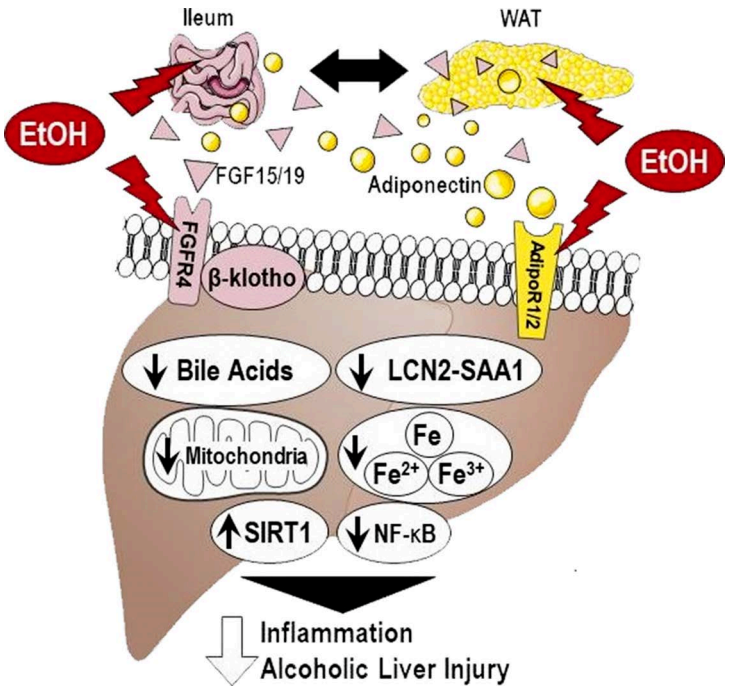

Figure 1. Proposed mechanisms that underlie the protective action of endocrine adiponectin–FGF15/19 signaling against ethanol-induced inflammation and liver injury. Adiponectin–FGF15/19 signaling exerts its protective actions against alcoholic liver injury through coordinating several crucial signaling molecules and cascades including LCN2, SAA1, bile acid metabolism, iron homeostasis, mitochondrial function, and SIRT1–NF-κB axis. AdipoR, adiponectin receptor; FGFR4, fibroblast growth factor receptor 4; LCN2, lipocalin-2; Fe, iron; Fe^{2+}, ferrous; Fe^{3+}, ferric; NF-κB, nuclear factor-κB; SAA1, serum amyloid A1; SIRT1, sirtuin 1.

this elevation. In a cellular model of alcoholic steatosis, knocking down LCN2 completely prevented the fat accumulation induced by ethanol[27].

Hepatic and circulating LCN2 levels were markedly elevated in response to chronic or chronic-binge ethanol administration in mice and rats[27,39]. The drastically elevated LCN2 levels were closely linked with the development and progression of alcohol-induced fatty liver injury in those animals. Consistently, LCN2 knockout mice were resistant to fat accumulation and liver injury after alcohol intake[27]. In line with these findings, liver samples from patients with alcoholic fatty liver had abnormal gene expression of LCN2-regulated molecules.[27] Furthermore, in patients with alcoholic steatohepatitis, LCN2 promotes liver inflammation after alcohol intake by mediating neutrophil infiltration into the liver and prolonging neutrophil life span[40].

FGF15/19 downregulates LCN2 in cultured hepatocytes[12]. In mouse AML-12 hepatocytes, treatment with recombinant FGF19 inhibited mRNA expressions of LCN2 dose dependently. While LCN2 mRNA levels were significantly increased by ethanol or lipopolysaccharide (LPS), a putative agent of ALD, coincubation with recombinant FGF19 completely abolished the ability of LPS or ethanol to induce LCN2 gene expression in AML-12 cells[12]. Similarly, coadministration of recombinant adiponectin abolished the ability of ethanol to upregulate LCN2 in AML-2 hepatocytes (M.Y., unpublished data).

In concordance with concerted elevation of adiponectin and FGF15 levels, myeloid cell-specific lipin-1 deficiency reduced hepatic and circulating levels of LCN2 and protected mice from liver damage after ethanol challenge, suggesting that adiponectin–FGF15/19 signaling regulated the ethanol-induced inflammation and alcoholic liver injury via targeting LCN2[12].

It is important to note the contradictory relationship between adiponecitn-FGF15/19 signaling and LCN2 in the development of alcoholic steatohepatitis. While concurrently elevated levels of adiponectin and FGF15 ameliorated ethanol-induced liver injury in mitoNEET knockout mice, the levels of hepatic and serum LCN2 in these mice were paradoxically elevated[13]. LCN2 has also been suggested to serve as a protective role in the pathogenesis of liver diseases by acting as a "help me" signal[42]. MitoNEET deficiency-mediated elevation of LCN2 may trigger anti-inflammatory signaling and protect mice from ethanol-induced liver damage[13]. Furthermore, given that both mitoNEET and LCN2 play vital roles in regulating iron homeostasis, the adiponectin–FGF15/19–LCN2 signaling in mitoNEET knockout mice after ethanol intake may be mainly regulated via iron metabolism-dependent

mechanisms[13]. Studies are required to further dissect the mechanism underlying this intriguing phenotype.

Adiponectin–FGF15/19–Serum Amyloid A1 Signaling and Ethanol

Serum amyloid A1 (SAA1) is an inducible acute response protein, which is largely produced by liver in response to injury, infection, stress, trauma, and inflammation[36]. SAA1 can potentially transduce signals by binding to several receptors, including the N-formyl peptide receptor 1[43], toll-like receptor 2[44], toll-like receptor 4[45], type B scavenger receptor I[46], and receptor for advanced glycation end product[47]. During the acute phase of inflammatory response, the liver secretes a large amount of SAA1, markedly elevating the level of circulating SAA1[36]. Although the liver is the principal source of SAA1, other organs have been documented to express SAA1. For example, during the nonacute phase, adipose tissue is the main source of SAA1 in obese subjects[48]. SAA1 can activate NF-κB and mitogen-activated protein kinases pathways. In addition, SAA1 elicits multiple proinflammatory effects, including induction of immune cell migration and stimulation of cytokine/chemokine production[36]. Elevation of SAA1 expression can therefore promote inflammatory conditions.

Similar to LCN2, SAA1 plays a key role in the pathogenesis of alcoholic steatohepatitis. Liver and serum SAA1 levels were drastically elevated in response to ethanol administration in mice or rats. Importantly, the increased SAA1 in those animals was closely linked with the development of ethanol-induced steatosis, inflammation, and liver injury[12,27,34,39,41].

Ethanol or LPS significantly elevated SAA1 gene expression in cultured AML-12 hepatocytes. However, the ability of LPS to induce SAA1 gene expression was largely blunted by FGF19 treatment[12]. Consistently, stimulated adiponectin–FGF15 axis was associated with markedly reduced hepatic expression and circulating levels of SAA1 in myeloid cell-specific lipin-1 knockout mice in response to ethanol challenge[12].

It is worthwhile to note that LCN2 deficiency selectively attenuated gene expression of hepatic SAA1 in ethanol-administrated mice, suggesting that LCN2 and SAA1 may regulate each other[27]. The intriguing interplay among the disrupted adiponectin–FGF15/19 signaling and aberrant LCN2–SAA1 axis and their contributions to alcoholic steatohepatitis merit future investigation.

Adiponectin–FGF15/19 Signaling Normalizes Bile Acid Homeostasis

Bile acids modulate inflammatory responses in various organs including the liver and intestine. Bile acids are increasingly being recognized as the most sensitive markers of inflammation and liver dysfunction. Abnormal bile acid homeostasis contributes to the development and progression of experimental alcoholic steatohepatitis in rodents[49,50]. Clinically, alcohol consumption induces cholestasis in all stages of ALD in patients[51].

As discussed above, FGF15/19 is firmly established as a negative regulator of bile acid synthesis via CYP7A1 inhibition in the liver[8]. Growing evidence has revealed a potential role of adiponectin in regulating bile acid metabolism. Serum adiponectin levels are inversely correlated with hepatic bile acid synthesis, serum bile acid levels, and hepatocellular injury in patients with nonalcoholic liver disease[52]. Adiponectin also directly regulates bile acid homeostasis-related genes such as Cyp7a1[52]. Furthermore, adiponectin is capable of alleviating inflammation induced by toxic bile acids, such as deoxycholic acid, in esophageal adenocarcinoma cells[53].

Concurrently elevated circulating levels of adiponectin and FGF15 ameliorated ethanol-mediated perturbation of bile acid homeostasis in the mitoNEET or myeloid cell-specific lipin-1 knockout mice[12,13]. The normalized hepatic and serum bile acids in these mice might also limit hepatic accumulation of toxic bile acids and ameliorated ethanol-induced liver damage. Given that both FGF15/19 and adiponectin can regulate bile acid homeostasis, this may partly explain the protective role of adiponectin–FGF15/19 signaling against ethanol-induced liver injury in those genetically modified mice[12,13]. The definitive role of adiponectin–FGF15/19 signaling in regulating bile acid homeostasis and its relationship to ALD need further investigation, potentially by performing ethanol feeding studies utilizing a genetically modified mouse model such as FGF15 or adiponectin null mice.

Adiponectin–FGF15/19 Signaling Ameliorates Ethanol-Induced Abnormality of Iron Homeostasis

Iron homeostasis is a major determinant of adiponectin levels[54,55]. The production of adiponectin from adipose tissue is modulated by iron[55]. In patients with diabetes and normal individuals, serum ferritin and transferrin levels are inversely associated with adiponectin[54]. In an animal model, iron accumulation in adipocytes, caused by either high iron diet feeding or ferroportin deficiency, can reduce adiponectin expression[55]. Mechanistically, iron signals through the reduction of acetylated forkhead box protein O1 levels to reduce the transcription of adiponectin in adipocytes[55]. To date, it is still uncertain whether iron directly regulates ileum FGF15/19 synthesis. However, given that adiponectin and FGF15/19 regulate each other, iron-mediated reduction of adiponectin can certainly reduce ileum FGF15/19 synthesis.

Ethanol and iron interact synergistically to cause liver injury[56], and aberrant iron homeostasis is implicated in the pathogenesis of ALD[57]. However, there is little knowledge

about the effects of ethanol on iron homeostasis in tissues, such as adipose and intestine, and their relationship with aberrant expression of adiponectin and FGF15/19. As discussed above, mitoNEET serves as an iron–sulfur cluster transfer protein due to its unique 39-amino acid CDGSH domain that binds to 2Fe-2S clusters. These 2Fe-2S clusters play crucial roles in mitochondrial iron homeostasis[30]. We recently found that ethanol feeding substantially increased concentrations of iron (Fe), ferrous (Fe^{2+}, reduced form), and ferric (Fe^{3+}, oxidized form) in adipose tissues of mice[13]. Interestingly, the circulating levels of total and HMW adiponectin and ileum FGF15 were decreased in these ethanol-fed mice[13]. We speculate that ethanol exposure may provoke release of the mitoNEET's 2Fe-2S cluster, which in turn causes mitochondrial iron overload and leads to concurrent reductions of adipose adiponectin and ileum FGF15/19 synthesis and production in mice.

Genetic ablation of mitoNEET in mice partially, but significantly, abolished the ability of ethanol to induce ferric contents in adipose and liver and protected mice from ethanol-induced liver damage via concerted elevations of adiponectin and FGF15[13]. These findings suggest that adiponectin–FGF15/19 signaling might exert prophylactic benefits against alcoholic liver injury via modulating iron metabolism. Additional studies are needed to address the role of adiponectin–FGF15/19 signaling in regulating iron homeostasis and its involvement in the pathogenesis of alcoholic steatohepatitis.

Adiponectin–FGF15/19 Signaling Improves Mitochondrial Function

Adequate mitochondrial function and biogenesis are critical determinants for the folding and secretion of adiponectin in adipocytes[58,59]. Interruption of mitochondrial function inhibits the expression of adiponectin in adipocytes, whereas the induction of mitochondrial biogenesis restores the production of adiponectin[58,59].

MitoNEET is an outer mitochondrial membrane protein and is involved in the regulation of adiponectin release and production through modifying mitochondrial activity in adipocytes[28,30,31]. By reducing mitochondrial activity, overexpression of adipose mitoNEET increases the production of adiponectin in adipocytes and elevates circulating total and HMW adiponectin[30]. CISD2 [nutrient-deprivation autophagy factor-1 (NAF-1)] is another member of the Fe-S protein NEET family[29]. CISD2 is closely related to mitoNEET, sharing 44% overall sequence identity and a highly similar structure and function[60]. Like mitoNEET, CISD2 primarily localizes in the outer mitochondrial membrane, regulates mitochondria functions[61], and promotes adipose adiponectin production and release[62]. The ability of mitoNEET or CISD2 to exert a constitutive stimulatory effect on adiponectin production is mediated by compromising mitochondrial activity in adipose tissues[30,62].

At this time, there is limited knowledge of the effects of ethanol on mitochondrial functions in adipose and intestine and on their relationship with the adiponectin–FGF15/19 axis. Ethanol administration to wild-type control mice markedly increased gene expression of uncoupling protein 1 (UCP1), a mitochondrial protein[13]. Accordingly, adipose mitochondrial DNA (mtDNA) copy number was significantly elevated, and production of adiponectin and FGF15 was disrupted in ethanol-fed wild-type mice[13]. However, ethanol administration to mitoNEET knockout mice decreased the adipose UCP1 expression, reduced mtDNA copy number, and increased adiponectin and ileum FGF15 synthesis[13]. Interestingly, adipose CISD2 gene expression levels were increased in these mitoNEET null mice fed with ethanol, suggesting that adipose CISD2 induction might act as a compensatory molecule in stimulating the adiponectin–FGF15/19 axis[13]. Performing ethanol feeding studies using genetically modified mouse models such as mitoNEET/CISD2 double knockout mice will provide more definitive mechanisms. Given that adiponectin and FGF15 were concurrently elevated in mitoNEET knockout mice after ethanol administration, mitochondrial activity might play a pivotal role in regulating synthesis and production of adipose adiponectin and ileum FGF15/19 in response to ethanol challenge.

Both adiponectin and FGF15/19 can improve mitochondrial health. Adiponectin increases mitochondria content by increasing their biogenesis[63,64]. Adiponectin is also able to rescue the damaged structure and compromised membrane potential[65–67]. The expression of oxidized phosphorylation genes encoded by mitochondria DNA is also restored by adiponectin[68]. In addition, adiponectin is critical to maintain healthy mitochondria in hepatocytes. For instance, adiponectin-deficient mice have reduced mitochondria, spontaneous mitochondrial damage, and a swelling phenotype in hepatocytes[69]. Clinically, elevated serum FGF19 improved mitochondrial health and overall diabetic remission in obese diabetic women undergoing bariatric surgery[70].

Unlike in adipose and intestine, it is well documented that alcohol intake alters hepatic mitochondria in multiple ways, causing liver dysfunction in rodents and humans[71,72]. Given the beneficial functions of adiponectin and FGF15/19 on mitochondria and liver, adiponectin–FGF15/19 signaling may protect the liver from ethanol-induced injury through rescuing mitochondria. In addition, mitochondria are the major source of ROS in nonphagocytic cells like hepatocytes[73]. MitoNEET deficiency attenuated the generation of hepatic oxidative stress in ethanol-administrated mice[13]. The role of adiponecitn–FGF15/19 signaling in mediating effects

of ethanol on hepatic mitochondrial functions warrants future investigation.

Adiponectin–FGF15/19 Signaling and Ethanol-Mediated Disruption of SIRT1–NF-κB Axis

NF-κB is a major master transcription factor regulating proinflammatory cytokines[74]. SIRT1 is an important molecule controlling the pathways of inflammation and lipid metabolism in organs such as the liver[75,76] SIRT1 exerts anti-inflammatory effects by deacetylation of the lysine residues on NF-κB[75–78]. Adiponectin directly upregulates SIRT1 in cultured hepatic cells[14]. More importantly, both adiponectin and FGF15/19 are able to exert anti-inflammatory effects via inhibiting NF-κB[12,13,41]. The SIRT1–NF-κB axis may be one of the critical signaling cascades in mediating adiponectin–FGF15/19 signaling.

It is well established that the aberrant SIRT1–NF-κB axis by ethanol exposure is, in whole or in part, responsible for ethanol-induced inflammation and development of alcoholic steatohepatitis in animals and humans[41,75,76]. Concomitantly elevated adiponectin and FGF15 were associated with elevated hepatic SIRT1 protein levels, reduced acetylated NF-κB, deactivated NF-κB, and attenuated inflammation in mitoNEET or myeloid cell-specific knockout mice after chronic or chronic-binge ethanol administration[12,13]. Conceivably, stimulated adiponectin–FGF15/19 signaling in these mice would attenuate ethanol-induced inflammation via ameliorating hepatic SIRT1–NF-κB signaling.

SUMMARY AND CONCLUSION

The adiponecitn–FGF15/19 axis has recently been gaining recognition as an interorgan crosstalking endocrine coordinator from adipose and gut to liver in response to ethanol challenge in animal models of alcoholic steatohepatitis. Ethanol exposure concomitantly decreases circulating levels of adiponectin and FGF15 and disrupts hepatic adiponectin–FGF15 signaling in rodents. More importantly, stimulation of adiponectin–FGF15/19 signaling profoundly improves alcoholic liver injury by blocking the signals leading to hepatopathogenesis, including inhibiting expression of the LCN2–SAA1 axis, normalizing bile acid homeostasis, preventing iron overload, ameliorating mitochondrial dysfunction, decreasing ROS generation, restoring SIRT1 activity, diminishing NF-κB activity, and limiting inflammatory response (Fig. 1).

The large body of evidence has suggested that ALD is driven by organ crosstalk[79]. Endocrine adiponectin–FGF15/19 axis controls adipose and gut to liver communication arm of an adipose–intestine–liver partnership in response to alcohol challenges. However, other organs such as muscle, bone, spleen, and brain may be within this communication axis regulated by the adiponectin–FGF15/19 axis and ethanol. Further studies will be necessary to clarify the effects of ethanol or its relationship with those crucial additional organs on the dynamics and impacts of the adiponectin–FGF15/19 axis-driven signaling cascades, which ultimately influence liver functions.

The detailed mechanisms whereby adiponectin–FGF 15/19 signaling exerts protective effects against ethanol-induced inflammation and alcoholic liver injury are incompletely understood. As discussed above, the LCN2–SAA1 axis is likely the critical component in mediating adiponectin–FGF15/19 signaling. It is necessary to further clarify the intriguing interplay between disrupted adiponectin–FGF15/19 signaling and the aberrant LCN2–SAA1 axis, and their contributions to ethanol-induced inflammation and liver injury. Performing ethanol feeding studies with various genetically modified animal models, including tissue-specific adiponectin, FGF15, LCN2, or SAA1 conditional knockout mice or transgenic mice will provide a clearer and better mechanistic picture of the interplay of these signaling molecules regulated by ethanol.

Additional aberrant processes, such as circadian rhythms[80], autophagy[81], and ER stress[82], are associated with pathogenesis of ALD. Both adiponectin and FGF15/19 are involved in regulating circadian rhythms[83,84], autophagy[85,86], and ER stress[87,88]. Therefore, it is worthwhile to explore whether and how adiponectin–FGF15/19 signaling ameliorates these disturbed processes and subsequently attenuates inflammatory responses and alleviates liver injury in response to ethanol challenge.

Growing evidence has revealed that disruption of gut microbiota homeostasis is closely associated with pathogenesis in rodents and humans[89]. For example, administration of ethanol to germ-free mice was associated with the absence of liver inflammation and injury, indicating that the presence of abnormal microbiota is necessary for the development and progression of ALD[90]. Furthermore, modulation of gut microbiota dysbiosis could attenuate ethanol-mediated hepatic injury in mice and humans[90–92]. It will be important to investigate the interplay between gut microbiota and ileum FGF15/19 synthesis and how the coordination of gut microbiota and ileum FGF15/19 is disrupted by ethanol. More importantly, it is necessary to investigate whether and how endocrine adiponectin–FGF15/19 signaling improves liver functions by remodeling gut microbiota during ethanol exposure.

The detailed mechanisms by which ethanol dysregulates the adiponectin–FGF15/19 axis will require further elucidation. As discussed above, regulation of iron metabolism represents an important mechanism for mitoNEET, CISD2, and LCN2, and their actions. Therefore, particular attention should be given to these newly emerged molecules. It is worthwhile to explore whether these molecules act as regulators affected by

ethanol in its dysregulation of the adiponectin–FGF15/19 axis via disrupted iron homeostasis. It will also be important to investigate whether reducing iron accumulation in tissues such as adipose, intestine, and liver is a plausible approach to alleviate alcoholic liver injury by boosting the protective adiponectin–FGF15/19 signaling. In addition, it is important to determine how ethanol impairs hepatic receptors for adiponectin and FGF15/19, particularly FGFR4/β-Klotho.

Gender differences are well known in ALD. It is well established in both human alcoholics and animal models of ethanol feeding that females develop more extensive liver injury than males[93]. Although it is unknown whether there are gender-specific changes in the expression of ileum FGF15/19, sexual dimorphism and sex-specific differences have been associated with adiponectin expression and its signaling[94]. Therefore, it is of great importance for future research projects focusing on gender differences in the regulation of adiponectin–FGF15/19 axis and their roles in susceptibility to ALD. In addition, adiponectin–FGF15/19 signaling may also play an important role in the progression of ALD from fibrosis–cirrhosis toward hepatocellular carcinoma. Changes in this signaling interaction may alter the progression of ALD and thus provide potential targets for therapeutic intervention.

The clinical relevance of adiponectin–FGF15/19 signaling in the pathogenesis of alcoholic steatohepatitis will need to be further evaluated. It will also require determining the correlation between the impaired adiponectin–FGF15/19 axis and the severity of liver injury (mild to moderate and severe liver injury in response to alcohol abuse). Prolonged exposure to FGF19 leads to the formation of hepatocellular carcinomas in rodents. This may limit clinical applications of FGF19. Therefore, it is important to explore the possibility of using nontumorigenic FGF19 variants of FGF19. Nonetheless, endocrine adiponectin–FGF15/19 signaling has profound beneficial effects in normalizing ethanol-induced deranged inflammatory processes through targeting the liver. Therefore, the adiponecitn–FGF15/19 axis represents an excellent pathway for the treatment of human alcoholic steatohepatitis. Enhancing or optimizing the adiponectin–FGF15/19 signaling may serve as a potent strategy in the management and treatment of human ALD.

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