World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i6.802

World J Gastroenterol 2013 February 14; 19(6): 802-812
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

What is the role of adiponectin in obesity related non-alcoholic fatty liver disease?

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Received: June 26, 2012 Revised: December 3, 2012
Accepted: December 15, 2012
Published online: February 14, 2013

Abstract

Non-alcoholic fatty liver disease (NAFLD) is recognized as the most common type of chronic liver disease in Western countries. Insulin resistance is a key factor in the pathogenesis of NAFLD, the latter being considered as the hepatic component of insulin resistance or obesity. Adiponectin is the most abundant adipose-specific adipokine. There is evidence that adiponectin decreases hepatic and systematic insulin resistance, and attenuates liver inflammation and fibrosis. Adiponectin generally predicts steatosis grade and the severity of NAFLD; however, to what extent this is a direct effect or related to the presence of more severe insulin resistance or obesity remains to be addressed. Although there is no proven pharmacotherapy for the treatment of NAFLD, recent therapeutic strategies have focused on the indirect upregulation of adiponectin through the administration of various therapeutic agents and/or lifestyle modifications. In this adiponectin-focused review, the pathogenetic role and the potential therapeutic benefits of adiponectin in NAFLD are analyzed systematically.

Key words: Non-alcoholic fatty liver disease; Obesity; Adiponectin; Visceral fat; Adipokines

Finelli C, Tarantino G. What is the role of adiponectin in obesity related non-alcoholic fatty liver disease? *World J Gastroenterol* 2013; 19(6): 802-812 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i6/802.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i6.802

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common type of chronic liver injury in many countries[1,2]. NAFLD includes a spectrum of syndromes, ranging from simple steatosis, non-alcoholic steatohepatitis (NASH) to fibrosis, cirrhosis and hepatocellular carcinoma[3]. The overall prevalence of NAFLD is 15%-40% in Western countries and 9%-40% in the Asian population[4]. NAFLD has dramatically increased over the past 15 years, mainly as a consequence of its close association with two major worldwide epidemics, obesity and type 2 diabetes mellitus (T2DM)[5]. Mortality in patients with NAFLD is significantly higher than in the age and gender-matched general population[6]. Disease progression to NASH and cirrhosis appears to be very slow, and only a few patients develop life-threatening advanced liver disease.

In many cases of NAFLD, the risks of developing metabolic and cardiovascular morbidities are much higher than the risks of developing hepatic diseases[7,8]. In fact, NAFLD is considered as the hepatic manifestation of the metabolic syndrome, which refers to a cluster of cardiovascular risk factors associated with insulin resistance, including central obesity, hypertension, dyslipidemia and T2DM[9]. The association between NAFLD and metabolic syndrome has been established in many cross-sectional and prospective studies[8]. NAFLD significantly increases the risk of diabetes and is a better predictor of the development of metabolic disorders than obesity

itself[10]. Some studies have reported an association of NAFLD with multiple classical and non-classical risk factors for cardiovascular diseases[7]. NAFLD predicts future cardiovascular events independently of other prognostic factors, including the component of metabolic syndrome. In summary, NAFLD is associated with a future high incidence of cardiovascular and metabolic complications and should be considered beyond a liver disease confined to classical boundaries. Understanding the disease and its management is a vital issue in current clinical practice.

PATHOGENESIS OF NAFLD

Although the pathogenesis of NAFLD remains largely unknown, insulin resistance, oxidative stress and inflammation play important roles in the development and progression of NAFLD[11,12]. Fatty liver itself is a status of insulin resistance. Hepatic fat accumulation can lead to hepatic insulin resistance, which may occur before the alterations in peripheral insulin actions and may induce peripheral insulin resistance[13,14]. Insulin regulates the uptake, oxidation and storage of fuel within insulin-sensitive tissues including the liver, skeletal muscle and fat. Peripheral insulin resistance impairs glucose uptake from blood into skeletal muscle and adipose tissue; serum non-esterified fatty acid (NEFA) levels may also be elevated because of the failure of insulin to suppress lipolysis[15,16]. In the liver, insulin resistance is associated with increased cellular contents of fatty acids and their metabolites (fatty acyl-CoAs, diacylglycerides and ceramides)[17-19]. Hyperinsulinemia caused by insulin resistance, in the presence of increased circulating levels of NEFA, enhances the hepatic uptake of fatty acid and promotes lipogenesis[1,20]. In addition, defects in mitochondrial β-oxidation, enhanced fatty acid synthesis and impaired secretion of triacylglyceride-rich very low density lipoproteins also contribute to hepatic steatosis[21-23]. A growing body of evidence from animal models suggests a "two-hit" hypothesis as being responsible for the development of NAFLD[24-26]. According to this theory, the first hit is the occurrence of fatty liver (steatosis), followed by a second event leading to the development of NASH. The potential secondary hits include endotoxin exposure, alcohol consumption and virus infections, which expand hepatic lipid stores, cause hepatocellular injury, and promote oxidative stress and inflammation in the liver. Lipotoxicity, and the release of cytokines and other pro-inflammatory mediators, play important roles during this process. Moreover, inflammation in the development of NASH can further impede insulin signaling[27]. Histologically, NASH is manifested by hepatocyte nuclear ballooning, hepatocyte apoptosis, Mallory's hyaline and inflammation foci[28]. NAFLD patients have a high circulating free fatty acids (FFAs) level that correlates with the severity of liver disease. Overloaded FFAs may exhibit lipotoxicity by inducing the expression of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α)[29].

VISCERAL OBESITY, ADIPOKINES AND NAFLD

Obesity, especially visceral obesity, is frequently associated with NAFLD and their coexistence in the same individual increases the likelihood of having more advanced forms of liver disease[30,31]. NAFLD occurs in 60%-95% of people with obesity[32]. Visceral fat is a key mediator of NASH and is strongly associated with alanine aminotransferase (ALT) levels in the nondiabetic obese population[31,33,34]. The importance of visceral fat in the pathogenesis of NAFLD has also been shown in many animal models, including *fa/fa* obese rats. In these animals, surgical resection of intra abdominal fat depots reverses hepatic insulin resistance and steatosis[35].

Recent evidence suggests that visceral adipose tissue is a metabolic and inflammatory organ that signals and modulates the action and metabolism of the brain, liver, muscle and cardiovascular system[36,37]. The imbalanced production of pro- and anti-inflammatory adipokines secreted from fat contributes to the pathogenesis of NAFLD[38]. Modulation of endocrine/immune/inflammatory interactions of adipose tissue may provide novel therapeutic (pharmacological) targets for the treatment of NAFLD. For example, in patients with severe lipodystrophy, injection with leptin reverses nonalcoholic fatty liver diseases[39,40]. However, in cases of NAFLD associated with obesity, serum levels of leptin are increased, and the liver becomes refractory to the "anti-steatotic" effects of leptin[41-43]. Leptin infusion is therefore unlikely to be of therapeutic value for patients with NAFLD. TNF-α, a pro-inflammatory adipokine that interferes with insulin signaling and favors steatosis, may play a casual role in the pathogenesis of NASH[38]. Circulating levels of TNF-α and hepatic expression of its type 1 receptor are increased in NASH, but could not discriminate steatohepatitis from steatosis[44-46]. Neutralization of TNF-α activity improves fatty liver disease in animals[47]. Conversely, nutritional steatohepatitis can still be produced experimentally in both TNF-α and TNF-α type 1 receptor knockout mice, suggesting that this adipokine might not be an essential mediator of NAFLD[48,49]. In contrast to leptin and TNF-α, adiponectin is more closely implicated in the pathogenesis of NAFLD/NASH. Unlike other adipokines, serum levels of adiponectin are decreased in obesity and its associated medical complications[50]. A negative association between serum levels of adiponectin and liver enzyme levels has been shown in healthy subjects[51]. Numerous epidemiological investigations in diverse ethnic groups have identified lower adiponectin level as an independent risk factor for NAFLDs and liver dysfunctions[37]. Compared with healthy controls, adiponectin levels are lower by more than 50% in NASH patients[52]. Adiponectin expression is decreased by 20%-40% during the development of NAFLD, from simple steatosis to NASH[52,53]. Moreover, NASH patients with lower levels of adiponectin show higher grades of inflammation, suggesting that adiponectin deficiency is an important risk factor

for the development of fatty liver, steatohepatitis and other forms of liver injuries[52-55]. In patients with T2DM, plasma adiponectin concentrations are inversely related to hepatic fat content[56]. There is a direct relationship between hypoadiponectinemia and NASH, independent of insulin resistance[52]. Animal-based studies have demonstrated that adiponectin possesses potent protective activities against various forms of liver injury, including those induced by carbon tetrachloride, lipopolysaccharide (LPS)/*D*-galactosamine, pharmacological compounds, bile duct ligations and methionine-deficient diet[57-61]. In animal models of both alcoholic and nonalcoholic steatohepatitis, exogenous adiponectin reduces hepatomegaly, depletes lipid accumulation, quenches hepatic inflammation and decreases hepatic expression and plasma concentrations of TNF-α[62]. Adiponectin knockout mice exhibit an enhanced pattern of hepatic fibrosis induced by carbon tetrachloride[58]. The lack of adiponectin expression could accelerate hepatic tumor formation in a NASH model in mice[63]. Among the known adipokines, adiponectin stands out for its insulin-sensitizing and anti-inflammatory roles, and may be used as a promising drug candidate for the treatment of liver diseases.

HEPATOPROTECTIVE FUNCTIONS OF ADIPONECTIN: STRUCTURAL BASIS AND SIGNALLING MECHANISMS

Four independent groups originally identified adiponectin, also termed Acrp30, AdipoQ, apM1 or GBP28, in both mice and humans[64-67]. This adipokine has attracted much attention because of its multiple beneficial effects on a cluster of obesity-related metabolic and cardiovascular dysfunctions. Hypoadiponectinemia is a key etiological factor contributing to almost all the major pathological conditions associated with obesity[68]. The physiological functions and clinical relevance of adiponectin in obesity-related medical complications have been extensively reviewed elsewhere[50,69-72]. In the following sections, we will discuss recent advances on the structural regulations of adiponectin as well as the molecular evidence supporting the role of adiponectin as a major protective agent against obesity-related NAFLD.

Polymorphism of the multimeric structures of adiponectin

A unique feature of the structure of adiponectin is its ability to assemble into several characteristic oligomeric isoforms, including trimers [low molecular weight (LMW)], hexamers [middle molecular weight (MMW)] and the oligomeric complexes comprising 18 protomers or above [high molecular weight (HMW)][73]. Adiponectin presents predominantly in the circulation as these three oligomeric complexes[74-79]. Trimeric adiponectin is the basic building block of adiponectin. The subunits in the trimer are associated *via* hydrophobic interactions. Two LMW adiponectin molecules linked by disulfide bonds form hexameric adiponectin. The structural properties of the HMW adiponectin remain poorly characterized because of the heterogeneous nature of this isoform. Analysis of adiponectin oligomers by non-denaturing and non-heating gel electrophoresis shows that the human HMW adiponectin composes of a mixture of 18-30 mers, or even larger molecular weight species[73,78,80,81]. Dynamic light scattering and transmission electron microscopy shows that the bovine HMW adiponectin forms a bouquet-like architecture resembling that of complement C1q[82]. Six globular objects can be seen atop a thin stalk, which presumably correspond to the six LMW adiponectins. The stalks bunch together in a manner that is consistent with the requirement for NH2-terminal disulfide bonding. The side views of HMW adiponectin suggest a conical structure of the oligomer with the COOH-terminal portion forming the base. Interestingly, these globular domains are arranged in a tight ring. This circular arrangement might enable polyvalent interactions of the globular domains with a single receptor. Recently, the HMW oligomeric structures formed by multiples of adiponectin trimers have been determined by single-particle analysis of electron micrographs[83]. Pleiomorphic ensembles of collagen-like stretches of the trimers lead to a highly dynamic structure of HMW adiponectin, which can be classified into two major classes: the fan-shaped (Class Ⅰ) and bouquet-shaped (Class Ⅱ). In both of these conformations, the globular domains assume a variety of arrangements, covering an area of up to 4.9 × 105 Å^2 and up to 320 Å apart. The conformational flexibility of the HMW oligomer can allow it to access and cluster disparate target ligands or receptors, which may be necessary to activate cellular signaling leading to the remarkable functional diversity of adiponectin.

HMW adiponectin as a major bioactive form in liver

Obese individuals have different distribution of adiponectin oligomers compared with lean controls. Relatively lower content of HMW adiponectin is closely associated with obesity-related metabolic complications[81]. The increases in the ratio of HMW *vs* total adiponectin, but not total adiponectin level *per se*, correlate well with improved insulin sensitivity during treatment with the insulin-sensitizing drug thiazolidinediones, in both diabetic mice and patients with T2DM. On the other hand, weight reduction by either calorie restriction or gastric bypass surgery results in a selective elevation of the HMW adiponectin, but not the trimeric and hexameric complexes[84-86]. An independent inverse association exists between ALT and HMW adiponectin[87]. Taken together, these epidemiological and genetic data suggest that the beneficial effects of adiponectin in humans might be mediated primarily by its HMW isoform, and the deficiency of this oligomer is an important etiological factor that links obesity with its medical complications.

Evidence from both *in vitro* and animal-based studies also supports the role of the HMW oligomer as the major active form in mediating the multiple actions of adiponectin in liver tissue. Recombinant adiponectin pro-

duced from mammalian cells, which can form the HMW oligomers, potently decreases hyperglycemia in diabetic mice through inhibition of hepatic glucose production[88]. However, bacterially generated full-length adiponectin, which lacks the capacity to form the HMW adiponectin, is almost inactive. Intravenous injection of the HMW adiponectin, but not the hexameric adiponectin, leads to a dose-dependent decrease in serum glucose levels[81]. The formation of the HMW oligomers is obligatory to mediate the insulin sensitizing effects of adiponectin on suppression of hepatic gluconeogenesis in primary rat hepatocytes[80]. Acute injection of recombinant adiponectin enriched with the HMW oligomers results in a marked activation of AMP-activated kinase (AMPK) in the liver, while chronic infusion with this protein leads to prolonged alleviation of hyperglycemia and insulin resistance in *db/db* diabetic mice[89]. This animal-based evidence is consistent with the clinical observations showing that the ratio of HMW/total adiponectin correlates closely with hepatic insulin sensitivity[81]. The role of the HMW oligomer as a predominant active form of adiponectin mediating its hepatic actions is also supported by two recent independent reports demonstrating that the insulin-sensitizing effects of the peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists thiazolidinediones were diminished in *ob/ob* obese mice with the targeted mutation of the adiponectin gene[90,91]. Notably, treatment with thiazolidinediones causes a selective elevation of the HMW oligomeric adiponectin[79,81]. In addition to the hepatic insulin-sensitizing activity, the HMW adiponectin has also been suggested to be the most potent isoform for alleviation of fatty liver disease in high fat diet-induced obese mice[92], and inhibition of apolipoprotein B and E release from human hepatocytes[93]. HMW adiponectin dose-dependently suppressed growth factor-induced hepatic stellate cell proliferation[94]. Taken together, these data suggest that the HMW form predominantly mediates the beneficial effects of adiponectin in hepatic tissue.

Receptors and postreceptor signaling pathways mediating the hepato-protective functions of adiponectin

Two adiponectin receptors (adipoR1 and adipoR2) have been identified and found to be expressed in various tissues[95]. AdipoR1 is abundantly expressed in skeletal muscles, whereas adipoR2 is present predominantly in the liver, suggesting a role of adipoR2 in hepatic adiponectin signaling[68,96]. Recently, several laboratories have investigated the physiological roles of adipoR1 and adipoR2 in *adipoR1/2* knockout mice. Both *adipoR1* and *adipoR2* knockout mice exhibit mild insulin resistance[97]. In *adipoR1/R2* double knockout mice, the binding and actions of adiponectin are abolished, resulting in increased tissue triglyceride content, inflammation and oxidative stress[97]. *AdipoR2* knockout mice reported by Liu *et al*[98] displayed reduced diet-induced insulin resistance, but promoted T2DM. These data support the physiological roles of adipoR1 and adipoR2 as the predominant receptors for adiponectin in the regulation of glucose and lipid metabolism. Despite this information, the detailed roles and expression of adipoRs in NAFLD are not conclusive[38,99-102].

Adiponectin stimulates AMPK in almost all its major target tissues, including skeletal muscle, liver, heart, endothelium, adipocytes and brain[75,89,103-106]. Notably, most biological effects of adiponectin in these target tissues are abrogated by expression of a dominant negative version of AMPK, supporting its obligatory role in mediating adiponectin's multiple actions. The precise mechanisms whereby adiponectin activates AMPK through its receptors remain to be determined. APPL1, an adaptor protein containing a pleckstrin homology domain, a phosphotyrosine binding domain and a leucine zipper motif, appears to be a key signaling molecule that couples adiponectin receptors and its downstream AMPK activation[103,107]. Adiponectin enhances the binding of APPL1 to both adipoR1 and adipoR2, and these interactions are essential for subsequent phosphorylation and activation of AMPK. Studies also indicate the important role of APPL1 in the metabolic syndrome[108,109]. AMPK activation in turn phosphorylates acetyl Coenzyme A carboxylase (ACC) and attenuates ACC activity. Inhibition of ACC reduces lipid synthesis and enhances fatty acid oxidation by blocking the production of malonyl-CoA, an allosteric inhibitor of carnitine palmitoyl transferase 1, the rate-limiting enzyme in fatty acid oxidation. In addition, activation of AMPK downregulates the expression of sterol regulatory element-binding protein 1c (SREBP1c), a transcription factor that regulates cholesterol and lipid synthesis. Reduction of SREBP1c results in downregulation of genes involved in lipogenesis, including ACC, fatty acid synthase, and glycerol-3-phosphate acyltransferase[104,110,111].

PPARα is a transcription factor controlling the transcription of a panel of genes encoding fatty acid oxidation enzymes, such as FATP, acyl-CoA oxidase and long chain acyl-CoA synthetase. Adiponectin stimulates PPARα activity possibly through PPARγ coactivator-1α[112]. These adiponectin-mediated signaling pathways lead to enhanced fat oxidation, reduced lipid synthesis and prevention of hepatic steatosis (Figure 1).

Cellular mechanisms contributing to the anti-inflammatory activities of adiponectin in NAFLD

Inflammatory cytokines are key mediators of hepatic inflammation, cell death, and fibrosis, as well as regeneration after massive or focal liver injury[38,113]. Adiponectin levels are negatively associated with mediators of inflammation, including interleukin-6 (IL-6) and C-reactive protein; but positively related to anti-inflammatory cytokine IL-10[114,115]. It suppresses TNF-α functions by inhibiting its expression and antagonizing its activities[61,62,116,117]. In the liver, cytokines such as IL-6 and TNF-α, are mainly produced from Kupffer cells and hepatic stellate cells (HSC), and partly from inflamed hepatocytes[52,118,119]. Adiponectin ameliorates NASH and liver fibrosis by suppressing the activation of Kupffer

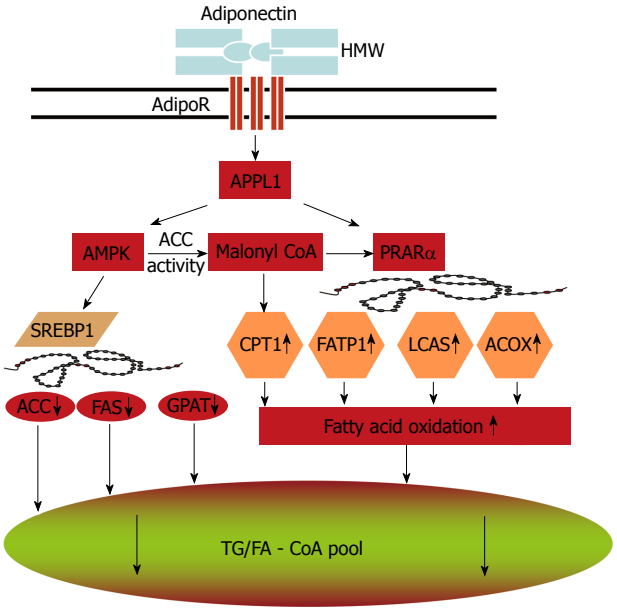

Figure 1 Summary of multiple signaling pathways that mediate the anti-steatotic effects of adiponectin. HMW: High molecular weight; AdipoR: Adiponectin receptor; APPL1: Adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1; AMPK: AMP-activated kinase; ACC: Acetyl Coenzyme A carboxylase; CPT1: Carnitine palmitoyl transferase 1; SREBP1: Sterol regulatory element-binding protein 1; FAS: Fatty acid synthase; GPAT: Glycerol-3-phosphate acyltransferase; ACOX: Acyl-CoA oxidase; LCAS: Long chain acyl-CoA synthetase; FATP: Fatty acid transport protein; PPARα: Peroxisome proliferator-activated receptor α; TG: Triacylglyceride; FA: Fatty acid.

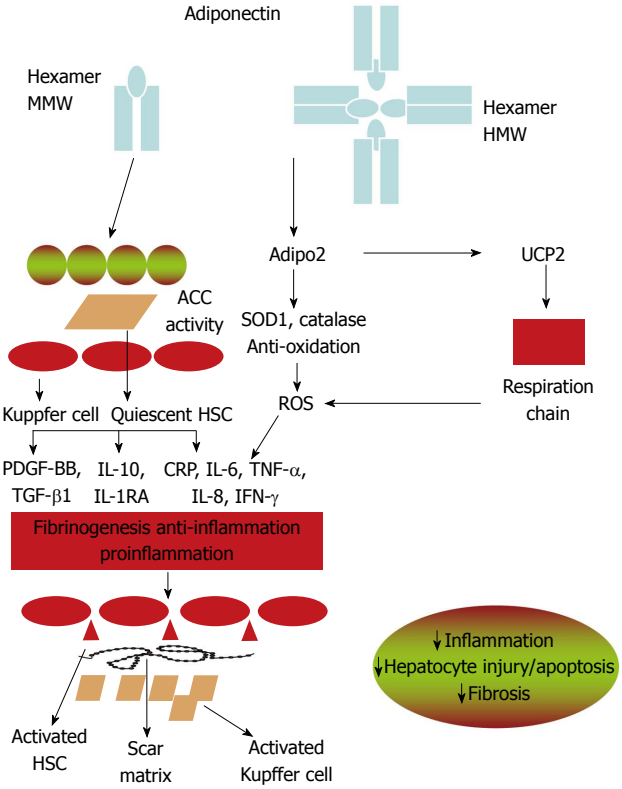

Figure 2 Summary of multiple pathways underlying the protective effects of adiponectin against liver injury. MMW: Middle molecular weight; HMW: High molecular weight; AdipoR: Adiponectin receptor; UCP: Uncoupling protein; SOD1: Superoxide dismutase 1; ROS: Reactive oxygen species; PDGF-BB: Platelet-derived growth factor BB; TGF-β1: Transforming growth factor-β1; CRP: C-reactive protein; IL: Interleukin; IL-1RA: Interleukin-1-receptor antagonist; TNF-α: Tumor necrosis factor-α; HSC: Hepatic stellate cells; IFN-γ: Interferon-γ.

cells and HSC (Figure 2). In porcine blood-derived macrophages, adiponectin suppresses both TNF-α and IL-6 production stimulated by LPS and induces IL10 expression. The attenuation of proinflammatory cytokine production by adiponectin is mediated in part by attenuating the translocation of nuclear factor kappa B (NF-κB) to the nucleus[120]. Adiponectin can also induce the expression of the anti-inflammation cytokine interleukin-1-receptor antagonist[121,122]. The anti-inflammatory effects of adiponectin in macrophages may involve the toll-like receptor-4 (TLR-4) signaling pathway. However, the mechanisms by which adiponectin suppresses TLR-4 mediated responses are not well understood[123].

The transformation of HSC into myofibroblasts is the key step that initiates the fibrotic process during liver injury[124,125]. The activated hepatic stellate cells increase the accumulation of extracellular matrix. Both adiponectin receptors, adipoR1 and adipoR2, are expressed in HSC. Adiponectin treatment maintains HSC quiescence, inhibits platelet-derived growth factor-stimulated proliferation and migration of human HSCs, and reduces the secretion and of monocyte chemoattractant protein-1 through AMPK-dependent mechanisms[94,125,126]. Additionally, adiponectin also regulates hepatic expression of TGFβ1, a pro-fibrotic factor involved in HSC activation[58,127] that plays an important role in neofibrogenesis of NAFLD[128].

Inhibition of adipoR2 expression by short hairpin RNAi-expressing adenovirus can induce TGFβ1 expression, and overexpression of adipoR2 diminishes TGFβ1 mRNA level.

Regulatory role of adiponectin on mitochondria activities

Mitochondrial dysfunction represents a central mechanism linking obesity with associated metabolic complications[129]. In patients with NASH, the hepatic mitochondria exhibit ultrastructural lesions and decreased activity of the respiratory chain complexes[130,131]. In this condition, the decreased activity of the respiratory chain results in accumulation of reactive oxygen species (ROS) that oxidize fat deposits to form lipid peroxidation products, which in turn, cause steatohepatitis, necrosis, inflammation and fibrosis. The increased mitochondrial ROS formation in steatohepatitis could directly damage mitochondria DNA and respiratory chain polypeptides, induce NF-κB activation and the hepatic synthesis of TNFα[132]. Oxidative phosphorylation reactions mediated by mitochondria respiratory chain (MRC) complexes are directly involved in regulating intracellular ROS activities and preventing accumulation of lipids and lipid peroxidation products in the liver.

Mice without adiponectin show an increased lipid

accumulation even under normal chow feeding[117]. This pre-existing hepatic steatotic condition might be the direct consequence of dysregulated mitochondria functions[117]. Adiponectin treatment restores the MRC activities, decreases the levels of mitochondrial lipid peroxidation products through regulating hepatic mitochondrial functions, which might represent a common mechanism underlying the multiple beneficial activities of this hormone in various obesity-related pathologies. Moreover, we have provided evidence supporting an essential role of uncoupling protein 2 (UCP2), a mitochondria inner membrane transporter, in mediating the beneficial effects of adiponectin on MRC activities. The protein and mRNA levels of UCP2 are decreased in the liver tissues of adiponectin knockout mice and can be significantly upregulated by adiponectin treatment. Overexpression of adipoR2 upregulates mRNA levels of UCP2, catalase, and superoxide dismutase 1 in the liver[97]. Furthermore, the effects of adiponectin on MRC activities are dramatically attenuated in *Ucp2*-deficient mice, suggesting that the increased UCP2 expression might be obligatory for adiponectin to elicit its activities on mitochondria functions (Figure 2). UCP2 possesses anti-oxidant activities through inhibition of ROS production from mitochondria[133]. It can also inhibit the production of pro-inflammatory cytokines in both macrophage and Kupffer cells[134]. A growing body of evidence suggests that UCP2 may play a beneficial role in various stages of fatty liver diseases[134,135]. These results suggest the existence of a reciprocal relationship between uncoupling proteins and adiponectin. However, the detailed signaling mechanisms underlying adiponectin-induced UCP2 expression are not clear and warrant further investigation.

ELEVATION OF ADIPONECTIN PRODUCTION AS A THERAPEUTIC STRATEGY FOR TREATMENT OF NAFLD

To date, there have been very few effective drug treatments for NAFLD and NASH. Early diagnosis and management of the underlying condition remains the mainstay of treatment. The present "gold standard" for treatment of NAFLD is weight reduction or a reduction of central obesity[4]. These "life-style adjustment" or anti-obesity measures (including bariatric surgery) impressively reduce liver cell injury, inflammation and hepatic fibrosis, as well as steatosis[136,137]. The potential for correcting steatosis by dietary or pharmacological approaches should provide a sound therapeutic approach for the treatment of steatosis and steatohepatitis. Strategies to block oxidative stress are of great interest, with some evidence that ALT normalization or histological improvement occurs with vitamin E (alone or with vitamin C or pioglitazone) and betaine[138].

Adiponectin and its agonists might represent emerging therapeutic agents for the treatment and/or prevention of liver dysfunctions[139-141]. Adiponectin replacement therapy is not yet available as a treatment option. Pharmacological intervention aimed at elevating adiponectin production might hold promise for the treatment and/or prevention of NAFLD.

CONCLUDING REMARKS

Based on our data, polymorphic UCP1 (AG + GG) obese patients with low adiponectin levels appear to be high-risk subjects for worsening of liver steatosis, an NAFLD, possibly requiring a second-step evaluation by liver biopsy[142].

The role of adiponectin in systemic inflammation and critical illness is not well defined. Early data suggest that plasma levels of adiponectin are decreased in critical illness[143]. Whether this is a result of the disease process itself or whether patients with lower levels of this hormone are more susceptible to developing a critical illness is not known. This observation of lower adiponectin levels then raises the possibility of therapeutic options to increase circulating adiponectin levels[143]. The various options for modulation of serum adiponectin (recombinant adiponectin, thiazolidinediones) are discussed.

Nevertheless, adiponectin-based therapeutics for NAFLD represent a promising area for further investigation.

CONCLUSION

Adiponectin is an abundant adipocyte-derived hormone with well established anti-inflammatory and insulin sensitizing properties. The significance of adiponectin in protecting obesity-related NAFLD has been increasingly recognized. Despite the advances made in recent years, the detailed molecular and cellular mechanisms underlying its hepato-protective functions remain largely uncharacterized.

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