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Adiponectin as an anti-fibrotic and anti-inflammatory adipokine in the liver

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Abstract

Hepatic fibrosis is a dynamic process resulting from excessive deposition of extracellular matrix in the liver; uncontrolled progression of fibrosis can eventually lead to liver cirrhosis and/or hepatocellular carcinoma. The fibrogenic process is complex and modulated by a number of both hepatic and extra-hepatic biological factors. Growing evidence indicates that adipokines, a group of cytokines produced by adipose tissue, impart dynamic functions in liver and are involved in modulation of hepatic fibrosis. In particular, two key adipokines, adiponectin and leptin, directly regulate many biological responses closely associated with development and progression of hepatic fibrosis. Leptin acts as a pro-fibrogenic cytokine, while adiponectin possesses anti-fibrogenic and anti-inflammatory properties. Adiponectin, acting via its cognate receptors, adiponectin receptors 1 and 2, potently suppresses fibrosis and inflammation in liver via multiple mechanisms. This review summarizes recent findings concerning the role of adiponectin in fibrogenic process in liver and addresses the underlying molecular mechanisms in modulation of fibrosis.

Keywords

Adiponectin; Fibrosis; Inflammation; Liver

Introduction

Hepatic fibrosis is a dynamic integrated process that occurs in response to liver injury, resulting from a repeated cycle of injury and activation of the wound healing process.

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Conflict of Interest

Pil-Hoon Park, Carlos Sanz-Garcia and Laura E Nagy declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

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Fibrosis is characterized by excessive accumulation of extracellular matrix (ECM), predominantly collagen 1, and can ultimately lead to irreversible cirrhosis [1]. Hepatic stellate cells (HSCs) act as central players in development and progression of liver fibrosis. In quiescent stage, HSCs reside in the Space of Disse and serve as the principal storage of retinyl esters in liver; additional significant biological functions of quiescent HSCs are not well understood. In response to liver injury, HSCs become activated, their morphological features are dramatically changed and they acquire new biological functions. In the activated state, the morphology of the cells is sharply changed from star-like shape to that of fibroblasts, associated with an increase in expression of cytoskeletal proteins, such as α-smooth muscle actin (α-SMA). Activated HSCs are proliferative and become resistant to apoptosis, secrete collagen and other extracellular matrix proteins, migrate to the sites of liver injury and secrete chemotactic factors that recruit immune cells to the sites of injury [2–4]. Therefore, activation of HSCs is considered a central event in the onset and progression of hepatic fibrosis.

It is well established that various cytokines are involved in the pathogenesis of hepatic fibrosis. For example, transforming growth factor (TGF)-β1, the proto-typical pro-fibrotic cytokine, stimulates HSCs to produce ECM [5]. A number of studies have also demonstrated that adipokines, a group of cytokines primarily derived from adipose tissue, exert a role in the regulation of hepatic fibrosis [6]. The two primary adipokines, adiponectin and leptin, are the best characterized adipokines affecting liver disease. Adiponectin is widely known to act as a potent anti-fibrotic cytokine, while leptin acts as a pro-fibrogenic cytokine. Interestingly, adiponectin impacts the development of hepatic fibrosis via multiple mechanisms, with both direct anti-fibrotic effects on HSCs, as well as indirect anti-fibrotic roles via its anti-inflammatory activities [7–9]. Recent evidence also suggests that adiponectin can influence the regulation of hepatocyte proliferation [10], which may also influence the fibrogenic response to liver injury. Herein, we review the recent findings regarding the protective effects of adiponectin in hepatic inflammation and fibrosis, as well as briefly summarizing the contributions of other key adipokines.

Overview of the effects of adiponectin and other adipokines on liver diseases

Adipose tissue acts as a dynamic endocrine organ via secretion of diverse biomolecules, collectively called adipokines. In addition to playing a critical role in the physiology of adipose tissue, adipokines regulate multiple non-adipose cellular and tissue targets and are involved in regulation of a variety of homeostatic functions, including energy metabolism, inflammation and immune function [11]. Once adipokines are secreted from adipose tissue, they circulate in the blood stream to reach their target organ(s). Adipokines then bind their cognate receptors and modulate various physiological functions. Liver is one of the major target organs affected by adipokines; adiponectin and leptin have particularly critical regulatory functions in the liver. Development and progression of various liver diseases, including ALD and NAFLD/NASH, are modulated by adiponectin and leptin. Here, we provide a general overview of the effects of adiponectin in liver disease, particularly focused

on its role in fibrosis, as well as a brief description of the contributions of other adipokines to fibogenesis.

ADIPONECTIN

Adiponectin is the most abundant adipokine in the plasma, comprising approximately 0.05% of the total plasma protein [12]. In addition to the crucial role in the lipid and glucose metabolism, adiponectin has multiple beneficial effects in the human body, including potent anti-inflammatory responses and modulation of reactive oxygen species production [13]. The two major receptors for adiponectin (AdipoR1 and AdipoR2) are present in liver and the signaling generated from binding with its receptors plays a protective role against various liver diseases (see Figure 1). In particular, growing evidence from both *in vitro* and *in vivo* models suggests that adiponectin suppresses development and progression of hepatic fibrosis. For example, injection of adenovirus producing adiponectin suppressed carbon tetrachloride (CCl_4)-induced liver fibrosis [7]. Adiponectin treatment also had a protective effect in acetaldehyde-induced collagen production in HSCs [14]. Moreover, hepatic fibrosis and tumor formation was enhanced by choline-deficient L-amino acid-defined (CDAA) diet in adiponectin knock-out compared to wild-type mice [15]. Progression of high-fat diet-induced liver injury, a common model of NAFL/NASH, to hepatic fibrosis was also significantly increased in adiponectin knock-out compared to wild-type mice [16], while adiponectin-overexpressing transgenic mice were resistant to fibrosis induced by exposure to thioacetamide [17].

These protective effects of adiponectin are due, at least in part, to its direct effects in regulating the activation state of HSCs. For example, adiponectin prevents proliferation and migration of HSCs [18], as well as decreases ECM deposition via alteration of molecular ratio of MMP-1 to TIMP-1 (by increasing TIMP-1 expression, and/or decreasing MMP-1 expression) [19]. Adiponectin also sensitizes activated HSCs to caspase-mediated apoptosis [20]. Collectively, these data implicate adiponectin in maintenance of HSCs in their quiescent state and promoting the reversal of HSC activation. The detailed molecular mechanisms underlying these anti-fibrotic effects of adiponectin will be discussed in the next sections.

Although adiponectin is predominantly produced from adipocytes, the plasma level of adiponectin is decreased in obesity, in contrast to other adipose tissue-derived hormones, such as leptin. Given this inverse relationship between obesity and the plasma level of adiponectin, lower availability of adiponectin has been implicated in the development of steatosis, inflammation and fibrosis in liver. For example, hypoadiponectinemia predicts the severity of hepatic fibrosis [21] and is associated with advanced fibrosis in patients with NAFLD [22]. Furthermore, lower plasma level of high molecular weight (HMW) adiponectin is a predictor of liver fibrosis in patients with HCV infection [23]. The circulating concentration of adiponectin is also negatively associated with chronic inflammation and accumulation of fat in liver in some rodent models of alcoholic liver disease [24]. Taken together, these data indicate that plasma concentrations of adiponectin might be a useful biomarker of hepatic steatosis, inflammation and fibrosis in liver diseases of varied etiologies.[25].

While many studies have identified adiponectin as an anti-inflammatory and anti-fibrotic cytokine, a few studies have reported that the circulating adiponectin concentration is positively associated with the development of liver diseases. For example, adiponectin concentration in the plasma is enhanced in severe hepatic fibrosis and declines with reduction in fibrosis in chronic hepatitis B patients [26]. Further, plasma adiponectin correlates with the progression of liver disease in HBV infection [27]. These contradictory results are most likely related to the stage of liver injury studied, with more severely impaired hepatic function perhaps impairing clearance of adiponectin from the circulation. Alternatively, the specific type of liver disease, i.e. HBV compared to HCV, may also contribute to these disparate findings. The impact of elevated adiponectin in more severe liver injury is not well understood and should be the focus of future investigations.

Given the predominant inverse correlation between lower adiponectin and progression of liver injury, studies have investigated the impact of restoring adiponectin in halting the progression of disease. For example, treatment with pioglitazone, an agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ), increased plasma level of adiponectin in NASH and also improved associated pathologies in NASH patients, including reducing hepatic steatosis, necro-inflammation and progression to fibrosis [28,29]. In addition, a recent study found that treatment with a synthetic peptide possessing adiponectin properties (ADD355) modulates various biochemical markers for fibrosis and reversed liver fibrosis induced by CCl_4 in mice [30]. These studies suggest that there is potential promise in the development of agents to enhance adiponectin production or activation of adiponectin receptor via agonists as interventions for the treatment or reversal of hepatic fibrosis.

Additional adipokines and liver fibrosis

Leptin, originally reported to regulate energy balance and appetite, was the first identified hormone produced from adipose tissue [31]. Leptin is also produced by other tissues, including skeletal muscle, placenta and vascular cells [32], as well as adipose tissue. Leptin is also secreted by activated, but not quiescent, HSCs and can interact with HSCs in an autocrine manner [33]. In contrast to the beneficial effects by adiponectin, leptin has been shown to promote hepatic fibrosis via up-regulation of TGF-β1 and other inflammatory cytokines by Kupffer cells and sinusoidal endothelial cells [34–36], as well as enhancing expression of collagens and facilitating proliferation of HSCs [37]. Moreover, the absence of leptin or leptin receptor causes a marked reduction of hepatic fibrosis in various *in vivo* models of fibrosis [38], indicating a critical role of leptin in the fibrogenic process in liver. The cognate receptors for leptin, members of the cytokine receptor family, are prevalently expressed in the body, such as brain (hypothalamus), lung, spleen and liver [39]. Upon binding of leptin with its full-length receptor, JAK/STAT signaling pathway is activated; JAK/STAT signaling plays a crucial role in leptin-induced ECM deposition and activation of HSCs [40].

In addition to adiponectin and leptin, a few additional adipokines can modulate liver fibrosis. Resistin, abundantly expressed in adipose tissue, was originally reported to antagonize the action of insulin and the circulating level of resistin is increased during obesity [41]. On the basis of these findings, resistin has been proposed as a link between

obesity and insulin resistance. In addition to its role in the regulation of insulin activity, recent studies suggest that resistin is also relevant in the pathophysiology of liver injury. For example, plasma resistin is enhanced in BDL-induced cirrhotic rats [42], as well as in patients with liver cirrhosis [43]. Furthermore, elevated plasma resistin positively correlated with increased mortality of cirrhotic patients [43], consistent with an involvement of resistin in hepatic fibrosis and advanced liver dysfunction. Moreover, resistin exerts pro-inflammatory effects in HSCs, increasing expression of inflammatory cytokines and chemokines by HSCs, including monocyte chemoattractant protein-1 (MCP-1/CCL2) and interleukin-8. These effects of resistin are mediated via NF-κB dependent mechanisms [44]. Resistin also increases expression of TGF-β1 by Kupffer cells, which in turn, enhances expression of collagen in HSCs [45], suggesting that resistin contributes to hepatic fibrosis through both direct and indirect activation of HSCs.

Plasminogen activator inhibitor-1 (PAI-1) inhibits urokinase plasminogen activator (uPA) and prevents production of plasmin. Since plasmin degrades extracellular matrix (ECM) both directly and through activation of matrix metalloproteinases (MMPs), PAI-1 induces accumulation of ECM and is involved in the development of hepatic fibrosis. Adipose tissue synthesizes and secretes PAI-1 into the circulation [46]. Hepatic stellate cells (HSCs) are also an important source of PAI-1, and expression level of PAI-1 is significantly enhanced during fibrosis [47]. Furthermore, knock-down of PAI-1 increases expression of MMPs (in particular, MMP9 and MMP13) and significantly improves hepatic fibrosis induced by dimethyl nitrosamine (DMN) and bile-duct ligation (BDL) models [48], suggesting that regulation of PAI-1 would be a promising strategy for the treatment of liver fibrosis.

Adipokines and inflammation in liver

Development of hepatic fibrosis occurs in response to repeated or sustained hepatocellular injury and is commonly preceded by chronic inflammation in liver, including infiltration of leukocytes and activation of macrophages resident in liver [49]. While activation of inflammatory responses is essential for a normal wound healing response to injury, dysregulated activation and/or resolution of this salutary inflammation can contribute to pathologic fibrogenic responses. Sustained/chronic inflammation contributes to fibrogenesis via multiple mechanisms. For example, chronic inflammation in liver induces necrosis and apoptosis of hepatocytes. Dead and dying hepatocytes stimulate Kupffer cells to secret inflammatory mediators and can also directly initiate the activation process of HSCs when HSCs phagocytose apoptotic hepatocytes [50]. Therefore, while the inflammatory process is a critical step in the response to injury, it can also be a harmful process itself in liver and contribute to progression of fibrosis. In established fibrosis, anti-inflammatory agents, immune-suppressants or anti-viral agents, all of which suppress inflammatory activity, can improve fibrotic status and even reverse fibrotic process [51–53].

In addition to its metabolic and anti-fibrotic effects, adiponectin is widely known to possess potent anti-inflammatory properties. It suppresses expression of inflammatory cytokines, including TNF-α, IL-6 and IL-1, as well as induction of anti-inflammatory signaling molecules, including IL-10, IL-1R antagonist and heme oxygenase-1 (HO-1). Interestingly, there is a significant inverse correlation between plasma adiponectin and TNF-α expression

[54]. Adiponectin and TNF-α negatively regulate each other's expression in adipose tissue, as well as other tissues. Treatment with adiponectin suppresses TNF-α expression in mice liver and decreases the plasma level of TNF-α, associated with the prevention of steatosis and inflammation in various models of chronic liver injury [55,56]. On the other hand, TNF-α also regulates the expression of adiponectin. For example, treatment with TNF-α suppresses adiponectin expression in human white adipose tissue [57] and decreases expression of adiponectin in adipocytes via suppressing transcriptional activity of PPAR-γ and CCAAT/enhancer binding protein (C/EBP), which act as transcriptional inducers of adiponectin [58,59] and preventing secretion of adiponectin through activation of c-Jun N-terminal kinase (JNK) [60].

In contrast to adiponectin, leptin stimulates inflammatory responses. Treatment with leptin enhanced acute CCl_4-induced necro-inflammatory responses in mice [61]. Leptin-deficient ob/ob mice are resistant to Concanavalin A (Con A)-induced hepatitis and production of inflammatory cytokines [62]. Taken together, these data suggest that, given the critical role of inflammatory processes in hepatic fibrosis, the modulation of chronic inflammatory responses by adiponectin and leptin could be one of the principal mechanisms underlying anti-fibrotic effects of adiponectin and fibrotic effect of leptin.

Relationship between obesity, hepatic fibrosis and plasma adiponectin

Obesity and associated metabolic syndrome is regarded as one of the key factors responsible for the progression of metabolic liver diseases, from NAFLD to NASH and the eventual progression to hepatic fibrosis. Obesity may contribute to hepatic fibrosis through multiple mechanisms. Abnormal accumulation of fat in liver creates what is considered to be a pro-fibrotic milieu, enhancing the production of reactive oxygen species, inducing cellular death in hepatocytes and dysregulating inflammatory responses [63]. In addition, circulating adiponectin is reduced in obesity, whereas leptin is increased. Given the complex pro/anti-fibrotic and pro/anti-inflammatory effects of leptin and adiponectin, this altered balance of adipokines likely contributes to the enhanced propensity of patients with obesity/metabolic syndrome to an increased progression of liver disease to the stage of fibrosis.

Molecular mechanisms underlying regulation of fibrosis and inflammation in liver by adiponectin

Molecular forms of adiponectin and adiponectin receptors involved in hepatic fibrosis

The adiponectin transcript encodes a 28–30KDa hydrophilic protein, with 247 amino acids and 4 clearly differentiated domains: the N-terminal domain, which contains the secretion signal domain; the variable region (28 aas); the collagenous domain with 22 Gly-X-Tyr (G-X-T) triplets; and the globular domain in the C-terminal region. The native adiponectin structure is a highly associated homo-trimer that forms via association through the collagenous domain. These homo-trimers can then associate into larger structures, including low molecular weight homo-hexamers (LMW), as well as higher order complexes of between 12–18 subunits (HMW). Moreover, a globular fragment is found in human plasma at very low concentrations; this globular adiponectin is thought to be the domain of adiponectin with maximal biological activity. Post-translational modifications, such as O-

glycosylation by disialic acid at the collagenous domain, as well as hydroxylation, can contribute to maximal activity. In addition to the role of TNFα in regulating adiponectin secretion discussed above, adiponectin secretion is also controlled by additional factors: Insulin-like Growth Factor 1 (IGF-1) enhances its secretion, while glucocorticoids, β adrenergic agonists, prolactin and insulin decrease secretion from adipose tissue [11].

The biological responses by adiponectin are mediated by binding with its receptors. Three different types of receptors for adiponectin have been identified to date. AdipoR1 and AdipoR2, a member of G protein-coupled receptors, are recognized as the cognate receptors for adiponectin. AdipoR1 is abundantly expressed in skeletal muscle and also exists in activated HSCs, while AdipoR2 is predominantly expressed in other types of liver cells [64]. Hepatic macrophages express both AdipoR1 and AdipoR2 [65]. AdipoR1 has a greater affinity for globular adiponectin while AdipoR2 binds full length and multimeric adiponectin more avidly [64].

Accumulating evidence indicates that there are functional differences between AdipoR1 and AdipoR2 signaling (Figure 2). Briefly, activation of AdipoR1 appears to be linked with activation of AMPK, while AdipoR2 signaling is more associated with activation of PPAR-α [66]. It is likely that both AdipoR1 and R2 signaling play important roles in the hepato-protective effects of adiponectin. Overexpression of AdipoR2 suppressed TGFβ-induced ROS production in hepatocytes via enhancing PPAR-α activity and expression of catalase [67], which prevents progression of NASH to the stage of fibrosis. In addition, AdipoR2 signaling plays a crucial role in the modulation of oxidative stress and inflammation in liver [68]. However, recent studies have also indicated that AdipoR1 signaling also plays a critical role in anti-fibrotic effect of adiponectin [69] and is required for disruption of the leptin-induced vascular ECM remodeling [70], suggesting a possibility of AdipoR1 signaling in anti-fibrotic effects of adiponectin. AdipoR1 also contributes to protection from fibrosis due to its potent anti-inflammatory impact on macrophages [71], as well as the ability of adiponectin to shift macrophages to an M2 phenotype [72]. Importantly, specific M2 macrophage subtypes are characterized by increased expression of MMPs and are likely involved in the resolution of fibrosis [73]. While the effect of adiponectin on expression of MMPs has not yet been studied, this could be an important area of future investigation.

T-cadherin, a member of cadherin family, was identified as a co-receptor required for transmission of metabolic signals by adiponectin [74]. Recent studies have demonstrated that T-cadherin could be implicated in adiponectin-mediated biological responses, including revascularization [75], suppression of pulmonary inflammation [76] and protection from stress-induced pathological cardiac remodeling [77]. Although, at this stage, the role of T-cadherin in hepato-protective effects of adiponectin has not been widely investigated, it would be interesting to examine the role of T-cadherin in adiponectin-induced anti-fibrotic and/or anti-inflammatory responses in liver.

AMP-activated protein kinase (AMPK)

The N-terminal domain of both AdipoR1 and AdipoR2 interacts with a pleckstrin homology adaptor protein, APPL1. This protein participates in the activation of different pathways including activation of AMP-activated protein kinase (AMPK), p38 MAPK, as well as

ERK1/2 and AKT [78]. In macrophages, activation of ERK1/2/AKT by adiponectin involves Cot/tpl2 signaling [79]. AMPK, a central signaling molecule regulating cellular metabolism, has long been considered as a key molecule mediating the metabolic effects of many hormones, including adiponectin, leptin, insulin, etc. [80]. Apart from the role in metabolism, AMPK signaling plays a critical role in anti-fibrotic effects induced by many natural products [81,82]. Moreover, AMPK signaling plays a key role in inhibiting proliferation of HSCs. Activation of AMPK by adiponectin leads to the increase in the expression of cyclin-dependent kinase inhibitors, including p27 (kip1) and p21 (cip1) and inhibition of AKT pathway [83]. In addition, 5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside (AICAR), a pharmacological activator of AMPK, blocked PDGF-induced phosphorylation of ribosomal S6 kinase (p70S6K) and 4E binding protein-1 (4EBP1), also consistent with a role for adiponectin in the regulation of cell cycle in HSCs [83]. Furthermore, activation of AMPK signaling inhibits TGFβ-induced expression of collagen (COL1A) and the myofibroblast marker, smooth muscle actin (α-SMA), in HSCs by regulating activity of the transcriptional coactivator, p300 [84].

Peroxisome proliferator-activated receptor-γ (PPAR-γ)

Peroxisome proliferator-activated receptor-γ (PPAR-γ), a nuclear receptor family member, plays essential roles in cellular differentiation, proliferation and metabolism through modulating expression of various target genes. It has been shown that expression level of PPAR-γ is decreased during liver fibrosis [85]. PPAR-γ might have inhibitory roles in development of hepatic fibrogenesis and is considered as a potential therapeutic target of hepatic fibrosis [86]. Agonists for PPAR-γ induce expression of adiponectin in adipocytes, indicating a critical role in transcriptional activation of adiponectin. Interestingly, treatment of HSCs with lentivirus encoding adiponectin also increased expression and activity of PPAR-γ. Furthermore, exposure with troglitazone, a PPAR-γ agonist, suppressed mRNA expression of collagen α1 and α-SMA in HSCs [17], suggesting a critical role of PPAR-γ in suppressing activation of HSCs and the fibrogenic process by adiponectin.

Modulation of ROS production

Excessive production of reactive oxygen species (ROS) plays a critical role in initiating inflammatory responses and promoting fibrogenesis in liver. Adiponectin has a negative impact on signaling pathways that generate ROS, which may contribute to its protective effects against inflammation and fibrosis. Adiponectin inhibits NADPH oxidase-dependent ROS production via induction of anti-oxidant enzymes in HSCs [87], associated with a suppression of proliferation of HSCs. Adiponectin also modulates ROS production in Kupffer cells. Adiponectin treatment normalizes LPS-stimulated ROS production in Kupffer cells after chronic ethanol feeding, which is critical for the regulation of TNF-α expression [65]. In addition, globular adiponectin prevents ethanol-induced ROS production via modulation of NADPH oxidase in macrophages [88]. In contrast, other studies have reported that adiponectin treatment increased ROS/RNS production, which induces of apoptosis in RAW 264.7 macrophages [89]. These differential effects of adiponectin on ROS production in macrophages could be due to different experimental conditions. For example, pretreatment with lower concentrations of globular adiponectin (0.1 μg/ml) decreased ethanol-stimulated ROS production [88], while higher concentration (10 μg/ml) increased

ROS formation in macrophages [89]. Detailed mechanisms underlying the differential impact of adiponectin in ROS production are not clearly understood. Identification of the mechanisms underlying differential effects of adiponectin on ROS production in different experimental conditions (e.g., different concentrations/activation of different receptors) would be valuable to understand the effects of adiponectin on ROS production, which in turn could impact design of therapeutic strategies to treat inflammatory diseases in liver.

Focal adhesion kinase (FAK)

Focal adhesions (FAs) make a link between extracellular environment and actin cytoskeleton. Assembly of focal adhesions is a critical process for maintaining myofibroblast phenotype of activated HSCs. Focal adhesion kinase (FAK), required for FAs assembly, therefore plays a crucial role in adhesion and migration processes of activated HSCs [90], and also modulates proliferation and collagen expression in HSCs [91,92]. Therefore, FAK signaling plays a crucial role in activation of HSCs and development of hepatic fibrosis. In fact, disruption of FAK signaling decreased mobility of cancer cells [93], sensitized activated HSCs to apoptosis [94] and attenuated synthesis of ECM and promoted ECM degradation [95]. In addition, FAK activation promotes cytoskeletal reorganization and fibrogenic phenotype of HSCs in HCV patients [96]. Taken together, these data suggest that FAK would be a potential therapeutic target for the treatment of fibrosis. A recent study reported that adiponectin modulated FAK activity in the generation of anti-fibrotic effects. Injection of adenoviral-adiponectin suppressed CCl_4-induced expression of integrins, collagen and α-SMA in liver. These effects were accompanied with dephosphorylation of focal adhesion kinase (FAK) in activated HSCs [97]. In this study, FAK signaling was required for adiponectin-induced TIMP-1 expression.

Tissue inhibitor of metalloproteinase-1 (TIMP-1)

ECM degradation process is mainly mediated by matrix metalloproteinases (MMPs) and enhanced expression and/or activity of MMPs are regarded as a promising strategy for the resolution of fibrosis. Tissue inhibitors of matrix metalloproteinase (TIMPs) reduce the activity of MMPs and are involved in progression of fibrosis. Among various TIMPs, TIMP-1 plays a crucial role in degradation of collagen and is considered as a promising therapeutic target for the prevention of fibrogenesis in liver [98]. Inhibition of TIMP-1 is a potential mechanism underlying anti-fibrotic effects of adiponectin [99]; however, the data from different studies are not all supportive of this hypothesis. In one study, treatment of HSCs with adiponectin promoted expression of TIMP-1 and binding of TIMP-1 with C63/β1-integrin complex reduced phosphorylation of FAK, which suppressed the migration of HSCs [18]. In addition, treatment with adiponectin increases mRNA level of TIMP-1 in dermal fibroblasts [100] and macrophages via Syk-dependent manner [78]. To date, studies have focused on the ability of adiponectin to regulate TIMP-1 expression by HSCs; however, since TIMP-1 is also expressed by resolution macrophages [73], it will also be important to investigate the effects of adiponectin on expression of TIMP-1 (and MMPs) by macrophages.

Negative regulation of leptin signaling

While both adiponectin and leptin are produced from adipose tissue, the biological actions by these adipokines are exactly opposite in many aspects. It has been suggested that these reciprocal functions of adiponectin and leptin contribute to the homeostatic maintenance of metabolic effects. The expression of adiponectin and leptin in HSCs are also reciprocally regulated. Adiponectin is abundantly present in quiescent HSCs, but the expression is significantly suppressed in activated HSC, while leptin expression is more abundant in activated HSCs, but not in quiescent cells [17]. Furthermore, adiponectin treatment has been shown to disrupt leptin-induced hepatic fibrosis. Adiponectin-induced activation of AMPK suppressed leptin-mediated Stat3 phosphorylation and SOCS-3 induction [19]. In addition, adiponectin treatment increased expression of protein phosphatase-1B (PTP1B), which negatively regulates leptin-induced JAK/STAT3 pathway, and blocked leptin-stimulated formation of TIMP1-MMP1 complexes in HSCs [99].

Conclusion and future perspectives

Hepatic fibrosis is a dynamic process under complex regulation by both intra- and extra-hepatic mediators. Emerging evidence has demonstrated that adipokines are closely associated with the pathogenesis of hepatic fibrosis, acting as one of multiple extra-hepatic factors regulating fibrosis. In particular, adiponectin prevents development of fibrosis via multiple mechanisms and is widely considered as a relevant target for the treatment of hepatic fibrosis, while leptin exerts an opposite role and promotes development of hepatic fibrosis. In liver diseases and obesity, the plasma level of adiponectin is usually decreased; these lower circulating concentrations of adiponectin could contribute to the fibrogenic process in liver. Development of agents enhancing the secretion of adiponectin from adipose tissue or activating adiponectin receptors in liver would be valuable for the prevention and/or treatment of hepatic fibrosis.

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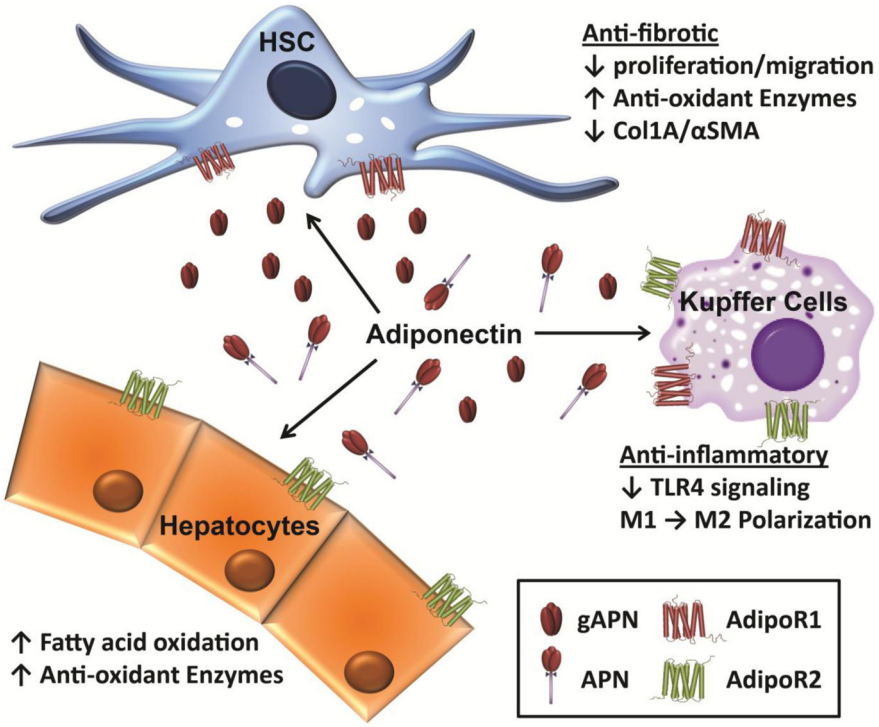

Figure 1. Adiponectin receptors in liver cells

AdipoR1 and AdipoR2 are differentially expressed on hepatocytes, hepatic stellate cells and Kupffer cells. Cellular responses to adiponectin interaction with receptors can have anti-oxidant, anti-inflammatory and anti-fibrotic effects within individual cell types in the liver.

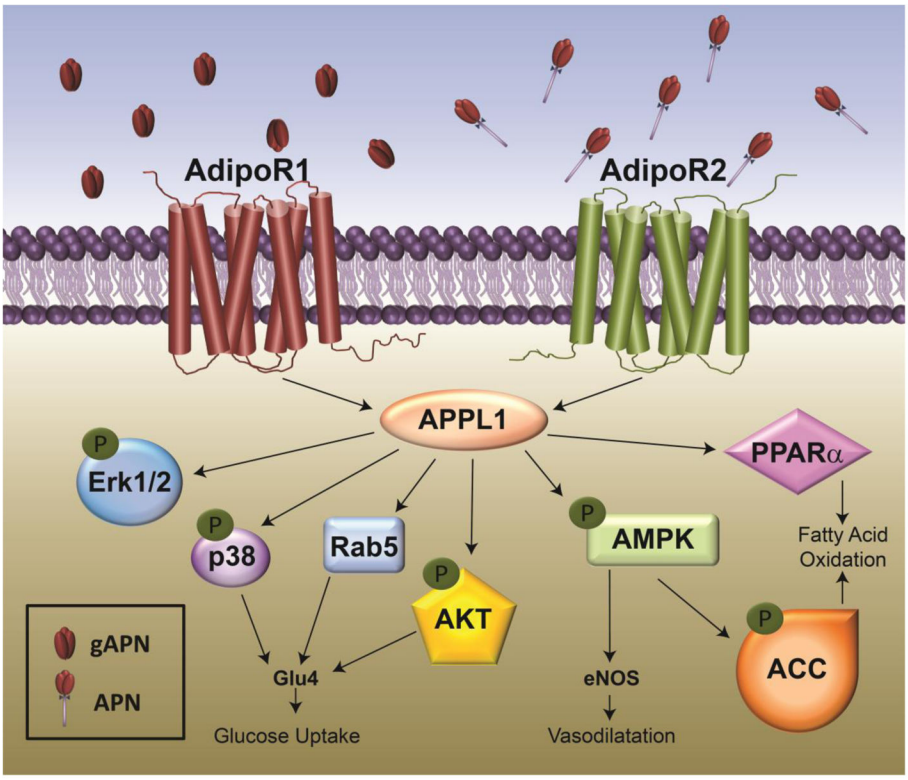

Figure 2. Signal transduction pathways activated by adiponect receptors

Adiponectin R1 and R2 dependent signaling is mediated via APPL; however, activation of down-stream signaling pathways is dependent on cell type and metabolic environment.