Disrupted Hepatic Adiponectin Signaling Impairs Liver Regeneration of Steatotic Rats

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Background: Individuals with non-alcohol fatty liver disease (NAFLD) exhibit impaired liver regeneration in a clinical setting and animal experiments. Adiponectin signaling is recognized as an important pathway of lipid metabolism, energy expenditure, anti-inflammation, and cellular proliferation. We herein investigate hepatic adiponectin signaling in dietary steatotic murine models undergoing hepatectomy, which has never been explored.

Methods: Sprague-Dawley rats fed with a normal diet (normal), high fat diet (HF), and a methionine-choline deficiency diet for 1 week (MCD 1W) and 5 weeks (MCD 5W), were used. The animals underwent 70% hepatectomy and were thereafter sacrificed at indicated time points.

Results: MCD 5W and HF displayed decreased Ki-67 labeling index and restituted liver mass compared to normal. Hepatic adiponectin, as well as TNF-α, of MCD5W and HF were increased compared to normal; whereas adiponectin receptor type 1 (AdipoR1) and adiponectin receptor type 2 (AdipoR2) were reciprocally decreased when compared to normal. PPARα, a downstream molecule of AdipoR2 axis, was decreased in MCD 5W compared to normal. Adenosine monophosphate-activated protein kinase (AMPK), a downstream molecule of AdipoR1 axis, was inactivated soon after hepatectomy in normal; whereas activation of AMPK persisted until day 3 after hepatectomy in MCD 5W and HF.

Conclusions: Reciprocal expression of adiponectin and its receptors in steatotic rats represents a unique form of adiponectin signaling disruption, which might be associated with impaired liver regeneration.

Key words: adiponectin signaling, liver regeneration, hepatectomy
disease, such as virus-related hepatitis, alcohol-related hepatitis, cirrhosis, cholestasis and non-alcohol fatty liver disease (NAFLD), functional liver reservoir is limited and liver regeneration is impaired following hepatectomy, patients are associated with a high morbidity and mortality. Of them, NAFLD is currently drawing particular attention because of its common occurrence in the general population, as well as in those with colorectal cancer and liver metastasis who have undergone chemotherapy. Steatohepatitis affects about 3% of the lean population, 19 percent of the obese population, and almost half of morbid obese people. In this “era of satiation”, NAFLD can be considered a hepatic representation of a metabolic syndrome, and is often accompanied by lifestyle disease, such as diabetes and obesity. Given the growing number of metabolic syndrome patients in recent years, the incidence of NAFLD is expected to increase further, particularly in North America, Europe, Asia, and the western Pacific countries, which has become a major concern for hepatic surgeons. An important factor in the regulation of liver injury occurring in the setting of obesity and insulin resistance is the influence of adipokines, including leptin, resistin, and adiponectin. Of them, adiponectin is currently drawing particular attention in the setting of NAFLD relevant problems. Adiponectin metabolically acts to reduce body fat, improve hepatic and peripheral insulin sensitivity, and decrease serum fatty acid levels in association with increased fatty acid oxidation. Furthermore, adiponectin has a significant anti-inflammatory effect, preventing liver damage caused by obesity, heptatoxin, and sepsis. These exciting evidences of the protective effects of adiponectin in liver injury raises the possibility that adiponectin may be a treatment for human NAFLD subject to hepatectomy. Therefore, specific knowledge of the hepatic adiponectin signaling involved in nutritional metabolism and affiliated signal transduction incurred in NAFLD would enable the development of interventional strategies to improve post-hepatectomy outcome.

METHODS

Induction of hepatic steatosis

All experiments were conducted in accordance with the Ethics Review Committee for Animal Experimentation of Chang Gung University. Male Sprague-Dawley rats, 250 gm on average, were used and housed under a 12-h light/dark cycle. Rats were fed either standard chow diet (5% fat), high fat diet (HF) (45% fat, cat. N0. D12451, Research Diets, Inc, Mount Prospect, NJ) for 14 weeks, or a standard methionine-choline deficiency diet (MCD) (Harlan CPB, Zeist, The Netherlands) for 1 and 5 weeks. A period of 1 week MCD was chosen to induce mild steatosis without inflammatory components, while a 5-week MCD diet period was applied to induce severe steatosis with prominent inflammation, however, without extensive fibrosis. For abbreviation, the experimental rats described above were designated as normal rats, HF rats, MCD 1W rats, and MCD 5W rats, respectively. The number of animals in each group at each indicated time point was 5-8.

Biochemical assays

Glucose was measured using a Glucometer Elite (Bayer, Elkhart, IN). The values of insulin and adiponectin (no. SRI-13K and no. MADP-60HK, respectively, Linco Research, St. Charles, MO), and triglycerides (no. 337-B, Sigma, St. Louis, MO) were measured using ELISA kits according to manufacturers’ instructions.

Surgical procedure

A 70% liver resection was used to induce liver regeneration. Briefly, rats were anesthetized by inhalation of methoxy-flurane. After midline laparotomy, the pedicles of median and left lateral lobes were ligated with fine silks and resected. The weight of the resected liver was determined. The experimental rats were thereafter sacrificed at indicated time points (12 hour, 1, 3, 5 and 7 days). The blood was collected by vena cava puncture, centrifuged (10 minutes, 3,000 g, 4°C) and the plasma then stored at –80°C. Livers were removed, weighed, and divided into two portions. One was immersed in 10% formalin and embedded in paraffin; 4 µm sections were routinely stained with hematoxylin and eosin for assessment of histology. Another portion was immediately frozen in liquid nitrogen and stored at –80°C for subsequent investigation.

Assessment of liver regeneration

Restituted liver mass was expressed as a per-
percentage of regenerated liver mass related to total liver weight; \( \% = \frac{A}{B \cdot 0.7} \), where \( A \) = the weight of the regenerated liver at sacrifice and \( B \) = resected liver weight. For assessment of hepatic proliferation, MiB-5, a rat equivalent of Ki-67 antibody was used, which detects all active parts of the cell cycle. Briefly, sections were deparaffinised and pretreated (citric acid pH 6.0, 2 bars, 120°C, 20 minutes). For primary and secondary antibodies, MiB-5 antibody (dilution 1:50, 60 minutes, DAKO, Copenhagen, Denmark) and Poly-HRP (dilution 1:1, 30 minutes, Invitrogen, Carlsbad, CA, U.S.A.), were used, respectively. The Ki-67 labeling index was determined by calculating the number of MiB-5-positive hepatocytes (magnification x400, 10 HPF) and expressed as mean positive cells per HPF.

**Quantitative real-time PCR for adiponectin, adiponectin receptor type 1 (AdipoR1), adiponectin receptor type 2 (AdipoR2), and peroxime proliferator-activated receptor-alpha (PPARα)**

Two micrograms of total RNA were treated with DNase 1 (Invitrogen) to remove DNA contamination. Then, the RNA was reverse-transcribed using MMLV reverse transcriptase (Invitrogen) in a 50-L reaction mixture. Taqman primers and probes for quantitative detection of adiponectin (Rn00595250-m1), AdipoR1 (Rn01483784-m1), AdipoR2 (Rn01463177-m1), PPARα (Rn00566193-m1) and GAPDH (Rn99999916-s1) were designed with Primer Express (ABI-Perkin-Elmer) using the GenBank accession number. cDNA samples were mixed with 2x universal TaqMan buffer containing the Taq enzyme, primers and probes in a total volume of 25L. The thermal cycle conditions were 50°C 2 min, 95°C 10 min, and 42 cycles of 95°C 15 sec and 60°C 1 min. All PCRs and analyses were performed using an ABI PRISM 7700 sequence Detection System (Applied Bio- systems). All samples were run in triplicate.

**Western blotting for TNF-α and phospho-adenosine monophosphate-activated protein kinase (p-AMPK)**

For Western blot analysis, we used a mixed protein (n = 5-8) retrieved from experimental animals for each time point, and each group, to represent one observation. Three observations were performed in total using different mixtures of retrieved proteins for each observation. Then, mean values were determined. Frozen tissue was cut and homogenized in 200 µl of ice-cold lysis buffer (10 mM Tris-HCl, pH 7.5, 1 mM MgCl2, 1 mM EGTA, 0.1 mM phenylmethylsulfonyl fluoride, 5 mM-mercaptoethanol, 0.5% Chaps, 10% glycerol). Following incubation for 30 min on ice, the samples were centrifuged at 14,000 rpm for 20 min at 40°C and the supernatant was then transferred to a new tube. Total protein was measured using a Bio-Rad Bradford kit (Bio-Rad Laboratories, CA, U.S.A.), and 30 µg of total protein was then run on a 12% SDS-polyacrylamide gel, and transferred to a nitrocellulose membrane which was blocked using non-fat dry milk in TBS-T (20 mM Tris-HCl, pH 7.6, 150 mM NaCl, 0.05% Tween 20) overnight at 4°C. The membrane was then probed using a primary antibody, washed several times with TBS-T, and incubated using a horseradish peroxidase (HRPO)-conjugated secondary antibody (goat anti-mouse HRPO, Transduction). Finally, the membrane was washed and developed using an enhanced chemiluminescence system (Pierce). The primary antibodies used were against TNF-α (BD Pharmingen, CA, U.S.A.) and p-AMPK (Cell Signaling, Danvers, MA, U.S.A.). Tubulin served as an internal control. Each targeted protein was normalized using the tubulin first, and then the ratio of normalized target protein to the sham was determined, which was represented as relative fold. Quantification of the autoradiographs was conducted using a Bio-Rad/GS 700 imaging densitometer.

**Immunofluorescence for hepatic adiponectin**

The frozen sections of the liver specimen were treated with a solution containing 4% paraformaldehyde, 0.2% Triton X-100, and 0.4% bovine serum albumin (BSA). The sections were incubated in blocking buffer containing 5% donkey serum (Sigma) and 1% BSA for 1h at room temperature. Primary antibodies against adiponectin (1:100, R & D) and Hoechst (0.5 µg/ml, Sigma) were used at 1:100 dilution in blocking buffer. The sections were imaged using a Leica, TCS SP2 confocal microscope. Images were imported to Adobe Photoshop (Adobe System, Inc., CA, U.S.A.) for processing.

**Statistical analysis**

Data were expressed as mean ± SD. Statistical
significance between groups was determined using one-way ANOVA, followed by post-hoc test (Scheffe’ method). \( p < 0.05 \) was considered statistically significant.

**RESULTS**

**Phenotypes of two dietary steatotic murine models**

The characteristics of two dietary steatotic murine models were shown (Table 1). HF exhibited over-weight, hyperglycemia, insulin resistance, and hyperlipidemia compared to those of normal. In contrast, MCD 5W exhibited decreased body weight, hypoglycemia, hypoinsulinemia, and hypolipidemia compared to those of normal.

**Histologic change of steatotic livers after heptectomy**

The representative histologic findings of steatotic murine models at baseline and day 7 after heptectomy were shown (Fig. 1). Normal exhibited normal micro-architecture before heptectomy and 7 days after heptectomy. HF showed microvesicular fatty change before heptectomy but became mixed macrovesicular and microvesicular 7 days after heptectomy. MCD 5W showed > 90% macrovesicular fatty change before heptectomy and approximately 70% fatty metamorphosis 7 days after heptectomy.

**Efficiency of liver regeneration**

Elevated serum level of ALT of experimental rats at day 1 following heptectomy was shown (Fig. 2A). Of them, HF displayed the highest serum level of ALT. The Ki-67 labeling indices of the experimental rats following heptectomy were shown (Fig. 2B). MCD 5W displayed the lowest Ki-67 labeling index, followed by HF, MCD 1W and normal, in increasing order (\( p < 0.01 \), ANOVA). The restituted liver masses of the experimental rats following heptectomy were shown (Fig. 2C). The MCD 5W displayed the lowest regenerative liver mass, followed by HF, MCD 1W, and normal, in increasing order (\( p < 0.01 \), ANOVA).

**Expression of hepatic TNF-\( \alpha \)**

The representative expression of hepatic TNF-\( \alpha \) detected by Western blot in experimental animals following heptectomy was demonstrated (Fig. 3A). MCD 5W exhibited the highest expression of TNF-\( \alpha \) during liver regeneration, followed by HF and normal, in decreasing order (Fig. 3B).

**Expression of hepatic adiponectin, AdipoR1, AdipoR2, and PPAR\( \alpha \) mRNA**

Expression of adiponectin, AdipoR1, AdipoR2, and PPAR\( \alpha \) mRNA of the experimental rats following heptectomy detected by quantitative real-time PCR were shown (Fig. 4). Expression of adiponectin mRNA in HF and MCD swiftly increased and arrived at their peaks at day 1 following heptectomy; whereas expression of adiponectin mRNA expression in normal remained relatively constant. Expression of AdipoR1 and AdipoR2 in HF and MCD 5W were reciprocally decreased compared to those of normal. Lastly, expression of PPAR\( \alpha \) was generally in parallel with AdipoR2, while HF exhibited a remarkable elevated level of PPAR\( \alpha \) along the entire course of the liver regeneration, and was even higher than that of normal.

**Localization of hepatic adiponectin protein**

The representative features of adiponectin protein of normal and MCD 5W following heptectomy detected by immuno-fluorescence were demonstrated.
The expression of adiponectin protein in experimental rats was predominantly expressed in hepatocytes *per se* rather than parenchymal cells. Notably, adiponectin protein was migrated and accumulated around the rim of fat droplets within hepatocytes of MCD 5W at day 7 after hepatectomy.

**Expression of hepatic p-AMPK protein**

The representative expression of p-AMPK protein of the experimental rats following hepatectomy detected by Western blotting was demonstrated (Fig. 6A). The expression of p-AMPK of normal declined soon after hepatectomy; while the expression of p-AMPK of HF and MCD5W increased modestly and peaked at day 3 after hepatectomy, and declined thereafter (Fig. 6B).

**DISCUSSION**

Several lines of evidences have demonstrated the adverse impact of NAFLD upon liver regeneration in a clinical setting and animal experiments.⁴-¹⁷

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**Fig. 1** Histologic changes of normal, HF and MCD 5W before and 7 days after hepatectomy. Hematoxylin-eosin stain, 400 x original magnification.
In the present study, we set-up two dietary steatotic murine models with different phenotypes: one is characterized by increased input of fatty acid, obesity, hyperglycemia, insulin resistance, and hyperlipidemia; while the other is characterized by decreased output of fatty acid, decreased body weight, hypoglycemia, hypoinsulinemia, and hypolipidemia. These two phenotypes represent the vast majority of subjects with NAFLD we may encounter in daily practice, therefore providing a wide-spectrum platform to investigate the mechanics of impaired liver regeneration occurring in individuals with NAFLD.

**Fig. 2** (A), serum levels of ALT at day 1 after hepatectomy. (B), Ki-67 labeling indices at indicated time points after hepatectomy. (C), restituted liver mass at indicated time points after hepatectomy. *+, † represented $p < 0.05$ and 0.01, respectively, compared to normal.
Recently, adiponectin signaling has been recognized as an important pathway of lipid metabolism, energy expenditure and cellular proliferation,\(^\text{18}\) all essential elements regarding liver regeneration.\(^\text{19}\) Thus, it is intriguing to investigate the role of hepatic adiponectin signaling involved in liver regeneration using our steatotic murine models. Novel findings observed in the present study included: 1) over-expression of hepatic adiponectin in subjects with NAFLD undergoing hepatectomy is possibly elicited by an excessive stimuli of the proinflammatory cytokine, TNF-\(\alpha\); 2) expression of hepatic adiponectin is derived from hepatocytes per se rather than migration from peripheral adipose tissues and hepatic sinusoids; 3) reciprocal expression of adiponectin and its receptors in NAFLD might represent a unique form of adiponectin signaling disruption; and 4) the expression of PPAR\(\alpha\) was tightly regulated by AdipoR2 axis; whereas the expression of AMPK, a downstream molecule of AdipoR1 axis, seemed to be relatively loosely regulated. The details of the above issues were discussed as follows. Adiponectin, an adipocytokine, is present exclusively in adipose tissue and blood, and its receptors are abundant in liver and muscle.\(^\text{20}\) Adiponectin has antidiabetic, anti-lipogenic, and antiatherogenic actions,\(^\text{21-23}\) as well as an anti-inflammatory effect.\(^\text{10-12}\) Based on our data, MCD 5W and HF displayed a higher level of hepatic adiponectin mRNA at basal line and regenerative process compared to that of normal.

It is worth mentioning that the expression of adiponectin was derived from the liver per se instead of production from the peripheral tissues, because the methodology employed in the present study was quantitative real-time PCR, which detected adiponectin mRNA. The result of immunofluorescence study further clarified that the expression of
Fig. 5 Expression of hepatic adiponectin in normal and MCD 5W at baseline, day 1 and day 7 after hepatectomy detected by immunofluorescence. The greenish spots represented adiponectin protein, whereas the blue ones represented nucleus. Original magnification, × 1000.

Fig. 6 Expression of p-AMPK in normal, HF, and MCD 5W detected by Western blot (A) and its quantitative analysis using densitometer (B). Each data derived from the mixture of proteins collected from different animals of the same group at each time point (n = 5-8) represent an observation. Three observations were performed using different mixture of proteins retrieved for each observation with same procedures, then, the mean values were determined.
adiponectin protein was predominately localized in hepatocytes. These findings were somewhat contradictory to the others’ reports. AdipoR2 was expressed in hepatocytes. Accordingly, it suggested that adiponectin protein adiponectin was mainly localized to endothelial cells of portal vessels and hepatic sinusoids, while AdipoR2 was exclusively detected in hepatocytes. Additionally, it suggested this hormone/receptor pair could function in a paracrine way. Our data however indicated that this adiponectin/AdipoR2 pair might function in an autocrine way. Interestingly, although the three-dimensional structure of adiponectin closely resembles that of TNF-α, these two proteins have completely opposite effects. Both in vivo and in vitro experiments demonstrated that adiponectin and TNF-α suppress each other’s action in their target tissues. Until now, we are not sure of the physiological significance between adiponectin and TNF-α following hepatectomy. A significant up-regulation of hepatic adiponectin has been observed under setting of acute hepatic inflammation elicited by ConA and CCl4, respectively. Adiponectin has also been shown to be a major antagonist of TNF-α production in several cell types. Taken together, we speculated that the induction of hepatic adiponectin in subjects with NAFLD undergoing hepatocyte might be elicited by an over-expressing TNF-α, to counteract the pro-inflammatory actions of TNF-α. Adiponectin activates AMPK and PPARα through its receptors (AdipoR1 and AdipoR2, respectively); By controlling AdipoR1, AdipoR2, or both genes with knockout mice, Yamauchi et al proved that the two receptors differ in their downstream signaling pathway. AdipoR1 is more tightly linked to the activation of the AMPK pathway and couples the activation of hepatic glucose production to increased activation of fatty acid oxidation, whereas AdipoR2 is mainly involved in the activation of PPARα pathway. The inhibition of AdipoR2 signaling in the liver caused the inhibition of PPARα signaling, increasing triglyceride accumulation in hepatocytes and also inhibiting the expression of ACO, a hepatic enzyme that contributes to fatty acid oxidation. Meanwhile, the inhibition of AdipoR2 signaling induced lipid peroxidation and oxidative stress, and it also reduced the expression of the antioxidant enzyme catalase. Vetelainen et al have shown that severe steatosis increases lipid peroxidation and decreases antioxidant response after 70% hepatectomy. In the present study, remarkably reciprocal expression of hepatic adiponectin versus AdipoR2 was observed during liver regeneration in HF and MCD groups. Worthy of mention, MCD 5W group exhibited the lowest level of AdipoR2 along the regenerative process. In turn, MCD 5W group exhibited the lowest level of PPARα. PPARα increases the expression of molecules involved in the reduction of oxidative stress, such as catalase and Cu/Zn-superoxide dismutase (SOD1). In addition, liver regeneration in PPARα- null mice is impaired and is associated with altered expression of genes involved in cell cycle, cytokine signaling, and fat metabolism. Accordingly, we suggested that the impaired liver regeneration of steatotic rats was partly due to down-regulation of PPARα through AdipoR2 axis, which causes increased peroxidation and decreased antioxidant response.

On the other hand, AMPK is a conserved sensor of cellular energy which protects cells by a low-fuel warning system. The activation of AMPK was modulated through adiponectin-AdipoR1 pathway, as previously described. Once activated, AMPK phosphorylates and inactivates a number of metabolic enzymes involved in ATP-consuming cellular events including fatty acid, cholesterol and protein synthesis, involving acetyl-Co enzyme A carboxylase (ACC) and HMG-CoA reductase, but also activates ATP-generating process. Recently, AMPK activation by AMP-mimetic 5-aminimidazole-4-carboxamide ribonucleoside (AICAR) has been shown to cause cell cycle arrest in several types of cells, which possibly involves accumulation of the tumor suppressor protein p53, and in turn the accumulated p53 up-regulates p21CIP. Furthermore, activated AMPK by energy starvation phosphorylates TSC2 at Thr-1227 and Ser-1345, and increases the activity of TSC1-TSC2 complex to inhibit mTOR. Taken together, AMPK activation may inhibit cell proliferation not only by activation of p53-p21 axis and inhibition of mTOR signaling, but also by suppression of the mevalonates synthesis pathway and de novo fatty acid synthesis. As shown in our data, AMPK was swiftly inactivated to promote hepatocyte proliferation 12 hours after hepatectomy in normal; while activation of AMPK persisted until day 3 after hepatectomy in HF and MCD 5W, which might lead to a time lag and derangement of liver restoration.
In conclusion, we, for the first time, audited the hepatic adiponectin signaling in subjects with NAFLD undergoing hepatectomy. Reciprocal expression of adiponectin and its receptors in steatotic rats represents a unique form of adiponectin signaling disruption, which might be of pathophysiological relevance in impaired liver regeneration. Our results further suggest that the downstream molecules of AdipoR1 and AdipoR2, such as PPARα and AMPK, rather than adiponectin per se, might be more appropriate targets to enhance liver regeneration.

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高血脂大鼠的肝臟內脂聯蛋白訊息傳遞阻斷
導致肝臟再生能力降低

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背景：非酒精性脂肪性肝病 (Non-alcohol fatty liver disease, NAFLD)，不論是在臨床或是動物實驗，皆會減弱肝臟再生能力。脂聯蛋白訊息傳導 (Adiponectin signaling) 被認為是在脂質代謝、能量消耗、抗發炎反應，以及細胞增生等作用上一個重要的路徑。基於以上概念，我們以不同高脂質飲食老鼠模擬群進行肝臟切除來探討其差異性，目前尚未有其他文獻有相同的討論。

方法：我們以接受正常飲食之大鼠做為對照組，實驗組三組包括高脂肪飲食組 (high fat, HF)，不含蛋氨酸膽鹼 (methioninecholine) 之飲食一週組 (MCD 1W) 及五週組 (MCD 5W)。這些大鼠均接受 70% 的肝臟切除，然後在特定時間點犧牲以進行探討。

結果：MCD 5W 組及 HF 組較對照組有較低的 Ki-67 標示比以及肝臟再生體積，但是在肝臟的脂聯蛋白和 TNF-α 則呈現較高的數值。與對照組比較，不論第一型脂聯蛋白接受體 (Adipo R1) 及第二型脂聯蛋白接受體 (Adipo R2) 皆是減少的。在 MCD 5W 組發現 PPARα 這個在 Adipo R2 路徑的下游產物比對照組來得低；針對 Adipo R1 路徑的下游產物，單磷酸腺嘌呤活化蛋白激酶 (adenosine monophosphate-activated protein kinase, AMPK) 在對照組則是在肝臟切除術後很快的被激活。但是在 MCD 5W 組及 HF 組，此激酶在肝臟切除術後甚至到第三天還是持續呈活化態。

結論：在高血脂大鼠身上觀察到脂聯蛋白及其接受體於肝切除後呈現反常狀態，代表某種獨特形式的脂聯蛋白訊息傳導阻斷，後者可能與肝臟再生能力降低有關。 (長庚醫誌 2011;34:248-59)

關鍵詞：脂聯蛋白訊息傳遞，肝臟再生，肝葉切除