

## Current Topics

Current Research Trends in the Exploration of  
Therapeutic Targets for Liver Disease

## Modulation of Cell Death and Survival by Adipokines in the Liver

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**Adipokines, hormones predominantly produced from adipose tissue, have been shown to impart dynamic functions in the liver. Emerging evidence has shown that adipokines are also involved in modulating liver cell survival and/or death. Among the various adipokines, adiponectin and leptin directly regulate proliferation of hepatocytes, Kupffer cells, and hepatic stellate cells. Moreover, these adipokines control apoptosis and cell cycle of hepatic cancer cells in a complex manner. Adiponectin possesses both pro- and anti-proliferative properties, whereas leptin appears to play roles as a pro-survival hormone. Recent studies have revealed that regulation of cell death and proliferation is one of the critical factors regulating liver physiology by adipokines. In this review, we summarize the effects of adipokines on apoptosis and survival of liver cells and also demonstrate their implications in regulating various liver functions and decipher the underlying molecular mechanisms.**

**Key words** adiponectin; apoptosis; leptin; liver; proliferation

## 1. INTRODUCTION

Adipose tissue acting as a dynamic endocrine organ plays crucial roles in the homeostasis of various physiological responses.<sup>1)</sup> Apart from being a storage site for excess energy (fat), growing evidence has highlighted that adipose tissue is involved in a variety of biological functions including lipid and glucose metabolism, inflammation and insulin resistance. Adipose tissue acts as an endocrine organ *via* secretion of numerous biologically active substances, collectively called “adipokines.” Among the various adipokines, adiponectin and leptin are considered as two key hormones that play critical roles in the maintenance of a number of biological responses. In particular, diverse biological responses in the liver such as lipid/glucose metabolism, inflammation, and fibrogenesis are modulated by adipokines.<sup>2)</sup> Therefore, the liver is considered as one of the major target organs affected by adipokines. Recent evidence has also revealed that cell death and/or survival of liver cells, as well as hepatic cancer cells, are directly regulated by adipokines. Interestingly, although adiponectin and leptin are produced from the same endocrine organ, the effects of these adipokines are quite different and oppose each other in many cases.<sup>3)</sup> Appreciating the effects of adipokines on the regulation of cell population and its underlying molecular mechanisms would be beneficial to understand the modulatory role of adipokines in many biological responses in the liver. In this review, we provide the recent findings regarding the pro-apoptotic and/or pro-survival role of adiponectin and leptin in primary liver cells and hepatic cancer cells with brief synopses of other key adipokines.

## 2. ADIPONECTIN AND LEPTIN

**2.1. Adiponectin** Adiponectin, the most abundant plasma protein (ranging from 2–10  $\mu\text{g/mL}$  in human), closely relates with the development of many diseases in clinical

situations. In particular, decrease in serum adiponectin levels closely associates with the development of various pathological conditions,<sup>4)</sup> indicating that adiponectin plays a beneficial role in normal physiology. Adiponectin generates biological responses *via* acting on adiponectin receptor 1 (adipoR1) or 2 (adipoR2) expressed throughout the body. During the initial years of adiponectin discovery, AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPAR)- $\alpha$  were considered key molecules to mediate the metabolic effects of adiponectin. Recent evidence has also demonstrated that adiponectin action requires various other signaling molecules. For example, heme oxygenase-1 (HO-1) and Fox3A are necessary for anti-inflammation and anti-proliferative effects on cancer cells,<sup>5,6)</sup> respectively.

**2.2. Leptin** The leptin receptor was originally identified in the brain as a regulator of appetite and body weight. Then, it was shown that leptin receptor is ubiquitously expressed throughout the body. Increasing evidence has shown that, in contrast to adiponectin, leptin is implicated in the development of many pathophysiological conditions including inflammation, immunity, and a diverse spectrum of metabolic processes.<sup>7)</sup> Janus kinase (JAK)-signal transducer and activator of transcription (STAT) (JAK/STAT pathway) has been considered as a key signaling pathway involved in the generation of biological actions by leptin.

## 3. PRO-APOPTOTIC AND/OR PRO-SURVIVAL EFFECTS OF ADIPONECTIN IN LIVER CELLS

In addition to its classical effects on metabolic disorders, adiponectin also affects development and progression of cancer. The role of adiponectin in cell survival or death is a matter of intense debate as many *in vivo* and *in vitro* studies have generated opposing results. It was originally reported that adiponectin suppresses tumor growth and circulating adiponectin levels were inversely associated with incidence

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of cancer.<sup>8)</sup> However, recent studies have also demonstrated proliferative properties of adiponectin, thereby progressing cancer.<sup>9)</sup> Adiponectin also controls cell death and/or survival of primary liver cells, raising the possibility that adiponectin modulates liver (patho)physiology through direct regulation of cell populations in liver.

**3.1. Anti-apoptotic and Pro-survival Effects of Adiponectin in Liver Cells** Adiponectin has been shown to protect liver cells from cell death induced by many insulting stimuli. For example, adiponectin protects mouse hepatocytes from iron overload-induced liver injury through HO-1 induction and activation of PPAR- $\alpha$ .<sup>10)</sup> In addition, globular adiponectin suppresses ethanol-induced apoptosis of liver cells through nuclear factor erythroid-related factor 2 (Nrf-2) signaling and HO-1 induction. Specifically, carbon monoxide (CO) was found to mediate protective effects against ethanol-induced apoptosis.<sup>11)</sup> Since hepatocellular apoptosis is a prominent early feature of alcoholic liver disease, adiponectin provides a promising therapeutic option for the treatment of alcohol-induced liver injury. In addition, adiponectin protects hepatocytes *via* inhibition of CD95 upregulation in chronic hepatitis C virus (HCV) patients.<sup>12)</sup> In rats undergoing ischemia-reperfusion injury in the liver, adiponectin treatment ameliorates hepatocyte apoptosis and inflammation, a process mediated through AMPK/endothelial nitric oxide synthase (eNOS) pathway.<sup>13)</sup>

Recent studies have revealed that adiponectin induces autophagy, a self-digestion process in response to the stressful condition, in liver cells and thereby protects liver cells from insults-induced abnormal cell death. Globular adiponectin promotes cell survival in rat hepatocytes *via* enhancing expression of autophagy-related genes.<sup>6)</sup> In this report, adiponectin induced nuclear translocation of FoxO3A *via* AMPK-dependent manner, which in turn transcribes autophagy-related genes. This autophagy induction contributes to restoration of ethanol-induced apoptosis in rat hepatocytes and HepG2 cells.<sup>6,14)</sup> In addition, autophagy induction plays a crucial role in liver protection from acetaminophen-induced hepatocyte damage,<sup>15)</sup> which occurs through mitochondria dysfunction, necrosis, and oxidative stress. However, the role of autophagy in cell death and survival is controversial. Although autophagy was originally reported as a type of cell death, recent evidence has demonstrated that autophagy would function as a survival mechanism against cellular stress,<sup>16)</sup> suggesting that autophagy may regulate cell proliferation (or death) in a context-dependent manner. Emerging findings suggest that adiponectin induces autophagy for overall survival of liver cells. Mechanistically, autophagy activation by adiponectin causes digestion of Bax, thereby preventing caspase activation.<sup>6)</sup> In addition, adiponectin enhances the expression of chemokine-like receptor 1 and CXCL8 by adipoR1 signaling in human hepatocytes,<sup>17,18)</sup> which behave as survival factors in the liver. Adiponectin also attenuates ceramide accumulation in liver. Both adipoR1 and R2 signaling mediate increased ceramidase activity and formation of sphingosine-1-phosphate (S1P). Since S1P is implicated in survival and proliferation of liver cells, adiponectin-induced S1P formation could be one of the plausible mechanisms responsible for pro-survival effect of adiponectin in liver.<sup>19)</sup>

**3.2. Apoptotic Effects of Adiponectin in Liver Cells** Although adiponectin prevents harmful stimulus-induced

apoptosis of hepatocytes as mentioned above, this adipokine hormone has also been shown to cause cell death in certain experimental conditions. For example, adiponectin represses late-stage regeneration of hepatocytes due to unavailability of growth factors in adiponectin knockout mice model.<sup>20)</sup> Mechanistically, hepatocyte growth factor (HGF) and fibroblast growth factor-2 (FGF-2) produced from hepatic stellate cells (HSCs) promote cell cycle progression of hepatocytes.<sup>21,22)</sup> However, adiponectin induces apoptosis and inhibits activation of HSCs.<sup>23)</sup> Therefore growth factors required for proliferation of hepatocytes are lacking and prevent hepatocytes proliferation. Adiponectin also affects survival rate of Kupffer cells. It promotes conversion into M2 phenotype and releases mediators that promote M1 macrophage apoptosis.<sup>24)</sup> In addition, globular adiponectin induces apoptosis of murine macrophage cell line by reactive oxygen species (ROS) production derived from reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and inducible nitric oxide synthase (iNOS).<sup>25,26)</sup> In addition, adiponectin has been shown to affect activated and/or quiescent status of HSCs. It prevents proliferation of HSCs and sometimes sensitizes activated HSCs to apoptosis.<sup>23)</sup> Adiponectin therefore has been widely considered as a potent anti-fibrotic cytokine. Adiponectin also exerts potent effects on apoptosis induction and anti-proliferation in hepatic cancer cells. Multiple underlying mechanisms have been proposed. For example, adiponectin induces expression of p53 and Bax and inhibits pro-survival pathway *via* glycogen synthase kinase-3 beta (GSK-3 $\beta$ ), thereby inhibiting  $\beta$ -catenin or cyclin D1 activity.<sup>8,27)</sup>

#### 4. EFFECTS OF LEPTIN ON PROLIFERATION OF LIVER CELLS

In contrast to adiponectin, leptin has been shown to possess mainly proliferative properties in the liver. Leptin has been widely known to potentially induce proliferation and activation of HSCs without eliciting significant effects on hepatocytes and Kupffer cells.

**4.1. Effects of Leptin on Proliferation of Hepatic Stellate Cells** Although leptin is predominantly produced from adipose tissue, it is also secreted from activated HSCs and this impairs resolution of hepatic fibrosis.<sup>23)</sup> Leptin inhibits tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis and suppresses FasL-induced apoptosis in HSCs.<sup>28)</sup> Leptin has also been shown to promote liver fibrosis through induction of transforming growth factor- $\beta$ <sup>23)</sup> and connective tissue growth factor<sup>29)</sup> in HSCs.

**4.2. Effects of Leptin on Hepatocytes and Kupffer Cells** While the effects of leptin on HSCs have been well documented in the literature, less is known regarding the apoptotic and/or survival effects of this adipokine on hepatocytes and Kupffer cells. A recent report indicates that leptin receptors are expressed in hepatocytes and involved in ROS production to a higher degree than HSCs *via* NADPH oxidase-dependent signaling.<sup>30)</sup> However, ROS production by leptin signaling did not affect functions and programmed cell death of hepatocytes.

**4.3. Effects of Leptin on Proliferation of Hepatic Cancer Cells** It is widely known that leptin induces proliferation and suppresses apoptosis of hepatic cancer cells. Plasma level of leptin is enhanced in obese individuals.<sup>31)</sup> Due to the higher

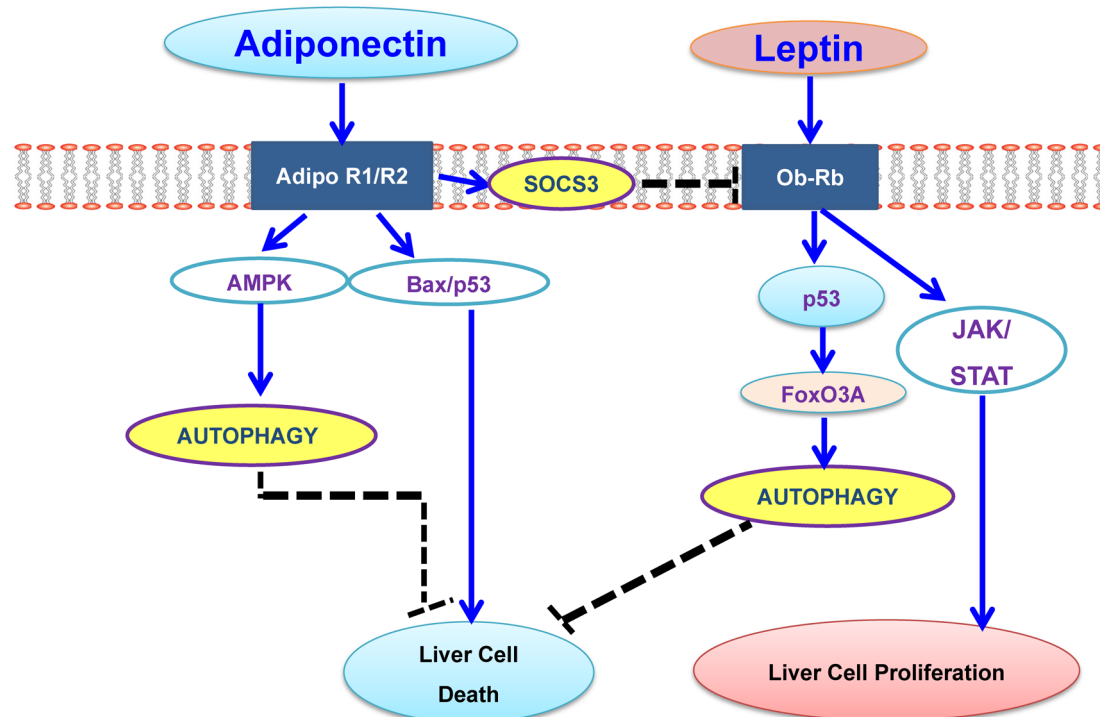


Fig. 1. Effects of Adiponectin and Leptin on Cell Death and Survival in the Liver

Adiponectin induces both apoptosis and proliferation of liver cells in a context-dependent manner. On binding with its receptor (adipoR1/R2), adiponectin activates a number of signaling pathways. Adiponectin induces apoptosis in hepatic cancer cells *via* expression of pro-apoptotic genes including Bax and p53. Adiponectin also interferes with leptin-induced JAK/STAT pathway required for cell proliferation through SOCS 3 signaling. In contrast to adiponectin, leptin mainly induces proliferation in HSCs and hepatic cancer cells without significant effects on cell death. Of the various signaling mechanisms, JAK/STAT signaling plays a crucial role in proliferation of liver cells. Both adiponectin and leptin induce autophagy activation. Autophagy induction leads to the inhibition of apoptosis and finally contributes to cellular proliferation.

circulating level of leptin in obesity, and the cardinal role of leptin in cancer progression, increased plasma level of leptin can be suggested as a possible mechanism underlying higher rate of cancer development in obese populations. Leptin induces cell cycle progression and increases the number of cells in S and G2–M phases, but reduces G0–G1 phase, suggesting enhanced DNA synthesis and mitotic activities by leptin.<sup>32)</sup> Inhibition of endoplasmic reticulum (ER) stress-associated apoptotic pathway was also proposed for leptin-induced increase in hepatic cancer cells.<sup>33)</sup> Additionally, methionine adenosyl-transferase (MAT) has been demonstrated responsible for mitogenic property of leptin in HepG2 and Huh7 cells. Interestingly, although leptin induces MAT in hepatic cancer cells, this hormone does not show mitogenic properties in human and mouse hepatocytes.<sup>34)</sup> We have recently found that leptin induces autophagy both in human hepatic and breast cancer cells similar to adiponectin. In this report, leptin-induced autophagy activation also contributes to the suppression of apoptosis of cancer cells, indicating that autophagy activation would be one of the survival mechanisms in hepatic cancer cells.<sup>35)</sup> In conjunction with the results from adiponectin, autophagy induction would be a promising target for the modulation of cancer cell survival by adipokines.

## 5. INTERACTION BETWEEN ADIPONECTIN AND LEPTIN SIGNALING

There is a growing appreciation for the cross-talk between adiponectin- and leptin-induced signaling pathways, whose interactions govern the final outcome in many liver disease

conditions. For example, adiponectin induces expression of suppressor of cytokine signaling-3 (SOCS-3) and protein tyrosine phosphatase 1B (PTP1B), which are negative regulators of JAK/STAT signaling.<sup>36,37)</sup> This interaction results in the suppression of leptin-induced hepatic fibrosis. Similarly, in hepatic cancer cell lines and HepG2 xenograft model, adiponectin-induced SOCS3 activation suppresses leptin-induced oncogenic effects.<sup>38)</sup> Moreover, adiponectin suppresses leptin-induced extracellular signal-regulated kinase (ERK) and AKT signaling through increased expression of PTP1B,<sup>39)</sup> leading to inhibition of leptin-mediated cancer growth. These findings indicate that adiponectin generates opposing effects on leptin-mediated proliferative, survival and oncogenic effects in hepatic cancer cells.

## 6. EFFECTS OF OTHER ADIPOKINES ON CELL DEATH AND SURVIVAL IN LIVER

**6.1. Visfatin and Resistin** Visfatin binds to insulin receptors at a site distinct from insulin binding and possesses insulin-like actions.<sup>40)</sup> In addition to hypoglycemic effects similar to insulin, visfatin also has modulatory effects on liver cell death. Visfatin protects hepatocytes from apoptosis and exerts hepatoprotective roles in non-alcoholic fatty liver disease (NAFLD) model.<sup>41)</sup> Resistin, originally regarded to play a role in insulin resistance, also mediates proliferation and migration of HSCs and suppression of apoptosis *via* interleukin-6 (IL-6) and MCP-1 dependent mechanism in these cells.<sup>42)</sup>

**6.2. Omentin** The plasma level of omentin is lowered in

obese and diabetic individuals, but positively correlates with adiponectin and high density lipoprotein (HDL) cholesterol levels,<sup>43)</sup> indicating a beneficial role in metabolic functions. Omentin promotes apoptosis of hepatocellular carcinoma through deacetylation of p53, thereby enhancing stability of this protein.<sup>44)</sup>

## 7. CONCLUSION AND FUTURE PERSPECTIVE

Adipokines play a key role in the pathogenesis of various types of liver diseases. Emerging evidence has demonstrated that adipokines, in particular adiponectin and leptin, regulate cell death and/or survival of liver cells and hepatic cancer cells *via* multiple mechanisms (Fig. 1). In general, adiponectin causes apoptosis of liver cancer cells; however, in the presence of damaging stimuli, it may prevent cell death possibly *via* autophagy activation. On the other hand, leptin causes proliferation of HSCs and hepatic cancer cells. Interestingly, leptin-induced autophagy activation causes degradation of pro-apoptotic proteins and thus inhibits cell death. Moreover, adiponectin interferes with leptin-mediated effects. Recent studies have clearly demonstrated that adiponectin and leptin modulate pathogenesis of hepatic fibrosis and liver cancer through direct regulation of proliferation of hepatic stellate cells and cancer cells. Herein, we summarize the effects of adiponectin and leptin in the regulation of proliferation of liver cells. Although, at this time, the major roles of other adipokines are not clearly understood, recent evidence suggests that visfatin and resistin have an impact on apoptosis and proliferation of liver cells. Future studies will unravel the effects of various different types of adipokines on cell death and proliferation of liver cells.

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