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TOPIC HIGHLIGHT

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Leptin in hepatocellular carcinoma

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Abstract

The risk factors for hepatocellular carcinoma (HCC) development have been established, and include chronic hepatitis B and C, heavy alcohol consumption, and aflatoxins. In fact, 5%-30% of patients with HCC still lack a readily identifiable risk factor. It has been reported that the majority of "cryptogenic" HCC may be attributed to nonalcoholic fatty liver disease, the hepatic presentation of the metabolic syndrome (MS). Obesity is associated with the development of the MS. Recently, adipose tissue has been considered as an endocrine organ because of its capacity to secrete a variety of cytokines, which are collectively known as the adipokines. Leptin, the product of the obese gene, is mainly produced by adipose tissue. Since leptin was first characterized in 1994, accumulated literature has demonstrated the involvement of this adipokine in several areas of human physiology. After binding to its receptor, leptin initiates a cascade of signaling events and subsequent cellular effects. In addition to being the regulatory mediator of energy homeostasis, several *in vitro* studies have demonstrated the fibrogenic role of leptin in the liver. Furthermore, the deregulated expression of leptin and its receptor have been demonstrated to be associated with a variety of metabolic disorders as well as human cancers. Most importantly, direct evidence supporting the inhibitory and/or activating role of leptin in the process of carcinogenesis and progression of human HCC has been accumulating rapidly. This review aims to provide important insights into the potential mechanisms of leptin in the development of HCC. Hopefully, further investigations will shed light on a new therapeutic target in HCC.

Key words: Adipokine; Hepatocellular carcinoma; Leptin; Liver cirrhosis; Metabolic syndrome; Obesity; Steatohepatitis

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most com-

mon cancer worldwide and the third leading cause of cancer death[1]. Due to its high mortality, the annual fatality ratio is close to 1.0, indicating that the patients who develop HCC will die within 1 year[2]. Furthermore, recent data have shown that there are 662 000 deaths per year from liver cancer[3]. In addition, using the linked Surveillance, Epidemiology and End Results and Medicare dataset to estimate the annual direct and indirect costs associated with HCC, Lang *et al*[4] pointed out the considerable economic impact of HCC on the health care system in the United States. Thus, further understanding of the causation and potential mechanisms of HCC is urgently needed.

Recently, obesity has become a worldwide health issue, because it increases the risk for a variety of human diseases. It is said that the prevalence of obesity has increased substantially over the past decade in most industrialized countries, and a further increase is expected in the future[5]. The International Association for the Study of Obesity reported that approximately 40%-50% of men and 25%-35% of women in the EU were overweight [defined as a body mass index (BMI) between 25.0 and 29.9 kg/m^2], and an additional 15%-25% of men and 15%-25% of women were obese (BMI $\geqslant$ 30.0 kg/m^2)[6]. A similar observation was also found in the US population and the prevalence continues to increase despite all efforts to oppose it[7]. Diseases which have been associated with obesity include hypertension, type 2 diabetes, dyslipidemia and coronary heart disease[8,9]. Further evidence suggests that obesity is also a risk factor for certain types of cancer[10].

In spite of many well-defined risk factors for HCC [including hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol], Caldwell *et al*[11] have shown that 5%-30% of patients with HCC lack a readily identifiable risk factor. The majority of "cryptogenic" HCC in the United States is attributed to nonalcoholic fatty liver disease (NAFLD)[12]. In addition, a number of studies have observed an increased risk (1.5 to 4-fold) of HCC among obese individuals[13-15]. Therefore, experts have attempted to elucidate the possible events by which obesity might be linked to these diseases. Of note, it should be remembered that adipose tissue is central to the understanding of metabolic abnormalities associated with the development of obesity. In recent years, adipose tissue has been considered as an endocrine organ because of its capacity to secrete a variety of proteins with broad biological activities[16]. These proteins, collectively referred to as adipokines, play an important role in the physiology of adipose tissue, including food intake and nutrient metabolism, insulin sensitivity, stress responses, reproduction, bone growth, and inflammation.

Leptin, the product of the obese (*ob*) gene, has undoubtedly been the most studied adipokine since this protein was first characterized by Zhang *et al*[17] in 1994. Leptin is best known as a regulator of food intake and energy expenditure *via* hypothalamic-mediated effects. It is currently appreciated that this adipokine has many additional effects, often as a consequence of direct peripheral actions. These include angiogenesis, hematopoiesis, lipid and carbohydrate metabolism and effects on the reproductive, cardiovascular and immune systems. More importantly, a recent study considered leptin as a fibrogenic factor in all types of chronic liver disease[18]. In addition, leptin has been demonstrated to be crucial in the progression of NAFLD, the hepatic presentation of the metabolic syndrome (MS), into liver fibrosis[19]. Thus, the aim of this review is to discuss the updated information on leptin and its receptor, the proinflammatory effects of leptin on chronic liver disease of different etiologies, and the potential impact of leptin on HCC progression. Hopefully, leptin will shed light on a new therapeutic target in HCC treatment.

LEPTIN - A VERSATILE ADIPOKINE

Leptin, the product of the *ob* gene, is mainly produced by adipose tissues and, to a lesser extent, by tissues such as the stomach, skeletal tissue and placenta[17]. Leptin is secreted into the blood stream in a circadian rhythm and proportional to body fat mass. Although leptin serves as a regulatory mediator between the brain and the periphery through modulating the hypothalamo-pituitary-adrenal (HPA) axis, its circulating level is also regulated by hormones secreted by the HPA system, including corticosteroids, prolactin, and insulin[20,21]. Furthermore, leptin expression can be negatively regulated by fasting, beta-adrenergic agonists and thiazolidinediones. In addition, leptin secretion is higher in females than in males for any given age and body fat mass, i.e. it is sexually dimorphic.

Leptin is known to regulate energy homeostasis[22]. However, leptin-deficient (*db*/*db*) mice are not only severely obese, but also have a number of abnormalities. Research efforts have since expanded to elucidate leptin's role in human physiology and have resulted in a fundamentally renewed understanding of its role in the regulation of neuroendocrine function, reproduction, gastroduodenal mucosa defense, and metabolism of bone[23]. Indeed, changes in plasma leptin concentrations or in leptin action have important and wide-ranging physiological implications.

Recently, mounting evidence has advocated leptin to have a regulatory function in immunity similar to the function of a pro-inflammatory cytokine. Several studies have found that circulating leptin levels increase during infection and inflammation, suggesting that leptin is part of the immune response and host defense mechanisms. Leptin levels are acutely increased by many acute phase factors, such as tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6, and during bacterial infection, or lipopolysaccharide (LPS) challenge[24]. Leptin acts on monocytes/macrophages by inducing eicosanoid synthesis, nitric oxide and several pro-inflammatory cytokines. Moreover, leptin induces chemotaxis of neutrophils and the release of oxygen radicals. The role of leptin in the innate and adaptive immune responses has also been reviewed recently[25].

LEPTIN RECEPTOR AND ITS SIGNALING PATHWAY

The leptin receptor (OBR), belongs to the class I cytokine

receptor family (which includes receptors for IL-6, IL-12 and prolactin), and exists in at least six alternatively spliced forms with cytoplasmic domains of different length, known as OBRa, OBRb, OBRc, OBRd, OBRe and OBRf. These receptors are membrane-spanning glycoproteins with fibronectin type Ⅲ domains in the extracellular region and with a shared 200-amino-acid module containing four conserved cysteine residues and two membrane proximal cytokine-like binding motifs, Trp-Ser-Xaa-Trp-Ser[26]. Only the long form of the leptin receptor can signal intracellularly, whereas the short forms do not[27]. The short forms of the leptin receptor are expressed by several non-immune tissues and seem to mediate the transport and degradation of leptin. The long form of OBR, known as OBRb, is expressed by the central nervous system in areas that are responsible for the secretion of neuropeptides and neurotransmitters that regulate appetite, body weight and energy homeostasis[28]. Interestingly, OBRb is also expressed by endothelial cells, pancreatic β-cells, the ovary, CD34+ hematopoietic bone-marrow precursors, monocytes/macrophages, and T and B cells[25].

After binding leptin, OBRb initiates a cascade of signaling events. Foremost, the receptor-associated Janus-family tyrosine kinase 2 becomes activated by auto- or cross-phosphorylation, and subsequently tyrosine phosphorylates the cytoplasmic domain of the receptor[29]. At least three phosphorylated tyrosine residues in the cytoplasmic domain of OBRb function as docking sites for cytoplasmic adaptors: Tyr_{985}, Tyr_{1077} and Tyr_{1138}. Each of these phosphorylation sites lies in a unique amino acid motif, and each of these residues thus recruits a distinct set of downstream signaling proteins when phosphorylated.

In cultured cells, phosphorylated Tyr985 recruits the SRC homology 2 domain-containing phosphatase 2 to mediate the first step in the activation of the extracellular signal regulated kinase cascade[30]. Phosphorylated Tyr1138 recruits the signal transducer and activator of transcription-3 (STAT3), a latent transcription factor that then becomes phosphorylated, translocates to the nucleus, and mediates the regulation of gene expression[31]. Tyr1138→STAT3 signaling promotes the expression of SOCS3, as the afferent arm of a feedback loop that attenuates OBRb signaling[32]. The phosphorylation of Tyr1077 promotes the recruitment, tyrosine phosphorylation and transcriptional activation of STAT5, although Tyr1138 may also play a minor role in the regulation of STAT5 phosphorylation[33].

LEPTIN AND MS

Obesity, particularly abdominal obesity, is associated with resistance to the effects of insulin on peripheral glucose and fatty acid utilization, often leading to type 2 diabetes mellitus. Insulin resistance, the associated hyperinsulinemia and hyperglycemia, and the production of adipokines may lead to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of atherosclerotic cardiovascular disease (CVD). Therefore, the co-occurrence of metabolic risk factors for both type 2 diabetes and CVD (abdominal obesity, hyperglycemia, dyslipidemia, and hypertension) suggests the existence of a "MS"[34].

A study by Zimmet *et al*[35] reported the association of leptin with fasting insulin in several populations, raising the possibility that hyperleptinemia was an additional component of the MS, or perhaps even underlay the syndrome. Subsequent study also found that leptin was strongly, positively correlated with BMI, fasting insulin, and mean blood pressure after adjusting for age and sex irrespective of glucose tolerance status. Linear regression models indicated that leptin was associated with insulin sensitivity independent of age, BMI, waist/hip ratio, triglycerides, HDL cholesterol, and hypertension[36]. The associations between leptin and components of the MS (insulin, blood pressure, triglycerides), independent of obesity measures, suggest that leptin is more than a mere "iostat" or indicator of obesity. Thus, hyperleptinemia or leptin resistance may also be an important etiological component of the MS, either directly or *via* its influence in regulating insulin sensitivity.

ESTABLISHED RISK FACTORS OF HCC AND THEIR POTENTIAL LINKS TO LEPTIN

The established risk factors for HCC include HBV or HCV infection, alcohol intake, tobacco smoking, and aflatoxins. Their respective hepatocarcinogenesis and potential relationship with leptin will be reviewed in this section.

Chronic hepatitis B

To date, two major HBV-specific mechanisms have been indicated to contribute to HCC development. The first is the integration of the viral genome into the host chromosome causing cis-effects, resulting in loss of tumor suppressor gene functions, and/or activation of tumor-promoting genes[37]. The second mechanism involves the expression of trans-activating factors derived from the HBV genome, which have the potential to influence intracellular signal transduction pathways and alter host gene expression. A major player involved in this form of viral transactivation is the X protein (HBx). The HBx protein has been found to display pleiotropic functions and has been implicated in the malignant transformation of chronically-infected liver cells. By disrupting cellular gene expression, viral products such as HBx may modulate cellular growth, repair and death, consequently resulting in the transformation of hepatocytes to an oncogenic state[37,38].

Recent clinical data, which investigated serum leptin concentrations in patients with chronic viral hepatitis, indicated that cirrhotic patients due to HBV infection had significantly higher leptin levels compared to the controls, and serum leptin levels were associated with the stage of liver fibrosis. In addition, it was suggested that increased serum leptin levels might represent a negative prognostic factor for response to lamivudine monotherapy in patients

with chronic hepatitis B[39]. Another report, which evaluated the expression of leptin and ObR in patients with chronic viral hepatitis, found that the HBV patients expressed significantly lower ObR mRNA levels in peripheral blood mononuclear cells and had decreased serum leptin levels in comparison to the healthy controls. This implied involvement of the leptin system in the immunopathology of chronic viral hepatitis[40].

Chronic hepatitis C

Chronic HCV infection is characterized by inflammatory lesions in the liver, often accompanied by intrahepatic lipid accumulation (steatosis) and progressive fibrosis of variable degree, and long-term progression to cirrhosis and HCC[41]. The mechanisms underlying the progression of HCV infection to HCC still remain ill-defined. Unlike HBV, HCV does not integrate into its host genome and has a predominantly cytoplasmic life cycle[42]. Hepatocarcinogenesis of HCV, therefore, must involve several indirect mechanisms including the interplay between chronic inflammation, steatosis, fibrosis and oxidative stress and their pathological consequences. For example, the accumulation of oxidative stress and DNA damage in a setting of restricted cell cycle checkpoint control and/or accelerated cell division is thought to compromise gene and chromosome stability and to form the genomic basis for malignant transformation. Markers of intracellular oxidative stress have also been found to be increased in patients with chronic HCV infection as well as HCV core transgenic mice[43]. In addition, several HCV proteins have been shown to have direct oncogenic effects and to upregulate mitogenic processes[44]. In fact, direct interactions of the various HCV proteins with host cell factors have also been shown to lead to changes in cellular signaling cascades involved in regulation of cell metabolism and division and seem to be sufficient to induce hepatocarcinogenesis. Overall, it is thought that the synergism between chronic inflammation and direct virus-host cell interactions triggers the malignant transformation of hepatocytes. The requirement for such a synergism would also explain the slow "multi-step" transformation process that underlies human HCC development[45,46].

A previous study has demonstrated that chronic HCV infection could induce abnormal lipid accumulation in the liver[41]. Therefore, the association of leptin with this metabolic disorder has been reviewed. Some authors showed the link between leptin and obesity as well as hepatic steatosis development in patients with chronic HCV infection, however, this observation was not found in another report[47,48]. Likewise, higher leptin levels were shown to be associated with cirrhosis development due to chronic HCV infection[39], but not with their histological features[49]. These controversial results regarding the association of leptin with chronic HCV hepatitis needs further investigation.

Alcohol consumption

Chronic alcohol consumption has long been associated with the development of hepatic cirrhosis and subsequent HCC. Many deleterious effects of alcohol have been attributed to alcohol metabolism in hepatocytes. In general, alcohol is almost metabolized by alcohol dehydrogenase (ADH) located in the cytoplasm of hepatocytes. Acetaldehyde, which forms *via* ADH-dependent alcohol metabolism, is clearly of great significance during the initiation and progression of alcohol-related liver disease. It is said that acetaldehyde can alter the integrity of DNA in a variety of ways[50]. Chronic alcohol consumption can alter the balance of bacterial flora within the GI tract and the permeability to LPS[51]. The vascular architecture linking the GI tract to the liver, thus, leads to increased intrahepatic LPS levels and the stimulation/activation of the liver's resident macrophage kupffer cell (KC) population[52]. Once activated, KCs synthesize and release a range of proinflammatory cytokines, which can act in both an autocrine and paracrine manner to further activate KCs or neighboring cell populations[53,54]. The activation of KCs and associated cytokine release may affect hepatic responsiveness to alcohol in several different ways. For example, hepatic stellate cells (HSCs) can undergo rapid activation in the presence of hepatic insult including increases in proinflammatory cytokines, oxidative stress, and/or levels of hepatotoxins[55]. A central mechanism underlying ethanol-induced activation of HSCs is dependent on the generation of reactive oxygen species[56].

As mentioned above, chronic alcohol consumption activates KCs and subsequently releases a number of proinflammatory cytokines. A study from India, investigating the effect of exogenous leptin and/or ethanol on the secretion of TNF-α, IL-6 and transforming growth factor (TGF)-β1 both *in vivo* and *in vitro*, found that leptin could downregulate ethanol-induced secretion of proinflammatory cytokines and growth factor[57]. This implies that leptin could be useful in preventing the damage produced by ethanol, which might be of therapeutic interest.

Aflatoxins

Ecological studies in the 1970s and 1980s first reported correlations between aflatoxin levels in crops or food and HCC rates[58]. Aflatoxin B1 (AFB1) is the most common and potent of the aflatoxins. In areas of high aflatoxin exposure, up to 50% of HCC patients have been shown to harbor a specific AGG to AGT point mutation in codon 249 of the TP53 tumor suppressor gene (codon 249^{ser} mutation)[59,60]. Interestingly, one prospective epidemiological study has shown a more than multiplicative interaction between HBV and aflatoxins in terms of HCC risk[61]. A number of potential mechanisms have been mentioned, for example, the fixation of AFB1-induced mutations in the presence of liver regeneration and hyperplasia induced by chronic HBV infection, and predisposition of HBV-infected hepatocytes to aflatoxin-induced DNA damage[62]. On the other hand, one recent study also suggested that aflatoxin-albumin adducts were associated with more advanced liver disease in individuals infected with HCV[63].

In addition to being a strong carcinogen, AFB1 is also

known to evoke a decrease in food intake and body weight gain. In one *in vitro* experiment, it was demonstrated that AFB1 had a weak effect on adipocytes, but no significant influence on leptin release[64]. Another animal model found that AFB1 could decrease food intake and body weight, and significantly depress serum leptin levels[65].

NAFLD: A NEW RISK FACTOR FOR HCC

NAFLD is a spectrum of disorders ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. It is believed to account for up to 90% of cases of elevated liver function tests in patients without an identifiable cause of liver disease (e.g. viral hepatitis, alcohol, inherited liver disease, and medications)[66]. Given the fact that patients with NASH can enter a final cirrhotic pathway similar to that in patients with alcoholic cirrhosis or in patients suffering from chronic hepatitis B or C, it is not surprising that NASH appears to be a new risk factor for HCC[67].

A close relationship between NFLD, obesity and the MS

Obesity is found in 30%-100% of subjects with NAFLD. In obese persons, steatosis is 4.6-fold higher than in normal weight persons[66]. Clinical, epidemiological and biochemical data strongly support the concept that NAFLD is the hepatic manifestation of the MS. According to Kotronen *et al*[68], 90% of individuals with NAFLD have at least one risk factor for MS, and 33% have all the features of MS. In addition, liver fat content is significantly increased in subjects with the MS as compared with those without the syndrome, independently of age, gender, and BMI. The presence of multiple metabolic disorders such as diabetes mellitus, obesity, dyslipidemia and hypertension is associated with a potentially progressive, severe liver disease[69].

Pathogenesis of NAFLD

Insulin resistance, oxidative stress, and an inflammatory cascade are believed to play integral roles in the pathogenesis and progression of NAFLD[70]. In insulin-resistant states, adipose and muscle cells preferentially oxidize lipids, resulting in the release of FFA. FFA can then be taken up by the liver, resulting in steatosis. Animal studies show that FFA, once released from muscle and adipose cells, can be incorporated into triglycerides in the liver or undergo oxidation in mitochondria, peroxisomes or microsomes. Oxidized by-products are harmful adducts that can cause liver injury, resulting in subsequent fibrosis[71]. Lipid peroxidation and oxidative stress result in increased production of hydroxynonenal and malondialdehyde that upregulate liver fibrosis *via* activation of stellate cells and result in increased production of TGF-β[72].

Recently, scientists have focused on the role of KCs in the pathogenesis of NAFLD. KCs are the resident macrophages of the liver and function in both innate and adaptive immunity as active phagocytosing agents and antigen-presenting cells (*via* toll-like receptors, among others) to T-cells. While inactivation of KCs is associated with NAFLD and impaired hepatic regenerative capacity, elimination of resident KCs has been associated with improvement of NASH, suggesting that overactivation of a Kupffer-cell-mediated immune response might underlie liver injury in NAFLD. It is thought that KC physiology becomes altered in the setting of increased hepatic lipid content possibly due to overcrowding of liver sinusoids resulting in prolonged exposure of KCs to antigens, reduced KC outflow, and a resulting sustained inflammatory response. Uncoupling proteins, are molecules that dissipate the proton gradient in the inner mitochondrial membrane and thereby reduce the energy needed for oxidative phosphorylation. Insufficient uncoupling protein production in KCs, possibly due to LPS-induced activity, might contribute to the pathogenesis of NAFLD[73].

Leptin in the pathogenesis of NAFLD

Leptin is thought to participate in the development of NAFLD. In animal models of NAFLD, leptin contributes to the development of insulin resistance and subsequently steatosis. Furthermore, in the context of liver insult, leptin has a proinflammatory role and is considered to be an essential mediator of liver fibrosis. In rats treated with carbon tetrachloride (CCl4), leptin injections have been shown to result in the increased expression of procollagen-I, TGFβ1 and smooth muscle actin, a marker of activated HSCs, and eventually to increased liver fibrosis[74].

In human studies, leptin levels were initially found to be significantly higher in 47 NASH patients than in 47 controls and correlated with the severity of hepatic steatosis but not to necroinflammation or fibrosis[75]. A subsequent study showed that leptin levels are significantly higher in NASH patients than in patients with chronic viral hepatitis and correlate with more severe fibrosis in univariate analysis[76]. However, another study failed to show any significant difference in leptin levels between NASH patients and controls or any independent association with liver fibrosis[77]. Thus, it is doubtful whether leptin is upregulated in patients with NASH and larger studies with a homogenous population and carefully matched healthy controls are needed. For the time being, leptin cannot be used as a noninvasive marker for the diagnosis of NASH.

LEPTIN PLAYS A FIBROGENIC ROLE IN THE LIVER

The development of fibrosis, which is critical for the progression of all chronic liver diseases, comprises a series of events, including inflammation, activation of fibrogenic myofibroblasts (e.g. HSCs), deposition of fibrillar extracellular matrix, and possibly neo-angiogenesis[78]. The data on the role of leptin in the regulation of these steps have been accumulating rapidly. Several *in vivo* studies, which evaluated the effect of leptin in animal models of chronic liver injury, including dietary steatohepatitis, bile duct ligation, and infection with eggs of *Schistosoma mansoni*, provided obvious support to the role of leptin as a critical mediator of fibrosis[79-81]. Importantly, when assessing

the response of ob/ob mice, the decreased fibrogenic response was reverted by supplementation with recombinant leptin. These findings suggest that leptin is a critical factor for the development of fibrogenesis in rodents.

Different cell types have been mentioned to participate in the response of leptin to liver injury, including KCs, sinusoidal endothelial cells and myofibroblast-like cells, which are derived from the activation of HSCs and from other mesenchymal cells. Ikejima *et al*[82] demonstrated that ObRb is expressed by sinusoidal endothelial cells and KCs, where exposure to recombinant leptin up-regulates the expression of TGF-β. A number of successive studies also indicated that HSCs express functional ObRb and are directly responsive to leptin. Expression of ObRb is low in quiescent HSCs, and increases during the activation process, suggesting that in activated HSCs the effects of leptin are amplified[83]. In addition, incubation of HSCs with recombinant leptin stimulates the expression of type I procollagen, potentiates the effects of TGF-b, and up-regulates expression of the tissue inhibitor of metalloproteinase-1, thus blocking collagen degradation[84,85].

A recently identified effect of leptin on fibrogenic cells is the induction of vascular endothelial growth factor (VEGF) *via* oxygen-independent activation of hypoxia-inducible factor 1a, a master switch of the angiogenic response[86]. These observations may potentially have an impact on liver fibrosis, as formation of new blood vessels is a key component of the wound-healing response and has been suggested to play a role in the irreversibility of established cirrhosis. Together, these observations suggest the fibrogenic role of leptin in the liver.

EVIDENCE REGARDING THE ASSOCIATION OF LEPTIN WITH HCC DEVELOPMENT

Yang *et al*[87] first explored whether obesity might increase the risk for HCC, and found that ob/ob mice developed liver hyperplasia at the earliest stage of NAFLD and eventually HCC. This observation raised the intriguing issue that obesity-related fatty liver, itself, might be a premalignant condition. A number of studies have attempted to elucidate the possible effects of leptin in HCC development. Wang *et al*[88], who investigated whether leptin might be involved in the etiogenesis of HCC in cirrhotic patients, found that increased serum leptin was significantly correlated with cirrhotic change, but not with HCC occurrence. This finding was consistent with previous studies, indicating the fibrogenic effect of leptin in the liver. Another study, which evaluated the expression of leptin and its receptor in HCC specimens and adjacent non-tumorous tissues, first pointed out the involvement of leptin in the carcinogenesis of HCC[89]. However, the authors suggested further investigations should be carried out to define the inhibitory and/or activating role of leptin in the process of carcinogenesis and progression of human HCC.

A recent study found that, without leptin signaling, neither fibrosis nor HCC developed in the rat NASH experimental model, suggesting that leptin might play a pivotal role in the progression of fibrogenesis and carcinogenesis in NASH[19]. Further *in vitro* assay demonstrated the necessity of leptin-mediated neo-vascularization coordinated with VEGF in this progression. The involvement of leptin/OBR in the angiogenesis of human HCC was also shown in a recent study[90]. Notably, one *in vitro* assay demonstrated the proliferative and anti-apoptotic effects of leptin in HCC cells *via* Janus kinase 2-linked signaling[91]. Taken together, these findings implied that leptin-induced effects implicated in HCC development seemed to be inhibitory.

In fact, several studies have reported the contradictory effects of leptin in HCC growth. Elinav *et al*[92] first showed that exogenous leptin significantly decreased tumor size and improved survival rate in a murine model of HCC. The authors further demonstrated that the majority of these leptin-induced inhibitory effects might be mediated by the induction of natural killer cell proliferation and activation. Moreover, Wang *et al*[93,94], who evaluated the expression of leptin and its receptor in HCC specimens by immunostaining, further correlated the expression profile with Ki-67 expression, intratumor MVD, as well as overall survival, provided clinical evidence on the prognostic roles of leptin and OBR in HCC patients. First, OBR expression was inversely correlated with vascular invasion of HCC. Furthermore, high leptin expression was associated with better survival in patients with HCC, treated postoperatively with medroxyprogesterone acetate, a synthetic variant of human progesterone. As a result, it was suggested that both high leptin and OBR expression in HCC tissues could predict better overall survival.

CONCLUSIONS AND FUTURE DIRECTIONS

Leptin has an increasingly crucial role in a variety of human metabolic disorders and cancers. This parallels the increasing prevalence of NAFLD in patients with HCC. This work reviews the updated information on leptin, including its receptor and related signaling pathway, and provides important insight into the association between leptin and the MS and NAFLD as well as well-known risk factors for HCC. Moreover, research studies have demonstrated that leptin can exert a fibrogenic effect in the liver. In addition, evidence regarding the direct link between leptin and HCC development has been accumulating rapidly. This demonstrates the potential of the leptin-mediated effects in the carcinogenesis and progression of HCC, however, there is ample room for further research on its inhibitory and/or activating role. In addition, the role of leptin in the response of HCC to hormonal therapy deserves further research.

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