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REVIEW

Chemoprevention of obesity-related liver carcinogenesis by using pharmaceutical and nutraceutical agents

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Abstract

Obesity and its related metabolic disorders are serious health problems worldwide, and lead to various health-related complications, including cancer. Among human cancers, hepatocellular carcinoma (HCC) is one of the most common malignancies affected by obesity. Therefore, obesity and its related disorders might be a key target for the prevention of HCC. Recently, new research indicates that the molecular abnormalities associated with obesity, including insulin resistance/hyperinsulinemia, chronic inflammation, adipokine imbalance, and oxidative stress, are possible molecular mechanisms underlying the pathogenesis of obesity-related hepatocarcinogenesis. Green tea catechins and branched-chain amino acids, both of which are classified as nutraceutical agents, have been reported to prevent obesity-related HCC development by improving metabolic abnormalities. The administration of acyclic retinoid, a pharmaceutical agent, reduced the incidence of HCC in obese and diabetic mice, and was also associated with improvements in insulin resistance and chronic inflammation. In this article, we review the detailed molecular mechanisms that link obesity to the development of HCC in obese individuals. We also summarize recent evidence from experimental and clinical studies using either nutraceutical or pharmaceutical agents, and suggest that nutraceutical and pharmaceutical approaches targeting metabolic abnormalities might be a promising strategy to prevent the development of obesity-related HCC.

Key words: Hepatocellular carcinoma; Obesity; Green tea catechins; Branched-chain amino acids; Acyclic retinoid

Core tip: Obesity and its related metabolic disorders increase the risk of hepatocellular carcinoma (HCC). In particular, the molecular abnormalities represented by insulin resistance/hyperinsulinemia, chronic inflammation, adipokine imbalance, and oxidative stress play a central role in the development of obesity-related HCC. Administration of green tea catechins, branched-chain amino acids, and acyclic retinoid has improved these metabolic abnormalities, and resulted

in the inhibition of HCC development in obese and diabetic mice models. In this review, we highlight the possibility that nutraceutical and pharmaceutical approaches targeting metabolic abnormalities are a promising strategy to prevent the development of obesity-related HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third leading cause of cancer-related deaths in the world. It accounts for more than 90% of primary liver cancers, and its incidence is increasing[1,2]. It is well known that HCC primarily develops from chronic liver inflammation and subsequent cirrhosis induced by persistent infection with the hepatitis B or hepatitis C viruses[3]. However, more recently, the incidence of HCC attributed to nonalcoholic fatty liver disease (NAFLD), which is related to obesity and systemic insulin resistance[4], has been rapidly increasing, especially in developed countries[5].

Obesity is now recognized as one of the most serious health problems worldwide, and its prevalence has dramatically increased in the last few decades[6]. It often causes a number of medical disorders, including type-2 diabetes mellitus, hypertension, and hyperlipidemia, which are collectively known as "metabolic syndrome". In addition, recent publications indicate that obesity and its related metabolic abnormalities, especially diabetes mellitus, are important risk factors for the development of many types of human malignancies, including HCC[7-16]. Moreover, obesity-associated neoplasms are likely to be more aggressive, and have an increased risk of recurrence, thereby resulting in higher mortality[17,18]. Indeed, in a prospective study conducted in a large cohort of American adults, Calle *et al*[19] reported that men with a body mass index (BMI) greater than 35 kg/m^2 had significantly higher mortality rates due to HCC when compared to men with a normal BMI.

Accumulating evidence from epidemiological and experimental studies indicates that several pathophysiological mechanisms link obesity to liver carcinogenesis, including insulin resistance and adipocytokine imbalance, alterations in the insulin-like growth factor-1 (IGF-1)/IGF-1 receptor (IGF-1R) axis, a state of chronic inflammation, and the induction of oxidative stress[9,10,15,20,21]. Meanwhile, several experimental studies have revealed that the improvement of chronic inflammation through the inhibition of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, plays an important role in the suppression of obesity-related colorectal cancer and HCC[22-25]. These facts suggest that pathophysiological disorders due to obesity and its related metabolic alterations could be critical targets for the chemoprevention of obesity-related liver carcinogenesis.

In this review, we summarize the multiple pathogenic mechanisms by which obesity and its related metabolic disorders induce the development of HCC, with a special focus on the emergence of insulin resistance and subsequent inflammatory cascades. We also discuss the possibility of nutraceutical or pharmaceutical approaches for targeting obesity-induced pathophysiological disorders for the prevention of obesity-related liver carcinogenesis.

LIVER STEATOSIS AND HCC

NAFLD has been referred to as the hepatic manifestation of obesity and metabolic syndrome and has become one of the most common liver diseases in developed countries[26]. NAFLD is mostly limited to liver steatosis, but approximately 20% of all cases present as nonalcoholic steatohepatitis (NASH) featuring hepatocyte injury, chronic liver inflammation, and various degrees of fibrosis with an elevated risk of developing liver cirrhosis and HCC[27-30]. Obesity is the main risk factor for NAFLD and up to 90% of obese people have some degree of liver steatosis[31]; however, NAFLD can be observed even in non-obese individuals with insulin resistance and hyperinsulinemia[4,32]. In contrast, obesity with only abdominal adiposity and without insulin resistance does not appear to play a role in liver steatosis[33]. These results indicate that obesity-induced metabolic abnormalities, especially insulin resistance, might be a crucial factor in the development of NAFLD.

Most NAFLD-related HCCs are believed to develop in the background of cirrhotic liver, similar to other etiologies such as chronic hepatitis virus infection[3]. Accumulating evidence indicates that NAFLD-induced cirrhosis increases the risk of HCC development in the absence of other risk factors[34-37]. Primary liver carcinomas, including HCC, often occur in patients with NASH, especially in those with advanced fibrosis and cirrhosis[38,39]. However, evidence is also accumulating indicating that NAFLD is strongly associated with the development of non-cirrhotic HCC[40-43].

A recent study from Yasui *et al*[44] revealed that approximately half of the 87 patients with HCC and biopsy-proven NASH had no established cirrhosis. In addition, a population-based study reported that 2863 cases of HCC (16% of the total number of HCC cases) were due to histologically confirmed NAFLD without other etiologies[45]. Notably, 1031 cases (36%) of NAFLD-related HCC were found in non-cirrhotic livers,

and 18% of these cases developed in simple fatty liver without steatohepatitis[45]. Thus, liver cirrhosis is not necessarily linked to the occurrence of obesity-related HCC.

As described above, NAFLD-related HCCs are likely to occur even in individuals with either NASH or simple fatty liver, in the absence of advanced liver fibrosis[34,40-44,46]. In these cases, the presence of metabolic syndrome, especially type 2 diabetes mellitus and obesity, plays a positive role in the development of HCC[47]. Notably, the features of HCC arising in these individuals are different from those arising in patients with chronic viral hepatitis, in terms of tumor size, the degree of tumor differentiation, and the extent of liver fibrosis[43]. Thus, given these differences between NAFLD-related and hepatitis virus-induced HCC, it is anticipated that specific pathophysiological mechanisms may present in the background of NAFLD-related hepatocarcinogenesis.

POTENTIAL PATHOPHYSIOLOGICAL MECHANISMS OF HEPATOCARCINOGENESIS ASSOCIATED WITH OBESITY

Although the pathways linking obesity to hepatocarcinogenesis remain poorly defined, accumulating evidence has led to the identification of potential pathophysiological mechanisms, including insulin resistance and the subsequent inflammatory cascades. Liver-specific and systemic insulin resistance are major consequences of obesity[20,48] and lead to fat accumulation in the hepatocyte by lipolysis and hyperinsulinemia, resulting in the development of liver steatosis, including NAFLD[32,47]. In addition, insulin resistance and hyperinsulinemia increase the biological activity of IGF-1, an important endocrine and paracrine regulator of tissue growth and metabolism[49-51].

The binding of insulin and IGF-1 to their respective cell surface receptors on tumors activates the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which is responsible for cellular processes like growth, proliferation, and survival[52,53] Indeed, alterations in the IGF-1/IGF-1R axis have been shown to contribute to the pathogenesis of HCC[52-55]. Moreover, insulin resistance also leads to an increased expression of pro-inflammatory cytokines, including TNF-α and IL-6, through the creation of an oxidative stress environment in the tissues[56]. The dysregulation of these cytokines is associated with the development of steatosis, chronic liver inflammation, and liver tumor formation[9,10,15,20,25,57]. Furthermore, DNA damage due to increased oxidative stress activates the PI3K/Akt pathway[58,59], suggesting that both of these may promote liver tumorigenesis in obese individuals. Thus, insulin resistance and its related inflammatory cascades are thought to be key factors involved in the development of obesity-associated HCC.

Excess fat accumulation in obesity results from a chronic increase in nutrient intake and a decrease in physical exercise, which leads to expansion of adipose tissue and recruitment of various immune cells, such as macrophages[60-62]. Hypertrophic adipocytes and infiltrated macrophages secrete free fatty acids and various pro-inflammatory cytokines, including TNF-α and IL-6[9,10,15,20], and contribute to the development of insulin resistance and low-grade, chronic inflammation[63,64]. Moreover, excess production of storage lipids causes an imbalance of serum adipokine levels, which is related to obesity-associated carcinogenesis[65,66].

The serum levels of adiponectin, an anti-inflammatory and tumor growth-limiting cytokine, are reduced in obese individuals[67] and are negatively correlated with obesity[68,69]. On the other hand, high-circulating levels of leptin, a major adipokine with pro-inflammatory and pro-fibrogenic effects, are observed in patients with obesity and NAFLD[70]. Notably, leptin has a growth-promoting effect through the activation of Janus kinase (JAK), a signal transducer and activator of transcription-3 (Stat3), PI3K/Akt, and extracellular signal-regulated kinase (Erk) signaling pathways[71]. In addition, leptin can induce the expression of TNF-α and IL-6[72,73], and result in tumor growth and progression as described above. Leptin also induces oxidative stress and inflammation in endothelial cells[74]. Indeed, in HCC patients, higher levels of serum leptin increase the risk of HCC recurrence after curative treatment[75]. Moreover, the positive association between leptin levels and the development of HCC has been elucidated by recent *in vitro* studies[71,76-79]. Taken together, these facts suggest that obesity-related metabolic abnormalities work simultaneously with, and complementary to, one another, and that they increase the risk of cancer, including HCC, in obese individuals (Figure 1).

OTHER POSSIBLE MECHANISMS LINKING OBESITY TO HEPATOCARCINOGENESIS: GENETIC RISK FACTORS

Recently published research has highlighted the relevance of genetic risk factors in the predisposition toward hepatocarcinogenesis in patients with NAFLD[80]. In particular, the I148M variant of patatin-like phospholipase domain-containing protein 3 (PNPLA3) is a risk factor for HCC development in obese and NAFLD patients[81,82]. Indeed, one recent cohort study involving 3473 obese individuals observed a high incidence of HCC development in the subjects with the I148M risk allele[83]. Interestingly, this risk allele is associated with HCC development independently of its effect on the progression of liver fibrosis and cirrhosis[82,84,85]. Given that NAFLD-related HCC is likely to occur in individuals without advanced liver fibrosis, it

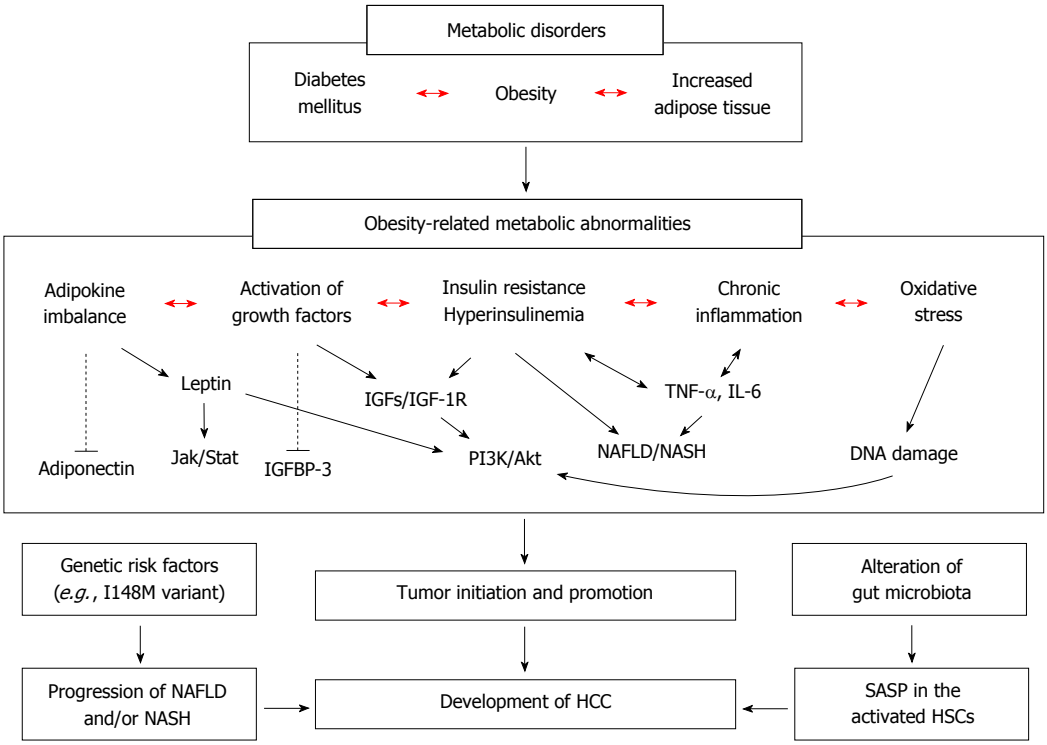

Figure 1 Proposed mechanisms linking obesity and its related metabolic abnormalities to the development of hepatocellular carcinoma. HCC: Hepatocellular carcinoma; HSCs: Hepatic stellate cells; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; IGF-1: Insulin-like growth factor-1; IGFBP-3: IGF-binding protein-3; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; Jak: Janus kinase; Stat: Signal transducer and activator of transcription; SASP: Senescence-associated secretory phenotype; PI3K: Phosphatidylinositol 3-kinase.

is believed that genetic risk factors, such as the I148M variant, also play an important role in the development of NAFLD-related HCC (Figure 1).

OTHER POSSIBLE MECHANISMS LINKING OBESITY TO HEPATOCARCINOGENESIS: MICROBIOME COMPOSITION

The relationship between the intestinal microbiome and metabolic regulation is attracting an increasing amount of attention. Indeed, several experimental studies have demonstrated that intestinal dysbiosis is associated with the development of metabolic disorders, including obesity, insulin resistance, and NAFLD[86-92]. Interestingly, obesity-induced alteration of gut microbiota promotes liver carcinogenesis through the activation of hepatic stellate cells (HSCs). Dietary and genetic obesity induced an alteration of gut microbiota, resulting in increased levels of deoxycholic acid (DCA)[93]. The enterohepatic circulation of DCA induced senescence-associated secretory phenotype (SASP) in the activated HSCs, leading to hepatocarcinogenesis via the secretion of various tumor-promoting factors in the liver[93]. Notably, the inhibition of DCA production or the reduction of gut bacteria prevented the development of HCC in obese mice[93]. Thus, these results indicate that the SASP in the activated HSCs due to obesity-induced gut microbial metabolites plays a key role in the development of obesity-related HCC (Figure 1).

BENEFICIAL EFFECTS OF WEIGHT REDUCTION IN PATIENTS WITH NAFLD

Although several agents have been evaluated in clinical trials, there are currently no well-established therapies for NAFLD[94]. However, several recent clinical studies have elucidated the beneficial effects of weight reduction in the improvement of NAFLD[95-100]. Notably, weight reduction based on dietary and lifestyle modifications improved the histological features of NAFLD in overweight subjects[101]. Interestingly, this beneficial effect was associated with an improvement in biological parameters (aspartate aminotransferase/alanine aminotransferase/γ-glutamyltransferase), metabolic ones (body mass index/fasting glucose/insulin resistance) or in the imbalance of adipocytokines[101]. Besides, recent studies examined the association between the magnitude of weight reduction and changes in histological features of liver steatosis, and reported that a weight loss of over 7% is essential to yield histological outcomes[96,97,100,102]. Moreover, Vilar-Gomez *et al*[103] reported that weight reduction of over 10% through lifestyle modification significantly reduced NASH-related histological features, including fibrosis and portal inflammation. Thus, weight reduction based on lifestyle modification can be effective in the

management of patients with NASH, and is currently recommended as a first line therapeutic intervention for this disease[94,103,104].

PREVENTION OF OBESITY-RELATED HCC USING THE NUTRACEUTICAL APPROACH: GREEN TEA CATECHINS

As stated earlier, obesity and its related metabolic abnormalities, including insulin resistance and chronic inflammation in the liver, play an important role in the development of HCC. This indicates that metabolic abnormalities induced by obesity may be a valuable target in the prevention of liver carcinogenesis in obese individuals. Indeed, genetic ablation of TNF-α and IL-6 signaling could reduce the incidence of obesity-promoted hepatocarcinogenesis through the reduction of liver steatosis and steatohepatitis[25]. In support of this idea, administration of adiponectin resulted in the reduction of leptin-induced liver tumorigenesis in nude mice[105]. Thus, targeting obesity-related metabolic abnormalities is a promising strategy for the prevention of HCC.

An improvement of metabolic abnormalities through nutraceutical or pharmaceutical intervention might be an effective strategy to inhibit obesity-related liver carcinogenesis, as has already been reported experimentally for colon carcinogenesis[106]. In order to verify this hypothesis, we experimentally investigated the chemopreventive effects of nutritional agents, including green tea catechins (GTCs) and branched-chain amino acids (BCAA) in obese and diabetic C57BL/KsJ-*db/db* (*db/db*) mice, and supplemented our findings by summarizing the relevant results of recent publications.

The *db/db* mice have a functional defect in the long-form leptin receptor, leading to hyperleptinemia and obesity due to overeating. Because of the obesity, hyperinsulinemia, and hyperleptinemia, these mice are regarded as a suitable animal model that mimics metabolic syndrome in humans[107]. In addition, the mice are susceptible to chemical carcinogens and develop *N*-diethylnitrosamine (DEN)-induced liver tumorigenesis through the activation of IGF/IGF-1R and the induction of chronic inflammation in the liver[54,55,108]. Thus, the *db/db* mice are thought to be a suitable mouse model of obesity-related hepatocarcinogenesis[54].

Recently, the beneficial effects of GTCs on the improvement of obesity have been reported[109]. A mechanistic review reported that the anti-obesity effects of GTCs results from underlying mechanisms that promote energy expenditure, fatty acid oxidation, and a reduction in nutrient absorption[110]. In addition, GTCs improved hyperglycemia, insulin resistance, and hyperleptinemia, and result in an improvement in liver steatosis and liver dysfunction in rodent diabetic models[111-113]. Treatment with GTCs decreases serum levels of insulin, TNF-α and IL-6 in insulin-resistant rats[114]. Thus, GTCs possess the ability to improve obesity and its related metabolic abnormalities.

In addition to the improvement of obesity, other studies have reported on the anti-cancer and cancer-preventative effects of GTCs[115-118]. A number of studies have demonstrated that GTCs inhibit the proliferation of, and induce apoptosis in, cancer cells by modulating the activation of several receptor tyrosine kinases (RTKs) and their downstream signaling pathways, such as Ras/Erk and PI3K/Akt[115-117,119,120]. Moreover, the down-regulation of IGF/IGF-1R and the activation of IGF-binding protein-3 (IGFBP-3), which negatively controls IGF/IGF-1R signaling, are responsible for the growth inhibition of colorectal and HCC cells[121,122]. Given that IGF/IGF-1R signaling plays an important role in the development of obesity-related HCC as stated above, GTCs are a promising candidate for the chemoprevention of this malignancy.

Indeed, our recent publication reported that (-)-epigallocatechin gallate (EGCG), a major biologically active component of green tea catechins, significantly inhibited the development of liver foci and adenoma in DEN-treated *db/db* mice[55]. Moreover, EGCG decreased the serum levels of insulin, IGF-1, IGF-2, and inhibited the phosphorylation of IGF-1R, Erk, Akt, and GSK-3β in the liver[55]. Furthermore, mRNA expression of TNF-α, IL-6, IL-1β, and IL-18 in the liver was reduced by EGCG treatment[55]. Thus, EGCG prevents obesity-related HCC development by modulating IGF/IGF-1R signaling, and by improving both insulin resistance and chronic liver inflammation. These data also indicate that GTCs, especially EGCG, may be useful for the chemoprevention of obesity-related HCC development (Figure 2).

To date there are no clinical studies that evaluate the chemopreventive effects of GTCs on obesity-related hepatocarcinogenesis in humans. However, our pilot study showed that oral supplementation of GTCs (1.5 g/d) for 1 year significantly reduced the incidence of metachronous colorectal adenomas after polypectomy[123]. In addition, a randomized, double-blinded, placebo-controlled study reported that oral administration of GTCs for 1 year prevented the progression of high-grade prostate intraepithelial neoplasia to prostate cancer[124]. Considering its chemopreventive effects in several human malignancies, an interventional approach using GTCs might also be effective in the prevention of obesity-related hepatocarcinogenesis. However, further clinical studies are needed in this field to verify our hypothesis.

PREVENTION OF OBESITY-RELATED HCC USING THE NUTRACEUTICAL APPROACH: BRANCHED-CHAIN AMINO ACIDS

As the liver plays an important role in the regulation of metabolism, patients with chronic liver disease are often

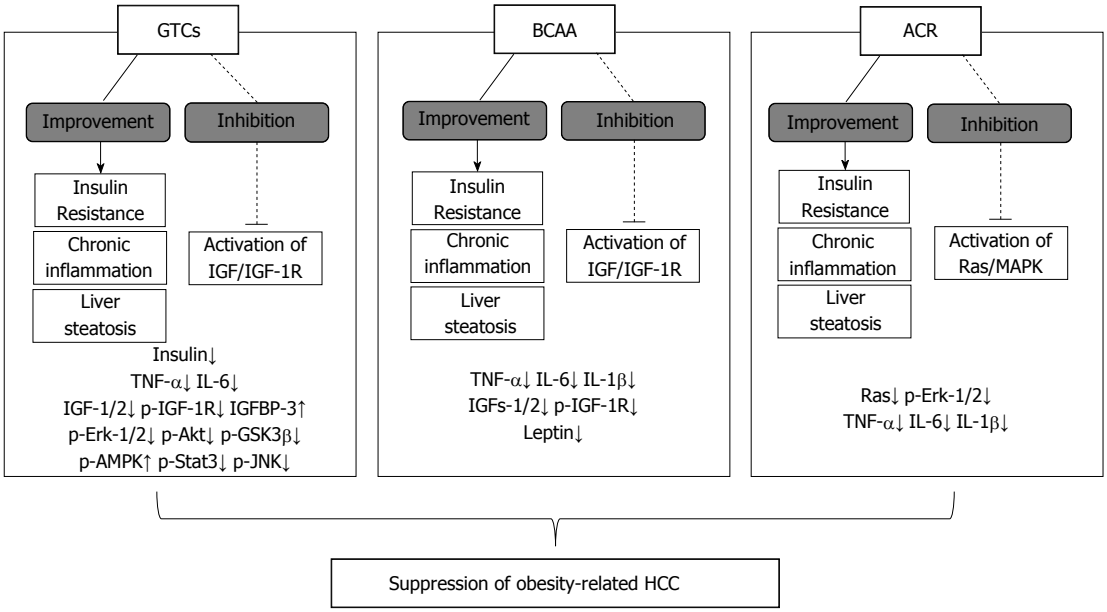

Figure 2 Mechanisms of action of green tea catechins, branched-chain amino acids, and acyclic retinoid in the inhibition of obesity-related liver carcinogenesis. HCC: Hepatocellular carcinoma; GTCs: Green tea catechins; BCAA: Branched-chain amino acid; ACR: Acyclic retinoid; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; IL-1β: Interleukin-1β; IGF-1: Insulin-like growth factor-1; IGF-1R: Insulin-like growth factor-1 receptor; IGFBP-3: IGF-binding protein-3; Stat3: Signal transducer and activator of transcription-3; Erk-1/2: Extracellular signal-regulated kinase-1/2; GSK-3β: Glycogen synthase kinase-3β; AMPK: AMP-activated kinase.

malnourished and have metabolic abnormalities, such as hypoalbuminemia and insulin resistance[125-128]. The decreased serum levels of BCAA (valine, leucine, and isoleucine) and hypoalbuminemia worsen the outcomes of cirrhotic patients; however, supplementation with BCAA improves protein-energy malnutrition and hypoalbuminemia, resulting in an improvement in the quality of life and in the prognosis of cirrhotic patients[125,127,129,130]. In addition, the beneficial effects of BCAA on the regulation of glucose metabolism have been demonstrated in recent clinical and experimental studies[131-134]. Thus, BCAA possesses the ability to improve not only malnutrition induced by chronic liver diseases, but also glucose intolerance, such as insulin resistance.

Notably, a long-term survival study reported that the continuous administration of BCAA was associated with a reduced incidence of HCC in obese cirrhotic patients[12]. This result also suggests the hypothesis that BCAA might have an anti-cancer effect on the development of HCC in obese cirrhotic patients. Therefore, in order to verify our hypothesis and clarify the detailed mechanisms of BCAA in the prevention of obesity-related HCC development, we conducted an experimental study by using a DEN-induced HCC model in obese and diabetic *db/db* mice[54]. In this study, BCAA supplementation significantly inhibited the incidence of liver neoplasms, including hepatic adenoma and HCC, through the inhibition of IGF-1, IGF-2, and IGF-1R protein expression in the liver[54]. The reduced incidence of liver neoplasms in this model was associated with improvements in insulin resistance, hyperleptinemia, and liver steatosis[54]. Moreover, our recent publication demonstrated that the administration of BCAA significantly suppressed the spontaneous development of liver neoplasms in *db/db* mice by inhibiting the expression of TNF-α, IL-6, and IL-1β mRNA in the liver[135]. Furthermore, BCAA inhibited the infiltration of macrophages into white adipose tissues, resulting in a reduction of TNF-α and IL-6 mRNA production from the tissue[135]. Thus, BCAA inhibited the development of liver tumorigenesis in obese rodents by regulating various obesity-induced metabolic abnormalities, especially insulin resistance and chronic inflammation, suggesting that BCAA is a promising agent for the chemoprevention of liver carcinogenesis in obese patients (Figure 2).

PREVENTION OF OBESITY-RELATED HCC USING THE PHARMACEUTICAL APPROACH: ACYCLIC RETINOID

Retinoids, derivatives of vitamin A, exert their biological functions by regulating the transcription of target genes through two distinct nuclear receptors - retinoic acid (RA) receptors (RARs) and retinoid X receptors (RXRs), both of which consist of three subtypes (α, β, and γ) characterized by a modular domain structure[136,137]. Among these receptors, RXRα is the most abundant RXR subtype in the adult liver[138]. Once RXRα is activated by its specific ligands, including RA or 9-cis-RA (9cRA), RXRα forms homodimers with itself or heterodimers with other RARs and then interacts with their respective DNA response elements, resulting in the regulation of proliferation, differentiation, and

apoptosis of liver cells. Thus, RXRα plays a crucial role in maintaining the homeostasis of liver cells.

Reduced expression of RXRα has been associated with carcinogen-induced rat hepatocarcinogenesis[139]. The impact of impaired receptor function of RXRα in the development of HCC is demonstrated through experimental studies. In HCC, RXRα is highly phosphorylated by an activated Ras-Erk 1/2 pathway, and accumulates in HCC by preventing its normal degradation through the ubiquitin-proteasome pathway[140]. The accumulated RXRα abrogates the function of the remaining intact RXRα in a dominant-negative manner, thereby inhibiting the formation of heterodimers with the partner molecules, including a tumor suppressor gene, *RAR*β[141-144]. In addition, phosphorylated RXRα is refractory to its potent ligand, 9cRA, and evades 9cRA-induced apoptosis[145]. Thus, the impaired receptor function of RXRα due to phospho-modification also plays a critical role in the development of HCC, suggesting that phosphorylated-RXRα may in the future be a key target for HCC chemoprevention and treatment.

Acyclic retinoid (ACR), which is equivalent to NIK-333 or peretinoin (Kowa Pharmaceutical Co., Tokyo, Japan), is a synthetic retinoid developed for HCC chemoprevention[139]. Recently, the chemopreventive effects of ACR were reported in our clinical studies. A randomized, controlled clinical trial examined the chemopreventive effects of ACR on secondary HCC in patients who underwent curative treatment for initial HCC[146-148]. In this study, oral administration of ACR (n = 44 patients; dose = 600 mg/d) for 12 mo significantly reduced the incidence of post-therapeutic recurrence or new HCC development compared to the placebo group (n = 45 patients) (median follow-up time = 38 mo; P = 0.04)[146,147]. Moreover, the preventative effects of ACR lasted for up to 3 years following the completion of ACR administration[148]. In addition, a subgroup analysis of a large-scale, randomized, placebo-controlled study (n = 401 patients) also showed that ACR (n = 100 patients; dose = 600 mg/d) reduced the risk of HCC recurrence or death by approximately 40% compared to placebo (n = 106 patients), especially in patients with Child-Pugh A and small tumors (size < 20 mm) (P = 0.0347)[149].

The possible molecular mechanisms by which ACR prevents the recurrence and the development of secondary HCC have been elucidated in experimental studies using HCC cell lines. We found that ACR restores the impaired receptor functions of RXRα by inhibiting RXRα phosphorylation. Namely, ACR inhibits the activated Ras-Erk 1/2 pathway independent of RXRα, and consequently prevents phospho-modification of RXRα, thereby restoring the function of RXRα in HCC cells[150]. Furthermore, we found that ACR inhibits not only the Ras-Erk 1/2 pathways but also several types of growth factors and their corresponding RTKs in several malignancies, including HCC[151-156]. Moreover, ACR itself functions as a ligand for RXRα and regulates the expression of its downstream genes such as *p21*, *RAR*β, and Cyclin D1, thereby preventing HCC development through inhibition of cell proliferation or induction of differentiation and apoptosis[145,153,157,158]. Thus, ACR may prevent the development of HCC *via* the pleiotropic responses of ACR target molecules, including phosphorylated RXRα.

Interestingly, our experimental study also elucidated the chemopreventive effects of ACR on the development of obesity-related HCC using the DEN-induced HCC model of obesity and diabetic *db/db* mice[108]. In this study, ACR significantly reduced the incidence of obesity-related HCC by inhibiting Ras activation and the phosphorylation of Erk-1/2 and RXRα, thereby restoring RXRα function in the liver[108]. Notably, the administration of ACR improved obesity-related metabolic abnormalities, such as insulin resistance and liver steatosis[108]. Moreover, ACR treatment decreased the levels of serum TNFα, as well as the expression of TNFα, IL-6, and IL-1β mRNA in the liver, resulting in an improvement of chronic inflammation[108]. As stated above, insulin resistance and chronic inflammation are significant risk factors for the development of obesity-related HCC. Therefore, the use of ACR in obese and cirrhotic patients with diabetes might be an effective strategy in preventing obesity-related HCC (Figure 2).

CONCLUSION

In this review, we highlighted nutraceutical and pharmaceutical approaches to targeting metabolic abnormalities as promising strategies to prevent the development of HCC in obese individuals. The molecular abnormalities represented by (1) insulin resistance/hyperinsulinemia; (2) chronic inflammation; (3) adipokine imbalance; and (4) oxidative stress, are regarded as the likely molecular mechanisms linking obesity to cancer development, including HCC. As stated above, the nutraceutical agents GTCs and BCAA prevented the development of obesity-related HCC by inhibiting those abnormalities in obese and diabetic mice. The safety of both GTCs and BCAA has been shown in recent clinical studies[123-125,127,129,130], suggesting that an intervention using GTCs and BCAA might be a practical approach for the chemoprevention of obesity-related HCC.

In addition, the pharmaceutical agent ACR has chemopreventive effects for recurrence or secondary HCC after curative treatment[146-149], and the safety of the agent was demonstrated in our recent clinical studies[146-149,159]. Moreover, ACR significantly reduced the incidence of obesity-related HCC in obese and diabetic mice, and this effect was associated with an improvement in metabolic abnormalities, including insulin resistance and chronic inflammation[108]. While the detailed mechanism by which ACR improves metabolic homeostasis remains unclear, the positive effects of ACR observed in the experimental study[108]

may encourage the use of the agent for the prevention of HCC in obese individuals.

In conclusion, recent evidence highlights that nutraceutical and pharmaceutical approaches that target metabolic abnormalities are a promising strategy for preventing the development of obesity-related HCC. GTCs, BCAA, and ACR might be candidates for this strategy. Further clinical studies are needed to investigate if active intervention using one or more of these agents can prevent the development of obesity-related HCC.

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