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**Pathogenesis of hepatocarcinogenesis in non-cirrhotic nonalcoholic fatty liver disease: Potential mechanistic pathways**

Perumpail RB *et al*. HCC in non-cirrhotic NAFLD

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**Abstract**

Although hepatocellular carcinoma (HCC) primarily arises in the background of liver cirrhosis, the development of HCC in nonalcoholic fatty liver disease (NAFLD) without cirrhosis is increasingly recognized. The pathogenesis of NAFLD associated non-cirrhotic HCC is distinct from that of cirrhotic HCC because the metabolic syndrome (MS) along with obesity and insulin resistance (IR) underlie several unique mechanisms that promote tumorigenesis. IR associated with MS, NAFLD, and type 2 diabetes mellitus lead to the release of multiple pro-inflammatory cytokines, including tumor necrosis factor alpha, interleukin-6, leptin and resistin, as well as decreased amounts of adiponectin. These processesfavor the development of hepatic steatosis and inflammation within the liver, which precede HCC development. Nevertheless, further investigation is necessary to elucidate the determinants for development of HCC in patients with NAFLD in the absence of cirrhosis.

**Key words:** Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Hepatocellular carcinoma; Metabolic syndrome

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**Core tip:** Although hepatocellular carcinoma (HCC) primarily arises in the background of liver cirrhosis, the development of HCC in nonalcoholic fatty liver disease (NAFLD) without cirrhosis is increasingly recognized. The pathogenesis of NAFLD associated non-cirrhotic HCC is distinct from that of cirrhotic HCC because the metabolic syndrome along with obesity and insulin resistance underlie several unique mechanisms that promote tumorigenesis.

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**INTRODUCTION**

Nonalcoholic fatty liver disease (NAFLD), obesity, type 2 diabetes mellitus (T2DM), and the metabolic syndrome (MS) are significant global health concerns that have been rising at alarming rates both in the Unites States and worldwide. Recent estimates suggest that, in the Unites States, the prevalence of obesity has risen to 33.8%, and the prevalence of T2DM among middle-aged adults has increased to 10.6%[1-3]. The epidemiology of NAFLD, the most common liver disorder in the Unites States and other industrialized countries, mirrors that of obesity and T2DM. Nonalcoholic steatohepatitis (NASH), a subset of NAFLD, can progress to cirrhosis and to hepatocellular carcinoma (HCC). A recently published prospective cohort study from the Unites States involving asymptomatic middle-aged patients determined the prevalence of NAFLD to be 46% and NASH 12.2%[2].

**HEPATOCARCINOGENESIS IN NON-CIRRHOTIC NAFLD**

Development of HCC in the setting of non-cirrhotic NAFLD is not common, but multiple studies have established obesity and T2DM - two major features of MS - as significant independent risk factors for HCC. Patients with cryptogenic cirrhosis, widely accepted as representing NASH, have a prevalence of T2DM and obesity similar to that of patients with NASH[4].The typical non-cirrhotic NASH patient who presents with HCC is older, male, and meets criteria for one or more features of MS[5].The majority of published data has been from Japanese studies, but similar observations have been made in studies from both Europe and South America[6-10].The largest group of NAFLD associated non-cirrhotic HCC patients studied to date once again showed an older male predominance with more than half exhibiting features of MS. This cross-sectional study of 87 Japanese patients with a median age of 72 years found that male patients appeared to develop HCC at a less advanced stage of liver fibrosis when compared to their counterparts, with the prevalence of cirrhosis at diagnosis significantly lower in men compared to women (39% *vs* 79%, *P* = 0.008) [10].However, an entirely Japanese cohort may not be generalizable to the U.S. The only reported case series from the Unites States of HCC arising from non-cirrhotic NAFLD was published in 2008. Guzman *et al*[11] describes three patients with non-cirrhotic HCC in the setting of NAFLD; all had at least two features of MS with a mean BMI of 33.5.A French study analyzed 128 patients with HCC and found that in 31 patients (24%), features of MS were the only risk factor for HCC[8]. Compared to the group of patients who had an overt cause for underlying liver disease (chronic HBV/HCV, genetic hemochromatosis, auto-immune liver disease, alcohol), the MS group was older (mean age 67.4 *vs* 59.4, *P* ≤ 0.01), had a higher BMI (29.7 *vs* 25, *P* ≤ 0.0001), and less background liver fibrosis (F0-F2: 65% *vs* 26%, *P* ≤ 0.001) [9]. Collectively, these data add to the growing evidence that HCC can occur in patients with non-cirrhotic patients with NAFLD, obesity, T2DM, or MS as risk factors. In addition, establishing the attributable risk of each component of MS for HCC requires further study. The pathogenesis of NAFLD associated non-cirrhotic HCC is distinct from that of cirrhotic HCC because MS and its` features of obesity and IR contain several unique mechanisms that help support a tumor-promoting environment. IR associated with MS, NAFLD, and T2DM lead to increased release of free fatty acids from adipocytes and the release of multiple pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), leptin and resistin. Decreased amounts of adiponectin are seen as well[5].These processes favor the development of both hepatic steatosis and inflammation within the liver[5].Increased levels of TNF-α lead to activation of NF-kB, a regulator of immune and inflammatory responses resulting in inhibition of apoptosis[5].

***Role of obesity in hepatocarcinogenesis***

Obesity is characterized by a low-grade chronic inflammatory response that is associated with increased cancer death rates, especially in HCC[12].Adipose tissue expansion promotes the release of the pro-inflammatory cytokines TNF-α and IL-6[13].TNF-α stimulates pro-oncogenic pathways involving NF-kB, c-Jun amino acid-terminal kinase (JNK), mammalian target of rapamycin complex (mTOR) and extracellular signal-related kinases[14].Additionally, IL-6 exhibits a major role in the inflammatory response and exerts tumor-promoting effects such as cell proliferation and anti-apoptosis[6].In the setting of obesity, IL-6 levels are elevated. It has been shown that weight loss results in reduced levels of both IL-6 and TNF-α leading to a decreased inflammatory and potentially carcinogenic response[15].A recent murine model demonstrated that obesity promoted malignant tumor growth in diethylnitrosamine-induced mice by enhancing the production of TNF-α and IL-6. This resulted in hepatic inflammation and activation of the pro-oncogenic signal transducer and activator of transcription (STAT3) pathway[16]. The investigators proposed that obesity, elevated IL-6, and activated STAT3 alone do not cause HCC. Rather, chronic activation of the IL-6/STAT3 axis leads to an increased probability that hepatocytes with previously acquired oncogenic mutations from exposure to environmental and dietary carcinogens will continue their malignant transformation[16].In the setting of a high fat diet, the activity of hepatic STAT3 increases and leads to accelerated liver tumor progression[17].Sorafenib, an anti-HCC agent that exhibits anti-tumor cell progression and anti-angiogenesis effects, acts mainly by blocking VwsEGF/PDGF and has recently been shown to block the STAT3 pathway, providing further evidence of the importance of STAT3 in HCC tumorogenesis[18].Adipokine imbalance *via* adipose tissue expansion plays a major role in obesity, diabetes and NAFLD[19].This imbalance leads to increased levels of leptin, a potent inflammatory cytokine, and decreased levels of adiponectin, a potent anti-inflammatory cytokine. Low adiponectin levels precipitate a vicious cycle of ectopic fat accumulation and further IR. Low adiponectin levels may also be insufficient to suppress inflammatory signaling in Kupffer cells and other macrophages[19] or to activate adenosine monophosphate-active protein kinase (AMPK), a potent inhibitor of the mTOR oncogenic pathway[6]. Adiponectin has also been demonstrated to play a pivotal role in anti-angiogenesis and apoptosis while leptin has been shown to promote angiogenesis in animal models, further substantiating the role of low adiponectin and elevated leptin levels in tumor formation and growth[20].

Intrahepatic lipid accumulation, derived from either lipolysis or excess dietary lipid intake, followed by lipid peroxidation contributes to inflammation and ultimately hepatocarcinogenesis[21]. PPARα upregulates fatty acid disposal in response to increased free fatty acid levels. However, in murine models, PPARα variants accelerate risk for hepatocarcinogenesis. Genetic variants affecting cell signaling (Akt, E-cadherin, β-catenin, ERK, MEK, MET, PI3K, Ras, Rat, mTOR and Wnt) as well as cell cycle regulation (p16, p53, INK4, cyclin’s and cdk’s) have all been implicated in HCC[21-23]. As differing classes of HCC have been observed in both humans and murine models, unique pathogenetic mechanisms linked to specific genetic variants may explain each class of HCC[22,23].

***Role of insulin resistance in hepatocarcinogenesis***

Obesity, T2DM, and NAFLD with its inherent activation of pro-inflammatory cytokines and lipotoxicity promote systemic and hepatic IR with resultant hyperinsulinemia. IR and hyperinsulinemia have been shown to upregulate the production of insulin-like growth factor-1 (IGF-1) and insulin receptor subtrate-1 (IRS-1). IGF-1 is a peptide hormone that stimulates cellular growth through proliferation and inhibition of apoptosis within the liver[24].IGF-1 activity increases expression of the proto-oncogenes c-fos and c-jun *in vitro* and activates mitogen activated protein kinases (MAPK), processes thought to contribute to HCC development[25]. Another important intracellular marker, JNK, is linked to obesity, IR, NASH, and HCC. JNK, a MAPK, is activated by IR, hyperinsulinemia, and obesity with an observed reduction of in JNK activity with weight loss[26].JNK has also been shown to phosphorylate and activate IRS-1, which subsequently leads to the pathway that is responsible for obesity- induced IR[27].Two main isoforms of JNK have been delineated in a mouse model: JNK1 appears to promote hepatic steatosis and inflammation, while JNK2 inhibits hepatocyte death[28].The activity of JNK and its relationship to the development of carcinogenesis has been slowly elucidated by a growing number of studies. Approximately 70% of HCC tissues show positive immunostaining for phosphorylated JNK, suggesting a role in hepatocarcinogenesis[29].

Increasingly, reports are linking the treatment of IR and hyperinsulinemia in diabetic patients to reducing the risk of HCC[30].Central to the effects of insulin-sensitizing therapy on the development of HCC is the interaction between AMPK, the tumor suppressor complexes TSC1 and TSC2, the mTOR oncogenic pathway, and autophagy. AMPK is increased in the setting of caloric restriction, starvation, and exercise and moderates cellular activities such as hepatic fatty acid and cholesterol biosynthesis[31].AMPK activation also increases the expression of TSC1/TSC2 through phosphorylation, which in turn reduces the activity of the mTOR oncogenic pathway[32].This reduced activity of the mTOR pathway leads to less uncontrolled cellular growth, proliferation, and survival and an increase in autophagy[33]. Autophagy is a cellular housekeeping strategy by which damaged proteins, organelles and invading microorganisms are removed by cellular auto-digestion[3,34].Defects in this process have been shown to play a pivotal role in a wide array of diseases, including NAFLD and HCC, where autophagy exhibits anti-tumor and anti-inflammatory properties[35]. In the setting of obesity and IR, AMPK is inhibited, leading to an increase in the activity of the oncogenic mTOR pathway as well as a decrease in autophagy[36].Increased mTOR activity leads to unabated cellular proliferation while decreased autophagy results in decreased removal of damaged mitochondria, enhanced oxidative stress, and activation of the JNK pathway, leading to inflammation and a tumor-promoting environment[34].However, the reason why only a small fraction of patients with risk factors develop non-cirrhotic HCC remains elusive.

**CONCLUSION**

The pathogenesis of NAFLD associated non-cirrhotic HCC is distinct from that of cirrhotic HCC because the MS along with obesity and IR underlie several unique mechanisms that promote tumorigenesis. IR associated with MS, NAFLD, and T2DM lead to the release of multiple pro-inflammatory cytokines, including tumor necrosis factor alpha, IL-6, leptin and resistin, as well as decreased amounts of adiponectin. These processesfavor the development of hepatic steatosis and inflammation within the liver, which precede HCC development.

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