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REVIEW

Pathogenesis of NAFLD-Related Hepatocellular Carcinoma: An Up-to-Date Review

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Abstract: With the epidemic of obesity, type 2 diabetes mellitus, and hypertension, non-alcoholic fatty liver disease (NAFLD) has become the most prevalent liver disease in the world. And the dysregulation of the metabolic microenvironment provides a favorable environment for the occurrence of liver cancer. In recent years, the incidence of hepatocellular carcinoma (HCC) caused by NAFLD is on the rise, especially in the United States, the UK, and France, where it is the fastest-growing cause of HCC. And due to the absence of disruptive symptoms in the early period and the lack of adequate surveillance in the population without cirrhosis, NAFLD associated-HCC is usually diagnosed at an advanced stage with larger tumors and lower cure rates, causing a substantial economic and social burden. Although many factors contribute to the occurrence and development of NAFLD-related HCC, the specific pathogenesis is still unclear. In this review, we focus on the research progress of its pathogenesis in recent years, including the role of insulin resistance, lipid accumulation and oxidative stress, gut microbiota, autophagy, the activation of the immune system, and hormonal disorders.

Keywords: non-alcoholic fatty liver disease, hepatocellular carcinoma, carcinogenic mechanisms, risk factors

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of chronic liver disease characterized by increased hepatocellular storage of triglycerides, including non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis which increases the risk of progression to hepatocellular cancer.[1]

Globally, liver cancer is the sixth most frequently diagnosed cancer and the third leading cause of cancer-related death. Hepatocellular carcinoma (HCC) represents the most common primary liver malignancy, accounting for 75–85% of all cases.[2] Although chronic viral hepatitis B (HBV) or C (HCV) has historically been considered the primary cause of the majority of HCC cases, greater vaccination coverage or the adoption of antiviral therapy for HBV and the adoption of direct-acting antivirals for HCV will change this trajectory.[1,3] At present, It is predicted that NAFLD's prevalence will increase to 28.4%, and the number of patients will reach 100.9 million. The total cases and prevalence of NAFLD are rapidly increasing in many countries, such as China, the United Kingdom, and Italy, and in a mathematical model we predict that these countries will have the highest number of cases, the fastest growth in cases, and the highest prevalence respectively, by 2030.[4] In the near future, NAFLD will inevitably become the predominant etiology of liver cancer in many countries.[3]

NAFLD Risk Factors

Several factors contribute to the development of NAFLD or NASH, and the subsequent occurrence of liver cancer, including obesity, diabetes, metabolic syndrome, genetic predisposition, some demographic risk factors and so on. Among them, metabolic syndrome includes hypertension, abdominal obesity, high triglycerides, elevated fasting blood sugar and dyslipidemia.[4]

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At present, it is estimated that more than 400 million people in the world have type 2 diabetes mellitus (T2DM) and 650 million people are obese.[5] And some studies revealed that compared with any other etiology, the proportion of HCC due to the prevalence of diabetes and obesity increased significantly in many countries, such as England, Japan and Korea.[5] The baseline diagnosis of diabetes is the independent predictor of hepatic cirrhosis and HCC, and the distribution of adipose tissue is directly related to liver inflammation and fibrosis.[6,7]

In addition, genetic polymorphisms in PNPLA3, TM6SF2, GCKR and MBOAT have been related to the increased risk of HCC, while HSD17B13 variants reduce the risk of HCC.[3] The demographic characteristics include older age (≥65 years), male sex, Hispanic individuals than white and African American individuals.[8] And moderate alcohol consumption and tobacco smoking were also associated with HCC in a multiethnic prospective cohort study that included 299 patients with NASH cirrhosis.[9] In addition, anti-diabetic medications, such as sulfonylureas and insulin, increased hepatocellular iron, and sedentary lifestyle also promote the occurrence of HCC.[5]

Pathogenesis

The pathological mechanisms of NAFLD-related HCC are multifactorial, and we will discuss the role of insulin resistance, lipotoxicity, oxidative stress, the activation of immune system, disturbance or imbalance in gut microbiota, autophagy dysregulation, and hormonal disorders in this review. These vital factors induce chronic inflammation, hepatocyte injury, cell proliferation and progression to HCC.

Insulin Resistance

Insulin resistance is a condition in which the decreased efficiency of insulin to promote glucose uptake and utilization, and the body secretes too much insulin to keep blood glucose levels stable.[10] The insulin signaling pathway is related to hyperinsulinemia, T2DM and obesity, and is one of the most frequently proposed mechanisms in the progression of NAFLD and hepatic fibrosis (Figure 1).[4] Hyperinsulinemia promotes the synthesis of insulin-like growth factor-1 (IGF-1) and induces the expression of insulin receptor substrate-1 (IRS-1), which shows the binding sites of many downstream molecules and pathways.[11] Insulin and IGF-1 bind to insulin receptor and insulin-like growth factor-1 receptor (IGF1R) on liver cell membrane respectively, activating IRS-1 which is followed by the activation of PI3K/AKT and Mitogen-activated protein kinase (MAPK) pathways. The former exerts effect on cell proliferation, growth and anti-apoptosis through activating different substrates, while the latter upregulates the transcription of proto-oncogenes such as c-fos and c-jun and subsequently facilitates the activation of the Wnt/β-catenin pathway, leading to liver fibrosis and tumor development.[12] Moreover, the tumor suppressor phosphatase and tensin homologue on chromosome 10 gene (PTEN) is the primary inhibitor of the PI3K/AKT pathway.[13]

Insulin resistance promotes hepatic lipid synthesis, inhibits hepatic fatty acid β-oxidation, and inhibits lipolysis, thereby causing hepatic lipid deposition and promoting hepatic steatosis, which in turn increases intermediate products of lipid metabolism, thus impairing tyrosine phosphorylation of IRS to inhibit insulin signal transduction.[14] Insulin resistance increases the expression of growth hormone receptor (GHR), which in combination with growth hormone (GH) promotes the activation of IGF-1 and pro-oncogenic pathways in liver cells.[15] In addition, oxidative stress, immune pathways, the disruption of intestinal flora and some endocrine pathways are also related to the pathogenesis of insulin resistance, and their roles will be described below.

Lipid Accumulation and Oxidative Stress

A distinctive feature of NASH is the accumulation of lipid droplets in the liver cells, particularly, increased mitochondrial oxidation of the fatty acids (FFAs) induces the formation of reactive oxygen species (ROS).[16,17] In addition, hyperinsulinemia/insulin resistance and chronic inflammation mainly drive the production of ROS and subsequent oxidative stress.[12] In this section, we discuss the role of various molecules and cancer-related signaling pathways, which are associated with lipid accumulation and oxidative stress, in the progression of hepatocellular carcinoma (Figure 2). ROS is involved in the process of necroptosis by acting in a positive feedback circle. Specifically, ROS contributes to the activation of receptor interacting protein 1 (RIP1) and RIP3, which in return causes the production of ROS and induces the recruitment and phosphorylation of mixed lineage kinase domain-like protein (MLKL).[18] Some studies have been

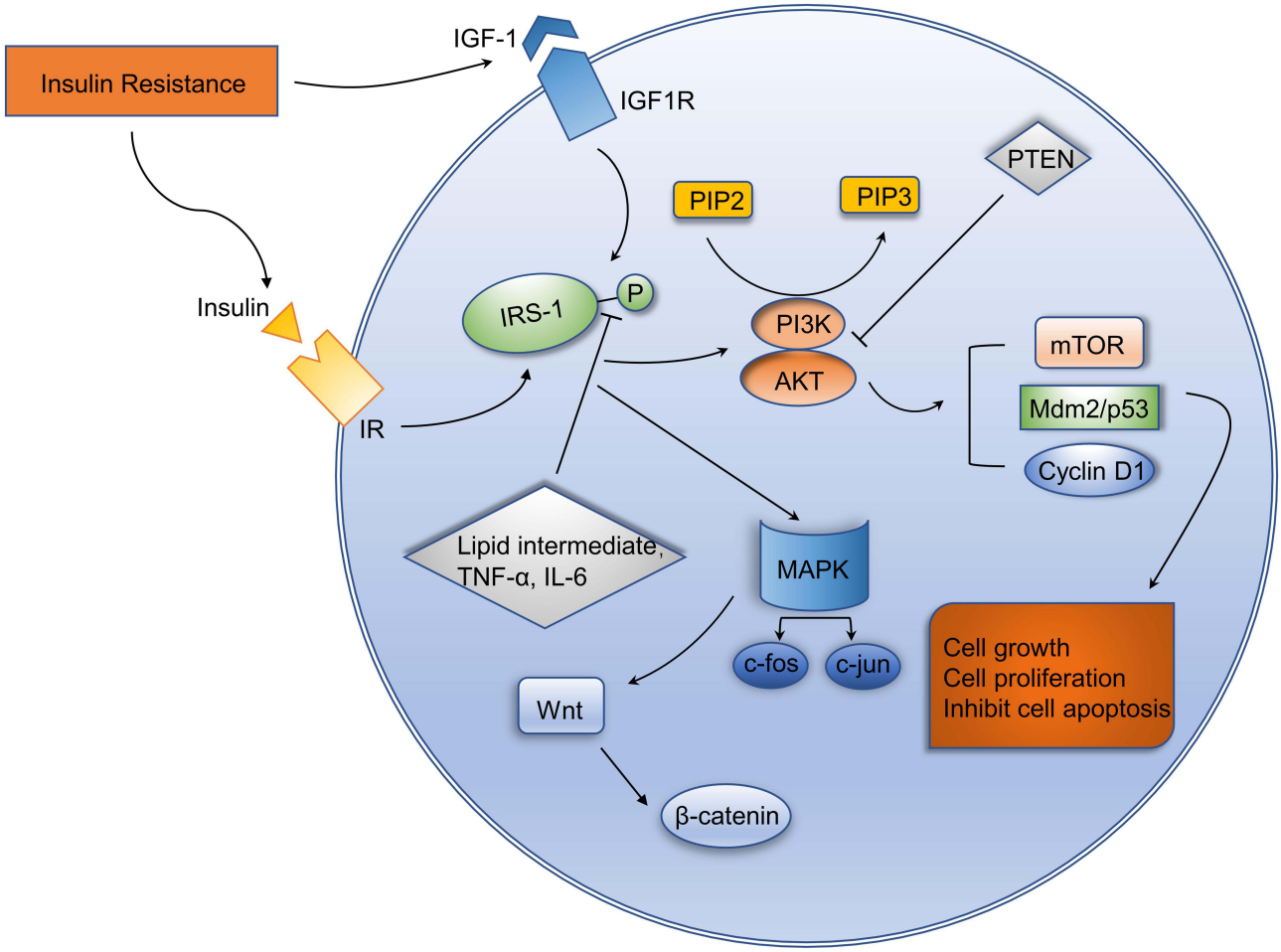

Figure 1 Molecular signaling pathways of insulin resistance in hepatocarcinogenesis. Activation of downstream signaling pathways is indicated by lines ending with arrows whereas inhibition of them is indicated by blunted lines.

Abbreviations: IR, insulin receptor; IGF-1, insulin growth factor-1; IGF1R, insulin-like growth factor-1 receptor; IRS-1, insulin receptor substrate-1; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; PIP2, phosphatidylinositol-3.4-bisphosphate; PIP3, phosphatidylinositol-3.4.5-triphosphate; PI3K, phosphoinositide 3-kinases; mTOR, mammalian target of rapamycin; PTEN, phosphatase and tensin homologue on chromosome 10 gene; MAPK, mitogen-activated protein kinase.

reported on animal models, aberrant lipid metabolism can cause selective loss of $CD4^+$ T lymphocytes, which produce more ROS derived from mitochondria compared with $CD8^+$ T lymphocytes, accelerating the occurrence of HCC. By specifically blocking ROS in vivo, it can reverse the reduction of liver $CD4^+$ T lymphocytes induced by NAFLD and delay the occurrence of HCC.[19] Additionally, the increased oxidation of FFA is linked to enhanced endoplasmic reticulum (ER) levels and oxidative stress in liver cells.[17] There is positive feedback between oxidative stress and ER through the former induces the increasing of calcium efflux from ER, which results in consequently increased permeability of mitochondria and lysosome, ER function disruption, cell damage and carcinogenesis in NASH.[20]

Furthermore, lipid hydroperoxide and ROS also affect the secretion of several cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, as well as leptin, and adiponectin, leading to chronic inflammation.[12] The elevated levels of IL-6 stimulate liver cell proliferation, inhibit apoptosis, and aid in the development of liver cancer by activating signal transducer and activator of transcription 3 (STAT3). Notably, it has been discovered that estrogen inhibits IL-6 production, thus explaining a lower prevalence of HCC in women.[21] TNF-α plays a role in liver disease development and tumorigenesis via mediating the activation of nuclear factor κB (NF-κB), which through JNK and phosphorylation of IκB kinase-β (IKKβ).[17] And TNF-α and IL-6 impair the insulin signaling pathway, through inhibiting the phosphorylation of IR, IRS and AKT, leading to insulin resistance.[22] Adiponectin (ADP) is the only factor secreted by adipocytes that decreases with the adipose tissue expansion. ADP has various physiological activities, including enhancing insulin

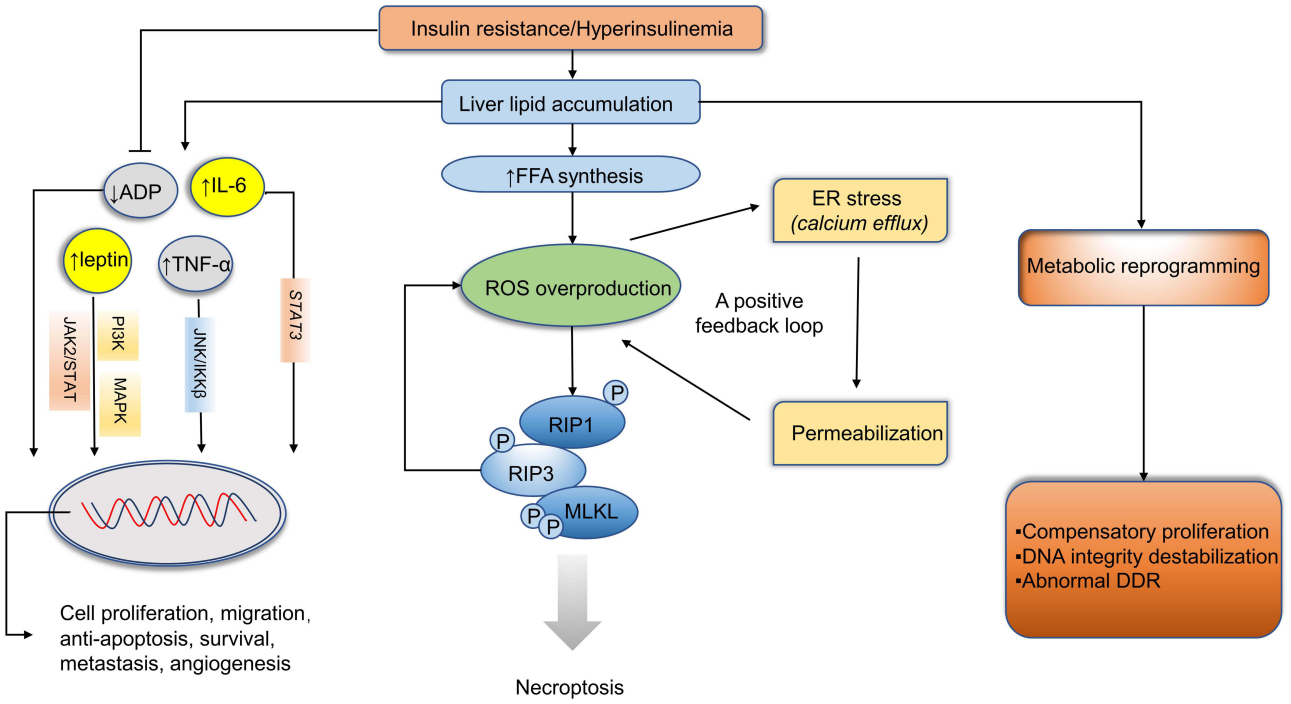

Figure 2 Mechanism of lipid accumulation and oxidative stress in liver tumorigenesis. Long lines ending with arrows or bars indicate activating or inhibitory effects respectively. Short arrows pointing up or down indicate up-regulated or down-regulated.

Abbreviations: FFA, free fatty acid; ROS, reactive oxygen species; ER, endoplasmic reticulum; RIP, receptor interacting protein; MLKL, mixed lineage kinase domain-like protein; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; JAK20, Janus kinase 2; JNK, Jun-(N)-terminal kinase; IKKβ, IκB kinase-β; STAT3, signal transducer and activator of transcription 3; PI3K, phosphoinositide 3-kinases; MAPK, mitogen-activated protein kinase; ADP, adiponectin; DDR, DNA damage response.

sensitivity, promoting fatty acid metabolism, and exerting anti-inflammatory and anti-atherogenic effects in the liver.[23] However, the exacerbated insulin resistance inhibits its action. Leptin plays an important role in maintaining energy stability and controlling the quality of adipose tissue. However, in obese patients, leptin receptor sensitivity is decreased and leptin resistance appears with the beneficial effects inhibited.[23] The interaction between leptin and many signaling pathways including PI3K, MAPK and JAK2/STAT contributes to the progression of HCC via promoting the tumor cell proliferation, migration, survival, angiogenesis and metastasis.[24]

Moreover, the accumulation of liver lipids contributes to metabolic reprogramming, characterized by decreased expression of genes related to lipolysis, lipogenesis and β-oxidation in the liver. The metabolic reprogramming leads to hepatocellular metabolic disturbance and the accumulation of potentially toxic metabolites that results in compensatory hepatocyte proliferation, the destabilization of DNA integrity and abnormal DNA damage response (DDR).[25]

The Gut Microbiota

Gut microbiota has an important impact on the maintenance of the intestinal barrier, nutritional support for hepatic cell growth, gut immune maturation, and the inhibition of liver inflammation.[26] The liver releases bile acids into the intestine through the biliary tract, and metabolic nutrients are transported to the liver via the portal vein. At the same time, metabolites and toxins produced by bacteria in the intestine also can enter the liver through the portal vein. Several studies have shown that disorders of the intestinal-liver axis, including dysbiosis of the intestinal microbiota, altered mucosal permeability and bacterial overgrowth, can significantly contribute to the development of NAFLD.[27]

In recent studies, we can learn that the abundance and composition of intestinal flora may change in patients with NAFLD. At the phylum level, *Proteobacteria, Actinobacteria, Verrucomicrobia* and *Fusobacteria* are overall more abundant in steatosis, while *Firmicutes* and *Bacteroidetes* are less abundant. The levels of *Streptococcus, Clostridium, Veillonella, Prevotella* and *Escherichia* are increased, as well as the decreased levels of *Lactobacillus, Lachnospira, Ruminococcus* could be observed in cirrhosis at the genus level.[28] Furthermore, a study cohort has shown that NAFLD-

HCC was characterized by the significantly enriched of *Bacteroides caecimuris* and *Veillonella parvula* compared to NAFLD-cirrhosis and non-NAFLD controls at the species level.[29] And at the family level, *Eubacteriaceae* enriched in NAFLD-cirrhosis, compared with the other two groups. The reduction of *Odoribacteraceae*, and *Prevotellaceae*, and the expansion of *Enterobacteriaceae* were observed in NAFLD-cirrhosis and NAFLD-HCC compared to non-NAFLD controls.[29] These changes in the relative abundance of different types of microbiota may provide a rapid, non-invasive diagnostic method for liver cirrhosis and HCC.[30]

Dysregulation of the gut microbiota plays a key role in the pathogenesis of NAFLD by disrupting the intestinal barrier, modifying choline metabolism, producing endogenous ethanol, promoting the release of inflammatory cytokines, and changing bile acid metabolism (Figure 3).[31] High-fat diets (HFDs) disrupt intercellular tight junctions in the gut via downregulating the expression of tight junction proteins and increasing the number of barrier-destroying species in the intestinal flora through small intestinal bacterial overgrowth (SIBO). SIBO also increases the expression of Toll-like receptor 4 (TLR4) and CD14, in the liver immune cells. Bacterial products, such as lipopolysaccharide (LPS), interact

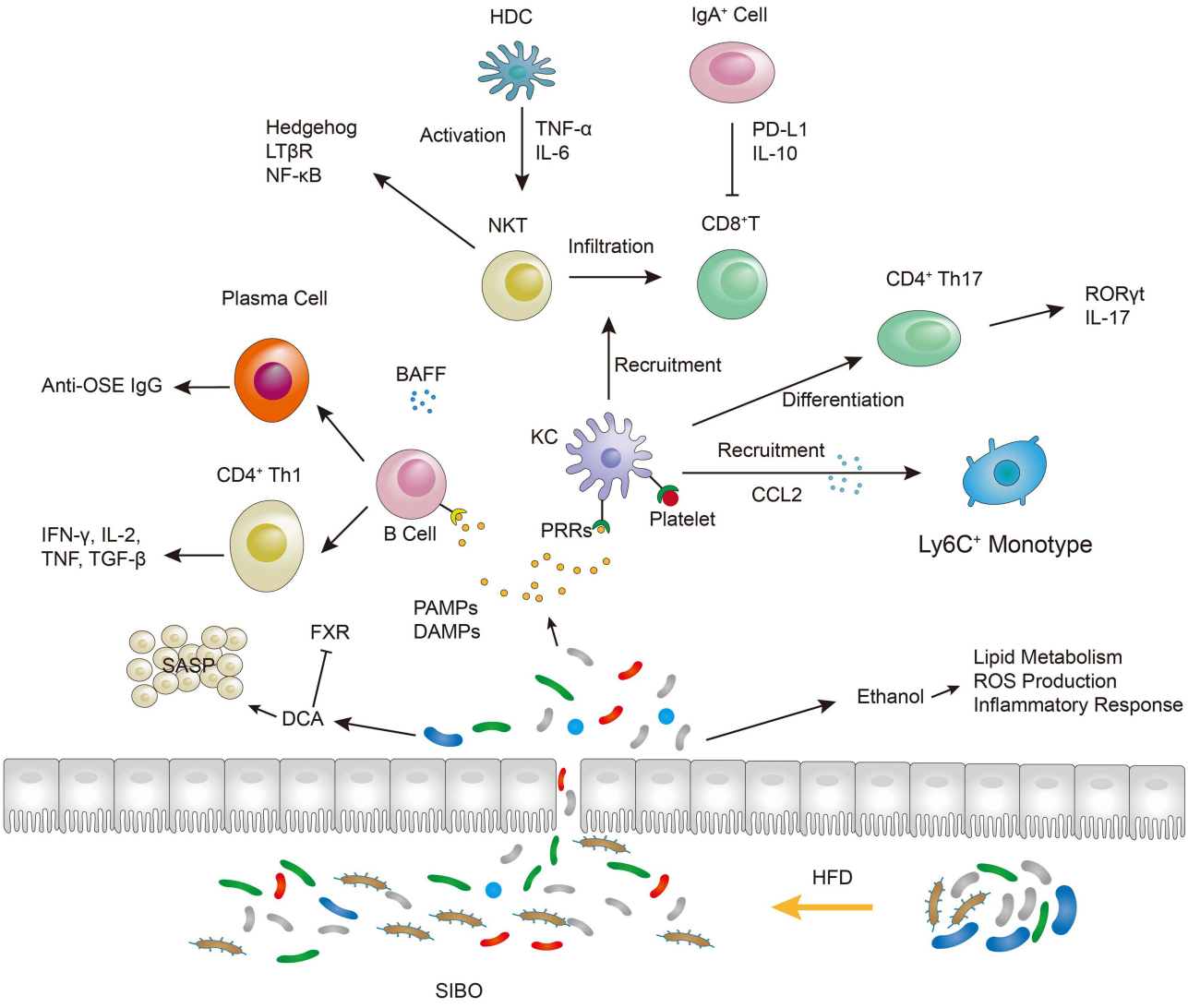

Figure 3 The role of intestinal microbiota dysbiosis and inflammatory response in hepatocarcinogenesis. Lines with arrows or bars are used to indicate facilitation or inhibition.

Abbreviations: HFD, high-fat diet; SIBO, small intestinal bacterial overgrowth; DCA, deoxycholic acid; SASP, senescence-associated secretory phenotype; FXR, farnesol X receptor; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PRRs, pattern recognition receptors; KC, Kupffer cell; NKT, natural killer T; TNF, tumor necrosis factor; IL-6, interleukin-6; TGF, transforming growth factor; IFN-γ, interferon-γ; CCL2, C-C motif chemokine ligand 2; HDC, hepatic dendritic cell; BAFF, B cell activating factor.

with TLRs to induce the production of IL-1β, TNF-α and IL-8, and the subsequent excessive lipid accumulation, insulin resistance, inflammatory responses and fibrosis.[31] Moreover, abnormal intestinal flora increases the relative levels of secondary bile acids such as deoxycholic acid (DCA), inducing gut permeability by acting as a detergent and producing ROS.[16] The enterohepatic circulation of DCA promotes senescence-associated secretory phenotype (SASP) in hepatic stellate cells (HSCs), which in turn secretes growth factors, chemokines, and pro-inflammatory cytokines in the liver and promotes liver cancer progression.[26] And the increased DCA, as an antagonist of farnesol X receptor (FXR), promotes the synthesis of fatty acids and triglycerides in the liver, induces the dysregulation of gluconeogenesis, and leads to insulin resistance in patients with NAFLD.[32] Ethanol is also constantly produced by intestinal flora, such as *Escherichia*, and increased in NASH patients. The production of endogenous ethanol increases the permeability of intestinal barrier by disrupting intercellular complexes and affects lipid metabolism via promoting lipid synthesis and reducing FFAs oxidation.[33] In addition, ethanol contributes to the development of NAFLD by inducing the ROS production and inflammatory response.[34]

Autophagy

Autophagy, also known as "self-eating", is a lysosomal catabolic pathway that regulates the delivery and degradation of misfolded proteins, damaged organelles, intracellular lipids and pathogens.[35] Depending on the pathway of cellular substances to lysosomes, the term autophagy encompasses: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy.[36] Autophagy exerts an important effect on cell survival, differentiation, and the maintenance of intracellular homeostasis. And impaired autophagy can be observed in many liver diseases, such as NAFLD, fibrosis, and NASH-associated HCC.[37]

Obesity and long-term HFDs influence the cellular autophagy mechanisms at various stages, which include preventing autophagosome formation, inhibiting autophagosome-lysosome fusion, and disrupting lysosome physiology.[37] In NAFLD, the reduced autophagy causes the accumulation of misfolded protein aggregates, resulting in the increased oxidative stress, DNA damage, and genomic instability, all of these are conducive to tumorigenesis.[38]

The loss of Beclin-1, ATG5 or ATG7 in mice leads to spontaneous HCC.[36] In addition, hepatocyte-specific deletion of TGF-β activated kinase 1 (TAK1) causes the inhibition of AMPK activity and autophagy, as well as the enhanced activity of mTORC1 that reduces the expression of peroxisome proliferator activated receptor α (PPARα). These above mechanisms lead to excessive lipid accumulation, spontaneous hepatic fibrosis and tumorigenesis.[39] And the lack of protein tyrosine phosphatase receptor type O (PTPRO) in mice (a known tumor inhibitor), also led to serious autophagy deficiency and liver damage. This conclusion can be confirmed based on immunohistochemical staining showed that hepatic PTPRO was decreased in NAFLD compared with normal livers, while p62/SQSTM1 was increased.[40] The impaired autophagy in NASH results in the accumulation of p62, which could affect the NF-κB, mTOR, Wnt/β-catenin, and NRF2 pathways.[41] P62 disrupts the combination of Kelch-like ECH-associated protein 1 (KEAP1) and nuclear factor erythroid-2-related factor 2 (NRF2), allowing NRF2 transfers into the nucleus, triggering the transcription of downstream targeted genes encoding for antioxidant proteins, detoxification enzymes, and drug transporters, and β-oxidation enzymes, protecting HCC cells from oxidative stress and the effects of anti-cancer drugs. Additionally, NRF2 promotes the expression of the p62 gene, thereby generating a positive feedback circle on the NRF2 pathway.[41] NRF2 also stimulates liver cancer cell proliferation and progenitor marker cytokeratin 19 expression, which is related to metastasis, vascular invasion, early relapse, poor prognosis, and resistance to chemotherapy, such as doxorubicin and 5-fluorouracil.[25]

Moreover, autophagy can clear the damaged mitochondria and subsequently generated ROS caused by the elevated metabolism of liver cancer cells, thus protecting the liver cancer cells. Autophagy also can maintain the metabolic supply of hepatocellular carcinoma cells by degrading damaged organelles, DNA, proteins and pathogens, under specific tumor microenvironments such as hypoxia and nutrient deficiency, which are caused by the rapid growth of the tumor at advanced stages.[35]

In conclusion, at the early stage of HCC development, autophagy exerts anti-tumorigenic effects through maintaining genomic stability, suppressing metastasis and oxidative stress, increasing anticancer immunogenicity, and so on.[42] However, once the tumor has progressed to an advanced stage, dysfunctional autophagy cells promote tumor progression.

This dual role highlights the complexity of targeting autophagy in the treatment of liver cancer, and it is necessary to determine the optimal therapeutic time window.[36]

The Activation of the Immune System

In human liver, various immune cells constitute the unique immune microenvironment, including Kupffer cells (KCs), $CD4^+$ T cells, $CD8^+$ T cells, B lymphocytes, HSCs, natural killer cells (NK cells), dendritic cells (DCs), and other immune cells.[43] Under NASH conditions, some pathobiological factors, such as the insulin resistance, lipid accumulation and oxidative stress, could recruit and activate these immune cells, then release molecules that result in inflammation, fibrosis, and HCC (Figure 3).[44]

KCs are the resident macrophages and one of the first lines of defense in the liver. KCs also express pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), recognizing the damage-associated molecular pattern molecules (DAMPs; eg, nuclear and mitochondrial DNA, uric acid and purine nucleotides) derived from injured liver cells, as well as pathogen-associated molecular patterns (PAMPs; eg, LPS) accumulated in portal vein circulation.[25] KCs bind of P62 induces into the M1-like proinflammatory phenotype and activates MAPK, ERK1/2, p38, JNK and NF-κB through the secretion of cytokines and chemokines, including TNF-α, IL-1β, IL-2, IL-6, IL-10, IFN-γ. The resulting hepatocyte apoptosis, steatosis, hepatic damage and the activation of HSCs, which followed by the production of extracellular matrix and hepatic fibrosis formation.[43] In addition, the interaction between KCs and platelets induces the recruitment of the NKT cell and $CD8^+$ T cell in the liver, and subsequent progression of NASH. Moreover, KCs can also cause the apoptosis-induced recruitment of $Ly6C^+$ monocyte, mediated by C-C motif chemokine ligand 2 (CCL2), and promote Th17 differentiation via the production of IL-23 or IL-6.[45]

In healthy livers, DCs are important to sustain immune homeostasis and tolerance, maintain the quiescent condition of the HSCs and suppress the activation of inflammasomes. While, under inflammatory conditions, hepatic DCs (HDCs) convert into the active state and induce the production of cytokines like TNF-α and IL-6, promoting T-cell proliferation and the activation of NKT cells. In NAFLD, the excessive lipid accumulation enhances the maturation of DCs and produces high lipid HDCs, which exert a stronger pro-inflammatory effect than lipid-low DCs.[46]

A mouse model induced by long-term feeding of a choline-deficient high-fat diet showed that the activation of $CD8^+$ T cells and NKT cells contribute to NASH and NASH-driven HCC development. Type I NKT (iNKT) cells induce the infiltration of $CD8^+$ T cells and activate hepatocellular LTβR and NF- κB signaling facilitating NASH-HCC transition.[47] In NASH, iNKT cells can trigger the signaling pathway Hedgehog that is required for maintaining cancer cell growth, proliferation and mesenchymal properties, and secrete the osteopontin, which leads to the HSC activation and fibrosis.[48]

In addition to innate immune mechanisms affect in the inflammatory process of NASH, recent evidence suggests that adaptive immunity also contributes to promoting the development of NASH, liver cirrhosis and HCC.[49] In NASH, adipocytes would secrete B cell activating factor (BAFF), in mouse models and human samples, which contributes to the impaired insulin sensitivity, the inflammation of adipose tissue, the survival and maturation of B cells and liver fibrosis.[50] B cells are activated through TLR4 by PAMPs and can differentiate into plasma cells which produce anti-OSE immunoglobulins (IgG) or induce IFN-γ, IL-2, TNF, TGF-β production in $CD4^+$ Th1 cells, then these cytokines induce immature macrophages to differentiate into the M1-like pro-inflammatory phenotype.[43] And Shalapour et al[51] reported that liver-resident immunoglobulin-A-producing (IgA^+) cells through expressing high levels of PD-L1 and IL-10 suppress the activation of cytotoxic $CD8^+$ T lymphocytes (CTL), their IFN-γ production and cytotoxic response to the tumor. Another $CD4^+$ T cell subtype exposed to the proinflammatory environment is $CD4^+$ Th17, which expresses RORγt and secretes IL-17, increasing the levels of PTEN that inhibit the PI3K/AKT pathway.[13,43] IL-17 also promotes the recruitment of neutrophils and macrophages, and induces the secretion of IL-6 aggravating insulin resistance, thereby promoting the inflammatory reactions and NAFLD progression. In contrast to the pro-inflammatory effects of Th17 cells, Treg cells have the opposite functions. The Treg/Th17 imbalance is related to the NAFLD pathogenesis. Treg cells contribute to the maintenance of immune homeostasis and restrict immune responses by the secretion of IL-10 and TGF-β.[52,53] However, in the tumor microenvironment, Treg cells might inhibit anti-tumor immune response and induce immunosurveillance escape of tumor cells.[45]

Endocrine Pathway

Due to the role of the hormones in metabolism and fat distribution, the endocrine pathway is another mechanism that contributes to the pathogenesis of NAFLD and HCC. Thyroid hormone is a key regulator of affecting cholesterol, lipid metabolism and blood lipid levels with a dual action on the synthesis and breakdown of fat and cholesterol, and the effect of promoting breakdown is more obvious than that of promoting synthesis. Hypothyroidism is thought to be related to the progression of NASH and HCC. Hypothyroidism promotes triacylglycerol synthesis by upregulating the expression of sterol regulatory element binding protein 1c (SREBP-1c), causing hyperlipidemia and steatosis. Additionally, hypothyroidism reduces oxidative metabolism and energy expenditure resulting in obesity and subsequent liver steatosis. By contrast, mild hypothyroidism ameliorates liver damage and fibrosis by the decreased production of ROS.[54]

Polycystic ovary syndrome (PCOS) usually coexists with NAFLD and is linked via insulin resistance and hyperandrogenism.[55] Androgens increase hepatic lipid production, aggravate IR in PCOS patients, and keep the organism in a mildly inflammatory state. Additionally, PCOS is related to the occurrence of metabolic syndrome, T2DM and cardiovascular disease.[54] The possibility of NAFLD should be considered when diagnosing and treating PCOS patients, especially in patients with insulin resistance, metabolic syndrome and obesity related risk factors, and liver function and/or ultrasound examination should be considered to facilitate early detection. Meanwhile, the possibility of PCOS should be excluded for women with NAFLD. GH contributes to energy homeostasis by promoting lipolysis and inhibiting glucose utilization. Several clinical observations demonstrate that GH deficiency is associated with the occurrence and development of NAFLD.[54] The decreased GH levels would aggravate IR and increase fat content, both of which are important risk factors for NAFLD and increase the incidence of NAFLD.[56] The upregulation of cell cycle-related kinase (CCRK), which is induced by IL-6/STAT3 and androgen receptor signaling, subsequently triggers the mTOR/4E-BP1 and mTOR/S6K/SREBP1 cascades, leading to lipid accumulation, inflammation and hepatocarcinogenesis.[57]

Conclusions

In recent years, due to the greater vaccination coverage or the adoption of antiviral therapy, the occurrence of virus-associated HCC has been decreasing, whereas the prevalence of NAFLD-related HCC is increasing rapidly, with the growing obesity epidemic, diabetes and metabolic syndrome. Targeting the above mechanisms, we can learn that avoiding sedentary and losing weight through lifestyle modification are the effective methods to prevent NAFLD-related HCC. And the role played by lipotoxicity, insulin resistance, oxidative stress, the disturbance or imbalance in gut microbiota, and hormonal disorders provide a possible way of pharmacology research for NASH treatment. Some drugs, the use of insulin sensitizers, such as glitazones through promoting the synthesis and intake of fatty acids in adipocytes, improving the insulin sensitivity and the hepatoprotective effect to impede the progression of steatohepatitis and fibrosis. Vitamin E and pentoxifylline could protect cells from oxidative damage induced by free radicals.[58] And the use of probiotics, prebiotics, symbiotic supplements, antibiotics and fecal microbiota transplantation might ameliorate the disorders of the gut microbiota.[31] However, the long-term safety and efficacy issues of these drugs remain unclear. Due to the role of proinflammatory molecules in accelerating liver cancer development, immunotherapy such as the use of thalidomide, infliximab and cetiniriviroc, may be a useful therapeutic strategy.[33] But owing to the NASH-induced aberrant T cells activation and subsequently defective anti-tumor surveillance, the immunotherapy has little effect on NASH-HCC.[59] And considering the role of endocrine disorders such as hypothyroidism, GH deficiency, and PCOS in the progression of liver disease, hormone replacement therapy can be used for NAFLD caused by hormonal disorders.

On the way to developing optimal therapies that target NASH and NASH-associated HCC, and improving early diagnostic methods and screening, we still have much work to do. At present, the pathogenesis of NAFLD-HCC is still not well-established, therefore, future studies are advised to concentrate on NAFLD-driven HCC investigations.

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Disclosure

The authors report no conflicts of interest in this work.

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