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CASE REPORT

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REVIEW

Multifunctional roles of inflammation and its causative factors in primary liver cancer: A literature review

Hong-Jin Chen, Ting-Xiong Huang, Yu-Xi Jiang, Xiong Chen, Ai-Fang Wang

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Abstract

Primary liver cancer is a severe and complex disease, leading to 800000 global deaths annually. Emerging evidence suggests that inflammation is one of the critical factors in the development of hepatocellular carcinoma (HCC). Patients with viral hepatitis, alcoholic hepatitis, and steatohepatitis symptoms are at higher risk of developing HCC. However, not all inflammatory factors have a pathogenic function in HCC development. The current study describes the process and mechanism of hepatitis development and its progression to HCC, particularly focusing on viral hepatitis, alcoholic hepatitis, and steatohepatitis. Furthermore, the roles of some essential inflammatory cytokines in HCC progression are described in addition to a summary of future research directions.

Key Words: Inflammation; Primary liver cancer; Hepatocellular carcinoma; Nonalcoholic fatty liver disease; Hepatitis virus

Core Tip: Primary liver cancer is the second most common tumor in the world, and the number of deaths due to this disease is increasing every year. A large number of studies have shown that inflammation has a certain regulatory effect in the occurrence and exacerbation of liver cancer. However, the function of inflammation in liver cancer remains to be studied. This review introduces the classification of hepatitis, the correlation between various inflammatory factors and hepatocellular carcinoma (HCC), and some of the anti-inflammatory drugs used in the treatment of HCC.

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INTRODUCTION

Liver cancer is categorized into primary and secondary liver cancer. Primary liver cancer involves hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and other rare cancer types. In contrast, secondary liver cancer is due to cancer cell metastasis from different body parts to the liver *via* the bloodstream[1]. Notably, HCC accounts for 95% of primary liver cancer cases and is one of the leading types and fatal liver cancer forms. HCC development is closely associated with hepatitis C virus (HCV), hepatitis B virus (HBV), and nonalcoholic fatty liver disease (NAFLD)[2]. Alcoholic fatty liver may cause alcoholic steatohepatitis (ASH), leading to progressive fibrosis and cirrhosis, and can develop into HCC[3]. All these processes leading to HCC involve a series of reactions from inflammation to cirrhosis, resulting in HCC. Therefore, inflammation is clinically significant as the initiating factor in HCC.

Inflammation is a defensive response of the human body against stimulation and is divided into acute and chronic inflammation. Acute or short-term hepatic inflammation is a nonfibrotic condition caused by lipopolysaccharide, hepatitis virus, and other factors, and disappears within hours or days. Chronic or long-term inflammation, driven by chronic oxidative stress, is one of the critical processes in HCC development and progression[4]. More studies are investigating the presence of inflammation in the occurrence and development of liver cancer, but its exact role remains unclear. Immune cells in the tumor microenvironment either suppress or promote tumorigenesis, participating in adaptive and innate immunity and defense mechanisms to eliminate foreign agents. Persistent chronic inflammation accelerates the growth and proliferation of tumor cells[5]. Bioactive molecules released from immune cells in the tumor microenvironment stimulate carcinogenesis programming and enhance tumor development[6]. Several inflammatory cytokines, including interleukin (IL)-22, a member of the IL-10 family[7], play a positive role in liver regeneration and the anti-inflammatory response. Other cytokines, including IL-1β and IL-17A, serve as tumor-promoting cytokines, inducing liver disease progression and hepatocarcinogenesis[8,9]. This review summarizes the recent evidence on HCC mechanisms caused by various hepatitis viruses and discusses the role of inflammatory signaling pathways in HCC progression and development (Figure 1).

DIFFERENT CAUSATIVE FACTORS IN INFLAMMATION AND HCC

Role of viral hepatitis in HCC

Viral hepatitis caused by infection with hepatitis viruses A, B, C, D, and E is a global epidemic leading to acute or chronic hepatitis, and even acute severe hepatitis related to a high mortality rate. Due to differences in the structure and features of viruses, they selectively infect the liver using various routes[10]. Approximately 80% of HCC cases are related to HBV or HCV infections, leading to cirrhosis and progressing to HCC.

Hepatitis B virus: Hepatitis B virus (HBV) can integrate its double-stranded DNA (dsDNA) into host cells to develop pregenomic RNA (pgRNA). Then, pgRNA is encapsulated into icosahedral capsids formed by the hepatitis B virus core antigen protein, meditated by polymerase action. Within the capsid, gpRNA is reverse-transcribed into single-stranded DNA (ssDNA), after which the DNA is enveloped to become infectious virions. HBV contains the gene fragments HBV X protein and HBV C protein in its genome. These gene fragments are critical regulatory proteins with crucial roles in HBV-induced HCC pathogenesis. They directly activate or inhibit the expression of hepatocyte growth-related genes, including CTbp2, HMBGA1, and CA10, affecting its transformation to HCC[11-13]. In addition to the direct effects on the host genome to attenuate stability and enhance gene mutations and chromosomal rearrangements with oncogenic or proto-oncogene expression, HBV accelerates HCC progression through multiple mechanisms. For instance, HBV promotes HCC by inducing inflammation and oxidative stress, and altering the immune cell interaction for immune evasion. Bing-Qing Zheng reported that HBsAg (surface antigen) suppressed STAT3 expression and activation in natural killer (NK) cells of chronic hepatitis B (CHB) patients by reducing the IL-21 stimulation response[14]. HBV also activates the phosphatase and tensin homolog (PTEN)/β-actin/c-Myc pathway to promote programmed cell death protein 1 expression, inhibiting T-cell activity and indirectly enhancing the immune evasion of HBV in CHB infection[15]. Furthermore, chronic HBV infection leads to CHB-induced inflammatory damage in hepatic cells due to the persistent activation of inflammatory cells and chemokines[16], causing chronic severe hepatitis or liver cancer. Overall, CHB linked

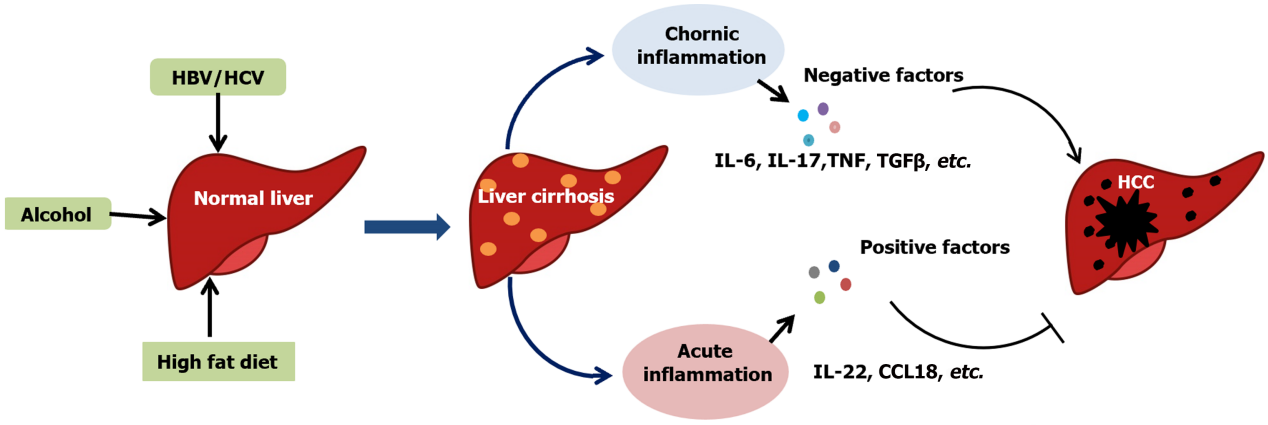

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Figure 1 The relationship between inflammation and hepatocellular carcinoma. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; IL: Interleukin; TNF: Tumor necrosis factor; TGF: Transforming growth factor.

with HBV infection has a weak direct stimulatory role in HCC progression. However, the infection depends more on regulating various immune-related active molecules within the hepatocyte microenvironment.

Hepatitis C virus: HCV belongs to the Flaviviridae family and is an enveloped ssRNA virus. Unlike HBV infection, HCV infection mainly presents as asymptomatic chronic hepatitis, of which 20%-30% of patients progress to liver cirrhosis, and 7% suffer liver cancer[10]. As the released immune cells form a complex HCV-induced HCC tumor microenvironment, Guo-He Song performed single-cell RNA sequencing on immune cells from nontumor and HCV-associated HCC liver tissues[17]. This discovery highlighted novel macrophage and T-cell subsets, of which M2 macrophages significantly expressing CCL18 were enriched in advanced HCC patients. CCL2, CCL20, CXCL8, or CXCL10 were highly induced by the synergistic activity of HCV core protein and chemokines such as interferon (IFN)-γ and IL-1β in fibroblasts or liver sinusoidal endothelial cells (LSECs). These chemokines result in HCV-induced hepatic injury of the LSECs by recruiting leukocytes and activating hepatic stellate cells (HSCs), enabling the development and progression of fibrosis and cirrhosis [18]. CCL2 and CXCL10 are upregulated in macrophages, promoted by the HCV core protein, by interacting with the gC1qR and nuclear factor-kappaB (NF-κB) signaling pathways[19]. Tumor necrosis factor (TNF)-α, IL-1β, IL-6, IL-10, IL-18, and transforming growth factor (TGF)-β are the most relevant inflammatory cytokines associated with HBV/HCV-induced HCC *via* multiple pathways[20]. The IL-6 GC and TGF-β1 TT genotypes promoted HCC development in the HCV-infected population by altering the transcription and stability of the protein structures. These could be potential markers for the early diagnosis of HCC[21].

Role of alcoholic hepatitis in HCC

Excessive alcohol consumption can cause alcoholic liver disease (ALD), such as steatosis, ASH, fibrosis, cirrhosis, and HCC. In the liver, alcohol is metabolized using three major oxidative pathways. First, alcohol is oxidized to acetaldehyde by alcohol dehydrogenase, with NAD^+ as the cofactor[22], cytochrome P450 2E1 (CYP2E1) in the microsomal ethanol oxidizing system[23], and the heme-containing enzyme catalase[24]. Subsequently, acetaldehyde is oxidized to acetate by aldehyde dehydrogenase (ALDH). Acetaldehyde damages DNA and impairs the antioxidant defense system, decreasing antioxidant and detoxification enzymes. Adducts from acetaldehyde can disturb cellular function, promoting alcohol-induced liver injury. CYP2E1 induced by chronic alcohol intake enhances alcohol metabolism to acetaldehyde, leading to liver injury and producing reactive oxygen species (ROS)[25]. These ROS attack the hepatocyte mitochondria and reduce ALDH activity. Additionally, mutagenic etheno-DNA adducts, stimulated by CYP2E1, are essential in genetic damage and liver carcinogenesis[26]. Long-term alcohol use causes excessive CYP2E1 along with oxidative stress, producing ROS [27]. Such exposure results in structural damage, mitochondrial dysfunction, mitochondrial stress in hepatocytes, and apoptotic signal upregulation.

Long-term alcohol consumption and liver dysfunction induce alcoholic hepatitis (AH), which is linked with severe ASH and high mortality rates in the short term[28]. Excessive consumption of alcohol causes damage to the microtubule structure and dysfunction of liver cells in patients with AH, which affects the efficiency of nutrient transport. Protein adducts formed by acetaldehyde can block DNA repair and hepatocyte mitochondria, contributing to the dysfunction of oxygen utilization, collagen synthesis, and extracellular matrix accumulation, resulting in liver fibrosis, cirrhosis, and carcinogenesis[29].

Interestingly, innate immunity activation leads to carcinogenesis in two ways: it leads to alcohol-induced liver injury and results in hepatoprotection, regeneration, and anti-inflammatory reactions to decrease alcohol-induced liver damage [30]. Alcohol consumption elevates lipopolysaccharides and activates the MyD88-independent TRIF/IRF-3 pathway using Toll-like receptor 4 (TLR4), causing oxidative stress, TNF-α release, and liver damage[31]. However, TLR4 and complement factors also promote Kupffer cells to secrete protective cytokines such as IL-6 and anti-inflammatory cytokines such as IL-10. Inflammatory cytokines such as TNF-α, IL-1, and IL-6 are enhanced in the serum of ALD patients [32]. IL-10 plays a positive hepatoprotective role *via* the STAT3 signaling pathway[33]. In contrast, IL-6 and p-STAT3 are

highly expressed in HCC patients[34]. TNF-α acts as a pro-tumorigenic cytokine and activates NF-κB and c-Jun N-terminal kinase (JNK) signaling pathways in liver carcinogenesis[35]. NK cells can develop IFN-γ to attenuate liver cell regeneration and kill hepatocytes[36]. However, the function of NK and NK T cells in hepatocytes remains unexplored. IL-1β plays an essential role in the progression of inflammation, alcohol-induced liver steatosis, and liver injury[37]. IL-22 has beneficial effects on hepatic inflammation and regeneration, while F-652, an IL-22 agonist, is a promising AH treatment candidate[38]. IL-17A functions as a tumor-promoting cytokine regulating inflammatory responses and cholesterol synthesis in developing hepatic steatosis, fibrosis, and HCC in an experimental alcohol-induced mouse model [9]. Some of the inflammatory factors have various roles in different stages. If their expression can be upregulated or downregulated during a specific period, these factors could exert their unique therapeutic effects on AH to HHC.

Role of NAFLD in HCC

NAFLD is a global disease characterized by excessive fat accumulation in the liver and is not associated with excessive alcohol use. NAFLD progression occurs through several stages, such as simple steatosis, steatohepatitis, fibrosis, and cirrhosis, leading to HCC. NAFLD encompasses a group of liver diseases from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH)[39]. NAFL is a simple steatosis of liver cells without inflammation[40]. Furthermore, NAFL development is accompanied by an inflammatory response, causing NASH and liver cancer with cirrhosis[41]. NASH is characterized by the long-term accumulation of triglycerides or clearance disorders in liver cells, progressing to HCC[42]. The presence of steatosis, inflammation, and hepatocyte damage typically characterizes NASH. These are associated with a higher incidence of cirrhosis and liver cancer with NASH mortality than in NAFL[43-45]. TLR9-MyD88 signaling stimulates Kupffer cells to synthesize IL-1β, which contributes to hepatocyte damage and activates HSCs, promoting NASH development[46]. IL-33 is released during chronic hepatocellular stress to activate ILC-2 in the liver and produce IL-13, facilitating HSC activation and the onset of hepatic fibrosis[47]. Notably, the IL-33/ST2 axis has dual roles in diet-induced NASH, wherein an IL-33 supplement ameliorates hepatic steatosis but exacerbates hepatic fibrosis [48]. TNF-α promotes liver fibrosis while cooperating with TIMP-1 produced by HSCs[49]. In a recent study, IL-17A was tested at a high concentration in early-stage fibrosis with increased expression of profibrotic markers in the tissue slice culture, which revealed a significant role of IL-17A in promoting liver fibrosis in human liver tissue[50]. IL-22 treatment ameliorated CXCL1/high-fat diet-induced NASH and methionine choline-deficient diet-induced NASH *via* multiple targets, suppressing liver inflammation[51].

Others

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease with chronic and persistent bile stasis in the liver while causing cirrhosis and liver failure[52]. Some case reports show that cirrhosis is an HCC risk factor in PBC patients [53,54]. Diabetes is categorized into type 1 (T1DM) and type 2 (T2DM) diabetes. Diabetes liver fibrosis (DHF) is a chronic complication that progresses to liver disease. The main reason for DHF is to activate quiescent HSCs *via* high glucose stimulation[55]. T2DM possesses an elevated risk of advanced fibrosis in NAFL patients[56]. Clinical analysis revealed that 1 out of 20 T1DM patients and 1 out of 5 T2DM patients have elevated liver hardness (an indicator to evaluate liver fibrosis), suggesting severe or advanced liver fibrosis. Obese or T2DM patients have an increased risk of developing NASH, which can progress to cirrhosis and HCC if unchecked.

KEY INFLAMMATORY FACTORS AND HCC

Interleukin family

The IL family, with more than 40 members, was first investigated in 1976. According to the structural homology of cytokines, the IL family has seven subfamilies, including IL-1, IL-2, IL-6/IL-12, IL-10, IL-17, and chemokine α subfamilies.

IL-1 subfamily: The IL-1 subfamily includes IL-1α, IL-1β, IL-18, and IL-37[57]. Inhibition of IL-1 signaling using its agonist weakens hepatic inflammation and promotes liver regeneration, helping recovery from liver injury in AH[58,59]. In NAFLD, mice lacking IL-1α and IL-1β had inhibition of hypercholesterolemia steatosis to steatohepatitis and liver fibrosis[60]. Lack of IL-1α in Kupffer cells of mice with hypercholesterolemia weakens liver inflammation and inflammatory cytokine expression[61]. IL-1α release at different locations affects the development direction of HCC differently. Urinary excretion of IL-1α suggests an HCC-promoting effect, wherein the antitumor immune response is inhibited through myeloid-derived suppressor cells recruitment into the tumor microenvironment. Simultaneously, systemic IL-1α administration directly activates T cells to inhibit HCC development[62]. IL-1β secretion by macrophages was reduced in HBV and hepatitis D virus (HDV) infection, while IL-1β inhibited HBV and HDV replication[63]. IL-1β exerts antiviral effects by inhibiting ERK2 activation by elevating IFN-α, which inhibits HCV replication[64]. IL-1 receptor antagonists improve inflammasome-dependent ASH in mice[37]. Mice lacking the IL-1β activation gene can inhibit the development of obesity-induced NAFLD[65]. IL-1β receptor antagonists can inhibit liver fibrosis in mice, while IL-1β, a component of the NLRP3 inflammasome, can reduce liver fibrosis in NASH mice[66]. IL-1β is highly involved in hepatic lipogenesis by enhancing triglyceride accumulation and induces pathogenic liver steatosis in obesity-induced NAFLD[67]. M1 macrophages induce programmed cell death ligand 1 (PD-L1) expression in hepatoma cells *via* IL-1β signaling. This key checkpoint molecule mediates HCC immune escape[68]. IL-1β-mediated homologous box C10 overexpression enhances HCC metastasis by upregulating 3-phosphoinositol-dependent protein kinase 1 (PDPK1) and vasodilator-stimulated phosphoprotein (VASP) expressions[69].

IL-6/IL-12 subfamily: This subfamily consists of IL-6, IL-12, IL-23, IL-27, and IL-35A[70]. A case-control experimental study unraveled the potential susceptibility of IL-6 gene polymorphisms against HBV infection[71]. IL-6 regulates microRNA-125b expression in HCV infection using the STAT3 pathway, causing HCV infection onset and possibly progressing to HCC[72]. In AH, IL-6 promotes microRNA-223-rich exosome production, mitigating NAFLD-associated fibrosis[73]. Additionally, caffeine improves NAFLD with a tandem between muscle production of IL-6 and liver STAT3 activation[74]. The activation of IL-6/STAT3 signaling enhances LCSC production by hepatoma cells and resists sorafenib in hepatoma cells. This is an essential factor in inducing the occurrence, development, and metastasis of liver cancer[75]. Inhibiting IL-6/STAT3 signaling can lead to HCC cell apoptosis[76].

IL-10 subfamily: This subfamily consists of IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26[77]. In a clinical study, polymorphisms in IL-19 increased susceptibility to HBV infection in children[78]. IL-19 inhibits the progression from NAFLD to NASH *in vitro*, while its deficiency in mice leads to pro-inflammatory cytokine expression in the liver[79]. IL-22 positively affects liver inflammation and impaired hepatic regeneration in AH patients and reduces ethanol-induced liver steatohepatitis in mice[38,80]. IL-22 exerts hepatoprotective effects in NAFLD-related liver fibrosis and injury[51,81,82]. However, the role of IL-22 in viral hepatitis is controversial, wherein some studies have reported its positive effects [83], while others indicated that it promotes liver fibrosis and HCC[84,85]. IL-22 exerts pro-tumorigenic effects on hepatocytes in HCC, while IL-22 BP ameliorates liver carcinogenesis[86]. IL-22 overexpression promotes HCC progression, while metformin treatment suppresses IL-22-induced liver cell proliferation, migration, and invasion by reacting with the Hippo signaling pathway[87].

IL-17 subfamily: The IL-17 subfamily comprises IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F[88]. IL-17 expression and the methylation status of its gene promoter can enhance CHB progression[89]. Polymorphisms in the IL-17 gene are related to HCV infection in humans[90,91]. In NAFLD, IL-17 promotes M1 macrophage polarization and exacerbates the hepatic inflammatory response, accelerating NAFLD progression in mice[92]. High-fat diets lead to IL-17A expression, accelerate NAFLD progression by inhibiting fatty acid β oxidation, and promote triglyceride accumulation[93]. This prevents fibrosis in steatohepatitis in mice by inhibiting IL-17-mediated inflammation[94]. In an experimental model of alcohol-induced HCC, IL-17 promotes HCC by regulating the inflammatory response of macrophages and cholesterol synthesis in fatty hepatocytes[9]. IL-17 can also promote non-ASH and HCC[95]. In particular, IL-17A can enhance HCC invasion *via* the AKT pathway and restrict the autophagy of HCC cells by inhibiting Bcl2 degradation[96,97]. IL-17 can improve HepG2 cell proliferation *in vitro* and *in vivo* by activating the IL-2/STAT6 pathway[98].

Chemokine α subfamily: Endoplasmic reticulum stress induces IL-8 transcription and inhibits interferon reactivity in human hepatocytes to increase HBV proliferation[99]. Interferon induces IL-8 to inhibit the production of HBV surface antigen using human hepatocytes[100]. Blocking the recruitment effect of IL-8 on neutrophils can reverse ASH in mice [101,102]. In NAFLD, liver TLR2 expression is positively associated with circulating IL-8 levels. TLR2-mediated pathways are critical for NAFLD/NASH progression, and NASH progression is slower in TLR2 knockout mouse models than in wild-type mouse models[103]. HBV-induced IL-8 inhibits antitumor immunity and elevates HCC metastasis[104]. IL-8 promotes the upregulated signaling of integrin-β3 and HCC cell invasion by activating the PI3K/Akt pathway[105]. Thus, inhibiting IL-8 expression can suppress HCC growth[106,107].

TNF

TNF is a cytokine and an adipokine that plays significant roles in various cellular events, including cell proliferation, cell differentiation, and cell death. As a pro-inflammatory cytokine, TNF is actively involved in inflammation-related carcinogenesis. Gene variation in TNF is associated with increased susceptibility to HBV and HCV infection[108,109]. One study evaluated the inhibition of TNF/NF-κB signaling and macrophage M1-type polarization, suggesting a promising approach for attenuating NAFLD progression to NASH[110]. Anti-TNFR1 treatment significantly reduces liver injury and fibrosis without affecting protective TNFR2 signaling in high-fat diet-induced NAFLD[111]. Anti-TNF-α compromises HCC progression and prolongs survival time in mice by decreasing tumor cell viability[112]. TNF-α induces mesenchymal stem cells mobilization to the injured liver site to participate in the inflammatory microenvironment formation and promotes liver cancer development[113]. TNF-α-mediated extracellular Ca^{2+} influx in HCC accelerates cell apoptosis, suggesting the function of TNF-α as a tumor-killing (pro-apoptotic) cytokine[114]. In addition, TNF-α polymorphism is associated with an elevated risk of HCC[115-117]. The role of TNF-α in the development and progression of HCC requires further exploration.

CXC motif chemokine family

Hepatic stellate cell–induced CXCL1 enhances the malignant development of HCC through the MIR4435-2HG/miR-506-3p/TGFβ axis, which could be a potential target in HCC therapy[118]. Inhibiting the CXCL1-CXCR2 loop improves doxorubicin efficacy in HCC, reducing macrophage recruitment in the tumor microenvironment and restricting tumor progression[119]. CXCL2 is a tumor suppressor, and its high expression significantly enhances the overall survival rate in HCC. Exogenous expression of CXCL2 inhibits cell proliferation in HCC by causing cell cycle arrest and apoptosis[120]. CXCL3 expression is upregulated in HCC and is highly associated with poor prognosis. This promotes CD133 + CSC proliferation through Erk1/2 phosphorylation[121]. CXCL5 knockdown inhibits cell proliferation and invasion through the miR-577/NF-κB axis, while CXCL5 overexpression is a potential indicator of poor prognosis in HCC patients[122]. Circ-HOMER1 causes cell growth and HCC aggressiveness by suppressing the miR-1322 function on CXCL6[123]. The expression level of CXCL6 in HCC tissues is significantly lower than in the adjacent normal tissues[124]. Tumor-associated macrophages caused by the CXCL8/miR-17 cluster enhance tumor cell growth and metastasis in HCC[125].

CXCL10 accelerates epithelial-mesothelial transition of HCC cells through MMP-2 activation[126]. CXCL10 remodels the intrahepatic tumor microenvironment of fibrosis-related HCC, while CXCL10 depletion promotes the invasion and infiltration of immune cells in the invasive tumor margin, resulting in an antitumorigenic microenvironment[127]. CXCL11/CXCR3 can positively regulate the stemness of α2δ1+ HCC tumor-initiating cells by improving self-renewal and tumorigenic properties *via* the ERK1/2 pathway[128]. SOX4-induced CXCL12 in HCC leads to tumor-distant metastasis by regulating CXCR4 in endothelial cells and reticular fibers while shaping the tumor microenvironment and neovascularization[129]. Compared with CHB patients or healthy control subjects, serum CXCL13 is significantly higher in HCC patients, and a positive result is associated with tumor size and metastasis[130]. In a clinical study, CXCL14 mRNA expression and serum CXCL14 levels were decreased in HBV-related HCC tissues. This indicates an advanced disease stage with severe hepatitis and impaired liver function[131]. CXCL14 represses cell proliferation in HCC and expedites apoptosis by inhibiting the Akt/mTOR signaling pathway[132]. Exogenous administration of CXCL14 prohibits angiogenesis in HCC and decelerates cell proliferation, invasion, and migration[133]. Allograft inflammatory factor 1 (AIF1)-induced M2 polarization macrophages secrete CXCL16, facilitating microvascular invasion and tumor progression [134]. Upregulated expression of CXCL17 in HCC promotes tumor cell proliferation and inhibits autophagy by controlling the LKB1-AMPK pathway[135]. MiR-325-3p overexpression attenuates angiogenesis, cell proliferation, migration, and invasion in HCC by restricting the CXCL17/CXCR8 axis[136]. Thus, CXCL2, CXCL6, and CXCL14 are negatively associated with HCC development and progression, while CXCL1, CXCL3, CXCL5, CXCL8, CXCL10, CXCL11, CXCL12, CXCL13, and CXCL17 play an inverse role.

TGF-β

TGF-β is a multifunctional regulator of various processes, including angiogenesis, immunity, and cancer[137,138]. TGF-β exists as three isoforms: TGF-β1, TGF-β2, and TGF-β3. All these can interrupt different stages of HCV propagation *via* the TGF-β/SMAD signaling pathway[139]. ECM1-mediated TGF-β activation promotes liver fibrosis by initiating HSCs[140]. TGF-β1 promotes HBV/HCV-induced fibrogenesis in hepatocytes and HSCs by interacting with the OCT4/Nanog pathway[141]. TGF-β inhibition significantly suppresses high-fat diet-induced inflammation and hepatic fibrosis, ameliorating obesity-related NAFLD and NASH[142,143]. Breviscapine and corosolic acid, TGF-β inhibitors, can alleviate NASH *via* multiple pathways by decreasing hepatic lipid accumulation, inflammation, and fibrogenesis[144,145]. In HCC, high TGF-β1 expression predicted shorter survival and poor disease prognosis in HCC patients[146]. In clinical studies, treating advanced HCC patients with the TGF-βR1/ALK5 inhibitor galunisertib can reduce AFP (alpha fetoprotein) and TGF-β1 in the body and prolong survival time[147,148]. In addition, galunisertib can improve sorafenib effectiveness in HCC patients[149]. In summary, TGF-β promotes the occurrence and development of HCC *via* inflammation-mediated cancer development (Table 1).

CURRENT CLINICAL THERAPIES

There is a significant correlation between inflammation and tumors, and regulating inflammation to treat the tumor could be an effective approach. The efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in treating tumors is evident. They can exert their anticancer effect regardless of whether administered alone or combined[150]. The therapeutic effect of NSAIDs on HCC has been demonstrated, and aspirin can decrease the risk of death from liver cancer induced by chronic liver disease[151]. Celecoxib also promotes the apoptosis of HCC cells by inhibiting Akt expression[152]. In addition, inhibiting certain inflammatory factors can inhibit HCC development. Inhibition of the NLRP3 inflammasome can hinder the growth of HCC cells and promote autophagy[153,154]. 17β-Estradiol (E2) can induce NLRP3 inflammasome activation, trigger pyroptosis, and inhibit HCC progression[155]. Furthermore, IL-6 inhibition can cause HCC cell senescence[156]. The IL-6/STAT3 pathway can enable the metastasis and proliferation of HCC. Thus, inhibiting this pathway can enhance malignant HCC progression[157,158]. Trilobolide-6-O-isobutyrate inhibited IL-6/STAT3 pathway activation to decrease HCC progression[159]. Ursodeoxycholic acid inhibited IL-8 induced ERK phosphorylation, suppressing IL-8 induced angiogenesis[160]. Neurotensin controls IL-8 expression and interferes with EMT (epithelial-mesenchymal transition)-mediated HCC invasion and migration[161]. Dicer collaborates with lenvatinib to downregulate the expression of IL-8 and inhibit HCC growth[106]. In an alcoholic hepatitis mouse model, IL-22 can improve non-ASH through multiple targets while inhibiting inflammation and anti-fibrosis. Moreover, metformin inhibits IL-22 expression, attenuating HCC cell proliferation, migration, and invasion, and promotes apoptosis[87]. Targeting IL-22 has performed well in early HCC clinical experiments, with a good safety and efficacy profile[38,162].

Notably, anti-inflammatory drugs are combined to treat HCC with beneficial therapeutic effects. Pre-clinical studies have indicated that aspirin, a nonsteroidal anti-inflammatory drug, can elevate the sensitivity to various anti-cancer drugs. These include sorafenib and doxorubicin while overcoming sorafenib resistance *in vitro* and *in vivo*[163]. Additionally, aspirin limits NF-κB activation of SLC7A11 transcription by B inhibits the growth of HCC, leading to ferroptosis[164]. However, aspirin is negatively related to the early reported incidence rate of HCC in the general population, which should be considered in the future, particularly in gastrointestinal ulcer patients[165,166]. Another cohort study discovered that using NSAIDs could decrease the risk of early HCC recurrence two years after radical hepatectomy, irrespective of the patient's age, hepatectomy range, viral hepatitis status, basic diabetes, and cirrhosis[167]. Curcumin, a traditional Chinese medicine extract, has excellent anti-inflammatory effects. Curcumin overcame lenvatinib resistance, a first-line treatment drug for unresectable advanced liver cancer, by inhibiting epidermal growth factor receptor[168]. Combining steroid anti-inflammatory drugs dexamethasone and N-acetylcysteine can be employed for post-thrombotic syndrome and post-conventional transcatheter arterial chemoembolization, which is the standard

Table 1 The key inflammatory factors in liver diseases

Disease	Promotion genes	Inhibition genes
Virus hepatitis	IL-6[71]; IL-8[101,102]; IL-17[90,91]; IL-22[84,85]; TNF[108,109]; TGF-β[139];	IL-1β[63,64]; IL-22[83]
Alcoholic hepatitis	IL-1β[37]; IL-8[101,102]	IL-6[73]; IL-22[38,80]
NAFLD	IL-1α[60 61]; IL-1β[60,67-69]; IL-8[103]; IL-17[92-94]; TNF[110-112]; TGF-β[144,145]	IL-19[79]; IL-22[51,81,82]
HCC	IL-1β[68,69]; IL-6[75,76]; IL-8[105-107]; IL-17[96-98]; IL-22[86,87]; CXCL1[118,119]; CXCL3[121]; CXCL5[122]; CXCL8[125]; CXCL10[126,127]; CXCL11[128]; CXCL12[129]; CXCL13[130]; CXCL16[134]; CXCL17[135]; CXCR3 [128]; CXCR4[129]; TGF-β[146-148]	CXCL2[120]; CXCL6[123, 124]; CXCL14[131,132]

IL: Interleukin; TNF: Tumor necrosis factor; TGF: Transforming growth factor; HCC: Hepatocellular carcinoma; NAFLD: Nonalcoholic fatty liver disease.

treatment for mid-term HCC. Only two out of 50 participants experienced mild allergic dermatitis[169,170]. Currently, only a few anti-inflammatory drugs have undergone clinical trials. More effective anti-inflammatory drugs can be applied in clinical trials of HCC by continuously enhancing fundamental experiments.

CONCLUSION

Emerging studies demonstrated that inflammation, particularly chronic inflammation, is crucial in liver deterioration. Moreover, uncontrolled inflammation is a critical factor in liver cancer development. However, at this stage, some acute inflammatory factors have the opposite effect on HCC, indicating that the role of inflammation in HCC requires more exploration regarding new regulatory factors. These factors have great development prospects for the mechanism underlying malignant HCC progression and future clinical treatment.

FOOTNOTES

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