**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 87121

**Manuscript Type:** REVIEW

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

Chen HJ *et al*. Inflammatory factors in primary liver cancer

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

**Hong-Jin Chen,** Department of Pharmacology, School of Basic Medical Sciences, Translational Medicine Research Center, Guizhou Medical University, Guiyang 550025, Guizhou Province, China

**Ting-Xiong Huang,** School of Clinical Medical, Translational Medicine Research Center, Guizhou Medical University, Guiyang 550025, Guizhou Province, China

**Yu-Xi Jiang,** Zhejiang Provincial Key Laboratory of Medical Genetics, Key Laboratory of Laboratory Medicine, Ministry of Education, Wenzhou 325035, Zhejiang Province, China

**Xiong Chen,** Department of Endocrinology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China

**Xiong Chen, Ai-Fang Wang,** Department of Endocrinology, The People's Hospital of Yuhuan, The Yuhuan Branch of The First Affiliated Hospital of Wenzhou Medical University, Yuhuan 317600, Zhejiang Province, China

**Author contributions:** Chen HJ and Chen X contributed to drafting the outline of this review; Chen HJ, Huang TX, and Jiang YX contributed to drafting the manuscript; Chen X and Wang AF contributed to finalizing the manuscript.

**Supported by** the National Natural Science Foundation of China, No. 82260567; Science and Technology Fund of Guizhou Provincial Health Commission, No. gzwkj2022-082; Excellent Young Talents Plan of Guizhou Medical University, No. 2023(112); Taizhou Social Development Science and Technology Plan Project, No. 23ywb146; and Start-up Fund of Guizhou Medical University, No. J2021032.

**Corresponding author: Ai-Fang Wang, MD, Associate Chief Physician,** Department of Endocrinology, The People's Hospital of Yuhuan, The Yuhuan Branch of The First Affiliated Hospital of Wenzhou Medical University, No. 18 Changle Road, Yucheng Street, Yuhuan 317600, China. 459081183@qq.com

**Received:** August 21, 2023

**Revised:** November 6, 2023

**Accepted:** November 24, 2023

**Published online:**

**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

Chen HJ, Huang TX, Jiang YX, Chen X, Wang AF. Multifunctional roles of inflammation and its causative factors in primary liver cancer: A literature review. *World J Hepatol* 2023; In press

**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.

**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](https://pubmed.ncbi.nlm.nih.gov/?term=Zheng+B&cauthor_id=31132315) 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 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 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 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 Die-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:** TheIL-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 Ca2+ 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 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.

**REFERENCES**

1 **Sia D**, Villanueva A, Friedman SL, Llovet JM. Liver Cancer Cell of Origin, Molecular Class, and Effects on Patient Prognosis. *Gastroenterology* 2017; **152**: 745-761 [PMID: 28043904 DOI: 10.1053/j.gastro.2016.11.048]

2 **Yamashita T**, Kaneko S. [Liver Cancer]. *Rinsho Byori* 2016; **64**: 787-796 [PMID: 30695467]

3 **Seitz HK**, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, Mathurin P, Mueller S, Szabo G, Tsukamoto H. Alcoholic liver disease. *Nat Rev Dis Primers* 2018; **4**: 16 [PMID: 30115921 DOI: 10.1038/s41572-018-0014-7]

4 **Refolo MG**, Messa C, Guerra V, Carr BI, D'Alessandro R. Inflammatory Mechanisms of HCC Development. *Cancers (Basel)* 2020; **12** [PMID: 32164265 DOI: 10.3390/cancers12030641]

5 **Anderson NM**, Simon MC. The tumor microenvironment. *Curr Biol* 2020; **30**: R921-R925 [PMID: 32810447 DOI: 10.1016/j.cub.2020.06.081]

6 **Wen Y**, Zhu Y, Zhang C, Yang X, Gao Y, Li M, Yang H, Liu T, Tang H. Chronic inflammation, cancer development and immunotherapy. *Front Pharmacol* 2022; **13**: 1040163 [PMID: 36313280 DOI: 10.3389/fphar.2022.1040163]

7 **Wu Y**, Min J, Ge C, Shu J, Tian D, Yuan Y, Zhou D. Interleukin 22 in Liver Injury, Inflammation and Cancer. *Int J Biol Sci* 2020; **16**: 2405-2413 [PMID: 32760208 DOI: 10.7150/ijbs.38925]

8 **Fischer J**, Long S, Koukoulioti E, Müller T, Fueloep B, Heyne R, Eslam M, George J, Finkelmeier F, Waidmann O, Berg T, van Bömmel F. Association of Common Polymorphisms in the Interleukin-1 Beta Gene with Hepatocellular Carcinoma in Caucasian Patients with Chronic Hepatitis B. *Pathogens* 2022; **12** [PMID: 36678401 DOI: 10.3390/pathogens12010054]

9 **Ma HY**, Yamamoto G, Xu J, Liu X, Karin D, Kim JY, Alexandrov LB, Koyama Y, Nishio T, Benner C, Heinz S, Rosenthal SB, Liang S, Sun M, Karin G, Zhao P, Brodt P, Mckillop IH, Quehenberger O, Dennis E, Saltiel A, Tsukamoto H, Gao B, Karin M, Brenner DA, Kisseleva T. IL-17 signaling in steatotic hepatocytes and macrophages promotes hepatocellular carcinoma in alcohol-related liver disease. *J Hepatol* 2020; **72**: 946-959 [PMID: 31899206 DOI: 10.1016/j.jhep.2019.12.016]

10 **Pisano MB**, Giadans CG, Flichman DM, Ré VE, Preciado MV, Valva P. Viral hepatitis update: Progress and perspectives. *World J Gastroenterol* 2021; **27**: 4018-4044 [PMID: 34326611 DOI: 10.3748/wjg.v27.i26.4018]

11 **Shen Z**, Wu J, Gao Z, Zhang S, Chen J, He J, Guo Y, Deng Q, Xie Y, Liu J, Zhang J. High mobility group AT-hook 1 (HMGA1) is an important positive regulator of hepatitis B virus (HBV) that is reciprocally upregulated by HBV X protein. *Nucleic Acids Res* 2022; **50**: 2157-2171 [PMID: 35137191 DOI: 10.1093/nar/gkac070]

12 **Liu X**, Zhu C, Li J, Xu F, Huang G, Xu L, Zhang B. HBV Upregulates CtBP2 Expression via the X Gene. *Biomed Res Int* 2018; **2018**: 6960573 [PMID: 30151388 DOI: 10.1155/2018/6960573]

13 **Chung KM**, Chen YT, Hong CC, Chang IC, Lin SY, Liang LY, Chen YR, Yeh CT, Huang SF. CA10 is associated with HBV-related hepatocarcinogenesis. *Biochem Biophys Rep* 2022; **31**: 101303 [PMID: 35800619 DOI: 10.1016/j.bbrep.2022.101303]

14 **Zheng B**, Yang Y, Han Q, Yin C, Pan Z, Zhang J. STAT3 directly regulates NKp46 transcription in NK cells of HBeAg-negative CHB patients. *J Leukoc Biol* 2019; **106**: 987-996 [PMID: 31132315 DOI: 10.1002/JLB.2A1118-421R]

15 **Sun Y**, Yu M, Qu M, Ma Y, Zheng D, Yue Y, Guo S, Tang L, Li G, Zheng W, Wang M, Guo D, Li C. Hepatitis B virus-triggered PTEN/β-catenin/c-Myc signaling enhances PD-L1 expression to promote immune evasion. *Am J Physiol Gastrointest Liver Physiol* 2020; **318**: G162-G173 [PMID: 31604033 DOI: 10.1152/ajpgi.00197.2019]

16 **Li JZ**, Ye LH, Wang DH, Zhang HC, Li TY, Liu ZQ, Dai EH, Li MR. The identify role and molecular mechanism of the MALAT1/hsa-mir-20b-5p/TXNIP axis in liver inflammation caused by CHB in patients with chronic HBV infection complicated with NAFLD. *Virus Res* 2021; **298**: 198405 [PMID: 33775752 DOI: 10.1016/j.virusres.2021.198405]

17 **Song G**, Shi Y, Zhang M, Goswami S, Afridi S, Meng L, Ma J, Chen Y, Lin Y, Zhang J, Liu Y, Jin Z, Yang S, Rao D, Zhang S, Ke A, Wang X, Cao Y, Zhou J, Fan J, Zhang X, Xi R, Gao Q. Global immune characterization of HBV/HCV-related hepatocellular carcinoma identifies macrophage and T-cell subsets associated with disease progression. *Cell Discov* 2020; **6**: 90 [PMID: 33298893 DOI: 10.1038/s41421-020-00214-5]

18 **Abouelasrar Salama S**, Gouwy M, De Zutter A, Pörtner N, Vanbrabant L, Berghmans N, De Buck M, Struyf S, Van Damme J. Induction of Chemokines by Hepatitis C Virus Proteins: Synergy of the Core Protein with Interleukin-1β and Interferon-γ in Liver Bystander Cells. *J Interferon Cytokine Res* 2020; **40**: 195-206 [PMID: 32031878 DOI: 10.1089/jir.2019.0115]

19 **Song X**, Gao X, Wang Y, Raja R, Zhang Y, Yang S, Li M, Yao Z, Wei L. HCV Core Protein Induces Chemokine CCL2 and CXCL10 Expression Through NF-κB Signaling Pathway in Macrophages. *Front Immunol* 2021; **12**: 654998 [PMID: 34531848 DOI: 10.3389/fimmu.2021.654998]

20 **Timperi E**, Barnaba V. Viral Hepatitides, Inflammation and Tumour Microenvironment. *Adv Exp Med Biol* 2020; **1263**: 25-43 [PMID: 32588321 DOI: 10.1007/978-3-030-44518-8\_3]

21 **Badshah Y**, Shabbir M, Khan K, Fatima M, Majoka I, Aslam L, Munawar H. Manipulation of Interleukin-6 (IL-6) and Transforming Growth Factor Beta-1(TGFβ-1) towards viral induced liver cancer pathogenesis. *PLoS One* 2022; **17**: e0275834 [PMID: 36215278 DOI: 10.1371/journal.pone.0275834]

22 **Meroni M**, Longo M, Rametta R, Dongiovanni P. Genetic and Epigenetic Modifiers of Alcoholic Liver Disease. *Int J Mol Sci* 2018; **19** [PMID: 30513996 DOI: 10.3390/ijms19123857]

23 **Jiang Y**, Zhang T, Kusumanchi P, Han S, Yang Z, Liangpunsakul S. Alcohol Metabolizing Enzymes, Microsomal Ethanol Oxidizing System, Cytochrome P450 2E1, Catalase, and Aldehyde Dehydrogenase in Alcohol-Associated Liver Disease. *Biomedicines* 2020; **8** [PMID: 32143280 DOI: 10.3390/biomedicines8030050]

24 **Ceni E**, Mello T, Galli A. Pathogenesis of alcoholic liver disease: role of oxidative metabolism. *World J Gastroenterol* 2014; **20**: 17756-17772 [PMID: 25548474 DOI: 10.3748/wjg.v20.i47.17756]

25 **Teschke R**. Alcoholic Liver Disease: Alcohol Metabolism, Cascade of Molecular Mechanisms, Cellular Targets, and Clinical Aspects. *Biomedicines* 2018; **6** [PMID: 30424581 DOI: 10.3390/biomedicines6040106]

26 **Jain D**, Murti Y, Khan WU, Hossain R, Hossain MN, Agrawal KK, Ashraf RA, Islam MT, Janmeda P, Taheri Y, Alshehri MM, Daştan SD, Yeskaliyeva B, Kipchakbayeva A, Sharifi-Rad J, Cho WC. Roles of Therapeutic Bioactive Compounds in Hepatocellular Carcinoma. *Oxid Med Cell Longev* 2021; **2021**: 9068850 [PMID: 34754365 DOI: 10.1155/2021/9068850]

27 **Tan HK**, Yates E, Lilly K, Dhanda AD. Oxidative stress in alcohol-related liver disease. *World J Hepatol* 2020; **12**: 332-349 [PMID: 32821333 DOI: 10.4254/wjh.v12.i7.332]

28 **Crabb DW**, Bataller R, Chalasani NP, Kamath PS, Lucey M, Mathurin P, McClain C, McCullough A, Mitchell MC, Morgan TR, Nagy L, Radaeva S, Sanyal A, Shah V, Szabo G; NIAAA Alcoholic Hepatitis Consortia. Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia. *Gastroenterology* 2016; **150**: 785-790 [PMID: 26921783 DOI: 10.1053/j.gastro.2016.02.042]

29 **Kong LZ**, Chandimali N, Han YH, Lee DH, Kim JS, Kim SU, Kim TD, Jeong DK, Sun HN, Lee DS, Kwon T. Pathogenesis, Early Diagnosis, and Therapeutic Management of Alcoholic Liver Disease. *Int J Mol Sci* 2019; **20** [PMID: 31159489 DOI: 10.3390/ijms20112712]

30 **Gao B**, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology* 2011; **141**: 1572-1585 [PMID: 21920463 DOI: 10.1053/j.gastro.2011.09.002]

31 **Hritz I**, Mandrekar P, Velayudham A, Catalano D, Dolganiuc A, Kodys K, Kurt-Jones E, Szabo G. The critical role of toll-like receptor (TLR) 4 in alcoholic liver disease is independent of the common TLR adapter MyD88. *Hepatology* 2008; **48**: 1224-1231 [PMID: 18792393 DOI: 10.1002/hep.22470]

32 **Szabo G**, Petrasek J, Bala S. Innate immunity and alcoholic liver disease. *Dig Dis* 2012; **30 Suppl 1**: 55-60 [PMID: 23075869 DOI: 10.1159/000341126]

33 **Miller AM**, Horiguchi N, Jeong WI, Radaeva S, Gao B. Molecular mechanisms of alcoholic liver disease: innate immunity and cytokines. *Alcohol Clin Exp Res* 2011; **35**: 787-793 [PMID: 21284667 DOI: 10.1111/j.1530-0277.2010.01399.x]

34 **Yang YM**, Kim SY, Seki E. Inflammation and Liver Cancer: Molecular Mechanisms and Therapeutic Targets. *Semin Liver Dis* 2019; **39**: 26-42 [PMID: 30809789 DOI: 10.1055/s-0038-1676806]

35 **Sethi JK**, Hotamisligil GS. Metabolic Messengers: tumour necrosis factor. *Nat Metab* 2021; **3**: 1302-1312 [PMID: 34650277 DOI: 10.1038/s42255-021-00470-z]

36 **Gao B**, Radaeva S, Park O. Liver natural killer and natural killer T cells: immunobiology and emerging roles in liver diseases. *J Leukoc Biol* 2009; **86**: 513-528 [PMID: 19542050 DOI: 10.1189/JLB.0309135]

37 **Petrasek J**, Bala S, Csak T, Lippai D, Kodys K, Menashy V, Barrieau M, Min SY, Kurt-Jones EA, Szabo G. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. *J Clin Invest* 2012; **122**: 3476-3489 [PMID: 22945633 DOI: 10.1172/JCI60777]

38 **Arab JP**, Sehrawat TS, Simonetto DA, Verma VK, Feng D, Tang T, Dreyer K, Yan X, Daley WL, Sanyal A, Chalasani N, Radaeva S, Yang L, Vargas H, Ibacache M, Gao B, Gores GJ, Malhi H, Kamath PS, Shah VH. An Open-Label, Dose-Escalation Study to Assess the Safety and Efficacy of IL-22 Agonist F-652 in Patients With Alcohol-associated Hepatitis. *Hepatology* 2020; **72**: 441-453 [PMID: 31774566 DOI: 10.1002/hep.31046]

39 **Hochreuter MY**, Dall M, Treebak JT, Barrès R. MicroRNAs in non-alcoholic fatty liver disease: Progress and perspectives. *Mol Metab* 2022; **65**: 101581 [PMID: 36028120 DOI: 10.1016/j.molmet.2022.101581]

40 **Paternostro R**, Trauner M. Current treatment of non-alcoholic fatty liver disease. *J Intern Med* 2022; **292**: 190-204 [PMID: 35796150 DOI: 10.1111/joim.13531]

41 **Murphy WA**, Adiwidjaja J, Sjöstedt N, Yang K, Beaudoin JJ, Spires J, Siler SQ, Neuhoff S, Brouwer KLR. Considerations for Physiologically Based Modeling in Liver Disease: From Nonalcoholic Fatty Liver (NAFL) to Nonalcoholic Steatohepatitis (NASH). *Clin Pharmacol Ther* 2023; **113**: 275-297 [PMID: 35429164 DOI: 10.1002/cpt.2614]

42 **Anstee QM**, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 411-428 [PMID: 31028350 DOI: 10.1038/s41575-019-0145-7]

43 **Rafiq N**, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, Younossi ZM. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol* 2009; **7**: 234-238 [PMID: 19049831 DOI: 10.1016/j.cgh.2008.11.005]

44 **Feldstein AE**, Canbay A, Angulo P, Taniai M, Burgart LJ, Lindor KD, Gores GJ. Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. *Gastroenterology* 2003; **125**: 437-443 [PMID: 12891546 DOI: 10.1016/S0016-5085(03)00907-7]

45 **Vonghia L**, Michielsen P, Francque S. Immunological mechanisms in the pathophysiology of non-alcoholic steatohepatitis. *Int J Mol Sci* 2013; **14**: 19867-19890 [PMID: 24084730 DOI: 10.3390/ijms141019867]

46 **Miura K**, Kodama Y, Inokuchi S, Schnabl B, Aoyama T, Ohnishi H, Olefsky JM, Brenner DA, Seki E. Toll-like receptor 9 promotes steatohepatitis by induction of interleukin-1beta in mice. *Gastroenterology* 2010; **139**: 323-34.e7 [PMID: 20347818 DOI: 10.1053/j.gastro.2010.03.052]

47 **McHedlidze T**, Waldner M, Zopf S, Walker J, Rankin AL, Schuchmann M, Voehringer D, McKenzie AN, Neurath MF, Pflanz S, Wirtz S. Interleukin-33-dependent innate lymphoid cells mediate hepatic fibrosis. *Immunity* 2013; **39**: 357-371 [PMID: 23954132 DOI: 10.1016/j.immuni.2013.07.018]

48 **Gao Y**, Liu Y, Yang M, Guo X, Zhang M, Li H, Li J, Zhao J. IL-33 treatment attenuated diet-induced hepatic steatosis but aggravated hepatic fibrosis. *Oncotarget* 2016; **7**: 33649-33661 [PMID: 27172901 DOI: 10.18632/oncotarget.9259]

49 **Osawa Y**, Hoshi M, Yasuda I, Saibara T, Moriwaki H, Kozawa O. Tumor necrosis factor-α promotes cholestasis-induced liver fibrosis in the mouse through tissue inhibitor of metalloproteinase-1 production in hepatic stellate cells. *PLoS One* 2013; **8**: e65251 [PMID: 23755201 DOI: 10.1371/journal.pone.0065251]

50 **Kartasheva-Ebertz D**, Gaston J, Lair-Mehiri L, Mottez E, Buivan TP, Massault PP, Scatton O, Gaujoux S, Vaillant JC, Pol S, Lagaye S. IL-17A in Human Liver: Significant Source of Inflammation and Trigger of Liver Fibrosis Initiation. *Int J Mol Sci* 2022; **23** [PMID: 36077175 DOI: 10.3390/ijms23179773]

51 **Hwang S**, He Y, Xiang X, Seo W, Kim SJ, Ma J, Ren T, Park SH, Zhou Z, Feng D, Kunos G, Gao B. Interleukin-22 Ameliorates Neutrophil-Driven Nonalcoholic Steatohepatitis Through Multiple Targets. *Hepatology* 2020; **72**: 412-429 [PMID: 31705800 DOI: 10.1002/hep.31031]

52 **Tanaka A**. Current understanding of primary biliary cholangitis. *Clin Mol Hepatol* 2021; **27**: 1-21 [PMID: 33264835 DOI: 10.3350/cmh.2020.0028]

53 **Natarajan Y**, Tansel A, Patel P, Emologu K, Shukla R, Qureshi Z, El-Serag HB, Thrift AP, Kanwal F. Incidence of Hepatocellular Carcinoma in Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis. *Dig Dis Sci* 2021; **66**: 2439-2451 [PMID: 32743773 DOI: 10.1007/s10620-020-06498-7]

54 **Sy AM**, Ferreira RD, John BV. Hepatocellular Carcinoma in Primary Biliary Cholangitis. *Clin Liver Dis* 2022; **26**: 691-704 [PMID: 36270724 DOI: 10.1016/j.cld.2022.06.011]

55 **Zhao B**, Li S, Guo Z, Chen Z, Zhang X, Xu C, Chen J, Wei C. Dopamine receptor D2 inhibition alleviates diabetic hepatic stellate cells fibrosis by regulating the TGF-β1/Smads and NFκB pathways. *Clin Exp Pharmacol Physiol* 2021; **48**: 370-380 [PMID: 33179312 DOI: 10.1111/1440-1681.13437]

56 **Singh A**, Garg R, Lopez R, Alkhouri N. Diabetes Liver Fibrosis Score to Detect Advanced Fibrosis in Diabetics with Nonalcoholic Fatty Liver Disease. *Clin Gastroenterol Hepatol* 2022; **20**: e624-e626 [PMID: 33434655 DOI: 10.1016/j.cgh.2021.01.010]

57 **Chan AH**, Schroder K. Inflammasome signaling and regulation of interleukin-1 family cytokines. *J Exp Med* 2020; **217** [PMID: 31611248 DOI: 10.1084/jem.20190314]

58 **Iracheta-Vellve A**, Petrasek J, Gyogyosi B, Bala S, Csak T, Kodys K, Szabo G. Interleukin-1 inhibition facilitates recovery from liver injury and promotes regeneration of hepatocytes in alcoholic hepatitis in mice. *Liver Int* 2017; **37**: 968-973 [PMID: 28345165 DOI: 10.1111/liv.13430]

59 **Szabo G**, Mitchell M, McClain CJ, Dasarathy S, Barton B, McCullough AJ, Nagy LE, Kroll-Desrosiers A, Tornai D, Min HA, Radaeva S, Holbein MEB, Casey L, Cuthbert J. IL-1 receptor antagonist plus pentoxifylline and zinc for severe alcohol-associated hepatitis. *Hepatology* 2022; **76**: 1058-1068 [PMID: 35340032 DOI: 10.1002/hep.32478]

60 **Kamari Y**, Shaish A, Vax E, Shemesh S, Kandel-Kfir M, Arbel Y, Olteanu S, Barshack I, Dotan S, Voronov E, Dinarello CA, Apte RN, Harats D. Lack of interleukin-1α or interleukin-1β inhibits transformation of steatosis to steatohepatitis and liver fibrosis in hypercholesterolemic mice. *J Hepatol* 2011; **55**: 1086-1094 [PMID: 21354232 DOI: 10.1016/j.jhep.2011.01.048]

61 **Olteanu S**, Kandel-Kfir M, Shaish A, Almog T, Shemesh S, Barshack I, Apte RN, Harats D, Kamari Y. Lack of interleukin-1α in Kupffer cells attenuates liver inflammation and expression of inflammatory cytokines in hypercholesterolaemic mice. *Dig Liver Dis* 2014; **46**: 433-439 [PMID: 24582082 DOI: 10.1016/j.dld.2014.01.156]

62 **Lin D**, Mei Y, Lei L, Binte Hanafi Z, Jin Z, Liu Y, Song Y, Zhang Y, Hu B, Liu C, Lu J, Liu H. Immune suppressive function of IL-1α release in the tumor microenvironment regulated by calpain 1. *Oncoimmunology* 2022; **11**: 2088467 [PMID: 35756844 DOI: 10.1080/2162402X.2022.2088467]

63 **Delphin M**, Faure-Dupuy S, Isorce N, Rivoire M, Salvetti A, Durantel D, Lucifora J. Inhibitory Effect of IL-1β on HBV and HDV Replication and HBs Antigen-Dependent Modulation of Its Secretion by Macrophages. *Viruses* 2021; **14** [PMID: 35062269 DOI: 10.3390/v14010065]

64 **Guo M**, Ye L, Yu T, Han L, Li Q, Lou P, Gan T, Jin X, Xiao H, Meng G, Zhong J, Xu Y. IL-1β Enhances the Antiviral Effect of IFN-α on HCV Replication by Negatively Modulating ERK2 Activation. *ACS Infect Dis* 2020; **6**: 1708-1718 [PMID: 32420725 DOI: 10.1021/acsinfecdis.9b00506]

65 **Mirea AM**, Stienstra R, Kanneganti TD, Tack CJ, Chavakis T, Toonen EJM, Joosten LAB. Mice Deficient in the IL-1β Activation Genes Prtn3, Elane, and Casp1 Are Protected Against the Development of Obesity-Induced NAFLD. *Inflammation* 2020; **43**: 1054-1064 [PMID: 32002713 DOI: 10.1007/s10753-020-01190-4]

66 **Mridha AR**, Wree A, Robertson AAB, Yeh MM, Johnson CD, Van Rooyen DM, Haczeyni F, Teoh NC, Savard C, Ioannou GN, Masters SL, Schroder K, Cooper MA, Feldstein AE, Farrell GC. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J Hepatol* 2017; **66**: 1037-1046 [PMID: 28167322 DOI: 10.1016/j.jhep.2017.01.022]

67 **Negrin KA**, Roth Flach RJ, DiStefano MT, Matevossian A, Friedline RH, Jung D, Kim JK, Czech MP. IL-1 signaling in obesity-induced hepatic lipogenesis and steatosis. *PLoS One* 2014; **9**: e107265 [PMID: 25216251 DOI: 10.1371/journal.pone.0107265]

68 **Zong Z**, Zou J, Mao R, Ma C, Li N, Wang J, Wang X, Zhou H, Zhang L, Shi Y. M1 Macrophages Induce PD-L1 Expression in Hepatocellular Carcinoma Cells Through IL-1β Signaling. *Front Immunol* 2019; **10**: 1643 [PMID: 31379842 DOI: 10.3389/fimmu.2019.01643]

69 **Dang Y**, Chen J, Feng W, Qiao C, Han W, Nie Y, Wu K, Fan D, Xia L. Interleukin 1β-mediated HOXC10 Overexpression Promotes Hepatocellular Carcinoma Metastasis by Upregulating PDPK1 and VASP. *Theranostics* 2020; **10**: 3833-3848 [PMID: 32206125 DOI: 10.7150/thno.41712]

70 **Scheller J**, Berg A, Moll JM, Floss DM, Jungesblut C. Current status and relevance of single nucleotide polymorphisms in IL-6-/IL-12-type cytokine receptors. *Cytokine* 2021; **148**: 155550 [PMID: 34217594 DOI: 10.1016/j.cyto.2021.155550]

71 **El-Maadawy EA**, Talaat RM, Ahmed MM, El-Shenawy SZ. Interleukin-6 promotor gene polymorphisms and susceptibility to chronic hepatitis B virus in Egyptians. *Hum Immunol* 2019; **80**: 208-214 [PMID: 30594561 DOI: 10.1016/j.humimm.2018.12.009]

72 **Dai CY**, Tsai YS, Chou WW, Liu T, Huang CF, Wang SC, Tsai PC, Yeh ML, Hsieh MY, Huang CI, Vanson Liu SY, Huang JF, Chuang WL, Yu ML. The IL-6/STAT3 pathway upregulates microRNA-125b expression in hepatitis C virus infection. *Oncotarget* 2018; **9**: 11291-11302 [PMID: 29541414 DOI: 10.18632/oncotarget.24129]

73 **Hou X**, Yin S, Ren R, Liu S, Yong L, Liu Y, Li Y, Zheng MH, Kunos G, Gao B, Wang H. Myeloid-Cell-Specific IL-6 Signaling Promotes MicroRNA-223-Enriched Exosome Production to Attenuate NAFLD-Associated Fibrosis. *Hepatology* 2021; **74**: 116-132 [PMID: 33236445 DOI: 10.1002/hep.31658]

74 **Fang C**, Cai X, Hayashi S, Hao S, Sakiyama H, Wang X, Yang Q, Akira S, Nishiguchi S, Fujiwara N, Tsutsui H, Sheng J. Caffeine-stimulated muscle IL-6 mediates alleviation of non-alcoholic fatty liver disease. *Biochim Biophys Acta Mol Cell Biol Lipids* 2019; **1864**: 271-280 [PMID: 30553055 DOI: 10.1016/j.bbalip.2018.12.003]

75 **Wang X**, Sun W, Shen W, Xia M, Chen C, Xiang D, Ning B, Cui X, Li H, Li X, Ding J, Wang H. Long non-coding RNA DILC regulates liver cancer stem cells via IL-6/STAT3 axis. *J Hepatol* 2016; **64**: 1283-1294 [PMID: 26812074 DOI: 10.1016/j.jhep.2016.01.019]

76 **Wang ST**, Huang SW, Liu KT, Lee TY, Shieh JJ, Wu CY. Atorvastatin-induced senescence of hepatocellular carcinoma is mediated by downregulation of hTERT through the suppression of the IL-6/STAT3 pathway. *Cell Death Discov* 2020; **6**: 17 [PMID: 32257389 DOI: 10.1038/s41420-020-0252-9]

77 **Wei H**, Li B, Sun A, Guo F. Interleukin-10 Family Cytokines Immunobiology and Structure. *Adv Exp Med Biol* 2019; **1172**: 79-96 [PMID: 31628652 DOI: 10.1007/978-981-13-9367-9\_4]

78 **Fan J**, Mu LH, Zhou L, Huang X, Huang YF. [Association between IL-19 gene polymorphisms and hepatitis B virus susceptibility in children]. *Zhongguo Dang Dai Er Ke Za Zhi* 2016; **18**: 1277-1281 [PMID: 27974122 DOI: 10.7499/j.issn.1008-8830.2016.12.016]

79 **Azuma YT**, Fujita T, Izawa T, Hirota K, Nishiyama K, Ikegami A, Aoyama T, Ike M, Ushikai Y, Kuwamura M, Fujii H, Tsuneyama K. IL-19 Contributes to the Development of Nonalcoholic Steatohepatitis by Altering Lipid Metabolism. *Cells* 2021; **10** [PMID: 34944021 DOI: 10.3390/cells10123513]

80 **Hendrikx T**, Duan Y, Wang Y, Oh JH, Alexander LM, Huang W, Stärkel P, Ho SB, Gao B, Fiehn O, Emond P, Sokol H, van Pijkeren JP, Schnabl B. Bacteria engineered to produce IL-22 in intestine induce expression of REG3G to reduce ethanol-induced liver disease in mice. *Gut* 2019; **68**: 1504-1515 [PMID: 30448775 DOI: 10.1136/gutjnl-2018-317232]

81 **Zai W**, Chen W, Wu Z, Jin X, Fan J, Zhang X, Luan J, Tang S, Mei X, Hao Q, Liu H, Ju D. Targeted Interleukin-22 Gene Delivery in the Liver by Polymetformin and Penetratin-Based Hybrid Nanoparticles to Treat Nonalcoholic Fatty Liver Disease. *ACS Appl Mater Interfaces* 2019; **11**: 4842-4857 [PMID: 30628769 DOI: 10.1021/acsami.8b19717]

82 **Abdelnabi MN**, Flores Molina M, Soucy G, Quoc-Huy Trinh V, Bédard N, Mazouz S, Jouvet N, Dion J, Tran S, Bilodeau M, Estall JL, Shoukry NH. Sex-Dependent Hepatoprotective Role of IL-22 Receptor Signaling in Non-Alcoholic Fatty Liver Disease-Related Fibrosis. *Cell Mol Gastroenterol Hepatol* 2022; **14**: 1269-1294 [PMID: 35970323 DOI: 10.1016/j.jcmgh.2022.08.001]

83 **Sertorio M**, Hou X, Carmo RF, Dessein H, Cabantous S, Abdelwahed M, Romano A, Albuquerque F, Vasconcelos L, Carmo T, Li J, Varoquaux A, Arnaud V, Oliveira P, Hamdoun A, He H, Adbelmaboud S, Mergani A, Zhou J, Monis A, Pereira LB, Halfon P, Bourlière M, Parana R, Dos Reis M, Gonnelli D, Moura P, Elwali NE, Argiro L, Li Y, Dessein A. IL-22 and IL-22 binding protein (IL-22BP) regulate fibrosis and cirrhosis in hepatitis C virus and schistosome infections. *Hepatology* 2015; **61**: 1321-1331 [PMID: 25476703 DOI: 10.1002/hep.27629]

84 **Zhang J**, Liu Z, Liu L, Huang M, Huang Y. Th22/IL-22 mediates the progression of HBV-related hepatocellular carcinoma via STAT3. *Cytotechnology* 2022; **74**: 203-216 [PMID: 35464167 DOI: 10.1007/s10616-021-00517-9]

85 **Wu LY**, Liu S, Liu Y, Guo C, Li H, Li W, Jin X, Zhang K, Zhao P, Wei L, Zhao J. Up-regulation of interleukin-22 mediates liver fibrosis via activating hepatic stellate cells in patients with hepatitis C. *Clin Immunol* 2015; **158**: 77-87 [PMID: 25771172 DOI: 10.1016/j.clim.2015.03.003]

86 **Giannou AD**, Lücke J, Kleinschmidt D, Shiri AM, Steglich B, Nawrocki M, Zhang T, Zazara DE, Kempski J, Zhao L, Giannou O, Agalioti T, Brockmann L, Bertram F, Sabihi M, Böttcher M, Ewald F, Schulze K, von Felden J, Machicote A, Maroulis IC, Arck PC, Graß JK, Mercanoglu B, Reeh M, Wolter S, Tachezy M, Seese H, Theodorakopoulou M, Lykoudis PM, Heumann A, Uzunoglu FG, Ghadban T, Mann O, Izbicki JR, Li J, Duprée A, Melling N, Gagliani N, Huber S. A Critical Role of the IL-22-IL-22 Binding Protein Axis in Hepatocellular Carcinoma. *Cancers (Basel)* 2022; **14** [PMID: 36551508 DOI: 10.3390/cancers14246019]

87 **Zhao D**, Xia L, Geng W, Xu D, Zhong C, Zhang J, Xia Q. Metformin suppresses interleukin-22 induced hepatocellular carcinoma by upregulating Hippo signaling pathway. *J Gastroenterol Hepatol* 2021; **36**: 3469-3476 [PMID: 34432321 DOI: 10.1111/jgh.15674]

88 **Meehan EV**, Wang K. Interleukin-17 Family Cytokines in Metabolic Disorders and Cancer. *Genes (Basel)* 2022; **13** [PMID: 36140808 DOI: 10.3390/genes13091643]

89 **Tian CH**, Dai J, Zhang W, Liu Y, Yang Y. Expression of IL-17 and its gene promoter methylation status are associated with the progression of chronic hepatitis B virus infection. *Medicine (Baltimore)* 2019; **98**: e15924 [PMID: 31169710 DOI: 10.1097/MD.0000000000015924]

90 **Massabayeva MR**, Aukenov NE, Mussazhanova ZB, Saenko VA, Rogounovitch TI, Shaimardanov NK, Kurmanova BR, Barkibaeva NR, Rakhypbekov TK. IL17A gene polymorphisms: relationship to predisposition for chronic viral hepatitis and progression to liver cirrhosis in kazakh population. *Vopr Virusol* 2016; **61**: 212-219 [PMID: 29323853 DOI: 10.18821/0507-4088-2016-61-5-212-219]

91 **Ren W**, Wu Z, Ma R, Liu Z, Wang Y, Wu L, Liu S, Wang Z. Polymorphisms in the IL-17 Gene (rs2275913 and rs763780) Are Associated with Hepatitis B Virus Infection in the Han Chinese Population. *Genet Test Mol Biomarkers* 2017; **21**: 286-291 [PMID: 28277785 DOI: 10.1089/gtmb.2016.0177]

92 **Yang Y**, Han CY, Guan QB, Ruan SL. [Interleukin-17-mediated inflammation promotes nonalcoholic fatty liver disease in mice with regulation of M1-type macrophage polarization]. *Zhonghua Gan Zang Bing Za Zhi* 2018; **26**: 916-921 [PMID: 30669784 DOI: 10.3760/cma.j.issn.1007-3418.2018.12.008]

93 **Shen T**, Chen X, Li Y, Tang X, Jiang X, Yu C, Zheng Y, Guo H, Ling W. Interleukin-17A exacerbates high-fat diet-induced hepatic steatosis by inhibiting fatty acid β-oxidation. *Biochim Biophys Acta Mol Basis Dis* 2017; **1863**: 1510-1518 [PMID: 28153707 DOI: 10.1016/j.bbadis.2017.01.027]

94 **Yamato M**, Sakai Y, Mochida H, Kawaguchi K, Takamura M, Usui S, Seki A, Mizukoshi E, Yamashita T, Yamashita T, Ishida K, Nasti A, Tuyen HTB, Komura T, Yoshida K, Wada T, Honda M, Kaneko S. Adipose tissue-derived stem cells prevent fibrosis in murine steatohepatitis by suppressing IL-17-mediated inflammation. *J Gastroenterol Hepatol* 2019; **34**: 1432-1440 [PMID: 30828861 DOI: 10.1111/jgh.14647]

95 **Gomes AL**, Teijeiro A, Burén S, Tummala KS, Yilmaz M, Waisman A, Theurillat JP, Perna C, Djouder N. Metabolic Inflammation-Associated IL-17A Causes Non-alcoholic Steatohepatitis and Hepatocellular Carcinoma. *Cancer Cell* 2016; **30**: 161-175 [PMID: 27411590 DOI: 10.1016/j.ccell.2016.05.020]

96 **Li S**, Lin Z, Zheng W, Zheng L, Chen X, Yan Z, Cheng Z, Yan H, Zheng C, Guo P. IL-17A inhibits autophagic activity of HCC cells by inhibiting the degradation of Bcl2. *Biochem Biophys Res Commun* 2019; **509**: 194-200 [PMID: 30579601 DOI: 10.1016/j.bbrc.2018.12.103]

97 **Xu QG**, Yu J, Guo XG, Hou GJ, Yuan SX, Yang Y, Yang Y, Liu H, Pan ZY, Yang F, Gu FM, Zhou WP. IL-17A promotes the invasion-metastasis cascade via the AKT pathway in hepatocellular carcinoma. *Mol Oncol* 2018; **12**: 936-952 [PMID: 29689643 DOI: 10.1002/1878-0261.12306]

98 **Hu Z**, Luo D, Wang D, Ma L, Zhao Y, Li L. IL-17 Activates the IL-6/STAT3 Signal Pathway in the Proliferation of Hepatitis B Virus-Related Hepatocellular Carcinoma. *Cell Physiol Biochem* 2017; **43**: 2379-2390 [PMID: 29073625 DOI: 10.1159/000484390]

99 **Tsuge M**, Hiraga N, Zhang Y, Yamashita M, Sato O, Oka N, Shiraishi K, Izaki Y, Makokha GN, Uchida T, Kurihara M, Nomura M, Tsushima K, Nakahara T, Murakami E, Abe-Chayama H, Kawaoka T, Miki D, Imamura M, Kawakami Y, Aikata H, Ochi H, Hayes CN, Fujita T, Chayama K. Endoplasmic reticulum-mediated induction of interleukin-8 occurs by hepatitis B virus infection and contributes to suppression of interferon responsiveness in human hepatocytes. *Virology* 2018; **525**: 48-61 [PMID: 30240958 DOI: 10.1016/j.virol.2018.08.020]

100 **Haga Y**, Kanda T, Nakamoto S, Nakamura M, Sasaki R, Wu S, Yokosuka O. Interferon induces interleukin 8 and bone marrow stromal cell antigen 2 expression, inhibiting the production of hepatitis B virus surface antigen from human hepatocytes. *Biochem Biophys Res Commun* 2017; **486**: 858-863 [PMID: 28363866 DOI: 10.1016/j.bbrc.2017.03.150]

101 **Wieser V**, Adolph TE, Enrich B, Kuliopulos A, Kaser A, Tilg H, Kaneider NC. Reversal of murine alcoholic steatohepatitis by pepducin-based functional blockade of interleukin-8 receptors. *Gut* 2017; **66**: 930-938 [PMID: 26858343 DOI: 10.1136/gutjnl-2015-310344]

102 **French SW**, Mendoza AS, Afifiyan N, Tillman B, Vitocruz E, French BA. The role of the IL-8 signaling pathway in the infiltration of granulocytes into the livers of patients with alcoholic hepatitis. *Exp Mol Pathol* 2017; **103**: 137-140 [PMID: 28818508 DOI: 10.1016/j.yexmp.2017.08.005]

103 **Auguet T**, Bertran L, Binetti J, Aguilar C, Martínez S, Sabench F, Lopez-Dupla JM, Porras JA, Riesco D, Del Castillo D, Richart C. Relationship between IL-8 Circulating Levels and TLR2 Hepatic Expression in Women with Morbid Obesity and Nonalcoholic Steatohepatitis. *Int J Mol Sci* 2020; **21** [PMID: 32545403 DOI: 10.3390/ijms21114189]

104 **Zhang C**, Gao Y, Du C, Markowitz GJ, Fu J, Zhang Z, Liu C, Qin W, Wang H, Wang F, Yang P. Hepatitis B-Induced IL8 Promotes Hepatocellular Carcinoma Venous Metastasis and Intrahepatic Treg Accumulation. *Cancer Res* 2021; **81**: 2386-2398 [PMID: 33653774 DOI: 10.1158/0008-5472.CAN-20-3453]

105 **Sun F**, Wang J, Sun Q, Li F, Gao H, Xu L, Zhang J, Sun X, Tian Y, Zhao Q, Shen H, Zhang K, Liu J. Interleukin-8 promotes integrin β3 upregulation and cell invasion through PI3K/Akt pathway in hepatocellular carcinoma. *J Exp Clin Cancer Res* 2019; **38**: 449 [PMID: 31684995 DOI: 10.1186/s13046-019-1455-x]

106 **Han X**, Wu J, Sha Z, Lai R, Shi J, Mi L, Yin F, Guo Z. Dicer Suppresses Hepatocellular Carcinoma via Interleukin-8 Pathway. *Clin Med Insights Oncol* 2023; **17**: 11795549231161212 [PMID: 37056297 DOI: 10.1177/11795549231161212]

107 **Krause GC**, Lima KG, Haute GV, Schuster AD, Dias HB, Mesquita FC, Pedrazza L, Marczak ES, Basso BS, Velasque AC, Martha BA, Nunes FB, Donadio MV, de Oliveira JR. Fructose-1,6-bisphosphate decreases IL-8 levels and increases the activity of pro-apoptotic proteins in HepG2 cells. *Biomed Pharmacother* 2017; **89**: 358-365 [PMID: 28242545 DOI: 10.1016/j.biopha.2017.01.178]

108 **Woziwodzka A**, Rybicka M, Sznarkowska A, Romanowski T, Dręczewski M, Stalke P, Bielawski KP. TNF-α polymorphisms affect persistence and progression of HBV infection. *Mol Genet Genomic Med* 2019; **7**: e00935 [PMID: 31441603 DOI: 10.1002/mgg3.935]

109 **Yue M**, Huang P, Wang C, Fan H, Tian T, Wu J, Luo F, Fu Z, Xia X, Zhu P, Li J, Han Y, Zhang Y, Hou W. Genetic Variation on TNF/LTA and TNFRSF1A Genes is Associated with Outcomes of Hepatitis C Virus Infection. *Immunol Invest* 2021; **50**: 1-11 [PMID: 31928491 DOI: 10.1080/08820139.2019.1708384]

110 **Zhou W**, Zhu Z, Xiao X, Li C, Zhang L, Dang Y, Ge G, Ji G, Zhu M, Xu H. Jiangzhi Granule attenuates non-alcoholic steatohepatitis by suppressing TNF/NFκB signaling pathway-a study based on network pharmacology. *Biomed Pharmacother* 2021; **143**: 112181 [PMID: 34649337 DOI: 10.1016/j.biopha.2021.112181]

111 **Wandrer F**, Liebig S, Marhenke S, Vogel A, John K, Manns MP, Teufel A, Itzel T, Longerich T, Maier O, Fischer R, Kontermann RE, Pfizenmaier K, Schulze-Osthoff K, Bantel H. TNF-Receptor-1 inhibition reduces liver steatosis, hepatocellular injury and fibrosis in NAFLD mice. *Cell Death Dis* 2020; **11**: 212 [PMID: 32235829 DOI: 10.1038/s41419-020-2411-6]

112 **Li W**, Jian YB. Antitumor necrosis factor-α antibodies as a noveltherapy for hepatocellular carcinoma. *Exp Ther Med* 2018; **16**: 529-536 [PMID: 30116311 DOI: 10.3892/etm.2018.6235]

113 **Zong C**, Meng Y, Ye F, Yang X, Li R, Jiang J, Zhao Q, Gao L, Han Z, Wei L. AIF1 + CSF1R + MSCs, induced by TNF-α, act to generate an inflammatory microenvironment and promote hepatocarcinogenesis. *Hepatology* 2023; **78**: 434-451 [PMID: 35989499 DOI: 10.1002/hep.32738]

114 **Zhu J**, Jin M, Wang J, Zhang H, Wu Y, Li D, Ji X, Yang H, Yin C, Ren T, Xing J. TNFα induces Ca(2+) influx to accelerate extrinsic apoptosis in hepatocellular carcinoma cells. *J Exp Clin Cancer Res* 2018; **37**: 43 [PMID: 29506556 DOI: 10.1186/s13046-018-0714-6]

115 **Heidari Horestani M**, Atri Roozbahani G, Sheidai M. The Potential Role of TNF-α (rs361525 and rs1800629) in Hepatocellular Carcinoma: Multivariate Analysis (Meta-Analysis). *J Gastrointest Cancer* 2019; **50**: 744-749 [PMID: 30027452 DOI: 10.1007/s12029-018-0135-y]

116 **Verma HK**, Merchant N, Bhaskar LVKS. Tumor Necrosis Factor-Alpha Gene Promoter (TNF-α G-308A) Polymorphisms Increase the Risk of Hepatocellular Carcinoma in Asians: A Meta-Analysis. *Crit Rev Oncog* 2020; **25**: 11-20 [PMID: 32865907 DOI: 10.1615/CritRevOncog.2020034846]

117 **Wungu CDK**, Ariyanto FC, Prabowo GI, Soetjipto, Handajani R. Association between five types of Tumor Necrosis Factor-α gene polymorphism and hepatocellular carcinoma risk: a meta-analysis. *BMC Cancer* 2020; **20**: 1134 [PMID: 33228594 DOI: 10.1186/s12885-020-07606-6]

118 **Li S**, Hu X, Yu S, Yi P, Chen R, Huang Z, Huang Y, Huang Y, Zhou R, Fan X. Hepatic stellate cell-released CXCL1 aggravates HCC malignant behaviors through the MIR4435-2HG/miR-506-3p/TGFB1 axis. *Cancer Sci* 2023; **114**: 504-520 [PMID: 36169092 DOI: 10.1111/cas.15605]

119 **Zhao H**, Wei S, Zhou D, Liu Y, Guo Z, Fang C, Pang X, Li F, Hou H, Cui X. Blocking the CXCL1-CXCR2 axis enhances the effects of doxorubicin in HCC by remodelling the tumour microenvironment via the NF-κB/IL-1β/CXCL1 signalling pathway. *Cell Death Discov* 2023; **9**: 120 [PMID: 37037815 DOI: 10.1038/s41420-023-01424-y]

120 **Ding J**, Xu K, Zhang J, Lin B, Wang Y, Yin S, Xie H, Zhou L, Zheng S. Overexpression of CXCL2 inhibits cell proliferation and promotes apoptosis in hepatocellular carcinoma. *BMB Rep* 2018; **51**: 630-635 [PMID: 30293547 DOI: 10.5483/BMBRep.2018.51.12.140]

121 **Zhang L**, Zhang L, Li H, Ge C, Zhao F, Tian H, Chen T, Jiang G, Xie H, Cui Y, Yao M, Li J. CXCL3 contributes to CD133(+) CSCs maintenance and forms a positive feedback regulation loop with CD133 in HCC via Erk1/2 phosphorylation. *Sci Rep* 2016; **6**: 27426 [PMID: 27255419 DOI: 10.1038/srep27426]

122 **Jia X**, Wei S, Xiong W. CXCL5/NF-κB Pathway as a Therapeutic Target in Hepatocellular Carcinoma Treatment. *J Oncol* 2021; **2021**: 9919494 [PMID: 34194499 DOI: 10.1155/2021/9919494]

123 **Zhao M**, Dong G, Meng Q, Lin S, Li X. Circ-HOMER1 enhances the inhibition of miR-1322 on CXCL6 to regulate the growth and aggressiveness of hepatocellular carcinoma cells. *J Cell Biochem* 2020; **121**: 4440-4449 [PMID: 32037619 DOI: 10.1002/jcb.29672]

124 **Wang J**, Zhang C, Chen X, Li Y, Li A, Liu D, Li F, Luo T. Functions of CXC chemokines as biomarkers and potential therapeutic targets in the hepatocellular carcinoma microenvironment. *Transl Cancer Res* 2021; **10**: 2169-2187 [PMID: 35116536 DOI: 10.21037/tcr-21-127]

125 **Yin Z**, Huang J, Ma T, Li D, Wu Z, Hou B, Jian Z. Macrophages activating chemokine (C-X-C motif) ligand 8/miR-17 cluster modulate hepatocellular carcinoma cell growth and metastasis. *Am J Transl Res* 2017; **9**: 2403-2411 [PMID: 28559990]

126 **Ren T**, Zhu L, Cheng M. CXCL10 accelerates EMT and metastasis by MMP-2 in hepatocellular carcinoma. *Am J Transl Res* 2017; **9**: 2824-2837 [PMID: 28670372]

127 **Brandt EF**, Baues M, Wirtz TH, May JN, Fischer P, Beckers A, Schüre BC, Sahin H, Trautwein C, Lammers T, Berres ML. Chemokine CXCL10 Modulates the Tumor Microenvironment of Fibrosis-Associated Hepatocellular Carcinoma. *Int J Mol Sci* 2022; **23** [PMID: 35897689 DOI: 10.3390/ijms23158112]

128 **Zhang Y**, Zhao W, Li S, Lv M, Yang X, Li M, Zhang Z. CXCL11 promotes self-renewal and tumorigenicity of α2δ1(+) liver tumor-initiating cells through CXCR3/ERK1/2 signaling. *Cancer Lett* 2019; **449**: 163-171 [PMID: 30771435 DOI: 10.1016/j.canlet.2019.02.016]

129 **Tsai CN**, Yu SC, Lee CW, Pang JS, Wu CH, Lin SE, Chung YH, Tsai CL, Hsieh SY, Yu MC. SOX4 activates CXCL12 in hepatocellular carcinoma cells to modulate endothelial cell migration and angiogenesis in vivo. *Oncogene* 2020; **39**: 4695-4710 [PMID: 32404985 DOI: 10.1038/s41388-020-1319-z]

130 **Li B**, Su H, Cao J, Zhang L. CXCL13 rather than IL-31 is a potential indicator in patients with hepatocellular carcinoma. *Cytokine* 2017; **89**: 91-97 [PMID: 27663978 DOI: 10.1016/j.cyto.2016.08.016]

131 **Lin Y**, Chen BM, Yu XL, Yi HC, Niu JJ, Li SL. Suppressed Expression of CXCL14 in Hepatocellular Carcinoma Tissues and Its Reduction in the Advanced Stage of Chronic HBV Infection. *Cancer Manag Res* 2019; **11**: 10435-10443 [PMID: 31849533 DOI: 10.2147/CMAR.S220528]

132 **Bi J**, Liu Q, Sun Y, Hu X, He X, Xu C. CXCL14 inhibits the growth and promotes apoptosis of hepatocellular carcinoma cells via suppressing Akt/mTOR pathway. *J Recept Signal Transduct Res* 2021; **41**: 593-603 [PMID: 33108937 DOI: 10.1080/10799893.2020.1837870]

133 **Liu Y**, Chang Q, Wu X, Yu Y, Zhang H. Effect of chemokine CXCL14 on in vitro angiogenesis of human hepatocellular carcinoma cells. *Arch Physiol Biochem* 2022; **128**: 1316-1322 [PMID: 32552011 DOI: 10.1080/13813455.2020.1769677]

134 **Cai H**, Zhu XD, Ao JY, Ye BG, Zhang YY, Chai ZT, Wang CH, Shi WK, Cao MQ, Li XL, Sun HC. Colony-stimulating factor-1-induced AIF1 expression in tumor-associated macrophages enhances the progression of hepatocellular carcinoma. *Oncoimmunology* 2017; **6**: e1333213 [PMID: 28932635 DOI: 10.1080/2162402X.2017.1333213]

135 **Wang L**, Li H, Zhen Z, Ma X, Yu W, Zeng H, Li L. CXCL17 promotes cell metastasis and inhibits autophagy via the LKB1-AMPK pathway in hepatocellular carcinoma. *Gene* 2019; **690**: 129-136 [PMID: 30597237 DOI: 10.1016/j.gene.2018.12.043]

136 **Li L**, Ji Y, Chen YC, Zhen ZJ. MiR-325-3p mediate the CXCL17/CXCR8 axis to regulate angiogenesis in hepatocellular carcinoma. *Cytokine* 2021; **141**: 155436 [PMID: 33515898 DOI: 10.1016/j.cyto.2021.155436]

137 **Larson C**, Oronsky B, Carter CA, Oronsky A, Knox SJ, Sher D, Reid TR. TGF-beta: a master immune regulator. *Expert Opin Ther Targets* 2020; **24**: 427-438 [PMID: 32228232 DOI: 10.1080/14728222.2020.1744568]

138 **Syed V**. TGF-β Signaling in Cancer. *J Cell Biochem* 2016; **117**: 1279-1287 [PMID: 26774024 DOI: 10.1002/jcb.25496]

139 **Zou LL**, Li JR, Li H, Tan JL, Wang MX, Liu NN, Gao RM, Yan HY, Wang XK, Dong B, Li YH, Peng ZG. TGF-β isoforms inhibit hepatitis C virus propagation in transforming growth factor beta/SMAD protein signalling pathway dependent and independent manners. *J Cell Mol Med* 2021; **25**: 3498-3510 [PMID: 33682288 DOI: 10.1111/jcmm.16432]

140 **Fan W**, Liu T, Chen W, Hammad S, Longerich T, Hausser I, Fu Y, Li N, He Y, Liu C, Zhang Y, Lian Q, Zhao X, Yan C, Li L, Yi C, Ling Z, Ma L, Zhao X, Xu H, Wang P, Cong M, You H, Liu Z, Wang Y, Chen J, Li D, Hui L, Dooley S, Hou J, Jia J, Sun B. ECM1 Prevents Activation of Transforming Growth Factor β, Hepatic Stellate Cells, and Fibrogenesis in Mice. *Gastroenterology* 2019; **157**: 1352-1367.e13 [PMID: 31362006 DOI: 10.1053/j.gastro.2019.07.036]

141 **Li W**, Duan X, Zhu C, Liu X, Jeyarajan AJ, Xu M, Tu Z, Sheng Q, Chen D, Zhu C, Shao T, Cheng Z, Salloum S, Schaefer EA, Kruger AJ, Holmes JA, Chung RT, Lin W. Hepatitis B and Hepatitis C Virus Infection Promote Liver Fibrogenesis through a TGF-β1-Induced OCT4/Nanog Pathway. *J Immunol* 2022; **208**: 672-684 [PMID: 35022275 DOI: 10.4049/jimmunol.2001453]

142 **Pahk K**, Lee SG, Joung C, Kim EO, Kwon HW, Kim DH, Hwang JI, Kim S, Kim WK. SP-1154, a novel synthetic TGF-β inhibitor, alleviates obesity and hepatic steatosis in high-fat diet-induced mice. *Biomed Pharmacother* 2022; **145**: 112441 [PMID: 34813997 DOI: 10.1016/j.biopha.2021.112441]

143 **Hui ST**, Wang F, Stappenbeck F, French SW, Magyar CE, Parhami F, Lusis AJ. Oxy210, a novel inhibitor of hedgehog and TGF-β signalling, ameliorates hepatic fibrosis and hypercholesterolemia in mice. *Endocrinol Diabetes Metab* 2021; **4**: e00296 [PMID: 34505423 DOI: 10.1002/edm2.296]

144 **Lan T**, Jiang S, Zhang J, Weng Q, Yu Y, Li H, Tian S, Ding X, Hu S, Yang Y, Wang W, Wang L, Luo D, Xiao X, Piao S, Zhu Q, Rong X, Guo J. Breviscapine alleviates NASH by inhibiting TGF-β-activated kinase 1-dependent signaling. *Hepatology* 2022; **76**: 155-171 [PMID: 34717002 DOI: 10.1002/hep.32221]

145 **Liu G**, Cui Z, Gao X, Liu H, Wang L, Gong J, Wang A, Zhang J, Ma Q, Huang Y, Piao G, Yuan H. Corosolic acid ameliorates non-alcoholic steatohepatitis induced by high-fat diet and carbon tetrachloride by regulating TGF-β1/Smad2, NF-κB, and AMPK signaling pathways. *Phytother Res* 2021; **35**: 5214-5226 [PMID: 34213784 DOI: 10.1002/ptr.7195]

146 **Peng L**, Yuan XQ, Zhang CY, Ye F, Zhou HF, Li WL, Liu ZY, Zhang YQ, Pan X, Li GC. High TGF-β1 expression predicts poor disease prognosis in hepatocellular carcinoma patients. *Oncotarget* 2017; **8**: 34387-34397 [PMID: 28415739 DOI: 10.18632/oncotarget.16166]

147 **Giannelli G**, Santoro A, Kelley RK, Gane E, Paradis V, Cleverly A, Smith C, Estrem ST, Man M, Wang S, Lahn MM, Raymond E, Benhadji KA, Faivre S. Biomarkers and overall survival in patients with advanced hepatocellular carcinoma treated with TGF-βRI inhibitor galunisertib. *PLoS One* 2020; **15**: e0222259 [PMID: 32210440 DOI: 10.1371/journal.pone.0222259]

148 **Faivre S**, Santoro A, Kelley RK, Gane E, Costentin CE, Gueorguieva I, Smith C, Cleverly A, Lahn MM, Raymond E, Benhadji KA, Giannelli G. Novel transforming growth factor beta receptor I kinase inhibitor galunisertib (LY2157299) in advanced hepatocellular carcinoma. *Liver Int* 2019; **39**: 1468-1477 [PMID: 30963691 DOI: 10.1111/liv.14113]

149 **Kelley RK**, Gane E, Assenat E, Siebler J, Galle PR, Merle P, Hourmand IO, Cleverly A, Zhao Y, Gueorguieva I, Lahn M, Faivre S, Benhadji KA, Giannelli G. A Phase 2 Study of Galunisertib (TGF-β1 Receptor Type I Inhibitor) and Sorafenib in Patients With Advanced Hepatocellular Carcinoma. *Clin Transl Gastroenterol* 2019; **10**: e00056 [PMID: 31295152 DOI: 10.14309/ctg.0000000000000056]

150 **Zappavigna S**, Cossu AM, Grimaldi A, Bocchetti M, Ferraro GA, Nicoletti GF, Filosa R, Caraglia M. Anti-Inflammatory Drugs as Anticancer Agents. *Int J Mol Sci* 2020; **21** [PMID: 32283655 DOI: 10.3390/ijms21072605]

151 **Yan LJ**, Yao SY, Li HC, Meng GX, Liu KX, Ding ZN, Hong JG, Chen ZQ, Dong ZR, Li T. Efficacy and Safety of Aspirin for Prevention of Hepatocellular Carcinoma: An Updated Meta-analysis. *J Clin Transl Hepatol* 2022; **10**: 835-846 [PMID: 36304506 DOI: 10.14218/JCTH.2021.00257]

152 **Leng J**, Han C, Demetris AJ, Michalopoulos GK, Wu T. Cyclooxygenase-2 promotes hepatocellular carcinoma cell growth through Akt activation: evidence for Akt inhibition in celecoxib-induced apoptosis. *Hepatology* 2003; **38**: 756-768 [PMID: 12939602 DOI: 10.1053/jhep.2003.50380]

153 **Wei Q**, Zhu R, Zhu J, Zhao R, Li M. E2-Induced Activation of the NLRP3 Inflammasome Triggers Pyroptosis and Inhibits Autophagy in HCC Cells. *Oncol Res* 2019; **27**: 827-834 [PMID: 30940293 DOI: 10.3727/096504018X15462920753012]

154 **Chen W**, Wei T, Chen Y, Yang L, Wu X. Downregulation of IRAK1 Prevents the Malignant Behavior of Hepatocellular Carcinoma Cells by Blocking Activation of the MAPKs/NLRP3/IL-1β Pathway. *Onco Targets Ther* 2020; **13**: 12787-12796 [PMID: 33363384 DOI: 10.2147/OTT.S260793]

155 **Awwad SF**, Assaf RH, Emam AA, Fouad AA, Arafa LF, El-Hanafy AA. NLRP3 inflammasome activation By 17β-estradiol is a potential therapeutic target in hepatocellular carcinoma treatment. *Med Oncol* 2023; **40**: 94 [PMID: 36763290 DOI: 10.1007/s12032-022-01945-z]

156 **Wang L**, Zhu L, Liang C, Huang X, Liu Z, Huo J, Zhang Y, Zhang Y, Chen L, Xu H, Li X, Xu L, Kuang M, Wong CC, Yu J. Targeting N6-methyladenosine reader YTHDF1 with siRNA boosts antitumor immunity in NASH-HCC by inhibiting EZH2-IL-6 axis. *J Hepatol* 2023; **79**: 1185-1200 [PMID: 37459919 DOI: 10.1016/j.jhep.2023.06.021]

157 **Liu D**, Luo X, Xie M, Zhang T, Chen X, Zhang B, Sun M, Wang Y, Feng Y, Ji X, Li Y, Liu B, Huang W, Xia L. HNRNPC downregulation inhibits IL-6/STAT3-mediated HCC metastasis by decreasing HIF1A expression. *Cancer Sci* 2022; **113**: 3347-3361 [PMID: 35848884 DOI: 10.1111/cas.15494]

158 **Xu J**, Lin H, Wu G, Zhu M, Li M. IL-6/STAT3 Is a Promising Therapeutic Target for Hepatocellular Carcinoma. *Front Oncol* 2021; **11**: 760971 [PMID: 34976809 DOI: 10.3389/fonc.2021.760971]

159 **Zhou XQ**, Mao XM, Fan R, Li SY, Shang J, Zhang T, Li RH, Li HQ, Hui Y, Chen WH, Wang ZX, Shen DY. Trilobolide-6-O-isobutyrate suppresses hepatocellular carcinoma tumorigenesis through inhibition of IL-6/STAT3 signaling pathway. *Phytother Res* 2021; **35**: 5741-5753 [PMID: 34355433 DOI: 10.1002/ptr.7233]

160 **Lin W**, Li S, Meng Y, Huang G, Liang S, Du J, Liu Q, Cheng B. UDCA Inhibits Hypoxic Hepatocellular Carcinoma Cell-Induced Angiogenesis Through Suppressing HIF-1α/VEGF/IL-8 Intercellular Signaling. *Front Pharmacol* 2021; **12**: 755394 [PMID: 34975472 DOI: 10.3389/fphar.2021.755394]

161 **Xiao P**, Long X, Zhang L, Ye Y, Guo J, Liu P, Zhang R, Ning J, Yu W, Wei F, Yu J. Neurotensin/IL-8 pathway orchestrates local inflammatory response and tumor invasion by inducing M2 polarization of Tumor-Associated macrophages and epithelial-mesenchymal transition of hepatocellular carcinoma cells. *Oncoimmunology* 2018; **7**: e1440166 [PMID: 29900041 DOI: 10.1080/2162402X.2018.1440166]

162 **Tang KY**, Lickliter J, Huang ZH, Xian ZS, Chen HY, Huang C, Xiao C, Wang YP, Tan Y, Xu LF, Huang YL, Yan XQ. Safety, pharmacokinetics, and biomarkers of F-652, a recombinant human interleukin-22 dimer, in healthy subjects. *Cell Mol Immunol* 2019; **16**: 473-482 [PMID: 29670279 DOI: 10.1038/s41423-018-0029-8]

163 **Wang J**, Hu F, Yu P, Wang J, Liu Z, Bao Q, Zhang W, Wen J. Sorafenib inhibits doxorubicin-induced PD-L1 upregulation to improve immunosuppressive microenvironment in Osteosarcoma. *J Cancer Res Clin Oncol* 2023; **149**: 5127-5138 [PMID: 36348018 DOI: 10.1007/s00432-022-04458-4]

164 **Wang YF**, Feng JY, Zhao LN, Zhao M, Wei XF, Geng Y, Yuan HF, Hou CY, Zhang HH, Wang GW, Yang G, Zhang XD. Aspirin triggers ferroptosis in hepatocellular carcinoma cells through restricting NF-κB p65-activated SLC7A11 transcription. *Acta Pharmacol Sin* 2023; **44**: 1712-1724 [PMID: 36829052 DOI: 10.1038/s41401-023-01062-1]

165 **Ricciotti E**, Wangensteen KJ, FitzGerald GA. Aspirin in Hepatocellular Carcinoma. *Cancer Res* 2021; **81**: 3751-3761 [PMID: 33893087 DOI: 10.1158/0008-5472.CAN-21-0758]

166 **Tan RZH**, Lockart I, Abdel Shaheed C, Danta M. Systematic review with meta-analysis: The effects of non-steroidal anti-inflammatory drugs and anti-platelet therapy on the incidence and recurrence of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2021; **54**: 356-367 [PMID: 34247393 DOI: 10.1111/apt.16515]

167 **Yeh CC**, Lin JT, Jeng LB, Ho HJ, Yang HR, Wu MS, Kuo KN, Wu CY. Nonsteroidal anti-inflammatory drugs are associated with reduced risk of early hepatocellular carcinoma recurrence after curative liver resection: a nationwide cohort study. *Ann Surg* 2015; **261**: 521-526 [PMID: 24950265 DOI: 10.1097/SLA.0000000000000746]

168 **Miyazaki K**, Morine Y, Xu C, Nakasu C, Wada Y, Teraoku H, Yamada S, Saito Y, Ikemoto T, Shimada M, Goel A. Curcumin-Mediated Resistance to Lenvatinib via EGFR Signaling Pathway in Hepatocellular Carcinoma. *Cells* 2023; **12** [PMID: 36831279 DOI: 10.3390/cells12040612]

169 **Simasingha N**, Tanasoontrarat W, Claimon T, Sethasine S. Efficacy of dexamethasone and N-acetylcysteine combination in preventing post-embolization syndrome after transarterial chemoembolization in hepatocellular carcinoma. *World J Gastroenterol* 2023; **29**: 890-903 [PMID: 36816622 DOI: 10.3748/wjg.v29.i5.890]

170 **Yang H**, Seon J, Sung PS, Oh JS, Lee HL, Jang B, Chun HJ, Jang JW, Bae SH, Choi JY, Yoon SK. Dexamethasone Prophylaxis to Alleviate Postembolization Syndrome after Transarterial Chemoembolization for Hepatocellular Carcinoma: A Randomized, Double-Blinded, Placebo-Controlled Study. *J Vasc Interv Radiol* 2017; **28**: 1503-1511.e2 [PMID: 28941589 DOI: 10.1016/j.jvir.2017.07.021]

**Footnotes**

**Conflict-of-interest statement:** All authors declare that they have no conflicts of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** August 21, 2023

**First decision:** September 27, 2023

**Article in press:**

**Specialty type:** Gastroenterology & Hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

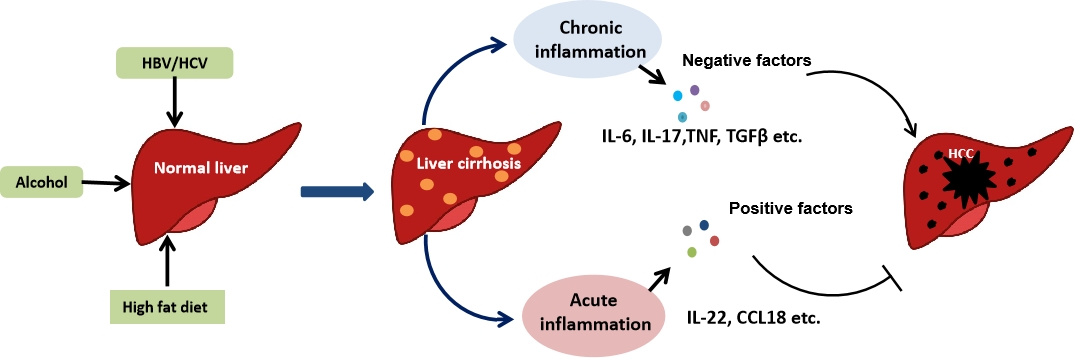
Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Massimi M, Italy; Tsoulfas G, Greece; Yang SS, Taiwan **S-Editor:** Liu JH **L-Editor:** Webster JR **P-Editor:**

**Figure Legends**



**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.

**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.