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REVIEW

Pathogenesis from Inflammation to Cancer in NASH-Derived HCC

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Abstract: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and one of the deadliest cancers worldwide. As opposed to the majority of patients with HCC, approximately 20–30% of cases of non-alcoholic steatohepatitis (NASH)-derived HCC develop malignant tumours in the absence of liver cirrhosis. NASH is characterized by metabolic dysregulation, chronic inflammation and cell death in the liver, which provide a favorable setting for the transformation of inflammation into cancer. This review aims to describe the pathogenesis and the underlying mechanism of the transition from inflammation to cancer in NASH.

Keywords: non-alcoholic steatohepatitis, hepatocellular carcinoma, inflammation to cancer transition, metabolic dysregulation, immune microenvironment

Introduction

Primary liver cancer is the sixth most common cancer and the third leading cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC), an inflammation-associated cancer, accounts for approximately 80% of all primary liver cancers.[1] Chronic inflammation has long been acknowledged as one of the essential hallmarks of tumorigenesis and can lead directly to cancer progression.[2] As early as the 19th century, Rudolf Virchow suggested that cancer arises from inflammation sites by observing leukocytes within cancerous tissues.[3] Accumulating evidence highlights the key role of chronic inflammation in the initiation, progression, invasion, and metastasis of cancer.[4] HCC frequently develops following a multi-step process from chronic inflammation to fibrosis, cirrhosis and carcinoma.[5] The majority of HCC cases occur in the setting of cirrhosis. However, approximately 12% of patients progress into HCC absence of cirrhosis.[6] A systematic review and meta-analysis of nineteen studies with a total of168571participants reported that non-alcoholic steatohepatitis (NASH) was the most common cause of non-cirrhotic HCC.[7] A single center retrospective cross-sectional study showed that 34.6% of NASH-derived HCC patients did not have cirrhosis.[8] The prevalence of NASH has shown a rapid upward trend accompanying the improvement of living standards. Consequently, over the course of 20 years between the periods of 1995–1999 to 2010–2014, the prevalence of NASH-derived HCC also increased from 2.6% to 19.5%.[9] NASH has already become the second leading cause of liver transplantation related to HCC in the United States.[10,11] Therefore, clarifying the exact mechanism of the inflammation-to-cancer transition in NASH is in urgent need. This review provides an in-depth discussion of the pathogenesis underlying the evolution from inflammation to malignancy with the intent to advance the prevention, diagnosis, and treatment of NASH-derived HCC.

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Metabolic Dysregulation Provides a Favorable Pro-Inflammatory Microenvironment for the Transition from Inflammation to Cancer in NASH

The pathogenesis of NASH involves an intricate relationship between a multitude of pathological mechanisms. Among them, insulin resistance (IR), lipotoxicity caused by accumulation of lipids and lipid metabolites, and the infiltration of pro-inflammatory cells are the most vital factors triggering chronic inflammation that leads to hepatocyte injury and progression to HCC (Figure 1).[12,13]

Lipid Metabolism and Insulin Resistance (IR)

The liver is a vital organ involved in lipid homeostasis. Dysregulation of hepatic lipid metabolism, resulting from lipid accumulation and IR, is considered to be a driving force toward NASH-derived HCC. Triglycerides have long been recognized as the predominant lipid accumulation in NASH. In the physiological state, the liver discards fat through oxidation or exporting it as very low-density lipoproteins (VLDLs), and storage fat by shunting excess lipids for the synthesis of triglycerides.[14] However, in chronic energy surplus conditions, adipose tissue could produce cytokines which prevent fatty acids from being absorbed by adipocyte and promote the adipose depots to release fatty acids. In response, the delivery of fatty acids to liver and fuels and hepatocyte triglyceride formation is increased.[14,15] Furthermore, IR also dysregulates the lipid metabolism by suppressing the inhibitory effect of insulin on adipose tissue lipolysis, increasing the flux of free fatty acids (FFAs) from adipocytes to the liver and causing overproduction of VLDLs. This in turn further exacerbates IR and decreases adiponectin synthesis by adipocytes.[16] Importantly, IR causes the liver to be overloaded by glucose and insulin. Hyperglycaemia and hyperinsulinaemia promote hepatic de novo lipogenesis (DNL) by inducing the carbohydrate-response element-binding protein (ChREBP) and sterol regulatory element-binding protein 1c (SREBP-1c), respectively, eventually resulting in lipid accumulation.[17] Subsequently, the

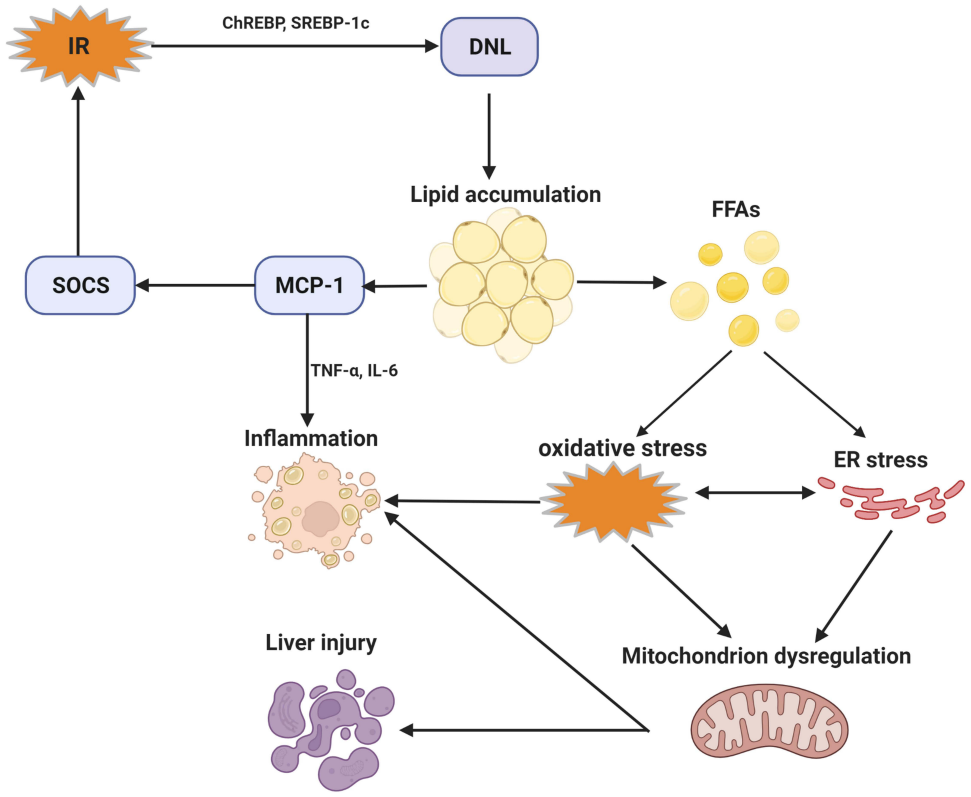

Figure 1 Metabolic dysregulation promotes the progression of inflammation in NASH.
Notes: Excessive accumulation of hepatic lipids and IR are both consequences of metabolic dysregulation. Increased IR and lipid accumulation mutually reinforce each other in NASH, inducing oxidative stress, ER stress, and mitochondrial dysregulation, resulting in inflammation and liver injury.

lipid-overloaded liver would initiate adaptive changes in FFA metabolism, which induces secretion of monocyte chemoattractant protein-1 (MCP-1) into circulation. The circulating monocytes would then be recruited to adipose tissues, followed by activation of macrophages and release of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) -α and interleukin (IL)-6 inducing a chronic inflammation.[17,18] In turn, IR could also be secondary to a chronic inflammation. Several pro-inflammatory cytokines are highly expressed in various tissues in NASH patients, including adipose tissue and the liver. Pro-inflammatory cytokines such as TNF-α and IL-6 have been reported to induce suppressor of cytokine signaling (SOCS) expression via the IKK/NF-κB and JAK/STAT3 signaling pathways, respectively. SOCS can phosphorylate insulin receptor substrates (IRS) 1 and IRS2 to inhibit the IRS1/2-mediated PI3K/Akt signaling pathway and contribute further to IR.[19–21] Furthermore, the TNF-α secreted by macrophage could promote lipolysis and downregulates triglyceride biosynthesis mediated by peroxisome proliferator-activated receptor-γ (PPAR-γ) and triglyceride storage in adipocytes, resulting in fatty acid oxidation, lipolysis, and the accumulation of triglycerides, which aggravates damage to hepatocytes.[22,23]

Free Fatty Acids (FFAs) and Reactive Oxygen Species (ROS)

It is well accepted that the lipid accumulating in patients with NASH mainly exists in the form of triglycerides. However, it has been shown that triglyceride content in hepatocytes is not the primary determinant of lipotoxicity, and that certain lipid classes are damaging to liver cells. Particularly, FFAs such as lysophosphatidylcholine, cholesterol, palmitic acid, and ceramides have emerged as key players in the development and progression of NASH.[24] Increased FFAs and lipid accumulation in hepatocytes induce mitochondrial damage and lead to the production of mitochondrial ROS.[25] The overproduction of ROS can lead to protein and lipid peroxidation, impede β-oxidation, cause mitochondrial damage, and ultimately result in cell death. Lipid peroxidation and oxidative damage to mitochondrial DNA could further diminish mitochondrial function and respiratory chain activity, leading to a reduced capacity for mitochondria to oxidize fatty acids and increase FFA and lipid accumulation, establishing a vicious cycle to exacerbate mitochondrial dysfunction and oxidative stress in NASH.[25–27]

Endoplasmic Reticulum(ER) Stress and Unfolded Protein Response (UPR)

The UPR is comprised of a complex network of interconnected signaling pathways initiated by activation of three major ER transmembrane proteins, inositol-requiring enzyme 1α (IRE1α), protein kinase R-like ER kinase (PERK), and activating transcription factor 6 (ATF6). These proteins are normally controlled by binding to the chaperone protein glucose-regulated protein 78 (GRP78) but could be released under ER stress.[28,29] UPR could activate by ER sensors to assist the cell in responding to the stress and rebalance ER function by underregulating protein translation and promoting protein folding, secretion, and degradation. Lipid accumulation in hepatocytes and consequent oxidative stress could trigger ER stress and activate the UPR. However, during prolonged or overwhelming ER stress due to lipid accumulation and oxidative stress in NASH, the UPR fails to restore ER homoeostasis, and eventually promotes apoptosis.[28,29] Under ER stress, released GRP78 could activate IRE1α, PERK, and ATF6, as well as their downstream signaling pathways, which promotes inflammation, apoptosis, and activity of related factors, including NF-κB, phosphorylation of eukaryotic initiation factor 2α (eIF2α), and expression of ER stress-related genes and proteins such as ATF4, c-Jun N-terminal kinase (JNK), and C/EBP homologous protein (CHOP), as well as the pro-apoptotic B-cell lymphoma-2 (Bcl-2) family member p53 up-regulated modulator of apoptosis (PUMA) and death protein 5 (DP5).[30–32]

Alteration of the Liver Immune Microenvironment Promotes the Transition from Inflammation to Cancer in NASH

Human liver contains a unique immune microenvironment that constitutes of various immune cells, including Kupffer cells (KCs), dendritic cells (DCs), natural killer (NK) cells, T lymphocytes, B lymphocytes, natural killer T (NKT) cells, $CD4^+$ T cells and other immune cells. The maintenance of immune homeostasis requires engaging a necessary immune response to pathogens while tolerating commensal microorganisms and self-antigens.[33–35] Under NASH conditions, various pathobiological factors, including IR, lipid accumulation, ROS, and ER stress, could affect immune cells and

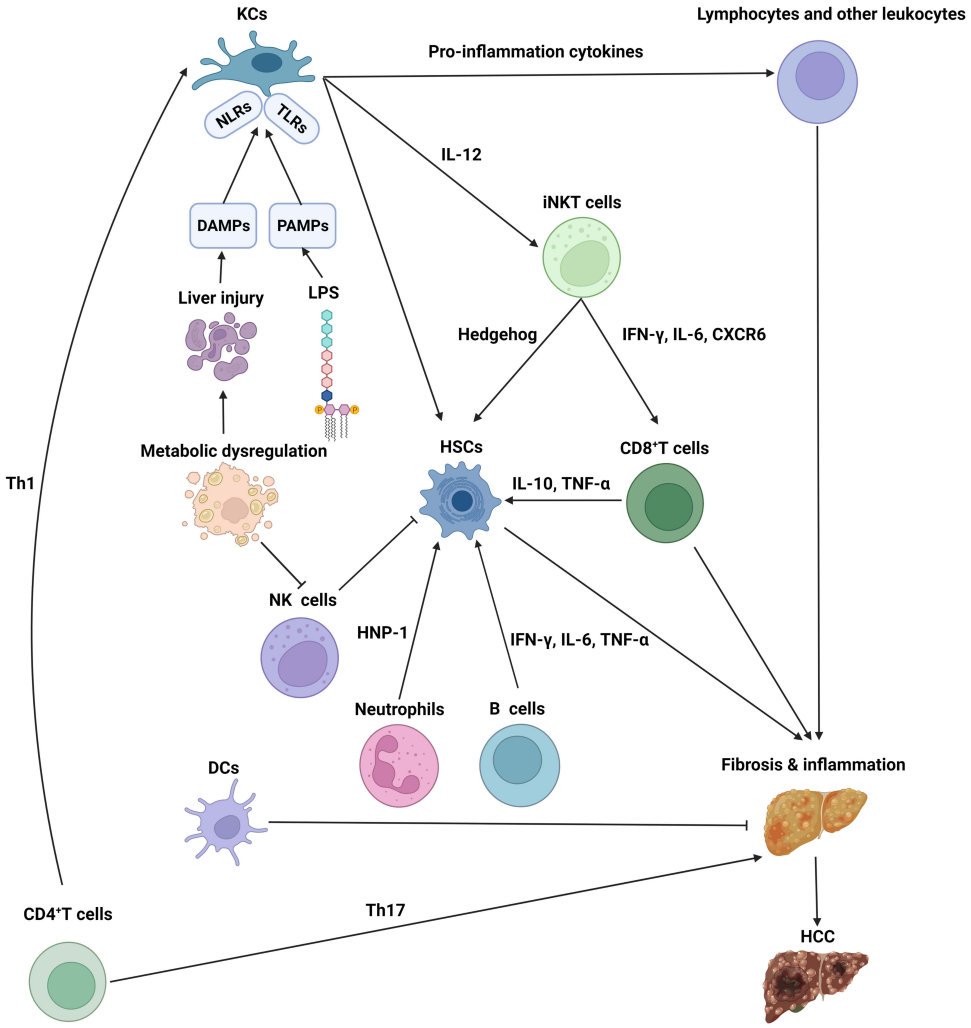

Figure 2 The immune microenvironment of NASH.

Notes: Under NASH conditions, a large number of immune cells are activated and induce the secretion of cytokines and chemokines, which initiates and promote inflammation. Activated immune cells also interact with other cells, especially HSCs, in the immune microenvironment of NASH, to promote fibrosis and inflammation which eventually lead to HCC. $CD4^+$ T cells exposed to a proinflammatory environment in NASH are biased toward Th1 and Th17 subtypes, promote polarization of macrophages into an M1-like proinflammatory phenotype, and contribute directly to the increase in inflammation through the production of inflammatory cytokines. In response to liver injury or LPS in NASH, KCs are activated by DAMPs and PAMPs, which produce cytokines that activate HSCs. iNKT cells, $CD8^+$ T cells, neutrophils, and B cells also contribute to the activation of HSCs. In contrast, NK cells inhibit the activation of HSCs. DCs also play a regulatory role in limiting inflammation and fibrosis. These immune cells play various roles in the immune microenvironment of NASH and can exacerbate NASH, thereby promoting the transition from NASH to HCC.

shape the immune microenvironment in the liver. Alteration of the immune microenvironment then results in chronic inflammation and fibrosis, and could eventually lead to HCC (Figure 2).[35,36]

Kupffer Cells (KCs)

KCs are resident macrophages in the liver, constituting the first line of host-defense against invading particles and microorganisms through robust phagocytic and efferocytic activity. As the liver's largest innate immune population, they play a crucial role in both innate and adaptive immune responses.[37,38] When liver injury occurs in NASH, KCs precede all other innate immune cells in the liver as the first cells to be recruited to sites of damage, and produce a range of cytokines and chemokines which could further recruit and instruct other immune cells for subsequent adaptive responses.[37–39] Normally, a periodic translocation of bacterial products, especially lipopolysaccharide (LPS), occurs through the portal vein from the intestines into the liver and is subsequently scavenged by KCs. In the context of NASH, metabolic dysregulation not only leads to liver injury but also provokes damage to the intestinal mucosal barrier. Enhanced intestinal permeability leads to greater translocation of pathogenic bacteria and LPS, and the subsequent release of various signals such as damage-

associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs).[40,41] Imbalance of M1/M2 KC homeostasis contributes to the occurrence and development of inflammation and fibrosis in NASH. PAMPs, including LPS and other enterogenous bacterial products, bind to Toll-like receptors (TLRs) on KCs, causing the induction of KCs into the classically activated (M1) pro-inflammatory phenotype and the production of inflammatory cytokines and chemokines, such as TNF-α, IL-1β, IL-2, IL-6, IL-10, interferon (IFN)-γ, C-C motif ligand (CCL) 2, and CCL5. These molecules trigger the recruitment of lymphocytes and other leukocytes, and promote the activation of MAPK family signaling pathways, including ERK1/2, p38, and JNK, as well as the activation of NF-κB signaling. The resulting chronic inflammation and activation of hepatic stellate cells (HSCs) eventually lead to liver injury.[42–45] In NASH, sustained liver injury could increase the release of DAMPs, which bind to TLRs and NOD-like receptors (NLRs), causing the assembly of inflammatory corpuscles, activation of the inflammatory response, and further amplification of liver injury, thereby facilitating a vicious circle of inflammation and liver injury.[41,46] Alternatively activated (M2) anti-inflammatory phenotype KCs have the capacity to counteract the proinflammatory functions of M1-like KCs by inducing apoptosis of them, and facilitating wound healing by increasing myofibroblast proliferation and collagen synthesis.[47,48] In the early stages of liver injury in NASH, KCs are pushed towards a M1-like proinflammatory phenotype, followed by polarization of these cells to a M2-like phenotype to promote wound healing. But with the persistence of chronic inflammation in NASH, this may lead to a dysregulated inflammation and tissue repair response that results in fibrillar connective tissue formation, ultimately causing fibrosis and development of protumorigenic properties.[38,48,49]

Hepatic Stellate Cells (HSCs) and Natural Killer Cells (NK Cells)

HSCs account for approximately 10–15% of all hepatic resident cells and reside in the subendothelial space of Disse where they store retinyl esters (vitamin A), cholesteryl esters, and triglycerides in lipid droplets.[50,51] The activation of HSCs is promoted by the recruitment of macrophages and circulating immune cells induced by the lipid accumulation, inflammation, and oxidative stress in NASH, as well as the release of several cellular signaling factors such as transforming growth factor (TGF)-β, TNF-α, IL-1β, and platelet-derived growth factor (PDGF). This leads to the formation of a fibrogenic extracellular matrix and results in hepatic fibrosis, thus hallmarking the transition to a key event in the progression of NASH.[52–54] Activated NK cells are able to kill newly activated and senescent HSCs directly by secreting IFN-γ and activation of NKG2D receptors, tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), and the p38/PI3K/AKT signaling pathway, thereby protecting the liver from an excessive fibrogenic response following tissue damage.[55–57] However, HSCs that are fully activated or fail to become senescent can resist NK cell-mediated killing. HSCs are chronically activated in NASH due to dysregulated senescence. A continuous cycle of hepatocyte death and HSC proliferation causes a surplus of activated HSCs to be produced than can be cleared, resulting in persistent inflammation and further fibrosis. The process may eventually trigger the aberrant proliferation and transformation of damaged hepatocytes, leading to HCC.[58–60]

Dendritic Cells (DCs)

DCs are key antigen-presenting cells in the liver immune microenvironment that initiate and direct the immune response towards antigens while maintaining tolerance to self-antigens, playing a prominent role in bridging innate and adaptive immunity.[61] Unlike immature and tolerogenic conditions in normal homeostatic conditions, hepatic DCs are transformed into a mature proinflammatory subset and produce numerous cytokines upon chronic inflammation in NASH, such as TNF-α and IL-6, promoting the T-cell mediated adaptive immune response and the activation of HSCs.[62,63] Surprisingly, depletion of DCs does not ameliorate disease and instead leads to increased hepatic fibrosis and inflammation in NASH.[64] One explanation for this may be the regulatory role of DCs in NASH, which involves clearance of apoptotic cells and necrotic debris, and the secretion of the anti-inflammatory cytokines, such as IL-10, thereby limiting sterile inflammation and fibrosis.[64–66] Indeed, the dual effects of DCs in NASH need to be further studied.

$CD4^+$ T Cells and Regulatory T (Treg) Cells

T cells are a diverse class of lymphocytes that mainly include $CD4^+$ helper T (Th) cells and $CD8^+$ cytotoxic T (Tc) cells, which play a pivotal role in the development and progression of NASH. It has been shown that T cells-deficient mice fail

to induce steatosis and hepatic inflammation by high fructose-diet fed.[67] $CD4^+$ T cells exposed to a proinflammatory environment in NASH are biased toward Th1 and Th17 subtypes, and worsen NASH. Th1 cells mainly secrete TNF-α, IFN-γ, and IL-2, which play a pro-inflammatory role by promoting the differentiation of immature macrophages into the M1-like pro-inflammatory phenotype.[35,68] Th17 cells mainly secrete IL-17, which increases the levels of phosphatase and tensin homologue deleted on chromosome 10 (PTEN), exacerbates JNK-mediated hepatotoxicity, and inhibits the activation of PI3K/AKT signaling pathway, thereby promoting the progression of hepatic steatosis and inflammation.[69,70] Interestingly, IL-22, a cytokine also produced by Th17 cells, may prevent JNK-mediated hepatotoxicity through the PI3K/AKT signaling pathway. However, the role of IL-22-mediated hepatoprotective activity is weakened in the presence of IL-17.[70,71] It is also worth to note that a recent study found that fibroblast growth factor 21 (FGF21) could attenuate IL-17 secretion by Th17 cells and even hepatocytes through Toll-like receptor 4 (TLR4), thus preventing NASH-HCC transition in DEN+HFMCD mice models.[72] Th17 cells can also produce multiple cytokines, such as CXCL1, CXCL2, CXCL6, and TGF-β, which induce recruitment of neutrophils and lymphocytes toward inflammation sites and activate HSCs, resulting in the progression of inflammation and fibrosis.[73–75] Hepatic Treg cells function as inhibitors of the immune response and are essential in maintaining immune homeostasis. Under chronic inflammation and dysregulated metabolic conditions, the number of Treg cells is markedly decreased due to ROS-induced apoptosis of Treg cells. Imbalance of the Th17/Treg cells ratio in NASH could reduce the immunosuppressive effect of Treg on Th17 cells and encourage inflammation.[76,77] In addition, $CD4^+$ T cells are able to detect and prevent malignant transformation of senescent hepatocytes. However, dysregulation of lipid metabolism in NASH results in selective loss of intrahepatic $CD4^+$ T cells and activation of cellular oncogene c-Fos (c-Fos) /liver X receptorα (LXRα) signaling, thereby accelerating HCC development.[78,79]

NKT Cells and $CD8^+$ T Cells

Unlike conventional T cells that recognize peptide antigens presented by major histocompatibility complex (MHC) molecules, NKT cells are unique lymphocytic sub-lineages that recognize glycolipid antigens presented by CD1d molecules. NKT cells are divided into two subsets based on T cell receptor (TCR) usage: type I NKT (iNKT) cells exclusively express an invariant TCR-α chain, and type II NKT cells express more diverse TCRs.[80,81] iNKT cells predominantly play proinflammatory roles, while type II NKT cells inhibit iNKT cell-mediated pro-inflammatory responses.[82] However, during liver injury in NASH, it is mainly the iNKT cells that are rapidly activated and accumulated, while the role of type II NKT cells is poorly understood due to the lack of specific markers.[83,84] In NASH, iNKT cells activate in an innate-like fashion and secrete inflammatory cytokines such as IFN-γ and IL-4 following recognition of lipid antigens presented by CD1d molecules.[84] Activated iNKT cells can trigger Hedgehog pathway and the secretion of cytokines such as osteopontin, resulting in HSC activation and fibrosis. In addition, activated iNKT cells could cause hepatic cell death directly via the Fas/FasL pathway or indirectly by activating NK cells.[82,85]

There is growing evidence from both human patients and animal models suggesting that $CD8^+$ T cells increase in the liver in NASH.[86–88] In NASH, $CD8^+$ T cells mainly produce cytokines such as TNF-α, IFN-γ, and IL-10, which drive the activation of HSCs and recruitment of macrophages.[88,89] It is interesting to note that $CD8^+$T cells alone may not be sufficient to cause observable liver injury, which would instead require iNKT cells to exert synergistic pro-inflammatory effects.[90] iNKT cells are able to secrete proinflammatory cytokines and chemokines such as IFN-γ, IL-4, and CXCR6, which induce the infiltration of $CD8^+$T cells and the activation of lymphotoxin β-receptor (LTβR) and the NF-κB signaling pathway, thereby promoting the transition from NASH to HCC.[87,90]

B Cells

Although it is limited, accumulating evidence implicates intrahepatic B cells as important participants in the progression of NASH. In NASH, adipocytes would secrete B cell activating factor (BAFF), an adipokine related to impaired insulin sensitivity, which promotes B cell development and maturation.[91,92] Several studies have shown that intrahepatic B cells gather in NASH where they promote the production of proinflammatory cytokines such as TNF-α, IFN-γ, IL-6, and TGF-β, and mediate the activation of T cells, KCs, and HSCs, thus elevating inflammation and fibrosis.[93–95] The level of

Immunoglobulin A (IgA) produced by B cells increases as NASH progresses, which has been shown to be a reliable predictor of fibrosis progression in NASH.[96,97] In addition, IgA^+ B cells and plasma cells can express high levels of programmed death-ligand 1 (PD-L1), IL-10, and TGF-β, which directly induce $CD8^+$T cell exhaustion and suppress their IFN-γ production and anti-tumor cytotoxicity, favoring the inflammation-to-cancer transition in NASH.[98,99]

Neutrophils

Infiltration of neutrophils is among the main characteristics of NASH and contributes to its progression through the production of cytokines, ROS, and neutrophil extracellular traps (NETs).[100,101] It has been shown that mice deficient of neutrophils or neutrophil effector molecules, such as proteases, elastase, and myeloperoxidase, were protected from diet-induced NASH.[102–104] Neutrophil-derived human neutrophil peptide (HNP)-1 induces the proliferation of HSCs, which leads to fibrosis and exacerbates NASH.[105] In addition, recent studies have shown that neutrophils are stimulated to form NETs in NASH, and inhibiting their release upon neutrophil cell death (NETosis) blocks macrophage infiltration, inflammatory cytokine production, and the transition from NASH to HCC.[106,107]

Therapeutic Perspective and Discussion

It is well known that cirrhosis is the precursor lesion for most instances of HCC and is the most common risk factor for HCC. However, approximately 20–30% of cases of NASH-derived HCC occur in the absence of cirrhosis.[7,108] The progression from NASH to HCC is a continuous process, which is affected by various factors, such as lipid accumulation, IR, oxidative stress, and alteration of the liver immune microenvironment. These factors culminate in a state of chronic inflammation in NASH. Inflammation-mediated cellular effectors and molecular mediators are important components of the tumor microenvironment.[109] It is currently believed that early inflammation has a beneficial effect by limiting tissue damage and promoting repair, but the chronic and persistent inflammatory state in NASH could be deleterious. The collaborative participation of various immune cells, oxidative stress, chronic liver injury, and inflammatory responses within the unique NASH immune microenvironment supports the continuous proliferation and expansion of pre-neoplastic cells, eventually leading to the transition from NASH to HCC.[110,111] Thus, NASH itself becomes a risk factor for HCC, even in the absence of cirrhosis.

NASH's microenvironment has been extensively studied, but the transition from inflammation to cancer in NASH has received insufficient attention. It is therefore urgent to develop an experimental model for identifying the transition from NASH to HCC, which should recapitulate the systemic metabolic and inflammatory microenvironment by increasing dyslipidemia and inflammatory cytokines. While a large number of models of NASH have been described, such as methionine and choline deficient diet model, choline-deficient L-amino-defined diet model, fructose and cholesterol diet model, high fat high sugar diet model, leptin deficiency (ob/ob mice) model, and leptin receptor deficiency (db/db mice) model.[112–114] These models have several limitations, including the necessity of non-physiological dietary manipulations, or the lack of insulin resistance or liver histology characteristic of NASH in humans, and rarely developed advanced fibrosis and do not lead to HCC.[112–114] Recently, an isogenic B6/129 hybrid strain of genetically modified mice was fed a western diet with a high-fructose-sugar solution and described as a new animal NASH-derived HCC model that faithfully recapitulates the progression of the human disease, and is expected to become a pre-clinical model in the transition from inflammation to cancer in NASH research.[114]

The annually increasing incidence of NASH-derived HCC implicates it as one of the leading causes of HCC in western countries.[8–10] Therefore, the primary risk factors for NASH, including IR, obesity, metabolic syndrome, and chronic inflammation, are also likely to be emerging risk factors for HCC. However, there are few studies on risk stratification in patients with these potential risk factors and minimal prevention and control strategies specifically targeting NASH-derived HCC.[115] As of now, weight loss through therapeutic lifestyle changes remains the only evidence-based means of preventing or delaying the transition from NASH to HCC, as there are no Food and Drug Administration (FDA)-approved medications for this condition.[116,117] Several drugs, such as aspirin, metformin, pioglitazone, and statins, have been shown to modulate risk factors and carcinogenic pathways in NASH-derived HCC, suggesting their potential to be included in prevention strategies.[118–122] However, several serious side effects, such as increased risk of bleeding from aspirin and bladder cancer from pioglitazone, may limit their use for long-term

prevention.[123,124] While metformin and statins have been suggested to be effective in reducing NASH-derived HCC risk, either they have little impact on liver histology or no convincing histological data are available.[125] As a result, metformin and statins are not recommended by the European Association for the Study of the Liver (EASL) or the American Association for the Study of Liver Diseases (AASLD) as a treatment for NASH, and the relevant effects of metformin and statins on NASH-derived HCC prevention still need to be ascertained through large, well-designed, randomized controlled trials.[126,127] Since various immune cells can trigger the secretion of proinflammatory molecules that facilitate NASH-derived HCC development, targeting pro-inflammatory cytokines may be a beneficial strategy to impede the transition from NASH to HCC.[128] Studies showed that Thalidomide and Infliximab, an anti-TNFα drug, alleviated inflammation, necrosis, and fibrosis in an experimental rat model of NASH.[129,130] Galunisertib (LY2157299), a TGF-β inhibitor, could inhibit SMAD2 phosphorylation and blocks collagens deposition, thus preventing fibrosis and NASH progression.[131] As a dual antagonist of chemokine receptor types 2 (CCR2) and 5 (CCR5), Cetiniriviroc hinders overactive inflammation and disrupts the activation of stellate cells, thereby targeting both inflammation and fibrogenesis in NASH.[132] Although these results are encouraging, their effects in human are controversial.[128] Immunotherapy has also shown potential therapeutic value for HCC in recent years.[133–135] However, recent study revealed that NASH-derived HCC might respond poorly to immunotherapy, owing to NASH-related aberrant T cell activation that leads to normal tissue damage.[136] Currently, there is still a lack of effective treatment for NASH and its derived HCC. Considering the complex pathophysiology of NASH, one targeted treatment may not suffice and that a combination of therapies targeting inflammation and metabolism might be the rational direction for treating NASH and its derived HCC.[137] However, there is still extensive research to be delivered to better understanding the complex mechanism behind inflammation–cancer transition. Furthermore, more clinical studies need to be conducted to better identify patients with inflammatory conditions that will respond to a specific therapy. Therefore, it is of great practical significance to reinforce our understanding of the mechanism underlying the transition from inflammation to cancer in NASH and pave the road towards individualized prevention, monitoring, and treatment strategies targeting NASH-derived HCC.

Abbreviations

HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; IR, insulin resistance; VLDLs, very low-density lipoproteins; FFAs, free fatty acids; DNL, de novo lipogenesis; ChREBP, carbohydrate-response element-binding protein; SREBP-1c, sterol regulatory element-binding protein 1c; MCP-1, monocyte chemoattractant protein-1; TNF, tumor necrosis factor; IL, interleukin; SOCS, suppressor of cytokine signaling; IRS, insulin receptor substrates; PPAR-γ, peroxisome proliferator-activated receptor-γ; ROS, reactive oxygen species; ER, endoplasmic reticulum; UPR, unfolded protein response; IRE1α, inositol-requiring enzyme 1α; PERK, protein kinase R-like endoplasmic reticulum kinase; ATF6, activating transcription factor 6; GRP78, glucose-regulated protein 78; eIF2α, eukaryotic initiation factor 2α; JNK, c-Jun N-terminal kinase; CHOP, C/EBP homologous protein; Bcl-2, B-cell lymphoma-2; PUMA, p53 up-regulated modulator of apoptosis; DP5, death protein 5; KCs, Kupffer cells; DCs, dendritic cells; NK, natural killer; NKT, natural killer T; LPS, lipopolysaccharide; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; TLRs, Toll-like receptors; IFN, interferon; CCL, C-C motif ligand; HSCs, hepatic stellate cells; NLRs, NOD-like receptors; TGF, transforming growth factor; PDGF, platelet-derived growth factor; TRAIL, tumor necrosis factor–related apoptosis-inducing ligand; Treg, regulatory T; Th, CD4+ helper T; Tc, CD8+ cytotoxic T; PTEN, phosphatase and tensin homologue deleted on chromosome 10; FGF21, fibroblast growth factor 21; TLR4, Toll-like receptor 4; c-Fos, cellular oncogene c-Fos; LXRα, liver X receptorα; MHC, major histocompatibility complex; TCR, T cell receptor; iNKT, type I NKT; LTβR, lymphotoxin β-receptor; BAFF, B cell activating factor; IgA, Immunoglobulin A; PD-L1, programmed death-ligand 1; NETs, neutrophil extracellular traps; HNP, human neutrophil peptide; FDA, Food and Drug Administration; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; CCR, chemokine receptor.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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