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Inflammation and Liver Cancer: Molecular Mechanisms and Therapeutic Targets

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Abstract

Hepatocellular carcinoma (HCC) is associated with chronic inflammation and fibrosis arising from different etiologies, including hepatitis B and C and alcoholic and nonalcoholic fatty liver diseases. The inflammatory cytokines tumor necrosis factor-α and interleukin-6 and their downstream targets nuclear factor kappa B (NF-κB), c-Jun N-terminal kinase (JNK), and signal transducer and activator of transcription 3 drive inflammation-associated HCC. Further, while adaptive immunity promotes immune surveillance to eradicate early HCC, adaptive immune cells, such as $CD8^+$ T cells, Th17 cells, and B cells, can also stimulate HCC development. Thus, the role of the hepatic immune system in HCC development is a highly complex topic. This review highlights the role of cytokine signals, NF-κB, JNK, innate and adaptive immunity, and hepatic stellate cells in HCC and discusses whether these pathways could be therapeutic targets. The authors will also discuss cholangiocarcinoma and liver metastasis because biliary inflammation and tumor-associated stroma are essential for cholangiocarcinoma development and because primary tumor-derived inflammatory mediators promote the formation of a “premetastasis niche” in the liver.

Keywords

NF-κB; apoptosis; hepatic stellate cells; ER stress; immune checkpoint inhibitor

Primary liver cancer encompasses hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and other types of liver cancer. Approximately 70 to 80% of cases are HCC and 15% are CCA.[1] The American Cancer Society estimates that 42,220 new cases of primary liver cancer will be diagnosed and 30,200 patients with liver cancer will die in 2018.[1] Patients with liver cancer are often asymptomatic in early stages and do not present with typical liver symptoms, such as jaundice, liver failure, and ascites, until they progress to advanced stages. Risk factors for HCC include hepatitis B (HBV) or C (HCV) virus infection, alcohol abuse, and fatty liver.[2,3] In Western countries, nonalcoholic fatty liver disease (NAFLD), a hepatic manifestation of metabolic syndrome, is one of the most common liver disease promoting HCC developoment.[4]

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Liver is constantly exposed to food antigens and low-dose endotoxins from the intestine. Accordingly, liver is highly tolerogenic, preventing unfavorable immune responses to physiological gut-derived substances.[5] This tolerogenic environment also contributes to the spontaneous acceptance of liver allografts in patients with liver transplantation. By con trast, the liver has self-defense mechanisms mediated by hepatic immune cells, including high numbers of natural killer (NK) and NKT cells, γδ T cells, and liver-resident macrophages (Kupffer cells).[6] These immune cells patrol the liver and promote the eradication of harmful substances, including exogenous pathogens and their products and food-derived poisons from the intestine. Hepatic immune cells also eliminate precancerous or early cancerous cells. However, insults, such as hepatitis virus infection, chronic alcohol abuse, and lipid accumulation, disrupt the tightly regulated hepatic immune system and induce harmful liver inflammation.

Chronic liver inflammation damages hepatic epithelial cells, including hepatocytes and biliaryepithelial cells. Because liver has a high regenerative capacity, this damage induces substantial cell proliferation. Simultaneously, inflammation induces reactive oxygen species (ROS) and deoxyribonucleic acid (DNA) damage, increasing the frequency of genomic DNA mutations. When the high rate of cell proliferation is coupled with DNA mutation, the incidence of malignant transformation increases. Further, chronic inflammation induces changes in the hepatic immune system, allowing cancer cells to easily evade immune surveillance. These changes include a decrease in the ratio of M1/M2 tumor-associated macrophages, the infiltration of myeloid-derived suppressor cells (MDSCs), the production of protumorigenic cytokines, the deregulation of the senescence-associated secretome, and the translocation of gut-derived metabolites and pathogens to the liver. Inflammation of biliary system is associated with CCA initiation and progression. Accordingly, several sources of biliary inflammation, including primary sclerosing cholangitis (PSC), liver fluke infection, and specific chemical exposure, are risk factors for CCA.[3,7] While the underlying molecular mechanisms of the etiologies vary, in most cases, chronic liver inflammation and the resultant cirrhotic microenvironment promote the initiation and progression of HCC and CCA.

Recent cohort studies have suggested that fatty or fibrotic liver increases the recurrence of colorectal cancer liver metastasis after curative resection,[8, 9]which contradicts earlier studies suggesting that the reduced hepatic blood flow in cirrhotic patients lowered metastatic incidence. Other recent studies indicate that the hepatic premetastatic niche is enhanced by underlying liver diseases or mediators secreted by primary cancers.[10,11]

This review highlights the inflammation-associated molecular signals involved in liver cancer. We will discuss the preclinical research and the translational implications for liver cancer. The in vivo mouse models described in this review are summarized in Table 1.

Inflammation Mediates HCC Development

Hepatocellular carcinoma is the fifth most common cancer type and the third leading cause of cancer-related death worldwide.[12] Approximately 80 to 90% of HCC cases have underlying cirrhosis caused by chronic liver inflammation.[13] The primary trigger for

inflammation that is associated with hepatocarcinogenesis is epithelial cell death. Presented below are the pathways, including cytokine signaling (tumor necrosis factor [TNF]-α, interleukin [IL]-6, nuclear factor kappa B [NF-κB], c-Jun N-terminal kinase [JNK], signal transducer and activator of transcription 3 [STAT3]), innate immune signaling, and adaptive immunity, that contribute to inflammation-mediated hepatocarcinogenesis.

NF-κB and JNK Contribute to Hepatocarcinogenesis through Liver Inflammation, Hepatocyte Death, and Compensatory Proliferation

TNFα is one of the best-characterized protumorigenic cytokines in hepatocarcinogenesis. It activates both the NF-κB and JNK signaling pathways (Fig. 1).[13,14] In experiments with TNF receptor type I (TNFRI)$^{-/-}$ mice, TNFRI knockout did not reduce diethylnitrosamine (DEN)-induced HCC, but did suppress high-fat diet (HFD)-promoted DEN-induced HCC, lymphotoxin α/β overexpression-induced HCC, and hepatocyte-specific transforming growth factor beta-activated kinase 1 (TAK1)-deletion-induced HCC.[15–17] NF-κB has dual functions in hepatocarcinogenesis. NF-κB-induced inflammation is known to promote tumorigenesis. In Mdr2$^{-/-}$ mice or mice overexpressing lymphotoxin α/β, inflammation-mediated HCC was suppressed by NF-κB inhibition.[16,18] Similarly, in a hepatocytespecific cylindromatosis-deficient (CYLD$^{\Delta hep}$) mouse model, which typically has increased hepatocyte TAK1 and NF-κB activation, TAK1 deletion decreased HCC development.[19] By contrast, basal NF-κB activity in hepatocytes prevents hepatocarcinogenesis by inhibiting hepatocyte apoptosis. In liver, hepatocyte apoptosis is coupled with compensatory proliferation, increasing the incidence of oncogenic mutations, which paradoxically induces hepatocarcinogenesis. For example, IκB kinase (IKK)β$^{\Delta hep}$ mice, which have reduced hepatocyte NF-κB activation, demonstrated enhanced hepatocyte apoptosis and compensatory proliferation, predisposing them to DEN-induced HCC.[20] Likewise, NF-κ-B essential modulator (NEMO)$^{\Delta hep}$ mice and TAK1$^{\Delta hep}$ mice, which lack hepatocyte NF-κB activation, spontaneously developed HCC.[21–23] Deletion of Fas-associated protein with death domain or caspase-8 in NEMO$^{\Delta hep}$ mice and TAK1$^{\Delta hep}$ mice reduced HCC development, underscoring that the antiapoptotic function of NF-κB can prevent HCC development by inhibiting compensatory proliferation.[21,24,25]

In addition to NF-κB, IKK and NEMO can regulate hepatocyte apoptosis through receptor-interacting protein kinase 1 (RIPK1). Recent studies of RIPK1 revealed multiple functions in hepatocyte death and HCC development. RIPK1 mediates apoptosis and HCC development via its kinase activity, which is suppressed by NEMO.[26] Inactivation of RIPK1 kinase activity suppressed spontaneous HCC development in NEMO$^{\Delta hep}$ mice.[26] By contrast, RIPK1 can prevent apoptosis and HCC through its scaffold function in NEMO$^{\Delta hep}$ mice.[26] However, RIPK1$^{\Delta hep}$ mice do not have a spontaneous HCC phenotype, suggesting that RIPK1 activity is not needed to maintain liver homeostasis.[26,27] A recent study revealed that TNF receptor-associated factor 2 (TRAF2) participates in the RIPK1 scaffold function that prevents spontaneous hepatocyte apoptosis and HCC in mice. This study also showed that HCC patients with low expression of RIPK1 and TRAF2 had a worse prognosis.[27] This finding suggests that RIPK1 and TRAF2 have an antihepatocarcinogenic effect.

JNK1 and JNK2 isoforms are expressed in liver. JNK1 but not JNK2 has been reported to promote tumorigenesis. The protumorigenic function of JNK1 was initially determined through its ability to induce apoptosis and compensatory proliferation in wild-type and IKKβ$^{\Delta hep}$ mice with DEN-induced HCC.[21,28] JNK1 also mediates HCC proliferation through p21 downregulation and c-Myc upregulation.[29] Recent studies showed that caspase-8-depenent apoptosis activated JNK in TAK1$^{\Delta hep}$ mice and RIPK1$^{\Delta hep}$ mice, which promoted hepatocyte proliferation (Fig. 1).[24,27] This result suggests that JNK is activated by hepatocyte apoptosis rather than promoting apoptosis. Several studies examined cell-specific functions of JNK and demonstrated a paradoxical role of JNK in HCC. Mice with whole-body JNK1 and JNK2 knockouts exhibited reduced DEN-induced HCC, increased p21 expression, and decreased c-Myc expression.[30] Surprisingly, JNK1$^{\Delta hep}$/JNK2$^{-/-}$ mice exhibited increased DEN-induced HCC and c-Myc expression.[30] In NEMO$^{\Delta hep}$ mice, JNK1 knockout increased spontaneous HCC.[31] In this model, JNK1 expressed in hematopoietic cells was relatively important for HCC development.[31] These findings suggest that JNK promotes HCC development by inducing an inflammatory environment and hepatocyte proliferation. Conversely, JNK expressed by hematopoietic cells and hepatocytes also have an antitumorigenic function.[30,31] Collectively, the TNFα, NF-κB, and JNK pathways can have either prosurvival or cell death functions, both of which can enhance HCC development. Therefore, HCC treatment strategies involving the inhibition of proinflammatory NF-κB and JNK should probably avoid excessive inhibition to prevent paradoxical HCC induction.

IL-6 and STAT3 Promote HCC Development

IL-6-mediated STAT3 activation is a major driver of hepatocyte repair and replication, which promotes hepatocarcino-genesis (Fig. 2).[13,14] Increased IL-6 levels and overactivated STAT3 have been observed in HCC patients.[32] Similarly, IL-6 and hepatocyte STAT3 activation promote DEN-induced HCC in mice.[33–35] In the DEN-induced mouse model and in TAK1$^{\Delta hep}$ mice, autocrine IL-6 production is required for the growth and malignant transformation of HCC progenitor cells (HcPCs), which give rise to HCC.[36] Once HCC has developed, paracrine IL-6 production from Kupffer cells plays a dominant role in HCC growth.[33] STAT3 is also activated by IL-22, which is produced by Th17 cells. In human HCC, IL-22 is overexpressed. Like IL-6, IL-22 promotes DEN-induced mouse HCC through STAT3 signaling.[37] STAT3 can also be activated by IL-17, but the contribution of IL-17 to HCC growth is IL-6 dependent.[38,39] These data implicate that IL-6 and STAT3 promote hepatocarcinogenesis and suggest that these proteins may be favorable targets for HCC therapy.

IL-6 is a Determinant of Gender Disparity for HCC Development

Seventy-three percent of HCC cases occur in men, and there is an association between sex hormones and IL-6 signaling in HCC development.[3] Estrogen receptor α and its coactivator NCOA5 cooperatively repress IL-6 production at the transcriptional level in Kupffer cells (Fig. 2).[33,40] As such, in DEN-induced HCC mouse models, IL-6 levels were higher in males than in females. Additionally, impairing estrogen receptor α-mediated repression in male mice with NCOA5 haploinsufficiency increased IL-6 levels, resulting in HCC development.[40] Conversely, IL-6 upregulated androgen receptor (AR) in HCC cells.[40] AR-

expressing HCC cells showed reduced expression of the tumor suppressor p53 and increased ROS production compared with AR-inactivated cells. Similarly, $AR^{\Delta hep}$ mice exhibited less DEN-induced HCC.[41] AR also promoted HBV-mediated HCC by enhancing HBV replication.[42] Thus, IL-6 plays an important role in the gender disparity in HCC prevalence.

Toll-Like Receptors and Damage-Associated Molecules Mediate HCC Development

Many studies suggest that activation of innate immune receptors, such as Toll-like receptors (TLRs), plays a role in hepatocarcinogenesis because IL-6 is induced through MyD88, a universal adaptor molecule for TLRs.[33,43] In HCC patients, TLR4 and TLR9 are overexpressed and associated with a poor prognosis.[44] Because the gut and the liver are linked anatomically through the portal vein, the liver is exposed to intestine-derived microbial products that activate hepatic TLRs. Lipopolysaccharide (LPS), a Gram-negative bacterial cell-wall component, is a ligand for TLR4.[43]

TLR4 plays a prominent role in HCC development. TLR4 knockout reduced the HCC burden compared with control mice in a DEN plus CCl_4 fibrosis-associated HCC mouse model and in $TAK1^{\Delta hep}$ mice and $PTEN^{\Delta hep}$ mice.[17,45,46] HCC burden reduced when gut-derived LPS was depleted by orally administering nonabsorbable antibiotics in the DEN plus CCl_4 model and in $PTEN^{\Delta hep}$ mice.[45,46] Continuous low-dose administration of LPS enhanced HCC development, whereas germ-free conditions decreased it.[45] These findings suggest that TLR4 and gut-derived LPS make an essential contribution to HCC development. Studies also determined the cells responsible for expressing TLR4 using bone marrowchimeric mice. In $PTEN^{\Delta hep}$ mice that developed nonalcoholic steatohepatitis (NASH)-associated HCC, bone marrow-derived TLR4 played an important role in HCC development.[46] Another report demonstrated that hepatic stellate cell (HSC)-derived tenascin C contributes to obesity-promoted HCC through TLR4 expressed by liver macrophages and hepatocytes.[47] Macrophage-expressed TLR4 could conceivably play a dominant role in NASH-associated HCC. By contrast, in the DEN plus CCl_4 model, TLR4 expressed by resident liver cells (including hepatocytes and HSCs) plays a greater role in HCC developmentcompared with that expressed by bone marrow-derived cells.[45] Specifically, HSCs produce epiregulin in a TLR4-mediated NF-κB-dependent manner, and epiregulin drives HCC development in the DEN plus CCl_4 model.[45]

The DEN plus CCl_4 model did not show that TLR9 contributes to HCC development;[48] however, TLR9 plays a significant role in HCC development in $TAK1^{\Delta hep}$ mice and hypoxia-mediated HCC growth.[17,49,50] This finding is unsur prising given the diverse mechanisms of HCC development in humans. Accordingly, different mouse HCC models should have similarly diverse and distinct molecular mechanisms.

With respected to damage-associated molecular patterns, in human HCC, high mobility group box 1 (HMGB1), a nuclear protein and endogenous ligand of TLR4 and receptor for advanced glycation end products (RAGE), is overexpressed and translocated to the cytosol.[51] Hypoxia, a prominent feature of all cancers, induces HMGB1 to translocate from nucleus to the cytosol and activate caspase-1 via TLR4 and RAGE, promoting HCC invasion and metastasis.[50,51] Hypoxia-induced HMGB1 translocation contributes to p38 activation and PGC1α-mediated mitochondrial biogenesis through TLR9.[50] In HCC cells, HMGB1 loss

causes mitochondrial dysfunction and reduces mitochondrial biogenesis and the ability to adapt to hypoxic conditions. In hypoxic HCC cells, TLR9 is overexpressed and is activated by HMGB1 bound to mitochondrial DNA.[49] HMGB1 also induces hypoxia-inducible factor 1-α-dependent aerobic glycolysis via YAP, promoting HCC cell growth.[52] In the DEN-induced HCC model, hepatocyte HMGB1 expression is required for the early stage but not in the late stage of HCC development.[50,52] Similarly, hepatocyte HMGB1 expression is crucial for HCC development in fibrosis-associated HCC models, such as the DEN plus CCl_4 model, the DEN plus 3,5-diethoxycarbonyl-1,4-dihydrocollidine-diet model, and $TAK1^{\Delta hep}$ mice, and hepatocyte RAGE expression is also crucial in the DEN plus CCL_4 model.[48] While hepatocyte HMGB1 expression did not play a role in fibrosis development in these models, it was crucial for ductular cell/progenitor cell proliferation.[48] HMGB1 bioactivity depends on its posttranscriptional modifications. Disulfide HMGB1 is proinflamma-tory and promotes ductular cell/hepatic progenitor cell proliferation in a RAGE-dependent and ERK- and CREB-phosphorylation-dependent manner.[48] Under autophagydeficient conditions, hepatocyte HMGB1 is also crucial for liver tumor development. NRF2 and caspase-11/caspase-1/gasdermin D activation are required for HMGB1 translocation.[53] This finding is clinically relevant because hepatocyte autophagy is diminished in advanced NAFLD and aged individuals, suggesting that autophagy deficiency-related HMGB1 translocation could be a mechanism for the development of NAFLD-associated HCC. Cold-inducible ribonucleic acid (RNA)-binding protein, another damage-associated molecule for TLR4, also can promote HCC development, likely through ROS production and cancer stem cell regulation.[54,55]

Alcohol intake and obesity increase the risk of HCV-mediated HCC. Mice with HCV-NS5A overexpression showed upregulation of hepatocyte TLR4, and additional alcohol exposure or a feeding a HFD enhanced HCC development via Nanog.[56,57] TLR4-Nanog signaling induced YAP and IGF2BP3, which suppressed the transforming growth factor (TGF)-β tumor suppressor function in HCC-initiating stem-like cells, suggesting that TLR4 promotes HCC initiation by suppressing TGF-β signaling.[58] The TLR4-Nanog pathway, in conjunction with the leptin-STAT3 axis, contributes to HCC initiation by promoting the Twist-mediated epithelialmesenchymal transition.[57] The TLR4-Nanog signaling can also repress mitochondrial respiration and enhance fatty acid oxidation, promoting HCC-initiating cell expansion and chemoresistance.[59] These studies revealed that TLR4 and its exogenous and endogenous ligands promote HCC development through multiple mechanisms. Therefore, inhibition of TLR signaling or HMGB1 function could be viable therapeutic approaches for HCC. However, anticancer strategies involving TLR activation to enhance tumor immunity have also been considered (discussed below).

The Intestinal Microbiome Contributes to HCC Development

The gut microbiome contributes to HCC development through both microbial product exposure (discussed above) and changes in microbial composition. A HFD alters the composition of gut microbiome.[60] Dysbiosis of the gut microbiome leads to the conversion of dietary choline into methylamines, which decreases plasma phosphatidylcholine and lipid transport from hepatocytes[61] and could augment chronic liver injury. The contributions of secondary bile acids and the gut microbiome in obesity-associated HCC has been discussed

previously.[60] Mice administered 7,12-dimethylbenz(a)anthracene, a chemical carcinogen that induces Ras mutation, developed HCC only when fed a HFD. A HFD increased the number of Gram-positive *Clostridium* in the intestine, which increased levels of circulating deoxycholic acids, inducing HSC senescence and senescence-associated secretory phenotype (SASP)-mediated HCC development.[60] Increased intestinal *Clostridium promoted* HCC development through TLR2.[60]

Intestinal *Clostridium* species regulate primary-to-secondary bile acid conversion. Ma et al recently reported that altered bile acid metabolism contributes to antitumor surveillance via NKT cells.[62] Primary bile acids increased and secondary bile acids decreased CXCL16 levels in liver sinusoidal endothelial cells. Increased levels of CXCL16, a ligand of CXCR6, accumulated $CXCR6^+$NKT cells to the liver and inhibited HCC growth. Taken together, alterations in the microbiome and gut–liver derangements can lead to hepatocarcinogenesis.

Adaptive Immunity has Anti- and Protumorigenic Roles in HCC

Ideally, nascent tumor cells are surveilled by the immune system and destroyed. Innate immune cells, such as macrophages, dendriticcells (DCs), and NK cells, are thefirst-linehost defense. Innate immune cells monitor external and internal pathogens and tumors, both directly and indirectly in conjunction with adaptive immune T and B cells. The antitumorigenic role of T cells is facilitated through immune surveillance by $CD4^+$T and $CD8^+$T cells. In NAFLD-promoted HCC, increased levels of linoleic acid, a dominant fatty acid in NAFLD, induced mitochondrial ROS production, promoting $CD4^+$T cell depletion and impairing tumor surveillance (Fig. 3).[63] Cytotoxic $CD8^+$T cells can be activated by $CD103^+$DC-mediated cross-presentation of tumor antigens, enhancing tumor immunity.[64] Bycontrast, studies have reported protumorigenic functions of $CD8^+$T, NKT, and Th17 cells. In mice fed a long-term cholinedeficient HFD, infiltration of $CD8^+$T cells and NKT cells in the liver promoted NAFLD-associated HCC; LIGHT, lymphotoxin, and NF-κB played roles in this process (Fig. 3). The cholinedeficient HFD also induced intrahepatic Th17 cell infiltration and IL-17A production.[65] Liver-derived IL-17A production affected peripheral adipose tissues, promoting insulin resistance and fatty acid release to the liver and eventually inducing NAFLD HCC. A study using a different inflammation-mediated HCC mouse model corroborated the protumorigenic functions of $CD8^+$T cells and lymphotoxin-β.[66] The role of B cells in HCC development is paradoxical. Depletion of B cells by an anti-CD20 antibody in a syngeneic HCC mouse model or inactivation of B cells in Hras12V Tg mice using a Bruton's kinase inhibitor enhanced HCC growth.[67,68] By contrast, an $Mdr2^{-/-}$ mouse model of HCC, mice treated with anti-CD20 antibody and B cell-deficient mice showed reduced inflammation-associated HCC.[69]

Levels of immunoglobulin A (IgA)-producing plasma cells converted from IgM-producing B cells were increased in human NASH livers and in mouse models of NASH-promoted HCC, including HFD-fed major urinary protein-urokinase type plasminogen activator (MUP-uPA) mice and HFD-fed streptozotocin-treated mice, but not in the HFD plus DEN model of HCC.[70] These IgA^+ cells expressed programmed death ligand 1 and IL-10 and suppressed antitumorigenic cytotoxic $CD8^+$T cells, promoting NASH-associated HCC. In

HFD-fed MUP-uPA mice, Th17 cells, regulatory T cells, and T follicular helper cells were increased and $CD4^+$T cells were decreased.

At sites of chronic inflammation, leukocytes accumulate and often form a functional immune microarchitecture, called “ectopic lymphoid-like structures (ELSs).”[71] While tumor-associated ELSs are associated with better prognosis in other cancer types, hepatic ELSs correlate with poor prognosis in HCC. The formation of hepatic ELSs is promoted by hepatocyte NF-κB activation and diminished by T cell ablation. These data suggested that adaptive immune cells play a significant role in HCC development, and that their roles are context and stage dependent.

Hepatic Stellate Cells are Components of the Tumor Microenvironment in HCC

Fibrosis is a significant risk factor for HCC. HSCs are collagen-producing cells involvedin fibrosispathogenesis.HSCs infiltrate tumors with immune cells, such as macrophages and monocytes, to form the tumor microenvironment, which promotes HCC development.[72–74] HSCs can shift macrophages and monocytes from an inflammatory (M1) to an immunosuppressive signature (M2), which promotes tumor progression.[74] Additionally, HSCs assist the escape of tumor cells from immune surveillance by increasing immunosuppressive cell populations of regulatory T cells and MDSCs.[75–78] The role of M1/M2 and MDSCs in cancer development have been reviewed in detail previously.[79,80]

The role of HSC-mediated SASP in hepatocarcinogenesis has been investigated. One senescence program is regulated by the p53 tumor suppressor, which controls SASP of HSCs.[81–83] p53-expressing senescent HSCs produce IL-6, interferon (IFNγ), and intercellular adhesion molecule 1, whereas p53-deficient proliferating HSCs secreted IL-3, −4, and −5.[83] p53-altered SASP affects macrophage polarization because p53 activation in HSCs triggers M2 (tumor-promoting)-to-M1 (tumor-suppressing) polarization, suppressing HCC development.[83] By contrast, the obesity-associated senescence secretome provokes HCC by secreting inflamma-tory and tumor-promoting factors.[60] In that study, SASP was induced in HSCs, and the obesity-induced microbial meta-bolite deoxycholic acids played a role.[60] Another study demonstrated that the cytoplasmic DNA-sensing pathway affected cellular senescence and SASP. In healthy cells, cytoplasmic DNases degrade cytoplasmic DNA, thereby restricting DNA to nuclei and mitochondria.[84] In senescent HSCs, DNase expression is diminished.[85] The nuclear DNA accumulating in the cytoplasm activates the cytoplasmic DNA-sensing pathway, stimulating cGAS-STING cytoplasmic DNA sensors, which enhances SASP. Thus, inhibiting this pathway prevented SASP in senescent HSCs, and attenuated obesity-associated HCC development.[85] Because the effect of HSC senescence on HCC is paradoxical, further studies are needed to determine whether modulating the tumor microenvironment by targeting HSCs could be a viable HCC treatment option.

MicroRNAs Regulate HCC Development by Functioning as Inflammation Modulators

MicroRNAs (miRNAs) are endogenous small noncoding RNAs that regulate protein expression by degrading target mRNAs or inhibiting translation.[86] MiRNAs contribute to inflammation, apoptosis, hepatocarcinogenesis, proliferation, invasion, and metastasis.[87–90]

MiRNAs can act as either oncogenes or tumor suppressors[91] and are dysregulated in HCC.[88] Circulating miR-122 and miR-21 levels potentially could be used as novel diagnostic biomarkers in HCC patients[92,93] because dysregu lated miR-122 and miR-21 expression is associated with liver inflammation and HCC (Fig. 4).

miR-122, the most abundant liver miRNA (~70% and ~50% of total miRNAs in mouse and human, respectively), is antitumorigenic and downregulated in human HCC.[94–96] Low miR-122 levels correlate with metastasis and poor prognosis in HCC.[97–99] miR-122$^{-/-}$ mice spontaneously developed steatohepatitis, fibrosis, and HCC.[100,101] miR-122 targets genes involved in proliferation and differentiation.[102] Many of these targets were identified using miR-122$^{-/-}$ mouse livers and human HCC samples.[103] BCL9 is a miR-122 target that is associated with HCC patient survival.[103] miR-122 is also anti-inflammatory and targets CCL2.[101] miR-122 deficiency led to the infiltration of inflammatory CD11b^{hi}Gr1^{+}CCR2^{+}cells that produce protumorigenic IL-6 and TNFα to the liver.[101] Reciprocally, IL-6 and TNFα decreased miR-122 levels via c-Myc-mediated C/EBPα inhibition.[104] Unsurprisingly, miR-122 expression was reduced in c-Myc-induced HCC.[105] Chronic inflammation amplifies the IL-6/TNFα/miR-122 inflammatory feedback circuit, inducing inflammation-driven HCC.[101,104] Notably, nuclear miR-122 directly binds pri-miR-21 to inhibit maturation of the oncomiR miR-21, decreasing chemoresistance and HCC growth.[106]

miR-21 is overexpressed in HCC and intrahepatic CCA.[107,108] miR-21 contributes to cancer cell growth, migration, and invasion by inhibiting PTEN.[107] Serum miR-21 levels correlate with clinical stage and metastasis,[109] and increased miR-21 expression in HCC was correlated with poor outcomes, suggesting it could be used as a biomarker for predicting the prognosis of HCC patients.[110,111] Three miR-21 targets (CAMSAP1, DDX1, and MARCKSL1) were correlated with survival in HCC patients.[112] Additionally, miR-21 antagomiR treatment reduced HCC growth.[113]

IL-6 can transactivate miR-21 through STAT3.[114,115] HBV × protein (HBx) induces miR-21 via IL-6.[116] HBx-mediated miR-21 induction inhibited cell apoptosis by suppressing IL-12 and programmed cell death 4 (PDCD4), thereby promoting HCC.[117,118] miR-21-mediated PDCD4 repression indirectly activated AP-1, which increased miR-21 transcription, creating an miR-21-PDCD4-AP-1 positive feedback loop that enhances HCC migration and invasion.[119] CCL2, which is induced by myeloid-derived angiogenic endothelial progenitor cells, increased miR-21 levels through the CCR2/JNK/AP-1 signaling pathway, promoting HCC migration, invasion, and metastasis.[120] miR-21 is transcriptionally regulated by the p65 subunit of NF-κB, which plays a role in chronic inflammation and tumorigenesis (described above).[121] Moreover, Aurora-A, an essential mitosis regulator, upregulated miR-21 transcription through NF-κB, contributing HCC chemoresistance.[122] The contribution of other miRNAs to HCC development is summarized in Table 2. Overall, measurement of circulating miRNAs could be a good tool for diagnosing various liver diseases, and targeting miRNA may be a good therapeutic strategy for HCC.

Endoplasmic Reticulum Stress Mediates Liver Inflammation and HCC

Endoplasmic reticulum (ER) stress is triggered by inflammation, hypoxia, and genome instability and induces the unfolded protein response (UPR).[123] ER stress and the UPR contribute to various biological processes, including glucose and lipid metabolism, inflammation, cell differentiation, apoptosis prevention, and cancer chemoresistance. They are upregulated in cancers, including HCC.[123–126] ER stress promotes obesity-associated HCC in a TNF-dependent manner.[127] Specifically, macrophage-derived TNF enhanced lipogenesis and promoted HCC through the TNF receptor TNFRI.[127] TNF-TNFRI-IKKβ-NF-κB signaling played a role in HcPC transformation and perpetuated tumor-elicited inflammation.[127] With respected to the UPR, inositol-requiring enzyme 1α (IRE1α) is an ER-localized transmembrane RNase that transduces the UPR pathway by cleaving XBP1 mRNA. Mice with a hepatocyte-specific deletion of IRE1α had reduced hepatocyte proliferation, HFD-induced steatosis, and HCC development.[128] Hepatocyte-specific IRE1α deletion suppressed the IKKβ-NF-κB pathway and attenuated liver inflammation.[128]

Endoplasmic reticulum stress regulates immune cells by increasing the expression of lectin-type oxidized low-density lipoprotein receptor-1 (LOX-1), a cell surface marker for polymorphonuclear (PMN)-MDSCs.[129] The number of LOX-1$^+$CD15$^+$PMN-MDSCs were increased in HCC patients and positively associated with the prognosis.[129] ER stress-induced LOX-1$^+$CD15$^+$PMN-MDSCs suppressed T cell proliferation, implicating them in immune tolerance to tumor cells.[129] Because ER stress contributes to HCC development, suppression of ER stress could be an HCC treatment option. For example, tauroursodeoxycholic acid, an ER stress reducer, suppressed ER stress-mediated NASH HCC.[127]

Etiologic Factors Associated with Inflammation and Liver Cancer

Viral Hepatitis-induced HCC

In the United States, 45 to 55% new cases of HCC are associated with HCV, and 10 to 15% with HBV.[3] Worldwide, up to 54% of HCC patients are linked to HBV.[130] HBV and HCV are noncytopathic. Chronic inflammation and liver damage are caused primarily by the immune response to virus-infected hepatocytes.[130] The majority (70–90%) of HBV- or HCV-related HCC is developed in cirrhotic liver, although HCC can presents in HBV or HCV patients without cirrhosis.[3] During hepatitis B, CD8$^+$T cells that specifically respond to HBV surface (HBs) and core antigens play a role in HCC development. An HBsAg Tg mouse line that did not have a spontaneous HCC liver phenotype developed HCC after administration of HBsAg-specific CD8$^+$T cells.[131] Another HBsAg Tg mouse line spontaneously developed liver injury and HCC, and NF-κB was activated in their hepatocytes, indicating HBsAg alone is sufficient to induce NF-κB activation and HCC.[132] In these mice, IKKβ inhibition increased ER stress and DNA damage, enhancing HCC. NF-κB regulates the UPR and prevents ER stress and DNA damage.[132] Collectively, HBsAg-mediated chronic inflammation is a driving factor for HBV HCC.

While chronic inflammation is crucial for HBV HCC development, HBV directly affects tumorigenesis by integrating its genome into the host genome, and p53-associated pathways

play a role in HBV-mediated hepatocarcinogenesis.[130,133,134] HCV, an RNA virus, has limited capacity for genome integration and therefore its direct carcinogenic capacity is less than HBV. HCV-induced HCC is more associated with host pathways related to cell survival, inflammation, oxidative stress, insulin resistance, hepatic steatosis, and fibrosis. DNA damage occurs during HCV replication, causing genomic disturbances that lead to hepatocarcinogenesis.[135] Direct-acting antiviral (DAA) treatments that eliminate hepatitis viruses are currently the most effective strategy to prevent hepatitis virus-mediated HCC. However, some HCV patients who achieved sustained virologic response with DAA still develop HCC or show high rate of recurrence of previously treated HCC.[136–138] Potential mechanisms for this outcome include: (1) the loss of the antitumorigenic effect of inflammation in HCV infection, (2) a DAA treatment-mediated reduction in HCV enhancing tumor surveillance (e.g., via induction of IFN target genes) in the HCC microenvironment, [136] and (3) upregulation of VEGF and angiopoietin-2 enhancing angiogenesis following DAA therapy.[139] Notably, this outcome was seen less frequently when patients were treated with IFN therapy, possibly because of IFN's antitumorigenic and immunomodulatory effects. Although DAA therapy for HCV is the frontline therapy, further investigation of HCC prevention after DAA therapy is still required.

NAFLD-Associated HCC

The incidence of HCC in NAFLD patients is relatively low compared with other etiologies. However, NAFLD HCC patients constitute a significant proportion of the HCC population because approximately 25% of adults presently have NAFLD in the United States.[4] Approximately 30 to 40% of new HCC cases are related to metabolic syndrome.[3] Type 2 diabetes is a risk factor for NAFLD and increases HCC incidence to two- to threefold.[3] The antidiabetic drug metformin reduces HCC incidence.[3] Hyperlipidemia is also associated with NAFLD, and statin treatment reduces the risk of HCC.[3] Among NAFLD HCC patients, 80 to 90% present with cirrhosis, but nonfibrotic fatty livers can also develop HCC.[4]

As mentioned above, the composition of the gut micro-biome was altered in an NAFLD HCC mouse model. Similarly, patients with NAFLD cirrhosis had increased fecal *Enterobacteriaceae* and *Streptococcus* and decreased *Akkermansia* compared with healthy controls. In patients with NAFLD HCC, fecal *Bacteroides* and *Ruminococcaceae* were increased and *Bifidobacterium* was decreased compared with those in NAFLD patients without HCC.[140] There was a negative correlation between the *Akkermansia/Bifidobacterium* ratio and the level of fecal calprotectin, a marker of intestinal inflammation. Fecal calprotectin concentration in NAFLD HCC patients was higher than NAFLD patients without HCC. NAFLD HCC patients had increased levels of IL-13, which can activate MDSCs and promote tumor progression by inhibiting tumor immunity.[140]

Another mechanism of NAFLD HCC is PNPLA3 polymorphisms, which are associated with general NAFLD progression, possibly by enhancing inflammatory signals, including IL-6/STAT3 and CCL5 pathways.[141–145] The PNPLA3-I148M variant has been reported to increase the risk of progression to NASH, fibrosis, and cirrhosis. Mice bearing PNPLA3-I148M spontaneously develop hepatic steatosis.[146,147] Mechanistically, HCC cells with PNPLA3-I148M showed increased proliferation via the IL-6/STAT3 pathway following

administration of low-dose free fatty acids in vitro and in a HFD-fed xenograft HCC model in vivo.[148] The PNPLA3-I148M variant also enhanced HSC activation through CCL5 production.[149]

Overall, NAFLD is a rapidly growing cause of liver transplantation and could become the most common cause of HCC in the future. Both the microbiome andgenetic association studies are hot research topics in the push to understand inflammation-mediated pathogenesis in NAFLD HCC development.

Alcohol-Associated HCC

About 18 to 33% of liver cancer is attributed to alcohol consumption and alcoholic cirrhosis.[150] The majority of alcohol is metabolized in the liver. Alcohol dehydrogenase (ADH) and CYP2E1 metabolize ethanol into acetaldehyde. Then, acetaldehyde is converted to acetate by acetaldehyde dehydrogenase 2 (ALDH2). Acetaldehyde is hepatocytotoxic and can react with protein complexes. These modified proteins are antigenic, triggering immune reactions and DNA damage.[151] CYP2E1 can potentiate binge alcohol-mediated gut leakiness, hepatocyte apoptosis, and inflammation.[152] Further, selective inhibition of CYP2E1 prevented DEN-induced carcinogen-esis.[153] Similarly, ALDH2 activity can affect alcohol-induced liver pathology. ALDH2-deficient mice had less steatosis but more inflammation and fibrosis.[154] ALDH2 polymorphisms in combinations with the ADH2 SNP (ALDH2*1/*2 and ADH2*2/*2) were correlated with HCC incidence in moderate drinkers.[155] Interestingly, the PNPLA3-I148M variant (discussed above) influenced HCC occurrence in patients with alcoholic cirrhosis.[156] PNPLA3-I148M in conjunction with transmembrane 6 superfamily member 2 variants is further associated with alcohol-associated HCC.[157] Thus, chronic alcohol consumption is a major risk factor for HCC development, particularly in individuals with certain gene polymorphisms. As such, polymorphism assessment could be a useful tool to identify populations at high risk for alcohol-associated HCC.

Modulation of Hepatic Immune Signals is a Potential Approach to Prevent and Treat HCC

Escape from immune surveillance is crucial for tumor progression. Regulatory T cells, MDSCs, M2 macrophages, and Th2 cytokines suppress tumor surveillance. Thus, enhancing the hepatic immune system is a potential HCC treatment strategy. Above, we discussed the protumorigenic role of TLR signaling. However, TLR ligands, such as agonists of TLR7 (resiquimod, imiquimod) and TLR9 (CpG oligonucleotides), have antitumorigenic effects via enhancing tumor antigen presentation to DCs.[158,159] Furthermore, the TLR3 agonist poly I:C increases NK cell tumoricidal activity through IFN production.[160,161] Bacterial products, such as bacillus Calmette–Guerin, an attenuated strain of *Mycobacterium* used as a tuberculosis vaccine, and monophosphoryl lipid A can boost tumor immunity via TLR2/4.[162–164]

Notably, immune checkpoint molecules play a crucial role in inhibiting tumor immunity. Programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte 4 (CTLA-4) are well-studied immune checkpoint proteins.[165] Their activation suppresses T cell-mediated tumor

immunity and enhances regulatory T cell activity.[165] Inhibitors of these proteins can suppress tumor growth by enhancing tumor immunity. Previous and ongoing clinical trials have tested the use of tremelimumab, a monoclonal CTLA-4 antibody, and nivolumab, a monoclonal PD-1 antibody, for HCC.[166–168] These trials demonstrated satisfactory results for tumor growth and patient survival. Radiofrequency ablation or chemoablation could enhance the antitumorigenic effects of immuno-modulating therapies, such as immune checkpoint inhibitors or TLR ligands, by releasing tumor antigens to prime adaptive immunity.[167] A more detailed review of the HCC immunotherapy has been discussed elsewhere.[165,169]

Inflammation Drives the Progression of CCA

Among intrahepatic, perihilar, and distal CCA,[170] intrahepatic CCA is the second most common primary liver cancer. The prognosis of CCA is poor (5-year survival rate < 5%), and most patients present with advanced stage disease. Risk factors for CCA include PSC and liver fluke infection. Approximately 7 to 15% of PSC patients develop CCA.[3] Liver fluke infection increases CCA incidence by 10-fold.[3,170] HBVand HCV infection increases CCA risk by twofold.[3] These factors suggest an association between inflammation and CCA. Mechanistic studies using mouse models have revealed the contribution of liver inflammation to CCA development. ST2, the IL-33 receptor, was overexpressed in human CCA.[171] IL-33 is a critical promoter for mouse CCA development when genetically primed by constitutively active Akt (myr-Akt) and Yap (YapS127A).[171,172] IL-33-dependent mouse CCA development occurs via IL-6.[171] Interestingly, both biliary cells and hepatocytes can give rise to intrahepatic CCA.[173–177] Hsp60$^{\Delta hep}$ mice spontaneously developed CCA due to ROS overproduction caused by mitochondrial dysfunction.[177] Kupffer cell-derived TNFα plays a role in this process.[177] JNK is also an essential factor for CCA; CCA development was reduced in mice treated with a JNK inhibitor or with a hepatocyte-specific JNK deletion.[177] Tumor-reactive stroma enriched with extracellular matrix, cancer-associated fibroblasts (CAFs), and inflammatory cells, including tumor-associated macrophages, also play a role in CCA development, increasing the stiffness and malignant potential of CCA tumors.[178] Reduced CCA formation was observed in mice that had CAFs inactivated by a BH3 mimetic,[179] suggesting a critical role of CAFs in CCA growth. However, CAF inactivation in this study might not be cell specific, and further investigations are warranted. Collectively, these reports suggest that IL-33, JNK, and CAFs could be potential targets for CCA treatments.

Inflammation Mediates the Establishment and Growth of Liver Metastases

Visceral cancers, including gastric, colon, and pancreatic cancer, preferentially metastasize to the liver due to their anatomical link through portal circulation. Liver metastasis is a prognostic determinant for these cancers. Recent studies provided new evidence that primary tumors secrete factors that form a “premetastatic niche” in the liver and promote the development of liver metastases. Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer that frequently develops liver metastases. Costa-Silva et al showed that exosomes secreted from primary PDAC travel to the liver, enhancing the production of TGF-β in Kupffer cells and fibronectin in HSCs and forming a premetastatic niche.[10] Migration

inhibitory factor and the fibronectin receptor integrin αvβ5 in PDAC-derived exosomes were essential for premetastatic niche formation in the liver.[10,11] Other studies demonstrated that tissue inhibitor of metalloproteinases-1 (TIMP-1) secreted from primary colorectal cancer or PDAC enhanced neutrophil recruitment to the liver by stimulating HSCs to produce stromal cell-derived factor 1 and TIMP-1 via CD63, creating a premetastatic niche.[180,181] Thus, primary cancers could promote liver metastasis by priming liver-resident cells. Underlying liver diseases, such as liver fibrosis, were thought to suppress liver metastasis due to reduced blood flow to the liver. However, several studies in humans suggest that fatty liver and liver fibrosis may enhance liver metastasis.[8,9,182–188] A large prospective cohort study of 2,715 patients who underwent resection for colorectal cancer liver metastases demonstrated that liver metastasis recurrence was higher in steatotic livers.[8] Another study of 953 patients with liver metastases after curative resection of colorectal cancer showed a fourfold increase in the risk of liver metastasis in fibrotic livers.[9] Various animal studies support these findings, suggesting that underlying liver diseases and inflammatory signals are associated with premetastatic niche formation.[189–193]

Conclusion

While the mortality of many cancers, such as lung, prostate, colorectal, and gastric, has decreased, the mortality of liver cancer has increased. The overall 5-year survival of HCC is 18%, though patients diagnosed in the localized stage have a 5-year survival of 31%.[1] Partial hepatectomy is the primary treatment strategy for HCC, and liver transplantation can also be indicated. Sorafenib has been used for the treatment of HCC, but many reports have identified a sorafenib-resistant HCC.[194,195] Recently, regorafenib was approved to treat HCC patients who were previously treated with sorafenib. However, regorafenib only extends survival 2 to 3 months, similar to sorafenib. Thus, the currently available chemotherapies are unsatisfactory.

Cell-death pathways, DNA damage and mutations, and inflammation are the drivers of HCC initiation. Inhibiting these pathways could prevent early HCC development, but this treatment strategy may not be effective for advanced HCC. Antiapoptotic strategies would also inhibit cancer cell death, which could enhance HCC growth. Inflammation and tumor-reactive stroma play important roles in many cancers, including HCC, CCA, and metastatic liver tumors. Further, an inflammatory liver microenvironment promotes the formation of a premetastatic niche. Therefore, blocking tumor-promoting inflammatory signals and enhancing tumor immunity through immune checkpoint inhibitors could be an effective strategy for treating these cancers. Recent advancements in immune checkpoint inhibitors have been significant but still require optimization. In 2017, the Food and Drug Administration expanded approval of the PD-1 inhibitor nivolumab as a second-line HCC therapy. In 2018, lenvatinib was approved as a new frontline treatment option for HCC in Japan based on data from the Phase 3 REFLECT trial.[196] Data suggest combination therapy with tumor ablation is more effective than monotherapy.[167] However, a better understanding of inflammation and immune signals in liver cancer is required to develop new therapies and to improve the efficacy of existing therapies.

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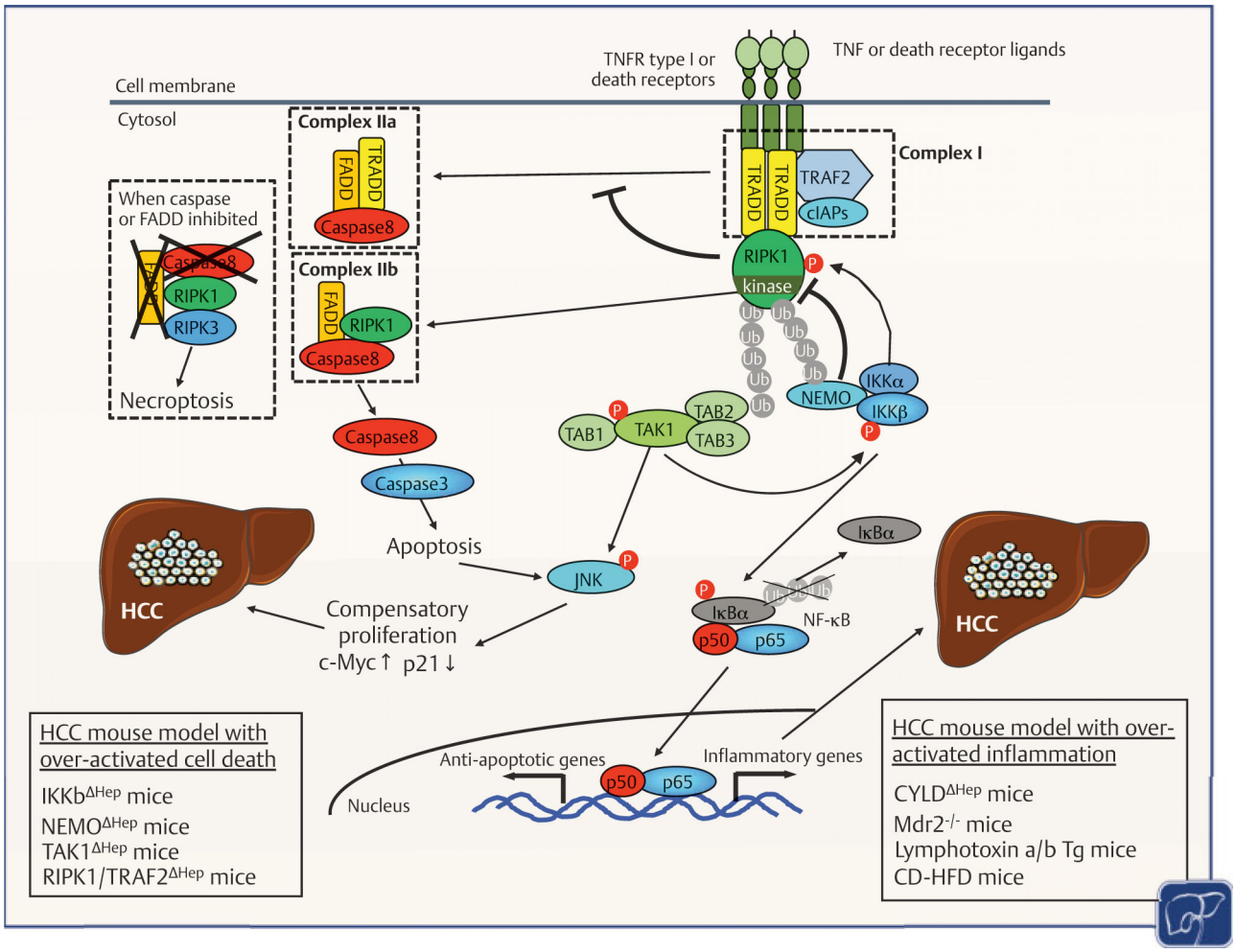

Fig. 1.

Tumor necrosis factor (TNF) receptor, IkappaB kinase/nuclear factor kappa B (IKK/NF-κB), c-Jun N-terminal kinase (JNK), and apoptosis in hepatocellular carcinoma (HCC) development. In the development of inflammation-associated HCC, the IKK/NF-κB, JNK, and apoptosis pathways play both pro- and antitumorigenic roles. Activation of death receptors, including TNF receptor type I, leads to the formation of "complexI," consisting of TNF receptor-associated death domain (TRADD), TNF receptor-associated factor 2 (TRAF2), and cellular inhibitor of apoptosis protein (cIAP). Polyubiquitination of receptor-interacting protein 1 (RIP1) recruits and activates the TAK1 and IKK complexes (IKKα/IKKβ/NF-kappa-B essential modulator [NEMO]). TAK1 activates the JNK mitogen-activated protein kinase (MAPK) pathway in a phosphorylation-dependent manner. TAK1 also phosphorylates and activates the IKK complex, leading to the phosphorylation, ubiquitination, and degradation of IκBα. This degradation results in the nuclear translocation and activation of NF-κB, comprising the p50 and p65 subunits. NF-κB promotes tumorigenesis by inducing inflammatory factors but prevents tumorigenesis by suppressing apoptotic pathways. NEMO regulates NF-κB activation and directly prevents the formation of the complex IIb (RIP kinase 1 [RIPK1], Fas-associated protein with death domain [FADD], caspase-8). RIPK1 kinase induces complex IIb-mediated hepatocyte

apoptosis. NEMO and RIPK1 negatively regulate the formation of complex IIa (TRADD, FADD, caspase-8). Inhibition of caspase-8 and/or FADD leads to phosphorylation of RIP1 and RIP3 and induction of necroptosis. JNK is crucial for compensatory proliferation by increasing c-Myc and decreasing p21.

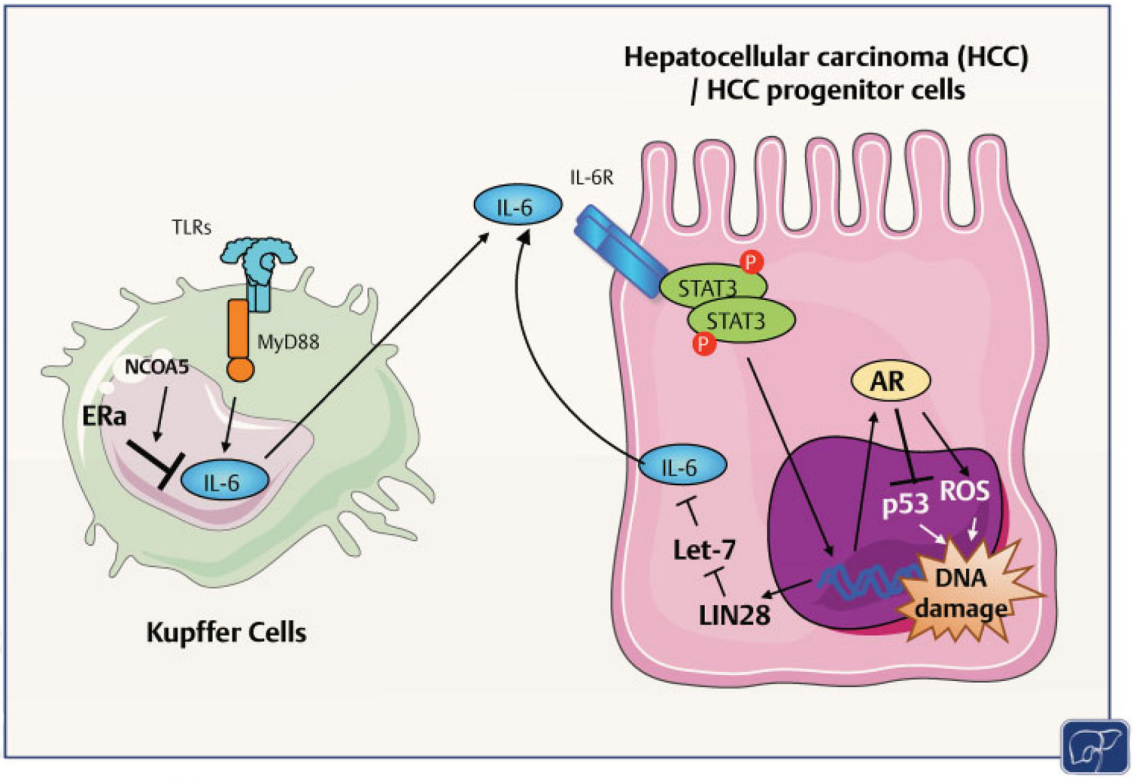

Fig. 2.

Interleukin (IL)-6 and the gender effect in hepatocellular carcinoma (HCC) development. In early HCC, IL-6 production is mediated by Toll-like receptor/MyD88 signaling in Kupffer cells and is negatively regulated by estrogen receptor α (ERα) signaling. NCOA5 is involved in ERα-mediated suppression of IL-6. IL-6 signaling promotes liver cancer cell growth by activating signal transducer and activator of transcription 3 (STAT3). IL-6 signaling also upregulates androgen receptor (AR) expression. AR inhibits the tumor suppressor p53 and enhances reactive oxygen species (ROS) production, promoting deoxyribonucleic acid (DNA) damage and mutation. In HCC progenitor cells, IL-6 is produced in an autocrine manner through upregulation of LIN28 and suppression of Let-7 and contributes to malignant transformation.

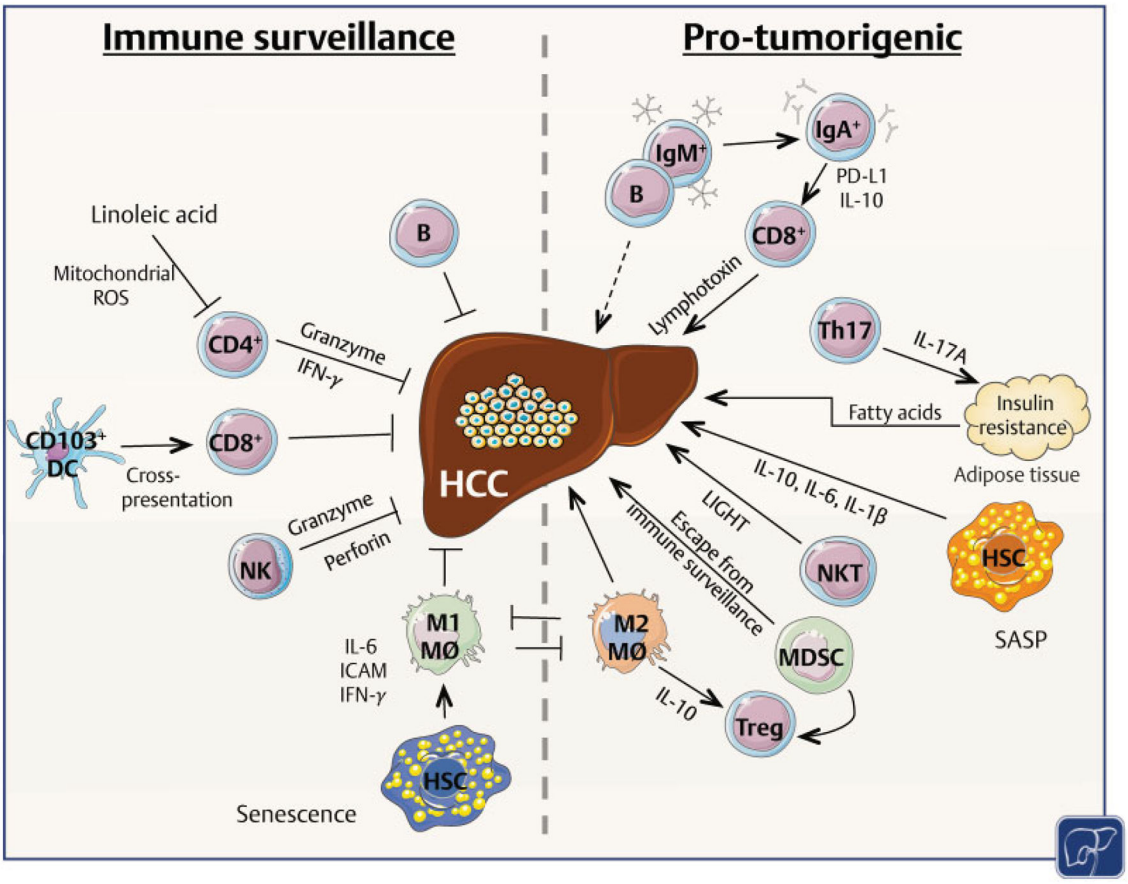

Fig. 3.

Anti- and protumorigenic roles of the immune cell network in hepatocellular carcinoma (HCC) development. Various immune cell networks have both anti- and protumorigenesis effects. Immune surveillance by natural killer (NK) cells, $CD4^+$, $CD8^+$ T cells, and B cells suppresses HCC development. However, the expansion of $CD8^+$ T cells, immunoglobulin A (IgA)-producing plasma cells, Th17 cells, NKT cells, regulatory T cells, myeloid-derived suppressor cells (MDSCs), and M2 macrophages promotes HCC development. HSC senescence has been proposed to play both pro- and antitumorigenic roles by inducing the senescence-associated secretory phenotype (SASP) and by promoting M1 polarization, respectively.

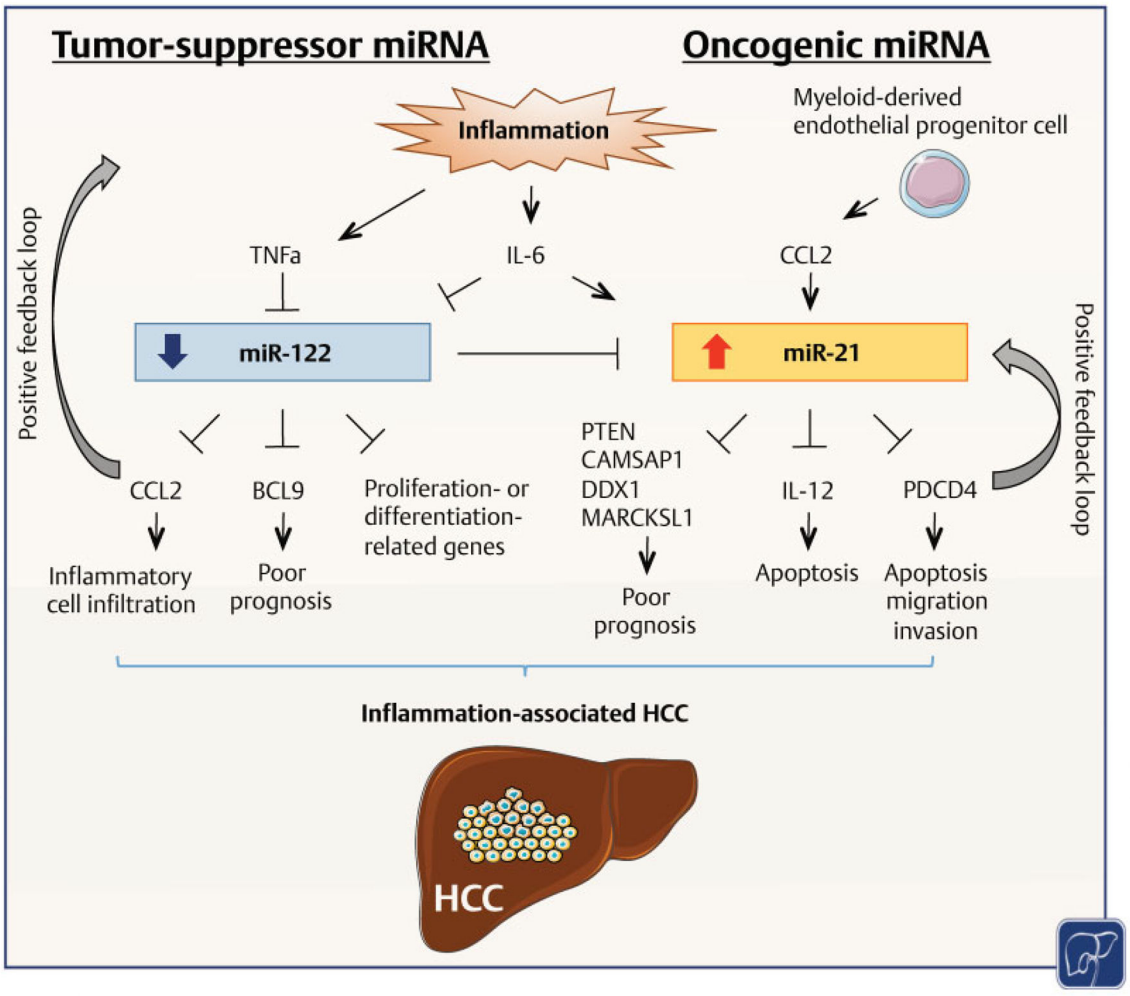

Fig. 4.

miR-122 and miR-21 regulate inflammation-associated hepatocellular carcinoma (HCC). Tumor suppressor miR-122, the expression of which is reduced in HCC, is inhibited by tumor necrosis factor (TNF)-α or interleukin (IL)-6. Decreased miR-122 levels increase CCL2 levels, leading to the infiltration of inflammatory cells (e.g., $CD11b^{hi}Gr1^{+}$ cells expressing CCR2) that produce TNFα and IL-6. Dysregulation of miR-122 induces BCL9 and many genes involved in proliferation and differentiation. miR-122 also negatively regulates the oncomiR miR-21. miR-21 is upregulated by IL-6 and CCL2. miR-21 targets PTEN, CAMSAP1, DDX1, MARCKSL1, and IL-12. miR-21 also targets programmed cell death 4 (PDCD4), creating a positive feedback loop. Dysregulation of miR-122 and miR-21 contributes to inflammation-associated HCC.

Table 1

Summary of mouse liver tumor models

Type of model	Method for inducing tumor	References
Chemically induced HCC	• DEN	20,28,30,33,35,36,50,52,104
Genetically engineered mouse models	• Lymphotoxin β/α overexpression	16
	• $Tak1^{fl/fl}$; Alb-Cre, $Tak1^{fl/fl}$; Alfp-Cre	22,23
	• $Mdr2^{-/-}$	18
	• $NEMO^{fl/fl}$; Alfp-Cre	21
	• $PTEN^{\Delta hep}$	46
	• Hras12V Tg	68
	• tet-o-*MYC*; LAP-tTA	101,105
	• $Fah^{-/-}$	66
Implantation models	• Syngeneic tumor model	67
Obesity- or NASH-associated HCC	•DEN + HFD	15,47
	• DMBA + HFD	60,85
	• MCD-fed MYC-ON	63
	• HFD-fed MUP-uPA	70,127
	• HFD-fed streptozotocin-treated	70
	• Xenograft HCC model with HFD feeding	148
	• CD-HFD diet	65
	• $PTEN^{\Delta hep}$	46
Fibrosis-associated HCC	• DEN + CCl_4	45,48
	• DEN + DDC diet	48
	• $Tak1^{\Delta hep}$	17,22,48
	• CD-HFD diet	65
	• $PTEN^{\Delta hep}$	46
Viral hepatitis-induced HCC	• HBsAg Tg	131,132
CCA	• Myr-Akt	171,172,175

Type of model	Method for inducing tumor	References
	• thioacetamide	166,169
	• CRISPR/Cas9-induced ICC	177
	• Akt/Nras-induced ICC	177
	• Akt/Notch-induced ICC	177
	• HDTV Kras	177
	• Syngeneic tumor model	179
	• TGFBR2/PTEN$^{\Delta Hep}$	176
Liver metastasis	• Intrasplenic injection	10,11
	• Intravenous injection	180,181

Abbreviations: CCA, cholangiocarcinoma; DDC, 3,5-diethoxycarbonyl-1,4-dihydrocollidine; DEN, diethylnitrosamine; DMBA, 7,12-dimethylbenz(a) anthracene; HCC, , hepatocellular carcinoma; HFD, high-fat diet; ICC, immunocytochemistry; MCD, methionine-choline deficient; MUP-uPA, major urinary protein-urokinase type plasminogen activator; NASH, nonalcoholic steatohepatitis; NEMO, nuclear factor kappa-B essential modulator.

Table 2

miRNAs associated with immune cell regulation in HCC

miRNAs	Target and effect	Cell type	Downstream effects	Ref
miR-26a	↓M-CSF	HCC	Inhibits TAM infiltration; inhibits tumor growth	197
miR-28–5p	↓IL-34	HCC	Inhibits TAM infiltration; better survival	198
miR-101	↓DUSP1	M2 macrophages	Promotes macrophage-induced HCC growth	199
miR-214	↓β-catenin	TAM	Antitumor (M1 polarization)	200
miR-17–92 cluster (miR-20a, miR-93, and miR-106b)	↓MICA/B	HCC	Inhibits NK cell-mediated cytotoxicity	201
miR-889	↓MICB	HCC	Inhibits NK cell-mediated cytotoxicity	202
miR-146a	↓STAT1	NK	Inhibits NK cell-mediated cytotoxicity	203
miR-615–5p	↓IGF-1 R	NK	Inhibits NK cell-mediated cytotoxicity	204
miR-152	↓HLA-G	HCC	Promotes NK cell-mediated cytotoxicity	205
miR-182	↑pore-forming protein	NK	Promotes NK cell-mediated cytotoxicity	206
miR-486–5p	↑IGF-1	NK	Promotes NK cell-mediated cytotoxicity	207

Abbreviations: DUSP1, dual specificity phosphatase 1; HCC, hepatocellular carcinoma; HLA-G, human leucocyte antigen-G; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; IL-34, interleukin-34; M-CSF, macrophage colony-stimulating factor; MIC, MHC class I-related chain molecules; miRNA, micro ribonucleic acid; NK, natural killer; STAT1, signal transducer and activator of transcription 1; TAM, tumor-associated macrophage.