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Review Article

Role of Noncoding RNAs in the Tumor Immune Microenvironment of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies. It has high mortality and poor clinical outcomes, but the molecular mechanisms in the pathogenesis of HCC are not understood. The tumor immune microenvironment (TIME) is a highly intricate system with distinct populations of innate and adaptive immune cells, as well as other stromal cells. They interact and evolve with tumor cells to influence tumor growth, migration, invasion, immune evasion, and response to therapy. Emerging evidence has shown noncoding RNAs (ncRNAs) are prominent regulators of TIME in HCC. In this review, we elaborate on the functions and molecular mechanisms of ncRNAs in remodeling TIME of HCC and discuss their diagnostic and therapeutic potential for HCC treatment.

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Introduction

Hepatocellular carcinoma (HCC), is the predominant form of primary liver cancer, the fifth most common malignancy, and the fourth leading cause of cancer-related death globally.[1–3] Major risk factors for HCC have been well established and include hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, abnormalities of lipid metabolism, excessive alcohol consumption, intake of dietary toxins like aristolochic acid or aflatoxin B1, diabetes.[3] HCC is a biologically complex and highly heterogeneous disease, and the detailed mechanisms underlying hepatocarcinogenesis are still poorly understood. In recent decades, various preventive and therapeutic approaches have been approved and widely applied in HCC management, including antihepatitis vaccine, surgical resection, liver transplantation, and systemic treatment, etc.[4,5] Notably, cancer immunotherapies have achieved pronounced clinical benefits, however, a large proportion of the immunotherapies still remain ineffective.[6] Considering that worldwide mortality from HCC is continuously increasing, it is important to improve our understanding of the molecular pathogenesis of HCC, while novel diagnostic/prognostic biomarkers and therapeutic strategies are urgently needed to deal with this major public health concern.

It is now clear that tumor formation and progression involve the co-evolution of neoplastic cells and surrounding stromal components. In recent years, the TIME has received significant attention as it is recognized to closely interact and co-evolve with tumor cells, affecting tumor growth, metastasis, immune escape, and the efficacy of immunotherapy. The TIME of HCC is a highly intricate and integrated system that consists of diverse cellular and noncellular components. The cellular components comprise immune cells including macrophages, neutrophils, myeloid-derived suppressor cells (MDSCs), natural killer (NK) cells, dendritic cells (DCs), T cells, B cells, cancer stem cells (CSCs), hepatic stellate cells (HSCs), vascular cells, cancer-associated fibroblasts (CAFs), and other stromal cells. The noncellular parts include the extracellular matrix and abundant soluble factors (e.g., cytokines, chemokines, growth factors) (Fig. 1). All these components dynamically interact to foster an immunosuppressive TIME. Many studies have revealed that TIME has a critical role in regulating immune evasion and the development of HCC.[6–9] However, the detailed molecular mechanisms underlying TIME reprogramming in HCC are not understood.

Noncoding RNAs (ncRNAs) refer to transcripts with no or minimal protein-coding ability. In the human genome, less than 2% of the transcripts encode proteins, while the remaining 98% are transcribed into different species of ncRNAs. ncRNAs can be classified into two major categories based on their molecular structure, including linear RNAs and circular RNAs (circRNAs). The linear RNAs can be broadly divided into two groups by their length, small noncoding RNAs (sncRNAs,

Keywords: ncRNAs; TIME; HCC; Biomarker; Therapeutic strategy.

Abbreviations: CAF, cancer-associated fibroblast; ceRNA, competitive endogenous RNA; circRNA, circular RNA; CSC, cancer stem cell; CTL, cytotoxic T cell; DC, dendritic cell; EMT, epithelial-mesenchymal transition; EV, extracellular vesicle; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; Hh signaling, Hedgehog signaling; HSC, hepatic stellate cell; lncRNA, long noncoding RNA; MDSC, myeloid-derived suppressor cell; miRNA, microRNA; NA, not available; ncRNA, noncoding RNA; NK cell, natural killer cell; PBMC, peripheral blood mononuclear cell; piRNA, PIWI-interacting RNA; sncRNA, small noncoding RNA; snoRNA, small nucleolar RNA; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; Th cell, T-helper cell; TIME, tumor immune microenvironment; Treg, regulatory T cell; tsRNA, transfer RNA-derived small RNA.

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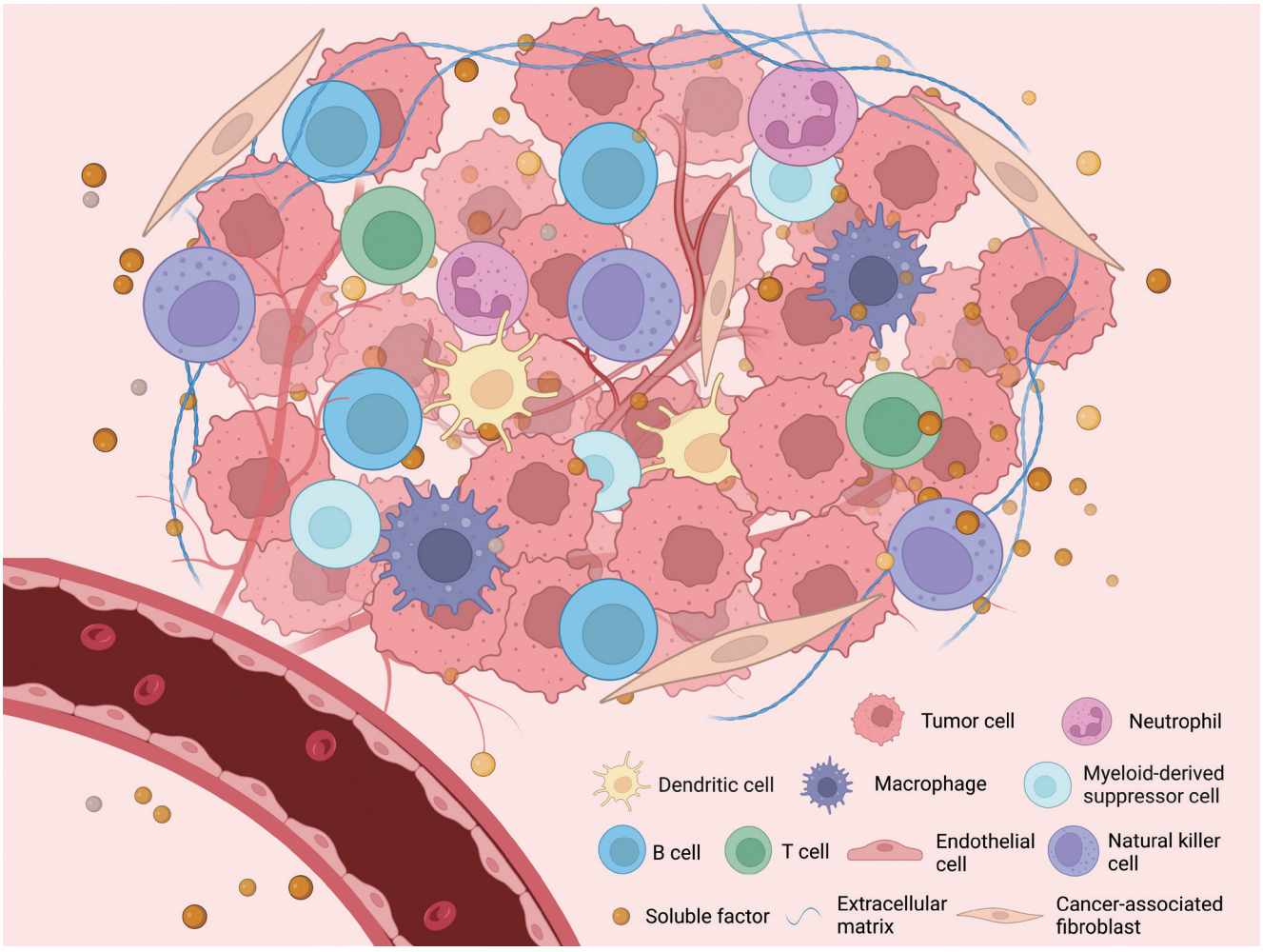

Fig. 1. Key players in the TIME of HCC. The TIME of HCC is a highly sophisticated system consisting of diverse cellular and noncellular components. The cellular components comprise various immune cells (macrophages, neutrophils, myeloid-derived suppressor cells, natural killer cells, dendritic cells, T cells, B cells), endothelial cells, cancer-associated fibroblasts, and other kinds of stromal cells. The noncellular counterparts include the extracellular matrix and diverse soluble factors secreted by both tumor cells and stromal cells. HCC, hepatocellular carcinoma; TIME, tumor immune microenvironment.

<200 nt) and long noncoding RNAs (lncRNAs, >200 nt). sncRNAs consist of microRNAs (miRNAs), small nucleolar RNAs (snoRNAs), transfer RNA-derived small RNAs (tsRNAs), and PIWI-interacting RNAs (piRNAs).[10,11] Emerging evidence has shown that ncRNAs can reprogram TIME, which has profound influences on HCC tumorigenesis and progression. In this review, we systematically discuss the functional roles and molecular mechanisms of ncRNAs within the TIME of HCC, and discuss the diagnostic/therapeutic potential of ncRNAs in HCC treatment.

NcRNAs and innate immune cells in TIME

The TIME of HCC is a complex ecosystem that has various types of innate immune cells and adaptive immune cells, both have established roles in host defense against tumors through diverse mechanisms. Innate immune cells establish the body's first line of defense against tumors, set up by macrophages, neutrophils, MDSCs, NK cells, and DCs, which recognize and act on tumor cells nonspecifically to maintain homeostasis of the host. However, under pathological conditions like cancer, the immune responses of these cells are often disturbed by TIME, which may fuel tumor growth and progression. Recently, extensive studies have indicated that ncRNAs exert a vital role in regulating the differentiation, activation, recruitment, and function of various innate immune cells during the pathogenesis of HCC, which will be discussed in the section below (Table 1, Fig. 2).[12–26]

NcRNAs and macrophages

Macrophages are the major component of the innate immune cells within TIME. It is acknowledged that macrophages largely originate from circulating bone marrow-derived monocytes.[27] Macrophages are a highly plastic and heterogeneous cell population whose phenotypes and functions are regulated by the surrounding microenvironment. In response to specific microenvironmental stimuli, macrophages generally polarize into two phenotypes, classically activated macrophages (M1) and alternatively activated macrophages (M2). M1 macrophages elicit pro-inflammatory effects and have an antitumorigenic role. Conversely, M2 macrophages enhance anti-inflammatory response and have pro-tumorigenic functions. Most tumor-associated macrophages (TAMs) in the tumor have an M2 phenotype. Under the inductions of

Table 1. ncRNAs involved in the regulation of innate immune cells

NcRNA	Expression in HCC	Related immune cell	Target molecules/pathways	Function in TIME	Impact on HCC	Reference
miR-28-5p	Downregulated	TAMs	IL-34/FAK/ERK1/2	Promote TAM recruitment and infiltration into HCC tissue	Promote angiogenesis, tumor growth, and metastasis	12
circASAP1	Upregulated	TAMs	miR-326/miR-532-5p/CSF-1	Promote TAM infiltration	Promote HCC growth and metastasis	13
hsa_circ_0110102	Downregulated	TAMs	miR-580-5p/PPARα/CCL2	Inhibit macrophage activation and infiltration	Inhibit HCC growth and metastasis	14
lncRNA LINC00662	Upregulated	TAMs	miR-15a/16/107/WNT3A/Wnt/β-catenin	Promote M2 macrophage polarization	Promote tumor growth and metastasis	15
lncRNA PART1	Upregulated	TAMs	miR-372-3p/TLR4 axis	Promote M2 macrophage polarization	Promote HCC cell proliferation, EMT, and metastasis	16
lncRNA TUC339	Upregulated	TAMs	NA	Promote macrophage activation, M2 polarization, and pro-tumorigenic activity	Promote HCC progression	17
hsa_circ_0003410	Upregulated	TAMs	miR-139-3p/CCL5	Recruit and polarize M2 macrophages	Promotes HCC tumor growth and metastasis	18
miR-223	Downregulated	Neutrophils	NA	Attenuate neutrophil maturation and activation	Inhibit HCC progression	19
miR-122	Downregulated	Neutrophils	CCL2	Inhibit recruitment of neutrophils	Inhibit tumor progression	20
miR-561-5p	Upregulated	NKs	CX_3CL1/ CX_3CR1^+/STAT3	Inhibit CX_3CR1^+ NK-cell infiltration and activation	Promote pulmonary metastasis	22
circRNA UHRF1	Upregulated	NKs	miR-449c-5p/TIM-3	Induce NK-cell exhaustion and promote NK-cell dysfunction	Promote immune evasion and resistance to anti-PD1 therapy	23
lncRNA GAS5	Downregulated	NKs	miR-544/RUNX3	Enhance the killing effect of NK cells	Inhibit immune evasion and tumor progression	24
circRNA hsa_circ_0007456	Downregulated	NKs	miR-6852-3p/ICAM-1	Strengthen the cytotoxicity of NK cells	Inhibit immune evasion and inhibit tumor growth	25
circRNA ARSP91	Downregulated	NKs	ULBP1	Strengthen the cytotoxicity of NK cells	Enhance innate immune surveillance, suppress HCC proliferation	26
lncRNA HOTAIR	Upregulated	MDSCs	CCL2	Promote recruitment of MDSCs	Promote tumor growth and metastasis	21

HCC, hepatocellular carcinoma; MDSCs, myeloid-derived suppressor cells; NA, not available; ncRNAs, noncoding RNAs; NKs, natural killer cells; TAMs, tumor-associated macrophages; TIME, tumor immune microenvironment.

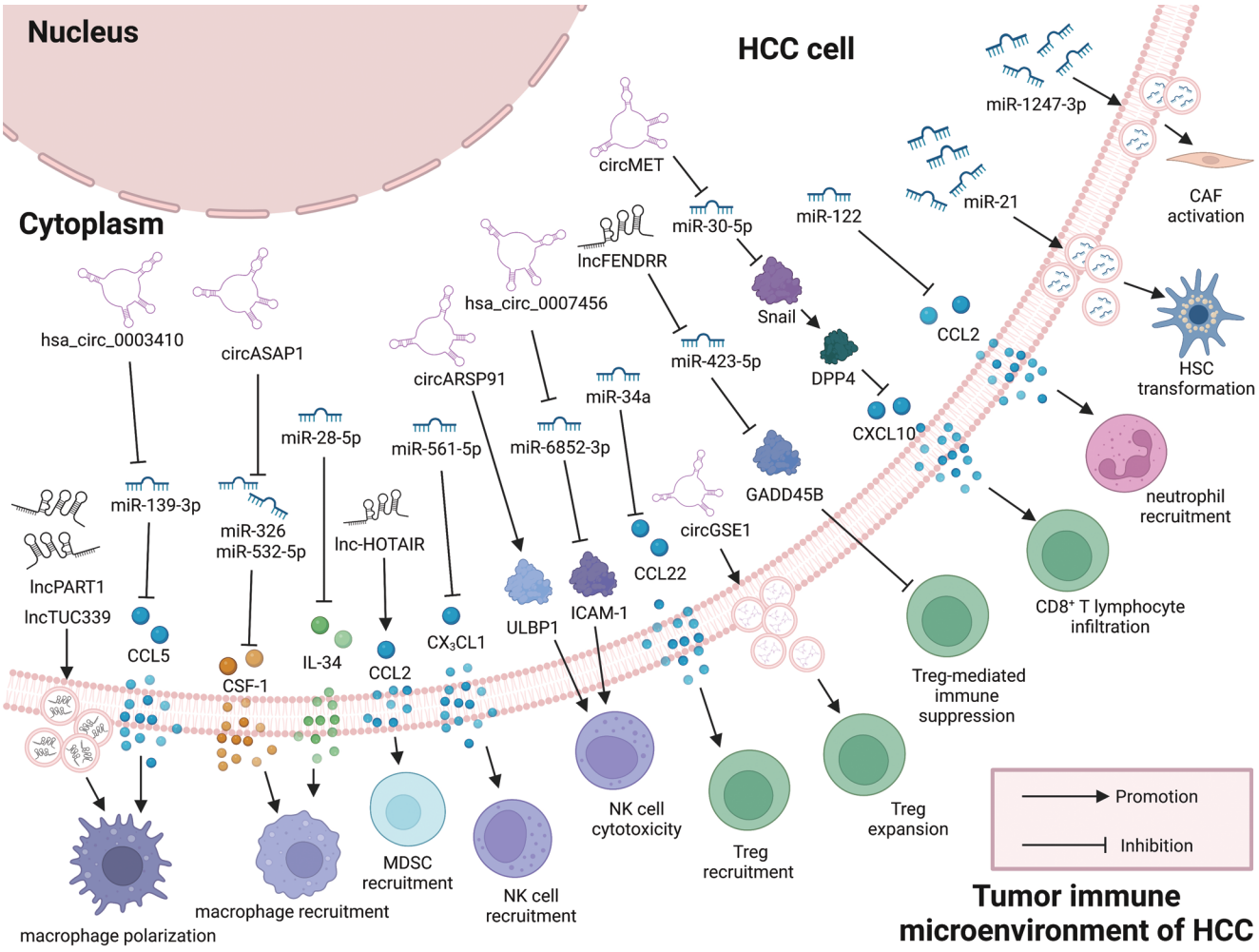

Fig. 2. ncRNA-mediated regulation of TIME. ncRNAs (miRNAs/lncRNAs/circRNAs) regulate the development, activation, recruitment, and cellular function of multiple cell types within TIME of HCC by diverse mechanisms. CAF, cancer-associated fibroblast; circ, circular RNA; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; lnc, long noncoding RNA; MDSC, myeloid-derived suppressor cell; NK, natural killer; Treg, regulatory T cell; TIME, tumor immune microenvironment.

various signaling molecules in TIME, TAMs are recruited to the primary and metastatic tumor tissues where they suppress the immune response by secreting a plethora of protumorigenic proteases, cytokines, chemokines, and growth factors, and promote tumor growth, migration, invasion, angiogenesis, and immunosuppression.[28,29]

An increasing number of studies show the extensive involvement of ncRNAs in macrophage recruitment and polarization in multiple cancer types, including HCC. For example, in HCC, miR-28-5p deficiency promotes the expression of interleukin (IL)-34, and activates FAK and ERK1/2 signaling in macrophages, leading to enhanced recruitment and infiltration of macrophages into HCC tumor sites.[12] Similarly in another study, highly expressed circASAP1 in HCC cells functions as a competitive endogenous RNA (ceRNA) that sponges miR-326 and miR-532-5p, alleviating the repression of CSF-1 expression. CSF-1, as a potent chemoattractant, survival, and differentiation factor for macrophages,[30] positively modulates TAM infiltration to HCC tumor bed, which is considered to contribute to HCC growth and metastasis.[13] Another circRNA hsa_circ_0110102, which is markedly downregulated in HCC cell lines, triggers macrophage activation and hepatic infiltration via miR-580-5p/PPARα/CCL2 pathway, while increasing the production and release of proinflammatory cytokines COX-2/PGE2 from macrophages, and ultimately enhancing HCC cell proliferation, migration, and invasion.[14]

Uncontrolled macrophage polarization is commonly implicated in HCC progression, and deregulation of ncRNAs plays an essential role in mediating M1/M2 macrophage polarization. As an example, LINC00662 induces macrophage M2 polarization in a paracrine manner to potentiate HCC tumor growth and metastasis. Mechanistic studies reveal that LINC00662 acts as a ceRNA for miR-15a/16/107 to stimulate WNT3A expression and secretion from HCC cells. WNT3A then activates Wnt/β-catenin pathway in macrophages, triggering their polarization toward the M2 subtype.[15] It is also reported that lncRNA PART1 is transferred from HCC cells to surrounding macrophages via HCC cell-derived extracellular vesicles (EVs) that triggers macrophage polarization toward the M2 subtype by targeting miR-372-3p/TLR4 axis.[16] Similarly, TUC339, a lncRNA enriched in HCC-secreted exosomes, is transmitted from HCC cells to peri-tumor macrophages and greatly affects macrophage polarization and activity.

Overexpression of TUC339 in human macrophage cell lines THP-1 contributes to M2 phenotype, polarization, and decreased phagocytic activity, decreased pro-inflammatory cytokine (IL1β and TNF-α) production, reduced costimulatory molecule expression, and augmented viability of macrophages, therefore diminishing the antitumor immune response against tumor cells.[17] Cao *et al*.[18] found that upregulated_circ_0003410 in HCC cells promoted HCC tumor growth and metastasis by elevating the ratio of M2/M1 macrophage. Mechanistically, hsa_circ_0003410 stimulates the expression of CCL5 by competitively binding miR-139-3p to recruit and polarize M2 macrophages. Many other ncRNAs have been shown to change M1/M2 macrophage polarization, such as lncRNA MALAT1,[31] lncRNA TP73-AS1,[32] hsa_circ_0074854,[33] which promote M2 polarization, and lncRNA cox-2,[34] lncRNA GAS5,[35] which inhibit M2 polarization.

Both ncRNAs expressed in HCC cells or exosomal ncRNAs secreted by HCC cells are known to orchestrate macrophage recruitment, polarization, and activity, and macrophages reciprocally impact HCC cell behavior by regulating ncRNAs. Intercellular communication between tumor cells and microenvironmental stromal cells mediated by ncRNAs have a strong impact on HCC initiation and malignant progression. A notable example is the miR-28-5p. Specifically, TAMs induced and recruited to HCC tissues by the miR-28-5p/IL-34/FAK/ERK1/2 signaling axis suppressed the expression of miR-28-5p in HCC cells by secretion of TGF-β1, hence forming an miR-28-5p/IL-34/TAM/TGF-β1 positive feedback loop to modulate HCC growth and metastasis.[12] A study by Liu *et al*.[36] reported that miR-92a-2-5p in exosomes transported from tumor-infiltrating macrophages to HCC tumor cells increased the invasive capacity of HCC tumor cells by altering the intrinsic AR/PHLPP/p-AKT/β-catenin signaling. Likewise, RBPJ-overexpressed macrophages transmit hsa_circ_0004658 to neighboring HCC cells via shuttling exosomes, which restrains proliferation and induces apoptosis in HCC cells through the miR-499b-5p/JAM3 pathway.[37]

ncRNAs and neutrophils

Neutrophils, generated in the bone marrow from myeloid precursors, participate in innate immunity against cancer. Like macrophages, neutrophils have various polarization phenotypes with either tumor-suppressive or tumor-promoting immune function. Tumor-associated neutrophils (TANs) can mediate cytotoxicity toward tumor cells. Besides, TANs also promote tumor growth and metastasis by stimulating angiogenesis, orchestrating the behavior of other immune cells, and enhancing tumor cell motility, migration, and invasion.[38,39] Increased neutrophil infiltration has been linked to HCC progression and poor prognosis in patients with HCC.[40] Mounting evidence has indicated that ncRNAs participate in controlling the activation, polarization, recruitment, and function of neutrophils in multiple cancer types, but it remains largely unexplored in HCC.[8,9] MiR-223 is abundantly expressed in neutrophil cells and serves as a modulator of neutrophils in many advanced liver diseases, including HCC and hepatitis virus infection, cirrhosis, nonalcoholic fatty liver disease, and alcohol-induced liver injury, which are important risk factors of HCC. Functionally, miR-223 has a critical role in attenuating neutrophil maturation and activation, although the exact molecular mechanism has not been clarified.[19,41] In another study by Hsu *et al*.,[20] by examining the immune cells that infiltrate hepatic parenchyma in miR-122-KO mice and control group, found that miR-122 depletion stimulated recruitment of neutrophils to the liver, driving hepatic inflammation and producing a higher level of tumor-promoting cytokines. Mechanism dissection reveals that miR-122 deficiency triggers neutrophil recruitment through upregulating CCL2. As the cellular behavior and function of neutrophils are regulated by HCC-derived exosomes, further investigation of the contents of the exosomes is warranted.[42]

NcRNAs and MDSCs

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature cells predominately originating from bone marrow precursor cells. Under pathological conditions like HCC, MDSCs and expand accumulate in TIME, and have strong immunosuppressive activity that impairs various immune responses, such as T-cell function, therefore contributing to tumorigenesis and tumor progression.[43] several studies have implicated ncRNAs in the differentiation, expansion, and immunosuppressive function of MDSCs,[44–46] their contribution to developing HCC is not clear. A recent study showed that strong expression of lncRNA HOTAIR in HCC cell lines was positively associated with enhanced recruitment of MDSCs. The proportion of MDSCs in peripheral blood mononuclear cells (PBMCs) increased when they were co-cultured with HCC cells overexpressing HOTAIR. It was further confirmed that HOTAIR increased the secretion of CCL2 from HCC cells into the tumor milieu. CCL2 was a well-documented chemoattractant and was speculated to be responsible for the HOTAIR-mediated accumulation of MDSCs into the TIME.[21]

NcRNAs and NK cells

Natural killer (NK) cells are an indispensable part of the innate immune system and a subgroup of innate lymphoid cells. They are primarily developed in the bone marrow and migrate into the blood circulation as they mature. The status of NK-cell activation is dictated by the interactions between specific ligands and diverse activating or inhibitory receptors expressed on the NK-cell surface. NK cells have cytotoxic activity and can directly kill target cells. Beyond its cytotoxic capacity, NK cells are also producers of large amounts of cytokines, chemokines, and growth factors that contribute to innate and adaptive immune responses, such as interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), CCL3. Therefore, NK cells can also influence the immune state and function of other immune cells in TIME.[47–49] Thus, NK cells mainly serve as important players in boosting antitumor immune response against tumors. NK-cell dysfunction can lead to severe immune deficiency that allows tumor cells to escape immune surveillance and thrive in the TIME. It is noteworthy that NK-cell dysfunction has been reported in the TIME of HCC,[50] but the mechanism underlying the abnormal behavior of NK cells in HCC is unknown.

To the best of our knowledge, studies describing the role of ncRNAs in mediating NK-cell activity, including infiltration, activation, exhaustion, and function during HCC progression are increasing. Chen *et al*.[22] found that upregulation of miR-561-5p expression suppressed CX_3CR1^+ NK-cell infiltration and activation by targeting CX_3CL1, thereby promoting HCC tumorigenesis and pulmonary metastasis. miR-561-5p in HCC tumor cells reduced secretion of CX_3CL1, a chemokine known to be associated with lymphocyte migration. Loss of CX_3CL1 in TIME interfered with chemotaxis and activation of CX_3CR1^+ NK cells by inactivating STAT3 signaling in NK cells. As CX_3CR1^+ NK cells have strong tumor-killing activity, inhibiting the infiltration and cytotoxic activity of CX_3CR1^+ NK cells enabled HCC cells to escape immune surveillance, and promoted HCC proliferation and metastasis. A recent study reported that HCC cell-derived exosomal circUHRF1 contributed to immune evasion and resistance to anti-PD1 immunother-

apy in HCC by inducing NK-cell exhaustion and suppressed IFN-γ and TNF-α production in NK cells. circUHRF1-mediated exhaustion and dysfunction of NK cells was attributed to increased expression of inhibitory receptor TIM-3 in NK cells.[23]

In HCC, the cytotoxicity of NK cells is governed by multiple ncRNAs. Low expression of the lncRNA GAS5 in the NK cells of HCC patients inhibits cytotoxic activity and accelerates tumor metastasis. Mechanistic studies show that lncRNA GAS5 deficiency inhibited RUNX3 expression in NK cells by upregulating miR-544, which suppressed the NCR1/NKp46 axis. NKp46 is a stimulatory receptor on the NK cell surface, and its inactivation impairs the killing activity of NK cells. The evidence indicates that the miR-544/RUNX3/NCR1/NKp46 pathway accounted for the GAS5-mediated regulation of NK-cell cytotoxicity.[24,51] Another study reported that downregulated hsa_circ_0007456 in HCC cells reduced the cytotoxicity of NK cells toward tumor cells, which promoted immune evasion and aggressiveness of HCC. To be specific, hsa_circ_0007456 deficiency restored miR-6852-3p level and interfered with the expression of ICAM-1. ICAM-1 was reported to regulate the adhesion of cancer cells and NK cells. Hsa_circ_0007456-mediated interference of ICAM-1 decreased the susceptibility of HCC cells to NK cytolysis.[25–53] Similarly, circRNA ARSP91 was found to enhance the cytotoxicity of NK cells toward HCC cells by upregulating UL16 binding protein 1, an NKG2D ligand that activates stimulatory receptors associated with the tumor-killing function of NK cells.[26,54,55] Many other ncRNAs are also known to modulate the cytotoxicity of NK cells against HCC cells, such as miR-615-5p,[56] miR-146a,[57] miR-30c-1,[58] and miR-506.[59] The available evidence supports a role of ncRNAs in the regulation of NK cells during the development of HCC. Some of the ncRNAs may be potential therapeutic targets to enhance the efficacy of NK cell-based anticancer immunotherapy in the treatment of HCC.

ncRNAs and DCs

DCs are considered the most efficient antigen-presenting cells with a key role in linking innate and adaptive immune system. They take up and process antigens, converting them into peptides that are presented to T cells by major histocompatibility complex molecules that trigger activation and protective immune responses. In the tumor milieu, normal DC activity is disturbed and often has immunosuppressive and tolerogenic effects that boosts the malignant progression of tumors.[60,61] Studies of dendritic cells in HCC are relatively scarce despite considerable evidence showing they have a critical role in many malignancies. ncRNAs have been shown to regulate the development, differentiation, recruitment, and function of DCs in many cancers, but their regulatory roles in the pathogenesis of HCC have not been extensively studies.[8,9,62] In recent years, several ncRNAs were reported to mediate the infiltration of dendritic cells in HCC. For example, Wu *et al*.[63] found that the expression level of lncRNA ASB16-AS1 was negatively correlated with tumor-infiltrating neutrophils in HCC, as shown by CIBERSORT, TIMER, xCell, quanTIseq, EPIC and MCP-counter.[63] The CIBERSORT algorithm confirmed that that MIR210HG was negatively correlated with, and LINC01224 was positively correlated, with DC infiltration.[64] The detailed molecular mechanisms were not described in the studies.

ncRNAs and adaptive immune cells in TIME

Despite being prominent regulators for many types of innate immune cells within TIME of HCC, emerging evidence has revealed that ncRNAs also participate in the regulation of adaptive immune cells, including various T and B cell subgroups (Table 2, Fig. 2).[65–73]

ncRNAs and T cells

T lymphocytes are the primary effector cells in cellular immunity and include subsets with distinct roles in immunity and immune-mediated pathologies.[74] Cytotoxic T cells (CTLs) kill and eradicate malignant cells.[75] T-helper (Th) cells are differentiated from $CD4^+$ T cells and have subpopulations with either pro- or antitumorigenic activity in the tumor milieu.[76] Regulatory T cells (Tregs) are differentiated from $CD4^+$ T cells and suppress antitumor responses of other immune cells, with immunosuppressive activity in the TIME. Infiltration of a large number of Tregs into tumor tissue is often associated with poor prognosis.[77] Additionally, In the setting of HCC, recent studies have shown that substantial changes in the expression profiles of ncRNAs occur during T-cell development, activation, and differentiation, indicating a crucial role of ncRNAs in regulating T-cell activity.

Increasing evidence shows the pivotal role of ncRNAs in mediating the antitumor response of CTLs against malignant HCC cells. For example, lncRNA NEAT1 was shown to contribute to the immune escape of HCC by affecting the antitumor activity of $CD8^+$ T cells. The lncRNA NEAT1 was significantly upregulated in the PBMCs of HCC patients, and overexpression of lncRNA NEAT1 induced $CD8^+$ T-cell apoptosis and impaired the cytolysis of HCC cells via regulating miR-155/Tim-3 signaling. Tim-3 is an inhibitory immune checkpoint receptor expressed on T cells; its activation enforces T-cell exhaustion and induces T-cell apoptosis and dysfunction.[65,78] The lncRNA lnc-Tim3 was shown to stimulate $CD8^+$ T-cell exhaustion by targeting Tim-3, and was linked to immunosuppression and malignant behavior in HCC. Mechanistically, lnc-Tim3 competitively bound to Tim-3 in $CD8^+$ T cells, resulting in release of Bat3 from the C-terminal end of Tim-3 and accumulation of the catalytically inactive form of Lck, which suppressed downstream T-cell signaling (ZAP70/AP-1/NF-AT1 signaling) and endogenous cytokine production (IL2/IFN-γ). The released Bat3 formed a complex with p300, which increased its nuclear translocation and enhanced p300-dependent p53 and RelA transcriptional activation of anti-apoptosis genes and promoted survival of $Tim\text{-}3^+$ exhausted $CD8^+$ T cells. The dual mechanism contributed to $CD8^+$ T-cell exhaustion.[66] In addition, the circRNA circMET is preferentially expressed in HCC tumors and associated with poor clinical outcomes. CircMET overexpression hinders $CD8^+$ T-cell infiltration in HCC tissues through the miR-30-5p/Snail/DPP4/CXCL10 axis, which enhances the immunosuppressive properties of TIME that favor HCC cell survival and metastasis.[67]

Th cell differentiation results from regulation of genes and involves transcription factors, including STAT3, RUNX-1, and others.[79] However, ncRNAs are also emerging as important regulators of Th cell differentiation. Feng *et al*.[68] observed that overexpression of miR-132 promoted Th17 differentiation and production of IL22 and IL17 possibly by targeting of the downstream protein SNIP1. IL22 activated hepatic stellate cells (HSCs), which then promoted HCC cell migration and epithelial-mesenchymal transition (EMT).[68]

ncRNAs are also implicated in the modulation of Tregs in HCC. For example, HBV infection-activated TGF-β signaling suppresses the expression of microRNA-34a, resulting in increased production of CCL22, which facilitates recruitment of $CD4^+CD25^+$ Tregs into the TIME. Sustained activation of TGF-β-miR-34a-CCL22 axis promotes the development of intrahepatic venous metastasis in HCC patients via generating an immunosuppressive TIME that favors tumor cell survival and dissemination.[69] ncRNAs have also been found to partici-

Table 2. ncRNAs involved in the regulation of adaptive immune cells

NcRNA	Expression in HCC	Related immune cell	Target molecules/pathway	Function in TIME	Impact on HCC	Reference
lncRNA NEAT1	Upregulated	$CD8^+$ T cells	miR-155/Tim-3	Induce $CD8^+$ T cells apoptosis and dampen its cytolysis activity against HCC cells	Promote immune evasion and tumor progression	65
lncRNA lnc-Tim3	Upregulated	$CD8^+$ T cells	Tim-3/Bat3/Lck/ZAP70/AP-1/NF-AT1 and Bat3/p300/p53/RelA	Stimulate $CD8^+$ T-cell exhaustion	Promote immunosuppression and tumor growth	66
circRNA circMET	Upregulated	$CD8^+$ T lymphocytes	miR-30-5p/Snail/DPP4/CXCL10	Stimulate $CD8^+$ lymphocyte infiltration	Enhance immunosuppression	67
microRNA-132	Upregulated	Th17	SNIP1	Promote Th17 differentiation and function	Promote HCC cell migration and EMT	68
microRNA-34a	Downregulated	Tregs	CCL22	Suppress Treg recruitment	Enhance immune surveillance, suppress tumor growth, and metastasis	69
lncRNA EGFR	Upregulated	Tregs	EGFR/AP-1/NF-AT1	Stimulate Treg differentiation, inhibit CTL activity	Promote immunosuppression and HCC growth	70
circRNA circGSE1	Upregulated	Tregs	miR-324-5p/TGFBR1/Smad3/FOXP3 axis	Induce the expansion of Tregs	Promote immune escape, enhance tumor growth and metastasis	71
lncRNA FENDRR	Downregulated	Tregs	miR-423-5p/GADD45B	Inhibit Treg infiltration	Suppress immune escape and tumor growth	72
lncRNA LINC00261	Downregulated	B cells	miR105-5p/SELL	Promote B-cell dysfunction	Promote HCC progression	73

HCC, hepatocellular carcinoma; NA, not available; ncRNA, noncoding RNA; Th, T-helper cell; TIME, tumor immune microenvironment; Treg, regulatory T cells.

pate in the differentiation of Tregs during HCC development, as shown by lncRNA lnc-EGFR. Lnc-EGFR is highly expressed in Tregs of HCC patients and is positively correlated with HCC immune evasion and tumor growth. Lnc-EGFR specifically binds to epithelial growth factor receptor (EGFR) and stabilizes it by blocking its ubiquitination by c-CBL. Persistent activation of EGFR triggers a. downstream signaling cascade (RAS/ERK/AP-1/NF-AT1). It is important to note that the NF-AT transcription factors are widely expressed in a variety of leukocytes, including T cells, and regulate genes involved in lymphocyte development. lnc-EGFR-activated AP-1/NF-AT1 signaling has been shown to stimulate Treg differentiation, as shown by an increased ratio of Tregs in $CD4^+$ T cells and in TIME. Intriguingly, the AP-1/NF-AT1 complex enhanced transcription of lnc-EGFR, EGFR, and Foxp3 by binding to their promoters, thus forming a forward-feedback loop in Tregs that impaired antitumor immunity and promoted HCC progression.[70] Similarly, exosomal circGSE1 from HCC cells promoted immune escape, tumor growth, and metastasis by promoting Treg differentiation and proliferation by regulating an miR-324-5p/TGFBR1/Smad3/FOXP3 axis.[71] In addition, Yu *et al*.[72] reported that poorly expressed lncRNA FENDRR in HCC cells acted an miR-423-5p sponge to downregulate GADD45B, enhance the immune-suppressive activity of Tregs, and allow HCC cells to escape from immune surveillance.[72] Taken together, the studies underscore the crucial role of ncRNAs in T cell-mediated immunosuppression and might inspire immunotherapy.

NcRNAs and B cells

The importance of T cells in tumor immune surveillance is well established, but the contribution of B cells has been studied to a much lesser extent. B cells contribute to humoral immunity by producing antibodies. Recent advances in B-cell biology have revealed that B cells participate in antigen presentation, promote T-cell responses, and release a variety of cytokines. B cell subsets have protumor or antitumor activities, including regulatory B cells with immunosuppressive activity.[80,81] Recent studies have shown tumor-infiltrating B cells were associated with tumor progression and immunotherapy response in human cancers, including HCC.[82–84] The regulatory role of ncRNAs during B-cell development, differentiation, apoptosis, and function have been described,[8,85,86] but little is known of ncRNA-mediated B-cell regulation of the pathogenesis of HCC. A recent bioinformatics analysis revealed that the LINC00261/MiR105-5p/SELL signaling axis was involved in B-cell dysfunction and was associated with overall survival in HCC patients. Details of the molecular mechanism were not clarified.[73]

ncRNAs and other stromal components in the TIME

In. addition to immune cells, CSCs, HSCs, CAFs, and many other stromal cells are components of the TIME in HCC.[6] Evidence of the regulatory effects of ncRNAs on a variety of non-immune cells is increasing (Table 3, Fig. 2).[87–92–99]

ncRNAs and CSCs

Cancer stem cells (CSCs) are a rare population of cells within the tumor bulk that share many intrinsic features with normal stem cells, such as self-renewal and differentiation. CSCs have been found to exist in many solid tumors, including HCC. The stem-cell like properties of liver CSCs may contribute to the heterogeneity, resistance to treatment, metastasis, and high rate of recurrence of HCC, which makes CSCs an attractive target for cancer therapy.[100,101] Recently, increasing studies have described the ability of ncRNAs to modulate self-renewal, differentiation, and stemness of liver CSCs through activating diverse CSC-related signaling pathways, such as Wnt-β-catenin signaling, YAP signaling, Hedgehog signaling, STAT3 signaling, TGF-β signaling, or cell cycle-related signaling.[101] LncRNA lncTCF7 and lnc-β-Catm, both are seen highly expressed in HCC tumor tissues and liver CSCs and correlate with poor prognosis in HCC, promote self-renewal maintenance of liver CSCs through activation of Wnt-β-catenin signaling pathway. Mechanistically, lncTCF7 recruits the SWI/SNF chromatin remodeling complex to the promoter region of target gene TCF7 to promote its transcription. TCF7 then triggers downstream Wnt signaling cascade, which primes the self-renewal of liver CSCs and tumor propagation. Lnc-β-Catm associates with EZH2 to catalyze methylation of β-catenin, thus hindering β-catenin ubiquitination and stabilizing it, allowing β-catenin to start Wnt signaling and sustain the self-renewal of liver CSCs.[87,88] Similarly, lncBRM sequesters BRM to form BRG1-BAF complex, starting YAP1 signaling in liver CSCs, which drives CSC self-renewal process.[89] lncHDAC2 is highly expressed in the $CD13^+CD133^+$ subset of liver CSCs, where it contributes to self-renewal maintenance by recruiting the nucleosome remodeling and deacetylase (NuRD) complex to promote PTCH1 and activate Hedgehog signaling.[90] Another lncRNA lncSOX4 mediates liver CSCs self-renewal via STAT3-SOX4 signaling axis. LncSOX4 interacts with and recruits STAT3 to bind to SOX4 promoter, triggering SOX4 expression, which is required for liver CSCs self-renewal and tumor initiation.[91] In addition, lncRNA-DILC is examined significantly downregulated in $EPCAM^+$ CSCs; it abrogates IL6 transcription and abolishes STAT3 activation, thus repressing self-renewal and expansion of liver CSCs. Lnc-DILC depletion helps with HCC start and progression.[92]

NcRNAs and HSCs

HSCs play vital roles in the tumorigenesis and progression of HCC, largely because activation of HSCs contributes to hepatic fibrosis. HSCs can secrete a variety of bioactive contents to maintain liver inflammation and regulate tumor-associated pathways, which then trigger immunosuppression, angiogenesis, and therapy resistance of HCC. Under pathological conditions, HSCs are changed from the quiescent stage to the active stage, and the activated HSCs eventually differentiate into myofibroblast-like cells.[102,103] Increasing studies have described the molecular mechanisms underlying HSC activation, and ncRNAs emerge as prominent participants in the regulation of HSC activation. For example, as the Wnt-β-catenin signaling pathway is documented to be generally hyperactivated in HSCs during liver fibrosis to orchestrate cell activation, proliferation, and maintain homeostasis,[104] many ncRNAs have been revealed to regulate HSC activation via Wnt-β-catenin pathway, as exampled by microRNA-145 and microRNA-708. MicroRNA-145 and microRNA-708 are both poorly expressed in fibrotic liver tissues and activated HSCs, and their deregulations are both able to activate the Wnt-β-catenin pathway via increasing expression of ZEB2 and ZEB1, respectively. The hyperactivated Wnt-β-catenin pathway thus accelerates the activation and proliferation of HSCs.[93,94] Hedgehog (Hh) signaling is another cascade activated in HSCs and regulates hepatic fibrogenesis. Hh signaling is also regulated by various ncRNAs, such as lncRNA-MEG3, microRNA-378, etc. LncRNA-MEG3 inhibits Hh signaling-mediated EMT process in HSC activation via associating with SMO protein and sponging miR-212. While microRNA-378 limits HSC activation by suppressing Gli3 expression, which is a downstream transcription factor of Hh signaling.[95,96] Zhou *et al*.[97]

Table 3. ncRNAs involved in the regulation of other stromal cells in TIME

NcRNA	Expression in HCC	Related stromal cell	Target molecules/ pathways	Function in TIME	Impact on HCC	References
lncRNA lncTCF7	Upregulated	CSCs	TCF7/Wnt signaling	Promote self-renewal of human liver CSCs	Promote tumor propagation	87
lncRNA lnc-β-Catm	Upregulated	CSCs	EZH2/Wnt-β-catenin	Sustain liver CSC self-renewal	Promote tumor propagation	88
lncRNA LncBRM	Upregulated	CSCs	YAP signaling	Promote CSC self-renewal	Promote tumor propagation	89
lncRNA lncHDAC2	Upregulated	CSCs	Hedgehog signaling	Promote self-renewal of liver CSCs	Promote tumor growth	90
lncRNA lncSOX4	Upregulated	CSCs	STAT3/SOX4 signaling	Sustain liver CSC self-renewal	Promote tumor initiation	91
lncRNA lnc-DILC	Downregulated	CSCs	IL-6/JAK2/STAT3 a signaling	Suppress self-renewal of liver CSCs	Inhibit tumor initiation and progression	92
microRNA-145	Downregulated	HSCs	ZEB2/Wnt-β-catenin	Repress HSC activation and proliferation	Repress liver fibrosis and tumorigenesis	93
microRNA-708	Downregulated	HSCs	ZEB1/Wnt-β-catenin	Repress HSC activation and proliferation	Repress liver fibrosis and tumorigenesis	94
lncRNA-MEG3	Downregulated	HSCs	miR-212/SMO/ Hh signaling	Inhibit HSC activation	Inhibit liver fibrosis	95
microRNA-378	Downregulated	HSCs	Hh signaling	Limit HSC activation	Inhibit liver fibrosis	96
microRNA-21	Upregulated	HSCs, CAFs	PTEN/PDK1/ AKT signaling	Convert HSCs to CAFs	Promote HCC angiogenesis	97
microRNA-124	Downregulated	HSCs	IQGAP1/NF-κB axis	Inhibit cytokine secretion of HSCs	Reduce inflammatory response	98
miR-1247-3p	Upregulated	CAFs	B4GALT3, β1-integrin/ NF-κB axis	Induce CAF activation	Foster lung metastasis of HCC	99

CAF, cancer-associated fibroblast; CSC, cancer stem cell; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; NA, not available; ncRNA, noncoding RNA; TIME, tumor immune microenvironment.

identified that tumor-derived exosomal miRNA-21 was internalized by HSCs and it directly targeted phosphatase and tensin homolog (PTEN), resulting in activation of PDK1/AKT signaling in HSCs, which primed the conversion from normal HSCs to CAFs and promoted angiogenesis of HCC. ncRNAs can also impair the HSC function to produce inflammatory cytokines. One such example is microRNA-124, which inhibits HSC secretion of TNF-α, IL-1β, and IL-6 by targeting the IQGAP1/NF-κB axis.[98]

ncRNAs and CAFs

As the most important and abundant component of the stromal cell population in TIME, CAFs are crucial players during the occurrence and malignant progression of HCC. Upon stimulation by the TIME, fibroblasts are activated and converted into CAFs. CAFs have been reported to modulate HCC progression through diverse mechanisms, including remodeling the extracellular matrix, secreting soluble factors or exosomes, and regulating the behavior of various immune cells, which can either potentiate or oppose HCC progression.[105–107] Many ncRNAs are known to regulate CAF formation and activation during HCC development. For example, the abovementioned HCC cell-derived miR-21 could convert HSCs into CAFs via targeting PTEN and activating PDK1/AKT signaling cascade in HSCs. Activated CAFs release various angiogenic factors to stimulate angiogenesis in HCC tumors.[97] Fang and colleagues unveil that HCC cell-derived exosomal miR-1247-3p potentiates CAFs activation to foster lung metastasis of HCC. Mechanistically, miR-1247-3p is transferred from HCC cells to fibroblasts in lung pre-metastasis niche via exosomes. MiR-1247-3p subsequently drives normal fibroblast transformation to CAFs by decreasing its target gene B4GALT3 expression to activate β1-integrin-NF-κB signaling. Activated CAFs promote stemness, EMT, chemoresistance, and tumorigenicity of HCC cells by releasing IL-6 and IL-8.[99] Finally, dynamic intercellular communications mediated by exosomes are widely seen between CAFs and HCC cells and strongly affect HCC progression and therapy response.[108] Therefore, as a major cargo in exosomes, ncRNAs are speculated to play important roles during the interaction, which deserves further elucidation.

Diagnostic/therapeutic potential of ncRNAs in HCC

One reason leading to the high mortality of HCC is that a significant percentage of patients is diagnosed at advanced stages. The diagnosis of HCC relies on serum α-fetoprotein measurement and ultrasonography imaging, etc. However, these diagnostic modalities still remain insufficient, especially for diagnosis of early-stage HCC.[5] Therefore, novel biomarkers with higher sensitivity and specificity are urgently needed. Emerging evidence indicates that a myriad of ncRNAs show aberrant and tissue-specific/cell-specific expression patterns in HCC, and many are detectable and relatively stable in body fluids. These unique properties of ncRNAs make them promising noninvasive biomarkers for HCC detection. Besides, ncRNAs also display prognostic value since the expression levels of multiple ncRNAs are closely correlated with tumor stage and clinical outcomes of HCC, such as metastasis and recurrence.[11] In addition, certain ncRNAs that modulate resistance are proven to be associated with treatment response, indicating their potential to predict treatment response.[23,109] Of note, many ncRNAs are encapsulated in circulating exosomes, which protect them from being degraded by RNase. And exosomal ncRNA detection has the advantage of noninvasive, repeatable, and real-time tracking.[110,111] Taken together, ncRNAs could serve as potential diagnostic/prognostic biomarkers, however, further efforts must validate the sensitivity and specificity of them as biomarkers.

Despite a lack of reliable biomarkers, effective therapeutic options/targets are also limited for HCC treatment.[5] Recently, ncRNAs have been documented to play widespread roles in gene regulation and participate in diverse signaling cascades.[112] Most important, ncRNAs function as a pivotal regulator in TIME during HCC progression by influencing the differentiation, activation, recruitment, and function of various types of cells within TIME, including diverse immune cells and many other nonimmune stromal cells. The ncRNA-mediated regulation of the TIME and cancer type-specific deregulation of ncRNAs indicate that ncRNAs are highly promising therapeutic targets for HCC treatment. To date, many approaches have been developed to target ncRNAs and govern their expression or function, including small molecule inhibitors, aptamers, antisense oligonucleotides, RNA interference, and CRISPR/Cas9 gene editing technology.[113–115] RNA-based therapeutic method is still in its infancy and many difficulties and limitations have emerged during its application. For example, difficulty of using antisense oligonucleotides is to optimize their specific delivery to target cells and to augment their stability *in vivo*.[113] One challenge of CRISPR/Cas9 is to avoid adverse off-target effects. Besides, there are concerns like whether these treatments might cause unwanted side effects, such as affecting other parts within TIME.[112,114] In addition, many ncRNAs exist in regulatory feedback loops, thus, it might be difficult to modulate their expression. Overcoming these challenges will improve the efficacy of these RNA-based cancer therapies.

It is important to highlight that ncRNA-based therapy is a promising approach in HCC immunotherapy. Given their vital roles in TIME, it might be possible to modulate the immune response of multiple immune cells within TIME by manipulating the expression pattern of specific ncRNA, such as facilitating recruitment of various antitumor immune cells to the tumor site, enhancing cytotoxicity of NK cells, inhibiting the function of immunosuppressive cells, which could be effective to boost antitumor immune response and restrain immune escape, ultimately hindering tumor growth and malignant progression. In addition, targeting different ncRNAs combined with other therapeutic strategies might show significant benefit in the treatment of HCC. For example, given that circUHRF1 has been proven to drive resistance to anti-PD1 immunotherapy in HCC patients,[23] the combined therapy of ncRNA-targeted drugs and anti-PD1 immunotherapy may therefore display synergistic effects in inhibiting tumor progression.

Conclusions and perspectives

TIME is an integrated system consisting of diverse cellular and noncellular parts. It closely interacts with tumors and greatly contributes to the occurrence and progression of HCC. And as summarized in this review, ncRNA is emerging as a prominent regulator in reprogramming the TIME of HCC. An impressive number of ncRNAs exhibit aberrant expression patterns in HCC, and they can modulate the development, biological behavior, and function of various cell types within the TIME, which ultimately elicit profound influences on tumorigenesis, tumor growth, metastasis, angiogenesis, and immune evasion in HCC. Of note, the current knowledge regarding the regulatory role of ncRNAs in TIME principally focuses on miRNAs and lncRNAs, but novel classes of ncRNA like circRNAs and piRNAs await further investigation. Accumulating evidence has indicated ncRNAs as important me-

diator in the crosstalk between TIME and neoplastic cells in various cancer types, but their mediatory role has not been elucidated in HCC. Apart from focusing on regulating ncRNAs on TIME, it is also important to dissect the exact mechanisms of how ncRNAs are dysregulated in TIME of HCC, which lets us gain a more comprehensive understanding of the complex regulatory network between TIME and ncRNAs in HCC pathogenesis. Because of the roles of ncRNAs within TIME of HCC, novel diagnostic/prognostic biomarkers and therapeutic interventions based on ncRNAs are under development for treating HCC, however, the majority are still in the experimental stages due to various limitations. Further investigations must translate those research findings into clinical applications.

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Conflict of interest

KY has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2023. The other authors have no conflicts of interest related to this publication.

Author contributions

Drafting of the manuscript (YL), critical revision of the manuscript for important intellectual content (ZW, KY). All authors made significant contributions to the study and approved the final manuscript.

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