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Review Article

miRNA and lncRNA as potential tissue biomarkers in hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is primary liver cancer, frequently diagnosed at advanced stages with limited therapeutic options. MicroRNAs (miRNAs) regulate target gene expression and through inhibitory competitive binding of miRNA influence cellular processes including carcinogenesis. Extensive evidence proved that certain miRNA's are specifically expressed in neoplastic tissues of HCC patients and are confirmed as important factors that can participate in the regulation of key signalling pathways in cancer cells. As such, miRNAs have a great potential in the clinical diagnosis and treatment of HCC and can improve the limitations of standard diagnosis and treatment. Long non-coding RNAs (lncRNAs) have a critical role in the development and progression of HCC. HCC-related lncRNAs have been demonstrated to exhibit abnormal expression and contribute to transformation process (such as proliferation, apoptosis, accelerated vascular formation, and gain of invasive potential) through their interaction with DNA, RNA, or proteins. LncRNAs can bind mRNAs to release their target mRNA and enable its translation. These lncRNA-miRNA networks regulate cancer cell expression and so its proliferation, apoptosis, invasion, metastasis, angiogenesis, epithelial-mesenchymal transition (EMT), drug resistance, and autophagy. In this narrative review, we focus on miRNA and lncRNA in HCC tumor tissue and their interaction as current tools, and biomarkers and therapeutic targets unravelled in recent years.

1. Introduction

Hepatocellular carcinoma (HCC) can arise from different aetiology, it can develop from simple steatosis, later progressing to fibrosis and cirrhosis [1]. HCC can be divided into three classes macrovesicular steatosis MaS-HCC, microvesicular steatosis MiS-HCC, and conventional HCC depending on the extent of fatty acid change and the size of lipid droplets each category displayed unique clinicopathological traits. The baseline level of liver steatosis was also significantly worse in patients with MaS-HCC compared to those with cHCC [2]. The main risk factors are hepatitis B virus (HBV) infection, hepatitis C (HCV) infection, chronic alcohol consumption and metabolic disorder such as obesity, type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [3,4]. Different genotoxic exposures, such as oxidative stress, reactive oxygen species (ROS), and reactive nitrogen species (RNS), which are typical metabolic byproducts of several oxidation-reduction (redox) processes, lead to different molecular pathogenesis of HCC. However, improvements in our understanding of the disease's biology and underlying causes have not yet been used in therapeutic settings. About 25 % of HCC tumors have therapeutically-relevant mutations, although the incidence of most mutations is less than 10 %, making proof-of-concept studies more difficult. In fact, untargetable mutations in telomerase reverse transcriptase (TERT), Tumor protein P53 (TP53), and Catenin beta-1 (CTNNB1) are still the leading causes of HCC [5]. The ideal way to convert molecular and immunological categorizations into biomarkers that guide therapy is currently an open area of investigation. The tumor microenvironment, especially immunological and platelet activation,

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has been shown to play a significant role in the pathophysiology of NASH-associated HCC, according to new findings that have defined the processes underlying this illness [6,7]. The converging underlying mechanisms is chronic inflammation assumed to account for 90 % of HCC [8]. It is well established that cirrhosis can be seen in between 80 and 90 % of HCC patients who have any underlying liver disease, it is also the most significant risk factor for HCC [9]. In 2020, HCC ranked as the 6th most common type of cancer and the 3rd leading cause of cancer-related mortality [10]. The oncogenic transformation of hepatocytes is a complex biological process caused by several genetic and epigenetic modifications [11]. miRNAs play a vital role in cell life activities, and various studies have confirmed that the abnormal miRNA expression in HCC is associated with increased proliferation, metastasis and apoptosis of HCC cells through various pathways [12]. In the early stage of HCC, surgical resection and liver transplantation are successful therapeutical options. The recurrence rate after resection is between 8.3 and 35 % [13,14]. However, major challenge is the lack of therapeutic options in advanced stages of HCC. Table 1 summarizes the stages of HCC and the therapeutic options available.

2. miRNA and lncRNA function and biogenesis

In recent years, non-coding RNAs (ncRNAs) including miRNAs and lncRNAs have been widely reported as a new class of clinical biomarkers and potential therapeutic targets for cancers including liver cancer [15]. ncRNAs can be divided into two groups. According to the molecular size of ncRNA, it can be classified as either small non-coding RNA (sncRNA), measuring under 200 nucleotides in length, or long non-coding RNA (lncRNA), measuring over 200 nucleotides in length [16].

miRNAs are a class of single stranded ncRNAs, about 18–25 nucleotides long, which may regulate gene expression [17]. They can bind to the 3′UTR of target mRNAs and inhibit their translation or lead to degradation [15] (Fig. 1). Inside the nucleus, the miRNA genes are transcribed to pri-miRNA by RNA polymerase II. Pri-miRNAs are cleaved by endonuclease Drosha producing pre-miRNAs, which are then transported to the cytoplasm by exportin-5. In the cytoplasm, the pre-miRNAs are processed by a type of RNase III endonuclease, Dicer, to generate a double-stranded miRNA protein complex. One of the strands becomes mature miRNA, and binds to RNA-mediated silencing complexes (RISC) immediately. In the RISC, the mature miRNA targets the 3′-untranslated regions (3′UTR) of its target mRNAs to regulate translational inhibition or mRNA cleavage [18].

lncRNAs also play an important role in regulating gene expression, and therefore cell proliferation, differentiation in various diseases including cancers [16]. These transcripts include some that are polyadenylated at the 3′ and 5′ ends as well as spliced, just like mRNAs. lncRNA has both *trans* and *cis*-acting roles. The *cis* role is to either activate or inhibit the transcription of neigh boring genes that communicate with transcription factors (TFs), changing the epigenetic state of chromatin or the chromosomal loop. lncRNAs also work in the nucleus to carry out *trans*-specific tasks, such as helping to build paraspeckles or interacting with nuclear proteins. Among others, lncRNAs' functions are represented by engaging with cytoplasmic proteins to lengthen or shorten their half-life or by connecting with mRNA to activate or repress translation. To inhibit miRNAs in the cytoplasm, lncRNAs sequester them after exiting the nucleus and engage in interactions with cytoplasmic proteins, which may prolong their lifespan and lncRNAs can secure, or "sponge", miRNAs can interfere with their ability to bind to their target molecules these two categories should always be studied in conjunction with one another, particularly when it comes to functional research you can see in Fig. 2 [19,20].

3. The role of miRNAs in HCC

Numerous studies have shown that miRNAs can modulate the cell cycle influencing control of cell growth and death [51]. For example by targeting the enhancer of zeste homolog 2 (EZH2), increased expression of miR-98 prevented growth of HCC cells in the G0/G1 phase [51]. Another example is miR-7, which according to Wu et al. could potentially be involved in the development of various human malignancies, including HCC [15]. In their study, they identified Kruppel-like Factor (KLF-4) as the target of miR-7, leading to dysregulation of PI3K/Akt axis [21]. Analysis of 50 surgically resected HCC specimens in pairs with matching peritumor tissues proved, that miR-7 is downregulated in HCC, and further functional studies revealed that it may act as a tumor suppressor by preventing cell migration and proliferation [21]. The overexpression of miR-10b in HCC induced the HOXD10/RhoC/u-PAR/MMPs pathway, which promoted HCC cell motility and invasion [22]. The Cancer Genome Atlas (TCGA) dataset of 363 HCC tumor tissues and 50 nontumor liver revealed a substantial overexpression association between miR-10b-5p, miR-18a-5p, miR-215-5p, and miR-940 and poor OS in HCC patients [23]. miR-21 was identified as particularly significant in HCC, being upregulated in tumor tissue and its elevated levels have been associated with poor overall survival in HCC patients [24]. The levels of miR-21 and miR-122 have been demonstrated to have a direct relationship with creatinine. miR-21 was proven as a diagnostic marker it has been hypothesized that the diagnostic value of miR-21 may potentially be influenced by the functioning of the HCC as well as for other malignant disorders such gastric and colorectal cancers [25]. Through bioinformatics prediction, literature research, and real-time PCR, they showed enhanced miR-32-5p was discovered to play tumorigenic role in multiple cancer types, including HCC [26] However, whether it contributes to HCC's multidrug resistance is still unknown [26]. miR-32-5p increased expression in HCC tissues acts as a negative prognostic marker [27]. Likewise, miR-92a [28], and miR-221 [29], due to their elevated expression in tumor tissues, are prognostic markers for fatal HCC [27]. Low expression of miR-92b in tumor tissue act as a prognostic marker [30]. List of miRNA functions in HCC are collected in Table 2.

According to the data from TCGA, significant downregulation of miR-122-5p is reported in HCC patients suggesting its potential involvement in the development and progression of HCC when it compared healthy control [55]. miR-122-5p regulates various genes and pathways associated with crucial cellular processes, including cell proliferation, apoptosis, metabolism, and tumor suppression, which may slow down tumor growth by reducing genome replication. Moreover, using data from the GEO database, it was found that miR-122-5p downregulation was highly correlated with tumor vascular invasion,

Table 1
Hepatocellular Carcinoma stages, therapeutic targets, and treatments based on Barcelona Clinic Liver Cancer.

Hepatocellular carcinoma						
Stages	Stage 0 Very early stage 1 nodule< 2 cm/High portal pressure and bilirubin	Stage A-C Early stage 3 nodules <3 cm diseases associated		Intermediate >3 lesions of any size	Advanced	Stage D Terminal stage
Treatment	Resection	Yes Radio frequency ablation/ Percutaneous ethanol injection	No Liver Transplantation	Transarterial chemoembolization	Atezolizumab+Bevacizumab Sorafenib	Palliative care

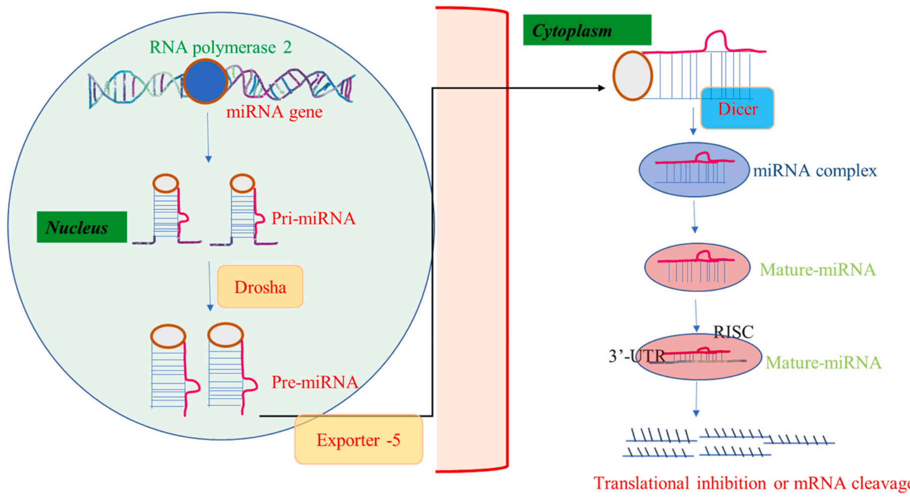

Fig. 1. Biosynthesis of miRNA.

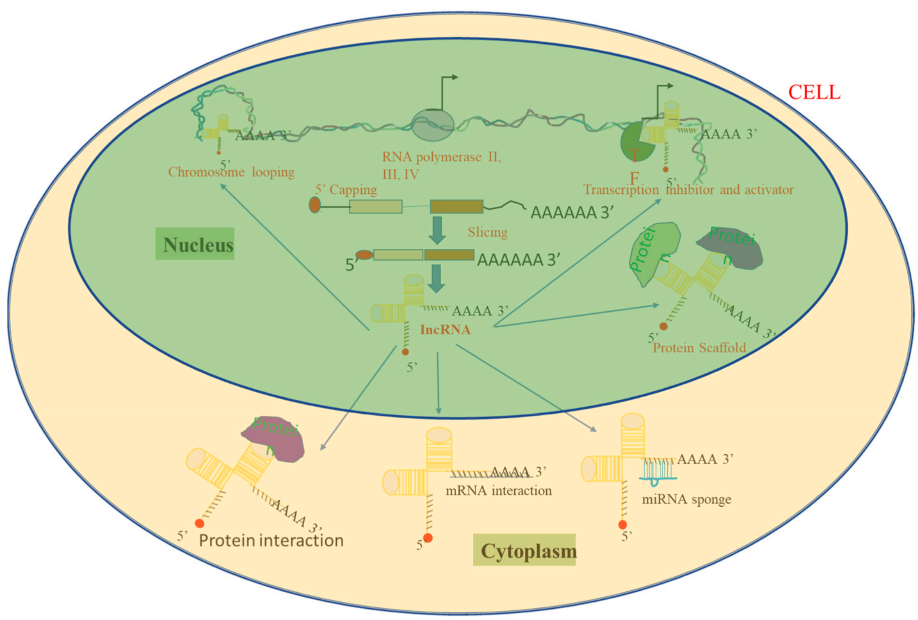

Fig. 2. lncRNA biogenesis: lncRNAs are generated and processed very similarly to mRNAs.

metastasis, sex, and viral infection in HCC tissues compared to healty control [55]. In earlier research, mice deficient in the miR-122 gene were shown to have characteristics that included hepatic steatosis, liver inflammation, fibrosis, and HCC, miR-122 was found to regulate the Hippo pathway by targeting multiple genes including Taz and Ppp1cc [56], and Wnt1/β-catenin pathway [57], proving the function of miR-122 in liver development and pathology discovered in the bio-informatical studies mentioned earlier.

miRNA-125b suppresses Akt phosporylation and cell proliferation in hepatoma cells. according to Li et al. miRNA −125b presents specific microarray profiles that can be used for early HCC diagnosis [58]. Most HCC cases had low levels of miRNA-125b expression, which is inversely correlated with the cell proliferation index [59,60]. According to Liang et al. and Haixia et al., miRNA-125b suppresses the expression of oncogenic LIN28B in HCC, which has been shown to have tumor-suppressive effects index [59]. miR-139-3p correlate positively with HCC according to a TCGA data analysis, which comprised 387 HCC patient tissues and 62 adjacent tissue samples [61]. miR-139-5p can be used to accurately predict the three-year survival rate of HCC patients [61]. In 2017, Devhare et al. demonstrated a substantial increase of miR-146a, miR-150, and miR-155 in HCV-infected African American patients when compared to Caucasian American patients. miR-150 was highly expressed in liver cirrhosis but also in HCV infected of HCC-tissue African American patients [62]. Latest research found that miR-155-5p was associated with high-risk HCC TNM stage and led to HCC malignancy both in vitro and in vivo. miR-155-5p was discovered to enhance HCC cell line increasing proliferation while inhibiting apoptosis but prevented apoptosis by suppressing PTEN, which increased PI3K/Akt pathway activation. miR-155-5p′s carcinogenic function in BALB/c nude mice by utilizing antagomiR to downregulate it and angomiR to upregulate it [32]. miR-296-5p was downregulated in HCC tissues and through axis of brahma-related gene-1/spalt-like transcription factor 4 (Brg1/Sall4) inhibits HCC cells stemness potential [63]. miR-203a-3p.1 was discovered to be upregulated in HCC, which promotes the growth of HCC cells [64].

miR-199b-5p is overexpressed in HCC, which is one of the reasons it is able to decrease EMT as well as HCC's potential for metastasis. In addition, miR-199b-5p is able to inhibit the tendency of HCC to spread

Table 2
Up/down regulation of miRNAs affect hepatocellular carcinoma compared to adjacent normal liver tissue.

miRNA	Function	Target	Regulation	References
miR-7	Autophagy, drug resistance	mTOR	Down	[18]
miR-10b	Migration, invasion	CSMD1	Up	[18,31]
miR-15b	Proliferation, apoptosis	BCL-2	Up	[3]
miR-21	Proliferation, apoptosis	MARCKSL1	Up	[32]
miR-21	To regulate the tumor microenvironment	Not defined	Down	[33–35]
miR-23b	To promote hepatocyte proliferation	Not defined	Down	[33]
miR-25	EMT, apoptosis	Not defined	Up	[18]
miR-26a	Cell cycle	CDK6, IL-6, cyclin D2, E1, E2	Down	[3]
miR-92a	Cell growth	FBXW7		[18]
miR-150-3p	To regulate the tumor microenvironment	Not defined	Down	[33–35]
miR-155-5p	Proliferation, apoptosis, invasion, migration	PTEN	Up	[36]
miR-181a	Autophagy	Atg5	Up	[18,37]
miR-203a-3p.1	Cell growth, proliferation, metastasis	Interleukin (IL) 24	Up	[18]
miR-214-5p	Migration, invasion, EMT	WASL		[38]
miR-4417	Proliferation	TRIM35	Up	[39]
let-7a	Apoptosis, proliferation	STAT3	Down	[3]
miR-32	Prognostic marker	Not defined	Up	[40]
miR-107	Prognostic Marker	Axin2, HMGA2, HMGCS2	Up	[41]
miR-221	Prognostic marker	Not defined	Up	[42]
miR-487a	Prognostic marker	SPRED2, PIK3R1	Up	[43]
miR-33a	Prognostic marker	Not defined	Down	[44]
miR-92a	Prognostic marker	FBXW7	Up	[18]
miR-105-1	Diagnostic and prognostic marker	NCOA1	Down	[45]
miR-122	Prognostic marker	PKM2, DLX4	Down	[46]
miR-138	Prognosis marker	Cyclin D3, SP1	Down	[47]
miR-1271-5p	Prognosis marker	FOXK2	Down	[48]
miR-21	Prognosis marker/ Diagnosis marker	Maspin	Up	[15,49]
miR-122	Diagnosis/prognosis marker	Snail1, Snail2	Down	[15,50, 51]
miR-665	Prognosis marker	Not defined	Up	[52]
miR-148a	Diagnosis marker	c-Met, E-cadherin, c-Myc	Down	[53]
miR-215-5p	Prognosis marker	Not defined	Down	[23]
miR-362-3p	Poor prognosis	ZC3H13	Down	[54]
miR-425-5p	Poor prognosis	ZC3H13	Down	[54]

to other organs [65]. Contrary, miR-199a, belonging to the same family, is crucial for maintaining liver homeostasis and is downregulated in HCC [66]. In an experimental model of HCC induced by diethyl nitrosamine (DEN) in male Balb/C mice, miRNA-199a was discovered to be a therapeutical tool. After miRNA-199a therapy, the levels of alpha-fetoprotein (AFP), vascular endothelial growth factor (VEGF), and tumor necrosis factor (TNF) decreased, moreover, the tumor regressed with the restoration of normal liver architecture [67]. In vivo studies in three different mice models of HCC and therapeutic intervention with miR-342-3p, according to Komoll RM et al., have clinical significance for human HCCs. Targeting the monocarboxylic acid transporter 1 (MCT1), miR-342-3p has a role in metabolic reprogramming in HCC and serves as a tumor suppressor in HCC [68]. Wang et al. examined miRNA expression profiles by microarray in 12 pairs of HCC and matched non-HCC tissues from patients with and without HBV. Specifically, miR-223, was linked to HCC unrelated to HBV. A function for miR-335 were active in the calcium signalling pathway, glycan structures - biosynthesis 1, and Wnt signalling pathway and they also interacted with cytokine-cytokine receptors in HBV infection. Specifically altered miRNAs in HCC brought on by HBV include miR-376c-3p, and miR-663 [69]. miR-1246 expression was found to be upregulated, which facilitated HCC cells' invasion and migration [70]. Chen et al. used TCGA datasets and identified miR-3682-3p as highly expressed in HCC, and verified his results in an analysis of HCC and adjacent peritumoral tissues in a different cohort [71].

Research reveals that miRNA patterns in HCC are associated with disease aetiology, e.g. Hepatitis B or C infection, liver cirrhosis or steatosis [72]. HCC aetiology across the globe varies depending on vaccination status, way of living, excess intoxicant etc. Some of the known HCC miRNA biomarkers discovered in different populations are shown (Table 3).

4. LncRNA and their function in HCC

In HCC, the lncRNA PNUTS binds ZEB1 to promote cell proliferation and dispersion in order to activate the EMT pathway [78]. By maintaining beta-catenin's stability, lncRNA02273 stabilizes transcription of downstream genes such as c-Myc, cyclin D1, survivin, MMP-7, and COX-2. LncRNA02273 significantly boosts Hep3B and MHCC97 cell motility, invasion, and proliferation while decreasing apoptosis in HCC [79]. Through its interaction with miR-665, lncRNA LIMT influences the EMT process, and causes sorafenib resistance in HCC [80]. LncRNA 02362 increases SOCS2 expression levels and prevents HCC progression by sponging miR-516b [81]. lncRNAs are crucial in the pathophysiology of HCC caused by HBV/HBx, too. Qiu et al. demonstrated that lncRNAs HULC and HOTAIR are upregulated, these lncRNAs accelerate cell proliferation, invasion, and metastasis while decreasing apoptosis and chemosensitivity. They do this by controlling the expression of numerous protein-coding genes as well as various signalling pathways [82]. It has been demonstrated that HULC and UCA1 function as miRNA

Table 3
miRNA indicators for HCC in different populations based on previous studied.

Population	miRNAs	Regulation	Aetiology/origin	References
Chinese	miR-375 and miR-122	Up	HCC, Chronic hepatitis and healthy control/serum	[72]
	miR-88	N/A	HBV/serum	[73]
Korean	miR-10b-5p and miR-215–5p	Up	HBV/serum exosomes	[23]
Italian	miR-1246 miR-101–3p	Up Down	HCC, Cirrhosis and healthy control/ plasma	[74]
Egypt	miR-182	Up	HCV/serum	[75]
	miR-122	Down	HCC and healthy control/plasma	[76]
Indian	miR-21 miR-122	Up Down	HCC, Chronic hepatitis and healthy control/serum	[51]
Japan	miR-21	Up	HCC and Chronic hepatitis/plasma	[77]
	miR-199a	Down	HCC and Chronic hepatitis/serum	

sponges that compete with mRNA for miRNA binding [83] In relation to HCC, various lncRNAs' roles in assessment, prognosis, and treatment are highlighted below Table 4.

lncRNAs in HCC in different populations is shown (Table 5) below.

The relationship between lncRNAs and miRNAs has a direct impact on the respective target genes expression and governs the translation of proteins. Its dysregulation is crucial for tumorigenesis and the development of numerous forms of malignancies, including HCC [15] as can be seen in Table 6. Some miRNAs that function as tumor suppressors are downregulated while others that function as oncogenic miRNAs are upregulated during the onset and development of malignancies, which can be further promoted, or balanced by their interacting lncRNAs [3].

Table 4
The role of lncRNA in HCC.

lncRNA	Function	Target	Regulation	References
HULC	Resistance to chemotherapy by activating protumoural autophagy	USP22	Up	[19,84]
H19	Promotes angiogenesis, Metastasis	MAPK1	Up	[19]
NEAT1	Sorafenib resistance developed	ATGL	Up	[85]
BANCR	Decrease in response to sorafenib	Not defined	Down	[86]
MIAT	Proliferation, Invasion	β-catenin; SIRT1	Down	[87,88]
MCM3AP-AS1	Proliferation, cell cycle, and apoptosis	FOXA1	Down	[89]
MT1DP	Cell proliferation	Not defined	Down	[90]
HOXD-AS1	Metastasis	SOX4; ARHGAP11A	Up	[91,92]
CDKN2BAS	Proliferation, metastasis	ARHGAP18	Up	[92]
CRNDE	Proliferation, migration, and invasion	POU2F1	Up	[93]
AGAP2-AS1	Metastasis and EMT	Not defined	Up	[94]
CDKN2B-AS1	Proliferation, metastasis	ANXA11	Up	[95]
PTENP1	Tumor growth and proliferation	Not defined	Down	[90]
HEIH	Metastasis	Not defined	Up	[90]
LINC00853	Diagnosis marker	Not defined	Up	[96]
TSPAN12	Diagnosis/ prognosis marker	Not defined	Up	[97]
LINC00161	Diagnosis marker	Not defined	Up	[98]
lncRNA-ATB	Prognosis marker Yes/ diagnosis marker no	Not defined	Up	[19]
LOC101926913	Prognosis marker	Not defined	Up	[99]
CTD-2510F5.4	Prognosis marker	Not defined	Down	[100]
LINC00152	Diagnosis marker Yes/ prognosis marker No	Not defined	Up	[19]
LINC00942	Prognosis marker	Not defined	Up	[100]
NONHSAT053785	Diagnosis marker	Not defined	Up	[101]

Table 5
lncRNA biomarkers for HCC in different populations based on literatures.

Population	miRNAs	Regulation	Aetiology/source	References
Chinese	lnc00152	Up	HCC and healthy control/plasma	[77]
	HULC	Up	HCC and healthy control/plasma	
	lnc00978	Down	HCC, Chronic hepatitis and healthy control/ serum	[102]
	Lnc-GPR89B-15	Not defined	HCC and healthy control/serum exosome	[103]
Korean	lnc00853	Not defined	HCC, Chronic hepatitis, liver cirrhosis and healthy control/serum exosome	[96]
Japanese	MALAT1	Up	HCC and Chronic hepatitis/plasma	[77]
Egyptian	UCA1 WRAP53	Up Not defined	HCC, chronic hepatitis C infection and healthy control/serum	[104]

Table 6
mechanisms of action of lncRNA in HCC.

LncRNA	Sponge miRNA	Affected mRNA	Functions	References
RAET1K	miR-100-5p	Lactate dehydrogenase isoform A (LDHA)	Improves HCC glycolysis and development	[3]
TUG1	miR-455-3p	Hemikinase 2 (HK2)	stimulates HCC progression and metabolism	[105]
HULC	miR-107	Sphingosine kinase 1 (SPHK1)	Stimulates angiogenesis	[3]
	miR-200a-3p	Zinc Finger E-Box Binding Homeobox 1 (ZEB1)	HCC growth	[3]
	miR-372-3p	Ras-related protein Rab-11A (Rab11a)	HCC growth	[106]
LINC00488	miR-330-5p	Talin-1 (TLN1)	Enhances angiogenesis	[107]
LINC00662	miR-15a, miR-16, and miR-107	Not defined	HCC growth and metastasis	[108]
LINC00473	miR-345-5p	Forkhead box protein P1 (FOXP1)	Encourages HCC cells to become radioresistant	[109]
FOXD2-AS1	miR-150-5p	Transmembrane protein 9 (TMEM9)	Promotes sorafenib resistance in HCC	[110]
SNHG16	miR-140-5p	Not defined	Raises sorafenib resistance in HCC	[111]
	let-7b-5p	Not defined	Oxaliplatin-resistant HCC is increased	[112]
GAS6-AS2	miR-493-5p	OTU Deubiquitinase, Ubiquitin Aldehyde Binding 1 (OTUB1)	Promote HCC growth, metastasis and invasion	[113]

5. Therapeutic potential of miRNAs and lncRNAs in HCC

The characteristics of aberrant microRNA expression in HCC tissues have prompted researchers to look at these microRNAs as potential diagnostic and prognostic markers for HCC. For instance, let-7 and miR-34 have been regarded as significant diagnostics for predicting cancer survival and treatment as well as innovative cancer therapeutic approaches [32]. Twelve microRNAs were discovered to be expressed differently in HCC compared to healthy individuals across three cohorts. Indicators of cirrhosis diagnosis include miR-34a-5p, while miR-122-5p, miR-125b-5p, miR-885-5p, miR-100-5p, and miR-148a-3p are potential biomarkers for chronic hepatitis B infection [114]. There are four microRNAs in particular that can identify HCC patients from healthy controls: miR-1972, miR-193a-5p, miR-214-3p, and miR-365a-3p [114]. Liu et al. finding high levels of let-7a in tumor tissues have been linked to serosal and vein invasion, therefore, let-7a has the makings of a promising biomarker for predicting tumor invasion outcomes [115].

In the development of HCC, lncRNAs a novel type of RNA, are important player, several HCC therapeutic techniques, such as immunotherapy, chemotherapy, and surgery, may use lncRNAs as biomarkers [116].

The first-line treatment for advanced HCC is sorafenib. miR-7 was recently shown to override sorafenib resistance by inhibiting TYRO3 via the PI3-Kinase/AKT route [117]. Another investigation found that sorafenib significantly decreased miR-142-3p levels by affecting the transcription factor PU.1 [118]. miR142-3p upregulation could make HCC cells more sensitive to sorafenib by targeting genes autophagy-related 5 (ATG5) and autophagy-related 16-like (ATG16L1) [118].

miRNAs may function as diagnostic and prognostic indicators in HCC. According to Zhang K et al. the TNM stages of HCC and the size of the tumor can also be determined using miRNAs. miR-32 expression was found to be strongly expressed in tumors that were at least <5 cm in size compared to > 5 cm [44]. Several studies have reported that high expression of miR-221 [42] and miR-487a [43] were negative prognostic factors in HCC. A poor outcome was seen in HCC patients with a reduced level of miR-33a [44]. Forkhead box K2 (FOXK2) protein overexpression has been associated with poor overall survival (OS) and disease-free survival (DFS) rates. FOXK2 is a target of miR-1271-5p [42]. Some important miRNAs like miR-122 mimic/miR-221 inhibitor has shown significant result in reduction of neo angiogenesis, proliferation, and as a pro-inflammatory marker as they mimic or inhibit the target [119]. A novel approach to cancer treatment that has been gaining popularity recently is known as molecular targeted therapy. Sorafenib (SOR), lenvatinib, regorafenib, cabozantinib, and ramucirumab are only a few of the targeted medications now being utilized to treat HCC [120]. Patients late stage of HCC are especially in need of sorafenib as a first-line treatment because it prolongs patient survival [121]. Nevertheless, a lot of patients continue growing sorafenib developed resistance [120]. However according to recent studies, there are numerous routes involved in the development of sorafenib resistance [122] Two interventional clinical trials studies such as (NCT02507882) and (NCT01829971).

6. Conclusion

Several study limitations persist, and there is still a critical need for improvement despite recent advancements in tumor identification and therapy. The onset and development of HCC are (on the molecular level) complicated processes, and are associated with dysregulated gene expression due to not only mutations arising in the coding regions of genomic DNA, but also due to dysregulation on the translational level.

Non-coding RNAs are gaining ever more attention for their potential as diagnostic and prognostic biomarkers, but also as therapeutical means. Precise understanding of miRNA/lncRNA mediated competitive endogenous RNA network will help us to more accurately detect and treat HCC. However, it is crucial to study ncRNAs in their complexity because of their close functional relation and dysregulation of one component of the whole cascade may not provide sufficient information about the overall outcome.

Conclusions of the study Since studies on ncRNAs in HCC are not thoroughly investigated in European nations, the bulk of studies from Asian countries, shedding light on various aetiologies, will help advance HCC research in the future.

Ethics approval and consent to participant

Not applicable.

Consent of publication

Not applicable.

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Author contributions

Conceptualization, V.R.M., K.H., and F.A.; writing—original draft, V.R.M., and M.R.; writing—review and editing, V.R.M., M.R., A.T., K.H., V.L., and F.A.; supervision, F.A. and K.H; funding acquisition, K.H., and V.L. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

No potential conflict of interest relevant to this article was reported.

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List of abbreviations

HCC	hepatocellular carcinoma
HBV	hepatitis B Virus
HCV	hepatitis C Virus
NASH	non-alcoholic steatohepatitis
ALD	alcoholic liver diseases
NcRNA	non-coding ribonucleic acid
MiRNA	micro ribonucleic acid
LncRNA	long non-coding ribonucleic acid
Cir-cRNA	circular ribonucleic acid
PiRNA	piwi-interacting ribonucleic acid
ROS	reactive oxygen species
CLD	chronic liver diseases
T2DM	type 2 diabetes mellitus
NAFLD	non-alcoholic fatty liver diseases
CVD	cardiovascular diseases
TERT	telomerase reverse transcriptase
TP53	tumor protein p53
CTNNB1	catenin beta-1

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