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Methods Review

The mechanistic, diagnostic and therapeutic novel nucleic acids for hepatocellular carcinoma emerging in past score years

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Abstract

Despite *The Central Dogma* states the destiny of gene as 'DNA makes RNA and RNA makes protein', the nucleic acids not only store and transmit genetic information but also, surprisingly, join in intracellular vital movement as a regulator of gene expression. Bioinformatics has contributed to knowledge for a series of emerging novel nucleic acids molecules. For typical cases, microRNA (miRNA), long noncoding RNA (lncRNA) and circular RNA (circRNA) exert crucial role in regulating vital biological processes, especially in malignant diseases. Due to extraordinarily heterogeneity among all malignancies, hepatocellular carcinoma (HCC) has emerged enormous limitation in diagnosis and therapy. Mechanistic, diagnostic and therapeutic nucleic acids for HCC emerging in past score years have been systematically reviewed. Particularly, we have organized recent advances on nucleic acids of HCC into three facets: (i) summarizing diverse nucleic acids and their modification (miRNA, lncRNA, circRNA, circulating tumor DNA and DNA methylation) acting as potential biomarkers in HCC diagnosis; (ii) concluding different patterns of three key noncoding RNAs (miRNA, lncRNA and circRNA) in gene regulation and (iii) outlining the progress of these novel nucleic acids for HCC diagnosis and therapy in clinical trials, and discuss their possibility for clinical applications. All in all, this review takes a detailed look at the advances of novel nucleic acids from potential of biomarkers and elaboration of mechanism to early clinical application in past 20 years.

Key words: noncoding RNA; lncRNA; miRNA; ctDNA; hepatocellular carcinoma; therapy

Introduction

In 2018, liver cancer had presented the sixth incidence (4.7%) and third mortality (8.2%) in malignancies worldwide [1]. According to statistics, there were approximately 840 000 new cases and 780 000 of liver cancer reported [1]. Liver cancer comprises hepatocellular carcinoma (HCC) (75–85%), intrahepatic cholangiocarcinoma (10–15%) and other rare types [1]. As the most common form of liver cancer, HCC often develops in patients

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with a history of hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, obesity, type 2 diabetes or alcohol-related liver disease [2–5]. In the past near 100 years, studies in HCC pathology have expanded our understanding on mechanism of tumorigenesis and development from the early stage to the advanced. Scientists got breakthrough achievements when confronting the knotty disease, for typical cases serum α-fetoprotein (AFP) as diagnostic biomarker, as well as sorafenib, regorafenib and lenvatinib approved by U.S. Food and Drug Administration (FDA) for treating HCC [6]. However, these efforts were helpful but remained limited, in which the measurement of AFP levels was with lower specificity and sensitivity in early stage HCC [7] and drug resistance trapped HCC therapies into a greater dilemma.

Bioinformatics has provided a very useful framework for studying different biomolecules contributing to the process of biology and medical science [8–10]. Despite *The Central Dogma* states the destiny of gene as 'DNA makes RNA and RNA makes protein', the nucleic acid molecules are not only engaged in roles as the carrier and transmitter of genetic information but also held responsible for gene regulation by the study of omics techniques. In recent score years, the expanding knowledge for genome and continuous reclamation for gene desert with the help of high-throughput sequencing have contributed to the emergence of multifarious nucleic acid molecules and modification, such as emergence of circulating tumor DNA (ctDNA) [11], extrachromosomal circular DNA [12], DNA methylation [13], microRNA (miRNA) [14], long noncoding RNA (lncRNA) [15], circular RNA (circRNA) [16], PIWI-interacting RNA (piRNA) [17], small nucleolar RNA (snoRNA) [17] and so on. Interestingly, cancer cells employed almost all of the above molecules and modifications to sustain physiological and developmental requirements. As an extremely heterogeneous malignant disease among all tumors, HCC initiated more complicated mechanism for adjusting living environment, resulting in a considerable challenge on diagnosis and therapy [18–20]. These emerging novel molecules and modifications had brought about new insight of tumorigenesis, alternative tools for diagnosis and potential therapeutic approach in clinic for HCC. In this perspective, we take a detailed look at recent contribution focusing on mainstream nucleic acids (ctDNA, DNA methylation, miRNA, lncRNA and circRNA) as potential biomarkers and discuss their function and mechanism of gene regulation regarding HCC as a paradigm. Advances in understanding roles of these molecules on HCC development have contributed to a vast number of publications in the past score years (Figure 1).

Noncoding RNA in HCC

miRNA

MicroRNA (miRNA) is a class of endogenous noncoding RNA containing approximately 22 nucleotides (nts) that can exert critical roles in the regulation of gene expression by complementarily targeting specific messenger RNA (mRNA), therefore leading to mRNA degradation or translational process inhibition [21]. Four key enzymes, including Drosha, exportin 5, Dicer and argonaute 2 (AGO2), participate in and regulate the process of human miRNAs biogenesis [22, 23]. Drosha and Dicer have been reported to deregulate in several types of cancers, which results in change of miRNAs expression and triggers signaling pathway of tumor progression [24–28]. In the past few decades, miRNAs have served as a paradigm for noncoding RNAs and provided numerous insights into how nucleic acids contributed to oncogenesis and the development of cancers [29].

Recent efforts of HCC researches concentrate on two facets: (i) excellent performance of miRNA for HCC diagnosis and (ii) miRNA's responsibility for HCC tumor progression.

A growing list of studies has described that miRNAs were hallmarks of HCC expressed in both of humor and liver tissue. Altered expression in HCC conduced that miRNAs may sever as available tools in clinic to discriminate HCC from liver cirrhosis, HBV, HCV or healthy people. Tomimaru *et al.* found that plasma miR-21 was upregulated in HCC patients than in chronic hepatitis patients and healthy volunteers. Thereinto, miR-21 could distinguish between HCC and chronic hepatitis with 61.1% sensitivity and 83.3% specificity, as well as healthy volunteers with 87.3% sensitivity and 92.0% specificity, which was more optimal than AFP [30]. Zhou's group found that the expression of serum miR-224 was higher in early-stage HCC than in liver cirrhosis, HBV and healthy controls, and it had a better distinguishable performance (95% CI: 0.838–0.923; sensitivity: 86.5%, specificity: 76.7%) between HCC and each of the three control groups than AFP (AUC: 0.700, 95% CI: 0.633–0.767; sensitivity: 71.9%, specificity: 63.7%) [31]. Investigators considered miR-16 as a potential biomarker also for early HCC diagnosis. The serum level of miR-16 in HCC patients was significantly lower HCC than in HCV. Moreover, miRNA-16 level could discriminate HCC from HCV patients with a cutoff value of 0.904, a sensitivity of 57.5% and a specificity of 70%, and combination of miR-16 with AFP could improve sensitivity and diagnostic accuracy to 85 and 87.5%, respectively [32]. Abdalla *et al.* found that using urinary miR-618/miR-650 for detecting HCC among HCV-positive patients was with 64/72% sensitivity and 68/58% specificity [33].

Apart from in humor, miRNA in tissues was also an effective tool in HCC diagnosis. One study showed that the expression of miR-221 was increased in HCC tissues than in matched normal tissues, and positively correlated with tumor stage, number of tumor nodes and microvascular invasion in HCC patients. In addition, survival analysis indicated that HCC patients with higher miR-211 expression had a worse survival rate than the lower miR-221 patients [34]. Researchers also found that the combination of several miRNAs acted as HCC indicators was efficient and may be more accurate or applicable than using single miRNA. In Wen's study, eight selected miRNAs (miR-20a-5p, miR-25-3p, miR-30a-5p, miR-92a-3p, miR-132-3p, miR-185-5p, miR-320a and miR-324-3p) were dramatically upregulated in the HBV-positive HCC patients compared with the HBV-positive noncancerous patients and showed a sensitivity of 86.6% and a specificity of 64.6%. Specially, miRNA panel consisting of miR-20a-5p, miR-320a, miR-375 (a miRNA reported in previous study) and miR-324-3p could be an indicator for blood-based early HCC detection [35]. Lin *et al.* established that an miRNA classifier (Cmi), which consists of miR-29a, miR-29c, miR-133a, miR-143, miR-145, miR-192 and miR-505, had better sensitivity (70.4–85.7%) than AFP of 20 ng/mL cutoffs (AFP20) (40.7–69.4%) for HCC diagnosis in four cohorts, while the specificity (80.0–91.1%) was similar to that of AFP20 (84.9–100%). Besides, Cmi could be more sensitive in detecting small size and early-stage HCC than AFP and even could detect AFP-negative HCC [36].

MicroRNAs (miRNAs) regulate intracellular signal pathway generally via a unique manner. The innate duty of almost all miRNAs is controlling gene expression via complementarily targeting 3′ untranslated region (UTR) of specific mRNA, which could mediate mRNA degradation and translation repression. In malignant tumor, miRNAs directly targeting mRNAs of oncogene are committed to affairs of tumor suppressor, while miRNAs directly inhibiting mRNAs of tumor suppressor exert tumor-promoting role. Recent mechanism research has revealed that

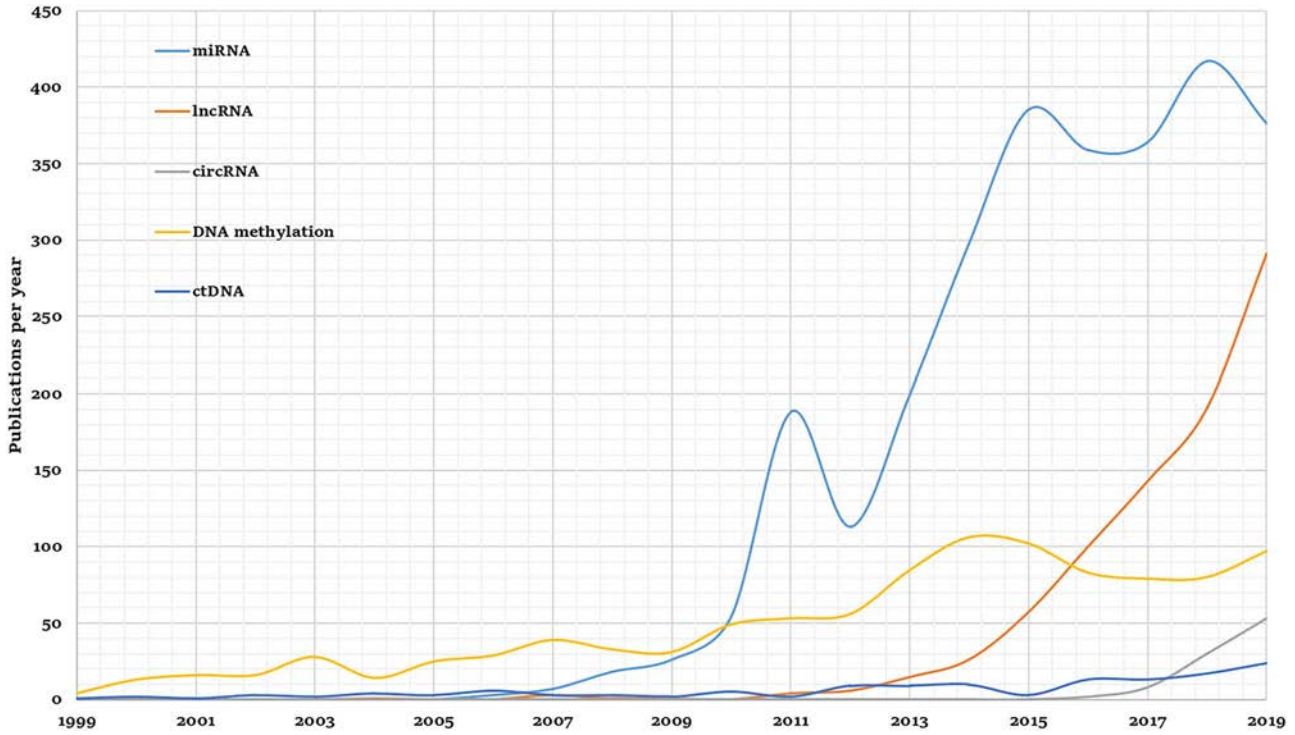


Figure 1. Twenty years of popular nucleic acids (miRNA, lncRNA, circRNA, DNA methylation and ctDNA) literature. The graph indicates trends of publications from 1999 to 2019 identified in PubMed using the keywords each nucleic acid combination with HCC.

miRNAs were involved in the regulation of vital gene in HCC by direct mode.

miR-148a targeted the 3′UTR of SMAD2 in HCC cell, leading to the inhibition of the expression and function of SMAD2 [37]. miR-24 inhibited p53 expression by binding to the 3′UTR of its mRNA and, thus, promote metastasis and invasion of HCC [38]. miR-542-3p can directly target TGF-β1 3′UTR and subsequently suppressed the protein expression of TGF-β1 as well activation TGF-β/Smad signaling in HCC [39].

However, the line that miRNAs regulate mRNAs of target gene is not sole but network-like. 3′UTR of one mRNA could be bound by multiple miRNAs, in return one miRNA could also target various mRNAs. For example, miR-101 could inhibit the gene expression of TGFβ-R1, Smad2 and VE-cadherin by binding to the 3′UTR of these mRNAs in HCC, respectively [40]; miR-26b, miR-342-3p and miR-195 could target different sites of TAB3 mRNA to inhibit its translational progression in HCC [41–44].

In fact, miRNAs could bind to not only 3′UTR of special mRNA but also its 5′UTR even coding region. For several cases (not in HCC), miR-10a can interact with 5′UTR of ribosomal protein mRNAs so as to enhance their translation [45]; miR-10b down-regulated the protein expression of MBNL1–3, SART3 and RSRC1 by targeting 5′UTRs of these genes [46]; Expression of GFRA3 was directly inhibited by miR-34a via its coding region [47]; miR-96 directly bound to the coding region of RAD51 and downregulated its expression [48].

In addition, a series of miRNAs associated with HCC were listed at Table 1 with more detail information.

lncRNA

Long noncoding RNA (lncRNA) is a type of transcript more than 200 nts in length with no protein coding performance [49, 50], many of which express in the tissues and organs under specified or pathological conditions such as malignancies. According to location in genome with respect to protein-coding genes, lncRNAs can be divided into six types that included intergenic lncRNA, antisense lncRNAs, bidirectional lncRNAs, intronic lncRNAs and overlapping sense transcripts [51]. Unlike miRNA, lncRNAs execute more complicated function as regulators in the process of gene transcription events [52], posttranscriptional control [53] and epigenetic regulation [54]. Besides, the new identity of lncRNAs is still continuously excavating. Accumulating evidence indicated that many lncRNAs participate in the biological progression of tumorigenesis and could be potential clinical indicators or anticancer targets of HCC [55–57].

LINC00161, a serum and exosome lncRNA, was detected in serum exosome, exosome-free and urine samples, with an increased expression in HCC patients compared with matched healthy controls. And the lncRNA showed excellent stability and specificity with an AUC of 0.794 (95% CI, 0.712–0.877), a sensitivity of 75% and a specificity of 73.2% [58]. A study by Wang *et al.* indicated that serum LRB1 had a potential distinguishing ability between patients with HCC and the healthy. It can be acted as a marker for the diagnosis of HCC with an AUC of 0.892 (95% CI, 0.843–0.922), a sensitivity of 92.43% and a specificity of 71.85%, and combination with AFP and des-γ-carboxy prothrombin results in better detection efficiency with an AUC of 0.971 (95% CI, 0.942–0.988), a sensitivity of 86.33% and a specificity of 87.64% [59].

Due to their diversity and complexity, lncRNAs employ multiplex mechanism to regulate intracellular signal pathway in HCC. (i) 'Act as a sponge binding miRNA, resulting in the failure of miRNA to target specific mRNA'. Li *et al.* found that SNHG5 could competitively bind miR-26a-5p and relieve its inhibition to target gene GSK3β, activating Wnt/β-catenin signal pathway [60]; Study by Sun *et al.* suggested that PITPNA-AS1 modulated

Table 1. A series of miRNAs associated with HCC

miRNAs	Role in HCC	Cancer phenotype	Mechanism	References
miR-122	Tumor suppressor	metastasis	miR-122 – PKM2 >> metastasis	[152]
miR-125b	Tumor suppressor	metastasis	miR-125b – Angpt2 >> VETC >> metastasis	[153]
miR-133b	Tumor suppressor	proliferation, migration, invasion	miR-133b – LASP1 >> proliferation, migration, invasion	[154]
miR-144	Tumor suppressor	metastasis	miR-144 – AKT3 >> metastasis	[155]
miR-144	Tumor suppressor	growth, motility	miR-144 – ZFX >> growth, motility	[156]
miR-145	Tumor suppressor	proliferation	miR-145 – IGF axis >> proliferation	[157]
miR-148b	Tumor suppressor	tumor initiation, metastasis, angiogenesis	miR-148b – Neuropilin-1 >> tumor initiation, metastasis, angiogenesis	[158]
miR-187	Tumor suppressor	proliferation, migration, invasion	miR-187 – IGF-1R >> proliferation, migration, invasion	[159]
miR-188-5p	Tumor suppressor	proliferation, metastasis	miR-188-5p – FGF5 >> proliferation, metastasis	[160]
miR-193b	Tumor suppressor	invasion, metastasis	miR-193b – Mcl-1 >> invasion, metastasis	[161]
miR-199a	Tumor suppressor	invasion	miR-199a – DDR1 >> invasion	[162]
miR-200a	Tumor suppressor	invasion, migration	miR-200a – GAB1 >> invasion, migration	[163]
miR-206	Tumor suppressor	migration, invasion	miR-206 – cMET >> migration, invasion	[164]
miR-214-3p	Tumor suppressor	proliferation	miR-214-3p – PIM-1 >> proliferation	[165]
miR-218	Tumor suppressor	growth	miR-218 – Bmi-1 >> growth	[166]
miR-218	Tumor suppressor	metastasis	miR-218 – SERBP1 >> metastasis, EMT	[167]
miR-22	Tumor suppressor	metastasis	miR-22 – YWHAZ >> metastasis	[168]
miR-23c	Tumor suppressor	proliferation	miR-23c – ERBB2IP >> proliferation	[169]
miR-28-5p	Tumor suppressor	proliferation, migration	miR-28-5p – IGF-1 >> proliferation, migration	[170]
miR-28-5p	Tumor suppressor	growth, metastasis	miR-28-5p – IL-34 >> TAM >> growth, metastasis	[171]
miR-299-3p	Tumor suppressor	migration, invasion, proliferation	miR-299-3p – SIRT5 >> migration, invasion, proliferation	[172]
miR-29a	Tumor suppressor	growth, metastasis	miR-29a – IFITM3 >> growth, metastasis	[173]
miR-29a	Tumor suppressor	proliferation	miR-29a – SIRT1 >> proliferation	[174]
miR-29b	Tumor suppressor	angiogenesis, invasion, metastasis	miR-29b – MMP-2 >> angiogenesis, invasion, metastasis	[175]
miR-302b	Tumor suppressor	proliferation	miR-302b – AKT2 >> proliferation	[176]
miR-30b	Tumor suppressor	transition, metastasis	miR-30b – Snail >> transition, metastasis	[177]
miR-33b	Tumor suppressor	proliferation	miR-33b – SALL4 >> proliferation	[178]
miR-340	Tumor suppressor	proliferation, invasion	miR-340 – JAK1 >> proliferation, invasion	[179]
miR-34a-5p	Tumor suppressor	proliferation	miR-34a-5p – AXL >> proliferation	[180]
miR-363-3p	Tumor suppressor	proliferation, migration, invasion	miR-363-3p – specificity protein 1 >> proliferation, migration, invasion	[181]
miR-375	Tumor suppressor	proliferation, clonogenicity, migration, invasion	miR-375 – AEG-1 >> proliferation, migration, invasion	[182]
miR-377	Tumor suppressor	proliferation, invasion	miR-377 – TIAM1 >> proliferation, invasion	[183]
miR-449a	Tumor suppressor	growth, metastasis	miR-449a – c-Met >> growth, metastasis	[184]
miR-485-5p	Tumor suppressor	proliferation, metastasis	miR-485-5p – EMMPRIN >> proliferation, metastasis	[185]
miR-504	Tumor suppressor	proliferation, invasion	miR-504 – Frizzled-7 >> Wnt/β-catenin >> proliferation, invasion	[186]
miR-508-5p	Tumor suppressor	migration, invasion, proliferation	miR-508-5p – MESDC1 >> migration, invasion, proliferation	[187]
miR-542-3p	Tumor suppressor	migration, invasion	miR-542-3p – UBE3C >> migration, invasion	[188]
miR-615-5p	Tumor suppressor	growth, metastasis	miR-615-5p – RAB24 >> growth, metastasis	[189]
miR-663a	Tumor suppressor	proliferation, motility	miR-663a – HMGA2 >> proliferation, motility	[190]
miR-9-3p	Tumor suppressor	proliferation	miR-9-3p – TAZ >> proliferation	[191]
miR-98	Tumor suppressor	migration, invasion	miR-98 – IL-10 >> migration, invasion	[192]
miRNA-340	Tumor suppressor	proliferation, migration, invasion	miRNA-340 – SKP2 >> proliferation, migration, invasion	[193]
miR-200b	Tumor suppressor	proliferation	miR-200b – DNMT3a >> proliferation	[194]

Continued.

Table 1. Continued

miRNAs	Role in HCC	Cancer phenotype	Mechanism	References
miR-466	Tumor suppressor	proliferation, migration, invasion	miR-466 – MTDH >> proliferation, migration, invasion	[195]
miR-106b-5p	Oncogene	invasion	miR-106b-5p – RUNX3 – invasion	[196]
miR-1180	Oncogene	proliferation	miR-1180 – TNIP2 – proliferation	[197]
miR-182	Oncogene	metastasis	miR-182 – TP53INP1 – metastasis	[198]
miR-197	Oncogene	invasion, metastasis	miR-197 – Axin-2, NKD1, DKK2 – Wnt/β-catenin signaling >> invasion, metastasis	[199]
miR-21	Oncogene	proliferation	miR-21 – HEPN1 – proliferation	[200]
miR-27a	Oncogene	proliferation	miR-27a – PPAR-γ – proliferation	[201]
miR-301a-3p	Oncogene	proliferation, invasion	miR-301a-3p – VGLL4 – proliferation, invasion	[202]
miR-3188	Oncogene	cell growth, migration, invasion	miR-3188 – ZHX2H – Notch1 signaling pathway >> growth, migration, invasion	[203]
miR-500a	Oncogene	proliferation	miR-500a – BID – proliferation	[204]
miR-519a	Oncogene	proliferation	miR-519a – PTEN – proliferation	[205]
miR-616	Oncogene	migration, invasion, transition	miR-616 – PTEN – migration, invasion, transition	[206]
miR-92b	Oncogene	proliferation, metastasis	miR92b – Smad7 – proliferation, metastasis	[207]

N.A. means not available. '–' represents inhibition and '>>' represents promotion.

WNT5A expression by mediating abrogation of miR-876-5p inhibition on WNT5A [61]. Yang *et al.* identified that HCC cell forced NORAD to bind to miR-202-5p, thereupon then eliminating miR-202–5p inhibition to TGFBR [62]. (ii) 'Regulate gene transcription via directly binding to DNA'. Sun's study indicated that p65 transcription was strongly inhibited by LINC000607 binding to its promoter region [63]. Wang *et al.* reported that lnc-DILC complementarily bound to IL-6 promoter region and hampered IL6 transcriptional progress [64]. (iii) 'Promote mRNA degradation by binding to mRNA'. Li *et al.* found that lncARSR physically interacted with PTEN mRNA and promotes its degradation, activating PI3K/Akt pathway [65]. (iv) 'Affect protein stabilization and activity as an interactor'. Sun's group proved that lncRNA-hPVT1 bound to NOP2 protein and sustained its stability, thus promoting proliferation and stem cell-like property of HCC cell [66]. Research by Ding *et al.* revealed that HNF1A-AS1 could directly interact with the C-terminal of SHP-1 with a high binding affinity and enhance phosphatase activity of SHP-1 in HCC [67].

We also provided a list of lncRNAs with more useful information in Table 2 which were related with the pathogenesis of HCC.

circRNA

Circular RNA (circRNA), generated from precursor mRNA back-splicing of exons, is a type of single-stranded RNA differentiated from traditional linear RNA, in the form of covalently closed continuous loop [68–70]. CircRNAs usually present low abundance and express in specific cells, tissues and pathological status [70]. Generally, they function as miRNA sponges and relieve the association between miRNA and target gene, therefore leading to the expression of target gene [68]. And circRNAs can be classified into four types that include exonic circRNAs, circular RNAs from introns, exonintron circRNAs and intergenic circRNAs [71]. Recent years, emerging circRNAs have been found to regulate HCC progression by acting as sponges to interact miRNAs. And they participated in multiple signaling pathways in HCC pathogenesis and presented good potential on the diagnosis and therapeutic targets of HCC [72–74].

However, many research focusing on circRNAs in HCC are not rich. And we reviewed several cases that circRNAs involved in HCC carcinogenesis. A study by Yu's group showed circRNA-104,075 was significantly overexpressed in HCC issues, cell lines and serum, and transcriptionally regulated by hepatocyte nuclear factor 4-alpha (HNF4a) with binding to its promoter. More importantly, circRNA-104,075 could increase the expression of YAP via interfering the connection between miR-218-5p and YAP 3′UTR, thus contributing to the translation of YAP. Besides, circRNA-104,075 had excellent diagnostic performance with an AUC-ROC of 0.973, a sensitivity of 96.0% and a specificity of 98.3% for HCC detection [75]. Han *et al.* picked up circMTO1 downregulated in HCC tissues from the expression profile of human circRNA and found that HCC patients with lower circMTO1 expression had the shorter survival rate. And the researchers identified that the circRNA as sponge of miR-9 could inhibit cell proliferation and invasion via regulating p21 of HCC. Hence, circMTO1 would be a potential target in HCC treatment and a prognosis predictor for HCC detection [76]. Luo's research indicated that circRNA-101,505 expression was reduced in HCC tissue (including cisplatin-sensitive and cisplatin-resistant groups) than in the adjacent groups, and HCC patients with high circRNA-101,505 had the worse survival rate than the low. And the researchers further determined its tumor-suppressive role in HCC that the overexpression of the circRNA-101,505 inhibited cell proliferation and enhanced cisplatin toxicity by sponging miR-103 to increase oxidored-nitro domain-containing protein 1 (NOR1) expression [77]. Another research found that circRNA-104,718 acted as an oncogene to promote HCC progression. First, circRNA-104,718 could be found expressed higher in HCC tissues than in the normal group and that the lower expression of the gene led to better prognosis in HCC patients. Then, mechanistically, circRNA-104,718 supported cell proliferation, migration, invasion and inhibited apoptosis by binding to miR-218-5p as a competing endogenous RNAs (ceRNAs) so as to enhance the translation of thioredoxin domain-containing protein 5 (TXNDC5) [78]. As described in the examples above, circRNAs often regulate gene expression such as miRNAs according to given pattern that

Table 2. A number of lncRNAs linked with HCC

LncRNAs	Role in HCC	Cancer phenotype	Mechanism	References
hDREH	Tumor suppressor	proliferation, migration	N.A.	[208]
ELMO1-AS1	Tumor suppressor	proliferation, migration, invasion	ELMO1-AS1 – ELMO1 >> proliferation, migration, invasion	[209]
lncRNA-LET	Tumor suppressor	metastasis	lncRNA-LET – NF90 >> CDC42 >> metastasis	[210]
FENDRR	Tumor suppressor	immune escape, proliferation, tumorigenicity	FENDRR – miR-423-5p – GADD45B – immune escape, proliferation, tumorigenicity	[211]
MEG3	Tumor suppressor	proliferation, migration, invasion	MEG3 >> miRNA-10a-5p – PTEN – AKT/MMP-2/MMP-9 signaling >> proliferation, migration, invasion	[212]
GMDS-DT	Tumor suppressor	N.A.	N.A.	[213]
CASC15	Oncogene	EMT	CASC15 – miR-33a-5p – TWIST1 >> EMT	[214]
CCAT2	Oncogene	N.A.	N.A.	[215]
DBH-AS1	Oncogene	tumorigenesis	DBH-AS1 – miR-138 – FAK/Src/ERK pathway >> tumorigenesis	[216]
DCST1-AS1	Oncogene	proliferation, metastasis	DCST1-AS1 >> AKT/mTOR signaling >> proliferation, metastasis	[217]
DLEU2	Oncogene	proliferation, migration, invasion	DLEU2 + EZH2 >> proliferation, migration, invasion	[218]
DSCAM-AS1	Oncogene	proliferation, migration, invasion	DSCAM-AS1 – miR-338-3p – CyclinD1 + SMO >> proliferation, migration, invasion	[219]
EIF3J-AS1	Oncogene	proliferation, migration, invasion	EIF3J-AS1 – miR-122–5p – CTNND2 >> proliferation, migration, invasion	[220]
ENST00000522221	Oncogene	N.A.	N.A.	[221]
HULC	Oncogene	proliferation	HUL >> HBx + STAT3 >> miR-539 – APOBEC3B – proliferation	[222]
H19	Oncogene	growth	H19 >> angiogenin, FGF18 >> growth	[223]
URHC	Oncogene	proliferation	URHC – ZAK >> ERK/MAPK pathway – proliferation	[224]
PVT1	Oncogene	proliferation	lncRNA-hPVT1 >> NOP2 >> proliferation	[66]
XIST	Oncogene	growth	XIST – miR-139-5p – PDK1 >> growth	[225]
ROR	Oncogene	radioresistance	ROR – miR-145 – RAD18 >> radioresistance	[226]
PTTG3P	Oncogene	growth, metastasis	PTTG3P >> PTTG1 >> PI3K/AKT signaling >> growth, metastasis	[227]
HOTAIR	Oncogene	viability, proliferation	HOTAI – miR-218 – Bmi-1 >> viability, proliferation	[228]
UCA1	Oncogene	N.A.	N.A.	[229]
PDPK2P	Oncogene	proliferation, metastasis, invasion	PDPK2P + PDK1 >> PDK1/AKT/caspase 3 pathway >> proliferation, metastasis, invasion	[230]
TATDN1	Oncogene	proliferation	TATDN1 – miR-6089 – LIX1L >> proliferation	[231]
SOX9-AS1	Oncogene	metastasis	SOX9 >> SOX9-AS1 – miR-5590-3p – SOX9 >> Wnt/β-catenin pathway >> metastasis	[232]
SNHG20	Oncogene	transformation	SNHG20 >> STAT6 >> transformation	[233]
LINC01296	Oncogene	proliferation, cell cycle	LINC01296 >> BUB1, CCNA2, CDK1 >> proliferation, cell cycle	[234]
PCNAP1	Oncogene	growth	PCNAP1 – miR-154 – PCNA >> growth	[235]
GAPLINC	Oncogene	EMT, invasion, migration	GAPLINC >> SNAI2 >> EMT, invasion, migration	[236]
LINC00668	Oncogene	cell division, cell cycle, mitotic nuclear division	N.A.	[237]
MALAT1	Oncogene	metastasis	MALAT1 – miR-124-3p – Slug >> metastasis	[238]
HOXA11-AS	Oncogene	migration, invasion	HOXA11-AS + EZH2 – miR-124 – migration, invasion	[239]
TGLC15	Oncogene	proliferation	TGLC15 + Sox4 >> proliferation	[240]
MIAT	Oncogene	proliferation	MIAT – miR-22-3p – sirt1 >> proliferation	[241]
PDIA3P1	Oncogene	chemoresistance	hMTR4 + PDIA3P1 – miR-125/124 – TRAF6 >> NF-κB signaling >> chemoresistance	[101]
LINC01638	Oncogene	proliferation	LINC01638 >> glucose uptake >> proliferation	[242]
SNHG7	Oncogene	proliferation, migration, invasion	SNHG7 >> RPL4 >> proliferation, migration, invasion	[243]

N.A. means not available. '–' represents inhibition, and '>>' represents promotion.

circRNAs are acted as ceRNA binding to miRNAs and relieve target gene's inhibition of miRNAs. Besides, circRNAs also act by associated proteins [70, 79]. For example, when the MBL protein was expressed in excess, circMbl could sponge out MBL through binding to it [80]. Luo *et al.* concluded that the types of circRNA-binding proteins containing transcription factors, RNA processing proteins, proteases and some other RNA-binding proteins, and the interaction contributes to the occurrence and development of multiple pathological processes [81]. Some circRNAs were found to been translated [70]. An investigation reported that circ-ZNF609, with an open reading frame containing start and stop codon, can encode a protein and regulate myoblast proliferation [82]. Another research found that circMbl can be translated through a cap-independent way and its UTR element might play a promoting role during translation process [83].

In addition, Table 3 listed a number of circRNAs added available information which were linked with the pathogenesis of HCC.

Other noncoding RNAs

Except for the three types above, some noncoding RNA such as piRNA, snoRNA in HCC was also identified to exert special function in HCC.

PIWI-interacting RNA (piRNA) is a type of small noncoding RNA in length 21–35 nts that regulates gene expression by guiding PIWI proteins to cleave target RNA [84]. In malignancies, piRNAs have been found to participate in cell proliferation, metastasis and apoptosis, by regulating DNA methylation and phosphorylation of some key protein of cancer [85–88]. However, knowledge for functions of piRNAs in cancer still remained not thorough [15]. A few reports have shown that some piRNAs play an impact role and have potential performance as good biomarker for HCC. piR-Hep1 was highly expressed in HCC tumor tissues compared with that in nontumoral liver. Silencing of piR-Hep1 led to the inhibition of cell viability and invasion and reduced AKT phosphorylation [89]. Rizzo *et al.* found that distinct piRNAs were expressed in liver tissues under different pathology, as piR-LLi-24,894 in low-grade lesions only, increasing piR-LLi-30,552 and piR-020498 from high-grade dysplastic nodules, early HCC to progressed HCC and piR-013306 in progressed HCC [90].

Small nucleolar RNA (snoRNA) is a class of noncoding RNA range 60–300 nts in length, which traditionally exerts important responsibility for rRNA and snRNA modification, such as uridine isomerization and ribose methylation [91–93]. In recent years, a new role of snoRNA has been presented as a regulator of cellular pathways, especially in cancer [92]. Accumulating evidence suggested that snoRNAs employed some signaling pathway which are important for tumor to control the progression of HCC. SNORD113–1, a snoRNA downregulated in HCC tissues, inhibited HCC cell viability and proliferation via involvement of MAPK/ERK and TGF-β pathway [94]. SNORA18L5 promoted HCC tumorigenesis and increased MDM2-mediated p53 degradation by retaining RPL5 and RPL11 in the nucleolus [95].

Noncoding RNA in key signaling pathways of HCC

HCC was documented to hire assorted signaling pathways in order to meet its abnormal physiological requirements. Well-described pathways dominant in HCC were TLR4/NF-kB [96], HGF/c-Met [97], Wnt/β-catenin [98], TGF-β [99] and MDM2-p53 signaling pathway [100]. Therewith, we portrayed these five prominent signaling pathway sketches in HCC, with added regulatory noncoding RNA available of key components (Figure 2) and all components (Figures 3–7).

In mechanism, lncRNAs or circRNAs, as sponges of miRNAs, could absorb miRNAs and relieve target's inhibition caused by miRNAs, finally expression of target genes. Therefore, in this pattern, lncRNA (PDIA3P1 [101], LINC00657 [102], SBF2-AS1 [103]) or circRNA (circHIAT1 [104], circZFR [105]) led to expression of target genes, and miRNA (miR-124/125 [101], miR-3171 [104], miR-106a-5p [102], miR-3615-5p [105], miR-140-5p [103], miR-24 [38]) resulted in the suppression of target genes. In addition, lncRNA-NEF physically bound with β-catenin and enhanced interaction between GSK3β and β-catenin, therefore inhibiting phosphorylation of β-catenin [106]. LncRNA MEG3 interacted with P53, fostering its stabilization and transcriptional activity [107]. Cooperation of the five pathways contributes to the tumorigenesis in HCC via exerting crucial roles in inflammation, survival, growth, EMT and apoptosis (Figure 2).

Databases of noncoding RNA

There has been a variety of well-constructed databases that describe the contents of several noncoding RNAs containing general information, associations with disease, expression level and regulatory network (Table 4). A majority of these resource platforms were based on considerable sequencing and experimental data in diseases, and the resources' utilization would facilitate the understanding for noncoding RNA and be helpful to the treatment of the diseases.

Emerging novel DNA and DNA modification of HCC

ctDNA

Circulating tumor DNA (ctDNA), a special circulating cell-free DNA (cfDNA), is released into circulation from tumor cells with carrying cancer-specific genetic and epigenetic aberrations, such as point mutations [108], copy number variations [109], chromosomal rearrangements [110] and DNA methylation patterns [111]. The half-life of ctDNA was approximately 1.5 h [112], so its transient existence indicated the real-time status of tumor. Many research have suggested that ctDNA could become a useful tool for liquid biopsy of HCC diagnosis, especially in early stage.

Ikeda's study performed a ctDNA next-generation sequencing and analyzed gene alteration on 26 patients. Several genes occurred mutations including TP53 (61.5%), CTNNB1 (30.8%) and ARID1A (23.1%) [113]. Another research by Howell *et al.* detected the mutation level of ctDNA and found that 35% of HCC patients existed various degrees of ctDNA mutation of liver cancer-specific primer panel for eight genes. Frequent mutations were detected in ARID1A (11.7%), CTNNB1 (7.8%) and TP53 (7.8%). And using ctDNA with these eight genes had a specificity of 100% for HCC detection [114]. Besides, Xu *et al.* performed methylation analysis on tumor DNA in HCC and ctDNA in matched plasma and found close correlation between the two groups. By screening and filtering of markers in HCC patient and normal blood samples, two models were established to make diagnostic and prognostic prediction, named as combined diagnostic score (cd-score) and combined prognosis score (cp-score), respectively. Thereinto, a cd-score system, consisting of 10 methylation markers, had superior sensitivity and specificity than AFP level detection for HCC diagnosis in biopsy-proven HCC patients with 0.969 AUC of cd-score versus 0.816 AUC of

Table 3. A list of circRNAs associated with HCC and corresponding information

circRNAs	Role in HCC	Cancer phenotype	Mechanism	References
cSMARCA5	Tumor suppressor	growth, metastasis	cSMARCA5 – miR-17-3p/miR-181b-5p – TIMP3 – growth, metastasis	[244]
circMTO1	Tumor suppressor	proliferation, invasion	circMTO1 – miR-9 – p21 – proliferation, invasion	[76]
circTRIM33–12	Tumor suppressor	proliferation, migration, invasion, immune evasion	circTRIM33–12 – miR-191 – TET1 – proliferation, migration, invasion, immune evasion	[245]
circSETD3	Tumor suppressor	proliferation	circSETD3 – miR-421 – MAPK14 – proliferation	[246]
circSMAD2	Tumor suppressor	migration, invasion, EMT	circSMAD2 – miR-629 >> migration, invasion, EMT	[247]
circ-103,809	Tumor suppressor	proliferation, migration, invasion	circ-103,809 – miR-620 >> proliferation, migration, invasion	[248]
circ-0001445	Tumor suppressor	proliferation, migration, invasion	circ-0001445 – proliferation, migration, invasion	[249]
circADAMTS13	Tumor suppressor	proliferation	circADAMTS13 – miR-484 >> proliferation	[250]
circ-0079929	Tumor suppressor	growth	circ-0079929 – PI3K/AKT/mTOR >> growth	[230]
circRNA-104,075	Oncogene	tumorigenesis	circRNA-104,075 – miR-582-3p – YAP >> tumorigenesis	[75]
circRNA-100,338	Oncogene	proliferation	circRNA-100,338 – miR-141–3p – RHEB > > proliferation	[251]
circRNA-0078710	Oncogene	proliferation, migration, invasion	circRNA-0078710 – miR-31 – HDAC, CDK2 >> proliferation, migration, invasion	[252]
circFBLIM1	Oncogene	proliferation, invasion	circFBLIM1 – miR-346 – FBLIM1 >> proliferation, invasion	[253]
circ-0067934	Oncogene	growth, metastasis	circ-0067934 – miR-1324 – FZD5 >> Wnt/β-catenin pathway >> growth, metastasis	[254]
circRHOT1	Oncogene	growth, metastasis	circRHOT1 + TIP60 >> NR2F6 >> growth, metastasis	[255]
circ-ZEB1.33	Oncogene	proliferation	circ-ZEB1.33 – miR-200a-3p – CDK6 >> proliferation	[256]
circPTGR1	Oncogene	migration, invasion	circPTGR1 – miR-449a – MET >> migration, invasion	[257]
circRNA-101,505	Oncogene	proliferation	circRNA-101,505 – miR-103 – NOR1 >> proliferation	[77]
circ-10,720	Oncogene	EMT	circ-10,720 – miR-490-5p – vimentin >> EMT	[258]
circRNA-101,368	Oncogene	migration	circ-101,368 – miR-200a – MGB1/RAGE signaling >> migration	[259]
cdr1as	Oncogene	proliferation, migration	cdr1as – miR-1270 – AFP >> proliferation, migration	[260]
circRNA-104,718	Oncogene	growth, metastasis	circRNA-104,718 – miR-218-5p – TXNDC5 >> growth, metastasis	[78]
circRNA-103,809	Oncogene	proliferation, cycle progression, migration	circRNA-103,809 – miR-377-3p – FGFR1 >> proliferation, cycle progression, migration	[261]
circ-0103809	Oncogene	growth	circ-0103809 – miR-490-5p – SOX2 >> growth	[262]
circ-0005075	Oncogene	proliferation, migration, invasion	circ-0005075 – miR-431 – proliferation, migration, invasion	[263]

'–' represents inhibition, and '>>' represents promotion.

AFP; a cp-score model, comprising of eight markers, showed more effective performance to distinct between HCC patients with other non-HCC than using AFP [111].

DNA methylation

DNA methylation is an epigenetic modification that methyl groups are attached to DNA molecules. Aberrant DNA methylation, a main way of epigenetic deregulation, has emerged as a driver in oncogenesis and the development of almost type of cancer [115–117]. DNA methylation typically turns the gene on when located in promoter, so oncogenes often are hypomethylated and tumor suppressive genes are hypermethylated in cancer. Accumulating reports have discussed the association between DNA methylation and HCC.

Liu *et al.* reported that the promoter methylation level of two tumor suppressors (SOX1 and VIM) in HCC patients was remarkably higher than that in non-HCC groups (liver cirrhosis, chronic hepatitis B and healthy controls) and closely associated with tumor stage and tumor size. Besides, promoter methylation of two genes in serum could show a higher sensitivity and specificity (SOX1: 72.08 and 84.21%, VIM: 61.67 and 83.16%) than that of AFP (56.67 and 83.16%) in discrimination between HCC and liver cirrhosis and chronic hepatitis B [118]. Research by Qiu *et al.* explored the connection between methylation of TRIM58 and HCC. Methylation level of TRIM58 in many HCC

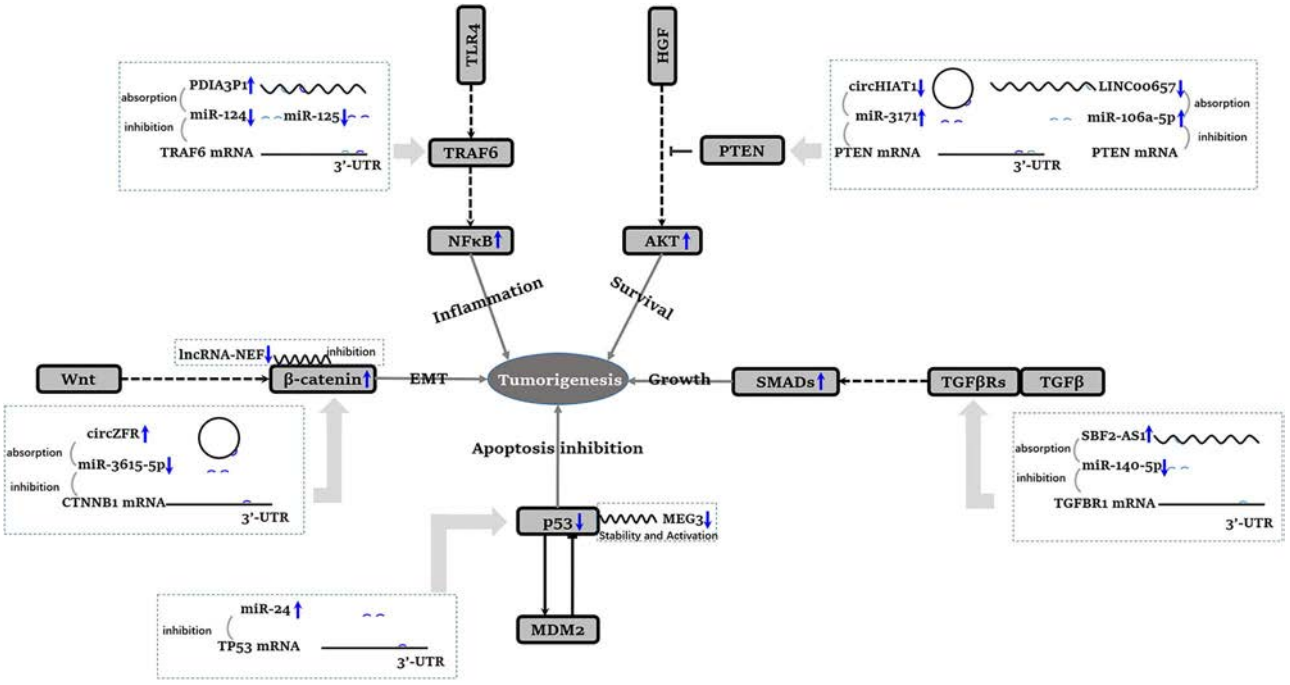


Figure 2. Cooperation of TLR4/NF-kB, HGF/c-Met, Wnt/β-catenin, TGF-β and MDM2-p53 signaling pathway directs HCC tumorigenesis via diverse intracellular process. The detailed mechanism by noncoding RNA is added into key components in each pathway.

Table 4. A list of databases associated with noncoding RNA and corresponding information

Database name	Noncoding RNAs containing	Expression Level	Regulatory network	Description	References
miRCancer	miRNA	√	×	miRNA dysregulation in cancer	[264]
Oncomir	miRNA	×	×	miRNA dysregulation in cancer	[265]
HMDD	miRNA	√	×	miRNA dysregulation in disease	[266]
TANRIC	lncRNA	√	×	function and clinical relevance of lncRNA in cancer	[267]
LncRNADisease	miRNA, lncRNA	√	×	lncRNA dysregulation in disease	[268]
Lnc2Cancer	miRNA, lncRNA	√	√	lncRNA dysregulation in cancer; lncRNAs-miRNA regulation	[269]
CircNet	miRNA, circRNA	√	√	tissue-specific circRNA expression profiles and circRNA-miRNA-gene regulatory network	[270]
circRNA disease	circRNA	√	×	circRNA dysregulation in disease	[271]
Circ2Disease	miRNA, circRNA	√	√	circRNA dysregulation in disease; circRNA-miRNA regulation	[272]
CCRDB	circRNA	√	×	HCC-related circRNA	[273]
MNDR	miRNA, lncRNA, piRNA, snoRNA	×	×	association between diverse noncoding RNAs and diseases	[274]

tissues was higher compared with nontumor tissues and normal liver tissues, and TRIM58 expression was decreased in HCC. In the study, TRIM58 hypermethylation was detected in 51 of 181 HCC patients with the 10% of threshold. Conclusively, the detection method using TRIM58 methylation level was potential strategy for HCC clinical prognosis [119]. Kuo *et al.* found that IRAK3 showed a dramatically increased promoter methylation frequency and intensity compared with that in the adjacent non-tumor tissues and normal parts of liver hemangiomas. Moreover, IRAK3 promoter methylation was closely associated with tumor stage, and the HCC patients with hypermethylation of IRAK3 had the worse prognosis [120]. Besides, Table 5 shows a vast of gene with aberrant DNA methylation.

Other types of DNA in HCC

Covalently closed circular DNA (cccDNA), existing in HBV not in human cells essentially, could be detected in HBV-related HCC [121]. In one study, researchers tested the levels of cccDNA in HCC tissues which was higher than that of the nontumor tissues [121]. Huang *et al.* developed a method using cccDNA detection in single cells and serum, with an 89.9% positive rate in HCC [122]. In fact, circular DNA exists in not only bacteria and viruses but also animals, for example, mitochondrial DNA (mtDNA). mtDNA can be transcribed and translated. An investigation suggested that mtDNA haplogroup N9a had an inverse correlation with the incidence of HCC and its expression suppressed tumorigenic activity *in vivo* [123].

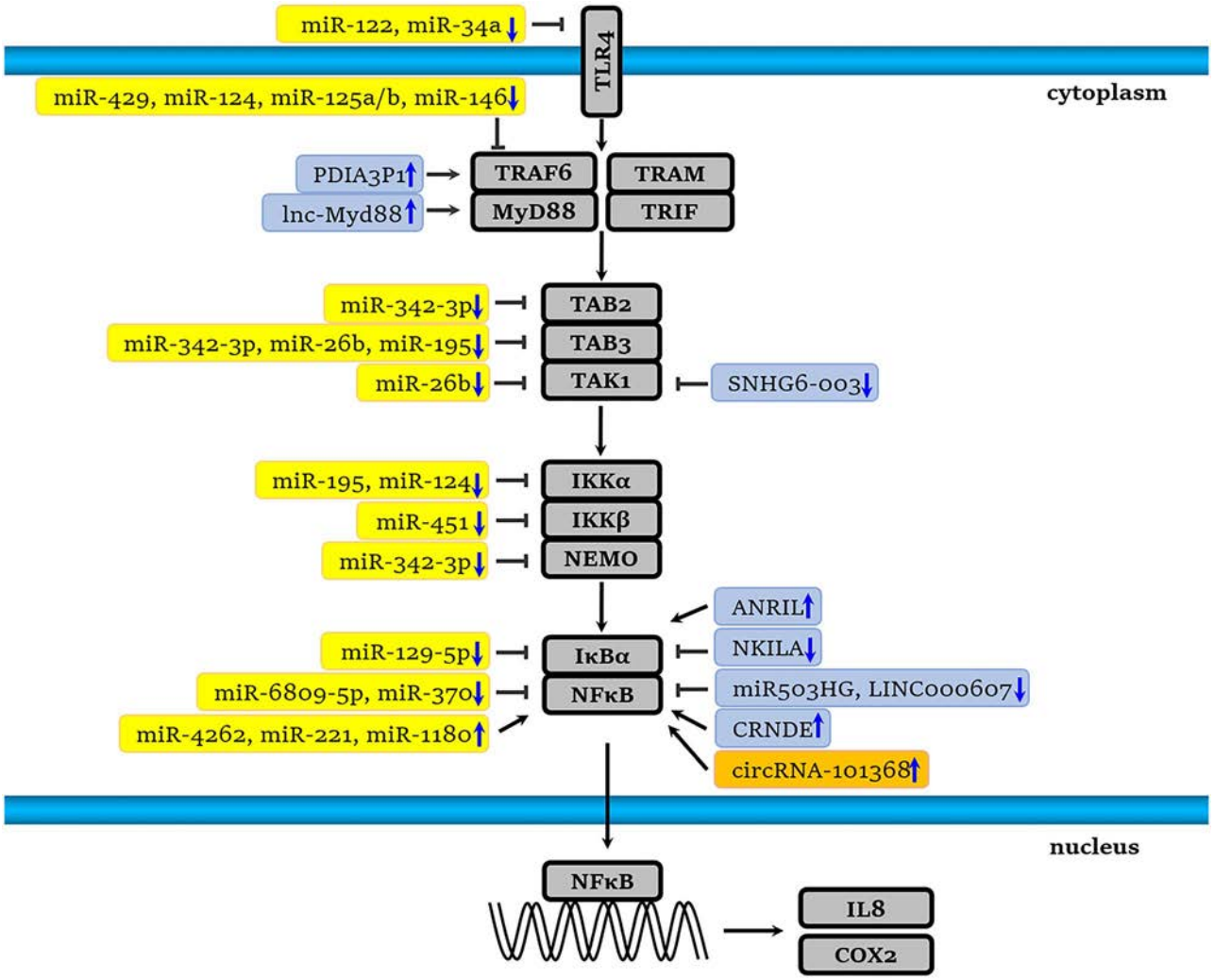


Figure 3. The sketch of TLR4/NF-kB signaling pathway with regulating three types of RNA for each component. Yellow, blue and orange modules represent miRNAs, lncRNAs and circRNAs, respectively.

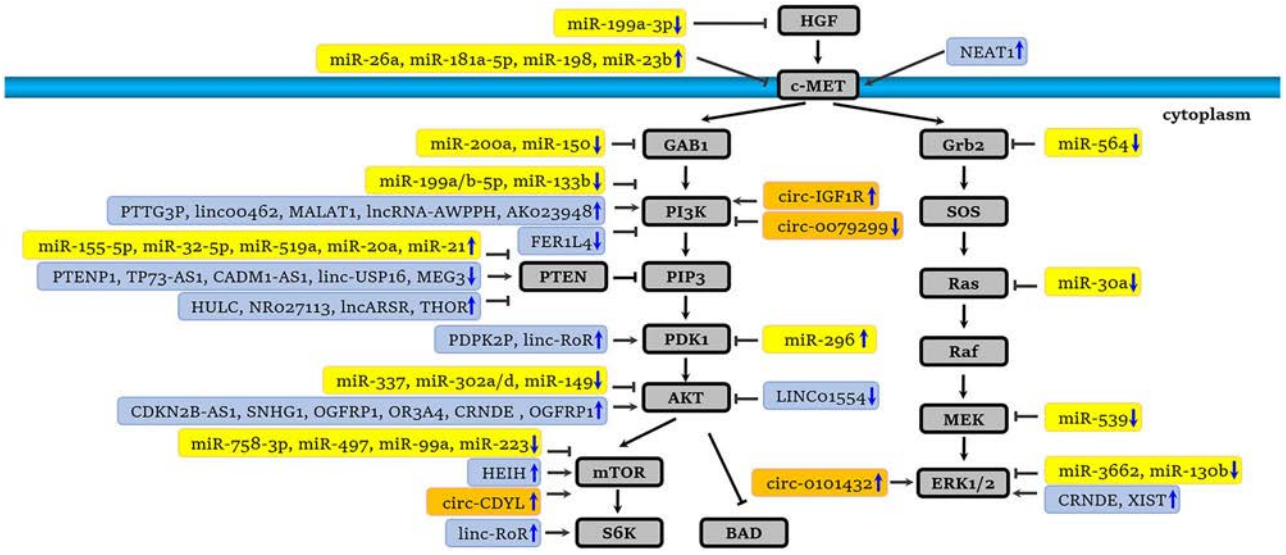


Figure 4. The sketch of HGF/c-Met signaling pathway with regulating three types of RNA for each component. Yellow, blue and orange modules represent miRNAs, lncRNAs and circRNAs, respectively.

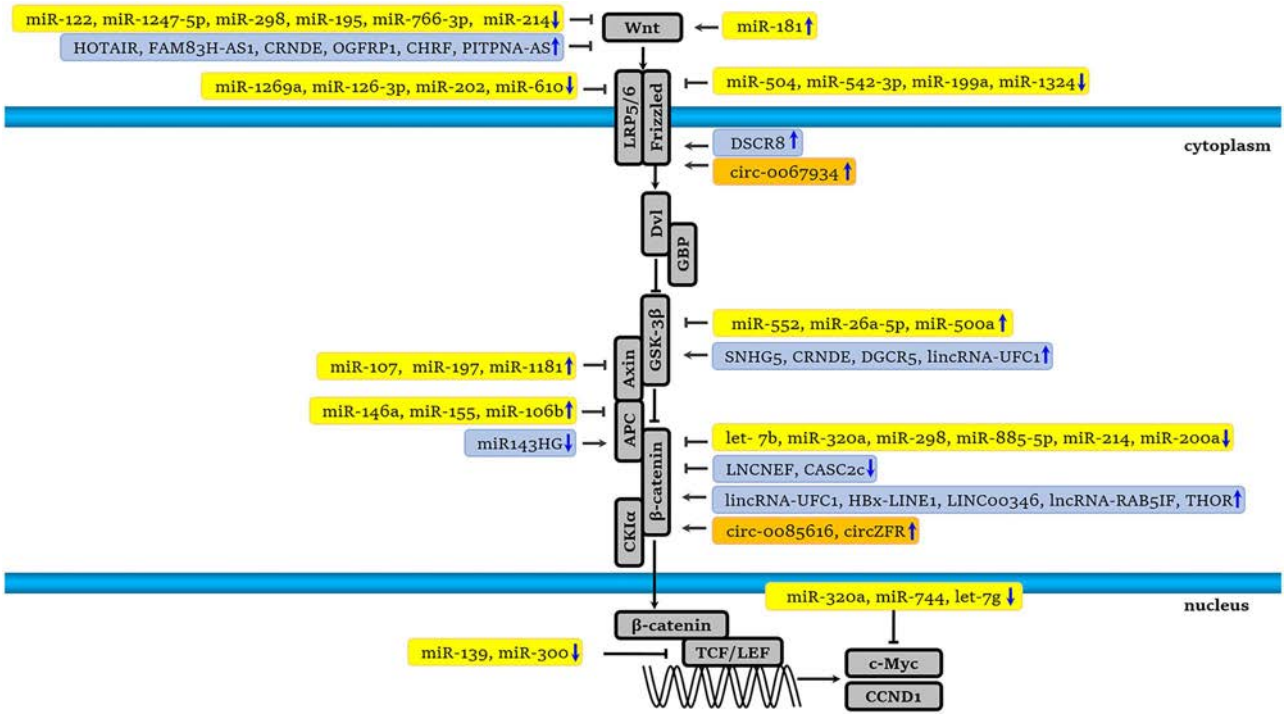


Figure 5. The sketch of Wnt/β-catenin signaling pathway with regulating three types of RNA for each component. Yellow, blue and orange modules represent miRNAs, lncRNAs and circRNAs, respectively.

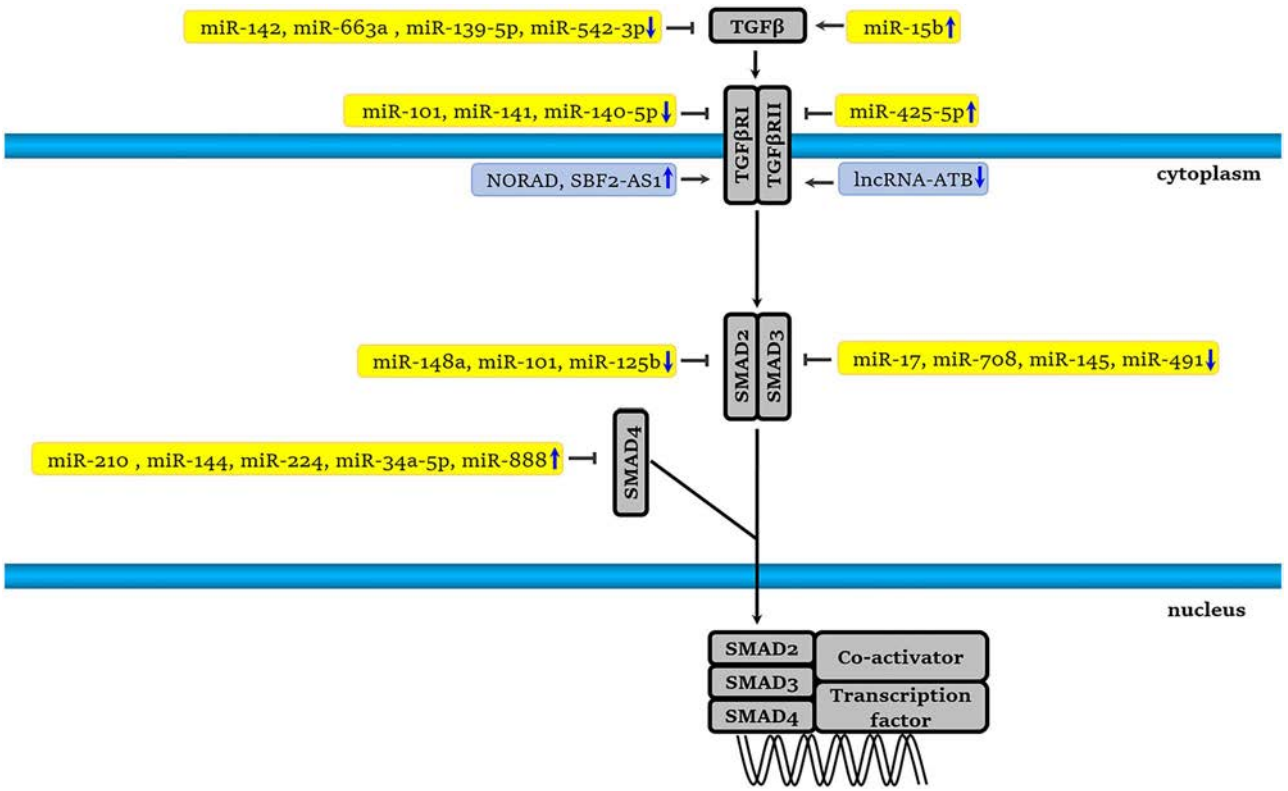


Figure 6. The sketch of TGF-β signaling pathway with regulating three types of RNA for each component. Yellow and blue modules represent miRNAs and lncRNAs, respectively.

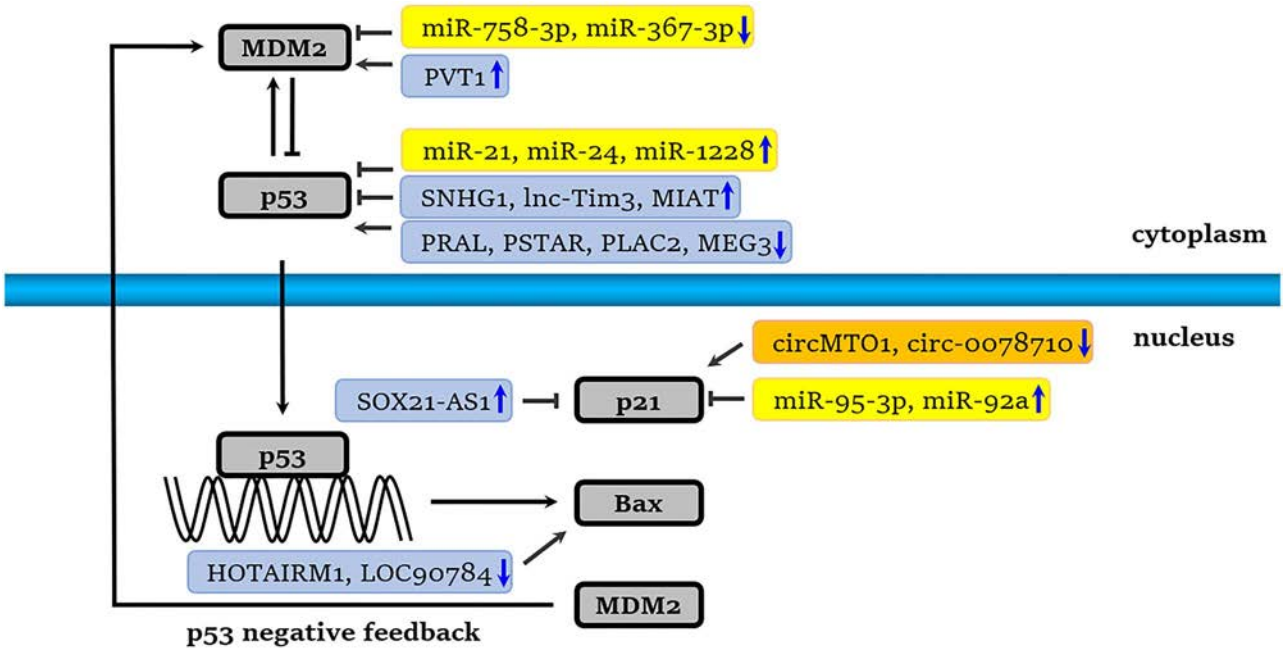


Figure 7. The sketch of MDM2-p53 signaling pathway with regulating three types of RNA for each component. Yellow, blue and orange modules represent miRNAs, lncRNAs and circRNAs, respectively.

Progress of nucleic acids research in clinical trial and research for HCC

Clinical trials

Like vanguard of nucleic acid molecules, miRNAs have made unparalleled progress in HCC diagnosis compared with other noncoding RNA. There have been numerous clinical trials showing at Table 6 using miRNAs as diagnostic biomarkers in HCC patients. Besides, in 2013, Mirna Therapeutics Inc. initiated one phase I clinical trial (NCT01829971) termed 'A Multicenter Phase I Study of MRX34, MicroRNA miR-RX34 Liposomal Injection'. Before this, miR-34, like a star in miRNAs, has attracted substantial attention with downregulation in HCC [124] and other types of cancer [125–130] and roles in a wide spectrum of tumorigenic pathways including P53 pathway [131], E2F pathway [132], c-Met pathway [124] and so on. In this research, 155 participants suffering from primary liver cancer, small cell lung cancer, lymphoma, melanoma, multiple myeloma, renal cell carcinoma or non-small cell lung cancer were intravenously given MRX34 (an analog of miR-34). However, the program was terminated due to the patients undergoing five immune-related serious adverse events in 2017. Until now, no miRNA-mimic therapeutics has been approved for treating HCC. Maybe the approach is quite a challenge (discuss in the following section).

In addition, DNA methylation for some genes was served as helpful tools in clinical trials for HCC diagnosis, which is shown in Table 7.

Drug design in research

There have been considerable nucleic acid molecules and epigenetic characteristics above showing excellent performance in HCC detection, and some of these participated in crucial pathways contributing tumorigenesis and the development of HCC, which implied these molecules presented potential therapeutic indication.

In early days, many researchers identified that miR-122 was frequently downregulated in HCC and targeted Cyclin G1 and Bcl-w to trigger apoptosis in HCC cell lines, which indicated that miR-122 may be a potential target for HCC treatment [133–135]. And in 2010, professor Deiters and colleagues developed two inhibitors (named **NSC 158959** and **NSC 5476**) and one activator (named **NSC 308847**) of miR-122. NSC 158959 and NSC 5476 showed reduction of HCV RNA therefore inhibiting of HCV replication by targeting miR-122. And NSC 308847 could increase in the activity of caspase-3 and -7 and induce excessive apoptosis in HCC cell lines through increase of miR-122 level [136, 137].

Studies have shown that miR-34a was significantly downregulated in HCC tissues than the normal and could inhibit the migration and invasion of HCC cell lines through the c-Met signaling pathway [124]. In 2014, study by Xiao *et al.* used a luciferase reporter system and picked up a lead candidate (**Rubone**), which acted as a small-molecule modulator of miR-34a to upregulate it. Mechanistically, Rubone inhibited cell proliferation and induced apoptosis with downregulation of cyclin D1 and Bcl-2 in HCC cell lines. Moreover, the researchers found that Rubone could activate the transcription of miR-34a through increasing P53 activities. Besides, in transplantation tumor animal model, Rubone exhibited more effective inhibition abilities of tumor growth than sorafenib at the dosage of 50 mg/kg [138].

Besides, researchers reported that miR-21, miR-96, miR-210 and miR-544 were abnormally expressed in HCC cells or tissues compared with the normal and involved in the multiple signal pathways of tumorigenesis of HCC [139–142]. And drug designs for these miRNAs have emerged and displayed excellent anticancer effect.

'Compound AC1MMYR2', a small-molecule inhibitor of miR-21, could block the development from precursor miR-21 to mature miR-21 and induced the reversion of epithelial–mesenchymal transition as well as tumor growth in several types of tumors [143]. 'Compound 1' reported by Velagapudi *et al.*, which inhibited biogenesis of precursor miR-96, showed

Table 5. Detailed information of aberrant methylation in plenty of genes

Gene name	Methylation type	Frequency	Locus	Reference
HOXD10	hypermethylation	76.90%	promoter	[275]
PDCD4	hypermethylation	59.10%	promoter	[276]
HCCS1	hypermethylation	62.50%	promoter	[277]
FOXD3	hypermethylation	57.70%	promoter	[278]
NKAPL	hypermethylation	77.80%	promoter	[279]
DENND2D	hypermethylation	75%	promoter	[280]
miR-148a	hypermethylation	N.A.	promoter	[281]
CDH1	hypermethylation	N.A.	promoter	[282]
9-Sep	hypermethylation	N.A.	promoter	[283]
P16	hypermethylation	58.50%	N.A.	[284]
GNAO1	hypermethylation	N.A.	promoter	[285]
GSTP1	hypermethylation	85%	promoter	[286]
MT1G	hypermethylation	N.A.	promoter	[287]
PGLYRP2	hypermethylation	N.A.	promoter	[288]
miR-192–5p	hypermethylation	N.A.	promoter	[289]
NQO1	hypermethylation	50%	promoter	[290]
KCNQ1	hypermethylation	N.A.	promoter	[291]
RASSF1A	hypermethylation	92.50%	promoter	[292]
CD82	hypermethylation	N.A.	promoter	[293]
RECK	hypermethylation	55.40%	promoter	[294]
COX-2	hypermethylation	N.A.	promoter	[295]
SAMSN1	hypermethylation	N.A.	promoter	[296]
FBLN1	hypermethylation	50%	promoter	[297]
MEG3	hypermethylation	N.A.	promoter	[298]
BNC1	hypermethylation	49.60%	promoter	[299]
GADD45B	hypermethylation	N.A.	promoter	[300]
MTAP	hypermethylation	N.A.	promoter	[301]
RUNX3	hypermethylation	41.10%	promoter	[302]
SOCS3	hypermethylation	48.03%	promoter	[303]
DUOX1	hypermethylation	90%	promoter	[304]
CEBPB	hypomethylation	N.A.	enhancer	[305]
BORIS	hypomethylation	41.90%	promoter	[306]
LINE-1	hypomethylation	87.30%	promoter	[307]
HAI-1	hypomethylation	N.A.	promoter	[308]
MGAT3	hypomethylation	N.A.	promoter	[309]
RASA3	hypomethylation	N.A.	promoter	[310]
UBE2Q1	hypomethylation	N.A.	promoter	[311]
CD147	hypomethylation	N.A.	promoter	[312]
DNAH17	hypomethylation	N.A.	amplicon	[313]
ZEB1-AS1	hypomethylation	N.A.	promoter	[314]
FOXK1	hypomethylation	N.A.	N.A.	[315]

N.A.: not available.

Table 6. Information of miRNAs as biomarker in clinical trials

miRNA	Applicable disease	Detection approaches	Enrollment	ClinicalTrials.gov identifier	Sponsor
Certain circulating miRNAs	HCC	Serum	126	NCT03227510	People's Friendship University
miR-145, miR-31, miR-92a	Lymph node metastasis in HCC	Tissue	150	NCT03416803	Shanghai Zhongshan Hospital
miR-221, miR-222	HCC	Tissue, blood	10	NCT02928627	University of Aberdeen
Certain miRNAs	HCV-related HCC	Serum	100	NCT03429530	HMHamed

N.A.: not available.

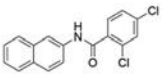
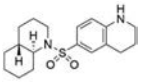
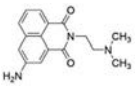
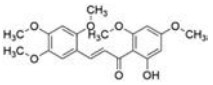
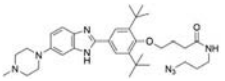
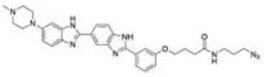
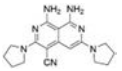
90% inhibition at 40 μM and upregulated the expression of FOXO1, therefore inducing apoptosis in cancer cells [144]. 'Compound Targapremir-210', a small molecule inhibitor of miR-210, inhibited Dicer processing of the miR-210 precursor and suppressed tumor growth in a mouse model [145, 146]. Christopher *et al.*, reported that a small molecule compound an inhibitor of miR-544 and also named as MLS000054131, impeded miR-544 biogenesis and repressed tumor growth *in vivo* [147]. Complete information of these compounds has been exhibited in Table 8.

Table 7. Information of DNA methylation as biomarker in clinical trials

Methylation location	Applicable Disease	Detection Approaches	Enrollment	ClinicalTrials.gov identifier	Sponsor
cfDNA	Liver cancer	Blood	1600	NCT03694600	Laboratory for Advanced Medicine, Indiana
cfDNA-based SEPT9-promoter	HCC	N.A.	440	NCT03311152	Central Hospital, Nancy, France
ctDNA	HCC	Blood	400	NCT03483922	HKGepitherapeutics
Liver cancer prognosis-related gene	Liver cancer	N.A.	300	NCT01786980	Eastern Hepatobiliary Surgery Hospital
SEPT9-promoter	HCC	Blood	220	NCT03804593	Epigenomics, Inc
VTRNA2–1 promoter	HCC	Tissue	92	NCT04177316	Chang Gung Memorial Hospital

N. A.: not available.

Table 8. Potential compounds targeting miRNAs of HCC

Compound Name	Target	Activity	Structure	Reference
NSC 158959	miR-122	EC50 = 3 μM		[136]
NSC 5476	miR-122	EC50 = 0.6 μM		[136]
NSC 308847	miR-122	IC50 = 3.8 μM		[136]
Rubone	miR-34a	IC50 = 3 μM		[138]
AC1MMYR2	miR-21	N.A.		[143]
Compound 1	miR-96	40 μM 90% inhibition		[144]
Targapremir-210	miR-210	IC50 = 200 nM(MDA-MB-231 cell)		[145]
MLS000054131	miR-544	N.A.		[147]

N.A.: not available.

Future remarks

Over the past several decades, scientists' understanding of genome has been substantially transformed. In the 1960s, it was widely believed that noncoding DNA (junk DNA) holding 98% region in genome was with no function and produced junk fragments. But now it seems that the noncoding region concealed huge potential functioning as gene regulators. Therewith, emergence of noncoding RNA or DNA has received considerable attention especially in malignant diseases. In this perspective and taking the extraordinarily heterogeneous cancer HCC as paradigm, we discussed incredible progress on some mainstream nucleic acids above and other popular ones, which included miRNA, lncRNA, circRNA, ctDNA and DNA methylation.

Methylation is a switch for gene expression. On/off of tumor gene is often managed by hypo/hypermethylation particularly in promoter. In HCC, methylation based on a few genes including the promoters of SEPT9 and VTRNA2–1 was also under research in clinical trial. Malignant tumors shed DNA into the circulation [148, 149]. Ephemeral life of ctDNA means it carried real-time information of tumor. Therefore, the features of ctDNA including mutation and methylation may be useful for HCC diagnosis.

All three noncoding RNAs showed promising performance in HCC detection, but miRNA was quite remarkable, some of which has entered to clinical trial stage such as miR-221 and miR-222. Furthermore, the three noncoding RNA regulated gene expression in terms of different patterns. miRNA and circRNA generally followed specified mode that miRNA inhibited target gene by binding to its 3′UTR and degrading its mRNA and circRNA turned on expression of target gene via sponging special miRNA and disassociating the link between miRNA and target gene. Unlike single model of miRNA and circRNA that the former consists of about 22 nts and the latter forms a covalently closed continuous

loop, lncRNA is in length range tens to even tens of thousands nts and possesses mRNA-like structure with a poly(A) tail and a promoter [150] even forms secondary and tertiary structures [151]. Therefore, the mRNA- and protein-like structures endow lncRNA with a variety of ability to regulate expression in gene and protein levels.

For drug therapy of HCC, all single-target drugs ended in failure finally. Hence, all drugs for HCC approved by FDA target multiple proteins such as sorafenib and regorafenib targeting VEGFR, RET and KIT. As for miRNA, it could not act as the direct executor of function for vital movement. In one facet, it can bind to several special mRNAs and lead to the inhibition of multiple proteins so as to launch the regulation of vital movement, thus probably targeting several targets of HCC, which may benefit for therapy. In the other facet, unlike compounds synthesized *in vitro* with clear targets, endogenous miRNA targets not only some proteins known but also other ones that we may not know yet, which may make against therapy. Maybe MRX34 with five immune-related serious adverse events is one example. In reality, put HCC aside, no miRNA therapeutics have been approved by FDA in any diseases. However, small interfering RNAs (siRNAs), another small RNA similar with miRNA, have contributed to the approval of Patisiran in 2018. This may be not occasional, because (i) siRNA is synthetic with higher specificity and generally targets one mRNA, but miRNA is endogenous molecules and targets multiple mRNAs and (ii) the sequence of siRNA is completely complementary to the target mRNA, while that of miRNA is partially matched, probably leading to more unknown events. Till now, miRNA as vanguard of noncoding RNA is so, and lncRNA and circRNA may be no much better off. Anyhow, to answer whether benefits outweigh harms or not, there is still much work to be done.

Key Points

- A variety of nucleic acids (miRNA, lncRNA, circRNA, ctDNA and DNA methylation) could act as effective biomarkers in humor or tissue of HCC patients.
- Regulatory patterns of three key noncoding RNA were summarized that lncRNA employed four distinct mechanisms and miRNA or circRNA generally hire the unique one.
- Some novel nucleic acids (miRNA, ctDNA and DNA methylation) have contributed to clinical trials research in HCC diagnosis and therapy.
- miRNA, as vanguard of nucleic acid molecules, showed difficulty as tool for HCC therapy.

Supplementary Data

Supplementary data are available online at https://academic.oup.com/bib.

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