The Role of MicroRNAs in Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers, leading to the second cancer-related death in the global. Although the treatment of HCC has greatly improved over the past few decades, the survival rate of patients is still quite low. Thus, it is urgent to explore new therapies, especially for more accurate biomarkers for early diagnosis, treatment and prognosis in HCC. MicroRNAs (miRNAs), small noncoding RNAs, are pivotal participants and regulators in the development and progression of HCC. Great progress has been made in the studies of miRNAs in HCC. The key regulatory mechanisms of miRNAs include proliferation, apoptosis, invasion, metastasis, epithelial-mesenchymal transition (EMT), angiogenesis, drug resistance and autophagy in HCC. And exosomal miRNAs also play important roles in proliferation, invasion, metastasis, and drug resistance in HCC by regulating gene expression in the target cells. In addition, some miRNAs, including exosomal miRNAs, can be as potential diagnostic and prediction markers in HCC. This review summarizes the latest researches development of miRNAs in HCC in recent years.

Key words: microRNAs; hepatocellular carcinoma; exosomes; regulatory mechanism; diagnosis; prediction; marker

Introduction

Hepatocellular carcinoma (HCC) has become the second most common cause of cancer-related death worldwide [1], with approximately 782,500 new cases and 745,500 deaths occurring in the global during 2012 [2]. In the early stage of HCC, surgical resection, liver transplant, local ablation and other curative therapies can improve patient’s survival [3]. However, the 5-year recurrence rate is very high, it may reach as high as 80%-90% even the HCC patients have received potentially curative therapies [4]. It has been already advanced stage for most people when HCC was diagnosed [5]. For the advanced stage, the small molecule targeted therapeutics drugs sorafenib and regorafenib are the standard treatments that have been approved by the US Food and Drug Administration (FDA). Sorafenib is the only standard first-line systemic therapy available for advanced HCC, but the median survival was reported only 3 months [6]. Regorafenib is a second-line drug when HCC patients were progressing on sorafenib treatment, whereas, the median survival was still only 10.6 months according to a phase 3 clinical trial report [7]. Even though sorafenib and regorafenib can improve overall survival of HCC patients, it is not too long. Furthermore, the worries for drug resistance and adverse action of these drugs are rising as well. Therefore, it is urgent to explore new therapies, especially seek for more accurate markers for early
diagnosis, treatment and prognosis in HCC. Nucleic acid-based drugs such as microRNAs (miRNAs) may have the promising therapeutic potential for HCC treatment. MiRNAs are pivotal participants and regulators in the development and progression of HCC. And exosomal miRNAs also play important roles in the development and progression in HCC. In addition, some miRNAs, including exosomal miRNAs, can be as diagnostic and prediction markers in HCC. In this review, we summarize the latest researches development of miRNAs in HCC in recent years.

Biogenesis of miRNAs

The sequence of the human genome has been finished in 2003, and it was reported that only 20,000-25,000 genes, about 1.5% of the total human genome, can encode protein [8]. In other words, noncoding RNAs (ncRNAs), including miRNAs, long noncoding RNAs (lncRNAs), small nuclear RNAs (snRNAs) and circularRNAs (circRNAs), are the major components of the human transcriptome [9]. MiRNAs are the pivotal members of this noncoding RNA family [10]. MiRNAs, ~ 23 nucleotides in length, act as important gene regulators in animals and plants [11]. MiRNAs control the expression of their target miRNAs principally by binding to the 3'-untranslated region (3'-UTR) [12]. A mature miRNA formation goes through a series of complicated process. It was described in the Figure 1. At first, miRNA genes are transcribed to primary microRNAs (pri-miRNAs) by RNA polymerase II in the nucleus [13]. Pri-miRNAs are cleaved by the RNase III type endonuclease Drosha the next, resulting in releasing the precursor miRNAs (pre-miRNAs), which have about ~70 nucleotides and stem-loop structures [14]. After that, being transported by exportin-5 from nucleus to cytoplasm, pre-miRNAs are processed by another RNase III type endonuclease Dicer to generate a miRNA protein complex with two strands [15, 16]. One strand will become a mature miRNA, and then the mature miRNA is bound to RNA-mediated silencing complexes (RISC) immediately [17]. In the RISC, the mature miRNA targets the 3'-UTR of its target mRNAs to regulate gene posttranscriptional expression, including translational inhibition and mRNA cleavage [18]. The other one will be degraded. It has been proved that miRNAs play crucial roles in multiple biological processes by regulating gene expression, and the abnormal expression of miRNAs are related to numerous cancers and many other diseases [19].

miRNAs and HCC

The research in miRNAs and their relevant functional mechanisms of cancer will contribute to the development of the therapeutics. Thus, we summarize recent researches development in regulating miRNAs in HCC. Some miRNAs have been found to be upregulated in HCC, which can be seen in the Table 1 [20-53], and some downregulated can be seen in the Table 2 [54-146]. The key regulatory mechanisms of miRNAs in these studies include proliferation, apoptosis, invasion,
metastasis, epithelial-mesenchymal transition (EMT), angiogenesis, drug resistance and autophagy in the development and progression of HCC. In addition, some miRNAs can also be as potential diagnostic and prediction markers in HCC.

**Table 1. Upregulated miRNAs in HCC**

| miRNA | Targets | Mechanisms |
|-------|---------|------------|
| miR-10b | CSMD1 | Migration, invasion | [20] |
| miR-21 | CAMSA1P1, DDX1, MARCKS1 | No mentioned | [21] |
| miR-25 | RhoGD1, TRAIL | EMT, apoptosis | [22, 23] |
| miR-32 | No mentioned | Prognostic marker | [24] |
| miR-92a | FBXW7 | Cell growth, prognostic marker | [25] |
| miR-96-5p | Caspase-9 | Apoptosis | [26] |
| miR-107 | Asn2, HMGA2, HMGC5 | Proliferation, prognostic marker | [27-29] |
| miR-135a | FOXO1 | Migration, invasion | [30] |
| miR-135-5p | PTEN | Proliferation, apoptosis, invasion | [31] |
| miR-181a | Atg5 | Autophagy | [32] |
| miR-182 | TP53INP1 | Drug resistance | [33] |
| miR-197 | CD82 | Migration, invasion | [34] |
| miR-203a-3p-1 | IL-24 | Cell growth, proliferation, metastasis | [35] |
| miR-210 | FGFR1L1, YES1 | Metastasis, angiogenesis, proliferation | [36, 37] |
| miR-214-5p | WASL | Migration, invasion, EMT | [38] |
| miR-216a/217 | PTEN, SMAD7 | Drug resistance | [39] |
| miR-221 | No mentioned | Prognostic marker | [40] |
| miR-332-3d | TGFBR2 | Cell growth, apoptosis, migration | [41] |
| miR-331-3p | ING5 | Proliferation, apoptosis | [42] |
| miR-336 | FBXL2 | Proliferation, migration, invasion | [43] |
| miR-454 | CHD5 | Proliferation, EMT, prognostic marker | [44] |
| miR-467a | SPRED2, PIK3R1 | Proliferation, metastasis, prognosis marker | [45] |
| miR-765 | LINP4B | Proliferation, migration, invasion | [46] |
| miR-873 | TSLC1 | Proliferation, migration, invasion | [47] |
| miR-892a | CD226 | Proliferation, invasion | [48] |
| miR-1246 | CADM1 | Migration, invasion, diagnostic and prognostic marker | [49] |
| miR-1249 | PTH11 | Cell growth, migration, invasion | [50] |
| miR-1468 | CITED2, UF1 | Proliferation, apoptosis | [51] |
| miR-3910 | MST1 | Cell growth, migration | [52] |
| miR-4417 | TRIM35 | Proliferation, apoptosis | [53] |

**MiRNAs and proliferation and apoptosis of HCC**

Cell growth, proliferation and apoptosis are the significant processes that guarantee the internal stability and balance of cell number and biological functions [14]. Cell proliferation is achieved through the cell cycle, a strictly and orderly controlled process of cell activity. The cyclin dependent kinases (CDKs) are the core regulators of the cell cycle [147]. Any cell proliferation process follows certain rules. When the cell cycle is out of control and cell unlimited proliferate, it will develop into a tumor cell [148]. Apoptosis is also called as programmed cell death [149]. Apoptosis contributes to maintain the internal balance between cell death and renewal [150]. Disorder of apoptosis is often associated with human diseases, for example, deficient apoptosis may lead to tumor [151]. In short, cell unlimited proliferation and abnormal regulation of apoptosis will promote the formation of cancer, including HCC.

**Table 2. Downregulated miRNAs in HCC**

| miRNA | Targets | Mechanisms |
|-------|---------|------------|
| miR-7 | mTOR, TYRO3 | Autophagy, drug resistance | [54, 55] |
| miR-7/21/107 | Maspin | Drug resistance, prognostic marker | [56] |
| miR-26 | ULP1 | Autophagy | [57] |
| miR-29a | CLDN1 | Proliferation, migration | [58] |
| miR-30a-5p | AEG-1 | Cell growth, apoptosis | [59] |
| miR-30e | MT1A | EMT | [60] |
| miR-31 | NDRG3 | Drug resistance | [61] |
| miR-31-5p | SPI | Proliferation, migration, invasion | [62] |
| miR-33a | No mentioned | Prognostic marker | [63] |
| miR-33a-5p | No mentioned | Drug resistance | [64] |
| miR-33b | SALL4 | Proliferation, metastasis | [65] |
| miR-98 | EZH2 | Proliferation | [66] |
| miR-101 | Mit-1, RAB5A, STMN1, ATG4D | Apoptosis, autophagy, diagnostic marker | [67-69] |
| miR-105-1 | NCOA1 | Diagnostic and prognostic marker | [70] |
| miR-122 | Snail1, Snail2, PKM2, DLX4 | EMT, proliferation, apoptosis, prognostic marker | [71-73] |
| miR-124-3p | MAPK14, RELA, CDK2, CDK4, SPI | No mentioned | [74] |
| miR-126 | VEGF | Angiogenesis | [75] |
| miR-137 | EZH2 | Proliferation, invasion | [76] |
| miR-138 | Cyclin D3, SPI | Proliferation marker, invasion, migration | [77, 78] |
| miR-142 | THBS4, TGF-β | Migration, invasion, cell growth, metastasis | [79, 80] |
| miR-142-3p | ATG5, ATG16L1, LDHA | Autophagy, drug resistance, proliferation | [81, 82] |
| miR-143 | TLR2 | Proliferation, invasion | [83] |
| miR-144 | ZFX | Proliferation, invasion, migration | [84] |
| miR-146a | HAB18G | Metastasis, angiogenesis | [85] |
| miR-152 | RTKN, DNM1 | Cell growth | [86, 87] |
| miR-186 | YAPI | Migration, invasion, proliferation | [88] |
| miR-187-3p | S100A4 | EMT | [89] |
| miR-194 | MAFK4 | Proliferation, diagnostic and prognostic marker | [90] |
| miR-195 | Wnt3a, CXB4, FGFR2, VEGFA | Proliferation, metastasis, angiogenesis | [91-93] |
| miR-199 | RGS17 | Proliferation, migration, invasion | [94] |
| miR-199a-3p | VEGFA, VEGFR1, VEGFR2, HGF, MMP2, YAPI | Angiogenesis, proliferation, apoptosis | [95, 96] |
| miR-199a-5p | CLTC | Cell growth | [97] |
| miR-199b-5p | TGF-β | EMT | [98] |
| miR-200a | CXCL1, GAB1 | EMT, invasion, migration | [99, 100] |
| miR-203 | IL-10, Snail1, Twist1 | Proliferation, metastasis, apoptosis | [101] |
| miR-206 | CCND1, cMET, CDK6 | Proliferation, apoptosis | [102] |
| miR-211 | SPARC | Proliferation, migration, invasion | [103] |
| miR-212 | FOXL1 | Migration, cell growth | [104] |
| miR-217 | MTDH | Proliferation, apoptosis, migration, invasion | [105] |
| miR-223 | Rab1 | Proliferation, apoptosis | [106, 107] |
| miR-296 | FGFR1 | Proliferation, apoptosis | [108] |
Recent studies have indicated that aberrant expressions of miRNAs were linked to HCC cells proliferation and apoptosis. Some miRNAs promoted cell proliferation and apoptosis of HCC, and the others were repressive. Therefore, these miRNAs can be as potential cancer inhibitors to control the development and progression of HCC by regulating cell proliferation and apoptosis.

Plenty of miRNAs were reported that they could mediate cell proliferation and apoptosis by controlling cell cycle in HCC. Overexpression of miR-1468 promoted cell cycle transition from G1 to S phase and apoptosis resistance [51]. Increased expression of miR-98 arrested HCC cell cycle in G0/G1 phase to repress cell proliferation via targeting enhancer of zeste homolog 2 (EZH2) [66]. Overexpression of miR-195 induced G1 phase cell cycle arrest and promoted apoptosis by directly targeting Wnt3 in HCC [91]. MiR-506 was reported to induce HCC cell cycle G1/S phase arrest and apoptosis [127]. MiR-1299 overexpression inhibited HCC cell cycle from G0/G1 phase entering into S phase, and its target cyclin dependent kinase 6 (CDK6) was the key regulator in the G0/G1 phase arrest [145].

Some aberrant expression of miRNAs could promote HCC cell proliferation and apoptosis by binding to their target genes. Inhibition of miR-25 expression was showed via PTEN/PI3K/Akt/Bad signaling pathway to enhance HCC cells apoptosis caused by the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [23]. MiR-107 was observed to be upregulated in HCC. Zhang JJ et al. reported that overexpression of miR-107 contributed to HCC cells proliferation via targeting Axin2 [27]. However, Wang Y et al. got that repressing miR-107 by targeting high mobility group A2 (HMGA2) could increase HCC cells proliferation [28]. MiR-155-5p was found to elevate HCC cells proliferation ability but inhibit apoptosis [31]. High expression of miR-203a-3p.1 could improve HCC cell proliferation by targeting interleukin-24 (IL-24) in HCC [35].

In addition, other miRNAs, which abnormally expressed, were proved to inhibit cell proliferation and apoptosis in HCC. MiR-96-5p was observed to inhibit apoptosis by targeting caspase-9 [26]. MiR-122 appeared abundant and downregulated in HCC cells. Xu Q et al. reported that overexpression of miR-122 repressed proliferation but induced apoptosis by targeting pyruvate kinase muscle 2 (PKM2) in HCC [72]. Another report found that miR-122 could downregulate the expression of oncogenic distal-less 4 (DLX4), knockdown the expression of this oncogene would inhibit HCC cells proliferation [73]. Overexpression of miR-137 was reported to reduce HepG2 cells proliferation by targeting EZH2 [76]. MiR-217 overexpression was revealed to inhibit cells apoptosis by targeting metaladherin (MTDH) in HCC [105]. MiR-337 and miR-370 overexpression were also found to inhibit cell proliferation and promote apoptosis in HCC by HMGA2 and PIM1 [110] [118]. Decreased levels of miR-377 could suppress HCC cell apoptosis through inhibiting Bcl-xL expression [120].

The above reports have shown that miRNAs serve important roles in proliferation and apoptosis of liver cancer. In addition, it was indicated that many miRNAs participate in the development and progression of HCC by mediating proliferation and apoptosis.

MiRNAs and metastasis of HCC

Invasion and metastasis are the essential characteristics of the tumor cells. Metastasis is one of the most dominative causes of cancer death [152]. And 90% of cancer deaths are because of metastasis [153]. Tumor metastasis is a very complex process; it usually undergoes these major procedures: (1) local
migration and infiltration, (2) vascular invasion, (3)
survival in the circulating blood, (4) homing and
implantation of metastatic organs in the distant place,
(5) substantial infiltration, (6) adaptation to new
environment, (7) secondary tumor growth [154]. EMT
is a biological process that epithelial cells transform
into mesenchymal cells by a specific procedure [155].
EMT participates in cancer metastasis through
empowering tumor cells with migratory and invasive
biological properties [156].

The latest researches have demonstrated that
miRNAs can regulate HCC cells by promoting or
suppressing HCC cells invasion, EMT and metastasis.
How to prevent tumor metastasis has become one of
the most important problems in the treatment of
HCC. The discoveries of miRNAs may provide us
with choices of anti-metastatic therapies.

These miRNAs dysregulated expression would
contribute to HCC metastasis. MiR-25 overexpression
could facilitate EMT formation by inhibiting Rho GDP
dissociation inhibitor alpha (RhoGDII) in HCC [22].
Overexpression of miR-135a promoted HCC cells
migration and invasion by targeting forkhead box O1
(FOXO1) [30]. High expression of miR-203a-3p.1
could improve HCC migration and invasion by
targeting IL-24 in HCC [35]. Upregulated miR-892a
[48] and miR-1246 [49] expression were observed to
enhance HCC cells migration and invasion. Downregulation miR-30e was showed to heighten
metastasis and EMT of HCC cells by enhancing MTA1
[60]. Additionally, loss levels of miR-345 [114] and
miR-638 [136] would heighten invasion and EMT of
HCC cells.

Above miRNAs aberrant expression could
motivate cell invasion, EMT and metastasis in HCC.
Of course, some were the opposite. Downregulation
of miR-197 was identified to inhibit HCC cells
migration and invasion by targeting KAI1/CD82 [34].
Overexpression of miR-214-5p could inhibit the
migration and invasion of HCC cells; besides,
miR-214-5p could also suppress EMT [38]. MiR-212
overexpression was observed to inhibit the migration
of HCC cells by targeting forhead box M1 (FOXM1)
and suppress the Wnt/β-Catenin signaling pathway
[104]. MiR-495 and miR-613 overexpression were
showed to inhibit cell proliferation and invasion in
HCC by targeting IGF1R and YWHAZ [124] [133].
Upregulation of miR-122 expression in HCC
repressed cell proliferation, invasion and EMT by
targeting Snail1 and Snail2 [71]. Overexpression of
miR-187-3p [89], miR-199b-5p [98] and miR-1301 [146]
in HCC were also reported to inhibit EMT and
metastasis. Besides, some miRNAs overexpression
could repress invasion, migration and metastasis in
HCC, for instance, miR-137 [76], miR-146a [85],
miR-186 [88], miR-199 [94], miR-365 [116], miR-370
[118], miR-520f [128], miR-634 [134], miR-1207-5p
[143], and so on.

Thus, miRNAs have been demonstrated to
regulate metastasis of HCC. Absolutely, these
miRNAs might be used to treat metastasis in HCC.

**MiRNAs and angiogenesis of HCC**

Abundant angiogenesis provides the necessary
nutrition for tumor growth and metastasis, thus, it is
essential for tumor growth and metastasis in solid
tumor [157]. As one of the common solid tumors,
HCC usually has affluent and deformed blood vessel
tissue [158]. In the process of angiogenesis, vascular
endothelial growth factor (VEGF), a highly conserved
homodimeric glycoproteina, is identified as one of the
most effective cytokines [159]. VEGF is a superfamily
with seven subtypes, for example, VEGF-A, VEGF-B,
VEGF-C, and so on. VEGF receptors have three types,
VEGFR1, VEGFR2 and VEGFR3. VEGF family
members combine with their receptors VEGFRs to
induce tumor angiogenesis [160]. High expression of
VEGF in tumor tissue or circulation blood frequently
implies tumor may be invasion and metastasis [161].

Great deals of miRNAs were reported to regulate
angiogenesis in HCC by VEGF. Overexpression of
miR-146a was showed to repress HCC angiogenesis
and tumor metastasis by downregulating VEGF [85].
MiR-199a-3p was proved to repress angiogenesis by
directly decreasing VEGF secretion and suppressing
expression of its receptors VEGFR1 and VEGFR2 on
HCC cells [95]. MiR-451 could suppress VEGF
production and block VEGFR2 pathway to reduce
angiogenesis [122]. Overexpression of miR-638 was
reported to suppress angiogenesis and tumor growth
of HCC cells by inhibiting VEGF in HCC [135].
MiR-1301 overexpression was found to inhibit HCC
angiogenesis by downregulating VEGFA, BCL9, and
β-catenin [146].

On the contrary, some miRNAs could enhance
angiogenesis by VEGF. Suppression miR-338-3p
could upregulate VEGF expression to promote
angiogenesis in HCC [112]. Furthermore,
downregulating miR-497 promoted angiogenesis and
metastasis by directly inhibiting VEGFA [125].

In consequence, miRNAs were proved the vital
regulators in the process of HCC angiogenesis. What’s
more, miRNAs could act as inhibitors of tumor
angiogenesis.

**MiRNAs and drug resistance of HCC**

Chemotherapy is currently one of the most
commonly used treatment methods, when most
patients with HCC are diagnosed at advanced stages
[162]. Large numbers of trials that tested the efficacy

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of various drugs have manifested that HCC has low sensitivity to chemotherapy [163]. And several chemotherapies fail due to the intrinsic or acquired drug resistance [164]. Thus, how to reverse drug resistance and improve the effectiveness of chemotherapy are crucial problems to be solved urgently. Many reports have showed that miRNAs could act as regulators to promote or reverse drug resistance in HCC, indicating miRNAs might have the promising therapeutic potential for drug resistance.

Sorafenib is as known the first-line drug for advanced HCC, but its curative effect is limited due to acquired resistance, which may be the primary factor [165]. MiRNAs could reverse this effect. MiR-7 was proved to overcome sorafenib resistance by suppressing its target TYRO3 via PI3-Kinase/AKT pathway [55]. Overexpression of miR-216a/217 activated TGF-β pathway to induce sorafenib resistance, but interdicting TGF-β pathway would reverse this resistance in HCC [39]. MiR-367-3p increased sorafenib efficacy to suppress HCC metastasis through changing the MDM2/AR/FKBP5/PHLPP/(pAKT and pERK) signals [117]. Another report has shown that sorafenib significantly reduced miR-142-3p levels by acting on the transcription factor PU.1; however, miR142-3p upregulation could sensitize HCC cells to sorafenib through targeting autophagy-related 5 (ATG5) and autophagy-related 16-like 1 (ATG16L1) to reduce sorafenib-induced apoptosis, enhance sorafenib-induced autophagy and inhibit cell growth [82].

For the drug resistance induced by other chemotherapeutic drugs, miRNAs also can promote or reverse drug resistance in HCC. Upregulating miR-182 was observed to increase cisplatin resistance in HCC treatment by regulating tumor protein 53-induced nuclear protein1 (TP53INP1) [33]. Inhibition of miR-33a-5p expression could also reduce cisplatin sensitivity and increased its drug resistance in HCC [64]. MiR-7/21/107 was enhanced by HBV X protein to promote HCC cells drug resistance by directly suppressing its target maspin expression [56]. MiR-31 and its target gene NDRG3 made HCC cells sensitize to chemotherapeutic drug Adriamycin [61]. MiR-375 was combined with hollow mesoporous silica nanoparticles (HMSN) to overcome doxorubicin hydrochloride resistance in HCC [119]. Additionally, miR-539 overexpression was reported to increase sensitivity to antagonize arsenic trioxide resistance in HCC [130].

Therefore, miRNAs were involved in drug resistance of HCC. Furthermore, miRNAs could prove a new therapeutic strategy for how to improve the effectiveness of chemotherapy when treating HCC.

**MiRNAs and autophagy of HCC**

Autophagy has been reported for many years ago, but it has recently gained more attention, especially the Nobel Prize in Physiology or Medicine awarding to the great discovery of autophagy in 2016 makes it a popular topic again. Autophagy, a self-digestive catabolism process [166], depends on lysosomes to degrade and recycle proteins or cell organelles [167]. Autophagy can regulate cell survival, differentiation, senescence, death and many other biological processes [168]. It has been proved that autophagy has a dual regulation role in HCC occurrence and suppression [169].

MiRNAs might participate in the process of HCC development and progression through autophagy. MiR-181a was reported to repress autophagy in HCC by targeting pro-autophagic protein Atg5, leading to reducing apoptosis of HCC cells and accelerate hepatoma growth [32]. MiR-7 was confirmed to induce HCC cells autophagy by targeting mammalian target of rapamycin (mTOR), and inhibition of autophagy heightened the antitumor activity of miR-7 to repress HCC cells proliferation [54]. MiR-26 could improve HCC cells sensibility to chemotherapy and facilitated apoptosis of HCC cells through inhibiting autophagy initiator ULK1 [57]. MiR-101 was found to enhance cisplatin-induced apoptosis through repressing autophagy in HCC [68].

Thus, miRNAs participate in the process of HCC tumorigenesis and development through autophagy. To sum up, miRNAs appear to play crucial roles in modulating HCC development and progression. The aberrant expression of miRNAs in HCC was summarized in the Figure 2. These studies indicated that miRNAs have the promising therapeutic potential for HCC treatment.

**Exosomal miRNAs and HCC**

Exosomes, one type in extracellular vesicles (EVs), are small vesicles with a size range of 40-150 nm and a lipid bilayer membrane [170]. Exosomes, which now considered as an additional mechanism for intercellular communication [171], are generated inside multivesicular endosomes or multivesicular bodies (MVBs) [172]. Exosomes exist in all body fluids, such as serum, urine, and saliva [173]. Exosomes have been shown to act as shuttles between cells including RNA, proteins, miRNAs, long noncoding RNAs (lncRNAs), or DNA fragments [174-177]. Tumor-derived exosomes are recognized as a critical determinant of the tumor progression [178]. Studies have demonstrated the mechanism of HCC-derived exosome-mediated miRNA transfer is
important in the growth and progression of HCC [179]. The studies of exosomal miRNAs in HCC in recent years were summarized in the Table 3 [180-194].

Exosomal miRNAs were involved in proliferation, migration, metastasis, drug resistance in HCC. Exosomal miR-9-3p, lower level in HCC patients, could reduce HCC cell viability and proliferation, and additionally reduced ERK1/2 expression by targeting fibroblast growth factor 5 (HBGF-5) [180]. Exosomal miR-32-5p was testified to activate the PI3K/Akt pathway, and induce multidrug resistance by modulating angiogenesis and EMT in HCC [183]. Exosomal miR-103 was proved to increase vascular permeability and promote metastasis by targeting junction proteins [184]. Zhang Z et al. found that the expression of exosomal miR-320a in cancer-associated fibroblasts (CAFs) was lower than paracancer fibroblasts (PAFs), leading to the cancer cells towards a more malignant phenotype. Furthermore, they revealed that miR-320a could suppress HCC cell proliferation, migration and metastasis by directly targeting PBX3 [186]. Tumor-derived exosomal miR-1247-3p was observed

| Proliferation | Apoptosis | Invasion, EMT and metastasis |
|---------------|-----------|-----------------------------|
| miR-29a ↓     | miR-320a ↓| miR-10b ↑                  |
| miR-30a-5p ↓  | miR-331-3p ↑| miR-340 ↓                  |
| miR-31-5p ↓   | miR-337 ↑  | miR-25 ↑                   |
| miR-33b ↓     | miR-30a-5p ↓| miR-345 ↓                  |
| miR-33b ↓     | miR-96-5p ↑| miR-30e ↑                  |
| miR-107 ↑     | miR-331-3p ↑| miR-306 ↓                  |
| miR-122 ↑     | miR-31-5p ↓| miR-30-1p ↓                |
| miR-137 ↑     | miR-317 ↑  | miR-361-5p ↓               |
| miR-138 ↑     | miR-370 ↑  | miR-33b ↑                  |
| miR-142 ↓     | miR-454 ↓  | miR-365 ↓                  |
| miR-142-3p ↓  | miR-487a ↓| miR-370 ↓                  |
| miR-143 ↓     | miR-495 ↓  | miR-370 ↓                  |
| miR-144 ↓     | miR-506 ↓  | miR-206 ↓                  |
| miR-152 ↓     | miR-520f ↓ | miR-217 ↓                  |
| miR-155-5p ↑  | miR-542-3p ↓| miR-4417 ↑                 |
| miR-155-5p ↑  | miR-613 ↓  | miR-138 ↓                  |
| miR-186 ↓     | miR-634 ↓  | miR-487a ↑                 |
| miR-194 ↓     | miR-663a ↓ | miR-495 ↓                  |
| miR-195 ↓     | miR-708 ↓  | miR-497 ↓                  |
| miR-199 ↓     | miR-765 ↑  | miR-494 ↓                  |
| miR-199a-3p ↓ | miR-873 ↑  | miR-142 ↑                  |
| miR-199a-5p ↓ | miR-874 ↑  | miR-143 ↑                  |
| miR-203 ↓     | miR-874-3p ↑| miR-144 ↑                  |
| miR-203a-3p ↑ | miR-892a ↑ | miR-146a ↓                 |
| miR-206 ↓     | miR-1207-5p ↑| miR-520f ↓                 |
| miR-210 ↑     | miR-1249 ↑ | miR-155-5p ↓               |
| miR-212 ↓     | miR-1271-5p ↓| miR-187-3p ↓               |
| miR-217 ↓     | miR-1299 ↓ | miR-195 ↓                  |
| miR-223 ↓     | miR-1468 ↑ | miR-197 ↑                  |
| miR-296 ↓     | miR-3910 ↑ | miR-199 ↓                  |
| miR-302d ↑    | miR-4417 ↑ | miR-199b-5p ↓              |

**Figure 2.** Summary of miRNAs in the development and progression of HCC. Red arrow means: increased expression of miRNA, blue arrow means: decreased expression of miRNA.
to convert fibroblasts to cancer-associated fibroblasts (CAFs) via downregulating B4GALT3, to activate β1-integrin-NF-κB signaling pathway to promote lung metastasis of liver cancer [190].

Therefore, exosomes can transfer miRNAs between cells, and these miRNAs play important roles in proliferation, invasion, metastasis, and drug resistance in HCC by regulating gene expression in the target cells.

**Acting as diagnostic and prediction markers in HCC**

When HCC are diagnosed, many patients have already been advanced stage. It would have far-reaching influence on the prevention and treatment of HCC if the cancer could be early diagnosed and detected. It is well recognized that alpha fetoprotein (AFP) is the most common used hematology diagnosis marker of HCC in the clinical. But its false negative rate may be 40% with early stage HCC [195]. Moreover, some non-tumor diseases, such as hepatitis and cirrhosis, these patients’ serum AFP levels may also elevate [196]. Therefore, it is necessary to seek for some new markers to diagnose and predict HCC. MiRNAs may have the potential functions according to the above mechanisms.

Numerous researches have supported that miRNAs could act as diagnostic and prediction markers in HCC. MiRNAs could be used to diagnose and distinguish HCC. For example, miR-101 levels in the serum were found to be significantly downregulated in the HBV-related HCC patients compared with the HBV-related liver cirrhosis patients, chronic hepatitis B patients and healthy controls, indicating that miR-101 could severe as a potential hematological marker of to diagnose and distinguish HBV-related HCC [69]. MiRNAs could also diagnose tumor size and TNM stages of HCC. High miR-32 expression was observed that large tumor size (≥5cm) had significantly decreased [24]. High expression of miR-1246 and its target gene CADM1 low expression were correlated with stage 1 of TNM stages in HCC [49]. Low expression of miR-296 in HCC patients might have large tumor size and advanced TNM stage [108]. Low expression of miR-137 was significantly closely related with lymph node metastasis, vein invasion and advanced clinical stage in HCC [76].

Besides, miRNAs were reported to be as useful prognosis markers as well. High expression of miR-92a [25], miR-221 [40], miR-487a [45] and miR-1468 [51] might indicate poor prognosis in HCC. Low expression of miR-33a [63], miR-122 [72], miR-137 [76], miR-194 [90] and miR-940 [142] in HCC patients were observed to have unfavorable prognosis. High levels of miR-7/21/107 and low expression of maspin implied poor survival of HBV-related HCC [56]. Low expression of miR-138 combined with high expression of its target cyclin D3 showed worse clinical prognosis in HCC [77]. High expression of forhead box K2 (FOXX2) protein, the target of miR-1271-5p, had poor overall survival (OS) and disease-free survival (DFS) of HCC patients [144].

Exosomal miRNAs have been as novel biomarkers for HCC diagnoses and prognosis in clinical in recent years. For example, high expression of exosomal miR-32-5p and low expression of its target PTEN were positively associated with poor prognosis [183]. HCC patients with lower levels of serum exosomal miR-638 had poor overall survival than those with higher levels of exosomal miR-638 in serum [188]. The expression level of serum exosomal miR-21 was significantly higher in patients with HCC than those with chronic hepatitis B (CHB) or healthy volunteers. Besides, high level of miR-21 expression correlated with cirrhosis and advanced tumor stage [181]. MiR-122, miR-148a, and miR-1246 were significantly elevated in serum exosomes from HCC patients compared to liver cirrhosis (LC) and normal control (NC) individuals [191].

Taken together, all of the above researches suggested that these miRNAs, including exosomal miRNAs, could be valuable of diagnostic and prediction markers in HCC.

**Conclusions and future directions**

Great progress has been made in the study of miRNAs in HCC. MiRNAs are pivotal participants...
and regulators in the development and progression of HCC. Proliferation, apoptosis, invasion, metastasis, EMT, angiogenesis, drug resistance and autophagy of miRNAs may be the primary regulatory mechanisms in HCC. Exosomal miRNAs have been focused on in recent years, and the researches are progressing rapidly. Recent studies have shown that exosomes can transfer miRNAs between cells in proliferation, invasion, metastasis, and drug resistance of HCC. In addition, exosomal miRNAs could be as biomarkers for HCC diagnoses and prognosis. The above studies indicated miRNAs could be used valid therapeutic targets and acted as valuable early diagnostic and prediction markers in HCC. Understanding the regulatory mechanisms of miRNAs in the HCC development and progression will help us to develop more effective new therapies and molecular therapeutic drugs.

However, there are also some problems in the studies of miRNAs. Lots of studies only stay in the experimental stage and do not really be used into the clinic. Secondly, the security and reliability of miRNAs acting as HCC early diagnosis and treatment markers also need to further research. In addition, Exosomal miRNAs are mostly concentrated in the observation of the content of miRNAs in serum exosomes, but their specific mechanisms of HCC are not fully understood. And the lack of sensitive preparatory and analytical technologies for exosomes are also big challenges to clinical translation [197].

Therefore, the future studies should pay more attention to make the acquired achievement of miRNAs in HCC translate into clinical application, for instance, develop available miRNA inhibitors for clinical. Besides, the research in security and reliability of miRNAs for HCC early diagnosis and treatment should also be more concerned. For the research of exosomal miRNAs in HCC, the mechanisms of exosome-mediated miRNAs transfer should be focused on in the future studies. Meanwhile, the analytical technologies also need to be improved.

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Competing Interests

The authors have declared that no competing interest exists.

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