Abstract. Hepatocellular carcinoma (HCC) is one of the most common malignancies, which accounts for 90% of primary liver cancer. HCC usually presents with poor outcomes due to the high rates of tumor recurrence and widespread metastasis. However, the underlying mechanism of HCC initiation and progression, which significantly hindered the development of valid approaches for early detection and treatment remain to be elucidated. As a group of small non-coding RNAs, microRNAs (miRNAs) have been demonstrated to be involved in many types of diseases especially human malignancies. Numerous miRNAs are deregulated in HCC, which may shed some light on current investigations. Since miRNAs are stable and detected easily, their ectopic expression has been reported in HCC tissues, serum/plasma and cell lines. As previously described, miRNAs serve as tumor suppressors or oncogenes, indicating that miRNAs may be useful as diagnostic, therapeutic and prognostic markers of HCC. In the present review, we assessed the latest data regarding dysregulated miRNAs in HCC and reviewed the reported functions of these miRNAs as they apply to the diagnosis and prognosis of HCC.

1. Introduction
Globally, hepatocellular carcinoma (HCC) is the fifth most common human cancer and the third leading cause of cancer-associated mortalities (1). In spite of the great achievements of novel therapies and diagnostic techniques, the early detection of HCC is difficult, resulting in a poor 5-year survival for HCC patients (ranging from 0 to 14%) (2,3). Therefore, the identification of the most specific and sensitive biomarkers for HCC is crucial.

MicroRNAs (miRNAs) are a large set of small non-coding RNAs, ~22 nucleotides in length, that mainly bind to the seed sequences located within the 3' untranslated region (3'UTR) of target mRNAs. miRNAs can promote the degradation or suppress the translation of target mRNAs, eventually inhibiting the biological functions of their target genes. Different genes can be regulated by the same miRNA, while different miRNAs can be regulated by the same gene (4,5). Over 2,500 human miRNAs have been found to play important roles in various physiological and pathological processes such as embryonic development, cell proliferation, differentiation, cell cycle progression, apoptosis, autophagy, angiogenesis and metabolism (6,7). Recently, it has been demonstrated that miRNAs exhibit tissue- and disease-specific patterns in human cancers, indicating that miRNAs may be novel biomarkers for the early diagnosis and prognosis prediction of HCC (8). In the present review, we summarized the known alterations of miRNAs and their biological roles in the development of HCC.

2. Biogenesis of miRNAs
Primary miRNAs (pri-miRNAs, containing stem-loop structures) are first transcribed by RNA polymerase II and then processed into the hair-shaped precursor miRNA (pre-miRNA, 70-90 nucleotides in length) by the complex comprising RNAase III (also known as Drosha) and DGCR8/Pasha in the nucleus (Fig. 1). Pre-miRNAs are transported into the cytoplasm by the exportin-5 complex and cleaved into mature miRNAs by Dicer (9-13). Earlier studies have identified enhancers and silencers of miRNA transcription (11,14,15). Recently, other mechanisms including DNA methylation and...
histone modification have been shown to regulate the production of miRNAs (16,17).

3. miRNAs in cancer

During the past decade, the multiple roles of miRNAs in the initiation and progression of human cancer have been well established. miRNAs are commonly dysregulated in tumor tissues and act as oncogenes or tumor suppressors, respectively. miRNAs are able to manipulate tumor proliferation, migration, invasion, metastasis, angiogenesis, cell cycle progression, apoptosis and autophagy. Consistently, the crucial roles of miRNAs in tumorigenesis and development have been further demonstrated in several animal models. For example, miRNA-15a/miRNA-16-1 knockout mice were predisposed to develop chronic lymphocytic leukemia (18). In addition, Eμ-miRNA-155 transgenic mice were prone to develop a proliferative B-cell malignancy in lymph nodes (19). Collectively, these results indicated that miRNAs may be valid therapeutic targets for treating human cancers.

4. miRNAs in HCC

Numerous studies have focused on the ectopic expression (up- or downregulation) of miRNAs in HCC. A panel of miRNAs have been identified to be candidate tumor suppressors or oncogene inducers and further proven to be critical factors in the regulation of malignant tumor behaviors. A brief description of these miRNAs is provided below.

Downregulation of miRNAs in HCC. The most common downregulated miRNAs in HCC are summarized in Table I. Of these miRNAs, let-7g, miR-122 and miR-199 are particularly noteworthy.

The miRNA let-7g is a member of the large let-7 family. It is significantly downregulated in human HCC tissues and is closely associated with the metastasis and poor overall survival of HCC. In vitro, restoration of let-7g markedly inhibited tumor proliferation and migration, suppressed the epithelial-mesenchymal transition (EMT), and induced cell apoptosis and cell cycle arrest by blocking the K-Ras/HMG2/Snail signaling pathway (20). Let-7g also targets Bcl-xL and collagen type I α2, thus promoting apoptosis and inhibiting migration in HCC cells.

The liver-specific miRNA-122 is significantly downregulated in a large number of HCC patients and is often inversely associated with a poor prognosis and metastasis. Restoration of miR-122 inhibits proliferation and migration, and increases apoptosis by targeting AKT3 in HCC cell lines (21). miR-122 was able to directly bind to the 3'UTR of the DLX4 gene (Distal-less 4) and downregulate its expression, which markedly suppressed HCC cell proliferation. Considering that miR-122 is associated with tumor invasion and metastasis in HCC, Wang et al (22) performed a panel of experiments and demonstrated that miR-122 was capable of triggering the EMT, induce disruption of the cellular cytoskeleton, block the RhoA/Rock signaling pathway, enhance adhesion and suppress invasion in HCC cells. Recently, it has been suggested that cell morphology and mitochondrial functions can be markedly regulated by miR-122, proposing that miR-122 is critical for hepatocarcinogenesis (23). Thus, miR-122 knockout mice eventually developed spontaneous tumors resembling human HCC. In particular, in the Huh7, HepG2 and QSG-7701 HCC cell lines, the expression of miR-122 has been shown to be significantly inhibited by the methylation of its promoter, which was restored by treatment with the demethylation agent 5-aza-dC. Additionally, the overexpression of miR-122 induced further cell apoptosis in these HCC cells (24).
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<td>Let-7g</td>
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<td>miR-122</td>
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<td>DNMT1</td>
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<td>PCMT1, Wnt3a</td>
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<td>miR-200a</td>
<td>CDK6</td>
<td>A potential tumor suppressor in HCC</td>
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<td>miR-202</td>
<td>LRP6</td>
<td>A potential tumor suppressor in HCC</td>
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<td>miR-203</td>
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<td>ABCB1</td>
<td>A therapeutic biomarker for HCC</td>
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<td>miR-302b</td>
<td>EGFR, AKT2</td>
<td>An effector in gene therapy of HCC, proliferation and growth</td>
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miR-199a-1, miR-199a-2 and miR-199b belong to the miR-199 family. In HCC tissues, miR-199a was significantly downregulated, correlating with a higher recurrence rate and a poor prognosis. In HCC cell lines, miR-199a was able to suppress tumor proliferation and induce apoptosis and cell cycle arrest by regulating the expression of matrix metalloproteinase-9 (MMP-9), frizzled type 7 receptor (FZD7) and hypoxia-inducible factor-1α. In a similar manner, miR-199a-3p expression was significantly reduced in a panel of human HCC cell lines. In addition, it was shown that miR-199a-3p directly targeted CD44 and inactivated the c-Met signaling pathway. The other known targets of miR-199a-3p include the mammalian target of rapamycin (mTOR) and c-Met, which play important roles for the biological functions of miR-199a-3p as a tumor suppressor. Downregulation of miR-199a-5p was observed in more than two-thirds of HCC samples and notably associated with an advanced tumor stage. In vitro experiments suggested that miR-199a-5p directly inhibits the expression of discoidin domain receptor-1 (DDR1) and that the loss of miR-199a-5p leads to the upregulation of DDR1 and enhances the invasion of HCC cells. In addition, it was shown that miR-199a-3p directly targeted CD44 and inactivated the c-Met signaling pathway. The other known targets of miR-199a-3p include the mammalian target of rapamycin (mTOR) and c-Met, which play important roles for the biological functions of miR-199a-3p as a tumor suppressor. Downregulation of miR-199a-5p was observed in more than two-thirds of HCC samples and notably associated with an advanced tumor stage. In vitro experiments suggested that miR-199a-5p directly inhibits the expression of discoidin domain receptor-1 (DDR1) and that the loss of miR-199a-5p leads to the upregulation of DDR1 and enhances the invasion of HCC cells. In another study, it was found that upregulated miR-199a-5p directly inhibited the activity of E2F3 and sensitized HCC cells to routine chemotherapies (25). Of note, miR-199a-5p significantly enhanced the suppressive effects of cisplatin on cell proliferation (26), while cisplatin downregulated the level of miR-199a-5p and then induced autophagy by activating autophagy-associated gene 7, a direct target of miR-199a-5p. These controversial results remain to be clarified in the future using more powerful experimental approaches (25-34).

In addition, the marked reduction of miR-20a, miR-138, miR-503, miR-218 and miR-376a expression was detected in HCC tissues. These miRNAs have been shown to be involved in tumor proliferation, apoptosis and cell cycle regulation (35-37). Collectively, a large number of miRNAs are downregulated in human HCC and have been found to be closely associated with tumor progression and prognosis.

Upregulation of miRNAs in HCC. miRNAs can also serve as oncogenes in human cancers. In HCC, a group of onco-miRNAs (listed in Table II) has been identified, and their functions have been well defined. Of these, miR-21, miR-221 and miR-224 are the best studied. Consequently, the roles in HCC of these miRNAs are reviewed.

miR-21 is one of the most common dysregulated miRNAs in human cancers and is involved in the regulation of cell proliferation, differentiation, apoptosis, angiogenesis, migration and invasion (38-40). Recent studies have suggested that miR-21 functions as a pro-metastatic miRNA in HCC (41) and can promote the invasion and metastasis of HCC by targeting phosphatase and tensin homolog (PTEN) and heparin-degrading endosulfatase-1 (hSulf-1) and activating the AKT/ERK signaling pathways (42). The HEPN1 gene is another target of miR-21, and its silence induced by miR-21 significantly accelerated the tumor growth of HCC. In addition, mitogen-activated protein kinase kinase 3 (MAP2K3), reverse-inducing-cysteine-rich protein with kazal motifs (RECK), and programmed cell death 4 (PDCD4) were the direct targets of miR-21, and their expression and functions were notably suppressed in HCC (41,43,44).

Another overexpressed miRNA in human HCC is miR-221, and its expression is significantly correlated with a poor overall survival and recurrence-free survival. It was found that miR-221 causes rapid S-phase entry and enhances tumor growth by targeting phosphatase and tensin homolog (PTEN) and heparin-degrading endosulfatase-1 (hSulf-1) and activating the AKT/ERK signaling pathways (42). The HEPN1 gene is another target of miR-21, and its silence induced by miR-21 significantly accelerated the tumor growth of HCC. In addition, mitogen-activated protein kinase kinase 3 (MAP2K3), reverse-inducing-cysteine-rich protein with kazal motifs (RECK), and programmed cell death 4 (PDCD4) were the direct targets of miR-21, and their expression and functions were notably suppressed in HCC (41,43,44).

Another overexpressed miRNA in human HCC is miR-222, and its expression is significantly correlated with a poor overall survival and recurrence-free survival. It was found that miR-221 causes rapid S-phase entry and enhances tumor growth by targeting phosphatase and tensin homolog (PTEN) and heparin-degrading endosulfatase-1 (hSulf-1) and activating the AKT/ERK signaling pathways (42). The HEPN1 gene is another target of miR-21, and its silence induced by miR-21 significantly accelerated the tumor growth of HCC. In addition, mitogen-activated protein kinase kinase 3 (MAP2K3), reverse-inducing-cysteine-rich protein with kazal motifs (RECK), and programmed cell death 4 (PDCD4) were the direct targets of miR-21, and their expression and functions were notably suppressed in HCC (41,43,44).
histone deacetylase 6 (HDAC6) and enhance the malignant progression of HCC.

miR-224 is upregulated in HCC, and recent studies have shown that miR-224 can act as an onco-miRNA in HCC through activating the AKT signaling pathway (46). In a previous study, we demonstrated that miR-224 can promote migration and invasion in HCC cells by targeting the homeobox D10 (HOXD10) gene (47).

Thus, dysregulated miRNAs are frequently involved in almost every step of the initiation and progression of HCC, indicating that these miRNAs are potential targets for the diagnosis and prognosis prediction for HCC patients.

5. miRNAs in HCC diagnosis and prognosis

Since a large number of HCC patients are diagnosed at an advanced stage of disease, the development of novel valid approaches to detect HCC earlier is crucial. Currently, α-fetoprotein is the only marker commonly used for HCC detection in the clinic. However, its reliability is questionable and its accuracy is not satisfactory (6). Based on the amount of evidence from clinical and basic research, it has been suggested that miRNAs have potential characteristics as diagnostic markers for HCC. Technically, miRNAs in circulation and in the cytoplasm are abundant and stable enough for detection using commercial kits. For example, a recent study has shown that miR-127 is significantly downregulated in HCC and that it is a potential diagnostic biomarker for HCC (48).

In addition, aberrant DNA
methylation of miRNA is potentially a useful parameter for the early diagnosis of HCC, and it has been found that single locus hypermethylation of miR-129-2 functions as a highly specific marker to distinguish HCC from chronic hepatitis and healthy liver tissues (50). Circulating miRNAs are also valuable for the early detection and prognosis prediction of HCC. The circulating miRNAs present in the serum and plasma of HCC patients are provided in Table III.

As previously reported, miRNAs are a powerful predictor of prognosis for cancer patients. Recently, several studies have shown the validity of miRNAs as prognostic markers in HCC (35,51-70). Upregulation of miR-9, miR-17-5p, miR-18, miR-25 and miR-590-5p/3p presented a high metastatic potential and a shorter survival in patients with HCC (35,67-70). Another study has indicated that concordant DNA methylation at certain miRNA loci correlated with a poor survival for HCC patients. Therefore, methylation may be used as a biomarker to predict the prognosis for HCC patients (50). In other studies, either a single miRNA or a panel of several miRNAs was proven to be a good predictor of prognosis for HCC patients (71,72).

Taken together, all of the abovementioned studies suggest that miRNAs can act as valuable biomarkers for the early diagnosis and prognosis prediction of HCC. However, controversies regarding the application of these markers in the clinic remain, thus further investigations are required.

6. miRNAs in HCC treatment

miRNAs function as tumor suppressors or oncogenes in HCC. Therefore, targeting these miRNAs may be a novel approach to treat HCC (24,35,60,61,64,73-102). Currently, the therapeutic application of miRNAs mainly consists of two strategies: miRNA inhibition and miRNA replacement.

**miRNA inhibition.** The aim of miRNA inhibition is to suppress oncogenic miRNAs using miRNA antagonists that usually involve some chemical changes to heighten binding, reduce nuclease resistance and promote cellular intake (6). Evidence has suggested that miR-146a, miR-182, miR-184, and miR-190b can act as therapeutic targets for HCC (98-102).

**miRNA replacement.** The aim of miRNA replacement is to restore the level of tumor suppressor miRNAs. In HCC cell lines, restoration of miR-26a/b was able to increase their chemosensitivity, which was favorable for the targeted molecular therapy of HCC (75-77). A previous study has shown that miR-26a replacement using an adeno-associated (AAV) delivery system decreased the tumorigenicity in a mouse model of HCC (49). Another example is that miR-122 can be used as a tumor suppressor through AAV-mediated delivery in a mouse model of HCC (49). Of these miRNAs, miR-34a is particularly noteworthy as it is the first miRNA mimic to reach the clinic (49) and is capable of inducing sensitivity to the antitumor effect of sorafenib in the treatment of HCC (79,80).

Furthermore, miR-425-3p is a promising prognostic marker in HCC treated with sorafenib (93).

The therapeutic application of miRNAs is a promising strategy for HCC treatment. However, it is well known that one miRNA regulates multiple target genes and that artificially up- or downregulating the level of miRNAs may result in undesirable off-target effects. Thus, the application of miRNAs for HCC treatment remains to be examined in clinical trials.

7. miRNA and radiosensitivity: A new direction for HCC treatment

The rapid development of radiation techniques has led to radiotherapy becoming a major treatment for HCC. However, a subgroup of HCC patients present intrinsic or acquired resistance to routine radiotherapy, which significantly hinders the therapeutic effects and patient outcomes. Therefore, determining methods to improve the effects of radiotherapy is of interest to oncologists and radiologists. Recent findings have shown that miRNAs are closely associated with radiotherapy outcomes and are involved in radiosensitivity (103). Some miRNAs can act as biomarkers to predict the cellular sensitivities to radiotherapy, while others enhance or reduce...
Acknowledgements

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