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.

Contents

1. Introduction
2. Biogenesis of miRNAs
3. miRNAs in cancer
4. miRNAs in HCC
5. miRNAs in HCC diagnosis and prognosis
6. miRNAs in HCC treatment
7. miRNA and radiosensitivity: A new direction for HCC treatment
8. Conclusions

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 Drosophila and DGC8/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
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 *vivo*, 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).
| microRNA | K-Ras/HMGA/Snail | Proliferation and migration | Refs. |
|----------|------------------|----------------------------|-------|
| Let-7g   | K-Ras/HMGA/Snail | Proliferation and migration | (8)   |
| miR-1    | ET1              | Proliferation              | (9)   |
| miR-7    | CUL5, CCNE1      | A tumor suppressor and therapeutic application in HCC | (59) |
| miR-20a  | Mcl-1            | Proliferation, G1 arrest and apoptosis | (10) |
| miR-22   | NP               | Differentiation, metastasis and prognosis of HCC | (39) |
| miR-23a  | TOP1             | A potential target in regulating chemo sensitivity of HCC | (60) |
| miR-26a  | PIK3C2α          | A potential therapeutic target and a new basis for targeted molecular therapy of HCC | (61) |
| miR-26b  | USP9X, TAK1, TAB3 | EMT, chemo sensitivity of HCC | (62,63) |
| miR-27a  | FZD7             | A promising chemo sensitizing strategy for the treatment of HCC | (64) |
| miR-29c  | SIRT1            | A tumor suppressor in HCC | (40) |
| miR-30a-3p | NP            | Proliferation, invasion and metastasis | (11) |
| miR-34a  | Bcl-2, c-Met     | Induces sensitivity to the antitumor effect of sorafenib in HCC, a critical targeted therapy for HCC | (65,66) |
| miR-34b  | NP               | An important component of the tumor suppressor network during carcinogenesis | (41) |
| miR-99   | Ago2             | A potential strategy for HCC | (67) |
| miR-100  | plk 1            | A prognostic marker and molecular therapeutic target in HCC | (68) |
| miR-101  | NLK              | A tumor suppressor in liver cancer | (42) |
| miR-122  | Cyclin G1, Bcl-w, AKT3, MMP-17 | Proliferation and apoptosis of HCC, regulation of morphology and cyto-architecture of HCC, a tumor suppressor and a potential therapeutic candidate | (12-14) |
| miR-124  | STAT3            | A tumor suppressor and a biomarker for diagnosis and therapeutics in HCC | (43) |
| miR-125b | eIF5A2           | Prognosis of HCC | (44) |
| miR-127  | 7-Sep            | A tumor suppressor and a potential diagnostic biomarker for HCC | (37) |
| miR-134  | ITGB 1           | A novel metastasis suppressor in HCC and a potential therapeutic target for HCC | (69) |
| miR-137  | AKT2             | A valuable biomarker for HCC prognosis | (45) |
| miR-138  | CCND3            | Cell cycle | (9) |
| miR-139  | TCF-4            | A therapeutic strategy for the treatment of HCC | (106,107) |
| miR-141  | E2F3, ZEB2       | Growth and metastasis of HCC, a novel potential therapeutic target for HCC treatment | (15,16) |
| miR-144  | E2F3             | Proliferation and metastasis of HCC | (17) |
| miR-145  | ADAM17, IRS1     | A potential therapeutic and biological target for HCC and a potential molecular mechanism causing aberrant oncogenic signaling in HCC | (70-73) |
| miR-148a | DNMT1            | A tumor suppressor during HCC | (46) |
| miR-148b | NP               | An independent prognostic factor for HCC | (47) |
| miR-185  | DNMT1            | A potential prognostic biomarker for HCC in the early stage and a novel therapeutic strategy for HCC treatment | (48,49) |
| miR-181a-5p | c-Met         | Motility, invasion and branching morphogenesis | (18) |
| miR-195  | PCMT1, Wnt3a     | Increasing tumor life span, and a potential therapeutic strategy in the treatment of HCC | (74,75) |
| miR-199  | MMP-9            | Adhesion of HCC | (19) |
| miR-200a | CDK6             | A potential tumor suppressor in HCC | (50) |
| miR-202  | LRP6             | A potential tumor suppressor in HCC | (51) |
| miR-203  | Survivin         | Proliferation | (20) |
| miR-212  | RBP2             | May be important in the pathogenesis of HCC | (108) |
| miR-214  | FGFR-1           | Potential prognostic marker and therapeutic target in HCC | (52) |
| miR-218  | Bmi-1, CDK6      | Proliferation and apoptosis | (21) |
| miR-219-5p | GPC3        | Proliferation | (9) |
| miR-223  | ABCB1            | A therapeutic biomarker for HCC | (76) |
| miR-302b | EGFR, AKT2       | An effector in gene therapy of HCC, proliferation and growth | (22,23) |
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 inhibited 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 inhibited 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.

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 p27, p57 and aryl hydrocarbon nuclear translocator (Arnt) in HCC. Additionally, the upregulation of miR-221 has been associated with a more aggressive phenotype of HCC and can suppress cell apoptosis by targeting the Bmf gene (45). Recently, miR-221 was shown to be able to silence human HCC and have been found to be closely associated with tumor progression and prognosis.

### Table I. Continued.

| microRNA | Target genes | Characteristics | Refs. |
|----------|--------------|----------------|-------|
| miR-320  | GNA1 1       | A new therapeutic avenue for targeting HCC metastasis | (77)  |
| miR-363  | S1PR1        | A novel target for treatment of HCC | (78)  |
| miR-376a | PIK3R1       | Apoptosis, proliferation | (9)   |
| miR-424  | c-Myb        | A tumor suppressor in HCC, a potential biomarker and therapeutic target for HCC | (53)  |
| miR-425-3p | NP         | Elevated expression of miR-425-3p in tumor cells is a novel marker of better prognosis in HCC treated with sorafenib | (79)  |
| miR-433  | CREB1        | Migration       | (24)  |
| miR-449  | SIRT1        | A novel targeting mechanism for HCC therapy | (80)  |
| miR-450a | DNMT3a       | Proliferation   | (25)  |
| miR-451  | ATF2, IKK-β  | Migration, proliferation | (26-28) |
| miR-491  | MMP-2/9, EMT | A new clue for preventing tumor metastasis of HCC | (81)  |
| miR-503  | Cyclin D3, E2F3, ARHGEF19 | An important role in cell cycle regulation(G1/S) and in the molecular etiology of HCC | (30)  |
| miR-520c-3p | GPC3      | A prospective prognosis predictor and biological treatment target of HCC | (54)  |
| miR-612  | AKT2         | An effective molecular target for HCC therapy   | (82)  |
| miR-744  | c-Myc        | Potentially useful target for miRNA-based therapies of HCC | (83)  |
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). It has been previously demonstrated that miR-21, miR-26a, miR-27a, miR-122, miR-223 and miR-801 can discriminate between HCC and healthy, chronic hepatitis B and cirrhosis groups (6). miR-126, miR-141 and miR-200c are also able to differentiate HCC from metastatic liver cancer with a high accuracy (49). In addition, aberrant DNA

| microRNA | Target genes | Characteristics | Refs. |
|----------|--------------|-----------------|-------|
| miR-9    | KLF17        | A predictive marker of high metastatic potential in HCC     | (55)  |
| miR-10a  | EphA4, CADM1 | EMT, metastasis                                           | (9)   |
| miR-17-5p | p38 pathway | Multiple tumor nodules, vein invasion, shortened overall survival | (9)   |
| miR-18   | TNRC68       | Proliferation and adhesion, a diagnostic and prognostic marker for HCC progression | (56)  |
| miR-21   | PTEN, RECK, PDCD4 | Migration and invasion of a stem-like population in HCC | (31,32) |
| miR-24   | SOX7         | Proliferation and invasion                                 | (109) |
| miR-25   | NP           | A predictive value on prognosis                             | (57)  |
| miR-135a | FOXM1, MTSS1 | Metastasis                                                 | (9)   |
| miR-143  | FNDC3B       | Metastasis                                                 | (9)   |
| miR-146a | NP           | A potential anti-angiogenic target for HCC therapy          | (84)  |
| miR-182  | TP53INP1     | A new target for chemotherapy of HCC                         | (85)  |
| miR-184  | INPP1L, SOX7 | As an oncogenic regulator in HCC                             | (86,87) |
| miR-190b | IGF-1        | A therapeutic target of HCC                                 | (88)  |
| miR-197  | CD82         | Migration and invasion                                      | (110) |
| miR-210  | VMP1, AIFM3  | Metastasis, apoptosis and proliferation                      | (9)   |
| miR-216a | TSCL1        | Tumorigenesis                                               | (9)   |
| miR-221  | BMF, BBC3, ANGPTL2 | Proliferation, clonogenicity, migration/invasion, G1 arrest, and apoptosis | (33)  |
| miR-222  | p27          | Proliferation                                               | (111) |
| miR-224  | PPP2R1B, NF-κB pathways, Homeobox D 10 | An onco-miRNA in HCC                                          | (34,35) |
| miR-301a | Gax          | Metastasis                                                 | (9)   |
| miR-373  | PPP6C        | Cell cycle                                                 | (9)   |
| miR-490-3p | ERCIC3    | EMT                                                        | (9)   |
| miR-519d | CDKN1A/p21, PTEN, AKT3, TIMP2 | Proliferation, invasion and apoptosis                       | (9)   |
| miR-525-3p | ZNF395    | Migration and invasion                                     | (112) |
| miR-550a | CPEB4        | Metastasis                                                 | (9)   |
| miR-590-5p/3p | PDCD4, PTEN | An important tumorigenic factor for HCC                     | (58)  |
| miR-615-5p | IGF-II     | Cell growth and migration                                   | (9)   |
| miR-657  | TLE1, NF-κB  | Proliferation                                               | (9)   |
| miR-1246 | CADM1        | Migration and invasion                                      | (113) |

| microRNA | Target genes | Characteristics | Refs. |
|----------|--------------|-----------------|-------|
| miR-222  | p27          | Metastasis                                               | (9)   |
| miR-224  | PPP2R1B, NF-κB pathways, Homeobox D 10 | An onco-miRNA in HCC                                          | (34,35) |
| miR-301a | Gax          | Metastasis                                               | (9)   |
| miR-373  | PPP6C        | Cell cycle                                                 | (9)   |
| miR-490-3p | ERCIC3    | EMT                                                        | (9)   |
| miR-519d | CDKN1A/p21, PTEN, AKT3, TIMP2 | Proliferation, invasion and apoptosis                       | (9)   |
| miR-525-3p | ZNF395    | Migration and invasion                                     | (112) |
| miR-550a | CPEB4        | Metastasis                                                 | (9)   |
| miR-590-5p/3p | PDCD4, PTEN | An important tumorigenic factor for HCC                     | (58)  |
| miR-615-5p | IGF-II     | Cell growth and migration                                   | (9)   |
| miR-657  | TLE1, NF-κB  | Proliferation                                               | (9)   |
| miR-1246 | CADM1        | Migration and invasion                                      | (113) |

Table II. Upregulated miRNAs in HCC.
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 (AAV8) 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...
radio-sensitivity in vitro and in vivo. For example, miRNA-381 promoted the radio-sensitivity of esophageal squamous cell carcinoma (ESCC), and its expression played a vital role in the radio-sensitivity of ESCC (104). In addition, miRNA-25 is overexpressed in radio-resistant non-small cell lung cancer (NSCLC) patients, and miRNA-25 affected radio-sensitivity by regulating BTG2 directly in NSCLC cells. Overexpression of miRNA-145 promoted the radio-sensitivity of cervical cancer and is a potential new biomarker of radio-sensitizing treatment for cervical cancer (105). Based on the abovementioned data, miRNAs play a crucial role in radio-sensitivity for cancer. However, the relationship between miRNAs and HCC radio-sensitivity has yet to be reported. Therefore, in view of the importance of miRNAs on radio-sensitivity, their mechanisms in HCC should be elucidated.

8. Conclusions

In summary, miRNAs are widely used in many areas of cancer, especially in HCC, including the early diagnosis, prognosis prediction, follow-up monitoring and target therapies. Undoubtedly, miRNAs have important effects on radiosensitivity, their mechanisms in HCC should be elucidated.

Acknowledgements

The present review was supported by the National Natural Science Foundation of China (grant nos. 81272498, 30973457 and 30901764).

References

1. Forner A, Llovet JM and Bruix J: Hepatocellular carcinoma. Lancet 379: 1245-1255, 2012.
2. Schwartz M, Roayaie S and Konstadoulakis M: Strategies for the management of hepatocellular carcinoma. Nat Clin Pract Oncol 4: 424-432, 2007.
3. Poon RT and Fan ST: Hepatectomy for hepatocellular carcinoma: Patient selection and postoperative outcome. Liver Transpl 10 (2 Suppl 1): S39-S45, 2004.
4. He L and Hannon GJ: MicroRNAs: Small RNAs with a big role in gene regulation. Nat Rev Genet 5: 522-531, 2004.
5. Kloosterman WP and Plasterk RH: The diverse functions of microRNAs in animal development and disease. Cell 111: 441-450, 2002.
6. D'Anneo M, Faloppi L, Scartozi M, Giampieri R, Bianconi M, Del Prete M, Silvestris N and Cascini S: The role of micro-RNAs in hepatocellular carcinoma: From molecular biology to treatment. Molecules 19: 6393-6406, 2014.
7. Carthew RW and Sontheimer EJ: Origins and mechanisms of miRNAs and siRNAs. Cell 136: 642-655, 2009.
8. Garajová I, Le Large TY, Frampton AE, Rolfo C, Voortman J and Giovannetti E: Molecular mechanisms underlying the role of micro-RNAs in the chemoresistance of pancreatic cancer. Biomed Res Int 2014: 678401, 2014.
9. Ambros V: The functions of animal micro-RNAs. Nature 431: 350-355, 2004.
31. Henry JC, Park JK, Jiang J, Kim JH, Nagorney DM, Roberts LR, Banerjee S and Schmittgen TD: miR-199a-3p targets CD44 and reduces proliferation of CD44 positive hepatocellular carcinoma cell lines. Biochem Biophys Res Commun 403: 120-125, 2011.

32. Jia XQ, Cheng HQ, Qian X, Shi ZM, Zhang JP, Jiang BH and Feng ZQ: Lentivirus-mediated overexpression of microRNA-199a inhibits cell proliferation of human hepatocellular carcinoma. Cell Biochem Biophys 62: 237-244, 2012.

33. Shen Q, Cacciottl VR, Zhang X, Iacob S, Weber F, Sotiropanou GC, Radtke A, Lu M, Paul A, Gerken G, et al: Role of microRNA-199a-5p and discoidin domain receptor 1 in human hepatocellular carcinoma invasion. Mol Cancer 9: 227, 2010.

34. Song J, Gao L, Yang G, Tang S, Xie H, Wang Y, Wang J, Zhang Y, Jin J, Guo Y, et al: MiR-199a regulates cell proliferation and invasion via targeting Fzd7. PLoS One 9: e99074, 2014.

35. Otsuka M, Kishikawa T, Yoshikawa T, Ohno M, Takata A, ia XQ, Cheng HQ, Qian X, Bian CX, Shi ZM, Zhang j P, Henry jC, Park jK, jiang j, Kim jH, Nagorney DM, Roberts LR, He Y, jiang X, et al: MicroRNA-20a functions as an onco-miRNA in hepatocellular carcinoma cells by activating AKT/ERK pathways. Cancer Lett 337: 226-236, 2013.

36. Xiao F, Zhang W, Chen L, Chen F, Xie H, Xing C, Yu X, Ding S, Chen K, Guo H, et al: MicroRNA-503 inhibits the G1/S transition by downregulating cyclin D3 and E2F3 in hepatocellular carcinoma. FEBS Lett 577: 191-196, 2013.

37. Chen J and Wang X: MicroRNA-21 in breast cancer: Diagnostic and prognostic potential. Clin Transl Oncol 16: 225-233, 2014.

38. Huang Y, Yang YB, Zhang XH, Yu XL, Zhang B and Cheng XC: MicroRNA-21 gene and cancer. Med Oncol 30: 376, 2013.

39. Pan X, Wang ZX and Wang R: MicroRNA-21: A novel therapeutic target in human cancer. Cancer Biol Ther 10: 1224-1232, 2010.

40. Zhou L, Yang ZX, Song WJ, Li QI, Yang F, Wang DS, Zhang N and Dou KF: MicroRNA-21 regulates the migration and invasion of a stem-like population in hepatocellular carcinoma. Int J Oncol 45: 661-669, 2014.

41. Bao L, Yan Y, Xu C, Ji W, Shen Y, Xu G, Zeng Y, Sun B, Qian H, Chen L, et al: MicroRNA-21 suppresses PTEN and hSulf-1 expression and promotes hepatocarcinoma carcinoma progression through AKT/ERK pathways. Cancer Lett 337: 226-236, 2013.

42. Hu S, Tao R, Wang S, Wang C, Zhao X, Zhao H, Li L, Zhu S, He Y, Jiang X, et al: MicroRNA-21 promotes cell proliferation in human hepatocarcinoma partly by targeting HEPN1. Tumour Biol 2818: 179-188, 2016.

43. Shen Q, Cicinnati VR, Zhang X, Iacob S, Weber F, Calin GA, Grazi GL, Croce CM, Bolondi L and Negrini M: MicroRNA-21 promotes hepatocellular carcinoma HepG2 cell proliferation and suppresses cell growth in hepatocellular carcinoma cells. FEBS Lett 588: 1913-1920, 2014.

44. Wang j, Li j, Wang X, Zheng C and Ma W: Downregulation of microRNA-214 and overexpression of FGFR1 contribute to hepatocarcinoma carcinoma metastasis. Biochem Biophys Res Commun 439: 47-53, 2013.

45. Lyu L, Ding GF, He C, Sun L, Jiang Y and Zhu L: MicroRNA-424 is down-regulated in hepatocellular carcinoma and suppresses cell migration and invasion through c-Myc. PLoS One 9: e91661, 2014.

46. Miao HL, Lei CJ, Qiu ZD, Liu ZK, Li R, Bao ST and Li MY: MicroRNA-520c-3p inhibits hepatocellular carcinoma cell proliferation and induces cytochrome c-independent apoptosis by targeting glypican-3. Hepatol Res 44: 338-348, 2014.

47. Sun Z, Han Q, Zhou N, Wang S, Lu S, Bai C and Zhao RC: MicroRNA-9 enhances migration and invasion through KLF17 in hepatocellular carcinoma. Mol Oncol 7: 884-894, 2013.

48. Murakami Y, Tamori A, Itami S, Tanahashi T, Toyoda H, Tanaka M, Wu W, Brojigin N, Kaneoka Y, Maeda A, et al: The expression level of miR-18b in hepatocellular carcinoma is associated with the grade of malignancy and prognosis. BMC Cancer 13: 99, 2013.

49. Su ZX, Zhao J, Rong ZH, Geng WM, Wu YG and Qin CK: Upregulation of micro-RNA-25 associates with prognosis in hepatocellular carcinoma. Diagn Pathol 9: 47, 2014.

50. Yang H, Zheng W, Zhao W, Guan C and An J: Roles of miR-590-5p and miR-590-3p in the development of hepatocellular carcinoma. Nan Fang Yi Ke Da Xue Xue Bao 33: 804-811, 2013 (in Chinese).

51. Jin G, Cheng Q, Ju Z, Zhang BH and Zhang M: Circulating microRNAs as biomarkers in hepatocellular carcinoma screening: A validation set from China. Medicine 94: e603, 2015.

52. Wen Y, Han J, Chen J, Dong J, Xia Y, Liu J, Jiang Y, Dai J, Lu J, Jin G, et al: Plasma microRNAs as early biomarkers for detecting hepatocellular carcinoma. J Cancer 5: 1679-1690, 2015.

53. Zhang X, Hu S, Zhang X, Wang L, Zhang X, Yan B, Zhao J, Yang A and Zhang R: MicroRNA-7 arrests cell cycle in GI phase by directly targeting CCNE1 in human hepatocellular carcinoma cells. Biochem Biophys Res Commun 443: 1078-1084, 2014.

54. Wang Y, Zhu M, Tao L, Yang W, Chen Z and Yang Y: MiR-23a-mediated inhibition of topoisomerase I expression potentiates cell response to etoposide in human hepatocellular carcinoma. Mol Cancer 12: 119, 2013.
92. Zhou P, Huang G, Zhao Y, Zhong D, Xu Z, Zeng Y, Zhang Y, Zhang H, Feng Z, Huang R, Xia Z, Xiang G and Zhang J: MicroRNA-26b inhibits epithelial-mesenchymal transition in hepatocellular carcinoma by targeting UPRX9. BMC Cancer 14: 593, 2014.

93. Zhao N, Wang R, Zhou L, Zhu Y, Gong J and Zhuang SM: GNAI1 suppresses tumor cell migration and invasion and is post-transcriptionally regulated. Cell Signal 25: 2693-2701, 2013.

94. Yang Y, Li L, et al: MicroRNA-34a targets Bcl-2 and sensitizes human hepatocellular carcinoma cells to sorafenib treatment. Technol Cancer Res Treat 13: 77-86, 2014.

95. Liu Y, Wu C, Wang Y, Wen S, Wang J, Chen Z, He Q and Feng D: MicroRNA-145 inhibits cell proliferation by directly targeting IRS1 and its downstream Akt signaling. Biochem Biophys Res Commun 446: 1255-1260, 2014.

96. Li T, Yin J, Yuan L, Wang S, Yang L, Du X and Lu J: Downregulation of microRNA-139 is associated with hepatocellular carcinoma risk and short-term survival. Oncol Rep 31: 1699-1706, 2014.

97. Gu W, Li X and Wang J: miR-139 regulates the proliferation and invasion of hepatocellular carcinoma by targeting the WNT/TFC-4 pathway. Oncol Rep 31: 397-404, 2014.

98. Liu Z, Zeng J, Wang L, Fang M, Wang Q, Zhao M, Xu X, Liu Z, Li W, Liu S, et al: Histone demethylase retinoblastoma binding protein 2 is overexpressed in hepatocellular carcinoma and negatively regulated by hsa-miR-212. PLoS One 8: e69784, 2013.

99. Ma Y, She XG, Ming YZ and Wen QQ: miR-24 promotes the proliferation and invasion of HCC cells by targeting SOX7. Tumour Biol 35: 10731-10736, 2014.

100. Dai W, Wang C, Wang F, Wang Y, Shen M, Chen K, Cheng P, Zhang Y, Yang J, Zhu R, et al: Anti-miR-197 inhibits migration in HCC cells by targeting KAI1/CD82. Biochem Biophys Res Commun 446: 541-548, 2014.

101. Yang WF, Fang F, Xiao JJ, Song Y, Zhao YY, Cao Y, Bei YH and Yang QQ: MiR-222 overexpression promotes proliferation of human hepatocellular carcinoma HepG2 cells by downregulating p27. Int J Clin Exp Med 7: 893-902, 2014.

102. Fang F, Zha R, Zhao Y, Wang Q, Chen D, Zhang Z, Chen T, Yao M, Gu J and He X: MiR-525-3p enhances the migration and invasion of liver cancer cells by downregulating ZNF395. PLoS One 9: e90867, 2014.

103. Man M, Menz C, Wang S, Zhou N, Guan M, Bai C, Lu S, Han Q and Zhao RC: MicroRNA-124 enhances migration and invasion through CADD1 in hepatocellular carcinoma. BMC Cancer 14: 616, 2014.

104. Köberle V, Kronenberger B, Pleli T, Trojan J, Imelmann E, Peveling-Oberhug J, Welter MW, Elhendawy M, Zeuzem S, Piotrowska A, et al: Serum miR-122 and miR-21 are prognostic markers in patients with hepatocellular carcinoma. Eur J Cancer 39: 3442-3449, 2013.
115. Ge W, Yu DC, Li QG, Chen X, Zhang CY and Ding YT: Expression of serum miR-16, let-7f, and miR-21 in patients with hepatocellular carcinoma and their clinical significances. Clin Lab 60: 427-434, 2014.

116. Meng FL, Wang W and Jia WD: Diagnostic and prognostic significance of serum miR-24-3p in HBV-related hepatocellular carcinoma. Med Oncol 31: 177, 2014.

117. Luo J, Chen M, Huang H, Yuan T, Zhang M, Zhang K and Deng S: Circulating microRNA-122a as a diagnostic marker for hepatocellular carcinoma. Onco Targets Ther 6: 577-583, 2013.

118. Zhang ZQ, Meng H, Wang N, Liang LN, Liu LN, Lu SM and Luan Y: Serum microRNA 143 and microRNA 215 as potential biomarkers for the diagnosis of chronic hepatitis and hepatocellular carcinoma. Diagn Pathol 9: 135, 2014.

119. Li J, Wang Y, Yu W, Chen J and Luo J: Expression of serum miR-221 in human hepatocellular carcinoma and its prognostic significance. Biochem Biophys Res Commun 406: 70-73, 2011.

120. Zhan MX, Li Y, Hu BS, Shao Pj, Meng QW, He X, Huang JW and Lu LG: Expression of serum microRNAs (miR-222, miR-181, miR-216) in human hepatocellular carcinoma and its clinical significance. Zhonghua Yi Xue Za Zhi 93: 1830-1832, 2013 (In Chinese).