The functions and targets of miR-212 as a potential biomarker of cancer diagnosis and therapy

Wenjun Chen1,2,3 | Jing Song3 | Hongjun Bian4 | Xia Yang1 | Xiaoyu Xie1 | Qiang Zhu1,2 | Chengyong Qin1,2 | Jianni Qi2,5

Abstract
Cancer is a major health problem worldwide. An increasing number of researchers are studying the diagnosis, therapy and mechanisms underlying the development and progression of cancer. The study of noncoding RNA has attracted a lot of attention in recent years. It was found that frequent alterations of miRNA expression not only have various functions in cancer but also that miRNAs can act as clinical markers of diagnosis, stage and progression of cancer. MiR-212 is an important example of miRNAs involved in cancer. According to recent studies, miR-212 may serve as an oncogene or tumour suppressor by influencing different targets or pathways during the oncogenesis and the development and metastasis of cancer. Its deregulation may serve as a marker for the diagnosis or prognosis of cancer. In addition, it was recently reported that miR-212 was related to the sensitivity or resistance of cancer cells to chemotherapy or radiotherapy. Here, we summarize the current understanding of miR-212 functions in cancer by describing the relevant signalling pathways and targets. The role of miR-212 as a biomarker and its therapeutic potential in cancer is also described. The aim of this review was to identify new methods for the diagnosis and treatment of human cancers.

KEYWORDS
Hedgehog, Hippo/YAP, miR-212, oncogenesis, Wnt
1 | INTRODUCTION

For many years, cancer has been the main cause of death worldwide. Recently, a large number of researchers have devoted themselves to the identification of targets or pathways involved in cancer and the development of targeted therapies that may efficiently kill cancer cells. Abnormal expression of miRNAs can be seen in different types of human cancers and correlates with proliferation, differentiation, invasion and other biological aspects of cancer.

miRNAs, about 18-25 nucleotides in length, are non-coding RNA molecules that can regulate the expression of genes involved in various biological processes, including proliferation, apoptosis, differentiation and survival of cellular processes, at the post-transcriptional level. miRNAs can participate in both physiological and pathological processes, such as tumour development, via interaction with the 3’ untranslated regions (UTRs) of their target mRNAs. According to the role they play in cancers, miRNAs are classified as tumour promoters or tumour suppressors. For instance, miR-802, as an oncogenic miRNA, promotes the proliferation of osteosarcoma (OS) cells via the suppression of p27, which is a kind of cell-cycle inhibitor, while miRNA-223 acts as a tumour suppressor in non–small-cell lung cancer (NSCLC) by interacting with the insulin-like growth factor-1 receptor. It was also recently demonstrated that miRNAs may play a role in drug resistance.

miR-212, found on chromosome 17q13.3, shares highly conserved sequences with miR-132 among vertebrates. miR-132 and miR-212 play an essential role in different aspects of neural development, maturation, morphogenesis and function. Therefore, the abnormal expression of miR-132 and miR-212 may cause a series of neurodegenerative diseases, such as Alzheimer’s disease, epilepsy, tauopathies and schizophrenia. Thus, miR-132/212 is sometimes called ‘neurimmiR’. Although the initial research on miR-212 emerged from studies performed in the neuronal context as well as studies on inflammation and other biological (dys)functions, studies on tumorigenesis and cell transformation have become the most popular in recent miR-212 research. More and more studies are reporting the abnormal expression of miR-212 in various cancers and that miR-212 can act as a marker to diagnose or predict the outcome of cancer. In previous studies, miR-212-3p/5p was reported to be suppressed in hepatocellular carcinoma (HCC), of cancer. In previous studies, miR-212-3p/5p was reported to be suppressed in hepatocellular carcinoma (HCC), and showed antitumour effect. Two other studies indicated that miR-212 functions as an oncogene, with a higher expression in pancreatic cancer. The different functions performed by miR-212 in cancer depend on the tumour types, targets or pathways involved. In addition, evidence has emerged that the decreased expression of miR-212-3p may be due to DNA hypermethylation, which weakens the effect of miR-212-3p and regulates the biological characteristics of tumour cells. However, another study found that it was histone modifications, not DNA hypermethylation that led to the decreased expression of miR-212-3p in lung cancer. Recently, growing evidence has indicated that miR-212 affects the response to radiotherapy or chemotherapy. This review discusses the pathways or targets of miR-212 involved in cancer, summarizes its function as a marker for the diagnosis or prediction of the outcome of cancer and, finally, analyses the therapeutic potential of miR-212 for malignant tumours.

2 | THE ROLE OF MIR-212 IN CANCER

2.1 | miR-212 and cell apoptosis

Apoptosis, a process characterized by programmed cell death, occurs in both the physiological state, such as for maintaining cell populations in tissues, as well as pathological states, such as during injured cells. Both intrinsic and extrinsic pathways may lead to apoptosis. When stimulated by specific growth factors or cytokines, apoptosis usually occurs through the extrinsic pathway. To our knowledge, not only precancerous cells, but also tumour cells can be induced to undergo apoptosis by p53. Recent research showed that miR-212 is associated with cancer cells apoptosis through various targets.

A study performed by Zhou et al demonstrated that overexpression of miR-212 inhibited prostate cancer (PCa) cell proliferation and induced PCa cell apoptosis via targeting EN-2, whereas the restoration of EN-2 led to the opposite effect. Lu et al verified that miR-212-3p inhibited the apoptosis induced by cisplatin through interaction with AChE-S in NSCLC cells. A study performed by Haihao Wang revealed that overexpression of miR-212-5p significantly suppressed the expression of the CCND3 protein by targeting the CCND3 gene and that upregulation of CCND3 positively correlated with cell growth in miR-212-5p overexpressing adult T-cell leukaemia/lymphoma cells, which was accompanied by restoration of cell cycle progression and reduction of apoptotic death. It was also reported that CCND3, encoding protein cyclin D3, played an important role in controlling the advancement through the G0/G1 phase of the cell cycle. XIAP, a key molecule of the cell apoptosis pathway, could prohibit cell apoptosis by inhibiting caspase-3, caspase-7 and caspase-9. In renal cell carcinoma (RCC), it was found that miR-212-5p inhibited the progression of RCC cells via interaction with XIAP. The remarkable mechanism of competing endogenous RNA (ceRNA) has recently attracted a lot of attention. One study found that miR-212-5p may induce degradation or inhibit the expression of NDUFA4. Moreover, LncMIF-AS1 was found to promote the expression of NDUFA4 in GC cells by binding miR-212-5p, and the recovered NDUFA4 strengthened the proliferative ability and prevented apoptosis of GC cells in vitro.

2.2 | miR-212 and the cell cycle

A number of molecular pathways and checkpoints regulate the cell cycle in most adult mammalian cells. Many miRNAs take part in these pathways. For example, some miRNAs are involved in the anti-proliferation of cells by inhibiting mitogenic pathways responsive to the activation of cyclin-CDK complexes. In contrast, other miRNAs may...
facilitate tumour cell proliferation by interacting with CDK inhibitors, such as p53 and ATM/ATR.\textsuperscript{32} SIRT1, which was shown to modulate both physiological and pathological processes in cells via acting on cell cycle proteins, including Rb, is now verified to be targeted by miR-212 in some cancers.\textsuperscript{33,34} miR-212-3p was shown by Ramalinga et al\textsuperscript{35} to prevent autophagy and angiogenesis while inducing cellular senescence by targeting SIRT1 in PCa. Likewise, it was demonstrated that miR-212-3p can suppress thyroid cancer cell growth through SIRT1.\textsuperscript{36} One study conducted by Bo Hu demonstrated that miR-212-3p has an antitumour role in PCa by means of targeting MAPK1.\textsuperscript{37} MAPK1, which belongs to the MAPK family, is closely associated with PCa, especially in the aspects of cell proliferation, cell cycle and apoptosis.\textsuperscript{38} Ji-ping Zeng demonstrated that miR-212-3p suppressed GC growth by modulating P21\textsuperscript{CIP1} and P27\textsuperscript{kip1}.\textsuperscript{39} It was verified that P21\textsuperscript{CIP1} and P27\textsuperscript{kip1} are associated with cell cycle arrest, and they showed a tendency for lower expression in GC.\textsuperscript{40} Jong-Kook Park found that upregulated miR-132-3p/-212-3p in pancreatic ductal adenocarcinoma (PDAC) increased cell proliferation via targeting the tumour suppressor Rb1.\textsuperscript{15} pRb, a protein produced by the gene Rb1, participates in the regulation of the cell cycle, specifically the transition of G1/S and G2/M.\textsuperscript{41} In HCC, it is suggested that downregulated hsa-miR-212-3p expression can lead to overexpression of RBP2 and promote cell proliferation. The authors of the study that revealed this concluded that there was a link between the hsa-miR-212-3p/RBP2/CDK1 pathways and progression of HCC.\textsuperscript{42} Likewise, for lung cancer cells, miR-212/132 can inhibit the development of tumour cells and affect the cell cycle by targeting p21 and cyclin D1.\textsuperscript{43} Thus, functional studies of miR-212 can help us better understand the role of miR-212 in cell cycle regulation.

2.3 | miR-212 and immune responses

miRNAs participate in both innate and adaptive immunity by interacting with various immune cells, including monocytes, macrophages, NK cells and T helper cells, in differentiation, activation and other functions. The relationship between miRNAs and immunity has important effects on cancer progression.\textsuperscript{44}

An earlier study on the biological functions of miRNA-212 found it to interact with the neurons as well as inflammation.\textsuperscript{11} Studies performed recently demonstrated that miRNA-212-3p can interact with immune cells and inflammatory cytokines in the occurrence or development of cancer. It was shown that downregulated miRNA-212-3p regulates the development of PCs through the secretion of inflammatory cytokines via the NF-κB pathway.\textsuperscript{45} Another study showed that the regulatory effect of miR-212-3p in CD80 expression can be disrupted by the SNP rs1599795 in the 3′-UTR of CD80, which may induce GC tumorigenesis.\textsuperscript{46} Ding et al\textsuperscript{47} suggested that IFN-γ could be used as an immunological method to treat pancreatic cancer as it inhibits miR-212-3p expression and the subsequent upregulation of RFXAP and MHC class II. It was also found that miR-212-3p may induce immunologic tolerance of pancreatic tumour cells by affecting dendritic cell functions.\textsuperscript{48} The findings of these studies indicate that targeting miR-212 will become a promising cancer immunotherapy approach.

2.4 | miR-212 as a diagnostic or prognostic biomarker

Multiple data indicate that miRNAs participate in human carcinogenesis. It was shown that some miRNAs were significantly upregulated or downregulated in comparison with paired normal tissues in various cancers, emphasizing the tremendous potential of miRNAs as diagnostic and therapeutic markers in cancer. Additionally, some miRNAs were found to be linked with the outcome of certain cancers. Importantly, these miRNAs can exist either in cells or in cell-free body fluids such as urine and saliva. This stability of miRNAs in body fluids allows them to be easily tested as biomarkers of disease.\textsuperscript{49}

Emerging researches have reported that the aberrant expression of miR-212 can be seen in different cancers and can be used for the diagnosis or prediction of outcome of cancer. One study on 386 patients revealed that a miRNA signature, including hsa-miR-212, may help identify early-stage breast cancer.\textsuperscript{50} After examining 45 PDAC and 20 adjacent normal pancreatic tissue specimens, miR-212-3p was found to correlate with tumour growth and disease stage in PDAC, and high levels of miR-212-3p were associated with poor outcome.\textsuperscript{51} In oesophageal cancer (EC), one study involving 46 patients revealed that, with other factors, such as treatment or staging of comparable disease, high miR-212 expression was accompanied with poor outcome.\textsuperscript{52} Contrarily, in acute myeloid leukaemia (AML), according to a study involving 576 patients, the high expression of miR-212 was associated with a better outcome of patients and its role in predicting cancer was found to not be affected by other factors.\textsuperscript{53} One study, including 15 cases associated with lymph node (LN) metastasis and another 15 cases without LN metastasis, found that there was a link between downregulated hsa-miR-212 expression and LN metastasis in GC and suggested that the level of hsa-miR-212 may serve as a clinic marker for GC.\textsuperscript{54} The effect of miR-212 on lung cancer is controversial. One study involving 418 lung adenocarcinoma (LUAD) patients found that high miR-212 levels predicted a poor recurrence-free survival (RFS),\textsuperscript{55} whereas another study, including 34 adenocarcinoma and squamous cell carcinoma tissue samples, indicated that low expression of miR-212 in patients represented the severity of the disease.\textsuperscript{56} This discrepancy may be caused by the different histological types of lung cancer involved in these studies. More researches enrolling a larger number of patients with a unified disease type are required to elucidate the controversial role of miR-212 in lung cancers. In breast cancer, after comparing the expression of miR-212-5p in 125 triple-negative breast cancer (TNBC) patients, it was revealed that the low expression of miR-212-5p predicted an unfavourable outcome.\textsuperscript{57} miRNAs can be tested not only in cells but also in cell-free body fluids, such as saliva and urine. In a study involving 173 HCC patients, serum miR-132/212 was shown to assist in diagnosis and prediction of the progression as well as outcome.
of HCC. Chao-hui Gu studied samples from 60 patients with RCC and found that a poor outcome was often indicated in RCC patients with down-regulated miR-212-5p. In chronic lymphocytic leukaemia (CLL), Tavolaro et al. evaluated the basal expression of miR-212 in 20 CLL cases and found that the downregulation of miR-132 and miR-212 was associated with progressive disease and a poor prognosis of CLL. A summary of the diagnostic and prognostic functions of miR-212 is shown in Table 1.

| miR-212 | Level | Cancer types | Diagnosis or prognosis | Ref. |
|---------|-------|--------------|------------------------|------|
| miR-212 | Up    | Breast cancer | Poor prognosis         | 85   |
| miR-212-3p | Up    | PDAC         | Poor prognosis         | 86   |
| miR-212 | Up    | Esophageal cancer | Poor prognosis         | 87   |
| miR-212 | Up    | AML          | Better survival        | 88   |
| miR-212 | Up    | Gastric cancer | Lymph node metastasis | 89   |
| miR-212 | Up    | LUAD         | Poor prognosis         | 90   |
| miR-212 | Down  | NSCLC        | Poor prognosis         | 91   |
| miR-212-5p | Down  | TNBC        | Poor prognosis         | 23   |
| miR-212 | Down  | Hepatocellular carcinoma | Improved diagnosis, Poor prognosis | 92 |
| miR-212-5p | Down  | Renal cell carcinoma | Poor prognosis         | 52   |
| miR-212 | Down  | CLL          | Poor prognosis         | 93   |

Abbreviations: AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; LUAD, lung adenocarcinoma; NSCLC, non–small-cell lung carcinoma; PDAC, pancreatic ductal adenocarcinoma; TNBC, triple-negative breast cancer.

FIGURE 1 miR212 and Wnt/β-catenin signaling
Both chemotherapy and radiotherapy are important treatments for cancer and growing evidence shows that the response to chemotherapy or radiotherapy is affected by miRNAs. Recently, miR-212 was found or proposed to participate in the regulation of cancer sensitivity to chemotherapy or radiotherapy. Xie et al. found that miR-132/-212-3p may induce drug resistance of breast cancer via the miR-132/-212-3p/PTEN/AKT/NF-κB/BCRP pathway. Further, they suggested that it could improve the treatment effects of doxorubicin, and they identified novel therapeutic targets for breast cancer by modulating miR-132/-212-3p. In contrast, another study found that miR-212-3p increases the sensitivity of NSCLC cells to TRAIL because there is a negative relationship between miR-212-3p and PED/PEA-15. Turrini et al. showed that imatinib downregulated miR-212-3p expression, causing the restoration of ABCG2. They showed a regulatory relationship between imatinib treatment, miRNA and ABCG2 in vitro for the first time. Further research is necessary to illuminate this link in vivo. According to a study by Hiromitsu Hatakeyama, down-regulated miR-212-3p may augment the expression of HB-EGF, which is a possible mechanism of drug resistance of head and neck squamous cell carcinoma cells to cetuximab. With regard to radiosensitivity, it was reported that the BRCA1 gene is regulated by miR-212-3p and affected the sensitivity of glioma cells to radiotherapy. More studies should, thus, focus on the role of miR-212-3p and BRCA1 in radioresistance. With the progress of research on miR-212, a miR-212-based treatment will be available for cancer. For example, the expression of miR-212 can be replaced or reduced to alter the response of cancer cells to chemotherapy or radiotherapy. Excitingly, further experiments utilizing miR-212 to treat cancer are on the way.

3 | THE PATHWAYS AND TARGETS OF MIR-212 IN CANCER

3.1 | The Wnt signalling pathway

The dysregulation of the Wnt/β-catenin pathway is believed to be central to the pathogenesis of cancer, chronic inflammation and progression, and metastasis.
degenerative diseases. The phosphorylation, degradation and regulation of β-catenin by Wnt are considered to form the core of this pathway. Without Wnt, Wnt target genes are significantly inhibited because of the persistent degradation of the β-catenin protein by the Axin complex.\textsuperscript{64-66} It was reported that the dysregulation of miR-212 participated in different cancers through the Wnt/β-catenin pathway via specific targets (Figure 1).

Zhi-dong Lv and colleagues showed that miR-212-5p may target Prrx2, which plays an important role in the proliferation, invasion and migration of breast cancer cells via the Wnt/β-catenin signalling pathway.\textsuperscript{56} Recently, miR-212-3p was found to regulate Wnt signalling pathways by acting on LEF-1, c-Myc and β-catenin in HCC, which is why miR-212-3p can inhibit the tumorigenesis and growth of HCC cells.\textsuperscript{67} The inhibition of the Wnt/β-catenin signalling pathway by miR-212-5p was also found in AML, and FZD5 was reported as the target gene of miR-212-5p.\textsuperscript{68} Zhou C showed that miR-212-3p suppressed cervical cancer through the downregulation of its downstream target gene TCF7L2,\textsuperscript{69} while TCF7L2 is thought to be the pivotal element in the Wnt signalling pathway.\textsuperscript{70,71}

3.2 | The Hedgehog signalling pathway

The Hedgehog (Hh) pathway has a role in embryonic development, tissue patterning and wound healing.\textsuperscript{72} Aberrant functioning of this pathway is connected with the development of cancer in several organs.\textsuperscript{73,74} The Hh pathway is often triggered by ligands. SHH, one of the identified ligands of the Hh pathway, is the most studied.\textsuperscript{75} Without SHH, PTCH1 can hinder the expression of smoothened (SMO), a target protein of the Hh pathway. As a result of the interaction between SHH and PTCH1, SMO and the subsequent activation of GLi transcription factors can be reduced, and the functions of GLi1, GLi2 and GLi3 are affected in the end.\textsuperscript{75} Thus, PTCH1 is called the “gatekeeper” of the Hh pathway.

In some kinds of cancer, miR-212 may play a role as an oncogene targeting PTCH1 (Figure 2). miR-212-3p was shown by Chen-chao Ma and colleagues to promote PDAC progression and metastasis via modulation of the Hh signalling pathway receptor PTCH1.\textsuperscript{16} In the case of NSCLC, Yuan Li found miR-212-3p may act as an oncogene to promote cell proliferation and other aggressive behaviour of tumour cells by acting on PTCH1.\textsuperscript{76}

3.3 | The Hippo/YAP signalling pathway

The Hippo/YAP signalling pathway was found to be associated with liver size.\textsuperscript{77,78} YAP and TAZ, the main effectors of the Hippo signalling pathway, are controlled by a series of kinase cascades. The main proliferative and oncogenic function performed by YAP and TAZ is associated with the members of the TEAD/TEF transcription factor family (TEAD1-4).\textsuperscript{79} For example, it was reported that YAP has the potential to induce liver tumorigenesis.\textsuperscript{80} FOXA1 has been previously reported to promote YAP transcription by Wen-jun Yu.\textsuperscript{81}
Recently, the relationship between miR-212 and FOXA1 was reported in various cancers.

Dou et al.\textsuperscript{12} reported that miR-212-3p repressed the expression of YAP via FOXA1 in HCC, emphasizing the significance of the miR-212-3p/FOXA1/Hippo/YAP pathway in HCC. In accordance with this finding, Hua-hua Tu demonstrated that miR-212-3p can inhibit HCC cell proliferation by targeting FOXA1.\textsuperscript{17} In OS, Chu-hai Xie reported that TUG1 can sponge miR-212-3p to upregulate FOXA1, with the subsequent effect of regulating cell proliferation and apoptosis in tumour cells.\textsuperscript{82} Liu et al.\textsuperscript{83} suggested that the anti-migration effect of miR-212-3p in OS cells was implemented via targeting FOXA1. In the latter two studies, although FOXA1 was the target of miR-212-3p, whether they are all involved in the same FOXA1/Hippo/YAP pathway requires further study.

### 3.4 The other targets of miR-212

miRNAs participate in various physiological and pathological processes by interacting with their target mRNAs. Apart from the pathways described above, miR-212 acts on a series of targets. The interaction between miR-212 and its targets may result in different functions depending on the target or tumour types. The targets and the effects of miR-212 are clearly shown in Table 2.

| No. | miR-212 | Target genes | Cancer types | Related functions | Ref. |
|-----|---------|--------------|--------------|-------------------|-----|
| 1   | 3p      | USP9X        | NSCLC        | Migration, invasion | 70  |
| 2   | 3p      | USP9X        | PDAC         | EMT, apoptosis, autophagy | 71  |
| 3   | 3p      | SOX4         | Breast cancer | Metastasis        | 72  |
| 4   | 3p      | SOX4         | Prostate cancer | Invasion, metastasis | 73  |
| 5   | 5p      | SOX4         | NSCLC        | Migration, invasion | 74  |
| 6   | 5p      | SOX4         | Osteosarcoma | Proliferation, Invasion | 75  |
| 7   | 3p      | SOX4         | NPC          | Migration, invasion | 76  |
| 8   | 3p      | SOX4         | Ovarian cancer | EMT              | 77  |
| 9   | 3p      | MnSOD        | Colorectal cancer | Metastasis     | 78  |
| 10  | 3p      | ZO-1         | Colorectal cancer | Metastasis   | 79  |
| 11  | 3p      | SMAD2        | Cervical cancer | Cell growth, migration, invasion | 80  |
| 12  | 3p      | PXN          | Gastric cancer | Metastasis and invasion | 81  |
| 13  | 3p      | MeCP2        | Gastric carcinoma | Carcinogenesis | 82  |
| 14  | 3p      | Lin28B       | AIPC         | Carcinogenesis | 83  |
| 15  | 3p      | SGK3         | GBM          | Proliferation | 84  |
| 16  | 3p      | HBEGF        | Ovarian cancer | Proliferation, migration, invasion | 85  |

Abbreviations: AIPC, androgen-independent prostate cancer; GBM, glioblastoma multiforme; NPC, nasopharyngeal carcinoma; NSCLC, non–small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

miR-212 may target different genes having different functions in colorectal cancer and NSCLC.\textsuperscript{84,88,92,93} Moreover, in cervical cancer, miR-212-3p was reported to play a role of tumour suppressor via targeting SMAD2.\textsuperscript{94} Meanwhile, in gastric cancer, miR-212-3p was indicated to take part in gastric carcinogenesis through targeting MeCP2.\textsuperscript{14} And in androgen-independent prostate cancer (AIPC), miR-212-3p and Lin28B were reported to form a potential regulatory loop to modulate c-Myc and prostate carcinogenesis.\textsuperscript{95} Yet, in glioblastoma multiforme (GBM), miR-212-3p was revealed to suppress the proliferation of GBM cells via targeting SGK3.\textsuperscript{82} In addition, miR-212-3p/miR-132-3p and SOX4 can interact with each other, creating a feedback loop in ovarian cancer cells. Specifically, the SOX4/EZH2 complex can silence miR-212-3p/132-3p expression, while miR-212-3p and miR-132-3p can inhibit the expression of SOX4 and modulate EMT of ovarian cancer cells.\textsuperscript{91} According to computer prediction, each miRNA can regulate about 200 mRNAs. Meanwhile, one protein-encoding gene also can also be modulated by multiple miRNAs, indicating that miRNAs are important regulators of mRNAs.\textsuperscript{97} Thus, it is essential to further explore the regulatory network of miRNA-212 in different human cancers.

### 4 CONCLUSION AND PERSPECTIVES

In general, a plenty of evidences show that miR-212 can interact with different targets and participate in multiple pathways, as
well as immune responses, in cancer. Dysregulated miR-212 may function as a promoter or suppressor in different aspects of tumorigenesis including cell proliferation, invasion, metastasis and apoptosis. Both DNA hypermethylation and histone modification may lead to the dysregulation of miR-212 in different cancers. MiR-212, downregulation or upregulation, may act as a biomarker for the diagnosis or prognosis of cancer. Especially, since miR-212 can also be detected in serum and plasma, which are much more readily obtainable than tissues, it attracts increased clinical attention as a biomarker. The controversial findings regarding miR-212 in some cancers require further study. miR-212 participates in chemoresistance and radioresistance, significantly affecting cancer treatment. Identifying vital miR-212 targets and developing safe, effective methods to address miR-212 involvement in the resistance to chemotherapy or radiotherapy will become an important focus in the field of cancer therapy.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (81600469, 81772626, 81570551, 81770607), the Science and Technology Development Projects of Shandong Province (2017GSF218053), the Clinical Medical Science and Technology Innovation Program of Jinan City (201704114), the Natural Science Foundation of Shandong Province (ZR2018PH003) and the Shandong Province Medical and Health Science and Technology development project (2017WS194).

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Jianni Qi and Hongjun Bian. Collection and assembly of data: Wenjun Chen, Jing Song, Xia Yang, Xiaoyu Xie. Data analysis and interpretation: Wenjun Chen and Hongjun Bian. Manuscript writing: Jianni Qi and Wenjun Chen. Administrative support: Qiang Zhu and Chengyong Qin. Final approval of manuscript: All authors.

ORCID

Jianni Qi https://orcid.org/0000-0002-9512-7762

REFERENCES

1. Liu X, Luo Z, Peng H, Jiang H, Xu L. Prognostic role of miR-9 expression in various human malignant neoplasms: a meta-analysis. Onco Targets Ther. 2016;9:3039-3047.
2. Croce CM. Causes and consequences of microRNA dysregulation in cancer. Nat Rev Genet. 2009;10(10):704-714.
3. Bian H, Zhou Y, Zhou D, Zhang Y, Shang D, Qi J. The latest progress on miR-374 and its functional implications in physiological and pathological processes. J Cell Mol Med. 2019;23(5):3063-3076.
4. Wang W, Bian H, Li F, et al. HBeAg induces the expression of macrophage miR-155 to accelerate liver injury via promoting production of inflammatory cytokines. Cell Mol Life Sci. 2018;75(14):2627-2641.
5. Li F, Bian H, Wang W, et al. HBV infection suppresses the expression of inflammatory macrophage miR-210. Mol Med Rep. 2019;19(3):1833-1839.
6. Inamura K, Ishikawa Y. MicroRNA in lung cancer: novel biomarkers and potential tools for Treatment. J Clin Med. 2016;5(3). pii:E36.
7. Nana-Sinkam SP, Croce CM. Clinical applications for microRNAs in cancer. Clin Pharmacol Ther. 2013;93(1):98-104.
8. Cao ZQ, Shen Z, Huang WY. MicroRNA-802 promotes osteosarcoma cell proliferation by targeting p27. Asian Pac J Cancer Prev. 2013;14(12):7081-7084.
9. Zhao FY, Han X, Chen XW, et al. miR-223 enhances the sensitivity of non-small cell lung cancer cells to erlotinib by targeting the insulin-like growth factor-1 receptor. Int J Mol Med. 2016;38(1):183-191.
10. Bourguignon LY. Matrix hyaluronan promotes specific MicroRNA upregulation leading to drug resistance and tumor progression. Int J Mol Sci. 2016;17(4):517.
11. Wanet A, Tacheny A, Arnould T, Renard P. MiR-212-132 expression and functions: within and beyond the neuronal compartment. Nucleic Acids Res. 2012;40(11):4742-4753.
12. Dou C, Wang Y, Li C, et al. MicroRNA-212 suppresses tumor growth of human hepatocellular carcinoma by targeting FOXA1. Oncotarget. 2015;6(15):13216-13228.
13. Wei LQ, Liang HT, Qin DC, Jin H-F, Zhao Y, She M-C. miR-212 exerts suppressive effect on SKOV3 ovarian cancer cells through targeting HBEFG. Tumour Biol. 2014;35(12):12427-12434.
14. Wada R, Akiyama Y, Hashimoto Y, Fukamachi H, Yuasa Y. miR-212 is downregulated and suppresses methyl-CpG-bindingproteinMeCP2 in human gastric cancer. Int J Cancer. 2010;127(5):1106-1114.
15. Park JK, Henry JC, Jiang J, et al. miR-132 and miR-212 are increased in pancreatic cancer and target the retinoblastoma tumor suppressor. Biochem Biophys ResCommun. 2011;406(4):518-523.
16. Ma C, Nong K, Wu B, et al. miR-212 promotes pancreatic cancer cell growth and invasion by targeting the hedgehog signaling pathway receptor patched-1. J Exp Clin Cancer Res. 2014;33:54.
17. Tu H, Wei G, Cai Q, et al. Microrna-212 inhibits hepatocellular carcinoma cell proliferation and induces apoptosis by targeting FOXA1. Onco Targets Ther. 2015;8:2227-2235.
18. Li D, Li Z, Xiong J, et al. MicroRNA-212 functions as an epigenetic-silenced tumor suppressor involving in tumor metastasis and invasion of gastric cancer through down-regulating PXN expression. Am J Cancer Res. 2015;5(10):2980-2997.
19. Incoronato M, Urso L, Portela A, et al. Epigenetic regulation of miR-212 expression in lung cancer. PLoS ONE. 2011;6(11):e27722.
20. Elmore S. Apoptosis: a review of programmed cell death. Toxicol Pathol. 2007;35(4):495-516.
21. Norbury CJ, Hickson ID. Cellular responses to DNA damage. Annu Rev Pharmacol Toxicol. 2001;41:367-401.
22. Mortezaee K, Salehi E, Mirtavvos-Mahyari H, et al. Mechanisms of apoptosis modulation by curcumin: implications for cancer therapy. J Cell Physiol. 2019;234(8):12537-12550.
23. Zhou Y, Ji Z, Yan W, Zhou Z, Li H. The biological functions and mechanism of miR-212 in prostate cancer proliferation, migration and invasion via targeting Engrailed-2. Oncol Rep. 2017;38(3):1411-1419.
24. Lu L, Zhang X, Zhang B, Wu J, Zhang X. Synaptic acetylcholinesterase targeted by microRNA-212 functions as a tumor suppressor in non-small cell lung cancer. Int J Biochem Cell Biol. 2013;45(11):2530-2540.
25. Wang H, Guo Q, Yang P, Long G. Restoration of microRNA-212 causes a G0/G1 cell cycle arrest and apoptosis in adult T-cell leukemia/lymphoma cells by repressing CCND3 expression. J Investig Med. 2017;65(1):82-87.
26. Chi Y, Huang S, Liu M, Guo L, Shen X, Wu J. Cyclin D3 predicts disease-free survival in breast cancer. Cancer Cell Int. 2015;15:89.
27. Asselin E, Mills GB, Tsang BK. XIAP regulates Akt activity and caspase-3-dependent cleavage during cisplatin-induced apoptosis in human ovarian epithelial cancer cells. Cancer Res. 2001;61(5):1862-1868.
28. Chai J, Shiozaki E, Srinivasula SM, et al. Structural basis of caspase-7 inhibition by XIAP. Cell. 2001;104(5):769-780.
29. Asselin E, Mills GB, Tsang BK. XIAP regulates Akt activity and caspase-9. Mol Cell. 2003;11(2):519-527.
30. Gu C, Wang Z, Jin Z, et al. MicroRNA-212 inhibits the proliferation, migration and invasion of renal cell carcinoma by targeting X-linked inhibitor of apoptosis protein (XIAP). Oncotarget. 2017;8(5):92119-92133.
31. Li D, Li Y, Huang Y, et al. Long non-coding RNA MIF-AS1 promotes gastric cancer cell proliferation and reduces apoptosis to upregulate NDUFA4. Cancer Sci. 2018;109(12):3714-3725.
32. Ouyang Q, Xu L, Cui H, Xu M, Yi L. MicroRNAs and cell cycle of malignant glioma. Int J Neurosci. 2016;126(1):1-9.
33. Lin Z, Fang D. The roles of SIRT1 in cancer. Genes Cancer. 2013;4(3-4):97-104.
34. Roth M, Chen WY. Sorting out functions of sirtuins in cancer. Oncogene. 2014;33(13):1609-1620.
35. Ramalinga M, Roy A, Srivastava A, et al. MicroRNA-212 negatively regulates starvation induced autophagy in prostate cancer cells by inhibiting SIRT1 and is a modulator of angiogenesis and cellular senescence. Oncotarget. 2015;6(33):34446-34457.
36. Li D, Bai I, Wang T, et al. Function of miR-212 as a tumor suppressor in thyroid cancer by targeting SIRT1. Oncol Rep. 2018;39(2):695-702.
37. Hu B, Jin X, Wang J. MicroRNA-212 targets mitogen-activated protein kinase 1 to inhibit proliferation and invasion of prostate cancer cells. Oncol Rep. 2018;26(7):1093-1102.
38. Chen QG, Zhou W, Han T, et al. MiR-378 suppresses prostate cancer cell growth through downregulation of MAPK1 in vitro and in vivo. Tumour Biol. 2016;37(2):2095-2103.
39. Jiping Z, Ming F, Lixiang W, et al. MicroRNA-212 inhibits proliferation of gastric cancer by directly repressing retinoblastoma binding protein 2. J Cell Biochem. 2013;114(12):2666-2672.
40. Xia J, Wu Z, Yu C, et al. miR-124 inhibits cell proliferation in gastric cancer through downregulation of SPHK1. J Pathol. 2012;227(4):470-480.
41. Semizarov D, Kroeger P, Fetsik S. SIRNA-mediated gene silencing: a global genome view. Nucleic Acids Res. 2004;32(13):3836-3845.
42. Liang X, Zeng J, Wang L, et al. Histone demethylase retinoblastoma binding protein 2 is overexpressed in hepatocellular carcinoma and negatively regulated by hsa-miR-212. PLoS ONE. 2013;8(7):e69784.
43. Liang X, Chen X, Chen L, et al. Upregulation of the miR-212/132 cluster suppresses proliferation of human lung cancer cells. Oncol Rep. 2015;33(2):705-712.
44. Cortez MA, Anfossi S, Ramapiyani R, et al. Role of miRNAs in immune responses and immunotherapy in cancer. Genes Chromosomes Cancer. 2019;58(4):244-253.
45. Qu HW, Jin Y, Cui ZL, Jin XB. MicroRNA-212 participates in the development of prostate cancer by upregulating BMI1 via NF-κB pathway. Eur Rev Med Pharmacol Sci. 2018;22(11):3348-3356.
46. Wu R, Li F, Zhu J, et al. A functional variant at miR-132-3p, miR-212-3p, and miR-361-5p binding site in CD80 gene alters susceptibility to gastric cancer in a Chinese Han population. Med Oncol. 2014;31(8):60.
47. Ding G, Zhou L, Shen T, et al. IFN-γ induces the upregulation of RFXAP via inhibition of miR-212-3p in pancreatic cancer cells: a novel mechanism for IFN-γ response. Onco Lett. 2018;15(3):3760-3765.
48. Ding G, Zhou L, Qian Y, et al. Pancreatic cancer-derived exosomes transfer miRNAs to dendritic cells and inhibit RFXAP expression via miR-212-3p. Oncotarget. 2015;6(30):29877-29888.
49. Mitchell PS, Parkin RK, Kroh EM, et al. Circulating microRNAs as stable blood based markers for cancer detection. Proc Natl Acad Sci U S A. 2008;105(30):10513-10518.
50. Yerukala Sathipati S, Ho SY. Identifying a miRNA signature for predicting the stage of breast cancer. Sci Rep. 2018;8(1):16138.
51. Wu Z, Zhou L, Ding G, Cao L. Overexpressions of miR-212 are associated with poor prognosis of patients with pancreatic ductal adenocarcinoma. Cancer Biomark. 2017;18(1):35-39.
52. Qi B, Liu SG, Qin XG, et al. Overregulation of microRNA-212 in the poor prognosis of esophageal cancer patients. Genet Mol Res. 2014;13(3):7800-7807.
53. Sun SM, Rockova V, Bullinger L, et al. The prognostic relevance of miR-212 expression with survival in cytogenetically and molecularly heterogeneous AML. Leukemia. 2013;27(1):100-106.
54. Wu WY, Xue XY, Chen ZJ, et al. Potentially predictive microRNAs of gastric cancer with metastasis to lymph node. World J Gastroenterol. 2011;17(31):3645-3651.
55. Lin K, Xu T, He BS, et al. MicroRNA expression profiles predict progression and clinical outcome in lung adenocarcinoma. Onco Targets Ther. 2016;9:5679-5692.
56. Ly ZD, Yang DX, Liu XP, et al. MiR-212-5p suppresses the epitheliomesenchymal transition in triple-negative breast cancer by targeting Prx2. Cell Physiol Biochem. 2017;44(5):1785-1795.
57. Wang F, Wang J, Lu L, Chen L, Cai W, Yang J. Diagnostic and prognostic potential of serum miR-132/212 cluster in patients with hepatocellular carcinoma. Ann Clin Biochem. 2018;55(5):576-582.
58. Tavolaro S, Colombo T, Chiaretti S, et al. Increased chronic lymphocytic leukemia proliferation upon IgM stimulation is sustained by the upregulation of miR-132 and miR-212. Genes Chromosomes Cancer. 2015;54(4):223-234.
59. Xie M, Fu Z, Cao J, et al. MicroRNA-132 and microRNA-212 mediate doxorubicin resistance by down-regulating the PTEN-AKT/NF-κB signaling pathway in breast cancer. Biomed Pharmacother. 2018;102:286-294.
60. Incoronato M, Garofalo M, Urso L, et al. miR-212 increases tumor necrosis factor-related apoptosis-inducing ligand sensitivity in non-small cell lung cancer by targeting the antiapoptotic protein PED. Cancer Res. 2010;70(9):3638-3646.
61. Turriani E, Haenisch S, Laechelt S, Diewock T, Bruhn O, Cascorbi I. MicroRNA profiling in K562 cells under imatinib treatment: influence of miR-212 and miR-328 on ABCG2 expression. Pharmagenet Genomics. 2012;22(3):198-205.
62. Hatakeyama H, Cheng H, Wirth P, et al. Regulation of heparin-binding EGF-like growth factor by miR-212 and acquired cettuximab-resistance in head and neck squamous cell carcinoma. PLoS ONE. 2010;5(9):e12702.
63. He X, Fan S. Hsa-miR-212 modulates the radiosensitivity of glioma cells by targeting BRCA1. Oncol Rep. 2018;39(3):977-984.
64. Gordon MD, Nusse R. Wnt signaling: multiple pathways, multiple receptors, and multiple transcription factors. J Biol Chem. 2006;281(32):22429-22433.
65. Komiya Y, Habas R. Wnt signal transduction pathways. Organogenesis. 2008;4(2):68-75.
66. MacDonald BT, Tamai K, He X. Wnt/β-catenin signaling: components, mechanisms, and diseases. Dev Cell. 2009;17(1):9-26.
67. Jia P, Wei G, Zhou C, et al. Upregulation of MiR-212 inhibits migration and tumorigenicity and inactivates Wnt/β-catenin signaling in human hepatocellular carcinoma. Technol Cancer Res Treat. 2018;17:153304618765221.
68. Lin JF, Zeng H, Zhao JQ, MiR-212-5p regulates the proliferation and apoptosis of AML cells through targeting FZD5. Eur Rev Med Pharmacol Sci. 2018;22(23):8415-8422.
69. Zhou C, Tan DM, Chen L, et al. Effect of miR-212 targeting TCF7L2 on the proliferation and metastasis of cervical cancer. Eur Rev Med Pharmacol Sci. 2017;21(2):219-226.
70. Boj SF, van Es JH, Huch M, et al. Diabetes risk gene and Wnt effector Tcf7l2/TCF4 controls hepatic response to perinatal and adult metabolic demand. Cell. 2012;151(7):1595-1607.

71. Yue W, Sun Q, Dacic S, et al. Downregulation of Dkk3 activates beta-catenin/TCF-4 signaling in lung cancer. Carcinogenesis. 2008;29(1):84-92.

72. Gan GN, Jimeno A. Emerging from their burrow: Hedgehog pathway inhibitors for cancer. Expert Opin Investig Drugs. 2016;25(10):1153-1166.

73. Ramalho-Santos M, Melton DA, McMahon AP. Hedgehog signaling and related signaling pathways in colorectal tumorigenesis. Curr Opin Genet Dev. 2002;12(5):503-511.

74. Dong J, Feldmann G, Huang J, et al. Elucidation of a universal size-control mechanism in Drosophila and mammals. Cell. 2007;130(6):1120-1133.

75. Zhao B, Ye X, Yu J, et al. TEAD mediates YAP-dependent gene induction and growth control. Genes Dev. 2008;22(14):1962-1971.

76. Wang J, Ma L, Weng W, et al. Mutual interaction between YAP and CREB promotes tumorigenesis in liver cancer cells. Hepatology. 2013;58(3):1011-1020.

77. Xie C, Chen B, Wu B, Guo J, Cao Y. LncRNA TUG1 promotes cell proliferation and suppresses apoptosis in osteosarcoma by regulating miR-212-3p/FOXA1 axis. Biomed Pharmacother. 2018;97:1645-1653.

78. Liu H, Li C, Shen C, et al. MiR-212-3p inhibits glioblastoma cell proliferation by targeting SOX4. Prostate. 2015;76(16):1560-1570.

79. Tang T, Huan L, Zhang S, et al. MicroRNA-212 functions as a tumor-suppressor in human non-small cell lung cancer by targeting SOX4. Oncol Rep. 2017;38(4):2243-2250.

80. Luo XJ, Tang DG, Gao TL, et al. MicroRNA-212 inhibits osteosarcoma cell proliferation and invasion by down-regulation of Sox4. Cell Physiol Biochem. 2014;34(6):2180-2188.

81. Li Y, Zhang D, Chen C, Ruan Z, Li Y, Huang Y. MicroRNA-212 displays tumor-promoting properties in non-small cell lung cancer cells and targets the hedgehog pathway receptor PTCH1. Mol Biol Cell. 2012;23(8):1423-1434.

82. Camargo FD, Gokhale S, Johnnidis JB, et al. YAP1 increases organ size and expands undifferentiated progenitor cells. Curr Biol. 2007;17(23):2054-2060.

83. Dong J, Feldmann G, Huang J, et al. Elucidation of a universal size-control mechanism in Drosophila and mammals. Cell. 2007;130(6):1120-1133.

84. Zhao B, Ye X, Yu J, et al. TEAD mediates YAP-dependent gene induction and growth control. Genes Dev. 2008;22(14):1962-1971.

85. Wang J, Ma L, Weng W, et al. Mutual interaction between YAP and CREB promotes tumorigenesis in liver cancer cells. Hepatology. 2013;58(3):1011-1020.

86. Yu W, Qiao Y, Tang X, et al. Tumor suppressor long non-coding RNA, MT1DP is negatively regulated by YAP and Runx2 to inhibit FoxA1 in liver cancer cells. Cell Signal. 2014;26(12):2961-2968.

87. Xie C, Chen B, Wu B, Guo J, Cao Y. LncRNA TUG1 promotes cell proliferation and suppresses apoptosis in osteosarcoma by regulating miR-212-3p/FOXA1 axis. Biomed Pharmacother. 2018;97:1645-1653.

88. Liu J, Chen B, Yue B, Yang J. MicroRNA-212 suppresses the proliferation and migration of osteosarcoma cells by targeting forkhead box protein A1. Exp Ther Med. 2016;12(6):4135-4141.

89. Chen W, Huang Y, Zhang S, et al. MicroRNA-212 suppresses nonsmall lung cancer invasion and migration by regulating ubiquitin-specific protease-9. J Cell Biochem. 2019;120(4):6482-6489.

90. Chen W, Zhou Y, Zhi X, et al. Delivery of miR-212 by chimeric peptide-condensed supramolecular nanoparticles enhances the sensitivity of pancreatic ductal adenocarcinoma to doxorubicin. Biomaterials. 2019;192:590-600.

91. Lin L, Wang Z, Jin H, Shi H, Lu Z, Qi Z. MiR-212/132 is epigenetically downregulated by SOX4/EZH2-H3K27me3 feedback loop in ovarian cancer cells. Tumor Biology. 2016;37(12):15719-15727.

92. Wang J, Ma L, Weng W, et al. Mutual interaction between YAP and CREB promotes tumorigenesis in liver cancer cells. Hepatology. 2013;58(3):1011-1020.

93. Borrego-Díaz E, Powers BC, Azizov V, et al. A potential regulatory loop between Lin28B: miR-212 in androgen-independent prostate cancer. Int J Oncol. 2014;45(6):2421-2429.

94. Liu H, Li C, Shen C, et al. MiR-212-3p inhibits glioblastoma cell proliferation by targeting SGK3. J Neurooncol. 2015;122(3):431-439.

95. Zhou Y, Ferguson J, Chang JT, Kluger Y. Inter- and intra-combinatorial regulation by transcription factors and microRNAs. BMC Genom. 2007;8:396.

How to cite this article: Chen W, Song J, Bian H, et al. The functions and targets of miR-212 as a potential biomarker of cancer diagnosis and therapy. J Cell Mol Med. 2020;24:2392-2401. https://doi.org/10.1111/jcmm.14966