Emerging role of microRNA-21 in cancer (Review)

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Abstract. MicroRNAs (miRs) are a class of single-stranded RNA molecules of 15-27 nucleotides in length that regulate gene expression at the post-translational level. miR-21 is one of the earliest identified cancer-promoting 'oncomiRs', targeting numerous tumor suppressor genes associated with proliferation, apoptosis and invasion. The regulation of miR-21 and its role in carcinogenesis have been extensively investigated. Recent studies have focused on the diagnostic and prognostic value of miR-21 as well as its implication in the drug resistance of human malignancies. The further use of miR-21 as a biomarker and target for cancer treatments is likely to improve the outcome for patients with cancer. The present review highlights recent findings associated with the importance of miR-21 in hematological and non-hematological malignancies.

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Abbreviations: miRNA, microRNA; IL, interleukin; AP-1, activated protein-1; NFI, nuclear factor I; PDCD4, programmed cell death protein 4; BTG2, B-cell translocation gene 2; RECK, reversion-induced cystine-rich protein with Kazal motifs; TIMP3, tissue inhibitor of metalloproteinases 3; HPV, human papilloma virus; PTEN, phosphatase and tensin homologue deleted on chromosome 10; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; CLL, chronic lymphocytic leukemia; T-ALL, T-cell acute lymphoblastic leukemia; HER2, human epidermal growth factor receptor 2; STAT3, signal transducer and activator of transcription 3; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor

Key words: microRNA-21, carcinogenesis, hematological malignancy

Contents

1. Introduction

MicroRNAs (miRs) are a class of naturally occurring short non-coding RNA molecules of 15-27 nucleotides in length that regulate eukaryotic gene expression at the post-transcriptional level. Almost 2,000 human miRNAs have been identified through cloning and/or sequence analysis (1). They have key regulatory roles in the development, differentiation and apoptosis of normal cells, as well as in the determination of the final phenotype of cancer cells, affecting carcinogenesis and metastatic potential (2). miR-21 is an abundantly expressed miRNA in mammalian cells, whose upregulation is associated with numerous types of cancer (3,4). By generation of a conditional miR-21 knock-in mouse, it was demonstrated that miR-21 functions as an oncogene with its overexpression resulting in malignant B-cell lymphoma (5). Indeed, miR-21 was found to be the only consistently upregulated miRNA in a study that profiled 540 clinical samples from cancer patients (6). The majority of studies on miR-21 have focused on its role in carcinogenesis and its clinical application. miR-21 is also expressed in hematopoietic cells of the immune system, including B/T cells, monocytes, macrophages and dendritic cells. High miR-21 levels are, therefore, considered to be a marker of immune cell activation (7). Regarding pathological necrosis, miR-21 enhances cellular necrosis by negatively regulating tumor suppressor genes associated with the death receptor-mediated intrinsic apoptotic pathway (8).

2. Biological function of miR-21

The biological functions of various miRNAs, including miR-21, have been extensively investigated and miR-21 is

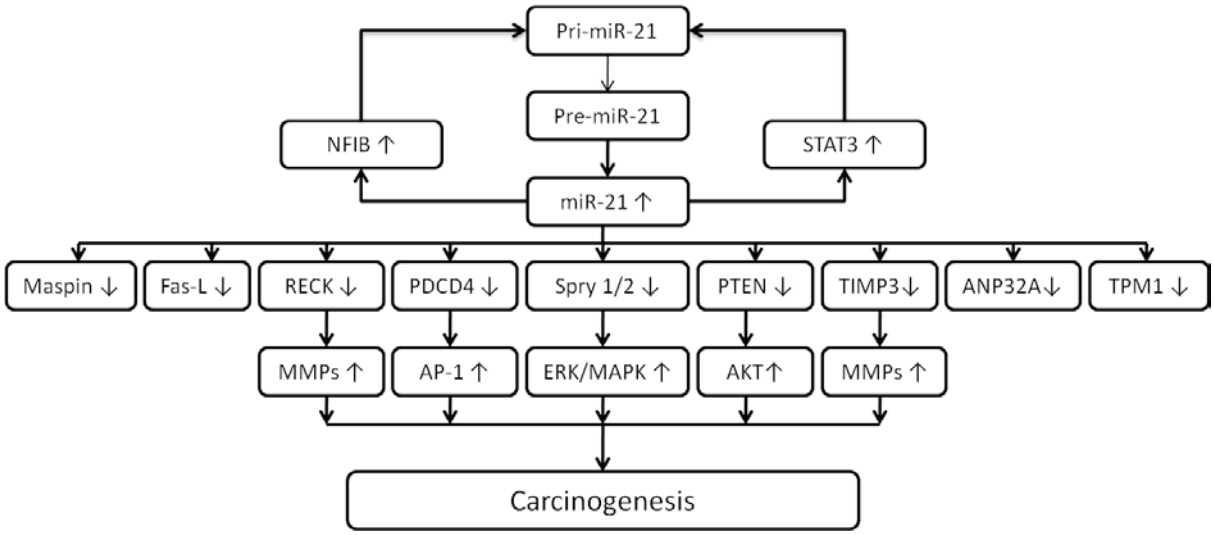

Figure 1. Pathways of the involvement of miR-21 in carcinogenesis. miR, microRNA; pri-mRNA, primary mRNA; pre-mRNA, precursor mRNA; AP-1, activated protein-1; NFI, nuclear factor I; Maspin, mammary serine protease inhibitor; Fas-L, Fas ligand; Spry 1/2, sprouty homolog 1/2; PDCD4, programmed cell death protein 4; TPM1, tropomyosin 1; RECK, reversion-induced cystine-rich protein with Kazal motifs; TIMP3, tissue inhibitor of metalloproteinases 3; ANP32A, acidic nuclear phosphoprotein 32 family, member A; MMP, matrix metalloproteinase; PTEN, phosphatase and tensin homologue deleted on chromosome 10; STAT3, signal transducer and activator of transcription 3; JNK, c-Jun N-terminal kinase; MDR, multi-drug resistance; ERK, extracellular signal-regulated kinase; MAPK, mitogen-associated protein kinase.

evolutionarily conserved across a wide range of vertebrate species (9). However, the location of the gene encoding miR-21 in the genome is different between humans and other vertebrate species. In rats and mice, the miR-21 gene is located on chromosome 10 and 21, respectively, whereas in humans, it is located on chromosome 17q23.2. The primary transcript of the miR-21 gene is independently transcribed from a conserved promoter located within the intron of the overlapping protein-coding gene (10). Experimental data have shown that in numerous cell types, miR-21 functions as an anti-apoptotic and pro-survival factor (11,12). High expression levels of miR-21 may be a characteristic of cancer cells and represent a common feature of pathological cell growth or cell stress. For instance, miR-21 was shown to be upregulated in a mouse model of cardiac hypertrophy and vascular neointimal lesion formation (13,14). The induction of miR-21 is associated with cellular de-differentiation. A noteworthy example is the restricted thyroid cell line FRTL-5, which depends on the presence of thyroid-stimulating hormone (15). These findings led to the hypothesis that relatively low levels of miR-21 may be temporarily and spatially required for differentiation and development, whereas high levels may exert oncogenic effects. Regarding the immune system, miR-21 has been shown to regulate T-cell immunity (16). Pro-inflammatory T helper (Th)1 and anti-inflammatory Th2 cells exist in a balanced state by counter-regulating each other's differentiation and function. miR-21 is induced in activated dendritic cells and directly targets the mRNA that encodes the p35 sub-unit of Th1-promoting interleukin (IL)-12, and in miR-21-deficient mice, increased secretion of IL-12 by dendritic cells as well as enhanced Th1 development have been observed (17). In addition to dendritic cell-derived miR-21, T-cell intrinsic miR-21 has been shown to promote Th2 differentiation by inhibiting the expression of Sprouty homolog (Spry)1 transcript, a mitogen-activated protein kinase (MAPK) pathway inhibitor (18). Furthermore, miR-21 has been found to be overexpressed in $CD4^+$ T cells derived from patients with lupus, as well as from lupus-prone MRL/lpr mice, indicating a strong association with autoimmune disease.

3. Regulation of miR-21

In *Homo sapiens*, miR-21 is located on chromosome 17q23.2, where it overlaps with the protein-coding gene transmembrane (TMEM)49, a human homolog of rat vacuole membrane protein. However, Fujita *et al* (19) reported that miR-21 and TMEM49 are independently regulated. Analysis of the consensus sequences within the miR-21 protein region identified several conserved enhancer elements, including binding sites for activation protein 1 (AP-1), Ets family transcription factor PU.1, CCAAT/enhancer-binding protein-α, nuclear factor I (NFI), serum response element, p53 and signal transducer and activator of transcription 3 (STAT3) (20). A chromatin immunoprecipitation assay showed that AP-1 activated miR-21 transcription through conserved AP-1 and PU.1 binding sites and downregulated the expression of NFIB, a potential target of miR-21. Furthermore, the NFIB protein usually binds to the miR-21 promoter and acts as a negative regulator; therefore, a double-negative feedback mechanism operates between miR-21 and NFIB, which sustains miR-21 expression (21). Epigenetic modification appears to be involved in the regulation of miR-21 expression in specific cell types. One study revealed that miR-21 was among several miRNAs strongly induced in the ovarian cell line OVCAR3 by treatment with the demethylating agent 5-aza-2'-deoxycytidine and suggested that hypomethylation may be the mechanism responsible for its overexpression *in vivo* (22). Programmed cell death protein 4 (PDCD4), a direct target of miR-21 in solid and hematological malignancies, acts as a negative regulator of AP-1 (23). The activation of miR-21 by AP-1 in response to RAS oncoprotein led to downregulation of the expression of its target gene PDCD4, which then contributed to the increase

in AP-1 activity. Hatley *et al* (24) provided the first *in vivo* evidence that miR-21 targets antagonists of RAS, including Spry1 and 2, B-cell translocation gene 2 (BTG2) and PDCD4, resulting in activation of the RAS/MAPK kinase/extracellular signal-regulated kinase pathway. In two studies, two-dimensional proteomics, luciferase reporter assays and western blot analysis were used to identify that tropomyosin 1 and acidic nuclear phosphoprotein 32 family, member A are targeted by miR-21, suppressing their translation (25,26). As with TPM1 and PDCD4, maspin was found to be directly targeted by miR-21, which reduced the invasiveness of breast cancer cells. Therefore, the levels of PDCD4 and maspin are inversely correlated with miR-21 in human breast cancer (27). In addition, miR-21 regulates multiple genes associated with cell apoptosis, migration and invasiveness, including reversion-induced cystine-rich protein with Kazal motifs (RECK) and tissue inhibitor of metalloproteinases 3 (TIMP3), which are suppressors of malignancy and inhibitors of matrix metalloproteinases. mRNAs carrying RECK and TIMP3 have been predicted to be conserved miR-21 targets with one and two putative binding sites, respectively (Fig. 1) (28).

4. Carcinogenesis

miR-21 has been shown to be the most commonly upregulated miRNA in solid and hematological malignancies (6). Extensive studies have implicated its role in tumor pathogenesis and during all other stages of carcinogenesis. To date, the following functional studies have been performed, which strongly suggest that miR-21 exerts oncogenic activity: i) Knockdown of miR-21 in cultured glioblastoma cells triggered the activation of caspases and led to an increase in apoptotic cell death, suggesting that miR-21 acts as an anti-apoptotic factor (11); ii) the human miR-21 gene is located in the fragile site FRA17B within the 17q23.2 chromosomal region, which is one of the human papilloma virus (HPV) integration loci. Integration of HPV into the host cell genome caused genetic and epigenetic alterations, suggesting that the location of the miR-21 gene at or near HPV integration sites may contribute to its elevation in cervical cancer (29); iii) knockdown of miR-21 in hepatoma cells increased the expression level of tumor suppressor phosphatase and tensin homologue deleted on chromosome 10 (PTEN), a direct target of miR-21, and decreased tumor cell proliferation, migration and invasion (30). Furthermore, in colorectal cancer, miR-21 expression was found to be inversely correlated with Spry2 and PTEN leading to cancer progression (3); and iv) miR-21 was shown to promote hepatic lipid accumulation and cancer progression by interacting with the HMG-box transcription factor 1-p53-sterol regulatory element-binding transcription factor 1 pathway. An antisense oligonucleotide specific for miR-21 impaired liver lipid accumulation in mice and growth of xenograft tumors (31).

5. miR-21 and hematological malignancies

miR-21 has been identified as an 'oncomiR' in pre-B-cell lymphoma, and inhibition of miR-21 induced biological and behavioral alterations in diffuse large B-cell lymphoma (DLBCL) (5,32). DLBCLs are known to be associated with the AKT signaling pathway, which is activated during carcinogenesis (33,34). Furthermore, AKT activation is associated with poor prognosis of DLBCL patients (35). miR-21 activates the phosphoinositide-3 kinase (PI3K)/AKT signaling pathway by directly suppressing forkhead box protein O1 expression and downregulating PTEN expression (36). Natural killer (NK)-cell leukemia is a cancer type derived from NK cells, whose onset and development are, to a great extent, governed by Epstein-Barr virus (EBV). In addition, miR-21 was found to negatively regulate the tumor suppressors, PTEN and PDCD4 in NK-cell leukemia. EBV infection may contribute to the upregulation of various miRNAs, including miR-21 and miR-155, and infection with EBV is associated with immortalization of lymphoid cells (37,38). In a study on a Chinese cohort with DLBCL, miR-21 expression was found to be elevated in the serum and correlated with the sub-type of activated B-cell lymphoma, as well as with early-stage disease (39). Jones *et al* (40) reported that circulating miR-21 along with miR-494 and miR-1973 was elevated in patients with classic Hodgkin lymphoma and indicated the disease response to therapy. These results suggest the potential use of miR-21 as non-invasive diagnostic markers.

Patients with chronic myeloid leukemia in the blastic phase show a poor response to clinical treatment (41); furthermore, retinol-binding protein 2, a histone H3 lysine 4 demethylase, was found to be underexpressed during the blastic phase of chronic myeloid leukemia, leading to epigenetic downregulation of miR-21 (42). Together with miR-155, miR-21 was found to be markedly overexpressed in patients with chronic lymphocytic leukemia (CLL) (4). IL-4 induces B-cell differentiation and survival of CLL cells, and regulation of miR-21 by IL-4 contributes to evasion of apoptosis of CLL cells (43). A study using an miR-21-based scoring system showed that miR-21 expression levels were significantly higher in CLL patients with chromosome 17 deletion (compared with CLL patients without chromosome 17 deletion), which was associated with poor prognosis (44). Although the investigation of miR-21 in acute leukemia is relatively insufficient, miR-21 is frequently overexpressed in myeloid blasts of patients with nucleophosmin-mutant acute myeloid leukemia and associated with a marked downregulation of PDCD4 protein (45). Lineage-tracing experiments revealed that Dicer1 deficiency led to apoptosis of T-cell acute lymphoblastic leukemia (T-ALL) cells. Microarray-based miRNA profiling revealed that miR-21 was deregulated in mouse and human T-ALL cells. Furthermore, miR-21 was shown to regulate T-ALL cell survival via repression of the tumor suppressor PDCD4 (46). In addition, the tumor suppressor Spry2 was revealed to be negatively correlated with miR-21 expression in myeloma cells. Inhibition of miR-21 led to upregulation of PTEN and downregulation of phosphorylated AKT in xenografts of myeloma (47,48). These results suggested that miR-21 is important in hematological malignancies.

6. miR-21 and solid tumors

Extensive studies have implicated the integral role of miR-21 in tumor pathogenesis and during all other stages of carcinogenesis. Growing evidence supports miR-21 expression as an important biomarker of poor prognosis in human

malignancies (49). Generally, the expression level of miR-21 has been found to be higher in more advanced malignancies. A previous study indicated that high-grade glioma tended to have higher expression levels of miR-21 than low-grade glioma (11). In breast cancer, overexpression of miR-21 was significantly correlated with advanced clinical stage, lymph node metastasis and poor prognosis (50). Increased expression of miR-21 has been found in human breast cancer cell lines *in vitro* as well as in tissue samples, with a key role in all phases of breast cancer pathogenesis (51). Overexpression of the receptor tyrosine kinase HER2 accounts for a clinically aggressive breast cancer sub-type with an increased incidence of metastasis. STAT3 co-opts the function of nuclear HER2 by recruiting it as its co-activator at the response elements in the promoter of miR-21. miR-21, in turn, was found to downregulate the expression of the metastasis suppressor protein PDCD4 in breast cancer (52). Further studies disclosed that serum and urine miR-21 may be a potential diagnostic biomarker for breast cancer; however, prior to its implementation in the clinic, further investigation is warranted (53,54).

The expression of miR-21 is also critical in colon cancer. During the carcinogenesis of colon cancer, miR-21 induces stemness by downregulating transforming growth factor β receptor 2 and stimulating invasion, as well as metastasis by suppressing PDCD4 (55,56). miR-21 has been extensively investigated for its prognostic potential in at least ten independent trials involving 2,039 patients since 2008 (57). Nielsen *et al* (58) evaluated the expression of miR-21 using semi-quantitative *in situ* hybridization analysis of formalin-fixed, paraffin-embedded tissue samples from 197 patients with stage II colorectal cancer. Strong staining for miR-21 was significantly associated with shorter disease-free survival and overall survival. Furthermore, a large multicenter retrospective trial assessed the association between miRNAs and stage II colon cancer in a Chinese population. Six selected indicator miRNAs, comprising four upregulated miRNAs (miR-21, miR-20, miR-103 and miR-106) and two downregulated miRNAs (miR-143 and miR-215) were assessed to predict disease recurrence. Forty-six percent of the high-risk patients experienced a relapse and 15% of the low-risk group exhibited recurrence (59).

In non-small cell lung cancer (NSCLC), miR-21 enhances oncogenic K-ras activation and modulates tumorigenesis by targeting Spry2, BTG2 and PDCD4 (24). The epidermal growth factor receptor (EGFR) pathway has been regarded as an important mechanism in lung adenocarcinoma. miR-21 expression was found to be significantly increased in cases of lung adenocarcinoma with EGFR mutations, and activated EGFR signaling enhanced miR-21 expression (60). A meta-analysis of eight eligible studies revealed that miR-21 expression is a significant negative prognostic factor in Asian populations (61). The association of miR-21 with reduced overall survival has been evidenced in head and neck carcinoma, as well as in carcinoma of the digestive system (62). In addition, serum miR-21 was found have prognostic value in hepatoma and to promote the development of hepatoma by regulating PDCD4 and PTEN (63). Extensive studies have investigated the role of miR-21 in prostate carcinogenesis driven by the androgen receptor (64). Downregulation of RECK and loss of BTG2 mediated by miR-21 was shown to contribute to prostate cell transformation (65,66). Furthermore, miR in prostate cancer tissues and in serum and urine samples of prostate cancer patients was revealed to be an independent diagnostic and prognostic biomarker (67-69).

Furthermore, miR-21 has been associated with the resistance of cancer to drug treatments. Inhibition of miR-21 may effectively reverse drug resistance in various cancer types (70). miR-21 is also implicated in drug resistance of breast cancer. In estrogen-positive breast cancer, downregulation of PDCD4 was found to be mediated by upregulation of HER2 via the MAPK and AKT signaling pathways, as well as miR-21 in aromatase inhibitor-resistant breast cancer cells (71). An *in vitro* study on breast cancer reported that silencing of miR-21 conferred sensitivity to tamoxifen and fulvestrant by enhancing autophagic cell death through inhibition of the PI3K-AKT-mammalian target of rapamycin pathway (72). Induction of miR-21 by interaction of hyaluronan-CD44 with protein kinase C and c-Jun has also been reported to contribute to chemotherapy resistance (73). Regarding anti-HER2 therapy of breast cancer, upregulation of miR-21 conferred resistance to trastuzumab along with a reduction of PTEN expression (74). The Geparquinto trial showed a negative association of circulating miR-21 with overall survival in HER2-positive breast cancer patients treated with neoadjuvant chemotherapy and trastuzumab or lapatinib (75). In HT-29 colon cancer cells, miR-21 targeted the human nuts homolog 2, leading to the expression of thymidine phosphorylase and dihydropyrimidine dehydrogenase. These mechanisms conferred resistance of colon cancer cells to fluorouracil (76). In addition to the well-known platinum-based chemotherapy for lung cancer, miR-21 has been shown to be involved in the resistance to the EGFR inhibitor. EGFR-tyrosine kinase inhibitor (TKI) has been regarded as an important treatment option for NSCLC and miR-21 overexpression was found to be associated with acquired resistance to EGFR-TKI (77,78). A pilot study using plasma miRNA profiles identified miR-21 to be involved in the primary resistance to EGFR-TKI in patients with advanced NSCLC with an activating EGFR mutation. The application of this non-invasive approach may be considered for monitoring responses of lung cancer patients to EGFR-TKI treatment (79). Furthermore, the implication of miR-21 in chemotherapy resistance has been investigated for a wide range of solid cancer types, including pancreatic and prostate cancer, hepatoma, ovarian cancer, glioma, and head and neck, stomach and bladder cancer (Table I) (68-71,75,77-94). These results support the clinical application of miR-21 inhibition in cancer treatments in the future.

7. Conclusion

Evidence supports that miR-21 is an oncogenic miRNA and regulates various downstream effectors associated with cancer. Overexpression of miR-21 is strongly associated with hematological and solid malignancies. miR-21 may be utilized as a diagnostic and prognostic biomarker for various types of cancer and as a potential therapeutic target. Based on this concept, further research on miRNA signaling pathways has begun with the aim of elucidating their effects on conventional protein signaling pathways. The implication of miR-21 in resistance to anticancer agents highlights the possible clinical

Table I. Studies on the involvement of miR-21 in the resistance of solid malignancies to anticancer agents.

Cancer type	Anticancer agent	Signaling pathway	Model	Author, year (Refs.)
Breast	Aromatase inhibitor	HER2/PDCD4	Cell, human	Chen *et al*, 2015 (71)
Breast	Tamoxifen/fulvestrant	PI3K-mTOR	Cell	Yu *et al*, 2016 (72)
Breast	Doxorubicin/paclitaxel	HA-CD44	Cell	Bourguignon *et al*, 2009 (73)
Breast	Trastuzumab	PTEN	Cell, mice, human	Gong *et al*, 2011 (74)
Lung	Gefitninb	PTEN	Cell, mice	Shen *et al*, 2014 (78)
Breast	Gemcitabine	PTEN/AKT	Cell, mice	Wu *et al*, 2016 (80)
Colon	5FU/oxaliplatin	TGFβ	Cell	Yu *et al*, 2012 (81)
Colon	5FU	Sprouty2	Cell	Feng *et al*, 2012 (82)
Lung	Cisplatin	PTEN	Cell, human	Liu *et al*, 2013 (83)
Pancreas	5FU	PTEN/PDCD4	Cell	Wei *et al*, 2016 (84)
Pancreas	Gemcitabine	PDCD4	Cell	Paik *et al*, 2013 (85)
Prostate	Docetaxel	PDCD4	Cell	Shi *et al*, 2010 (86)
Liver	Interferon-α/5FU	PTEN/PDCD4	Cell, human	Tomimaru *et al*, 2010 (87)
Liver	Sorafenib	PTEN/AKT	Cell, mice	He *et al*, 2015 (88)
Ovary	Cisplatin	JNK/c-JUN	Cell	Echevarria-Vargas *et al*, 2014 (89)
Ovary	Paclitaxel	MDR-1/P-gp	Cell	Xie *et al*, 2013 (90)
Brain (glioma)	Temozolomide	Wnt/β-catenin	Cell	Lan *et al*, 2015 (91)
Brain (glioma)	Temozolomide	Bax/Bcl-2	Cell	Shi *et al*, 2010 (92)
Head and neck (oral cancer)	Cisplatin	PTEN/TIMP3/PDCD4	Cell, mice	Zhou *et al*, 2014 (93)
Head and neck	Cisplatin	HA-CD44/PDCD4/IAP	Cell	Bourguignon *et al*, 2012 (94)
Head and neck (nasopharyngeal cancer)	Cisplatin	PDCD4/Fas-L	Cell	Yang *et al*, 2013 (95)
Stomach	Cisplatin	PTEN	Cell	Yang *et al*, 2013 (96)
Bladder	Doxorubicin	PTEN	Cell	Tao *et al*, 2011 (97)

FU, fluorouracil; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide-3 kinase; JNK, c-Jun N-terminal kinase; PTEN, phosphatase and tensin homologue deleted on chromosome 10; PDCD4, programmed cell death protein 4; MDR, multi-drug resistance; P-gp, p-glycoprotein; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; TIMP3, tissue inhibitor of metalloproteinases 3; HA, hyaluronan; IAP, inhibitor of apoptosis; Fas-L, Fas ligand.

application of miR-21 inhibition for reducing the resistance of cancer to drugs, with the potential to use targeted therapeutic strategies in addition to conventional cytotoxic agents. In 2013, a clinical trial using an miRNA was launched (NCT01829971; ClinicalTrial.gov). The study evaluates the safety of an miRNA-RX34 liposomal injection in patients with primary liver cancer as well as other selected solid tumor types and hematological malignancies. To the best of our knowledge there are no ongoing miR-21-based clinical trials on cancer patients. Further studies are required prior to implementing miRNA-based cancer therapeutic strategies into clinical practice. Furthermore, development of effective delivery methods of synthetic therapeutic miRNAs to desired target tissues may enhance the efficacy of miRNA-mediated treatments, enabling the adoption of this type of therapy in cancer medicine in future.

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