

Role of miRNA-214-3p in cancer (Review)

ZESHAN CHEN¹, XIN DENG², YUANHONG LU¹, LING LU¹, YIJUE QIN¹,
HAISHUN QU¹ and SHAOHANG LAN¹

¹Department of Traditional Chinese Medicine, Guangxi Zhuang Autonomous Region People's Hospital, Nanning, Guangxi 530016, P.R. China; ²School of Basic Medical Sciences, Guangxi University of Traditional Chinese Medicine, Nanning, Guangxi 530200, P.R. China

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Abstract. microRNA-214-3p (miRNA-214-3p) can be mapped to the human chromosome 1q24.3 and is ~22 nucleotides in length. It has been garnering considerable attention due to its aberrant expression profile in various different types of cancer and its apparent role in regulating tumor progression. In malignant tumors, miRNA-214-3p can serve as a tumor suppressor or oncogene. This can be mediated by mainly inhibiting the expression of target genes by binding to the 3'-untranslated region of target mRNAs, thereby regulating multiple downstream cellular processes, such as cell proliferation, metastasis, invasion and apoptosis. However, the role of miRNA-214-3p in cancer remains unclear. Therefore, in the present review, the role of miRNA-214-3p in cancer was summarized, whilst analyzing its potential as a biomarker for cancer diagnosis, prognosis and response to treatment. In addition, the present review evaluates its effects on sensitivity to chemotherapy, targeted therapy and radiotherapy. The current proposed strategies for the systemic delivery of miRNA-214-3p in cancer were also discussed.

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1. Introduction

In 2022, 20 million new cases of cancer and 9.7 million cancer-related mortality occurred worldwide (1). According to the Global Report 2022, 2,041,910 new cases of cancer and 618,120 cancer-related mortality cases were predicted in the United States in 2025 (2). Treating cancer remains a major challenge. Early diagnosis and prevention of distant metastasis remain difficult in the clinical diagnosis and treatment of cancer (3). Therefore, additional in-depth investigation of cancer pathogenesis and the identification of molecular markers for early diagnosis are essential for the clinical diagnosis and treatment of cancer. Recent studies on microRNAs (miRNAs) have reported that they can serve important roles in cancer development. Specifically, they can function either as tumor suppressors or oncogenes in the proliferation, metastasis and invasion of cancer. In turn, they can be associated with the diagnosis, prognosis and treatment of cancer (4,5).

miRNA is a single-stranded non-coding RNA molecule that is ~22 nucleotides in length, which is widely found in eukaryotes (6). miRNA mainly negatively regulate gene expression by binding to the 3'-untranslated regions (UTR) of target mRNAs, which leads to the degradation or translational repression of the latter (7). This process involves several steps: i) In the nucleus, miRNA genes are transcribed into primary miRNAs by RNA polymerase II, where primary miRNA are further processed into precursor miRNA by the Drosha enzyme-DiGeorge syndrome critical region 8 complex and transported to the cytoplasm (8); ii) in the cytoplasm, the precursor miRNA is sheared by the Dicer enzyme into a mature double-stranded miRNA of ~22 nucleotides in length, where one strand of the mature double-stranded miRNA (the guide strand) is subsequently loaded into the Argonaute protein to form an RNA-induced silencing complex; and iii) this complex binds to the 3'-UTR of the target mRNA through sequence complementation, resulting in the degradation of the mRNA and the formation of an RNA-induced silencing

Correspondence to: Professor Xin Deng, School of Basic Medical Sciences, Guangxi University of Traditional Chinese Medicine, 13 Wuhe Avenue, Nanning, Guangxi 530200, P.R. China
E-mail: ricedx@126.com

Professor Yijue Qin, Department of Traditional Chinese Medicine, Guangxi Zhuang Autonomous Region People's Hospital, 6 Taoyuan Road, Qingxiu, Nanning, Guangxi 530016, P.R. China
E-mail: qinyijue888@126.com

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complex. In this manner, mRNA degradation and translational repression is achieved (8).

A number of studies have shown that miRNA-214-3p expression is dysregulated in different cancers, where it can regulate their progression by inhibiting the expression of its target genes (9,10). In the present review, the role of miRNA-214-3p in different types of cancer was summarized, whilst also analyzing its potential effects on cancer chemotherapy, targeted therapy and radiotherapy. In addition, the present review aimed to analyze the potential of miRNA-214-3p as a biomarker and its delivery strategy.

2. miRNA-214-3p regulation in cancer

Competitive endogenous RNA (ceRNA). Long-stranded non-coding RNA (lncRNA) and circular RNAs (circRNA), the expression of which has also been found to be dysregulated in cancer, can competitively bind to miRNA-214-3p through the ceRNA mechanism, in turn promoting the expression of its downstream target mRNAs. The circRNA nuclear factor IX (NFIX) can bind to and inhibit the expression of miRNA-214-3p to upregulate the expression of TP53 regulation of apoptosis inhibitor 1, which promotes lung cancer progression (11). This finding suggests that the circRNA NFIX can target miRNA-214-3p to act as an oncogene in lung cancer. In addition, circRNA 0038718 can target and inhibit miRNA-214-3p function, which in turn inhibits breast cancer cell proliferation and invasion (12), suggesting that circRNA 0038718 can target miRNA-214-3p to serve as a tumor suppressor.

DNA methylation. DNA methylation is an important epigenetic modification that can regulate miRNA expression (13). In Pediatric central nervous system germ cell tumors, the expression of miRNA-214-3p is negatively correlated with its methylation status (14). Further studies revealed that the expression of miRNA-214-3p is significantly upregulated when the DNA demethylating agent 5-aza-2'-deoxycytidine was added (14).

Transcription factors. Twist1 is a transcription factor, which is a transcription factor with a highly conserved basic helix-loop-helix motif (15). In ovarian cancer, Twist1 can positively regulate the level of miRNA-214-3p expression (16).

Others. In medullary thyroid carcinoma, the expression of miRNA-214-3p is downregulated under hypoxia (17).

3. Role of miRNA-214-3p in different types of cancers

In humans, miRNA-214 is mapped to chromosome 1q24.3, where the amplification of 1q24.3 has been associated with the histological typing of liposarcoma (18). miRNA-214 cyclic precursor is sheared by the Dicer enzyme to form miRNA-214-3p and miRNA-214-5p (19). miRNA-214-3p has been shown to be involved in lung cancer (11,20), nasopharyngeal carcinoma (21), esophageal cancer (22,23), gallbladder cancer (24), colorectal cancer (25,26), cervical cancer (9,27), endometrial cancer (28), prostate cancer (29,30), leukaemia (31), medullary thyroid cancer (17),

retinoblastoma (32) and Ewing sarcoma of bone (33), where they appear to mainly serve the role of tumor suppressor. In liver cancer (34-36), gastric cancer (37,38), pancreatic cancer (39-41), breast cancer (42,43), ovarian cancer (44,45), renal cell carcinoma (46,47), glioma (48,49) and osteosarcoma (50,51), miRNA-214-3p was found to mediate a dual role of both oncogene and tumor suppressor. By contrast, in bladder cancer (52) miRNA-214-3p was found to function as an oncogene. miRNA-214-3p can regulate various cellular processes, such as tumor cell proliferation and metastasis, by targeting downstream target genes (Fig. 1). However, miRNA-214-3p itself can also be regulated by various lncRNAs and circRNAs (Fig. 2). Table I summarizes the role of miRNA-214-3p in different types of cancers.

Lung cancer. Lung cancer accounts for ~12.4% of all cancers and can be divided into small-cell lung cancer and non-small cell lung cancer (NSCLC), with NSCLC accounting for 80-85% of all cases (1). miRNA-214-3p is typically downregulated in NSCLC, inhibition of which can promote cell proliferation and inhibit apoptosis in NSCLC (11). Fibroblast growth factor receptor 1 (FGFR1) is a member of FGFR that promotes cancer metastasis and drug resistance through epithelial-mesenchymal transition (EMT) (53). miRNA-214-3p can directly target the 3'-UTR of FGFR1 to inhibit EMT and the Wnt/MAPK/AKT pathways in NSCLC cells, which in turn inhibits cell proliferation, migration and invasion (20). These studies highlight the role of miRNA-214-3p in inhibiting the progression of lung cancer.

Nasopharyngeal cancer (NPC). Nasopharyngeal cancer (NPC) is a malignant epithelial tumor that has a subtle onset and is prone to metastasis (54). Although radiotherapy combined with chemotherapy for NPC can produce a 5-year survival rate of 85-90%, but recurrence and metastasis can still occur in 8-10% patients (55). Therefore, it is important to assess its pathogenesis and novel therapeutic targets for NPC. Bisphenol A was previously found to induce NPC cell proliferation by inhibiting the expression of miRNA-214-3p, leading to the upregulation of β -catenin expression (21). These findings indicate that miRNA-214-3p can function as a tumor suppressor in NPC.

Esophageal cancer. Esophageal cancer is a common tumor occurring in the digestive system (1). CircRNA fibronectin type III domain-containing 3B (circFNDC3B) can sponge miRNA-214-3p to upregulate the expression of cell division cycle 25 homologue A (CDC25A), which promotes esophageal cancer cell proliferation, migration and invasion (22). Therefore, restoring the expression of miRNA-214-3p or targeting the circFNDC3B/miRNA-214-3p/CDC25A axis may be a promising therapeutic approach for esophageal cancer (22). Additionally, miRNA-214-3p expression was observed to be significantly lower in esophageal cancer cells and tissues compared with that in non-malignant oesophageal tissues (23). In addition, overexpression of miRNA-214-3p was able to inhibit the ability of esophageal cancer cells to proliferate, migrate and invade, thereby exerting an oncogenic effect by targeting Ras-related protein 14 (23). These

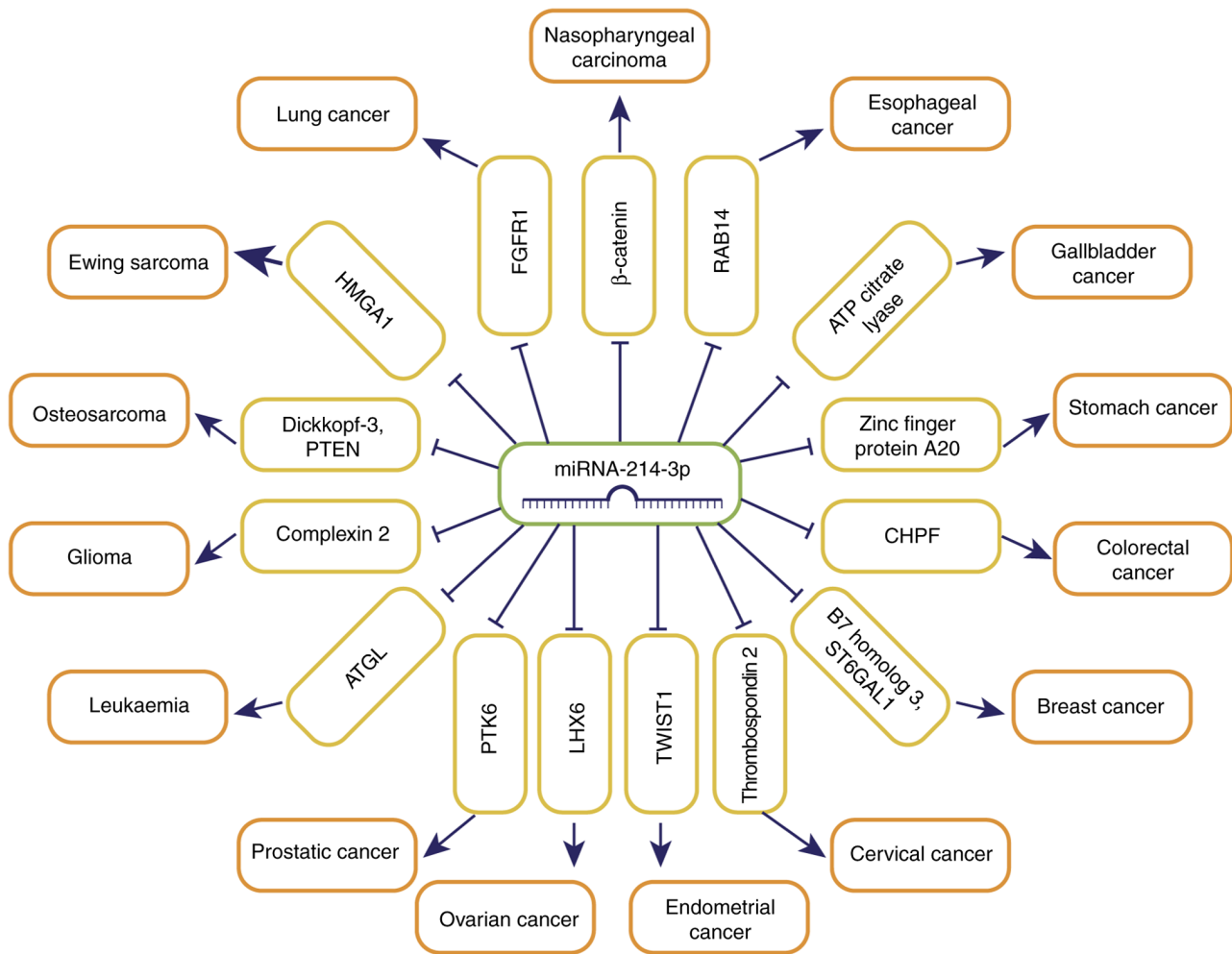


Figure 1. miRNA-214-3p regulates tumor progression by targeting downstream target genes. miRNA, microRNA; FGFR1, fibroblast growth factor receptor 1; RAB14, Ras-related protein 14; CHPF, Chondroitin polymerizing factor; ST6GAL1, β -galactoside α -2,6-sialyltransferase 1; LHX6, LIM homeobox domain 6; PTK6, Protein Tyrosine Kinase 6; ATGL, Adipose triglyceride lipase; HMG1A, high mobility group AT-hook 1.

findings suggest the tumor-suppressive role of miRNA-214-3p in esophageal cancer, where that restoring its expression may be a viable therapeutic approach.

Liver cancer. Hepatocellular carcinoma (HCC) is the most common primary liver cancer (56). Its incidence is the highest in Asia, where it accounts for ~72% of all global cases (56). Ji *et al* (57) shown that the expression of miRNA-214-3p is reduced in HCC cells and tissues compared with that in normal tissues, cells and non-hepatitis B virus-infected cells. miRNA-214-3p is a downstream target of the lncRNA polymerase (RNA) II subunit J4, pseudogene β -secretase (BACE1) antisense RNA (BACE1-AS) and plasmacytoma variant translocation 1, which serve as oncogenes by promoting the progression of HCC. The overexpression of miRNA-214-3p can counteract the oncogenic effects of these three aforementioned lncRNAs. This suggests the tumor suppressor role of miRNA-214-3p in HCC (34,35,37). However, hsa_circRNA_102049 can bind to miRNA-214-3p to upregulate reelin expression, which promoted the sensitivity of HCC cells to sorafenib (36). Therefore, miRNA-214-3p may yet serve as an oncogene and a tumor suppressor in HCC. This dual-identity appear likely to be associate with whether its upstream

regulators and downstream target genes are oncogenes or tumor suppressors.

Gallbladder cancer. Gallbladder cancer is a highly aggressive malignancy that is prone to liver metastasis and lymphatic metastasis (58). Liu *et al* (24) previously reported that human umbilical cord mesenchymal stem cells-derived exosomal miRNA-214-3p can targets ATP citrate lyase whilst down-regulating the expression of glucose transporters 1, which then inhibits the proliferation and migration of gallbladder cancer cells (24). These findings indicate that stem cell exosomes may be a treatment option for gallbladder cancer.

Gastric cancer. Gastric cancer is a malignant tumor that is subtle and prone to metastasis (2). In gastric cancer vascular endothelial cells, exosomal miRNA-214-3p can reverse the anti-angiogenic effect of apatinib by inhibiting the ferroptosis pathway toward (through zinc finger protein A20) (37). However, Jiang *et al* (38) found opposite trends in the same cancer. Specifically, the lncRNA hepatocellular carcinoma up-regulated EZH2 (HEIH) can bind to miRNA-214-3p, where the overexpression of miRNA-214-3p can reverse the effects of lncRNA HEIH in promoting the proliferation,

Table I. Summary of the role of miRNA-214-3p in different types of cancers.

Type	Upstream regulator	Target	Biological function	Role	(Refs.)
Lung cancer	circRNA NFIX	TRIAP1	Inhibits tumor cell proliferation and promotes apoptosis	Tumor suppressor	(11)
	-	FGFR1	Inhibits tumor cell proliferation, migration and invasion	Tumor suppressor	(20)
Nasopharyngeal Carcinoma	-	β -catenin	Inhibits tumor cell proliferation	Tumor suppressor	(21)
Esophageal cancer	circRNA FNDC3B	CDC25A	Inhibits tumor cell proliferation, migration and invasion	Tumor suppressor	(22)
	-	RAB14	Inhibits tumor cell growth, migration and invasion	Tumor suppressor	(23)
Liver cancer	LncRNA BACE1-AS	Apelin	Inhibits tumor cell proliferation, migration, invasion and promotes apoptosis	Tumor suppressor	(34)
	LncRNA PVT1	GPX4	Inhibits tumor cell viability and promotes iron death	Tumor suppressor	(35)
	Hsa_circRNA_102049	-	Inhibits cellular sensitivity to sorafenib	Oncogene	(36)
Gallbladder cancer	-	ATP citrate lyase	Inhibits tumor cell proliferation and migration	Tumor suppressor	(24)
Gastric cancer	-	Zinc finger protein A20	Attenuating the anti-angiogenic effect of apatinib on tumor cells	Oncogene	(37)
	LncRNA HEIH	-	Inhibits tumor cell proliferation, migration and invasion	Tumor suppressor	(38)
Pancreatic cancer	Hsa_circ_0014784	YAP1	Inhibits tumor cell proliferation, migration, EMT and tumor angiogenesis	Tumor suppressor	(39)
	LncRNA HLA complex P5	HDGF	Inhibits tumor cell proliferation, migration and invasion	Tumor suppressor	(40)
	-	-	Promoting stellate cell proliferation in pancreatic cancer	Oncogene	(41)
Colorectal cancer	LncRNA BACE1-AS	Tuftelin 1	Inhibits tumor cell invasion, migration and liver metastasis	Tumor suppressor	(25)
	-	CHPF	Inhibits glycolysis and promotes cellular iron death in tumor cells	Tumor suppressor	(26)
Breast cancer	-	B7 homolog 3	Enhancing the tumor immune microenvironment and inhibiting tumor cell proliferation	Tumor suppressor	(42)
	-	ST6GAL1	Promote tumor cell viability, migration and invasion	Oncogene	(43)
Cervical cancer	-	Thrombospondin 2	Inhibits tumor cell viability, invasion and metastasis	Tumor suppressor	(9)
	LncRNA HOTAIR	β -catenin	Inhibits tumor cell proliferation and promotes apoptosis	Tumor suppressor	(27)
Endometrial carcinoma		TWIST1	Inhibits tumor cell migration, invasion and EMT	Tumor suppressor	(28)
Ovarian cancer	LncRNA SNHG17	CDK6	Inhibits tumor cell growth	Tumor suppressor	(44)
	-	LHX6	Promote tumor cell proliferation and inhibit apoptosis	Oncogene	(45)
Renal cell cancer	Hsa_circ_0065217	ALPK2	Inhibits tumor cell proliferation and invasion	Tumor suppressor	(46)
	LncRNA ASB16-AS1	LARP1	Promotes tumor cell proliferation, migration and invasion	Oncogene	(47)

Table I. Continued.

Type	Upstream regulator	Target	Biological function	Role	(Refs.)
Bladder cancer	CircRNA LRIG1	-	Promotes tumor cell growth, migration, invasion and inhibits apoptosis	Oncogene	(52)
Prostate cancer	circRNA DHPS	CCL5	Inhibiting osteoblastic metastasis of tumor cells	Tumor suppressor	(29)
	-	PTK6	Inhibits tumor cell growth and EMT	Tumor suppressor	(30)
Leukaemia	-	ATGL	Inhibits tumor cell growth	Tumor suppressor	(31)
	LncRNA HOXA11-AS	EZH2	Inhibits tumor cell growth and metastasis	Tumor suppressor	(48)
Glioma	-	Complexin 2 Dickkopf-3	Inhibits tumor cell sensitivity to temozolomide Promotes tumor cell viability, migration, invasion and inhibits apoptosis	Oncogene Oncogene	(49) (50)
Osteosarcoma	LncRNA LINC01535	KCNC4	Inhibits tumor cell proliferation, migration, invasion and promotes apoptosis	Tumor suppressor	(51)
Medullary thyroid cancer	LncRNA ZFAS1	UCHL1	Inhibits tumor cell proliferation and invasion	Tumor suppressor	(17)
Retinoblastoma	Hsa_circ_0007534	-	Inhibits tumor cell viability, proliferation, colony formation and promotes apoptosis	Tumor suppressor	(32)
Ewing sarcoma	-	HMGA1	Inhibits tumor cell growth and migration	Tumor suppressor	(33)

miRNA, microRNA; circRNA, circular RNA; lncRNA, long non-coding RNA; circRNA NFIX, circRNA nuclear factor IX; EMT, epithelial-mesenchymal transition; FGFR1, fibroblast growth factor receptor 1; TRIAP1, TP53 regulation of apoptosis inhibitor 1; circFNDC3B, Circ RNA Fibronectin Type III Domain Containing 3B; CDC25A, cell division cycle 25 homologue A; lncRNA POLR2J4, lncRNA RNA polymerase II subunit J4 (pseudogene); RAB14, Ras-related protein 14; lncRNA BACE1-AS, lncRNA β -secretase 1 antisense RNA; ST6GAL1, β -galactoside α -2,6-sialyltransferase 1; lncRNA PVT1, lncRNA plasmacytoma variant translocation 1; GPX4, glutathione peroxidase 4; lncRNA HEIH, hepatocellular carcinoma upregulated EZH2-associated lncRNA; YAP1, yes-associated protein 1; HDGF, hepatoma-derived growth factor; circ COL1A1, circ collagen, type I, α 1; GLS1, glutaminase 1; lncRNA HOTAIR, lncRNA HOX transcript antisense intergenic RNA; lncRNA SNHG17, Small nucleolar RNA host gene 17; CDK6, cyclin-dependent kinase 6; ALPK2, α -Protein Kinase 2; lncRNA ASB16-AS1, lncRNA ankyrin repeat And SOCS Box-Containing 16 antisense RNA1; LARP1, La-related protein 1; circLRIG1, circ Leucine-rich repeats and immunoglobulin-like domains 1; lncRNA SNHG3, lncRNA small nucleolar RNA host gene 3; TGFB1, transforming growth factor β receptor 1; circ-DHPS, circular RNA-deoxyhypusine synthase; CCL5, C-C motif chemokine ligand 5; lncRNA VPS9D1-AS1, lncRNA VPS9D1 antisense RNA 1; GPX1, glutathione peroxidase 1; lncRNA HOXA11-AS, lncRNA HOXA11 antisense RNA; EZH2, enhancer of zeste homolog 2; KCNC4, Potassium Voltage-Gated Channel Subfamily C Member 4; lncRNA ZFAS1, lncRNA zinc finger antisense 1; UCHL1, Ubiquitin carboxyterminal hydrolase L1; CHPF, Chondroitin polymerizing factor; LHX6, LIM homeobox domain 6; PTK6, Protein Tyrosine Kinase 6; ATGL, Adipose triglyceride lipase; HMGA1, high mobility group AT-hook 1.

migration and invasion of gastric cancer cells, highlighting the possible anticancer effects of miRNA-214-3p (38). These studies suggest that miRNA-214-3p can serve as both an oncogene and a tumor suppressor in gastric cancer, which may be associated with the cancer secretion of exosomes for carcinogenesis.

Pancreatic cancer. Pancreatic cancer is one of the leading causes of cancer-related mortality (59). Yes-associated protein 1 (YAP1) is a downstream target of the hsa_circ_0014784/miRNA-214-3p axis, where silencing the miRNA-214-3p was found to promote YAP1 expression, which in turn promoted pancreatic cancer cell proliferation, migration, EMT and tumor angiogenesis (39). Anti-tumor cell angiogenesis is also important to improve therapy in

pancreatic cancer. Inhibiting the expression of vascular endothelial growth factor receptor (VEGFR)-2 can inhibit pancreatic cancer invasion (60). In addition, the lncRNA human leukocyte antigen complex P5 can competitively bind to miRNA-214-3p to upregulate the expression of hepatoma-derived growth factor, which can promote pancreatic cancer proliferation, migration and invasion (40). Both of the aforementioned studies therefore support the anticancer role of miRNA-214-3p in pancreatic cancer.

However, another previous study (41) revealed that miRNA-214-3p can promote the proliferation of pancreatic cancer stellate cells and that the activation of stellate cells can result in the release of various cytokines (such as hepatocyte growth factor, basic fibroblast growth factor and IL-8) to promote the progression of pancreatic cancer (41,61,62).

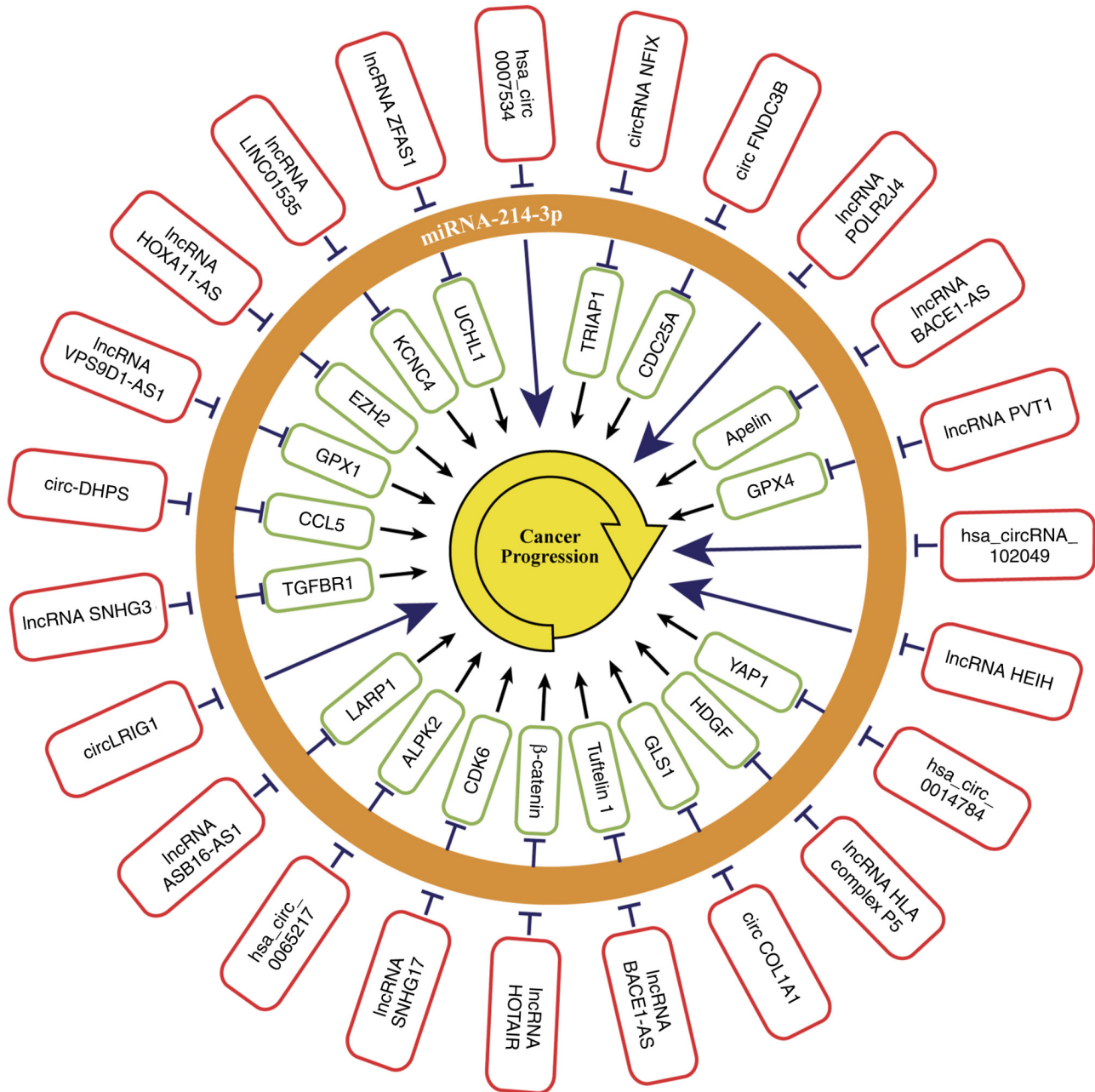


Figure 2. miRNA-214-3p is regulated by a variety of lncRNA and circRNA that affect miRNA-214-3p or downstream target gene expression, which in turn regulates cancer progression. miRNA, microRNA; circRNA, circular RNA; lncRNA, long non-coding RNA; circRNA NFIX, circRNA nuclear factor IX; TRIAP1, TP53 regulation of apoptosis inhibitor 1; circFNDC3B, Circ RNA Fibronectin Type III Domain Containing 3B; CDC25A, cell division cycle 25 homologue A; lncRNA POLR2J4, lncRNA RNA polymerase II subunit J4 (pseudogene); lncRNA *BACE1-AS*, lncRNA β -secretase 1 antisense RNA; lncRNA PVT1, lncRNA plasmacytoma variant translocation 1; GPX4, glutathione peroxidase 4; lncRNA HEIH, hepatocellular carcinoma upregulated EZH2-associated lncRNA; YAP1, yes-associated protein 1; HDGF, hepatoma-derived growth factor; circ COL1A1, circ collagen, type I, α 1; GLS1, glutaminase 1; lncRNA HOTAIR, lncRNA HOX transcript antisense intergenic RNA; lncRNA SNHG17, Small nucleolar RNA host gene 17; CDK6, cyclin-dependent kinase 6; ALPK2, α -Protein Kinase 2; lncRNA ASB16-AS1, lncRNA ankyrin repeat And SOCS Box-Containing 16 antisense RNA1; LARP1, La-related protein 1; circLRIG1, circ Leucine-rich repeats and immunoglobulin-like domains 1; lncRNA SNHG3, lncRNA small nucleolar RNA host gene 3; TGFBR1, transforming growth factor β receptor 1; circ-DHPS, circular RNA-deoxyhypusine synthase; CCL5, C-C motif chemokine ligand 5; lncRNA VPS9D1-AS1, lncRNA VPS9D1 antisense RNA 1; GPX1, glutathione peroxidase 1; lncRNA HOXA11-AS, lncRNA HOXA11 antisense RNA; EZH2, enhancer of zeste homologue 2; KCNC4, Potassium Voltage-Gated Channel Subfamily C Member 4; lncRNA ZFAS1, lncRNA zinc finger antisense 1; UCHL1, Ubiquitin carboxyterminal hydrolase L1.

Therefore, miRNA-214-3p may yet have dual roles as both an oncogene and a tumor suppressor in pancreatic cancer.

Colorectal cancer. The major cause of death from colorectal cancer is metastasis (63). The lncRNA *BACE1* antisense RNA (*BACE1-AS*)/miRNA-214-3p/Tuftelin 1 axis and the

circ collagen type I α 1/miRNA-214-3p/glutaminase 1 axis are potential treatment targets for colorectal cancer, whereby silencing miRNA-214-3p expression was observed to promote colorectal cancer progression (25,64). Chondroitin polymerizing factor (CHPF) is a type II transmembrane protein that can promote the progression of colorectal cancer (65).

miRNA-214-3p can directly bind to the 3'-UTR of CHPF to inhibit its expression, which in turn increases ferrous iron and reactive oxygen species levels to inhibit cellular glycolysis. This resulted in ferroptosis in colorectal cancer cells (26). These findings suggest the existence of a therapeutic miRNA-214-3p/CHPF pathway. Therefore, miRNA-214-3p likely functions as a tumor suppressor in colorectal cancer.

Breast cancer. Breast cancer is a common malignancy in women. From 1990 to 2019, the global incidence of breast cancer in young women increased from 89,174 to 168,776 cases (66). miRNA-214-3p was previously found to promote the killing of breast cancer cells by CD8+ T cells and natural killer cells by targeting B7 homolog 3 (42). These findings indicate that miRNA-214-3p can inhibit the progression of breast cancer cells by favoring a more hostile tumor microenvironment. In another study, berberine was reported to inhibit the proliferation, migration and invasion of triple-negative breast cancer cells (67). The mechanism involved the upregulation of miRNA-214-3p expression by berberine, which suppressed secretin expression (67). These studies support the cancer suppressive role of miRNA-214-3p.

However, Tao *et al* (43) reported that miRNA-214-3p expression is elevated in both triple-negative breast cancer cells and tissues compared with that in their normal adjacent tissues. miRNA-214-3p, which targets ST6 β -galactoside α -2,6-sialyltransferase 1, can increase breast cancer cell viability, migration and invasion (43). The dual role of miRNA-214-3p in breast cancer may be associated with the complex network of molecular interactions and different functions of downstream target genes in cancer cells.

Cervical cancer. In total, 760,000 new cases of cervical cancer and 411,000 mortality cases are predicted to occur globally in 2030 (68). miRNA-214-3p was found to be expressed at low levels in patients with cervical cancer, where this low expression of miRNA-214-3p was suggested to promote its progression (9). Mechanistically, miRNA-214-3p can directly target thrombospondin 2 to inhibit cervical cancer cell viability, invasion and metastasis (9). In addition, the lncRNA HOX transcript antisense intergenic RNA can sponge miRNA-214-3p to upregulate β -catenin expression, which promoted cervical cancer cell proliferation and inhibited apoptosis (27). This suggests that miRNA-214-3p serve the role of a tumor suppressor in cervical cancer.

Endometrial cancer. Endometrial cancer is a malignancy of the female reproductive system (69). TWIST1 is an EMT-associated transcription factor that can promote metastasis and maintains the stemness of cancer stem cells (70). Fang *et al* (28) found that compared with that in normal tissues and human endometrial epithelial cells, miRNA-214-3p expression in endometrial cancer cells and tissue is downregulated and that the overexpression of miRNA-214-3p can target TWIST1 to inhibit endometrial cancer cell migration, invasion and EMT (28). In addition, miRNA-214-3p is inhibited by the lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1), leading to the upregulation of high mobility group A1, c-Myc and MMP-9 expression. This in turn promoted the proliferation, invasion and metastasis of endometrial cancer cells (71).

These studies indicate that miRNA-214-3p likely functions as a tumor suppressor in endometrial cancer.

Ovarian Cancer. Ovarian cancer is a malignant tumor of the female reproductive system, where its 5-year survival rate is <50%. Therefore, it can gravely threaten the lives and health of women (72). Liu *et al* (73) revealed that the lncRNA NEAT1 can bind to miRNA-214-3p to promote angiogenesis and metastasis in ovarian cancer cells (73). Furthermore, miRNA-214-3p can be suppressed by the lncRNA small nucleolar RNA host gene 17 (SNHG17). Specifically, since cyclin-dependent kinase 6 (CDK6) is a downstream target of miRNA-214-3p, CDK6 was found to mediate the pro-carcinogenic role of lncRNA SNHG17 in ovarian cancer (44). These studies suggest the tumor suppressor role of miRNA-214-3p.

However, Yang *et al* (45) previously reported a positive association between serum exosomal miRNA-214-3p levels and pathological malignancy degree of ovarian cancer. In patients with ovarian cancer, miRNA-214-3p expression was increased ~7.9-fold in borderline tissues, 21.8-fold in low-grade serous ovarian cancer tissues and 31.8-fold in platinum-sensitive high-grade serous ovarian cancer tissues compared with that in benign tissues (45). The lncRNA X-inactive specific transcript (XIST) can also serve a tumor suppressor role in ovarian cancer by inhibiting the expression of miRNA-214-3p, such that the overexpression of miRNA-214-3p can reverse the anticancer effect of lncRNA XIST (74). Overall, miRNA-214-3p may yet serve a dual-role as an oncogene and a tumor suppressor in ovarian cancer.

Renal cell carcinoma (RCC). RCC accounts for ~2% of all cancer diagnoses worldwide (75). The most common histopathological type of RCC is clear renal cell carcinoma (75). Previous studies have shown that hsa_circ_0065217 can inhibit miRNA-214-3p to upregulate α -protein kinase 2 expression, which then promotes the proliferation and invasion of RCC (46). However, lncRNA ankyrin repeat and SOCS box-containing 16-AS1 can inhibit the proliferation, migration and invasion of clear renal cell carcinoma cells by sponging miRNA-214-3p to upregulate the expression of LA-related protein 1 (47). The dual role of miRNA-214-3p in RCC may be associated with its different upstream regulators and different downstream targets.

Bladder cancer. Bladder cancer is a common urological malignancy, ranking fourth in cancer incidence among men in the United States in 2024 (69). The expression of miRNA-214-3p was found to be significantly upregulated in bladder cancer tissues (52). Circ leucine-rich repeats and Ig-like domains protein 1 can target miRNA-214-3p to increase E-cadherin expression, which downregulates the protein expression levels of N-cadherin and Vimentin. This in turn inhibited the proliferation, migration and invasion of bladder cancer cells and promoted their apoptosis (52). These findings indicate that miRNA-214-3p serves an oncogenic role in bladder cancer.

Prostate cancer. Androgen deprivation therapy is the main treatment for patients with advanced prostate cancer (76). Knocking down androgen receptor expression was revealed

Table II. miRNA-214-3p as biomarkers.

Type	Expression	Indication	(Refs.)
Lung cancer	Down	Low expression is associated with poor prognosis	(10)
Prostate cancer	Down	Low expression is associated with poor prognosis	(30)
Ovarian cancer	Up	Positive association between serum exosomal miRNA-214-3p levels and pathological malignancy degree of ovarian cancer	(45)
Osteosarcoma	Up	High expression is associated with poor prognosis	(50)
Breast cancer	Up	High expression positively associates with chemotherapy resistance	(85)

to upregulate the expression of circular RNA-deoxyhypusine synthase (circ-DHPS) in prostate cancer cells (29). Circ-DHPS can bind to miRNA-214-3p to upregulate the expression of C-C motif chemokine ligand 5, thereby promoting the metastasis of prostate cancer cells to osteoblasts (29). In addition, the lncRNA small nucleolar RNA host gene 3 (SNHG3) can competitively bind to miRNA-214-3p, which upregulates the expression of TGF- β receptor 1 and activates its signaling pathway, in turn promoting the bone metastasis of prostate cancer cells (77). These studies emphasize the anticancer role of miRNA-214-3p in prostate cancer.

Leukemia. Leukemia is a hematological malignancy that includes acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (78). miRNA-214-3p is typically expressed at low levels in T-cell ALL (T-ALL), which may be associated with the development of T-ALL (79). The lncRNA VPS9D1 antisense RNA 1 (VPS9D1-AS1) can bind to miRNA-214-3p to upregulate glutathione peroxidase 1 expression, which in turn promotes the proliferation of ALL cells whilst inhibiting apoptosis (80). Additionally, miRNA-214-3p can inhibit adipose triglyceride lipase expression, downregulate peroxisome proliferator-activated receptor α expression and inhibit the production of diacylglycerol and free fatty acids, thereby inhibiting the proliferation of AML cells (31). These studies suggest that miRNA-214-3p primarily functions as a tumor suppressor in leukemia.

Glioma. Glioma is a common malignancy of the central nervous system (81). The lncRNA homeobox A11 (HOXA11)-AS has been reported to be highly expressed in glioblastoma, which is associated with poor prognosis (48). The lncRNA HOXA11-AS can bind to miRNA-214-3p to upregulate the expression of enhancer of zeste homolog 2, which in turn promotes the proliferation and metastasis of glioma cells (48). However, the expression of miRNA-214-3p is elevated in temozolomide-resistant glioma compared with that in temozolomide-sensitive tissues (49). In particular, inhibiting the expression of miRNA-214-3p was found to promote the sensitivity of glioma cells to temozolomide, which inhibited cell proliferation and promoted apoptosis. The underlying mechanism was associated with miRNA-214-3p targeting Complexin 2 (49). Therefore, the miRNA-214-3p duality in glioma is likely to be dependent on its upstream regulators and corresponding downstream targets.

Osteosarcoma. Osteosarcoma is high-grade malignant bone tumor that commonly develops in adolescents and has a poor prognosis, with rapid proliferation, high mortality and high chances of disability (82). miRNA-214-3p was observed to be highly expressed in osteosarcoma tissues and cells (50). It can promote the viability, migration and invasion of osteosarcoma cells whilst inhibiting apoptosis by binding to the 3'-UTR of Dickkopf-3 and activating the Wnt/ β -catenin/lymphoid enhancer-binding factor 1 signaling pathway (50). Li *et al* (83) previously found that miRNA-214-3p can also target PTEN, enhancing osteosarcoma cell viability and inhibiting apoptosis. By contrast, the long intergenic non-coding RNA 01535 can inhibit the expression of miRNA-214-3p to upregulate potassium voltage-gated channel subfamily C member 4 expression, which promoted cell proliferation, migration and invasion, whilst inhibiting apoptosis (51). These studies suggest that miRNA-214-3p also has a dual role as both an oncogene and a tumor suppressor in osteosarcoma.

Other cancers. lncRNA zinc finger antisense 1 has been demonstrated to serve as an miRNA-214-3p sponge to upregulate ubiquitin carboxyterminal hydrolase L1 expression, which promoted the proliferation and invasion of medullary thyroid cancer cells (17). In retinoblastoma, elevated levels of miRNA-214-3p may serve a tumor-suppressing effect (32). In another study, osthole (Chinese Herbal Extract of *Cnidium Officinale*) was found to inhibit the PI3K/AKT/mTOR pathway by decreasing hsa_circ_0007534 expression and increasing the level of miRNA-214-3p expression, which suppressed the viability, proliferation and colony formation ability of retinoblastoma cells and promoted their apoptosis (32). Additionally, miRNA-214-3p can repress high mobility group AT-hook 1 expression and inhibit the proliferation and migration of bone Ewing sarcoma cells (33).

4. miRNA-214-3p as a biomarker

With technological advancements, the detection and quantification of miRNA have become more efficient (84), such that a multitude of studies have identified miRNA-214-3p as having the potential to serve as a biomarker for cancer diagnosis, prognosis and therapeutic response (Table II) (10,45,85).

Diagnostic biomarkers. Yang *et al* (45) revealed that miRNA-214-3p is highly expressed in exosomes of ovarian cancer tissues. However, miRNA-214-3p expression was increased 7.9-fold in borderline tissues, 21.8-fold in low-grade

Table III. Effect of miRNA-214-3p on cancer chemotherapy.

Chemotherapeutic drugs	Cancer	Role	Target	(Refs.)
Cisplatin	Pediatric central nervous system germ cell tumors	Induced cisplatin resistance	Bcl2-like 11	(14)
	Ovarian cancer	Reduced cisplatin sensitivity	-	(74)
	Oral squamous cell carcinoma	Inhibits cisplatin resistance	PIM1	(93)
	Esophageal cancer	Enhanced cisplatin sensitivity	Survivin and CUG-BP1	(94)
Vincristine and carboplatin	Retinoblastoma	Promotes vincristine and carboplatin sensitivity	ABCB1 and XIAP	(96)
Temozolomide	Glioblastoma	Inhibits temozolomide resistance	MGMT	(95)
Temozolomide	Glioma	Promotes temozolomide resistance	CPLX2	(49)
Gemcitabine	Pancreatic cancer	Inhibits gemcitabine resistance	HDGF	(40)

PIM1, proto-oncogene serine/threonine-protein kinase; MGMT, O⁶-methylguanine-DNA methyltransferase; CPLX2, Complexin 2; ABCB1, ATP Binding Cassette Subfamily B Member 1; XIAP, X-linked inhibitor of apoptosis; HDGF, hepatoma-derived growth factor; CUG-BP1, CUG-binding protein 1.

serous ovarian cancer tissues and 31.8-fold in platinum-sensitive high-grade serous ovarian cancer tissues compared with that in benign tissues (45). Receiver operating characteristic curve results in another previous study suggested that four miRNAs (including miRNA-214-3p) can be used to distinguish between patients with HCC and non-HCC patients. In addition, miRNA-214-3p alone could distinguish between patients with HCC and patients with chronic hepatitis B or normal healthy individuals, but could not accurately distinguish between patients with HCC and those with cirrhosis, which may be due to the smaller sample size of patients with cirrhosis in that particular study (86). These findings suggest that miRNA-214-3p can be used as a diagnostic biomarker for ovarian and liver cancers.

Prognostic biomarkers. Low expression of miRNA-214-3p has been shown to be associated with poor prognosis in patients with colorectal cancer (87), liver cancer (88), prostate cancer (30) and lung cancer (10). By contrast, in NPC, high expression of miRNA-214-3p is associated with tumor recurrence and metastasis (89). Unfortunately, this study (89) did not go further to overexpress or knockdown the expression of miRNA-214-3p in NPC cells. Therefore, the effect of miRNA-214-3p expression on various processes, such as proliferation, migration and apoptosis in NPC cells, was not investigated (89). In another previous study, a Cox regression model consisting of miRNA-199a-3p, miRNA-214-3p and three clinicopathological factors was used to predict overall survival in patients undergoing radical cystectomy, where the hazard ratio (95% CI) for miRNA-214-3p is 3.30 (1.11-9.77), P=0.031 (90). Therefore, clinicians can predict the prognosis of patients with colorectal cancer, liver cancer, prostate cancer, lung cancer, NPC and bladder cancer based on the level of expression of miRNA-214-3p, which may be beneficial for the timely intervention in these patients.

Treatment response biomarkers. The therapeutic response can affect the prognosis and survival of patients with cancer.

Therefore, it is necessary to identify cancer therapeutic response biomarkers. Xing *et al* (85) previously found that high expression of miRNA-214-3p was associated with chemotherapy resistance in breast cancer, where a logistic regression signature consisting of five miRNAs, including miRNA-214-3p, was more stable compared with each single miRNA at accurately predicting chemotherapy resistance in breast cancer (AUC=0.839; 95% CI, 0.730-0.949) (85). miRNA-214-3p may therefore have clinical potential as a treatment response biomarker for improving the individualized cancer treatment protocols.

5. miRNA-214-3p in chemotherapy, targeted therapy and radiotherapy

Chemotherapy, and radiotherapy are important tools in cancer treatment. Drug resistance poses a major obstacle and is primary cause of cancer recurrence and poor prognosis (91). Several studies have previously suggested that miRNAs can serve a key role in regulating drug resistance to cancer chemotherapy and radiotherapy (92-96), to which miRNA-214-3p is no exception (Table III).

Platinum-based chemotherapeutics. Common platinum-based chemotherapeutic agents include cisplatin, carboplatin and oxaliplatin. Wang *et al* (93) previously reported that miRNA-214-3p can inhibit cisplatin resistance in oral squamous cell carcinoma cells by targeting PIM1, a key promoter of hypoxia-induced chemotherapy resistance (97). In pediatric central nervous system germ cell tumor cells, high expression of miRNA-214-3p was found to promote cisplatin resistance through a mechanism associated with targeting BCL2-like 11, a pro-apoptotic protein, leading to the suppression of apoptosis (14). In esophageal cancer, miRNA-214-3p can bind to the 3'-UTR of survivin and embryo deadenylation element-binding protein, an antiapoptotic protein, to upregulate the expression of caspase-3 and promote sensitivity to cisplatin (94). In

addition, miRNA-214-3p was observed to target ATP-binding cassette subfamily B member 1 and X-linked inhibitor of apoptosis protein (an antiapoptotic protein), promoting the sensitivity of retinoblastoma to vincristine and carboplatin (96). These studies collectively suggest that the anticancer efficacy of platinum-based chemotherapeutic agents can be promoted by either increasing or decreasing the expression of miRNA-214-3p. The mechanism by which miRNA-214-3p regulates platinum-based chemotherapeutic agent sensitivity may be associated with regulation of the tumor microenvironment and the targeting of apoptotic proteins, since tumor microenvironment and inactivation of the apoptotic pathways tended to cause chemotherapy resistance in tumors (98).

Other chemotherapeutic agents. Liu *et al* (40) previously revealed that miRNA-214-3p can target hepatoma-derived growth factor and promote the sensitivity of pancreatic cancer cells to gemcitabine (40). In glioma, miRNA-214-3p was found to promote resistance to temozolomide by targeting complexin 2 (49). Notably, in glioblastoma, miRNA-214-3p can target O6-methylguanine-DNA methyltransferase to reverse glioblastoma resistance to temozolomide (95).

Radiotherapy. Mesenchymal stem cell extracellular vesicular miRNA-214-3p can ameliorate thoracic vascular injury, inflammatory response and pulmonary fibrosis after radiotherapy, which in turn attenuates lung injury caused by radiotherapy (99). Therefore, administering radiotherapy for treating thoracic malignancies whilst increasing miRNA-214-3p expression was proposed to be a strategy to attenuate radiotherapy-induced lung injury (99).

Targeted therapy. Through the in-depth study of the molecular mechanisms of tumor progression, targeted therapy has advanced considerably and is becoming one of the primary modes of cancer treatment (100). However, acquired resistance poses a major dilemma for targeted therapeutics (101). A previous study revealed that miRNA-214-3p can target transducin (β)-like 1 X-linked receptor 1 to promote the sensitivity of prostate cancer cells to nituzumab (102). In addition, miRNA-214-3p can target zinc finger protein A20 and inhibit the anti-vascular effects of apatinib on gastric cancer vascular endothelial cells (37).

6. Strategies for delivering miRNA-214-3p

Although miRNA have potential for disease therapy, difficulties exist that limit the efficiency of their delivery. miRNAs are readily degraded by some nucleases (103-105). Furthermore, their negative charge, high molecular mass and hydrophilicity of nucleic acids renders it difficult to cross cell membranes (106). Therefore, delivering miRNAs to target cells efficiently and accurately remains a considerable challenge for miRNA anti-tumor therapy. Viral and non-viral nanocarrier systems have been developed for delivering miRNA-214-3p, with non-viral carrier systems including exosomes and nanocarrier systems.

Exosome carriers. Exosomes are nanoscale vesicles secreted by cells, with diameters of 30-100 nm. They can transfer

biologically active components, such as proteins, miRNAs and mRNA, to recipient cells (107). When exosomes interact with surrounding cells, cell surface receptors are activated, where vesicle contents can be translocated to the corresponding cells. The lipid bilayer membrane of exosomes also prevents cargoes, such as miRNAs, from being degraded, thereby exerting a regulatory effect on target cells (107). Liu *et al* (24) previously reported that exosomes released from human umbilical cord mesenchymal stem cells contained miRNA-214-3p. After adding exosomes to gallbladder cancer cells, miRNA-214-3p can inhibit cell proliferation by suppressing the expression of facilitative glucose transporter 1 and ATP-citrate lyase (24).

However, in cases of exosomes of tumor origin that can mediate miRNA expression, they may promote cancer progression (108). Wang *et al* (37) revealed that exosomes secreted by gastric cancer contain miRNA-214-3p, which can be taken up and enter vascular endothelial cells to increase their own miRNA-214-3p expression, in turn increasing glutathione expression and decreasing lipid reactive oxygen species production. This culminated in reversing the anti-angiogenic effects of apatinib (37).

It must be acknowledged that the functional role of exosome-associated miRNA-214-3p is likely to be context-dependent, potentially either promoting or inhibiting tumor progression depending on its origin and target.

Viral vectors. Viral vectors commonly used to deliver miRNA include lentiviruses, adenoviruses, adeno-associated viruses and retroviruses (109). Phatak *et al* (23) previously used lentiviral vectors to deliver miRNA-214-3p into esophageal cancer cells, which was followed by a significant increase in the expression of miRNA-214-3p, which then targeted RAB14 to inhibit the migration and invasion of esophageal cancer cells. Furthermore, colorectal cancer cells with low miRNA-214-3p expression were constructed using a lentiviral vector system to deliver an inhibitor of miRNA-214-3p (87). miRNA-214-3p inhibition promoted colorectal cancer cell proliferation and metastasis, whereas overexpression of miRNA-214-3p reversed this process (87). Although lentiviral vectors are effective methods for delivering miRNA, their immunogenicity and potential induction of mutations cannot be ignored. Viruses bind to cell surface receptors through their envelope proteins (110). Lentiviruses are capable of delivering vectors to both normal and tumor cells. Consequently, standard lentiviral vectors lack tumor specificity and may infect both healthy and malignant cells (110,111). However, when the selective targeting of tumor cells is desired, this can be achieved by modifying the viral receptor, either through pseudotyping or the incorporation of receptor-specific ligands. Miletic *et al* (112) designed lentiviral vectors pseudotyped with lymphocytic choriomeningitis virus glycoproteins that selectively targeted G62 human glioma cells (112). Therefore, viral delivery systems for delivering miRNA-214-3p into cancer cells for anticancer therapy remain desirable, but studies on this topic remain limited.

Nanoparticles (NPs) vectors. Liposomes, inorganic nanoparticles and polymer nanoparticles are commonly used carriers for delivering molecules (113). Delivering nanoparticles and cargoes specifically to tumor tissues remains a major challenge in the nanoparticle transport field. NPs can bind specifically

to receptors overexpressed on cancer cells by targeting ligands (surface functionalization of ligands, such as antibodies, peptides and small molecules), ensuring the selective accumulation of nanoparticles in the tumor microenvironment (114). Folate receptor is frequently overexpressed in cancer, rendering it a common target for liposomal nanoparticle delivery systems (115). Rong *et al* (116) previously developed lactobionic acid-modified liposomal nanoparticles that efficiently delivered sialic acid and miRNA-145 specifically to HCC cells expressing salivary acid glycoprotein receptors, which promote apoptosis with negligible side effects. Therefore, engineering the nanoparticle ligands to specifically target tumors would facilitate NP and the cargo accumulation at the tumor site.

A representative 3D DNA nanostructured material known as tetrahedral framework nucleic acid (tFNA) consists of four single-stranded DNAs of equal lengths, which has reported advantages of satisfactory biocompatibility, editability, high stability, low biotoxicity and ease of preparation (117). Survivin is an inhibitor of apoptosis that is highly expressed only in tumor cells and embryonic cells, whilst being largely undetectable in normal tissues. Therefore, it was proposed as an anticancer target (118). Li *et al* (119) previously modified miRNA-214-3p to one of the vertices of tFNA and synthesized tFNA-miRNA-214-3p, which was shown to target survivin in NSCLC cells and induce the mitochondrial apoptotic pathway, in turn promoting apoptosis (119). Although the delivery of miRNAs using nanoparticles is a promising strategy for treating cancer, its limitations cannot be ignored. It is difficult for liposomes to load high quantities of therapeutic drugs into a lipid matrix (120). Additionally, polymer nanoparticles encapsulated with molecular drugs are difficult to allow prolonged release, and the biodegradation of polymers can become cytotoxic (120). Similarly, the low solubility and toxicity of inorganic nanoparticles remain major challenges that need to be addressed (121).

7. Clinical significance and future challenges

Abnormal proliferation, metastasis and invasion of tumor cells are the three main features of cancer that can affect the prognosis and treatment options for patients. Therefore, the inhibition of tumor cell proliferation, metastasis and invasion is key to halting cancer progression. However, the role of miRNA-214-3p in cancer has been receiving attention. In lung cancer, miRNA-214-3p was found to target FGFR1 to inhibit cell proliferation, metastasis and invasion (20). Overexpression of miRNA-214-3p can suppress drug resistance in retinoblastoma, which in turn promoted apoptosis (96). Conversely, as an oncogene, high expression of miRNA-214-3p can promote the proliferation, migration and invasion of bladder cancer cells (52). In addition, miRNA-214-3p can affect the sensitivity of cancer cells to chemotherapy, radiotherapy and targeted therapy. Therefore, regulating the expression of miRNA-214-3p during cancer treatment can inhibit cancer progression. miRNA-214-3p can also be used as a biomarker for cancer diagnosis, prognosis and therapeutic response, which may prove beneficial for early the diagnosis and personalized treatment of cancer. The effective systemic delivery of miRNA-214-3p would then avoid enzymatic hydrolysis and enables its stable expression in tumor cells.

However, the role of miRNA-214-3p in cancer faces challenges. The complexity of upstream regulators and downstream targets of miRNA-214-3p allows it to serve a dual role as an oncogene and a tumor suppressor in cancers dependent on the type involved. The interactions among the multiple downstream target genes of miRNA-214-3p warrant further investigation. Viral vectors may also induce an immune response, leading to cytotoxic damage after entering host cells. Additionally, the extensive nature of miRNA regulation leads to unexpected regulatory effects that may cause off-target effects and trigger the development of other diseases (such as leukemia) (122). Therefore, the clinical application of miRNA therapy may have promise at this stage, but its efficacy and safety require further investigation.

8. Conclusions

In the present review, the role of miRNA-214-3p in a range of cancers was summarized. The expression of miRNA-214-3p can be affected by ceRNA, transcription factors, DNA methylation and hypoxic conditions. miRNA-214-3p can serve as a tumor suppressor in the majority of cancer types. In liver cancer, gastric cancer, pancreatic cancer, breast cancer, ovarian cancer, renal cell cancer, glioma and osteosarcoma, miRNA-214-3p can also function as both an oncogene and a tumor suppressor. However, in bladder cancer, miRNA-214-3p functions as an oncogene. Additionally, miRNA-214-3p can serve as a biomarker for the diagnosis, prognosis and therapeutic response of some types of cancer. The expression of miRNA-214-3p can also affect sensitivity of chemotherapy, radiotherapy and targeted therapy. Finally, the systemic delivery strategy of miRNA-214-3p holds promise for miRNA-based therapies for cancer. These findings provide novel ideas for cancer treatment and drug development.

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Authors' contributions

ZC wrote the manuscript and constructed figures and tables. YL and LL reviewed and edited the manuscript. SL and HQ analyzed the literature. XD and YQ conceptualized the review and oversaw the process. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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