Role of miR-181a-5p in cancer (Review)

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Received February 9, 2023; Accepted July 13, 2023

DOI: 10.3892/ijo.2023.5556

Abstract. MicroRNAs (miRNAs) are non-coding RNAs (ncRNAs) that can post-transcriptionally suppress targeted genes. Dysregulated miRNAs are associated with a variety of diseases. MiR-181a-5p is a conserved miRNA with the ability to regulate pathological processes, such as angiogenesis, inflammatory response and obesity. Numerous studies have demonstrated that miR-181a-5p exerts regulatory influence on cancer development and progression, acting as an oncomiR or tumor inhibitor in various cancer types by impacting multiple hallmarks of tumor. Generally, miR-181a-5p binds to target RNA sequences with partial complementarity, resulting in suppression of the targeted genes of miR-181a-5p. However, the precise role of miR-181a-5p in cancer remains incompletely understood. The present review aims to provide a comprehensive summary of recent research on miR-181a-5p, focusing on its involvement in different types of cancer and its potential as a diagnostic and prognostic biomarker, as well as its function in chemoresistance.

Contents

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Key words: miR-181a-5p, cancers, biomarker, chemoresistance

1. Introduction

MicroRNA (miRNAs/miRs) are small non-coding (nc) RNAs with the size of 17-25 nucleotides. The first miRNA was identified in 1993 when a small ncRNA was discovered in *Caenorhabditis* elegans heterochronic gene lin-4 (1). Subsequently, other small RNAs were found in *Caenorhabditis elegans*, *Drosophila* and humans (2-4). Later, researchers realized that small ncRNAs are functional products that have an impact on development outside of translating proteins (5-7). The discovery of miRNAs shed light on post-transcriptional regulation of gene expression. Briefly, miRNA genes are transcribed into primary miRNAs and processed into mature miRNA duplexes by pol-II, Drosha and Dicer. Then, the miRNA duplex is loaded into argonaute protein to form the RNA-induced silencing complex, which navigates the mature miRNA to the 3'UTR of their targeted mRNA through base pairing, resulting in mRNA transcriptional inhibition or mRNA degradation (8). In the past few years, studies on miRNAs have increased, and as of June 2023, 38,589 miRNAs have been annotated in the miRBase miRNA database (https://www.mirbase.org/). Abundant studies have substantiated the intricate association between dysregulated miRNAs and a multitude of diseases, notably carcinogenesis (9,10). These miRNAs are powerful regulators of various cellular processes including cell proliferation, differentiation, development and apoptosis (11,12). As a pivotal constituent of the ncRNA network, miRNAs possess the ability to occupy numerous nodes owing to their capacity to target a considerable number of mRNAs (13). With the development of computational and sequencing technology, researchers can easily predict the target genes of a miRNA through its sequence for target recognition called the 'seed sequence', which is the nucleotides 2-8 of a miRNA (13,14). In recent years, studies have deciphered the biological function of miRNAs extensively, but understanding of the role of miRNAs still requires a tremendous amount of work.

MiR-181a-5p has been extensively studied as a regulatory miRNA with altered expression in various diseases. For

instance, studies have revealed that miR-181a-5p alleviates vascular inflammation, atherosclerosis and inflammatory response in monocrotaline-induced pulmonary arterial hypertension (15,16). In addition, it is associated with obesity and insulin resistance (17). Currently, numerous research has identified upregulated or downregulated expression levels of miR-181a-5p in different tumors, highlighting its role in regulating tumorigenesis through post-transcriptional suppression of its targeted genes (18,19). The present review summarizes the recent studies on miR-181a-5p, explain its role in cancer and chemotherapy and outlines its potential as a biomarker.

2. Regulation of miR-181a-5p in cancer

MiR-181a-5p is a conserved miRNA belonging to the miR-181 family, which comprises four mature miRNAs. These mature miRNAs, namely miR-181a, miR-181b, miR-181c and miR-181d, all share the identical 'seed' sequence 'ACAUUCA'. In humans, miR-181a is located in chromosome 1. MiR-181a-5p is a mature single strand of miR-181a with the sequence 'AACAUUCAACGCUGUCGGUGAGU', while miR-181a-3p is a passenger strand (15,20).

Numerous studies have suggested that dysregulation of miR-181a-5p in tumors is regulated the following factors: *i) Competing endogenous RNAs (ceRNAs)*. MicroRNAs have the ability to bind to specific sequences on target RNA transcripts called microRNA recognition elements (MREs). Through these MREs, ncRNAs that are upstream mediators of miRNAs, such as lncRNAs and circRNAs, can bind to miRNA and function as a miRNA sponge to inhibit its expression (21,22). Numerous ncRNAs, such as colon cancer-associated transcript 1 (CCAT1) and nuclear enriched abundant transcript 1 (NEAT1), have been demonstrated to be sponges of miR-181a-5p in multiple systems of cancer (23-25).

ii) Transcription factors (TFs). NF-κB is positively correlated with the expression of miR-181a-5p. NF-κB short interfering (si)RNA decreases the expression of miR-181a-5p (26). In addition, STAT1 inhibits the expression of miR-181a-5p by binding to its promoter (27). These results indicate that activation or downregulation of miR-181a-5p is modulated by TFs.

iii) DNA methylation. DNA methylation occurs in the CpG island of the promoter region. It is a crucial mechanism of miRNA downregulation. In colorectal cancer, hypermethylation of CpG islands transcriptionally represses the expression of miR-181a-5p (28).

iv) Other factors. Hypoxia also leads to the dysregulation of miR-181a-5p. However, the effects of hypoxia for miR-181a-5p were reversed in different types of cancer. Moreover, the concrete mechanism has not yet been clarified (29,30).

3. MiR-181a-5p in different types of cancer

The growth of cancer is associated with its malignant cell hallmarks, which include the capabilities for sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing/accessing vasculature, activating invasion and metastasis, reprogramming cellular metabolism and avoiding immune destruction (31). MiR-181a-5p exerts its influence on various tumor properties, including cell proliferation, metasitasis, angiogenesis, epithelial-mesenchymal transition (EMT) and autophagy (Fig. 1). It is important to note that the expression of miR-181a-5p is specific to certain tissues and it can simultaneously target multiple genes, potentially playing dual roles. The function of miR-181a-5p is not reliant on a specific target, but rather on the collective impact of its targets, which may encompass both tumor suppressor genes and oncogenes (32). The present study summarizes the existing studies on miR-181a-5p in different tumors and has described them in various systems. The summary of results is provided in (Table I).

Tumors of the digestive system

Colorectal cancer. Colorectal cancer (CRC) is the third most common cancer worldwide and also the most frequent tumor of the digestive tract. The high migratory and invasive properties of CRC cells promote the progression of CRC and lead to poor prognosis of patients with CRC (33).

MiR-181a-5p inhibits proliferation and induces apoptosis. In CRC, results indicate that miR-181a-5p suppresses tumor growth by regulating the Wnt/β-catenin signaling pathway. It has been observed to inhibit cell proliferation, 5-FU sensitivity and promote apoptosis (34,35). The inhibitory effect of miR-181a-5p has also been confirmed in microsatellite-instable CRC, where its expression of miR-181a-5p is reduced and miR-181a-5p directly binds to the 3'UTR of pleomorphic adenoma gene 1 (PLAG1) (28). Another well-established target of miR-181a-5p is p53. Upregulation of miR-181a-5p promotes apoptosis by modulating Bax and Bcl-2 (24). In addition, a previous study revealed that lncRNA-ANRIL can sponge miR-181a-5p, inhibiting apoptosis and radiosensitivity in colon cancer cells (36).

MiR-181a-5p inhibits migration and invasion. The lncRNA-SNHG6 has been identified to be positively correlated with tumor progression and distant metastasis (37). MiR-181a-5p is the direct target of both SNHG6 and E2F5. By inhibiting E2F5, miR-181a-5p induces G_0/G_1 arrest and suppresses CRC cell migration and invasion (38). Additionally, a study revealed that miR-181a-5p reverses the effects of circRNA-NSUN2 on promoting cell proliferation and migration by binding to the 3'UTR of Rho-associated coiled-coil-containing protein kinase 2 (ROCK2) (39).

MiR-181a-5p promotes CRC growth and metastasis. MiR-181a-5p have been demonstrated to be associated with liver metastasis of CRC. This may be attributed to the enrichment of miR-181a-5p in extracellular vesicles of CRC, which alters the tumor environment (TME) (40). MiR-181a-5p promotes motility, invasion and tumor growth by directly targeting Wnt inhibitory factor 1 (WIF-1). Notably, it participates in the regulation of EMT, which is considered a crucial process in cancer metastasis (41). MiR-181a-5p also promotes metastasis and cell proliferation in CRC by inhibiting PTEN, a tumor suppressor gene (42). Multiple studies have showed that miR-181a-5p binds to the 3'UTR of PTEN mRNA, leading to reduced PTEN expression and subsequent activation of the phosphorylated (p)-AKT pathway (27,43). In these cases, the expression of miR-181a-5p is upregulated by IL-1β/NF-kb signaling (26), while STAT1 acts as an inhibitor of miR-181a-5p (27). Furthermore, miR-181a-5p induces metabolic shifts in CRC, favoring glycolysis over oxidative

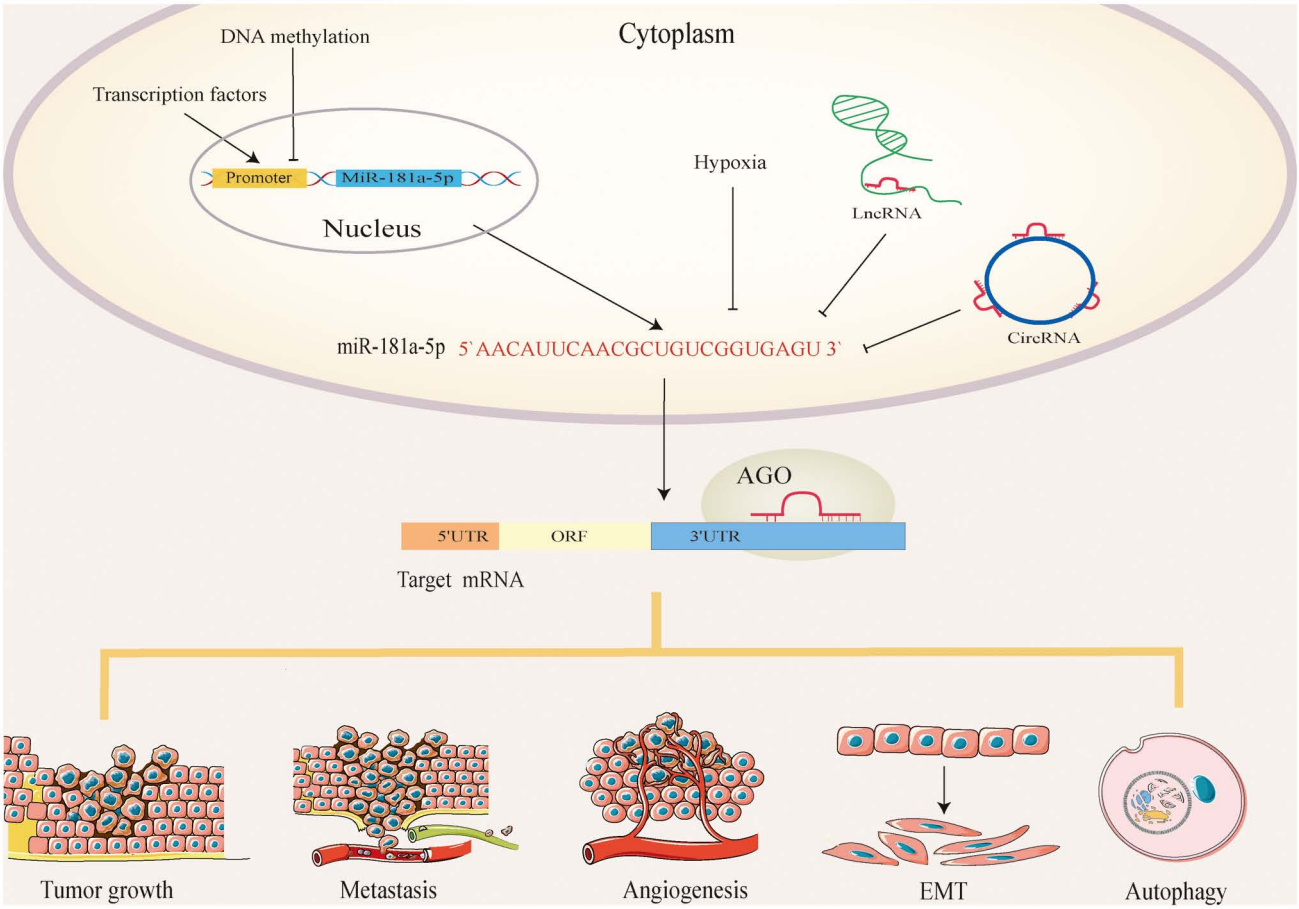

Figure 1. MiR-181a-5p inhibits target mRNA by binding to its 3'UTR and regulates multiple harmarks of tumor cells. In addition, miR-181a-5p is modulated by multiple factors, such as ncRNAs, transcription factors, DNA methylation and hypoxia. EMT, epithelial-mesenchymal transition; ORF, Open Reading Frame; AGO, argonaute; lncRNA, long non-coding RNA; circRNA, circular RNA; miR, microRNA; UTR, untranslated region.

pathways and resulting in increased lactic acid release (43). Finally, angiogenesis is an important feature for tumor growth and metastasis. The pro-angiogenic ability of miR-181a-5p has been demonstrated, and it inhibits the expression of SRC kinase signaling inhibitor 1 (SRCIN1) and reversion-inducing cysteine-rich protein with Kazal motifs (RECK) to promote angiogenesis (Fig. 2) (44,45).

Gastric cancer. Gastric cancer (GC) is a major health burden worldwide. It is the second cause of cancer-related mortalities after lung cancer (46).

MiR-181a-5p promotes GC cell proliferation. A previous study has reported an elevation of miR-181a-5p in GC tissues, which is corelated with tumor progression (47). Meanwhile, TGF-β level is decreased in GC tissues compared with normal tissues. Experimental results indicate that miR-181a-5p directly interacts with TGF-β, thereby facilitating tumor cell proliferation *in vivo* and *in vitro* (48). The Ras association domain family (RASSF) is a crucial contributor in the formation of tumors. Another study has demonstrated that miR-181a-5p promotes GC cell proliferation and G_1/S transition, and suppresses apoptosis by inhibiting RASSF1A (49). MiR-181a-5p also inhibits ATP4B and tyrosine-protein phosphatase megakaryocyte 2 to promote GC tumor growth (50,51).

MiR-181a-5p promotes GC metastasis. MiR-181a-5p modulates the RASSF6/MAPK pathway, promoting proliferation, migration, invasion, metastasis and inducing EMT in GC (52). The role of miR-181a-5p in promoting metastasis in GC is further confirmed by evidence showing that it inhibits caprin-1 to promote cell proliferation, invasion and migration, while reducing apoptosis *in vitro* and *in vivo* (53).

MiR-181a-5p inhibits GC growth and metastasis. MiR-181a-5p has been reported to negatively regulate autophagy of cisplatin resistant cells. MiR-181a-5p increases sensitivity of drug-resistant cells to cisplatin and the tumor volume of nude mice. In this context, ATG5 is a potential target of miR-181a-5p (54). Lin *et al* also revealed that miR-181a-5p blocks GC cell proliferation, migration and invasion (55). Oncogenic factor, Prox1, was considered to be a downstream target of miR-181a-5p (55). In gastric adenocarcinoma, miR-181a-5p has been indicated to inhibit cell proliferation and increase apoptosis by modulating the AKT pathway (Fig. 2) (56).

Hepatocellular carcinoma. Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for 75-85% of all types of liver cancer, which caused ~830,000 mortalities worldwide as of 2020 (46). Several experimental results indicate that miR-181a-5p may plays its role as a tumor inhibitor in HCC (Fig. 2).

MiR-181a-5p suppresses HCC metastasis. MiR-181a-5p inhibits c-Met to promote branching-morphogenesis

Table I. Role of miR-181a-5p in different types of cancer.

Tumor type	Upstream regulator	Target	Mechanism	Role	(Refs.)
Colorectal cancer	-	WIF-1	Promotes tumor growth and liver and EMT metastasis	oncomiR	(41)
	-	PTEN	Triggers metabolic shift	oncomiR	(43)
	-	PTEN	Promotes liver metastasis	oncomiR	(42)
	NF-κB	PTEN	Promotes tumor growth	oncomiR	(26)
	STAT1	PTEN	Promotes tumor growth	oncomiR	(27)
	-	SRCIN1	Promotes angiogenesis	oncomiR	(44)
	BAP31	RECK	Promotes angiogenesis	oncomiR	(45)
	CRNDE	Wnt/β-catenin	Inhibits tumor development and promotes the sensitivity to 5-FU	inhibitor	(34)
	-	PLAG1	Inhibits tumor development	inhibitor	(28)
	ZEB1-AS1	Wnt/β-catenin/	Suppresses tumor growth and promotes the sensitivity to 5-FU	inhibitor	(35)
	SNHG6	E2F5	Inhibits cell migration, invasion and induces G_0/G_1 arrest	inhibitor	(38)
	CCAT1	P53	Induce cell apoptosis	inhibitor	(24)
	CircNSUN2	ROCK2	Inhibits tumor growth	inhibitor	(39)
	ANRIL	-	Increase tumor apoptosis and radio resistance	inhibitor	(36)
Gastric cancer	-	MEG2	Promotes tumor growth	oncomiR	(51)
	-	TGF-β	promotes cell proliferation	oncomiR	(48)
	-	RASSF1A	promotes cell proliferation, G_1/S transition	oncomiR	(49)
	-	RASSF6	Promotes tumor metastasis and EMT	oncomiR	(52)
	-	caprin-1	Promotes cell migration and invasion	oncomiR	(53)
	MEG3	ATP4B	Promotes tumor growth	oncomiR	(50)
	-	ATG5	Inhibits autophagy and cisplatin resistance	inhibitor	(54)
	-	Prox1	Inhibits tumor growth and metastasis	inhibitor	(55)
	MALAT1	AKT	Inhibits tumor growth	inhibitor	(56)
Hepatocellular carcinoma	XIST	PTEN	Enhances cell proliferation and invasion	oncomiR	(60)
	-	c-Met	Diminishes branching-morphogenesis	inhibitor	(18)
	-	Egr1	Suppresses tumor proliferation	inhibitor	(58)
	CCAT1	ATG7	Inhibits autophagy	inhibitor	(59)
Esophageal adenocarcinoma	-	CBLB	Enhance the sensitivity of cisplatin	inhibitor	(61)
Pancreatic cancer	ANRIL	HMGB1	Inhibit tumor growth and gemcitabine resistance	inhibitor	(64)
	-	PTEN and MAP2K4	Promotes cells invasion	oncomiR	(63)
Non-small cell lung cancer	-	Kras	Inhibits cell proliferation and migration	inhibitor	(67)
	-	CDK1	Inhibits tumor growth	inhibitor	(68)
	-	VCAM-1	Inhibits tumor growth	inhibitor	(70)

Table I. Continued.

Tumor type	Upstream regulator	Target	Mechanism	Role	(Refs.)
	NEAT1	HMGB2	Inhibits cell migration and invasion	inhibitor	(25)
	SNHG7	E2F7	Suppresses tumor growth and metastasis	inhibitor	(69)
Laryngeal cancerous	MYCAT1	NPM1	Inhibits tumor growth	inhibitor	(74)
	ANRIL	Snai2	Inhibits EMT	inhibitor	(75)
Bladder cancer	circ0068871	-	Inhibits cell proliferation and migration	inhibitor	(103)
Renal cancer	-	KLF6	Promotes tumor growth and EMT	oncomiR	(105)
Thyroid cancer	ZNF674-AS1	SOCS4	Aggravates tumor growth, metastasis and EMT	oncomiR	(109)
	-	KDM5C	Promote tumor growth	oncomiR	(107)
	-	SLC5A5	Decrease efficacy of radioiodine treatment	oncomiR	(110)
	-	MIL3	Promotes angiogenesis	oncomiR	(29)
	-	KLF15	Promote tumor growth	oncomiR	(108)
Salivary adenoid cystic carcinoma	circ001982	-	Inhibits cell migration and invasion	inhibitor	(111)
Chondrosarcoma	-	RGS16	Promote tumor growth, metastasis and angiogenesis	oncomiR	(142)
	-	VEGF	Increases expression of VEGF	oncomiR	(30)
Osteosarcoma	CASC2	RASSF6	Promotes cell proliferation and invasion	oncomiR	(139)
	TUSC7	RASSF6	Promotes cell proliferation and invasion	oncomiR	(140)
Breast cancer	TGF-β	-	Promotes anoikis resistance	oncomiR	(78)
	SOX2	TUSC3	Promotes tumor metastasis	oncomiR	(79)
	-	PHLPP2 and INPP4B	Promotes S-phase entry and proliferation	oncomiR	(77)
	-	PIAS3	Promotes tumor growth	oncomiR	(19)
	-	NDRG2	Facilitates metastasis and glycolysis	oncomiR	(80)
	-	PGRMC1	Inhibits tumor growth	inhibitor	(82, 83)
	ERβ	-	Blocks cholesterol biosynthesis	inhibitor	(81)
	LUCAT1	KLF6 and KLF15	Inhibits cell proliferation and invasion	inhibitor	(84)
Cervical cancer	-	PRKCD	Inhibit irradiation-induced apoptosis and decreases G_2/M block	oncomiR	(88)
	-	PTEN	Promotes tumor growth	oncomiR	(87)
	-	INPP5A	Promotes tumor growth	oncomiR	(86)
	-	GRP78	Inhibits tumor growth and oxaliplatin resistance	inhibitor	(89)
	CDKN2B-AS1	TGFβ1	Inhibits tumor metastasis	inhibitor	(90)
	LUCAT1	-	Inhibits tumor growth and EMT	inhibitor	(91)
	CCAT1	MMP14	Inhibits cell proliferation and invasion	inhibitor	(23)

Table I. Continued.

Tumor type	Upstream regulator	Target	Mechanism	Role	(Refs.)
Endometrial carcinoma	CCAT1	-	Inhibits tumor growth	inhibitor	(95)
	DLEU2	-	Inhibits EMT and glycolysis	inhibitor	(96)
Ovarian cancer	-	Smad7	Promotes tumor growth and EMT	oncomiR	(97)
	-	SFRP4	Promotes stem cell frequency and platinum resistance	oncomiR	(98)
Prostate cancer	LEF1	-	Promotes tumor growth and EMT	oncomiR	(101)
	MIIP	KLF17	Promotes EMT	oncomiR	(102)
	MBNL1-AS1	PTEN	Promotes tumor growth	oncomiR	(100)
Melanoma	CASC2	PLXNC1	Promotes tumor growth	oncomiR	(133)
	LEFPL3-AS1	-	Induces apoptosis of melanoma stem cells	inhibitor	(134)
Cutaneous squamous cell carcinoma	-	TGF R3	Promotes tumor development	oncomiR	(136)
	-	Kras	Decelerates proliferation	inhibitor	(137)
Glioma	CASC2	PTEN	Promotes tumor growth and TMZ resistance	oncomiR	(128)
	circ0076248	SIRT1	Inhibits tumor growth and TMZ resistance	inhibitor	(122)
	-	KLF6	Increases permeability of BTB	inhibitor	(127)
	-	OPN	Decreases tumor progression and OPN production	inhibitor	(126)
	-	-	Inhibits tumor growth and camustine resistance	inhibitor	(124)
	-	Notch2	Suppresses the formation of glioblastoma stem cell	inhibitor	(125)
Neuroblastoma	-	ABI1	Induces tumor growth and metastasis	oncomiR	(130)
Medulloblastoma	-	Ras	Promotes cell invasion and migration	oncomiR	(132)
Leukemia	-	ATM	Promotes proliferation and G_1/S transition	oncomiR	(113)
	-	RalA	Suppresses tumor growth	inhibitor	(116)
	-	W1F1	Promotes tumor growth	oncomiR	(114)
	-	STAT3	Inhibits the sensitivity to FAS-mediated apoptosis	inhibitor	(115)
Myeloma	CCAT1	HOXA1	Inhibits tumor growth	inhibitor	(118)
	MALAT1	Hippo-YAP	Inhibits tumor growth	inhibitor	(117)
Lymphoma	-	NF-κB	Inhibits cell proliferation and survival	inhibitor	(120)

OPN, Osteopotin.

and invasion of HCC cells (18). Additionally, it induces glucose metabolism reprogramming, which is associated with the progression and early lung metastasis of HCC. Mechanistically, miR-181a-5p reduces the expression of mitochondrially encoded (mt)-Cytochrome B and mt-Cytochrome C oxidase subunit 2 proteins, thus decreasing the electron transport chain (ETC). This reduction in ETC activity results in an increase in hexokinase 2 (HK2) and glucose transporter 1, enhancing glucose uptake, lactic acid release and LDH activity (57).

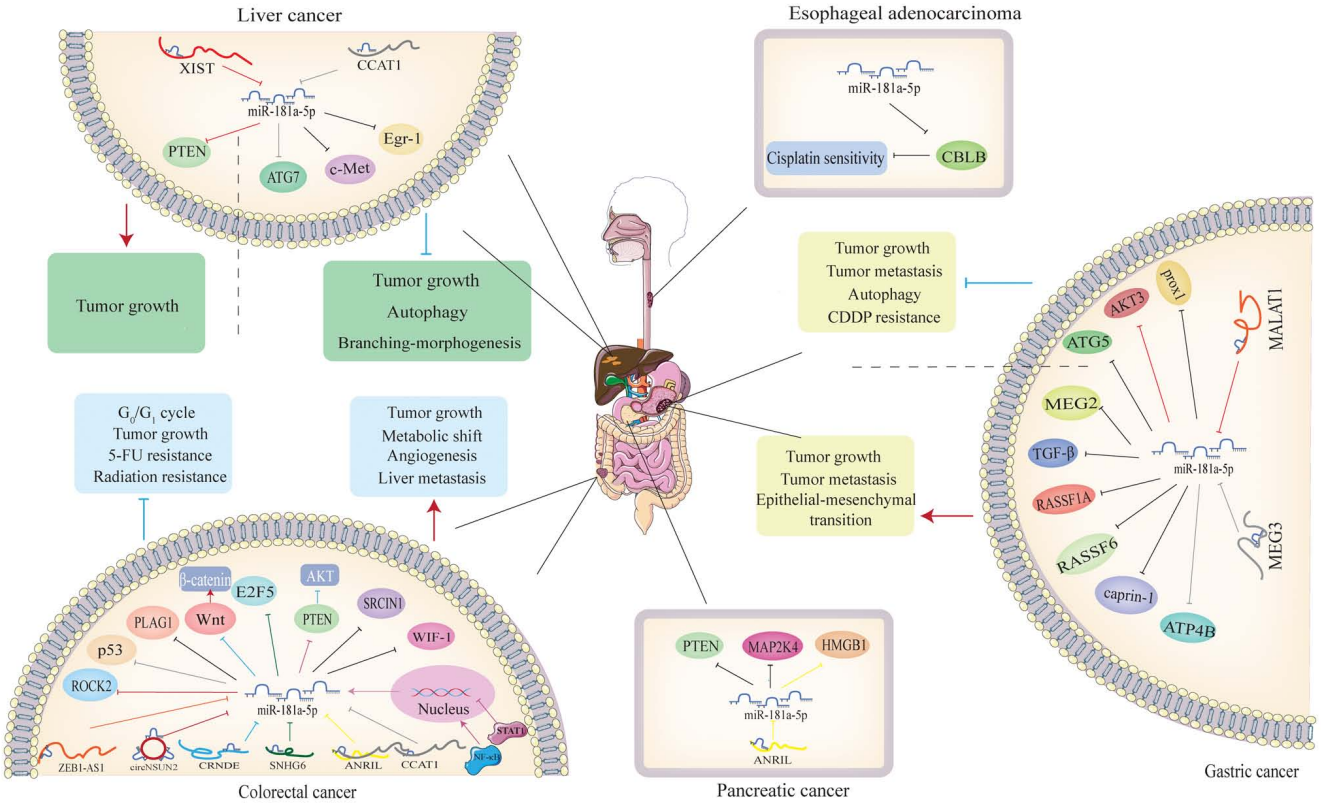

Figure 2. Role of miR-181a-5p in different tumors of the digestive system. Targets confirmed in the same report are connected with arrows with same colors and the factors producing different effects are separated by dotted lines (→, promote; -|, inhibit). miR, microRNA; CCAT1, colon cancer-associated transcript 1; Egr-1; c-Met; ATG, autophagy-related gene; ROCK2, Rho-associated coiled-coil-containing protein kinase 2; PLAG1, pleomorphic adenoma gene 1; E2F5, E2f transcription factor family member 5; SRCIN1, SRC kinase signaling inhibitor 1; WIF-1, Wnt inhibitory factor-1; ZEB1-AS1, zinc-finger E homeobox-binding1 antisense1; circ, circular RNA; NSUN2, NOP2/Sun domain family, member 2; CRNDE, Colorectal Neoplasia Differentially Expressed; SNHG6, small nucleolar RNA host gene 6; ANRIL, Antisense non-coding RNA in the INK4 locus; CCAT1, colon cancer associated transcript 1; HMGB1, high-mobility group box 1 protein; prox1, Prospero-related homeodomain transcription factor1; MEG3, maternally expressed gene 3; RASSF, Ras association domain family; MALAT1, metastasis associated lung adenocarcinoma transcript 1; CBLB, second member of the E3 ubiquitin ligase CBL family; XIST, X-inactive specific transcript; PTEN, Phosphatase and Tensin Homolog deleted on Chromosome 10.

MiR-181a-5p inhibits HCC growth. Early growth response factor1 (Egr1) plays a crucial role in cancer progression by activating the TGF-β/Smad pathway. Evidence has demonstrated that miR-181a-5p inhibits Egr1 by binding to its 3'UTR, resulting in tumor proliferation suppression in HCC (58). Assays have showed that miR-181a-5p inhibits HCC cell autophagy by targeting ATG7, which is positively correlated with autophagy (59).

However, a previous report suggested that lncRNA-XIST increases the cancer suppressor gene PTEN through the inhibition of miR-181a-5p. Restored miR-181a-5p expression promotes the HCC cell proliferation and invasion (60).

Esophageal adenocarcinoma. MiR-181a-5p inhibits cisplatin resistance in esophageal adenocarcinoma. In comparison with constructed cisplatin-resistant EAC cells, the miR-181a-5p expression is significantly higher in normal EAC cells. Furthermore, miR-181a-5p exhibits stronger cisplatin-induced inhibition of proliferation and promotion of apoptosis. In addition, CBLB, which is involved in ubiquitination to aggravate cisplatin resistance, is identified as a direct target of miR-181a-5p (Fig. 2) (61).

Pancreatic cancer. Pancreatic cancer (PC) is the most malignant tumor of the digestive system, which is extremely aggressive (62). Although early findings have revealed that miR-181a-5p, which indirectly inhibits the PTEN and MAP2K4, enhances the invasion capability of PC (63), another report after 8 years revealed that miR-181a-5p inhibits PC by targeting high mobility group box 1 (HMGB1). It inhibits PC cell proliferation, invasion, migration and resistance of gemcitabine, while reducing the expression of miR-181a-5p attenuates these effects. In addition, lncRNA-ANRIL decreases HMGB1 by sponging miR-181a-5p to activate cell autophagy (Fig. 2) (64).

Respiratory system tumors

Non-small cell lung cancer (NSCLC). Lung cancer is the most commonly diagnosed cancer in the world and is characterized by a high rate of metastasis and delayed diagnosis (65). NSCLC accounts for 80-85% of all types of lung cancer (66). The following studies indicate that miR-181a-5p is a tumor inhibitor in NSCLC. It can inhibit tumor growth and metastasis by targeting multiple pro-tumorigenic factors. MiR-181a-5p targets the recognized oncogene Kras by binding to its 3'UTR, thereby slowing cell proliferation and migration (67). It has also been found to target CDK1 and E2F7, which regulate the cell cycle and promote tumor proliferation (68,69). Additionally, miR-181a-5p has been demonstrated to target

HMGB2 to inhibit NSCLC cell migration and invasion (25). It is worth mentioning that NF-κB has been indicated to promote miR-181a-5p expression in colorectal cancer (26). However, a report has demonstrated that IL-17 inhibits miR-181a-5p by activating NF-κB (70). Furthermore, vascular cell adhesion molecule 1 has been demonstrated to be a direct target of miR-181a-5p. This laterally proves that miR-181a-5p can reduce vascular oxygen supply (70). In these cases, lncRNA NEAT1 and SNHG7 have been demonstrated to be up-stream regulators of miR-181a-5p as a miRNA sponge (25,69,71). Notably, miR-181a-5p can alleviate immunosuppression and anti-PD-1 resistance of NSCLC, providing a novel strategy for enhancing the efficacy of immunotherapy (72).

Laryngeal cancer. MiR-181a-5p has a tumor suppressor property in laryngeal cancer. Myc target protein 1 (MYCT1) is known to regulate cell apoptosis (73). Recently, Wang *et al* revealed that MYCT1 collaborates with MYC-associated protein X to enhance the promoter of miR-181a-5p, which binds to the 3'UTR of nucleophosmin 1 (NPM1), thus inhibiting laryngeal cancerous cell viability, colony formation and promoting apoptosis (74). Another study has demonstrated that miR-181a-5p inhibits EMT of laryngeal cancer by targeting Snai2 (75).

Cancer of the reproductive system

Breast cancer (BC). BC is one of the leading causes of mortality among women worldwide (76).

MiR-181a-5p promotes tumor growth of BC. Exosome-derived miR-181a-5p is upregulated in BC. By targeting PIAS3, it promotes the expansion of early-stage myeloid-derived suppressor cells, which in turn exacerbate cell proliferation, induce tumor growth and evade immune destruction (19). In addition, miR-181a-5p increases the level of p-AKT by co-targeting PH-domain leucine-rich repeat-containing protein phosphatase 2 and Inositol polyphosphate 4-phosphatase type II phosphatases in luminal breast cancer, resulting in cell proliferation and S phase entry (77). TGF-β has been demonstrated to upregulate the expression of miR-181a-5p through mediation of its transcription. Increased miR-181a-5p reduces apoptosis and sensitivity to anoikis (78).

MiR-181a-5p promotes BC cell migration and invasion. It has been reported that lncRNA-SOX2 is downregulated and correlates with poor survival of BC. A tumorigenesis experiment conducted on nude mice has demonstrated that SOX2 suppresses tumor development and metastasis by sponging miR-181a-5p. In this case, miR-181a-5p promotes BC metastasis by inhibiting Tumor suppressor candidate 3 (79). MiR-181a-5p also targets the NDRG2 to reduce activation of PTEN, thus facilitating proliferation, invasion and glycolysis of BC (80).

MiR-181a-5p is an inhibitor of BC. MiR-181a-5p is upregulated in TNBC tissues and cells. This may be associated with the suppressive effect of ER-β, which modulates the expression of miRNA to inhibit TNBC. Upregulation of miR-181a-5p is an auxiliary mechanism of ER-β-induced cholesterol biosynthesis inhibition (81). In addition, miR-181a-5p has been revealed to be positively correlated with Bax and Caspase-9, which promote cell apoptosis (82,83). Functional experiment has revealed that miR-181a-5p inhibits cell proliferation, migration and invasion by targeting oncogenes Kruppel-like factor (KLF) 6, KLF15 and progesterone receptor membrane component 1 (Fig. 3) (84).

Cervical cancer (CC). CC is the fourth leading cause of cancer-associated mortality among women, accounting for >2.6 million deaths worldwide every year (46,85).

MiR-181a-5p promotes CC cell proliferation and inhibits apoptosis. MiR-181a-5p expression is elevated in CC tissues. It negatively targets INPP5A to promote CC cell proliferation and invasion while inhibiting apoptosis (86). MiR-181a-5p also post-transcriptionally inhibits PTEN in CC. Inhibition of miR-181a-5p can impede cell cycle progression by increasing P21, P27, Bax and decreasing Bcl-2 (87). Moreover, miR-181a-5p is upregulated in human CC specimens and cell lines that are not responsive to radiation therapy. It suppresses radiation-induced apoptosis and G_2/M cell cycle arrest by inhibiting protein kinase C delta type (PRKCD) (88).

MiR-181a-5p inhibits CC cell proliferation. A study revealed that miR-181a-5p is aberrantly reduced in CC and inhibits proliferation and resistance of oxaliplatin. In this case, GRP78 is identified as the direct target of miR-181a-5p (89).

MiR-181a-5p inhibits CC metastasis. MiR-181a-5p has direct binding sites with TGFβ1, promoting the expression of TGFβ1 to inhibit CC proliferation, migration and invasion (90). Another group showed that miR-181a-5p inhibits invasion, migration and EMT of CC (91). LncRNA-CCAT1 is located on chromosome 8q24, where human papillomavirus integration usually occurs (92). Overexpression of CCAT1 promotes CC cell proliferation and invasion. MiR-181a-5p is identified as a downstream target of CCAT1and decreases the expression of MMP14. CCAT1 indirectly upregulates the MMP14 by suppressing miR-181a-5p to promote CC progression (Fig. 3) (23).

Endometrial carcinoma (EC). EC is one of the most common malignancies in women and a leading cause of cancer-associated mortalities worldwide (93).

MiR-181a-5p is a tumor inhibitor in EC. A preliminary experiment revealed that the PTEN is decreased and miR-181a-5p is increased in non-obese patients with EC, suggesting that PTEN is negatively correlated with miR-181a-5p (94). More focused work revealed that miR-181a-5p inhibits EC cell proliferation and migration, while miR-181a-5p inhibitor can neutralize these effects (95). Accumulation of HK2 in EC promotes EMT and glycolysis. MiR-181a-5p is an inhibitor of HK2. An experiment has confirmed that DLEU2 interacts with enhancer of zeste homolog 2 to silence miR-181a-5p, thus inducing EMT and glycolysis (96) (Fig. 3).

Ovarian cancer. Ovarian cancer is a common tumor of the gynecological malignancy. Clinical data has demonstrated that miR-181a-5p is increased in advanced epithelial ovarian cancer and promotes tumor development (97). In an *in vivo* and *vitro* experiment, miR-181a-5p has been further indicated to promote cell proliferation, migration, invasion and EMT. SMAD family member 7 (Smd7), an inhibitor of TGF, has been identified as a direct target of miR-181a-5p (97). In high-grade serous ovarian cancer, miR-181a-5p increases stem-cell frequency and resistance of cisplatin by activating

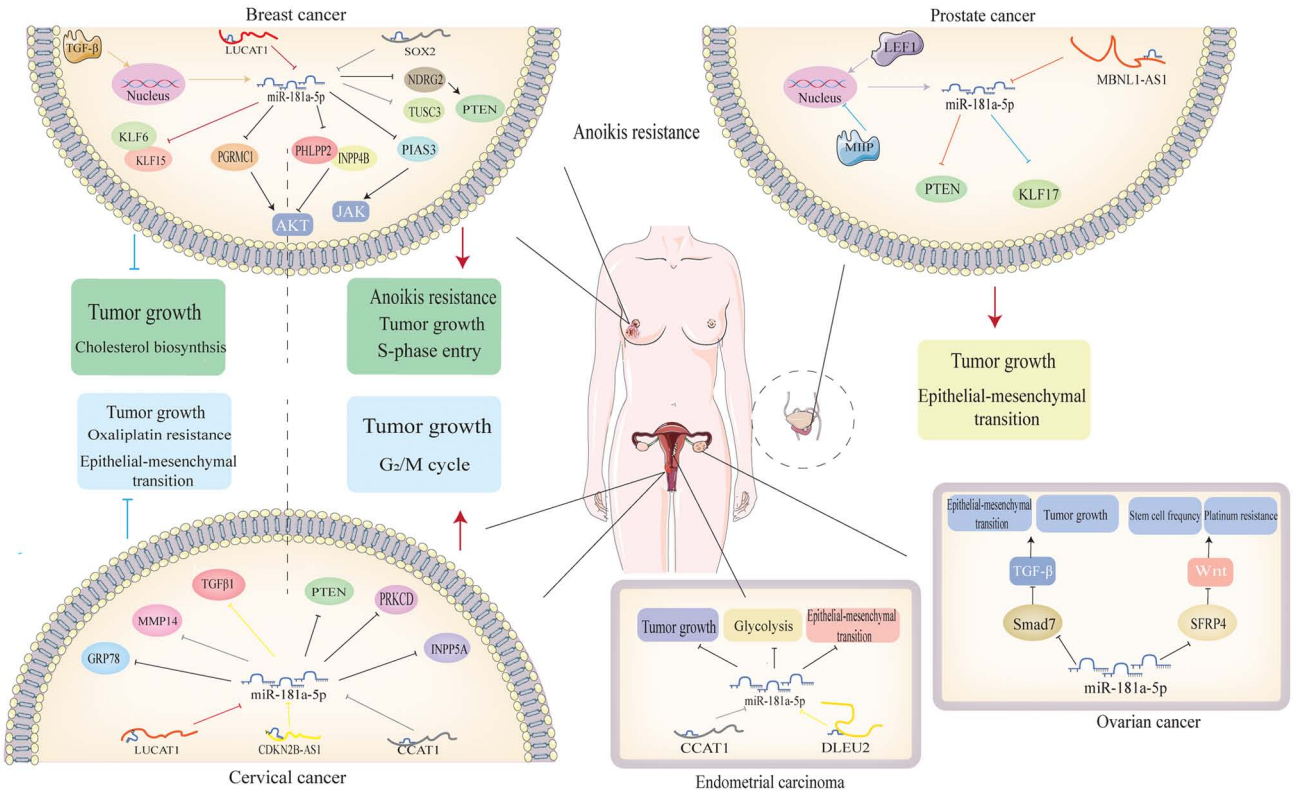

Figure 3. Role of miR-181a-5p in different tumors of reproductive system. Targets confirmed in the same report are connected with arrows with the same colors, and the factors producing different effects are separated by dotted lines (→, promote; -|, inhibit). miR, microRNA; KLF, Kruppel-like factors; PGRMC1, progesterone (P4) receptor membrane component 1; PHLPP2, PH domain leucine-rich repeat-containing protein phosphatase 2; INPP4B, Inositol polyphosphate 4-phosphatase type II; PIAS, protein inhibitor of activated STAT; TUSC3, tumor suppressor candidate 3; NDRG2, N-myc downstream-regulated gene 2; SOX2, sex-determining region Y-box 2; LUCAT1, lung cancer-related transcript 1; GRP78, Glucose-Regulated Protein 78; PRKCD, Protein kinase C delta; INPP5A, Inositol Polyphosphate-5-Phosphatase A; DLEU2, deleted in lymphocytic leukemia 2; SFRP4, Secreted Frizzled Receptor Protein 4; LEF1, Lymphoid enhancer factor; MMP, membrane-type matrix metalloproteinase; MBNL1-AS1, Muscle blind-like-proteins antisense 1.

the Wnt/β-catenin signaling pathway. This activation is achieved by directly targeting Secreted frizzled-related protein 4 (SFRP4), an inhibitor of the Wnt/β-catenin pathway (Fig. 3) (98).

Prostate cancer (PCa). PCa is the second most frequently diagnosed cancer and the sixth leading cause of cancer-associated mortality among men worldwide (99).

MiR-181a-5p may promotes EMT and tumor growth in PCa (Fig. 3). The inhibitory effect of miR-181a-5p on PTEN has been observed in PCa. In this context, miR-181a-5p enhances cell proliferation, migration and invasion (100). To the best of our knowledge, two studies have investigated the effect of miR-181a-5p on EMT. The results revealed that miR-181a-5p promotes EMT with high E-cadherin expression by inhibiting the EMT negative regulator, KLF17. Notably, lymphoid enhancer-binding factor 1 and migration and invasion-inhibitory protein have been identified to downregulate the expression of miR-181a-5p in PCa (101,102).

Tumors of the urinary system

Bladder cancer (BCa). To the best of our knowledge, there is only one report focused on the role of miR-181a-5p in BCa. MiR-181a-5p is a tumor inhibitor in BCa. A group demonstrated that expression of circRNA-0068871 is increased, while miR-181a-5p is expressed at a low level in BCa. circRNA-0068871 intensifies cell proliferation, migration and suppressed apoptosis *in vivo* and *vitro*. Mechanistically, circRNA-0068871 acts as a sponge for miR-181a-5p, which directly targets EGFR3, indicating that miR-181a-5p is a tumor inhibitor in BCa (103).

Renal cancer. A preliminary experiment indicated that miR-181a-5p may play a role as an oncomiR in renal cancer. Compared with normal tissues and cells, miR-181a-5p is upregulated in both renal cancer tissues and cell lines. *In vitro*, miR-181a-5p inhibits apoptosis and promotes proliferation, invasion and migration of 786-O and ACHN cell lines (104). In addition, miR-181a-5p has been identified to be associated with tumor size and TNM stages in clear cell renal cell carcinoma. MiR-181a-5p directly binds to KLF6, which induces apoptosis, promoting renal cancer progression and metastasis (105).

Cancer of the endocrine system

Thyroid cancer (TC). According to 2020 statistics, TC is the most common endocrine cancer. Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, accounting for ~85% of thyroid cancer worldwide (106). The following experiments suggest that miR-181a-5p promotes the progression of TC by modulating multiple target genes. *In vivo* and *vitro*, a group demonstrated that miR-181a-5p inhibits papillary demethylase and lysine-specific demethylase 5C (KDM5C) to

induce cell proliferation and migration, thus promoting the tumor growth (107). In addition, it is widely acknowledged that angiogenesis is a key factor in PTC recurrence and metastasis. By inhibiting MIL3, exosomal miR-181a-5p promotes tumor angiogenesis and growth. In this case, it decreases DACT2 and increases VEGF and YAP (29). Other reports further validated that miR-181a-5p promotes metastasis of PTC. MiR-181a-5p promotes cell proliferation, invasion and EMT to aggravate PCT metastasis, while its downstream target KLF15 and suppressor of cytokine signaling 4 can counteract these effects (108,109). In addition, miR-181a-5p reduces the efficacy of radioactive iodine treatment by suppressing sodium iodide symporter (NIS), which is a potent iodine transporter. A report has indicated that miR-181a-5p directly inhibits sodium/iodide cotransporter (SLC5A5) to regulate NIS (110).

Salivary adenoid cystic carcinoma. To the best of our knowledge, one study explored the role of miR-181a-5p in salivary adenoid cystic carcinoma (SACC) with lung metastasis. Compared with SACC-83 cells (cells from patients with SACC), Ju *et al* revealed that miR-181a-5p is decreased in SACC-LM cells (SACC patients with lung metastasis). Furthermore, miR-181a-5p is sponged by circRNA-001982, resulting in stronger ability of migration and invasion (111).

Cancer of the circulatory system

Leukemia. Leukemia, the most common circulatory system tumor, with >470,000 new cases worldwide in 2020 (46). It can be divided into myeloid leukemia and lymphocyte leukemia according to the pathological cells. Targeting miRNAs associated with leukemia may be an effective approach to treat leukemia. MiR-181a-5p has been identified to be associated with acute myeloid leukemia (AML). Clinical data has demonstrated that miR-181a-5p is decreased in children with AML, along with a decrease in TGF-β and an increase in Smad7 (112). However, there is a conflicting study that suggests miR-181a-5p promotes AML cell proliferation and G_1/S transition by targeting ataxia telangiectasia mutated (113). In addition, miR-181a-5p has also been found to promote the progression of acute lymphoblastic leukemia (ALL) and lymphocyte leukemia by inhibiting WIF1 and STAT3 (114,115). However, another study revealed that miR-181a-5p has an inhibitory effect on myelogenous leukemia. MiR-181a-5p directly binds to the 3'UTR of Ra1A, thus inhibiting proliferation and promoting G_2 cell cycle arrest and apoptosis (116).

Myeloma. Multiple myeloma (MM) is the second most common hematologic tumor with 176,404 new cases worldwide in 2020 (46). MM is a hematological tumor characterized by abnormal proliferation of plasma cells. MiR-181a-5p appears to be a potential therapeutic target for MM. *In vitro* experiments, miR-181a-5p is associated with lower CDK2, Cyclin E1 and Bcl2 and higher p21, Bax and caspase 3 to regulate proliferation and apoptosis of MM cells by inhibiting the Hippo/YAP axis (117). In addition, miR-181a-5p induces cell cycle to G_0/G_1 phase arrest, and directly targets homeobox transcription factor A1 (HOXA1), which has been demonstrated to promote cell growth and tumor progression (118). These findings suggest that miR-181a-5p plays a suppressive role in MM.

Lymphoma. Lymphoma is a malignant tumor originating in the lymphatic hematopoietic system. Diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype of non-Hodgkin lymphoma, accounting for 31% in Europe and the USA (119). Common standard treatments cure only about half of patients. MiR-181a-5p suppresses the proliferation and survival of DLBCL, and it modulates NF-kB by directly targeting NF-kB regulatory factors caspase recruitment domain-containing protein 11, encoding nuclear factor of κ-light polypeptide gene enhancer in B-cells inhibitor-α, p50, p65 and c-Rel. Study using xenograft models revealed that miR-181a-5p prevents tumor growth rate and prolongs the animal survival in NF-kB-dependent DLBCL (120).

Cancer of the nervous system

Glioma. Glioma is a highly malignant tumor in the central nervous system, which develops rapidly and is prone to metastasis from early stage (121). The clinical data reveal a decrease in miR-181a-5p in glioma tissues and cell lines. It has been determined that circRNA 0076248 acts as an upstream regulator of miR-181a-5p, indirectly increasing the expression of Sirtuin 1 (SIRT1) (122). Overexpression of miR-181a-5p inhibits cell proliferation, invasion and sensitizes cells to Temozolomide (TMZ) (122). An investigation has also demonstrated that miR-181a-5p acts as a suppressive regulator of glioblastoma multiform (GBM), the most malignant glioma (123). In a study involving patients with GBM treated with carmustine, miR-181a-5p has been shown to enhance G_1 cell cycle arrest and apoptosis by regulating caspase-9, Bcl-2 and SIRT1. Mechanistically, miR-181a-5p inhibits the PI3K/AKT signaling pathway to promote GBM cell apoptosis and carmustine sensitivity (124). MiR-181a-5p also decreases glioblastoma stem-like cells formation and Osteopontin production of GBM, thus inhibiting the tumor development and progression (125,126). In addition, miR-181a-5p has been demonstrated to increase the permeability of the blood-tumor barrier (BTB), thereby improving the delivery of therapeutic drugs (127). However, a study conducted by Liao and coworkers demonstrated that increased expression of miR-181a-5p promotes cell proliferation and TMZ sensitivity through the regulation of the PTEN/AKT signaling pathway (128).

Neuroblastoma and medulloblastoma (MB). Neuroblastoma is the most frequent extracranial solid tumor in infants worldwide, with 25-50 cases per million individuals. More than 50% of patients already have distant metastases by the time they are diagnosed (129). In a study, researchers attributed the oncogenic role of miR-181a-5p to inhibit ABI1 mRNA. *In vitro* experiments, it promotes cell proliferation, migration and invasion. Furthermore, a nude mice xenograft model provided further evidence that consolidates the pro-tumorigenic effect of miR-181a-5p (130). MB is an aggressive cerebral tumor, divided into four molecular subtypes: i) WNT; ii) SHH; iii) 3 group; and iv) 4 group. Among them, 3 group has the worst prognosis and the majority of patients have metastasized at the time of diagnosis (131). A previous report provides novel treatment strategies for 3 group-MB. Experimental evidence indicates that miR-181a-5p expression is increased in 3 group-MB cells compared with SHH-MB cells. SHH-MB cells treated with 3 group-MB exosomal miR-181a-5p demonstrate

increased aggressiveness and mobility. The tumor-promoting effects of exosomal miR-181a-5p are attributed to activation of the RAS/MAPK signaling pathway (132).

Skin cancer

Melanoma. Melanoma is an aggressive cancer of the skin. MiR-181a-5p promotes melanoma cell proliferation and invasion, suggesting that miR-181a-5p has a role of tumor inhibitor. Then, miR-181a-5p is found to directly bind to the 3'UTR of Plexin C1 and is sponged by lncRNA-CASC2 (133). However, another study provided evidence that miR-181a-5p reduces the expression of Bcl2 and induces apoptosis of melanoma stem cells (134).

Cutaneous squamous cell carcinoma. Cutaneous squamous cell carcinoma (cuSCC) is the second most commonly diagnosed malignant cancer of the skin after melanoma, accounting for 20% of skin cancer worldwide (135). Two reports came to opposite conclusions on the role of miR-181a-5p in CSCC. In normal epidermal keratinocytes (HaCaT), a group uncovered that expression of miR-181a-5p increases in cuSCC tissues and inhibits apoptosis of UV induced HaCaT cells. In addition, miR-181a-5p suppresses TGF R3 to increase the expression of TGF, which promotes multiple tumorigenic functions (136). The other study demonstrated that miR-181a-5p blocks the Kras/MAPK pathway to slow SCC13 cell proliferation (137). Notably, the two reports treated the cells in different ways and utilized different cell lines for *in vitro* experiments.

Cancer of the motor system. Osteosarcoma (OS) is a common malignant tumor in adolescents and children (138).

MiR-181a-5p is involved in the progression and metastasis of OS. In OS, miR-181a-5p has been observed to target RASSF6 to promote cell proliferation and invasion. TUSC7 and CASC2 were established as upstream regulators of miR-181a-5p (139,140). Chondrosarcoma is a primary osteosarcoma in which mortality is usually due to lung metastasis. The expression of miR-181a-5p is upregulated significantly in chondrosarcoma (141). By regulating VEGF and G-protein signaling 16, miR-181a-5p has been shown to promote angiogenesis, which is critical for the progression and metastasis of OS (22,142).

4. MiR-181a-5p as a biomarker

With the development of technology, miR-181a-5p can be accurately and conveniently quantitatively detected (143), which makes it a potential biomarker. The following studies showed the potential of using miR-181a-5p as one of the biomarkers for diagnosis, prognosis and assessment of chemotherapy response. These studies are summarized in Table II.

Biomarkers for diagnosis. Although tissue biopsies remain the gold standard for cancer diagnosis, there is evidence that miR-181a-5p can be used as a biomarker for early diagnosis. For example, serum miR-181a-5p level is decreased in patients with BC compared with normal subjects, and the sensitivity of miR-181a-5p level in early diagnosis of BC is higher compared with that of conventional tumor markers CA153 and carcinoembryonic antigen (144). Another study found that plasma exosomal miR-181a-5p is significantly increased in patients with CRC, suggesting that it has the potential as a marker for diagnosing CRC (145). In addition, miR-181a-5p can also be used to determine the subtype or stage of a certain cancer. Researchers found that compared with controls, patients with early esophageal cancer have significantly lower level of miR-181a-5p, which can be used as a novel biomarker for early diagnosis of esophageal cancer (146). In endometrial carcinoma (EC), it is identified to be increased in type I EC and type II EC, while the increase in type II EC was significantly higher compared with that in type I (147). In addition, miR-181a-5p level is elevated in the tissues of Chinese males with lung squamous cell carcinoma (148).

Biomarker for prognosis. Numerous studies have found that the level of miR-181a-5p may predict the risk of progression and survival of multiple types of cancer. In the majority of reports, increased miR-181a-5p in tumor tissue or serum is correlated with poor outcome and shorter overall survival (149-152). For example, in pediatric acute lymphoblastic leukemia, miR-181a-5p increases the risk of central nervous system of leukemia. The expression of miR-181a-5p provides a novel marker for the course of pediatric ALL. In addition, its expression in bone marrow and peripheral blood samples is significantly decreased to the 33rd day of treatment (153). But in NSCLC (154,155) and AML (156), miR-181a-5p is positively associated with an improved prognosis. Moreover, extracellular vesicle-delivered miR-181a-5p may indicate the risk of tumor metastasis. For example, miR-181a-5p is significantly upregulated in patients with bone metastatic prostate cancer (157), while in rectal cancer with lymph node metastasis, it is decreased (158).

Overall, miR-181a-5p may be an effective tool for predicting cancer prognosis. However, more studies are warranted to provide evidence for clinical application.

Biomarker for response to therapy. The level of miR-181a-5p expression can predict the treatment response of patients with cancer, which can improve the reference for the selection of clinical treatment strategy. For example, EGFR-tyrosine kinase inhibitors (TKIs), such as gefitinib, are the first-line treatment of advanced NSCLC in the presence of allergenic mutations. Circulating miR-181a-5p was quantified in plasma samples of 39 patients with advanced EGFR-mutated NSCLC treated with EGFR-TKIs, and the results showed that patients with partial/complete response (PR/CR) had higher baseline miR-181-5p compared with patients with stable/progressive disease (SD/PD) (159). This trend is similar in patients with colorectal cancer treated with EGFR-TKI. A low level of miR-181a-5p indicates poor progression-free survival (PFS) (160). Uniformly, the level of miR-181a-5p is positively associated with the outcomes of anti-tumor treatment, such as EOX (epirubicin/capecitabine/oxaliplatin) regimen, bortezomib, sorafenib or stem cell transplantation. In these cases, serum miR-181a-5p in PR patients may be significantly higher than that in PD patients (161-164). However, in advanced unresectable epithelial ovarian cancer, patients with higher miR-181a-5p expression have shorter overall survival and PFS accompanied by elevated smad2. Combined analysis of p-smad2 and miR-181a-5p

Table II. MiR-181a-5p as a biomarker.

Tumor	Expression	Indication	(Refs.)
Breast cancer	Down	Early diagnosis of breast cancer.	(144,160)
Colorectal cancer	Up	Diagnosis of colorectal cancer. Lower prognosis and survival outcome.	(143,149)
	Down	Low expression reflects poor PFS of colorectal cancer treated with EGFR-TKIs.	(143)
Endometrial carcinoma	Down	Significantly high in type II endometrial carcinoma.	(147)
Non-small cell lung cancer	Up	Diagnosis of Chinese male lung squamous cell carcinoma. High expression has an improved outcome with EGFR-TKIs.	(148,159)
	Down	Shorter overall survival and poor prognosis.	(154,155)
Prostate cancer	Up	Significantly high in bone metastatic prostate cancer patients.	(157)
Acute lymphoblastic leukemia	Up	Upregulated miR-181a-5p predicts higher risk of central nervous system.	(154)
Acute myeloid leukemia	NA	Significantly higher in better prognosis patients. Positively associates with outcome treated with intensive induction chemotherapy.	(156,163)
Rectal cancer	Down	Lymph node metastasis and N-positive disease.	(159)
Multiple myeloma	Up	Short progression and poorer prognosis.	(151)
	Down	Bortezomib resistance.	(161)
Pancreatic cancer	NA	Lower in non-progressive stagy.	(145)
Hepatocellular carcinoma	NA	Low expression implicates poor outcome afte treating with sorafenib.	(162)
Gastric cancer	Down	Downregulation of miR-181a-5p is associated with progressive disease treated with EOX regimen.	(164)
Ovarian cancer	NA	High expression reflects shorter overall survival and progression-free survival.	(150,165)
Esophageal cancer	Down	Diagnosis of esophageal cancer.	(146)

NA, not available.

may potentially identify those patients with ovarian cancer with a lower chance of responding to platinum-based neoadjuvant chemotherapy (165).

5. MiR-181a-5p in chemotherapy

Chemotherapy is one of the main therapeutic methods used against cancer, and the response of patients with cancer to chemotherapy is influenced by various factors, such as PTEN and the Wnt/β-catenin pathway (166,167). Numerous genes have been identified as being involved in chemotherapy. Therefore, miRNA can impact cancer chemotherapy by binding to chemotherapy-related targets (168,169). Recent research has focused on the role of miR-181a-5p in chemotherapy. These findings provide a foundation for the clinical use of miR-181a-5p mimics or inhibitors to enhance the sensitivity of chemotherapeutics. In this section, the present study discusses the interaction between miR-181a-5p and platinum, as well as other chemotherapeutic agents (Table III).

Platinum. Platinum drugs, such as cisplatin, carboplatin and oxaliplatin, are one of the most commonly used drugs in chemotherapy and are often used in combination with other chemotherapeutic drugs (170). A recent study has shown that miR-181a-5p can enhance the sensitivity of platinum drugs by targeting some oncogenes in certain types of cancer. It has been observed that in cisplatin resistant cells, the level of miR-181a-5p is reduced. Conversely, CUGBP Elav-like family member 1, which is inhibited by miR-181a-5p, increases in cisplatin resistant cells in lung squamous cell carcinoma and as an oncogene. MiR-181a-5p can decrease the IC_{50} of cells and effectually recover the cisplatin resistance (171).

Vitamin D receptor (VDR) is a nuclear receptor that regulates autophagy (172). In BC cell lines HS578T, miR-181a-5p induces autophagy to promote apoptosis and inhibit proliferation by suppressing VDR, thus increasing the sensitivity of cisplatin (173). Similarly, other studies have also demonstrated that miR-181a-5p can induce apoptosis and promote the sensitivity of cisplatin in NSCLC (174), GC (175) and esophageal cancer (61). In additon, these *in vitro* results were

Table III. Impact of miR-181a-5p on chemotherapy.

Chemotherapy Drug	Cancer	Role	Target	(Refs.)
Platinum	NSCLC	Promotes the sensitivity of cisplatin	CELF1, and SP1	(171,176)
	Breast cancer	increases the sensitivity of cisplatin	Vitamin D receptor	(173)
	Gastric cancer	Promotes the sensitivity of DDP	cyclinG1	(175)
	Esophageal cancer	increases the sensitivity of cisplatin	CBLB	(61)
	Cervical cancer	Promotes the sensitivity of oxaliplatin	GRP78	(89)
	Ovarian cancer	Inhibits the sensitivity of cisplatin	SFRP44	(98)
Dabrafinib	Melanoma	Reverses dabrafinib resistance	TFAM	(189)
5-FU	Colorectal cancer	Increases 5-FU sensitivity	Wnt/β-catenin, PLAG1	(28,34)
Melphalan	Seeded retinoblastoma	Enhances the efficacy of melphalan	BCL-2, MAPK1 and Bax	(180)
Carmustine	Glioma	Promotes sensitivity of Carmustine	/	(124)
Gemcitabine	Pancreatic cancer	Suppresses chemoresistance to gemcitabine	HMGB-1	(64)
Ara-c	Leukemia	Inhibits Ara-c resistance	/	(177)
Gefitinib	Non-small cell lung cancer	Promotes gefitinib resistance	GAS7	(178)

confirmed *in vivo*. In a mouse xenograft model, miR-181a-5p expression in tumors increased significantly in the group treated with Xiaoji decoction (XJD) combined with cisplatin comparing with the mice treated with XJD alone. In this case, transcription factor SP1, which promotes tumor progress, is a target of miR-181a-5p. Upregulation of miR-181a-5p inhibits SP1 to increase the sensitivity to cisplatin and reduce the tumor size and weight (176). In cervical cancer, miR-181a-5p indirectly binds to glucose related protein GRP78, which promotes tumor progression and resistance to oxaliplatin, thus attenuating oxaliplatin resistance in drug-resistant cells and mouse model (89). Notably, another study revealed that miR-181a-5p/SFRP4 axis activates the Wnt/β-catenin pathway to reduce cisplatin sensitivity in ovarian cancer (98). These findings suggests that the effect of miR-181a-5p on the same drugs may be different in different types of cancer.

Overall, the studies indicated that miR-181a-5p can increase the sensitivity to platinum except in ovarian cancer. Using miR-181a-5p mimics to increase the miR-181a-5p expression may be a potential strategy for platinum resistance patients.

Other chemotherapeutic agents. MiR-181a-5p showed different effects on various chemotherapeutic agents. For example, it inhibits resistance of gemcitabine (64) and Ara-c (177), but promotes gefitinib resistance (178). Wnt/β-catenin pathway promotes resistance to 5-FU in colorectal cancer. MiR-181a-5p has been identified as an inhibitor of Wnt and PLAG1, and increases the 5-FU sensitivity of colorectal cancer cells (28,34). In melanoma, miR-181a-5p decreases in BRAF inhibitor (dabrafenib) resistant patients. MiR-181a-5p mimics inhibit mitochondrial transcription factor A and reverses dabrafenib resistance (179). In addition, promoting sensitivity of chemotherapy by using miR-181a-5p has been applied in a rat-seeded retinoblastoma model, which demonstrated that using lipid nanoparticles to co-deliver miR-181a-5p and melphalan can enhance the efficacy while reducing cytotoxic side effects by inhibiting BCL-2, MAPK1 and promoting Bax (180). In addition, Carmustine and TMZ are alkylating agents for glioma, and miR-181a-5p can promote sensitivity of carmustine (124); however, results of the effect of miR-181a-5p on TMZ was opposite in two independent studies (122,128).

6. Controversies

The present study elucidates the role of miR-181a-5p in cancers of different systems. These studies helped to understand the effects of miR-181a-5p on tumor progression, chemotherapy and revealed that it has the potential to be a biomarker. However, as a kind of miRNAs, miR-181a-5p is environment-dependent. Since miR-181a-5p can simultaneously bind to multiple targets (possibly oncogenes or tumor suppressor genes), and these targets express differently in different types of cancer, scientists often get conflicting results in the study of miR-181a-5p. Due to this uncertainty, it is difficult to actually put miR-181a-5p into clinical use. More research and clinical trials are needed to provide a further understanding of miR-181a-5p.

7. Conclusions

The present review summarizes some interesting studies on miR-181a-5p for its role in different systems of cancer. The dysregulation of miR-181a-5p has been implicated in various types of cancer and functions as an oncomiR or tumor inhibitor. Mechanistically, miR-181a-5p targets multiple mRNAs to regulate intricate and diverse signaling pathways. Additionally, numerous factors, such as ncRNAs and TFs, serve as upstream regulators that modulate the expression of miR-181a-5p.

MiR-181a-5p is capable of mediating cellular processes, such as proliferation, apoptosis, autophagy, angiogenesis and the regulation of tumor growth in xenograft models. It can also either promote or suppress the cell migration, invasion, EMT and tumor metastasis. In addition, miR-181a-5p shows promise as a potential biomarker and target to increase the sensitivity for chemotherapy. These findings may provide implications for oncological research and treatment strategies of cancer.

Acknowledgements

Not applicable.

Funding

This work was supported by the Project of Science and Technology Department of Sichuan Province (grant no. 2021YJ0445).

Availability of data and materials

Not applicable.

Authors' contributions

JL wrote the major parts of the manuscript and prepared the figures and tables. JS and YZ revised the manuscript. FD, ML, XW and YC prepared the manuscript. SW and ZX oversaw the process and wrote the manuscript. ZW conceptualized the study and oversaw the process. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

Authors declare that they have no competing interests.

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