

MicroRNA-195: a review of its role in cancers

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Abstract: MicroRNAs (miRNAs) are small and highly conserved noncoding RNAs that regulate gene expression at the posttranscriptional level by binding to the 3'-UTR of target mRNAs. Recently, increasing evidence has highlighted their profound roles in various pathological processes, including human cancers. Deregulated miRNAs function as either oncogenes or tumor suppressor genes in multiple cancer types. Among them, miR-195 has been reported to significantly impact oncogenicity in various neoplasms by binding to critical genes and signaling pathways, enhancing or inhibiting the progression of cancers. In this review, we focus on the expression of miR-195 in regulatory mechanisms and tumor biological processes and discuss the future potential therapeutic implications of diverse types of human malignancies.

Keywords: miR-195, cancers, biological processes, biomarker

Introduction

Cancer is one of the prevalent and deadly diseases threatening human health worldwide.¹ In recent decades, although great improvements have been achieved in the treatment of cancer, such as surgery, radiochemotherapy and chemotherapy, the 5-year survival rate for most cancer patients has remained very low due to the lack of efficient early biomarkers.² Therefore, the exploration of new diagnostic biomarkers and potential therapeutic strategies is urgently needed.

MicroRNAs (miRNAs) are tiny, highly conserved, noncoding silencing RNA molecules of ~22 nucleotides, which regulate gene expression by switching off gene expression or degrading mRNA at the posttranscriptional level.³ The first miRNA, lin-4, was identified in 1993, which regulates developmental timing by inhibiting the protein expression of lin-14 via binding the 3'-UTR of its mRNA.⁴ Until now, more than 2,500 known mature miRNAs have been identified in the human genome and recorded in the public miRbase database.⁵⁻⁷ More than ~30% of human protein coding genes are regulated by miRNAs.^{8,9} miRNAs are encoded by the noncoding region of gene, including intergenic or exonic regions or other genes.^{3,10} A single miRNA can effectively influence the expression of several dozen or even hundreds of different mRNAs, and each mRNA can simultaneously be regulated by multiple miRNAs.^{11,12} miRNAs play an unavoidable role in both physiological and pathological processes, such as embryogenesis, metabolism, proliferation, differentiation and apoptosis.¹³⁻¹⁶

Emerging data have revealed that miRNAs can target many of the programs that are tightly related to almost all aspects of cancer biopathological features, suggesting that miRNAs can play crucial roles in the pathogenesis of cancer, including initiation, promotion, malignant conversion, progression and metastasis of the oncogenic state.^{17,18} Based on the miRNA expression and its validated targets, miRNAs might function as oncogenes (oncomiRs) or tumor suppressors in cancer.¹⁹ Therefore, miRNAs are considered as diagnostic, prognostic and therapeutic biomarkers in almost all cancers.

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miR-195

miR-195 is one of the miR-15/107 family members, which are stress inducible and activated in multiple diseases, such as cancers, heart failure and schizophrenia. Members of the miR-15/107 group have a similar sequence, AGCAGC, near the 5' end of the mature miRNA, named AGCx2 miRNA.²⁰ The human miR-195 gene originates from intron 7, which is located on chromosome 17p13.1 and on the reverse strand of the mRNA gene AK098506, encoding an unknown functional protein.^{21,22} The predicted stem-loop structure of miR-195 determined using the miRBase (<http://mirbase.org/>) is shown in Figure 1A. The miR-195 hairpin gives rise to the “guide strand” miR-195-5p and the sister “passenger” strand miR-195-3p (Figure 1B). Dysregulation of miR-195 may contribute to the pathogenesis of multiple diseases. For example, miR-195 has been reported to be related to Alzheimer's disease (AD), regulating important brain growth factors related to schizophrenia.²³ In addition, miR-195 has been found to be upregulated during cardiac hypertrophy, and cardiac overexpression of miR-195 results in pathological cardiac growth and heart failure in transgenic mice.²⁴ In particular, miR-195 exerts its function by targeting the mRNAs of multiple proteins as oncogenes or tumor suppressors in several cancers, including breast cancer,²⁵ lung cancer,²⁶ prostate cancer (PCa),²⁶ gastric cancer (GC),²⁷ colorectal cancer (CRC),²⁸ hepatocellular cancer (HCC) and bladder cancer (BC).²⁹ In this review, we discuss the current knowledge about the effects and mechanisms of miR-195 in diverse types of malignancies (Table 1).

miR-195 in various cancers

miR-195 and digestive system cancer

HCC

HCC, ranked as the second leading cause of cancer mortality in human beings, is one of the most prevalent malignancies

worldwide.³⁰ HCC is difficult to diagnose at an early stage due to a lack of understanding of HCC formation and progression. Therefore, identifying novel tumor-suppressive molecules for HCC is urgently needed.

Xu et al³¹ discovered that miR-195 suppresses HCC to form colonies in vitro and to develop tumors in mice. The Rb-E2F signaling axis acts as a key checkpoint in cell cycle progression. In addition, miR-195 blocks the G1/S transition by repressing Rb-E2F signaling through regulating the expression of target genes, such as *CCND1*, *CDK6* and *E2F3*. In addition, Yang et al³² confirmed that miR-195 upregulation can promote apoptosis of HCC cells by increasing the expression of large tumor suppressor kinase 2 (*LATS2*) and *P53* while decreasing *CDK2* expression. *LATS2*, considered as a tumor suppressor gene, has been believed to cause cell cycle arrest via inhibition of *CDK2* activity.³³ Numerous studies have confirmed the essential roles of NF- κ B as a link between inflammation and cancer.³⁴ Ding et al³⁵ corroborated that miR-195 suppresses HCC development via the downexpression of multiple NF- κ B downstream effectors by directly targeting *IKK α* and *TAB3*. In addition, the suppression of HCC angiogenesis and metastasis by miR-195 was affirmed by Wang et al,³⁶ partly via targeting the proangiogenic factor *VEGF* and prometastatic factors *VAV2* and cell division control protein 42 homolog (*CDC42*). Protein-L-isoaspartate (D-aspartate) O-methyltransferase 1 (*PCMT1*), a member of the type II class of protein carboxyl methyltransferase enzymes, has been verified to be involved in increasing the cancer cell life span. *PCMT1* has been found to be negatively regulated in HCC by miR-195, which targets putative binding sites in its 3'-UTR.³⁷ Yang et al³⁸ presumed that miR-195 overexpression is important to regulate cell proliferation, cell cycle and apoptosis by targeting *WNT3A* in HCC. *WNT3A*, a member of the Wnt family, has been reported to serve as a key therapeutic

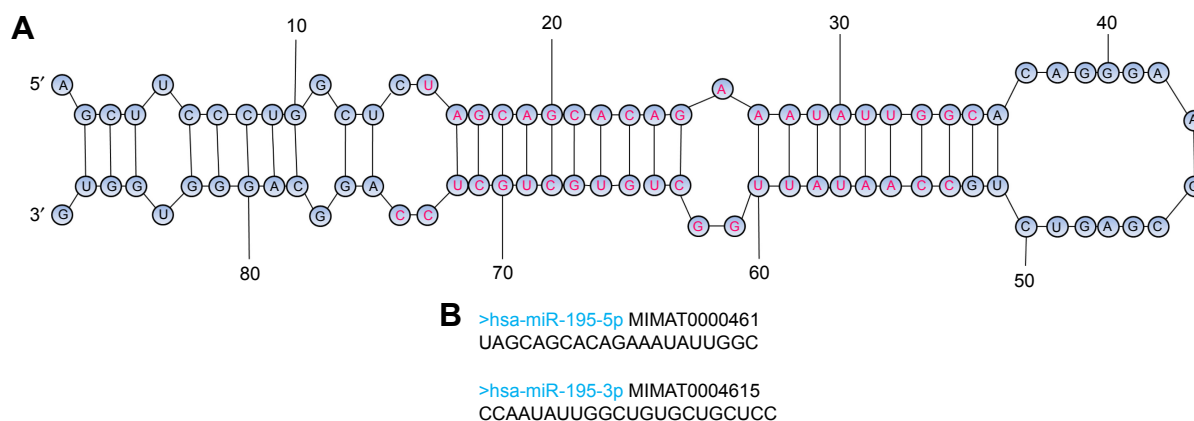


Figure 1 The structure and sequence of miR-195.

Notes: (A) Stem-loop structure of miR-195. (B) Mature sequence of miR-195. Two different mature miR-195 sequences, namely miR-195-5p and miR-195-3p.

Table 1 miR-195 alterations in cancers

Cancer type		Regulated expression	Target gene	Related functions	References
Digestive system cancer	HCC	Downregulated	<i>CCND1</i> , <i>CDK6</i> , <i>E2F3</i> , <i>Lats2</i> , <i>IKKα</i> , <i>TAB3</i> , <i>VEGF</i> , <i>PCMT1</i> , <i>WNT3A</i> , <i>SRC-3</i> , <i>CBX4</i> , <i>PHF19</i> , <i>FGF2</i> , <i>VEGFA</i> , <i>YAP</i> , <i>CDC42</i> , <i>VAV2</i>	Cell cycle, proliferation, migration, angiogenesis, metastasis, apoptosis, invasion	31, 32, 35–38, 41–45
	CRC	Downregulated	<i>BCL-2</i> , <i>CARMA3</i> , <i>YAP</i> , <i>CDK2</i> , <i>CDK8</i> , <i>FGF2</i> , <i>IGF2BP2</i> , <i>RAF1</i> , <i>CARM1</i> , <i>BCL2L2</i> , <i>WEE1</i> , <i>CHK1</i>	Apoptosis, viability, metastasis, proliferation, metastasis, migration, EMT, radioresistance, chemotherapy resistant	52–54, 56, 58, 61, 64, 67, 68
	GC	Downregulated	<i>CDK6</i> , <i>AKT3</i> , <i>bFGF</i>	Cell cycle, proliferation, migration, migration, invasion, chemotherapy resistant	27, 73, 75
Respiratory system cancer	EC	Downregulated	<i>CDC42</i>	Proliferation, invasion	81
	Lung cancer	Downregulated	<i>MYB</i> , <i>IGF1R</i> , <i>HDGF</i> , <i>CHK1</i>	Proliferation, migration, invasion, radiosensitivity	85, 86, 88, 89
	BC	Downregulated	<i>CDK4</i> , <i>GLUT3</i> , <i>BIRC5</i> , <i>WNT7A</i> , <i>CDC42</i> , <i>ARL2</i>	Cell cycle, proliferation, apoptosis, migration, invasion, viability	29, 96, 97, 101, 103
Urinary system cancer	Kidney cancer	Downregulated	<i>VEGFR2</i>	Proliferation, migration, invasion, metastasis	108
Bone cancer	OS cancer	Downregulated	<i>FASN</i> , <i>CCND1</i> , <i>NKD1</i>	Migration, invasion, metastasis	124, 127, 128
Brain cancer	Glioma	Downregulated	<i>E2F3</i> , <i>CCND3</i> , <i>CCND1</i> , <i>CCNE1</i>	Proliferation, invasion	133, 134
		Upregulated	Unknown	Chemotherapy resistant	136
		Downregulated	<i>CCND1</i> , <i>BCL-2</i>	Proliferation, apoptosis	138
Head and neck cancer	TSCC	Downregulated	Unknown	Prognosis biomarker	140
	HNSCC	Upregulated	<i>DCUN1D1</i> , <i>BCL-2</i>	Growth, invasion, apoptosis	142, 143
	LSCC	Downregulated	<i>TRIM14</i> , <i>CDK6</i>	Proliferation, invasion, migration	145, 146
Skin cancer	Melanoma	Downregulated	<i>PHB1</i>	Proliferation	150
		Upregulated	<i>WEE1</i>	Migration, invasion	148
		Downregulated	Unknown	Predictive biomarker for patient survival	174
Endocrine cancer	ACC	Downregulated			
	Thyroid cancer	Downregulated	<i>RAF1</i> , <i>CCND1</i> , <i>FGF2</i>	Proliferation, migration, invasion	176, 177
	PC	Downregulated	<i>DCLK1</i>	Proliferation, migration, invasion	179
Reproductive system cancer	Breast cancer	Downregulated	<i>CCNE1</i> , <i>ACACA</i> , <i>FASN</i> , <i>HMGCR</i> , <i>CYP27B1</i> , <i>RAF1</i> , <i>WNT3A</i> , <i>IRS1</i>	Cell cycle, EMT, angiogenesis, invasion, chemotherapy resistant	25, 154, 162, 163, 166, 168
		Downregulated	<i>HDGF</i> , <i>CCND1</i> , <i>CCND2</i> , <i>MYB</i> , <i>SMAD3</i>	Proliferation, migration, invasion	111–115
	CC	Downregulated	<i>BCOX1</i> , <i>FGF2</i> , <i>FRA-1</i> , <i>RPS6KBI</i> , <i>PRRI1</i>	Proliferation, metastasis, EMT, angiogenesis, migration	117–121
Reproductive system cancer	PCa	Downregulated			
		Downregulated			
		Downregulated			

Abbreviations: ACC, adrenocortical cancer; BC, bladder cancer; CC, cervical cancer; CRC, colorectal cancer; EC, esophageal cancer; EMT, epithelial–mesenchymal transition; GC, gastric cancer; HCC, hepatocellular cancer; HNSCC, head and neck squamous cell cancer; LSCC, laryngeal squamous cell carcinoma; OS, osteosarcoma; OSCC, oral squamous cell carcinoma; PC, pancreatic cancer; PCa, prostate cancer; TSCC, tongue squamous cell carcinoma.

target in tumorigenesis.³⁹ The steroid receptor coactivator-3 (*SRC-3*) is frequently amplified and overexpressed in multiple human cancers.⁴⁰ However, its molecular mechanism remains largely unexplored in HCC. The underlying mechanism of the miR-195 anti-proliferation activity in HCC occurs through the suppression of *SRC-3*.⁴¹ Furthermore, based on two other studies in 2015, miR-195 showed antiproliferative, anti-invasive and anti-migratory characteristics by inhibiting chromobox homolog 4 (*CBX4*) and PHD finger protein 19 (*PHF19*) gene expression in HCC.^{42,43} The lung is the most frequent metastatic organ site of HCC. Wang et al⁴⁴ found

that the expression of miR-195 is significantly downregulated in lung metastatic cell lines. Furthermore, they claimed that miR-195 functions as a vital suppressive regulator in lung metastasis of HCC by targeting angiogenesis-related gene fibroblast growth factor 2 (*FGF2*) and vascular endothelial growth factor A (*VEGFA*). Recently, Yu et al⁴⁵ demonstrated that miR-195 inhibits epithelial–mesenchymal transition (EMT) in HCC by suppressing *YAP*.

In another study, lncRNA small nucleolar RNA host gene 1 (*SNHG1*) was identified as a potential sponge of miR-195.⁴⁶ The function and clinical analysis of *SNHG1*

showed that it enhances HCC tissues and cell lines compared with normal tissues and cell lines. Downregulation of SNHG1 represses the proliferation and invasion of HCC cells and promotes the expression of miR-195. Furthermore, miR-195 has been reported to enhance the susceptibility of HCC cells to 5-fluorouracil (5-FU), at least in part by inhibiting the expression of Bcl-w.⁴⁷

Moreover, miR-195 has been recognized as a circulating miRNA, and its serum levels have been shown to be a diagnostic marker. The analysis of circulating exosomes isolated from HCC patients, together with chronic hepatitis (CHB) and liver cirrhosis (LC) patients, has also revealed the presence of miR-195 (downregulation in HCC), supporting serum exosomal miR-195 as a novel serological biomarker for HCC.⁴⁸ These studies indicate that miR-195 may participate in the pathogenesis of HCC and contribute to the diagnosis and prognosis of this disease.

CRC

CRC is the third most commonly diagnosed cancer and the third leading cause of cancer-related death in the USA, with more than 1 million people diagnosed annually.⁴⁹ Despite improvements in clinical diagnosis and treatment technology for CRC treatment, the 5-year survival rate of CRC is low due to a lack of effective interventions and specific diagnostic markers for early diagnosis.⁵⁰ Thus, it is essential to find novel therapy targets and valuable biomarkers for CRC.

Liu et al⁵¹ found that miR-195 is markedly decreased in surgically removed CRC tissues and cell lines compared with adjacent non-tumor tissues and normal cells. There is evidence that the upregulation of miR-195 can inhibit CRC cell proliferation via the downregulation of *CDK2* and *CDK8*^{52,53} and further promote CRC cell apoptosis and reduce cell viability by repressing expression of the antiapoptotic protein BCL-2.⁵⁴ Another study showed that miR-195 is significantly reduced in CRC patients with lymph node metastasis and an advanced tumor stage.⁵⁵ Furthermore, Wang et al⁵⁶ showed that miR-195 suppresses CRC cell proliferation and invasion in vitro by downregulating caspase recruitment domain and membrane-associated guanylate kinase-like domain protein 3 (*CARMA3*), which has been believed to play a vital role in tumorigenesis.⁵⁷ Signaling pathways, such as Hippo/YAP, also play crucial roles in CRC progression,⁵⁸ similar to the role of miR-195 described in HCC.⁴⁵ Previous studies have revealed that *FGF2* plays a significant role in cell growth, differentiation and function in CRC, and Wnt signaling was identified as a key pathway in tumor development and

progression.^{59,60} Zhang et al⁵² reported that miR-195 exerts antiproliferative functions by targeting *FGF2* and blocking the Wnt/ β -catenin pathway. Recently, insulin-like growth factor (IGF2) mRNA-binding protein 2 (*IGF2BP2*) was identified as a posttranscriptional regulatory mRNA-binding factor that contributes to CRC carcinogenesis.⁶¹ *RAF1*, also known as cRaf, is a member of the MAPK pathway and can be bound by miR-195 at its 3'-UTR.^{25,62} However, the expression of miR-195 is negatively correlated with *IGF2BP2* and *RAF1*, and *IGF2BP2* regulates *RAF-1* mRNA stability by affecting miR-195 synthesis in CRC.⁶¹

Furthermore, miRNA can serve as a target for the development of novel miRNA-based therapeutic strategies to overcome radioresistance.⁶³ A very recent study showed that miR-195 sensitizes CRC cells to radiation through the regulation of genes involved in cell proliferation and survival, such as coactivator-associated arginine methyltransferase 1 (*CARM1*).⁶⁴ *CARM1*, also known as *PRMT4*, can exert both oncogenic and tumor-suppressive functions.^{65,66} Recent studies have also reported that miR-195 is significantly associated with the regulation of drug resistance. For example, miR-195 has been demonstrated to sensitize the CRC lines, HT29 and LOVE, to doxorubicin by directly targeting *BCL2L2*, which is described as an important antiapoptotic regulator by suppressing the death-promoting activity.⁶⁷

Nevertheless, a puzzling result was reported by Kim et al,⁶⁸ in which miR-195 desensitized human CRC HCT-116 cells to 5-FU through direct inhibition of the expression of the G2 checkpoint kinase *WEE1* and checkpoint kinase (*CHK1*). Although it is difficult to determine why miR-195 has opposite functions in the regulation of drug sensitivity in CRC, we inferred that the role of miR-195 might be affected by the disease stage and cell type-specific environment. In addition, miR-195 expression levels might be used as a predictive factor for early detection and screening of CRC in the meta-study by Li et al.⁶⁹ Thus, miR-195 may be a novel marker reflecting the development of CRC.

GC

GC, which develops from the lining of the stomach, is one of the most lethal malignancies of the digestive system.⁷⁰ The 5-year survival rate of GC patients is unsatisfactory due to its recurrence and metastasis.⁷¹ The majority of GC patients are diagnosed at an advanced stage given the lack of appropriate biomarkers and specific early symptoms. Therefore, it is urgent to discover novel and suitable prognostic biomarkers

of GC. Until now, dysregulation of miRNA expression is considered to play a crucial role in GC development.⁷²

In the study by Deng et al,²⁷ miR-195 was found to be abnormally expressed and epigenetically regulated in GC cell lines and tissues via the suppression of CDK6 and VEGF signaling. In addition, miR-195 played a critical role in suppressing tumor progression in human GC in vitro and in vivo, probably exerting its role by modulating its target gene *AKT3*.⁷³ AKT3 is a member of the AKT subfamily of serine/threonine protein in the PI3K/AKT signaling pathway, which plays a significant role in many human cancers including GC.⁷⁴ Moreover, miR-195 has a significant effect on the chemotherapy sensitivity of cisplatin and clinical prognosis.⁷³ Another investigation revealed that, by interacting with *bFGF* 3'-UTR, overexpression of miR-195 could decrease *bFGF* expression and repress cellular migration and invasion of the GC cell lines, SNU-1 and KATO-3, as well as tumor formation in a xenograft mouse model.⁷⁵ bFGF is a pro-tumor factor that is involved in cancer angiogenesis, metastasis and tumor infiltration.⁷⁶

Emerging studies have examined the prognostic role of miR-195 in GC. The levels of miR-195 are highly decreased in patient-derived GC tissue and plasma of GC patients compared with paracancerous tissue and plasma in the healthy control group. In addition, decreased miR-195 is negatively associated with distant lymph node metastasis, an advanced clinical stage and infiltration in GC patients.⁷⁷ Overall, these data suggest that miR-195 could be used as a diagnostic and prognostic marker of GC.

Esophageal cancer (EC)

EC, as a major global health challenge, is the eighth most common malignancy and sixth leading cause of cancer-related death worldwide.⁷⁰ There are two major subtypes of EC in terms of distinct etiology and epidemiology: esophageal squamous cell carcinoma and esophageal adenocarcinoma (OAC). Oral squamous cell carcinoma (OSCC) is the predominant histological type of EC, accounting for more than 90% of all EC cases globally.⁷⁸ Despite extensive studies and significant improvements in diagnosis and treatment, the overall 5-year survival is still dismal at <10%–15%.⁷⁹ Thus, it is imperative to discover molecular biomarkers for early tumor detection and novel effective therapeutic methods.

Several published papers suggest miR-195 as a tumor suppressor in OSCC. First, by using a microarray assay, miR-195 was found to have decreased expression in OSCC compared with paired non-OSCC tissue.⁸⁰ Another study

demonstrated that miR-195 reduces the proliferation and invasion of OSCC cells. The researchers argue that the antiproliferative and anti-invasion effects of miR-195 can be attributed to its suppression of *CDC42*.⁸¹ *CDC42*, a Rho family GTPase, is involved in the regulation of the cell cycle and has been shown to be overexpressed in various human cancers.⁸² Furthermore, Sun et al⁸³ observed that combined expression of miR-195/*CDC42* is a more efficacious prognostic marker for progression-free survival and overall survival of OSCC patients than miR-195 or *CDC42* alone. These studies lay the foundation for further analysis of miR-195 as a novel therapy for EC.

miR-195 and the respiratory system cancer

Lung cancer

Lung cancer is the number one cause of cancer mortality in both sexes worldwide. Non-small-cell lung cancer (NSCLC) is a major class of lung cancer, accounting for nearly 80% of all lung cancer cases.⁸⁴ Thus, a better understanding of the mechanism underlying NSCLC progression is urgently needed.

miR-195 has been shown to serve as a tumor suppressor by inhibiting NSCLC cell proliferation, migration and invasion via targeting *MYB*.⁸⁵ In addition, miR-195 has been found to diminish NSCLC cell proliferation and metastasis, partly by targeting insulin-like growth factor 1 receptor (*IGF1R*),⁸⁶ which plays a positive role in tumorigenesis.⁸⁷ Another two studies have expanded the suppressive role of miR-195 in NSCLC. Guo et al⁸⁸ suggested that miR-195 is a tumor suppressor in NSCLC by targeting hepatoma-derived growth factor (*HDGF*), which is expressed in many cancers. In addition, checkpoint kinase 1 (*CHK1*), a potential target for cancer therapy, is downregulated by miR-195 according to Liu et al.⁸⁹

Furthermore, Wu et al⁹⁰ showed that an oncogenic LncRNA (PVT1) regulates the effect of NSCLC cells on radiosensitivity by sponging miR-195 and that these effects can be reversed by miR-195 overexpression. Therefore, miR-195 might be used as a promising biomarker for the diagnosis and as a potential target for the treatment of NSCLC in the future.

miR-195 and urinary system cancer

BC

BC is believed to be one of the most prevalent genitourinary tract malignancies in both sexes worldwide.⁹¹ Approximately

386,000 new cases of BC patients and 150,000 deaths occur globally each year.⁹² Many factors contribute to the carcinogenesis of BC, such as genetic and epigenetic alterations, especially the downregulation of tumor suppressors.⁹³ However, the molecular mechanisms of bladder tumorigenesis remain unclear. Therefore, it is necessary to elucidate new detailed mechanisms and to identify effective diagnostic biomarkers in BC.

Canturk et al⁹⁴ aimed to construct miRNA regulatory networks of BC-related miRNAs and their target genes using microarray and Kyoto Encyclopedia of Genes and Genomes enrichment analysis. The results of their study revealed reduced expression of hsa-miR-195-5p in human BC compared with normal bladder urothelium. Moreover, they showed that hsa-miR-195-5p, hsa-let-7c and hsa-miR-125b-5p hub miRNAs along with *CDK6*, *CDK4* and *ERBB3* hub genes might exist in the same BC pathway. Perturbation of *CDK4*, the key regulator of the G1/S transition, together with cyclin D1 is linked to cancer and tumorigenesis.⁹⁵ In another paper, *CDK4* has also been verified as a direct target of miR-195, which exerts a growth-suppressing function in the BC cell line, T24.⁹⁶ Another report has demonstrated that miR-195 decreases T24 glucose uptake and inhibits cell proliferation while inducing cell apoptosis by negatively regulating GLUT member 3 (*GLUT3*).⁹⁷ GLUT3 is a member of GLUTs, which has greater transport capacity and a higher affinity for glucose to support tumorigenesis compared with other GLUT members.⁹⁸ By using deep sequencing technology, Itesako et al²⁹ confirmed that the downregulation of the miR-195/497 cluster contributed to BC progression and metastasis. Transfection of mature miR-195 or miR-497 into two BC cell lines (BOY and T24) significantly inhibited cancer cell proliferation, migration and invasion, suggesting that the miR-195/497 cluster functioned as a tumor suppressor in BC by directly targeting *BIRC5* and *WNT7A*.²⁹ *BIRC5* is a member of the inhibitor of apoptosis (IAP) family regarded as an oncogene and reported as a diagnostic biomarker for BC.^{99,100} In addition, Zhao et al¹⁰¹ found that miR-195 could significantly inhibit the proliferation of BC cells in vitro, partially via the inhibition of Cdc42/STAT3 signaling.

Urothelial cancer-associated 1 (UCA1) is an lncRNA that is highly expressed in BC tissues and has been reported to play oncogenic roles in BC progression.¹⁰² A recent paper indicated that UCA1 enhances mitochondrial function and BC cell viability by functioning as an important ceRNA for miR-195 to regulate its target gene ADP-ribosylation factor-like GTPase 2 (*ARL2*) in vivo and in vitro.¹⁰³ *ARL2*

is an activator of ATP/ADP transporters belonging to the ADP-ribosylation factor family,¹⁰⁴ functions in both cytosol and mitochondrial and is located in the inner membrane space of mitochondria.¹⁰⁵ Elucidation of UCA1/miR-195/*ARL2* signaling network provides important clues for understanding the molecular pathology of BC. Collectively, these studies indicate that miR-195 could be used as a potentially valuable biomarker for BC diagnosis and therapy.

Kidney cancer

Renal cell carcinoma (RCC) is one of the most malignant diagnostic urological cancers of the adult kidney. RCC accounts for approximately 3% of cancers and resulted in an estimated 13,860 deaths in the USA in 2014.¹⁰⁶ Clear cell RCC (ccRCC) is the main histological category of RCC, accounting for 75% of cases.¹⁰⁷ Based on Sun et al,¹⁰⁸ the expression levels of miR-195 in ccRCC samples were significantly reduced compared with the control groups. Moreover, the overexpression of miR-195 could suppress the proliferation, migration, invasion and apoptosis of a human ccRCC cell line (ACHN) through inhibiting both the Raf/MEK/ERK and the PI3K/AKT signaling pathways by targeting *VEGFR2*. In addition, Wang et al¹⁰⁹ showed that miR-195-5p together with miR-29a-3p/29 c-3p participates in androgen receptor (AR)-enhanced ccRCC cell metastasis, which indirectly confirmed that miR-195 functions as a suppressor in RCC. Overall, these findings help to define miR-195 as a tumor suppressor in RCC, yet more work is needed to elucidate its use as a potential therapeutic approach for RCC.

miR-195 and reproductive system cancer Cervical cancer (CC)

Among women worldwide, CC is one of the most prevalent gynecological malignancies, ranked as the fourth leading cause of cancer-associated mortality.⁷⁰ However, the mechanisms underlying the oncology of CC are still largely unknown. Therefore, novel biomarkers and effective therapeutic targets for early detection and treatment of CC are urgently needed.

The miR-195 level in serum can be used for the diagnosis of CC. Zhang et al¹¹⁰ conducted a study of miRNA markers in CC patients' serum and found that the levels of four miRNAs (miR-195, miR-16-2*, miR-2861 and miR-497) were differentially expressed in the serum of CC patients compared with normal controls and considered them as novel noninvasive biomarkers for the detection of CC. Song et al¹¹¹

analyzed the behavior of CC tumors by MTT using a dual luciferase reporter assay and showed that the overexpression of miR-195 inhibited cell proliferation, migration and invasion by suppression of *HDGF*. The anti-tumorigenic role of miR-195 in CC was not solely due to *HDGF*, as miR-195 also targets *CCND1*, *CCND2*, *MYB* and *SMAD3* in CC.^{112–115} *SMAD3*, a member of the SMAD family, is related to tumor growth in cancer progression.¹¹⁶ In general, miR-195 shows advantageous characteristics as a novel biomarker for early diagnosis and as a therapeutic target in CC.

PCa

PCa is the most commonly diagnosed cancer in the male population worldwide and accounted for approximately 30,000 American deaths in 2014.¹⁰⁶ The dramatic decrease in the survival rate in late-stage PCa is largely attributed to metastasis, highlighting the need to develop therapeutic options for advanced PCa. Studies investigating PCa have revealed that miR-195 acts as a tumor suppressor, and mechanistically, researchers have identified several miR-195 targets in PCa. Concretely, miR-195 can regulate the invasiveness of PCa cells and metastasis of PCa xenografts by regulating breast cancer-overexpressed gene 1 (*BCOX1*).¹¹⁷ In addition, Liu et al¹¹⁸ demonstrated that miR-195 specifically inhibits the EMT process of PCa cells through its target gene *FGF2*. In addition, in PCa cell lines, miR-195 shows an inhibitory effect on cell migratory ability by targeting Fra-1, which is overexpressed in several tumors.¹¹⁹ In addition, miR-195 can be implicated into the progression of PCa by regulating ribosomal protein S6 kinase B1 (*RPS6KB1*) signaling, and thus the miR-195-*RPS6KB1* axis represents a novel potential therapeutic target for PCa treatment.¹²⁰ A follow-up study from this group in 2018 claimed that miR-195 could directly inhibit the expression of proline rich 11 (*PRR11*) and that the upregulation of miR-195 or knockdown *PRR11* could suppress PCa angiogenesis and proliferation in vivo and in vitro.¹²¹ Overall, miR-195 could serve as a biomarker and therapeutic target in PCa.

miR-195 and bone cancer

Osteosarcoma (OS)

OS is a prevalent primary malignant bone cancer with high morbidity and mortality in youths, the incidence of which is approximately 4 million per year worldwide.¹²² Due to the high metastasis and recurrence potential, it is of great importance to explore new targets for the treatment of OS metastasis. The circulating miRNAs present in the serum

and plasma of OS patients are valuable for the early detection and prognosis prediction of OS. For example, a low level of circulating miR-195-5p and miR-199a-3p levels in plasma was significantly associated with metastasis among patients with OS.¹²³ In OS, miR-195 was observed to suppress tumorigenicity by targeting multiple pro-survival genes. In the OS cell line, U2OS, restoration of miR-195 markedly inhibited cell invasion and migration by directly targeting fatty acid synthase (*FASN*).¹²⁴ *FASN*, an enzyme that is crucial in endogenous lipogenesis, plays a key role in cancer cell metastasis.^{125,126} In addition, miR-195 also targets *CCND1* and naked cuticle homolog 1 (*NKDI*) in independent studies, thus inhibiting OS cell proliferation and metastasis in vivo and in vitro.^{127,128} As one negative regulator of Wnt signaling pathway, *NKDI* is overexpressed in certain types of cancer.^{129,130} Overall, these findings indicate the crucial role of miR-195 in OS and the potential ability of miR-195 to serve as a promising prognostic factor for OS.

miR-195 and brain cancer

Glioma

Glioma is the most lethal primary malignant brain neoplasm, leading to significant mortality worldwide annually.¹³¹ Some research papers have reported that miR-195 has the ability to diminish the progression of glioma. Lakomy et al¹³² demonstrated a significant downregulation of miR-195 in glioblastoma multiforme samples compared with control nonmalignant brain tissues. Based on the study by Zhang et al,¹³³ miR-195 plays a role in impairing glioblastoma cell proliferation and invasion by targeting *E2F3* and *CCND3*. Furthermore, Hui et al reported that miR-195 can inhibit the proliferation of human glioma cells by directly targeting *CCND1* and *CCNE1*.¹³⁴

In stark contrast to the abovementioned studies, there is evidence that miR-195 is an oncogenic miRNA in glioma. Ujifuku et al¹³⁵ concluded that miR-195 along with miR-455-3p and miR-10a* are upregulated in glioblastoma multiforme, inducing enhanced temozolomide resistance, yet the knockdown of miR-195 can reverse temozolomide resistance. In a separate study, miR-195 showed a sevenfold decrease in the expression of cyclosporin A (CsA)-treated U-87 MG glioma cells, suggesting that miR-195 might act as an oncogene in glioma.¹³⁶ These studies revealed that miR-195 overexpression might assist with the spread of glioma, while others have demonstrated its suppressive effects.

miR-195 and head and neck cancer

Head and neck cancer, which ranks fifth among all carcinomas, is a group of cancers that start within the mouth, larynx, nose, throat, sinuses or salivary glands with an incidence of 500,000 new cases annually.¹³⁷ Cumulative data clearly suggest that miR-195 should be explored as a prognostic marker for various types of head and neck cancers. Jia et al¹³⁸ demonstrated a decrease in miR-195 expression in tongue squamous cell carcinoma (TSCC) compared with adjacent nonmalignant tissues and provided evidence that miR-195 may be a prognostic factor for TSCC patients. Moreover, the antitumor effects of miR-195 in TSCC may be partially mediated by its inhibition of *CCND1* and *BCL-2* expression.¹³⁸ Based on the study by Santos et al,¹³⁹ miR-195, miR-17, miR-132 and miR-221 seem to play crucial roles as tumor suppressors in salivary function. However, Summerer et al¹⁴⁰ reported opposite data in a study of differential plasma miRNA expression between head and neck squamous cell cancer (HNSCC) patients and healthy individuals. They observed that high plasma expression of miR-195-5p in a panel of four miRNAs (miR-142-3p, miR-185-5p, miR-574-3p, miR-374-5p) is correlated with worse HNSCC prognosis.

Laryngeal squamous cell carcinoma (LSCC) is accounting for about 25% of the total head and neck cancer cases.¹⁴¹ Recently, two papers from the same group have reported that miR-195 significantly suppresses the growth and invasion of LSCC by targeting defects in cullin neddylation 1, domain containing 1 (*DCUN1D1*).¹⁴² In addition, it favors Hep-2 apoptosis by silencing *BCL-2*,¹⁴³ which would provide candidate targets for LSCC therapy. OSCC is also a common head and neck neoplasm with a poor prognosis.¹⁴⁴ Repression of tripartite motif-containing protein 14 (*TRIM14*), which is involved in many biological processes through the NF- κ B signaling pathway, by miR-195 in OSCC cells results in proliferation, migration and invasion inhibition.¹⁴⁵

Oral verrucous carcinoma (OVC) is a verrucous variant of OSCC. A study suggested a negative relationship between miR-195 and *CDK6* and further verified that miR-195 and its target gene *CDK6* could be regarded as potential diagnostic biomarkers and therapeutic targets of OVC.¹⁴⁶ These results suggested that miR-195 could serve as a potential therapeutic target and promising biomarker in head and neck cancer. Thus, miR-195 merits further exploration in future studies.

miR-195 and skin cancer

Melanoma

By far, melanoma is one of the most aggressive and deadly forms of skin cancer. Approximately 200,000 new cases and

46,000 deaths worldwide have been reported to be due to melanoma, with a 5-year survival rate of <15%.^{1,147} Therefore, the diagnostic biomarkers and research to identify more effective treatment modalities are essential. Studies on the function of miR-195 in melanoma have drawn various but sometimes conflicting conclusions. One study on miR-195 in melanoma investigated the biological relevance of *WEE1* and miR-195 in melanoma cell lines in vitro. Concretely, the authors discovered that miR-195 overexpression could enhance the migration and invasion of melanoma cells by directly inhibiting *WEE1* expression.¹⁴⁸ *WEE1*, a G2 checkpoint regulator, influences cell entry into mitosis by inhibiting *CDC2*, which induces G2/M progression in the cell cycle.¹⁴⁹

Nevertheless, contrasting results have been revealed by Cirilo et al,¹⁵⁰ who showed that miR-195 functions as an antiproliferative role in melanoma cells by targeting human prohibitin 1 gene (*PHB1*). *PHB1* is a highly conserved protein, which is best known as a mitochondrial chaperone, and is required for the proliferation and growth of cancer cells.¹⁵¹ As a result, we explored whether miR-195 could function as an enhancer or a suppressor in the progression of melanoma tumors.

miR-195 and endocrine cancer

Breast cancer

Globally, breast cancer is the leading cause of cancer death among females, accounting for approximately 1.5 million new cases per year.¹⁵² Distant metastasis and drug resistance have been regarded as major challenges in the treatment of breast cancer.¹⁵³ Hence, it is a priority to identify reliable biomarkers that can predict tumor progression and drug responsiveness.

Several independent research groups have demonstrated an inhibitory effect of miR-195 on breast cancer development. Luo et al¹⁵⁴ demonstrated that miR-195 is capable of inhibiting proliferation and colony formation in breast cancer cells in vitro by directly targeting a key cell cycle-related gene, *CCNE1*. *CCNE1*, which is one of the members of the cyclin family that drives cells from G1 to S phase, functions as an oncogene in many types of human cancers.^{155,156} In addition, miR-195 is also involved in lipid metabolism, which plays an important role in breast cancer. Acetyl-CoA carboxylase alpha (*ACACA*) and *FASN* are two key enzymes in de novo fatty acid synthesis, and they are highly elevated in breast cancer.^{157,158} As an important enzyme for de novo cholesterol synthesis, 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*) is a potential

anticancer molecule for breast cancer as well as other cancer types.¹⁵⁹ Cytochrome P450 superfamily 27, subfamily B member 1 (CYP27B1) is upregulated in breast cancer and participates in calcium homeostasis and steroid biosynthesis, among other functions.^{160,161} miR-195 can significantly attenuate EMT in breast cancer via the downregulation of *ACACA*, *FASN*, *HMGCR* and *CYP27B1* by co-targeting their 3'-UTR regions.¹⁶² Wang et al¹⁶³ established that miR-195 may be relevant to angiogenesis in the development of breast cancer. Mechanistically, miR-195 functions as a tumor suppressor in breast cancer via the IRS1-VEGF axis. It is well known that IRS1 is a signaling adapter protein involved in cancer progression, including breast cancer.¹⁶⁴ The control of miR-195 expression may be related to epigenetic events, such as DNA methylation in breast cancer. Based on bisulfate restriction analysis and bisulfite sequencing, Li et al²⁵ found that miR-195 and miR-197 are downregulated in human breast cancer tissues and cell lines due to the CpG islands upstream of the miR-195/497 gene methylation state. The authors identified miR-195 as a tumor suppressor that inhibits breast cancer cell colony formation and invasion in vitro partially by downregulating *Raf-1*.²⁵ Raf-1 is a part of the MAPK/REK signal transduction pathway and has been reported to undergo mutation into an oncogene in human tumors.¹⁶⁵ Another study has illustrated that through inhibition of *Raf-1*, miR-195 upregulation sensitizes MCF-7 breast cancer cells to adriamycin treatment.¹⁶⁶ Triple-negative breast cancer (TNBC) is a heterogeneous subtype of breast cancer characterized by the absence of estrogen, progesterone and HER-2 receptor expression, accounting for approximately 12%–17% of breast cancer cases, having a poor prognosis, and accompanied by a high risk of recurrence.¹⁶⁷ Furuya et al¹⁶⁸ reported that eribulin treatment strongly increases miR-195 levels in a non-basal-like type of TNBC cell line, MDA-MB-231,¹⁶⁸ and miR-195 was reported to downregulate Wnt3a in the same work.

There is emerging evidence supporting the prognostic role of miR-195 in breast cancer. For example, serum levels of miR-195 were clearly higher in the earliest stage of disease in Turkish breast cancer patients compared with disease-free controls.¹⁶⁹ In addition, miR-195 has demonstrated utility in the prognosis of breast cancer, as reported by Nadeem et al,¹⁷⁰ who demonstrated that the decrease in the expression of miR-195 in plasma samples of breast cancer patients was strikingly correlated with clinicopathological features, including a higher differentiation grade, lymph node metastasis and the clinical stage. Likewise, Zhao et al¹⁷¹ noted that

the expression of miR-195 was notably downregulated in the serum of breast cancer patients and could be used to discriminate breast cancer from control samples with a sensitivity of 69.0% and specificity of 89.2%. These results suggest that serum miR-195 may represent a novel diagnostic biomarker for breast cancer.

Adrenocortical cancer (ACC)

ACC is a rare but aggressive type of endocrine malignancy that occurs in approximately one to two people per million in the population. Patients with ACC generally have a poor outcome, with a 5-year survival rate of 30%.¹⁷² Therefore, it is urgent to identify diagnostic and therapeutic biomarkers for this disease. According to the study by Soon et al,¹⁷³ miR-195 is significantly downregulated in ACC and often inversely associated with poorer disease-specific survival. Subsequently, Carbra et al¹⁷⁴ found that patients suffering from ACC have low circulating miR-195 and high miR-483-5p levels in serum, implying that circulating miR-195 and miR-483-5p could be promising predictive biomarkers with high prognostic value for ACC patients.

Thyroid cancer

Thyroid cancer is the most common endocrine-relevant cancer, and the incidence of which has been dramatically increasing worldwide in recent years.¹⁷⁵ A study by Wang et al¹⁷⁶ sought to expound the role of miR-195 in thyroid cancer. They reported that miR-195 was downregulated in 50 pairs of thyroid tumor tissues relative to the adjacent non-tumor tissues. Functional studies have suggested that miR-195 acts as a tumor suppressor by inhibiting thyroid cancer cell proliferation, and in vitro experiments have identified the proto-oncogene *RAF-1* as a direct target of miR-195.¹⁷⁶ A similar study has shown that miR-195 is underexpressed in papillary thyroid carcinoma (PTC).¹⁷⁷ In that study, functional analyses suggested that miR-195 inhibits tumor growth by targeting *CCND1* and suppresses migration and invasion by targeting *FGF2* in PTC cells. Furthermore, miR-195 might suppress the Wnt/ β -catenin signaling pathway, which is critical in PTC pathogenesis.¹⁷⁷ Thus, the abovementioned studies support miR-195 as a promising potential therapeutic target for thyroid cancer.

Pancreatic cancer (PC)

PC, the fourth leading cause of cancer-related mortality in USA, continues to be one of the most aggressive malignancies, which is estimated to become the second leading cause of cancer death by 2030.¹⁷⁸ There is a single report

that miR-195 is a tumor-suppressive miRNA in PC, as miR-195 was expressed less in PC tissues and cell lines compared with normal controls.¹⁷⁹ The overexpression of miR-195 in the PC cell line, AsPC-1, caused a reduction in proliferation, migration and invasion by negatively regulating doublecortin-like kinase 1 (*DCLK1*), whereas the down-regulation of miR-195 had an opposite effect.¹⁷⁹ *DCLK1*, a microtubule-binding member of the calmodulin-dependent kinase family, plays a key role in initiation and progression, which can also negatively regulate several tumor suppressor miRNAs.^{180,181}

Overall, all the abovementioned studies suggest that miR-195 can act as a valuable biomarker for the diagnosis and prognosis of endocrine cancer.

Conclusion

In this review, we have focused on multiple mechanisms of miR-195 in various types of cancer and their potential roles in cancer diagnosis, differential prognosis and therapy evaluation. miR-195 is oncogenic or tumor suppressive and involved in a broad range of cancerous cellular

processes, including proliferation, metastasis, invasion, apoptosis, angiogenesis (Figure 2) and chemosensitivity (Figure 3) or as a tumor promoter. The mechanisms by which miR-195 mediates its action are extremely complicated and involved in various signaling pathways, such as Rb-E2F, PI3K/AKT, NF- κ B, MAPK/REK, Wnt/ β -catenin and Hippo/YAP. In molecular genetics, the 3'-UTR represents one section of mRNA that contains various binding sites for regulatory proteins as well as miRNAs that posttranscriptionally influence gene expression. Based on luciferase assays from all the studies reviewed herein, we determined that miR-195 could function as a tumor suppressor or promoter by binding to the 3'-UTR in the mRNA of its target genes in various cancers.^{25,37,75,86,112,162} In addition, the miR-195 and lncRNA regulatory paradigms modulate gene expression patterns that regulate tumor progression (such as cell proliferation, invasion and radiosensitivity; Figure 4). Greater recognition of the roles of miR-195 and lncRNAs in carcinogenesis could provide new insights into the mechanisms of tumor development and identify new diagnostic markers and therapeutic

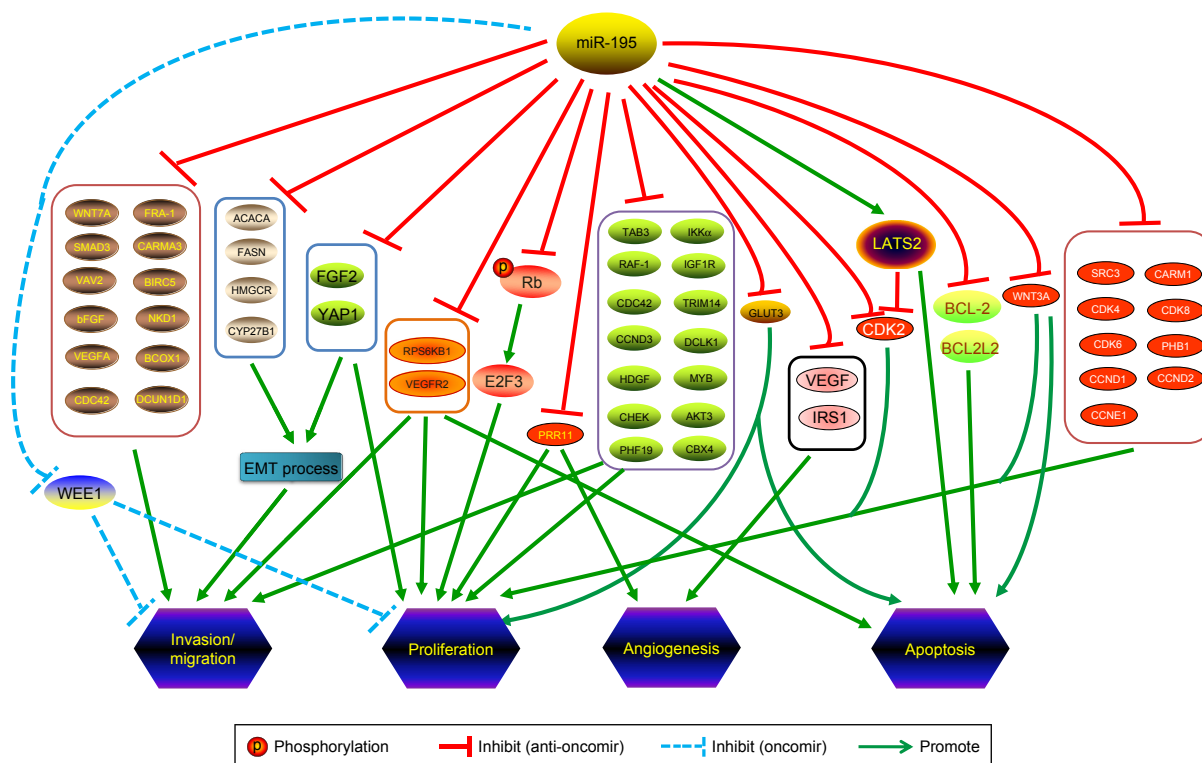


Figure 2 Roles of miR-195 in the progression and development of malignant tumors and its target genes.

Note: The direct targets and indirect effectors of miR-195 are shown with their multiple functions in cancer cell processes (EMT, invasion/migration, proliferation, angiogenesis and apoptosis).

Abbreviation: EMT, epithelial–mesenchymal transition.

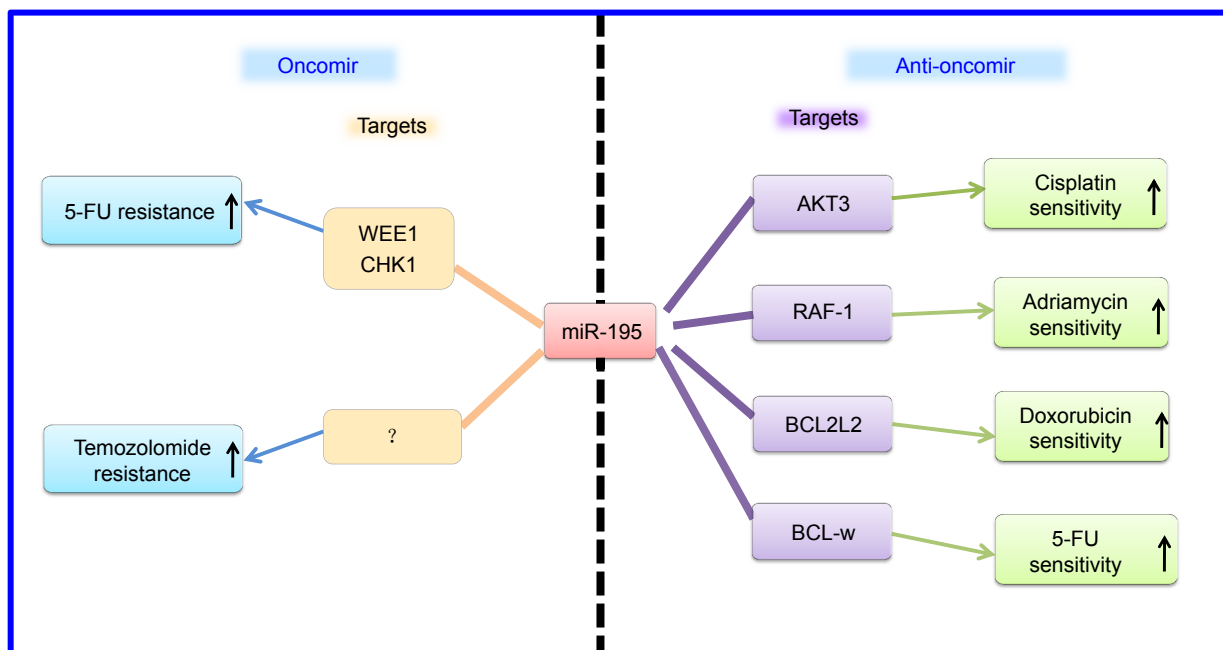


Figure 3 Summary of the diverse roles of miR-195 in drug sensitivity.

Abbreviation: 5-FU, 5-fluorouracil.

approaches for anticancer drug development. Nevertheless, the complex mechanisms of miR-195 involved in cancer development are still in the early stage, which should be systematically explored. Therefore, multicenter studies are needed before the experimental findings for miR-195 can be applied in the clinic to treat various types of human cancers.

In conclusion, the current review indicates that miR-195 may act as a potentially useful tumor biomarker for cancer diagnosis and therapy. Combined use of miR-195 and other conventional tumor markers may be a promising direction for clinical diagnosis.

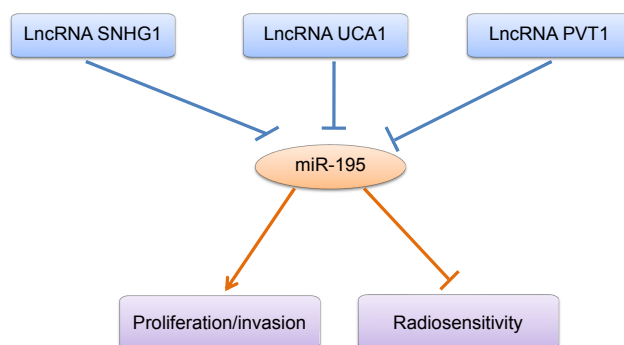


Figure 4 Roles of miR-195 and LncRNA-miR-195 interactions in regulating tumor progression.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (grant no 31601194) and Natural Science Foundation of Shandong Province (JQ201815).

Disclosure

The authors report no conflicts of interest in this work.

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