Review - miR-495–3p as a promising tumor suppressor in human cancers

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Review

miR-495–3p as a promising tumor suppressor in human cancers

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ABSTRACT

Noncoding RNAs are a type of cellular RNA not having the ability to translate into proteins. As an important type of ncRNA with a length of about 22 nucleotides (nt), microRNAs were revealed to contribute to regulating the various cellular functions via regulating the protein translation of target genes. Among them, available studies proposed that miR-495–3p is a pivotal player in cancer pathogenesis. These studies showed that the expression level of miR-495–3p decreased in various cancer cells, suggesting its tumor suppressor role in cancer pathogenesis. Long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) are the important regulators of miR-495–3p via sponging it, leading to increased expression levels of its target genes. Moreover, miR-495–3p was shown to have a promising potential to be a prognostic and diagnostic biomarker in cancer. MiR-495–3p also could affect the resistance of cancer cells to chemotherapy agents. Here, we discussed the molecular mechanisms of miR-495–3p in various cancer including breast cancer. In addition, we discussed the miR-495–3p potential as a prognostic and diagnostic biomarker as well as its activity in cancer chemotherapy. Finally, we discussed the current limitations regarding the use of microRNAs in clinics and the future prospects of microRNAs.

1. Introduction

MicroRNAs (miRNAs), as a type of noncoding RNAs (ncRNAs) with a length of about 22 nucleotides (nt), modulate the post-transcriptional processes by interacting with the 3′-untranslated region (3′-UTR) or open reading frame (ORF) of target messenger RNAs (mRNAs). mRNAs could be modulated by various miRNAs, and each miRNA could regulate multiple mRNAs. As a result of their effect on various signaling genes, miRNAs are regarded as crucial regulators in pathophysiological situations. Moreover, secreted miRNAs could circulate in biological fluids like blood, saliva, and urine, suggesting that they can be regarded as promising diagnostic and prognostic biomarkers in diseases [1]. MicroRNAs, after identifying in the 1990 s, alter our knowledge regarding the regulation of gene expression [2]. After that, accumulating results showed that miRNAs are the pivotal modulators of a variety of biological processes, including cell differentiation, cell death, and development. Additionally, miRNAs have been linked to the development of a number of human diseases, including cancer, cardiovascular conditions, and neurological problems [3].

By modulating the various genes engaged in cancer-related processes like cell cycles, apoptosis, and DNA damage, miRNAs are becoming crucial regulators of carcinogenesis. Various cancers usually exhibited

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various miRNA expression, and some miRNAs have been suggested as a possible prognostic and diagnostic biomarker. In preclinical investigations, manipulating miRNA targets using miRNA-based therapeutics showed promising results with lower unwanted side effects [3]. The delivery of miRNAs to specific cells and the possible unwanted outcomes are still problems in the creation of successful miRNA-based therapeutics. So, further research is needed to improve the efficacy of miRNA-based therapy and better in cancer pathophysiology, additional study is required [4]. Emerging data suggested that miR-495–3p may contribute to cancer pathogenesis by regulating the signaling pathway related to cancer onset and metastasis. These data showed that the expression level of miR-495–3p decreased in various cancers like colorectal cancer [5], melanoma [6], breast cancer [7], gastric cancer [8], leukemia [9], pancreatic cancer [10], lung cancer [11], bladder cancer [12], cervical cancer [13], oral cancer [14], renal cancer [15], ovarian cancer [16], prostate cancer [17], and esophagus cancer [18], suggesting that miR-495–3p may be a tumor suppressor in cancer pathogenesis. This research revealed that miR-495–3p affects cancer by modulating cancer-related signaling pathways like angiogenesis, migration, invasion, cell cycle, proliferation, viability, and apoptosis. In addition, other research showed that miR-495–3p is involved in chemosensitivity as well as may be a promising diagnostic and prognostic biomarker in cancer.

Considering the importance of miR-495–3p in regulating the various cancer-related signaling pathways as well as its potential to affect cancer chemotherapy and be a prognostic and diagnostic biomarker in cancer, this study was designed to present the latest knowledge regarding the function of miR-495–3p in cancer. In addition, this study discussed the current limitations in using miRNAs as a therapeutic target in cancer as well as the future prospects regarding miRNA's capability to become a promising therapeutic strategy in cancer diagnosis and treatment.

2. MicroRNAs biogenesis and function

The initial transcript of miRNA (Pri-miRNA) is a single-strand RNA synthesized by RNA polymerase II having multiple hundred nucleotides [19]. Cleaving of the Pri-miRNA by the Microprocessor complex, a group of enzymes that comprises the RNase III enzyme DROSHA and the cofactor DiGeorge critical region 8 (DGCR8), is the initial stage in miRNA maturation [20], leading to cleavage of stem-loop structure and formation of Pre-miRNA. After exporting pre-miRNA into the cytoplasm, the RNase III enzyme Dicer further processed the pre-miRNA to produce duplex-miRNA. The duplex-miRNA loaded into miRNA-induced silencing complex (miRISC), leading to the degradation of one strand of duplex miRNA. The mature single-strand miRNA could interact with the 3′-UTR of the target miRNA to decrease their translation [21,22]. The miRNA targets have a sequence with 2–6 nucleotides known as miRNA response element (MRE), which interacted with the seed sequence of miRNA with partial or complete matching [23]. MiRNAs are crucial regulators of post-transcriptional processes and gene expression [24] (Fig. 1).

3. Roles of microRNAs in cancer pathogenesis

Cancer is a complicated condition that develops as a result of epigenetic and genetic modifications in cells. Cancer is characterized by the deregulation of gene expression, and miRNAs have been identified as key participants in this process. MicroRNAs may be one of the main elements driving the development of cancerous cells, according to a 2002 theory [25]. Numerous forms of cancer have been linked to dysregulated miRNA expression, making miRNAs an appealing target for cancer treatment [26–28].

Many miRNAs function as oncogenes by suppressing apoptosis and encouraging the growth of cancer cells. For instance, miR-155 has been demonstrated to enhance tumor growth and metastasis and is overexpressed in numerous malignancies. Apoptosis, the cell cycle, and the

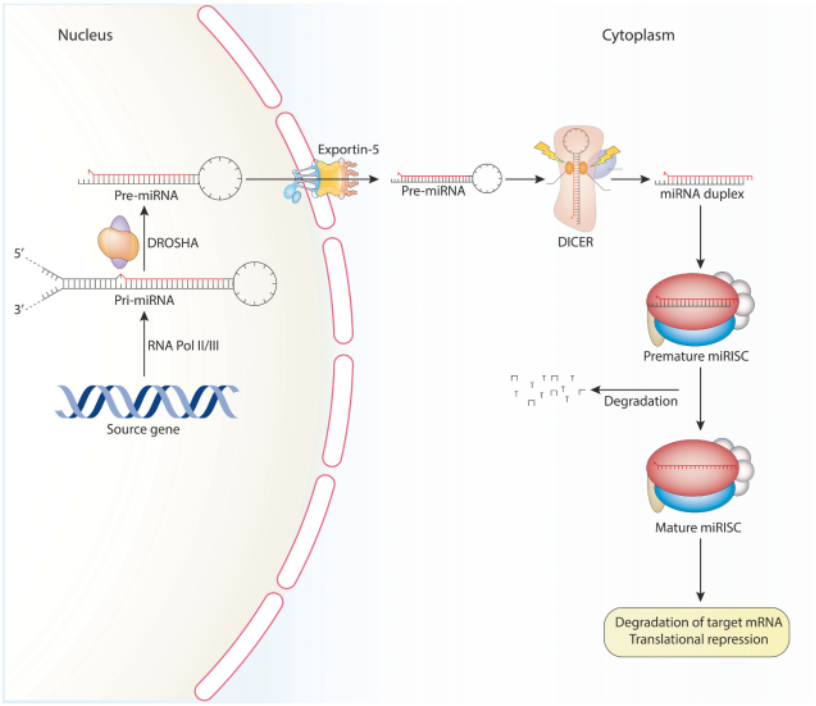

Fig. 1. Mechanism of microRNA biogenesis and function. As it clears, Pri-miRNA is synthesized by RNA polymerase II, which is processed by DROSHA to produce Pre-miRNA. Pre-miRNA is exported by Exportin-5 into the cytoplasm and further cleaved by Dicer, leading to miRNA duplex biogenesis. In a miRISC-dependent pathway, miRNA duplex converts to mature miRNA to suppress the translation or degrade the target miRNA. mRNA: messenger RNA, miRNA: microRNA, miRISC: miRNA-induced silencing complex. RNA Pol II: RNA polymerase II.

response to DNA damage are all regulated by proteins that MiR-155 targets [29,30]. Similar to this, miR-21, which has been demonstrated to block apoptosis and increase cell proliferation, is elevated in several malignancies. MiR-21 has been linked to a poor prognosis in cancer patients and targets multiple tumor suppressor genes, namely phosphatase and tensin homolog (PTEN) and programmed cell death protein 4 (PDCD4) [30,31]. On the other hand, certain miRNAs function as tumor inhibitors by preventing the development of cancer cells and encouraging apoptosis. One tumor suppressor miRNA, miR-34a, is downregulated in numerous malignancies. MiR-34a causes apoptosis and stops the cell cycle while targeting several oncogenes, such as MYC, B-cell lymphoma 2 (Bcl-2), and cyclin-dependent kinases 4/6 (CDK4/6) [32]. Likewise, to miR-15/16, which is frequently deleted or decreased in leukemia as well as other malignancies, miR-15/16 is a tumor inhibitor miRNA. Several genes essential in the survival and proliferation of cells are targeted by miR-15/16, notably BCL-2, cyclin D1 (CCND1), and WNT3A [33,34].

An indicator for the diagnosis and prognosis of malignancy can be the reduction of miRNA levels in cancer cells. MiRNAs are easily discovered using a variety of techniques, including qPCR and microarray analysis, as they are stable in bodily fluids. For instance, it has been discovered that many malignancies, such as lung, breast, and colon cancer, have elevated miR-21 transcription. In cancer patients, elevated amounts of miR-21 are linked to a poor prognosis and a higher chance of recurrence. Similarly, it has been discovered that several hematological malignancies upregulate miR-155 expression, and leukemia patients with excessive levels of miR-155 have poor prognoses [35,36]. Cancer cells are desirable targets for cancer therapy due to the abnormalities of miRNA expression in these cells. Oncogenic miRNAs can be inhibited or tumor suppressor miRNAs can be restored using miRNA-based therapies. For instance, tumor-suppressing miRNAs can be restored by using miRNA mimics or viral vectors, while oncogenic miRNAs can be suppressed by using antisense oligonucleotides or small compounds [37,38]. For the treatment of cancer, a number of miRNA-based therapies are now undergoing clinical trials, such as the miR-34a mimic for solid tumors [39] and miR-16 mimic for chronic lymphocytic leukemia [40,41].

4. The clinical implication of miR-495–3p in cancer

4.1. MiR-495–3p and chemoresistance

Chemoresistance is a major problem in managing the treatment of cancer-affected patients. The efficacy of therapeutic strategy in cancer is limited because cancer cells can acquire new mechanisms making them resistant to chemotherapy drugs [42]. With the failure in the efficacy of the primary treatment strategy, the rate of metastasis and patient survival increased and decreased, respectively [43]. MicroRNAs have been proposed to be important mediators in response to chemotherapy agents. In this regard, a study showed that resistant MDA-MB-231 cells have a decreased expression level of miR-495–3p but have higher levels of the glucose-regulated protein 78 (GRP78). They used a siGRP78 plasmid in MDA-MB-231R cells and reported that it reduced the expression level of GRP78 and restored their sensitivity to pirarubicin. Additionally, miR-495–3p expression was shown to increase and its upregulation was shown to reverse pirarubicin resistance in MDA-MB-231R cells. According to their research, miR-495–3p upregulation inhibits the p-AKT/mammalian target of the rapamycin (mTOR) axis, which in turn decreases GRP78 expressions in triple-negative breast cancer (TNBC) cells [7]. Another study showed that miR-495–3p upregulation reduced the rate of proliferation of imatinib-resistant leukemia cells. Also, it was discovered that overexpressing miR-495–3p decreased the activity of multidrug resistance mutation 1 (MDR1) to efflux imatinib [9]. Further study indicates that inhibiting miR-495–3p activity lessened the impact of depletion of lncRNA NORAD on chemotherapeutic resistance, hypoxia-induced EMT, and vasculogenic mimicry (VM). This research indicated that lncRNA NORAD sponges miR-495–3p to increase the chemoresistance, EMT, and VM, and its inhibition may reduce hypoxia-induced malignancy in colorectal cancer [44].

4.2. MiR-495–3p as a diagnostic and prognostic biomarker

MicroRNAs can regulate a wide range of physiological functions, including differentiation, growth, metabolism, immunity, cell division, and apoptosis [24,45]. Additionally, miRNAs can regulate gene expression by interacting with a specific mRNA, enhancing the breakdown of mRNA, and impeding mRNA translation [46]. Furthermore, earlier studies demonstrated that miRNAs are involved in the regulation of tumor development, growth, and progression [2], and other research verified the relationship between the concentrations of specific miRNAs and the overall survival of cancer-affected patients. Therefore, miRNAs can be cancer biomarkers for diagnosis or prognosis. So, some studies investigated the potential of miR-495–3p as a diagnostic and prognostic biomarker. A study suggested that acute myeloid leukemia (AML)-affected patients with higher expression of miR-495–3p targets have a worse prognosis than patients with lower expression levels of miR-495–3p [9]. Another research showed a lower expression level of miR-495–3p in patients affected by melanoma. This study proposed that the expression level of miR-495–3p in melanoma had a negative correlation with patient survival rate [6]. Some investigations explored the importance of miR-495–3p-targeting circRNAs and lncRNAs as possible prognostic and diagnostic biomarkers in cancer. For example, research showed that patients with oral squamous cell carcinoma (OSCC) with higher expression levels of circKRT1 have a poor prognosis than OSCC patients with lower levels of circKRT1. This study discovered that the higher expression of circKRT1 may be a promising biomarker for the prognosis of OSCC patients [15]. Another research revealed a direct association between the increased expression of LINC01133 and the survival rate of patients with ovarian cancer [17]. Moreover, a study proposed that CRC patients with higher levels of lncRNA LUNAR1 had a lower survival rate, indicating that LUNAR1 may be a promising biomarker in CRC prognosis [47]. More investigation proved that the expression level of lncRNA FAM83A-AS1 had a positive correlation with lymphatic and distant metastasis in patients with esophageal cancer. In addition, their Kaplan-Meier curves revealed that FAM83A-AS1 levels are indirectly associated with lower survival rates of patients [18] (Table 1).

5. Mechanistic view of miR-495–3p in cancer pathogenesis

Numerous studies conducted to explore the potential molecular mechanisms of miR-495–3p in various cancers. Overall, these

Table 1
Mir-495–3p as a prognostic and diagnostic biomarker in cancer.

cancer	miR-495–3p	Result	Ref
AML	Down	The higher expression level of miR-495–3p targets is linked to an unfavorable prognosis–	[9]
MEL	Down	Lower miR-495–3p levels had a decreased survival rates	[6]
OSCC	Down	The levels of circKRT1 associated with unfavorable prognosis	[15]
OC	Down	The higher levels of LINC01133 associated with a decreased survival rate	[17]
CRC	Down	The higher levels of LUNAR1 is correlated with the mortality of CRC patients	[47]
ESCC	Down	The higher levels of FAM83A-AS1 is negatively associated with patient survival rate	[18]

AML: acute myeloid leukemia, MEL: melanoma, OSCC: oral squamous cell carcinoma, OC: ovarian cacner, CRC: colorectal cancer, ESCC: esophageal squamous cell carcinoma, Down: downregulated

investigations have shown that miR-495–3p expression levels are decreased in cancer, indicating that miR-495–3p serves as a tumor suppressor in cancer pathogenesis. here, we have discussed the mechanistic roles of miR-495–3p in various cancers to reveal the potential mediators contributing to cancer pathogenesis (Fig. 2 and Table 2).

5.1. miR-495–3p and colorectal cancer

Zhang et al. in 2020 showed that miR-495–3p expression levels decreased in colorectal cancer (CRC) cells and clinical specimens. They discovered that miR-495–3p promoted apoptosis while inhibiting the growth and migration of colorectal cancer cells. Their bioinformatics analysis and dual-luciferase reporter assay revealed that miR-495–3p directly targeted high mobility group box 1 (HMGB1). Moreover, their in vivo and in vitro assays showed that miR-495–3p restricted the growth of CRC via interacting with HMGB1. Overall, this research suggested that miR-495–3p-mediated downregulation of HMGB1 might be a therapeutic strategy for the management of CRC [5].

Another research was conducted to find the molecular mechanism of lncRNA LUNAR1 in CRC development. According to their findings, LUNAR1 expression levels were strongly increased and had a poor correlation with survival rates of CRC-affected patients. They also demonstrated that LUNAR1 depletion decreased CRC cell motility, invasion, and growth, but increased cell apoptosis. Based on the results of their bioinformatics and luciferase assays, it was shown that LUNAR1 served as a sponging factor for miR-495–3p. Further functional investigations revealed that overexpressing miR-495–3p reduced CRC cell proliferation, migration, and invasion while enhancing apoptosis. Additionally, miR-495–3p was shown to interact with Myc binding protein (MYCBP), leading to a hypothesis that LUNAR1 inhibited CRC growth through the miR-495–3p/MYCBP axis. These findings eventually showed that the miR-495–3p/MYCBP contributes to the progression of CRC and proposed that LUNAR1 may be used as a predictor of disease progression for patients with CRC [47].

A recent work by Rittavee et al. in 2023 discovered that the expression level of lncRNAs NORAD and hypoxia-inducible factor-1 (HIF-1α) were increased in CRC tissues. They showed that the resistance to 5-FU in CRC cells was associated with increased levels of NORAD, and this process was enhanced after exposure of CRC cells to hypoxia. The researchers also discovered that NORAD knockdown inhibited the development of hypoxia-induced vasculogenic mimicry (VM) and the expression of the VE-cadherin. Furthermore, it was proved that NORAD suppression made CRC cells more sensitive to 5-FU by raising cell apoptosis and lowering cell viability. In addition, NORAD suppression was shown to decrease the expression level of HIF-1α and subsequent epithelial-to-mesenchymal transition (EMT) via decreasing N-cadherin and increasing E-cadherin. They revealed that NORAD acts as a sponging factor for miR-495–3p to increase the expression levels of HIF-1α. In addition, they showed that miR-495–3p depletion reversed the effects of NORAD silencing on VM, EMT, and chemoresistance. These results indicate that NORAD suppression may be a promising treatment strategy for treating the malignancy of hypoxia-stimulated CRC patients by preventing chemoresistance and VM development via acting as a sponging factor for miR-495–3p to upregulate the levels of HIF-1 and enhance EMT [44].

5.2. miR-495–3p and melanoma cancer

Geng et al. in 2022 revealed that miR-495–3p levels decreased in melanoma. They discovered that miR-495–3p overexpression enhances the viability of melanoma cells. They revealed that CAMP-responsive element binding protein 1 (CREB1) directly targeted miR-495–3p, and CREB1 upregulation increase the viability of melanoma cells by suppressing miR-495–3p. moreover, their data proved that miR-495–3p interacted with karyopherin 2 (KPNA2) mRNA, and CREB1 enhance KPNA2 levels and cell viability via suppressing miR-495–3p.

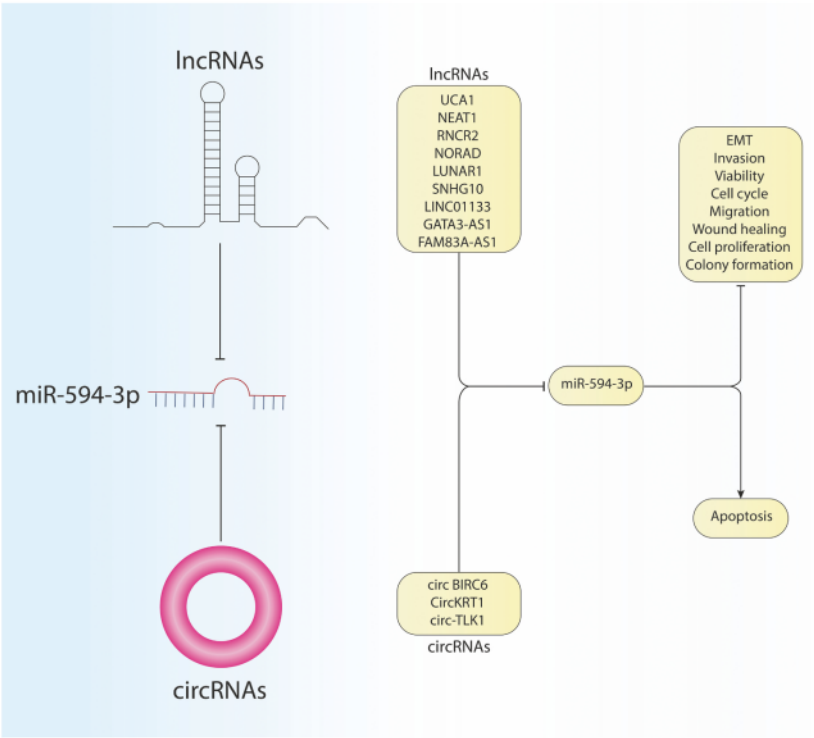

Fig. 2. The molecular mechanism of lncRNA and circular RNAs in sponging miR-495–3p in various cancer. As it clears, circular RNAs and lncRNAs could act as a sponging factor to suppress the expression of miR-495–3p. In various cancer, it was proved that miR-495–3p decreased in various cancer and it may be a tumor suppressor in cancer pathogenesis. lncRNAs and circular RNAs could act as a sponging factor to suppress the expression of miR-49–3p, leading to an increase in the expression of target genes. lncRNA: long non-coding RNA, circRNA: circular RNA, miR: microRNA. UCA1: urothelial carcinoembryonic antigen 1, NEAT1: nuclear paraspeckle assembly transcript 1, PNCR2: prolinerich nuclear receptor coregulatory protein 2, NORAD: Non-coding RNA activated by DNA damage, LUNAR1: leukemia-induced non-coding activator RNA-1, SNGH10: small nucleolar RNA host gene 10, GATA3: GATA3 binding protein, FAM83A: family with sequence similarity 83 member A.

Table 2
The expression levels of miR- 495–3p in melanoma tissues and cells as well as its in Vivo and in Vito effects.

cancer	Source	miR- 495–3p	Circ/ lncRNA	miR	Target	In vitro effects	In vivo effects	ref
CRC	Cell Tissue	Down Down	-	miR- 495–3p	HMGB1	↓ Migration ↑ Apoptosis	Reduce the size and weight of the tumor	[5]
CRC	Cell Tissue	Down Down	LUNAR1	miR- 495–3p	MYCBP	↓ Proliferation ↓ Migration ↓ Invasion ↑ Apoptosis	-	[47]
CRC	Cell Tissue	Down Down	-	miR- 495–3p	HIF-1α	↓ Proliferation ↓ Migration ↓ Invasion ↓ Viability ↓ Chemoresistance ↑ Apoptosis	-	[44]
MEL	Cell Tissue	Down Down	-	miR- 495–3p	CREB1	↓ Migration ↓ Invasion ↓ Viability	-	[6]
MEL	Cell	Down	NEAT1	miR- 495–3p	E2F3	↓ Proliferation ↓ Migration ↓ Invasion	Reduce both the growth and weight of the tumor	[48]
BC	Cell Tissue	Down Down	-	miR- 495–3p	GRP78	↓ Proliferation ↓ Migration ↓ Chemoresistance	-	[7]
BC	Cell Tissue	Down Down	GATA3-AS1	miR- 495–3p	CENPU	↓ Proliferation	-	[32]
GC	Cell	Down	UCA1	miR- 495–3p	SATB1	↓ Colony formation ↓ Migration ↓ Invasion ↓ Viability ↑ Apoptosis	Inhibit tumor growth while promoting apoptosis	[8]
GC	Cell Tissue	Down Down	SNHG10	miR- 495–3p	CTNNB1	↓ Colony formation ↓ Migration ↓ Invasion ↓ Viability ↑ Apoptosis	-	[49]
CML	Cell	Down	-	miR- 495–3p	BCR-ABL	↓ Cell growth	-	[9]
PTC	Cell	Down	-	miR- 495–3p	-	↓ Proliferation ↓ Migration ↓ Invasion ↓ Viability	-	[10]
NSCLC	Cell Tissue	Down Down	-	miR- 495–3p	Sphk1	↓ Proliferation ↓ Cell cycle ↓ Wound healing ↓ Colony formation	-	[11]
BLC	Cell	Down	circ-BIRC6	miR- 495–3p	XBP1	↓ Proliferation ↓ Invasion ↓ Migration ↓ EMT ↓ Colony formation	Tumor size and weight should be decreased	[12]
CC	Cell Tissue	Down Down	-	miR- 495–3p	CDK1	↓ Proliferation ↓ Invasion ↓ Migration ↓ Cell cycle ↑ Apoptosis	Reduce the size and weight of the tumor	[13]
OSCC	Cell Tissue	Down Down	CircKRT1	miR- 495–3p	PDL1	↓ Proliferation ↓ Invasion ↓ Migration ↓ EMT	diminution of the tumor's size and weight	[14]
RCC	Cell Tissue	Down Down	TLK1	miR- 495–3p	CBL	↓ Invasion ↓ Migration ↓ Cell cycle ↑ Apoptosis	Suppress tumor growth	[15]
OC	Cell	Down	LINC01133	miR- 495–3p	TPD52	↓ Invasion ↓ Migration	Inhibit tumor metastasis	[16]
PCa	Cell Tissue	Down Down	NORAD	miR- 495–3p	TRIP13	↓ Invasion ↓ Migration ↓ Proliferation ↑ Apoptosis	Reduce the size and mass of the tumor	[17]
ESCC	Cell Tissue	Down Down	FAM83A-AS1	miR- 495–3p	-	↓ Migration	-	[18]

CRC: colorectal cancer, HMGB1: High mobility group box 1 protein, LUNAR1: Leukemia-Associated Non-Coding IGF1R Activator RNA 1, MYCBP: c-MYC binding protein, HIF-1α: Hypoxia-Inducible Factor, MEL: melanoma cancer, CREB1: CAMP Responsive Element Binding Protein 1, HK2: Human Kallikrein 2, 1NEAT1: nuclear-enriched abundant transcript, BC: breast cancer GRP78: Glucose-regulating protein 78, CENPU: centromere protein U, GC: gastric cancer, UCA1: urothelial carcinoma-associated 1, SATB1: Special AT-rich sequence-binding protein-1, CML: Chronic myeloid leukemia, PTC: Papillary thyroid carcinoma, NSCLC: Non-small cell lung cancer, SPHK1: sphingosine kinase 1, BLC: bladder cancer, XBP1: X-box binding protein 1, CC: Cervical cancer, CDK1: Cyclin-dependent kinase 1, OSCC: oral squamous cell carcinoma, PD-L1: programmed cell death ligand 1, RCC: Renal cell carcinoma, OC: ovarian cancer, TPD52: Tumor protein D52, Prostate cancer, TRIP13: thyroid

hormone receptor interacting protein 13, ESCC: esophageal squamous cell carcinoma, FAM83A: Family with sequence similarity 83 A, Down: downregulated, UCA1: urothelial carcinoembryonic antigen 1, NEAT1: nuclear paraspeckle assembly transcript 1, PNCR2: prolinerich nuclear receptor coregulatory protein 2, NORAD: Non-coding RNA activated by DNA damage, LUNAR1: leukemia-induced non-coding activator RNA-1, SNGH10: small nucleolar RNA host gene 10, GATA3: GATA3 binding protein, FAM83A: family with sequence similarity 83 member A.

Collectively, this study suggested that CREB1/miR-495–3p/KPNA2 axis could modulate the progression of melanoma, suggesting the new molecular mechanism in melanoma pathogenesis [6].

In a study published in 2018 by Xia and colleagues, it was discovered that lncRNA NEAT1 was upregulated in melanoma cells. This study revealed that NEAT1 depletion decreased the growth of melanoma cells, whereas NEAT1 upregulation increased melanoma cell invasion and migration. Further research revealed that NEAT1 sponges miR-495–3p. Additionally, they proved that melanoma cells had lower levels of miR-495–3p. Furthermore, their data demonstrated that miR-495–3p bind directly to E2F3 mRNA, and E2F3 levels were suppressed when miR-495–3p was overexpressed. This study also showed that miR-495–3p reduced E2F3-induced carcinoma cell invasion, migration, and proliferation. Moreover, using the xenograft mice model, they showed that NEAT1 accelerated melanoma growth via modulating the miR-495–3p/E2F3 axis. These results indicate that NEAT1 induces E2F3 and inhibits miR-495–3p, acting as an oncogene in melanoma progression [48].

5.3. miR-495–3p and breast cancer

Liu et al. in 2022 showed that pirarubicin-resistant MDA-MB-231 cells had higher levels of the protein glucose-regulated protein 78 (GRP78) and lower levels of the miR-495–3p than non-resistant MDA-MB-231 cells. They used a plasmid expressing siGRP78 to silence GRP78 expression in MDA-MB-231R and revealed that it increased sensitivity to pirarubicin. Similar to this, miR-495–3p upregulation in MDA-MB-231R cells boosted miR-495–3p levels, reversed pirarubicin chemotherapy resistance, and inhibited cell migration and proliferation. In triple-negative breast cancer (TNBC) cells, they proved that miR-495–3p upregulation reduced the expression levels of GRP78 via the protein kinase B (AKT)/mammalian target of the rapamycin (mTOR) pathway. Importantly, in chemo-resistant and chemo-sensitive TNBC clinical specimens, GRP78 and miR-495–3p levels have an inverse pattern. They proved that miR-495–3p and GRP78 levels have a direct and indirect association with BC prognosis, respectively. collectively, they proposed that the miR-495–3p/GRP78/Akt axis has an important role in TNBC pathogenesis and pirarubicin resistance, suggesting a novel and promising therapeutic target in TNBC [7].

Another research suggested that the expression levels of centromere protein U (CENPU) were higher in breast cancer (BC) clinical specimens than in healthy tissues, and this upregulation of its levels correlated with clinicopathological characteristics. Furthermore, it was discovered that BC patients with higher levels of CENPU had a poor prognosis. They proposed miR-495–3p as a possible regulator of CENPU expression. Collectively, they indicated that lncRNA GATA3-AS1 could sponge miR-495–3p to enhance the expression levels of CENPU, and this pathway was strongly associated with poor prognosis of BC patients. In addition, they revealed that CENPU is engaged in the regulation of the cell cycle via modulating polo-like kinase 1 (PLK1) levels [32].

5.4. miR-495–3p and gastric cancer

In 2019, Yuan et al. found that lncRNA SNHG10 was highly expressed in gastric cancer (GC) cells. SNHG10 depletion impeded the invasion and migration of GC cells as well as decreased the expression levels of the WNT axis. Further research showed that SNHG10 sponge miR-495–3p levels, to upregulates the levels of catenin 1 (CTNNB1). Collectively, this study proposed that SNHG10 the miR-495–3p/CTNNB1 axis activates the WNT signaling pathway, which leads to the progression of GC [8].

Another research showed that the expression levels of special AT-rich sequence binding protein 1 (SATB1) and lncRNA UCA1 increased while miR-495–3p decreased in GC tissue compared to normal tissues. This research proved that miR-495–3p interacted with SATB1 mRNA, and SATB1 depletion and miR-495–3p upregulation decreased the expression levels of UCA1. It was also shown that UCA1 acts as a sponging factor for miR-495–3p to upregulate the expression levels of SATB1. This study suggested that SATB1/miR-495–3p/lncRNA-UCA1 axis contributes to the invasion and growth of GC cells, proposing a novel regulatory pathway in modulating GC pathogenesis [49].

5.5. miR-495–3p chronic myeloid leukemia

Rittavee et al. designed a study to explore the underlying molecular mechanism of miR-495–3p in the chemo-sensitivity of chronic myelogenous leukemia (CML). Their in vitro analysis showed that BCR-ABL1 cells exhibited reduced levels of miR-495–3p. Their loss-of-function analysis increased proliferation, triggered the cell cycle, and induced Imatinib resistance. MiR-495–3p upregulation was shown to inhibit the proliferation and tyrosine kinase inhibitors (TKIs) resistance of imatinib-resistant T315I-mutant cells and decrease MDR1-mediated drug resistance. The function of miR-495–3p in CML patients was further investigated, and it was discovered that the expression levels of miR-495–3p increased in patients and their levels were correlated with poor prognosis. Overall, considering the importance of miR-495–3p in CML malignant behaviors and its effect on CML resistance to chemotherapy drugs, miR-495–3p may be a promising therapeutic target in CML treatment [9].

5.6. miR-495–3p and thyroid carcinoma

A study in 2023 showed that papillary thyroid cancer (PTC) cells with the BRAFV600E mutation have a higher potential for invasion and migration. This study showed that miR-495–3p upregulation inhibited the invasion and migration of PTC cells with the BRAFV600E mutation by inhibiting the expression levels of target genes, including transforming growth factor beta 2 (TGFB2), epiregulin (EREG), and cyclin D1 (CCND1). These findings suggest that the lack of miR-495–3p expression in PTC may have a major impact on the progression of the disease [10].

5.7. miR-495–3p and non-small cell lung cancer

Based on a recent study, individuals with non-small cell lung carcinoma (NSCLC) who had elevated levels of sphingosine kinase 1 (SPHK1) had a poor prognosis. This study revealed that miR-495–3p specifically targets SPHK1 and inhibits the progression of tumors by lowering LDH-A (lactate dehydrogenase-A) action, colony formation, and cell proliferation. Additionally, once miR-495–3p was restored, it resulted in G0/G1 phase cell cycle arrest. Following SPHK1 suppression, scientists also saw a sizable rise in ceramide levels, which resulted in mitochondrial malfunction. Researchers discovered that even in the presence of SPHK1deficiency, dynamin-related protein 1 (Drp1), parkin (PARK2), and LC3 significantly increased, while PTEN-induced kinase 1 (PINK1) and mitofusin-2 (MFN2) were destroyed, resulting in a disruption in mitochondrial fission/fusion and stimulation of mitophagy. In addition, it was discovered that miR-495–3p upregulation decreased mitochondrial energy homeostasis, increased reactive oxygen species (ROS) production, and increased mitochondrial membrane potential, all of which contributed to the development of apoptosis. According to the study, miR-495–3p could be utilized to target SPHK1 and promote lethal mitophagy to reduce NSCLC carcinogenesis and change the sphingolipid rheostat toward ceramide, opening up a novel therapeutic option for

NSCLC [11].

5.8. miR-495–3p and bladder cancer

In a study done in 2021 by Zhou et al., it was discovered that bladder cancer (BLC) cell lines have increased circBIRC6 expression. The scientists found that the growth, invasion, migration, and EMT of BLC cells were all considerably inhibited by the suppression of circBIRC6. likewise, the miR4953p inhibitor prevented the inhibition effect. The research also showed that circBIRC6 served as a miR495p sponge to control the expression of X-box-binding protein 1 (XBP1). Additionally, the xenograft studies demonstrated that the expression of miR-495p and circ-BIRC6 was knocked down, which significantly slowed the growth of tumors. In comparison to the circBIRC6 suppression group, the expression rates of XBP1, Ki-67, and EMT-associated proteins were also recovered in the co-transfection group. These results highlight a prospective therapeutic target for the management of BC by demonstrating that the control of the miR-495/3p/XBP1 signaling pathway by circ-BIRC6 knockdown inhibits BC carcinogenesis and development [12].

5.9. miR-495–3p and cervical cancer

Tang et al.'s work, which was published in 2021, showed that miR-143–3p and miR-495–3p specifically target the cyclin-dependent kinases 1 (CDK1) gene in cervical carcinoma (CC). They discovered that miR-495–3p and miR-143–3p decreased in CC tissues and cells, whereas CDK1 was upregulated. Inhibiting miR-143–3p or miR-495–3p elevated levels or suppressing CDK1 increased apoptosis and decreased the survival rate in CC cells. Also, in vivo, tests revealed that increasing CDK1 blocked the upregulation effects of miR-143–3p or miR-495–3p on the tumor formation of CC cells. Overall, the findings imply that miR-143–3p and miR-495–3p jointly target CDK1, meaning that CC treatment options may include blocking this process [13].

5.10. miR-495–3p and oral squamous cell carcinoma

In 2020, Yang et al. showed that oral squamous cell carcinoma (OSCC) tissues and cells had elevated levels of circKRT1 and PDL1 (programmed cell death ligand 1). CircKRT1 depletion was shown to increase CD8 +T cell cytotoxicity while suppressing OSCC cell invasion, migration, proliferation, EMT, and apoptosis. The inhibitory impacts of circKRT1 on immune evasion and progression of OSCC were linked to PDL1 inhibition. This study suggested that circKRT1 acts as a sponge to upregulate the expression level of PDL1. It seems that circKRT1 modulates OSCC immune evasion and progression by regulating the miR-495–3p/PDL1 axis. Their in vivo results also proved that circKRT1 regulates the metastasis and progression of OSCC via modulating miR-495–3p and PDL1 levels [14].

5.11. miR-495–3p and renal cell carcinoma

Lei et al. explored the function of circTLK1 in renal cell carcinoma (RCC) and showed the expression levels of casitas B-lineage lymphoma (CBL) proto-oncogene increased in RCC cells and clinical specimens. Their result showed that the depletion of circTLK1 or CBL decreased the metastasis and proliferation and increased the cell apoptosis of RCC cells. Moreover, their results proved that circTLK1 acts as a sponging factor to enhance the expression levels of CBL. In addition, they proved that circTLK1 depletion suppressed the RCC progression via the miR-495–3p/CBL axis, suggesting a promising target in treating RCC [15].

5.12. miR-495–3p and ovarian cancer

Liu et al. in 2020 designed a study to investigate the underlying mechanism of LINC01133 in epithelial ovarian cancer (EOC) and discovered that LINC01133 was highly elevated in EOC clinical specimens and cells and its levels correlated with clinicopathological features and metastasis. Their functional experiments showed that LINC01133 increased tumor metastasis in vivo as well as cancer cell migration and invasion in vitro. Mechanistically, they revealed that LINC01133 negatively modulates miR-495–3p levels. Additionally, they found that miR-495–3p interacted with tumor protein D52 (TPD52) mRNA, which mediates the metastasis-promoting impact of LINC01133. Overall, this study showed that LINC01133 modulates the miR-495–3p/TPD52 axis to enhance EOC metastasis, making it a promising therapeutic target in EOC [16].

5.13. miR-495–3p and prostate cancer

A study in 2020 found that miR-495–3p decreased in prostate cancer (PC) clinical specimens and cells, whereas lncRNA NORAD and thyroid hormone receptor-interacting protein 13 (TRIP13) were both increased. In PC cells, NORAD depletion or miR-495–3p overexpression induced cell death and inhibited cell invasion, migration, and proliferation. Furthermore, NORAD suppression was shown to decrease tumor progression in vivo. NORAD was demonstrated to act as a miR-495–3p sponge to upregulate TRIP13 levels. Additionally, suppression of miR-495–3p was shown to restore the effects of NORAD suppression on PC cell behaviors. Moreover, miR-495–3p upregulation inhibits the invasion, migration, and proliferation of PC cells and enhances cell apoptosis. overall, their findings indicated that NORAD depletion suppressed the PC progression by regulating the miR-495–3p/TRIP13 axis, which makes this axis a novel therapeutic strategy in PC management [17].

5.14. miR-495–3p and esophageal carcinoma

Huang et al. in 2020 investigated the expression and role of the lncRNA FAM83A-AS1 in esophageal cancer (EC) and discovered that levels of FAM83A-AS1 enhanced in both EC clinical specimens and cells, and its levels were linked to elevated lymphatic metastases as well as decreased rate of survival. They also showed that FAM83A-AS1 enhanced the migration of EC cells. They also discovered that miR-495–3p was a direct target of FAM83A-AS1 and that FAM83A-AS1 inversely controlled miR-495–3p expression, which was lower in esophageal cancer tissues. Importantly, they revealed that overexpression of miR-495–3p in EC cells inhibited the stimulatory effect of FAM83A-AS1 on cell migration [18].

6. Conclusion and future prospects

Recent years have seen an increase in interest in miR-495–3p as a possible oncogene that may influence tumor development by hitting many genes through distinct cancer signaling pathways (Table 2). This review investigates miR-495–3p's function in cancer and how it contributes to treatment resistance. Despite advancements in the field of cancer therapy, cancer cells continue to develop resistance to treatments like radiation therapy, chemotherapy, and specific treatments via a variety of processes, including genetic or epigenetic modifications in the cancer cell. Due to their potential as therapeutic targets, miRNAs have recently become prominent biomarkers in several cancers. Multiple cancer types have been associated with increased miRNA expression, which has been linked to cancer progression. MiRNA-based therapeutics have opened up new possibilities for the treatment of cancer in the present era of conventional therapy. MiRNA mimics and antagomirs, for instance, have been created to alter the tumor microenvironment and stop the growth of tumors.

Additionally, miRNA-based medicines have advanced in clinical studies, which will shed more light on this cutting-edge strategy for treating cancer. MRX34 is a liposomal double-strand RNA mimic to mitigate the function of miR-34 which enters the clinical trials as a first miRNA mimic in patients with HCC, melanoma, and renal cell

carcinoma [39]. MesomiR-1 is a miR-16 mimic that enters clinical trials in patients with mesothelioma [50]. Another agent known as MRG-106 with target miR-155, enters phase I and phase II clinical trials in patients with leukemia and lymphoma [51,52]. In 2019, another agent, RGLS5579, was introduced to inhibit miR-10, but it currently is in the pre-clinical stages [53]. The accurate and effective distribution of miRNAs and a thorough understanding of the biological functions of circulating miRNAs are two obstacles that this strategy also has. Regardless of these difficulties, the targeted miRNA method has enormous potential for treating cancer. Regular therapies could only be partly successful and might eventually cause resistance. As a result, combining miRNA-based treatment with other techniques could lead to the development of fresh cancer treatment options. MiR-495–3p has the potential to be a useful biomarker in the detection, diagnosis, and prognostication of cancers in numerous cancer types. In conclusion, addressing miR-495–3p with cutting-edge methods might grow into a promising therapy for patients who acquire resistance to traditional medications, giving people with cancer new hope.

CRediT authorship contribution statement

Seyed Reza Hosseini Fard, Rosario Mireya Romero-Parra: Conceptualization, Supervision, Illustration. **Yasir Qasim almajidi, Ahmed Hjazi, Hashem O. Alsaab, Khulood H. Oudaha**: Writing – original draft. **Huldani Huldani, Shadia Hamoud Alshahrani, Beneen M. Hussien, Muhja Ahmed**: Writing – review & editing.

Declaration of Competing Interest

The authors declare they have no conflict of interests.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9