MicroRNA-490-3p and -490-5p in carcinogenesis: Separate or the same goal? (Review)

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Abstract. MicroRNA (miR)-490-3p and miR-490-5p, located on chromosome 7q33, are two independent mature products of miR-490 exerting distinct effects on tumor progression. miR-490-3p and miR-490-5p possess antitumor properties. miR-490-3p dysfunction has been associated with malignancies including colorectal cancer, while the abnormal function of miR-490-5p has been more considerably associated with bladder cancer (for example). At present, there are 30 and 11 target genes of miR-490-3p and miR-490-5p, respectively, that have been experimentally verified, of which the cyclin D1 (CCND1) gene is a common target. Through these target genes, miR-490-3p and miR-490-5p are involved in 7 and 3 signaling pathways, respectively, of which only 2 are shared regulatory signaling pathways. The present review introduces two competing endogenous RNA (ceRNA) regulatory networks centered on miR-490-3p and miR-490-5p. These networks may be important promoters of tumor cell proliferation, invasiveness, metastatic potential and apoptosis. Unlike miR-490-5p, miR-490-3p plays a unique role in promoting cancer. However, both are promising molecular markers for early cancer diagnosis and prognosis. In addition, miR-490-3p was also found to be associated with the chemical resistance of cisplatin and paclitaxel. The present review focuses on the abnormal expression of miR-490-3p and miR-490-5p in different tumor types, and their complex ceRNA regulatory networks. The clinical value of miR-490-3p and miR-490-5p in cancer diagnosis, prognosis and treatment is also clarified, and an explanation for the opposing effects of miR-490-3p in tumor research is provided.

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Contents

1. Introduction

Noncoding RNAs (ncRNAs) refers to RNAs that do not have a protein-coding function after gene transcription, and include microRNAs (miRNAs/miRs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). With the development of molecular biological techniques, the status of ncRNA has changed from 'transcription junk' to an important entity that mediates the regulation of cellular functions, serving a considerable role in disease development, especially cancer (1). miRNAs are highly conserved endogenous small RNAs, which primarily bind to the 3'-untranslated region (3' UTR) of target mRNA to downregulate gene expression (1,2). Some miRNAs are involved in the pathogenesis of various malignant tumors (3). A number of these cancer-related miRNAs possess oncogenic properties, such as miR-155 (4), and some, miR-488 for instance, exert cancer-suppressive effects (5). It is worth noting that some miRNAs can simultaneously exhibit cancer-promoting and -suppressing effects. For example, miR-155 was found to be downregulated in ovarian and gastric cancer (GC), suggesting that it acts as an oncogenic molecule, but is upregulated in breast and pancreatic cancers (4). In addition, in colon cancer, miR-155 showed contradictory roles in the same cancer type, and its expression patterns, also found for miR-490-3p, suggest that miR-490-3p acts as a tumor regulator with complex mechanisms (6-8). In addition, studies have shown that miRNA expression patterns are related to cancer types and clinical parameters,

making miRNA analysis an effective tool for cancer diagnosis and prognosis (3). The emergence of miRNA mimics and miRNA-targeted molecules (antimiRs), as well as research on miRNAs in drug resistance, also indicate miRNAs as novel targets for cancer therapy (9,10).

Numerous studies have reported the association between miRNAs and oncogenic effects. However, miR-490 and its two mature products (miR-490-3p and miR-490-5p) have a unique appeal. miR-490 is located in the cholinergic receptor muscarinic 2 (CHRM2) gene in the 7q33 region. CHRM2 encodes a muscarinic acetylcholine receptor, a G protein-coupled receptor that responds to acetylcholine and plays an important signaling role in the nervous system, inhibiting glioblastoma proliferation through the Notch-1/EGFR signaling pathway (11). As such, activation of CHRM2 is a viable strategy for the treatment of glioblastoma (12). miR-490 is an miRNA transcribed from the intron of CHRM2 (13). miR-490 is transcribed in the same direction as the intron, suggesting a co-transcriptional relationship, with the precursor miRNA being excised from the intron. The miR-490 precursor comprises a stem-loop structure composed of 128 bases (Fig. 1), which matures in the cytoplasm (3), and generates two mature products, miR-490-3p (22 bp) and miR-490-5p (20 bp). In glioblastoma, CHRM2 affects the level of mature miR-490 due to low expression of epigenetic modifications, and may be responsible for miRNA dysregulation (13). Growing research on miR-490-3p and miR-490-5p has been reported not only in neurological tumors, such as glioblastoma, but also in a wide range of cancer types and pathogenic networks, such as respiratory, gastrointestinal and hematological tumors, and sarcomas. miR-490-5p was initially reported in deeply-sequenced bladder cancer (BC) tissues, and was the most significantly decreased miRNA (14), followed closely by miR-490-3p, which was found to be expressed at low levels in high-throughput sequenced colorectal adenocarcinoma (15). Thereafter, an in-depth study of miR-490-3p in hepatocellular carcinoma (HCC) revealed that miR-490-3p could act as an oncogene, which differs from the general oncogenic effect of miRNAs (8), and this is what prompted the investigation of these two miRNAs in the present review. As a closely related entity, miR-490-5p may also be a factor that plays a two-sided role in cancer. The current study indicates that miR-490-5p only plays the role of an oncogene, while miR-490-3p is indicated as a double-edged sword with regard to cancer. Due to the difference in sequence, and the expression and functionality of '3p' and '5p' miRNAs, it is possible that miR-490-5p also serves both beneficial and detrimental roles in cancer (16).

The low expression levels of miR-490-3p and miR-490-5p in most cancer types suggests that they are associated with the inhibition of tumorigenesis (6,17). This was exemplified by Wang *et al* (6), who initially identified a substantial downregulation in miR-490-3p levels in paired and unpaired HCC tissues analyzed from a cohort of The Cancer Genome Atlas. Secondly, in 50 paired HCC tissues, fluorescence *in situ* hybridization revealed that miR-490-3p expression was downregulated in HCC tissues compared with adjacent non-tumor tissues, primarily in the cytoplasm, which may be associated with the maturation of intron miRNA cleavage in the cytoplasm (3). Subsequent reverse transcription-quantitative PCR analysis revealed that miR-490-3p expression levels were lower in HepG2 hepatocellular carcinoma cells than in normal liver tissue. Furthermore, cell function assays (MTT analysis, agar assays and Transwell analysis) showed that HepG2 cells transfected with miR-490-3p mimics exhibited decreased viability, as well as decreased proliferative capacity, anchorage-dependent growth and invasive potential. These results suggest that miR-490-3p is dysregulated in tumor expression and influences tumor cell behavior. Moreover, Kaplan-Meier analysis revealed that low miR-490-3p expression levels were detrimental to patient survival, and univariate and multifactorial Cox regression analyses indicated that miR-490-3p expression was an independent prognostic factor for poor survival and tumor recurrence in patients with HCC (6). However, miR-490-3p has also been found to be highly expressed in HCC (8), lung cancer (18), thyroid carcinoma (19), multiple myeloma (MM) (20) and skin squamous cell carcinoma (SSCC) (21). Therefore, it would be interesting and meaningful to study the underlying mechanisms of miR-490-3p and miR-490-5p in cancer. The current article reviews the different roles of these two miRNAs in cancer formation, competing endogenous RNA (ceRNA) regulatory networks, chemoresistance, and patient diagnosis and prognosis (Table I). The review also discusses the potential diagnostic, prognostic and therapeutic value of miR-490-3p and miR-490-5p in cancer.

2. Aberrant expression of miR-490-3p and miR-490-5p in cancer

Current research shows that the expression levels of miR-490-3p and miR-490-5p are low in the majority of tumors. Tumor types with low expression levels of miR-490-3p include colorectal cancer (CRC) (22-24), GC (25-27), cholangiocarcinoma (CCA) (28), lung cancer (29-31), prostate cancer (32), ovarian cancer (OC) (33-37), endometrial cancer (Eca) (38-40), breast cancer (BCa) (41,42), osteosarcoma (Osa) (43) and acute myeloid leukemia (AML) (44). Tumor types with low expression levels of both miR-490-3p and miR-490-5p include HCC (6,45-55), esophageal squamous cell carcinoma (56-59) and glioma (13,60,61). In addition, tumor types with low miR-490-5p expression also include BC (17,62,63), renal cell carcinoma (64), neuroblastoma (65) and pharyngolaryngeal cancer (66). The aforementioned results have been confirmed in corresponding tumor tissues or tumor cells, and subsequent cell function experiments further supported the tumor suppressor effects of high levels of miR-490-3p and miR-490-5p, including inhibition of proliferation, epithelial-mesenchymal transition (EMT), invasiveness and metastasis, as well as apoptosis promotion (Fig. 2). The effects of miR-490-3p and miR-490-5p on cancer cell behavior are achieved through 27 and 11 target genes, respectively (Table II). Among them, only CCND1 is a common target gene (Table I).

In addition, unlike miR-490-5p, miR-490-3p is highly expressed in HCC (8), lung cancer (18), thyroid carcinoma (19), SSCC (21) and MM (20). Zhang *et al* (8), reported the upregulation of miR-490-3p in 20 cases of HCC tissues and liver cancer cell lines (HepG2, SK-Hep-1 and PLC/PRF/5), which is in contrast to the low expression of miR-490-3p

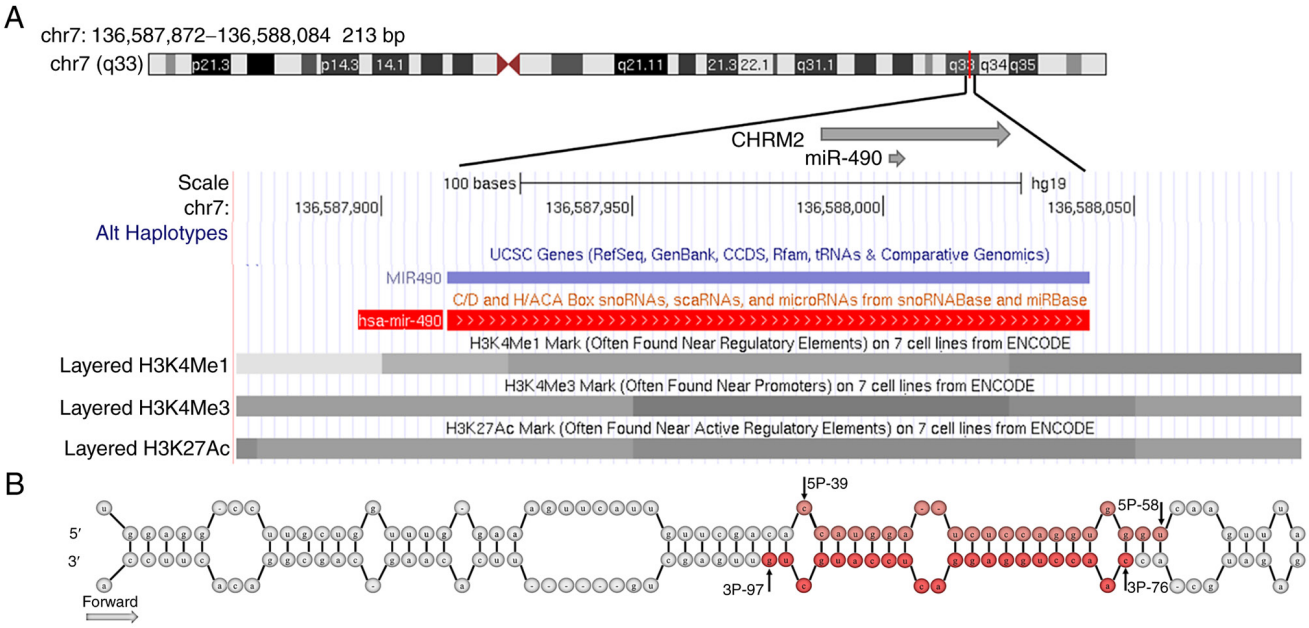

Figure 1. Chromosomal location and sequences of miR-490-3p and miR-490-5p. (A) miR-490 is mapped to chr7 (q33), and the host gene is CHRM2. (B) Precursor miR-490 produces two mature products, miR-490-3p and miR-490-5p, from the stem-loop. Reference information was acquired from the UCSC Genome Browser (99) on Human, Feb. 2009 (GRCh37/hg19) (http://genome.ucsc.edu/) and the miRbase (http://mirbase.org/). Permission is granted for reuse of all graphics produced by the UCSC Genome Browser website. miR, microRNA; CHRM2, cholinergic receptor muscarinic 2; chr, chromosome.

in other HCC tissues and HepG2 liver cancer cells (47,52). Xia *et al* (21) observed high expression of miR-490-3p in the SSCC cell line CD34 + COLO-16. In addition, Li *et al* (18) and Zhang *et al* (19) observed high expression of miR-490-3p in lung cancer and thyroid cancer, respectively. In plasma specimens, Jiang *et al* (20) reported the upregulation of miR-490-3p in 35 patients with MM. However, the sample for these research results was from Chinese hospitals with limited sample size. Therefore, future verification of these findings in larger sample cohorts from other regions is necessary.

In cancers with high expression levels of miR-490-3p, the target sites of miR-490-3p are concentrated within the ERGIC and golgi 3 (ERGIC3) and poly (rC) binding protein 1 (PCBP1) genes. As an oncogene, abnormal activation of ERGIC3 can promote the occurrence of cancer (67), and silencing ERGIC3 can inhibit the proliferation of lung adenocarcinoma cells (68). In HCC, the high expression levels of miR-490-3p did not predictably silence the gene expression of ERGIC3, but abnormally, significantly promoted ERGIC3 expression, thereby promoting cellular proliferation, migration, invasiveness and EMT (8). In cancer, the promotion of ERGIC3 expression by miR-490-3p is likely to be associated with argonaute RISC catalytic component 2 (Ago2), a key component of the RNA-induced silencing complex (8). The Ago2 protein has been shown to promote both protein translation and translation inhibition, depending on the differential effect of the cell cycle and cellular stress (69). However, the underlying mechanism of Ago2 on miR-490-3p in HCC is yet to be elucidated. PCBP1 is a tumor suppressor gene, which can promote the immune response to tumors, the deletion of which leads to a reduction in T cell-mediated antitumor immune responses and promotes tumor metastasis and progression (70). In SSCC (21), lung cancer (18) and thyroid cancer (19), PCBP1 is post-transcriptionally inhibited by the high expression levels of miR-490-3p, which enhances tumor immune escape and promotes cancer proliferation, migration and invasiveness, ultimately promoting the occurrence of cancer. Zhang *et al* (71) reported high expression levels of miR-490-3p in thyroid cancer. Their study revealed that even with low expression of miR-490-3p, the high expression of E3 ligase ubiquitin ligation factor E4 also promoted PCBP1 degradation after translation. This suggests the existence of other post-transcriptional modifications in conjunction with miR-490-3p in carcinogenesis. Therefore, the tumor suppressor and oncogenic mechanism of miR-490-3p is achieved by the regulation of oncogene and tumor suppressor gene expression.

3. Signaling pathways associated with miR-490-3p and miR-490-5p

Identification of the signaling pathways associated with miR-490-3p and miR-490-5p are important for understanding their complex regulatory mechanisms in cancer. The target genes of miR-490-3p and miR-490-5p are involved in 7 and 3 signaling pathways respectively, (Fig. 3).

AKIRIN2 is the direct target gene of miR-490-3p. gp130 is the signal transduction subunit of IL-6, STAT3, VEGFA and the IL-6 receptor in the hypoxia inducible factor 1 subunit α (HIF-1A) signaling pathway (28,72). In CCA, the high expression of AKIRIN2 increases the expression of gp130, indicating that miR-490-3p regulates the HIF-1A signaling pathway to inhibit the proliferation, invasion and migration abilities of CCA cells (28). FRAT regulator of WNT signaling pathway 1 (FRAT1) and tankyrase 2 (TNKS2) are the other two target genes of miR-490-3p. FRAT1 is a cofactor for DVL for the inhibition of GSK-3β in the Wnt signaling pathway (73). TNKS2 induces Axin-1 degradation, thereby weakening the inhibition of β-catenin by GSK-3β, and ultimately enhancing

Table I. Clinical value and comparison of the roles of miR-490-3p and miR-490-5p in cancer development.

Variable	miR-490-3p	(Refs.)	miR-490-5p	(Refs.)
Carcinostatic	Glioma[a], ESCC[a], HCC[a], Osa, AML, GC, CCA, CRC, lung cancer, BCa, OC, Eca, PC	(23,25,28,31,32,35,38,41,43,44, 52,59,60)	Glioma[a], ESCC[a], HCC[a], RCC, BC, pharyngolaryngeal cancer, neuroblastoma	(54,57,61,62,64-66)
Carcinogenesis	HCC, Lung cancer, Thyroid carcinoma, SSCC, MM	(8,18-21)	N/A	-
Target genes	CCND1[a], ABCC2, AKIRIN2, ATG7, AURKA, CDK1, ERGIC3, FRAT1, HDAC2, HK2, HMGA2, hnRNPA1, MAPK1, MMP2, MMP9, PCBP1, POU3F2, PPM1F, RAB14, RHOA, RSF1, SMARCD1, SP1, TGFα, TGFβR1, TGIF2, TNKS2, TWIST1, VDAC1, VIM	(6,8,13,20-24,26-32,34,35,38-42, 45,46,52,59,85,100,101)	CCND1[a], BUB1, E2F2, ECT2, ROBO1, EGFR, PIK3CA, MYEOV, SOX2, c-FOS, MAP3K9	(17,50,51,53,54,57, 61,62,65,66)
Signaling pathways	MAPK[a], TGF-β[a], HIF-1A, Wnt, EGFR, AMPK, AKT	(13,22-24,28,40-42,44)	MAPK[a], TGF-β[a], PI3K-AKT	(54,64,66)
ceRNA network	Hsa_circ_SLC3A2, Hsa_circ_0006948, Hsa_circ_101237, PPM1F, HMGA2, LncRNA BCYRN1, lncRNA CCAT1, lncRNA DLEU1, lncRNA LINC00173, lncRNA LINC00483, lncRNA RP11-81H3.2, lncRNA SNHG6, lncRNA SNHG15, lncRNA SNHG16, lncRNA TP73-AS1, lncRNA TONSL-AS1, POU3F2, MAPK1, TGFβR1, CDK1, hnRNPA1, TNKS2, RSF1, HDAC2, HK2	(6,25,26,29,30,33-35,38,44,46-48, 55,56,85,86,102)	Hsa_circ_0103809, Hsa_circ_0023642, SOX2, EGFR, lncRNA LINC02532, LncRNA XLOC_001659, PIK3CA	(17,50,57,87)
Diagnosis	In tissue and plasma	(6,20)	In tissue	(93)
Chemoresistance	Increase paclitaxel resistance and decrease CDDP resistance	(36,94)	N/A	-
Prognosis	GC[a], HCC[a], Glioma, CRC, Osa	(6,13,22,90,91)	GC[a], HCC[a]	(51,87)

miR, microRNA; ESCC, esophageal squamous cell carcinoma; AML, acute myeloid leukaemia; GC, gastric cancer; CCA, cholangiocarcinoma; CRC, colorectal cancer; BCa, breast cancer; OC, ovarian cancer; Eca, endometrial carcinoma; PC, prostate cancer; HCC, hepatocellular carcinoma; Osa, osteosarcoma; SSCC, skin squamous cell carcinoma; MM, multiple myeloma; RCC, renal cell carcinoma; BC, bladder cancer; CDDP, cisplatin. [a]Common between miR-490-3p and miR-490-5p.

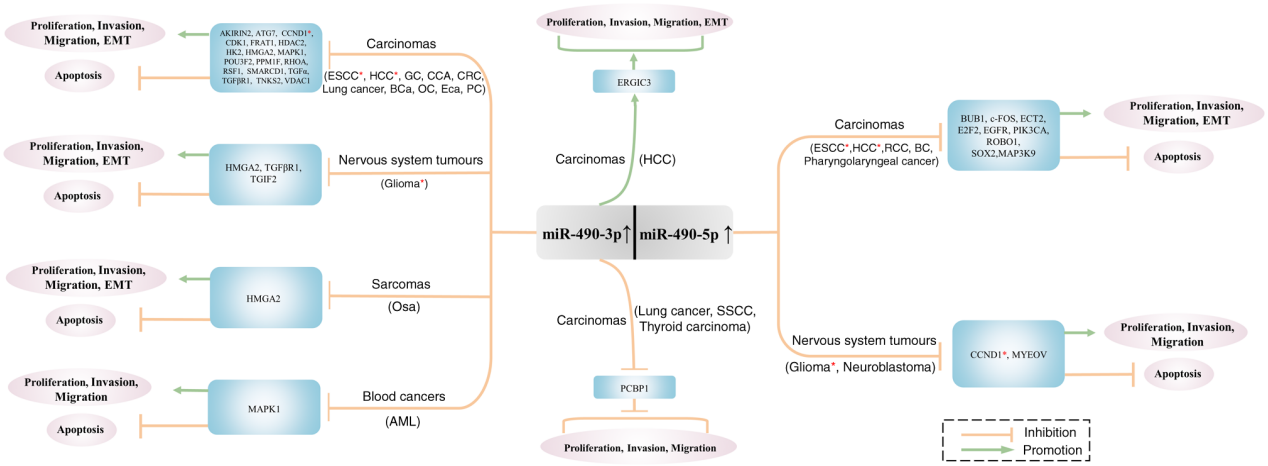

Figure 2. Cell behavioral functions of miR-490-3p and miR-490-5p target genes. miR-490-3p and miR-490-5p have their own target genes. Expression of miR-490-3p and miR-490-5p can inhibit cancer cell proliferation, migration, invasiveness and EMT by inhibiting target genes and promoting apoptosis. Among them, CCND1 is a common target gene. Additionally, miR-490-3p promotes cellular proliferation, invasiveness, migration and EMT by promoting the expression of ERGIC3. miR-490-3p promotes cellular proliferation, migration and invasiveness by increasing the expression of PCBP1. *Common target gene of miR-490-3p and miR-490-5p. miR, microRNA; EMT, epithelial-mesenchymal transition; CCND1, cyclin D1; ERGIC3, endoplasmic reticulum-Golgi intermediate compartment protein 3; PCBP1, poly(RC) binding protein 1; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; GC, gastric cancer; CCA, cholangiocarcinoma; CRC, colorectal cancer; BCa, breast cancer; OC, ovarian cancer; Eca, endometrial carcinoma; PC, prostate cancer; Osa, osteosarcoma; AML, acute myeloid leukemia; SSCC, skin squamous cell carcinoma; RCC, renal cell carcinoma; BC, bladder cancer.

β-catenin activity (74). Therefore, in CRC and BCa, the low expression levels of miR-490-3p can promote β-catenin accumulation and Wnt signaling pathway activation, thereby enhancing the cancer cell aggressiveness (23,42).

In AML, miR-490-3p is associated with the MAPK signaling pathway. Inhibition of miR-490-3p by lncRNA-colon cancer associated transcript 1 (CCAT1) causes the accumulation of MAPK1 and c-Myc in the MAPK signaling pathway. As a nucleoprotein, c-Myc stimulates the expression of lncRNA CCAT1 to form a positive feedback loop, and enhance cancer cell proliferation and invasiveness (44).

In BCa, P70S6 kinase (P70S6K) is the downstream effector of Transforming protein RhoA, a target gene of miR-490-3p (41). Through the P70S6K/P85S6K pathway, miR-490-3p may affect the proliferation and apoptosis of BCa T47D and MCF-7 cells (41,75). In Eca, the high expression of TGFα is the possible reason for the activation of the EGFR signaling pathway. Upregulation of TGFα can promote the expression of EGFR downstream proteins NF-kB, MMP-2, cyclin D1 and survivin, and inhibit the production of pro-apoptotic protein Bax (40). miR-490-3p is involved in the development of Eca by inhibiting TGFα and the EGFR pathway (40). Transfection of miR-490-3p mimics reduced the level of voltage-dependent anion-selective channel protein 1 and increased the level of phosphorylated AMPK in CRC (22). The activated AMPK pathway inhibits the mTOR signaling pathway through tuberous sclerosis complex subunit 1 and 2 (76), indicating that miR-490-3p plays an anticancer role through its regulation of the AMPK signaling pathway (22). The target genes of miR-490-3p comprise TGFβR1 and TGFB induced factor homeobox 2, which regulate the TGF-β signaling pathway to promote cancer (13,24,77,78).

The target genes of miR-490-5p are also involved in the regulation of the TGF-β signaling pathway. BUB1 is an activator of TGF-β. By inhibiting the expression of BUB1, miR-490-5p inhibits the TGF-β signaling pathway, suppresses the proliferation, migration and invasiveness, and increases the apoptosis of HCC cells (54). miR-490-5p is also associated with the MAPK signaling pathway, and MAP3K9 is the direct target of miR-490-5p. The phosphorylation activation of MAP3K9 can sequentially activate MAPKK and MAPK, and promote cellular proliferation, migration, invasiveness and EMT (66). Furthermore, miR-490-5p directly targets PIK3CA to regulate the PI3K/Akt signaling pathway and inhibit the carcinogenicity of renal cancer cells (64,79,80).

Although both miR-490-3p and miR-490-5p are involved in regulating the TGF-β and MAPK signaling pathways, their molecular mechanisms are different (13,44,54,66). This indicates that miR-490-3p and miR-490-5p have different mechanisms for inhibiting cancer development.

To the best of our knowledge, there are currently no published studies on the oncogenic signaling pathway of miR-490-3p (81). Notably, the antioncogene PCBP1 was reported to be an immune checkpoint required for effector T-cell function, as well as a key molecule in the conversion of the TGF-β signaling pathway from a growth factor inhibitor to a tumor growth promoter in advanced cancer stages (70). PCBP1 was also reported to be associated with the HIF and Akt signaling pathways (82,83). However, the role of miR-490-3p in the regulation of these pathways is yet to be elucidated. By contrast, ERGIC3 has not been reported in association with a corresponding signaling pathway; however, in non-small cell lung cancer (NSCLC), ERGIC3 is negatively regulated by miR-230a and no effect of miR-490-3p on ERGIC3 was observed (84). Whether this is affected by tissue specificity, or perhaps other influencing factors, may be worthy of further investigation.

4. Primary ceRNA regulatory networks of miR-490-3p and miR-490-5p

In cancer, the dysregulation of miR-490-3p and miR-490-5p is significantly associated with ncRNAs, including circRNA

Table II. Key roles of miR-490-3p and miR-490-5p in cancer.

Cancer type	Target gene	miR	Expression level	Regulatory mechanism	Effect *in vitro*	(Refs.)
CRC	FRAT1, VDAC1, TGFβR1, MMP2, MMP9	miR-490-3p	Low	Inhibit FRAT1/Wnt /β-catenin signaling pathway	Proliferation↓, apoptosis↑, EMT↓	(22-24)
				Inhibit VDAC1/AMPK/ mTOR signaling pathway	Proliferation↓, migration and invasion↓, apoptosis↑	
				Inhibit TGFβR1/SMAD2/4/TGF-β signaling pathway	Migration and invasion↓	
GC	SMARCD1, MAPK1, hnRNPA1	miR-490-3p	Low	LncRNA CCAT1/miR-490-3p/ hnRNPA1 axis	Migration↓	(25-27)
				LncRNA LINC00483/miR-490-3p/ MAPK1 axis	Proliferation↓, migration and invasion↓, apoptosis↑	
HCC	PPM1F, ATG7, HDAC2, POU3F2, CDK1, TNKS2, AURKA	miR-490-3p	Low	Hsa_circ_SLC3A2 /miR-490-3p/PPM1F axis	Proliferation↓, invasion↓	(6,45-48, 51,52,55)
				LncRNA BCYRN1/miR-490-3p/POU3F2 axis	Proliferation↓, migration and invasion↓	
				LncRNA CCAT1/miR-490-3p/CDK1 axis	Proliferation↓, invasion↓	
				LncRNA RP11-81H3.2/miR-490-3p/ TNKS2 axis	Proliferation↓, migration and invasion↓	
				LncRNA SNHG15/miR-490-3p/HDAC2 axis	Proliferation↓, migration and invasion↓	
HCC	ECT2, E2F2, ROBO1, SOX2, BUB1	miR-490-5p	Low	Hsa_circ_0103809/miR-490-5p/SOX2 axis	Proliferation↓, migration↓, apoptosis↑	(49-51, 53,54)
				Inhibit BUB1/TGF-β signaling pathway	Proliferation↓, migration and invasion↓, apoptosis↑	
CCA	AKIRIN2	miR-490-3p	Low	Inhibit AKIRIN/IL-6/gp130/STAT3/ VEGFA signaling pathway	Proliferation↓, migration and invasion↓, EMT↓	(28)
ESCC	HMGA2, MAPK1	miR-490-3p	Low	Hsa_circ_0006948/miR-490-3p/HMGA2 axis	Proliferation↓, migration and invasion↓, EMT↓	(56,58,59)
ESCC	PIK3CA	miR-490-5p	Low	LncRNA XLOC_001659/miR-490-5p/ PIK3CA axis	Proliferation↓, invasion↓	(57)
Lung cancer	CCND1, MAPK1, RSF1	miR-490-3p	Low	Hsa_circ_101237/miR-490-3p/MAPK1 axis	Proliferation↓, migration and invasion↓	(29-31)
				LncRNA SNHG6/miR-490-3p/RSF1 axis	Proliferation↓, apoptosis↑	
Pharyngolaryngeal cancer	MAP3K9	miR-490-5p	Low	Inhibit MAP3K9/MAPKK/MAPK signaling pathway	Proliferation↓, migration and invasion↓, EMT↓	(66)
PC	HDAC2	miR-490-3p	Low	-	Proliferation↓, migration and invasion↓, apoptosis↑	(32)
BC	EGFR, c-FOS	miR-490-5p	Low	Hsa_circ_0023642/miR-490-5p/EGFR axis	Invasion↓	(17,62,63)
RCC	PIK3CA	miR-490-5p	Low	Inhibit PIK3CA/PI3K- Akt signaling pathway	Proliferation↓, migration and invasion↓	(64)

Table II. Continued.

Cancer type	Target gene	miR	Expression level	Regulatory mechanism	Effect *in vitro*	(Refs.)
Glioma	HMGA2, TGFβR1, TGIF2	miR-490-3p	Low	Inhibit TGIF2/TGF-β signaling pathway	Proliferation↓, EMT↓	(13,60)
Glioma	CCND1	miR-490-5p	Low	-	Proliferation↓	(61)
Neuroblastoma	MYEOV	miR-490-5p	Low	-	Proliferation↓, migration and invasion↓, apoptosis↑	(65)
OC	ABCC2, TGFβR1, CDK1	miR-490-3p	Low	LncRNA CCAT1 /miR-490-3p/TGFβR1 axis	Migration and invasion↓, EMT↓	(33-37)
				LncRNA DLEU1/miR-490-3p/CDK1 axis	Proliferation↓, migration and invasion↓, apoptosis↑	
				LncRNA TONSL-AS1/miR-490-3p/CDK1	Proliferation↓	
Eca	SP1, HK2, TGFα	miR-490-3p	Low	axis LncRNA SNHG16/miR-490-3p/HK2 axis Inhibit TGFα/EGFR signaling pathway	Proliferation↓	(38-40)
					Proliferation↓, migration and invasion↓, apoptosis↑	
BCa	TNKS2, RHOA	miR-490-3p	Low	Inhibit RHOA/P70S6K/P85S6K signaling pathway	Proliferation↓, apoptosis↑	(41,42)
				Inhibit TNKS2/β-catenin/AXIN/ Wnt signaling pathway	Proliferation↓, migration and invasion↓	
Osa	HMGA2	miR-490-3p	Low	-	Proliferation↓, apoptosis↑	(43)
AML	MAPK1	miR-490-3p	Low	Inhibit lncRNA CCAT1/miR-490-3p/ MAPK1/c-Myc positive feedback loop in MAPK signaling pathway	Proliferation↓, migration and invasion↓, apoptosis↑	(44)
HCC	ERGIC3	miR-490-3p	High	-	Proliferation↑, migration and invasion↑, EMT↑	(8)
Lung cancer	PCBP1	miR-490-3p	High	-	Proliferation↑, migration and invasion↑, EMT↑	(18)
Thyroid	PCBP1	miR-490-3p	High	-	Neoplasia↑	(19)
carcinoma SSCC	PCBP1	miR-490-3p	High	-	Maintenance of cancer stem cells↑	(21)

miR, microRNA; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; ESCC, esophageal squamous cell carcinoma; PC, prostate cancer; BC, bladder cancer; RCC, renal cell carcinoma; OC, ovarian cancer; Eca, endometrial carcinoma; BCa, breast cancer; Osa, osteosarcoma; AML, acute myeloid leukemia; SSCC, skin squamous cell carcinoma; EMT, epithelial-mesenchymal transition.

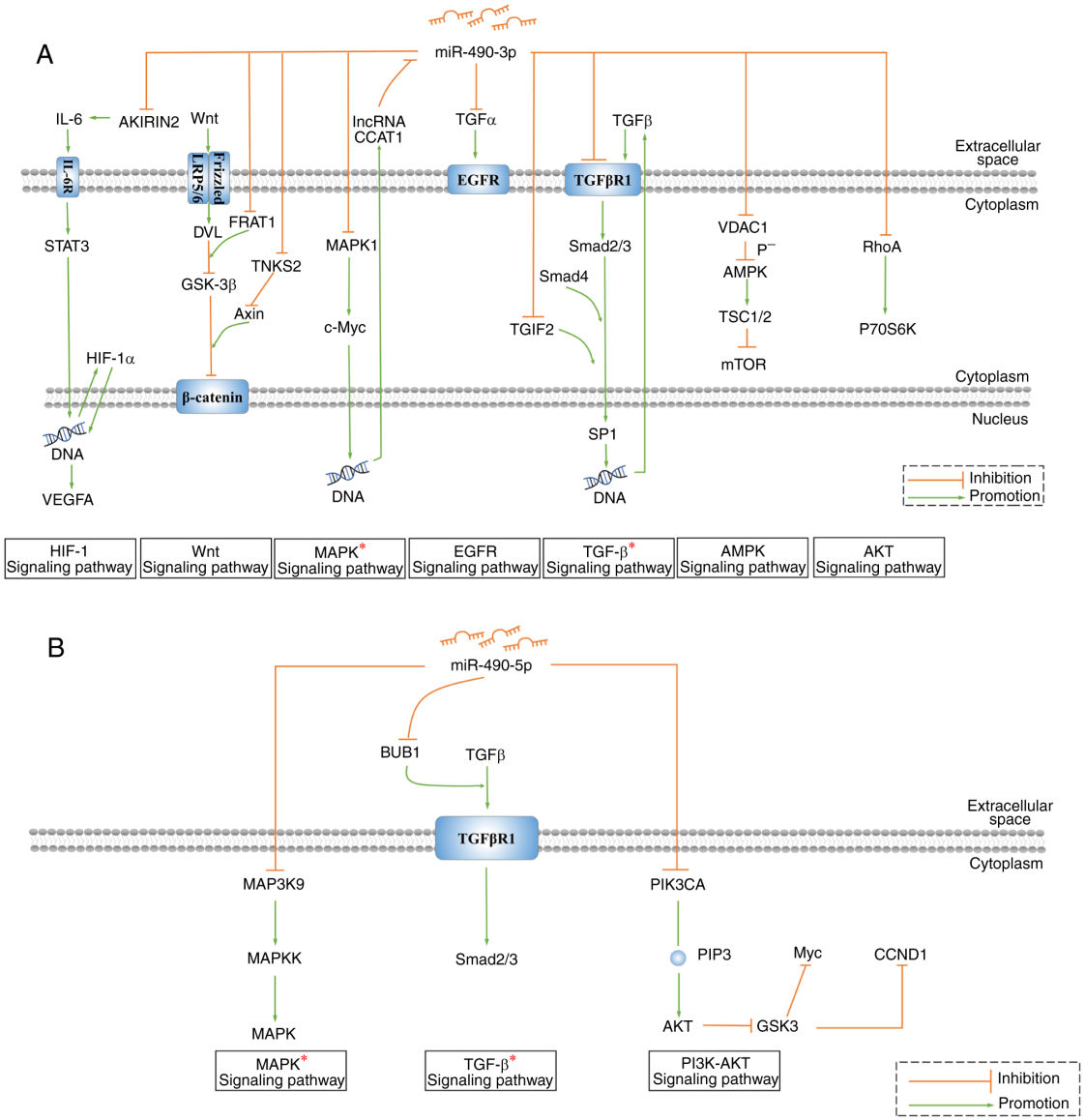

Figure 3. Target genes and signaling pathways of miR-490-3p and miR-490-5p. (A) miR-490-3p participates in the regulation of 7 signaling pathways through 9 target genes. (B) miR-490-5p participates in the regulation of 3 signaling pathways through 3 target genes. *Common signaling pathway of miR-490-3p and miR-490-5p. miR, microRNA.

and lncRNA (Fig. 4). In the HepG2 liver cancer cell line, circSLC3A2 can sponge miR-490-3p, and thus promote the expression of protein phosphatase 1F, and increases tumor proliferation and invasion (6). In the TE-1 and KYSE30 ESCC cell lines, Hsa_circ_0006948 can reverse the inhibition of high mobility group AT-hook 2 expression by miR-490-3p, thereby promoting cancer (56). In NSCLC cell lines (A549 and H1299), enhancement of the circRNA_101237/miRNA-490-3p/MAPK1 pathway was found to have a cancer-promoting effect (29).

In AML, there is a positive feedback loop associated with lncRNA CCAT1/miR-490-3p/MAPK1/c-Myc. Within this, the downregulation of miR-490-3p can lead to the upregulation of MAPK1 and c-Myc, which in turn increases the expression of CCAT1 and accelerates tumorigenesis (44). lncRNA CCAT1 is also involved in the development of GC, and the lncRNA CCAT1/miR-490-3p/heterogeneous nuclear ribonucleoprotein A1 axis can promote the migration of GC cells (26). In addition, the lncRNA CCAT1/miR-490-3p/CDK1 axis was also found in HCC (55). In OC cell lines (SKOV3 and CaOV3), the lncRNA CCAT1/miR-490-3p/TGFβR1 axis can promote EMT (34).

In the H460 NSCLC cell line, lncRNA small nucleolar RNA host gene (SNHG) 6 promotes the expression of oncogene remodeling and spacing factor 1 (RSF1) through the miR-490-3p/RSF1 axis, and also indirectly promotes the expression of anti-apoptotic protein Bcl-2, and inhibits the expression of apoptosis-related proteins (cleaved caspase-3 and Bax) (30). In the MKN-45GC cell line, LINC00483 not only regulates the miR-490-3p/MAPK1 axis, but also indirectly promotes the expression of anti-apoptotic proteins c-Myc and MMP9, and inhibits the expression of pro-apoptotic protein Bax (25). Furthermore, In HCC cell lines (Huh-1 and Huh-7), lncRNA SNHG15 promotes HCC progression by regulating the miR-490-3p/histone deacetylase 2 axis (48). In other liver cancer cell lines (HepG2 and Huh7), the lncRNA RP11-81H3.2/miR-490-3p/TNKS2 pathway was also identified

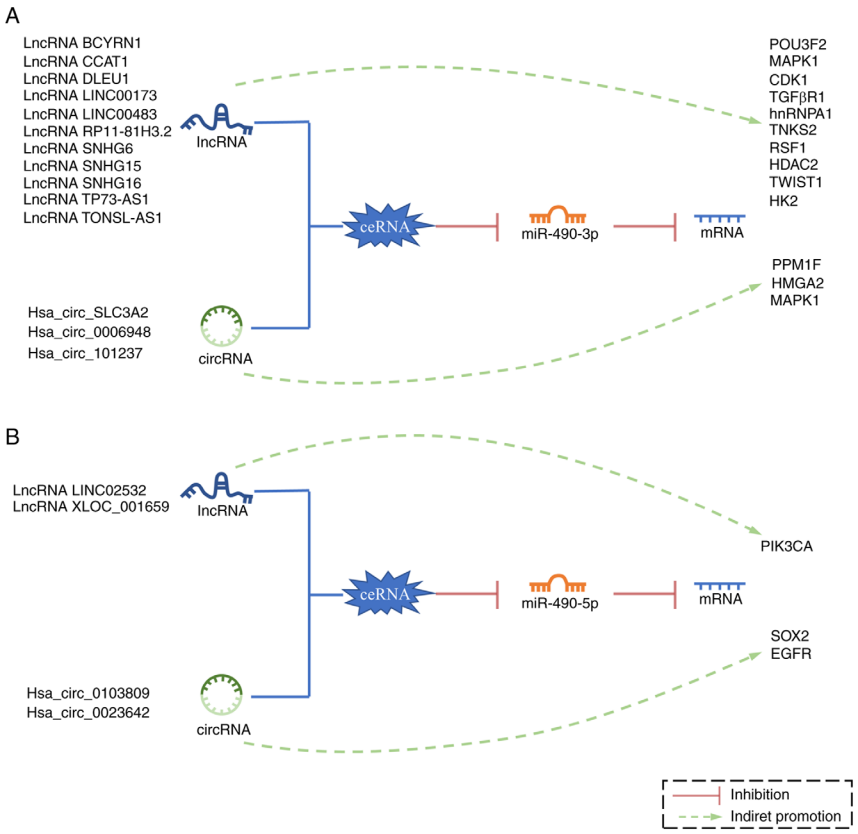

Figure 4. Schematic diagram of the ceRNA networks centered on miR-490-3p and miR-490-5p. (A) Upstream ncRNAs of miR-490-3p include 11 lncRNAs and 3 circRNAs. ncRNAs inhibit the expression of miR-490-3p through endogenous competition and release miR-490-3p's control of 12 target genes. (B) Upstream ncRNAs of miR-490-5p include 2 lncRNAs and 2 circRNAs, and it regulates 3 downstream target genes. ceRNA, competing endogenous RNA; miR, microRNA; ncRNA, noncoding RNA; circRNA, circular RNA; lncRNA, long non-coding RNA.

to be active. miR-490-3p is not only the downstream target of RP11-81H3.2, but is also responsible for the degradation of RP11-81H3.2; the positive feedback loop between RP11-81H3.2 and miR-490-3p can promote the proliferation, migration and invasiveness of tumor cells (47). Additionally, there exists a dysregulation of the lncRNA BCYRN1/miR-490-3p/POU3F2 axis in the HepG2 cell line (46). In OC cell lines (OVCAR3 and A2780), the inhibition of lncRNA deleted in lymphocytic leukemia 1 on miR-490-3p increased the expression of CDK1, CCND1 and SMARCD1 protein, and indirectly promoted the expression of anti-apoptosis-related proteins MMP2, Bcl-xL and P70S6K (35). In addition, there is also a dysfunction of the lncRNA TONSL-AS1/miR-490-3p/CDK1 axis in the OVCAR3 OC cell line (33). In Eca, the TFAP2A/lncRNA SNHG16/miR-490-3p/HK2 axis can promote cancer. The transcription factor TFAP2A can activate SNHG16 transcription, thereby reversing the inhibitory effect of miR-490-3p on HK2, and ultimately promoting the proliferation and glycolysis of Eca (38). In the MDA-MB-231 triple-negative BCa (TNBC) cell line, the lncRNA TP73-AS1/miR-490-3p/TWIST1 axis can promote the formation of vasculogenic mimicry, thereby promoting tumor progression (85). In addition, the inhibitory effect of lncRNA LINC00173 on miR-490-3p was identified in TNBC (86).

Members of the ceRNA regulatory network centered on miR-490-5p are different from those of the miR-490-3p network. In the BC cell lines (J82 and UMUC3), the ERα/circ_0023642/miR-490-5p/EGFR pathway can inhibit the progress of BC (17). In liver cancer cell lines (HepG2 and Huh7), highly expressed Hsa_circ_0103809 promotes the development of cancer through the Hsa_circ_0103809/miR-490-5p/ SRY-box transcription factor 2 (SOX2) signaling pathway (50). Additionally, in ESCC cell lines (EC9706 and EC-1), the highly expressed lncRNA XLOC_001659 inhibited miR-490-5p and promoted the expression of PIK3CA, which ultimately promoted the proliferation and invasiveness of ESCC cells (57). Furthermore, in GC, the highly expressed lncRNA LINC02532 can inhibit the expression of miR-490-5p (87).

5. Clinical diagnostic and prognostic values of miR-490-3p and miR-490-5p

Early diagnosis of cancer is a hot spot of clinical concern, and early cancer discovery is conducive to improved prognosis. As shown in Table III, the abnormal expression of miR-490-3p in tumor tissues has been applied to the diagnosis of a variety of tumors, including HCC (6,88), rectal adenocarcinoma, ESCC, GC and CRC (89). In addition, plasma miR-490-3p may be a diagnostic biomarker for CRC (22) and MM (20).

Current research shows that miR-490-3p also plays an important role in predicting the prognosis of cancer patients (Table III). Liu *et al* (22) reported that the low expression levels of miR-490-3p in CRC tissues were not only associated with poorer clinicopathological characteristics, but also with shorter overall survival (OS) in patients with CRC. Wang *et al* (6)

Table III. Diagnostic and prognostic values of miR-490-3p and miR-490-5p.

miR	Cancer type	Sample type	Expression level	Target gene	Diagnostic/prognostic value	(Refs.)
miR-490-3p	CRC	457 patients from TCGA	Low	-	AUC=0.797	(89)
miR-490-3p	CRC	55 plasma	Low	VDAC1	Prognostic factor of OS, AUC=0.66, sensitivity=65.45%, specificity=71.43%	(22)
miR-490-3p	ESCC	90 patients from TCGA	Low	-	AUC=0.826	(89)
miR-490-3p	GC	446 patients from TCGA	Low	-	AUC=0.798	(89)
miR-490-3p	Glioma	58 patients	Low	TGIF2	Prognostic factor of OS	(13)
miR-490-3p	GC	36 paired tissues and 82 patients	Low	SMARCD1	Prognostic factor of OS, DFS and Survival rate	(27,91)
miR-490-3p	HCC	114 patients	Low	PPM1F	Prognostic factor of OS, relapse, AUC=0.63	(6)
miR-490-3p	HCC	41 patients and 375 patients	Low	POU3F2	Prognostic factor of Survival rate, AUC=0.695	(46,88)
miR-490-3p	MM	35 plasma	High	-	AUC=0.87, sensitivity=60%, specificity=85%	(20)
miR-490-3p	Osa	148 patients	Low	-	Prognostic factor of OS and RFS	(90)
miR-490-3p	READ	162 patients from TCGA	Low	-	AUC=0.965	(89)
miR-490-5p	CRC	115 patients	Low	-	AUC=0.737, sensitivity=70.79%, specificity=64.52%	(93)
miR-490-5p	HCC	41 patients	Low	-	AUC=0.715	(92)
miR-490-5p	HCC	50 patients and 92 patients	Low	E2F2, ECT2	Prognostic factor of OS, DFS and survival rate	(49,51)

miR, microRNA; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MM, multiple myeloma; Osa, osteosarcoma; READ, rectum adenocarcinoma; OS, overall survival; RFS, relapse-free survival; DFS, disease-free survival; AUC, area under curve; TCGA, The Cancer Genome Atlas.

found that the low expression of miR-490-3p was associated with a lower OS and tumor recurrence in patients with HCC. Li *et al* (88) showed that the low expression of miR-490-3p represents the low OS rate of patients with HCC, and Ding *et al* (46) found that the low expression of miR-490-3p decreased the OS of patients with HCC. In Osa, Tang *et al* (90) found that low expression of miR-490-3p was associated with OS and relapse-free survival. Qu *et al* (91) showed that in helicobacter pylori-infected patients with GC, low expression of miR-490-3p was associated with shorter OS and disease-free survival (DFS) times. Shen *et al* (27) found that low expression levels of miR-490-3p promotes the expression of SMARCD1, and is associated with shorter OS times in patients with GC. In addition, Vinchure *et al* (13) showed that higher expression levels of miR-490-3p in patients with the mesenchymal subtype of glioblastoma is associated with improved OS (13).

miR-490-5p also has potential diagnostic capabilities in HCC (92) and CRC (93). Fang *et al* (51) revealed that the expression level of miR-490-5p is associated with the OS and DFS rate of patients with HCC. Other studies have also found that low expression levels of miR-490-5p are associated with lower OS (49,92) and DFS (49) in patients with HCC. In GC, high expression of LINC02532 can result in reduced expression of miR-490-5p, which is associated with poor prognosis (87).

6. miR-490-3p-related anticancer drug resistance

Tumor chemoresistance frequently results in recurrence and poor prognosis. Tian *et al* (36) ascertained that miR-490-3p promotes chemosensitivity to cisplatin (CDDP) by downregulating the target gene ATP binding cassette subfamily C member 2 in OC cells, suggesting that it may be a potential therapeutic target for the treatment of patients with CDDP-resistant OC. In addition, Chen *et al* (94) revealed that miR-490-3p can upregulate the protein expression levels of P-gp and GST-π, thereby enhancing the resistance of A2780 OC cells to paclitaxel. At present, research on miR-490-3p and chemoresistance is limited, and the underlying mechanism of its differential action on the sensitivity of different chemotherapeutic agents towards cancer may be associated with miR-490-3p targeting of different downstream genes.

7. Discussion

The dysfunction mechanism of miR-490-3p and miR-490-5p in cancer is worthy of attention. Hypermethylation of the miR-490 promoter results in decreased expression of the precursor miR-490 (27), which influences the maturation of miR-490-3p and miR-490-5p. In addition, the competitive inhibition of miR-490 by oncogenic ncRNAs (such as lncRNAs and circRNAs) is one of the reasons for the low expression of miR-490-3p and miR-490-5p (Fig. 4). However, numerous studies have shown that miR-490-3p has a different mechanism of action than miR-490-5p in tumorigenesis. Due to the difference in base sequence between the two mature miRNAs (Fig. 1B), miR-490-3p not only suppresses oncogenes to exert anticancer effects, but also suppresses the cancer suppressor gene PCBP1 and promotes cancer development. In addition, miR-490-3p has a role in promoting the expression of target genes, which may be associated with the Ago2 protein (69) and the 5'-UTR of mRNAs that encode ribosomal proteins (95). Therefore, the molecular mechanism by which miR-490-3p inhibits or promotes cancer warrants further investigation.

The ceRNA regulatory network is an important factor in cancer regulation by miR-490-3p and miR-490-5p. Through an endogenous competition mechanism, these ncRNAs downregulate the expression of miR-490-3p and miR-490-5p, and relieve their inhibitory effects on downstream target genes (Fig. 4). The existence of feedback loops suggests that the aberrant expression of miR-490 is not only the initiating factor for cancer, but also the effector of accelerated cancer development (44). The ceRNA network of miR-490-3p includes 11 lncRNAs, 3 circRNAs and 12 protein-coding genes. In the ceRNA network of miR-490-5p, there are 2 lncRNAs, 2 circRNAs and 3 protein-coding genes. The two ceRNA networks also communicate with each other. For example, SOX2 in the miR-490-5p regulatory network can activate lncRNA CCAT1 in the miR-490-3p regulatory network, thereby promoting the progression of squamous cell carcinoma (96). This shows that the ceRNA regulatory network is more complex and sophisticated than the current findings indicate.

Numerous studies have shown that miR-490-3p and miR-490-5p have high specificity and sensitivity in the early diagnosis of tumors (Table III). The diagnostic capabilities of miR-490-3p can be applied to bodily fluids such as tissue, blood and urine. miR-490-3p and miR-490-5p are also independent prognostic factors for HCC and GC (51,91). At the same time, the imbalance of miR-490-3p is also related to the chemoresistance of cancer (36,94). In addition, though it is not clear whether miR-490-3p or miR-490-5p is involved, miR-490 exists in the exosomes of mast cells. This suggests the possibility of using exosomes as miR-490 vectors to transform the tumor microenvironment (97).

At present, it is necessary to further understand the specific mechanisms of the ceRNA regulatory networks associated with miR-490-3p and miR-490-5p. At the same time, the unique cancer-promoting mechanism of miR-490-3p remains to be clarified. Besides the involvement of Ago2, whether there are other influencing factors that make miR-490-3p a unique cancer-promoting factor remains to be studied. There are also conflicting results regarding the role of miR-490-3p in OC drug resistance (36,94), and further experimental verification is required. At present, there is a lack of clinical studies using miR-490-3p and miR-490-5p as therapeutic targets, and the side effects of related therapies are not yet clear.

Previously, Vinchure and Kulshreshtha (81) reviewed miR-490 as a potential biomarker and therapeutic target in cancer and other pathologies. However, the differences between miR-490-3p and miR-490-5p in this context were not well distinguished. According to current research, it is necessary to treat the two mature products of miR-490 differently. Further research is required to focus on the ceRNA networks centered on miR-490-3p and miR-490-5p, which will provide a solid theoretical foundation for their applications in early clinical diagnosis, tumor prognosis prediction and chemotherapeutic resistance.

We hypothesize that further investigation is required to thoroughly explore the molecular mechanisms of miR-490-3p and miR-490-5p in tumors. In addition, there is still a lack of research surrounding the effects of miR-490-3p and miR-490-5p on chemoresistance. In the future, whether miR-490-3p and miR-490-5p can be targeted as tumor

treatment options will be an interesting topic (9), as well as their value in the treatment of non-cancer diseases (98).

8. Conclusions

miR-490-3p and miR-490-5p are derived from the same precursor miRNA and both exhibit low expression levels in glioma, ESCC and HCC. Both have a common target gene, CCND1, and both function in the MAPK and TGF-β pathways to regulate cancer cell characteristics, such as proliferation, migration and invasiveness. However, the differences between miR-490-3p and miR-490-5p are of interest. Firstly, miR-490-3p is involved in a wider range of cancer types, with dysregulated expression in up to 13 cancers, while miR-490-5p has been more widely studied in BC, RCC and pharyngeal cancer. Secondly, miR-490-3p targets a higher number of downstream genes. miR-490-5p targets 11 downstream genes, while miR-490-3p targets 30. Furthermore, miR-490-3p is involved in more signaling pathways, including those of HIF-1A, Wnt, EGFR, AMPK and AKT; and compared with miR-490-5p, miR-490-3p has a more complex ceRNA regulatory network. Notably, the current review suggests that miR-490-3p has both oncogenic and pro-oncogenic effects, while miR-490-5p has only oncogenic effects. It has been well documented that tissue and plasma miR-490-3p have diagnostic capacities in malignancies such as CRC, MM and HCC, and that miR-490-3p has a higher value as an independent prognostic factor in CRC, glioma, GC, HCC and Osa than miR-490-5p. In addition, focusing on miR-490-3p may help to address the resistance of OC to chemotherapeutic drugs such as cisplatin and paclitaxel.

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Authors' contributions

The article was conceived by YL and SD. YL, DT, HC, YC and SC collected and analyzed the associated publications, and drafted the manuscript. SD and YL critically revised the work and gave the final approval of the submitted version. All authors have read and approved the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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