

## Review Article

# The potential role of microRNA-497 in different cancers

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**Abstract:** microRNA-497 (miR-497) is located on chromosome 17 which belongs to the miR-15 family, affecting a variety of life processes, including cell proliferation, apoptosis, cell differentiation, epithelial-mesenchymal transition, angiogenesis, cell cycle, invasion and metastasis through post-transcriptional regulation of target genes. Increasing evidences have shown miR-497 plays an important role in the occurrence and development of a variety of tumors. Cytology and animal experiments also demonstrate that miR-497 can inhibit the progression of some tumors and promote the efficacy of certain chemotherapy drugs. However, miR-497 play different regulatory role in different tumors, not only function as a diagnostic marker for cancer, but also as a new target for cancer therapy. In this paper, we focused on the role and mechanism of miR-497 in different tumors, and investigated accumulating data to provide the basis for clinical tumor-specific targeted therapy.

**Keywords:** microRNA-497, tumor, suppressor gene, targeted therapy

## Introduction

MicroRNAs (miRNAs) are a class of evolutionarily conserved non-coding RNA molecules comprising ~22 nucleotide. miRNAs inhibit the expression of genes through binding to 3' untranslated region (3'-UTR region) at the post-transcriptional level [1, 2]. miRNAs participate in a variety of cellular processes to regulate cell growth, differentiation and apoptosis under physiological and pathological conditions [3]. In recent years, multiple studies have shown that microRNAs may serve as a tumor suppressor gene or oncogene, in which specific miRNA expression changes may closely related to the tumor occurrence and development [4-6]. The gene encoding microRNA-497 (miR-497) is located within chromosome 17 which plays different roles in the development of a variety of tumors. In this paper, expression and potential role of miR-497 in different tumors and its associated mechanisms are reviewed.

## miR-497

miR-497 is a cluster of highly conserved miRNA located on the short arm of chromosome 17

(17p13.1), belonging to miR-15/16/195/424/497 cluster, with each mature miRNAs member of the family contains a AGCAGC sequence in the 5' end and has a high expression abundance [7]. Increasing evidences have shown that, by binding to a different target gene, miR-497 inhibits expression of the target genes which involved in the regulation of cell proliferation, apoptosis, cell cycle arrest, epithelial-mesenchymal transformation, cell differentiation, cell invasion and metastasis, therefore influence the development and progression of tumors (**Figure 1**).

## Expression and function of miR-497 in different tumors

miR-497 expression levels in various tumors vary differently, which may play tumor suppression or promotion effects (**Table 1**).

### Ovarian cancer

By analyzing 326 cases of serous ovarian cancer genome in the Cancer Genome Atlas (TCGA) meta-analysis database, our group has found a poor prognosis mesenchymal subtype of microRNA regulatory networks. miR-497 is a



**Figure 1.** miR-497 and its downstream targets and signaling pathways.

key microRNA in the network, and was negatively correlated with epithelial-mesenchymal transition associated gene expression. Further *in vitro* experiments confirmed that, miR-497 can inhibit epithelial-mesenchymal transition and tumor invasion in ovarian cancer cells by directly binding the 3'-UTR of SMURF1 to suppress the expression of SMURF1 [8]. Delfino et al [9] employed Gene Ontology and KEGG analysis to explore the survival and recurrence-related target genes in ovarian cancer, and the results confirmed miR-521 and miR-497 is associated with ovarian cancer survival and recurrence, high expression of miR-497 is correlated to earlier FIGO stage and longer survival time in ovarian cancer patients, which may be used as potential predictors to assess the prognosis of patients with ovarian cancer. In addition, miR-497 can also inhibit angiogenesis of tumor cells in ovarian cancer. miR-497 may directly bind to the VEGFA 3'-UTR to inhibit PI3K/AKT and MAPK/ERK signaling pathway [10]. VEGFA is recognized as angiogenesis inducible factor, which is a potential prognostic factor in lung cancer, VEGFA can promote angiogenesis by binding to FLT1 and KDR to trigger downstream signaling pathways [11]. These studies suggest that miR-497 functions as tumor suppressor gene in the progression of ovarian cancer.

**Breast cancer**

In breast cancer, miR-497 expression was significantly decreased compared with that in the normal breast tissues [12], and in male breast cancer, miR-497 is one of the main expression

down-regulated miRNAs [13]. The levels of miR-497 expression in several different breast cancer cell lines, including SW1990, ZR-75-30, MDA-453, MiaPaCa-2 pancreatic ductal adenocarcinoma (PDAC) and MDA-231 are also very low [14]. Luo et al [15] found that exogenous miR-497 transfection into MDA-MB-231 cell line can cause cell cycle arrest at G1 phase. In ZR-75-30 and MCF-7 cell lines, overexpression of miR-497 was found to directly targeted Raf-1 gene, with the binding site region even more conservative than

the well-known CCND-1 3'-UTR binding sites. In addition, SHEN et al [16] reported that miR-497 can induce apoptosis of breast cancer cells by directly binding target gene Bcl-w. These studies indicated that miR-497 plays an important role in the inhibition of breast cancer and may be a potential diagnostic and therapeutic targets.

**Colorectal cancer**

Lin Wang et al [17] reported that miR-497 was downregulated in colorectal cancer tissues, and its expression level was negatively associated with tumor size, lymph node invasion, TNM stage and metastasis. *In vitro* studies have demonstrated that over-expression of miR-497 inhibited the proliferation, metastasis and invasion of colon cancer cells. miR-497 can inhibit proliferation and metastasis of colorectal cancer cells through inhibition of the MAPK/ERK signaling pathway by directly combining with KSR1 3'-UTR thus. In addition, miR-497 upregulated or EZH2 downregulated may decrease β-catenin expression. miR-497-EZH2 inhibit tumor growth and metastasis by inhibiting Wnt/β-catenin pathway. Qiu et al [18] reported in colorectal cancer, VEGF-A is a direct target of miR-497, thereby by inhibiting the expression of VEGF-A/ERK/MMP-9 signal pathways, miR-497 may prevent the metastasis of colorectal cancer cells.

**Liver cancer**

miR-497 was inhibited in HCC tissues, and its expression was negatively correlated with

**Table 1.** Expression levels and target genes of miR-497 in different tumors

Cancers	Expression of miR-497	Targets of miR-497	References
Ovarian cancer	Endogenous miR-497 expression was down-regulated in the more aggressive ovarian cancer cell lines	SMURF1	[8, 9]
Breast cancer	The relative level of miR-497 expression in BC tissues was significantly lower than that in corresponding noncancerous breast tissues	Raf-1, Bcl-w	[12-16]
Colorectal cancer	MiR-497 was downregulated in colorectal cancer tissues and cell lines.	KSR1, EZH2, VEGF-A	[17, 18]
Liver cancer	miR-497 was significantly down-regulated in HCC tissue samples and cell lines.	VEGFA, AEG-1, CCNE1, CDC25A, BTRC, CDK4	[19, 20]
Non-small cell lung cancer	miR-497 is downregulated in NSCLC tumors and cell lines	HDGF, BCL2	[21, 22]
Melanoma	Endogenous miR-497 expression was downregulated in A375 cells	BRAF	[27]

VEGFA, AEG-1 in HCC. AEG-1 is overexpressed in a variety of tumors, and can promote invasion and metastasis of HCC tumor cells. By binding to AEG-1 3'-UTR, miR-497 inhibit the proliferation of liver cancer cells [19]. In HCC, miR-497 may also targeting ROCK1 by binding to 3'-UTR to inhibit its expression in HCC tissues. Further experiments confirmed that miR-497 inhibited the expressions of CCNE1, CDC25A, BTRC and CDK4, etc., inducing cell cycle arrest and apoptosis, thereby suppressing the proliferation of liver cancer cells [20].

#### Lung cancer

Zhao et al [21] applied Real-time PCR, Western Blot and immunohistochemistry assay to detected miR-497 expression in 51 cases of tumor tissue in patients with non-small cell lung cancer and 30 cases of adjacent tissue, the results showed that miR-497 expression was significantly higher in non-small cell lung cancer than that in adjacent tissues. Moreover, the high expression of miR-497 was correlated to the late clinical stage. However, Kaplan-Meier analysis showed that miR-497 was highly expressed in II/III patients. Although miR-497 expression in lung cancer tissues was significantly higher than that in the adjacent tissues, further animal experiments confirmed that miR-497 in lung cancer xenograft model can inhibit tumor growth. The study also suggested miR-497 plays the role of pro-apoptotic factor in lung small cell lung cancer. miR-497 can directly bind to BCL2 3'-UTR to reduce lung cancer cell viability and inhibit cancer cell proliferation. In normal cells (non-cancerous lung cells HLF1), no such effect was observed in miR-497 [22]. SGC7901 and multidrug-resistant cell line A549 was used to investigate the regulation role of miR-497 in lung cancer drug resistance in rats. The results showed that

miR-497 expression was significantly decreased SGC7901 and A549 cell lines, and the expression of BCL2 increased. *In vitro* drug sensitivity test showed that overexpression of miR-497 increased drug sensitivity and promote apoptosis of SGC7901 and A549 cell lines by targeting BCL2, suggesting that miR-497 plays a potential role in promoting apoptosis of lung cancer.

#### Melanoma

A recent work reported that miR-125b, miR-211 and miR-196a can reduce melanoma cell cancerization and invasion, and aberrant miR-182 can promote melanoma cell cancerization and invasion [23-26]. Recently, Poell et al systematically investigated the genome-wide miRNA human lentivirus expression library and found that miR-15/16, miR-141/200a, miR-96/182 and miR-203 was the most powerful inhibitor of the proliferation of A375 melanoma cells. Ectopic expression of these miRNAs *in vivo* can long-termly inhibit melanoma cell proliferation. For exogenous introduction of the synthetic miRNAs in several different melanocyte cell lines, miR497 and miR182 are efficient effectors [27]. MiR-47 and miR-182 influences melanocyte proliferation by targeting different genes which providing promising candidates for the application of the melanoma treatment.

#### Other tumors

In bladder cancer miR-497 expression is suppressed. miR-497 plays anti-tumor effect through inhibiting expressions of GLUT3 and CDK4. miR-497 induces cervical carcinoma cell cycle arrest in G1/S phase, suppresses bladder cancer cell proliferation, tumor growth and metastasis, and increases chemosensitivity of cervical cancer cells. Thus, miR-497 in bladder cancer has tumor suppression effect

[28, 29]. In renal cell carcinoma, miR-497 was down-regulated, and its expression was negatively correlated with pathological grade, clinical stage, lymph node metastasis and distant metastasis. In addition, low miR-497 expression in renal cell carcinoma patients was negatively correlated with poor prognosis. Multivariate survival analysis showed that the expression level of miR-497 may be a potential independent prognostic indicator in renal cell carcinoma. Further experiments confirmed that miR-497 inhibits cell invasion and metastasis in renal cell carcinoma HK-2 cell lines [30]. Xu et al [31] applied *in situ* hybridization technology to find that miR-497 expression in 10 cases of pancreatic cancer tissues was significantly lower than that in adjacent normal tissue. *In vitro* experiments confirmed miR-497 inhibit cell proliferation of pancreatic cancer cells by binding to the 3'UTR of target gene IGF-1R through affecting IGF-1R/AKT signaling pathway. Compared with normal nasopharyngeal epithelium, miR-497 expression level was lower in NPC cells. Further *in vitro* studies confirmed that miR-497 inhibited target genes (HSPA4L and ANLN) expressions and therefore suppressed the proliferation and invasion of nasopharyngeal carcinoma cells, which may play tumor suppression function in nasopharyngeal [32]. Wald et al [33] used gene chips and qRT-PCR to detect miRNA expression profiles in HPV-16 (human papillomavirus, HPV) positive and negative SCCHN cell lines, and found that compared to normal oral keratinocytes, three miRNAs (miR-63, miR-33 and miR-497) were up-regulated in HPV-negative head and neck squamous cell carcinoma cell line (squamous cell carcinoma of the head and neck, SCCHN) and HPV-positive cells, whereas the other eight miRNAs were downregulated, suggesting that these differentially expressed miRNAs may serve as biomarkers in SCCHN cell lines.

#### miR-497 in cancer therapy

Our research group preliminarily constructed two mice transplanted tumor model by intraperitoneally inoculated with ovarian cancer SKOV3-IP1 and HeyA8-IP1 cell lines, and transfected with Nanoliposomes packaged miR-497 mimics or negative control. Compared with mice given the negative control miRNA, miR-497 mimics group mice have smaller tumor size [data not shown], suggesting that miR-497 can inhibit the growth and spread of ovarian

cancer. In addition to direct anti-tumor effect, miR-497 can inhibit KSR1 expression to increase the sensitivity of colorectal cancer cells to 5-fluorouracil [34]. Thus, miR-497 in combination with platinum or PARP inhibitor, may enhance the efficacy of these anticancer drugs. However, Xu et al [35] reported that miR-497 was correlated to chemotherapy resistance in pancreatic cancer. By inhibiting the expression of FGFR1/2, miR-497 thereby increased gemcitabine/erlotinib resistance to pancreatic cancer cells.

#### Summary and outlook

In summary, miR-497 can inhibit the progression of ovarian cancer, liver cancer, colorectal cancer, breast cancer, pancreatic cancer, nasopharyngeal carcinoma, renal cell carcinoma and melanoma. Although miR-497 expression in lung cancer tissues was significantly higher than in adjacent normal tissues and high expression of miR-497 was correlated with later clinical stage [19], animal experiments have confirmed that miR-497 inhibit the growth of lung cancer cells [19, 20]. Expression of miR-497 in specific tumor subtypes still require multi-center, large sample studies to explore its different functions and the underlying mechanisms, so as to provide a theoretical basis for the clinical intervention and treatment opportunity.

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#### Disclosure of conflict of interest

None.

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