

## Review Article

# Role and mechanism of miR-187 in human cancer

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**Abstract:** MicroRNAs (miRNAs) are short non-coding RNAs, approximately 22 nucleotides in length, and involved in the post-transcriptional regulation of gene expression. MiRNAs play fundamental roles in many biological processes such as the development and progression of tumors. In this review, we briefly describe the expression of miR-187 in various types of cancer and discuss the role of miR-187 in cancer development and drug resistance. It is also possible to take miR-187 as an important indicator of diagnosis and prognosis of tumors.

**Keywords:** MiR-187, cancers, biological processes, drug resistance, biomarker, prognosis

### Introduction

MicroRNAs (miRNAs) are a group of short non-coding RNA with ~22 nucleotides found in all eukaryotic cells [1, 2]. They usually function as critical gene regulators by binding to the complementary sites in 3'-untranslated regions (3'-UTR), thus leading to gene translational repressions [3]. MiRNAs play significant roles not only in normal cells but also in cancers. Mounting evidence suggests that various miRNAs have important roles in carcinogenesis such as proliferation, apoptosis, migration and invasion through regulating downstream target genes [2, 4-6]. Furthermore, abnormal expression of miRNAs in cancer tissue suggests these miRNAs may serve as one of the diagnostic indicators of cancer in the future [7-9].

Among the cancer-related miRNAs, the study of miR-187 has caused special attentions in recent years. The human gene miR-187 is located at the 18q12.2 [10]. It has been found that miR-187 expression is significantly varied in different tumor types. In gastric cancer (GC) [11-13] and non-small cell lung cancer (NSCLC) [14-17], the expression of miR-187 is controversial. Moreover, miR-187 exerts its function via the regulation of various target genes. Therefore, we systematically review the role of miR-187 in cancers and the detailed mechanisms, to gain a better comprehension of its

potential as a novel biomarker and an indicator of diagnosis, treatment and prognosis.

### *The expression of miR-187 in cancers*

MiR-187 is expressed variously in a wide range of cancers, which known as tissue specificity (**Table 1**). MiR-187 expression was reduced in osteosarcoma (OS), which has a high incidence in adolescents [10, 18, 19]. Ectopic expression of miR-187 is also common in male genitourinary tumors. For instance, miR-187 expression decreased in Prostate cancer (Pca) compared with benign prostatic hyperplasia (BPH) [20]. Similarly, the expression of miR-187 decreased in bladder cancer (BC\*) [21]. Zhao J, et al. identified that high expression of miR-187 in the tissues of clear cell renal cell carcinoma (ccRCC) [22]. A reduction of miR-187 was also observed in cancers of the digestive system, such as colorectal cancer (CRC) and hepatocellular carcinoma (HCC) [23-25]. MiR-187 played a carcinogenic role in oral squamous cell carcinoma (OSCC) and a significantly high level of miR-187 was detected in patient's plasma [26, 27]. Also, abnormal expression of miR-187 in the top diseases causing death among female patients are being studied extensively. The reduced expression of miR-187 was reported in cervical cancer (CC), which is the most common gynecological malignancy in women [28-30]. whereas, in ovarian cancer (OC),

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**Table 1.** Expression pattern of miR-187 in a variety of human cancers

Cancer type	Expression	Level	Reference
GC	Downregulation	Tissue and Cell	[11]
	Upregulation	Tissue and Cell	[12, 13]
NSCLS	Upregulation	Tissue and Cell	[14, 16]
	Downregulation	Tissue and Cell	[15, 17]
OS	Downregulation	Tissue and Cell	[10, 18, 19]
Pca	Downregulation	Urine and Cell	[20]
BC*	Upregulation	Tissue and Cell	[21]
ccRCC	Downregulation	Tissue and Plasma	[22]
CRC	Downregulation	Tissue and Cell	[23]
HCC	Downregulation	Tissue and Cell	[24, 25]
OSCC	Upregulation	Tissue and Plasma	[26, 27]
CC	Downregulation	Tissue and Cell	[28-30]
OC	Upregulation	Tissue and Cell	[31]
BC	Upregulation	Cell	[32]
ALL	Upregulation	Bone marrow and Cell	[33]
DLBCL	Downregulation	Cell	[34]

GC: gastric cancer; NSCLS: non-small cell lung cancer; OS: osteosarcoma; Pca: prostate cancer; BC\*: bladder cancer; ccRCC: clear cell renal cell carcinoma; CRC: colorectal cancer; HCC: hepatocellular carcinoma; OSCC: oral squamous cell carcinoma; CC: cervical cancer; OC: oral cancer; BC: breast cancer; ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma.

which is second only to cervical cancer in morbidity, the expression of miR-187 was up-regulated [31]. Additionally, miR-187 expression was up-regulated in breast cancer cell lines especially in lumen B cell lines [32]. In acute lymphoblastic leukemia (ALL), a common malignancy in children, miR-187-5p elevation was found in b-line lymphocytes [33]. Whereas, in diffuse large b-cell lymphoma (DLBCL), miR-187 expression level was decreased [34]. The expression of miR-187 in gastric cancer (GC) is somewhat controversial. Specifically, two previous studies published in 2017 showed that the expression of miR-187 was up-regulated in GC [12, 13], while the study published in 2018 showed a downregulation of miR-187 in GC [11]. In addition, controversy over the expression of miR-187 in NSCLS also still exists [14-17]. The exact reason has not yet been revealed by more researches.

### *MiR-187 as a non-invasive diagnostic indicator*

MiRNAs are a new class of circulating nucleic acids in serum and other body fluids and are expected to be useful clinical biomarkers.

Because the early symptoms of prostate cancer (PCa) are very similar to prostatic hyperplasia, the misdiagnosis rate is high and the best treatment opportunity is easily delayed. It is recognized that continuous detection of serum prostatespecific antigen (PSA) is of high predictive value for PCa. The downregulation of miR-187 was observed in urine samples and tissue samples from prostate cancer patients. The median expression of miR-187 in prostate tissue was negatively correlated with the PSA [35]. Acetaldehyde dehydrogenase 1A3 (ALDH1A3), a downstream target of miR-187 in PCa, could be detected in urine as a new biomarker for PCa [20]. These new studies showed that miR-187 and its regulated target genes was also expected to be added as a new biomarker for PCa [36]. Compared with normal non-cancerous tissues, miR-187 in oral cancerous tissues was significantly up-regulated. ROC analysis showed that the level of miR-187 in plasma could distinguish between

malignant and non-malignant states to some extent [26]. Moreover, ROC analysis results obtained by F. Mirzadeh Azad et al. demonstrated the dysregulated of miR-187 in lung cancer could be used as a reliable marker for distinguishing tumor tissue from normal tissue [37]. In the study of Li et al., it was found that some miRNAs including miR-187 could be used in the early diagnosis of GBC. Their roles are similar to that of CEA CA199, which can be used as early diagnostic markers of GBC [38]. The group set consisting of miR-187, miR-221, miR-222, miR-146b, miR-155, miR-224 and miR-197 can accurately distinguish malignant tumors and proliferative nodules [39].

### *MiR-187 as predictors of prognosis*

The abnormal expression of MicroRNAs in a variety of tumors might be closely correlated with the prognosis of cancer patients. In metastatic breast cancer (MBC), one study reported that upregulation of miR187-3p and miR342-3p were verified to be associated with increased progression-free survival (PFS) and overall survival (OS) respectively. These two miRNAs

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also played a role in response to systemic therapy. KEGG pathway analysis predicted miR-342-3p and miR-187-3p regulated the MAPK signaling pathway [40]. MAPK pathway, as it was known, was participated in proliferation, survival and chemoresistance, as well as a poor outcome of patients with BC [41, 42]. On the contrary, another study reported that high miR-187 expression was negatively correlated with BC prognosis. MiR-187 in low-risk breast cancer is lower than that in high-risk breast cancer and could promote cancer to be more invasive [43]. In GC, the role of miR-187 in invasion depth, lymph node metastasis and distant metastasis is reported controversial as well [11-13]. In NSCLS, the effect of miR-187 is as controversial as that in BC and GC. MiR-187 was associated with TNM staging, lymph node metastasis and smoking history. The high expression of miR-187 indicated a good prognosis in NSCLS [15, 17, 44], while the conclusion was reversed in another study [16].

MiR-187 predicts a better prognosis in some cancers because of its anticancer effects. In OS, the downregulation of miR-187 was correlated with poor survival [18]. Additionally, in HCC, abnormal expression of miR-187 and its downstream target gene S100A4 were associated with poor prognostic factors, such as adjacent organ infiltration, advanced TNM tumors, microscopic vascular infiltration, and degree of cirrhosis [25]. Similarly, in female patients with high incidence of CC and OC, the expression level of miR-187 in patients with good prognosis was higher than that in patients with poor prognosis [27, 29]. Moreover, Decreased miR-187 expression was associated with shortened overall survival and relapse-free survival in CRC patients [23]. According to 5-year survival rate, miR-187 played an anti-tumor role in ccRCC and promoted better prognosis of patients [22, 45].

However, the high expression of miR-187 in some tumors has a poor prognosis. Patients with high miR-187 expression in BC\* had an increased risk of recurrence which is a risk of bad prognosis [21]. The level of miR-187 expression in plasma could predict the prognosis of patients after tumor resection. The sharp decline of miR-187 in the plasma after OSCC resection suggested that the high expression of miR-187 would lead to poor prognosis in

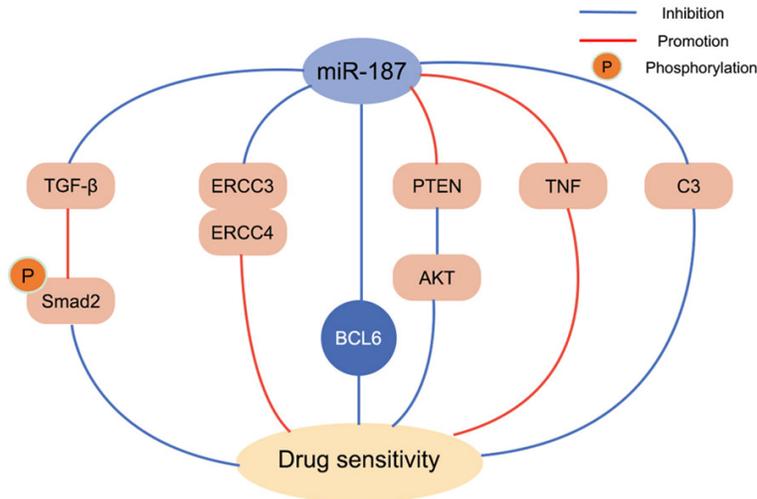
patients [26]. MiRNAs differentially expressed in BDC were identified by TCGA publicly available database. Among these miRNAs, hsa-miR-625 and hsa-miR-187 were most closely related to prognosis could be used as prognostic factors of BDC [46]. MiR-212, miR-675, miR-187 and miR-148a were predictors of PCa overall survival, independent of gender, age, tumor stage and differentiation [47]. These evidences suggested that miR-187 could be used as a non-invasive predictor of prognosis in cancer patients.

### *Relationship between miR-187 and drug sensitivity*

In tumor cells, chemoresistance remains a big challenge for modern medicine. Many researchers are studying the role of miRNAs in Chemotherapeutic insensitivity and the specific mechanism is still under investigation [48-53].

The protein expressions of TGF- $\beta$ 1, p-Smad4, ERCC3 and ERCC4 were remarkably fallen following overexpression of miR-187 [54]. SMAD family member 4 (Smad4) is the downstream target gene of transforming growth factor beta-1-like (TGF- $\beta$ 1) [55]. Western blot revealed that the protein levels of TGF- $\beta$ 1 and p-Smad4 were down-regulated, revealing that miR-187 had a remarkable influence on DDP-resistance of gastric cancer cells by inhibiting the TGF- $\beta$ /Smad signaling pathway. Previous studies have also concluded that TGF- $\beta$ /Smad may be involved in the sensitivity of gastric cancer cells to DDP [56, 57]. ERCC (excision repair cross complementing) is a member of the nucleotide excision repair (NER) family and many previous trials have confirmed that ERCC is associated with resistance to platinum compounds, affecting survival in cancer patients [58-62]. By upregulation of ERCC3 and ERCC4 expression in NER pathway, miR-187 could increase cisplatin resistance by enhancing DNA damage repair ability of gastric cancer cells [54]. These findings provided a new idea for the clinical treatment of DDP resistance in GC. Additionally, Paclitaxel and docetaxel have been used in the standard treatment of BC extensively. Uhr K, et al. reported that miR-187 was associated with the pathway "Cell cycle G2-M checkpoint" and the "MTOR signaling" pathway. As we all know, Paclitaxel works by blocking cell growth between the G2 and mitotic phases of the

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**Figure 1.** Regulation of drug sensitivity by miR-187. BCL6 was proved to be a direct downstream target of miR-187, which inhibited the sensitivity of Doxorubicin (DOX), vincristine (VCR) and bortezomib. TGF- $\beta$ 1, p-Smad4, ERCC3 and ERCC4 are important proteins in TGF- $\beta$ 1/Smad and NER signaling pathways, respectively. MiR-187 affects DDP resistance in gastric cancer cells by regulating the expression of these proteins. The negative regulation of miR-187 on PTEN, TNF and C3 was associated with the potential mechanism of Esophageal adenocarcinoma (EAC) resistance. PTEN reduced AKT activation, increasing the sensitivity of EAC to X-ray radiation and cisplatin.

cell cycle. Notably, this study observed that genes involved in the G2-M checkpoint pathway were mainly down-regulated in cell lines with elevated expression of miR-187. Thus, miR-187 served a role in breast cancer patients who are chemoresistant. However, the exact mechanisms responsible for the regulatory function were not described in detail [63]. Nevertheless, miR-187 has been shown to have no effect on cell sensitivity to tamoxifen or fluvastatin [64]. These conflicting data may be due to the tumor and/or tissue-specific functions of miR-187, or to the different ways in which these cytotoxic agents act in.

The prognosis of neoadjuvant chemoradiotherapy (CRT) for esophageal adenocarcinoma (EAC) is poor, so it is important to find potential novel markers to guide clinical treatment. X-ray radiation combined with cisplatin can cause DNA damage. Some targets regulated by miR-187 were selected from KEEG analysis. The expression levels of these targets in cells overexpressing miR-187 were then verified by qPCR. The results of qPCR showed that PTEN and TNF were the most significant. This suggests that the down-regulated genes of miR-187 may be overactive in EAC tumors with

poor sensitivity [65], PI3K/PTEN/Akt pathway has been mentioned in many literatures involved in drug resistance, proliferation and apoptosis of various cancers [66-69]. It also revealed miR-187 had the negative effect on immune regulator complement component 3 (C3) for the first time. Though the mechanism remains uncertain, the new effect of miR-187 has attracted a lot of attention. In conclusion, the new adjuvant chemoradiotherapy is highly sensitive to esophageal cancer patients with high expression of miR-187 [65].

MiR-187 expression in b-cell lymphoma cells was significantly reduced. Overexpressed miR-187 significantly reduced cell sensitivity to Doxorubicin (DOX), vincristine (VCR)

and bortezomib. Overexpression of miR-187 attenuated the expression of BCL6 in SUDHL2 cells, proving that miR-187 was a negative regulator of BCL6. In conclusion, miR-187 inhibited multidrug resistance in diffuse large b-cell lymphoma by targeting BCL6 [34] (**Figure 1**).

### *MiR-187 regulates the process of tumor proliferation and apoptosis*

In recent years, miR-187 is considered to be an important miRNA related to tumor cell proliferation and apoptosis (**Table 2**). In OS, miR-187 was a tumor suppressor that could inhibit the proliferation of osteosarcoma cells. S100A4 was a direct downstream target of miR-187 and S100A4 3'-UTR contained the binding sequence of miR-187. When S100A4 is overexpressed, cell growth inhibition regulated by miR-187 is reversed [18]. Similarly, cui et al. also revealed that miR-187 was down-regulated in OS. MAPK12 was confirmed to be the direct target of miR-187. Downregulated miR-187 could raise MAPK12 expression and further promote the progress of osteosarcoma cancer [19]. MiR-187 may also exert its proliferation inhibitory effect in OS by targeting MAPK7 and zinc finger E-box binding homeobox

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**Table 2.** The target genes of miR-187 and the biological processes involved in different tumors

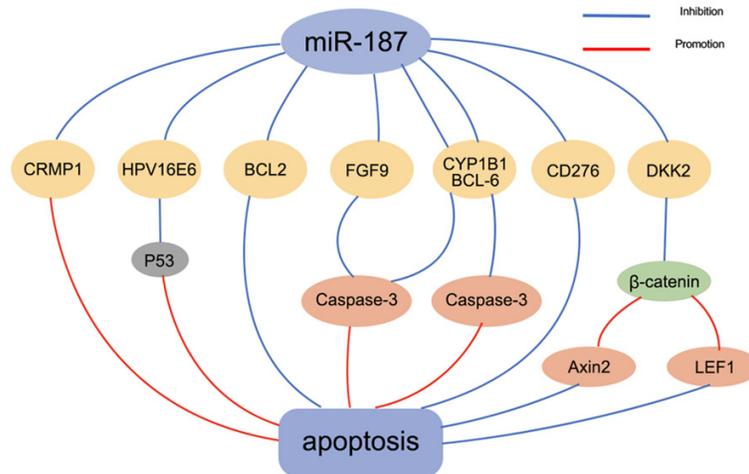
Cancer type	Downstream target	Biological process	References
GC	FOXA2	proliferation, migration and invasion	[11]
	CRMP1	proliferation, apoptosis, migration and invasion	[13]
	MAD2L2	proliferation, cell cycle	[71]
	STOML2	migration, and invasion	[71]
NSCLC	BCL6	proliferation, apoptosis, migration and invasion	[15]
	PTRF	proliferation, migration and invasion	[16]
	CYP1B1	proliferation, apoptosis, migration and invasion	[17]
	FGF9	proliferation, cell cycle	[44]
OS	S100A4	proliferation, migration and invasion	[18]
	MAPK12	proliferation, migration and invasion	[19]
	ZEB2	proliferation, migration, and invasion	[10]
	MAPK7	proliferation, cell cycle, migration, and invasion	[70]
ccRCC	B7-H3	proliferation, migration and invasion	[22]
CRC	CD276	proliferation, apoptosis and invasion	[23]
	SOX4	migration, invasion	[73]
	NT5E	migration, invasion	[73]
	PTK6	migration, invasion	[73]
HCC	IGF-1R	proliferation, migration and invasion	[24]
	S100A4	migration, invasion	[25]
OSCC	BARX2	migration, invasion	[27]
CC	HPV16 E6	proliferation, apoptosis, and invasion	[28]
	FGF9	proliferation, apoptosis	[29]
	Bcl-2	apoptosis	[30]
OC	Dab2	proliferation, migration	[31]
ALL	DKK2	proliferation, apoptosis	[33]
DLBCL	BCL6	apoptosis	[34]

GC: gastric cancer; NSCLS: non-small cell lung cancer; OS: osteosarcoma; ccRCC: clear cell renal cell carcinoma; CRC: colorectal cancer; HCC: hepatocellular carcinoma; OSCC: oral squamous cell carcinoma; CC: cervical cancer; OC: oral cancer; ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma.

2 (ZEB2). The mechanism of growth inhibition triggered by MAPK7 negatively regulated by miR-187 is cell cycle arrest in the G2/M phase. G2/M cell cycle arrest was also associated with a decrease in Cyclinb-B1 expression [10, 70]. Interestingly, Chao et al. found that Dab2, the downstream target of miR-187 in ovarian cancer (OC) has a dual role in cancer development. A lot of evidence underline that Dab2 is a tumor suppressor. However, the role of Dab2 as a tumor suppressor has been shown only in the early stages of OC. Specifically, upregulated miR-187 in the initial stage of OC inhibited cell proliferation. Whereas, as miR-187 continued to increase, Dab2-mediated EMT could be suppressed in the terminal stage of OC [31]. As a tumor suppressor in GC, miR-187 downregulated expression of MAD2L2 and STOML2 consistently and substantially.

MAD2L2, as a member of the gene family that mitotic checkpoint control mechanisms, possibly inhibiting the cell cycle to stagnate in the G0/G1 phase [71]. Likewise, miR-187 inhibits cell proliferation by targeting MAD2L2 to induce cell cycle arrest in the G0/G1 phase [11]. In contrast, the other studies have shown that miR-187 acted as an oncogene in GC. MiR-187 could promote the proliferation of GC cells in vivo and vitro. FOXA2 was the downstream target of miR-187 in GC cells and overexpression of miR-187 inhibited FOXA2 expression [11]. By targeting tumor suppressor CRMP1, miR-187 promoted cell proliferation, and inhibited cell apoptosis in GC [13]. In lung cancer cells, MiR-187 played an essential role in cell cycle regulation. Overexpression of miR-187 could block the G1-S phase and inhibit the proliferation of lung cancer cells [37]. It has also been

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**Figure 2.** Regulation of apoptosis by miR-187. HPV16E6 promotes apoptosis by suppressing tumor suppressor gene p53. Bcl-2, CYP1B1 and Bcl-6 all promoted the genes of Caspase family (caspase-3 and caspase-7) to promote apoptosis. miR-187 modulates the Wnt/ $\beta$ -catenin signaling pathway through DKK2 to inhibit cell apoptosis, Axin2 and LEF1 are the downstream targets of the Wnt/ $\beta$ -catenin signaling pathway.

reported that the miR187/HPV16 E6 axis in CC caused the loss of cell regulation, infinite proliferation and malignant transformation [28]. Additionally, cervical cancer tissues showed significantly decreased level of miR-187. Concretely, FGF9 as the downstream target of miR-187 played a central role in cell growth. Downregulation the expression of FGF9 was critical for inhibiting proliferation and promoting apoptosis [29]. As a tumor suppressor in CC, MiR-187 negatively regulated the expression of B-cell lymphoma 2 (Bcl-2). Downregulation of Bcl-2 further inhibited the activation of caspase-3, resulting in inducing cell apoptosis [30]. In HCC, upregulation of miR-187 inhibited cell proliferation, colony formation via suppression of IGF-1R expression [24]. Regarding NSCLC, the effect of miR-187 on cell proliferation and apoptosis is controversial. Bcl-6 down-regulated the expression of caspase-3 and caspase-7, which are responsible for inhibiting apoptosis mediated by miR-187 [15]. Mao et al. revealed that the anti-apoptotic effect of CYP1B1 in NSCLC is the same as that of BCL-6 [17]. MiR-187 may induce cell cycle arrest in the G0/G1 phase by regulating the expression of cyclin D1, CDK4 and CDK6, thereby inhibiting cell proliferation. It was also proved that FGF9 was a target of miR-187 [44]. On the contrary, PTRF, as the target of miR-187 in NSCLC in another study, was a tumor suppressor to inhibit the activity of cell proliferation [16]. In

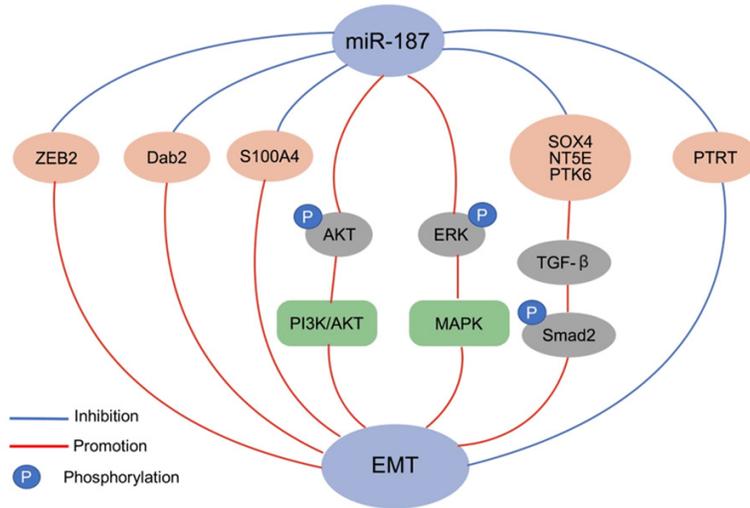
CRC and ccRCC, miR-187 inhibited cell proliferation and promoted apoptosis through decreasing CD276 which is proved to be the direct downstream target of miR-187 [22, 23]. In nalm-6 B cells, miR-187-5p inhibiting DKK2 expression resulted in inappropriate activation of Wnt/ $\beta$ -catenin signaling, which is important for cell growth and apoptosis [33] (Table 2; Figure 2).

*MiR-187 regulates the process of tumor migration and invasion*

The migration and invasion is a common event and the initial step in human cancer progression. MiR-187 is also involved in regulating migration and invasion in a variety of tumors. Several studies have demonstrated that miR-187 acted as epithelium-mesenchymal transformation (EMT)-associated downstream effectors of receptor signaling or protein kinases For example, TGF-mediated Smad, MAPK and PI3K/AKT signaling and matrix metalloproteinase-2/7/9 (MMP-2/7/9) are all participate in the process of EMT.

During differentiation, epithelial cells dedifferentiate and move further away, then differentiate again to form aggressive phenotype of cancer cells. This transient and reversible phenomenon is called epithelial-mesenchymal transformation (EMT). Increasing evidence supports that EMT is a key stage in tumor invasion and migration [72]. TGF $\beta$  is a master inducer of EMT via classical Smads and complementary non-Smad pathways. In CRC, miR-187 partially neutralized the activation of the TGF $\beta$ -mediated Smad pathway by lowering the phosphorylation level of Smad2. Smad2, one of the intermediates of TGF $\beta$  signaling, was activated after Smad2 phosphorylation increased. SOX4, NT5E and PTK6 were direct targets of miR-187 and these three targets were considered to be essential upstream effectors of TGF $\beta$ . Therefore, miR-187 played an important regulatory role in controlling TGF $\beta$ /smad-mediated EMT by regulating SOX4, NT5E and PTK6 expression [73]. Besides, Cai et al. confirmed that miR-187

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**Figure 3.** Regulation of EMT by miR-187. TGF $\beta$  is an inducer of EMT via Smad and non-Smad pathways, such as MAPK and PI3K/AKT. MiR-187 activated the mitogen-activated protein kinase (MAPK) pathway through the phosphorylation of ERK and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling via the phosphorylation of AKT. MiR-187 inhibited the expression of TGF $\beta$  by inhibiting the three target genes of SOX4, NT5E and PTK6. TGF $\beta$  works positively by promoting Smad2 phosphorylation, thereby activating Smad signaling and inducing EMT. In addition to PTRT, ZEB2 and S100A4, the three downstream target genes of miR-187, all promoted EMT. EMT: epithelial-to-mesenchymal transition.

activated non-Smad pathways by phosphorylating proteins related to MAPK and PI3K/AKT pathway such ERK and AKT in NSCLC. PTRF, as a direct target of miR-187, significantly inhibited miR-187-induced EMT [14]. Dab2 is a well-known tumor suppressor and is negatively regulated by miR-187 in OC. But in advanced cancer, it also played an important role in the promotion of tumors by promoting EMT-mediated metastasis. As western blot results showed, the overexpression of miR-187 suppressed Dab2, increased E-cadherin, and suppressed vimentin and phosphor FAK protein levels [31]. Hypoxia is known to cause irreversible damage to liver cells. Dou et al. confirm that miR-187-3p reversed the promotion effect of hypoxia on HCC cell metastasis and EMT by regulating S100A4 expression negatively [25]. Moreover, Through directly targeting the zinc finger E-box binding homeobox 2 (ZEB2), miR-187 reversed EMT in osteosarcoma cells and inhibited cell migration and invasion [10] (Figure 3).

In addition to the effect of EMT on the ability of cell proliferation and migration, miR-187 can promote or inhibit cancer metastasis by regulating downstream target genes (Table 2). S100A4, MAPK12, MAPK7 and ZEB2, men-

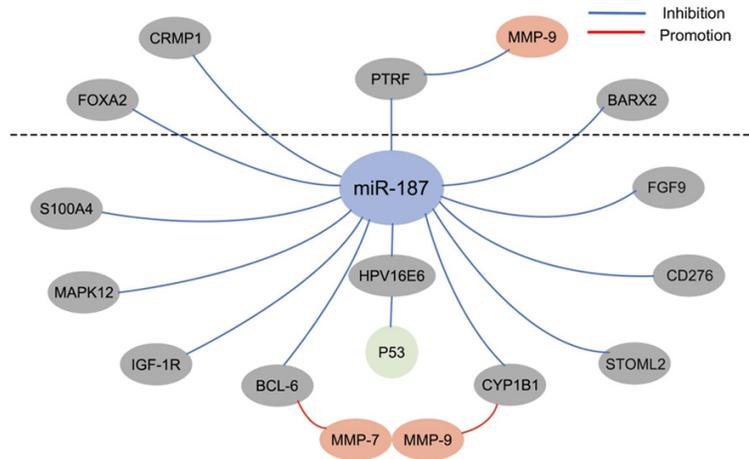
tioned above, exerted a role in the regulation of tumor proliferation and also affected the migration and invasion of OS cells [10, 18, 19, 70]. CD276 (also called B7-H3), the target of miR-187, could induce tumor invasion and migration in CRC and ccRCC [22, 23]. MiR-187 acted as a tumor suppressor in GC by inhibiting invasive capacity via STOML2 [11]. Contrary to STOML2, FOXA2 and CRMP1 inhibited miR-187's role in promoting migration and invasion in GC [12, 13]. Furthermore, BARX2, as a transcription factor, can control the expression of adhesion molecules and cytoskeletal elements to promote migration and invasion in OSCC [27]. It is well known that human papillomavirus is one of the major causes of cervical cancer. Based on this theory, HPV16 E6 was found

to be the downstream of miR-187. E6AP (e6-related protein) inactivated the tumor suppressor gene P53, resulting in impaired ability to regulate normal cell. In a word, miR-187 inhibited the metastasis of cancer cells by negatively regulating HPV16 E6 mRNA [28]. Matrix metalloproteases (MMPs) are a class of proteolytic enzymes that degrade the structural components of the extracellular matrix and could cause the loss of intercellular connections and promote cell migration and invasion. BCL-6 and CYP1B1 is downstream targets of miR-187 in NSCLC. They could increase the invasion capacity of cancer cells through promoting the expression of MMP-7 and MMP-9 [15, 17] (Figure 4).

### Discussion

Although there are many related studies on miRNAs, many specific mechanisms have not been clearly elucidated. As we all know the gene regulation of miRNAs is a complex network structure [74]. A miRNA can affect multiple downstream genes and biological processes. Different miRNA may have different effects which may be added together or cancelled out on the same gene. In this review, the tumor-

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**Figure 4.** Regulation of cell metastasis by miR-187. Apart from the EMT, miR-187 regulated cell metastasis in cancers through other pathways. MiR-187 promoted metastasis of cancer cells by targeting FOXA2, CRMP1, BARX2 and PTRF (above the dotted line), while miR-187 inhibited cell migration and invasion in cancers via the suppression of S100A4, MAPK12, IGF-1R, among others (below the dotted line). In particular, MMP and p53 are involved, with MMP promoting metastasis and p53 inhibiting metastasis. EMT: epithelial-to-mesenchymal transition.

related aspects were summarized from a number of studies on miR-187.

MiRNA is found to be expressed stably in serum and plasma and to express specific expression profiles in different diseases [75]. Several studies have found that miR-187 can be detected in plasma and urine. These findings could be used as non-invasive indicators in the future and made significant contributions to the prevention, diagnosis, treatment and prognosis of tumors. However, a large amount of research need to be undertaken to incorporate miRNAs into clinical diagnostic guidelines.

MiRNA expression may be affected by various mechanisms, such as chromosomal instability, DNA methylation, and even some oncogenes [74, 76]. As in one type of tumor cell, miR-187 may act as either a suppressor or a promoter. The reason for the differences among different studies could be the complex regulation mechanism of miRNA, the problem of sample selection, unreasonable experimental design and data processing. In this paper, multiple downstream target genes of miR-187 and a series of important processes such as proliferation, apoptosis, migration and invasion are integrated. However, these conclusions are also drawn from preclinical experiments and have not been applied to clinical investigation.

## Conclusion

This review summarizes the functions of miR-187 in tumor. MiR-187 has different expression and regulation in various cancers and can be used as either a tumor suppressor gene or an oncogene. The expression of miR-187 can be detected in plasma and urine which makes it possible to be used as a promising predictor. Remarkably, the level of miR-187 in tissues and plasma may also evaluate prognosis in cancer patients. Furthermore, miR-187 is able to sensitize chemotherapy and radiotherapy for some cancers. MiR-187 is involved in multiple cellular processes of cancer, including proliferation, ap-

optosis, migration, invasion, and cell cycle regulation. Taken together, miR-187 is closely related to the development, prediction, treatment and prognosis of a variety of tumors.

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## Disclosure of conflict of interest

None.

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