

Pleiotropic functions of miR107 in cancer networks

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Abstract: MicroRNAs are short regulatory RNAs that posttranscriptionally modulate gene expression and thus play crucial roles in controlling cancer-onset, growth, and progression processes. miR107, a highly conserved microRNA that maps to intron 5 of the *PANK1* gene, contributes to the regulation of normal and tumor biological processes. Studies have reported that miR107 has oncogenic or tumor-suppressor functions in different human tumors. The pleiotropic functions of miR107 in various cancers are achieved via its targeting different genes that are involved in tumor proliferation, invasiveness, metastasis, angiogenesis, and chemotherapy-response pathways. The carcinogenicity or cancer-suppressor effects of miR107 occur in a tissue- and cell-specific manner, and the expression level of miR107 can be affected by various factors, including epigenetic and genetic factors, treatment exposure, and daily diet. A comprehensive analysis of the current literature suggests that miR107 functions as a central element in the regulation of cancer networks and can be used as a potential diagnostic and prognostic biomarker and drug target for therapeutic intervention.

Keywords: microRNA, miR107, cancer, suppressor, proto-oncogene

Background

MicroRNAs (miRNAs) are a family of small (20–25 base pair nucleotides long) noncoding RNAs, most of which play important regulatory roles in regulating normal development and physiology.^{1,2} miRNAs cause these biological effects through sequence-specific binding of a seed sequence to the 3'-end of the untranslated regions (UTRs) of a target mRNA, which causes either mRNA degradation or inhibition of translation and further leads to posttranscriptional downregulation of target-protein expression.³ Thousands of miRNAs have been identified in humans, and it is thought that expression of two-thirds of all genes are regulated by miRNAs.⁴ Deregulated expression levels of many miRNAs are associated with carcinogenesis, and have been proposed to be novel prognostic and predictive biomarkers.^{5–7}

Tumor cells are distinguished from normal cells by several peculiar biological traits, such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, angiogenesis, and activating invasion and metastasis.⁸ The alternation of miRNA expression has a crucial role in cancer, as miRNAs can act either as oncogenes or tumor suppressors in the early disease stages, and they can also influence the progression of invasion and metastasis, as well as predict the clinical outcomes of antitumor therapies.^{9,10}

This review focuses on the pleiotropic functions of miR107 in cancers. miR107 is a highly conserved miRNA that maps to intron 5 of the *PANK1* gene. miR107 belongs to

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the miR15/107 group, whose members regulate genes involved in cell division, metabolism, stress response, and angiogenesis in vertebrate species. All miRNAs in this group share the sequence AGCAGC, starting at either the first or the second nucleotide from the 5'-end of the mature miRNA sequence.¹¹ miR107 is ubiquitously expressed in a range of tissues, with relatively high abundance in the brain. Altered expression of miR107 has been reported in metabolism diseases, such as adipogenesis and diabetes, as well as in neurological diseases and cancers.¹²

The biological functions of miR107 vary significantly in physiological and pathological processes of various cancers, probably as a result of being targeted to different pathways or genes.^{13,14} Both clinical and non- or preclinical studies have shown that miR107 is deregulated in several human tumors and its expression level significantly associated with disease staging, metastasis, and treatment outcomes.^{15,16} We present a systematic review of the complex roles of miR107 in tumor pathogenesis, progression, and prognosis, and of the factors that regulate miR107-expression levels.

Carcinogenic effects of miR107 in various types of cancer

The association between miR107-expression level and carcinogenic effects has been widely researched in various human cancers. However, the functions of miR107 in carcinogenesis are controversial and highly cell-type-dependent, as it acts as either a tumor suppressor or an oncogene by presenting different expression levels in various human tumors. The opposing results found between and within studies are not an uncommon phenomenon in the field of miR107 biology, and these inconsistencies may be due to variations in its mechanism of action.¹⁷ To help decipher miR107's function in specific cancer, Table 1 lists detail of miR107's function by tumor type.

Table 1 miR107 function by cancer type

Cancer	Function
Hepatocellular carcinoma	Oncogenic
Pituitary adenomas	Oncogenic
Prostate cancer	Oncogenic
Colorectal cancer	Oncogenic
Glioma	Tumor suppressor
Non-small-cell lung cancer	Tumor suppressor
Hematological malignancies	Tumor suppressor
Bladder cancer	Tumor suppressor
Renal clear-cell carcinoma	Tumor suppressor
Cervical cancer	Tumor suppressor
Head and neck/oral cancer	Oncogenic and tumor suppressor
Pancreatic cancer	Oncogenic and tumor suppressor
Gastric cancer	Oncogenic and tumor suppressor
Breast cancer	Oncogenic and tumor suppressor

miR107 functions as an oncogenic miRNA

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common type of live cancer and the third leading cause of cancer-related death in the world. Previous studies have shown that miRNAs play a fundamental role in HCC, thereby opening a novel avenue for investigating the molecular mechanisms of HCC pathogenesis. The function of miR107 in HCC continues to be researched, as it has been found to have increased expression in HCC tumors compared to paired non-HCC tissue in cancer patients.^{18,19} Serum miR107 levels are higher in HCC patients compared with healthy controls, and a logit prediction model has shown that the serum levels of miR107, miR92a-3p, miR3126-5p, and α -fetoprotein can serve as sensitive, specific, and noninvasive biomarkers for the diagnosis of HCC, especially in patients at early stages or with low α -fetoprotein levels.²⁰ Moreover, high miR107 expression has been significantly correlated with poor outcome (tumor differentiation and tumor vascular invasion) in HCC by repressing the expression of *HMGCS2*.²¹

Pituitary adenomas

Pituitary adenomas are common benign neoplasms that often grow invasively, but very rarely progress to true carcinomas. miR107 expression is significantly upregulated in both sporadic growth hormone-secreting pituitary adenomas and in nonfunctioning pituitary adenomas when compared with normal pituitaries.²² miR107 acts as an oncogenic miRNA in pituitary adenomas, negatively regulating the expression of the pituitary tumor-suppressor gene *AIP*.

Prostate cancer

Prostate cancer is the most commonly diagnosed male malignancy and the second leading cause of male cancer-related death. A study investigating changes in circulating miRNA levels associated with prostate cancer found that miR107 had higher concentrations in the urine of men with prostate cancer compared with controls.²³ There is also evidence that the growth factor granulin is dysregulated via miR107 in prostate cancer, which may provide a potential common therapeutic target.²⁴

Colorectal cancer

Colorectal cancer (CRC) is the fourth most common cancer in the world, with a high mortality rate. Researchers first found that miR107 is a prometastatic miRNA in CRC, in which the expression level of miR107 was positively correlated with the metastatic potential of different CRC cell lines.¹³

Elevated levels of miR107 have been observed in stage III compared with stage II tumors, and higher expression of miR107 is associated with lymph node metastasis and distant metastasis.¹³ miR107 exerts its prometastatic function by negatively regulating two metastasis suppressors: DAPK and KLF4. The expression level of miR107 has also been associated with both progression-free survival and overall survival (OS), and overexpression of miR107 is significantly associated with improved objective response to chemotherapy in CRC patients.²⁵ A recent study showed that miR107 expression was aberrantly increased in human CRC tumor tissue and cell lines when compared with colonic control tissues and colon epithelial cells.²⁶

miR107 as a tumor suppressor

Glioma

Glioma is the most common primary malignant tumor in the central nervous system, and is associated with poor prognosis and rapid mortality. Perhaps the strongest evidence of miR107 acting as a tumor suppressor has been found in glioma studies. miR107 is ubiquitously expressed in a range of tissue, with relatively high abundance in the brain. The expression level of miR107 has been shown to be significantly downregulated in human glioma tissue and cell lines when compared with normal brain tissue.¹⁵ Low levels of miR107 expression are also significantly associated with advanced pathological features and poor prognosis of human gliomas, such as larger tumor size, lower Karnofsky performance score, and shorter OS and progression-free survival.¹⁶

The antitumorigenic roles of miR107 in glioma include the inhibition of cell apoptosis, migration, and invasion. Upregulation of miR107 inhibits the proliferation of gliomas by repressing the expression of *SALL4* and activating the *FADD*–caspase 8–caspase 3/7 cell-apoptosis pathway.¹⁵ miR107 exerts its anti-invasion effects through the *NOTCH2*-signaling pathway.^{14,27} Overexpression of miR107 inhibits the proliferation of gliomas by arresting the cell cycle at the G₀–G₁ phase, and also downregulates the expression of *CDK6* and *NOTCH*.²⁸

Non-small-cell lung cancer

Lung cancer (LC) is one of the most common and deadliest cancers in the world, and non-small-cell LC (NSCLC) accounts for 80%–85% of all LC. Two studies have shown that miR107 expression is reduced in lung tumors and LC cell lines compared to normal lungs.^{29,30} Furthermore, low miR107 expression has been found to be significantly correlated with higher clinicopathological staging stage, regional lymph-node involvement, and tumor differentiation, as well

as poor prognosis.²⁹ Recently, it was shown that miR107 suppresses LC-cell proliferation, inhibits metastasis, impedes the cell cycle, and promotes apoptosis by directly targeting *EGFR*.³¹

Hematological malignancies

There is limited information on miR107 in hematological cancers. miR107 was initially reported to be upregulated in acute promyelocytic leukemia (APL) cells treated with all-*trans* retinoic acid (ATRA) compared with untreated cells.³² Further study showed that miR107 was downregulated in APL blasts compared with normal promyelocytes differentiated in vitro from CD34⁺ progenitors, and its expression level was upregulated after cells had been treated with ATRA.³³ Chronic lymphocytic leukemia (CLL) is the most common leukemic disorder, and is characterized by an accumulation of mature B cells in the blood, bone marrow, and secondary lymphoid organs. A recent study assessed global miRNA expression between purified B cells from treatment-naïve CLL patients and healthy controls, and found that miR107 was downregulated in CLL patients.³⁴ Evidence has shown that miR107 acts in CLL by targeting a calcium-channel protein (*Cacna2d1*) to promote erythroid differentiation.³⁵

Bladder cancer

Bladder cancer is the most prevalent malignant tumor of the urinary system, ranks ninth in cancer incidence around the world, and is the 13th most common cause of death by cancer. Expression of miR107 is decreased in bladder carcinomas in situ when compared with normal bladders from UPK II SV40 mice.³⁶ CircRNAs, a type of noncoding RNA, have been shown to exert major functions in gene regulation. A recent study showed that mechanisms underlying circRNAs in cancer-related pathway might involve miRNA sponge effects via interactions with miRNAs.³⁷ Further results on circRNA in bladder carcinoma found that circTCF25 was significantly more highly expressed in carcinoma tissue compared with control tissue.³⁸ An additional study on the circRNA–miRNA–mRNA axis in bladder cancer showed that overexpression of circTCF25 downregulated miR107, increased CDK6 expression, and promoted proliferation and migration in vitro and in vivo.³⁸

Renal clear-cell carcinoma

Renal cell carcinoma (RCC), which accounts for approximately 85% of all kidney cancers, is the most common type of kidney cancer. Clear-cell RCC occupies the major proportion of RCC cases.³⁹ miR107 plays a tumor-suppressor

role in clear-cell RCC by inhibiting cell proliferation and invasiveness.³⁹

Cervical cancer

Cervical cancer is the second most prevalent type of cancer among women worldwide and a complex disease involving numerous oncogenes or the abnormal expression of tumor suppressors. miR107 contributes to the development of cervical cancer by directly targeting *CCR5*, which acts as a tumor oncogene in cervical cancer.⁴⁰

Controversy

Head and neck/oral cancer

Head and neck/oral cancer (HNOC) is the sixth most common cancer worldwide, accounting for 4% of cancers in men and 2% of cancers in women.⁴¹ miR107 was first found to be highly expressed in nine HNOC cell lines.^{41,42} However, subsequent studies showed that miR107 is downregulated in oral squamous cell carcinoma (SCC) cell lines and tongue SCC.⁴³⁻⁴⁵ Molecular research has found that downregulation of miR107, which targets the *PRKCE* gene, is a pathogenetic event in HNSCC, and miR107 may thus be a potential anticancer therapeutic for this patient population. Another recent study unraveled the tumor-suppressor role of miR107 in esophageal carcinogenesis, by targeting *CDC42*.⁴⁶ HNOC can divide into a severe subtype, and the roles of miR-107 were poorly studied in some kinds of HNOC.⁴⁷ Based on these *in vitro* studies, we concluded that further clinical and *in vivo* studies should be conducted to identify roles of miR107 in HNOC.

Pancreatic cancer

Pancreatic cancer (PCa) is a devastating disease with a poor 5-year survival rate, and local recurrence and systematic metastasis are the major reasons for treatment failure. A study analyzing global miRNA expression in 12 nontumor pancreas and 44 pancreas primary tumors, including 12 insulinomas, 28 nonfunctioning endocrine tumors, and four acinar carcinomas, showed that miR107 is overexpressed in pancreatic endocrine tumors versus normal pancreatic tissue.⁴⁸ Data from this study suggest that alteration in miR107 expression is related to endocrine and acinar neoplastic transformation, but its expression cannot be used as a biomarker of PCa, due to the very small sample.

In contrast to this result, there is evidence suggesting that miR107 is a tumor-suppressive factor in PCa. BxPC3LN, a lymphatic PCa cell line that exhibits highly metastatic stem-cell-like properties, expresses lower levels of miR107 than the parental BxPC3 cell line.⁴⁹ Another recent study found

that plasma miR107 levels were significantly downregulated in PCa patients compared with healthy volunteers.⁵⁰ Moreover, low plasma miR107 levels were significantly associated with advanced T and N stage, liver metastasis, and shown to be an independent factor predicting poor prognosis in PCa patients.⁵⁰ miR107 plasma levels were increased in PCa patients who had undergone curative pancreatectomy compared with preoperative expression levels.⁵⁰

Gastric cancer

Gastric cancer (GC) is the fourth most common malignancy and the second leading cause of cancer-related death across the world.⁵¹ Gastric adenocarcinoma accounts for over 90% of GC cases. miR107 is commonly upregulated in GC and can promote GC-cell migration, invasion, and metastasis, both *in vitro* and *in vivo*.⁵² The first study on miR107 in GC investigated miR107 expression levels in tissues from 50 cases of GC and matched normal tissue by quantitative reverse-transcription polymerase chain reaction.⁵³ The authors discovered that miR107 is frequently upregulated in GC and its overexpression significantly associated with GC metastasis.⁵³ A subsequent study conducted with a larger sample showed that miR107 expression was significantly higher in tumor tissue, and showed significant associations with tumor invasion, lymph-node metastasis, and stage.⁵⁴ In addition, OS and disease-free survival of patients with high miR107 expression were significantly worse than those of patients with low miR107 expression.⁵⁴ The overexpression of miR107 in GC has also been evidenced in other studies.⁵⁵⁻⁵⁸ Furthermore, circulating miR107-expression levels are also higher in diffuse-type GC in a mouse model.⁵⁹

In contrast to previous findings, one study reported that miR107 expression was significantly decreased in GC (determined by comparing miRNA-expression profiles between 80 gastric tumor tissues and matched adjacent nonneoplastic tissues), and the reexpression of miR107 in GC cells significantly decreased proliferation by targeting *CDK6*.⁶⁰ In contrast to the mouse model, plasma miR107 levels are not altered in the patients with diffuse-type GC.⁶⁰

Because of the complex results, it is critical to expand sample sizes and affirm the function of miR107 in the pathogenesis of GC. Also, several questions remain. Dose the expression level of miR107 alter with cancer stage? Why does miR107 expression correlate with response to GC-treatment outcome? Finally, how can miR107 have opposing effects in the same cancer in two different studies? As these questions are answered, researchers will gain a better understanding of the precise function of miR107 in GC.

Breast cancer

Breast cancer is a common highly heterogeneous malignancy and one of the main gynecological cancers worldwide. In breast cancer, hormone-receptor status is one of the most important predictive factors. In one study, miR107 expression was decreased in 30 breast cancer specimens compared with adjacent normal breast tissue,⁶¹ and miR107 can inhibit the proliferation and migration of MDA-MB231 cells in a dose- and time-dependent manner. There is also evidence that miR107 is markedly downregulated in both breast cancer cell lines and breast tumors.⁶²

These results are different from previous studies, in which miR107 was shown to be upregulated in breast tumors and cells and elevated miR107 levels associated with more advanced tumor status, increased lymph-node metastasis, and increased metastasis in distant organs.^{63–65} The complex behavior of miR107 presented in breast cancer are possibly the result of high tumor heterogeneity and hormone responsiveness. Since the expression of miR107 can be downregulated by estrogen treatment, endogenous estrogen levels may significantly influence miR107 levels.⁶⁶ As breast cancer can be classified into different subgroups based on the state of ER, PR, and HER2, differences in the carcinogenicity of miR107 may also be caused by the statuses of ER, PR, and HER2 in different breast cancer patient groups.

miR107 functions and downstream targets in cancer

Understanding the functions of miRNAs will provide broad prospects for understanding and overcoming tumors. Altered miR107-expression levels in several cancers have led numerous researchers to investigate its tumor-specific functions and identify its targets in various steps of tumor formation and development. The pleiotropic roles and direct targets of miR107 are further summarized in Figure 1 and discussed in detail herein.

Proliferation, cell cycle, and apoptosis

Altered levels of miR107 have been demonstrated to be associated with proliferation, differentiation, and cell-cycle progression in cancer cells. However, the existing data are controversial. miR107 is effective in suppressing the tumorigenicity of HNSCC in vitro and in vivo by inhibiting proliferation, blocking DNA replication and colony formation, and inhibiting cell invasion. It acts by downregulating the expression of *PRKCE*, which plays critical roles in the signal-transduction pathways involved in proliferation, differentiation, apoptosis, and migration.⁶⁷ Evidence has also

shown that miR107 can suppress cell proliferation in two LC cell lines and induces G₁ cell-cycle arrest by downregulating *CCNE1* and *CDK6*.³⁰ Upregulation of miR107 suppresses glioma cell growth through direct targeting of *SALL4*, *CDK6*, and *NOTCH*, leading to the activation of the *FADD*–caspase 8–caspase-3/7 apoptosis-signaling pathway.^{15,28} The antitumor effects of miR107 in inhibiting proliferation and inducing cell-cycle arrest in HNSCC, LC, and glioma need further verification.

Data from Song et al suggested that miR107 promotes the proliferation of GC cells by posttranscriptionally targeting *CDK8*, a key protein in the regulation of cell cycle and cell growth, and thus promoting the development and progression of GC.⁵⁶ In addition, it also promotes cell proliferation by targeting the transcription factor *FOXO1*, repressing expression of the cell-cycle inhibitors p21^{Cip1} and p27^{Kip1} and increasing the expression of cell-cycle regulator cyclin D1.⁵⁷ Furthermore, miR107 regulates the expression of *GRN*, a mitogen and growth factor, in multiple human cancers, implying that a therapeutic strategy of restoring the expression of the miR-15/107 gene group may decrease the malignant potential of tumors by attenuating *GRN* expression.^{24,68} Li et al found that miR107 expression was decreased in breast cancer, while overexpression of miR107 suppressed MDA-MB231 breast cell proliferation by targeting *CDK8*, leading cells to arrest at the G₀–G₁ phase.⁶¹

Revascularization

Tumor vascularization, partly driven by hypoxia, plays a critical role in the progression of solid tumors. *HIF1* is significant in hypoxic signaling in tumors. miR107 can decrease hypoxia signaling and inhibit the differentiation of endothelial progenitor cells by targeting *HIF1B*.⁶⁹ Overexpression of miR107 in HCT116 colon cancer cells suppresses angiogenesis, tumor growth, and tumor *VEGF* expression in mice. These in vitro results support the hypothesis that miR107 can act as a tumor suppressor by inhibiting tumor vascularization in tumor-cell lines and tissue.

Migration, invasion, and metastasis

Migration is one of the main reasons for failure of tumor therapy and neoplasm recurrence. High miR107 expression can increase the tumorigenic and metastatic potential of breast cancer by inhibiting *LET7* and *DICER*,^{64,65} and the expression level of miR107 is significantly elevated in triple-negative metastatic breast cancer patients compared with disease-free patients.⁶³ However, there is also evidence that overexpression of miR107 suppresses breast cancer-cell migration by targeting

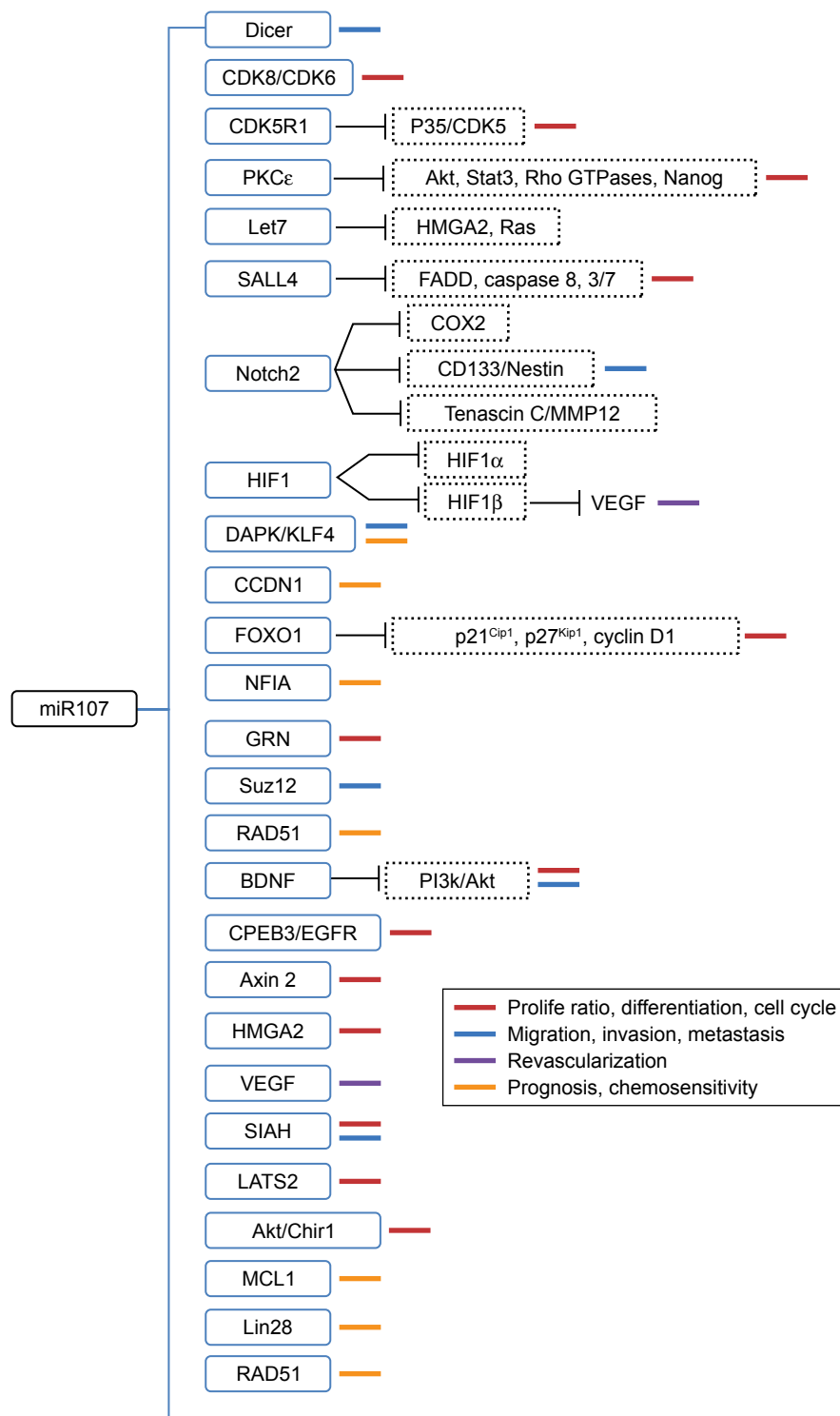


Figure 1 miR107 directs target genes and their multiple functions in cancer cells.

CDK8.⁶¹ miR107 has been shown to function as a prometastatic factor in CRC by negatively regulating the expression of two metastasis suppressors: *DAPK* and *KLF4*.¹³

miR107 overexpression is not only an important factor in the pathological process of GC but also related to increased tumor invasion, metastasis, prognosis, and tumor stage.^{53,54}

In addition, circulating miR107 was significantly increased in a mouse model of early- and late-stage diffuse-type GC.⁵⁹ miR107 functions as a positive metastatic regulator for GC by targeting *DICER*.^{53,54} In contrast, Feng et al found that miR107 was decreased in gastric tumor tissues and could inhibit the invasion of GC cells by targeting *CDK6*.⁶⁰

Table 2 Pleiotropic effects of miR107 expression on sensitivity to cancer therapy

Cancer	Therapeutic method	Association between miR107 expression and treatment sensitivity	Reference
NSCLC	Cisplatin	Low expression of miR107 significantly correlated with poor prognosis	29
		Transfected with miR107, mimics significantly increased cisplatin resistance by targeting the CDK8 protein	71
Gastric cancer	Chemotherapy	Patients with high miR107 expression had lower OS and DFS	54
		High miR107-expression levels correlated strongly with increased distant disease-free survival relative to tumors with low miR107	53
Colorectal cancer	Chemotherapy	Overexpression of miR107 associated with improved objective response to chemotherapy in colorectal cancer patients	25
Acute myeloid leukemia	Cytarabine	miR107 expression positively associated with worse OS	71
Triple-negative breast cancer	Chemotherapy	Low miR107 expression significantly associated with lower OS and RFS	63
Glioma	Chemotherapy	Low miR107 expression associated with poor prognosis	16
Gastrointestinal stromal tumor	Imatinib	miR107 overexpressed in gastrointestinal stromal tumor specimens, which was associated with imatinib resistance	72

Abbreviations: NSCLC, non-small-cell lung cancer; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival.

High miR107 expression probably serves a metastasis-inhibiting role in PCa.^{49,50} Additional studies have shown that the inhibitory effects on the migration and invasion exerted by miR107 in glioma and cervical cancer are due to its involvement in the modulation of *NOTCH2-TNC-MMP12* and *NOTCH2-COX2* signaling through direct targeting of *NOTCH2*^{14,27} and through activation of the *ATR-CHK1* pathway,⁷⁰ respectively.

Cancer therapy resistance mediators

Vast evidence has shown that the expression level of miR107 is associated with chemotherapeutic sensitivity in different cancers, as shown in Table 2. For example, low miR107 expression significantly correlated with poor prognosis for NSCLC patients, and mimics transfected with miR107 significantly increased cisplatin resistance by targeting the CDK8 protein in NSCLC cells.^{29,73} miR107 expression can mediate the sensitivity of *PARP* inhibitors by targeting genes or factors in the DNA-damage-response pathway, such as *RAD51*.⁷⁴

In the previous section, we summarized that miR107 has oncogenic and tumor-suppressive effects by suppressing both tumor-suppressive mRNAs and oncogenic mRNAs in different cancer types. Due to the opposite roles of miR107 in the pathogenesis of different cancer types, it also has various influences on treatment outcomes. Most studies on miRNA-expression levels in cancer have viewed positive correlations between miRNA-expression levels and increased survival as evidence that the miRNA is tumor-suppressive. However, this kind of interpretation can be misleading sometimes. It is critical first to validate the association between miR107-expression levels and clinical treatment outcomes if further studies aim to explore the roles of miR107 in the

treatment outcome of cancers. Authors should also further illuminate molecular mechanisms via *in vitro* and animal studies. We are still far from using miR107 as a potential biomarker for personalized treatment strategies and a potential therapeutic target.

Factors influencing miR107 expression in cancer cell lines

The roles of miRNAs in human disease and treatment response have been widely studied. However, which factors influence the expression and stability of miRNAs have barely been considered. In this section, we summarize various factors that can influence miR107 expression, including genetic and epigenetic factors, treatment exposure, and multiple dietary factors.

Epigenetic and genetic factors

Epigenetic factors

Epigenetic mechanisms, including promoter methylation and histone modification, are critical in the regulation of gene expression. Previous studies have underscored the role of epigenetic regulation of noncoding miRNAs in human cancer, typically through the methylation of CpG islands within miRNA primary transcript-promoter regions.⁷⁵⁻⁷⁷ Recently, Lee et al reported that miR107 was a candidate miRNA that may undergo transcriptional silencing through the methylation of a conserved CpG island in its promoter sequence in pancreatic carcinomas.⁷⁸ The primary transcript of miR107 (located at chromosome 10q23.31) is coexpressed from an intronic segment of *PANK1*, a coding gene on chromosome 10. We used two commonly used DNA-methylation prediction programs (MethPrimer and CpG Island Searcher) to predict CpG-island distribution 1,000 base pairs upstream

from the 5'UTR, and confirmed that a CpG island exists immediately upstream (−442 to −338) of the *PANK1*-transcription starting site. Interestingly, a recent study showed that the promoter CpG islands of *mir107* were not methylated in NSCLC,⁷⁹ suggesting that epigenetic silencing of *miR107* by DNA methylation is cell-specific and any epigenetic alteration of *miR107* in other tumors should not be ignored in further studies.

circRNAs are a class of single-stranded closed RNA molecules and produced from precursor mRNA back-splicing of thousands of genes in eukaryotes.⁸⁰ circRNAs function as an miRNA- or RNA-binding protein sponge and regulate splicing or transcription. circRNAs are involved in cancer pathogenesis.⁸¹ Recent research demonstrated that circTCF25 has a miRNA sponge effect that sequesters *miR107* and finally increases CDK6 expression and promotes proliferation and migration in bladder carcinoma.³⁸

lncRNAs are transcripts with no protein-coding function that are longer than 200 nucleotides. lncRNAs are emerging as new factors in the cancer paradigm, demonstrating potential roles in both oncogenic and tumor-suppressive pathways.⁸² lncRNAs can regulate the expression of miRNA by various mechanisms. *miR107*-expression levels are regulated by lncRNAs. As an lncRNA, *HULC* is correlated with the development of HCC. *HULC* sequesters *miR107* and promotes tumor angiogenesis in liver cancer through *miR107*–E2F1–SPHK1 signaling in liver cancer.⁸³ *NEAT1* plays an oncogenic role in human laryngeal SCC and regulates CDK6 expression of laryngeal SCC cells, mediated by *miR107*.⁸⁴ *c-Myc* is an inducible gene that is regulated by specific growth signals in a cell-cycle-dependent manner. *c-Myc* upregulates the expression and strengthens the activity of lncRNA *H19*, and *H19* promotes cell-cycle progression of NSCLC cells by downregulating *miR107* and upregulating CDK6 expression.⁸⁵

Genomic and transcription factors

The tumor suppressor *p53* is a transcription factor that responds to stress and maintains cellular control by deregulating stress responses and thereby maintaining cell and tissue integrity. Mutations in *P53* or other disruptions in the *p53* pathway are associated with tumor growth and angiogenesis.^{86,87} *P53* can activate the transcription of a group of miRNAs, which in turn suppresses the transcription of genes that regulate apoptosis, DNA repair, and cell-cycle progression.^{88,89}

Computer analysis reveals a potential *p53*-binding site (1,811 base pairs upstream) of the *PANK1*/*miR107*-

transcription starting site, and several studies have demonstrated that *miR107* belongs to the group of miRNAs regulated by *p53*.⁸⁹ Chen et al demonstrated that *p53* inhibits the proliferation of glioma cells by targeting *miR107*, and wild-type *p53* protein binding to the promoter region of *miR107*, leading to increased *miR107* expression relative to that of glioma cells expressing mutated *P53*.²⁸ Furthermore, Toll-like receptors modulate the expression of multiple miRNAs. *TLR4* can downregulate *miR107* expression through the *NFKB* pathway, and it can further influence the innate immune system by increasing macrophage adhesion via *CDK6*.⁹⁰

Treatment exposure

Surgery

Circulating miRNAs have been identified as potentially convenient biomarkers for many diseases, as they can be easily measured without invasive biopsies. miRNAs in circulation are protected from RNase degradation by binding to protein complexes. It has been hypothesized that circulating miRNAs enter the circulation by passive leakage from apoptotic or necrotic cells or by active secretion of microvesicle-free miRNA or miRNA containing microvesicles,⁹¹ and many circulating miRNAs have been used to determine the diagnosis and prognosis of human cancer.^{92,93} Changes in circulating miRNA levels between pre- and postsurgery samples may be used as biomarkers for cancer diagnosis.^{67–69} However, it has not yet been explained why miRNA levels change between before and after surgery.

Kodahl et al investigated changes in the circulating miRNA profiles of 24 postmenopausal women with ER-positive early-stage breast cancer before surgery and 3 weeks after tumor resection, and found that the postoperative patients had significant higher *miR107* levels compared with preoperative samples.⁹¹ On the other hand, Cookson et al showed the opposite result, in which circulating *miR107* levels were decreased after surgery in a group of 10 breast cancer patients assessed before and after resection.^{92–94} To explain this difference, we propose several possible hypotheses. First, if surgery can influence miRNA expression, the time at which samples are taken after surgery should be considered carefully. Second, as *miR107* levels in breast cancer are associated with tumor status, increased lymph-node metastasis, and increased metastasis in distant organs, the histopathological stage of the cancer before surgery should be taken into account. Third, since estrogen levels can influence *miR107* expression, pre- and post-surgery ER status should also be considered carefully.

Drug exposure

miRNAs are not only associated with disease pathogenesis but also with treatment response to many drugs. Interestingly, disease and drug exposure can inversely influence miRNA expression.⁹⁵⁻⁹⁹ As shown by studies on miR107 and drug treatment, miR107-expression level is not only associated with treatment response but can also be regulated by treatment with various drugs.

Evidence has shown that miR107 is upregulated during ATRA and arsenic trioxide treatment in APL cells.^{32,100,101} Zhou et al showed that the effects of taxol in attenuating migration and invasion are due to the upregulation of miR107 expression in cervical cancer cells, in which miR107 plays an important role in regulating the expression of MCL1.¹⁰² In addition to chemotherapy, radiotherapy can also significantly influence miR107 expression. miR107 is overexpressed in mouse renal cortical tissue after administration of ¹⁷⁷Lu-octreotate, which is a radiopharmaceutical used for treatment of neuroendocrine cancers.¹⁰³ However, a recent study found that long-term and excessive use of 900 MHz radiofrequency radiation downregulated rno-miR107 expression in Wistar albino adult male rat brains.¹⁰⁴

There is also evidence that chronic morphine treatment can significantly upregulate miR107 and miR103 levels, leading to downregulation of downstream target genes *in vivo* and *in vitro*.¹⁰⁵ Soluble β -amyloid peptides have specific repression effects on miR107 expression on neuronal.¹⁰⁶ Since miR107 plays a critical role in many cancers, we propose the hypothesis that the antineoplastic effects and treatment resistance of some antitumor drugs are partly due to the exceptional expression of miR107 under treatment exposure.

Lipopolysaccharide (LPS) is recognized as the most potent microbial mediator presaging the threat of invasion of Gram-negative bacteria. Blood miR107 expression levels are upregulated in mice exposed to LPS.¹⁰⁷ Another study showed that LPS downregulated miR107 expression level in an MyD88- and p65-dependent manner, as well as PANK1 α and PPAR α , and then upregulated the expression of CDK6.⁹⁰

Dietary factors

In addition to drug factors, dietary factors (such as fats, carbohydrates, proteins, vitamins, minerals, and trace elements) may also influence cellular processes by regulating endogenous miRNA expression.¹⁰⁸ Davidson et al showed that exposure to fish oil, in which the main effective constituent is a chemoprotective *n3*-polyunsaturated

fatty acid, can selectively upregulate the expression of miR107 in rat colons.¹⁰⁹ Studies have further demonstrated that dietary lipids modulate the expression of miR107¹¹⁰ and plant-derived polyphenols can regulate the expression of miR103/107 and prevent diet-induced fatty liver disease in hyperlipidemic mice.¹¹¹ There is also evidence that miR107 expression can be altered by chronic ethanol feeding.¹¹²

Conclusion

We can conclude that miR107 has pleiotropic functions in cancer by controlling the expression of genes involved in several cancer cell-signaling networks. miR107 is involved in tumor proliferation, cell-cycle progression, apoptosis, invasiveness, metastasis, angiogenesis, and chemotherapy response.

As miR107 levels are potential biomarkers for the diagnosis and prognosis of multiple cancers,^{13,16,29} the diagnostic/prognostic value of circulating miR107 should be explored further in various tumors. Almost all clinical studies on the association between miR107 deregulation and cancer onset compared the expression levels between tumor tissue and corresponding healthy tissue. The results of a study by Boominathan supported the view that circulating miR107 can be used as a novel diagnostic biomarker for breast cancer, as patients with newly diagnosed ER-positive breast cancer had higher circulating miR107 levels than healthy controls.⁸⁹ Whether circulating miR107 can be used as a novel cancer diagnostic and prognostic biomarker requires further investigation in various cancers.

miR107 can significantly influence the treatment outcomes of various cancers. Conversely, exposure to therapy can also affect the expression of miR107 through unknown mechanisms, a similar phenomenon as observed for other miRNAs.^{90,91} Based on the complex association between miR107 expression and drug exposure, the relationship between miR107-expression levels, cancer susceptibility, and therapy sensitivity must be considered in future studies. Finally, and most importantly, as miRNA-based *in vivo* therapy attempts have already been successful,^{113,114} the potential use of miR107 as a therapeutic target merits careful investigation.

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Disclosure

The authors report no conflicts of interest in this work.

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