

# Role and potential mechanisms of miR-100 in different diseases (Review)

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**Abstract.** In recent years, the role of microRNAs (miRNAs) in disease has attracted considerable interest, underscoring their potential utility as diagnostic biomarkers. miR-100, belonging to the miR-99 family, is integral to the pathophysiological processes underlying numerous diseases. miR-100 has been found to influence the pathogenesis of a variety of noncancerous diseases. As for cancer, this factor plays a significant role in various tumors throughout diverse systems, influencing essential processes including cell proliferation, invasion, migration and apoptosis of cancerous cells. This review examines the existing literature on miR-100 in the context of non-cancerous diseases and cancer, investigates its mechanisms of action across different diseases and considers its potential role as a diagnostic biomarker as well as its involvement in cancer drug resistance.

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## 1. Introduction

MicroRNAs (miRNAs) are highly conserved non-coding RNAs consisting of 21-24 nucleotides that target specific 3' untranslated regions of mRNAs through the RNA-induced silencing complex to regulate the expression of target genes (1,2). In recent years, a large number of studies have confirmed the important role of miRNAs in cancer and non-cancer diseases (3,4).

One of the most important members of the miR-99 family, miR-100 regulates a wide variety of biological processes, including migration, cell death, metabolism and response to drugs. For instance, Liu *et al* (5) demonstrated that miR-100-5p can target and reduce the expression of myotubularin related protein 3 (MTMR3), thereby activating the PIP3/AKT and ERK signaling pathways and promoting the proliferation of epidermal stem cells, which in turn is beneficial to the healing of skin wounds. Wang *et al* (6) found that miR-100-5p promotes proliferation and inhibits differentiation of myofibroblasts by downregulating tribbles pseudokinase 2. Numerous studies have shown that miR-100 has atypical expression patterns in different forms of cancer, where it can either restrict or promote tumor growth, depending on the tumor setting. Of note, in recent years, an increasing number of studies have focused on the exosome-mediated miR-100 delivery system, exploring its application in regulating tumor progression and providing new strategies for the clinical translation of miR-100. In addition, miR-100 plays an important role in the pathogenesis of noncancerous diseases, such as osteoporosis, cerebral infarction, Parkinson's disease, atherosclerosis, rheumatoid arthritis and autoimmune dacryoadenitis. The present study was the first systematic review of the dual regulatory roles of miR-100 in cancers of different systems and comprehensively summarizes the application of exosome-delivered miR-100 in the regulation of tumor progression, as well as the research progress of miR-100 in non-cancerous diseases, with the aim of elucidating its molecular mechanism and biological

function, and providing new insights for disease diagnosis, prognosis assessment and treatment.

## 2. miR-100-overview

miR-100, belonging to the miR-99 family, is composed of three distinct members: miR-99a, miR-99b and miR-100, all of which exhibit a shared seed region sequence (ACCCGUA) (7). This molecule originates from the miR-100/let-7/miR-125 miRNA cluster and is transcribed from the third intron of the multi-exonic MIR-100HG gene, which is situated on human chromosome 11. As one of the oldest miRNAs, tracing its origins back to bilaterian ancestors, miR-100 is highly conserved and functionally diverse. This miRNA exists in two mature forms: miR-100-5p (mature sequence: AACCCGUA AUCCGAACUUGUG) and miR-100-3p (mature sequence: CAAGCUUGUAUCUAUAGGUAUG) (<https://www.mirbase.org/>) (8-10). These forms exhibit distinct sequences, implying they target different mRNA sequences and fulfill separate roles. For instance, in gastric cancer (GC), miR-100-3p targets bone morphogenetic protein receptor type 2 (BMPR2), whereas miR-100-5p targets mTOR (11,12).

## 3. miR-100 and non-cancerous diseases

### *Diseases of the skeletal system*

**Osteoporosis.** The growth and osteogenic differentiation of human bone marrow mesenchymal stem cells (hBMSCs) play a crucial role in mitigating bone loss in individuals with osteoporosis. Wang *et al.* (13) found that miR-100-5p is upregulated in hBMSCs from patients with osteoporosis, where it directly targets and suppresses transmembrane protein 135 expression. This suppression negatively regulates the proliferation and osteogenic differentiation of hBMSCs, thereby disrupting the bone formation process in osteoporosis (13). In a comparable study, Ai *et al.* (14) noted an increase in miR-100-5p expression within the knee joint tissues of individuals with osteoporosis, indicating that miR-100-5p plays a role in the downregulation of lysine demethylase 6B (KDM6B) expression. This reduction in KDM6B's capacity to eliminate histone H3K27 (H3K27me3) methylation from the RUNX family transcription factor 2 (RUNX2) promoter led to diminished RUNX2 expression and hindered osteoblast differentiation, ultimately affecting the bone formation ability in these patients (14). Of note, several clinical studies have confirmed the potential diagnostic value of miR-100 for osteoporosis. The miR-100 expression levels were compared in 120 plasma samples taken from patients with osteoporosis and 120 samples taken from healthy controls using reverse transcription-quantitative PCR (RT-qPCR), in a study by Ding *et al.* (15). The researchers found that the osteoporosis group had significantly higher levels of miR-100 expression. An area under the curve (AUC) of 0.8916 was determined by the receiver operating characteristic (ROC) curve analysis to indicate that miR-100 has diagnostic potential for osteoporosis (15). This result can be corroborated with the study by Chen *et al.* (16), who also observed an upregulation of miR-100 expression in the serum of patients with osteoporosis and obtained a similar diagnostic efficacy (AUC=0.8875). These studies not only revealed the key

regulatory role of miR-100-5p in the pathogenesis of osteoporosis, but also provided an important theoretical basis for the development of miRNA-based early diagnostic methods and targeted therapeutic strategies.

**Osteoarthritis (OA).** Wu *et al.* (17) demonstrated that infrapatellar fat pad MSC-derived exosomes could deliver miR-100-5p into chondrocytes, reduce mTOR expression and promote autophagy activation, thereby inhibiting apoptosis and maintaining cartilage homeostasis to protect articular cartilage from damage and alleviate the condition of OA. Lai *et al.* (18) used RT-qPCR to detect the expression level of miR-100-5p in the serum of 150 patients with knee OA (KOA) and 150 normal controls, and found that its expression was downregulated, with an AUC of 0.845, which suggests that miR-100-5p is closely related to KOA, and it also has a high diagnostic value.

**Non-traumatic osteonecrosis of the femoral head (NONFH).** Yang *et al.* (19) identified an upregulation of miR-100-5p in exosomes derived from bone tissue of patients with NONFH. The research found that miR-100-5p inhibits osteogenic differentiation of hBMSCs and angiogenesis of human umbilical vein endothelial cells by inactivating the BMPR2/Smad1/5/9 signaling pathway. The results suggest that miR-100-5p could be a promising target for NONFH therapy (19).

### *Diseases of the nervous system*

**Cerebral infarction.** In the acute phase after stroke, neuronal abnormalities are one of the key factors promoting the formation and expansion of infarct foci, whereas microglia activation plays an important role in the progression of neuroinflammation (20,21). The study by Xin *et al.* (22) found that ischemia induced hyperactivation of M1 neurons, which in turn upregulated miR-100-5p expression in neurons and promoted its enrichment in extracellular vesicles (EVs). These miR-100-5p-carrying EVs can be taken up by neighboring microglia and neurons, and subsequently, miR-100-5p specifically binds to and activates the Toll-like receptor (TLR)7 through its U<sub>18</sub>U<sub>19</sub>G<sub>20</sub> motif, which in turn activates the NF-κB signaling pathway. This process not only leads to neuronal overexcitation and apoptosis but also exacerbates the neuroinflammatory response, ultimately exacerbating the pathology of ischemic brain injury (22). However, Cao *et al.* (23) found that miR-100-5p can target to reduce the expression level of mTOR, activate autophagy response, inhibit apoptosis and thus alleviate the condition of cerebral infarction. This suggests a possible dual regulatory role for miR-100 in cerebral infarction.

**Parkinson's disease (PD).** It has been shown that MSC-derived exosomes (MSC-Exo) are effective in attenuating dopaminergic (DA) neuronal damage and reducing oxidative stress levels in PD models. The molecular mechanism is that miR-100-5p, delivered by MSCs-Exo, inhibits the expression of its target gene NADPH oxidase 4 (NOX4) and upregulates the expression levels of the antioxidant factors Keap-1, nuclear factor erythroid 2-related factor 2, heme oxygenase 1, superoxide dismutase (SOD)-1 and SOD-2, which reduces the accumulation of reactive oxygen species and attenuates the damage of DA neurons, and improves the motor deficit in PD (24). Loss of DA neurons caused by microglia

activation is considered an important pathological factor in PD. Adipose-derived stem cells with small EVs reduce microglia activation by delivering miR-100-5p, targeting downregulation of deltex E3 ubiquitin ligase 3L expression, which in turn reduces the expression level of STAT1 and attenuates microglial cell activation, thereby decreasing the loss of DA neurons and ameliorating motor deficits (25).

**Spinal cord injury (SCI).** It was found that the regulation of inflammation and microenvironment after SCI was beneficial to the recovery of neural tissues. miR-100 could attenuate the inflammatory response induced by microglia by inhibiting the activation of the NF- $\kappa$ B pathway by downregulating the expression level of TLR4. miR-100 also inhibited neuronal apoptosis by decreasing the expression of apoptosis-related proteins. These anti-inflammatory and anti-apoptotic effects together promoted the repair of neural tissues, which ultimately significantly improved motor function after SCI (26).

#### Heart diseases

**Coronary atherosclerosis.** As key effector cells of allergic inflammation, eosinophils and the cytotoxic granule proteins they release have been shown to promote atherosclerotic plaque development (27). Gao *et al* (28) found that miR-100-5p in human umbilical cord MSC exosomes (hUCMSC-Exo) could target and downregulate frizzled class receptor (FZD)5, inhibit the Wnt/ $\beta$ -catenin pathway, significantly reduce the migration ability of eosinophils, promote apoptosis and reduce the release of eosinophil cationic protein and inflammatory factors, thus improving the atherosclerotic lesions in mice. Similarly, Ji *et al* (29) found that knockdown of circ-0004104 in vascular endothelial cells (VECs) with atherosclerosis-induced injury resulted in upregulation of miR-100 expression, which targeted and downregulated of TNF- $\alpha$ -induced protein 8 expression levels, and attenuation of VEC injury, thereby inhibiting the progression of atherosclerosis.

**Cardiac hypertrophy.** Zeng *et al* (30) observed upregulation of miR-100-5p expression in tissues of a rat model of cardiac hypertrophy induced by abdominal aortic constriction and in a model of cardiac hypertrophic cells generated by angiotensin II stimulation. Their molecular pathogenic mechanism is that miR-100-5p promotes the activation of autophagy by decreasing the expression of mTOR, leading to an increase in the surface area of cardiomyocytes, a decrease in cardiac function and the progression of cardiac hypertrophy (30).

**Heart failure.** Zhong *et al* (31) constructed a heart failure cell model by adriamycin induction. It was found that hUCMSC-EVs could inhibit oxidative stress and apoptosis by delivering miR-100-5p and targeting to reduce the expression level of NOX4, thus alleviating the condition of heart failure (31).

**Autoimmune diseases.** Liu *et al* (32) demonstrated that miR-100-5p expression was downregulated in EVs derived from macrophages in the rheumatoid arthritis microenvironment. Overexpression of miR-100-5p can target and reduce the expression level of mTOR, inhibit the proliferation of synovial cells and the exacerbation of inflammation and attenuate the disease progression of rheumatoid arthritis. Li *et al* (33) found that hUCMSC-sEVs deliver miR-100-5p, promote macrophage polarization toward an anti-inflammatory M2 phenotype and

increase the proportion of regulatory T cells, thus playing an important role in the treatment of autoimmune dacryoadenitis.

**Other diseases.** The incidence of acute kidney injury (AKI) caused by ischemia/reperfusion (IR) injury has been increasing year by year. Chen *et al* (34) found that hUCMSC-sEVs could deliver miR-100-5p into HK-2 cells exposed to IR injury, which could inhibit apoptosis by decreasing the expression of FKBP5 and activating the AKT pathway. The hUCMSC-sEVs were injected intravenously into mice with IR injury and found to significantly inhibit apoptosis and protect the kidneys from damage. This provides a new approach for the treatment of AKI (34). Wu *et al* (35) found that miR-100-5p can treat atopic dermatitis. miR-100-5p exerts anti-inflammatory effects by downregulating the expression of forkhead box (FOX)O3, thereby inhibiting the activation of the downstream NLR family pyrin domain containing 3 signaling pathway. Zhang *et al* (36) demonstrated that miR-100 from hUCMSC-EVs promotes endometriosis development by inhibiting HS3ST2 expression and promoting endometrial stromal cell proliferation, invasion and migration. Furthermore, in the context of a high-fat diet, mice that overexpress miR-100 exhibited a reduction in weight gain, a decrease in both visceral and subcutaneous fat, lower levels of serum low-density lipoprotein cholesterol, as well as enhanced glucose tolerance and insulin sensitivity. The results indicate that miR-100 could provide protective advantages in the context of metabolic syndrome and hepatic steatosis induced by a high-fat diet (37).

#### 4. miR-100 function and molecular mechanisms in different systemic cancers

A multitude of research findings has illustrated that miR-100 is crucial in diverse systemic cancers, influencing the proliferation, invasion, migration and apoptosis of malignant tumor cells. As illustrated in Table I and Figs. 1 and 2, the mechanisms by which miR-100 influences tumor development can be summarized as follows: i) miR-100 directly targets and regulates its downstream genes, impacting tumor progression (12,38-50); ii) interactions between miR-100 and long non-coding RNAs (lncRNAs) (11,51-55), circular RNAs (circRNAs) (56,57) and cytokines (58-61) modulate its expression, indirectly affecting the expression of downstream target genes; and iii) miR-100 regulates the expression of target genes and further modulates tumor progression by affecting key signaling pathways (53,58,62-66). Furthermore, increasing attention has been given to the use of miRNAs in clinical treatments. Exosomes are membrane-bound vesicles released by diverse cells found in mammalian tissues or body fluids, and they are crucial for facilitating communication between cells (67-69). Research indicates that the administration of miR-100 through exosomes into neoplastic cells can modulate tumor advancement, highlighting a potentially beneficial pathway for oncological therapy (62,63,70-72).

##### Digestive system tumors

**Liver cancer.** Ge *et al* (38) showed that miR-100 downregulates C-X-C motif chemokine receptor 7 (CXCR7) expression in hepatocellular carcinoma (HCC) LM3 cells, which decreases proliferation, migration and invasion. The cancer stem cells

Table I. microRNA-100 target genes and their roles in different cancers.

Type of cancer	Targets	Roles	(Refs.)
Liver cancer	CXCR7	Direct inhibition of cell proliferation, migration and invasion	(38)
	IGF2	Inhibition of the PI3K/AKT/mTOR pathway reduces tumor stem cell stemness	(58)
	CLDN11	Activation of PI3K/AKT pathway to enhance cell migration and invasion	(62)
	mTOR	Inhibition of cell-dependent VETC migration	(73)
Gastric cancer	LDHA	Inhibits glycolysis and thus cell proliferation and invasion	(75)
	mTOR	Promotes autophagy, which in turn inhibits cell proliferation and migration	(11)
	BMPR2	Direct inhibition of cell proliferation and promotion of apoptosis	(12)
Esophageal cancer	CXCR7	Direct inhibition of cell proliferation	(39)
	CXCR7	Direct inhibition of cell proliferation, migration and invasion	(40)
	mTOR	Direct inhibition of cell proliferation and invasion	(56)
Colorectal cancer	IGF1R	Promotes lymphangiogenesis and enhances metastasis	(63)
	Smad4	Promotes cell proliferation, migration and invasion	(51)
	mTOR	Direct inhibition of cell proliferation, migration and invasion	(70)
Breast cancer	FOXA1	Direct inhibition of cell proliferation, migration and invasion	(41)
	CDC25A	Direct inhibition of cell proliferation, migration and invasion	(42)
	FZD8	Inhibition of the Wnt/ $\beta$ -catenin pathway, which in turn inhibits cell migration and invasion	(64)
	mTOR	Inhibition of HIF-1 $\alpha$ expression, which in turn inhibits cell proliferation, migration and invasion	(72)
	mTOR	Maintenance of tumor-associated macrophage phenotype for tumor progression	(83)
Endometrial cancer	mTOR	Promotes autophagy and induces apoptosis	(87)
Cervical cancer	SATB1	Inhibits the AKT/mTOR signaling pathway and suppresses cell proliferation, migration and invasion	(65)
Ovarian cancer	EPDR1	Promotes tumor progression	(52)
Nasopharyngeal carcinoma	HOXA1	Direct inhibition of tumor progression	(43)
	IGF1R	Direct inhibition of cell motility and invasion	(44)
	ATG10	Activates PI3K/AKT pathway, inhibits autophagy, inhibits cell proliferation and migration	(53)
Chordoma	RASGRP3	Promotes cell proliferation, migration and invasion	(61)
	IGF1R	Direct inhibition of tumor progression	(45)
Thyroid cancer	FZD8	Inhibits the Wnt/ $\beta$ -catenin signaling pathway, inhibits cell proliferation and promotes apoptosis	(66)
Non-small cell lung cancer	HOXA1	Direct inhibition of cell proliferation, motility and invasion	(46)
	SOAT1	Direct inhibition of cell proliferation and migration	(47)
	SMARCA5	Direct inhibition of cell proliferation, migration, and invasion	(54)
	ACKR3	Direct inhibition of tumor progression	(57)
Prostate cancer	mTOR	Inhibits NOX4, inhibits cell proliferation, migration and invasion	(94)
Renal cell carcinoma	NOX4	Inhibits mTOR, promotes autophagy and inhibits cell migration and invasion	(95)
Mantle cell lymphoma	mTOR	Inhibition of cell proliferation	(48)
Acute myeloid leukemia in children	ATM	Promotes cell proliferation and inhibits apoptosis	(49)
Multiple myeloma	MTMR3	Promotes cell migration and inhibits apoptosis	(50)

CXCR7, C-X-C motif chemokine ligand 7; IGF2, insulin-like growth factor 2; CLDN11, claudin 11; mTOR, mammalian target of rapamycin; LDHA, lactate dehydrogenase A; BMPR2, bone morphogenetic protein receptor type 2; IGF1R, insulin-like growth factor 1 receptor; Smad4, mothers against decapentaplegic homolog 4; FOXA1, forkhead box protein A1; CDC25A, cell division cycle 25A; FZD8, frizzled-8; SATB1, Special AT-rich sequence-binding protein 1; EPDR1, ependymin-related protein 1; HOXA1, homeobox A1; ATG10, autophagy-related 10; RASGRP3, RAS guanyl releasing protein 3; SOAT1, sterol O-acyltransferase 1; SMARCA5, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 5; ACKR3, atypical chemokine receptor 3; NOX4, NADPH oxidase 4; ATM, Ataxia Telangiectasia Mutated; MTMR3, myotubularin related protein 3; VETC, vessels encapsulating tumor clusters.

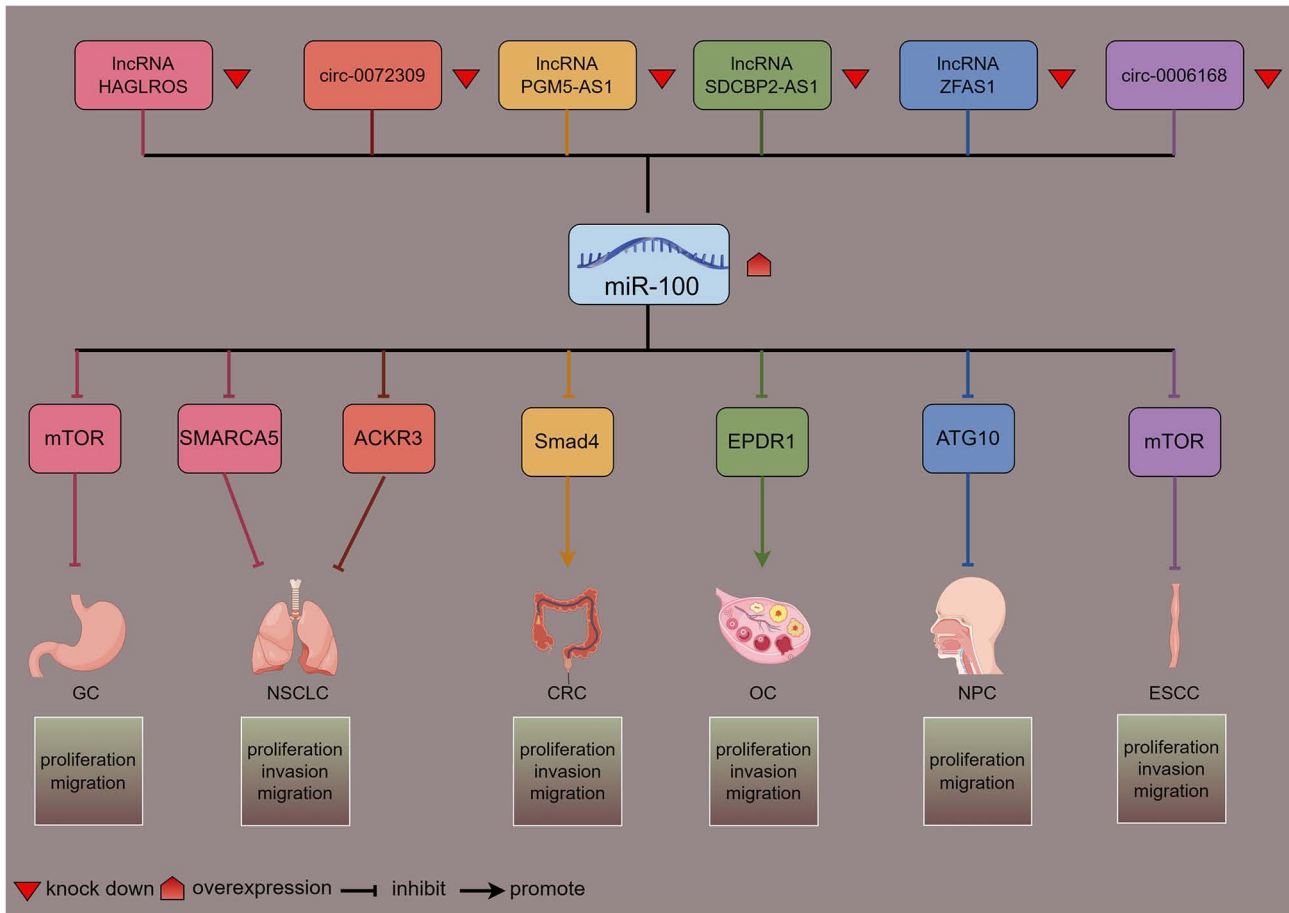


Figure 1. Network diagram of lncRNAs/circRNAs regulating miR-100: Down-regulation of lncRNAs/circRNAs results in upregulation of miR-100, which in turn targets downstream target genes to regulate cancer progression (figure generated with figdraw). mTOR, mechanistic target of rapamycin; SMARCA5, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 5; ACKR3, atypical chemokine receptor 3; Smad4, SMAD family member 4; EPDR1, epithelial-derived protein 1; ATG10, autophagy related 10; GC, gastric cancer; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; OC, ovarian cancer; NPC, nasopharyngeal carcinoma; ESCC, esophageal squamous cell carcinoma; lncRNA, long non-coding RNA; circRNA, circular RNA; miR, microRNA.

of HCC showed a marked downregulation of miR-100 and miR-125, according to another study (58). In addition, the study demonstrated that stemness regulators, including SOX2, OCT4 and NANOG, reduced miR-100 and miR-125 expression, which in turn increased insulin-like growth factor (IGF)2 expression, activated the PI3K/AKT/mTOR pathway and preserved tumor stem cell characteristics (58). Vessels encapsulating tumor clusters (VETC) are a typical vascular architecture in HCC that allows complete tumor clusters to enter the bloodstream non-invasively. Elevated levels of angiopoietin 2 (Angpt2) in HCC cells are critical for the formation of VETCs. miR-100 targets and reduces mTOR expression, which in turn diminishes p70S6K phosphorylation, leading to a decrease in Angpt2 levels. This action inhibits VETC-dependent metastasis of HCC cells, preventing their migration into the bloodstream in a non-invasive manner (73). The ‘Warburg effect’ is a characteristic of cancer metabolism; it occurs when cancer cells generate energy primarily through glycolysis (74). Tumor cell metabolism and survival are greatly impacted by lactate dehydrogenase A (LDHA), an essential glycolysis enzyme. By focusing on and reducing LDHA expression, miR-100-5p blocks glycolysis in cancer cells when oxygen levels are low. This inhibits HCC cell proliferation and invasion by reducing

lactate generation and glucose uptake (75). The results of these investigations provide credence to the idea that miR-100 can slow the development of HCC. Nevertheless, there is evidence that miR-100 may contribute to the aggressive development of HCC, according to certain research. Wang *et al* (62) found that MHCC-97H, a highly metastatic HCC cell line, which has high expression of  $\beta$ -galactoside  $\alpha$ 2,6 sialyltransferase I (ST6Gal-I), was better able to invade and migrate than its ST6Gal-I-knockdown counterpart. The stimulation of  $\alpha$ -2,6 sialylation by ST6Gal-I was thought to be responsible for this action. It led to an increase in the activity of nerve sheath phospholipase-2 and caused miR-100-5p to be sorted into exosomes. When these exosomes were co-cultured with low-invasive HCC cells (HepG2), miR-100-5p was transferred into the HepG2 cells, resulting in reduced claudin 11 expression, increased PI3K expression and AKT phosphorylation. These changes led to the activation of the PI3K/AKT signaling pathway and enhanced the migratory and invasive potential of HCC cells (62).

GC. Peng *et al* (12) demonstrated that BMP2 expression could be enhanced by removing miR-100-3p, and that BMP2 expression could be suppressed by increasing the levels of miR-100-3p. Subsequently, this inhibition slowed GC cell

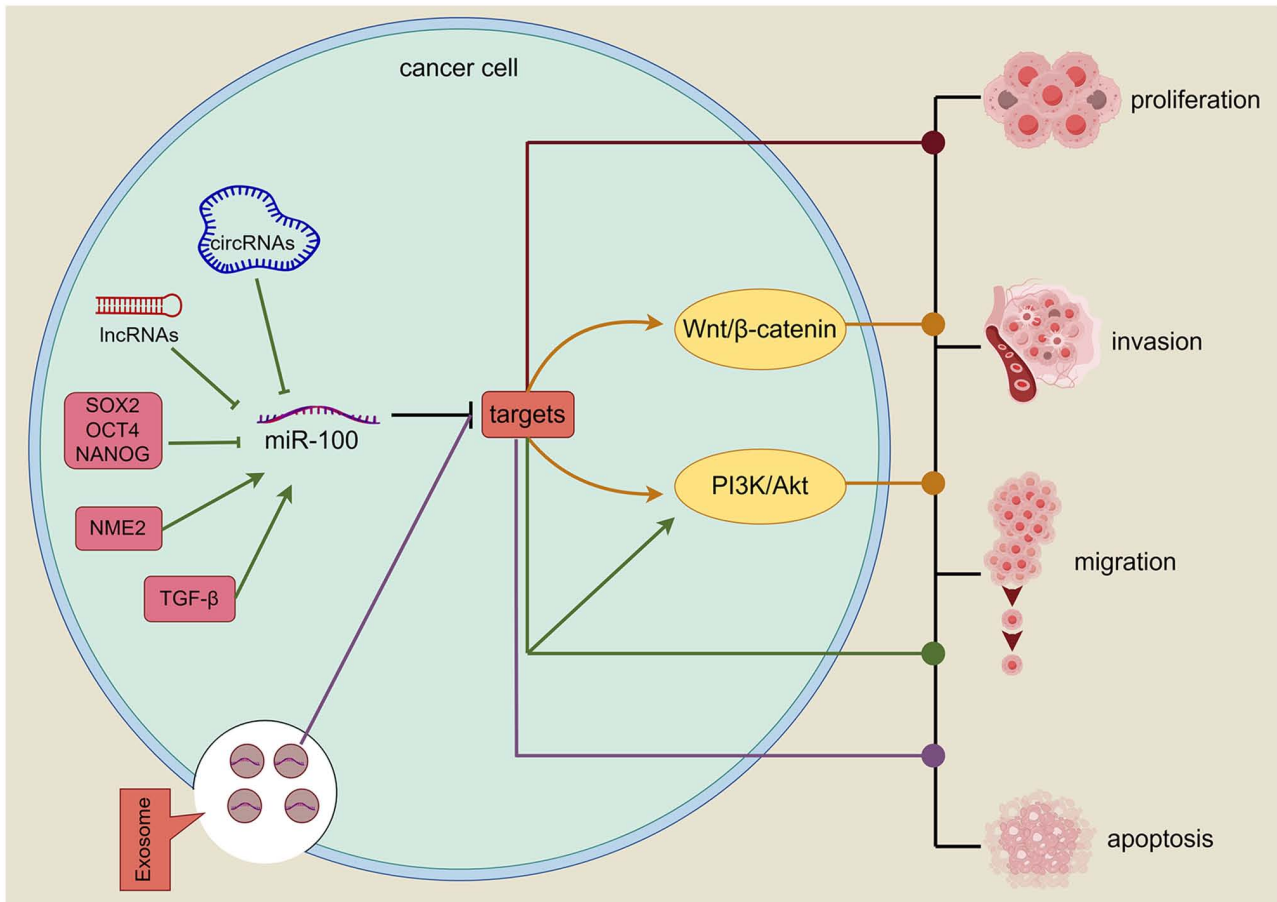


Figure 2. Mechanism of miR-100. Red pathway: miR-100 directly inhibits relevant target genes regulating tumor proliferation, invasion, migration and apoptosis. Green pathway: LncRNAs, circRNAs, cytokines (SOX2, OCT4, NANOG, NME2, TGF- $\beta$ ) upregulate/downregulate the level of miR-100 and inhibit the level of target genes, and the relevant target genes regulate tumor progression by activating the relevant signaling pathways or directly. Yellow pathway: miR-100 activates relevant signaling pathways by inhibiting target genes and plays corresponding roles in tumors. Purple pathway: miR-100 is delivered into tumor cells via exosomes, inhibiting the expression of target genes and regulating tumor progression (figure generated with figdraw). LncRNA, long non-coding RNA; circRNA, circular RNA; miR, microRNA; SOX2, sex determining region Y-box 2; OCT4, octamer binding transcription factor 4; NANOG, recombinant NANOG homeobox protein; NME2, NME/NM23 nucleoside diphosphate kinase 2; TGF- $\beta$ , transforming growth factor- $\beta$ ; -, inhibition;  $\rightarrow$ , promotion.

proliferation and set off cell death. Cao *et al* (39) found that miR-100 could target and reduce CXCR7 expression, which in turn suppressed GC-cell proliferation. The ability of LncRNAs to operate as competing endogenous RNAs allows for the regulation of miRNA activity (76). To inhibit miR-100-5p expression, Chen *et al* (11) found the LncRNA HAGLROS. After HAGLROS knockdown increased miR-100-5p and decreased mTOR expression, autophagy was improved and GC-cell proliferation and migration were suppressed (11). Evidence indicates, on the other hand, demonstrated that miR-100 expression is elevated in GC tissues and cells, and that levels show marked increases in relation to tumor aggressiveness. The transcription factor NME/NM23 nucleoside diphosphate kinase 2 (NME2) plays a critical role in miR-100 transcription. To achieve this, it acts with RNA polymerase II at its C-terminal domain, specifically targeting serine 5 for phosphorylation. This leads to an increase in miR-100 expression, which prevents GC cells from terminating their lives (59).

**Esophageal cancer (EC).** Through its direct targeting of CXCR7, miR-100 inhibits EC cell proliferation, migration and invasion (40). Additionally, circ-0006168 serves as an oncogenic circRNA, with its expression being markedly elevated in esophageal squamous cell carcinoma (ESCC) tissues and cell

lines. Reducing circ-0006168 expression increased miR-100 expression and decreased mTOR expression, which suppressed ESCC cell motility, invasion and proliferation (56). Patients with ESCC have a poor prognosis due to lymphangiogenesis, which is a critical component of metastasis (77). There are multiple routes by which cancer-associated fibroblasts (CAF), an important part of the tumor microenvironment (TME), can promote tumorigenesis and progression (78). The study demonstrated that in ESCC, overexpression of IGF1R was caused by the deletion of miR-100-5p in CAF-derived exosomes. This overexpression activated the PI3K/AKT pathway, which in turn promoted the creation of lymphatic vessels and enhanced the metastasis of ESCC to lymph nodes. Based on these results, miR-100-5p may be able to target the lymphatic metastases of ESCC via exosome-mediated transport and suppress lymphangiogenesis (63).

**Colorectal cancer (CRC).** Relative to non-metastatic CRC tissues, miR-100 expression is substantially higher in lymph node metastatic CRC tissues, according to various studies. By reducing the expression of targets such as mTOR, IGF1R, Fas and X-linked inhibitor of apoptosis, overexpression of miR-100-5p can prevent CRC metastasis (79). Furthermore, Jahangiri *et al* (70) discovered that miR-100, which was

delivered via MSCs-Exo, reduced mTOR expression and indirectly increased miR-143. The expression of hexokinase 2 and KRAS was subsequently downregulated as a result of this, thereby inhibiting CRC cellular activities (70). Of note, Zhou *et al* (51) found that lncRNA PGM5-AS1 could target and inhibit miR-100-5p. The elevation of miR-100-5p expression and the subsequent downregulation of Smad4 promoted the proliferation, migration and invasion of CRC cells when PGM5-AS1 was knocked down (51).

**Pancreatic ductal adenocarcinoma (PDA).** Ottaviani *et al* (60) discovered that the SMAD2/3 signaling pathway is activated by TGF- $\beta$ , leading to an increase in miR-100 transcription and the progression of PDA. However, miR-100-5p was found in significant levels in exosomes from hUCMSCs, according to Ding *et al* (71). Pancreatic cancer cells sped up the disease's development after absorbing these exosomes, which allowed miR-100-5p to enter the cells and stimulate cell proliferation and invasion.

#### *Cancer of the reproductive system*

**Breast cancer (BC).** Through downregulating FOXA1 expression, Xie *et al* (41) discovered that miR-100 impeded BC-cell proliferation, migration and invasion. In a similar study, Li *et al* (42) showed that miR-100-5p may reduce cell division cycle 25A expression, which in turn delayed BC cell migration, invasion and proliferation while speeding up apoptosis. The Wnt/ $\beta$ -catenin system is crucial in the genesis of cancer and regulates numerous key biological processes. It is also a highly conserved pathway. After being engaged, the Wnt pathway makes  $\beta$ -catenin more stable, which encourages it to go to the nucleus and take part in cellular activities (80,81). To enhance Wnt/ $\beta$ -catenin signaling, FZD8, a receptor for Wnt proteins, activates signaling pathways that are dependent on  $\beta$ -catenin, as well as those that are independent of it (82). According to Jiang *et al* (64), miR-100 suppresses the migration and invasion of BC cells by downregulating FZD8, which in turn reduces the expression of  $\beta$ -catenin, MMP-7, transcription factor 4 and lymphoid enhancer binding factor 1. Ultimately, this leads to inactivation of the Wnt/ $\beta$ -catenin pathway (64). Separately, Pakravan *et al* (72) transported miR-100 into BC cells using exosomes produced by MSCs. Once inside, miR-100 reduced mTOR expression, which in turn reduced hypoxia-inducible factor 1 $\alpha$  expression, leading to less VEGF transcription and a reduction in BC cell proliferation, migration and invasion (72). Remarkably, a different study proposed that miR-100 could enhance the tumor-associated macrophage phenotype, which in turn promotes BC metastasis. Angiogenesis, tumor migration and anti-tumor immunity are all promoted by tumor-associated macrophages (TAM), an important part of the TME immune cell population. In BC, TAM express a high level of miR-100, which helps to preserve their phenotype by reducing the production of mTOR, an enzyme that promotes tumor growth. Furthermore, the Hedgehog pathway can be activated to improve the stemness and migration of BC cells, as miR-100-induced reductions in mTOR expression result in an increase in STAT5A-mediated IL-1R secretion (83).

**Endometrial, cervical and ovarian cancer (OC).** Cancer cells may die when autophagy, a mechanism of cellular breakdown, is stimulated (84). There is a strong correlation between the amount of autophagosomes and the expression

of light chain (LC)3; therefore, an increase in LC3 often correlates with an increase in autophagosome numbers. Beclin1 is involved in autophagosome formation during the early stages of autophagy (85,86). By reducing mTOR expression, Cai *et al* (87) demonstrated that miR-100-5p accelerates autophagy and promotes autophagosome formation. Endometrial cancer cells die and the disease advances more slowly as a result of this upregulation of Beclin1 and LC3 expression (87). By reducing SATB homeobox 1 expression, miR-100 suppressed cervical cancer cell proliferation, migration and invasion, as well as epithelial to mesenchymal transition (EMT) and the AKT/mTOR pathway, according to research by Huang *et al* (65). In OC, the lncRNA SDCBP2-AS1 was shown by Liu *et al* (52) to modulate miR-100-5p expression. Through inhibition of SDCBP2-AS1, miR-100-5p was upregulated, leading to the suppression of epithelial-derived protein 1 expression. This, in turn, enhanced migration, invasion and proliferation of OC cells while preventing their apoptosis (52).

#### *Head and neck tumors*

**Nasopharyngeal carcinoma (NPC).** Through its direct targeting and suppression of homeobox (HOX)A1 expression, He *et al* (43) showed that miR-100 suppresses the growth of NPC cells. A different team of researchers discovered that miR-100 can decrease IGF1R expression, which in turn decreases NPC cell motility and invasion (44). In RNA, the reversible methylation of the sixth position of adenine, called N6-methyladenosine (m6A), is dynamically regulated by methyltransferases and demethylases. The methyltransferases that play a role include methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit (METTL3), METTL14, RNA binding motif protein 15B and zinc finger CCCH-type containing 13, with METTL3 serving as the primary catalytic enzyme. Research has demonstrated that m6A alteration modulates RNA function through controlling RNA expression, splicing, translocation, stabilization of lncRNAs and miRNA processing (88-91). Peng *et al* (53) discovered a variety of differentially expressed m6A-associated genes in NPC, including METTL3 and alkB homolog 5, RNA demethylase. The expression of METTL3 was observed to be markedly elevated in tumor tissues. METTL3 promotes the expression of the lncRNA ZFAS1 by decelerating RNA degradation processes and providing stability to the methylated ZFAS1 transcripts. The increased levels of ZFAS1 expression are significantly associated with unfavorable outcomes in NPC. The depletion of ZFAS1 led to an increase in miR-100-3p levels, which subsequently reduced autophagy-related 10 expression, stimulated the PI3K/AKT pathway and suppressed autophagy in tumor cells. The increased autophagy within the TME supplies tumor cells with additional energy, leading to the conclusion that the inhibition of autophagy by miR-100-3p diminishes the proliferation and migration of NPC cells (53,92). However, additional research indicates that miR-100-5p could also be involved in the advancement of NPC. The downregulation of FOXA1, a pioneer factor implicated in multiple tumors (93), resulted in heightened expression of miR-100-5p. This increase subsequently diminished RAS guanyl releasing protein 3 expression, thereby facilitating cell proliferation, migration and invasion in NPC (61).

*Chordoma and thyroid cancer.* Zhang *et al* (45) discovered that miR-100-5p has the capacity to suppress the proliferation of chordoma cells while enhancing apoptosis through the downregulation of IGF1R expression. Furthermore, it notably reduced the levels of N-calmodulin and waveform protein, while simultaneously enhancing the expression of E-calmodulin. This modulation effectively hinders the migration and invasion of chordoma cells by disrupting the EMT process (45). In a distinct investigation, Ma and Han (66) demonstrated that miR-100-5p has the capacity to inactivate the Wnt/ $\beta$ -catenin pathway through the suppression of FZD8 expression, subsequently leading to the inhibition of thyroid cancer cell proliferation and the induction of apoptosis.

*Tumors of the respiratory system.* The two main histological subtypes of lung cancer (LC) are small cell LC (SCLC) and non-SCLC (NSCLC), the former of which is more frequent. The development and progression of NSCLC are regulated by miR-100, according to multiple studies. Based on what we know about its upstream regulators, miR-100 is frequently downregulated in NSCLC. For instance, in NSCLC, brain metastasis is reduced when circ-0072309 is downregulated and miR-100 is upregulated. This, in turn, decreases atypical chemokine receptor 3 expression (57). A similar pattern was observed when the lncRNA HAGLROS was knocked down: miR-100 was upregulated, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 5 was downregulated and NSCLC cell proliferation, migration, and invasion were all reduced (54). Furthermore, it has been demonstrated that miR-100 can lower HOXA1 expression, which in turn inhibits NSCLC cell proliferation, motility and invasion (46). Sevoflurane inhibited cell proliferation and migration by re-establishing miR-100-3p expression, which in turn decreased sterol O-acyltransferase 1 expression, as discovered by Fu *et al* (47), who noted that miR-100-3p was downregulated in A549 NSCLC cells.

*Other tumors.* The expression of miR-100 is negatively impacted by a number of cancers and is strongly linked to the advancement of tumors. By reducing the expression of NOX4, for instance, miR-100-5p blocks the proliferation, colony formation, migration and invasion of prostate cancer (PC) cells. This is achieved by targeting and suppressing the expression of mTOR (94). In renal cell carcinoma (RCC), Liu *et al* (95) discovered that miR-100 inhibits mTOR pathway expression, which in turn induces autophagy and downregulates NOX4 expression. As a result, the migration and invasion of RCC cells are suppressed (95). In mantle cell lymphoma, miR-100 inhibits cell growth via targeting mTOR (48). On the other hand, miR-100 is overexpressed and targets ATM in child acute myeloid leukemia, which promotes the proliferation of leukemia cells while preventing their death (49). In their study, Wei *et al* (50) discovered that miR-100-5p inhibits apoptosis and increases the survival and metastatic capacity of multiple myeloma cells by targeting and downregulating MTMR3 expression. Diffuse large B-cell lymphoma cells are unable to proliferate, migrate or invade when the lncRNA HAGLROS is silenced; this is because miR-100 is upregulated in this tumor type (55).

## 5. Value in cancer diagnosis and prognostic assessment

A significant contributor to high cancer mortality is the failure to diagnose tumors early, which leads to missed treatment opportunities. Furthermore, inadequate or ineffective methods for assessing prognosis can result in suboptimal treatment for patients. These issues, including missed early diagnoses and improper prognostic assessments, contribute to increased mortality rates in cancer patients (96). Early diagnosis and accurate prognostic evaluation are thus critical. While most tumor markers currently used in clinical settings are protein-based, only ~2% of human genome genes are translated into proteins, meaning that relying solely on protein markers may not provide a comprehensive view of the tumor. The non-coding regions of the genome contain a wealth of information beyond that found in the protein-coding regions. Therefore, a deeper exploration of the role of these non-coding regions is essential for improving early cancer diagnosis and prognostic assessments (97). miRNA expression is generally tissue-specific, with changes in expression levels corresponding to the growth or regression of tumor tissue (98). Additionally, miRNAs are highly stable in body fluids, making them detectable and valuable for diagnostic purposes (99). Consequently, miRNAs, including miR-100, are increasingly recognized for their potential as biomarkers in clinical cancer diagnosis and prognosis.

*Diagnostic value.* There is strong evidence that miR-100 could be used as a diagnostic tool in a number of cancer types, such as PC (100), multiple myeloma (50), BC (101), nephroblastoma (102) and bladder cancer (103), based on studies that measured miR-100 levels in cancer patients' tissues or sera and compared those results to other relevant factors (Table II). One study looked at 100 men with PC and 100 men with benign prostatic hyperplasia to see how miR-100-5p was expressed in their tissues. They discovered that miR-100-5p expression was lower in PC and that this decrease was increasingly pronounced as the tumor grade rose. With an AUC of 0.72, miR-100-5p may be useful as a PC biomarker, according to an ROC curve analysis (100). Similarly, miRNA sequencing and RT-qPCR both indicated that patients with multiple myeloma had significantly higher miR-100-5p expression levels than those with iron deficiency anemia. With an AUC of 0.983, miR-100-5p is clearly a highly useful biomarker for the diagnosis of multiple myeloma (50). Wang *et al* (101) found that miR-100-5p, miR-191-5p and miR-342-3p were all considerably higher in the plasma of 108 patients with BC compared to 103 healthy controls. These levels were particularly high in stages I and II of the disease. Together and separately, these three miRNAs successfully differentiated patients with BC from healthy controls; however, miR-191-5p and miR-100-5p demonstrated superior diagnostic performance in the early detection of BC. In comparison, more conventional biomarkers like CEA and CA153 showed less diagnostic efficacy (101). Similarly, Ludwig *et al* (102) found that the serum expression level of miR-100-5p was significantly higher in 32 patients with nephroblastoma (or Wilms' tumor) compared to normal controls, with an AUC value of 0.90. When Motawi *et al* (103) compared miR-92a, miR-100 and miR-143 levels in the blood of 62 healthy controls with those of 70 patients with bladder

Table II. Potential utility of miR-100 in cancer diagnosis.

Diagnostic	Cases	Sample type	Testing technology	Expression	AUC	Sensitivity, specificity, %	(Refs.)
MM	5 MM vs. 5 IDA	Plasma cells	MiRNA-seq	Upward	0.983	-	(50)
PC	100 PC vs. 100 BPH	Tissue	RT-qPCR	Downward	0.720	-	(100)
BC	108 BC vs. 103 HC	Plasma	RT-qPCR	Upward	0.961	93.5, 93.2	(101)
Nephroblastoma	32 WT vs. 12 HC	Serum	RT-qPCR	Upward	0.900	-	(102)
BIC	70 BIC vs. 62 HC	Plasma	RT-qPCR	Downward	0.823	90.0, 66.7	(103)
CC	46 CC vs. 34 HC	Serum	RT-qPCR	Downward	0.879	91.2, 80.4	(104)
Leukemia	85 ALL vs. 12 HC	Bone marrow	RT-qPCR	Downward	0.642	64.7, 62.5	(105)

HC, healthy control; RT-qPCR, quantitative reverse-transcription PCR; miRNA-seq, microRNA sequencing; AUC, area under the receiver operating characteristic curve; IDA, iron deficiency anemia; PC, prostate cancer; BPH, benign prostate hyperplasia; MM, multiple myeloma; BC, breast cancer; WT, Wilms' tumor; BIC, bladder cancer; CC, cervical cancer; ALL, acute lymphoblastic leukemia.

Table III. Potential utility of miR-100 in cancer prognostic assessment.

Cancer type	Characteristics	(Refs.)
Liver cancer	Low expression is associated with shorter OS	(106)
Liver cancer	Decreased OS with low expression	(107)
Liver cancer	Low expression associated with poorer RFS and OS	(108)
Breast cancer	Low expression associated with poorer EFS and OS	(109)
Esophageal cancer	Reduced 3- and 5-year survival with low expression	(110)
Skin melanoma	Low expression associated with shorter survival time	(111)
Oral squamous cell carcinoma	High expression associated with poorer OS and PFS	(112)
Bladder cancer	High levels of miR-182/miR-100 ratio significantly associated with shorter survival	(113)

OS, overall survival; PFS, progression-free survival; EFS, event-free survival; RFS, recurrence-free survival; miR, microRNA.

cancer, they discovered that the cancer patients' levels were substantially lower. miR-100 showed a 90% sensitivity and 66.7% specificity with an AUC of 0.823. When miR-143 and miR-92a were added to the mix, the assay's sensitivity and specificity went up to 94.3 and 83.3%, respectively, with an AUC of 0.926. Therefore, miR-92a, miR-100 and miR-143 in plasma show promise as circulating biomarkers for the clinical identification of bladder cancer (103). Alongside the previously discussed malignancies, miR-100 demonstrates promise as a diagnostic biomarker in conditions such as cervical cancer (AUC 0.879) (104) and leukemia (AUC 0.642) (105). Overall, the unusual expression of miR-100-5p in the context of cancer development suggests its potential as a valuable candidate for cancer diagnosis. However, to improve its reliability, additional validation is necessary across a wider spectrum of cancer types and more extensive patient groups.

**Prognostic assessment value.** Several studies have shown that miR-100-5p is important for predicting cancer outcomes. Studying the link between miR-100-5p expression levels and patient survival, overall survival (OS), recurrence-free survival (RFS) and event-free survival (EFS) allowed to determine miR-100-5p's prognostic importance (Table III). In a survival

analysis, Liao *et al* (106) found that patients whose miR-100-5p expression was lower had worse survival results. A subsequent study revealed that the overexpression of polo-like kinase 1 (PLK1), an oncogene associated with adverse outcomes in HCC, was caused by miR-100-5p's insufficient targeting and repression of PLK1 (106). A related study by He *et al* (107) found that low-expression patients with HCC had a much lower OS rate compared to high-expression individuals. Furthermore, tumor grade, metastasis and tumor stage were significantly correlated with miR-100-5p levels, which are important clinicopathological indicators (107). Additionally, Song *et al* (108) found that miR-100-5p was downregulated in HCC cases with major vascular invasion and that its low expression was significantly associated with poorer RFS and OS. A potential prognostic factor in HCC is overexpression of miR-100-5p, which was associated with improved clinical outcomes. Overexpression of miR-100-5p in HER2-positive non-luminal subtype BC cells improved EFS and OS, according to Fuso *et al* (109). Overexpression of miR-100-5p in combination with let-7a-5p, miR-101-3p and miR-199a-3p improved EFS and OS (109). Patients had significantly better 3- and 5-year survival rates when miR-100-5p expression was downregulated in EC tissues, as reported by Zhang and Tang (110). Higher levels of

miR-100-5p were associated with improved survival rates in patients. According to Wang *et al.* (111), greater expression of miR-100-5p is strongly related to cutaneous melanoma patient survival, suggesting improved clinical prognosis. Conversely, Jakob *et al.* (112) found that patients with oral squamous cell carcinoma with high miR-100-5p expression had poorer OS and progression-free survival. A research team has proposed using the miR-182/miR-100 ratio as a predictive biomarker for patients with bladder cancer after finding an association between this ratio and the pT stage, histologic grade, recurrence and carcinoma *in situ*. Multifactorial Cox regression analysis demonstrated that the miR-182/miR-100 ratio is an independent predictor for OS. Kaplan-Meier curve analysis showed that individuals with bladder cancer had a much shorter survival time when the miR-182/miR-100 ratio was high. Accordingly, this ratio shows promise as a novel biomarker for survival prediction (113). In addition, OC (114), glioblastoma (115) and gastric adenocarcinoma (116) are just a few of the cancers where miR-100 has demonstrated prognostic value. The importance of miR-100 as a predictive biomarker for various cancer types is underscored by these findings.

## 6. Impact on cancer drug resistance

Although multidrug resistance is still a major problem in cancer treatment, researchers have made great strides in understanding its molecular processes and regulatory pathways, with miRNAs being named as key intracellular regulators (117). It has been acknowledged that miR-100 plays a major role in the development of treatment resistance in several cancer types. To illustrate the point, tyrosine kinase inhibitor (TKI) resistance is substantially related to elevated miR-100-5p expression in NSCLC cell lines. A drop in cell viability rates is observed when miR-100-5p expression is suppressed with lock nucleic acid, which greatly increases the sensitivity of cancer cells to TKI therapy (118). These results highlight the critical role of miR-100-5p in promoting NSCLC resistance to TKIs. Reduced miR-100-5p expression causes mTOR levels to rise in LC, which in turn makes LC cells resistant to cisplatin therapy (119). In addition, treatment resistance and metastasis in malignant cells, commonly called dormant cancer cells, are often associated with the presence of residual tumor cells and disseminated tumor cells. Malignant cells in PC can evade conventional treatments by entering a dormant phase, which they can then progress through to castration-resistant prostate cancer (CRPC) and transdifferentiated neuroendocrine prostate cancer (NEPC). These latent cells consistently showed an increase of miR-100-5p, which is involved in the development of CRPC and NEPC. Knockdown of miR-100-5p promotes apoptosis in dormant prostate cancer cells and thus inhibits CRPC and NEPC progression (120). A possible involvement for miR-100-5p in the development of paclitaxel resistance in this cancer was suggested by the significantly higher levels of miR-100-5p in paclitaxel-resistant PC cell lines compared to non-resistant ones (121). Notably, in the setting of cervical cancer, hypoxia-induced overexpression of miR-100 slowed the pace of cell viability reduction following paclitaxel treatment. On the other hand, paclitaxel sensitivity was enhanced in cells lacking miR-100, suggesting that overexpression of miR-100 may promote paclitaxel resistance in cervical

cancer cells (122). These studies highlight the various roles of miR-100 in the development of resistance to drugs in various cancer types. Although further research is needed to determine the exact mechanisms of action, miR-100 is a potential option for future oncology therapeutic treatments due to its evident involvement in cancer drug resistance.

## 7. Conclusion

The exploration of diagnostic markers and therapeutic strategies for cancer remains a pivotal area of investigation, as numerous previously daunting challenges are progressively being resolved. In recent years, miRNAs have been acknowledged for their crucial functions in tumor development and the advancement of cancer. Of note, miR-100 has been identified as a significant factor that can either facilitate or suppress cancer progression, contingent upon the specific tumor type. For instance, in various studies, miR-100 has demonstrated tumor-suppressive effects in esophageal cancer (40,56,63), endometrial cancer (87), cervical cancer (65), chordoma (45), thyroid cancer (66), NSCLC (46,47,54,57), PC (94), RCC (95), mantle cell lymphoma (48) and diffuse large B-cell lymphoma (55). In the context of PDA (60,71), OC (52), acute myeloid leukemia in children (49) and multiple myeloma (50), miR-100 exhibits a role that promotes tumorigenesis. In various malignancies, including liver cancer (38,58,62,73,75), GC (11,12,39,59), CRC (51,70,79), BC (41,42,64,72,83) and NPC (43,44,53,61), the function of miR-100 is still a subject of debate, as it may either facilitate or suppress tumor development. The analysis of molecular mechanisms has demonstrated that miR-100 plays a significant role in regulating essential processes in cancer cells, primarily through the targeting of various downstream genes. Furthermore, the expression of miR-100 is regulated by upstream signaling factors that influence tumor progression through the modulation of target genes. miR-100 plays a role in modulating cancer-associated signaling pathways, thereby impacting the behavior of tumor cells. Furthermore, the application of exosomes for the delivery of miR-100 has demonstrated potential in effectively modulating tumor progression. Consequently, a more profound comprehension of these molecular mechanisms aids in clarifying the processes that contribute to cancer development and provides fresh insights for therapeutic approaches to cancer. The expression patterns specific to certain tissues and the notable dysregulation of miR-100 across different cancer types underscore its potential utility as a biomarker for the early detection of cancer. Furthermore, the relationship between miR-100 expression levels and patient survival following treatment highlights its importance as a prognostic indicator. In addition, the varying levels of miR-100 expression observed in both drug-sensitive and drug-resistant cell lines indicate its potential role in the mechanisms underlying cancer drug resistance. Subsequent research could yield novel approaches to address chemoresistance in clinical applications. It is worth noting that miR-100 also has an important role in the disease development of numerous non-cancer diseases, and in-depth exploration of its molecular mechanism and study of the clinical translational approach may provide new ideas for the treatment of diseases. Despite its promising potential, there are still several limitations in current research: i) The

specific behavior and mechanisms of miR-100 in the complex cancer microenvironment remain to be further explored; ii) efficient utilization of miR-100 for early diagnosis and accurate prognostic assessment remains an unresolved challenge; iii) much of the current research on miR-100 is primarily at the basic experimental level, with insufficient integration into clinical applications. Consequently, future research should focus on advancing the molecular mechanisms of miR-100, facilitating its clinical translation, and improving its diagnostic and therapeutic applications. At the basic research level, deeper exploration is needed to better understand miR-100's dual role in cancer and to analyze its dynamic mechanisms in the TME. Regarding therapeutic development, efforts should focus on optimizing targeted delivery systems using exosomes or nanocarriers, and exploring the combined effects of miR-100 mimetics or inhibitors with conventional therapies. In diagnostic applications, establishing body fluid-based miR-100 detection systems and developing precise tools for early diagnosis and prognosis assessment, possibly integrating artificial intelligence, should be prioritized. By adopting a 'basic-translational-clinical' research model, miR-100 can be accelerated from a molecular marker to a clinical diagnostic and treatment strategy, ultimately offering new hope and possibilities for patients.

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#### Availability of data and materials

Not applicable.

#### Authors' contributions

JL and HD conceived and designed the study and were responsible for manuscript writing. YS and JL were responsible for the collection and assembly of data. YS and HD were responsible for data analysis and interpretation. GH participated in the revision of the paper. All authors have read and approved the final manuscript. Data authentication is not applicable.

#### Ethics approval and consent to participate

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#### Competing interests

The authors declare that they have no competing interests.

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