Review

Multiple Roles of MicroRNA-100 in Human Cancer and its Therapeutic Potential

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Key Words

MiR-100 • Biogenesis • Cellular pathways • Tumor suppressor • Tumor promoter

Abstract

MicroRNAs (miRNAs) are a recently discovered class of endogenous, small (about 22 nucleotides) non-coding RNAs, which play important roles in cancer development and progression. Emerging evidence shows that microRNAs exert their regulatory effects by directly binding to the 3'- untranslated regions (UTRs) of their target genes. MicroRNA-100 (miR-100) is aberrantly expressed and functions in many human cancers by regulating multiple cell processes, such as cell cycle, proliferation, differentiation, migration, invasion and apoptosis, via post-transcriptionally regulating various target genes. A better understanding of the molecular mechanisms involved in miR-100-mediated tumor progression will provide an opportunity for exploring novel miR-100-based targeted therapies for human cancers. This review aims to summarize the recently published literature on the roles of miR-100 in regulating tumorigenesis, and explore its potential clinical applications for cancer diagnosis, prognosis and clinical treatment.

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Introduction

As the most studied non-coding RNAs, miRNAs are short (about 22 nucleotides) endogenous non-coding RNAs, which regulate gene expression at a posttranscriptional level to promote mRNA degradation and repress translation by binding to the 3'-UTR of targets [1, 2]. Studies demonstrate that more than 50% of the miRNAs are located in so-called "fragile sites" on chromosomes which are frequently deleted, amplified, or rearranged to involve cancers [3]. Since their discovery in 1993, aberrant expression patterns and functional abnormalities of miRNA expressions have been identified to be associated with a variety of

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human diseases, including cancers [4, 5]. MiRNAs play vital roles in the regulation of almost every cellular process, including proliferation, apoptosis, differentiation and angiogenesis. Considering their implications in multiple biological processes, current research of miRNAs is mainly focused on clarifying their physiological and pathological functions, exploring potential miRNAs target genes, as well as deciphering the molecular mechanism underlying transcriptional regulation of miRNAs.

Comparative studies indicate that the origin of miR-100 which is a member of the miR-99 family could date back to the bilaterian ancestor [6]. The expression patterns and effects of miR-100 in tumor progression have not been fully elucidated, and the recent studies have shown controversial results [7, 8]. In human cancers, miR-100 has been reported to function as either a oncogenic miRNA or a tumor suppressive miRNA, which depends on tumor types and microenvironment [9]. Many studies have revealed that miR-100 functions in numerous important biological processes such as metabolism, cell cycle, migration, epithelial-mesenchymal transition (EMT), differentiation and cell survival. Moreover, dysregulation of miR-100 is associated with a poor prognosis for different cancers, indicating that miR-100 may be a good candidate for using as a prognostic biomarker and a potential therapeutic target for human cancers. This review aims to summarize recent research on the target genes of miR-100 and its roles in regulating tumorigenesis as well as its implication for clinical therapy.

Dysregulation of miR-100 in many human cancers

The miR-100 gene is located on chromosome 11 at 11q24.1 (Gene ID: 406892) [10]. A unique biogenesis pathway including at least 4 steps produces mature miRNA, including miR-100 [11] (Fig. 1). The first step in miRNA biogenesis is the formation of a long primary miRNA (pri-miRNA) with a 5'm7G cap and a 3' poly-A tail, which is initially transcribed by RNA Polymerase II in the nucleus [12]. Secondly, the pri-miR-100 is cropped into a ~65-nt stem-loop structure by a nuclear protein complex consisting of the nuclear RNase III enzyme Drosha, the double-stranded RNA binding protein Pasha / DiGeorge Critical Region 8 (DGCR8) and multiple RNA-associated proteins [13, 14]. This cleavage event is important for the necessity that it predetermines mature miRNA sequence and lays a foundation for the subsequent events [15]. Thirdly, after nuclear processing, the pre-miR-100 is exported into the cytoplasm with the help of the nuclear export factor Exportin 5 (Exp5) [16, 17]. Here, a second RNase III enzyme termed Dicer, subsequently removes the loop region of the pre-miRNA to produce a ~22bp double-stranded RNA duplex [16]. One strand of this short-lived duplex is degraded by an unknown nuclease, while the other strand with the less stable 5'-end remains as a mature miRNA [15, 18]. Finally, the miR-100 strand of the duplex is incorporated into a large protein complex, termed the RNA induced silencing complex (RISC), where miR-100 guides RISC to bind with 3'-UTR of the target gene mRNA, thereby functions to inhibit protein translation and/or promote mRNA degradation [10, 19].

Recently, dysregulation of miR-100 has been reported to be involved in tumor occurrence, development, and drug resistance [20] (Table 1). Some highly expressed miRNAs act as oncogenes by repressing tumor suppressors, whereas low-level miRNAs act as tumor suppressors by negatively regulating oncogenes. One hand, down-regulation of miR-100 has been reported in a variety of human tumors, such as head and neck squamous cell carcinoma (HNSCC) [21-23], nasopharyngeal cancer (NPC) [24], oral squamous cell carcinoma (OSCC) [25], esophageal squamous cell carcinoma (ESCC) [26-31], breast cancer [32-34], non-small cell lung cancer (NSCLC) [35, 36], gastric cancer (GC) [8], hepatocellular carcinoma (HCC) [37-41], pancreatic adenocarcinoma [42-44], adrenocortical cancer [45], bladder cancer [46-55], ovarian cancer [56-60], endometrioid endometrial carcinoma (EEC) [61], cervical cancer [62, 63], small cell carcinoma of the cervix (SCCC) [64], prostate cancer (PC) [65-70], colorectal cancer (CRC) [71-73], chondrosarcomas [74], osteosarcoma [75, 76], glioblastoma (GBM) [77], acute lymphoblastic leukemia (ALL) [78-81], and on the other hand, overexpression

Fig. 1. MiRNA biogenesis. Drosha together with Pasha/DGCR8 cuts pri-miRNA to form the stem-loop structural pre-miRNA, and then Dicer removes the loop region from pre-miRNA, leaving the mature sequence miRNA.

Table 1. Dysregulation of miR-100 in different human cancers

Cancer type	MiR-100 expression	Sample	Main Target gene	References
Gastric cancer	Up regulation	Cell lines	HS3ST2	[7]
		serum		[9]
	Down regulation	Tissues		[85]
		Tissues		[8]
Head and neck squamous cell carcinoma (HNSCC)	Down regulation	Tissues	IGF1R/ mTOR	[21-23]
Nasopharyngeal cancer (NPC)	Down regulation	Cell lines	PIK1	[24]
Oral squamous cell carcinoma (OSCC)	Down regulation	Cell lines	FGFR3	[25]
Esophageal squamous cell carcinoma (ESCC)	Down regulation	Tissues	mTOR	[26, 27, 30, 31]
Breast cancer	Up regulation	Serum	PIK1,Wnt/ β -catenin, IGF2,SMARCA5 ,HOXA1, EphB6	[28, 29]
	Down regulation	Cell lines		[33, 34]
Non-small cell lung cancer (NSCLC),		Tissues	PLK1	[32]
		Cell lines		[35]
Hepatocellular carcinoma (HCC)	Up regulation	Pleural effusion	ICMT-Rac1,PLk1,mTOR ,IGF-1R	[36, 84]
	Down regulation	Tissues		[83]
Pancreatic adenocarcinoma	Up regulation	Tissues	IGF1-R, FGFR3	[37-41]
		Serum		[86]
Adrenocortical cancer	Down regulation	Tissues/ Metastatic cell lines	IGF - mTOR	[87-89]
	Down regulation	Cell lines, stem cell, serum		[42-44]
Bladder cancer	Down regulation	Tissues	IGF - mTOR	[45]
Ovarian cancer	Down regulation	Tissues	FGFR3,mTOR,	[46-55]
Endometrioid endometrial carcinoma	Down regulation	Tissues	PLK1,FRAP1 /mTOR	[56-60]
Cervical cancer	Down regulation	Tissues	mTOR	[61]
Small cell carcinoma of the cervix (SCCC)	Down regulation	Tissues	PLK1	[62, 63]
Prostate cancer	Down regulation	Tissues	Not clear	[64]
Colorectal cancer(CRC)	Down regulation	Tissues/Cell lines	SMARCA5,BAZ2A,THAP2, mTOR, FGFR3, Argonaute 2	[65-70]
Chondrosarcomas	Down regulation	Tissues	RAP1B	[71-73]
Osteosarcoma (OS)	Down regulation	Cell lines	mTOR	[74]
Glioblastoma (GBM)	Down regulation	Tissues	Cyr61,FGFR3.	[75, 76]
Acute lymphoblastic leukaemia(ALL)	Down regulation	Cell lines	SMRT/NCOR2	[77]
Small cell lung cancer (SCLC)	Down regulation	myeloid cells	FKBP51, IGF1R/mTOR	[78-81]
Renal cell carcinoma(RCC)	Up regulation			
Acute myeloid leukemia (AML)	Up regulation			

Fig. 2. Overview of numerous target genes of miR-100. Numerous genes have been confirmed as targets for miR-100, which covers multiple biological signaling pathways, including cellular proliferation, apoptosis, invasion, metastasis and differentiation. Symbols: → activation; ⊥ inhibition.

of miR-100 has been also found in small cell lung cancer (SCLC) [82], NSCLC [83, 84], GC [7, 9, 85], HCC [86], pancreatic adenocarcinoma [87-89], renal cell carcinoma (RCC) [90], acute myeloid leukemia (AML) [91-94]. However, the expression levels of miR-100 in the same cancer type could be different, which is dependent on the tumor samples obtaining in cancer cell lines or in cancer tissues, as well as plasma. The discrepant expression is still difficult to explain at the time.

The different roles of miR-100 in tumorigenesis might depend on tumor types and its target genes in different cells. Previously, Zheng and his colleague reported that miR-100 was up-regulated in childhood AML and overexpression of miR-100 inhibited the differentiation of granulocyte and monocyte cells and promoted cell survival [94]. On the contrary, they found that miR-100 was down-regulated in childhood ALL and ectopic expression of miR-100 inhibited cell proliferation and enhanced dexamethasone-induced cell apoptosis [80]. Also, Leite's study showed that the expression of miR-100 was reduced during the transition from high grade localized prostate cancer to metastasis [68]. However, conversely, patients with higher levels of miR-100 expression were more prone to suffer biochemical recurrence after radical prostatectomy [69]. Based on experimental results, they pointed out that miR-100 was a context-dependent miRNA in prostate cancer which influenced the fate of tumor cells. On the one hand, oncogenic miR-100 increases cell proliferation through the pRb pathway by down-regulating SMARCA5, BAZ2A and THAP2; on the other hand, miR-100 could also act as a tumor suppressor, cooperating with other factors to down-regulate the mTOR pathway [66]. So far, the molecular bases of these interactions and status of downstream targets of miR-100 have been studied by many scientists. However, the mechanisms responsible for its dysregulation are largely unknown and need to be further elucidated.

The functions of miR-100 and its target genes in human cancers

To date, numerous genes have been testified as target genes of miR-100, which covers multiple biological signaling pathways, affecting formation of many malignant phenotypes

including cellular proliferation, differentiation, invasion, metastasis, angiogenesis and apoptosis in heterogeneous tumors (Fig. 2). For example, miR-100 could suppress proliferation, induce apoptosis and cell cycle arrest in tumor cells by targeting multiple tumor-related genes such as mTOR, PI3K, AKT1, IGF1-R, HS3ST2, HOXA1, RAP1B, FGFR3, PIK1, Cyr61, FKBP51 [7, 58, 61, 72, 75, 76, 80, 87, 95]. Direct regulation of some oncogenes involved in tumor cell invasion and metastasis, such as HOXA1, Rac1, ICMT, EphB6, AGO2 by miR-100 has been identified in many cancers [32, 41, 67, 96]. In addition, there is evidence that miR-100 has an important role in regulating cell differentiation by targeting core reprogramming factors including Plk1, Wnt, β -catenin or RBSP3 [34, 94]. Although miR-100 exerts a potent tumor-regulatory effect by regulating multiple target genes, the number of target genes is still growing, which suggests a complicated regulatory network for miR-100 in human cancers.

MiR-100 in cancer proliferation and apoptosis

The phosphatidylinositol 3-kinase (PI3K) / v-akt murine thymoma viral oncogene homolog 1 (AKT1) / mammalian target of rapamycin (mTOR) pathway is a key signaling system related to tumor cell proliferation and apoptosis [58, 97]. As a member of PI3K-related kinase family, mTOR (locus 1p36.2) interacts with special proteins to form two distinct complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2) and regulates protein synthesis and cell growth [61, 98]. Torres et al. described down-regulation of miR-100 in EEC, which was accompanied by increasing expression of its target gene mTOR to regulate cell proliferation [61]. Similarly, mTOR is also involved in the ability of miR-100 ability to suppress cell proliferation and colony formation in bladder cancer [50]. It was demonstrated by Sun et al. that miR-100 was significantly decreased in ESCC and the tumor suppressor function of miR-100 resulted from inhibiting tumor cell growth and inducing apoptosis by targeting mTOR [27]. As an mTOR inhibitor, the rapamycin analog RAD001 has recently been shown to decrease tumor growth in a xenograft model of clear cell ovarian cancer [95]. Ankur et al. showed that up-regulation of miR-100 inhibited mTOR signaling and enhanced sensitivity to RAD001 [58]. Interestingly, Huang and his colleagues identified for the first time that miR-100 might act as a tumor suppressor in the progression of osteosarcoma by controlling the direct target gene Cyr61 [75, 99]. It has been reported that Cyr61 promotes cell proliferation and inhibit cell apoptosis by binding to different types of integrin molecules, which resulted in down-regulating p53 expression and up-regulating NF- κ B expression through PI3K/Akt/mTOR pathways [100, 101]. Therefore, targeting miR-100/mTOR signaling pathway will be a potential strategy for inhibition of proliferation and induction of apoptosis in human cancers.

Bi et al. reported lower levels of miR-100 and higher levels of fibroblast growth factor receptor 3 (FGFR3) in the osteosarcoma specimen compared to the paired normal bone tissues, and their further research work indicated that miR-100 could inhibit growth of osteosarcoma cells through binding to the 3'-UTR of FGFR3 mRNA [76, 102]. Similarly, Blick et al. showed that low expression of miR-100 could increase FGFR3 expression to stimulate cell proliferation in non-muscle invasive bladder cancer [48]. As well, Morais and his colleagues showed that miR-100 is involved in bladder urothelial carcinogenesis by changing the expression levels of mRNA and proteins of genes related to cell proliferation, survival, apoptosis and chromosomal stability [54]. In addition, Peng et al. showed that miR-100 functioned as a tumor suppressor in colorectal cancer by targeting RAP1B [72].

The process of tumorigenesis is the result of a variety of complex factors, in which evasion of apoptosis is one of the crucial acquired capabilities used to promote cancer cell survival and proliferation [103-106]. However, the molecular bases of miR-100 involved in regulation of apoptosis in tumor cells remain uncharacterized. Insulin growth factor-1 receptor (IGF1-R) plays an important role in cell longevity and proliferation and its down-regulation can lead to cell death [107]. Huang et al. indicated that overexpression of miR-100 in pancreatic adenocarcinoma directly targeted IGF1-R to control cell apoptosis [87]. Previous studies have shown that the mTOR signaling is closely interconnected with the IGF

pathway since it can be activated by upstream IGF receptor signaling. Chen et al. showed that down-regulation of miR-99 family contributed to HNSCC tumorigenesis, in part by targeting IGF1-R/mTOR signaling to regulate cell proliferation and apoptosis [22]. Similarly, the IGF-mTOR signaling is also involved in regulation of adrenocortical cancer cell apoptosis by miR-100 [45]. FKBP51, a 51-kDa FK506 binding protein, exerts proliferative and anti-apoptotic properties via inactivation of the glucocorticoid receptor (GR) signaling pathway by reducing GR activity and impairing GR nuclear translocation [108-110]. Li and other researchers' experimental data indicated that miR-100, a tumor suppressor in ALL, was involved in two essential signaling pathways to inhibit cell growth and initiate cell apoptosis: (i) influencing GR activity by targeting FKBP51; (ii) down-regulating the expression of the anti-apoptotic gene MCL1 by suppressing the IGF1R/mTOR pathway [80]. In another report, Ge et al. showed that overexpression of miR-100 could lead to autophagy of HCC cells by inhibiting expression of mTOR and IGF-1R [38]. As the target gene of miR-100, HS3ST2 gene was reported to encode an important enzyme participating in the final modification of heparan sulfate proteoglycans (HSPGs), which plays vital roles in tumor progression. Also, the absence of HS3ST2 would result in aberrant modulation of key HS biosynthetic enzymes in several cancers including breast, lung, pancreatic, and colorectal cancers [111, 112]. Based on Yang's investigation, miR-100 functions as a key suppressor of apoptosis in GC by down-regulating expression of HS3ST2 to inactivate the Notch signaling pathway [7, 113]. In addition, Ghose and Bhattacharyya's work firstly reported transcriptional regulation of microRNA-100, -146a, and -150 genes by p53 and NF-kappaB p65/RelA in mouse striatal STHdh/ Hdh cells and human cervical carcinoma cells [114].

Liu and his colleagues firstly reported that miR-100 was significantly lower in NSCLC tissues than in normal tissues and its overexpression could lead to G₂/M cell cycle arrest in NSCLC cell by binding the 3'-UTR of polo-like kinase 1 (PIK1) transcripts [36]. PIK1, a kind of conserved serine/threonine kinases, is involved in the control of the G₂/M phase, and its overexpression is significantly correlated with malignant phenotypes including higher clinical stage, advanced tumor classification and lymph node metastasis of cancers [115-117]. In HCC, PIK1 is also reported to be involved in miR-100's ability to impair the growth ability of cancer cells and their capability to form colonies [39]. Bao et al. showed a gradually decreased tendency of miR-100 expression in cervical cancer tissues, and further results indicated that downregulation of miR-100 leads to an increase in Plk1 leading to cell cycle progression in cervical cancer [62]. Consistent with these results, the miR-100-induced G₂/M arrest is mediated by PIK1 in nasopharyngeal cancer progression [24]. Similarly, Dong et al. also revealed that miR-100 could affect the growth of epithelial ovarian cancer cells by post-transcriptionally regulating target PIK1 expression [60].

MiR-100 in cancer invasion and metastasis

Metastasis is one of the causes of tumor recurrence and cancer mortality. The ability of tumor cells to invade and destroy neighboring tissues and organs, as well as migrate to other parts of the body, is crucial to the metastatic process [118, 119]. It has been increasingly recognized that miRNAs play important roles in tumor invasiveness and metastasis [120-122]. For example, Shi et al. showed that lower expression of miR-100 could promote the migration and invasion of gastric cancer cells without significant alteration of proliferation [8]. Also, Fu et al. showed that miR-100 was involved in ESCC metastasis and introduction of miR-100 could strikingly inhibit cell invasion and migration of ESCC cells [26]. Rac1, the most extensively studied isoform in Rac subfamily, is found to be significantly overexpressed in metastatic and aggressive HCCs [123]. As the upstream regulator of Rac1, ICMT is an essential post-prenylation-processing enzyme, which methylates a group of proteins including Rho GTPases [124]. Zhou et al. found that miR-100 exerted its anti-metastasis function by directly repressing expression of ICMT and Rac1, and consequently abrogating the Rac1 signaling [41]. In addition, miR-100 inhibits the motility and invasiveness of mammary tumor cells through direct repressing HOXA1 [32]. EphB6 can affect the expression of a variety of proteins, which are involved in cytoskeleton, signal transduction,

metabolism and energy homeostasis [125]. In previous research, the expression of EphB6 receptor has been reported to be transcriptionally silenced in invasive breast carcinoma cells [126]. Bhushan et al. showed that miR-100 in breast cancer could target the kinase-deficient EphB6 receptor to initiate signal transduction from the cell surface to the nucleus and alter tumorigenesis and invasion [96]. Moreover, Zhang et al. demonstrated that miR-100 modulated the migration and invasion of ESCC cells by targeting the mTOR 3'-UTR, and its downregulation in ESCC tissues was significantly correlated with status of lymph node metastasis in patients [30]. Argonaute 2 (AGO2), the core effector protein of the miRNA-induced silencing complex promotes tumor metastasis. Wang et al. showed that loss of miR-100 promoted the metastatic ability of prostate cancer cells through modulating migration, invasion, epithelial-mesenchymal transition (EMT) and stemness of cancer cells by upregulating AGO2 expression [67, 127]. With biological properties similar to normal adult stem cells, cancer stem cells (CSCs) play central roles in malignant tumor onset, progression, recurrence, metastasis and drug resistance [128]. In addition, EMT allows cancer cells to metastasize by changing proliferating cells from an aplanetic state to a motile state and one of its biomarker is the loss of E-cadherin [129]. Shimamura et al. applied Network Profiler to microarray gene expression and extracted the system changes that were related to EMT, and further found that higher expression of miR-100 could significantly decrease E-cadherin expression and induce morphological changes of EMT [130].

The roles of miR-100 in differentiation of cancer stem cells

Studies performed over the past years have demonstrated that miRNAs can sustain stemness of embryonic stem cells (ESCs), regulate ESC differentiation, as well as controlling self-renewal and differentiation of CSCs [131-133]. CSCs are characterized by self-renewal and high tumorigenic capacity and can be formed during the process of EMT. Petrelli et al. found that miR-100 induced a differential program by the Wnt / β -catenin pathway which is one of the main signal pathways involved in differentiation of CSCs and could inhibit maintenance and expansion of CSCs in basal-like cancer through the down-regulation of Plk1 [34]. In addition, Zheng and his colleagues revealed that miR-100 could modulate the cell cycle effectors pRB / E2F1 including regulating G1/S transition and S-phase entry and blocked granulocyte / monocyte differentiation in acute myeloid leukemia (AML) by targeting RBSP3, which is a phosphatase-like tumor suppressor [94].

MiR-100 in cancer diagnosis and prognosis

Specific miRNAs have been found to be differentially expressed in the majority of tumor cases, suggesting that miRNA expression patterns are capable of distinguishing between malignant and normal tissues [134, 135]. There is increasing evidence to show that tumor-derived circulating miRNAs have diagnostic or prognostic potential because of their remarkable stability in blood and their characteristic expression in cancers [136-138]. During the past few years, the roles of miR-100 in diagnosis of human cancers are increasingly reported. For example, a noticeable decrease in miR-100 was observed in human PC tissues compared to normal prostate tissues and in bone metastatic PC tissues compared to primary PC tissues [67]. Also, Shi et al. showed that the expression of miR-100 was lower in GC tissues as compared with control tissues [8]. In contrast, Yang et al. detected up-regulation of miR-100 in human epithelium-derived GC cells [7]. The discrepant expression is still difficult to explain at the time. In another study, miR-100 was observed to be reduced about fourfold in invasive human breast cancer tissues as compared with benign patient samples [33]. Similarly, miR-100 was found to be down-regulated in all subtypes of breast cancers including luminal A, luminal B, basal-like and HER2 subtypes, compared with paired normal breast tissues [32]. Recently, the lower expression of miR-100 in bladder cancer tissues compared to adjacent noncancerous tissues is reported to be correlated with low-grade, non-invasive bladder urothelial cancer [50, 52, 54]. In ESCC, miR-100

demonstrated markedly lower expression in tumor tissues than in controls as validated by quantitative reverse transcription-polymerase chain reaction [30]. Feng et al. found that the expression of miR-100 in docetaxel-resistant lung adenocarcinoma cell line (SPC-A1/DTX) is significantly lower than that in parental SPC-A1 cells [35]. Also, the expression level of miR-100 was significantly decreased in osteosarcoma tissues in comparison with the adjacent normal tissues [75, 139]. Likewise, miR-100 was also found to be markedly under-expressed in both pancreatic cancer cell lines and tumor cells from patients [42]. Using microarray analysis to compare the expression of miR-100 in five pancreatic cancer cell lines of which two that can metastasized *in vivo* and three that did not metastasize, Huang et al. showed that miR-100 is significantly up-regulated in metastatic tumor cells [87].

Recently, as a non-invasive, blood-based diagnostic tool, cell-free miRNA has obtained much interest [140, 141]. By comparing blood serum samples from 50 gastric patients and 47 healthy controls, Wang et al. confirmed the diagnostic value of serum miR-100 higher regulation in human GC [9]. The Solexa sequencing results from Zhang et al. demonstrated marked upregulation of 25 serum miRNAs including miR-100 in ESCC patients compared with controls [29]. Similarly, together with the other six serum miRNAs, miR-100 was found to be significantly higher in ESCC than in controls [28]. From those above studies, it was concluded that miR-100 might be a more reliable diagnostic biomarker for human cancers as a result of its aberrant expression in tumorigenesis.

Meanwhile, the associations of miR-100 with clinical outcome of human cancer patients were also reported. In terms of SCLC, Xiao et al. confirmed that the expression level of miR-100 was inversely correlated with the expression of its target gene HOXA1 and associated with the poor prognosis of SCLC patients [82]. Wang et al. showed that overexpression of miR-100 in RCC tissues was associated with advanced tumor T stage, grade, the presence of metastasis and poor prognosis of patients [90]. Moreover, low expression of miR-100 was testified to be a negative prognostic factor, associating with gene signatures of high grade undifferentiated breast cancer [34]. Wang et al. showed that down-regulation of miR-100 in bladder cancer tissues was associated with shorter overall survival and poor progression-free survival of patients [51]. In addition, by detecting the expression of miR-100 in 120 self-paired specimens of ESCC and adjacent normal tissues by RT-PCR, Zhou et al. found that the expression of miR-100 in ESCC tissues was significantly lower than that in the adjacent normal tissues and could predict advanced clinical stage, depth of tumor invasion, and the presence of distant metastasis [31]. In CRC, low miR-100 expression was observed to be significantly connected with advanced TNM stage, larger tumor size, and higher incidence of lymph node metastasis, together with shorter overall survival, suggesting that miR-100 could serve as an independent unfavorable prognostic predictor [71]. Similarly, low miR-100 expression was found to be closely correlated with higher clinical stage, advanced tumor classification and lymph node metastasis of NSCLC patients, suggesting that low miR-100 expression might be a poor prognostic factor in NSCLC [36]. At the same time, Zhou et al. showed that down-regulation of miR-100 in HCC tissues was significantly associated with advanced TNM stage, poorer cell differentiation, venous invasion, tumor nodule without complete capsule and shorter recurrence-free survival of patients [41]. In other two studies, miR-100 was reported to function as a tumor suppressor by targeting plk1 in HCC and be correlated with higher incidence of lymph node metastasis and poor prognosis in HCC patients [37, 142]. Therefore, it was concluded that low expression level of miR-100 could not only predict unfavorable prognosis of HCC patients but also have the capacity to predict further risk stratification in the treatment of HCC. What's more, overexpression of miR-100 in pediatric AML was found to be associated with poor relapse-free and overall survival of patients [91]. In contrast, Li et al. observed that miR-100 was down-regulated in 111 ALL patients, especially in high-risk groups and its lower expression level was correlated with shorter 5-year survival of patients [80]. In another study, Peng et al. showed that low miR-100 expression was closely correlated with higher serum CA125 expression level, lymph node involvement, advanced FIGO stage and short overall survival of epithelial ovarian cancer (EOC) patients, suggesting that the status of miR-100 expression could be an independent

predictor of overall survival in EOC [60]. Taken together, miR-100 can serve as a candidate prognostic indicator, but further investigation of a larger patient population is necessary to confirm prognostic evaluation of miR-100 in human cancers.

MiR-100 in cancer therapy

MiR-100 can be overexpressed or under-expressed in different cancers, so silencing of miR-100 that is overexpressed or replacement of miR-100 that is under-expressed are two distinct and novel approaches to treat tumors driven by miR-100 dysregulation [143]. The observation of decreased levels of tumor suppressive miRNAs including miR-100 in cancers has led to the concept of miRNA replacement therapy. For example, Li et al. reported that transfection of lentiviral vector containing miR-100 mimics in pancreatic cancer cells could inhibit cancer cell proliferation and increase sensitivities to cisplatin through targeting FGFR3 [42]. Zhu et al. also highlighted miR-100 as a tumor suppressor in chondrosarcoma and obtained evidence that overexpression of miR-100 could reverse the chemoresistance of cisplatin-resistant chondrosarcoma cells to cisplatin by directly targeting mTOR [74]. In addition, upregulated miR-100 with oncogenic potential in specific cancer types can be potential therapeutic targets for inhibition by using antisense oligonucleotides, sponges or locked nucleic acid (LNA) constructs [144-146]. However, the inhibition of miR-100 for therapy has not been demonstrated in certain cases.

On the other hand, differentiation therapy is a promising therapeutic strategy which is achieved by using drugs to force malignant cells to terminally differentiate and taking advantage of differentiation molecules that are specifically expressed in the selected tissue. Therefore, this therapy can reduce side effects in patients, since it avoids indiscriminately killing proliferating cells and instead concentrates its efficacy on cancer cells. Interfering with estrogen receptor (ER) activation is currently the gold standard for the treatment of breast cancer [147]. By promoting the expression of a functional ER, converting a basal like phenotype into luminal, miR-100 renders basal-like BrCSCs responsive to hormonal therapy [34]. In addition, despite the great advances achieved in radiotherapy and cytotoxic drug development, long term cure rates by standard therapies are disappointing owing to disseminated disease at diagnosis and chemotherapeutic resistance [148]. Ectopic miRNAs are involved in various drug resistant mechanisms including EMT, CSC, apoptosis avoidance, androgen signaling and multiple drug resistance (MDR) transporters [78, 149, 150]. Additionally, miR-100 can influence the sensitivity of tumors to chemo- or radiation therapy, so a combination of miR-100 chemo- or radiation therapy proves to be a novel antitumor strategy. In the study of Feng et al. showed that introduction of miR-100 could significantly sensitize SPC-A1/DTX cells to docetaxel via inducing significant suppression of cell proliferation, cell arrest in G₂/M phase of cell cycle and enhancement of apoptosis by targeting Plk1 [35, 151]. Lobert et al. initially reported that down-regulation of miR-100 could increase β -tubulin class V expression level to promote the continuing survival and proliferation of tumor cells, suggesting special implications for paclitaxel resistance and potential miR-100 replacement therapy in combination with paclitaxel [152]. Also, Ng et al. demonstrated for the first time that overexpression of miR-100 promoted the low expression of activating ataxia telangiectasia mutated (ATM, an important checkpoint regulator for promoting homologous recombination repair) in human glioma cell line and restoration of miR-100 could sensitize tumor cells to radiotherapy or chemotherapy [153].

Conclusions and Future Directions

In summary, much evidence indicates that aberrant miR-100 expression is commonly found in different human cancers and miR-100 functions as a potent tumor suppressor / promotor. More importantly, the expression patterns and effects of miR-100 in tumor

progression are not fully elucidated and the recent studies have reported controversial results. Since miR-100 has been reported to be significantly dysregulated in different cancer types, it is expected to be a valuable molecular marker for cancer diagnosis and prognosis. Understanding the roles of these altered miRNAs and its possible molecular mechanisms in physiological and pathological processes of cells will be helpful to provide an opportunity for possible therapeutic intervention in disease processes by targeting either the regulatory pathways or the miRNAs themselves. Since transfection of miR-100 could improve the sensitivity to chemotherapy agents and radiation therapy in cancer cells, targeting miR-100 may provide a new strategy for overcoming therapy resistance in clinic. Research into miR-100-based therapy, however, is at an early stage, and further investigation of miR-100 may lead to novel therapeutic strategies for human cancers in future.

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Disclosure Statement

The authors declare that they have no conflicts of interest related to this work.

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