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Review Article

MiR-101: a potential therapeutic target of cancers

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Abstract: MicroRNAs (miRNAs) are small noncoding RNAs that could regulate gene expressions transcriptionally or post-transcriptionally through binding to 3' untranslated region (3'UTR) of target messenger RNAs (mRNAs), which were identified to be associated with tumorigenesis in various neoplasms. Among them, miR-101, encoded by two precursor transcripts (miR-101-1 and miR-101-2), was recognized to serve as a tumor suppressor via targeting critical oncogenes or anti-oncogenes. Additionally, studies have shown that miR-101 was participated in multiple cancer-related biological processes, including proliferation, apoptosis, angiogenesis, drug resistance, invasion and metastasis. In this review, we aim to summarize the function of miR-101 in different biological processes by figuring out the underlying target gene networks and explore its potential role as a biomarker in diverse neoplasms, which will provide a brand-new insight in molecular targeting cancer treatment.

Keywords: miR-101, cancers, biomarker, therapeutic targets

Introduction

In modern society, an increasing number of people are in great danger of malignant neoplasms under the pressure of fast-paced work and heavy-burdened life [1]. In spite of the application of traditional treatments, like surgery, chemotherapy and radiotherapy, many cancer patients are still suffering from limited effects, owing to metastasis, recurrence and drug resistance [2]. So it is urgent for us to identify molecular targets and develop effective agents for molecular targeting treatment. Fortunately, microRNAs (miRNAs), potential therapeutic targets, entered into the public view and brought hope for cancer patients.

MicroRNAs (miRNAs), 18-25 nucleotides in length, are a series of evolutionally conserved, single-stranded, small non-coding RNA molecules, which can modulate gene expressions at both transcriptional and post-transcriptional level via binding to the 3' untranslated region (3'UTR) of target messenger RNAs (mRNAs), thus leading to mRNA degradation or translational inhibition [3]. Among them, miR-101, generating from two precursor transcripts: miR-101-1 on chromosome 1p31 and miR-101-2 on chromosome 9p24, was recently acknowledged to be a tumor suppressor in the incidence and development of various neoplasms [4]. Based on available researches, miR-101 was down-regulated in gastric cancer (GC) [5], intrahepatic cholangiocarcinoma (ICC) [6], osteosarcoma (OS) [7], hepatocellular carcinoma (HCC) [8], non-small-cell lung cancer (NSCLC) [9], oral squamous cell carcinoma (OSCC) [10], bladder transitional cell carcinoma (BTCC) [11], cervical cancer [12], intraductal papillary mucinous neoplasm of the pancreas (IPMN) [13], ERα-positive breast cancer [14] and so on. In detail, miR-101 was also reported to take part in many cancer-related biological processes, including proliferation, apoptosis, angiogenesis, drug resistance, invasion and metastasis [15-17]. What's more, the gene network involved in multiple biological processes was found to be more complex than we could imagine. MiR-101 was influenced by many extrinsic and intrinsic factors, like atmospheric particles, viruses, pro-inflammatory cytokines and so on. Meanwhile, downstream targets of miR-101 were complicated, which means that miR-101 could modulate diverse target genes while a single target gene could be regulated by multiple microRNAs, including miR-101. Therefore, it could be seen

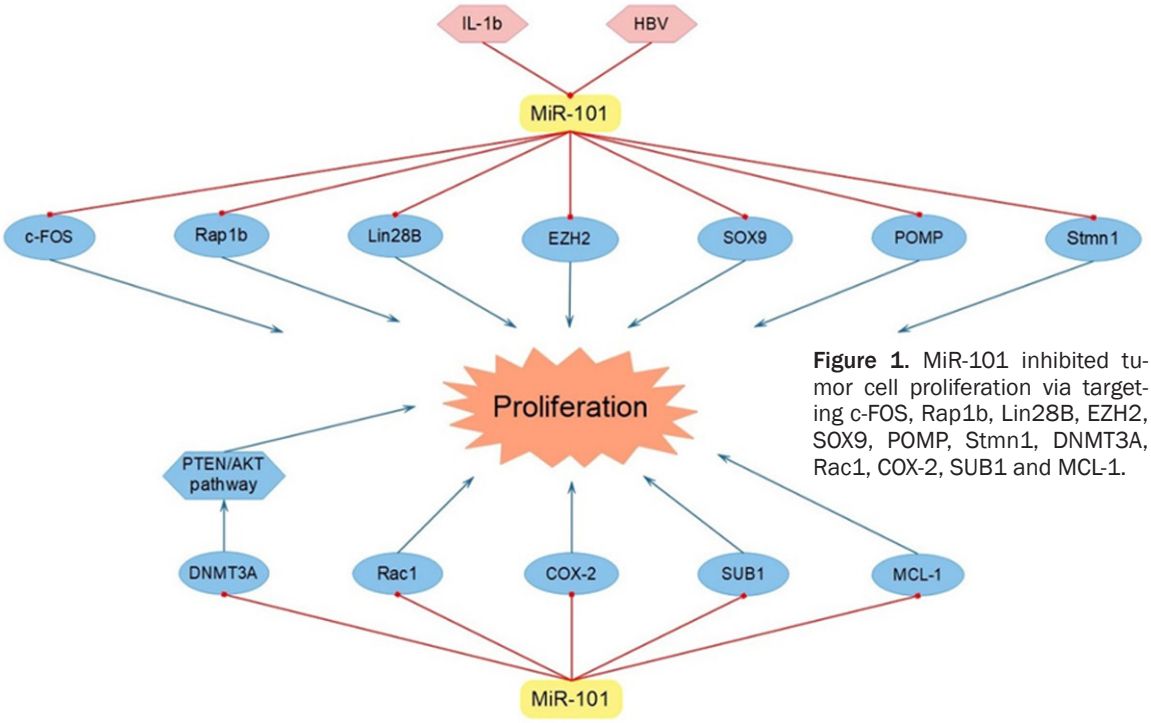

Figure 1. MiR-101 inhibited tumor cell proliferation via targeting c-FOS, Rap1b, Lin28B, EZH2, SOX9, POMP, Stmn1, DNMT3A, Rac1, COX-2, SUB1 and MCL-1.

that the distinct molecular mechanism deserves for further exploration in future. Apart from its role in cancers, miR-101 was claimed to be related with kinds of non-malignant diseases, such as multiple system atrophy (MSA) [18], hepatopulmonary syndrome (HPS) [19], cardiac fibroblasts (CFs) [20], HBV-associated chronic hepatitis [21], Alzheimer [22], pulmonary fibrosis [23], acute kidney injury (AKI) [24], gestational diabetes mellitus (GDM) [25] and so on. Evidence had been proven that miR-101 played a pivotal role in the initiation and development of multifarious diseases, especially malignant neoplasms.

In this review, we will focus on the function of miR-101 in cancer-related biological processes, including proliferation, apoptosis, angiogenesis, drug resistance, invasion and metastasis, and explore the potential role of miR-101 as a biomarker in various neoplasms, which might offer a novel guidance in molecular targeting cancer treatment.

MiR-101 in proliferation

Cell proliferation is crucial in cellular processes and miR-101 has been recognized to suppress tumor proliferation by regulating several target genes. It was demonstrated that miR-101 inhibited cell proliferation directly by decreasing the expression of enhancer of zeste homolog 2 (EZH2) in lung cancer [17], BTCC [11] and embryonal rhabdomyosarcoma (eRMS) [26]. EZH2, a member of the polycomb group (PcG) protein family, functioned as a histone methyltransferase by catalyzing histone H3 lysine 27 (H3-K27) trimethylation, which played an important role in maintaining gene silence and was greatly participated in the process of proliferation in various neoplasms [27]. Besides, in mesenchymal stem cell of Wilms tumor, miR-101, cooperating with miR-26a and Wilm's tumor suppressor gene1 (WT1), remarkably suppressed cell proliferation by targeting EZH2 [28]. Moreover, in SiO_2 particle-induced lung cancer, SiO_2 particle stimulated the accumulation of IL-1b, which negatively modulated miR-101. Then miR-101, suppressed by IL-1b, inhibited the EZH2 expression and thus restrained cell proliferation [29]. Interestingly, it was also announced that miR-101 reduced the expression of Lin28B in NSCLC and thereby inhibited cell proliferation, which could be restrained by IL-1b via the COX2-HIF1α pathway [30]. In addition, miR-101 refrained cell proliferation of HCC directly by targeting SOX9 [31]. What's more, miR-101 was also discovered to be diminished by HBV in HCC and possessed a great potential

Table 1. Target genes and dysregulation of miR-101 in proliferation, apoptosis, angiogenesis, drug resistance

MiR-101	Disease	Target genes	Reference	Participation
Downregulated	NSCLC	DNMT3A	Liu J, et al.	Proliferation
		Lin28B	Wang L, et al.	Proliferation
		EZH2	Zhang JG, et al.	Proliferation
		Caspase 3	Yin J, et al.	Apoptosis
	HCC	Rap1b	Sheng Y, et al.	Proliferation
		SOX9	Zhang Y, et al.	Proliferation
		EZH2	Xu L, et al.	Drug resistance
		MCL-1	He H, et al.	Drug resistance
	Breast Cancer	POMP	Zhang X, et al.	Proliferation
		Stmn1	Wang R, et al.	Proliferation
		DNMT3A	Liu J, et al.	Proliferation
		EYA1	Guan H, et al.	Apoptosis
		VHL	Liu N, et al.	Apoptosis
		SOX2	Wang J, et al.	Apoptosis
		Jak2	Wang L, et al.	Apoptosis
		MCL-1	Liu X, et al.	Drug resistance
	Bladder cancer	EZH2	Friedman JM, et al.	Proliferation
		c-FOS	Long Y, et al.	Proliferation
	PCa	SUB1	Chakravarthi BV, et al.	Proliferation
		COX-2	Hao Y, et al.	Proliferation
		RLIP76	Yang J, et al.	Apoptosis
	Wilms Tumor	EZH2	Akpa MM, et al.	Proliferation
	Cervical Cancer	COX-2	Lin C, et al.	Proliferation
	GC	VEGF-C	Li G, et al.	Apoptosis
			Liu HT, et al.	Angiogenesis
	PDA	RRM1	Fan P, et al.	Apoptosis
	CRC	Sphk1	Chen MB, et al.	Angiogenesis
	PTC	Rac1	Lin X, et al.	Proliferation
	OS	DNA-PKcs	Zhen YF, et al.	Apoptosis
		mTOR	Lin S, et al.	Apoptosis
	T-ALL	Notch 1	Qian L, et al.	Drug resistance
	NPC	ITGA3	Tang XR, et al.	Angiogenesis
	GBM	GSK3β	Tian T, et al.	Drug resistance
	ACC	Pim-1	Liu XY, et al.	Drug resistance
	eRMS	EZH2	Vella S, et al.	Proliferation
Upregulated	-	-	-	-

in decreasing cell proliferation via targeting ras-associated protein-1b (Rap1b) [32]. Rap1b was one of the isoforms of Rap1. Rap1, a member of Ras superfamily of G proteins, was a little GTPase located in cellular membranes and had been reported to be associated with cell proliferation [33]. Furthermore, miR-101 was elucidated to dilute the level of DNA methyltransferase 3A (DNMT3A) in breast cancer, accordingly suppressing cell proliferation [34]. Meanwhile, it was also discovered that DNMT3A accumulated in NSCLC and accelerated tumor cell proliferation via activating the PTEN/AKT pathway, which could be repressed by miR-101 [35]. Additionally, in breast cancer, miR-101 worked as a suppressor in cell proliferation through targeting proteasome maturation protein (POMP) and Stathmin 1 (Stmn1) [14, 36]. Notably, enhancing the expression of miR-101 could dilute the level of Ras-related C3 botuli-

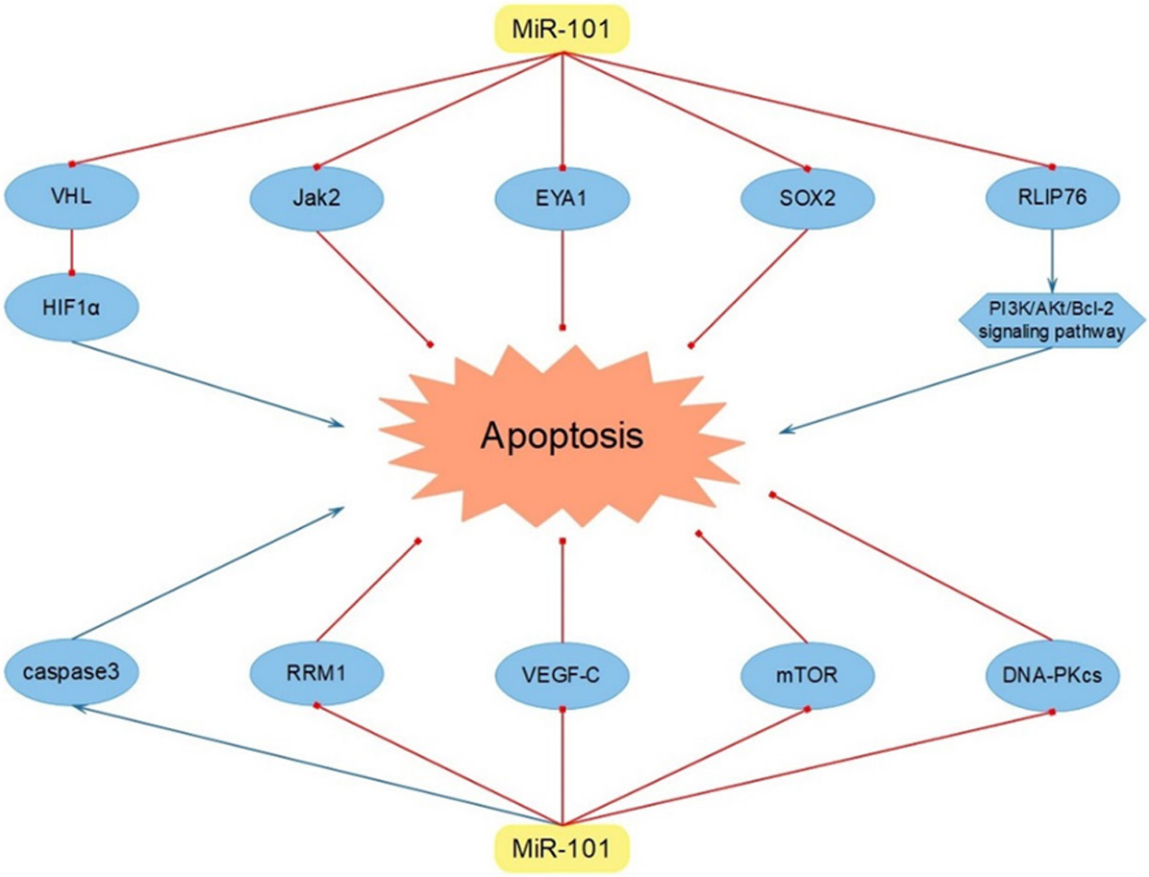

Figure 2. MiR-101 promoted tumor cell apoptosis via targeting VHL, Jak2, EYA1, SOX2, RLIP76, caspase3, RRM1, VEGF-C, mTOR and DNA-PKcs.

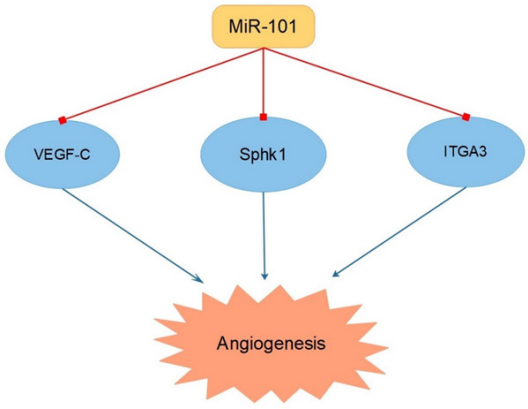

Figure 3. MiR-101 suppressed tumor cell angiogenesis via targeting VEGF-C, Sphk1 and ITGA3.

num toxin substrate 1 (Rac1), thereby leading to inhibited cell proliferation of papillary thyroid carcinoma (PTC) [37]. Also, it was claimed that the miR-101/c-FOS signaling pathway contributed to the weakened proliferation in bladder cancer [38]. In addition, the suppressed cell proliferation of cervical cancer was proven to be related with the high-expressed miR-101, via negatively regulating COX-2 [12]. What's more, miR-101 was also affirmed to weaken prostate cancer (PCa) cell proliferation via down-regulating COX-2 and SUB1 [39, 40]. Besides, in endometrial cancer, miR-101 restrained the level of MCL-1, thereby contributing to the decreased tumor proliferation [41] (**Figure 1** and **Table 1**).

MiR-101 in apoptosis

Tumor cell apoptosis is an indispensable step in cellular processes and miR-101 has been clarified to serve as a promoter in apoptosis of diverse cancers. It was confirmed that miR-101 increased cell apoptosis of breast cancer directly through decreasing the expression of Janus Kinase 2 (Jak2), eyes absent homolog1 (EYA1) and sex-determing region Y-box2 (SOX2) [42-44]. What's more, the capacity of breast cancer cell apoptosis was regulated by more

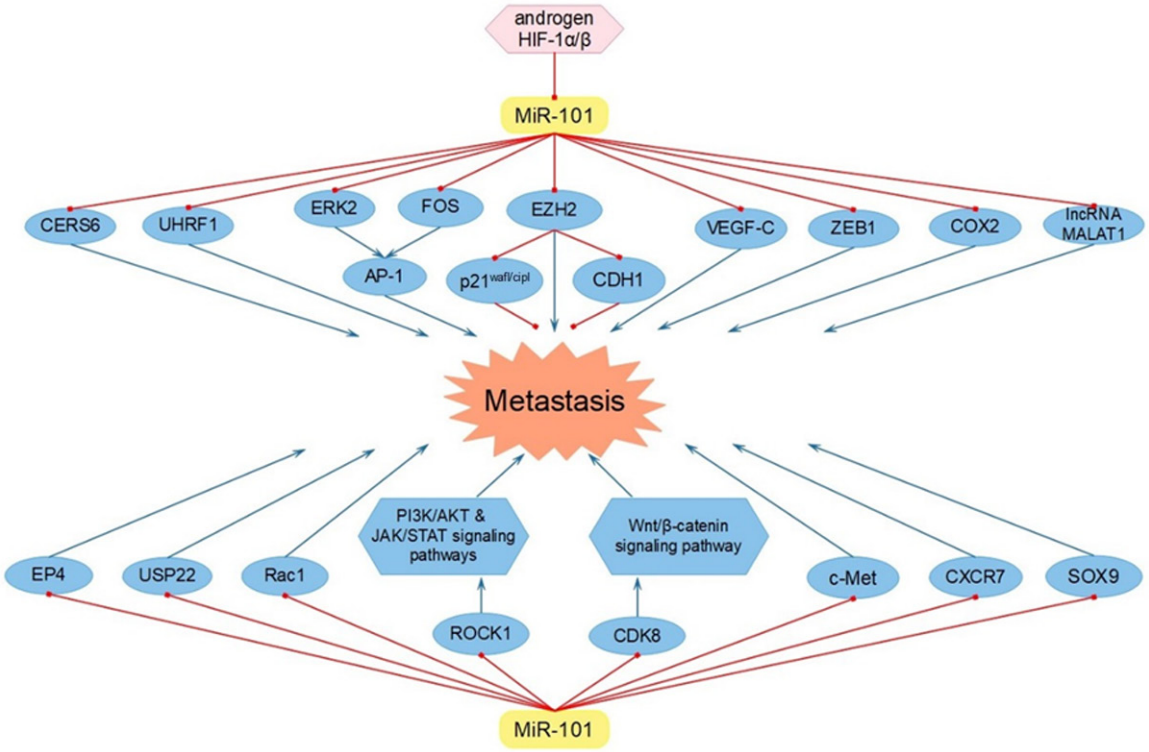

Figure 4. MiR-101 refrained tumor cell metastasis via targeting CERS6, UHRF1, ERK2, FOS, EZH2, VEGF-C, ZEB1, COX2, lncRNA MALAT1, EP4, USP22, Rac1, ROCK1, CDK8, c-Met, CXCR7 and SOX9.

complex mechanisms. In detail, miR-101 reduced the level of von Hippel-Lindau (VHL), which could negatively regulate hypoxia inducible factor-1α (HIF1α), thus leading to enhancing HIF1α-dependent cell apoptosis in breast cancer [45]. In addition, miR-101 served as a promotor in PCa cell apoptosis via inhibiting the level of Ral binding protein 1 (RLIP76), accordingly down-regulating the activation of PI3K/Akt/Bcl-2 signaling pathway [46]. Besides, miR-101 enhanced NSCLC cell apoptosis directly via stimulating the augmentation of caspase 3 [47]. What's more, in pancreatic ductal adenocarcinoma (PDA), miR-101 impaired the expression of ribonucleotide reductase M1 (RRM1), thus leading to the induced progression of cell apoptosis [48]. Meanwhile, it was proclaimed that miR-101 contributed to the increased GC cell apoptosis via diluting the VEGF-C expression level [49]. Furthermore, in OS, the action of miR-101 in promoting apoptosis attributed to its negative regulation of mTOR and DNA-dependent protein kinase catalytic subunit (DNA-PKcs) [50, 51]. Based on available researches, we found that some classical apoptosis-related genes, like p53, Fas, ATM, had not been mentioned. So it is still urgent for us to find out whether miR-101 can modulate other apoptosis-related genes in diverse neoplasms in future (**Figure 2** and **Table 1**).

MiR-101 in angiogenesis

Tumor angiogenesis is based on the interaction between neoplasm cells and endothelial cells, which plays a significant role in the initiation and development of cancers. It was indicated that miR-101 acted as an inhibitor of tube formation in human umbilical vascular endothelial cells (HUVECs) in GC via targeting VEGF-C [52]. VEGF-C, a member of the VEGF family, was reported to be related with higher lymphatic density [53]. However, other VEGF family members, like VEGF-A, VEGF-B, VEGF-D and PGF, are also involved in the regulation of hemangiogenesis or lymphangiogenisis. So more efforts should be put to find out whether they could also serve as target genes of miR-101. In addition, the repression of angiogenesis caused by miR-101 was clarified in colorectal cancer (CRC), by the way of targeting sphingosine kinase 1 (SphK1) [54]. SphK1

Table 2. Target genes and dysregulation of miR-101 in metastasis

MiR-101	Disease	Target genes	Reference
Downregulated	NSCLC	CERS6	Suzuki M, et al.
		EZH2	Cho HM, et al.
	HCC	VEGF-C	Liu Z, et al.
		ERK2	Liu JJ, et al.
		c-FOS	Liu JJ, et al.
		FOS	Li S, et al.
		ZEB1	Zhao S, et al.
	Bladder Cancer	c-Met	Hu Z, et al.
	PCa	EZH2	Cao P, et al.
	RCC	UHRF1	Goto Y, et al.
	Cervical Cancer	COX-2	Huang F, et al.
	EOC	EZH2	Semaan A, et al.
	GC	EZH2	Carvalho J, et al.
	ESCC	Onco-lncRNA MALAT1	Li RQ, et al.
	CRC	EP4	Chandramouli A, et al.
	PTC	Rac1	Wang C, et al.
		USP22	Zhao H, et al.
	OS	EZH2	Zhang K, et al.
		ROCK1	Jiang R, et al.
		c-FOS	Wang Z, et al.
	GBM	SOX9	Liu N, et al.
	LSCC	CDK8	Li M, et al.
	OSCC	CXCR7	Hui Y, et al.
		ZEB1	Wu B, et al.
Upregulated	-	-	-

mediated the phosphorylation of sphingosine to S1P, which had been found to be connected with angiogenesis [55]. What's more, it was disclosed that, in nasopharyngeal carcinoma (NPC), increasing the level of miR-101 could negatively modulate the expression of integrin subunit alpha 3 (ITGA3), accordingly leading to the weakened capacity of angiogenesis [56] (**Figure 3** and **Table 1**).

MiR-101 in invasion and metastasis

Tumor invasion and metastasis is frequently known as the main cause of cancer-related deaths and miR-101 shows a great potential in inhibiting tumor cell invasion and metastasis in multifarious neoplasms. It was found that miR-101 decreased cell metastasis in OS through directly reducing the expression of v-fos FBJ murine osteosarcoma viral oncogene homolog (FOS) [8]. Meanwhile, miR-101 was discovered to repress cell metastasis of HCC via regulating the miR-101-ERK2/c-FOS-AP-1 feedback loop [7, 57]. In detail, miR-101 inhibited the expression of ERK2 and c-FOS, which were two critical components of activator protein-1 (AP-1), thus suppressing AP-1-dependent cell metastasis. AP-1, as a transcription factor (TF), could promote miR-101 transcription, which made the pathway a feedback loop. In addition, EZH2 was participated in the process of invasion and metastasis as well. It was elucidated that miR-101 restrained cell metastasis by downregulating the level of EZH2 in lung cancer and OS [58, 16]. Moreover, in epithelial ovarian cancer (EOC), miR-101 decreased the expression of EZH2, which mediated the transcriptional repression of p21 wafl/cipl, thus leading to the inhibition of cell metastasis [59]. Meanwhile, miR-101 was demonstrated to down-regulate the EZH2 level in GC and thereby enhanced the restoration of E-cadherin (CDH1), which weakened the capacity of cell metastasis [60]. Besides, it was recognized that miR-101 was negatively regulated by androgen and HIF-1α/HIF-1β in PCa and miR-101 functioned as a suppressor via diluting EZH2 in the process of invasion and metastasis [61]. What's more, a variety of signaling pathways were explored to play a critical role in the process of tumor invasion and metastasis. For instance, miR-101 inhibited tumor metastasis in OS by impairing the activation of PI3K/AKT and JAK/STAT signaling pathways via targeting ROCK1 [62]. Moreover, the inhibition of the Wnt/β-catenin signaling pathway was proven in laryngeal squamous cell carcinoma (LSCC), which was caused by miR-101 through targeting CDK8 [63]. Apart from the above-mentioned complex molecular mechanisms, there were still a number of target genes which were mediated by miR-101 and directly pro-

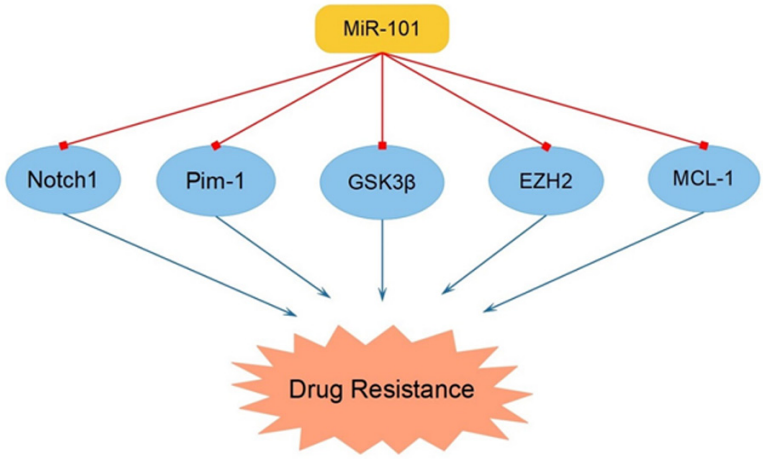

Figure 5. MiR-101 modulated tumor cell drug resistance via targeting Notch1, Pim-1, GSK3β, EZH2 and MCL-1.

duced effects on the process of invasion and metastasis in multifarious cancers. For example, in NSCLC, miR-101 inhibited cell metastasis through targeting ceramide synthase 6 (CERS6) [9]. CERS6 played a key role in ceramide synthesis in cellular membrane, which was connected with the formation of lamellipodia and metastasis [64]. Besides, the reduced capacity of metastasis was reported to be regulated by miR-101 through targeting Ubiquitin-like with PHD and ring finger domains 1 (UHRF1) and VEGF-C [6, 65, 66]. In addition, it was recognized that miR-101 decreased cell metastasis via inhibiting the expression of zinc finger E-box binding homeobox 1 (ZEB1) in HCC and OSCC [67, 10]. ZEB1 was confirmed to possess a great potential in organ fibrosis and cancer metastasis via reducing E-cadherin and triggering epithelial-to-mesenchymal transition (EMT) [68]. Moreover, in cervical cancer, the miR-101/COX2 regulatory axis was indicated to be negatively correlated with tumor metastasis [69]. Interestingly, miR-101, cooperating with miR-217, down-regulated the level of onco-lncRNA MALAT1 and refrained cell metastasis in esophageal squamous cell carcinoma (ESCC) [70]. It was clarified that miR-101 reduced the expression of EP4 and inhibited CRC cell metastasis [71]. Subsequently, the suppressed ability to invade caused by miR-101 was explored in PTC, as it negatively modulated Ubiquitin-specific protease 22 (USP22) and Rac1 [72, 73]. It was affirmed that miR-101 was also participated in the miR-101/c-Met pathway in bladder cancer to prevent cell metastasis [74]. Notably, in OSCC, the function of miR-101 in decreasing metastasis resulted from targeting CX chemokine receptor 7 (CXCR7) [75]. Furthermore, the accumulation of miR-101 was illustrated to suppress the level of sex-determining region Y-box9 protein (SOX9), thereby controlling invasion and metastasis in glioblastoma multiforme (GBM) [76] (**Figure 4** and **Table 2**).

MiR-101 in drug resistance

Drug resistance is a major obstacle in chemotherapy and increasing evidences had indicated that miR-101 took part in the regulation of drug resistance in sorts of cancers. It was disclosed that, in triple-negative breast cancer, high-expressed miR-101 enhanced tumor cell chemotherapeutic sensitivity to paclitaxel via decreasing the MCL-1 expression level [15]. Moreover, the chemotherapeutic sensitivity to fluorouracil in HCC cell was indicated to be promoted by the up-regulated miR-101, via targeting EZH2 [77]. Interestingly, based on previous researches, miR-197 was illustrated to promote paclitaxel resistance while inhibiting fluorouracil resistance in cancers [78, 79]. This phenomenon contributed to the synergistic effect or the antagonistic effect in drug resistance remained to be obscure and urged for more investigation. In addition, miR-101 was clarified to induce chemotherapeutic sensitivity to adriamycin in T-cell acute lymphoblastic leukemia (T-ALL) and HCC via targeting Notch 1 and MCL-1 respectively [80, 81]. Besides, the chemotherapeutic sensitivity to cisplatin in salivary gland adenoid cystic carcinoma (ACC) cell was indicated to be promoted by miR-101, via targeting provirus integration site for moloney murine leukemia virus 1 (Pim-1) [82]. Furthermore, the augmentation of miR-101 in GBM suppressed the level of glycogen synthase kinase 3β (GSK3β), accordingly leading to the increased ability to sensitize resistant GBM cells to temozolomide [83]. The above-mentioned researches almost focused on single drug resistance. However, an increasing number of cancer patients are suffering from multi-drug resis-

tance, whose molecular mechanism is still unclear and worthy of further investigation (**Figure 5** and **Table 1**).

MiR-101 in clinical application

Based on mounts of researches, miR-101 was speculated to have the potential of serving as a biomarker in multifarious neoplasms, which might bring guidance for the molecular targeting treatment. It was claimed that down-regulated miR-101 was remarkably associated with increased tumor size, advanced TNM classification and poor survival in GC cell [52]. Moreover, an underlying connection between the miR-101 expression, T3-4 tumor grade and worse prognosis was announced in LSCC [63]. Besides, the poor prognosis of cancer patients caused by the low level of miR-101 was demonstrated in OSCC [10]. Additionally, it was also reported that the level of miR-101 played a critical role in the pathological grade and TNM classification in breast cancer cell [42]. With ample evidences in cancer, we considered miR-101 as a considerable biomarker in multifarious cancers, which might offer a novel sight for clinical application.

Discussions and conclusions

In this review, on account of available researches, miR-101 was reported to be down-regulated in almost carcinoma tissues, which disclosed that miR-101 could function as a tumor suppressor in diverse malignant neoplasms. Nonetheless, no one had claimed the up-regulation of miR-101 in any carcinoma tissue. This phenomenon of tissue specificity was different from that of other microRNAs. For instance, the majority of miR-29a was down-regulated in human cancers while a few was illustrated to be overexpressed in some cancers, like cholangiocarcinoma and CRC [84]. Consequently, it is controversial that miR-101 could be up-regulated in some neoplasms and possess the possibility to serve as oncogene or tumor suppressed gene. The distinct tissue specificity of miR-101 still deserves for further exploration.

Besides, we discovered that miR-101 could modulate various target genes while one single target gene could be regulated by multifarious miRNAs, which added the difficulty of identifying specific downstream targets of miR-101 in clinical application. Fortunately, an increasing number of new materials have entered into public view, like extracellular vesicles (EVs), long non-coding RNAs (lncRNAs) and so on, which possess the potential of carrying functional miRNAs and delivering them to specific targets. However, the connection between miR-101 and new materials is still mysterious and more attention should be paid for further research.

In conclusion, miR-101 greatly contributed to the incidence and development of a variety of neoplasms. Kinds of physiological and pathological cell processes were discovered to be under the regulation of miR-101, such as cell proliferation, apoptosis, angiogenesis, drug resistance, invasion, metastasis and so on. In addition, miR-101 was also detected to possess the potential to be a biomarker for diverse neoplasms. However, the connection between miR-101 and its target genes was complex and there were still a lot of mysterious mechanisms remaining unknown, which urged us for further exploration before the research findings turning to clinical application. We suggest that miR-101 might provide a novel, secure and effective insight in the future molecular targeting treatment and could bring dawn for people suffering from cancers.

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Disclosure of conflict of interest

None.

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