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REVIEW

The Emerging Roles of miR-125b in Cancers

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Abstract: MicroRNAs (miRNAs) are endogenous, noncoding, single-stranded RNA molecules of 22 nucleotides in length. MiRNAs have both tumor-suppressive properties and oncogenic properties that can control critical processes in tumors. Mature miR-125b originates from miR-125b-1 and miR-125b-2 and leads to the degradation of target mRNAs or the inhibition of translation through binding to the 3′ untranslated regions (3′-UTR) of target mRNAs. Importantly, miR-125b is involved in regulating NF-κB, p53, PI3K/Akt/mTOR, ErbB2, Wnt, and another signaling pathways, thereby controlling cell proliferation, differentiation, metabolism, apoptosis, drug resistance and tumor immunity. This review aims to summarize the recent literature on the role of miR-125b in the regulation of tumorigenesis and to explore its potential clinical application in the diagnosis, prognosis and clinical treatment of tumors.

Keywords: miR-125b, cancer, biomarker, pathway

Introduction

MicroRNAs (miRNAs) are endogenous, noncoding, single-stranded RNA molecules of 22 nucleotides in length that regulate approximately 30% of human genes.[1] MicroRNAs are involved in the regulation of multiple cellular functions, including apoptosis,[2] metabolism,[3] proliferation and differentiation. In addition, miRNAs play a critical role in the communication of tumor microenvironmental cells, influence the tumor microenvironment, and are involved in tumor-related inflammation, hypoxia and immunity.[4–7] Meanwhile, miRNAs exist in various biological fluids as circulating miRNAs, and changes in circulating miRNAs are indicative of pathophysiological conditions in cancers. Thus, circulating miRNAs can be effective biomarkers in cancer diagnosis.[8] Interestingly, miRNAs have both tumor-suppressive properties and oncogenic properties that can control critical components of signaling pathways. Dysregulation of miRNAs can lead to the generation of surrogate and compensatory signals (parallel or downstream pathways to drug-blocked pathways), thereby maintaining drug resistance.[9]

Mature miR-125b originates from miR-125b-1 and miR-125b-2. MiR-125b-1 is derived from a long noncoding RNA (lncRNA)–MIR100HG (miR-100/let-7a-2/miR-125b-1, chromosome 11), and miR-125b-2 is derived from a miRNA cluster (miR-99a/let-7c/miR-125b-2, chromosome 21). Recently, miR-125b has emerged as an important regulator in human cancers, and it is incorporated into the RNA-induced silencing complex (RISC), which leads to the degradation of target mRNAs or the inhibition of translation through binding to the 3′ untranslated regions (3′-UTRs) of target mRNAs.[10] In addition to targeting mRNAs encoding proteins, miR-125b can also target lncRNAs such as MALAT1 and inhibit its expression. Moreover, miR-125b can produce a synergistic effect when combined with miRNAs from the same miRNA cluster. It has been reported that miR-125b and miR-100 coregulate the resistance of cetuximab or vincristine.[11,12]

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Dysregulation of miR-125b in Cancers

The dysregulation of miR-125b is shown in Table 1. Upregulation of miR-125b as an oncogene has been reported in various cancers: nasopharyngeal carcinoma (NPC),[13,14] retinoblastoma (RB),[15] glioblastoma (GBM),[16–20] poorly differentiated non-small-cell lung cancer (NSCLC),[21] acute lymphoblastic leukemia (ALL),[22] acute myeloid leukemia (AML),[23] and gastric cancer.[24–26] On the other hand, miR-125b, as a tumor suppressor, is downregulated in the following cancers: non-small-cell lung cancer (NSCLC),[27] esophageal squamous cell carcinoma (ESCC),[28,29] anaplastic thyroid cancer,[30] bladder cancer,[31–35] hepatocellular carcinoma (HCC),[36–39] melanoma,[40,41] ovarian cancer,[42–44] osteosarcoma,[45–47] chondrosarcoma,[48] breast cancer,[49–55] gallbladder cancer (GBC),[56] endometrioid endometrial cancer (EEC),[57] colorectal cancer (CRC),[58,59] multiple myeloma (MM),[60] and Ewing's sarcoma (ES).[61]

The function of miR-125b diverges in different cancers depending on the different molecular contexts and the tumor microenvironment. At present, many genes have been

Table 1 The Target Genes of miR-125b in Different Cancers

Cancer Type	Expression in Tumor	Sample	Target Gene	References
Nasopharyngeal carcinoma (NPC)	Upregulation	Tissues	A20	13
	Downregulation in DDP-resistant cell	Cell lines	Bcl2	14
Retinoblastoma (RB)	Upregulation	Cell lines	DRAM2	15
Glioblastoma (GBM)	Upregulation	Tissues, cell lines	p53, P38mapk, NKIRAS2, PIAS3, FZD6	16–19
	Upregulation in TMZ-resistant cell	Cell lines	Bak1	20
Non-small cell lung cancer (NSCLC)	Upregulation in poorly differentiated NSCLC	Cell lines	TP53INP1	21
	Downregulation in tumor	Cell lines	KLC2	27
Acute lymphoblastic leukemia (ALL)	Upregulation	Leukemic cells	A20, Bcl2	22,99
Acute myeloid leukemia (AML)	Upregulation	Leukemic cells	CBFβ	23
Gastric cancer	Upregulation	Tissues	STARD13, NEU1, PPP1CA	24–26
Esophageal squamous cell carcinoma (ESCC)	Downregulation	Tissues	HMGA2, STAT3	28,29
Anaplastic thyroid cancer cell (ATC)	Downregulation	Tissues	PIK3CD	30
Bladder cancer	Downregulation	Tissues	Trop-2, SphK1, E2F3, SIRT7, MALAT1, MMP13	31–35
Hepatocellular carcinoma (HCC)	Downregulation	Tissues	Angpt2, SMAD2, SMAD4, Mcl-1, Bcl-w, IL-6R, EIF5A2	36–39
Melanoma	Downregulation	Tissues	ITGA9, NEDD9, c-jun	40,41
Ovarian Cancer	Downregulation	Tissues	SET, EIF4EBP1, BCL3	42–44
Osteosarcoma	Downregulation	Tissues	Bcl2, STAT3, HK2	45–47
Chondrosarcoma	Downregulation	Tissues	ErbB2	48
Breast cancer	Downregulation	Tissues	TSTA3, MAP2K7, STARD13, ETS1, ENPEP, CK2-α, CCNJ, MEGF9, EPO, EPOR, MUC1	49–55
Gallbladder cancer (GBC)	Downregulation	Tissues	Bcl2	56
Endometrioid endometrial cancer (EEC)	Downregulation	Tissues	ErbB2	57
Colorectal cancer (CRC)	Downregulation	Tissues	NA	58,59
	Upregulation in cexutimab-resistant CRC	Tissues	DKK3, ZNRF3, RNF43, APC2	11
Cervical cancer (CC)	Upregulation	Cell lines	HMGA1	100
Multiple myeloma (MM)	Downregulation	Cell lines	MALAT1, STAT3	60,101
Ewing's sarcoma (ES)	Downregulation	Tissues	PIK3CD	61

confirmed as target genes of miR-125b, covering a variety of biological signaling pathways and affecting the formation of many malignant phenotypes such as proliferation, differentiation, migration, apoptosis, cell cycle and drug resistance in different cancers [Figure 1]. In tumors that upregulate miR-125b, tumorigenesis is promoted by inhibiting proapoptotic genes and genes that inhibit proliferation and invasion. Conversely, in tumors where miRNA-125b is downregulated, tumorigenesis is promoted by reducing the inhibition of genes that promote proliferation, differentiation, and apoptosis inhibition.

Upregulation of miR-125b in Cancer

In previous studies of many cancers, miR-125b participated in tumor proliferation and cell cycle regulation as a suppressor mechanism. In NPC and ALL, miR-125b was shown to directly suppress A20, which inhibits proliferation and induces apoptosis by negatively regulating the NF-κB signaling pathway.[13,22,62] The study showed that downregulation of CBFβ by miR-125b prevents granulocyte differentiation and maturation, indicating that miR-125b promotes hematopoietic malignancies through the CDX2/miR-125b/CBFβ pathway.[23] Overexpression of miR-125b in gastric cancer results in downregulation of PPP1CA and then promotes phosphorylation of Rb protein and activation of E2F, a transcription factor, to promote gene transcription. This indicates that miR-125b participates in the pathogenesis of gastric cancer through the PPP1CA-Rb-E2F signaling pathway.[26] Upregulation of miR-125b decreased the level of FZD6 in GBM. Unexpectedly, in this mechanism, FZD6 acted as a negative regulator to inhibit the Wnt pathway while promoting STAT3 and NF-kB signaling, and miR-125b was shown to be an important regulator of GBM tumorigenesis. NEU1 and STARD13 are direct targets of miR-125b. NEU1 acts as a tumor suppressor gene to regulate downstream molecules by encoding NEU1 sialidase. One of the functions of NEU1 is sialylation, which can reduce protein phosphorylation and attenuate FAK, ERK1/2, and MMP17.[55] Our data suggest that autophagy is reduced in triple-negative breast cancer (TNBC), likely leading to the deregulation of the EGFR-MUC1-NEU1 complex and its associated cellular pathways. Another function of NEU1 is to form the EGFR-MUC1-NEU1 complex that controls autophagy and associated cellular pathways.[63] Zheng et al indicated that the mRNA of StarD13 as a ceRNA regulated the expression of TP53INP1, thereby regulating the migration and invasion of breast cancer cells.[64]

MiR-125b can inhibit apoptosis to promote tumorigenesis. In RB and GMB, miR is significantly upregulated, and then it apparently suppresses DRAM2, p53, and P38.[15,16,65] DRAM2 is a crucial component of the p53 signaling pathway, and the induction of autophagy by DRAM is a potential mechanism contributing to cell death. DRAM2 encodes a transmembrane lysosomal protein that is thought to play a key role in

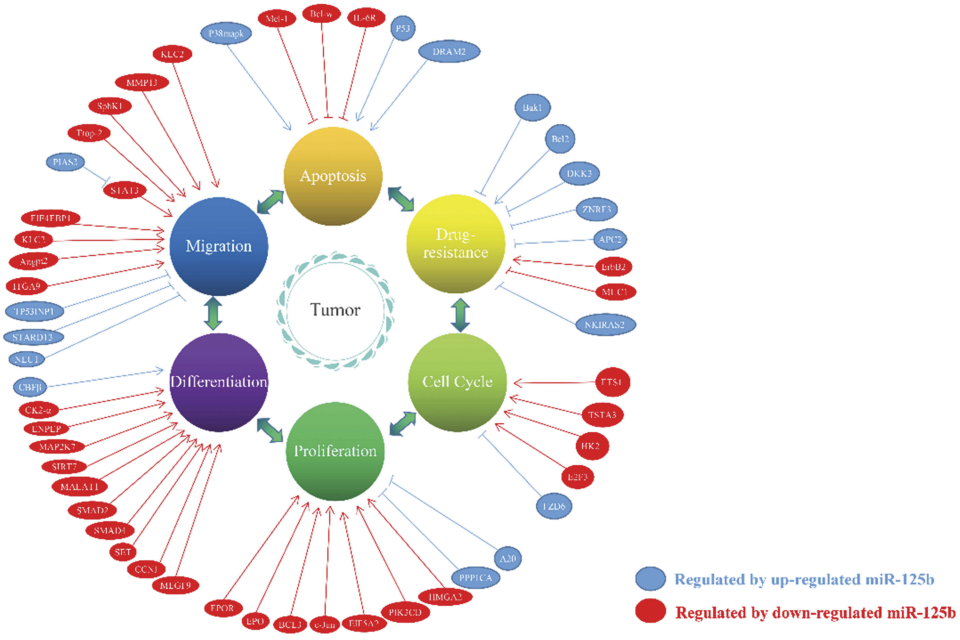

Figure 1 The role of miR-125b in the development of cancer.

autophagy initiation, and the autophagy induced by DRAM2 is an underlying mechanism of p53-mediated cell death.[15,65] Both p53 and p38MAPK are direct target genes of miR-125b, and p53 is known to activate the apoptotic pathway, while p38MAPK can induce mitochondrial apoptosis.[16,66] Zheng et al reported that miR-125b expression was significantly higher in poorly differentiated NSCLC cells with high metastatic potential and that it reduced the level of TP53INP1. TP53INP1 is considered a tumor suppressor gene with proapoptotic and antimetastatic functions.[64]

Downregulation of miR-125b in Cancer

In terms of the downregulation of miR-125b in various tumors, the low expression of miR-125b promotes cell proliferation, migration and invasion by controlling HMGA2 and STAT3 in ESCC.[28,29] HMGA2 alters the structure of DNA and regulates gene transcription. In both Ewing's sarcoma and ATC, miR-125b regulates the PI3K/Akt/mTOR pathway by regulating PIK3CD. MiR-125b in bladder cancer upregulates Trop-2, SphK1, E2F3, SIRT7, MALAT1, and MMP13 to promote cancer tumorigenesis and metastasis.[67,68]

In HCC, miR-125b regulates many genes involved in various mechanisms. The downregulation of miR-125b causes the overexpression of EIF5A2, which is known to be associated with proliferation and poor prognosis in patients with CRC and NSCLC.[39,69–71] MiR-100 reduces the protein level of Angpt2, which is an essential molecule for angiogenesis, by blocking the mTOR/p70S6K signaling pathway. It has been demonstrated that miR-125b can cause excessive angiogenesis by affecting the proliferation of endothelial cells.[36] MiR-125b downregulation facilitates the epithelial-mesenchymal transition (EMT) of HCC cells by targeting SMAD2 and SMAD4, which are both signal transducers of the TGFβ signaling pathway.[37,72] Moreover, miR-125b is downregulated in macrophage exosomes of HCC and can target CD90 to mediate the stem cells of HCC.[73] EMT can increase tumor stem cell-like properties, such as migratory and invasive capabilities and chemoresistance. Furthermore, the levels of Mcl-1, Bcl-xL and Bcl-w, the antiapoptotic members of the Bcl-2 family, are increased via miR-125b. The Bcl-2 family plays a crucial role in suppressing apoptosis largely through binding to proapoptotic proteins (Bax and Bak1).[38,74]

ITGA9, NEDD9, and c-jun are controlled by miR-125b and contributed to melanoma development. One study showed that ITGA9 promotes EMT by promoting the dissociation of E-cadherin and beta-catenin.[75] The NEDD9/Src/FAK signaling complex plays an important role in mediating the movement of growth factors and converting mechanical forces into biochemical signals. These signals promote cancer metastasis by regulating migration, invasion, and infiltration.[76] Interestingly, miR-125b can bind within the coding sequence (CDS) of c-Jun mRNA and thus regulate c-Jun protein expression.[41] In ovarian cancer, SET, EIF4EBP1, and BCL3 are the targets of miR-125b.[43] Zhao et al indicated that BCL3 serves as an oncogene and is regulated by its downstream target gene, STAT3.[77] SET proteins, also known as TAF-1β, I2PP2A and INHAT, belong to the multifunctional protein family which is involved in apoptosis, transcription, nucleosome assembly and histone binding.[42]

The decrease in miR-125b expression in breast cancer may be due to the enhancement of DNA methylation in the promoter region.[52] Downregulation of miR-125b induces cell survival by inducing the expression of erythropoietin (EPO) and its receptor EPOR through the ERBB2/Her2 pathway.[78] In addition, miR-125b downregulates the expression of the oncogene ETS1 involved in cell cycle transformation and proliferation. Further, ENPEP is thought to be an important and highly specific enzyme that metabolizes and inactivates bioactive peptides such as angiotensin II (AngII) in the renin-angiotensin system. ENPEP is expressed in cervical neoplasm lesions and is upregulated as lesions develop from invasive intraepithelial neoplasias to invasive squamous cell carcinomas.[79] In addition, MAP2K7 and TSTA3 are upregulated by miR-125b. MiR-125b-mediated EMT may occur through the MAP2K7–JNK cascade in breast cancer. TSTA3 is an NADP(H)-binding protein that is involved in electron carrier activity, GDP-l-fucose synthase activity, glycoprotein biosynthesis, cell-cell adhesion, and biopolymer glycosylation.[49] Wang et al reanalyzed GEO data and speculated that the TSTA3-related network regulates cell apoptosis, cyclin-dependent protein kinase activity, cell migration, insulin secretion, transcription, and cell proliferation in HCC.[80] MiR-125b is also downregulated in EECs, and Shang et al demonstrated that miR-125b inhibits EEC cell invasion by downregulating ErbB2. Several studies have indicated ErbB2 as the target of miR-125b that mediates tumor development and invasion.[57,81] It is worth considering that patients with overexpression of ERBB2 have an important genotype in breast cancer. It has been reported that miR-125b is involved in drug resistance in these patients.[48] However, the significance of miR-125b in the diagnosis and treatment of breast cancer patients deserves further study.

MiR-125b Controls Drug Resistance in Cancer

As in the mechanism of tumorigenesis, miR-125b also has two sides in the mechanism of drug resistance. Multidrug resistance (MDR) is a major clinical obstacle in the successful treatment of patients with NPC. In a study by Yuan et al a significant reduction in miR-125b expression levels was observed in cisplatin (DDP)-resistant cells compared with parental NPC cells. The results of the study suggest that miR-125b may regulate the sensitivity of NPC cells to DDP by modulating the expression levels of the antiapoptotic factor BCL-2. Additionally, Tang et al found that miR-125b acts as a tumor suppressor to inhibit glucose metabolism by targeting ErbB2 in chondrosarcoma, thereby inhibiting glucose metabolism. The results showed that miR-125b is downregulated in chondrosarcoma patient tissues and doxorubicin-resistant cells compared to normal tissues. MiR-125 overexpression enhances doxorubicin sensitivity in parental and doxorubicin-resistant cells by directly targeting ErbB2-mediated upregulation of glycolysis.[48]

In contrast, miR-125b was found to be overexpressed in glioblastoma stem cells (GSCs) compared to normal brain tissues and GBM tissues. The repression of miR-125b before temozolomide (TMZ) treatment in GSCs resulted in increased inhibition of cell proliferation compared to that with TMZ treatment alone, and a study indicated that miR-125b enhances TMZ resistance by targeting Bak1.[20] Similarly, Haemmig et al showed that GBM cells overexpressing miR-125b exhibit increased NF-κB activity and antiapoptotic activity and upregulation of cell cycle genes by targeting TNFAIP3 and NKIRAS2, both of which contribute to NF-κB activity. This is significantly related to the resistance of GBM cells to TNFα- and TMZ-induced apoptosis.[17] Furthermore, Shi et al showed that a miR-125b inhibitor enhanced the anti-invasion activity of TMZ in GSCs by targeting PIAS3, which contributed to reduced STAT3 transcriptional activity and subsequently decreased the expression of MMP-2 and MMP-9.[18] Remarkably, miR-125b overexpression was clearly associated with shorter overall survival of patients treated with TMZ. The evidence suggests that miR-125b may be a predictor of TMZ response in GBM patients.

Recently, studies have shown that miR-125b is associated with resistance to ERBB-targeted therapies by activating downstream signal transducers or parallel pathways.[9,24,82] In research on cetuximab resistance in CRC, miR-100 and miR-125b derived from lncRNA MIR100HG were found to be overexpressed in cetuximab-resistant cells. MiR-100 and miR-125b coordinately repressed five Wnt/β-catenin negative regulators, resulting in increased Wnt signaling and cetuximab resistance. In this mechanism, miR-125b inhibited DKK3, ZNRF3, RNF43, and APC2. LncRNA TINCR has been reported to sponge miR-125b and release HER-2, resulting in trastuzumab resistance in breast cancer.[83]

The Role of miR-125b in Tumor Immunity

MiR-125b also plays an important role in tumor immunity. Studies have shown that miR-125b is involved in the regulation of immune cells such as T cells, B cells, DC cells and macrophages.[84–87] MiR-125b regulates T cell proliferation and activation, is highly expressed in naive CD4 T cells and can inhibit the T cell immune response, while miR-125b can promote T cell apoptosis.[84,88] Overexpression of miR-125b in the B cells of tumor patients prevents the release of immature B cells from the bone marrow into the blood. Overexpression of miR-125b also leads to defects in the development of pre-B cells, and miR-125b inhibits differentiation of primary B cells into plasma cells.[89]

Macrophages can be polarized into two different types of macrophages (M1 and M2). The M1 type promotes the inflammatory response, while the M2 type inhibits the inflammatory response. MiR-125b regulates the polarization of macrophages and is highly expressed in M1 macrophages and promotes tumor immune responses by targeting IRF4.[85] In an ovarian cancer study, nanoparticles coated with miR-125b repolarized tumor-associated macrophages (TAMs) in the peritoneal cavity to M1 macrophages. Nanoparticles combined with paclitaxel enhanced anti-ovarian cancer efficacy compared to that with pacitaxel alone.[90] Nanoparticles encapsulating miR-125b also successfully reprogrammed TAMs to the M1 phenotype in non-small-cell lung cancer (NSCLC), which may play an important role in immunotherapy.[91]

MiR-125b in Cancer Diagnosis and Prognosis

MiRNAs in solid tissues or circulating miRNAs can be used as a basis for the diagnosis of tumors and prognosis. Currently available tumor markers for HCC are of little clinical relevance. Zuo et al suggested that a panel of serum miRNAs (including miR-125b) combined with

alpha-fetoprotein (AFP) had a higher sensitivity (82%) and specificity (75%) for the diagnosis of early-stage HCC compared to that of a single marker.[92] In 150 patients, 90 patients with HCC and 60 patients without cancer, serum expression of four miRNAs was assessed. The results indicated that the combination of miR-125b, miR-223, miR-27a, and miR-26a could serve as a valuable biomarker with an AUC of 0.874 in distinguishing the HCC group from the noncancer group in AFP-negative subjects. Moreover, the diagnostic accuracy of miR-125b in cancer diagnosis was assessed by a meta-analysis, which included 695 patients with various kinds of cancers and 370 healthy controls from 8 qualified studies. In this meta-analysis, the sensitivity and specificity of miR-125b in cancer diagnosis were 82% (95% CI, 76–87%) and 77% (95% CI, 70–84%), respectively. A high AUC of 0.84 reflected the high overall level of diagnostic accuracy.[93]

Studies have suggested that the high expression of miR-125b could be an independent and poor prognostic factor in patients with HER2-positive gastric cancer. Wu et al detected the expression of miR-125b in fresh tissues of 50 gastric cancer patients and 6 gastric cancer cell lines. MiR-125b was detected by in situ hybridization, and its clinicopathological diagnosis and clinical parameters were studied. The results demonstrated that the 5-year survival rate of patients with gastric cancer and with high levels of miR-125b expression was significantly lower than that of patients with low levels of expression in stages I, II, and III. In addition, this high expression level of miR-125b in gastric cancer tissues was associated with lymph node and distant metastases.[26] Sui et al collected a total of 132 samples of gastric cancer and 38 noncancerous samples, and the analyzed results showed that the OS rate of patients with HER2-positive gastric cancer and higher miR-125b expression was significantly reduced compared to those with lower miR-125b expression (P=0.034).

Several studies have indicated miR-125b as a biomarker to predict prognosis in breast cancer.[49,94–96] Sun et al performed a study to analyze miR-125b in breast cancer, and they followed up with the patients who provided 175 pairs of fresh breast cancer and normal control samples for 80 months. The results showed that TSTA3 was highly regulated by miR-125b, highly expressed in breast cancer tissues and tumor cells, and closely related to TNM stage. TSTA3-overexpressing patients had low survival rates.[49] In 2019, a study showed that miR-125b is upregulated in the blood of untreated breast cancer patients. We were able to differentiate between breast cancer patients and normal women by the amount of miR-125b in plasma (AUC = 0.85).[97] In addition, the combination of miR-125b and CA153 provided better diagnostic accuracy (89% vs 70%) than CA153 alone. In the prognosis of breast cancer, analysis in the combined TCGA and METABRIC databases showed that patients with high miR-125b had a better prognosis (HR = 0.72, P = 0.0015).[97]

Moreover, in small intestinal neuroendocrine tumors (SBNETs), four serum miRNAs (miR-125b, −362, −425 and −500a) had high diagnostic value (AUC=0.951) in SBNETs. The effectiveness after surgical resection of SBNET was evaluated, and the results showed that miR-125b-5p returns to normal levels in patients without disease and remains upregulated in patients with residual tumors one month after surgery.[98]

Signaling Pathways Regulated by miR-125b

As mentioned above, miR-125b may play different roles in different cancers, and miR-125b's anticancer or procancer function may also be regulated by different signaling pathways. In terms of cancer promotion, miR-125b can target DRAM2 and p53 and then inhibit the P53 tumor suppressor signaling pathway.[16,66] In addition, miR-125b can target A20 to activate the NF-κB signaling pathway and target FZD6 to activate STAT3 and the Wnt signaling pathway.[13,19,22,62] As tumor suppressors, miR-125b can promote the PI3K/Akt, TGFβ, and ERBB2/Her2 signaling.[67,68,72,78]

Conclusions and Future Directions

In conclusion, emerging evidence further demonstrates that miR-125b dysregulation is a general feature in many cancers and plays an important role in tumorigenesis and clinical therapy. MiR-125b may serve as a potent tumor promoter or inhibitor in different tumors, depending on the different molecular contexts. MiR-125b is involved in various aspects of tumor cell proliferation, differentiation, invasion, migration, drug resistance, and tumor immunity. Importantly, miR-125b can serve as a diagnostic and prognostic marker for multiple tumors. However, the roles of miR-125b have not been fully elucidated in different tumor subtypes, and defining its potential molecular mechanisms in the pathological processes of tumors will be helpful to provide an opportunity for possible intervention in cancer therapy by targeting either the regulatory pathways or the miRNAs themselves. The current problem encountered with miR-125b is that it has dual functions in

tumor regulation. We need to adopt different analysis and interference strategies for miR-125b in different tumors. However, at present, miR-125b as a therapeutic target needs to overcome many obstacles, such as the stability of the drug, the efficiency of the delivery system, and the off-target effect of the drug.

In the future, miR-125b can be studied more to determine the interaction between miR-125b and other functions in immunotherapy or as a biomarker for diagnosis and therapy and to determine the more precise regulation of miR-125b in different cancers. Therefore, it is proposed that miR-125b could be regarded as a new therapeutic target in the treatment of cancer.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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