Review Article
MiR-145: a potential biomarker of cancer migration and invasion

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Abstract: MircoRNAs (miRNAs) are a diverse family of highly-conserved small non-coding RNAs, which range from approximately 18 to 25 nucleotides in size. They regulate gene expression transcriptionally or post-transcriptionally via binding to the 3'-untranslated region (3'-UTR) of target message RNAs (mRNAs). MiRNAs have emerged as molecular regulators that participate in physiological and pathological processes of diverse malignancies. Among them, miRNA-145 (miR-145) played a profound role in tumorigenesis and progression of various neoplasms. In this review, we summarized the recent findings regarding miR-145, to elucidate its functional roles in cell invasion and migration of diverse human malignancies, and considered it a potential biomarker for cancer diagnosis, screening, and prognosis.

Introduction

Global cancer statistics alarm that cancers rank as the leading cause of death, and cancer-caused mortality is soaring globally. Treatment and regular surveillance contribute to relieving the remarkably rising economic burden of cancers [1]. Cell invasion and migration are the major characteristics of metastatic tumors, which account for high mortality rate and poor prognosis of cancers. Despite the advances in surgical resection, radiotherapy and chemotherapy, it is urgent to search and develop novel and alternative therapeutic approaches of cancers. In this regard, mircoRNAs (miRNAs) have been verified to stress their roles as metastasis activators or suppressors, which may serve as diagnostic biomarkers and therapeutic targets [2].

MiRNAs, a novel class of small noncoding RNAs, regulate gene expression at the transcriptional or post-transcriptional level through binding to the 3' untranslated regions (3'-UTR) of target message RNAs (mRNAs) [3]. A variety of miRNAs have multiple target genes involved in cell growth and signaling pathways, dysregulation of which may participate in many fundamental cellular processes of various cancers, including tumorigenesis, proliferation, apoptosis, metastasis and drug-resistance. Among them, miRNA-145 (miR-145) appears to be a vital factor for tumor aggressiveness and prognosis. MiR-145, located in a fragile region of chromosome 5q, was first reported in mouse heart muscle, and later verified in humans [4-6]. It was remarkably expressed in germ lines and mesoderm-derived tissues, including ovary, uterus, prostate, testis, spleen and heart [7]. Based on available researches, miR-145 down-regulated in a wide range of cancers, including colorectal cancer (CRC), non-small-cell lung cancer (NSCLC), breast cancer (BCa), osteosarcoma (OS), cervical cancer, prostate cancer (PCa), gastric cancer (GC), ovarian cancer (OC), glioma (GBM) and bladder cancer. In this review, we summarized the roles of miR-145 in invasion and migration of various tumors, and explored its potential role as a candidate biomarker for cancer diagnosis, monitoring and prognosis in humans, shedding new light on potential treatment of cancers.
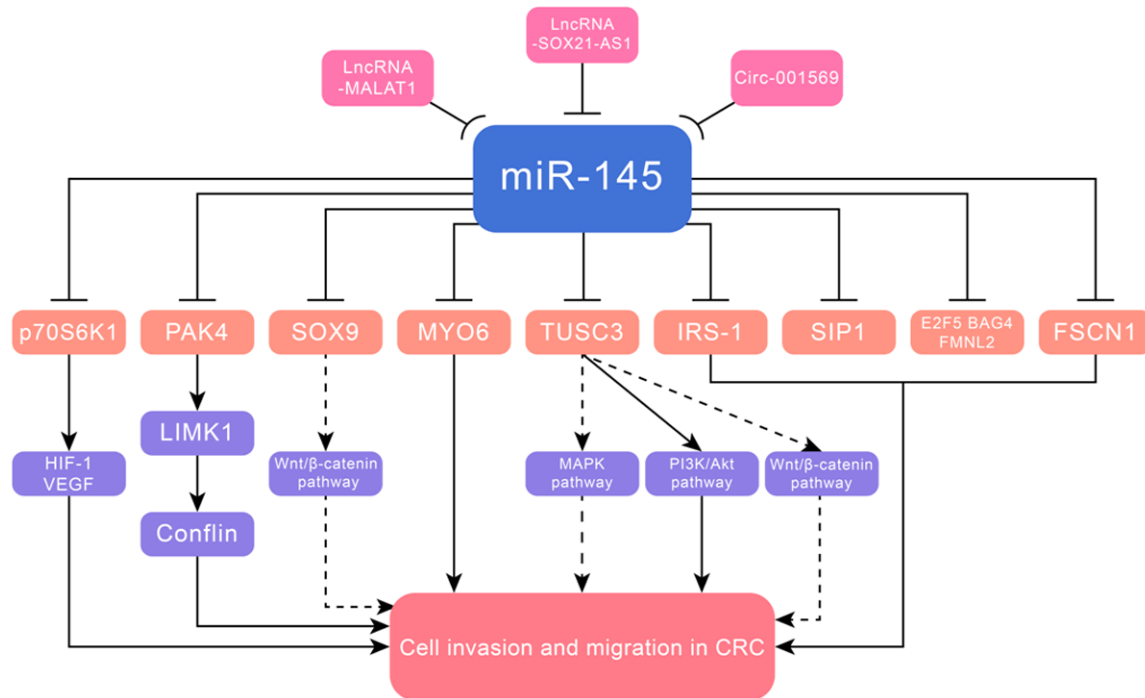
MiR-145 in tumor invasion and migration

MiR-145 in CRC

MiR-145 played an inhibitory role in CRC in that it reduced cell migration and invasion, apparently by suppressing P21-activated kinase 4 (PAK4) [8], tumor suppressor candidate 3 (TUSC3) [9], p70S6K1 [10], sex-determining region Y-box 9 (SOX9) [11], myosin VI (MYO6) [12], insulin receptor substrate-1 (IRS-1) [13], SMAD-interacting protein 1 (SIP1) [14] and fascin-1 (FSCN1) [15]. MiR-145 targeted PAK4 to suppress cell migration through inhibition of the LIMK1-conflin signaling pathway. PAK4, a subfamily of serine/threonine kinases, modulated actin cytoskeleton reorganization by phosphorylating LIMK1 [16]. Subsequently, activated PAK4 stimulated LIMK1 to phosphorylate cofilin, which acted synergistically to facilitate cell migration [17]. Besides, miR-145 was clarified to block mitogen-activated protein kinase (MAPK) pathway by targeting TUSC3. TUSC3, located on chromosome region 8p22 [18], was reported to enhance epithelial-mesenchymal transition (EMT) and cancer progression through regulating MAPK, PI3K/Akt and Wnt/β-catenin pathways in CRC [19]. However, whether miR-145 regulated the latter two pathways warranted further investigation. EMT is a critical step of tumor cell metastasis [20]. The MAPK pathway participated in gene expression and cell growth by phosphorylating specific target protein substrates. MAPKs were composed of three well-characterized subfamilies: extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinase (JNK), and p38 protein kinases [21]. MiR-145 downregulated hypoxia-inducible factor 1 (HIF-1) and vascular endothelial growth factor (VEGF) by targeting p70S6K1, both were important regulators in tumor angiogenesis. P70S6-K1, one downstream mammalian target of rapamycin (mTOR), acted as a key regulator in protein synthesis. Additionally, the mTOR/p70S6K1 is a vital signaling pathway in regulating cellular functions [10, 22-24]. LncRNA MALAT1 functioned as an endogenous RNA (ceRNA) to sponge miR-145, and inhibited malignant progression of CRC via the lncRNA MALAT1/miR-145/SOX9 axis. LncRNA MALAT1, expressed from chromosome 11q13, is a noncoding RNA of more than 8000 nt [25]. SOX9 was determined as an oncogene, which was reported to regulate metastasis by activating Wnt/β-catenin signal [26], but it was unclear whether this pathway functioned in CRC. Similarly, lncRNA SOX21-AS1/miR-145/MYO6 axis aggravated the malignant development of CRC. LncRNA SOX21-AS1 was identified as a cancer-correlated molecular in human cancers, low expression level of which was associated with advanced stage in oral squamous cell carcinoma, while its upregulation positively correlated with tumor size and advanced stage in lung adenocarcinoma [27, 28]. Of note, sponging miRNA was also a significant regulatory mechanism of circRNA functions. Circ_001569 exerted its tumor promoting function via inhibiting miR-145, and subsequently up-regulated E2F5, BAG4 and FMNL2, which were all targets of miR-145 [29] (**Figure 1** and **Table 1**).

MiR-145 in BCa

MiR-145 mediated targets directly related to cell invasion and migration in BCa were ADP-ribosylation factor 6 (ARF6) [30], fascin, junctional adhesion molecule-A (JAM-A) [31], c-Myc [32], Rho-associated protein kinase 1 (ROCK1) [33], cyclin E2 (CCNE2) [34], octamer-binding transcription factor 4 (OCT4) [35], matrix metalloproteinase 11 (MMP11), Rab GTPase family 27a (Rab27a) [36], RTKN [37] and metastasis gene mucin 1 (MUC1) [38]. LncRNA-RoR/miR-145/ARF6 pathway was demonstrated to inhibit invasion in BCa. The small GTPase ARF6, a novel target of miR-145, participated in membrane traffic or cytoskeleton organization, and regulated E-cadherin localization [39]. Similarly, the KCNQ1 opposite strand/antisense transcript 1 (KCNQ1OT1) gene, located at 11p15.5, interacted with miR-145 to modulate its target CCNE2, forming a KCNQ1OT1/miR-145/CCNE2 axis [40]. In addition, miR-145 inhibited cell invasion and migration by targeting fascin and JAM-A, which were major contributors to the cytoskeletal phenotype. The cell-cell adhesion JAM-A influenced epithelial cell morphology and migration. Knockdown of JAM-A reduced β1-integrin expression, which was implicated in BCa via effects on growth, and whether miR-145/JAM-A/β1-integrin functioned in BCa required further exploration [41, 42]. P53 indirectly inhibited the oncogene c-Myc through directly binding the promoter of miR-145 at the p53 response element [32]. Moreover, eIF4E and CDK4 were direct target genes of c-Myc [43, 44]. The regulation mechanisms of miR-145 through DNA methylation and p53 gene mutation were first reported in prostate cancer [45].

Figure 1. MiR-145 suppressed cell invasion and metastasis in CRC via targeting PAK4, TUSC3, p70S6K1, SOX9, MYO6, IRS-1, SIP1, FSCN1, E2F5, BAG4 and FMNL2.

MiR-145 inhibited growth and migration via targeting ROCK1, a serine/threonine protein kinase, which was a critical regulator of actin cytoskeleton reorganization [46]. MUC1, a member of extensively O-glycosylated proteins, created a physical barrier that protected epithelia from damage [47]. MiR-145/MUC1 also exerted its tumor inhibitory function in NSCLC, and the exact mechanism will be elucidated in the next segment (**Figure 2** and **Table 1**).

MiR-145 in NSCLC

MiR-145 inhibited cell invasion and migration in NSCLC by targeting MUC1 [48], NEDD9 [49], forkhead box transcription factor M1 (FOXM1) [50] and metadherin (MTDH) [51]. MiR-145 was downregulated in NSCLC, due to its methylation, correlated with a more aggressive tumor phenotype via targeting MUC1. Abnormal promoter DNA hypermethylation, a vital epigenetic signature, was associated with transcriptional repression of various miRNAs, resulting in signaling activation that could enhance invasion and migration [52]. ERβ could promote NSCLC vasculogenic mimicry formation and cell invasion by modulating ERβ/MALAT1/miR-145/ NEDD9 signaling. Moreover, ERβ upregulated expression of lncRNA-MALAT1 via binding to

the estrogen response elements, which were located on the promoter of lncRNA-MALAT1. Consequently, it inhibited miR-145 and increased NEDD9 as miR-145 directly targeted NE-DD9. LINC00339 acted as a ceRNA to sponge miR-145, and inhibited malignant progression of NSCLC cells via LINC00339/miR-145/ FOXM1 axis. FOXM1, a transcription factor from the FOX family, was a vital component of the KRAS/ERK pathway in respiratory epithelial cells [53]. LncRNA small nucleolar RNA host gene 1 (SNHG1) modulated MTDH by acting as a miR-145 sponge. MTDH, also named astrocyte elevated gene-1 (AEG-1), was identified as an oncogene that controlled growth and aggressiveness of cancers [54]. A close association of MTDH with PI3K/AKT pathway was unveiled in numerous studies, however, it warranted further research to identify whether miR-145 affected migration and invasion of NSCLC cells via regulating this pathway [55] (**Figure 3** and **Table 1**).

MiR-145 in GBM

MiR-145 was reported to play a tumor-suppressive role in GBM, and its several gene targets were identified, including A disintegrin and metalloproteinase 17 (ADAM17) and EGFR [56],

Table 1. Target genes of miR-145 in cancer invasion and metastasis

MiR-145	Disease	Target genes	Reference
Downregulated	CRC	PAK4	[8]
		TUSC3	[9]
		p70S6K1	[10]
		SOX9	[11]
		MYO6	[12]
		IRS-1	[13]
		SIP1	[14]
		FSCN1	[15]
		E2F5, BAG4 and FMNL2	[29]
	BCa	ARF6	[30]
		fascin and JAM-A	[31]
		c-Myc	[32]
		ROCK1	[33]
		CCNE2	[34]
		OCT4	[35]
		MMP11 and Rab27a	[36]
		RTKN	[37]
		MUC1	[38]
		FSCN1	[84]
	NSCLC	MUC1	[48]
		NEDD9	[49]
		FOXM1	[50]
		MTDH (AEG-1)	[51]
		FSCN1	[85, 86]
	GBM	ADAM17 and EGFR	[56]
		ROCK1	[57]
		ABCG2	[58]
		CTGF	[59]
		SOX9 and ADD3	[60]
	OC	MTDH	[68]
		RASA1	[69]
		DNMT3A and HK2	[70]
		HMGA2	[71]
	Bladder cancer	PAK1	[78]
		ZEB1/2 and FSCN1	[79]
		KLF4	[88]
		CDK6	[91]
		Sp1	[92]
	PCa	FSCN1	[87]
		SWAP70	[93]
		HEF1 (NEDD9 or Cas-L)	[94]
	GC	FSCN1	[82]
		Ets1	[101]
		SOX9	[104]
		CTNND1	[105]
		N-cadherin and ZEB2	[106]
	Cervical cancer	SIP1	[107]
		MYPT1	[110]

ROCK1 [57], ABCG2 [58], connective tissue growth factor (CTGF) [59], SOX9 and adducin 3 (ADD3) [60]. ADAM17 originally validated as the protease of the tumor necrosis factor-α (TNF-α) [61]. The miR-145/ADAM17 axis also played a role in hepatocellular carcinoma (HCC) [62] and renal cell carcinoma [63]. Besides, LncUCA1/miR-145/ADAM17 was shown to activate EMT and take part in the metastasis of nasopharyngeal carcinoma [64]. MiR-145 significantly inhibited cell invasion at least partially via downregulation of the RhoA/ROCK1 pathway. ABCG2 was an ATP-binding cassette transporter protein, which correlated with the phenotype of cancer stem cells [65]. MiR-145 targeted CTGF, which in turn downregulated downstream SPARC and focal adhesion kinase (FAK)/pFAK, leading to suppression of cell migration. CTGF could activate the FAK and extracellular signal-regulated kinase (ERK) pathways in chondrosarcoma cells [66]. CTGF, located on chromosome 6q23.1, is a member of the CCN family and a cell-adhesion factor [67]. Besides, miR-145 modulated proliferation, adhesion, and invasion of glioblastoma cells by targeting SOX9 and ADD3. The former was presumed to downregulate expression of cell cycle progression-related genes, including c-Myc, N-Myc and cyclin D1, resulting in inhibition of cell cycle progression. The latter inhibited the transcription of genes involved in cell

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	OS	VEGF	[112]
		MMP16	[113]
		CDK6	[114]
	HCC	ADAM17	[62]
	Renal cell carcinoma	ADAM17	[63]
	ESCC	FSCN1	[80]
	LSCC	FSCN1	[83]
		MYO5A	[120]
	Pancreatic cancer	MUC13	[121]
	OSCC	c-Myc and CDK6	[122]
	Endometrial cancer	SOX11	[123]
	Melanoma	NRAS	[124]
	ICC	NUAK1 (ARK5)	[125]
	Retinoblastoma	ADAM19	[126]
	Thyroid cancer	AKT3	[130]
Upregulated	esophageal cancer	SMAD5	[131]

migration (E-cadherin, N-cadherin), contributing to inhibition of cell invasion (**Figure 4** and **Table 1**).

MiR-145 in OC

MiR-145 suppressed cell invasion and migration of OC, whose mediated targets were identified, including MTDH [68], RASA1 [69], DNA methyltransferases 3A (DNMT3A), hexokinase-2 (HK2) [70] and high-mobility group A2 (HMGA2) [71]. MiR-145 inhibited tumor growth and metastasis by targeting MTDH in high-grade serous OC, the most common and aggressive subtype of epithelial ovarian cancer. Circ-ITCH interacted with miR-145 to modulate its target RASA1, forming a circ-ITCH/miR-145/RASA1 axis. Circ-ITCH generated from several exons of itchy E3 ubiquitin protein ligase (ITCH), which was located on chromosome 20q11.22 on the plus strand [72]. RASA1, a member of the RAS-GAP family, could stimulate the GTPase activity of normal RASp21, resulting in aberrant intracellular signaling through RAF-MEK-ERK and PI3K-Akt pathways [73]. MiR-145 perturbed the Warburg effect by targeting DNMT3A and HK2, thereby inhibiting cell growth. The former was one of DNA methyltransferases that could promote the Warburg effect, and the latter was one of glycolytic enzymes controlled the Warburg effect. DNA methylation, which is controlled by DNMT, is a major epigenetic rule that controlled chromosomal stability and gene expression. Of note, DNMT3A did not interact with HK2, which was mediated by miR-145. MiR-145 overexpression correlated with DNMT3A downregulation, and DNMT3A also suppressed miR-145 through DNA methylation, suggesting the existence of a mutual negative feedback between miR-145 and DNMT3A [74, 75]. The Warburg effect described by Warburg in the 1930s, is a well-known feature in cancer-specific metabolism and its emergence is associated with tumor progression [76, 77] (**Figure 5** and **Table 1**).

MiR-145 in bladder cancer

MiR-145 inhibited bladder cancer cell invasion via targeting PAK1, which promoted EMT through phosphorylating Snail. Both miR-145 and PAK1 modulated the activity of MMP-9, which was a critical step in tumor invasion [78]. LncRNA-UCA1, acting as an inducer of EMT, enhanced bladder cancer invasion and metastasis through the miR-145-ZEB1/2-FSCN1 pathway. Additionally, lncRNA-UCA1 and miR-145 constituted a reciprocal repression regulatory loop. Both ZEB1 and ZEB2 bound the E-BOX sequence in the E-cadherin promoter, thus repressing the initiation of EMT [79]. A recent study also reported a similar mechanism, in which up-regulation of lncRNA ROR regulated FSCN1 by serving as a molecular sponge for miR-145, contributing to inhibition of cell invasion and migration in ESCC [80]. FSCN1, an actin-binding protein, is involved in the formation of cytoplasmic microfilament bundles and actin-based cell surface protrusions [81]. MiR-145/FSCN1 also played a role in gastric cancer [82], laryngeal squamous cell carcinoma (LSCC) [83], BCa [84], NSCLC [85, 86] and PCa [87]. MiR-145 targeted Kruppel-like factor 4 (KLF4), which regulated PTBP1, resulting in impairment of the Warburg effect (the PTBP1/PKMs axis) [88]. KLF4, a zinc-finger transcription factor expressed in the epithelium of various tissues, played a pivotal role in maintaining the self-renewal of embryonic stem cells [89, 90]. Circ_0058063 served as a ceRNA that absorbed miR-145 to regulate its expression in bladder cancer. It regulated cell growth and migration of bladder cancer through modulating miR-145, which was mediated by CDK6 [91]. Overexpression of miR-145 obviously
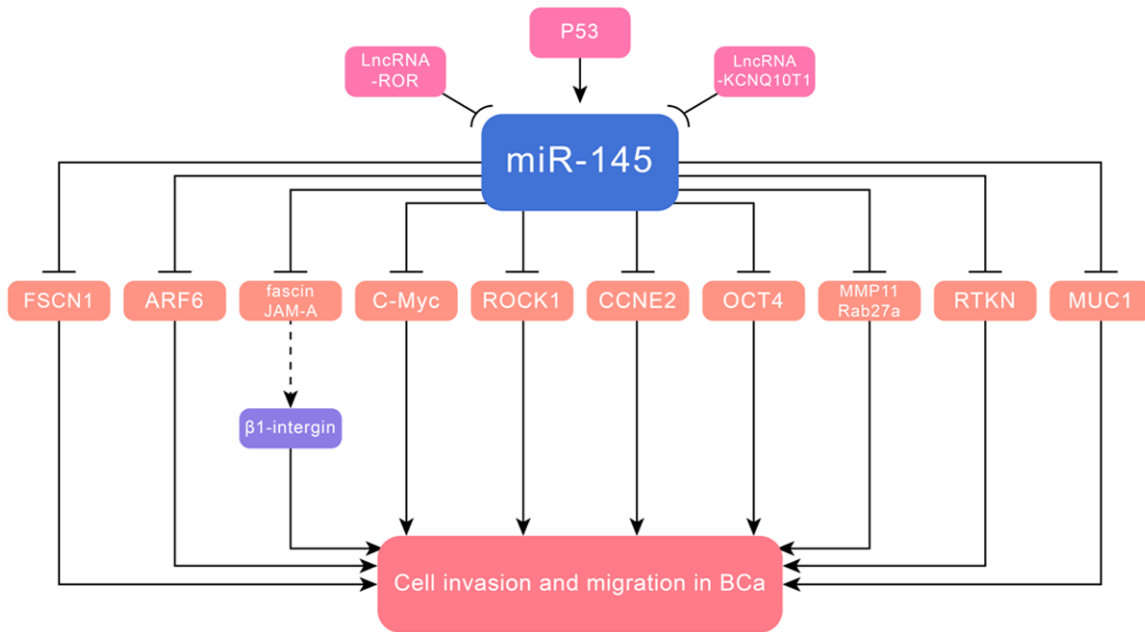
Figure 2. MiR-145 inhibited cell invasion and metastasis in BCa via targeting ARF6, fascin, JAM-A, c-Myc, ROCK1, CCNE2, OCT4, MMP11, Rab27a, RTKN, MUC1 and FSCN1.
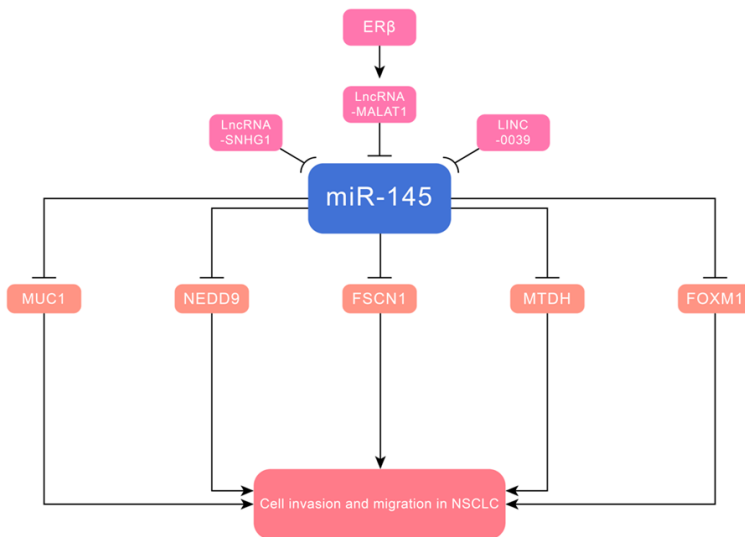
Figure 3. MiR-145 suppressed cell invasion and metastasis in NSCLC via targeting MUC1, NEDD9, FOXM1, MTDH and FSCN1.

inhibited the transcription of Slug via down-regulating the specificity protein 1 (Sp1)/nuclear factor-κB (NF-κB) signaling pathway, which was an EMT-associated transcription factor [92] (**Table 1**).
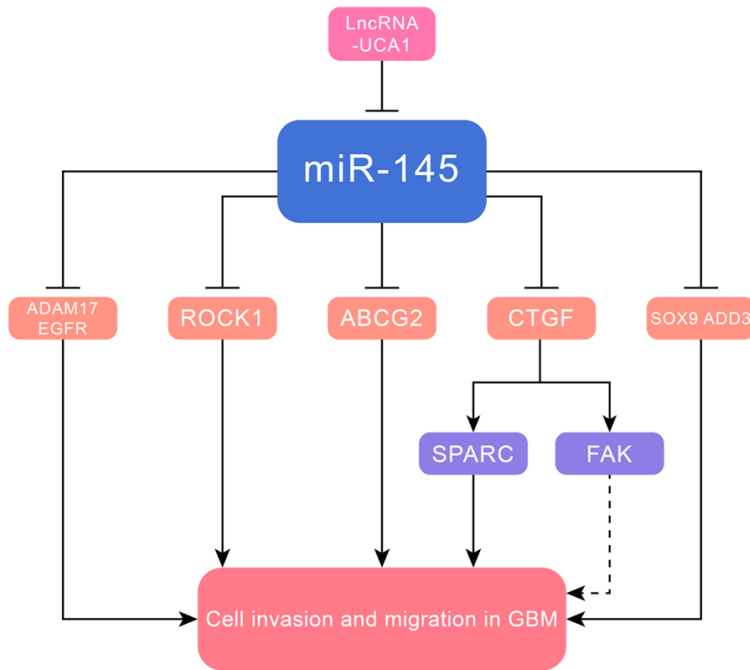
MiR-145 in PCa

MiR-145 mediated targets directly related to cell invasion and migration in PCa were FSCN1 [87], SWAP70 [93] and human enhancer of fila-

mentation 1 (HEF1) [94]. The PCAT-1/miR-145/FSCN1 regulatory axis inhibited cell invasion and migration in prostate cancer. Prostate cancer associated lncRNA transcript 1 (PCAT-1), a highly specific lncRNA, was a prostate-specific regulator located in the chromosome 8q30 gene [95, 96]. SWAP70 was a 70-kDa nuclear protein originally isolated from activated B lymphocytes, whose overexpression altered the actin organization and lamellipodial morphology [97, 98]. HEF1, also known as NEDD9 or Cas-L, is a cytoplasmic scaffolding protein that dramatically decreased E-cadherin and promoted EMT in prostate cancer, which were directly targeted by miR-145. HEF1 was also implicated to the TGF-β signaling pathway, which was important in EMT [94, 99]. However, it was unclear whether miR-145/HEF1/TGF-β functioned in PCa (**Table 1**).

MiR-145 in GC

LncRNA taurine-upregulated gene 1 (TUG1) enhanced cell invasion in GC via negatively regulating miR-145 [100]. MiR-145 repressed the

Figure 4. MiR-145 inhibited cell invasion and metastasis in GBM via targeting ADAM17, EGFR, ROCK1, ABCG2, CTGF, SOX9 and ADD3.
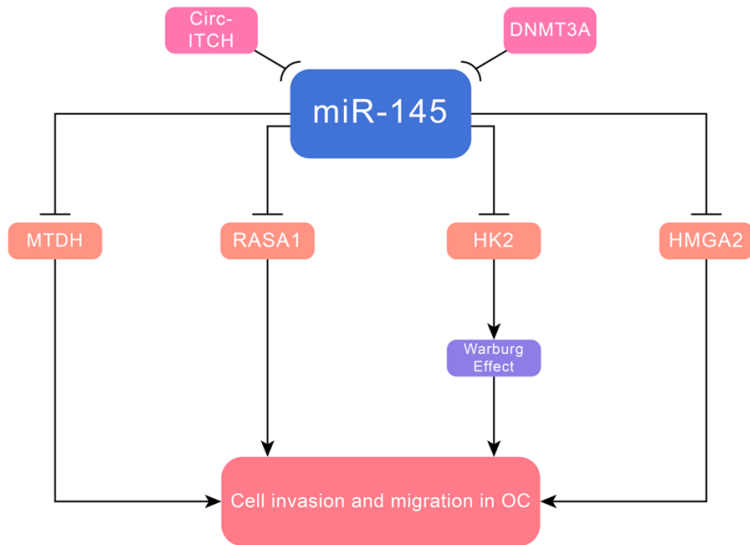
Figure 5. MiR-145 suppressed cell invasion and metastasis in OC via targeting MTDH, RASA1, DNMT3A, HK2 and HMGA2.

V-ets erythroblastosis virus E26 oncogene homolog 1 (Ets1) expression at the posttranscriptional level through directly targeting its 3'-UTR in GC cells [101]. The cellular homolog of retroviral V-ets oncogene, was a member of the Ets transcription factor family that participated in the migration, invasion, and angiogenesis of cancer cells [102, 103]. LncRNA SNHG14 was

remarkedly up-regulated in GC and could sponge miR-145, thus upregulating SOX9 and involving in PI3K/AKT/mTOR pathway [104]. Catenin-δ1 (CTNND1) was a member of the cadherin-catenin complex, and its cytoplasmic expression was inhibited by miR-145. Additionally, the miR-145 mediated decrease of N-cadherin rescued the membranous localization of E-cadherin and CTNND1, thus inhibiting cell invasion [105]. ZEB2, bound the E-BOX sequence in the E-cadherin promoter and suppressed EMT, leading to GC invasiveness [106] (**Table 1**).

MiR-145 in cervical cancer

MiR-145 inhibited migration and invasion of cervical cancer cells through targeting SIP1, a key activator of EMT. It also modulated the expression of Snail (SNAI1), up-regulation of which correlated with up-regulation of vimentin (VIM) and down-regulation of E-cadherin (CDH1), both of which were EMT-associated markers [107]. The zinc finger protein SIP1, also known as ZEB2, functioned as a transcriptional repressor of CDH1 [108]. MiR-145 expression in cervical cancer cells was wild-type p53-dependent, which enhanced the effects of p53 by suppressing the p53 inhibitors, thus inhibiting cell invasion [109]. MiR-145 negatively regulated cell invasion through targeting MYPT1 by directly binding to its 3'-UTR, thus increasing phosphorylation of myosin light chain (pMLC) and inhibiting cervical cell viability, migration and invasion. Besides, pMLC was involved in migration and invasion through modulating actomyosin contractile activity and cytoskeletal reorganization post-translationally [110]. MiR-145 could induce cancer stem cell (CSC) differentiation, whose overexpression down-regulated

core stem cell transcription factors, such as OCT4, SOX2 and KLF4, which were essential for CSC maintenance, thereby decreasing tumor invasion and colony formation in cervical cancer [111] (**Table 1**).

MiR-145 in OS

MiR-145 was reported to play a tumor-suppressive role in OS, and its several gene targets were identified so far, including VEGF [112], MMP16 [113], CDK6 [114]. VEGF, an apparently endothelial cell-specific mitogen, was a signal protein that played a significant role in tumor development and metastasis [115, 116]. MMP16 was one of the most significant MMPs in cell migration and tissue remodeling, which could directly degrade a few matrix molecules and triggered pro-MMP2 [117, 118]. MMPs were the family of zinc- and calcium-dependent endopeptidases that played a crucial role in tumor metastasis and angiogenesis [119]. Futhermore, MMPs shared a number of features with another family of ADAMs, as mentioned above (**Table 1**).

MiR-145 in other cancers

MiR-145 could inhibit cell invasion and migration by targeting MYO5A in LSCC [120], mucin 13 (MUC13) in pancreatic cancer [121], c-Myc and CDK6 in oral squamous cell carcinoma (OSCC) [122], SOX11 in endometrial cancer [123], NRAS in melanoma [124], Novel (nua) kinase family 1 (NUAK1) in intrahepatic cholangiocarcinoma (ICC) [125] and ADAM19 in retinoblastoma [126]. Among these target genes, NRAS, belonging to the RAS superfamily of GTPases, were upstream factors of MAPK (RAS/RAF/MEK/ERK) signaling pathway and played an essential role in the progression of various cancers [127]. In addition, overexpression of miR-145 suppressed growth and invasion of ICC by targeting NUAK1/Akt/FOXO1 signaling, which was also associated with downregulation of MMP. NUAK1, an AMP-activated protein kinase also known as ARK5, could be phosphorylated and activated by Akt [128, 129]. Futhermore, miR-145 inhibited growth and metastasis of thyroid cancer cells mediated by the PI3K/Akt pathway, as it directly targeted AKT3 and thus reducing Akt phosphorylation [130]. MiR-145 was a potential protective miRNA of most cancers, but intriguingly, its upregulation stimulated both migration and invasion by targeting SMAD5 in esophageal cancer, serving as a positive regulator of SMAD5 expression an independent prognostic factor for overall survival of esophageal cancer [131] (**Table 1**).

MiR-145 in potential clinical application

Accumulating evidence suggested that miR-145 played profound roles in tumor migration and invasion via targeting key transcription factors or critical pathways, and miR-145 expression was of promising clinical utility. Low miR-145 expression was associated with advanced stage disease and tumor aggressiveness, indicating it might serve as a powerful predictor of outcomes and a potential biomarker of poor prognosis in cancer patients. A number of studies reported that dysregulated miRNAs showed alterations at the early stages of tumorigenesis. Moreover, miRNAs can be circulated in body fluid, suggesting their values as non-invasive biomarkers. Circulating miRNAs were uniquely useful for stratification and of intriguing quality, which made them potential biomarkers for cancers [132]. The biomarkers found in patient biofluids (i.e. blood and urine) were likely to be more representative of the whole tumor's genomic landscape compared to tumor sampling [133, 134]. With a better understanding of miR-145 and its targets, along with its associated pathways, we could disclose a brand new mechanism in malignancy therapy. Taken together, miR-145 might serve a useful biomarker of poor prognosis, monitor cancer progression and treatment response, and optimize personalized treatment regimens.

Discussion and prospects

There was growing body of evidences on the functions of miRNAs in regulating cell migration and invasion of diverse malignancies, which attracted much attention and research interest. MiR-145 functioned via regulating its downstream molecules, either directed or indirectly through its upstream RNA molecules, such as lncRNA and circRNAs, which both served as the ceRNAs to sequester miRNAs away from target mRNAs, or lncRNAs derepressed target mRNAs expression by competitively binding to miRNAs [135]. MiRNAs were characterized as critical components of cancer biological processes, including tumorigenesis, proliferation, differentiation, apoptosis, metas-

tasis, angiogenesis, drug-resistance and EMT regulation. Notably, EMT and angiogenesis could trigger tumor invasion and metastasis. For instance, miR-145 played a profound role in angiogenesis and vascular development via targeting the friend leukemia virus integration 1 (Fli1), an early marker of hemangioblast transcription and differentiation, thus inhibiting migration [136, 137]. Tumor migration and invasion, the commonly known causes of cancer-related deaths, were involved in advanced stages of tumor progression. In this review, we summarized the recent findings regarding miR-145 and focused on its mechanistic involvement in cell migration and invasion of multiple cancers. In conclusion, miR-145 could be a good candidate for the targeted therapy of cancers, especially the invasive cancers. Above all, miRNA-based therapeutics is promising, and elevation or inhibition of miR-145 has been proposed as a possible therapeutic strategy of cancers, but further investigation is needed prior to clinical application.

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Disclosure of conflict of interest

None.

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