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Review

miR-136–5p: A key player in human cancers with diagnostic, prognostic and therapeutic implications

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ABSTRACT

MiRNAs have emerged as crucial modulators of the expression of their target genes, attracting significant attention due to their engagement in various cellular processes, like cancer onset and development. Amidst the extensive repertoire of miRNAs implicated in cancer, miR-136–5p has emerged as an emerging miRNA with diverse roles. Dysregulation of miR-136–5p has been proved in human cancers. Accumulating evidence suggests that miR-136–5p mainly functions as a tumor suppressor. These data proposed that miR-136–5p is engaged in the regulation of various cellular processes, like cell proliferation, migration, invasion, EMT, and apoptosis. In addition, miR-136–5p has demonstrated substantial potential as a prognostic and diagnostic marker in human cancers as well as an effective mediator in cancer chemotherapy. Furthermore, miR-136–5p was shown to be correlated with clinicopathological features of affected patients, proposing that it could be used for cancer staging and patient survival. Therefore, a comprehensive comprehension of the precise molecular basis governing miR-136–5p dysregulation in different cancers is vital for unraveling its therapeutic importance. Here, we have discussed the molecular basis of miR-136–5p as a potential tumor suppressor as well as its importance in cancer diagnosis, prognosis, and chemotherapy. Finally, we have discussed the challenge of using miRNAs as a therapeutic target as well as the prospect regarding the importance of miR-136–5p in human cancers.

1. Introduction

Cancer remains a formidable and worldwide health challenge [1–3], and despite considerable improvement in research and treatment, necessitating the continuous pursuit of new therapeutic strategies [4,5]. Recently, we have encountered emerging progress in identifying and

Abbreviations: BC, Breast cancer; BLC, Bladder cancer; BCL2, B-cell lymphoma 2; CBX4, Chromobox 4; CAFs, Cancer-associated fibroblasts; CC, Cervical cancer; ceRNA, competing endogenous RNA; DGCR8, DiGeorge critical region 8; EC, Endometrial cancer; EMT, Epithelial mesenchymal transition; GC, Gastric cancer; GNAS, Guanine nucleotide binding protein, alpha stimulating; HOXC10, Homeobox C10; HCC, Hepatocellular carcinoma; LC, Lung cancer; LncRNA, Long noncoding RNA; LSCC, Laryngeal squamous cell carcinoma; LUSC, Lung squamous cell carcinoma; MAT2B, Methionine adnosyltransferase 2B; miRs., MicroRNAs.; miRNAs, MicroRNAs; mRNA, Messenger RNA; MTDH, Metadherin; NSCLC, Non-small cell lung cancer; OS, Osteosarcoma; OSCC, Oral squamous cell carcinoma; RAP2C, Ras-related protein Rap-2c; PBX3, Pre-B-cell leukemia transcription factor 3; PC, Pancreatic cancer; PPP2R2A, Protein phosphatase 2 regulatory subunit balpha; Pre-miRNA, Precursor miRNA; Pri-miRNA, Primary miRNA; PTX, Paclitaxel; RAB9A, Ras-related protein Rab-9A; RCC, Renal cell carcinoma; RISC, RNA-induced silencing complex; ROCK1, Rho-associated protein kinase 1; SKA2, Spindle and kinetochore associated complex subunit 2; SMAD3, Mothers against decapentaplegic homolog 3; TNBC, Triple negative breast cancer; TRIM27, Tripartite motif-containing protein 27; UTR, Untranslated region; YWHAZ, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta.

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treating the various pathophysiological states [6–10], and in cancer, miRNAs have emerged as crucial modulators of expression of their target genes [11–14], attracting significant attention due to their engagement in various cellular processes, like cancer onset and development [15]. Amidst the extensive repertoire of miRNAs implicated in cancer, miR-136–5p has emerged as an emerging miRNA with diverse roles [16–18]. Dysregulation of miR-136–5p has been proved in human cancers, such as LC [16,17,19], BC [18,20], CC [21], EC [22], BLC [23, 24], HCC [25], PC [26], GC [27], RCC [28], LSCC [29], glioma [30], and melanoma [31]. Accumulating evidence suggests that miR-136–5p mainly functions as a tumor suppressor [22,25,31,32]. Therefore, a comprehensive comprehension of the precise molecular basis governing miR-136–5p dysregulation in different cancers is vital for unraveling its therapeutic importance. This article aims to provide a comprehensive review of the available improvement of miR-136–5p's involvement in cancer pathogenesis. We will delve into its regulatory functions, target genes, and signaling pathways, emphasizing its impact on key cancer behaviors, including cell invasion, proliferation, migration, and apoptosis. Moreover, we will explore the clinical applications of miR-136–5p dysregulation, including its capability as a diagnostic and prognostic biomarker. The therapeutic potential of miR-136–5p in cancer is particularly intriguing, as its alteration opens up novel avenues for the suggesting of miRNA-based therapeutic strategies. We will provide an extensive overview of the current approaches employed to modulate miRNA activity and expression, encompassing the utilization of anti-miRNA oligonucleotides and synthetic miRNA mimics. Additionally, we will discuss the future directions and challenges in harnessing the treatment importance of miRNAs, such as overcoming off-target effects and improving delivery systems. In conclusion, miR-136–5p represents a promising avenue for both cancer research and therapy. By elucidating the regulatory mechanisms and functional roles of miR-136–5p, valuable insights can be obtained into the intricate landscape of cancer pathology.

2. Biogenesis and function of microRNAs

MiRNAs are a vital class of small RNA molecules and play a crucial function in modulating post-transcriptional expression of target genes [33,34]. They are engaged in various biological processes, including disease pathogenesis and progression [35,36]. The biogenesis of miRNAs is a multi-step phenomenon, initiating with the Pri-miRNA transcription by RNA polymerase II/III in the nucleus [37,38]. The pri-miRNA has a hairpin structure which is processed by DROSHA/DGCR8 complex, leading to the generation of Pre-miRNA [39,40]. Afterward, in the Exportin-5-mediated transportation, the pre-miRNA is released to the cytoplasmic space for further processing [41]. In the cytoplasm, the pre-miRNA is recognized and cleaved by the Dicer, releasing an RNA duplex [42]. In the RISC-mediated process, one of the strands of duplex RNA, known as the mature miRNA, target mRNA molecules through base-pairing interactions [34]. This interaction can lead to either mRNA degradation or translation repression, thereby regulating gene expression [34,43]. The function of miRNAs largely depends on their specific target genes. Through base-pairing interactions with the 3′ UTR of targets mRNAs, miRNAs can regulate gene expression post-transcriptionally. They can inhibit translation by preventing ribosome binding or induce mRNA degradation by promoting deadenylation and subsequent decay [44,45]. By modulating the expression of target genes, miRNAs contribute to the regulation of various biological behaviors, including cell metabolism, apoptosis, differentiation, and proliferation [46,47]. Moreover, miRNAs can exhibit regulatory functions beyond post-transcriptional gene regulation by modulating chromatin remodeling [48] (Fig. 1).

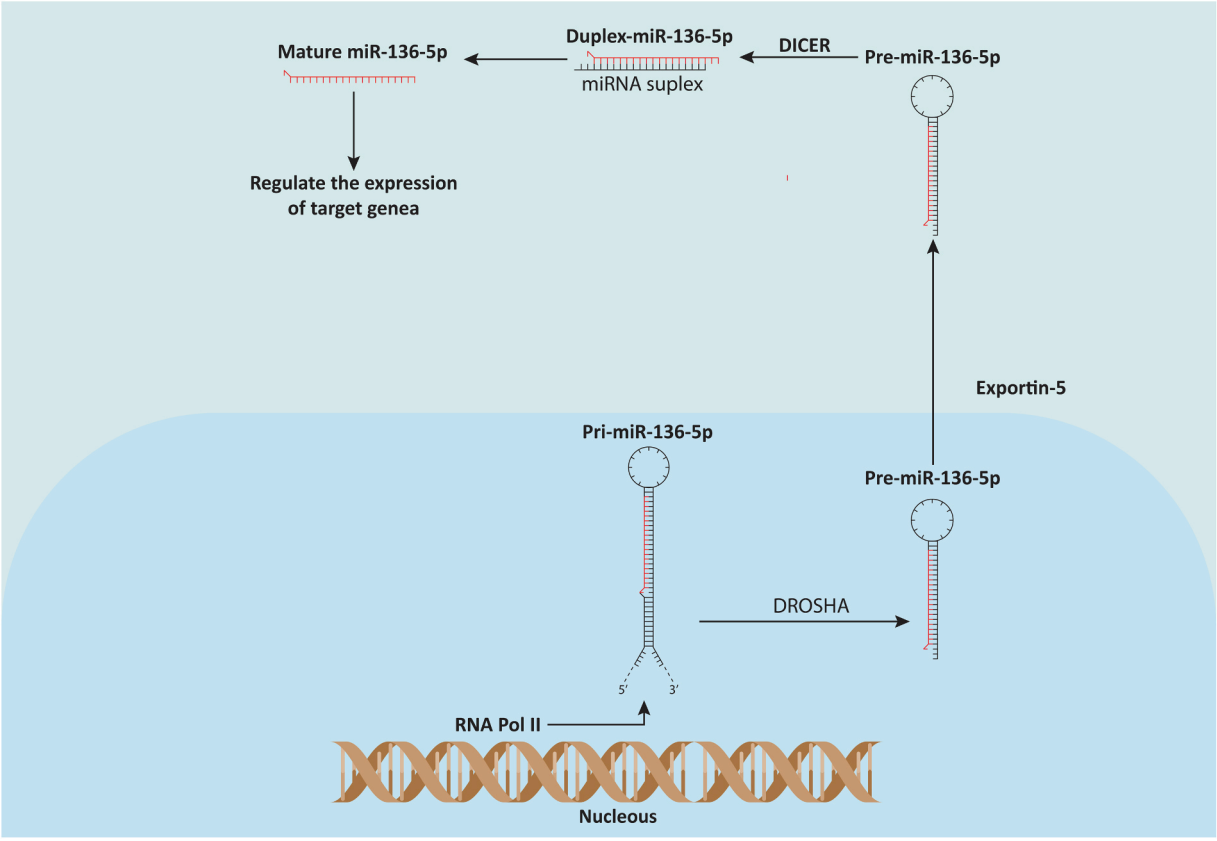

Fig. 1. An illustration representing miR-136–5p biogenesis. As indicated, RNA polymerase II produce Pri- miR-136–5p transcript, which further processed in nucleus by Drosha to release Pre-miR-136–5p. It transported into cytoplasmic space in Exportin-52 dependent mechanism. In cytoplasm, Pre- miR-136–5p is further cleaved by Dicer to produce diplex miR-136–5p. One of the strand of mature miR-136–5p will be choice to repress target mRNA translation or degrade the target mRNA.

3. Dysregulation of miRNAs in human cancers

The dysregulation of miRNAs is commonly observed in human malignancies [49,50]. These small RNA molecules have a critical importance in post-transcriptional modulation of target genes and contribute to cancer progression [51]. In cancer, miRNAs can act as tumor promoters or tumor suppressors, which depend on the specific context and cancer type [52]. Tumor suppressor miRNAs are often decreased in cancer and function by downregulating the oncogene expression or genes engaged in important cellular behaviors such as metastasis, apoptosis, and cell cycle progression [53]. Conversely, oncogenic miRNAs are frequently increased and enhance tumor growth, angiogenesis, and chemotherapy by downregulating tumor suppressor genes or DNA repair-related genes [53]. Numerous miRNAs are engaged in cancer biology. For example, miR-542–3p is frequently downregulated in various cancers and is inversely correlated with cell metastasis, invasion, migration, proliferation, apoptosis, and cell cycle [54]. Another microRNA, miR-495–3p, has a potential to be a promising tumor suppressor in cancer biology [55]. The let-7 microRNA, which is found to be reduced in LC [56], plays a crucial role in targeting the oncogene RAS. Similarly, miR-16 and miR-15, which are downregulated in chronic lymphocytic leukemias, target the antiapoptotic factor BCL2 [57]. A research has shown that miR-127 is abundantly expressed in normal PC and BLC but significantly silenced or decreased in the corresponding tumor samples. Moreover, another study has identified the proto-oncogene BCL6 as one of the targets of miR-127, suggesting that miR-127 acts as a tumor suppressor [58]. On the other hand, miR-1290, a well-known oncogenic miRNA, is often overexpressed in malignancy and contributes to tumor growth and resistance to therapy [59]. miR-10b plays an active role in cancer development by promoting the invasion and migration of tumor cells [60]. The miR-17–92 cluster is found to be enhanced in OS, resulting in the dysregulation of several genes involved in apoptosis, cell cycle control, and differentiation [61]. In GC, Kim et al. have identified a group of miRNAs associated with tumor penetration through the distant metastasis, lymph node metastasis, and serosa [62]. In OSCC, miR-130b-3p, miR-141–3p, miR-96–5p, and miR-21–3p have been found to be deregulated [63]. Notably, inhibiting these four miRNAs simultaneously results in decreased cell proliferation and reduced levels of Cyclin D1 protein [63]. The dysregulation of miRNAs in cancer can occur through various routes. Genetic alterations, such as chromosomal abnormalities, copy number variations, and mutations, can directly impact the expression or function of miRNAs [64–66]. Additionally, changes in the components of the miRNA biogenesis machinery, including exportin-5, Dicer, and Drosha, can lead to dysregulated miRNA levels in cancer [67–69]. The dysregulation of miRNAs in cancer has significant clinical implications. Altered expression levels of specific miRNAs have been associated with prognosis, treatment response, and patient outcomes in various cancer types [70,71]. Furthermore, miRNAs have demonstrated potential as diagnostic and prognostic biomarkers, as their expression patterns.

4. Role of miR-136–5p in cancer

The miR-136–5p has been found to have an important role in cancer, acting mostly as a tumor suppressor [17,18,26,32]. As a tumor suppressor, miR-136–5p functions by negatively regulating oncogenes or genes involved in promoting cancer progression. It induced cell cycle arrest, inhibit cell proliferation, and enhance cell apoptosis in human cancers [17,18,26,32]. Additionally, miR-136–5p can suppress tumor progression and inhibit cancer metastasis by targeting genes involved in these processes. Moreover, available research showed that the most engaged miR-136–5p-related signaling pathways are related to Wnt, SMAD, and Bcl2-related pathways [23,30]. Understanding the function of miR-136–5p in cancer is crucial for unraveling its underlying molecular mechanism as well as its importance as a biomarker or therapeutic target. Further research is needed to reveal the factors that determine whether miR-136–5p acts as a tumor suppressor or an oncogene in different cancer types.

5. miR-136–5p in human cancers: mechanism and function

5.1. Lung cancer

Zhang et al. revealed the upregulation of circTIMELESS in LUSC cells and clinical specimens. They found a positive correlation between circTIMELESS levels and the TNM stage, suggesting its importance as a prognostic biomarker. The researchers further investigated the function of circTIMELESS and demonstrated that its depletion significantly inhibited invasion in vitro and disrupted proliferation in cellular experiment and animal model. Further investigations proved that circTIMELESS functions as a miR-136–5p sponge. By sequestering miR-136–5p, circTIMELESS was shown to effectively modulates miR-136–5p levels. miR-136–5p overexpression mirrored the results observed upon circTIMELESS depletion, as both interventions decreased the invasion and proliferation of cell line. Moreover, this study identified ROCK1 as a direct interacting mRNA of miR-136–5p. They performed recovery experiments, which revealed that overexpression of ROCK1 partially rescued the effects of miR-136–5p overexpression and circTIMELESS depletion on cell proliferation and invasion. In conclusion, this research highlighted the presence of circTIMELESS in LUSC and demonstrated its role as a tumor stimulator via miR-136–5p/ROCK1. These findings suggest that circTIMELESS may serve as a potential treatment strategy for LUSC [19].

Gao et al. demonstrated the high expression of lncRNA NORAD in NSCLC cells and clinical specimens. They found that NORAD upregulation enhanced the glycolysis and proliferation of NSCLC cells. Their data indicated that NORAD functions as a ceRNA for miR-136–5p. Their loss-and gain-of-function experiments highlighted that miR-136–5p could rescue the activatory effects of NORAD in NSCLC. This suggests that NORAD may be an oncogene in NSCLC by targeting miR-136–5p. Targeting the NORAD/miR-136–5p interaction may hold potential as a therapeutic strategy for the NSCLC management. Overall, this study sheds light on the importance of NORAD in NSCLC and suggests valuable insights into the molecular basis of NSCLC pathogenesis [16].

Geng et al. put forward the notion that the levels of hsa_circ_0014130 is markedly elevated in NSCLC clinical specimens. The researchers observed that when hsa_circ_0014130 was decreased, it led to a notable inhibition of invasion and proliferation of LC cells by triggering apoptosis. Furthermore, the depletion of hsa_circ_0014130 demonstrated a suppressive effect on tumorigenesis of xenograft mice. Through mechanistic analysis, it was revealed that the downregulation of hsa_circ_0014130 resulted in a decrease in the level of Bcl-2, a gene targeted by miR-136–5p. This downregulation occurred because hsa_circ_0014130 acted as a sponging factor for miR-136–5p, thereby sequestering it and preventing it from targeting Bcl-2. In summary, they discovered that hsa_circ_0014130 is upregulated in NSCLC clinical specimens and acts as a tumor promoter in NSCLC by enhancing tumor growth. This promotion occurs, at least in part, through the upregulation of Bcl-2 via function as a sponging factor for miR-136–5p. The findings of this study provide valuable insights into hsa_circ_0014130 function in NSCLC and shed light on the underlying molecular mechanisms involved [17] (Table. 1 and Fig. 2).

5.2. Breast cancer

Han et al. conducted a study that revealed elevated levels of FAM83H-AS1 in BC clinical specimens and cells. They observed that suppressing FAM83H-AS1 decreased in the invasion, migration, and proliferation of BC cells, while its overexpression exerted opposite impacts. Theirbioinformatics analysis proposed that the researchers identified miR-136–5p as a potential target mRNA for FAM83H-AS1. In addition, they found that the levels of miR-136–5p decreased in BC

Table 1
The mechanistic view of miR-136–5p and their related ceRNA and target genes in human cancers.

Cancer type	ceRNA	microRNA	Target	In vitro effects	In vivo effects	Ref.
LC	circTIMELESS	miR-136–5p	ROCK1	Inhibited cell invasion and proliferation	Inhibited tumor growth	[19]
	NORAD		-	Inhibited glycolysis and cell proliferation	-	[16]
	circ_0014130		BCL2	Inhibited invasion and cell proliferation	-	[17]
BC	FAM83H-AS1		MTDH	Inhibited invasion, migration, and proliferation	Inhibited tumor growth	[18]
	circ_0069094		YWHAZ	Inhibited cell invasion and proliferation and induced cell apoptosis	-	[32]
	Circ_0001387		SKA2	Inhibited cell invasion and proliferation	-	[20]
HCC	circ_0091579		TRIM27	Inhibited cell cycle, invasion, migration, proliferation, and EMT, and decreased cell apoptosis	Inhibited tumor growth	[72]
	-		-	-	-	[25]
BLC	PlncRNA-1		SMAD3	Inhibited cell invasion, migration, and proliferation	Inhibited tumor growth	[23]
	circSPECC1		GNAS	Inhibited cell migration and proliferation	-	[24]
PC	DSCAM-AS1		PBX3	Inhibited cell invasion, migration and proliferation	Inhibited tumor growth	[26]
CC	FOXP4-AS1		CBX4	Inhibited cell invasion, migration and proliferation	-	[21]
EC	DSCAM-AS1		-	Inhibited cell proliferation and enhanced cell apoptosis	-	[22]
GC	CYTOR		HOXC10	Inhibited cell growth	-	[27]
RCC	CYTOR		MAT2B	Inhibited cell invasion and proliferation and enhanced cell apoptosis	-	[28]
LSCC	circ_100290		RAP2C	Inhibited cell invasion, migration and proliferation and enhanced cell apoptosis	Inhibited tumor growth	[29]
Glioma	CRNDE		-	Inhibited cell invasion, migration and proliferation	-	[30]
Melanoma	Circ_0013359		RAB9A	Inhibited glycolysis, invasion, migration, and proliferation		[31]

BCL2: B-cell lymphoma 2, BC: Breast cancer, BLC: Bladder cancer, CBX4: Chromobox 4, CC: Cervical cancer, EC: Endometrial cancer, GC: Gastric cancer, GNAS: Guanine nucleotide binding protein, alpha stimulating, HCC: Hepatocellular carcinoma, HOXC10: Homeobox C10, LC: Lung cancer, MAT2B: Methionine adnosyltransferase 2B, LSCC: Laryngeal squamous cell carcinoma, MTDH: Metadherin, PBX3: Pre-B-cell leukemia transcription factor 3, PC: Pancreatic cancer, RAB9A: Ras-related protein Rab-9A, RAP2C: Ras-related protein Rap-2c, RCC: Renal cell carcinoma, ROCK1: Rho-associated protein kinase 1, SKA2: Spindle and kinetochore associated complex subunit 2, SMAD3: Mothers against decapentaplegic homolog 3, TRIM27: Tripartite motif-containing protein 27, YWHAZ: Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta.

clinical specimens and that its upregulation resulted in the suppression of TNBC cell migration, invasion, and proliferation. The study also demonstrated that suppressing miR-136–5p reversed the inhibitory effects of FAM83H-AS1 depletion on BC cell migration, invasion, and proliferation, proposing that FAM83H-AS1 exerts its tumor promoting impact by suppressing miR-136–5p. Additionally, the researchers indicated that MTDH as direct target mRNA for miR-136–5p and showed that MTDH expression was increased in human BC clinical specimens. The increased expression of MTDH induced invasion, migration, and proliferation of TNBC cells. Notably, data from BC mouse xenografts demonstrated that FAM83H-AS1 also promoted the growth of tumor. Overall, the results of this study indicate that FAM83H-AS1 may be an oncogenic mediator that modulates MTDH expression and miR-136–5p during BC development. The findings suggest that showed the FAM83H-AS1/miR-136–5p/MTDH axis may be a novel treatment target for BC [18].

Kong et al. revealed the overexpression of circ_0069094 in paclitaxel (PTX)-resistant BC cells and clinical specimens. They found that depletion of circ_0069094 resulted in decreased invasion, proliferation, and tumor growth, while also increasing sensitivity to PTX and apoptosis in PTX-resistant cell lines. Through their investigation, the researchers identified miR-136–5p as a target of circ_0069094. They further observed that inhibiting miR-136–5p reversed the effects induced by circ_0069094 depletion in PTX-resistant cells. The study also showed that the expression of miR-136–5p was decreased in PTX-resistant BC clinical specimens and cells, and that overexpressing miR-136–5p limited the malignant behaviors of BC cells by interacting with YWHAZ mRNA. Notably, circ_0069094 regulated the YWHAZ levels in BC by binding to miR-136–5p mRNA. Overall, the findings of this study indicate that circ_0069094 is enhanced in PTX-resistant BC, and its silencing leads to decreased tumor growth and cell aggressiveness, as well as increased cell apoptosis and PTX sensitivity. The study highlights the role of miR-136–5p as a target of circ_0069094 and demonstrates that its downregulation contributes to PTX resistance [32].

Xiong et al. (2023) investigated the expression levels of Circ_0001387, SKA2, and miR-136–5p in BC clinical specimens and cell lines. They found that Circ_0001387 and SKA2 increased, while miR-136–5p decreased. The researchers also observed that reducing the expression of Circ_0001387 inhibited the progression of BC cells in both animal models and laboratory experiments. Further analysis revealed that Circ_0001387 interacted with miR-136–5p mRNA, thereby affecting the malignant behaviors of BC cells. Additionally, miR-136–5p targeted SKA2, and when SKA2 was reintroduced, it counteracted the inhibitory effect of increasing miR-136–5p levels in BC cells. Overall, the study highlights the overexpression of SKA2 and Circ_0001387, as well as the low expression of miR-136–5p in BC. The findings emphasize the role of Circ_0001387 as a miR-136–5p sponge, which affects the malignant behaviors of BC cells. Additionally, the study identifies SKA2 as a target of miR-136–5p and demonstrates that SKA2 can reverse the inhibitory effect caused by enhancing miR-136–5p in BC cells [20] (Table. 1 and Fig. 2).

5.3. Hepatocellular carcinoma

Mao et al. conducted a study that demonstrated elevated levels of circ_0091579 in HCC clinical specimens and cell lines. They observed that HCC patients with upregulated circ_0091579 level had a lower survival rate. The researchers further found that depletion of circ_0091579 suppressed the cell cycle, migration, invasion, proliferation, and EMT of HCC cells, but induced apoptosis. In their investigation, the study revealed that circ_0091579 acted as miR-136–5p sponge. The effects mediated by circ_0091579 depletion were largely reversed when miR-136–5p was suppressed in HCC cells. Additionally, miR-136–5p bound to the 3′UTR of TRIM27, and the enhancement of TRIM27 attenuated the influences induced by miR-136–5p upregulation in HCC cells. The study demonstrated that circ_0091579 acted as a sponge for miR-136–5p, leading to the upregulation of TRIM27 expression in HCC cells. Moreover, the study showed that depletion of circ_0091579 suppressed the growth of xenograft tumors. Overall, the findings of this study indicate that circ_0091579 is upregulated in HCC and is associated

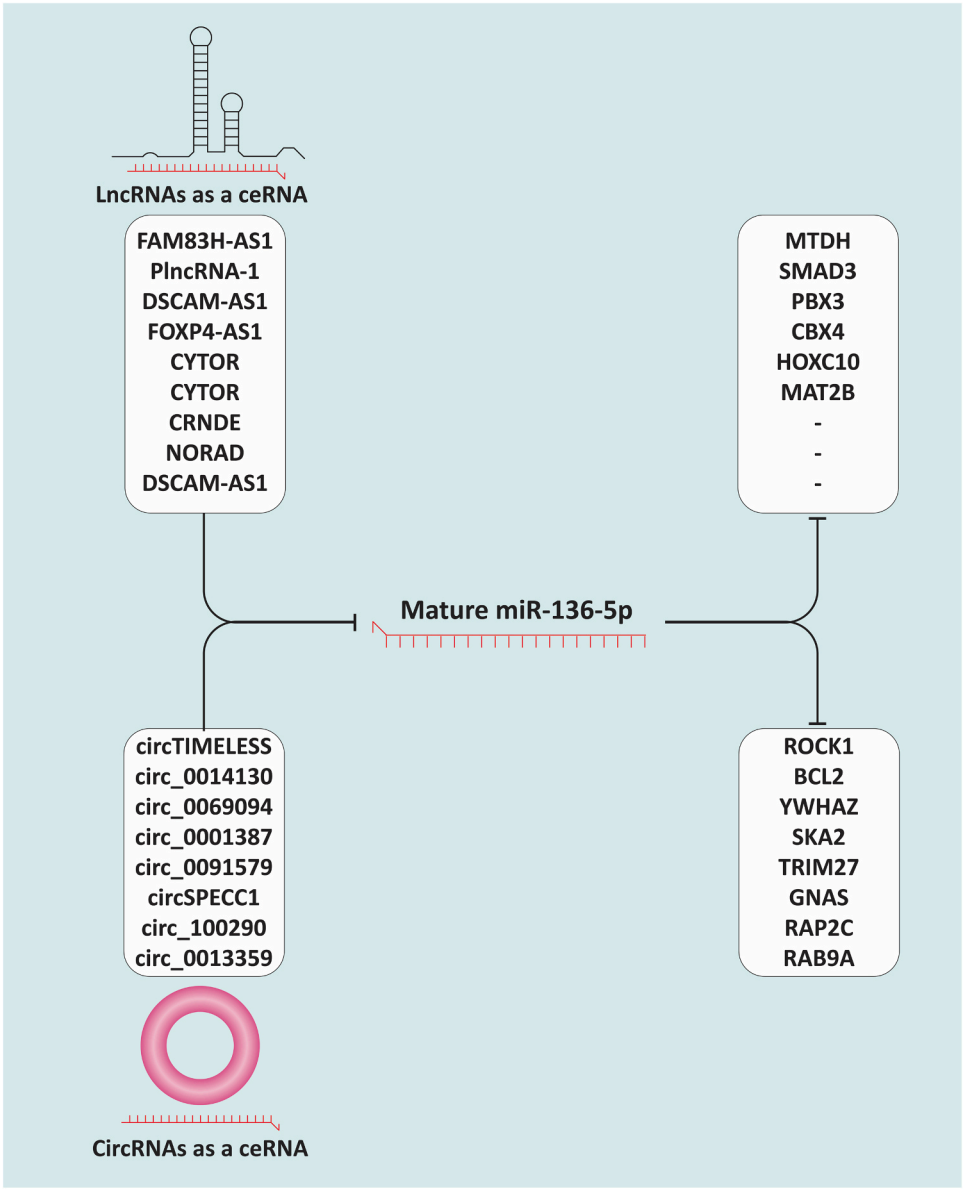

Fig. 2. the mechanistic view of miR-136–5p and its related ceRNAs and target genes. As indicated, various lncRNAs and circular RNAs can sponge miR-136–5p, leading to reduction in its inhibitory effect on the target genes. BCL2: B-cell lymphoma 2, CBX4: Chromobox 4, GNAS: Guanine nucleotide binding protein, alpha stimulating, HOXC10: Homeobox C10, MAT2B: Methionine adnosyltransferase 2B, MTDH: Metadherin, PBX3: Pre-B-cell leukemia transcription factor 3, RAB9A: Ras-related protein Rab-9A, RAP2C: Ras-related protein Rap-2c, ROCK1: Rho-associated protein kinase 1, SKA2: Spindle and kinetochore associated complex subunit 2, SMAD3: Mothers against decapentaplegic homolog 3, TRIM27: Tripartite motif-containing protein 27, YWHAZ: Tyrosine 3-monooxygenase/tryptophan 5-monooxyge nase activation protein zeta.

with lower survival of patients [72].

Ding et al. investigated miR-136–5p levels in HCC clinical specimens. They analyzed 101 pairs of HCC and adjacent clinical specimens using RT-qPCR. The researchers also utilized the TCGA and GEO database to further validate the clinical importance of miR-136–5p level in HCC. This study found that the expression of miR-136–5p was markedly suppressed in HCC clinical specimens. Moreover, the downregulation of miR-136–5p was associated with HCC patients who had vaso-invasion, portal vein tumor embolus, advanced TNM stage, and metastasis. Their findings suggested that the downregulation of miR-136–5p is a major player in aggressiveness and development of HCC. The study indicates that miR-136–5p functions as an anti-HCC microRNA and is important for HCC aggravation via modulation of various signaling axes [25] (Table. 1 and Fig. 2).

5.4. Bladder cancer

Kang et al. conducted research that showed the overexpression of PlncRNA-1 in 71.43% of BLC clinical specimens. The level of PlncRNA-1 was found to be correlated with number of tumors, T stage, tumor invasion, and age in BLC clinical specimens. Further experiments conducted by the researchers revealed that inhibiting the expression of PlncRNA-1 decreased the invasion, migration, and proliferation of BLC cell lines both in animal models and laboratory settings in. The study also observed that the promoter of PlncRNA-1 in BLC clinical specimens exhibited hypomethylation, which led to the overexpression of PlncRNA-1. Additionally, this study found that PlncRNA-1 influenced the SMAD3 and miR-136–5p levels. On the other hand, miR-136–5p enhanced SMAD3 and PlncRNA-1 levels. PlncRNA-1 was shown to interact with miR-136–5p and modulate the SMAD3 levels. Further analysis demonstrated that modulating miR-136–5p could reverse SMAD3 and levels the impairment of PlncRNA-1-related EMT markers. In summary, PlncRNA-1 has significant predictive importance and is engaged in the post-transcriptional modulation of SMAD3 [23].

Yang et al. made the discovery that circSPECC1, a type of circular RNA, exhibited significant up-regulation in both BLC cells and clinical specimens. The enhanced expression of circSPECC1 was found to be associated with a lower prognosis in BLC patients. Subsequent experiments conducted by the researchers further revealed that when circSPECC1 was knocked down, it hindered the migration and proliferation abilities of BLC cells. To investigate the molecular basis behind these observations, the study explored the role of circSPECC1 as a sponging

factor for miR-136–5p. It was found that circSPECC1 interacted with miR-136–5p and sequestered it, leading to an upregulation of the protein and mRNA levels of GNAS. Moreover, when the expression of GNAS was enforced, it effectively reversed the suppressed migration and proliferation mediated by circSPECC1 inhibition [24] (Table. 1 and Fig. 2).

5.5. Pancreatic cancer

Huang et al. explored the function of DSCAM-AS1 in PC. The researchers assessed the levels of DSCAM-AS1 using qRT-PCR and ISH assays. They proceeded to deplete DSCAM-AS1 in PC cells to investigate its impact on cell migration, invasion, and proliferation. The team also investigated the interaction between DSCAM-AS1, PBX3, miR-136–5p and through luciferase reporter assay and bioinformatic analysis. Furthermore, a mice model was developed to determine the effect of DSCAM-AS1 in growth of the tumor. The study findings revealed that DSCAM-AS1 levels was elevated in both clinical specimens and cells. After DSCAM-AS1 silencing, it effectively inhibited the invasion, migration, and proliferation of PC cells and led to the tumor growth inhibition in vivo. Further investigation demonstrated that DSCAM-AS1 was a miR-136–5p sponge, resulting in the promotion of PBX3 levels. The study suggested that DSCAM-AS1 in PC was partially done by modulation of the miR-136–5p/PBX3 axis [26] (Table. 1 and Fig. 2).

5.6. Cervical cancer

Zhao et al. made the discovery that FOXP4-AS1 levels was significantly higher in CC cells. When FOXP4-AS1 was forced to be expressed, it resulted in increased invasion, migration, and proliferation of CC cells. Conversely, when FOXP4-AS1 was depleted, the opposite impacts were observed. The researchers also investigated the molecular basis behind these findings and found that FOXP4-AS1 functions as a ceRNA for miR-136–5p in modulating the expression of CBX4. This indicates that FOXP4-AS1 have oncogenic properties in CC. The study suggests that targeting FOXP4-AS1 could be a novel therapeutic approach and may propose an emerging biomarker for CC treatment [21] (Table. 1 and Fig. 2).

5.7. Endometrial cancer

Li et al. conducted a study that unveiled the high DSCAM-AS1 levels in EC clinical specimens and cells. Importantly, they also observed a correlation between poorer overall survival and high DSCAM-AS1 expression in EC patients. In vitro experiments further demonstrated that depletion of DSCAM-AS1 decreased EC cell proliferation and promotion of cell apoptosis. Furthermore, the study uncovered that DSCAM-AS1 acts as a sponging factor for miR-136–5p, thereby exerting its oncogenic effects in EC. These findings provide preliminary evidence that DSCAM-AS1 enhances EC development by modulating miR-136–5p. This discovery enhances our comprehension of the roles played by lncRNAs in EC and may help in identifying emerging targets for anticancer therapies [22] (Table. 1 and Fig. 2).

5.8. Gastric cancer

Li et al. conducted a study presenting evidence of the upregulation of the lncRNA CYTOR in GC cells. They demonstrated that depletion of CYTOR inhibited the GC cell growth. Additionally, they identified miR-136–5p as a target of CYTOR in regulating GC development. It is noteworthy that miR-136–5p was found to be underexpressed in GC cells. The study also revealed that HOXC10 is a target of miR-136–5p. Overall, the findings proposed that CYTOR has a role in modulating the miR-136–5p/HOXC10 signaling, thereby promoting the progression of GC. Furthermore, the study demonstrated the involvement of CYTOR in GC progression in in vivo experiments [27] (Table. 1 and Fig. 2).

5.9. Renal cell carcinoma

Li et al. indicated that the lncRNA CYTOR is overexpressed in RCC cells and clinical specimens. Conversely, miR-136–5p revealed to be underexpressed in both RCC cells and clinical specimens. The study demonstrated that the downregulation of CYTOR suppressed cell invasion and proliferation, as well as enhanced apoptosis in RCC cells. Furthermore, the study uncovered that CYTOR acts as a sponging factor for miR-136–5p, which has an inhibitory impact on RCC development. Additionally, the study identified MAT2B is a miR-136–5p target gene. The protein MAT2B was found to directly interact with BAG3 protein, affecting the apoptosis, invasion, and proliferation of RCC cells. In vivo experiments further supported these findings, showing that the knockdown of CYTOR led to enhanced levels of miR-136–5p and decreased levels of MAT2B, ultimately inhibiting RCC development [28] (Table. 1 and Fig. 2).

5.10. Laryngeal squamous cell carcinoma

Wang et al. made the discovery that the expression of circ_100290 is considerably increased in both LSCC cells and clinical specimens. They also found that the circ_100290 levels directly associated with lymph node metastasis and advanced TNM stage in LSCC individuals. Their cell culture experiments indicated the higher levels of circ_100290 enhanced the invasion, migration, and proliferation, while inhibiting cell apoptosis in LSCC cells. Conversely, depletion of circ_100290 induced the opposite impacts. In vivo experiments further supported these findings, as circ_100290 upregulation significantly enhanced tumor growth. The study also revealed the mechanistic role of circ_100290 as miR-136–5p sponge. Inhibition of miR-136–5p in LSCC cell lines reversed the impacts of circ_100290 depletion. In addition, RAP2C was shown to be a miR-136–5p target gene, and depletion of RAP2C in LSCC cells partially reversed the tumor promoting impacts caused by the circ_100290 upregulation or miR-136–5p depletion [29] (Table. 1 and Fig. 2).

5.11. Glioma

Li et al. proved the elevated levels of CRNDE in glioma clinical specimens. Their in vitro assays discovered a new molecular basis of CRNDE in glioma development. By manipulating the expression of CRNDE, they observed a direct correlation between the expression of CRNDE and the invasive, migratory, proliferative capabilities of glioma cells, which were accompanied by a decrease in the rate of apoptosis. Their experiments also indicated downregulation of miR-136–5p mitigated these effects. Through predicted interactions between CRNDE, miR-136–5p, and related mRNA, the researchers found that both protein and mRNA expression analyses supported the notion that the protumoral actions of CRNDE are driven by the suppression of Wnt2 and Bcl-2 through miR-136–5p [30] (Table. 1 and Fig. 2).

5.12. Melanoma

The study conducted by Li et al. revealed that circ_0013359 and RAB9A exhibited increased expression, but miR-136–5p expression were decreased in both melanoma cell lines and clinical specimens. The researchers found that when Circ_0013359 was knocked down, it led to the inhibition of various melanoma cell behaviors, including glycolysis, invasion, migration and proliferation. Conversely, it increased cell cycle arrest and apoptosis in melanoma cell lines. These results proposed that circ_0013359 has a major role in regulating melanoma development. Furthermore, the study discovered that circ_0013359 acts as a miR-136–5p sponge, leading to its downregulation. They found that Their interactions promote melanoma development. In addition, the researchers found that miR-136–5p suppresses melanoma growth by interacting with RAB9A mRNA, indicating its tumor-suppressive role in

this context. Interestingly, the study also demonstrated that depletion of circ_0013359 resulted in the suppression of tumor growth in animal model. This suggests that circ_0013359 may have therapeutic potential as a target for melanoma treatment [31] (Table. 1 and Fig. 2).

6. Prognostic and diagnostic importance of miR-136–5p

miRNAs have emerged as promising indicators for the diagnosis and prognosis of cancer due to their stable levels and involvement in crucial cellular processes [73]. Among these miRNAs, miR-136–5p has demonstrated substantial potential as a prognostic and diagnostic marker in human cancers. This section focuses on the diagnostic and prognostic implications associated with dysregulated expression of miR-136–5p in cancer patients. Dysregulation of miR-136–5p expression has been observed across multiple cancer types, suggesting its potential as a diagnostic marker. Several studies have highlighted altered levels of miR-136–5p in cancerous specimens compared to normal specimens, making it a promising candidate for distinguishing between cancer and non-cancerous conditions [17,18,72,74]. In certain cancer types, downregulation of miR-136–5p linked with lower prognosis, suggesting its potential as a prognostic marker for predicting patient outcomes. Conversely, upregulated miR-136–5p expression correlated with favorable prognosis in other cancer types, indicating its potential as a positive prognostic indicator. The diagnostic and prognostic potential of miR-136–5p in cancer can be attributed to its involvement in critical cellular processes and its ability to regulate signaling pathways and target genes. Dysregulated expression of miR-136–5p can disrupt key pathways involved in cancer development and progression, influencing tumor growth, metastasis, and response to treatment. The identification and validation of target genes modulated by miR-136–5p, along with their functional implications in cancer biology, further support its significance as a diagnostic and prognostic marker. However, translating the diagnostic and prognostic potential of miR-136–5p into clinical practice faces challenges. Standardized methodologies for detecting and quantifying miR-136–5p need to be established to ensure reliable and reproducible results across different laboratories. Additionally, larger prospective studies involving diverse patient populations are required to validate the prognostic and diagnostic importance of miR-136–5p across various cancer types.

7. Therapeutic implications of targeting miR-136–5p in cancer

Research has demonstrated that miR-136–5p has a major role in the cancer pathogenesis. It exerts its influence by regulation of tumor suppressor genes and oncogenes, thereby impacting cancer cell behaviors [17,18,26]. Additionally, miR-136–5p has been found to modulate cell cycle progression [72], which is a critical process in the development of cancer. The cell abilities to invade and metastasize surrounding tissues is a hallmark of aggressive cancers. MiR-136–5p revealed to affect the process of EMT [72], which is engaged in the invasion and migration of cancer cells. The tumor microenvironment, which consists of various cell types and the extracellular matrix, has a significant function in cancer development. CAFs, immune cells, and components of the extracellular matrix have a major role in cancer cell fate in tumor microenvironment [75–77]. Understanding the precise role of miR-136–5p in these interactions will enhance our understanding for the introducing new treatment strategies affecting the tumor microenvironment. Drug resistance poses a significant obstacle in the treatment of cancer. Research has indicated that miR-136–5p plays a role in resistance to chemotherapy and targeted therapies [78,79]. Targeting miR-136–5p holds promise in overcoming drug resistance and improving treatment outcomes. In this regard, it was showed that the levels of miR-136–5p were found to be lower in BC cells and tissues that were resistant to PTX treatment. However, when miR-136–5p was artificially increased, it effectively inhibited the aggressive behaviors of BC cells. This inhibition was achieved by directly targeting the YWHAZ gene, which is known to be involved in promoting malignancy in BC cells [32]. Exosomes derived from anlotinib-resistant NSCLC cells carry miR-136–5p, which is responsible for conferring resistance to anlotinib in NSCLC cells. This resistance is achieved by targeting the PPP2R2A gene. These findings suggest that miR-136–5p could serve as a potential biomarker for predicting the response to anlotinib treatment in NSCLC [80]. In addition, circ_0003998 was found to play a role in regulating the formation of cell colonies, apoptosis, and sensitivity to DTX in NSCLC cells that are resistant to DTX. This regulation is achieved, at least in part, by controlling the expression of the CORO1C gene through its interaction with miR-136–5p. These findings shed light on the potential of circ_0003998 as a therapeutic target for treating chemoresistant NSCLC [79].

8. Future directions and perspectives of microRNA in cancer

The study of miRNAs in cancer has opened up new avenues for research and potential therapeutic interventions. As our perception of the roles and mechanisms of miRNAs in malignancies continues to expand, several future directions and perspectives have emerged. One important area of future research is the development of miRNA-based treatment strategies [81]. Another future direction is the identification of new miRNAs with prognostic and diagnostic importance in human cancers [82]. The integration of miRNA biomarkers with other clinical parameters can enhance the accuracy of cancer diagnosis and improve patient management. Furthermore, the emerging field of liquid biopsy holds promise for the non-invasive detection of miRNAs in body fluids such as blood, urine, and saliva. Liquid biopsies offer a minimally invasive approach for monitoring miRNA expression patterns in real-time, enabling the assessment of tumor dynamics and treatment response [83,84]. Understanding the interplay between miRNAs and the immune system in cancer could lead to the development of novel immunotherapeutic approaches [85]. In addition, emerging technologies like CRISPR/Cas9-mediated modulation of miRNAs and RNA interference-based approaches offer more precise and effective targeting of miRNAs [86,87]. Overall, future directions in miRNA research in cancer involve the development of targeted therapies, identification of novel biomarkers, exploration of liquid biopsy techniques, and investigation of miRNA's role in immunotherapy. Continued efforts in these areas have the potential to translate miRNA research into clinically valuable tools for cancer diagnosis, treatment, and patient management.

9. Conclusion

Accumulating data regarding the tumor-suppressor miR-136–5p in various cancers has proposed its promising importance as a treatment target. The miR-136–5p capabilities in suppressing the progression of cancers lies in its potential to repress the oncogenic genes and signaling pathways. Available data proposed that the expression of miR-8136–5p decreased in human cancers, like LC, BC, GC, PC, CC, EC, HCC, RCC, glioma, and melanoma. These studies revealed that the decreased levels of miR-136–5p is usually associated with higher aggressiveness, advanced tumor stages, and unfavorable prognoses. miR-136–5p has a wide-ranging and complex functions in modulating the important cellular processes invasion, migration, apoptosis, EMT, proliferation, and apoptosis. miR-136–5p bound to specific target mRNA, leading to suppression of signaling molecules, growth factors, and oncogenes. Moreover, miR-136–5p was shown to be engaged in sensitivity to cancer chemotherapy. Furthermore, the upregulation of miR-136–5p was shown to inhibit tumor promoting-related cellular processes, proposing that it may be a promising treatment target in cancer. In addition, other research showed that miR-136–5p has a potency to be a prognosis and diagnosis biomarker in cancer, highlighting its importance in human cancers. However, more studies will guarantee the application of miR-136–5p as an emerging and novel therapeutic target.

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CRediT authorship contribution statement

Omer Qutaiba B. Allela: Supervision, Conceptualization, Editing, Writing – original draft. **Chou-Yi Hsu:** Supervision, Conceptualization, Editing, Writing – original draft. **Sheereehan Adull-Hussein Mahdi:** Data collection, Writing – original draft. **Ojas Prakashbhai Doshi:** Writing – original draft, Editing. **Mohaned Adil:** Data collection, Writing – original draft. **Mohammed Shnain Ali:** Data collection, Writing – original draft.

Declaration of Competing Interest

We declare that we have no competing interests.

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