Non-coding RNA Research 12 (2025) 67–80

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Review Article

miR-135b: A key role in cancer biology and therapeutic targets

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ARTICLE INFO

Keywords:
miR-135b
Cancer
Drug resistance
Oncotherapy

ABSTRACT

miR-135b, a microRNA, is consistently up-regulated in various cancer tissues and cells, promoting cancer progression. By inhibiting one or more target genes, miR-135b regulates phenotypes such as cancer growth, apoptosis, migration, invasion, drug resistance, and angiogenesis, establishing it as a critical driver of cancer progression. Additionally, miR-135b is regulated by various oncogenes and therapeutic drugs, highlighting its complexity and therapeutic potential. Significant progress has been made in understanding miR-135b's impact on cancer cell behavior, establishing it as a promising biomarker for cancer diagnosis and prognosis, as well as a potential target for future cancer therapies. However, despite the extensive research on this topic, there has been no comprehensive review summarizing its role and mechanisms across different cancer types. This review aims to provide a detailed overview of the biological characteristics of miR-135b, its regulatory targets, upstream signaling pathways, and its therapeutic potential, including its influence on cancer chemoresistance. The review also addresses key controversies surrounding miR-135b in cancer research, aiming to deepen the understanding of its role, promote the transformation of its clinical application, and provide a theoretical foundation for developing more effective cancer treatment strategies.

1. Introduction

MicroRNAs (miRNAs) are a class of small noncoding RNAs [1–3], with tens of thousands of mature sequences identified [4–6]. Dysregulation of miRNA expression leads to abnormal gene regulation, contributing to cell dysfunction and carcinogenesis [7–9]. In recent years, research on various miRNAs has advanced from the laboratory to clinical applications. For example, the miR-16 mimic TargomiRs is undergoing a phase I clinical trial (NCT02369198) for malignant pleural mesothelioma and non-small cell lung cancer (NSCLC) [10–12]. Cobomarsen, an LNA antagomiR targeting miR-155, is in phase I clinical trials (NCT02580552) for cutaneous T-cell lymphoma and hematological malignancies [13–15]. TTX-MC138, which inhibits miR-10b expression, is being tested for its ability to halt the progression of advanced solid tumors [16–18] and is currently in phase I/II trials (NCT06260774). These developments highlight the promising role of miRNAs in anticancer drug development and therapeutic target selection.

As a prominent member of the miRNA family, miR-135b has shown substantial progress in cancer research. Numerous preclinical animal studies have demonstrated that its aberrant expression is closely linked to carcinogenesis across various organs (Table 1). This miRNA not only regulates critical biological processes in cancer cells [19–21] but also has significant associations with the quantity and functionality of cancer stem cells [22–24]. In cancer progression, miR-135b preferentially targets proteins involved in signaling pathways [25–27], thereby playing a broad role in multiple signaling pathways. Therefore, employing miR-135b mimics or inhibitors can modulate multiple signaling pathways and effectively manage cancer progression [28–30]. Furthermore, miR-135b levels are closely correlated with clinicopathological features, making it a valuable diagnostic and prognostic biomarker [31–33]. Thus, developing miR-135b-based therapeutic strategies holds great promise for cancer treatment. However, clinical research in this field remains limited. Gaining a more comprehensive insight into the biological traits, roles, and mechanisms of miR-135b, along with recent developments, is essential for creating novel therapies that target miR-135b.

This review systematically outlines the biological characteristics of miR-135b, offering a comprehensive summary of its recent research

Peer review under the responsibility of Editorial Board of Non-coding RNA Research.
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https://doi.org/10.1016/j.ncrna.2025.02.005
Received 13 November 2024; Received in revised form 13 January 2025; Accepted 17 February 2025
Available online 20 February 2025

advancements in oncology and its role in cancer drug resistance. Additionally, we explore the current controversies within the research and discuss the potential clinical applications of miR-135b. This review aims to enhance the understanding of miR-135b′s role in cancer biology and support its translation into clinical practice, paving the way for more effective cancer treatments.

2. Biological characteristics

miR-135b, an intronic miRNA within the *LEMD1* gene transcribed from miR-135B (1q32.1) [52,53], comprises two mature strands: miR-135b-5p (5′-UAUGGCUUUUCAUUCCUAUGUGA-3′) and miR-135b-3p (5′-AUGUAGGGCUAAAAGCCAUGGG-3′). As a multifunctional miRNA, miR-135b plays a critical role in various biological and pathological processes, with its functions and regulatory mechanisms directly influencing its specific roles in disease progression. For instance, miR-135b is involved in the regulation of cardiovascular diseases [54–56], obesity [57], diabetes [58], chronic inflammation [59], and cancers [20] by targeting multiple genes and signaling pathways. Its biological function is largely dependent on its interactions with target genes, while its expression is intricately regulated at multiple levels, including transcriptional control by transcription factors [60], epigenetic mechanisms such as DNA methylation [50] and histone modifications [61], and the modulation of its activity by competitive endogenous RNAs through the "sponge effect". In recent years, miR-135b has garnered significant attention due to its pivotal role as a potential biomarker and therapeutic target in various diseases, particularly cancer. In cancer research, miR-135b not only regulates numerous cancer suppressor genes but is also finely regulated by various protein-coding and non-coding RNAs (Table 2). These characteristics make miR-135b a key focus of research for understanding cancer pathogenesis and developing novel therapeutic strategies.

3. Carcinogenic effects of miR-135b

3.1. GC

miR-135b-5p is a small non-coding RNA with significant oncogenic effects, which plays an important role in the occurrence and progression of GC. miR-135b-5p showed significant upregulation in GC tissues, serum samples from patients with GC, and various GC cell lines [35,91,92]. Its high expression level not only serves as an early diagnostic tool for gastric abnormalities, but is also closely related to malignant progression and poor prognosis [93–95]. The mechanism of action of this small RNA is mainly reflected in its ability to promote the proliferation, migration and invasion of cancer cells by suppressing key cancer suppressors such as CAMK2D, TGFBR2, KLF4, APC, CLDN11, and CMTM3 [74,96,97] (Fig. 1A). Moreover, miR-135b-5p enhances its oncogenic properties by regulating various signaling pathways. For instance, IL-1α/β, Wnt/β-catenin, and PI3K/AKT pathways can upregulate the

Table 1
Preclinical animal studies of miR-135b in cancers.

Use animals	Cancer type	Mode of action of miR-135b	Mechanism of action of miR-135b	Research result	Reference
BALB/c nude mice	Gastric cancer (GC)	miR-135b-5p inhibitor lentivirus transfection SGC7901-xenografted mice	miR-135b-5p/CMTM3	miR-135b-5p inhibitor inhibits cancer growth *in vivo*	[34]
BALB/c nude mice	GC	miR-135b-5p overexpressing lentivirus-SGC7901 cells	miR-135b-5p/TGFBR2	miR-135b-5p promotes cancer growth *in vivo*	[35]
BALB/c nude mice	GC	AntagomiR-135b-5p was injected into tail vein xenografted mice	miR-135b-5p/CAMK2D	AntagomiR-135b-5p inhibits cancer growth and lung metastasis *in vivo*	[36]
K19-Wnt1/C2mE; Gan	GC	miR-135b-lnfl/fl transgenic knockout mice	miR-135b/RECK /FOXN3	Knockout of miR-135b inhibits the progression of GC	[37]
BALB/c nude mice	ADR and 5-FU-resistant GC	/	miR-135b-5p/ITGA2/MAPK/ERK	miR-135b-5p inhibits ADR/5-FU resistance	[38]
BALB/c nude mice	Cisplatin-resistant GC	miR-135b-5p mimic-MKN28 cells	miR-135b-5p/MST1/MAPK	miR-135b-5p promotes cisplatin-resistance	[39]
BALB/c nude mice	Pancreatic cancer (PC)	AntagomiR-135b-5p-AsPC-1 cells	miR-135b-5p/KLF4/GPRC5A	AntagomiR-135b-5p inhibits cancer growth	[40]
BALB/c nude mice	Gemcitabine-resistant PC	miR-135b-5p mimic-MIA PaCa-2 cells	miR-135b-5p/BMAL1/YY1	miR-135b-5p promotes gemcitabine-resistant	[41]
BALB/c nude mice	Colorectal cancer (CRC)	Anti-miR-135b-5p-SW480 cells	miR-135b-5p/ST6GALNAC2/PI3K/AKT	Anti-miR-135b-5p inhibits cancer growth	[42]
BALB/c nude mice	Oxaliplatin resistant CRC	Anti-miR-135b-5p-SW620 cells	miR-135b-5p/FOXO1	Anti-miR-135b-5p promotes anti-cancer effects	[43]
BALB/c nude mice	Oxaliplatin resistant CRC	miR-135b-5p inhibitor-HCT-116/LOHP cells	miR-135b-5p/MUL1/ULK1	Anti-miR-135b-5p promotes anti-cancer effects	[44]
BALB/c nude mice	Esophageal cancer (EC)	LV-miR-135b-5p-inhibitor-Eca109 cells	miR-135b-5p/TXNIP	miR-135b-5p inhibitor inhibites cancer growth	[45]
BALB/c nude mice	Breast cancer (BC)	miR-135b-5p overexpression vecter-MCF-7 cells	miR-135b-5p/AGR2	miR-135b-5p increases the sensitivity of MCF-7 cells to ADR	[46]
BALB/c nude mice	HER-2 positive BC	miR-135b-5p agomiR is injected directly	miR-135b-5p/cyclin D2	miR-135b-5p agomiR promotes anti-cancer effects	[47]
NOD/SCID mice	Lung metastasis of BC	AntagomiR-135b-5p is injected directly	miR-135b-5p/SDCBP	AntagomiR-135b-5p promotes lung metastasis of BC	[48]
BALB/c nude mice	NSCLC	miR-135b-5p overexpression vecter-H292 cells	miR-135b-5p/CYLD/NF-κB	miR-135b-5p promotes cancer progression	[49]
NOD-SCID	NSCLC	miR-135b-5p- lentiviral vector-CL1-0 cells	miR-135b-5p/Hippo	miR-135b-5p promotes lung cancer growth and metastasis	[50]
Athymic nu/nu mice	Osteosarcoma (OS)	miR-135b-5p overexpression vecter-Saos-2 cells	miR-135b-5p/Notch and Wnt/β-catenin	miR-135b-5p promotes CSC characteristics, lung metastasis, and cancer recurrence in OS	[51]

CMTM3: CKLF-like MARVEL transmembrane domain containing 3; TGFBR2: TGF-beta receptor 2; CAMK2D: Calcium/calmodulin-dependent kinase II-delta; RECK: Reversion-inducing cysteine-rich protein with kazal motifs; FOXN3: Forkhead box N3; ADR: Doxorubicin; 5-FU: 5-fluorouracil; ITGA2: Integrin subunit alpha 2: MAPK: Mitogen-activated protein kinase; MST1: Mammalian ste20-like kinase 1; KLF4: Krüppel-like factor 4; GPRC5A: G protein-coupled receptor class C group 5 member A; BMAL1: Brain and muscle ARNT-like 1; YY1: Yin Yang 1; ST6GALNAC2: GalNAc alpha-2,6-sialyltransferase 2; PI3K/AKT: Phosphatidylinositol 3-kinase/protein kinase B; FOXO1: Forkhead Box O1; TXNIP: Thioredoxin-interacting protein; AGR2: Anterior gradient 2; SDCBP: Syndecan binding protein; CYLD: CYLD lysine 63 deubiquitinase; CSCs: Cancer stem cells.

Table 2
Upstream regulators of miR-135b in cancers.

Upstream factors	miR-135b expression	Cancer type	References
Morin	Inhibits	NSCLC	[62]
Estradiol	Inhibits	CRC	[63]
Peucedanum chenur chloroformic extract	Inhibits	CRC	[64]
5-ASA	Inhibits	CRC	[65]
SD-208	Inhibits	CRC	[66]
SRC	Promotes	CRC	[67]
APC	Inhibits	CRC	[67]
PTEN/PI3K	Inhibits	CRC	[67]
TCF4/β-catenin	Promotes	CRC	[68]
PI3K/AKT Wnt/β-catenin	Promotes	GC	[69]
YAP	Promotes	Hepatocellular carcinoma (HCC)	[70]
JunB/AP-1	Promotes	HCC	[71]
P38	Promotes	BC	[72]
TAZ	Promotes	OS	[73]
LncRNA PCAT18	Inhibits	GC	[74]
LncRNA UCA1	Inhibits	PC	[75]
LncRNA GAS8-AS1	Inhibits	Papillary thyroid carcinoma (PTC)	[76]
LncRNA ZFAS1	Inhibits	PTC	[77]
LncRNA DANCR	Inhibits	Multiple myeloma	[78]
LncRNA HAGLROS	Inhibits	BC	[79]
Lnc SMAD5-AS1	Inhibits	Diffuse large B cell lymphoma	[80]
LncRNA GAS5	Inhibits	NSCLC	[81]
LncRNA LINC01339	Inhibits	Wilms' Tumor	[82]
CircCNIH4	Inhibits	BC	[83]
Circ_0044234	Inhibits	Triple-negative BC	[84]
Circ_0000977	Inhibits	Triple-negative BC	[85]
CircNOL10	Inhibits	CRC	[86]
Circ-LECRC	Inhibits	CRC	[87]
Circ_0000977	Inhibits	CRC	[88]
Circ_0000471	Inhibits	Ovarian cancer (OC)	[89]
CDR1as	Inhibits	OC	[90]

5-ASA: 5-aminosalicylic acid; SD-208: TGF-beta receptor I kinase inhibitor; SRC: Proto-oncogene tyrosine-protein kinase Src; APC: Activated protein C; PTEN: Phosphatase and tensin homolog; TCF4: Transcription factor 4; YAP: Yes-associated protein; JunB: Jun B proto-oncogene; AP-1: A activating protein-1; TAZ: Transcriptional coactivator with PDZ-binding motif.

expression of miR-135b-5p, thereby augmenting the characteristics of GC stem-like cells (Fig. 1A). This mechanism offers a significant molecular basis for the rapid progression and treatment of GC. Notably, exosomal miR-135b-5p released by GC cells has been shown to impair T cell function, potentially diminishing the efficacy of immunotherapy [98]. This suggests that miR-135b-5p is not only crucial for cancer proliferation and metastasis, but also exacerbates disease progression by altering the cancer microenvironment. In summary, the elevated expression of miR-135b-5p is evident throughout several critical pathological stages of GC. Its oncogenic effects encompass various mechanisms, including the regulation of cell signaling, modulation of gene expression, and evasion of immune responses.

3.2. PC

The oncogenic role of miR-135b-5p in PC is evident through multiple key aspects. First, the expression of miR-135b-5p is upregulated in clinical samples, tissues, and cell lines of PC [40,99]. Its elevated expression significantly enhances the proliferation, migration, invasion, and differentiation capabilities of PC stem cells, thereby accelerating cancer progression [100]. Second, it disrupts the circadian rhythm of the pancreas by targeting the core circadian clock factor BMAL1 [41]. This disruption not only impacts normal metabolic processes and cellular proliferation regulation but also creates conditions conducive to cancer development. Furthermore, the level of miR-135b-5p is closely associated with regional lymph node metastasis, vascular invasion, and cancer thrombus formation [101]. This upward trend not only signifies the malignancy of the disease but also directly influences patient prognosis. High levels of miR-135b-5p expression are significantly correlated with reduced overall survival and disease-free survival (DFS) in PC patients [102–104], further underscoring its role as an oncogene in PC. From a molecular mechanism perspective, the cancer-promoting effects of miR-135b-5p are linked to the mediation of pathways involving BMAL1-YY1, jade family PHD finger 1 (JADE-1)-AKT/mTOR, KLF4-GPRC5A, secreted frizzled-related protein 4 (SFRP4)-Wnt/β-catenin, and mineralocorticoid receptor (NR3C2)-EMT (Fig. 1B). These pathways collectively contribute to the cancerous properties of miR-135b-5p, highlighting its potential as a key molecular target for early diagnosis, prognosis, and therapeutic intervention in PC.

3.3. CRC

miR-135b exhibits a potent oncogenic role in CRC by influencing critical cellular and molecular processes. At the cellular level, miR-135b drives CRC progression by promoting cell proliferation, migration, invasion, and angiogenesis while simultaneously inhibiting apoptosis [42,105,106]. These activities facilitate the cancer's ability to grow, invade surrounding tissues, and establish a blood supply, which is essential for sustaining malignancy. On a molecular level, numerous studies have shown that miR-135b is upregulated in CRC tissues, positioning it as a potential diagnostic and prognostic biomarker [107–117]. Notably, miR-135b expression is markedly higher in metastatic sites, such as the peritoneum and liver, compared to primary CRC tissues [118], emphasizing its critical role in metastatic progression. Mechanistically, miR-135b exerts its oncogenic effects by downregulating ST6GALNAC2 [42], mismatch repair gene (MMR) [63], TGFBR2/death-associated protein kinase 1 (DAPK1)/APC [67], KLF9 [86], calcium-sensing receptor (CaSR) [107], metastasis suppressor-1 (MTSS1) [119], ubiquitin-specific peptidase 13 (USP13) [120], and TXNIP [121]. Furthermore, miR-135b enhances angiogenesis, a hallmark of cancer progression, by suppressing genes like ST6GALNAC2 [42], FOXO1 [106], and TXNIP [121], which normally inhibit vascular development. This ability to promote blood vessel formation is integral to supporting the metabolic demands of growing cancers and metastatic lesions. Interestingly, miR-135b's oncogenic effects can be modulated by various factors. Estradiol [63], 5-ASA [65], and SD-208 [66] have been shown to reduce its activity, while pathways involving APC and PTEN/PI3K [67] also counteract its effects. In contrast, heat shock factor 1 (HSF1) [44], SRC [67], and the TCF4/β-catenin signaling axis [68] amplify its oncogenic potential, further enhancing cancer growth and metastatic capability. The above effects of miR-135b on CRC were summarized in Fig. 1C. In conclusion, miR-135b plays a multifaceted and essential role in CRC progression, acting as both a driver of malignancy and a potential biomarker for disease diagnosis and prognosis.

3.4. EC

miR-135b-5p plays a pivotal oncogenic role in EC, where its elevated expression is closely linked to cancer progression and poor clinical outcomes. High levels of miR-135b-5p are consistently observed in EC tissues and cells, and its suppression has been shown to effectively inhibit cancer growth and proliferation [45] (Fig. 1D). Clinically, elevated miR-135b-5p expression is negatively associated with overall survival, while positively correlating with higher cancer grades and increased lymph node metastasis [122,123], emphasizing its role in driving disease aggressiveness. In patients with EC undergoing esophagectomy following chemoradiotherapy, lower miR-135b-5p expression is associated with a higher DFS [124]. These findings highlight the significant prognostic value of miR-135b-5p in EC.

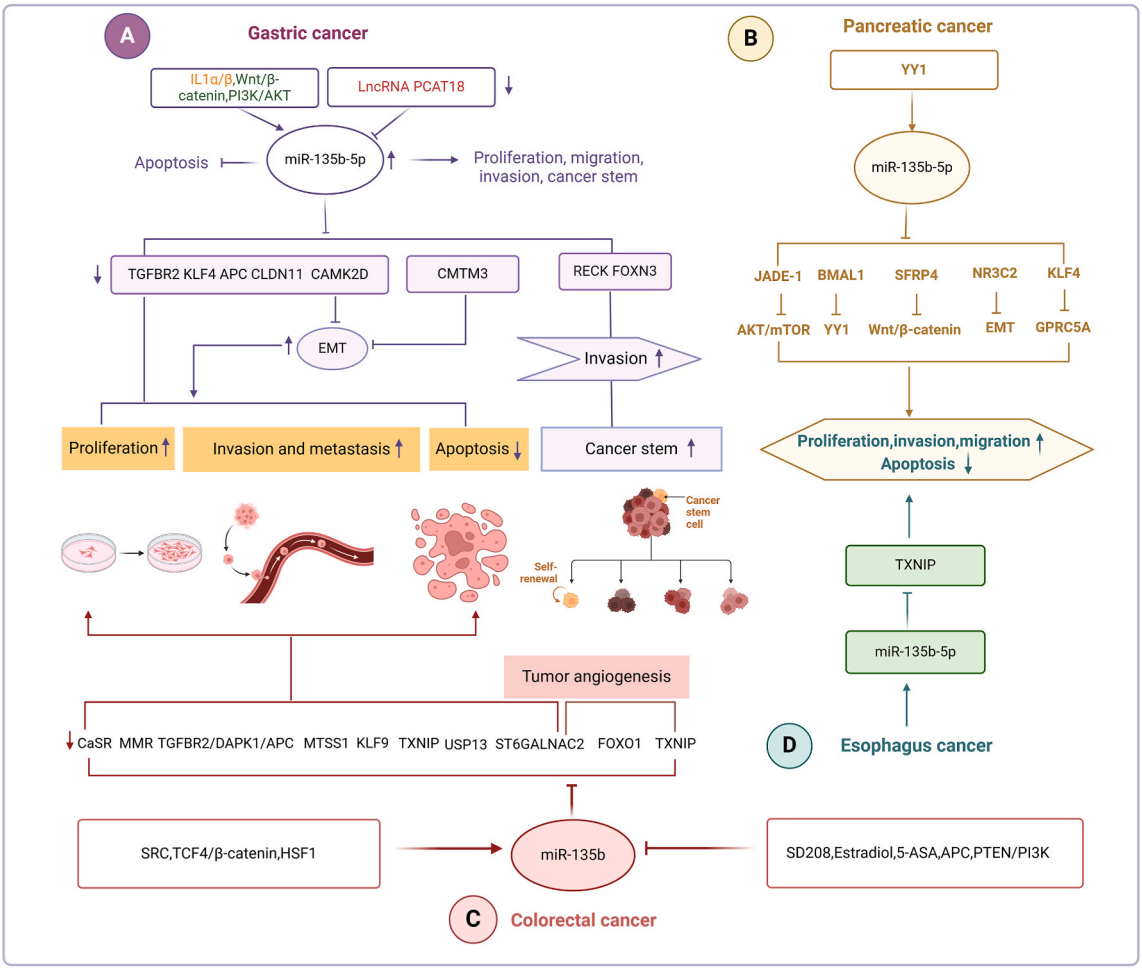

Fig. 1. The mechanism of action of miR-135b in gastrointestinal cancers. A miR-135b-5p promotes gastric cancer (GC) cell proliferation, migration, and invasion and inhibits apoptosis by suppressing TGFBR2, KLF4, APC, CAMK2D, and CMTM3 expression. The lncRNA PCAT18↓/miR-135b-5p↑/CLDN11↓ axis exacerbates GC progression. IL-1α/β enhances miR-135b expression, reducing RECK and FOXN3 expression, thereby increasing invasion and cancer stemness in GC cells. Wnt/β-catenin and PI3K/AKT signaling pathways further augment GC cell proliferation, migration, invasion, and stemness via miR-135b upregulation. **B** miR-135b-5p promotes pancreatic cancer cell proliferation, migration, and invasion and inhibits apoptosis by suppressing the JADE-1-AKT/mTOR, BMAL1-YY1-loop, SFRP4-Wnt/β-catenin, NR3C2-EMT, and KLF4-GPRC5A axes. **C** miR-135b promotes colorectal cancer cell proliferation, migration, and invasion and inhibits apoptosis by downregulating the expression of CaSR, MMR, TGFBR2, DAPK1, APC, ST6GALNAC2, MTSS1, USP13, TXNIP, and KLF9. Additionally, miR-135b facilitates cancer angiogenesis by suppressing FOXO1, TXNIP, and ST6GALNAC2. miR-135b is inhibited by SD208, Estradiol, 5-ASA, APC, and PTEN/PI3K, while upregulated by SRC, TCF4/β-catenin, and HSF1. **D** miR-135b-5p promotes esophageal cancer cell proliferation, migration, and invasion and inhibits apoptosis by downregulating TXNIP expression.

3.5. OC

Clinical studies have revealed elevated expression of miR-135b-5p in OC epithelial tissues [125], with experimental evidence showing that its suppression in OC cell lines, such as HO8910, A2780, KOV3, CAOV3, and OVCAR3, markedly reduces cell proliferation, migration, and invasion [89,90]. This effect is linked to the upregulation of hypoxia-inducible factor 1α inhibitor (HIF1AN) and dual specificity phosphatase 5 (DUSP5), which are downstream targets of miR-135b-5p (Fig. 2A). Additionally, the overexpression of miR-135b-3p in OC cell lines OVCAR3 and SKOV3 promotes cell growth, survival, invasion, and migration [126]. Therefore, miR-135b-5p and miR-135b-3p exhibit oncogenic effects in OC.

3.6. Cervical cancer (CC)

Clinical studies have revealed that miR-135b is highly expressed in the cervical tissues of CC patients, as well as in CC cell lines, suggesting its significant involvement in disease progression [127,128]. Additionally, Mi et al. [129] found that rs1131445 prevented miR-135b from inhibiting IL-16 by interfering with the interaction between miR-135b and IL-16 3′ UTR, thus leading to upregulation of IL-16 expression and increasing the risk of CC. Experimental evidence further shows that suppressing miR-135b expression leads to the upregulation of FOXO1, a cancer suppressor, which effectively inhibits CC cell proliferation [130] (Fig. 2B). These findings highlight miR-135b's pivotal role in CC development and progression, making it a promising biomarker for diagnosis and a potential target for therapeutic intervention.

3.7. BC

Clinical studies have shown that miR-135b is overexpressed in BC tissues compared to adjacent normal tissues [131–133]. This elevated expression is associated with advanced pathological features such as TNM stage and lymph node metastasis, underscoring its role in cancer progression and metastasis [134–136]. Functional studies reveal that

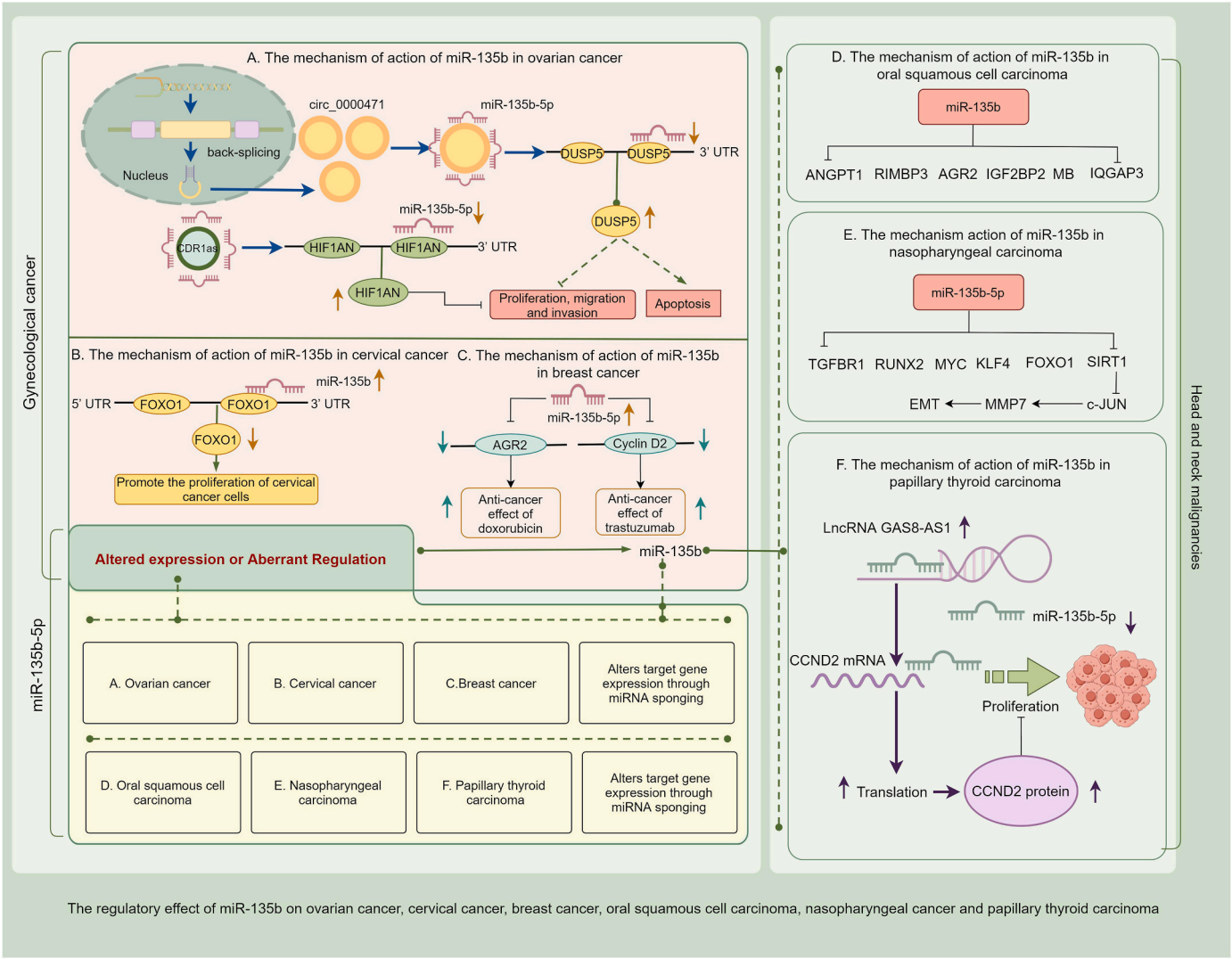

Fig. 2. The regulatory effect of miR-135b on gynecological cancer and head and neck malignancies. A Circ_0000471/miR-135b-5p/DUSP5 and CDR1as/miR-135b-5p/HIF1AN axes affect ovarian cancer progression. **B** miR-135b promotes cervical cancer progression by inhibiting FOXO1 expression. **C** miR-135b-5p enhances the anti-cancer effects of trastuzumab and doxorubicin in breast cancer cells by downregulating the expression of AGR2 and cyclin D2. **D** miR-135b may promote oral squamous cell carcinoma progression by downregulating ANGPT1, RIMBP3, AGR2, IGF2BP2, MB, and IQGAP3. **E** miR-135b-5p may promote nasopharyngeal carcinoma progression by downregulating the TGFBR1, RUNX2, MYC, KLF4, FOXO1, and SIRT1/c-JUN/MMP/EMT axis. **F** LncRNA GAS8-AS1/miR-135b-5p/CCND2 axis inhibits the proliferation of papillary thyroid carcinoma cells.

miR-135b is highly expressed in multiple BC cell lines, including MDA-MB-231, MCF-7, MDA-MB-436, HCC1937, MDA-MB-468, and BT20, where it promotes proliferation, migration, and invasion. Knockdown of miR-135b in these cell lines significantly suppresses these oncogenic behaviors, highlighting its role in driving cancer growth [131,134,137]. Furthermore, miR-135b enhances the sensitivity of cancer cells to treatments like trastuzumab and doxorubicin by targeting oncogenic proteins such as AGR2 and cyclin D2, potentially providing therapeutic benefits [46,47] (Fig. 2C). These findings collectively suggest that miR-135b acts as a crucial regulator of BC progression and treatment response, making it a potential target for therapeutic intervention.

3.8. *Oral squamous cell carcinoma (OSCC)*

Lopes et al. [138] discovered that has-miR-135b is expressed at higher levels in both para-cancer and cancer tissue samples of OSCC compared to non-cancerous tissues. This miRNA can effectively differentiate between non-cancerous, cancerous, and adjacent cancerous tissues, suggesting its role as a carcinogenic risk factor and a potential biomarker for distinguishing different tissue types [138–140]. Notably, miR-135b targets several downstream genes, including angiopoietin 1 (ANGPT1), RIMS-binding protein 3 (RIMBP3), AGR2, insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2), MB, and IQ motif-containing GTPase-activating protein 3 (IQGAP3) [141] (Fig. 2D), which are involved in various cellular processes. However, the exact interplay and functional dynamics among these targets remain unclear. Additionally, Scapoli et al. [142] reported that miR-135b expression is downregulated in patients with OSCC who exhibit lymph node metastasis compared to those without, indicating a possible association between miR-135b levels and OSCC metastasis. Current research mainly targets clinical samples to investigate the relationship between miR-135b and OSCC, leaving its mechanistic involvement in disease progression largely unexamined. Further research is needed to elucidate the specific mechanisms by which miR-135b influences OSCC progression and metastasis, providing insights into the disease and identifying potential therapeutic targets.

3.9. Nasopharyngeal carcinoma (NPC)

Tang et al. [143] identified that miR-135b-5p is significantly elevated in clinical samples of NPC and has significant diagnostic and prognostic value [144]. Subsequent research by Cheng et al. [145] explored the underlying mechanisms, revealing that miR-135b-5p acts as a sponge for sirtuin 1 (SIRT1), suppressing its expression and preventing sirt1 from binding to the matrix metalloproteinase 7 (MMP7) promoter at the c-JUN site. This displacement allows c-JUN to enhance MMP7 transcription, thereby promoting NPC progression (Fig. 2E). miR-135b-5p also plays a key role in regulating NPC metastasis. Mi et al. [146] observed upregulation of miR-135b-5p in metastatic NPC tissues, with predicted targets including TGFBR1, RUNX2, MYC, KLF4, and FOXO1 (Fig. 2E). However, further experiments are required to confirm its specific regulatory effects. Future studies should aim to investigate the connection between miR-135b-5p and the progression, survival, and resistance to anti-cancer treatments in NPC. While further research is warranted, miR-135b-5p continues to be a promising diagnostic marker for NPC.

3.10. PTC

The worldwide occurrence of PTC is increasing, considerably affecting patient survival rates and quality of life [147–149]. Studies have identified miR-135b-5p as a downstream target of the lncRNA GAS8-AS1, which normally acts as a cancer suppressor by inhibiting PTC development (Fig. 2F). Overexpression of miR-135b-5p counteracts the protective effects of lncRNA GAS8-AS1, highlighting its oncogenic potential [76]. Furthermore, research indicates that elevated miR-135b-5p levels are associated with greater cancer aggressiveness, suggesting its value as a prognostic biomarker for PTC progression [150]. Despite these findings, the specific molecular mechanisms by which miR-135b-5p promotes PTC development and aggressiveness remain largely unexplored. Further investigation is needed to clarify its regulatory pathways and to evaluate its potential as a therapeutic target in PTC management.

3.11. HCC

Clinically, miR-135b is significantly upregulated in HCC samples [70,151]. At the cellular level, its overexpression enhances proliferation, migration, and invasion in various HCC cell lines, including Hep3B, Huh7, SMMC7721, MHCC97-L, MHCC97-H, HB611, BEL-7404, and HepG2, underscoring its oncogenic role [70,151,152]. Mechanistically, miR-135b exerts oncogenic effects by inhibiting the MST1-Hippo signaling pathway [70], FOXO1 [71], RECK [60,151], and ecotropic viral integration site 5 (EVI5) [60]. Additionally, Zhang et al. [153] found that miR-135b is correlated with alpha-fetoprotein (AFP), a key biomarker for HCC screening, diagnosis, treatment, and prognosis. Patients with elevated miR-135b levels are more responsive to anti-PD-1 therapy. Yang et al.'s [154] research further supports miR-135b's role in enhancing the efficacy of anti-PD-1 therapy in HCC, suggesting that targeting miR-135b could be a promising therapeutic approach, as inhibiting its expression effectively suppresses HCC growth. Moreover, no existing research has examined the *in vivo* impact of miR-135b-5p on HCC. Thus, additional studies are needed to elucidate the function of miR-135b-5p in the progression of HCC and its response to treatment.

3.12. NSCLC

miR-135b-5p is one of the most significantly upregulated miRNAs in patients with NSCLC cancer tissues [155,156]. Higher miR-135b-5p expression is associated with lower overall survival [157] and a higher likelihood of visceral pleura invasion in NSCLC patients [158]. Functionally, miR-135b-5p promotes oncogenesis by enhancing cell proliferation, migration, invasion, and glycolysis, while inhibiting apoptosis [159]. These effects are mediated through the suppression of the Hippo signaling pathway, activation of the NF-κB pathway, and the PTEN/AKT/HIF-1α signaling pathway. Additionally, the IL-6/STAT3 (Fig. 3A) and NF-κB pathways (Fig. 3C) can enhance miR-135b-5p's effects, while Morin (Fig. 3D), lncRNA GAS5 (Fig. 3E) and circLARP4 (Fig. 3F) can inhibit its expression. In contrast, miR-135b-3p exhibits different functions. Wang et al. [160] demonstrated that melatonin inhibits the circ_0017109/miR-135b-3p/TOX3/Hippo axis (Fig. 3B), showing anti-cancer effects. Yin et al. [161] found that knocking down circUBAP2 suppresses NSCLC, with miR-135b-3p acting as a downstream target (Fig. 3B). These findings indicate that miR-135b-3p has a pro-apoptotic effect, in contrast to the anti-apoptotic effect of miR-135b-5p. Therefore, distinguishing between miR-135b-5p and miR-135b-3p is essential when designing anti-cancer strategies targeting miR-135b. The specific regulatory mechanisms of miR-135b in NSCLC are outlined in Fig. 3.

3.13. Glioblastoma

miR-135b-5p has been implicated in glioblastoma progression, with evidence suggesting its oncogenic potential. Studies have shown that miR-135b-5p is significantly upregulated in glioblastoma tissues and contributes to cancer growth by promoting cell proliferation and enhancing radioresistance [162,163]. Specifically, increased miR-135b-5p expression has been linked to the ability of glioblastoma cells to survive radiation therapy, highlighting its role in cancer resilience. These findings point to miR-135b-5p as a potential target for therapeutic intervention in glioblastoma. However, further research is needed to fully elucidate its molecular mechanisms and confirm its consistent role across diverse glioblastoma subtypes.

3.14. Melanoma

Research on miR-135b in human cutaneous melanoma remains limited; however, existing evidence underscores its potential significance in cancer progression. Hu et al. [164] reported that miR-135b expression is markedly elevated in melanoma tissue samples compared to adjacent non-cancerous tissues. Functional studies revealed that silencing miR-135b in primary melanoma cells and the A375 cell line significantly inhibited cell proliferation and migration, strongly suggesting an oncogenic role for miR-135b in melanoma. These findings imply that miR-135b may contribute to melanoma pathogenesis by promoting cancer growth and invasiveness, highlighting its potential as a target for therapeutic intervention.

3.15. OS

miR-135b is highly expressed in OS tissues and cell lines [165–168], playing a crucial role in advancing OS progression, recurrence, and lung metastasis [51,73,169]. Through its interactions with multiple target proteins such as phosphatase Mg2+/Mn2+ dependent 1A (PPM1A), translocation family protein 3 (TET3), glycogen synthase kinase-3β (GSK3β), beta-transducin repeat-containing protein (β-TrCP), casein kinase 1 alpha (CK1α), APC, FOXO1, large tumor suppressor kinase 2 (LATS2), and myocardin, miR-135b facilitates the degradation of mRNA via the miR-135b-mRNA degradation pathway, thereby contributing to disease exacerbation (Fig. 4A). These findings indicate that miR-135b holds promise as a therapeutic target for OS, with its inhibitors showing potential for effective treatment strategies.

3.16. Multiple myeloma (MM)

miR-135b is highly expressed in the serum, cancer tissues, MM cell lines, and mesenchymal stem cells of patients with MM [170–172]. Its expression correlates with the severity of osteolytic lesions [170] and the impairment of osteogenic differentiation in bone marrow

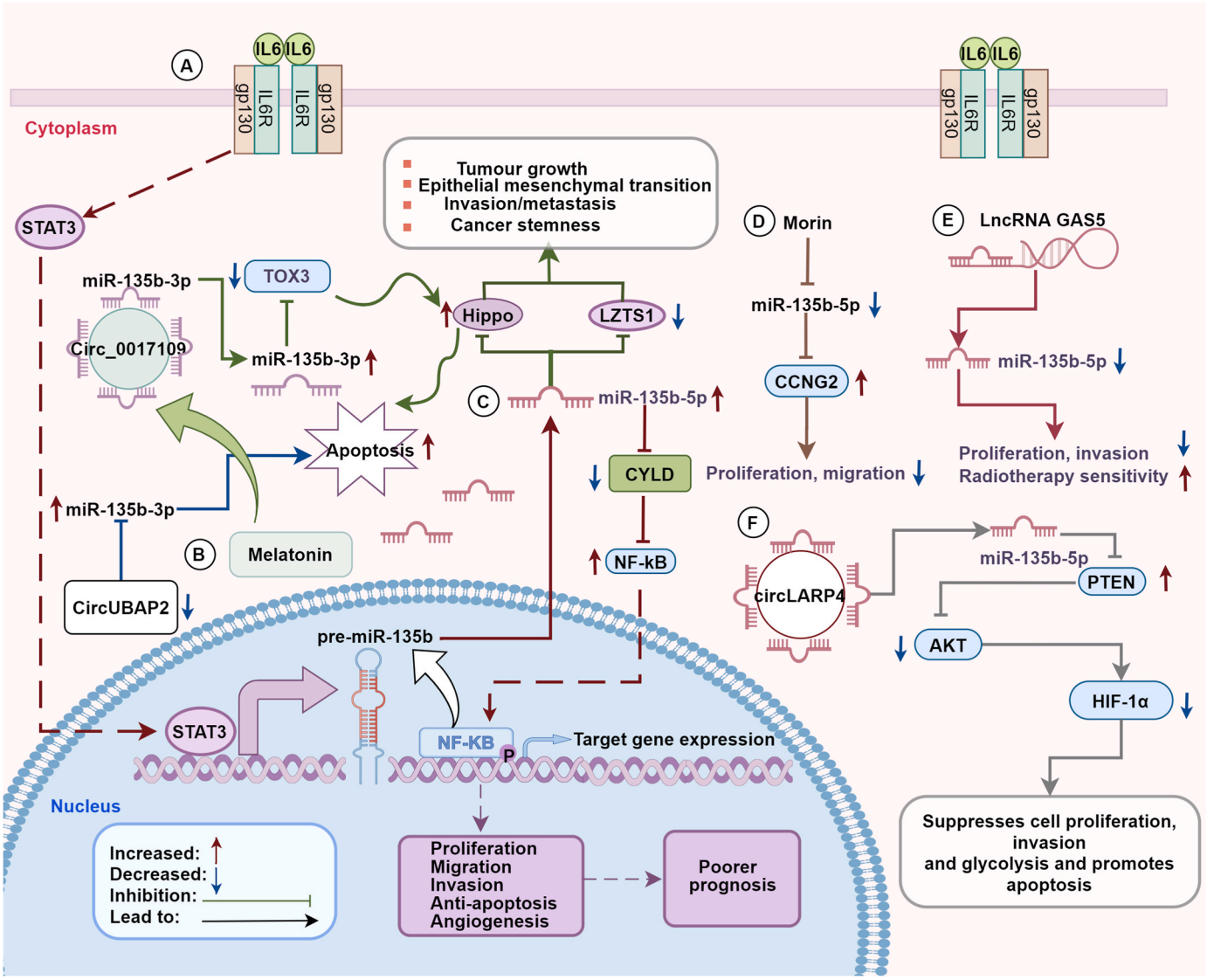

Fig. 3. The mechanism of action of miR-135b in non-small cell lung cancer (NSCLC). **A** The IL-6/STAT3↑-miR-135b-5p↑-CYLD↓-NF-κB↑ axis promotes the progression of NSCLC. **B** The Melation/circ_0017109↓/miR-135b-3p↑/TOX3↓/Hippo↑ and circUBAP2↓/miR-135b-3p↑ axes promote apoptosis in NSCLC. **C** The NF-κB↑/miR-135b-5p↑/LZTS1↓/Hippo↓ axis promotes NSCLC progression. **D** Morin inhibits the proliferation and migration of NSCLCs through the miR-135b-5p/CCNG2 axis. **E** The lncRNA GAS5 inhibits NSCLC by downregulating miR-135b-5p. **F** CircLARP4 inhibits NSCLC by targeting miR-135b-5p↓/PTEN↑/AKT↓/HIF-1α↓ pathway.

mesenchymal stem cells [172]. The carcinogenic mechanism of miR-135b in MM involves activation of the Wnt/β-catenin-versican pathway and downregulation of KLF9, factor-inhibiting HIF-1alpha (FIH-1), and SMAD5 (Fig. 4B). Notably, lncRNA DANCR can counteract miR-135b's carcinogenic effect (Fig. 4B). Additionally, miR-135b also plays a critical role in intercellular communication. Under hypoxic conditions, MM cells release exosomes enriched with miR-135b, which can be transferred to human umbilical vein endothelial cells (HUVECs), thereby promoting angiogenesis *in vivo* [173]. Thus, miR-135b can serve as a diagnostic biomarker for evaluating MM severity, and detecting miR-135b in exosomes may offer a new diagnostic approach.

4. Anti-cancer effects of miR-135b

miR-135b is a cancer-promoting gene in most cancers, but studies have shown that miR-135b plays a cancer suppressive role in prostate cancer (PCa) and renal cell carcinoma (RCC).

4.1. PCa

In clinical tissue samples from PCa patients, as well as in PCa cell lines DU145 and PC3, miR-135b expression is notably decreased [174]. Overexpression of miR-135b in PCa cells has been shown to promote the nuclear translocation of STAT6, thereby inhibiting cell migration and invasion [174]. Moreover, miR-135b negatively regulates the androgen receptor (AR) in PCa, suppressing cell proliferation [175,176]. miR-135b also inhibits PCa bone metastasis; Olivan et al. [177] found significant downregulation of miR-135b in PC3 bone-metastatic clone (PC3-BM) cells, where overexpression reduced PC3-BM cell migration. Additionally, lower levels of miR-135b expression in PCa with poor prognosis in patients, suggesting its potential as a prognostic biomarker for aggressive PCa [177]. These findings highlight the cancer-suppressive role of miR-135b in PCa, underscoring its potential as a therapeutic target for inhibiting PCa progression and metastasis.

4.2. RCC

Emerging evidence highlights the potential cancer-suppressive role

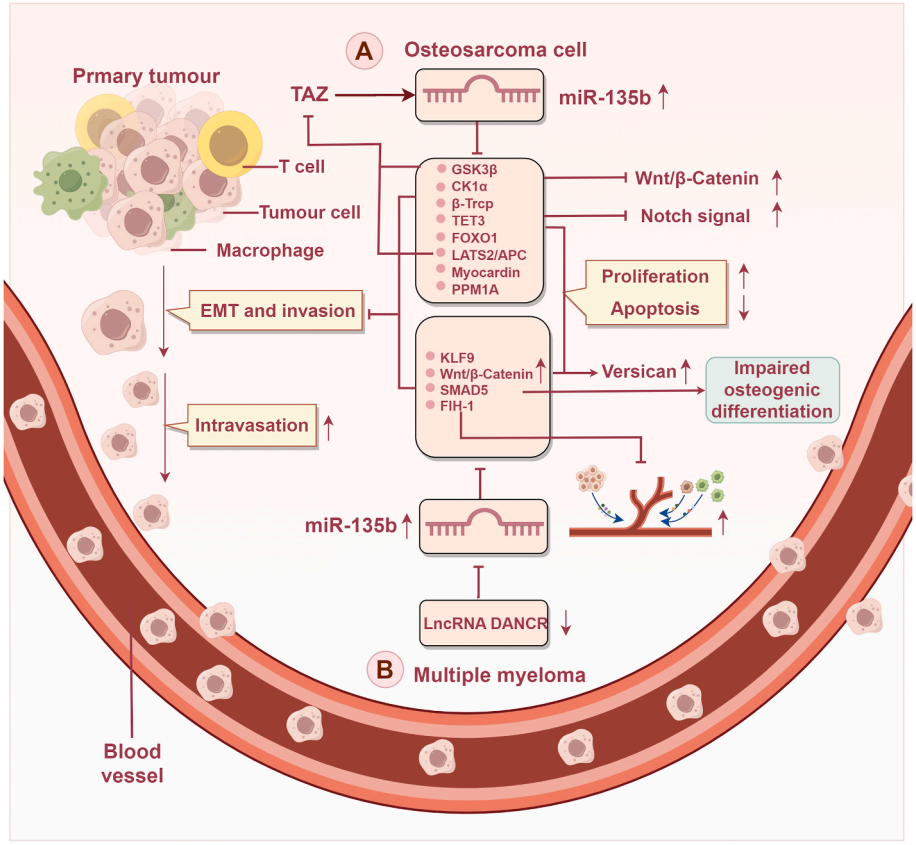

Fig. 4. The mechanism of action of miR-135b in osteosarcoma and multiple myeloma. A miR-135b aggravates osteosarcoma by downregulating the expression of PPM1A, FOXO1, and myocardin, and modulating the TET3/Notch↑, GSK3β/CK1α/β-TrCP/APC/Wnt/β-catenin↑, and LATS2/GSK3β/TAZ-loop pathway. **B** In multiple myeloma, miR-135b's carcinogenic mechanism involves activation of the Wnt/β-catenin-versican pathway and negative regulation of FIH-1 and SMAD5. The lncRNA DANCR↑/miR-135b↓/KLF9↑ axis reduces miR-135b's carcinogenic effects.

of miR-135b-5p in RCC. Wang et al. [178] reported a significant downregulation of miR-135b-5p in RCC cell lines A498 and OSRC-2 compared to normal kidney HK-2 cells. Functional assays demonstrated that the overexpression of miR-135b-5p effectively inhibited RCC cell proliferation and migration, underscoring its cancer-suppressive effects [178]. Mechanistically, the oncogenic effects in RCC are driven by the overexpression of lncRNA GAPLINC, which functions as a molecular sponge to sequester miR-135b-5p. This sequestration leads to the upregulation of CSF1, a key oncogene. The findings suggest that restoring miR-135b-5p expression or targeting the GAPLINC/miR-135b-5p/CSF1 axis could serve as promising therapeutic strategies for RCC. Therapies that inhibit GAPLINC or CSF1, or that reintroduce miR-135b-5p, may effectively suppress RCC progression by disrupting this oncogenic signaling pathway.

5. miR-135b and cancer resistance

Drug resistance poses a significant challenge in cancer therapy, diminishing treatment effectiveness, increasing the risk of recurrence and metastasis, and ultimately compromising patient survival [179–182]. Overcoming drug resistance is essential for improving treatment outcomes and prolonging patient life. Several studies have highlighted the significant role of miR-135b in influencing cancer cell response to chemotherapy. Elevated miR-135b levels reduce the sensitivity of ovarian, colorectal, gastric, and esophageal cancer cells to cisplatin [45,68,126,183], CRC cells to oxaliplatin, 5-FU and ADR [43,44,184–186] and PC cells to gemcitabine [41]. Conversely, overexpression of miR-135b can enhance the sensitivity of GC cells to 5-FU and ADR [38], BC cells to trastuzumab and ADR [46,47], and NSCLC cells to cisplatin [187]. Additionally, miR-135b plays a significant role in radiotherapy, where its inhibition has been shown to improve the sensitivity of NSCLC and glioblastoma cells to radiation [81,163]. These findings, summarized in Table 3, suggest that modulating miR-135b levels may offer a promising approach to overcoming drug resistance and enhancing the efficacy of cancer treatments.

6. Controversy over miR-135b in cancer

The role of miR-135b in BC, melanoma, glioblastoma, HCC, and RCC remains highly controversial. Conflicting findings have emerged regarding its expression levels and effects on cancer cell proliferation, migration, and invasion. For instance, multiple studies have consistently demonstrated that miR-135b is highly expressed in BC cell lines such as MDA-MB-231, MCF-7, and SK-BR-3, where it significantly promotes proliferation, migration, and invasion [131,134,137]. However, Pu et al.'s [48] findings present a stark contrast to these conclusions. Similarly, in melanoma, Hu et al. [164] observed elevated miR-135b levels in melanoma tissue samples compared to non-cancerous areas. Suppressing miR-135b in primary melanoma cells and A375 cells led to reduced proliferation and migration [164]. Conversely, Zhang et al. [188] reported that miR-135b expression was downregulated in melanoma clinical samples and A375 cell lines. Overexpressed miR-135b suppressed proliferation, and migration [188]. In glioblastoma, Yu et al. [162] and Xiao et al. [163] reported elevated miR-135b-5p expression in clinical glioblastoma tissue samples compared to normal tissues, which contradicted findings by Mokgautsi et al. [189]. Furthermore, the impact of miR-135b-5p on the proliferation of U87-MG glioblastoma cells also showed inconsistencies between Yu et al. [162] and Istiqamah et al. [190]. Discrepancies also exist in the role of miR-135b in HCC. While several studies reported that miR-135b

Table 3
Regulatory effect of miR-135b on cancer drug resistance.

Chemotherapy drug	Signaling pathway	Sensibility	Cancer	References
Cisplatin	miR-135b-5p/MST1/MAPK	Restrains	GC	[39]
Cisplatin	miR-135b-5p/TXNIP	Restrains	EC	[45]
Cisplatin	miR-135b-5p/KLF13	Restrains	CRC	[68]
Cisplatin	miR-135b-3p/PTEN	Restrains	OC	[126]
Cisplatin	miR-135b-5p/KLF4	Restrains	GC	[183]
Cisplatin	miR-135b-5p/FZD1	Promotes	NSCLC	[187]
ADR/5-FU	miR-135b-5p/ITGA2	Promotes	GC	[38]
ADR	miR-135b-5p/AGR2	Promotes	BC	[46]
ADR	miR-135b-5p/LATS2	Restrains	CRC	[184]
5-FU	miR-135b-5p/ST6GALNAC2/PI3K/AKT	Restrains	CRC	[185]
5-FU	miR-135b-5p/Spock1	Restrains	CRC	[186]
Gemcitabine	miR-135b-5p/BMAL1/YY1	Restrains	PC	[41]
Oxaliplatin	miR-135b-5p/FOXO1/Bim/Noxa	Restrains	CRC	[43]
Oxaliplatin	miR-135b-5p/MUL1/ULK1	Restrains	CRC	[44]
Trastuzumab	miR-135b-5p/Cyclin D2	Promotes	HER-2 positive BC	[47]
Radiation	LncRNA GAS5/miR-135b-5p	Restrains	NSCLC	[81]
Radiation	miR-135b-5p/GSK3β	Restrains	Glioblastoma multiforme	[163]

FZD1: Frizzled class receptor 1; Spock1: Sparc/osteonectin, cwcv and kazal-like domain proteoglycan 1; Bim: Bcl-2-interacting mediator of cell death; Noxa: Phorbol-12-myristate-13-acetate-induced protein 1.

promotes proliferation in Huh7 cells [70,151,152], Bao et al. [191] demonstrated that overexpression of miR-135b inhibits proliferation in the same cell line. Similar contradictions are observed in RCC. Wang et al. [178] found significant downregulation of miR-135b-5p in RCC cell lines, suggesting a cancer-suppressive role, while Zhang et al. [192] reported its upregulation in both RCC tissues and urine-derived extracellular vesicles, implicating it in cancer progression. To understand the basis of these discrepancies, we first performed a comparative analysis using the miRBase database, confirming that all studies focused on miR-135b-5p rather than miR-135b-3p. Despite this consistency, the effects of miR-135b-5p on cancer cell proliferation vary even within the same cell line (e.g., MDA-MB-231, A375, U87-MG, Huh7). Several factors may explain these inconsistencies. First, the heterogeneity of cancer tissue may be the key factor, and clinical samples from different sources may lead to changes in the expression level and functional role of miR-135b due to differences in molecular characteristics and pathological status. Second, as a multi-target miRNA, miR-135b has complex and variable functions in different cell lines and cancer types. Finally, inconsistencies in the expression and effects of miR-135b within the same cell line may be linked to variations in cellular survival conditions, culture environments, and experimental techniques, including differences in culture media, passage numbers, and gene manipulation methods.

Therefore, the role of miR-135b in BC, melanoma, glioblastoma, HCC, and RCC necessitates further in-depth research and validation. Future research should focus on resolving these controversies by standardizing experimental conditions, expanding sample sizes, and utilizing more advanced multi-omics techniques to clearly elucidate the specific roles of miR-135b in the initiation and progression of these cancers.

7. Conclusions and future perspectives

miR-135b is abnormally upregulated in GC, PC, CRC, EC, OC, CC, OSCC, NPC, PTC, NSCLC, osteosarcoma, and MM, where it plays a pro-carcinogenic role. It can promote the proliferation, migration, and invasion of the aforementioned cancer cells by regulating multiple targets, and can itself be modulated by various drugs, proteins, and non-coding RNAs (Fig. 5). The oncogenic effects of miR-135b are primarily linked to key signaling pathways such as Hippo, Notch, Wnt/β-catenin, TGF-β, PI3K/AKT, NF-κB, JAK/STAT, AKT/mTOR, and PTEN/AKT/HIF-1α (Fig. 5). Targeting miR-135b can disrupt cancer cell development, making it a promising candidate in cancer therapy. Furthermore, miR-135b shows potential as a diagnostic and prognostic biomarker, with its expression levels in tissues or blood correlating with cancer progression. It also influences the efficacy of chemotherapy and radiotherapy. Overall, miR-135b plays a critical role in cancer progression and holds promise as a potential target for early cancer diagnosis and gene therapy, as well as a valuable biomarker for prognostic evaluation and monitoring treatment efficacy. Therefore, intervention strategies targeting this miRNA have the potential to emerge as novel therapeutic approaches for effectively controlling cancer progression.

In this manuscript, we summarized the role and mechanism of miR-135b in cancer and highlighted that miR-135b-based intervention strategies may provide new directions for cancer treatment. Although current anti-cancer strategies targeting miR-135b have not yet progressed to clinical trials, numerous preclinical animal studies have demonstrated the significant cancer-inhibitory effects of miR-135b inhibitors across various cancer types (Table 1). Additionally, related research patents highlight that miR-135b can serve as a biomarker for cancer diagnosis and prognosis (CN112695095A), and its inhibitors have been shown to effectively suppress lung metastasis and recurrence in osteosarcoma (CN106692987A). These findings indicate that miR-135b-based anti-cancer strategies hold significant clinical translational potential, emphasizing further investigation and development.

Although foundational research highlights miR-135b's substantial clinical translational potential in anti-cancer strategies, several challenges must be addressed before it can be applied in practice. First, the stability and targeted delivery of miR-135b remain urgent issues. As miRNAs are prone to degradation in the bloodstream, developing reliable delivery systems is essential to ensure therapeutic doses are accurately delivered to cancer cells. Second, the safety of miR-135b-based treatments is a crucial concern. For example, MRX-34, the first miR-34 mimic to enter clinical trials, was discontinued due to severe immune reactions [193], underscoring the need to rigorously evaluate potential off-target effects and immune-related risks in miR-135b therapy. Additionally, the potential for resistance development with long-term therapy is another critical area requiring further investigation. Based on this, we propose that future research initially focus on developing liquid biopsy technologies utilizing blood or urine samples to detect miR-135b expression for early cancer diagnosis and personalized treatment monitoring. This approach not only shows great potential for clinical translation but also aligns with advancements in personalized medicine. Although preclinical studies have made progress in understanding miR-135b, further research is needed to address its toxicity, safety, targeting, and potential for drug resistance. Large-scale animal studies should be prioritized to validate the efficacy, safety, and resistance profiles of miR-135b inhibitors. Additionally, optimizing selective drug delivery systems and exploring their combination with existing anti-cancer therapies will be essential to improving therapeutic outcomes. Furthermore, while initial insights have been gained into miR-135b's expression changes and potential targets in cancer, advanced techniques such as single-cell sequencing could be utilized to

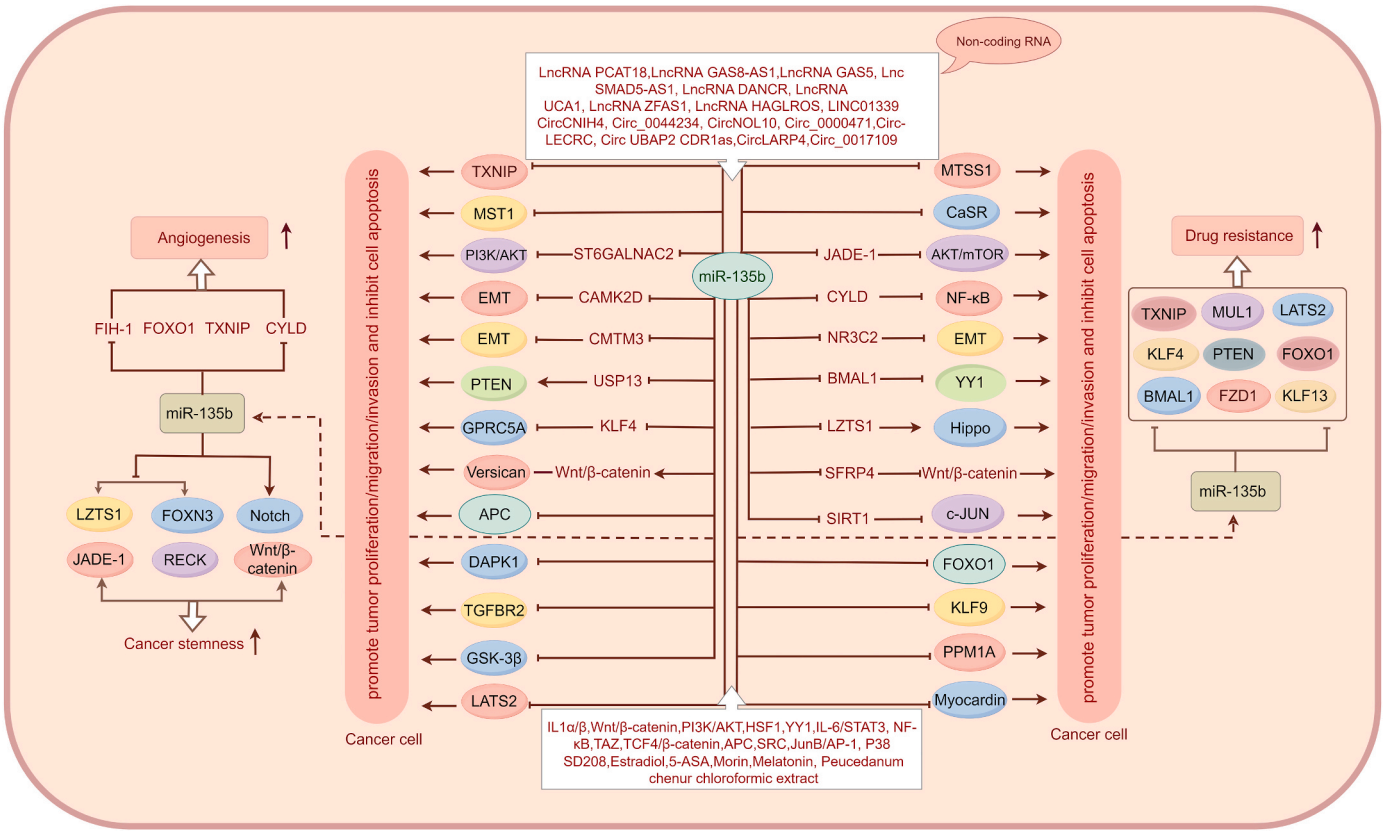

Fig. 5. The mechanism of miR-135b's action in cancer biology and the upstream factors regulating miR-135b. miR-135b regulates various biological characteristics of cancer cells, such as proliferation, apoptosis, migration, invasion, angiogenesis, cancer stemness, and drug resistance by inhibiting multiple target genes. Various non-coding RNAs, coding proteins, and drugs can modulate the expression of miR-135b.

investigate the dynamic behavior of miR-135b within the cancer microenvironment. These studies could elucidate its interactions with various cell types, including immune cells and cardiomyocytes, thereby providing a more comprehensive understanding of miR-135b's regulatory network and a theoretical foundation for its future clinical application.

CRediT authorship contribution statement

Yingchun Shao: Writing – review & editing, Writing – original draft, Conceptualization. **Shuangshuang Zhang:** Writing – review & editing, Validation, Investigation. **Yuxin Pan:** Writing – review & editing, Validation. **Zhan Peng:** Writing – review & editing, Validation. **Yinying Dong:** Writing – review & editing, Validation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (82400429; 81803058), Natural Science Foundation of Shandong Province (ZR2023QH007; ZR2023MH102), Chinese Society of Clinical Oncology (Y-QL2019-0337), MountTai Scholar Project Special Fund (tsqn202211363), and Natural Science Foundation of Qingdao Municipality (23-2-1-135-zyyd-jch). Fig. 1 was created using BioRender.com. Figs. 2–5 were drawn by Figdraw (www.figdraw.com).

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