MicroRNA-325: A comprehensive exploration of its multifaceted roles in cancer pathogenesis and therapeutic implications (Review)

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Abstract. MicroRNA (miRNA/miR) represents a category of endogenous, short-chain non-coding RNA molecules comprising ~22 nucleotides. Specifically, miR-325 is situated within the first sub-band of region 2 on the short arm of the X chromosome. Notably, aberrant expression of miR-325 has been observed across various tumor systems, spanning the nervous, endocrine, respiratory, reproductive and digestive systems. miR-325 exhibits the capacity to target a minimum of 20 protein-coding genes, thereby influencing diverse cellular processes, including cell proliferation, epithelial-mesenchymal transition, apoptosis, invasion and migration. Moreover, miR-325 serves a pivotal role in the formation of six competing endogenous RNA (ceRNA) regulatory axes, involving one circular RNA, four long non-coding RNA and one additional miRNA. By participating in various signaling pathways through gene targeting, the abnormal expression of miR-325 has been associated with clinicopathological conditions in diverse patients with cancer, significantly impacting both the clinicopathology and prognosis of affected individuals. Additionally, miR-325 has been associated with the development of resistance to oxaliplatin, cisplatin and doxorubicin in cancer cells. Its involvement in the anticancer molecular mechanisms of these agents underscores its potential significance in therapeutic contexts. However, it is noteworthy that the current study did not specifically address sex-based cell line selection. In conclusion, the present review provides a comprehensive summary of the relevant findings concerning miR-325, offering valuable insights for future research endeavors focused on determining the molecular mechanisms associated with this miRNA.

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Key words: cancer pathogenesis, competing endogenous RNA regulatory axes, therapeutic target, drug resistance

Contents

1. Introduction

MicroRNAs (miRNAs/miRs) are concise, endogenous non-coding RNAs, typically ~22 nucleotides in length, which serve a crucial role in the orchestration of gene expression within multicellular organisms, exerting influence over mRNA stability and translation (1). The dysregulation of miRNAs is frequently implicated in the malignant transformation of cells, as highlighted in previous research (2). miRNAs contribute significantly to biological processes underpinning cancer progression, metastasis, and the development of resistance to treatment (3).

One such miRNA of interest is miR-325, which resides in the first sub-band of region 2 on the short arm of the X chromosome (1). miR-325 has garnered attention due to its aberrant expression across >10 types of cancer. Given its location on the sex chromosomes, there is a hypothesis that the regulation of miR-325 expression may be linked to sex differences. However, prior investigations have often overlooked sex differences in the selection of cell lines, prompting the need for more comprehensive exploration in this area (2,4).

Further analysis of miR-325 regulation has unveiled its interaction with six competing endogenous RNAs (ceRNAs), comprising one circular RNA (circRNA), four long non-coding RNAs (lncRNAs) and one additional miRNA. miR-325 exerts its regulatory influence by targeting and inhibiting 20 protein-coding genes (PCGs), thereby modulating key cancer cell behaviors, including the cell cycle, proliferation,

epithelial-mesenchymal transition (EMT), apoptosis, invasion and migration (5-7). The present review also revealed a notable association between diminished expression of miR-325 and shortened overall survival (OS) and progression-free survival (PFS) across various types of cancer. Furthermore, miR-325 has been implicated in resistance to three anticancer drugs, and may actively participate in the molecular mechanisms of action associated with oxaliplatin (8), cisplatin (CDDP) (9,10) and doxorubicin (DOX) (11).

The aim of this review was to systematically examine the current state of research surrounding miR-325, including its abnormal expression, molecular mechanisms and clinical implications. By providing a consolidated overview of the knowledge on miR-325, this review seeks to offer valuable insights to guide future investigations in this field.

2. Abnormal expression of miR-325 in cancer

As illustrated in Table I, miR-325 exhibits consistent downregulation in both cellular and tissue contexts across eight distinct cancer types. Notably, miR-325 is downregulated in colorectal cancer (CRC) (4,5,11), gastric cancer (GC) (12,13), HCC (8,14,15), bladder urothelial carcinoma (BLCA) (6,16,17), non-small cell lung cancer (NSCLC) (18,19), oral squamous cell carcinoma (OSCC) (20) and papillary thyroid cancer (PTC) (21). In addition, miR-325 expression is downregulated in a T-cell acute lymphoblastic leukemia (T-ALL) cell line (5). Notably, miR-325 demonstrates heightened expression levels in glioblastoma multiforme and lower-grade glioma (GBM/LGG) (22) and nasopharyngeal carcinoma (NPC) (23). Meanwhile, the status of miR-325 expression in breast cancer (BC) (23,24) appears to be contentious.

As shown in Table I and Fig. 1, a comprehensive analysis was conducted by comparing the expression differences of miR-325 between cancer tissues and corresponding para-cancerous tissues, as well as between cancer cells and para-cancerous cells, across 11 cancer types.

3. miR-325 and cancer cell behaviors

As shown in Fig. 1 and Table II, miR-325 is considered a potent regulator that can inhibit 20 PCGs, thereby exerting control over various cancer cell behaviors, such as proliferation, EMT, apoptosis, invasion and migration.

Cell cycle orchestration involves a complex interplay of proteins, enzymes, cytokines and signaling pathways, which are crucial for cell proliferation and repair (25). In NSCLC, miR-325 has been shown to impede the progression of the cell cycle S phase or G_2/M phase in the HCT116 cell line by targeting the gene kinesin family member 2C (KIF2C) (7).

Cancer proliferation signifies a dysregulated balance between cell gain and loss, where mutant tumor cells proliferate faster than they die (26). miR-325 has been reported to curtail cancer cell proliferation in NSCLC, CRC, BLCA, HCC, skin cutaneous melanoma (SKCM), T-ALL, NPC, BC, PTC, GC and GBM/LGG by targeting 14 genes, including high mobility group box 1 (HMGB1) (8,18), glutathione peroxidase 2 (GPX2) (10), tripartite motif containing 14 (TRIM14) (5), metallothionein 3 (MT3) (27), C-X-C motif chemokine ligand 17 (CXCL17) (15), dolichyl-phosphate N-acetylglucosaminephosphotransferase 1 (DPAGT1) (10,12), aquaporin 5 (AQP5) (16), mitogen-activated protein kinase kinase kinase 2 (MAP3K2) (28), BAG cochaperone 2 (BAG2) (5), cell division cycle associated 5 (CDCA5) (23), lipocalin 15 (LCN15) (29), DEAD-box helicase 5 (21), human antigen R(HuR) (14) and forkhead box M1 (FOXM1) (22).

Apoptosis, a well-known form of programmed cell death, serves as a key physiological mechanism limiting cell population expansion (26). miR-325 has been shown to enhance cancer cell apoptosis in HCC, T-ALL and GC by targeting four genes, namely DPAGT1 (10,12), AQP5 (16), BAG2 (5) and HuR (14) .

EMT, a critical cell biological program, is implicated in development and wound healing, and its activation is associated with the formation of normal and cancer stem cells (30). It has been demonstrated that miR-325 impedes EMT progression in BLCA by targeting the gene MT3 (27). By contrast, in BC, miR-325 may promote EMT progression by targeting the gene S100 calcium binding protein A2 (S100A2) (24).

Cancer metastasis, the primary cause of cancer-related death, is reliant on an increase in cell migration during tumor progression, enabling tumor cells to escape the primary tumor and invade adjacent tissues to form metastases (31). miR-325 has been shown to inhibit the invasion and migration of cancer cells in NSCLC, CRC, BLCA, HCC, SKCM, NPC, BC and GBM/LGG by targeting 12 genes: KIF2C (7), HMGB1 (8,18), GPX2 (10), TRIM14 (5), MT3 (27), acid phosphatase 5 (ACP5) (32), HMGB1 (12), CXCL17 (15), MAP3K2 (28), CDCA5 (23), LCN15 (29), and FOXM1 (22). By contrast, miR-325 can promote the invasion and migration of BC cancer cells by targeting the gene S100A2 (24).

4. miR-325 and its ceRNAs

ceRNAs competitively bind to miRNA, thereby attenuating its inhibitory influence on target mRNA and regulating cellular activity at the post-transcriptional level (31). The ceRNA regulatory network of miR-325, as shown in Table III and Fig. 2, involves circRNAs and lncRNAs serving pivotal roles in cellular biology.

circRNAs exert diverse biological functions by serving as transcriptional regulators, miRNA sponges and protein templates (33). As depicted in Table III, the inhibitory impact of miR-325 on target genes was competitively counteracted by Circ_0069313. In OSCC, the Circ_0069313/miR-325/FOXP3 axis was implicated in inducing OSCC cell immune escape (20).

lncRNAs are RNA molecules exceeding 200 nucleotides in length, which are central to cellular regulation (34). The regulatory interplay involving four lncRNAs, AR, FOXD3-AS1, LINC01515 and MSC-AS1, has been shown to competitively inhibit miR-325 (11,22,26,30) (Table III; Fig. 2).

The lncRNA/miR-325/PCG axis has emerged as a potent regulator hindering cancer progression, including its inhibitory role in HCC. Notably, the AR/miR-325/ACP5 axis has been shown to exhibit the capability to impede invasion and migration of HCC cells (32). Additionally, three distinct lncRNA/miR-325/PCG axes have been implicated in promoting cancer progression. In SKCM, the FOXD3-AS1/miR-325/MAP3K2 axis can promote proliferation, migration and invasion of cancer cells (28). In NPC, the

Table I. Aberrant expression of miR-325 in various types of cancer.

A, Digestive system

First author, year	Cancer	miR-325 expression	Cell line	Tissue or serum	(Refs.)
Zhang, 2021	CRC	Downregulated	FHC versus HT29 and SW480	Paracancerous tissues versus CRC tissues from patients	(8)
He, 2021	CRC	Downregulated	NCM460 versus HT29, SW620, HCT116 and SW480	Paracancerous tissues versus CRC tissues from patients	(5)
Li, 2021	CRC	Downregulated	CT-26 versus CD115 and RANK	NA	(13)
Huang, 2023	GC	Downregulated	HGC-27c versus SGC-7901	NA	(14)
Sun, 2020	GC	Downregulated	NA	Adjacent normal gastric epithelium tissues versus GC tissues from the 137 patients	(9)
Li, 2021	HCC	Downregulated	NA	20 pairs of paracancerous tissues versus HCC tissues from patients	(15)
Zhang, 2019	HCC	Downregulated	HepG2 and Huh7 versus HepG2.2.15 and Huh70-1.3	20 pairs of paracancerous tissues versus HBV-HCC tissues from patients	(16)
Li, 2015	HCC	Downregulated	LO2 versus SMMC-7721, Hep3B, HepG2, Huh7 and Bel7404	Paracancerous tissues versus HCC tissue from the 99 patients	(12)

B, Urinary system

First author, year	Cancer	miR-325 expression	Cell line	Tissue or serum	(Refs.)
Lin, 2018	BLCA	Downregulated	HT-1197 and HS228 versus T24, RT4, 5637, HT-1376, J82, UM-UC-3 and TCCSUP	Paracancerous tissues versus BLCA tissues from 164 patients	(17)
Sun, 2020	BLCA	Downregulated	T24, J82 and UMUC3 versus SV-HUC-1, SW780 and HT1376	Paracancerous tissues versus BLCA tissues from 30 patients	(6)
Li, 2020	BLCA	Downregulated	T24 and 5637 versus 5637-R and T24-R cells	NA	(18)

C, Nervous system

First author, year	Cancer	miR-325 expression	Cell line	Tissue or serum	(Refs.)
Xiong, 2021	GBM/ LGG	Upregulated	NHA, SW1783 versus U87 and LN229	Paracancerous tissues versus BLCA tissues from 24 patients	(22)

D, Respiratory system

First author, year	Cancer	miR-325 expression	Cell line	Tissue or serum	(Refs.)
Gan, 2019	NSCLC	Downregulated	NA	Paracancerous tissues versus NSCLC tissues from patients	(7)
Yao, 2015	NSCLC	Downregulated	16HBE versus A549, H358, H1299, H1650 and SPCA1	107 pairs of paracancerous tissues versus NSCLC tissues from patients	(19)
Liu, 2021	NPC	Upregulated	NP69 versus 5-8F, C666-1, SUNE1 and 6-10B	Paracancerous tissues versus NPC tissues from patients	(23)

Table I. Continued.

E, Derma

First author, year	Cancer	miR-325 expression	Cell line	Tissue or serum	(Refs.)
Chen, 2022	OSCC	Downregulated	NA	Paracancerous tissues versus OSCC tissues from patients	(20)

F, Circulatory system

First author, year	Cancer	miR-325 expression	Cell line	Tissue or serum	(Refs.)
He, 2021	T-ALL	Downregulated	T cell versus Jurkat, CCRF-CEM, TALL-1 and KOPTK1	Paracancerous tissues versus T-ALL tissues from patients	(5)

G, Reproductive system

First author, year	Cancer	miR-325 expression	Cell line	Tissue or serum	(Refs.)
Wang, 2021	BC	Upregulated	MCF10A versus MDA-MB-231, MDA-MB-453, MDA-MB-468, BT-20 and MCF7	Noncancerous tissues versus primary BC tissues from 30 patients	(24)
Liu, 2023	BC	Downregulated	MB157 versus MDA-MB-231, MDA-MB-436, SK-BR-3 and CAMA-1	Paracancerous tissues versus BC tissue from 15 patients	(29)

H, Endocrine system

First author, year	Cancer	miR-325 expression	Cell line	Tissue or serum	(Refs.)
Xin, 2020	PTC	Downregulated	Nthyori3-1 versus BHP5-16, TPC1, K1 and BHP2-7	Paracancerous tissues versus PTC tissue from 24 patients	(21)

miR, microRNA; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; BLCA, bladder urothelial carcinoma; HCC, hepatocellular carcinoma; SKCM, skin cutaneous melanoma; OSCC, oral squamous cell carcinoma; T-ALL, T-cell acute lymphoblastic leukemia; NPC, nasopharyngeal carcinoma; BC, breast cancer; PTC, papillary thyroid cancer; GC, gastric cancer; GBM/LGG, glioblastoma multiforme and lower-grade glioma; NA, not applicable.

LINC01515/miR-325/CDCA5 axis has been shown to foster proliferation, migration and invasion, while inhibiting apoptosis (23). Similarly, in CRC, the MSC-AS1/miR-325/TRIM14 axis may stimulate proliferation, invasion and migration of cancer cells (5).

The base sequence of miR-325 is 3'-UGUGAAUGACCUGUGGAUGAUCC-5' (5) (Fig. 3A and C). Four target genes have been observed to bind to this sequence. Specifically, miR-325 forms a binding interaction with CDCA5 through the 3'-UgUGGAUGAUC-5' sequence (23), TRIM14 and MAP3K2 through the 3'-GAUGAUC-5' sequence (11,26), and BAG2 through the 3'-AUGAUC-5' sequence (5) (Fig. 3A). In addition, three lncRNAs have been shown to bind to the base sequence of miR-325. The binding interactions are as follows: miR-325 binds to LINC01515 through the 3'-UgAAuGA-CCU----gUgGAUGAUC-5' sequence (23), MSC-AS1 through the 3'-UgAAUgACCugUgGAUGAUC-5' sequence (5), and FOXD3-AS1 through the 3'-GAUGAUC-5' sequence (27).

As shown in Fig. 3B, the pre-miR-325 sequence has 13 target genes, and its base sequence is 3'-AACUAUCCCUCCAGGAGUUAUUUGUUUAAUA-5' (6). Pre-miR-325 forms specific binding interactions with the following genes: MT3 through the 3'-CCUCCagaaGUUAUU-5' sequence, heat shock protein family A member 12B (HSPA12B) through the 3'-CUCCAggaGUUAUUU-5' sequence, ACP5 and LCN15 through the 3'-AGUUAUU-5' sequence, LNX1, CXCL17, S100 calcium binding protein A4 (S100A4), S100A2 and HuR through the 3'-AGUUAUUU-5' sequence, and FOXP3, AOP5, GPX2, KIF2C and HuR through the 3'-GUUAUU U-5' sequence. Additionally, pre-miR-325 binds to FOXM1

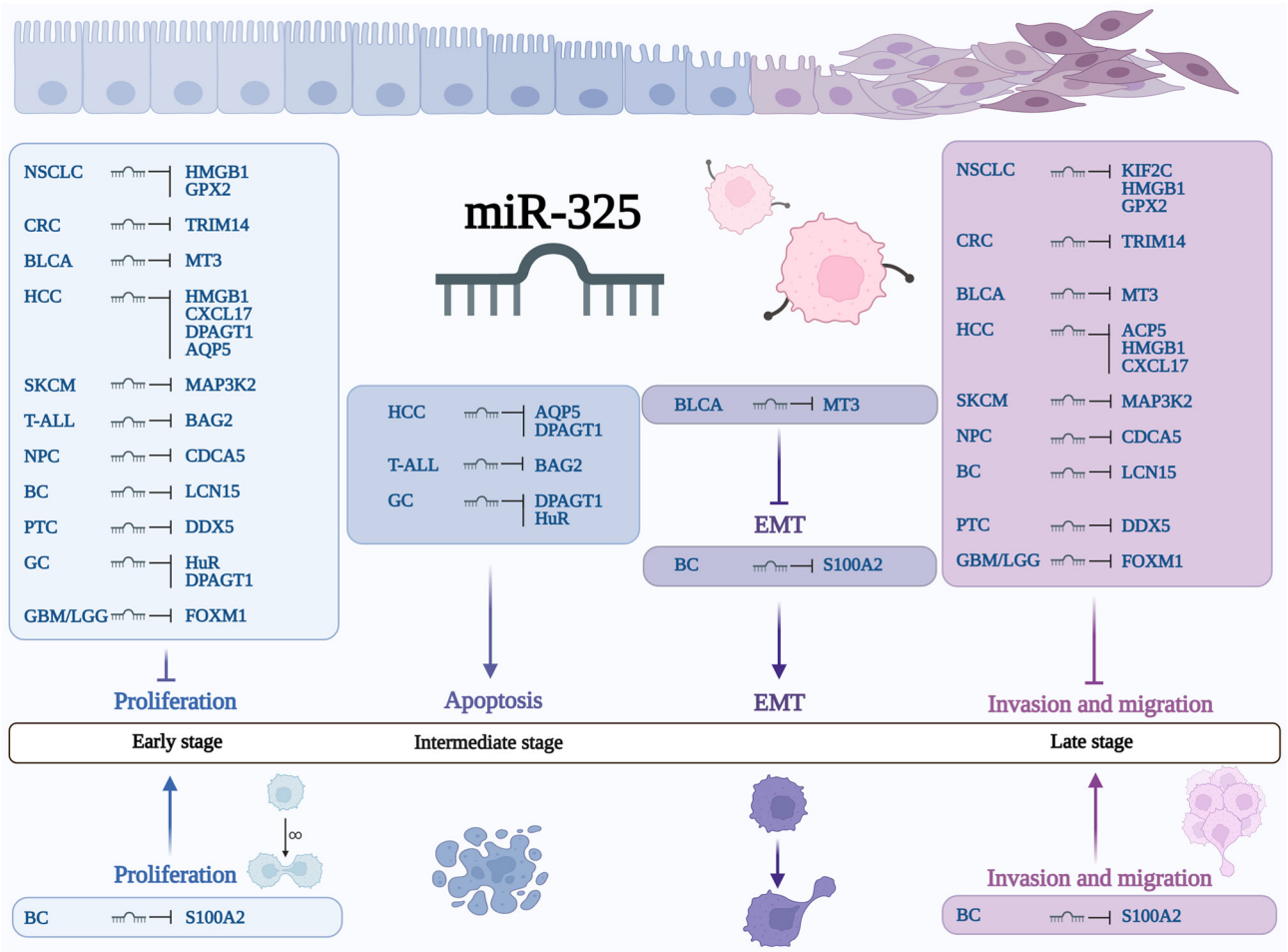

Figure 1. miR-325 and the regulation of cancer cell behaviors. miR-325 can regulate a variety of cancer cell biological behaviors through its competing endogenous RNA networks or target genes. Arrows indicate enhancement and flat lines indicate inhibition. miR, microRNA; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; BLCA, bladder urothelial carcinoma; HCC, hepatocellular carcinoma; SKCM, skin cutaneous melanoma; T-ALL, T-cell acute lymphoblastic leukemia; NPC, nasopharyngeal carcinoma; BC, breast cancer; PTC, papillary thyroid cancer; GC, gastric cancer; GBM/LGG, glioblastoma multiforme and lower-grade glioma; EMT, epithelial-mesenchymal transition.

through the 3'-GAGUUAUU-5' sequence. Furthermore, as shown in Fig. 3D, pre-miR-325 forms a binding interaction with Circ-0069313 through the 3'-GUUAUUU-5' sequence.

5. miR-325 and cancer therapy

As illustrated in Table IV, the prognostic significance of miR-325 is underscored by its dysregulation, and is associated with the pathological state of cancer tissues and diagnostic risk, influencing patient prognosis. In GC, HCC, NSCLC and BLCA, diminished miR-325 expression has been reported to be associated with adverse patient outcomes. In GC, reduced miR-325 expression has been shown to align with a shorter OS (9). Similarly, in HCC, low miR-325 expression corresponded to earlier TNM stage, and shorter OS and PFS, alongside factors such as tumor size and metastasis (12). Patients with NSCLC with low miR-325 expression exhibited shorter OS and PFS (15) (19). In addition, in BLCA, diminished miR-325 expression was associated with a shorter OS (17). Notably, miR-325 has been reported to target and inhibits KIF2C expression in NSCLC, with high KIF2C expression linked to shorter OS (7). In NPC, elevated LINC01515 expression, suppressing miR-325, has been shown to be associated with poor prognosis and OS in patients (23). Similarly, in NSCLC, heightened GPX2 expression, directly targeted by miR-325, was negatively associated with miR-325 expression, and associated with poor prognosis and OS (10). In OSCC, hsa_circ_0069313 can bind to miR-325, inhibiting its expression, and was thus revealed to be associated with poor prognosis and OS (20). Furthermore, in SKCM, FOXD3-AS1, targeted by miR-325, was upregulated and negatively associated with miR-325 expression, contributing to poor prognosis and OS in patients (28)

The development of drug resistance in tumor cells significantly contributes to the ineffectiveness of chemotherapy (35). As shown in Fig. 4A, miR-325 may serve a crucial role in modulating the response of cancer cells to various anticancer drugs. Oxaliplatin is a highly effective chemotherapy agent in CRC treatment. This third-generation platinum compound induces DNA cross-linking in cancer cells, resulting in apoptotic cell death. In CRC, miR-325 sensitized cancer cells to oxaliplatin-induced cytotoxicity by modulating the HSPA12B/PI3K/AKT/Bcl-2 pathway (8). CDDP, which is employed in treating diverse types of human cancer, such as bladder, head and neck, lung, ovarian and testicular cancer (36), has been shown to encounter regulatory influence

Table II. Target genes of miR-325 and effects of miR-325 by targeting PCGs *in vitro* and *in vivo*.

First author, year	Cancer	PCG	Effect *in vitro*	Cell line	Effect *in vivo*	Xenograft model	(Refs.)
Gan, 2019	NSCLC	KIF2C	Migration (+), invasion (-) and cell cycle (-)	A549, H1299, H226 and H520	NA	NA	(7)
Yao, 2015	NSCLC	HMGB1	Proliferation (-) and invasion (-)	A549, H1299, SPCA1, H1650, H358 and 16HBE	NA	NA	(19)
Wang, 2022	NSCLC	GPX2	Proliferation (-), migration (-), invasion (-), and cisplatin resistance (-)	A549 and NCIH1385	Tumor growth (-)	BEAS-2B cell xenograft in BALB/c male mice	(10)
Zhang, 2021	CRC	HSPA12B	Viability (-)	HT29 and SW480	NA	NA	(8)
He, 2021	CRC	TRIM14	Proliferation (-), migration (-) and invasion (-)	HT29, SW620, HCT116 and SW480	NA	NA	(5)
Li, 2021	CRC	S100A4	Osteoclasto-genesis (-)	CT-26	Tumor growth (-)	CT-26 cell xenograft in BALB/c male mice	(13)
Sun, 2020	BLCA	MT3	Proliferation (-), migration (-), invasion (-), and EMT (-)	T24	NA	NA	(6)
Han, 2013	HCC	ACP5	Migration (-) and invasion (-)	HA22T	Tumor metastasis (-)	HA22T xenograft in nude mouse	(31)
Li, 2015	HCC	HMGB1	Proliferation (-) and invasion (-)	LO2 versus SMMC-7721, Hep3B, HepG2, Huh7 and Bel7404	NA	NA	(12)
Li, 2021	HCC	CXCL17	Proliferation (-), migration (-), invasion (-) and angiogenesis (-)	HepG2, Bel-7402 and SMMC-7721	NA	NA	(15)
Li, 2019	HCC	DPAGT1	Proliferation (-), apoptosis (+) and DOX resistance (-)	Huh7-1.3 and HepG2.2.15	Tumor growth (-)	Huh7e1.3 and DOX-R xenograft in nude mice	(11)
Zhang, 2019	HCC	AQP5	Proliferation (-) and apoptosis (+)	Huh7-1.3 and HepG2.2.15	NA	NA	(16)
Sun, 2020	SKCM	MAP3K2	Proliferation (-), migration (-) and invasion (-)	A375 and SK-MEL-1	NA	NA	(27)
He, 2021	T-ALL	BAG2	Proliferation (-) and apoptosis (+)	Jurkat	NA	NA	(5)
Liu, 2021	NPC	CDCA5	Proliferation (-), migration (-) and invasion (-)	5-8F and C666-1	NA	NA	(23)
Liu, 2023	BC	LCN15	Proliferation (-), migration (-) and invasion (-)	SK-BR-3 and CAMA-1	NA	NA	(29)

Table II. Continued.

First author, year	Cancer	PCG	Effect *in vitro*	Cell line	Effect *in vivo*	Xenograft model	(Refs.)
Wang, 2021	BC	S100A2	Proliferation (+), invasion (+) and EMT (+)	MDA-MB-231 and MCF7	NA	NA	(24)
Xin, 2020	PTC	DDX5	Proliferation (-) and migration (-)	BHP5-16, TPC1, K1 and BHP2-7	NA	NA	(21)
Huang, 2023	GC	HuR	Proliferation (-) and apoptosis (+)	SGC-7901 and HGC-27	Tumor growth (-)	SGC-7901-GFP cells xenograft in larval zebrafish	(14)
Sun, 2020	GC	DPAGT1	Proliferation (-) and apoptosis (+)	MKN45	NA	NA	(9)
Xiong, 2021	GBM/LGG	FOXM1	Proliferation (-), migration (-) and invasion (-)	SW1783 and U87	Tumor growth (-)	U87 cell xenograft in BALB/c nude mice	(22)

miR, microRNA; PCG, protein-coding gene; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; BLCA, bladder urothelial carcinoma; HCC, hepatocellular carcinoma; SKCM, skin cutaneous melanoma; T-ALL, T-cell acute lymphoblastic leukemia; NPC, nasopharyngeal carcinoma; BC, breast cancer; PTC, papillary thyroid cancer; GC, gastric cancer; GBM/LGG, glioblastoma multiforme and lower-grade glioma; DOX, doxorubicin; EMT, epithelial-mesenchymal transition; NA, not applicable.

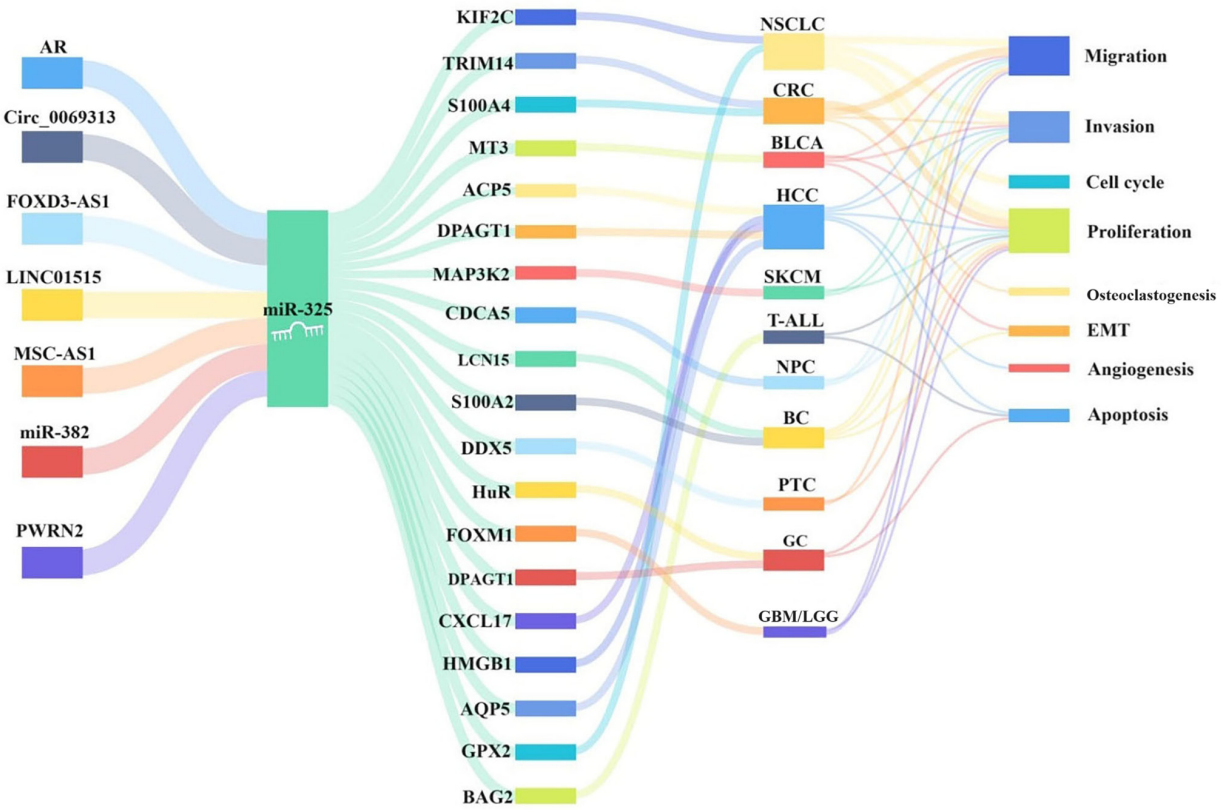

Figure 2. ceRNA networks associated with miR-325. This intricate network serves a pivotal role in the regulation of diverse biological processes within cancer cells. Notably, it exerts influence over essential cellular behaviors, including migration, invasion, cell cycle progression, proliferation, osteoclastogenesis, EMT, angiogenesis and apoptosis. Across a spectrum of 11 different cancer types, the impact of the miR-325 ceRNA networks underscores their significance in orchestrating intricate molecular mechanisms that contribute to cancer pathogenesis. ceRNA, competing endogenous RNA; miR, microRNA; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; BLCA, bladder urothelial carcinoma; HCC, hepatocellular carcinoma; SKCM, skin cutaneous melanoma; T-ALL, T-cell acute lymphoblastic leukemia; NPC, nasopharyngeal carcinoma; BC, breast cancer; PTC, papillary thyroid cancer; GC, gastric cancer; GBM/LGG, glioblastoma multiforme and lower-grade glioma; EMT, epithelial-mesenchymal transition.

Table III. ceRNAs of miR-325.

			Binding site of ceRNA and miR-325		Binding site of miR-325 and PCG		
First author, year	CeRNA axis	Cancer	ceRNA, 5'-3'	miR-325, 3'-5'	PCG, 5'-3'	miRNA, 3'-5'	(Refs.)
Han, 2013	AR/miR-325/ACP5	HCC	NA	NA	UCAAUAA	AGUUAUU	(31)
Chen, 2022	Circ_0069313/ miR-325/FOXP3	OSCC	CAAUAAA	GUUAUUU	CAAUAAA	GUUAUUU	(20)
Sun, 2020	FOXD3-AS1/ miR-325/MAP3K2	SKCM	CUACUAG	GAUGAUC	CUACUAG	GAUGAUC	(27)
Liu, 2021	LINC01515/ miR-325/CDCA5	NPC	AaUUgCUaGGAgu ugaAaCUACUAG	UgAAuGA-CCU-gUgGAUGAUC	AgACCUACUAG	UgUGGAUGAUC	(23)
He, 2021	MSC-AS1/miR-325/ TRIM14	CRC	AgUUAuUGGuaAua CUACUAGU	UgAAUgACCug UgGAUGAUC	CUACUAG	GAUGAUC	(5)
Zhang, 2019	miR-325/AQP5	HCC	NA	NA	CAAUAAA	GUUAUU	(16)
He, 2021	miR-325/BAG2	T-ALL	NA	NA	UACUAG	AUGAUC	(5)
Li, 2021	miR-325/CXCL17	HCC	NA	NA	UCAAUAAA	AGUUAUUU	(15)
Xiong, 2021	miR-325/FOXM1	GBM/LGG	NA	NA	CUCAAUAA	GAGUUAUU	(22)
Wang, 2022	miR-325/GPX2	NSCLC	NA	NA	CAAUAAA	GUUAUUU	(10)
Yao, 2015	miR-325/HMGB1	NSCLC	NA	NA	GUUAUAU	CAAUAUA	(19)
Zhang, 2021	miR-325/HSPA12B	CRC	NA	NA	GAGGUga-CAAUAAAA	CUCCAgga GUUAUUU	(8)
Huang 2023	miR-325/HuR	GC	NA	NA	UCAAUAAA-CAAUAAA	AGUUAUUU-GUUAUUU	(14)
Gan, 2019	miR-325/KIF2C	NSCLC	NA	NA	CAAUAAA	GUUAUUU	(7)
Liu, 2023	miR-325/LNC15	BC	NA	NA	UCAAUAA	AGUUAUU	(29)
Sun, 2020	miR-325/MT3	BLCA	NA	NA	GGAGGaauga CAAUAA	CCUCCagaa GUUAUU	(6)
Wang, 2021	miR-325/S100A2	BC	NA	NA	AGUUAUUU	UCAAUAAA	(24)
Li, 2021	miR-325/S100A4	CRC	NA	NA	AGUUAUUU	UCAAUAAA	(13)

miR, microRNA; ceRNA, competing endogenous RNA; PCG, protein-coding gene; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; BLCA, bladder urothelial carcinoma; HCC, hepatocellular carcinoma; SKCM, skin cutaneous melanoma; T-ALL, T-cell acute lymphoblastic leukemia; OSCC, oral squamous cell carcinoma; NPC, nasopharyngeal carcinoma; BC, breast cancer; GC, gastric cancer; GBM/LGG, glioblastoma multiforme and lower-grade glioma; NA, not applicable.

Table IV. Prognostic value of miR-325.

First author, year	Cancer	Sample size	miR-325 expression	Clinicopathological characteristics	Prognostic values of miR-325 overexpression	(Refs.)
Sun, 2020	GC	134	Downregulated	NA	Shorter OS	(9)
Li, 2015	HCC	99	Downregulated	Earlier TNM stage, larger tumor size and increased metastasis	Shorter OS and PFS	(12)
Li, 2021	NSCLC	20	Downregulated	NA	Shorter OS and PFS	(15)
Yao, 2015	NSCLC	107	Downregulated	NA	Shorter OS and PFS	(19)
Lin, 2018	BLCA	42	Downregulated	NA	Shorter OS	(17)

miR, microRNA; GC, gastric cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; BLCA, bladder urothelial carcinoma; OS, overall survival; PFS, progression-free survival; NA, not applicable.

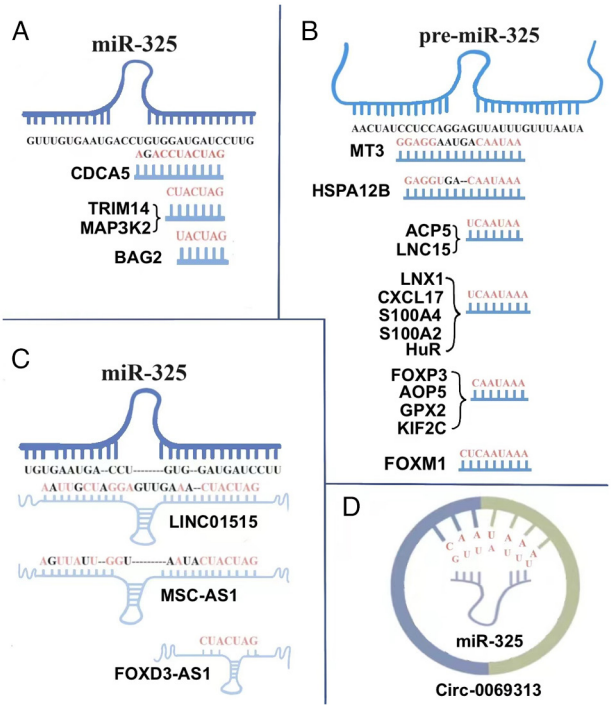

Figure 3. Interaction of miR-325 and pre-miR-325 with various RNA molecules. (A) miR-325 binds with four target genes. (B) Pre-miR-325 binds with 13 target genes. (C) miR-325 binds with 3 lncRNAs. (D) Pre-miR-325 binds with one circRNA. Specifically, miR-325 exhibits binding affinity towards four target genes and three lncRNAs, while pre-miR-325 demonstrates a more extensive interaction, binding to 13 target genes and one circRNA. This comprehensive depiction highlights the intricate network of molecular associations involving miR-325 and pre-miR-325 with their respective RNA counterparts. miR, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA.

from miR-325. In GC, SNHG6 can bind to miR-325-3p, interacting directly with GITR to regulate CDDP resistance. GITR, in turn, promotes CDDP resistance in GC cell lines, primarily by modulating Bcl2-mediated apoptosis (9). Notably, in NSCLC, GPX2 has been reported to drive malignant progression and CDDP resistance in KRAS-driven lung cancer (10). DOX is a standard systemic chemotherapy adjuvant drug for transarterial chemoembolization. Chemosensitivity to DOX has been reported to be markedly increased in cells overexpressing miR-325, and the inhibitory effects of miR-325 on chemoresistance have been shown to be diminished upon artificially restoring DPAGT1 expression. Meanwhile, miR-325 inhibits the expression of DPAGT1 gene in HCC. This regulatory mechanism has been shown to phenotypically mimic the effects of DPAGT1 silencing both *in vitro* and *in vivo*, consequently reducing the survival rate of DOX-resistant cells (11).

The CADDIE database (https://www.exbio.wzw.tum.de/caddie/) was used to search potential targeted drugs of PCGs, and the obtained results are shown in Fig. 4B. Among these, MAP3K2 has associations with bosutinib and fostatinib, HMGB1 with chloroquine, MT3 with zinc acetate and zinc chloride, GPX2 with glutathione, S100A4 with trifluoperazine, and S100A2 with zinc chloride, zinc acetate and olopatadine. Future investigations are warranted to elucidate the potential interactions between miR-325 and these drugs.

6. Discussion

The findings of the present study underscore the potential utility of miR-325 as a biomarker in various types of cancer. In NSCLC (7), miR-325 has emerged as a promising diagnostic and treatment target. Similarly, in HCC (15), miR-325 may hold promise as a biomarker for treatment. In NPC (23), LINC01515 has been shown to act as a molecular sponge for miR-325, influencing cell division cycle-related expression, and showcasing potential as a prognostic biomarker or therapeutic target. In BLCA (16,26), low-level expression of miR-325 has emerged as a biomarker for adverse clinicopathological characteristics and poor prognosis. In GBM/LGG (22), miR-325 was identified as a promising prognostic biomarker.

Collectively, these findings highlight the potential role of miR-325 as a diagnostic, therapeutic and prognostic biomarker across different types of cancer. However, the existing research on miR-325 has certain limitations. Notably, the expression of miR-325 in BC appears controversial. One dataset indicated the upregulation of miR-325 in the primary BC tissues of

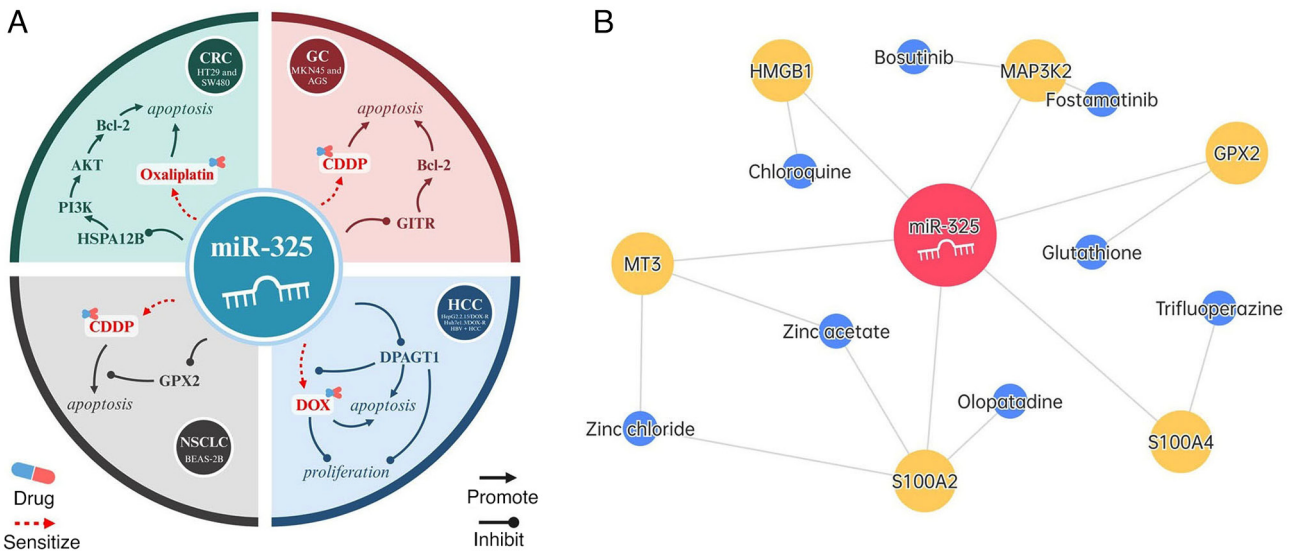

Figure 4. miR-325-related therapeutic drugs. (A) miR-325 is associated with resistance to three drugs (CDDP, DOX and oxaliplatin). (B) Target drugs of the PCGs of miR-325 and the competing endogenous RNA/miR-325/PCG axes in the CADDIE database. miR, microRNA; CDDP, cisplatin; DOX, doxorubicin; CRC, colorectal cancer; GC, gastric cancer; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma.

30 patients compared with in non-cancerous tissues (24), whereas another dataset suggested it was downregulated in the BC tissues of 15 patients compared with in adjacent tissues (29). Discrepancies in the choice of cell lines, small sample sizes and inconsistent tumor stages among patient samples may contribute to these variations in miR-325 expression patterns in BC.

Addressing these disparities, future research should delve into sex-specific differences in miR-325, explore the relationship between miR-325 and resistance to various anticancer drugs, and investigate how abnormal miR-325 expression in tumors is related to the efficacy of drug treatments. These areas of research will provide a more comprehensive understanding of the role of miR-325 in cancer, contributing to its potential as a robust biomarker in diagnosis, treatment and prognosis across diverse cancer types.

The present study comprised a comprehensive examination of miR-325, offering a review that highlights its potential as a potential focal point in cancer research. The review not only identified the promise of miR-325, but also provided valuable insights and directions for subsequent investigations into its various facets. Simultaneously, it addressed existing controversies and shortcomings within the current landscape of miR-325 research. Future endeavors in this field may concentrate on elucidating the aberrant molecular regulation of miR-325, identifying its molecular mechanisms associated with antitumor drug resistance and efficacy. An intriguing aspect is the chromosomal location of miR-325 on the X chromosome. Nevertheless, the existing literature has only described sex differences in miR-325 expression in specific tumor types, signifying a lack of emphasis on sex-specific cell line selection in ongoing research. To correct for this, forthcoming studies should aim to amass gene expression profiles from patient tissues of diverse sexes, integrating comprehensive statistical analyses with clinical data from both male and female patients with cancer. Such an approach promises to establish a robust theoretical foundation for the clinical application of miR-325 in tumor research.

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Figs. 1, 3 and 4A were created with BioRender.com.

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Availability of data and materials

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Authors' contributions

ZF, YaZ, YiZ, ZZ and YY collected and analyzed the literature, drafted the figures and wrote the paper. CY, JD and SD conceived and revised the article, and gave the final approval of the submitted version. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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