Recent findings on miR-370 expression, regulation and functions in cancer (Review)

LINGLING YE[1*], JINQIU WANG[2*], KUI YI[3*], FEN WANG[1], JINYAN WANG[1], HAO WU[1], HUI YANG[1], ZHAOHUI YANG[1] and QUAN'AN ZHANG[1]

[1]Department of Oncology, The Affiliated Jiangning Hospital with Nanjing Medical University, Nanjing, Jiangsu 211000; [2]Department of Oncology, Dafeng People's Hospital, Yancheng, Jiangsu 224000; [3]Department of General Surgery, The Affiliated Jiangning Hospital with Nanjing Medical University, Nanjing, Jiangsu 211000, P.R. China

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Abstract. MicroRNAs (miRNAs/miRs) are a group of small non-coding RNAs that serve as post-transcriptional gene modulators. miRNAs have been demonstrated to serve a pivotal role in carcinogenesis and the dysregulated expression of miRNAs is a well-understood characteristic of cancer. In recent years, miR-370 has been established as a key miRNA in various cancers. The expression of miR-370 is dysregulated in various types of cancer and varies markedly across different tumor types. miR-370 can regulate multiple biological processes, including cell proliferation, apoptosis, migration, invasion, as well as cell cycle progression and cell stemness. Moreover, it has been reported that miR-370 affects the response of tumor cells to anticancer treatments. Additionally, the expression of miR-370 is modulated by multiple factors. The present review summarizes the role and mechanism of miR-370 in tumors, and demonstrates its potential as a molecular marker for cancer diagnosis and prognosis.

Contents

Correspondence to: Dr Quan'An Zhang, Department of Oncology, The Affiliated Jiangning Hospital with Nanjing Medical University, 169 Hushan Road, Dongshan Street, Nanjing, Jiangsu 211000, P.R. China
E-mail: quananzhangjn@163.com

*Contributed equally

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1. Introduction

MicroRNAs (miRNAs/miRs) are a class of noncoding small RNAs ~22 nucleotides in length. It has been reported that one miRNA can target dozens of mRNAs by recognizing and binding to complementary sites in the 3'-untranslated regions (3'-UTRs) (1). Thus, the prediction of its impacts in different contexts is difficult (2). The potential target genes of miRNAs can be predicted using bioinformatics tools, such as TargetScan (3), RNA22 (4), miRDB (5), STarMir (6) and DIANA-microT-CDS (7); regular updating of these tools is important to ensure accurate results. A number of the tools are updated regularly, with TargetScan and miRDB being the ones most frequently updated (8). Moreover, it has been shown that miRNA-binding sites within coding sequences (CDSs) can also participate in the control of gene expression (9). Among the aforementioned tools, RNA22, miRDB and STarMir can identify miRNA targets in CDSs, 5'UTRs and 3'UTRs.

miRNAs are dysregulated in various types of human cancer, and are considered to function as oncogenes or tumor suppressors, depending on their target genes. Because of their broad regulatory activity, miRNAs are involved in numerous cellular processes, including proliferation (10), apoptosis (11) and metastasis (12). Moreover, miRNA expression is regulated by various factors, such as long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs). lncRNAs are RNAs that do not encode proteins and are >200 nt in length (13). lncRNAs regulate gene expression at different levels through various mechanisms, such as genomic imprinting, chromatin remodeling, cell cycle regulation and transcriptional regulation (14). circRNAs are a unique class of RNA with a closed-loop structure that can modulate linear RNA transcription, downstream gene expression and protein production (15). Competitive endogenous RNA is a mechanism that can explain the regulatory interactions among diverse RNAs. The theoretical core of this hypothesis is that some non-coding RNAs, such as lncRNAs, pseudogenes and circRNAs, can competitively bind to the same miRNA through a miRNA response element in order to modulate the expression levels of each other (16).

Among the numerous miRNAs, miR-370 has attracted great attention. The miR-370 family is located at chromosome 14q32.31 and includes two main members of the human

genome, miR-370-5p and miR-370-3p. At present, most research has focused on miR-370-3p, with only a few studies reporting on miR-370-5p (12,17). In general, miR-370 inhibits gene expression by specifically binding to the 3'-UTR of downstream target mRNAs, and can function as an oncogene or tumor suppressor to regulate the occurrence and development of cancer (18). In addition, it has been shown that miR-370 may act as small activator RNA for P21 in lung cancer (17). Similarly, accumulating evidence has indicated that miRNAs can activate gene expression by targeting promoters (19,20). The potential mechanism underlying miRNA-mediated gene activation is unclear. miR-370 has been reported to affect numerous biological behaviors, such as cell proliferation (21), apoptosis (22), migration (23), invasion (24), as well as cell cycle progression (25) and cell stemness (26). Furthermore, miR-370 may affect the response of cancer cells to anticancer therapy (27).

The present review systematically summarizes the expression and function of miR-370 in cancer, and predicts its potential as a novel biomarker, as well as a diagnostic and prognostic indicator.

2. The aberrant expression of miR-370 in cancer

The dysregulation of miR-370 is closely associated with the pathogenesis and progression of numerous types of cancer. Existing studies have reported that miR-370 is aberrantly expressed in various types of cancer, with both upregulation and downregulation reported (Table I). Among them, miR-370 has been shown to be downregulated in nine types of cancer, including oral squamous cell carcinoma (OSCC) (28), laryngeal squamous cell carcinoma (LSCC) (29), thyroid cancer (23,30), esophageal squamous cell carcinoma (ESCC) (31), hepatocellular carcinoma (HCC) (32,33), colon cancer (22), ovarian cancer (34), cervical cancer (21) and osteosarcoma (35). Conversely, miR-370 has been reported to be upregulated in melanoma (36).

Inconsistent results have been reported regarding miR-370 expression in four types of cancer, including acute myeloid leukemia (AML), breast cancer, gastric cancer and prostate cancer. Notably, overexpression of miR-370 has been reported in AML (37); however, it has also been demonstrated that miR-370 is significantly decreased in the peripheral blood of pediatric patients with AML (38). These two conflicting results may be due to the effect of age on the results or may be because miR-370 expression differs in tissue and peripheral blood. In addition, in breast cancer, one study reported downregulation of miR-370 expression (12), whereas two other studies have shown upregulation of miR-370 expression (26,39). In gastric cancer, three studies have indicated that miR-370 is upregulated (24,40,41), whereas one study reported that miR-370 is downregulated (42). In prostate cancer, inconsistent results regarding miR-370 expression have also been observed (43,44). Therefore, in most cancer types, miR-370 acts as a tumor suppressor; however, in some cancer types, it may promote tumor progression. In addition, there are inconsistent results regarding miR-370 expression in four types of cancer. The underlying mechanisms of these differences remain unclear and may be related to tumor heterogeneity.

3. The biological role of miR-370 in cancer

miR-370 and different signaling pathways. The role of miR-370 in signaling pathways associated with cancer occurrence and development has been extensively explored. Numerous studies have shown that miR-370 can influence cancer development and progression by participating in the Wnt/β-catenin, MAPK, NF-κB and PI3K/Akt signaling pathways, alongside others (Fig. 1).

The Wnt signaling pathway. Aberrant activation of the Wnt signaling pathway can facilitate the progression of multiple types of cancer (45). Core elements of the Wnt signaling pathway comprise the extracellular factor Wnt and the transmembrane receptor β-catenin (46). It has been reported that RuvB-like ATPase 1 (RUVBL1) can positively regulate Wnt/β-catenin signaling (47). miR-370-3p can directly target RUVBL to inhibit the interaction between RUVBL1 and β-catenin/LEF1 complex, thereby inhibiting Wnt/β-catenin signaling and further inhibiting osteosarcoma progression (35). Another study reported that DNA methylation-mediated reduction of miR-370 leads to upregulation of forkhead box M1 (FoxM1), thus activating the Wnt/β-catenin signaling pathway and promoting cell proliferation in osteosarcoma (48). Wnt family member 7A (Wnt7a) is a Wnt ligand that activates the classical Wnt/β-catenin signaling pathway to promote cancer progression (49). Wnt7a activates the Wnt signaling pathway, stimulates the invasion of bladder cancer cells and is inhibited by miR-370-3p (50). Furthermore, miR-370-3p has been reported to inhibit Wnt7a protein expression and Wnt/β-catenin signaling, further suppressing bladder cancer proliferation (51). In response to miR-370-3p overexpression, cyclin D1 and C-myc have been shown to be decreased in thyroid cancer, which is related to the Wnt signaling pathway (30). These results suggested that miR-370 may act as an oncosuppressor in the Wnt signaling pathway by regulating a range of targets associated with this pathway.

The MEK/ERK signaling pathway. The activity of the MAPK/ERK kinase (MEK)/ERK signaling pathway is crucial for promoting cancer progression. The serine/threonine kinase RAF1 serves a vital role in activating the MEK1/2 dual-specificity protein kinases, which then activate ERK1/2 (52). miR-370-3p can downregulate RAF1 expression, thereby inhibiting the MEK/ERK pathway in cervical cancer (21). In AML, miR-370-3p has been reported to inhibit MAPK1 expression, in turn suppressing ERK signaling, which further inhibits AML progression (53). These results indicated that miR-370 may function as a tumor suppressor in the MEK/ERK pathway by regulating different target genes.

The PI3K/AKT signaling pathway. The PI3K/Akt signaling pathway plays an essential role in the occurrence and development of tumors. The PI3K/AKT signaling pathway phosphorylates PI3K and AKT proteins, thus facilitating tumor cell proliferation and malignancy, and suppressing tumor cell apoptosis (54). miR-370 has been reported to inhibit cell proliferation in liver cancer by suppressing AKT, which in turn inhibits forkhead box O3a (FoxO3a) (32).

Table I. Expression patterns and target genes of microRNA-370 in various types of cancer.

Cancer type	Expression	Function	Target gene	(Refs.)
OSCC	Downregulation	Inhibits proliferation, migration and invasion	IRS-1	(28)
LSCC	Downregulation	Inhibits proliferation	FoxM1	(29)
Thyroid cancer	Downregulation	Inhibits proliferation, migration and invasion; induces apoptosis	FZD8/LMO4/MYH9	(23,30,75,77)
NSCLC	/	Inhibits proliferation, cell cycle, migration and invasion	p21/TRIM44	(17,81)
Breast cancer	Downregulation	Inhibits proliferation and invasion	LUC7L3	(12)
	Upregulation	Promotes proliferation migration, and invasion	FBLN5/ FGF14	(26,39)
ESCC	Downregulation	Inhibits proliferation and invasion; induces apoptosis	PIM1/Wnt7a	(31,70)
Gastric cancer	Downregulation	Inhibits proliferation, migration and invasion	EGFR	(42)
	Upregulation	Promotes proliferation, cell cycle, migration and invasion	FoxO1/UQCRC2/ TGFβ-RII	(24,40,41)
CRC	Downregulation	Inhibits proliferation, migration and invasion; induces apoptosis	β-catenin/ MDM4/EZH1	(22,84,86,88)
HCC	Downregulation	Inhibits proliferation; induces apoptosis	FoxO3a/ISG15	(32,33)
Ovarian cancer	Downregulation	Inhibits proliferation, cell cycle and invasion	CDK6/FoxM1/RAB17	(25,34,61)
Cervical cancer	Downregulation	Inhibits proliferation and migration; induces apoptosis	RAF1	(21)
Osteosarcoma	Downregulation	Inhibits proliferation, migration and invasion	RUVBL1/PIM1	(35,69)
Melanoma	Upregulation	Promotes proliferation, migration and invasion; inhibits apoptosis	PDHB	(36)
Prostate cancer	Upregulation	Promotes proliferation and cell cycle	FoxO1	(44)
	Downregulation	Inhibits proliferation, migration and invasion	DDX3X	(43)
Bladder cancer	/	Inhibits proliferation, cell cycle migration and invasion; induces apoptosis	Wnt7a/SLD5	(51,63)
AML	Downregulation	Inhibits proliferation, migration and invasion; induces apoptosis	MAPK1	(38,53)
	Upregulation	Promotes proliferation	NF1	(37)

OSCC, oral squamous cell carcinoma; LSCC, laryngeal squamous cell carcinoma; NSCLC, non-small cell lung cancer; ESCC, esophageal squamous cell carcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; AML, acute myeloid leukemia; /indicates that there is no article showing its expression level.

The NF-κB signaling pathway. Emerging research has suggested that dysregulated NF-κB pathway activity contributes to a variety of diseases, including cancer (55). The NF-κB signaling pathway affects cancer cell proliferation, apoptosis and metastasis, thereby influencing tumor progression (56). It has been reported that fibulin-5 (FBLN5) acts as a tumor suppressor to suppress cancer tumorigenesis and progression (57). miR-370-3p can promote breast cancer progression by directly targeting FBLN5 and activating the NF-κB signaling pathway (26). This result suggested that miR-370 may act as an oncogene, which is contradictory to the usual situation and may be related to tumor heterogeneity.

miR-370 and the cell cycle. The cell cycle is a complex process involving a number of regulatory proteins that guide the cell through a particular sequence of events, ultimately leading to mitosis and the creation of two daughter cells (58). The cell cycle is affected by various factors, such as cyclin D1, cyclin-dependent kinases (CDKs) and CDK inhibitors (59). A number of studies have confirmed that miR-370 may affect cell cycle progression by targeting different genes (Fig. 2). RAB proteins can modulate intracellular transport, and abnormal expression of RABs has been found in a variety of diseases, including cancer (60). Overexpressed RAB17 in ovarian cancer has been shown to promote the cell cycle, decreasing the number of G_1 phase cells and increasing the number of S phase cells (61). Notably, RAB17 is a direct target of miR-370-3p. Furthermore, miR-370-3p arrests the cell cycle and promotes apoptosis of ovarian cancer cell through inhibiting CDK6 (25). SLD5, a component of the GINS complex, is crucial for DNA replication (62). SLD5 has been reported to accelerate the cell cycle of bladder cancer cells and to be negatively regulated by miR-370 (63). Furthermore, miR-370 can induce non-small cell lung cancer (NSCLC) cell cycle arrest, through inhibiting the cyclin D1-CDK4/CDK6 pathway by activating p21 (17). It is proposed in this research that miR-370 may upregulate

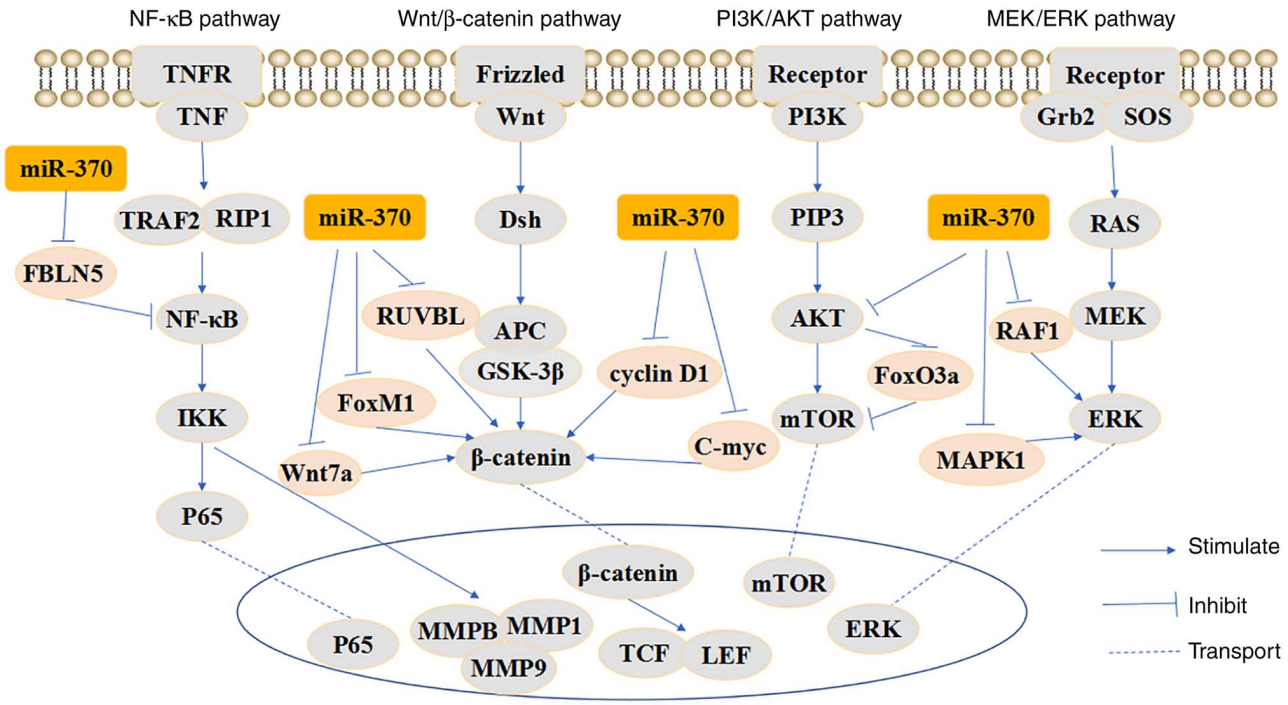

Figure 1. miR-370 related signaling pathways in cancer. miR-370 can regulate cancer progression through participating in the PIK3/AKT, Wnt/β-catenin, NF-κB and MEK/ERK signaling pathways. Grey, signaling pathway; pink, target gene; orange, miR-370. miR-370, microRNA-370.

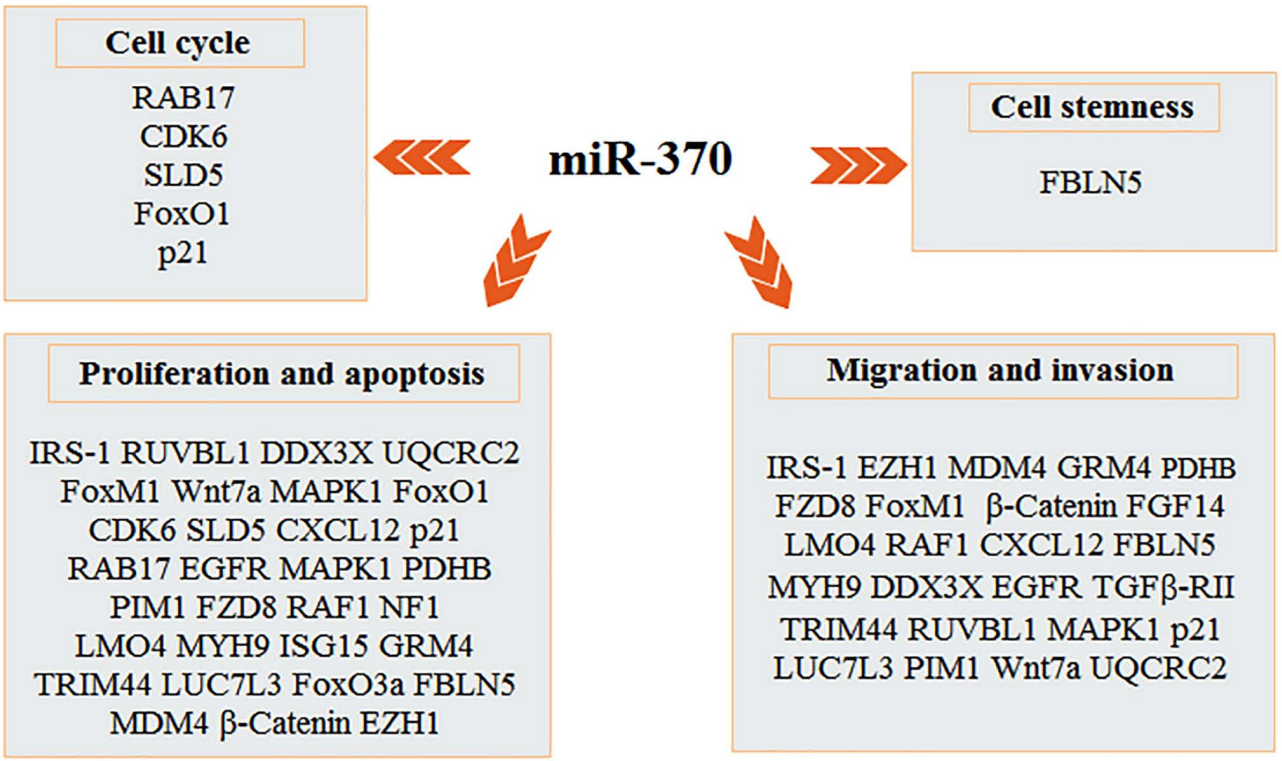

Figure 2. Biological role of miR-370 and its target genes in cancer. By promoting or suppressing cell proliferation, apoptosis, migration and invasion, miR-370 has oncogenic or tumor-promoting roles in different types of cancer. Besides, miR-370 can regulate the stemness of cancer cells by targeting FBLN5. Through targeting RAB17, CDK6, SLD5, FoxO1 and p21, miR-370 can affect the progression of the cancer cell cycle. miR-370, microRNA-370.

p21 gene expression in lung cancer through binding the p21 promoter; however, the mechanism involved is unknown.

In contrast to the aforementioned findings, a small number of studies have shown that miR-370 promotes cell cycle progression. Forkhead box transcription factor O1 (FoxO1), a member of the FoxO family of transcription factors, is crucial for modulating cytokine and chemokine secretion (64). FoxO1 acts as a tumor suppressor and has been demonstrated to be

involved in a variety of critical cell functions, such as cell proliferation, cell cycle, apoptosis and angiogenesis (65). In prostate cancer, miR-370 can accelerate the G_1/S cell cycle transition by inhibiting FoxO1, which increases the expression of p21Cip1 and p27Kip1 (44). Besides, similar findings have been observed in gastric cancer (40). In summary, miR-370 acts as a promoter or inhibitor in the cell cycle process, depending on the different targets.

miR-370 and cell proliferation and apoptosis. miR-370 has been reported to be involved in cell proliferation and apoptosis through directly regulating various targets (Fig. 2). FoxM1, a critical member of the FOX transcription factor family, regulates proliferation and invasion in a number of cancer types (66,67). miR-370 has been shown to function as an inhibitor in LSCC (29) and ovarian cancer (34) that regulates cell proliferation by decreasing FoxM1. PIM1, which is one of the Pim family kinases, has a critical role in the progression of human malignancies (68). miR-370 acts as a tumor suppressor in ESCC to suppress cell proliferation and induce cell apoptosis via downregulating PIM1 (31). Furthermore, miR-370 regulates osteosarcoma cell proliferation through downregulating PIM1 (69). Wnt7a can facilitate cell proliferation and decrease apoptosis, and is targeted by miR-370-3p in cisplatin-resistant esophageal cancer (70) and bladder cancer (51). These results suggested that miR-370 may regulate the same target to affect cell proliferation and apoptosis in various types of cancer.

Insulin receptor substrate-1 (IRS-1) is the substrate of insulin-like growth factor receptor, which activates AKT/mTOR signaling in malignant tumors (71). miR-370 can act as a suppressor to reduce the anchorage-independent growth of OSCC cells by downregulating IRS-1 (28). Frizzled class receptor 8 (FZD8), which is one of the Frizzled family of serpentine proteins, promotes the progression of various types of cancer by activating the Wnt pathway (72). In addition, FZD8 promotes the proliferation of thyroid cancer cells and is decreased by miR-370-3p (30). LIM domain-only 4 (LMO4) is a member of the LIM-only family of proteins and has been demonstrated to act as an oncogene in different types of cancer (73,74). miR-370-3p has been shown to function as a tumor suppressor to inhibit thyroid cancer cell proliferation and promote apoptosis through suppressing LMO4 (75). Myosin heavy chain 9 (MYH9) serves as an oncogene in multiple types of cancer, and MYH9 inhibition markedly inhibits the malignant phenotypes and chemoresistance of cancer cells (76). Notably, miR-370-3p can inhibit cell proliferation and induce cell apoptosis by decreasing MYH9 in 131I-resistant differentiated thyroid carcinoma cells (77).

In NSCLC, miR-370 can inhibit cell proliferation and colony formation by upregulating p21 (17). Furthermore, the knockdown of miR-370 can partially restore the inhibitory effect of silenced KCNK15-AS1 on lung cancer cell proliferation (78). Tripartite motif-containing 44 (TRIM44) is an atypical TRIM-family protein and emerging studies have demonstrated that TRIM44 stimulates cancer progression, including lung cancer (79,80). miR-370-3p acts as a tumor suppressor in NSCLC to inhibit cell proliferation by downregulating TRIM44 (81). In breast cancer, miR-370-5p suppresses cell proliferation through targeting LUC7-like 3 pre-mRNA splicing factor (LUC7L3), which is negatively regulated by miR-370-5p (12).

It has previously been reported that EGFR serves an important role in the pathogenesis of human malignancy (82). In gastric cancer, inhibition of EGFR can suppress cell proliferation, and miR-370 works as a potential regulator of EGFR (32,83). In colon cancer, miR-370-3p can restrain cell proliferation by targeting β-catenin (84). Mouse double minute 4 (MDM4) has been validated as an oncogene that can negatively regulate transcriptional activity of the tumor suppressor p53 (85). miR-370 functions as a suppressor to inhibit cell proliferation and promote apoptosis by targeting MDM4 in colorectal cancer (CRC) (22,86). Both zeste homologue 1 (EZH1), and its homolog EZH2, act as histone H3 lysine 27 (H3K27) methyltransferases that regulate target gene transcription. H3K27 has been reported to be involved in the development and progression of various types of cancer (87). Knockdown of miR-370-5p can facilitate the proliferative ability of CRC by targeting EZH1 (88).

FoxO3a is a member of a subfamily of forkhead transcription factors that had a crucial role in carcinogenesis (89). miR-370 works as a tumor suppressor to inhibit the proliferation of human liver cancer cells by inhibiting AKT, which further suppresses FoxO3a (32). The expression of IFN-stimulated gene 15 (ISG15) has been shown to be associated with the differentiation grade, migration and survival in patients with HCC (90). Furthermore, miR-370 regulates the IFN-α-induced apoptosis of HCC cells through downregulating ISG15 (33).

In ovarian cancer, miR-370-3p restrains cell proliferation and promotes apoptosis by targeting CDK6 (25). Furthermore, miR-370-3p can suppress colony formation of ovarian cancer cells via targeting RAB17 (61). miR-370-3p also suppresses the proliferation of cervical cancer cells by downregulating RAF1 (21). DDX3X, one of the DEAD-box helicase family members, has a key role in almost all stages of RNA metabolism and is involved in the progression of multiple diseases, such as viral infection and cancer (91). miR-370-3p overexpression can inhibit cell proliferation by directly targeting DDX3X in prostate cancer (43). In addition, it has been reported that miR-370 inhibits bladder cancer cell proliferation by downregulating SLD5 (63).

MAPK1 has previously been reported to regulate cell differentiation, proliferation and migration in various types of cancer (92,93). miR-370-3p inhibits the proliferation and promotes the apoptosis of AML cells by targeting MAPK1 (53). CXCL12, a member of the chemokine family, serves a critical role in tumor development (94). CXCL12 overexpression facilitates melanoma cell proliferation and is regulated by miR-370-3p (95). Moreover, miR-370-3p targets RUVBL1 directly to suppress the proliferation of osteosarcoma cells (35).

Contrary to the aforementioned findings, existing studies have shown that miR-370 can also promote proliferation in several types of cancer. Ubiquinol-cytochrome c reductase core protein 2 (UQCRC2) is a crucial mitochondrial respiratory complex III subunit, which has been confirmed to be involved in various types of cancer as either an oncogene or a tumor suppressor gene (96). Enhanced miR-370 has been reported to facilitate gastric cancer cell proliferation through suppressing

UQCRC2 (24). In gastric cancer (40) and prostate cancer (44), FoxO1 inhibits cell proliferation and is negatively regulated by miR-370. Furthermore, miR-370-3p can promote prostate cancer cell proliferation by downregulating P21 (97). Pyruvate dehydrogenase B (PDHB) is a mitochondrial enzyme that catalyzes the conversion of glucose-derived pyruvate to acetyl-CoA (98). Upregulation of miR-370 can facilitate melanoma cell proliferation and can inhibit apoptosis through targeting PDHB (36). A previous study revealed that microdeletions of NF1 are common events, resulting in decreased NF1 expression in AML (99). miR-370 has been shown to enhance AML cell proliferation potential by downregulating NF1, which is identified as a tumor suppressor (37). Glutamate metabotropic receptor 4 (GRM4), which is a member of the GRM protein family, has been reported to be involved in adaptive immunity reactions in cancer. Notably, GRM4 significantly inhibits breast cancer cell proliferation under the direct regulation of miR-370-3p (100). Moreover, FBLN5 inhibits the proliferation of breast cancer cells and is negatively regulated by miR-370-3p (26). Overall, miR-370 may have a critical role in cell proliferation in multiple types of cancer through regulating different targets. The conflicting results of miR-370 in different cancer types may suggest it has a context-dependent role.

miR-370 and cell migration and invasion. Metastasis is the process by which cancer cells spread from the tumor and acquire a more mesenchymal phenotype through epithelial-mesenchymal transition (EMT). When cancer cells migrate from the tumor they can invade the healthy stroma to produce new tumors (101). miR-370 is deemed to be a significant miRNA related to tumor cell migration and invasion (Fig. 2). In OSCC, miR-370 can regulate IRS-1 expression and restrain the tumor phenotype (28). In thyroid cancer, miR-370-3p has been shown to suppress cell migration and invasion by targeting FZD8 (30), LMO4 (75) and MYH9 (77). In addition, miR-370-3p suppresses NSCLC cell migration and invasion through regulating TRIM44 (81) and p21 (17). It has also been reported that miR-370-5p directly targets LUC7L3 to inhibit cell invasion in breast cancer (12). In ESCC, miR-370-3p suppresses cell invasion by downregulating Wnt7a (70). In bladder cancer, miR-370-3p directly targets Wnt7a and suppresses the Wnt signaling pathway, thereby inhibiting cell invasion (50). Overexpressed miR-370 has been shown to suppress gastric cancer cell migration by targeting EGFR (42). In colon cancer, enforced miR-370-3p can inhibit EMT through modulating β-catenin (84). miR-370 can also downregulate MDM4 and inhibit the metastatic ability of CRC cells (86). EZH1 has been shown to facilitate CRC cell invasion and has been identified as a target of miR-370-5p (88). Overexpressed miR-370 can suppress ovarian cancer cell invasion by downregulating FoxM1 (34). In cervical cancer, miR-370-3p inhibits cell migratory abilities by regulating RAF1 expression (21). Enforced expression of miR-370-3p can suppress prostate cancer cell migration, as well as invasion, and can lead to downregulation of the DDX3X protein (43). miR-370-3p may also suppress cell EMT by directly downregulating RUVBL1 in osteosarcoma (35). Overexpression of miR-370 inhibits osteosarcoma cell migration capacity by targeting PIM1, which is negatively regulated by miR-370 (69). By directly binding to the 3'-UTR of MAPK1, miR-370-3p has been reported to decrease its expression, and to inhibit the migration and invasion of AML cells (53). Elevated miR-370-3p may also inhibit the migration and invasion of melanoma cells by downregulating CXCL12 expression (95).

Several studies have shown that miR-370 can promote cell migration and invasion in breast cancer, stomach cancer and melanoma. Fibroblast growth factor 14 (FGF14) belongs to the FGF family and a recent study suggested that FGF14 functions as a tumor suppressor in colorectal cancer (102). FGF14 overexpression can decrease breast cancer cell migration and invasion, is negatively regulated by miR-370-3p (39). miR-370-3p facilitates breast cancer cell metastasis through suppressing FBLN5 and by activating the NF-κB signaling pathway (26). GRM4 may act as a potential tumor suppressor to inhibit breast cancer cell migration and invasion, is modulated by miR-370-3p (100). Blocking transforming growth factor-β (TGFβ) signaling in a gastric cancer model has been reported to promote tumor growth, and resistance to a TGFβ inhibitor appears to be a critical event in the occurrence of gastric cancer (103). miR-370 can increase the metastatic ability of gastric cancer cells by downregulation of TGFβ-RII (41). In addition, miR-370 may modulate EMT signaling pathways to facilitate tumor metastasis by targeting UQCRC2 in gastric cancer (24). Overexpressed miR-370 can also enhance melanoma cell invasion and glycolysis by downregulating PDHB (36). In most tumors, miR-370 inhibits cell metastasis; however, in some tumors, miR-370 both inhibits and promotes cell migration and invasion. The mechanisms underlying these effects are unknown and may be associated with tumor heterogeneity.

Stemness. Cancer stem cells (CSCs) are a small subpopulation of tumor cells with self-renewal, differentiation and tumorigenic properties (104). CSCs have been identified as one of the key factors contributing to tumor recurrence and drug resistance (105). NF-κB-mediated signaling pathways have been confirmed to be implicated in the maintenance of CSC characteristics associated with tumor progression (106). miR-370-3p has been shown to reduce FBLN5 expression and activate the NF-κB signaling pathway to stimulate breast cancer cell stemness (26).

MiR-370 and cancer treatment. Since miR-370 is involved in different signaling pathways, it has been considered a promising target for the development of anticancer treatments (Fig. 3). A previous study reported that RAB17 can affect the paclitaxel resistance of ovarian cancer cells through the CDK6/RB signaling pathway, is negatively regulated by miR-370-3p (61). Targeting of ISG15 by miR-370 can also regulate the sensitivity of HCC cells to IFN-α treatment (33). Upregulated Wnt7a expression has been reported to promote cisplatin resistance in esophageal cancer and to be negatively regulated by miR-370-3p (70). Furthermore, miR-370 enhances the radiosensitivity of NSCLC cells by downregulating EGFR and hypoxia-inducible factor 1α (107). miR-370-3p inhibits 131I resistance in thyroid cancer cells through downregulating MYH9 expression (77). Furthermore, it has been reported that miR-370-3p facilitates the therapeutic effect of anti-PD-1 treatment in melanoma

Table II. Regulatory factors regulate the expression of microRNA-370 in various cancers.

A, lncRNA

First author, year	Factor	Cancer type	(Refs.)
Li, 2019	lncRNA TUG1	AML	(53)
Peng, 2019	lncRNA KCNK15-AS1	Lung cancer	(78)
Li, 2021	lncRNA CASC9	Gastric cancer	(83)
Wang, 2019	lncRNA LINC00511	Ovarian cancer	(108)
Wang, 2021	lncRNA SNHG15	Ovarian cancer	(25)
Zhang, 2020	lncRNA BCAR4	Bladder cancer	(51)
Pan, 2021	lncRNA HCG18	Prostate cancer	(43)
Zhang, 2021	lncRNA SNHG3	CRC	(88)
Jin, 2020	lncRNA FGF14-AS2	Breast cancer	(39)

B, circRNA

First author, year	Factor	Cancer type	(Refs.)
Chen, 2018; Chen, 2021	circNEK6	Thyroid carcinoma	(30,77)
Liu, 2020	circ_0058124	Thyroid carcinoma	(75)
Xiong, 2021	circUBAP2	Thyroid carcinoma	(23)
Wang, 2022	circFBXW8	NSCLC	(81)
Zou, 2020	circ_001275	ESCC	(70)
Mo, 2022	circCCDC66	CRC	(86)
Guo, 2020	circ_0000714	Ovarian cancer	(61)
Chen, 2018	circ_0061140	Ovarian cancer	(34)
Wu, 2019	circAGFG1	Cervical cancer	(21)
Endo, 2020	circITGA7	Prostate cancer	(109)
Fang, 2020	circITGA7	Osteosarcoma	(69)
Chen, 2019	circMYO10	Osteosarcoma	(35)
Wei, 2020	circ_0020710	Melanoma	(95)

C, Others

First author, year	Factor	Cancer type	(Refs.)
Yamane, 2016	DNMT1	Bladder cancer	(63)
Pan, 2016	DNMT1	HCC	(111)
Zhang, 2017	DNMT1	Osteosarcoma	(48)
Han, 2016	Alpinumisoflavone	ESCC	(31)

AML, acute myeloid leukemia; circRNA, circular RNA; CRC, colorectal cancer; DNMT, DNA methyltransferase; NSCLC, non-small cell lung cancer; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma.

through downregulating the CXCL12 (95). These results indicated that it may be promising to use miR-370-targeted therapy in combination with other existing anticancer therapies to improve efficacy.

4. The regulation of miR-370 in cancer

Previous studies have identified multiple factors involved in the regulation of miR-370, such as lncRNAs, circRNAs, methyltransferases and other factors (Table II).

lncRNAs. lncRNAs are RNA molecules known to have gene regulatory functions similar to those of miRNAs. lncRNAs contain miRNA-binding sites and also act as miRNA sponges, which can lead to the reduced bioavailability of mature miRNAs. lncRNA TUG1 has been reported to modulate cell proliferation and migration in AML through modulating the miR-370-3p/MAPK1/ERK signaling pathway (53). Knockdown of KCNK15-AS1 can suppress lung cancer cell proliferation by upregulating miR-370 (78). Furthermore, lncRNA CASC9 acts as an oncogene to promote the progression of gastric

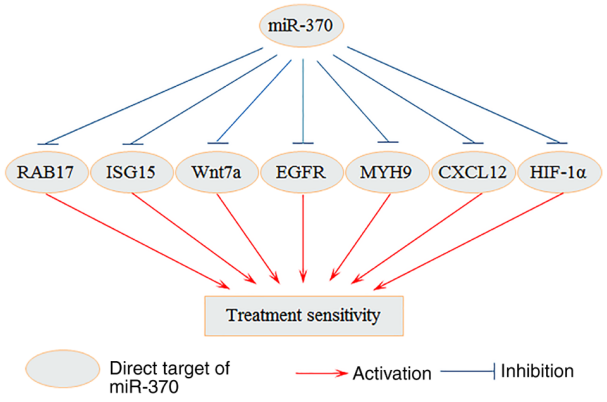

Figure 3. miR-370 affects cancer treatment by regulating different targets. miR-370 can regulate cancer treatment through targeting RAB17, ISG15, Wnt7a, EGFR, MYH9, CXCL12 and HIF-1α. miR-370, microRNA-370.

cancer by modulating the miR-370/EGFR axis (83). Through downregulating miR-370-5p, LINC00511 promotes the proliferation and invasion of estrogen receptor 1-expressing ovarian cancer cells (108). Similarly, lncRNA SNHG15 facilitates ovarian cancer progression through regulating CDK6 by sponging miR-370-3p (25). lncRNA BCAR4 affects the cell proliferation and apoptosis of bladder cancer by sponging miR-370-3p (51). In addition, through sponging miR-370-3p, lncRNA HCG18 can promote the proliferation and migration of prostate cancer cells by upregulating DDX3X (43). lncRNA SNHG3 enhances the proliferative and invasive ability of CRC through modulating the miR-370-5p/EZH1 axis (88). In addition, lncRNA FGF14-AS2 suppresses breast cancer cell migration and invasion through targeting FGF14 via acting as a sponge of miR-370-3p (39).

circRNAs. circRNAs can also function as miRNA sponges, and they carry several miRNA-binding sites. Multiple studies have shown that circRNAs are involved in miR-370 regulation. In thyroid carcinoma, circNEK6 (30,77), circ_0058124 (75), and circUBAP2 (23) have been identified to regulate miR-370 expression via direct sponging and ultimately promote cancer progression by modulating the expression of targets of miR-370. Furthermore, circFBXW8 promotes NSCLC progression by elevating TRIM44, through acting as a sponge of miR-370-3p (81). circRNA_001275 elevates Wnt7a expression through sponging miR-370-3p to promote esophageal cancer progression and cisplatin resistance (70). In CRC, circCCDC66 facilitates cancer progression through regulating the miR-370/MDM4 axis (86). In addition, circ_0000714 acts as a sponge of miR-370-3p and influences cell paclitaxel resistance and the cell cycle in ovarian cancer cells (61). circ_0061140 promotes cell proliferation and migration in ovarian cancer by inhibiting FoxM1 through sponging miR-370 (34). Moreover, circAGFG1 regulates cervical cancer cell proliferative and migratory abilities via the miR-370-3p/RAF1 axis (21). circITGA7 can serve as a sponge for miR-370-3p to inhibit prostate cancer cell proliferation (109). Furthermore, circITGA7 (69) and circMYO10 (35) function as sponges for miR-370-3p to promote cancer progression in osteosarcoma. circ_0020710 has been reported to act as an oncogene in melanoma cells to promote tumor progression through regulating the miR-370-3p/CXCL12 axis (95).

DNA methylation and other factors. DNA methyltransferase 1 (DNMT1) is essential for maintaining DNA methylation patterns during cell replication and has been demonstrated to participate in the regulation of miRNAs in cancer cells (110). IL-6-induced overexpression of DNMT1 inhibits miR-370, leading to upregulated SLD5, which promotes cell proliferation of bladder cancer (63). A previous study suggested that physcion (an active ingredient in the medicinal plant Radix et Rhizoma Rhei) can induce HCC cell apoptosis through upregulating miR-370 by regulating the AMPK/Sp1/DNMT1 signaling pathway (111). Osteosarcoma cells treated with the DNA methylation inhibitor, 5-AZA-2'-deoxycytidine, exhibit elevated miR-370 expression, which regulates osteosarcoma cell proliferation. This result indicates that DNA methylation is critical for miR-370 expression in osteosarcoma (48). Furthermore, the potential antitumor effects of alpinumisoflavone (AIF) have been demonstrated (112). AIF inhibits tumor growth via inducing cell apoptosis through modulating miR-370/PIM1 signaling in ESCC (31).

5. The diagnostic and prognostic value of miR-370 in cancer

The diagnostic value of miR-370 in cancer. Emerging research has demonstrated the potential of miR-370 as a diagnostic biomarker for different types of cancer, such as AML, breast cancer and gastric carcinoma (Table III). In particular, miR-370 is downregulated in the peripheral blood of pediatric patients with AML, with a sensitivity of 96.9% and specificity of 93.3%. In this previous study, the receiver operating characteristic (ROC) curve had an area under the curve (AUC) of 0.966 for miR-370 (38). In another study, serum miR-370 expression was shown to be markedly reduced in patients with AML, and high sensitivity and specificity were detected in AML serum samples (91.46 and 100.00%), with an AUC of the ROC of 0.909 (113). It has been shown that miR-370-3p is upregulated in the serum and exosome specimens of patients with breast cancer, with a sensitivity of 59.26% and specificity of 74.07%. The AUC of the ROC curve for miR-370-3p was 0.6735. Serum exosome miR-370 levels were also correlated with breast cancer tumor size, lymph node metastasis and TNM stage (26). This result was higher than other markers, such as carcinoembryonic antigen and neuron-specific enolase (sensitivity, 0.48 and 0.39, respectively) (114). Further studies are recommended to verify the value of miR-370 in diagnosis because of its relatively high specificity and sensitivity compared with other markers. In addition, miR-370 expression is markedly higher in the plasma of patients with gastric carcinoma compared with that in healthy controls. Patients with gastric carcinoma with more aggressive or advanced tumors have been shown to have higher miR-370 plasma levels (41). These results suggested that the role of miR-370 as a diagnostic biomarker is accompanied by its role as a biomarker of prognosis.

The prognostic value of miR-370 in cancer. Various studies have also shown that miR-370 is significantly associated with the prognosis of patients with cancer (Table III). miR-370 is

Table III. Diagnostic and prognostic value of microRNA-370 in various types of cancer.

Cancer type	Expression	Diagnostic or prognostic value	(Refs.)
AML	Downregulation	Diagnostic biomarker and associated with poor OS	(38,113)
Breast cancer	Upregulation	Diagnostic biomarker and associated with tumor size, lymph node metastasis and TNM stage	(26)
Gastric cancer	Upregulation	Diagnostic biomarker, and associated with more advanced lymph node metastasis and higher clinical stage	(41)
ESCC	Downregulation	Associated with TNM stage and pathological grade	(31)
HCC	Downregulation	Associated with tumor lymph node metastasis and vascular invasion, and poor OS	(115)

AML, acute myeloid leukemia; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; OS, overall survival.

decreased in ESCC, and miR-370 expression is negatively associated with ESCC clinicopathological characteristics, including TNM stage and pathologic grade (31). In gastric carcinoma, miR-370 has been shown to be upregulated. Compared with in the control tissues, the higher levels of miR-370 expression in gastric carcinoma tissues were revealed to be correlated with more advanced lymph node metastasis and higher clinical stage (41). It has also been reported that low miR-370 expression is significantly correlated with tumor lymph node metastasis and vascular invasion in patients with HCC. Furthermore, a low level of miR-370 is associated with poor prognosis in patients with HCC and miR-370 can serve as an independent prognostic marker (115).

6. Conclusion

miR-370 is widely involved in the occurrence and development of various types of cancer and is abnormally expressed in cancer. Notably, miR-370 affects cancer progression by regulating the Wnt/β-catenin, MAPK, NF-κB and PI3K/Akt signaling pathways, alongside others. Additionally, miR-370 can participate in various biological processes by regulating target genes, including cell proliferation and apoptosis, cell migration and invasion, cell cycle progression and cell stemness. miR-370 can also modulate the response of cancer cells to anticancer therapies by regulating their target genes. Furthermore, miR-370 may serve as a specific diagnostic and prognostic marker for various types of cancer. Through the regulation of miR-370, lncRNAs, circRNAs, methyltransferases and other factors are involved in the development and progression of cancer.

However, there are still a number of shortcomings in the studies on miR-370. First of all, available studies have revealed that miR-370 serves an inhibitory role in various types of cancer; however, it can act as a tumor promoter in melanoma. In addition, inconsistent expression levels of miR-370 have been detected in AML, breast cancer, gastric cancer and prostate cancer. The mechanisms underlying these differences need to be elucidated. Secondly, miR-370 is under the regulation of numerous factors, and the interaction of miR-370 with its targets constitutes its regulatory network. The complexity of this regulatory network provides miR-370 with diverse biological functions that depend specifically on the cellular environment. Future studies need to focus on the regulatory network of miR-370, which will contribute to a deeper understanding of the mechanisms underlying the effects of miR-370 on cancer. Furthermore, in spite of the fact that miR-370 plays different roles in chemotherapy for different types of cancer, it is still regarded as a promising treatment target for cancer therapy. Future research may focus on understanding more clearly the mechanisms of how miR-370 regulates treatment resistance in cancer. Finally, numerous studies have confirmed that miR-370 can efficiently modulate the cellular response to chemotherapy, thus indicating that the use of miR-370-targeted therapy in combination with chemotherapy may be promising in certain types of cancer to improve therapeutic efficacy.

In summary, miR-370 serves a significant role in the initiation and progression of multiple types of cancer. Hence, miR-370 may be the focus of future research for the treatment of cancer. The present review comprises an overview of the research progress regarding miR-370 in cancer, which may provide more insight into the molecular mechanisms of miR-370 and its functions in cancer.

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Availability of data and material

Not applicable.

Authors' contributions

LY, JinqW and QZ conceived the study. LY and KY wrote the original draft. JinyW and FW, reviewed and edited the manuscript, and performed supervision. HW, HY and ZY reviewed and edited the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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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