Investigating the molecular mechanisms of microRNA-409-3p in tumor progression: Towards targeted therapeutics (Review)

WENJIE XIE[1], ZHICHAO WANG[1], JUNKE WANG[2], XIU WANG[3] and HONGZAI GUAN[1]

[1]Department of Clinical Laboratory, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266000, P.R. China; [2]Department of Cardiology, Tianjin Medical University General Hospital, Tianjin 300052, P.R. China; [3]Key Laboratory of Medical Science and Laboratory Medicine of Jiangsu Province, School of Medicine, Jiangsu University, Zhenjiang, Jiangsu 212013, P.R. China

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Abstract. MicroRNAs (miRNAs) are a group of non-coding RNAs that exert master regulatory functions in post-transcriptional gene expression. Accumulating evidence shows that miRNAs can either promote or suppress tumorigenesis by regulating different target genes or pathways and may be involved in the occurrence of carcinoma. miR-409-3p is dysregulated in a variety of malignant cancers. It plays a fundamental role in numerous cellular biological processes, such as cell proliferation, apoptosis, migration, invasion, autophagy, angiogenesis and glycolysis. In addition, studies have shown that miR-409-3p is expected to become a non-invasive biomarker. Identifying the molecular mechanisms underlying miR-409-3p-mediated tumor progression will help investigate miR-409-3p-based targeted therapy for human cancers. The present review comprehensively summarized the recently published literature on miR-409-3p, with a focus on the regulation and function of miR-409-3p in various types of cancer, and discussed the clinical implications of miR-409-3p, providing new insight for the diagnosis and treatment of cancers.

Contents

1. Introduction

MicroRNAs (miRNAs/miRs) are a type of naturally occurring non-coding single-stranded RNA that range between 19 and 22 nucleotides in length. They are involved in the post-transcriptional regulation of gene by effectively recognizing the target genes' 3'-untranslated region (UTR) and cleaving

Correspondence to: Dr Hongzai Guan, Department of Clinical Laboratory, The Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao, Shandong 266000, P.R. China
E-mail: guanhongzai@qdu.edu.cn

Abbreviations: miRNA/miR, microRNA; UTR, untranslated region; NSCLC, non-small cell lung cancer; BC, breast cancer; CC, cervical cancer; GC, gastric cancer; CRC, colorectal cancer; OC, ovarian cancer; ccRCC, renal cell carcinoma; BCa, bladder cancer; PTC, papillary thyroid cancer; PC, pancreatic cancer; BTC, biliary tract cancer; DLBCL, diffuse large B-cell lymphoma; AML, acute myeloid leukemia; NPC, nasopharyngeal carcinoma; TSCC, tongue squamous cell carcinoma; PCa, prostate cancer; HCC, hepatocellular carcinoma; lncRNA, lncRNA; circRNA, circular RNA; LUAD, lung adenocarcinoma; CIRT, carbon ion radiotherapy; MET, MET proto-oncogene, receptor tyrosine kinase; SPIN1, spindlin1; ZB1-AS1, zinc finger E-box binding homeobox 1 antisense 1; ceRNA, competing endogenous RNA; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; DUXAP8, double homeobox A pseudogene 8; SOD1, superoxide dismutase 1; CBR3-AS1, CBR3 antisense RNA 1; AQP4, aquaporin4; AKT1, AKT serine/threonine kinase 1; circTRIM28, circular RNA tripartite motif-containing 28; HMGA2, high mobility group AT-hook 2; ATF1, activating transcription factor 1; circFAT1, circular RNA FAT atypical cadherin 1; CDK8, cyclin-dependent kinase 8; SLC7A11, solute carrier family 7 membrane 11; ELF2, E74-like factor 2; IGFBP3, insulin-like growth factor binding protein 3; PHF10, PHD finger protein 10; circNEK9, circRNA NIMA-related kinase 9; MAP7, microtubule associated protein 7; KLF17, Kruppel-like factor 17; NLK, nemo-like kinase; Oxa-R, oxaliplatin resistance; ERCC1, ERCC excision repair 1; RAB10, RAB10, member RAS oncogene family; CCDN2, cyclin D2; RDX, radixin; RSU1, Ras suppressor protein 1; DOCK1, dedicator of cytokinesis 1; HBVSMCs, human brain vascular smooth muscle cells; MCL1, myeloid cell leukemia sequence 1; HMGN5, high mobility group nucleosome binding domain 5; ANG, Angiogenin; EMT, epithelial-mesenchymal transition; TWIST1, Twist family bHLH transcription factor; MMP, matrix metalloproteinase; p-AKT, phosphorylated AKT; CTNND1, catenin-δ1; GAB1, GRB2 associated binding protein 1; circTRIM28, circRNA tripartite motif-containing 28; FABP4, fatty acid binding protein 4; HIF-1α, hypoxia-inducible factor-1α; BRF2, BRF2 RNA polymerase III transcription initiation factor subunit; ROS, reactive oxygen species; PDK1, 3-phosphoinositide dependent kinase 1; CTBP1, C-terminal binding protein 1; TCGA, The Cancer Genome Atlas; GEO, Gene Expression Omnibus

Key words: cancer, miR-409-3p, molecular mechanism, promotor, suppressor

mRNA molecules or partially performing complementary binding (1). By contrast, in certain circumstances, miRNAs also bind to the 5'-UTR or open reading frame of the target genes, resulting in translation activation (2). In addition, their generation proceeds through a series of complex processes from the nucleus to the cytoplasm (Fig. 1). An estimated 30% of human protein-coding genes are thought to be regulated by miRNAs (3). Furthermore, miRNAs are found on tumor-related chromosomes or fragile chromosomal sites, suggesting that miRNAs are often involved in the formation and progression of malignant carcinomas (4,5). In addition, individual miRNAs are engaged in more than one paramount physiological or pathological cellular process, such as cell proliferation (6), cell cycle (7), apoptosis (8), metastasis (9) and angiogenesis (10).

Among the numerous miRNAs, miR-409-3p has attracted a huge amount of attention. Initially found in embryonic stem cells (11), miR-409 (NCBI gene ID: 574413) consists of 79 bases located on chromosome 14q32.31. MiR-409 is being reprocessed to produce mature miR-409-3p (Fig. 2). Furthermore, increasing data point to the broad expression of miR-409-3p in malignancies, particularly non-small cell lung cancer (NSCLC) (12-21), breast cancer (BC) (22-30), cervical cancer (CC) (31-35), osteosarcoma (36-39), gastric cancer (GC) (40-44), colorectal cancer (CRC) (45-52), ovarian cancer (OC) (53-56), renal cell carcinoma (ccRCC) (57,58), bladder cancer (BCa) (59-61), papillary thyroid cancer (PTC) (62), pancreatic cancer (PC) and biliary tract cancer (BTC) (63), diffuse large B-cell lymphoma (DLBCL) (64), acute myeloid leukemia (AML) (65,66), oligodendroglioma (67), melanoma (68), nasopharyngeal carcinoma (NPC) (69), tongue squamous cell carcinoma (TSCC) (70), prostate cancer (PCa) (71-76), meningioma (77), intracranial artery tumors (78), glioma (79,80), fibrosarcoma (81), glioblastoma (82) and hepatocellular carcinoma (HCC) (83,84). Specifically, it has been shown that miR-409-3p exerts anti- or pro-tumorigenic roles in cancer progression by targeting downstream mRNAs or modulated by the upstream regulators of long non-coding RNAs (lncRNAs) or circular RNAs (circRNAs).

The present review outlines the expression, target genes and functional mechanisms of miR-409-3p in various malignancies, offering recommendations for future research and clinical applications regarding miR-409-3p.

2. Aberrant expression of miR-409-3p in cancers

Growing evidence has shown that multiple cancer types have abnormal miR-409-3p expression, with both upregulation and downregulation observed, as summarized in Table I. MiR-409-3p not only exists in tissues and cells but also stably exists in circulating body fluids. For the most part, miR-409-3p acts as a tumor suppressor and was reported to be downregulated in a minimum of 13 cancers, including NSCLC (12,14-17,19-21), BC (24,26,27,29,30), CC (31-35), osteosarcoma (36-39), GC (40-44), CRC (45,46,48-51), OC (53-55), ccRCC (57,58), BCa (59,61), PTC (62), AML (65,66), oligodendrogliomas (67), melanoma (68), TSCC (70), glioma (79), fibrosarcoma (81) and HCC (83,84). However, miR-409-3p also serves as an oncogene to promote tumor progression. MiR-409-3p was reported to be upregulated in carcinomas such as PC and BTC (63), meningioma (77), intracranial artery tumors (78) and glioblastoma (82). However, as shown in Table I, there are inconsistent results of miR-409-3p expression in NSCLC (13,18), BC (22,23,25,28), CRC (47,49), OC (56), DLBCL (64) and PC (71,73,74,76).

To sum up, it was found that miR-409-3p expression levels in tissues, cells and circulating fluids, such as plasma or serum, were inconsistent. While the exact regulatory mechanism is currently elusive, the reasons for the discrepancy found by certain scholars are as follows. First, various types of cancer cell are capable of selectively releasing specific miRNAs (85). Theoretically, the selective miRNAs released into the circulating fluids may lead to an increase in plasma or serum and a decrease in the level of tumor tissues/cells from which they are derived. In addition, miRNAs can be secreted into the extracellular space and packaged into all types of membrane-bound vesicles, including exosomes, microvesicles and apoptotic bodies (86), and influence the biological function of the recipient cells, thereby protecting these specific miRNAs from RNase-mediated degradation and upregulation in circulating fluids (87-89). Secondly, it has been hypothesized that miRNAs in the circulation may mainly represent by-products of dead cells (90,91). Furthermore, in consideration of the stromal compartment and tumor microenvironment, circulating miRNAs in the plasma/serum of cancer patients may also come from these parts (92). It was inferred that this may be due to differences in sample size, study cohort, batch effect, sensitivity and specificity of the assay and clinical factors such as gender, age and TNM stage. The contradictory findings on miR-409-3p in certain cancers require further exploration.

3. Clinical applications

MiR-409-3p as a biomarker in cancers. A huge effort has gone into finding acceptable miRNAs and it has been indicated that miRNAs are promising biomarkers for the diagnosis and monitoring of several malignancies. Circulating miR-409-3p was found to be dysregulated in various types of cancers (Table II). Zhou *et al* (13) examined six miRNAs, including miR-409-3p, in the plasma, which may contribute to the detection of LUAD to a certain extent. Similarly, Wang *et al* (18) revealed that miR-409-3p had high sensitivity and specificity in differentiating lung adenocarcinomas (LUADs) from healthy individuals and was able to detect early-stage LUAD in patients. In addition, it was able to diagnose stage I or II BC when compared to healthy controls (22). In patients with BC, miR-409-3p was shown to have the highest sensitivity and specificity for distinguishing patients with BC from healthy subjects (23,25). Besides, when combined with miR-32-5p, the sensitivity and specificity of the detection of CC in tissue and serum samples were the highest (31). The combined panel of ratios of five miRNAs possessed a diagnostic capability to make a distinction between CRC and colorectal adenoma (52). Furthermore, Wang *et al* (47) used a panel of miR-409-3p, miR-7 and miR-93, which had great diagnostic accuracy in distinguishing CRC from a healthy group. In PC and BTC, Kim *et al* (63) demonstrated that miR-409-3p was also downregulated by sequencing serum miRNAs. In AML, Li *et al* (65) discovered that miR-409-3p had the best diagnostic value, with a sensitivity of 93.3% and a specificity

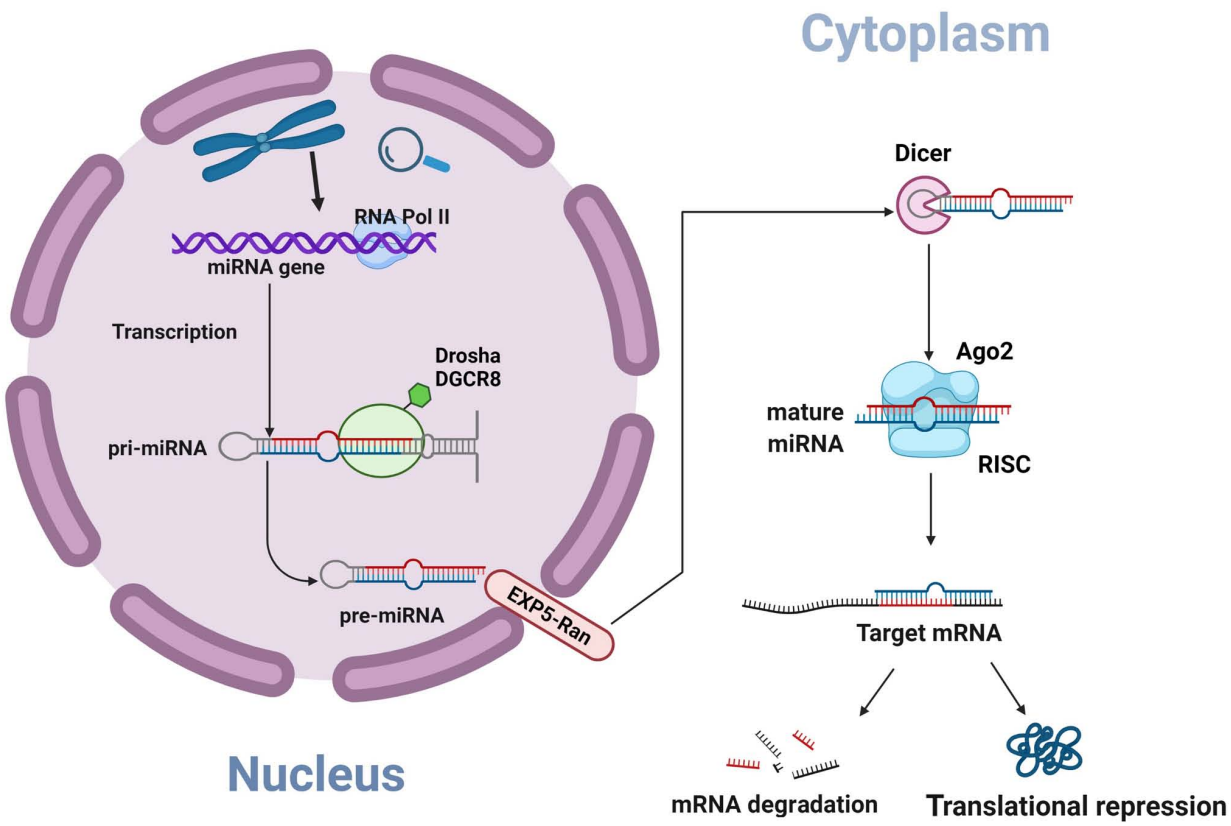

Figure 1. MiRNA biosynthesis and mechanisms. In eukaryotic cells, miRNAs first transcribe a long pri-miRNA within the nucleus and then are processed by Drosha and DGCR8 into a hairpin pre-miRNA containing 60-70 nucleotides, which are transported out of the nucleus with the help of EXP5-Ran, and cut into mature miRNA by Dicer in the cytoplasm, It is then integrated into the RISC to regulate gene expression based on complete or incomplete pairing with mRNA. Created with Biorender software (http://biorender.com). MiRNA, microRNA; Pol, polymerase; Drosha, Drosha ribonuclease III; DGCR8, DiGeorge syndrome chromosomal region 8; Dicer, Dicer ribonuclease III; Ago2, Argonaute 2; RISC, RNA-induced silencing complex.

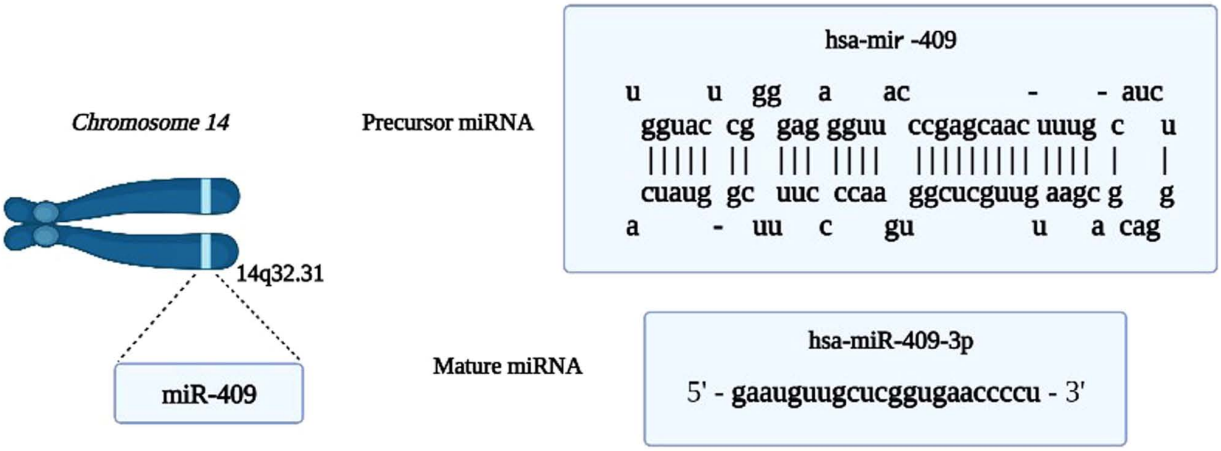

Figure 2. MiR-409-3p precursor and mature sequence. The precursors of miR-409-3p generate mature miR-409-3p under the involvement of transporters and enzymes. Created with BioRender software (http://biorender.com). miR, microRNA.

of 87.9%. In addition, miR-409-3p could be combined with other miRNAs to create a signature model for the diagnosis of NPC (69). Most strikingly, when comparing the serum concentrations of eight preoperative and postoperative patients with carbon ion radiotherapy (CIRT)-localized PCa, Yu *et al* (74) found that the expression level of miR-409-3p was higher than that of patients with CIRT following the surgical removal of primary tumors, and the patients with higher preoperative miR-409-3p levels had a better response to CIRT. The same result was found in the prediction of meningioma (68).

In general, the aforementioned results proved that miR-409-3p may serve as a promising biomarker for the diagnosis and therapeutic monitoring of cancers.

Prognostic value of miR-409-3p in cancers. MiR-409-3p has been discovered to be a prognostic marker in a variety

Table I. Expression of miR-409-3p in cancers based on published literature.

Authors, year	Type of cancer	Normal cells	Cancer cells	Cells expression (tumor/normal)	Tissues	Tissues expression (tumor/normal)	Plasma/ serum	Plasma/serum expression (tumor/normal)	(Refs.)
Wan *et al*, 2014	Lung cancer	HBE	A549, SPC-A1, PC9	Downregulation	34 pairs of NSCLC tissues and matched adjacent normal tissues	Downregulation	-	-	(12)
Zhou *et al*, 2017		-	-	-	19 pairs of NSCLC tissues and adjacent normal tissues	Upregulation	Plasma	Upregulation	(13)
Song *et al*, 2018		-	A549, H460	Downregulation	85 pairs of NSCLC tissues and matched adjacent normal tissues	Downregulation	-	-	(14)
Qu *et al*, 2018		HBE	A549, NCI-H1299, NCI-H1650, SPC-A1, PC-9	Downregulation	-	-	-	-	(15)
Yin *et al*, 2020		BEAS-2B	H1299, A549, H460, PC-9	Downregulation	66 pairs of NSCLC tissues and the adjacent normal tissues	Downregulation	-	-	(16)
Liu *et al*, 2020a		HBE	A549, PC-9, NCI-H1299, NCI, H460, NCI-H1650, NCI-H520	Downregulation	18 pairs of NSCLC tumor and adjacent normal tissue samples	Downregulation	-	-	(17)
Wang *et al*, 2020a		-	-	-	-	-	Serum	Downregulation	(18)
Wang *et al*, 2020b		BEAS-2B	A549, SK-MES-1, H1703, H460, H522	Downregulation	61 pairs of NSCLC tissues and adjacent normal tissues	Downregulation	-	-	(19)
Liu *et al*, 2022		HBE	A549, H1650, H520, H460, H1299, PC9	Downregulation	48 pairs of cancerous and paracancerous tissues	Downregulation	-	-	(20)
Yang *et al*, 2022b		MRC-5	A549, H2170	Downregulation	67 pairs of NSCLC tissues and adjacent normal tissues	Downregulation	-	-	(21)

Table I. Continued.

Authors, year	Type of cancer	Normal cells	Cancer cells	Cells expression (tumor/normal)	Tissues	Tissues expression (tumor/normal)	Plasma/ serum	Plasma/serum expression (tumor/normal)	(Refs.)
Cuk *et al*, 2013b	BC	-	-	-	-	-	Plasma	Upregulation	(22)
Cuk *et al*, 2013a		-	-	-	24 primary BC surgery tissue samples and 8 benign breast biopsies	Downregulation	Plasma	Upregulation	(23)
Li *et al*, 2013		-	-	-	21 pairs of DCIS and the corresponding normal tissues	Downregulation	-	-	(24)
Shen *et al*, 2014		-	-	-	-	-	Plasma	Upregulation	(25)
Zhang *et al*, 2016		HBL-100	MCF-7, T47D, MDA-MB-468, MDAMB-231	Downregulation	30 pairs of human BC tissues and adjacent non-tumor samples	Downregulation	-	-	(26)
Ma *et al*, 2016		HBL-100, MCF-10A	MCF-7, BT-474, MDA-MB-231, SK-BR3	Downregulation	40 pairs of tumor tissues and transitional tissues normal tissues	Downregulation	-	-	(27)
Venkatadri *et al*, 2016		-	MCF-7	Upregulation	-	-	-	-	(28)
Su *et al*, 2021		MCF-10A	MCF-7, SKBR-3	Downregulation	44 pairs BC tissue and adjacent normal tissue samples	Downregulation	-	-	(29)
Yang *et al*, 2022a		MCF10A	MCF7, MDA-MB-231	Downregulation	64 pairs BC tissue (including 30 sensitive and 30 resistant to tamoxifen) and 64 normal tissue samples	Downregulation	-	-	(30)
Shukla *et al*, 2019	CC	NCE	SiHa, Hela, CaSki	Downregulation	-	-	Serum	Downregulation	(31)
Sommerova *et al*, 2019			HeLa, CaSki, C4-I	Downregulation	Precancerous cervical lesions	Downregulation	-	-	(32)
Cui *et al*, 2020		ECT1/E6E	HeLa, Caski, C33A, Siha	Downregulation	55 pairs of CC tissues and adjacent non-tumor tissues	Downregulation	-	-	(33)

Table I. Continued.

Authors, year	Type of cancer	Normal cells	Cancer cells	Cells expression (tumor/normal)	Tissues	Tissues expression (tumor/normal)	Plasma/ serum	Plasma/serum expression (tumor/normal)	(Refs.)
Zhou *et al*, 2021		HcerEpic	SiHa, SW756, CaSki, C-33A	Downregulation	GEO datasets (GSE102686) and 47 pairs of CC tissues and marched normal tissues	Downregulation	-	-	(34)
Wu *et al*, 2021		HcerEpic	CaSki, HeLa	Downregulation	-	-	-	-	(35)
Wu *et al*, 2016	Osteosa-rcoma	hFOB	U2OS, MG-63, SAOS-2	Downregulation	58 pairs of osteosarcoma tissue specimens and adjacent non-tumorous tissue specimens	Downregulation	-	-	(36)
Zhang *et al*, 2017		NHOst, hFOB 1 19	MG63, SaOS-2, U2OS, G292	Downregulation	36 pairs of human osteosarcoma tissues and normal bone tissues	Downregulation	-	-	(37)
Wu *et al*, 2019		hFOB 1 19	HOS (GDC76), MG63 (GDC074)	Downregulation	49 pairs of osteosarcoma tumor and adjacent non-tumor tissues	Downregulation	-	-	(38)
Long *et al*, 2020		hFOB 1 19	SJSA1, U2OS	Downregulation	30 pairs of osteosarcoma and adjacent tissues	Downregulation	-	-	(39)
Li *et al*, 2012	GC	GES-1	MKN45, MKN28, SGC-7901, NCI-N87, AGS	Downregulation	67 pairs of primary GC tissues and its matched non-tumor tissues	Downregulation	-	-	(40)
Zheng *et al*, 2012		GES-1	SGC-7901, HGC-27, AGS, MGC-803, NCI-N87	Downregulation	90 paired of GC and their corresponding non-tumorous tissues	Downregulation	-	-	(41)
Yu *et al*, 2021		GES-1	XGC-1, MKN45	Downregulation	30 pairs of GC tissues and paracancerous normal tissues	Downregulation	-	-	(42)
Feng *et al*, 2021		GES-1	MKN45, BGC823,	Downregulation	94 pairs of GC tissues and adjacent	Downregulation	-	-	(43)

Table I. Continued.

Authors, year	Type of cancer	Normal cells	Cancer cells	Cells expression (tumor/normal)	Tissues	Tissues expression (tumor/normal)	Plasma/ serum	Plasma/serum expression (tumor/normal)	(Refs.)
			MGC803, HGC27, SGC7901		non-tumorous tissues				
Liu *et al*, 2015	CRC	-	SW480, SW1116	Downregulation	45 pairs of primary CRC and their corresponding adjacent non-tumor tissues	Downregulation	-	-	(45)
Bai *et al*, 2015		-	HCT116, RKO, DLD1, SW480	Downregulation	82 pairs of CRC samples and corresponding non-tumorous tissues	Downregulation	-	-	(46)
Wang *et al*, 2015		-	-	-	-	-	Plasma	Upregulation	(47)
Tan *et al*, 2016		FHC, CCD-18Co	LoVo, HCT 116, DLD-1, SW480, HT-29, RKO	Downregulation	20 human CRC tissue samples and 10 human normal tissues	Downregulation	-	-	(48)
López-Rosas *et al*, 2018		-	SW-480/ trophozoites, Caco2/ trophozoites	Downregulation	-	-	-	-	(49)
Han *et al*, 2020		-	HCT-116/	Downregulation	-	-	-	-	(50)
Chen *et al*, 2022			L-OHP SW480, HCT116	-	45 cases of CRC and adjacent non-tumorous tissues	Downregulation			(51)
Zhang *et al*, 2018a		-	-	-	-	-	Serum	Ratio of miR-130a-3p/ miR-409-3p and miR-148a-3p/ miR-409-3p upregulation	(52)
Gharpure *et al*, 2018	OC	IO180	HeyA8, HeyA8 MDR, A2780, A2780 CP20 SKOV3ip1,	Downregulation	GEO datasets (GSE15190)	Downregulation	-	-	(53)

Table I. Continued.

Authors, year	Type of cancer	Normal cells	Cancer cells	Cells expression (tumor/normal)	Tissues	Tissues expression (tumor/normal)	Plasma/ serum	Plasma/serum expression (tumor/normal)	(Refs.)
			Ovcar5, Ovcar3, Ovca432, IGROV, IGROV CP20, Ovcar8						
Cheng *et al*, 2018		SV40, iMOSEC	OV-1063, CoC1, CaoV-3, OVCAR3, and SKOV3	Downregulation	13 OC tumor samples and 12 tumor-adjacent normal tissue samples	Downregulation	-	-	(54)
Zhang *et al*, 2018b		IO180	KOV3_ip1, A2780_PAR and HEYA8	Downregulation	-	-	-	-	(55)
Li *et al*, 2020b		OSE80	SKOV3, Vcar	-	6 OC tissues	Upregulation	-	-	(56)
Zhu *et al*, 2016	ccRCC	-	-	-	13 cases of localized renal cell carcinoma and 15 cases of metastatic renal cell carcinoma	Downregulation	-	-	(57)
Wang *et al*, 2019		-	A-498, 769-P	Downregulation	56 pairs of ccRCC tissues and tumor-adjacent normal tissue samples	Downregulation	-	-	(58)
Xu *et al*, 2013	BCa	SV-HUC-1	T24, 5637, J82, UM UC3	Downregulation	10 pairs of human BCa tissues and adjacent normal mucosal tissues	Downregulation	-	-	(59)
Lian *et al*, 2018		-	-	-	-	-	Serum	Downregulation	(61)
Zhao *et al*, 2018	PTC	Nthy-ori3-1 cell l	B-CPAP, TPC-1, GLAG-66	Downregulation	20 pairs of primary PTC tissues and adjacent non-tumor	Downregulation	-	-	(62)
Kim *et al*, 2019		-	-	-	-	-	Serum	Upregulation	(63)
Leivonen *et al*, 2017	DLBCL	SV_Co10	SU-DHL-4	Upregulation	Discovery cohort: 7 pairs of DLBCL primary and relapse validation cohort:	Down in the relapse sample	-	-	(64)

Table I. Continued.

Authors, year	Type of cancer	Normal cells	Cancer cells	Cells expression (tumor/normal)	Tissues	Tissues expression (tumor/normal)	Plasma/ serum	Plasma/serum expression (tumor/normal)	(Refs.)
					13 pairs of DLBCL primary and relapse				
Li *et al*, 2020a	AML	-	-	-	73 patients with AML and 15 healthy controls	Downregulation	-	-	(65)
Xie *et al*, 2023	AML	HS-5	NB4, THP-1	Downregulation	-	-	-	-	(66)
Kumar *et al*, 2018	Oligodendr-ogliomas	-	HS683	-	TCGA: 153 Oligoden-drogliomassamples and 5 controls	Downregulation	-	-	(67)
Venza *et al*, 2015	Melanoma	NHEM	G361, GR-M, OCM-1	Downregulation	-	-	-	-	(68)
Chen and Dai, 2018	TSCC	HOK	Tca8113, SCC9, SCC25, Ca127	Downregulation	68 patients (38 males and 30 females)	Downregulation	-	-	(70)
Josson *et al*, 2014	PCa	-	$ARCaP_E$, $ARCaP_M$, $LNCaP^{Neo}$, $LNCaP^{RANKL}$	Upregulation in $ARCaP_M$ and $LNCaP^{Neo}$	Benign prostatic hyperplasia (n=14), Gleason 6 (n=26), and Gleason ≥7 (n=35)	Upregulation in Gleason ≥7 compared with Gleason 6; upregulation in Gleason 6 and Gleason ≥7 compared with benign prostatic hyperplasia	-	-	(71)
Josson *et al*, 2015		-	[SON, SOC, $HS\text{-}27a_{RWV}$, $HS\text{-}27a_{C4\text{-}2}$, $MG\text{-}63_{RWV}$, $MG\text{-}63_{LNCaP}$, $MG\text{-}63_{C4\text{-}2}$	Upregulation in the cancer-associated stromal cell (SOC, $HS\text{-}27a_{C4\text{-}2,}$ $MG\text{-}63_{LNCaP}$, $MG\text{-}63_{C4\text{-}2}$)	Gleason 6, (n=25) and Gleason score ≥7 (Gleason 7, 8, 10, n=30)	Upregulation in Gleason ≥7	-	-	(73)
Yu *et al*, 2018			-	-	-	-	Serum exosomes	Upregulation before carbon ion radiotherapy	(74)

Table I. Continued.

Authors, year	Type of cancer	Normal cells	Cancer cells	Cells expression (tumor/normal)	Tissues	Tissues expression (tumor/normal)	Plasma/ serum	Plasma/serum expression (tumor/normal)	(Refs.)
		-	-	-	PCa set (n=32) and benign prostatic hyperplasia set (n=43)	Downregulation	-	-	
Nguyen *et al*, 2013		-	-	-	42 primary tumors of low-risk, localized PCa and 28 normal prostate tissue	Downregulation in the low-risk, localized PCa	Serum	Downregulation in castration resistant PCa compared with low-risk	(76)
Zhi *et al*, 2016	Meningioma	-	-	-	-	-	Serum	Upregulation in pre-operative	(77)
Ding *et al*, 2021	Intracranial artery tumors	-	Human brain vascular smooth muscle cells exposed to H_2O_2	Upregulation	-	-	-	-	(78)
Cao *et al*, 2017	Glioma	HAs	172, SHG44, U251, U87	Downregulation	Glioma tissue (n=20) and normal brain tissue (n=8)	Downregulation	-	-	(79)
Ma *et al*, 2022		NHA	U-87 MG, U-138 MG, U-118 MG, T98-G, LN-229, LN-18	Downregulation	47 pairs of primary glioma tissues and adjacent non-tumor	Downregulation	-	-	(80)
Weng *et al*, 2012	Fibrosarcoma	-	HT1080, Cos-7	Downregulation	-	-	-	-	(81)
Khalil *et al*, 2016	Glioblastoma	-	98G, U251 and U373	Upregulation	Glioblastoma tissues (n=26)	Upregulation	-	-	(82)
Chang *et al*, 2023	HCC	-	Huh-7	Downregulation	45 pairs of liver HCC tissue and adjacent normal tissue; tumor (n=375) and normal tissues (n=50) based on TCGA and Genotype-Tissue Expression database	Downregulation	-	-	(83)

Table I. Continued.

Authors, year	Type of cancer	Normal cells	Cancer cells	Cells expression (tumor/normal)	Tissues	Tissues expression (tumor/normal)	Plasma/ serum	Plasma/serum expression (tumor/normal)	(Refs.)
Li *et al*, 2023		LX2	Hep3B, Huh7	Downregulation	5 liver transplant donors, 5 patients with liver cirrhosis, and 5 patients with HCC	Downregulation	-	-	(84)

MiR, microRNA; NSCLC, non-small cell lung cancer; BC, breast cancer; DCIS, ductal carcinoma *in situ*; CC, cervical cancer; GEO, Gene Expression Omnibus; GC, gastric cancer; CRC, colorectal cancer; OC, ovarian cancer; ccRCC, renal cell carcinoma; BCa, bladder cancer; PTC, papillary thyroid cancer; DLBCL, diffuse large B-cell lymphoma; AML, acute myeloid leukemia; TCGA, The Cancer Genome Atlas; TSCC, tongue squamous cell carcinoma; PCa, prostate cancer; HCC, hepatocellular carcinoma.

of malignancies. The varied expression of miR-409-3p in various neoplasms may indicate that miR-409-3p expression and survival have different relationships.

In NSCLC, miR-409-3p expression was an independent prognostic marker. In general, patients with low miR-409-3p expression exhibit poor prognosis. Patients with LUAD with low miR-409-3p expression display a lower overall survival (12,14,16,20), recurrence-free survival (12) and disease-free survival (14,20) than patients with high miR-409-3p expression. Furthermore, a low median survival time was associated with pTNM (III+IV) and lymph node metastasis. Clinically, reduced miR-409-3p expression was found to be substantially associated with poor tumor differentiation, tumor size, advanced pTNM stage, lymph node metastasis, pleural invasion and smoking (12,14,20). In BC, the level of tissue miR-409-3p was negatively associated with TNM stage, lymph node metastasis, pathological differentiation, tumor size and Ki-67 status (27). In osteosarcoma, miR-409-3p expression was associated with advanced clinical stage and distant metastasis (38). In addition, miR-409-3p was usually decreased in GC. Among patients with GC, changes in miR-409-3p expression were associated with local invasion, TNM stage and tumor size (40-42). Studies investigating miRNA profiles in CRC showed that downregulation of miR-409-3p was associated with tumor size, local invasion and metastasis (45,46). In addition, in OC, lower miR-409-3p levels were closely associated with the International Federation of Gynecology and Obstetrics stage (55). Furthermore, miR-409-3p, when combined with other miRNAs, was negatively associated with age and the age at which non-muscle-invasive BCa develops (61). In patients with AML, a low level of miR-409-3p was associated with poorer event-free survival and white blood cell count (65). Another study assessing oligodendrogliomas confirmed that miR-409-3p was inversely associated with progression-free survival (67). With regard to TSCC, downregulation of miR-409-3p was associated with TNM stage and lymph node metastasis (70). On the contrary, a previous study has shown that in other neoplasms, including PCa, patients with high miR-409-3p expression had a poorer prognosis than those with low miR-409-3p expression. More importantly, a higher Gleason score was positively associated with the expression of miR-409-3p (71). In addition, the high recurrence rate of meningioma was substantially connected with miR-409-3p expression, indicating that miR-409-3p may have predictive utility for patients with meningioma following tumor removal (77).

In summary, these findings suggested that miR-409-3p was significantly linked to the survival of cancer patients. Therefore, miR-409-3p may function as an independent prognostic molecular biomarker in malignancies.

4. Biological roles of miR-409-3p in cancers *in vitro*

MiR-409-3p plays a role in the initiation and progression of cancer, and its abnormal expression is involved in several biological processes (Table III). The specific mechanisms are described below.

Growth and apoptosis. Several diseases, particularly cancer, are caused by a disruption in the balance between cell growth

Table II. Diagnostic value of miR-409-3p in cancers.

Authors, year	Type of cancer	AUC	Sensitivity	Specificity	95% CI	Combined diagnostic molecular signature	(Refs.)
Zhou *et al*, 2017	Lung cancer	0.61	-	-	0.53-0.69	miR-19b-3p+miR-21-5p+miR-221-3p+miR-409-3p+miR-425-5p+miR-584-5p	(13)
Wang *et al*, 2020a		0.76	57.32%	86.67%	0.68-0.82	miR-409-3p+miR-142-5p+miR-223-3p+miR-146a-5p	(18)
Cuk *et al*, 2013b	BC	-	-	-	-	miR-127-3p+miR-148b+miR-376a+ miR-376c+ miR-409-3p+miR-652+miR-801	(22)
Cuk *et al*, 2013a		0.66	-	-	0.59-0.74	miR-148b+miR-409-3p+miR-801	(23)
Shen *et al*, 2014		0.78	-	-	-	miR-148b+miR-409-3p+miR-801	(25)
Shukla *et al*, 2019	CC	-	-	-	-	miR-32-5p+miR-409-3p	(31)
Wang *et al*, 2015	CRC	-	-	-	-	miR-409-3p+miR-7+miR-93	(47)
Zhang *et al*, 2018a		-	-	-	-	let-7b/miR-367-3p+miR-130a-3p/miR-409-3p+miR-148-3p/miR-27b+ miR-148a-3p/miR-409-3p+miR-21-5p/miR-367-3p	(52)
Li *et al*, 2020a	AML	0.93	93.30%	87.90%	0.86-1.00	-	(65)
Jiang *et al*, 2021	NPC					miR-134-5p+miR-205-5p+miR-409-3p+miR-484+miR-486-3p+miR-486-5p+ miR-92b-3p	(69)
Fredsøe *et al*, 2020	PCa	-	-	-	-	miR-375*+miR-33a-5p+miR-16-5p*+miR-409-3p	(75)
Zhi *et al*, 2016	Meningioma	-	-	-	-	miR-106a-5p+miR-219-5p+miR-375+miR-409-3p+miR-197+miR-224	(77)

MiR, microRNA; AUC, area under curve; BC, breast cancer; CC, cervical cancer; CRC, colorectal cancer; AML, acute myeloid leukemia; NPC, nasopharyngeal carcinoma; PCa, prostate cancer.

Table III. Targets and functions of miR-409-3p in human cancers.

Authors, year	Tumor type	Upstream genes	Downstream genes	Proliferation and apoptosis (used cells)	Invasion and migration (used cells)	Other functions (used cells)	(Refs.)
Wan *et al*, 2014	Lung cancer	-	MET	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑; ΔmiR-409-3p: Proliferation↑, (A549, SPC-1)	↑miR-409-3p: Invasion and Migration↓; Δ miR-409-3p: Invasion and Migration↑ (A549, SPC-1)	-	(12)
Song *et al*, 2018		-	SPIN1	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑; ΔmiR-409-3p: Proliferation↑ (A549)	↑miR-409-3p: Invasion and Migration↓; ΔmiR-409-3p: Invasion and Migration↑ (A549)	-	(14)
Yin *et al*, 2020		DUXAP8	HK2, LDHA	ΔmiR-409-3p: Cell viability↑, Colony formation↑ (A549, H1299)	ΔmiR-409-3p: Migration↑ (A549, H1299)	ΔmiR-409-3p: Glycolysis↑ (A549, H1299)	(16)
Liu *et al*, 2020a		-	SOD1	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑ (H1299)	-	-	(17)
Wang *et al*, 2020b		PSMA3-AS1	SPIN1	ΔmiR-409-3p: Proliferation↑, Apoptosis↓ (A549, H460)	ΔmiR-409-3p: Invasion and Migration↑ (A549, H460)	-	(19)
Liu *et al*, 2022		CBR3-AS1	SOD1	↑miR-409-3p: Proliferation↓ (H1650)	↑miR-409-3p: Invasion and Migration↓ (H1650)	ΔmiR-409-3p: Radiosensitivity↓ (H520)	(20)
Yang *et al*, 2022b		Hsa_circ_ 0079530	AQP4	↑miR-409-3p: Proliferation↓; ΔmiR-409-3p: Proliferation↑ (H1270, A549)	↑miR-409-3p: Invasion and Migration↓, EMT↓; ΔmiR-409-3p:Invasion and Migration↑ (H1270, A549)	↑miR-409-3p: Radiosensitivity↑; ΔmiR-409-3p: Radiosensitivity↓ (H1270, A549)	(21)
Zhang *et al*, 2016	BC	-	AKT1	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑ (MDA-MB-231, MDA-MB-468); ΔmiR-409-3p: Proliferation↑ (T47D)	↑miR-409-3p: Invasion and Migration↓ (MDA-MB-231, MDA-MB-468); ΔmiR-409-3p: Invasion and Migration ↑ (T47D)	-	(26)
Ma *et al*, 2016		-	ZEB1	↑miR-409-3p: Proliferation↓, Colony formation↓ (MDA-MB-231)	↑miR-409-3p: Invasion and Migration↓ (MDA-MB-231)	-	(27)

Table III. Continued.

Authors, year	Tumor type	Upstream genes	Downstream genes	Proliferation and apoptosis (used cells)	Invasion and migration (used cells)	Other functions (used cells)	(Refs.)
Su *et al*, 2021		CircCNOT2	TWIST1	↑miR-409-3p: Proliferation↓, Apoptosis↑ (MCF-7)	↑miR-409-3p: Invasion and Migration↓ (MCF-7)	↑miR-409-3p: EMT↓ (MCF-7)	(29)
Yang *et al*, 2022a		CircTRIM28	HMGA2	ΔmiR-409-3p: Proliferation↑, Colony formation↑, Apoptosis↓ (MCF7/R, MDA-MB-231/R)	ΔmiR-409-3p: Invasion and Migration ↑ (MCF7/R, MDA-MB-231/R)	ΔmiR-409-3p: Tamoxifen sensitivity↓ (MCF7/R, MDA-MB-231/R)	(30)
Shukla *et al*, 2019	CC	-	MTF2	↑miR-409-3p: Proliferation↓ (SiHa)	-	-	(31)
Sommerova *et al*, 2019		-	HPV16/ 18 E6	↑miR-409-3p: Proliferation↓; ΔmiR-409-3p: Proliferation↑ (C-4I, CaSki)	↑miR-409-3p: Migration↓; ΔmiR-409-3p: Migration↑, (CaSki)	-	(32)
Cui *et al*, 2020		Circ_0000745	ATF1	↑miR-409-3p: Colony formation↓ (CaSki, Siha)	↑miR-409-3p: Invasion and Migration↓ (CaSki, Siha)	↑miR-409-3p: Glycolysis↓ (CaSki, Siha)	(33)
Zhou *et al*, 2021		CircFAT1	CDK8	ΔmiR-409-3p: Proliferation↑, Apoptosis↓ (CaSki, C-33A)	ΔmiR-409-3p: Invasion and Migration ↑ (CaSki, C-33A)	-	(34)
Wu *et al*, 2016	Osteosarcoma	-	CTNND1	-	↑miR-409-3p: Invasion and Migration↓ (U2OS, SAOS-2)	-	(36)
Zhang *et al*, 2017		-	ELF2	↑miR-409-3p: Proliferation↓, Cell cycle↓, Apoptosis↑: ΔmiR-409-3p: Proliferation↑, Cell cycle↑, Apoptosis↓ (MG63, SaOS-2)	-	-	(37)
Wu *et al*, 2019		-	ZEB1	↑miR-409-3p: Proliferation↓ (MG63, HOS)	↑miR-409-3p: Invasion↓ (MG63, HOS)	-	(38)
Long *et al*, 2020		Circ0000285	IGFBP3	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑; ΔmiR-409-3p: Proliferation↑, Colony formation↑, Apoptosis↓ (SJSA1, U2OS)	↑miR-409-3p: Invasion and Migration↓; ΔmiR-409-3p: Invasion and Migration↑ (SJSA1, U2OS)	-	(39)

Table III. Continued.

Authors, year	Tumor type	Upstream genes	Downstream genes	Proliferation and apoptosis (used cells)	Invasion and migration (used cells)	Other functions (used cells)	(Refs.)
Zhang *et al*, 2021		CircATRNL1	LDHA	-	-	↑miR-409-3p: Glycolysis↓ (Saos-2); ΔmiR-409-3p: Glycolysis↑ (MG63)	(112)
Li *et al*, 2012	GC	-	PHF10	↑miR-409-3p: Proliferation↓, Colony formation↓, Cell cycle↓, Apoptosis↑ (SGC-7901)	-	-	(40)
Zheng *et al*, 2012		-	RDX	-	↑miR-409-3p: Invasion and Migration↓ (SGC-7901, HGC-27, MKN45)	-	(41)
Yu *et al*, 2021		CircNEK9	MAP7	↑miR-409-3p: Proliferation↓, Colony formation↓, Cell cycle↓; ΔmiR-409-3p: Proliferation↑, Colony formation↑, Cell cycle↑ (XGC-1, MKN45)	↑miR-409-3p: Invasion and Migration↓; ΔmiR-409-3p: Invasion and Migration↑ (XGC-1, MKN45)	-	(42)
Wang *et al*, 2020c		Circ0001023	PHF10	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑ (AGS); ΔmiR-409-3p: Proliferation↑, Colony formation↑, Apoptosis↓ (MKN-28, SGC-7901)	↑miR-409-3p: Invasion and Migration↓ (AGS); ΔmiR-409-3p: Invasion and Migration↑ (MKN-28, SGC-7901)	-	(44)
Liu *et al*, 2015	CRC	-	NLK	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑ (SW480, SW1116)	↑miR-409-3p: Invasion and Migration↓ (SW480, SW1116)	-	(45)
Bai *et al*, 2015		-	GAB1	-	↑miR-409-3p: Invasion and Migration↓; ΔmiR-409-3p: Invasion and Migration↑ (HCT116, RKO)	-	(46)
Tan *et al*, 2016		-	beclin-1	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑ (LoVo Oxa R)	-	↑miR-409-3p: Chemoresistance↓, autophagic activity↓ (LoVo Oxa R)	(48)

Table III. Continued.

Authors, year	Tumor type	Upstream genes	Downstream genes	Proliferation and apoptosis (used cells)	Invasion and migration (used cells)	Other functions (used cells)	(Refs.)
Han *et al*, 2020		-	ERCC1	↑miR-409-3p: Cell cycle↓, Apoptosis↑; ΔmiR-409-3p: Cell cycle↑, Apoptosis↓ (HCT-116/L-OHP)	↑miR-409-3p: Invasion and Migration↓: ΔmiR-409-3p: Invasion and Migration↑ (HCT-116/L-OHP)	↑miR-409-3p: Chemoresistance↓; ΔmiR-409-3p: Chemoresistance↑ (HCT-116/L-OHP)	(50)
Chen *et al*, 2022		LINC00630	HK2	↑miR-409-3p: Proliferation↓, Apoptosis↑ (SW480, HCT116)	-	↑miR-409-3p: Glycolysis↓ (SW480, HCT116)	(51)
Gharpure *et al*, 2018	OC	-	FABP4	-	↑miR-409-3p: Invasion and Migration↓; ΔmiR-409-3p: Invasion and Migration↑ (HeyA8 MDR, Ovcar5)	-	(53)
Cheng *et al*, 2018		-	FIP200	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑ (OV-1063, OV-1063R)	-	↑miR-409-3p: Chemoresistance↓; Autophagic activity↓ (OV-1063 R)	(54)
Li *et al*, 2020b		-	RAB10	↑miR-409-3p: Proliferation↓, Colony formation↓, Apoptosis↑; ΔmiR-409-3p: Proliferation↑, Colony formation↑, Apoptosis↓ (SKOV3)	Δ miR-409-3p: Migration↑ (SKOV3)	-	(56)
Wang *et al*, 2019	ccRCC	-	PDK1	-	-	↑miR-409-3p: Glycolysis↓ (A-498,769-P)	(58)
Xu *et al*, 2013	BCa	-	MET	-	↑miR-409-3p: Invasion and Migration↓ (T24, 5637)	-	(59)
Xu *et al*, 2016		-	MET	↑miR-409-3p: Cell motility↓ (T24, UM-UC-3)	-	-	(60)
Zhao *et al*, 2018	PTC	-	CCDN2	↑miR-409-3p: Proliferation↓, Colony formation↓, Cell cycle↓ (TPC-1, GLAG-66)	-	-	(62)

Table III. Continued.

Authors, year	Tumor type	Upstream genes	Downstream genes	Proliferation and apoptosis (used cells)	Invasion and migration (used cells)	Other functions (used cells)	(Refs.)
Leivonen *et al*, 2017	DLBCL	-	-	↑miR-409-3p: Cell viability↓ (SU-DHL-4, SV_Co10)	-	↑miR-409-3p: Chemoresistance↓ (SU-DHL-4, SV_Co10)	(64)
Xie *et al*, 2023	AML	-	RAB10	↑miR-409-3p: Proliferation↓, Apoptosis ↑ (THP-1)	-	-	(66)
Chen and Dai, 2018	TSCC	-	RDX	↑miR-409-3p: Proliferation↓; ΔmiR-409-3p: Proliferation↑ (Tca8113)	↑miR-409-3p: Invasion and Migration↓; ΔmiR-409-3p: Invasion and Migration↑ (Tca8113)	-	(70)
Josson *et al*, 2014	PCa	-	RSU1	ΔmiR-409-3p: Apoptosis↑ ($ARCaP_M$)	↑miR-409-3p: Invasion and Migration↑ ($ARCaP_E$-409), EMT↑ ($ARCaP_E$, LNCaP)	-	(71)
Gururajan *et al*, 2014		-	-	-	↑miR-409-3p: EMT↑; ΔmiR-409-3p: EMT↓ ($ARCaP_M$,$ARCaP_E$)	-	(72)
Josson *et al*, 2015		-	RSU1	↑miR-409-3p: Proliferation↑ ($ARCaP_E$, SON-409 CM, SON-C CM)	↑miR-409-3p: EMT↑ ($ARCaP_E$, SON-409 CM, C4-2B PCa)	-	(73)
Ding *et al*, 2021	Intracranial artery tumors	Circ_DOCK1	MCL1	↑miR-409-3p: Proliferation↓, PCNA↓, Apoptosis↑; ΔmiR-409-3p: proliferation↑, PCNA↑, Apoptosis ↓ (HBVSMCs)	-	-	(78)
Cao *et al*, 2017	Glioma	-	HMGN5	↑miR-409-3p: Proliferation↓, Colony formation↓, Cell cycle↓ (U251); ΔmiR-409-3p: Proliferation↑, Colony formation↑, Cell cycle↑ (U87)	↑miR-409-3p: Invasion↓ (U251); ΔmiR-409-3p: Invasion↑ (U87)	-	(79)
Ma *et al*, 2022		circATRNL1	PDK1	↑miR-409-3p: Cell cycle↓, Proliferation↓; ΔmiR-409-3p: Cell cycle↑, Proliferation↑ (LN-229 and T98-G)	-	-	(80)

Table III. Continued.

Authors, year	Tumor type	Upstream genes	Downstream genes	Proliferation and apoptosis (used cells)	Invasion and migration (used cells)	Other functions (used cells)	(Refs.)
Weng *et al*, 2012	Fibrosarcoma	-	ANG	↑miR-409-3p: Proliferation↓ (HUVEC, HT1080)	-	↑miR-409-3p: Vascularization↓ (HUVEC, HT1080)	(81)
Chang *et al*, 2023	HCC	-	BRF2	-	↑miR-409-3p: Invision and Migration↓; ΔmiR-409-3p: Invision and Migration↑ (Huh-7)	-	(83)
Li *et al*, 2023		LINC00886	RAB10	↑miR-409-3p: Proliferation↓, Apoptosis ↑; ΔmiR-409-3p: Proliferation↑, Apoptosis↓ (Hep3B, Huh7)	↑miR-409-3p: Invision and Migration↓; ΔmiR-409-3p: Invision and Migration↑ (Hep3B, Huh7)	-	(84)

↑, upregulation/enhancement; ↓, decrease; Δ, knockdown; MiR, microRNA; MET, MET proto-oncogene, receptor tyrosine kinase; SPIN1, spindlin1; DUXAP8, double homeobox A pseudogene 8; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; SOD1, superoxide dismutase 1; AQP4, aquaporin 4; EMT, epithelial-mesenchymal transition; BC, breast cancer; ; AKT1, AKT serine/threonine kinase 1; ZEB1, zinc finger E-box binding homeobox 1; TWIST1, twist family bHLH transcription factor 1; circTRIM28, circular RNA tripartite motif-containing 28; HMGA2, high mobility group AT-hook 2; CC, cervical cancer; MTF2,metal response element binding transcription factor 2; ATF1, activating transcription factor 1; circFAT1, circular RNA FAT atypical cadherin 1; CDK8, cyclin dependent kinase 8; CTNND1, catenin-δ1; ELF2, E74-like factor 2; ZEB1, zinc finger E-box binding homeobox 1; IGFBP3, insulin like growth factor binding protein 3; GC, gastric cancer; PHF10, PHD finger protein 10; RDX, radixin; CircNEK9, CircRNA NIMA-related kinase 9; MAP7, microtubule associated protein 7; CRC, colorectal cancer; NLK, nemo like kinase; GAB1, GRB2 associated binding protein 1; ERCC1, ERCC excision repair 1; OC, ovarian cancer; FABP4, fatty acid binding protein 4; RAB10, RAB10, member RAS oncogene family; ccRCC, renal cell carcinoma; PDK1, 3-phosphoinositide dependent kinase 1; BCa, bladder cancer; PTC, papillary thyroid cancer; CCDN2, cyclin D2; DLBCL, diffuse large B-cell lymphoma; AML, acute myeloid leukemia; TSCC, tongue squamous cell carcinoma; PCa, prostate cancer; RSU1, Ras suppressor protein 1; MCL1, myeloid cell leukemia sequence 1; HBVSMCs, human brain vascular smooth muscle cells; HMGN5, high mobility group nucleosome binding domain 5; ANG, angiogenin; HCC, hepatocellular carcinoma; BRF2, BRF2 RNA polymerase III transcription initiation factor subunit.

and death. Targeted genes of miR-409-3p are closely associated with the development and apoptotic processes of tumor cells. In most cases, miR-409-3p acts as a tumor suppressor. A tyrosine kinase receptor called MET proto-oncogene, receptor tyrosine kinase (*MET*) triggers the mitogenic signaling pathway, which leads to the development of tumors and malignant transformation (93,94).

In LUAD, miR-409-3p suppressed the proliferation of A549 and SPC-1 NSCLC cells and promoted caspase-3-dependent apoptosis by directly targeting *MET* (12). Subsequently, Song *et al* (14) reported that miR-409 upregulation clearly inhibited proliferation by inhibiting spindlin 1 (*SPIN1*), a component of the SPIN/SSTY gene family. A study by Qu *et al* (15) unveiled that lncRNA zinc finger E-box binding homeobox 1 antisense 1 (ZEB1-AS1) functioned as a competing endogenous RNA (ceRNA) to facilitate NSCLC tumorigenesis by regulating the ZEB1-AS1/miR-409-3p/*ZEB1* signaling pathway. Mounting evidence suggests that the ZEB1-AS1 signaling pathway may aggravate NSCLC cell proliferation and reduce apoptosis (15). Furthermore, Yin *et al* (16) revealed that by regulating the miR-409-3p/hexokinase 2 (*HK2*) and lactate dehydrogenase A (*LDHA*) axis, double homeobox A pseudogene 8 (DUXAP8) promoted the viability of A549 and H1299 NSCLC cells. Liu *et al* (17) also demonstrated that loss of miR-409-3p inhibited the expression of superoxide dismutase 1 (*SOD1*) and its oncogenic activity. Recently, a publication described carbonyl reductase 3 (CBR3)-AS1 as a ceRNA interacting with miR-409-3p in NSCLC. Furthermore, NSCLC development and miR-409-3p suppression were facilitated by the overexpression of CBR3-AS1. In addition, the CBR3-AS1/miR-409-3p/*SOD1* axis could promote the proliferation of H1650 NSCLC cells (20). In addition to CBR3-AS1, circ_0079530 also had an oncogenic role in NSCLC through the inhibition of miR-409-3p. Yang *et al* (21) revealed that the circ_0079530/miR-409-3p/aquaporin 4 (*AQP4*) axis promoted the proliferation and invasion of H1270 and A549 NSCLC cells.

According to Zhang *et al* (26), overexpression of miR-409-3p, which has a crucial role in cell development, significantly hampered the proliferation and colony formation of MDA-MB-231 and MDA-MB-468 BC cells and accelerated apoptosis by targeting AKT serine/threonine kinase 1 (*AKT1*), which was essential for cell growth (95). By contrast, anti-miR-409-3p led to the inhibition of the proliferation of T47D BC cells. In addition, despite the fact that upregulation of miR-409-3p did not affect *AKT1* mRNA, the protein level decreased, indicating that the regulation of AKT1 by miR-409-3p was post-transcriptional. Ma *et al* (27) also concluded that increased miR-409-3p expression impeded cell proliferation and regulated the process of BC by targeting the important nuclear transcription factor *ZEB1*. Furthermore, miR-409-3p was predicted to mainly target caspases, BCL2 and cell cycle cyclins involved in anti-tumor drug-induced apoptosis (27). However, the finding was not demonstrated by a corresponding functional analysis in animals. Recently, by targeting miR-409-3p, circRNA tripartite motif-containing 28 (circTRIM28) was reported to upregulate oncogenic high mobility group AT-hook 2 (*HMGA2*) in BC. Regulation of the miR-409-3p/*HMGA2* axis also accounted for the influence of circTRIM28 on cell proliferation and apoptosis (30).

The direct binding between miR-409-3p and HPV16/18 E6 mRNA was identified in cervical dysplasia tissues. Despite the regulation of miR-409-3p levels having no effect on colony development, miR-409-3p overexpression also attenuated the proliferation of CaSki, C-4I and Hela cells. Vice versa, miR-409-3p knockdown promoted the proliferation of CaSki and C-4I CC cells, but there was no change in HeLa CC cells (32). Cui *et al* (33) revealed that miR-409-3p was involved in CC progression through the ceRNA mechanism. On the one hand, circ0000745 regulated activating transcription factor 1 (*ATF1*) expression to regulate CC progression by sponging miR-409-3p. Of note, the proliferation of cells was negatively related to the expression level of miR-409-3p. Co-transfection of miR-409-3p with circ0000745 alleviated the promoting effects of overexpression of circ0000745 on CC cell proliferation (33). On the other hand, circRNA FAT atypical cadherin 1 (circFAT1) also had a crucial role in CC by acting as a sponge for miR-409-3p. Increased circFAT1 promoted CC progression, including enhancing proliferation and repressing apoptosis via the miR-409-3p/cyclin-dependent kinase 8 (*CDK8*) axis (34). In addition, Wu *et al* (35) reported that miR-409-3p, targeted by circEPSTI1, regulated the expression of solute carrier family 7 membrane 11 (*SLC7A11*) expression. The proliferation of Hela and CaSki cells in CC was influenced by the circEPSTI1-miR-409-3p-*SLC7A11* axis.

With regards to osteosarcoma, Zhang *et al* (37) revealed that E74-like factor 2 (*ELF2*), an ETS family transcription factor, served as an oncogene and played prominent roles in cell proliferation, differentiation and apoptosis. Therefore, the ectopic expression of miR-409-3p clearly hampered cell proliferation, induced G0/G1 arrest and promoted apoptosis in osteosarcoma cells. Shortly after, Wu *et al* (38) found that *ZEB1* was also regulated by miR-409-3p in HOS and MG63 osteosarcoma cells, thus inhibiting cell proliferation. Furthermore, Long *et al* (39) discovered that circ0000285, which is increased in osteosarcoma, acted as a ceRNA of miR-409-3p to promote insulin-like growth factor binding protein 3 (*IGFBP3*). More importantly, miR-409-3p overexpression clearly reduced cell viability and colony numbers of osteosarcoma cells, and enhanced cell apoptosis, which was reversed by *IGFBP3*. In conclusion, circ0000285 could promote the proliferation and suppress the apoptosis of osteosarcoma via the miR-409-3p/*IGFBP3* axis. It was also the first ceRNA mechanism to be explored in osteosarcoma.

MiR-409-3p was also mentioned in connection with the cellular biological processes in GC. The 2020 study by Wang *et al* (44) demonstrated that, compared with adjacent tissue, circ0001023 expression was conspicuously upregulated. Mechanistically, miR-409-3p was positively correlated with PHD finger protein 10 (*PHF10*), which was identified as a direct target of circ0001023 and negatively modulated by circ0001023 via the ceRNA network. Circ0001023 silencing could inhibit the proliferation and trigger the apoptosis of GC cells, while miR-409-3p inhibitors could partially inhibit apoptosis and promote the proliferation of GC cells. Similarly, Li *et al* (40) also found that miR-409-3p overexpression reduced the level of *PHF10*, thus markedly limiting the proliferation and colony numbers of tumor cells and slowing the transition from the G1 to the S phase of the cell cycle. CircRNA NIMA-related kinase 9, which is enhanced in GC cells,

could promote the proliferation of GC cells by targeting the miR-409-3p/microtubule associated protein 7 (*MAP7*) axis. MiR-409-3p has been shown to bind to *MAP7* mRNA directly, causing cell cycle arrest in the G0/G1 phase and limiting GC cell growth and colony formation (42). Furthermore, consistent with previous findings, the expression of miR-409-3p had been confirmed to decrease, and high levels of miR-409-3p were found to be able to inhibit proliferation and trigger apoptosis. Surprisingly, when GC cells were treated with precision hyperthermia, miR-409-3p could positively regulate the targeting gene Kruppel-like factor 17 (*KLF17*) and induce GC cell apoptosis (43).

Liu *et al* (45) showed that miR-409-3p overexpression in CRC targeted nemo-like kinase (*NLK*), which is implicated in the formation, progression and signaling pathways of cancer. In addition, in cells resistant to oxaliplatin, a platinum-based chemotherapeutic drug, such as oxaliplatin-resistant LoVo (Oxa-R) and HCT-116/L-OHP cells, miR-409-3p was found to regulate cell proliferation, the cell cycle and apoptosis by targeting *beclin-1* and ERCC excision repair 1 (*ERCC1*), respectively (48,50). This phenomenon was also observed in drug-resistant OV-1063 cells by inhibiting *FIP200* (54). In CRC, LINC00630 functioned as an endogenous sponge for miR-409-3p and relieved the inhibition of miR-409-3p on *HK2*. By repressing miR-409-3p, LINC00630 upregulated *HK2* and promoted cell proliferation, and inhibited apoptosis in the CRC cell lines SW480 and HCT116 (51).

In addition, another group provided evidence that miR-409-3p had effects on OC cells, including proliferation, colony formation and apoptosis, by targeting RAB10, member RAS oncogene family (*RAB10*), whereas its downregulation inhibited the apoptosis and promoted the proliferation as well as colony formation (56).

In BCa, Xu *et al* (60) also observed that *MET* could regulate 14q32.2 miRNA clusters, including miR-409-3p, and miR-409-3p could directly target *MET*. In addition, miR-409-3p participated in the miR-433-mediated inhibition of cell motility.

Of note, Zhao *et al* (62) reported that miR-409-3p upregulation in PTC weakened PTC cell proliferation and induced cell cycle arrest in G0/G1 phase by modulating cyclin D2. In DLBCL, miR-409-3p overexpression significantly inhibited the proliferation of SU-DHL-4 compared with SV_Co10 (64). In AML, Xie *et al* (66) revealed that miR-409-3p negatively regulated the expression of RAB10, sequentially inhibiting proliferation and promoting apoptosis. In TSCC, Chen and Dai (70) concluded that miR-409-3p negatively regulated the expression of radixin (*RDX*), sequentially inhibiting proliferation *in vitro*. Furthermore, miR-409-3p could act as an oncogene. In PCa, Josson *et al* (71,73) noted that through the negative regulation of Ras suppressor protein 1, miR-409-3p enhanced cell proliferation and inhibited cell apoptosis. Simultaneously, circular dedicator of cytokinesis 1, which promoted proliferation and inhibited apoptosis in human brain vascular smooth muscle cells through the miR-409-3p/myeloid cell leukemia sequence 1 (*MCL1*) axis, sponged miR-409-3p to boost *MCL1* expression, which helped inhibit certain targets in the treatment of intracranial artery tumors (78). Of note, a study by Cao *et al* (79) found that high mobility group nucleosome binding domain 5 (*HMGN5*) acted as an oncogene in glioma. By suppressing *HMGN5*, miR-409-3p suppressed glioma cell proliferation and colony formation and blocked glioma cells in the G0/G1 phase. Angiogenin (*ANG*), a gene involved in cell proliferation, has also been studied in the context of fibrosarcoma. HT1080 cell transfection with a miR-409-3p mimic could suppress cell proliferation by targeting *ANG* (81). In general, miR-409-3p has been strongly connected with cell growth and apoptosis in various cancers. In HCC, Li *et al* (84) found that silencing LINC00886 upregulated the expression of miR-409-3p, weakened the proliferation of HCC cells (Hep3B, Huh7) and promoted apoptosis. Conversely, it promoted the proliferation of Hep3B as well as Huh7 proliferation and inhibited apoptosis.

Migration and invasion. The process through which independent cells travel from the main tumor to distal organs through blood arteries or lymphatic vessels is referred to as metastasis and invasiveness of malignant tumors (96). Metastasis, the most prominent feature of malignant tumors, is responsible for the majority of cancer-related fatalities and has become a major impediment to cancer treatment. MiR-409-3p influences tumor migration and invasion by altering target genes to further regulate the progression of cancer (Fig. 3).

A consensus has been reached that epithelial-mesenchymal transition (EMT) plays a significant role in cancer metastasis (97), which is characterized by decreased E-cadherin expression and increased N-cadherin/vimentin expression (98,99) and allows the cells to acquire the properties of migration and invasion. Twist family bHLH transcription factor 1 could induce EMT and participate in cancer metastasis (100). A Transwell assay performed by Su *et al* (29) found that miR-409-3p overexpression could limit the EMT in MCF7 BC cells. *KLF17* is a member of a conserved family of transcription factors that regulates cell migration and invasion. A certain range of heat treatments accelerated the expression of miR-409-3p in SGC-7901 and BGC-823 GC cells and indirectly upregulated *KLF17*, further inhibiting the migration, invasion and the EMT pathway (43). In addition, Josson *et al* (71,73) found an elevated level of miR-409-3p/5p in PCa, suggesting that it may promote tumorigenesis, EMT and bone metastasis of PCa. In addition, increased miR-409-3p has also been observed in PCa cells and tissues in bone metastasis.

Matrix metalloproteinases (MMPs), a type of proteolytic enzyme that break down the structural components of extracellular matrix and contributes to the loss of intercellular connection, promote cell migration and invasion, in addition to the EMT process.

In NSCLC, miR-409-3p mimics were able to suppress the protein levels of phosphorylated AKT (p-AKT), ultimately resulting in the decrease of the expression of MMP2 and MMP9, which in turn reduced the migration and invasion of A549 and SPC-1 NSCLC cells (12). In addition, a study by Song *et al* (14) found that *SPIN1* is associated with cancer metastasis, as a direct miR-409-3p target in A549 NSCLC cells. In line with this, miR-409-3p overexpression evidently inhibited A549 NSCLC cell invasion and migration, but this inhibition could be reversed by anti-miR-409-3p. In addition, Yin *et al* (16) reported that the inhibition of miR-409-3p in NSCLC rescued the number of migrated H1299 and A549 NSCLC cells transfected with small interfering RNAs targeting

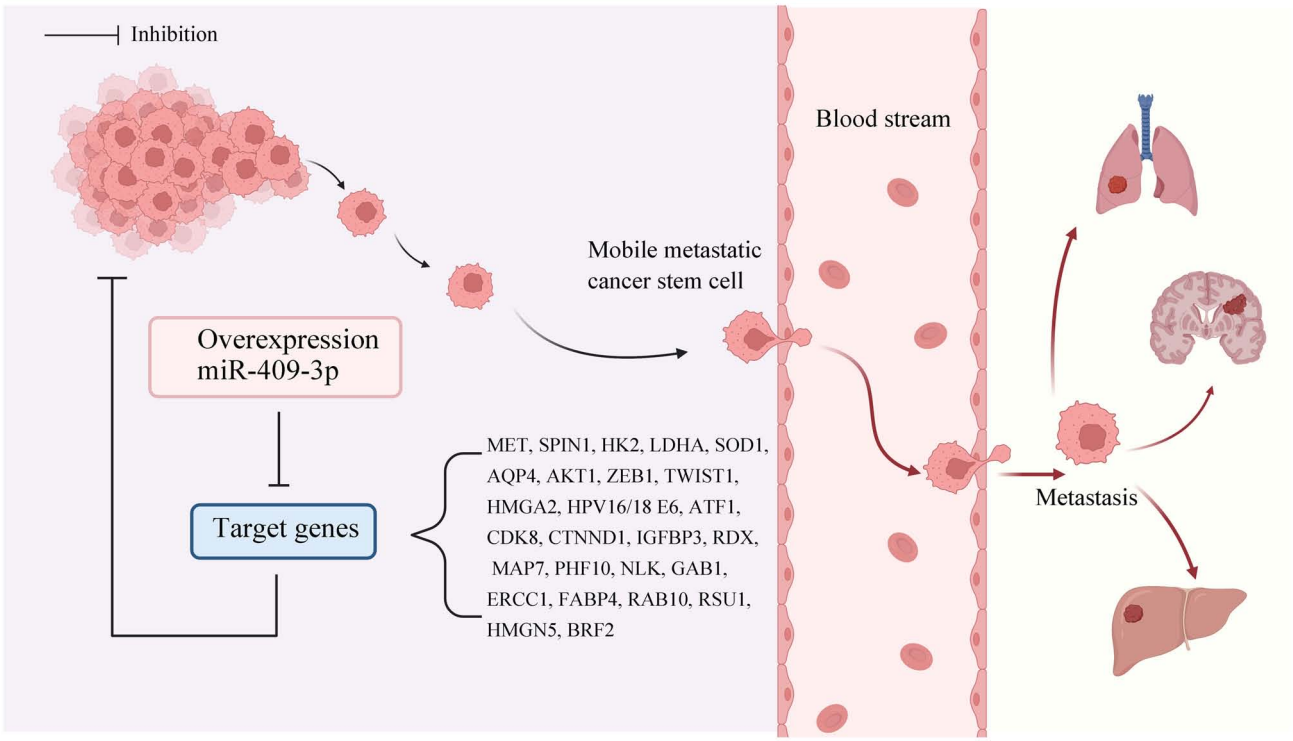

Figure 3. Effect of miR-409-3p target genes on migration and invasion of cancer cells. Overexpression of miR-409-3p inhibits downstream target genes, such as ZEB1, MET and CDK8, and further regulates cell invasion and metastasis. Created with BioRender software (http://biorender.com). MiR, microRNA; MET, MET proto-oncogene, receptor tyrosine kinase; SPIN1, spindlin1; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; SOD1, superoxide dismutase 1; AQP4, aquaporin 4; AKT1, AKT serine/threonine kinase 1; ZEB1, zinc finger E-box binding homeobox 1; TWIST1, Twist family bHLH transcription factor; HMGA2, high mobility group AT-hook 2; ATF1, activating transcription factor 1; CDK8, cyclin dependent kinase 8; CTNND1, catenin-δ1; IGFBP3, insulin like growth factor binding protein 3; RDX, radixin; MAP7, microtubule associated protein 7; PHF10, PHD finger protein 10; NLK, nemo like kinase; GAB1, GRB2 associated binding protein 1; ERCC1, ERCC excision repair 1; FABP4, fatty acid binding protein 4; RAB10, RAB10, member RAS oncogene family; RSU1, Ras suppressor protein 1; HMGN5, high mobility group nucleosome binding domain 5; BRF2, BRF2 RNA polymerase III transcription initiation factor subunit.

DUXAP8. Wang *et al* (19) verified the above mechanism in another NSCLC cell line, H1299. They used miR-409-3p inhibitor and negative control, leading to the weakening of the inhibitory effect on *SPIN1*, which then promoted H1299 NSCLC cell metastasis and invasion. Liu *et al* (20) showed that miR-409-3p mimics also mitigated the effects of CBR3-AS1 on NSCLC cell invasion and migration. A ceRNA named circ_0079530 was overexpressed in NSCLC cells and sequestered miR-409-3p. Increased rates of cell migration and invasion are carried on by low levels of the miRNA, on the contrary, the increase of migration and invasion rate (21).

By targeting *AKT1*, Zhang *et al* (26) found that miR-409-3p overexpression also hindered BC cell motility and invasion. Ma *et al* (27) also found that a low abundance of miR-409-3p and high expression of *ZEB1* in BC may be responsible for the high metastasis rate of BC. Yang *et al* (30) reported that circRNA tripartite motif-containing 28 (circTRIM28) contributed to the migration and invasion of BC cells by downregulating miR-409-3p.

An array of studies observed that when using particular inhibitors and mimics of miR-409-3p in SiHa CC cell lines, miR-409-3p displayed a pattern of overexpressed and downregulated HPV16/18 E6, boosting or inhibiting migration, respectively (32). Despite the inhibition of miR-409-3p on cell migration and invasion reported by Cui *et al* (33), miR-409-3p may suppress *ATF1* expression, and thus negatively regulate the migration and invasion of CaSki and Siha CC cells. The tumor suppressor role of miR-409-3p lies at least in part in the negative regulation of *CDK8*. miR-409-3p/*CDK8* modulated CaSki and C-33A CC cell invasion and migration behaviors (34).

In osteosarcoma, Wu *et al* (36) found that functionally decreased miR-409-3p markedly increased the migration and invasion of osteosarcoma cell lines (U2OS and SAOS-2) by directly targeting catenin-δ1, further promoting the metastasis of osteosarcoma. In a different study, the miR-409-3p-mediated inhibition of the invasion of another two osteosarcoma cell lines (MG63 and HOS) was examined and *ZEB1* was identified as a new target gene (38). Another publication reported that overexpression of miR-409-3p clearly reduced SJSA1 as well as U2OS cell invasion and migration in osteosarcoma, whereas its downregulation increased migration and invasion rates (39).

In GC, one group indicated that miR-409-3p functioned as a tumor suppressor by validating its targeting of *PHF10*, inhibiting AGS GC cell invasion and migration, and stimulating invasion and migration of MKN-28 and SGC-7901 GC cells (44). In addition, the constitutive expression of miR-409-3p in three GC cell lines, including SGC-7901, HGC-27 and MKN45, reduced their migration and invasion rates (41). Furthermore, Yu *et al* (42) also found that this miRNA could downregulate *MMP2* and *MMP9*, while *MAP7* was another gene tightly associated with EMT and could

partly rescue its expression, thereby boosting the invasion and migration of XGC-1 and MKN45 cells in GC. In addition, a similar regulation mechanism pattern was also observed by Xu *et al* (59) in T24 and 5637 BCa cells in that miR-409-3p may regulate cell migration and invasion in part by indirectly controlling *MMP2* and *MMP9*.

In CRC, Liu *et al* (45) showed that high expression of miR-409-3p induced SW480 and SW1116 CRC cell migration and invasion by repressing the expression of *NLK*. Furthermore, Bai *et al* (46) detected that miR-409-3p was a metastasis-specific miRNA in CRC. MiR-409-3p directly linked to cell invasion and migration in CRC through targeting GRB2-associated binding protein 1 (46). Another study found that miR-409-3p has an inhibitory role in CRC, where it noticeably reduced HCT-116 and HCT-116/L-OHP migration and invasion, which occurred by suppressing *ERCC1* under certain experimental conditions (50).

Simultaneously, Chen and Dai (70) also reported that miR-409-3p strongly modulated the development of TSCC by targeting *RDX*, thus inhibiting or stimulating the migration and invasion of Tca8113 TSCC cells.

In OC, miR-409-3p reversely regulated fatty acid binding protein 4 (*FABP4*) in OC cell lines (HeyA8 MDR and Ovcar5). In addition, hypoxia and hypoxia-inducible factor-1α (HIF-1α) could reduce miR-409-3p, which may eliminate its inhibitory effect on *FABP4*, leading to increased *FABP4* levels to further promote the metastasis of OC cells (53). MiR-409-3p suppressed cell migration of SKOV3 OV cells (56), whose mediated target *RAB10*, a type of small GTPases belonging to the Ras protein family (101). The *MET* oncogene is a tyrosine kinase with a well-defined receptor, which is generally upregulated in various cancers. Tumor invasion and metastasis are aided by *MET* activation caused by aberrant paracrine stimulation of hepatocyte growth factor (102). In NSCLC, miR-409-3p inhibited the invasion and migration of A549 and SPC-1 NSCLC cells by negatively regulating *MET*, thereby exerting a tumor-suppressive effect (12). Similarly, following the transfection of miR-409-3p into T24 and 5637 BCa cell lines, the expression of *MET*, which could induce migration and invasion, was directly reduced (59). In addition, the downregulation of *HMGN5* also accounted for the anti- and pro-metastatic action of miR-409-3p in U251 and U87 glioma cells, respectively. In addition, the downregulation of *HMGN5* also accounted for the anti-metastatic action of miR-409-3p in glioblastoma (79). In HCC, Chang *et al* (83) observed that the relative migration and invasion rate of Huh-7 cells treated with miR-409-3p mimics was significantly decreased by regulating BRF2 RNA polymerase III transcription initiation factor subunit (*BRF2*). After silencing LINC00886, the expression level of miR-409-3p was upregulated, which weakened the invasion and migration of HCC cells (Hep3B, Huh7). Conversely, overexpression of LINC00886 has the opposite effect (84).

Autophagy, chemoresistance and radioresistance. MiR-409-3p regulates numerous genes involved in autophagy, chemoresistance and radioresistance (Fig. 4).

Generally speaking, autophagy is a normal physiological process within cells, which involves loading damaged proteins and organelles from the cytoplasm into autophagosomes, and then fusing with lysosomes for degradation and reuse (103). Phosphatidylinositol 3-kinase class III and beclin-1 are involved in autophagosome formation (104). In a previous study, when the ratio of light chain (LC)3I and LC3II decreased, it was used as one of the criteria for autophagy. Autophagy is thought to be a primary mechanism of cancer cell chemoresistance (105,106). Recent studies have discovered that abnormal miRNA expression has a role in the molecular mechanisms of chemoresistance. The regulatory function of miR-409-3p on cancer cells' chemoresistance has been discussed in previous studies. In BC, circTRIM28 knockdown improved tamoxifen sensitivity through the miR-409-3p/*HMGA2* axis (30). Furthermore, miR-409-3p, as a promising therapeutic target in CRC, has been shown to improve CRC cell susceptibility to chemotherapeutic drugs such as oxaliplatin (48,50). Of note, Tan *et al* (48) found that miR-409-3p expression was clearly upregulated in CRC cells with sensitivity to oxaliplatin, and promoted the chemosensitivity of LoVo Oxa-R CRC cells by inhibiting beclin-1-mediated autophagy. Most importantly, the autophagy-related protein LCII was higher and lower expressed in LoVo Oxa-R and LoVo CRC cells, respectively. Furthermore, Han *et al* (50) discovered that curcumin treatment increased the expression of miR-409-3p in HCT-116/L-OHP CRC cells in a concentration-dependent manner, increasing the sensitivity of CRC cells to chemotherapeutic drugs through the partial inhibition of survivin, P-glycoprotein and multidrug resistance-related protein. Of note, Cheng *et al* (54) found that miR-409-3p acting as an anti-cancer factor enhanced the sensitivity of OC cells to cisplatin treatment by inhibiting *FIP200*-mediated autophagy. Furthermore, in contrast to OC cells responsive to cisplatin treatment, cells resistant to cisplatin treatment had a lower miR-409-3p expression and significantly higher autophagic activity. It was indicated that miR-409-3p could also be a therapeutic target in OC resistance. In addition, DLBCL is a heterogeneous disease and the most common lymphoid malignancy. Using lentiviral vectors, Leivonen *et al* (64) found that the functional overexpression of miR-409-3p improved the sensitivity of DLBCL cells to chemotherapeutic agents such as rituximab and doxorubicin. These findings suggested that miR-409-3p can enhance the effects of chemotherapeutic agents in several types of cancers and act as a chemosensitizer. Of note, despite abundant evidence pinpointing that chemoresistance is caused by autophagy, two research teams found the opposite results: The first was that L-6-hydroxymethyl-chiro-inositol 2[R]-2-O-methyl-3-O-octadecyl carbonate, an AKT inhibitor, could accelerate radiosensitivity by guiding autophagy (107), and the other was that rapamycin, an inhibitor of mTOR, radiosensitized HCC827 NSCLC cells by inhibiting the action of phosphatase and tensin homolog (108), a tumor suppressor, to positively regulate autophagy (109). Hence, based on the relationships between autophagy and treatment resistance, whether these contrasting findings reflect the differences between different treatment regimens such as chemotherapy or radiotherapy and different types of cancer is worthy of further exploration.

Another popular cancer treatment is radiotherapy. In NSCLC, Liu *et al* (20) found that CBR3-AS1/miR-409-3p/*SOD1* signaling reduced reactive oxygen species levels by reducing H2AX foci, which in turn decreased apoptosis following

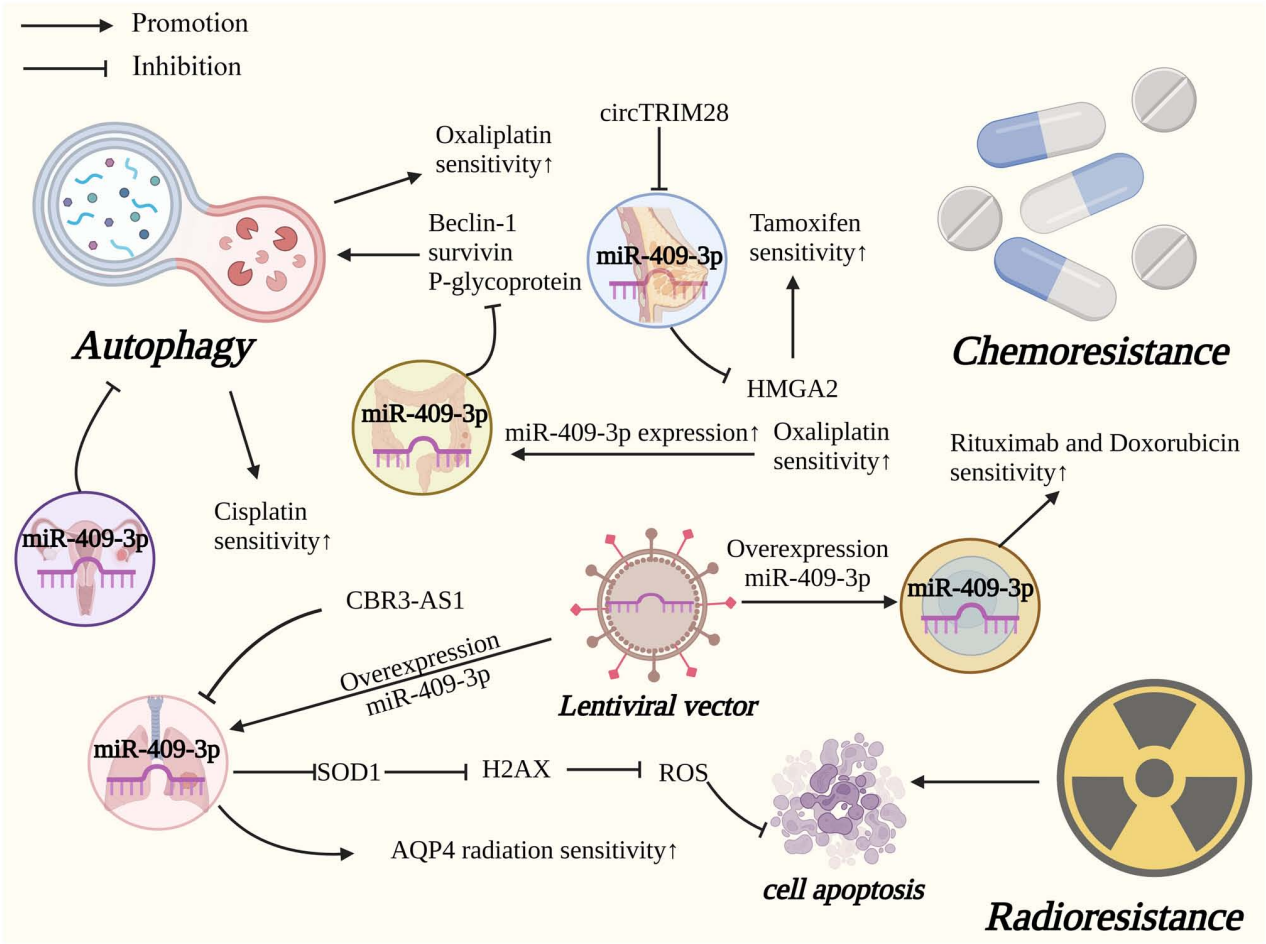

Figure 4. MiR-409-3p regulates cell autophagy, chemoresistance and radioresistance. MiR-409-3p regulates cell autophagy, chemoresistance and radioresistance by targeting certain molecules. Created with BioRender software (http://biorender.com). MiR, microRNA; circTRIM28, circRNA tripartite motif-containing 28; HMGA2, high mobility group AT-hook 2; SOD1, superoxide dismutase 1; CBR3-AS1, CBR3 antisense RNA 1; ROS, reactive oxygen species; AQP4, aquaporin 4.

ionizing radiation. In addition, H1270 and A549 NSCLC cells with high expression of miR-409-3p exhibited enhanced sensitivity to irradiation by direct targeting of *AQP4* (21).

Cell glycolysis. To meet their energy needs for proliferation and metastasis, cancer cells mostly rely on glycolysis. Aerobic glycolysis is an abnormal process of energy metabolism in cancer (110). Rate-limiting enzymes HK2, LDHA and GLUT1 are the key components of the glycolysis pathway. In NSCLC, DUXAP8 served as an miR-409-3p sponge to promote *HK2* and *LDHA* expression. By regulating the miR-409-3p/*HK2*/*LDHA* axis, DUXAP8 promoted glycolysis (16). In addition, Chen *et al* (51) demonstrated that LINC00630 controlled glycolysis primarily by targeting the miR-409-3p/*HK2* axis, which may explain the development of CRC and offer a possible target for its treatment. Likewise, *ATF1*, an miR-409-3p target, conspicuously reduced the extracellular acidification rate, glucose uptake and lactic acid generation in CC (33). A study by Wang *et al* (58) indicated that miR-409-3p served as a suppressor in glycolysis. In the A-498 and 769-P ccRCC cell lines, HIF-1α, an important molecule for cancer cells to respond to a hypoxic microenvironment (111), could induce the decrease of miR-409-3p expression and weaken the inhibitory effect of miR-409-3p on 3-phosphoinositide dependent kinase 1, a molecule required for metabolic activation. In osteosarcoma, miR-409-3p decreased *LDH2* expression, which was associated with a decrease in glucose absorption, lactate generation and extracellular acidification rate (112).

Angiogenesis. Angiogenesis refers to the process of producing new blood vessels from pre-existing posterior venules of capillaries and has a critical role in embryonic development, wound healing and inflammation (113). In addition, the growth and metastasis of tumors largely depend on angiogenesis (114). MiR-409-3p appears to have a significant role in tumor angiogenesis, according to new research. The capacity of HT1080 fibrosarcoma cells to form tubular structures on Matrigel® was significantly diminished when miR-409-3p was overexpressed compared with control cells, according to *in vitro* investigations. However, this inhibition could be reversed by *ANG* overexpression (81).

5. Biological roles of miR-409-3p in cancer *in vivo*

MiR-409-3p has been studied in various cancers and it has been found to have a conspicuous role in arresting tumorigenesis or promoting tumor progression (Table IV). A large number

Table IV. Outline of studies on the function of miR-409-3p in animal models.

Authors, year	Tumor type	Animal models	Results	(Refs.)
Song *et al*, 2018	Lung cancer	6-week-old BALB/c mice	↑miR-409-3p: Tumor growth↓, lung burden↓, photonic radiance intensity of the lungs↓	(14)
Zhang *et al*, 2016	BC	4-5-week-old nude mice	↑miR-409-3p: Tumor growth↓, average tumor volume and weight↓, Ki-67 antigen staining↓	(26)
Ma *et al*, 2016		5-week-old male athymic nude mice	↑miR-409-3p: Tumor size↓, tumor weight↓	(27)
Zhang *et al*, 2017	Osteosarcoma	6-8-week-old male nude BALB/c mice	↑miR-409-3p: Tumor volume↓, tumor weight↓	(37)
Li *et al*, 2012	GC	4-week-old male nude mice	↑miR-409-3p: Tumor growth↓, tumor weight↓, Ki-67 antigen staining↓, apoptosis↑	(40)
Zheng *et al*, 2012		week-old BALB/c-nu/nu	↑miR-409-3p: Pulmonary metastasis assays: Number and size of metastatic nodules↓; Peritoneal dissemination↓	(41)
Liu *et al*, 2015	CRC	4-week-old male BALB/C nude mice	↑miR-409-3p: Peritoneal nodules↓, metastasis↓	(45)
Bai *et al*, 2015		4-5-week-old female BALB/c-nu/nu mice	↑miR-409-3p: Pulmonary metastatic nodules↓, Ki-67 antigen staining↓	(46)
Tan *et al*, 2016		6-week-old female BALB/c nude mice	↑miR-409-3p: Chemosensitivity↓, autophagic activity↓	(48)
Gharpure *et al*, 2018	OC	Female athymic nude mice	↑miR-409-3p: Tumor weight↓, number of tumor nodules↓, metastasis↓	(53)
Cheng *et al*, 2018		5-6-week-old female BALB/c nude mice	↑miR-409-3p: Tumor volume↓	(54)
Xie *et al*, 2023	AML	4-week-old male SCID-Beige mice	↑miR-409-3p: Tumor volume↓, tumor weight↓	(66)
Chen and Dai, 2018	TSCC	4-6-week-old female BALB/C mice	↑miR-409-3p: Tumor volume↓, tumor weight↓, lymphatic metastasis↓, lymphatic microvessel density ↓	(70)
Josson *et al*, 2014	PCa	4-week-old male nude mice	↑miR-409-3p: Tumor size↑, Ki-67 antigen staining↑, EMT↑	(71)
Josson *et al*, 2015		Athymic mice	↑miR-409-3p: Tumor incidence↑, tumor size↑, Ki-67 antigen staining↑, EMT↑	(73)
Weng *et al*, 2012	Fibrosarcoma	4-6-week-old female BALB/c nude mice	↑miR-409-3p: Tumor growth↓, vascularization↓, metastasis↓, tumor sizes↓, Ki-67 antigen staining↓	(81)
Chang *et al*, 2023	HCC	4-5-week-old female nude mice	↑miR-409-3p: Lung and liver metastases↑	(83)

↑, upregulation/enhancement; ↓, decrease; MiR, microRNA; BC, breast cancer; GC, gastric cancer; CRC, colorectal cancer; OC, ovarian cancer; AML, acute myeloid leukemia; TSCC, tongue squamous cell carcinoma; PCa, prostate cancer; EMT, epithelial-mesenchymal transition; HCC, hepatocellular carcinoma.

of studies using xenograft models have indicated a tumor suppressor role for miR-409-3p, since its upregulation led to inhibitory effects on tumor growth and distant metastasis. By contrast, miR-409-3p could act as an oncogene to significantly promote tumorigenesis in the xenograft models of PCa (71,73). Most importantly, in the xenograft model of CRC, overexpression of miR-409-3p in LoVo Oxa-R CRC cells injected into nude mice restricted tumor growth and improved the sensitivity to chemotherapeutic drugs (48). Xie *et al* (66) found that overexpression of miR-409-3p could reduce the tumor volume and weight in SCID mice. In addition, Chen and Dai (70) discovered that the lymphatic microvessel density of TSCC nude mice transfected with miR-409-3p was considerably reduced when compared to the control group. At the same time, *in vivo*

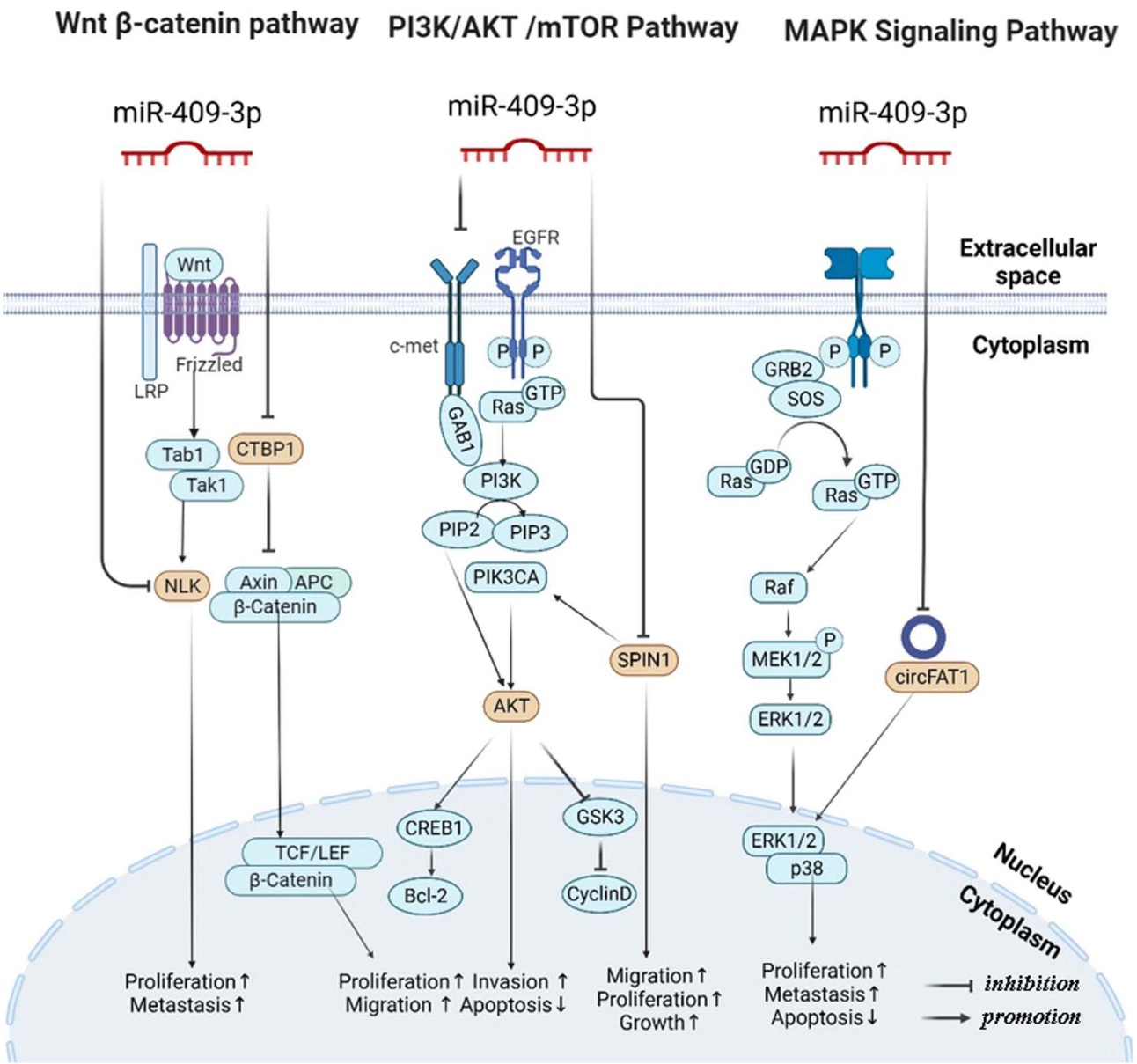

Figure 5. MiR-409-3p related signaling pathways in cancer. MiR-409-3p can influence cancer development and regulate the biological processes of cells by participating in the Wnt/β-Catenin, PIK3/AKT/mTOR, MAPK signaling pathways. Created with Biorender software (http://biorender.com). MiR, microRNA; LRP, low-density lipoprotein receptor-related protein; Tab1, TGF-β activated kinase 1/MAP3K7 binding protein 1; CTBP1, C-terminal binding protein 1; Tak1, TGF-β-activated kinase 1; NLK, nemo-like kinase; APC, adenomatous polyposis coli; TCF, T-cell factor; LEF, lymphoid enhancer-binding factor; EGFR, epidermal growth factor receptor; MET, MET proto-oncogene, receptor tyrosine kinase; GTP, guanosine triphosphate; GAB, growth factor receptor-bound protein 2-associated binder; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; AKT1, AKT serine/threonine kinase 1; GSK3, glycogen synthase kinase 3; CREB1, cAMP responsive element binding protein 1; Bcl-2, B-cell lymphoma 2; GRB2, growth factor receptor-bound protein 2; SOS, Son of sevenless; GDP, guanosine diphosphate; Ras, Rat sarcoma; Raf, rapidly accelerated fibrosarcoma; MEK1/2, mitogen-activated protein kinase kinase 1/2; circFAT1, circular RNA FAT atypical cadherin 1; ERK1/2, extracellular signal-regulated kinase 1/2.

experiments showed that the miR-409-3p overexpression group had fewer tubular structures, and miR-409-3p promoted the development of tumors by inhibiting cell proliferation and tumor vascularization (81). In HCC, Chang *et al* (83) discovered that decreased miR-409-3p led to the development of lung and liver metastases.

6. MiR-409-3p-related signaling pathways

Of note, by influencing target genes or being controlled by upstream genes, miR-409-3p can alter the activities of numerous signaling pathways. The most significant signaling pathways influenced by miR-409-3p that contribute to tumorigenesis include the Wnt/β-catenin pathway, PI3K/AKT/mTORC1 pathway and the MAPK pathway (Fig. 5).

Wnt/β-Catenin signaling pathway. The incidence and progression of malignancies are linked to the Wnt/β-Catenin signaling pathway, which enhances tumor stem cell proliferation, survival and differentiation (115). NLK is an evolutionarily conserved MAPK, highly expressed in nerve tissues (116,117). When NLK phosphorylation is activated, it can phosphorylate

substrates that participate in the Wnt/β-Catenin signaling pathway (118). Hence, in CRC, miR-409-3p downregulation could boost *NLK* expression and increase the expression of the Wnt/β-Catenin signaling pathway, regulating CRC cell proliferation and metastasis (45). In addition, using functional enrichment analysis, Zhang *et al* (55) demonstrated that the targeted genes of miR-409-3p are implicated in the pathway, and the negative regulatory association between miR-409-3p and C-terminal binding protein 1 (*CTBP1*) was verified using OC data in The Cancer Genome Atlas (TCGA). A study by Deng *et al* (119) indicated that *CTBP1* activates the expression gene of Wnt genes, thereby regulating the signaling pathway. Chang *et al* (83) found that miR-409-3p regulated *BRF2*, which enhanced invasion and metastasis in HCC via the Wnt/β-catenin signaling pathway.

PI3K/AKT signaling pathway. According to a vast number of studies, miR-409-3p is found in most oncogenic signaling pathways. One of the many signaling pathways involved in cell growth and survival is the PI3K/AKT/mTOR signaling pathway. MET is a tyrosine kinase protein in response to a hepatocyte growth factor that plays an essential part in cancer progression, including in morphogenesis, mitogenesis, metastasis, proliferation and survival (120). *In vitro* experiments confirmed that miR-409-3p has MET as its direct target; it inactivated AKT signaling and achieved the effect of inhibiting cancer proliferation, invasion and migration, as well as promoting apoptosis in NSCLC (12). Another group also found that, by inhibiting the expression of *SPIN1*, miR-409-3p could inhibit components of PI3K/AKT, including the expression of BCL2, cAMP responsive element binding protein 1, p-AKT and cyclin D, thereby blocking the progression of NSCLC (14). Besides, as previously mentioned, AKT1 is a crucial downstream target kinase in the PI3K signaling cascade (121). In GC, miR-409-3p/*AKT1* axis could influence GC cell lines, including MDA-ZMB-231, MDA-MB-468 and T47D cell proliferation and metastasis *in vivo* and *vitro* (26). In addition, in DLBCL, Leivonen *et al* (64) demonstrated that PIK3R1 was a targeted gene of miR-409-3p in SU-DHL-4 DLBCL cells by using lentiviral vectors. Most importantly, the PI3K/AKT pathway has been found to be involved in the progression of DLBCL, which exerts an obviously significant contribution to cellular processes and is expected to become a promising therapeutic target. Besides, in PCa, Yu *et al* (74) indicated that PCa cells subjected to CIRT delivered exosomal miR-409-3p, inhibiting AKT in the PI3K/AKT pathways in recipient cells, which is the main signaling pathway linked to apoptosis induction and proliferation inhibition, and which may be involved in the mechanism of action of CIRT.

MAPK signaling pathway. MAPK cascade pathways are highly conserved and modulate cell proliferation, differentiation and migration by phosphorylating specific target protein substrates. MAPK consists of the following subfamilies, including extracellular signal-regulated kinases, c-Jun N-terminal kinase, p38 protein kinases and extracellular-signal-regulated kinase 5 (122). Furthermore, circFAT1 promoted cancer progression in the C-33A and CaSki CC cell lines, stimulating proliferation and metastasis, as well as inhibiting their apoptosis by activating the ERK1/2 and p38 MAPK pathway (34). Of note, in malignant hematological diseases such as DLBCL, miR-409-3p has been indicated to suppress MAPK1 mRNA and ERK1/2 protein levels and improve the chemosensitivity of cells *in vitro*, indicating that the MAPK pathway is involved in the progression of DLBCL (64).

7. Discussion

The development of genomics, proteomics, high-throughput sequencing and array technology has resulted in the introduction of miRNA gene profiles of various malignancies, which are currently available in the respective databases, such as TCGA and Gene Expression Omnibus. The present review outlined that miR-409-3p, an important molecule in current research, has been proven to exert a role as a tumor suppressor or as an oncogenic miRNA in several malignancies. Molecular studies to analyze cancer development dependent on the levels of miRNAs have become a notable aspect of genetic research. Of note, miR-409-3p exhibits considerable promise for use as a diagnostic and therapeutic target for cancer based on the potent biological roles it possesses.

In the fight against cancer, miR-409-3p deserves to be a focus of research, since it has a critical role in the emergence of numerous cancers. Due to its stability in circulating body fluids, such as serum or plasma, miR-409-3p can also be used for cancer diagnosis and prognosis. It is frequently present at different concentrations in fluids from cancer patients compared to those from healthy individuals. These levels can even vary depending on the type of cancer, indicating the potential use of miR-409-3p as a noninvasive biomarker in the future. In addition, throughout the history of cancer treatment, resistance has become the most influential factor in the treatment effect. Interestingly, other experiments have shown that miR-409-3p could be used in combination therapy to fight different cancers. Of note, enhancing the expression of miR-409-3p can increase sensitivity to chemotherapy and radiotherapy of patients, significantly extend patient survival and hopefully brighten the outlook for patients. More importantly, changes in miR-409-3p expression levels could be used to evaluate the effectiveness of surgical treatment. The changes in miR-409-3p expression provide a reliable way to assess effectiveness.

However, at present, the roles of miR-409-3p in different cancer types are only now beginning to be investigated, with studies focusing solely on how miR-409-3p affects the apparent biological function of cancer. More in-depth mechanisms need to be further clarified. In the future, the biological processes through which miR-409-3p participates in tumorigenesis and development should be further explored. At present, the tumor microenvironment, ferroptosis, pyroptosis, necroptosis, cell senescence, mitophagy, fatty acid and amino acid metabolism and cancer stemness are research hot-spots. The association between miR-409-3p and these biological processes has remained largely elusive. In addition, research on the molecular mechanisms of miR-409-3p is mostly confined to its differential expression in cancer and tissues adjacent to cancer. It is necessary to further study the mechanisms of miR-409-3p affecting tumor growth at the transcriptional and post-transcriptional levels to analyze the complex interaction network of miR-409-3p in pan-cancer

panels. At this stage, miRNAs may combine with different target genes or corresponding upstream or downstream genes to form a network of mutual regulation to participate in the development of tumors, which is a widely recognized molecular mechanism. miR-409-3p has been proved to target *MET*, c-myc, *CyclinD1*, *MMP2*, *ZEB1* and *ELF2*, etc. In addition, these target genes also have prominent molecular regulatory functions, such as cell proliferation, apoptosis, migration, invasion, autophagy, resistance, angiogenesis and glycolysis. It is worth noting that few studies have been conducted on miR-409-3p in malignancies, such as hematological malignancies, melanoma and liver cancer, and the upstream signaling of miR-409-3p, such as lncRNAs or circRNAs. Studying the ceRNA mechanism in which miR-409-3p is widely involved can provide new ideas for disease discovery, diagnosis and treatment. In addition, current research shows that miR-409-3p is dysregulated in 23 types of cancer and brings into play the role of oncogenes or tumor suppressor genes in tumorigenesis. However, miR-409-3p has tumor specificity and its specific mechanism remains to be elucidated. In addition, in order to better study the functions and mechanisms of miRNAs, online tools such as miRDB (http://www.mirdb.org/) (123) and TargetScan (http://www.targetscan.org/) (124) may be used for miRNA target prediction and functional annotations. These websites have the function of predicting target genes. According to the prediction results, validation at the cellular and animal levels will greatly accelerate and boost the progress of miRNA research.

MiR-409-3p has been identified as a strong candidate molecule in cancer diagnosis and treatment. Increasing evidence shows that the combination of miR-409-3p with other biomarkers can improve the sensitivity and specificity of diagnosis. However, there is currently no mature miRNA detection technology in clinical practice, so miRNA as a biomarker has not been used in clinical practice. In addition, it is positive that, based on the rapidly developing targeted delivery strategy, treatment schemes involving miR-409-3p regulatory target tissues are expected to be applied in medical practice. However, due to the limitations of medical equipment and technology, how to better design targeted drugs for miR-409-3p remains elusive and there is still a long way to go to better deliver drugs to the designated sites. Although miR-409-3p-targeted therapy is a potentially effective therapeutic approach, the molecular mechanisms underlying the changes in miR-409-3p expression in various malignancies remain unclear, significantly diminishing the utility of miR-409-3p in clinical treatment. More research should be conducted in the future.

In summary, compared to previous studies, the present article is a comprehensive review that provides a detailed summary of the expression, function and clinical application prospects of miR-409-3p in various malignant tumors. It provided a more comprehensive perspective and demonstrated the importance of miR-409-3p in the field of cancer. In addition to emphasizing the importance of miR-409-3p in cancer, its potential as a biomarker and therapeutic target was also highlighted.

In addition, the current review not only summarized existing research results but also provided specific suggestions for future research directions. It emphasized the relationship between miR-409-3p and the tumor microenvironment, cell death mechanisms and other areas that have not been fully explored in current research. Proposing these future research directions provides guidance for further development in this field.

It is expected that the present review on miR-409-3p will prompt further research to fully understand the basic biological mechanisms of miR-409-3p, as well as its potential as a tool for clinical application in cancer management and therapy in the future.

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Authors' contributions

WJX and ZCW wrote major parts of the manuscript and prepared the figures and tables. XW and JKW revised the manuscript. HZG oversaw the process and wrote the manuscript. ZCW, XW and JKW conceptualized the study and oversaw the process. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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