Am J Transl Res 2022;14(4):2749-2766
www.ajtr.org /ISSN:1943-8141/AJTR0140214

Original Article

The promising role and prognostic value of miR-198 in human diseases

Xiaoping Wang, Yanxia Zhu, Qiuli Xie

Department of Infectious Diseases, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, P. R. China

Received October 31, 2021; Accepted April 6, 2022; Epub April 15, 2022; Published April 30, 2022

Abstract: The importance of microRNAs (miRNAs or miRs) has attracted more and more attention. MiRNA is an approximately 22-nucleotide, single-stranded, non-coding RNA molecule that affects the expression of downstream target genes. MiRNAs regulate the occurrence and development of human diseases. The objective of this article is to explore the abnormal expression of miR-198 in a variety of human diseases. The relationships between abnormally expressed miR-198 and clinicopathological characteristics are also summarized. Its roles in various diseases and potential molecular mechanisms include involvement in many biological processes, such as cell cycle regulation, proliferation, invasion, migration, apoptosis, and drug resistance. The potential value of miR-198 for disease diagnosis, treatment, and especially, prognosis, are discussed. More in-depth research on miRNA will support the conversion from basic research to clinical applications of this molecule.

Keywords: miR-198, function, molecular mechanism, prognosis, human diseases

Introduction

MicroRNAs (miRNAs or miRs) have attracted more and more attention [1]. MiRNA is a short, approximately 22-nucleotide, single-stranded non-coding RNA molecule that can directly bind to the 3'UTR of the target gene's mRNA and induce its degradation [2-4]. The process of miRNA production includes transcription to primary miRNA, conversion into precursor miRNA by Drosha ribonucleic acid enzyme III, and finally, cleavage into mature miRNA by Dicer [2, 5, 6]. MiRNA participates in almost all cellular processes and in a wide range of signal pathways and mechanisms. Disorders in miRNA expression are closely linked to a variety of human diseases, including cancer [7-10].

MiR-198 was first reported in 2007. Hansen et al. [11] found that miRNAs expressed in the brain, including miR-198, are related to the etiology of schizophrenia. Follistatin-like 1 (FSTL1) is a secreted glycoprotein. The primary transcript of FSTL1 also encodes miR-198 in primates [12]. The 'seesaw' of FSTL1-miR-198 seems to be a unique regulatory switch essential for wound healing [13]. Mattiotti et al. [12] indicated that the switch between FSTL1 protein and miR-198 expression is a significant regulatory factor in wound healing and cancer metastasis. The expression profiles of many diseases include miR-198. For example, Walter et al. [14] explored the importance of several miRNAs in 37 cases of prostate cancer; they found that miR-198 expression is elevated in prostate cancer cells. Compared with normal tissues, the miRNA expression profile in prostate cancer seems to have a unique expression pattern. Study results indicate that miR-198 participates in the progression of various diseases and is a potential research target.

In this study, we comprehensively summarize miR-198 expression in a variety of disease types and its relationships with clinicopathological characteristics, functions, and underlying molecular mechanisms. We also summarize and discuss the prognostic value of miR-198. The studies reviewed here reveal the powerful potential of miR-198 as a novel biomarker and therapeutic target. We also provide suggestions for further basic research and clinical applications.

The expression pattern in public databases

To further explore the expression of miR-198 in public database, we adopted The Cancer Genome Atlas (TCGA) cohort to assess the expression level of miR-198 in tumor and paired nontumor tissues across pancancer. As shown in the **Figure 1**, we observed that the expression of miR-198 was dysregulated in different tumor tissues. In details, we found that the miR-198 expression was upregulated in the tumor tissues in bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), kidney renal clear cell carcinoma (KIRC), pancreatic adenocarcinoma (PAAD), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), and thyroid carcinoma (THCA) (**Figure 1A-K**). However, there was no difference between tumor tissues and paired nontumor tissues in cholangiocarcinoma (CHOL), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and uterine corpus endometrial carcinoma (UCEC) (**Figure 1L-S**).

Expression and characteristics of miR-198 in clinical samples

Table 1 presents a summary of abnormal miR-198 expression that occurs in human diseases and the clinical significance. Although the expression of miR-198 is reduced in most diseases, current studies have found it is upregulated in chronic pancreatitis and pancreatic ductal adenocarcinoma [15], esophageal cancer [16], retinoblastoma [17], and lupus nephritis [18, 19]. Studies of renal cell carcinoma (RCC) revealed that miR-198 is lower in RCC tissues, compared to adjacent tissues [20]. Gigante et al. [21] isolated $CD8^+$ T cells from peripheral blood mononuclear cells of 25 patients with primary RCC and 15 healthy controls. RNA was extracted and quantitative RT-PCR was performed, and the levels of miR-198 in $CD8^+$ T cells from patients with RCC patients are increased. The researchers did not further examine miR-198 expression in RCC tissues. These two study findings are not contradictory. MiR-198 expression is complex, and the expression results may be different for different cell types.

In addition to examining expression of miR-198 in clinical tissue samples, researchers usually study associations between levels of miR-198 expression and clinical characteristics. Wang et al. [22] found that downregulated miR-198-5p expression was significantly associated with tumor size, lymph node metastasis, and tumor node metastasis (TNM) stage in patients with non-small cell lung cancer (NSCLC) [23]. Expression of miR-198 is also linked to degree of differentiation in patients with NSCLC. In LUSC cells, the expression of miR-198-5p was associated with TNM stage. One study found that the level of miR-198-5p expression was higher in patients with early TNM than that in patients with advanced TNM [24]. Similarly, in patients with LUAD clinical features such as age, TNM stage, vascular invasion, and lymph node metastasis were all related to the expression of miR-198 [25-27]. Huang and colleagues detected miR-198 expression in tissues from 95 cases of hepatocellular carcinoma (HCC), and they found that the level of miR-198 was low in HCC tissues. [28]. Low miR-198 expression is closely related with tumor capsular infiltration ($P<0.001$), hepatitis C virus infection ($P<0.001$), tumor node numbers ($P=0.013$), metastasis ($P<0.010$), vaso-invasion ($P=0.017$), and clinical tumor node metastasis stage ($P=0.024$). In osteosarcoma [29], colorectal cancer (CRC) [30], breast cancer (BC) [31], gastric cancer (GC) [32, 33], and oral squamous cell carcinoma (OSCC) [34], researchers found that miR-198 is closely related to some clinical features of these diseases. This finding indicates that miR-198 can be used as a predictive marker for most cancers. In addition to the cancer research findings, Cui et al. [18] also found there is a connection between miR-198 and lupus nephritis. miR-198 is upregulated in patients with lupus nephritis, compared with normal controls. There is a direct positive relationship between miR-198 expression and Systemic Lupus Erythematosus Disease Activity Index scores.

In summary, miR-198 is abnormally expressed in most cancers and is a part of non-cancer diseases. Abnormally expressed miR-198 is

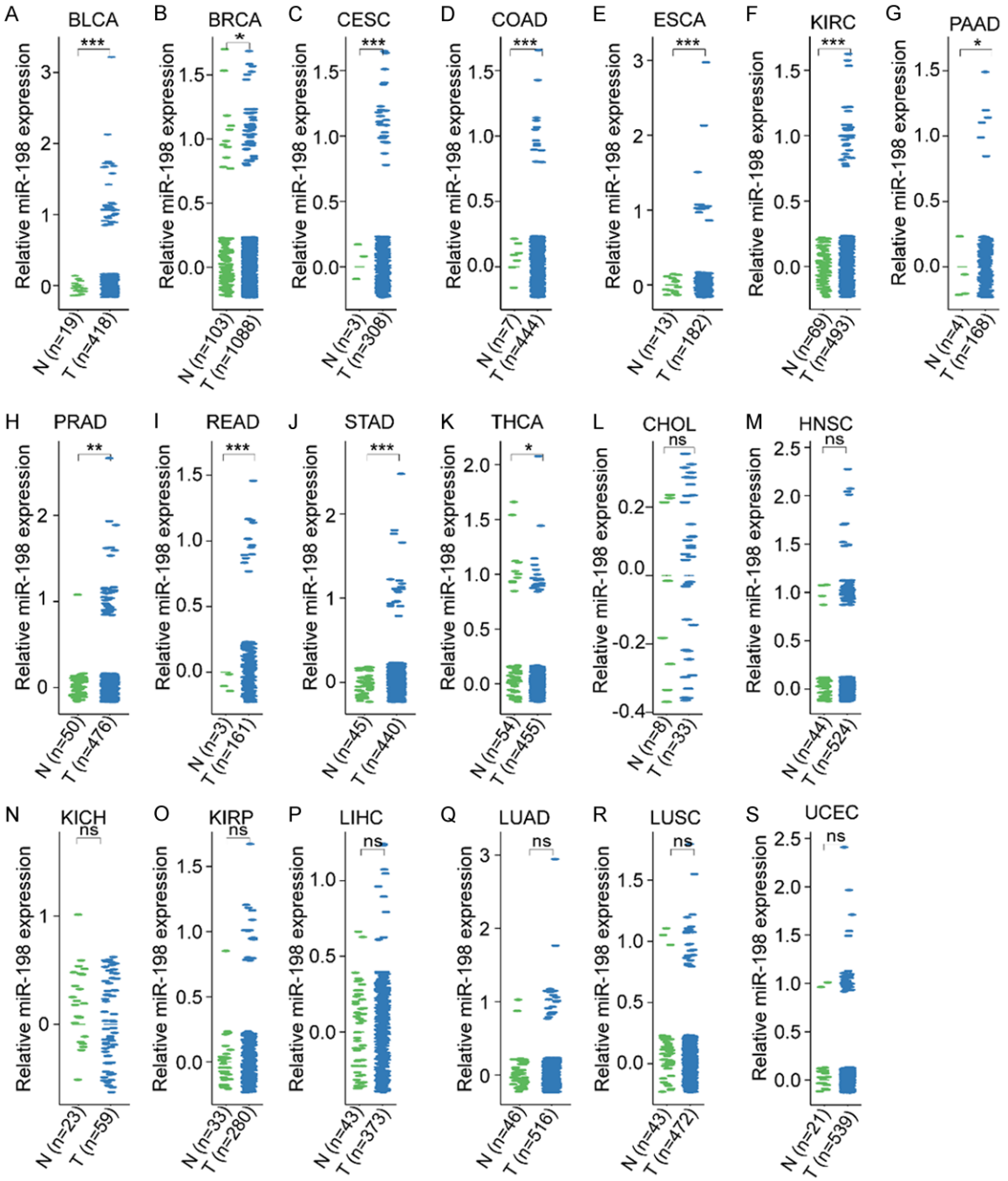

Figure 1. The expression level of miR-198 in tumor and paired nontumor tissues across pancancer. A-K. Upregulated miR-198 expression was observed in BLCA, BRCA, CESC, COAD, ESCA, KIRC, PAAD, PAAD, READ, STAD, and THCA. L-S. There was no significant difference between normal tissue and tumor tissue in CHOL, HNSC, KICH, KIRP, LIHC, LUAD, LUSC, and UCEC. This data was downloaded from TCGA database. The analysis was conducted by GraphPad prism 9. The statistical test used is t test. Denotes *P* value <0.1, **P* value <0.05, ***P* value <0.01, ****P* value <0.001. Abbreviations: BLCA, Bladder urothelial carcinoma; BRCA, Breast invasive carcinoma; CESC, Cervical squamous cell carcinoma and endocervical adenocarcinoma; COAD, Colon adenocarcinoma; ESCA, Esophageal carcinoma; KIRC, Kidney renal clear cell carcinoma; PAAD, Pancreatic adenocarcinoma; PRAD, Prostate adenocarcinoma; READ, Rectum adenocarcinoma; STAD, Stomach adenocarcinoma; THCA, Thyroid carcinoma; CHOL, Cholangiocarcinoma; HNSC, Head and neck squamous cell carcinoma; KICH, Kidney chromophobe; KIRP, Kidney renal papillary cell carcinoma; LIHC, Liver hepatocellular carcinoma; LUAD, Lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; UCEC, Uterine corpus endometrial carcinoma.

Table 1. Abnormal expression of miR-198 in human diseases and clinical significance

Disease type	miRNA	Number of cases	Expression level	the correlation of miR-198 expression with clinicopathologic characteristics	Refs
Glioma	miR-198	20 glioma samples and 15 normal brain tissues	Downregulated	/	[110]
Glioblastoma (GBM)	miR-198	25 tumor samples and 5 nontumorous brain specimens	Downregulated	/	[113]
Melanoma	miR-198	43 melanoma tumor samples and 18 paired adjacent normal tissues	Downregulated	/	[111]
NSCLC	miR-198-5p	20 pairs of NSCLC and the corresponding adjacent non-cancerous specimens	Downregulated	Tumor size, lymph node metastasis, TNM stage	[22]
	miR-198	124 NSCLC patients	/	TNM staging, differentiation	[23]
LUSC	miR-198-5p	23 LUSC tissues and corresponding noncancerous tissues	Downregulated	TNM stage	[24]
LUAD	miR-198-5p	101 paired LUAD tissues and adjacent normal lung tissues	Downregulated	Age, vascular invasion, TNM stage, lymph node metastasis	[25]
	miR-198	90 pairs of LUAD tissues and adjacent normal lung tissues	Downregulated	/	[48]
	miR-198	47 paired LUAD tissues and adjacent non-tumor lung tissues	Downregulated	TNM stage, lymph node metastasis	[26]
	miR-198	42 tumor specimens and pair-matched adjacent normal tissues	/	/	[49]
LUAD-associated malignant pleural effusion	miR-198	107 patients with pleural effusion	Downregulated	/	[27]
Liver cancer	miR-198	40 liver neoplasms and adjacent normal tissues	Downregulated	/	[53]
HCC	miR-198	50 HCC tissues and matched adjacent nontumorous liver tissues	/	/	[54]
	miR-198	95 HCC tissues and the para-cancerous liver tissues	Downregulated	Hepatitis C virus infection, tumor capsular infiltration, metastasis, number of tumor nodes, vaso-invasion, and clinical tumor node metastasis stage	[27]
Osteosarcoma (OS)	miR-198	40 OS tissues and adjacent normal tissues	Downregulated	/	[93]
	miR-198	76 OS tissues and paired adjacent non-tumor bone tissues	Downregulated	TNM stage and distant metastasis	[28]
	miR-198	51 paired osteosarcoma tissues and normal tissues	Downregulated	/	[91]
PTC	miR-198	30 PTC tissues and paired adjacent noncancerous thyroid tissues	/	/	[104]
CRC	miR-198	30 CRC tissues and matched adjacent non-tumor tissues	Downregulated	/	[61]
	miR-198	50 pairs of colorectal primary tumors and adjacent noncancerous colorectal tissues	Downregulated	/	[62]
	miR-198	116 CRC tissues and normal colorectal tissues 65 CRC tissues and normal colorectal tissues	Downregulated	Histological grade, tumor status, AJCC stage, and lymph node invasion	[29]
Ovarian cancer (OC)	miR-198	60 OC tissues and corresponding non-tumor adjacent tissues	Downregulated	/	[83]
	miR-198	10 OC tissues and 6 normal ovarian tissues	Downregulated	/	[86]
Chronic pancreatitis and pancreatic ductal adenocarcinoma	miR-198	74 tumor tissues, 18 tissues of chronic pancreatitis and 9 adjacent normal tissues	Upregulated	/	[15]
Diffuse large B-cell lymphoma (DLBCL)	miR-198	30 DLBCL tissues and normal control tissues	Downregulated	/	[112]
Prostate cancer (PCa)	miR-198	162 prostate cancer tissues	Downregulated	/	[80]
	miR-198	40 prostate cancer tissues and their corresponding noncancerous tissues	Downregulated	/	[82]

BC	miR-198	60 BC tissues and corresponding adjacent normal tissues	Downregulated	/	[110]
	miR-198	49 clinical breast tumor tissues and the adjacent tissues	Downregulated	Lymph node metastasis	[31]
RCC	miR-198	8 RCC tissues and adjacent normal tissues	Downregulated	/	[20]
	miR-198	25 patients treated with open radical nephrectomy or nephron-sparing surgery	Upregulated (in $CD8^+$ T cells)	/	[21]
ESCC	miR-198	52 ESCC tissues and corresponding paracarcinoma tissues	/	/	[72]
	miR-198	46 ESCC tissues and para-cancerous normal tissues	Upregulated	/	[16]
Retinoblastoma (RB)	miR-198	21 RB tissues and 7 normal retina tissues	Upregulated	/	[17]
GC	miR-198	106 pairs of GC specimens and adjacent noncancerous tissues	Downregulated	Tumor size, tumor depth, lymph node metastasis, and clinical stage	[32]
	miR-198	118 GC tissues and adjacent non-tumor gastric tissues	Downregulated	Tumor size, tumor depth, lymph node metastasis, and clinical stage	[33]
	miR-198	149 GC tissues	/	/	[68]
	miR-198	40 GC tissues and corresponding normal stomach mucosa tissues	Downregulated	/	[69]
OSCC	miR-198	80 OSCC tissues and adjacent non-tumor tissues	Downregulated	Metastasis	[34]
Lupus nephritis (LN)	miR-198	52 SLE patients	Upregulated	SLEDAI scores	[18]
	miR-198	42 LN patients and 10 healthy controls	Upregulated	/	[19]

also closely related to a series of clinical features. MiR-198 may participate in the occurrence and development of various diseases. In the future, more studies are needed that further examine the abundance and roles of miR-198 in various diseases.

Function and molecular mechanisms of miR-198 in different diseases

In vivo and *in vitro* studies reveal the expression and functions of miR-198 in various human diseases. However, the molecular mechanisms that may be involved are only briefly discussed. A large number of studies found that miR-198 affects biological processes such as proliferation, invasion, migration, cell cycles, apoptosis, and drug resistance. **Table 2** presents a comprehensive summary of these findings.

miR-198 and respiratory diseases

Lung cancer is the leading cause of cancer-associated deaths in the world and has high morbidity and mortality [35-37]. Smoke, air pollution, and ionizing radiation are the major causes of lung cancer [38, 39]. From the histological perspective, lung cancer can be separated into two subtypes, NSCLC and small cell lung cancer [40]. Of these subtypes, NSCLC is the most common one, which accounts for 80%-85% of all cases [41, 42]. NSCLC includes the three histological subtypes, LUAD (the most common subtype) [43-45], LUSC, and large cell carcinoma. Early detection, diagnosis, and treatment of lung cancer is a promising strategy for reduction of lung cancer mortality [46, 47]. Increasing numbers of studies have revealed the anti-tumor roles of miR-198 in lung cancer.

Yang et al. [48] examined the miR-198 role by overexpressing or knocking down the gene in lung cancer *in vivo* and *in vivo* studies. Their results indicated that miR-198 suppresses tumor cell growth and induces apoptosis lung cancer. Further investigation revealed that fibroblast growth factor receptor (FGFR1) is a direct target of miR-198. Wang and colleagues also found that miR-198-5p inhibits invasion and migration of NSCLC cells by targeting fucosyltransferase 8 (FUT8) [22]. In another study of NSCLC, researchers used qRT-PCR and western blot analysis to confirm that miR-198 inhibited the hepatocyte growth factor/cellular-mesenchymal-epithelial transition (HGF/c-Met) signaling pathway and relieved radiotherapy resistance [23]. Using samples from patients with LUAD, miR-198 and NC were separately transfected into 6-well plates to explore the function of miR-198 in A549 cells. CCK-8 assays and flow cytometric analysis were used to detect cell proliferation, apoptosis, and cell cycle. The results indicated miR-198 inhibits proliferation and induces apoptosis and cell cycle arrest. The miR-198/Livin/caspase-3 regulatory network affects cisplatin resistance and has a vital role in LUAD treatment [49]. Wu et al. [26, 50] found that hsa-circ-0025036 sponges miR-198 to upregulate serine hydroxymethyltrasferase 1 (SHMT1) and TGF-α expression, thereby having a role in LUAD.

miR-198 and digestive system diseases

HCC is the most widespread type of liver cancer and the fourth largest contributor to tumor-related deaths worldwide [51-53]. Duan et al. found that FOXP3 upregulates miR-198 expression by specifically binding to the miR-198 promoter sequence [54]; miR-198 targets the proto-oncogene MYC and inhibits MYC expression. High levels of miR-198 eventually promote hep G2 cell apoptosis while inhibiting proliferation. Li's and colleagues' *in vivo* and *in vitro* experimental results support the tumor-promoting effect of circular RNA circSP3 in HCC [55]. Circular RNA circSP3 (a type of ceRNA) sponges miR-198 and thereby upregulates cyclin-dependent kinase 4 (CDK4). Another study of HCC revealed that miR-198 expression is reduced in HCC cells. miR-198 inhibits synthesis of receptors and PIK3CA signal transducers and inhibits the signal pathways induced by mitotic IGF-1R and Met, which in turn leads to high expression of claudin-1 and E-cadherin. By controlling mitosis and movement pathways, miR-198 reduces growth and migration of HCC cells [56]. Tan et al. [57] also found that miR-198 inhibited the development of HCC cells through the HGF/c-MET pathway. c-MET is the key to the invasion ability of HCC cells [58]. After activated c-MET binds to the homologous ligand, HGF, it triggers many signaling pathways [59]. In summary, results indicate that miR-198 can be used as a tumor suppressor and has a potential role in the treatment of liver cancers.

Table 2. The functions and molecular mechanisms of miR-198 in different diseases

Disease type	miRNA	Assessed cell lines	Expression	Upstream	Downstream	Functional role (validated)	Effect in vivo	Related signaling pathways	Refs
Glioma	miR-198	U87, U251, U138, LN18, NHA	Downregulated	Circ-0005198	TRIM14	Inhibits proliferation, induces apoptosis, attenuates temozolomide resistance		/	[110]
GBM	miR-198	A172, U87, U251, U118, LN229, U138, T98, NHAs	Downregulated	/	MGMT	Enhances temozolomide sensitivity		/	[113]
Melanoma	miR-198	A375, SK-MEL-1, A2058, 293T, HEMn	Downregulated	Hsa-circ-0025039	CDK4	Inhibits proliferation, invasion and glucose metabolism		/	[111]
Lung cancer	miR-198	NCI-H460, A549, Hela	Downregulated	/	FGFR1	Inhibits proliferation, induces apoptosis		/	[48]
NSCLC	miR-198-5p	HCC827, NCI-H1650, NCI-H1299, A549, HEK293T	/	/	FUT8	Inhibits migration, invasion, EMT, and metastasis		/	[22]
	miR-198	A549, NCI-H460, SPCA-1, SK-MES-1, 16HBE	Downregulated	/	MET	Inhibits proliferation, migration, invasion, attenuates radiotherapy resistance, and induces apoptosis		HGF/c-MET signaling pathway	[23]
LUAD	miR-198-5p	/	/	/	/	/		p53 signaling pathway	[25]
	miR-198	A549	Downregulated	/	Livin	Inhibits proliferation, induces apoptosis, enhances cisplatin chemosensitivity		/	[48]
	miR-198	A549, Calu-3	/	/	SHMT1	Inhibits proliferation, induces apoptosis, and cell cycle arrest		/	[26]
	miR-198	A549, Calu-3 cells, NHBE, HEK-293T	/	Hsa-circ-0025036	SHMT1, TGF-α	Inhibits proliferation, and induces apoptosis	/	/	[49]
Liver cancer	miR-198	HepG2, 293T	/	FOXP3	MYC	Inhibits proliferation, and induces apoptosis	/	/	[53]
HCC	miR-198	Hep-3B, Huh-7, Bel-7402, SMMC-772, and HL-7702	Downregulated	Circ-SP3	CDK4	Inhibits proliferation, migration, and invasion		/	[54]
	miR-198	Huh-7, Hep3B, Pop10	Downregulated	/	/	Inhibits proliferation, and migration		/	[56]
	miR-198	HepG2, Hep3B, QGY-7701, QGY-7703, BEL-7404, SMMC-7721	Downregulated	/	c-MET	Inhibits migration, invasion	and	HGF/c-MET pathway	[57]
OS	miR-198	U2OS, HOS	Downregulated	Circ-0002060	ABCB1	Attenuates doxorubicin resistance		/	[93]
	miR-198	HOS LucF-GFP	Downregulated	/	c-MET	Inhibits migration, and invasion		/	[91]
	miR-198	HOS, MG63, G293, SAOS2, U2OS, hFOB, HEK293T	Downregulated	/	ROCK1	Inhibits proliferation, migration, and invasion		/	[28]
	miR-198	HOS, U2OS, hFOB	Downregulated	Hsa-circ-0010220	STX6	Inhibits proliferation, migration, invasion, induces cell cycle arrest and apoptosis	Inhibits tumor growth	/	[91]
TC	miR-198	K1, CAL-62, TPC1, Nthy-ori 3-1	Downregulated	Circ-ITGA7	FGFR1	/		/	[106]
PTC	miR-198	BCPAP, KTC-1, K1, HEK293, Nthy-ori 3-1	/	Circ-RAPGEF5	FGFR1	Inhibits proliferation, and metastasis		/	[104]
CRC	miR-198	SW480, HCT116, FHC	Downregulated	Circ-PRKDC	DDR1	Inhibits proliferation, migration, invasion, induces apoptosis		/	[61]
	miR-198	HT29, SW480, SW620, FHC	Downregulated	/	ADAM28	Inhibits proliferation, colony formation, induces apoptosis		JAK-STAT signaling pathway	[64]

	miR-198	SW620, CRL-1459	/	/	Tenascin C	/	/	/	[64, 70]
	miR-198	HCT116, SW480, HUVECs	Downregulated	Circ-0089153	SENP1	Inhibits proliferation, sphere formation, tube formation, induces apoptosis	Inhibits tumor growth	/	[62]
	miR-198	HCT116, SW1116	/	/	FUT8	Inhibits proliferation, migration, invasion	Inhibits tumor growth, metastasis	/	[29]
OC	miR-198	A2780, OVCAR3, SKOV3, Caov3, IOSE80	Downregulated	/	/	Inhibits proliferation, migration, invasion, induces apoptosis	/	PI3K/Akt signaling pathway	[83]
	miR-198	SKOV3, HeyA8, OVCAR429, HEK-293T	/	Circ-0004390	MET	Inhibits proliferation	/	/	[86]
PC	miR-198	HPDE, PaCa-2	Downregulated	MSLN, OCT-2	PBX-1, VCP	Inhibits proliferation, migration, invasion, induces apoptosis, enhances TNFα chemosensitivity	Inhibits tumor growth and metastatic spread	/	[71]
DLBCL	miR-198	CRL-2630	/	Bortezomib	HMGA1	Inhibits proliferation, colony formation, induces apoptosis	/	/	[112]
PCa	miR-198	LNCaP, DU145	/	/	MIB1	Inhibits proliferation, colony formation, induces G0/G1 cell cycle arrest	Inhibits tumor growth	/	[80]
	miR-198	RWPE-1, LNCap, 22Rv1, DU145, PC-3	Downregulated	SChLAP1	/	Inhibits proliferation, migration, invasion, induces apoptosis	/	MAPK1 signaling pathway	[82]
	miR-198	PC3, DU145	/	/	Livin	Enhances adriamycin chemosensitivity	/	/	[81]
BC	miR-198	MDA-MB-231, MCF-7, SK-BR-3, MDA-MB-453, MCF-10A	/	LINC00473	MAPK1	Inhibits proliferation, migration, invasion	/	/	[110]
	miR-198	MCF-7, MDA-MB-231, BT474, BT549, MCF10A	Downregulated	/	CDCP1	Inhibits proliferation, migration, promotes cell adhesion	/	/	[31]
RCC	miR-198	A498, ACHN	/	/	BIRC5	Inhibits cell viability, migration, invasion, induces apoptosis	Inhibits tumor growth	/	[20]
	miR-198	/	/	/	JAK3	leads to immune dysfunction	/	/	[21]
ESCC	miR-198	ECA109, TE-13, Kyse150, Kyse450, Kyse510, HET-1A	/	Circ-LPAR3	MET	Inhibits migration, invasion, metastasis	/	RAS/MAPK and the PI3K/Akt pathways	[72]
RB	miR-198	Y79, SO-RB50, WERI-RB1, ARPE-19	Upregulated	/	PTEN	Promotes proliferation, invasion	/	PI3K/AKT signaling pathway	[17]
GC	miR-198	SGC-7901, AGS, MGC803, MKN-28, BGC823, NGEC	Downregulated	/	FGFR1	Inhibits proliferation, induces apoptosis, cell cycle arrest	/	/	[33]
	miR-198	SGC7901, BGC823	Downregulated	Circ-AKT3	PIK3R1	Attenuates cisplatin resistance	/	PI3K/AKT signaling pathway	[68]
	miR-198	GES-1, SGC-7901, MGC-803	Downregulated	/	TLR4	Inhibits proliferation, migration, invasion, induces apoptosis	/	/	[70]
	miR-198	SNU-5, MGC-803, HGC-27, BGC-823, SGC7901, AGS	Downregulated	Circ-PLEC	MUC19	Inhibits proliferation, migration, invasion, induces apoptosis, attenuates paclitaxel resistance	/	/	[69]
OSCC	miR-198	Cal-27, SCC-9, SCC-25, HaCaT	Downregulated	/	CDK4	Inhibits proliferation, invasion, EMT, induces apoptosis	/	/	[34]
LN	miR-198	MMC, HEK-293	/	/	PTEN	Promotes glomeruli cell growth, proliferation	/	/	[18]
OP	miR-198-5p	hFOB1.19	/	Hsa-circ-0002060	Bax	/	/	/	[99]

CRC is one of the most common cancers [60, 61], and is an urgent global health burden [51]. Both circ-PRKDC and circ-0089153 can act as ceRNAs and change the level of downstream target genes by sponging miR-198. Via this mechanism, they can have a significant role in the progress of CRC [62-64]. Li et al. [65] used qRT-PCR to detect the expression of miR-198 in human CRC cell lines and normal colon cell lines. Subsequently, MTT, colony formation, flow cytometry, and western blot were used to detect effects of miR-198 on cell proliferation, colony formation, apoptosis, and expression of some pathway proteins. The results showed that miR-198 blocks CRC cells proliferation and promotes apoptosis by targeting ADAM28 and blocking the JAK/STAT pathway. Wang et al. [30] also found that miR-198 could inhibit CRC tumor growth and metastasis by targeting FUT8 *in vivo*.

GC is the fifth most universal cancer disease worldwide and the third leading cause of cancer-related deaths [51, 66, 67]. Patients with advanced GC generally can only rely on chemotherapy, and drug resistance is the main reason for GC treatment failures [68]. Huang et al.'s [69] *in vitro* study found that circAKT3 regulates expression of PIK3R1, activates the phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) signaling pathway, and ultimately promotes cisplatin resistance via targeting miR-198. Subsequently, the results of *in vivo* experiments supported this result. Their research suggested that treatment targeting miR-198 has a specific effect on alleviation of chemotherapy resistance in GC. Zhou and colleagues also reported the potential role of miR-198 in GC-related drug resistance [70]. MiR-198 inhibitor reverses the effect of downregulation of circPLEC in paclitaxel (PTX)-resistant GC cells. CircPLEC could inhibit miR-198, and promote PTX resistance through regulation of the expression level of mucin 19 (MUC19). Two other studies revealed the anti-tumor effect of miR-198 in GC. It is mainly manifested by inhibiting growth, invasion, and migration, and inducing GC cell apoptosis [33, 71].

In studies of pancreatic cancer (PC), researchers found that miR-198 is an antagonist of MSLN-mediated survival of autocrine PC cells and resistance to TNF-α-induced apoptosis. The upregulated expression of miR-198 can reduce tumor growth and metastasis *in vivo*. Regulation of miR-198-mediated interactors is of great significance for prevention of chemotherapy resistance of PC cells [72, 73]. In a study of esophageal squamous cell carcinoma (ESCC), Shi et al. found that the circLPAR3 upregulated the expression of MET via sponge miR-198 *in vivo* and *in vitro* (**Figure 2**).

miR-198 and urogenital system diseases

RCC is a common high-grade malignant urinary system tumor and the second primary cause of death in patients with urinary system tumors [74, 75]. Yuan et al. [20] examined the role of miR-198 in RCC. Highly expressed miR-198 could suppress cell viability, causes cell apoptosis, and inhibit tumor growth in nude mouse models. Mechanically, miR-198 exerts a tumor suppressor effect by targeting BIRC5. Gigante et al. [21] pointed out that dysregulation of miR-198 and miR-29b in $CD8^+$ T cells of patients with RCC is related to immune dysfunction. Research results suggest that future miRNA-targeted treatments will help correct this T cell defect.

Lupus nephritis is one of the most common complications of systemic lupus erythematosus [76, 77]. It is an immune complex-mediated glomerulonephritis [78]. Researchers found that miR-198 inhibits lupus nephritis progression by inhibiting PTEN expression [18].

Prostate cancer is the most common cancer in men [79, 80]. Current evidence supports the hypothesis that miR-198 is an important tumor suppressor in this cancer. RAY et al. [81] reported that miR-198 is less expressed in prostate cancer with a high Gleason grade, and that overexpression in mice can lead to impaired tumor formation. Overexpression of miR-198 can suppress proliferation of prostate cancer cell lines, increase G0/G1 cell cycle arrest, and significantly impair colony formation. Another study found that miR-198 combined with RNAi might enhance the chemosensitivity of PC3 cells to adriamycin obviously [82]. The SChLAP1/miR-198/MAPK1 axis is also joined in the process of inhibition of prostate cancer [83].

Ovarian cancer (OC) is one of the most typical gynecological cancers and the fifth primary cause of cancer-related deaths in women all

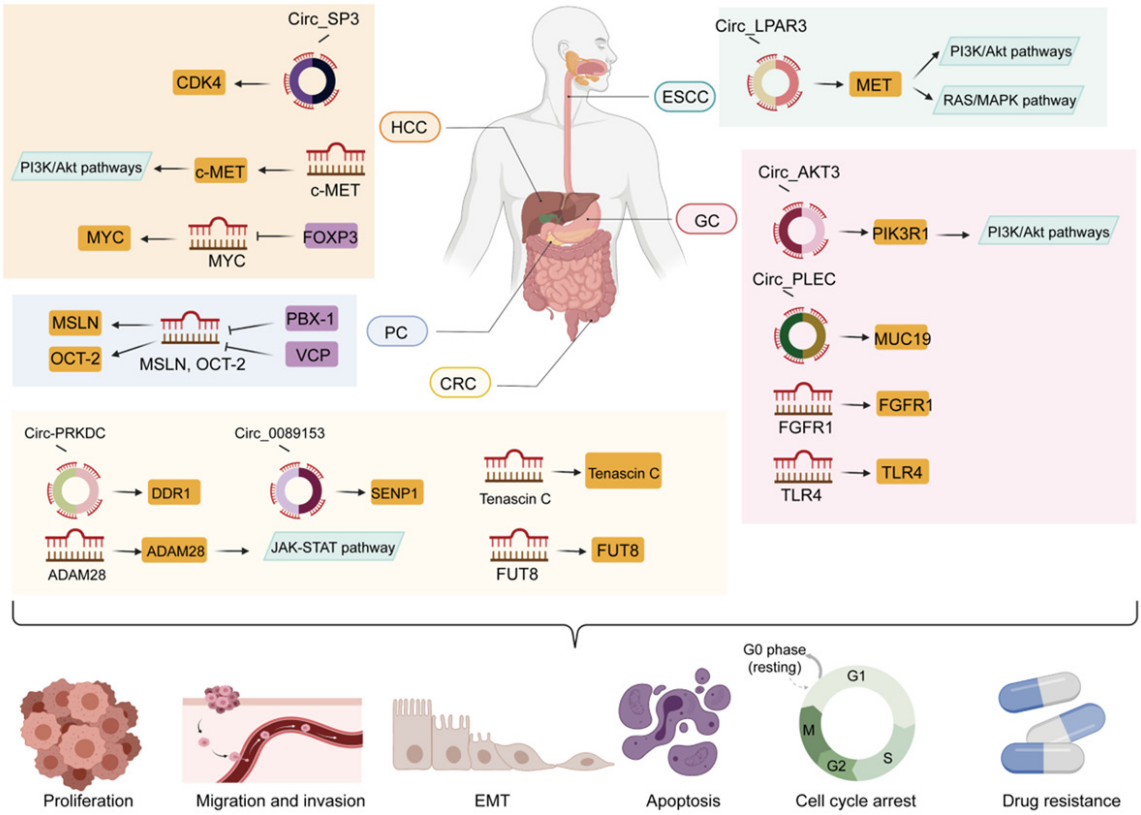

Figure 2. Summary of the roles and mechanisms of miR-198 in some digestive system diseases: ESCC, GC, HCC, PC, and CRC. Abbreviations: ESCA, Esophageal carcinoma; GC, Gastric cancer; HCC, Hepatocellular carcinoma; PC, Pancreatic cancer; CRC, Colorectal cancer.

around the world [66, 84]. Xiao et al. [85] selected normal human ovarian epithelial cells IOSE80 and the OC cell line OVCAR3 for their research. Their results suggested that miR-198 inhibited proliferation, migration, and invasion of OC cells by inhibiting the PI3K/Akt pathway. PI3K is an important regulator of macrophage phagocytosis, mainly by activating cell surface receptors to phosphorylate the second messenger of phosphatidylinositol. Akt binds to the PIP product of PI3K through the pleckstrin homology domain [86]. Previous studies found that abnormal activation of the PI3K/Akt pathway promotes the occurrence and development of OC [87]. Xu et al. [88] revealed the important role of the circ0004390/miR-198/MET axis in regulation of OC proliferation and that it provides a potential target for OC treatment.

miR-198 and skeletal system diseases

Osteosarcoma is the most common aggressive malignant bone tumor, which originates from the original transformed mesenchymal cells [89, 90]. It is also the second leading cause of tumor-related deaths in children and adolescents [91]. Georges [29], Zhang [92], and Lu et al. [93] revealed the tumor suppressor effect of miR-198 in osteosarcoma. Overexpression of miR-198 inhibits osteosarcoma cell proliferation, invasion, and migration, and induces apoptosis and cell cycle arrest. Drug resistance has always been a major obstacle to effective cancer chemotherapy [94]. Researchers found that circ-0002060 promotes doxorubicin (DOX) resistance and osteosarcoma progression by regulating the miR-198/ABC subfamily G member 1 axis [95]. Taken together, these results suggest that molecularly targeted drugs for miR-198 will bring new hope for osteosarcoma treatment.

Osteoporosis is a systemic bone disease in which bone resorption exceeds bone formation and leads to deterioration of bone tissue microstructure [96, 97]. With the intensification of population aging, osteoporosis has increasing-

ly become one of the main health problems of concern [98, 99]. Liu and colleagues found that Hsa-circ-0002060 gene knockdown could improve osteoporosis by targeting miR-198-5p, and Hsa-circ-0002060/miR-198-5p/Bcl-2-associated X protein (Bax) axis acted in an essential role in the occurrence and development of osteoporosis [100].

miR-198 and endocrine diseases

Thyroid cancer (TC) is the most common cancer of the endocrine system, and its incidence is rising rapidly [67, 101]. Papillary thyroid carcinoma (PTC) is the most common well-differentiated TC and accounts for 80%-85% of thyroid malignancies [102-104]. Although the efficacy of clinical treatment of TC has improved, the disease still has a high recurrence rate [105]. Two studies of potential new biomarkers for the diagnosis and treatment of TC revealed associations between miR-198 and TC. Liu et al.'s [106] results of *in vivo* and *in vitro* experiments indicated miR-198 has an anti-tumor effect in PTC. As a type of ceRNA, circRAPGEF5 sponges miR-198, inhibits binding of miR-198 and FGFR1, and thereby upregulates the level of FGFR1 and ultimately promotes PTC proliferation and metastasis. Li et al. [107] also found that circITGA7/miR-198/FGFR1 axis has an important role in TC development.

BC is a malignant tumor that occurs in breast epithelial tissue and is a common cause of death in women of all ages worldwide [108, 109]. The high mortality of patients with BC is related to recurrence, drug resistance, and the high frequency of metastasis [110]. Researchers have examined the miR-198 expression in BC and related functional mechanisms. RT-qPCR results revealed that miR-198 is downregulated in BC. Functional studies revealed that miR-198 inhibits cell proliferation and migration and promotes cell adhesion in invasive BC cells *in vitro*. Mechanistically, miR-198 acts by targeting CUB domain containing protein 1 (CDCP1) [76]. Niu and colleagues proposed a hypothesis that LINC00473 regulates MAPK1 expression via sponge miR-198 [111]. They co-transfected siLINC00473 and miR-198 inhibitor into MDA-MB-231. Their results indicated that changes in expression of Cyclin D1, p21, N-cadherin, E-cadherin, and MAPK1 induced by siLINC00473 are all rescued by miR-198 inhibitors. siLINC00473 promotes BC cell proliferation, invasion, and migration by targeting miR-198.

miR-198 and other diseases

In glioma [112], melanoma [113], diffuse large B-cell lymphoma [114], and OSCC [34], the expression level of miR-198 decreases and has a role in tumor inhibition. The anti-tumor effect mainly manifests as inhibition of tumor cell proliferation and promotion of apoptosis. Nie et al. [115] found that miR-198 induces the chemosensitivity of glioblastoma to temozolomide by targeting O6-methylguanine-DNA methyltransferase. Deng also found that circ-0005198/miR-198/tripartite motif containing 14 (TRIM14) axis could enhance temozolomide resistance of tumor cells in glioma [112]. To examine the biological role of miR-198 in retinoblastoma, researchers transfected Y79 and WERI-RB1 cells with miR-198 inhibitors to down-regulate the endogenous level. Down-regulation of miR-198 inhibited growth and invasion of retinoblastoma cells *in vitro*. MiR-198 could target phosphatase and tensin homolog deleted on chromosome ten (PTEN) and regulate PI3K/AKT pathway to promote tumor progression [17].

It seems reasonable that miR-198 has a dual role in its effects on disease progression. Because miR-198 can promote or inhibit disease progression in the same disease or among different diseases, the different effects of miR-198 are revealed by the different studies.

miR-198 acts as a prognostic biomarker

Abnormal expression of miR-198 in different diseases suggests that it can be used for disease diagnosis or prediction. **Table 3** presents a summary of the prognostic value of miR-198 in some diseases. In glioblastoma, researchers used the Chinese Glioma Genome Atlas database database and TCGA database to further analyze miR-198 expression and found that low expression of miR-198 is linked to a poor clinical outcome in patients with glioblastoma [115]. Wang et al. [25] divided the entire parameter into two groups (low expression and high expression) based on the median level of miR-198-5p in LUAD tissue, and the survival rate of patients with downregulated miR-198-5p was significantly ($P<0.001$). However, con-

Table 3. Prognostic value of miR-198 in human diseases

Disease type	miRNA	Prognostic implication of miR-198 down expression	HR	*P* value	Refs
GBM	miR-198	Poor	/	0.0255/0.0388	[113]
LUAD	miR-198-5p	Poor	0.272 (0.133-0.555)	0.001	[25]
CRC	miR-198	Poor	/	0.01	[29]
PC	miR-198	Poor	0.110 (0.03-0.42)	0.0014	[71]
Chronic pancreatitis and PDAC	miR-198	Better	/	0.0097	[15]
EC	miR-198	Poor	/	0.03	[16]
GC	miR-198	Poor	/	0.001	[32]
OSCC	miR-198	Poor	3.221 (1.443-4.113)	0.033	[34]

sidering that other factors seemed to have no predictive value, the researchers did not conduct further multi-factor analyses. In patients with PC, log-rank tests revealed that the survival rate of high miR-198 expression patients was significantly higher. The median survival of patients with low miR-198 expression was 15.5 months. In contrast, the median survival time of the miR-198 high expression group was 35.75 months. Multivariate analysis revealed that miR-198 was obviously related to overall survival [72]. However, another study of chronic pancreatitis and pancreatic ductal adenocarcinoma found that high expression of miR-198 was significantly associated with poor prognosis [15]. The researchers did not thoroughly examine the reasons for the contradiction, so multiple studies with large samples sizes are needed. Kang and colleagues examined the effect of miR-198 on OSCC prognosis [34]. Univariate Cox regression analyses revealed differences; TNM staging and miR-198 expression were significantly correlated with poorer overall and disease-free survival. The results of multivariate analysis suggest that TNM staging and miR-198 expression could serve as prognostic markers for OSCC. In addition, low expression of miR-198 is related to poor prognoses for CRC [30], EC [16], and GC [32]. We believe that miR-198 could be used as a prognostic tool to predict outcomes for some cancer patients. As a biomarker, miRNA has certain advantages, including stability, which means it is detectable for long period of time.

Conclusions and perspectives

We studied the effects of miR-198 on a variety of human diseases from multiple perspectives, including clinical studies, *in vivo* animal models, and *in vitro* cell experiments. Taken together, study results indicate that abnormal expression of miR-198 affects the occurrence, development, and outcome of the disease. The ceRNA mechanism is also widely involved in the process via which miR-198 regulates disease progression. Circ-0005198, Hsa-circ-0025039, Hsa-circ-0025036, Circ-SP3, Circ-0002060, Hsa-circ-0010220, Circ-ITGA7, Circ-RAPGEF5, Circ-PRKDC, Circ-0089153, Circ-0004390, SChLAP1, LINC00473, Circ-LPAR3, Circ-AKT3, Circ-PLEC, and Hsa-circ-0002060 are non-coding RNAs that sponge miR-198. Except for these non-coding RNAs, expression of miR-198 is also regulated by a variety of transcription factors and proteins.

We suggest that miR-198 has the potential to function as a biomarker for disease diagnosis and prognosis or as a target to reduce drug resistance when used in combination with existing drugs (**Figure 3**). However, given the apparent dual functions of miR-198 during the development of specific diseases, the numbers and depth of research studies have been limited. In the future, abundant basic and clinical research is needed to further clarify its functions and clinical significance. There is also a clear gap between the current research on miR-198 and clinical practice, and more large-scale patient and multi-type clinical sample (e.g., urine, serum) studies are needed to support its use as a new type of disease-related diagnostic and prognostic biomarker. We hope that by summarizing the potential role and prognostic value of miR-198 in human disease, we can provide direction for the treatment, diagnosis, and prognosis of diseases. In the future, using miRNA levels in blood, urine, and other body fluids to characterize disease and disease progress would be of great use clinically.

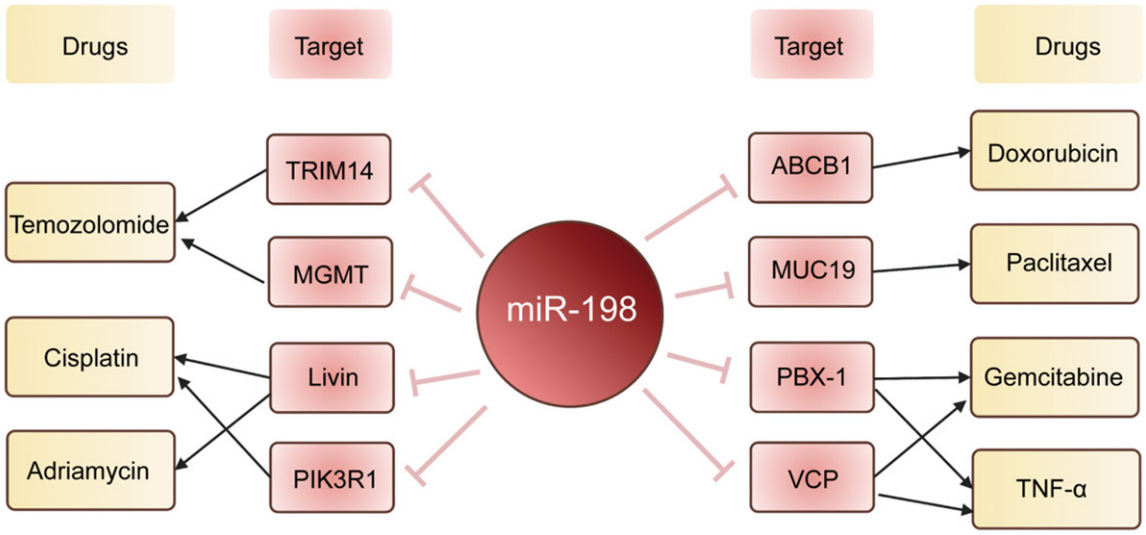

Figure 3. MiR-198 improves sensitivity to certain chemotherapeutic drugs by targeting its downstream target genes.

Disclosure of conflict of interest

None.

Address correspondence to: Xiaoping Wang, Department of Infectious Diseases, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, P. R. China. Tel: +86-371-67966941; E-mail: wangxp19731230@163.com

References

[1] Pritchard CC, Cheng HH and Tewari M. MicroRNA profiling: approaches and considerations. Nat Rev Genet 2012; 13: 358-369.

[2] Ambros V. The functions of animal microRNAs. Nature 2004; 431: 350-355.

[3] Sun HL, Cui R, Zhou J, Teng KY, Hsiao YH, Nakanishi K, Fassan M, Luo Z, Shi G, Tili E, Kutay H, Lovat F, Vicentini C, Huang HL, Wang SW, Kim T, Zanesi N, Jeon YJ, Lee TJ, Guh JH, Hung MC, Ghoshal K, Teng CM, Peng Y and Croce CM. ERK activation globally downregulates miRNAs through phosphorylating exportin-5. Cancer Cell 2016; 30: 723-736.

[4] Rückerl D, Jenkins SJ, Laqtom NN, Gallagher IJ, Sutherland TE, Duncan S, Buck AH and Allen JE. Induction of IL-4Rα-dependent microRNAs identifies PI3K/Akt signaling as essential for IL-4-driven murine macrophage proliferation in vivo. Blood 2012; 120: 2307-2316.

[5] O'Brien J, Hayder H, Zayed Y and Peng C. Overview of microrna biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne) 2018; 9: 402.

[6] Abe M and Bonini NM. MicroRNAs and neurodegeneration: role and impact. Trends Cell Biol 2013; 23: 30-36.

[7] Krützfeldt J and Stoffel M. MicroRNAs: a new class of regulatory genes affecting metabolism. Cell Metab 2006; 4: 9-12.

[8] Lionetti M, Musto P, Di Martino MT, Fabris S, Agnelli L, Todoerti K, Tuana G, Mosca L, Gallo Cantafio ME, Grieco V, Bianchino G, D'Auria F, Statuto T, Mazzoccoli C, De Luca L, Petrucci MT, Offidani M, Di Raimondo F, Falcone A, Caravita T, Omede' P, Morabito F, Tassone P, Boccadoro M, Palumbo A and Neri A. Biological and clinical relevance of miRNA expression signatures in primary plasma cell leukemia. Clin Cancer Res 2013; 19: 3130-3142.

[9] Wang M, Yang C, Liu X, Zheng J, Xue Y, Ruan X, Shen S, Wang D, Li Z, Cai H and Liu Y. An upstream open reading frame regulates vasculogenic mimicry of glioma via ZNRD1-AS1/miR-499a-5p/ELF1/EMI1 pathway. J Cell Mol Med 2020; 24: 6120-6136.

[10] Di Leva G, Garofalo M and Croce CM. MicroRNAs in cancer. Annu Rev Pathol 2014; 9: 287-314.

[11] Hansen T, Olsen L, Lindow M, Jakobsen KD, Ullum H, Jonsson E, Andreassen OA, Djurovic S, Melle I, Agartz I, Hall H, Timm S, Wang AG and Werge T. Brain expressed microRNAs implicated in schizophrenia etiology. PLoS One 2007; 2: e873.

[12] Mattiotti A, Prakash S, Barnett P and van den Hoff MJB. Follistatin-like 1 in development and human diseases. Cell Mol Life Sci 2018; 75: 2339-2354.

[13] Sundaram GM, Common JE, Gopal FE, Srikanta S, Lakshman K, Lunny DP, Lim TC, Tanavde V, Lane EB and Sampath P. 'See-saw' expression of microRNA-198 and FSTL1 from a single transcript in wound healing. Nature 2013; 495: 103-106.

[14] Walter BA, Valera VA, Pinto PA and Merino MJ. Comprehensive microRNA profiling of prostate cancer. J Cancer 2013; 4: 350-357.
[15] Vychytilova-Faltejskova P, Kiss I, Klusova S, Hlavsa J, Prochazka V, Kala Z, Mazanec J, Hausnerova J, Kren L, Hermanova M, Lenz J, Karasek P, Vyzula R and Slaby O. MiR-21, miR-34a, miR-198 and miR-217 as diagnostic and prognostic biomarkers for chronic pancreatitis and pancreatic ductal adenocarcinoma. Diagn Pathol 2015; 10: 38.
[16] Qi B, Yao WJ, Zhao BS, Qin XG, Wang Y, Wang WJ, Wang TY, Liu SG and Li HC. Involvement of microRNA-198 overexpression in the poor prognosis of esophageal cancer. Asian Pac J Cancer Prev 2013; 14: 5073-5076.
[17] Wei D, Miao Y, Yu L, Wang D and Wang Y. Down-regulation of microRNA-198 suppresses cell proliferation and invasion in retinoblastoma by directly targeting PTEN. Mol Med Rep 2018; 18: 595-602.
[18] Cui D, Zhu D, Ren H, Lin J, Lai W, Huang Q, Zhao J and Yang M. MicroRNA-198 contributes to lupus nephritis progression by inhibition of phosphatase and tensin homology deleted on chromosome ten expression. Mol Med Rep 2017; 16: 7813-7820.
[19] Lu J, Kwan BC, Lai FM, Tam LS, Li EK, Chow KM, Wang G, Li PK and Szeto CC. Glomerular and tubulointerstitial miR-638, miR-198 and miR-146a expression in lupus nephritis. Nephrology (Carlton) 2012; 17: 346-351.
[20] Yuan C, Su Z, Liao S, Li D, Zhou Z, Wang Y, Quan M, Zeng L, Lv C, Shen C, Gong W, Wu J, Chen X, Hu W, Lv X, Si W and Yu X. miR-198 inhibits the progression of renal cell carcinoma by targeting BIRC5. Cancer Cell Int 2021; 21: 390.
[21] Gigante M, Pontrelli P, Herr W, Gigante M, D'Avenia M, Zaza G, Cavalcanti E, Accetturo M, Lucarelli G, Carrieri G, Battaglia M, Storkus WJ, Gesualdo L and Ranieri E. miR-29b and miR-198 overexpression in CD8+ T cells of renal cell carcinoma patients down-modulates JAK3 and MCL-1 leading to immune dysfunction. J Transl Med 2016; 14: 84.
[22] Wang S, Zhang X, Yang C and Xu S. MicroRNA-198-5p inhibits the migration and invasion of non-small lung cancer cells by targeting fucosyltransferase 8. Clin Exp Pharmacol Physiol 2019; 46: 955-967.
[23] Zhu L, Xue F, Xu X, Xu J, Hu S, Liu S, Cui Y and Gao C. MicroRNA-198 inhibition of HGF/c-MET signaling pathway overcomes resistance to radiotherapy and induces apoptosis in human non-small-cell lung cancer. J Cell Biochem 2018; 119: 7873-7886.
[24] Liang YY, Huang JC, Tang RX, Chen WJ, Chen P, Cen WL, Shi K, Gao L, Gao X, Liu AG, Peng XT, Chen G, Huang SN, Fang YY and Gu YY. Clinical value of miR-198-5p in lung squamous cell carcinoma assessed using microarray and RT-qPCR. World J Surg Oncol 2018; 16: 22.
[25] Wang SS, Fang YY, Huang JC, Liang YY, Guo YN, Pan LJ and Chen G. Clinical value of microRNA-198-5p downregulation in lung adenocarcinoma and its potential pathways. Oncol Lett 2019; 18: 2939-2954.
[26] Wu S, Zhang G, Li P, Chen S, Zhang F, Li J, Jiang C, Chen X, Wang Y, Du Y, Sun Q and Zhao G. miR-198 targets SHMT1 to inhibit cell proliferation and enhance cell apoptosis in lung adenocarcinoma. Tumour Biol 2016; 37: 5193-5202.
[27] Han HS, Yun J, Lim SN, Han JH, Lee KH, Kim ST, Kang MH, Son SM, Lee YM, Choi SY, Yun SJ, Kim WJ and Lee OJ. Downregulation of cell-free miR-198 as a diagnostic biomarker for lung adenocarcinoma-associated malignant pleural effusion. Int J Cancer 2013; 133: 645-652.
[28] Huang WT, Wang HL, Yang H, Ren FH, Luo YH, Huang CQ, Liang YY, Liang HW, Chen G and Dang YW. Lower expressed miR-198 and its potential targets in hepatocellular carcinoma: a clinicopathological and in silico study. Onco Targets Ther 2016; 9: 5163-5180.
[29] Zhang S, Zhao Y and Wang L. MicroRNA-198 inhibited tumorous behaviors of human osteosarcoma through directly targeting ROCK1. Biochem Biophys Res Commun 2016; 472: 557-565.
[30] Wang M, Wang J, Kong X, Chen H, Wang Y, Qin M, Lin Y, Chen H, Xu J, Hong J, Chen YX, Zou W and Fang JY. MiR-198 represses tumor growth and metastasis in colorectal cancer by targeting fucosyl transferase 8. Sci Rep 2014; 4: 6145.
[31] Hu Y, Tang Z, Jiang B, Chen J and Fu Z. miR-198 functions as a tumor suppressor in breast cancer by targeting CUB domain-containing protein 1. Oncol Lett 2017; 13: 1753-1760.
[32] Cui Z, Zheng X and Kong D. Decreased miR-198 expression and its prognostic significance in human gastric cancer. World J Surg Oncol 2016; 14: 33.
[33] Gu J, Li X, Li H, Jin Z and Jin J. MicroRNA-198 inhibits proliferation and induces apoptosis by directly suppressing FGFR1 in gastric cancer. Biosci Rep 2019; 39: BSR20181258.
[34] Kang Y, Zhang Y and Sun Y. MicroRNA-198 suppresses tumour growth and metastasis in oral squamous cell carcinoma by targeting CDK4. Int J Oncol 2021; 59: 39.
[35] Altorki NK, Markowitz GJ, Gao D, Port JL, Saxena A, Stiles B, McGraw T and Mittal V. The lung microenvironment: an important regulator of tumour growth and metastasis. Nat Rev Cancer 2019; 19: 9-31.

[36] Yi Q, Cui H, Liao Y, Xiong J, Ye X and Sun W. A minor review of microRNA-338 exploring the insights of its function in tumorigenesis. Biomed Pharmacother 2021; 139: 111720.
[37] Wang R, Yamada T, Kita K, Taniguchi H, Arai S, Fukuda K, Terashima M, Ishimura A, Nishiyama A, Tanimoto A, Takeuchi S, Ohtsubo K, Yamashita K, Yamano T, Yoshimura A, Takayama K, Kaira K, Taniguchi Y, Atagi S, Uehara H, Hanayama R, Matsumoto I, Han X, Matsumoto K, Wang W, Suzuki T and Yano S. Transient IGF-1R inhibition combined with osimertinib eradicates AXL-low expressing EGFR mutated lung cancer. Nat Commun 2020; 11: 4607.
[38] Liu R, Wei S, Chen J and Xu S. Mesenchymal stem cells in lung cancer tumor microenvironment: their biological properties, influence on tumor growth and therapeutic implications. Cancer Lett 2014; 353: 145-152.
[39] Zhang T, Chen Y, Ge Y, Hu Y, Li M and Jin Y. Inhalation treatment of primary lung cancer using liposomal curcumin dry powder inhalers. Acta Pharm Sin B 2018; 8: 440-448.
[40] Zhang W, Gao Y, Li P, Shi Z, Guo T, Li F, Han X, Feng Y, Zheng C, Wang Z, Li F, Chen H, Zhou Z, Zhang L and Ji H. VGLL4 functions as a new tumor suppressor in lung cancer by negatively regulating the YAP-TEAD transcriptional complex. Cell Res 2014; 24: 331-343.
[41] Xue J and Zhang F. LncRNA LINC00511 plays an oncogenic role in lung adenocarcinoma by regulating PKM2 expression via sponging miR-625-5p. Thorac Cancer 2020; 11: 2570-2579.
[42] Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, Geisinger K, Hirsch FR, Ishikawa Y, Kerr KM, Noguchi M, Pelosi G, Powell CA, Tsao MS and Wistuba I. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015; 10: 1243-1260.
[43] Herbst RS, Morgensztern D and Boshoff C. The biology and management of non-small cell lung cancer. Nature 2018; 553: 446-454.
[44] Reck M, Heigener DF, Mok T, Soria JC and Rabe KF. Management of non-small-cell lung cancer: recent developments. Lancet 2013; 382: 709-719.
[45] Chen Z, Fillmore CM, Hammerman PS, Kim CF and Wong KK. Non-small-cell lung cancers: a heterogeneous set of diseases. Nat Rev Cancer 2014; 14: 535-546.
[46] Yee J, Sadar MD, Sin DD, Kuzyk M, Xing L, Kondra J, McWilliams A, Man SF and Lam S. Connective tissue-activating peptide III: a novel blood biomarker for early lung cancer detection. J Clin Oncol 2009; 27: 2787-2792.
[47] Tan X, Jiang L, Wu X, Feng W and Lin Q. MicroRNA-625 inhibits the progression of non-small cell lung cancer by directly targeting HOXB5 and deactivating the Wnt/β-catenin pathway. Int J Mol Med 2019; 44: 346-356.
[48] Yang J, Zhao H, Xin Y and Fan L. MicroRNA-198 inhibits proliferation and induces apoptosis of lung cancer cells via targeting FGFR1. J Cell Biochem 2014; 115: 987-995.
[49] Liang Y, Wang H, Sun Y, Chen S, Wang H, Huang R, Zhao X, Fu W and Yang C. miR-198-induced upregulation of Livin may be associated with the prognosis and contribute to the oncogenesis of lung adenocarcinoma. Oncol Rep 2017; 38: 2096-2104.
[50] Wu S, Li H, Lu C, Zhang F, Wang H, Lu X and Zhang G. Aberrant expression of hsa_circ_0025036 in lung adenocarcinoma and its potential roles in regulating cell proliferation and apoptosis. Biol Chem 2018; 399: 1457-1467.
[51] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
[52] Mirzaei HR, Sahebkar A, Mohammadi M, Yari R, Salehi H, Jafari MH, Namdar A, Khabazian E, Jaafari MR and Mirzaei H. Circulating microRNAs in hepatocellular carcinoma: potential diagnostic and prognostic biomarkers. Curr Pharm Des 2016; 22: 5257-5269.
[53] Kang L, Zhang ZH and Zhao Y. SCAMP3 is regulated by miR-128-3p and promotes the metastasis of hepatocellular carcinoma cells through EGFR-MAPK p38 signaling pathway. Am J Transl Res 2020; 12: 7870-7884.
[54] Duan X, Jiang B, Yang J, Zhou L, Tian B and Mao X. FOXP3 inhibits MYC expression via regulating miR-198 and influences cell viability, proliferation and cell apoptosis in HepG2. Cancer Med 2018; 7: 6182-6192.
[55] Li M, Chen H, Xia L and Huang P. Circular RNA circSP3 promotes hepatocellular carcinoma growth by sponging microRNA-198 and upregulating cyclin-dependent kinase 4. Aging (Albany NY) 2021; 13: 18586-18605.
[56] Elfimova N, Sievers E, Eischeid H, Kwiecinski M, Noetel A, Hunt H, Becker D, Frommolt P, Quasdorff M, Steffen HM, Nürnberg P, Büttner R, Teufel A, Dienes HP, Drebber U and Odenthal M. Control of mitogenic and motogenic pathways by miR-198, diminishing hepatoma cell growth and migration. Biochim Biophys Acta 2013; 1833: 1190-1198.
[57] Tan S, Li R, Ding K, Lobie PE and Zhu T. miR-198 inhibits migration and invasion of hepato-

cellular carcinoma cells by targeting the HGF/c-MET pathway. FEBS Lett 2011; 585: 2229-2234.
[58] Whittaker S, Marais R and Zhu AX. The role of signaling pathways in the development and treatment of hepatocellular carcinoma. Oncogene 2010; 29: 4989-5005.
[59] Trusolino L, Bertotti A and Comoglio PM. MET signalling: principles and functions in development, organ regeneration and cancer. Nat Rev Mol Cell Biol 2010; 11: 834-848.
[60] Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017; 66: 683-691.
[61] Sobhani I, Itti E, Luciani A, Baumgaertner I, Layese R, André T, Ducreux M, Gornet JM, Goujon G, Aparicio T, Taieb J, Bachet JB, Hemery F, Retbi A, Mons M, Flicoteaux R, Rhein B, Baron S, Cherrak I, Rufat P, Le Corvoisier P, de'Angelis N, Natella PA, Maoulida H, Tournigand C, Durand Zaleski I and Bastuji-Garin S. Colorectal cancer (CRC) monitoring by 6-monthly 18FDG-PET/CT: an open-label multicentre randomised trial. Ann Oncol 2018; 29: 931-937.
[62] Wang G, Li Y, Zhu H, Huo G, Bai J and Gao Z. Circ-PRKDC facilitates the progression of colorectal cancer through miR-198/DDR1 regulatory axis. Cancer Manag Res 2020; 12: 12853-12865.
[63] Fang G, Chen T, Mao R, Huang X and Ji L. Circular RNA circ_0089153 acts as a competing endogenous RNA to regulate colorectal cancer development by the miR-198/SUMO-specific peptidase 1 (SENP1) axis. Bioengineered 2021; 12: 5664-5678.
[64] Murakami T, Kikuchi H, Ishimatsu H, Iino I, Hirotsu A, Matsumoto T, Ozaki Y, Kawabata T, Hiramatsu Y, Ohta M, Kamiya K, Fukushima M, Baba S, Kitagawa K, Kitagawa M and Konno H. Tenascin C in colorectal cancer stroma is a predictive marker for liver metastasis and is a potent target of miR-198 as identified by microRNA analysis. Br J Cancer 2017; 117: 1360-1370.
[65] Li LX, Lam IH, Liang FF, Yi SP, Ye LF, Wang JT, Guo WW and Xu M. MiR-198 affects the proliferation and apoptosis of colorectal cancer through regulation of ADAM28/JAK-STAT signaling pathway. Eur Rev Med Pharmacol Sci 2019; 23: 1487-1493.
[66] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7-34.
[67] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.
[68] Yuan L, Xu ZY, Ruan SM, Mo S, Qin JJ and Cheng XD. Long non-coding RNAs towards precision medicine in gastric cancer: early diagnosis, treatment, and drug resistance. Mol Cancer 2020; 19: 96.
[69] Huang X, Li Z, Zhang Q, Wang W, Li B, Wang L, Xu Z, Zeng A, Zhang X, Zhang X, He Z, Li Q, Sun G, Wang S, Li Q, Wang L, Zhang L, Xu H and Xu Z. Circular RNA AKT3 upregulates PIK3R1 to enhance cisplatin resistance in gastric cancer via miR-198 suppression. Mol Cancer 2019; 18: 71.
[70] Zhou N, Wang W, Xu C and Yu W. Circular RNA PLEC acts as a sponge of microRNA-198 to promote gastric carcinoma cell resistance to paclitaxel and tumorigenesis. Pathol Res Pract 2021; 224: 153487.
[71] Quan XQ, Xie ZL, Ding Y, Feng R, Zhu XY and Zhang QX. miR-198 regulated the tumorigenesis of gastric cancer by targeting Toll-like receptor 4 (TLR4). Eur Rev Med Pharmacol Sci 2018; 22: 2287-2296.
[72] Marin-Muller C, Li D, Bharadwaj U, Li M, Chen C, Hodges SE, Fisher WE, Mo Q, Hung MC and Yao Q. A tumorigenic factor interactome connected through tumor suppressor microRNA-198 in human pancreatic cancer. Clin Cancer Res 2013; 19: 5901-5913.
[73] Shi Y, Fang N, Li Y, Guo Z, Jiang W, He Y, Ma Z and Chen Y. Circular RNA LPAR3 sponges microRNA-198 to facilitate esophageal cancer migration, invasion, and metastasis. Cancer Sci 2020; 111: 2824-2836.
[74] Wang G, Zhang ZJ, Jian WG, Liu PH, Xue W, Wang TD, Meng YY, Yuan C, Li HM, Yu YP, Liu ZX, Wu Q, Zhang DM and Zhang C. Novel long noncoding RNA OTUD6B-AS1 indicates poor prognosis and inhibits clear cell renal cell carcinoma proliferation via the Wnt/β-catenin signaling pathway. Mol Cancer 2019; 18: 15.
[75] Li J, Huang C, Zou Y, Ye J, Yu J and Gui Y. CircTLK1 promotes the proliferation and metastasis of renal cell carcinoma by sponging miR-136-5p. Mol Cancer 2020; 19: 103.
[76] Fu R, Guo C, Wang S, Huang Y, Jin O, Hu H, Chen J, Xu B, Zhou M, Zhao J, Sung SJ, Wang H, Gaskin F, Yang N and Fu SM. Podocyte activation of NLRP3 inflammasomes contributes to the development of proteinuria in lupus nephritis. Arthritis Rheumatol 2017; 69: 1636-1646.
[77] Reyes-Thomas J, Blanco I and Putterman C. Urinary biomarkers in lupus nephritis. Clin Rev Allergy Immunol 2011; 40: 138-150.
[78] Kuriakose J, Redecke V, Guy C, Zhou J, Wu R, Ippagunta SK, Tillman H, Walker PD, Vogel P and Häcker H. Patrolling monocytes promote the pathogenesis of early lupus-like glomerulonephritis. J Clin Invest 2019; 129: 2251-2265.
[79] Kaittanis C, Andreou C, Hieronymus H, Mao N, Foss CA, Eiber M, Weirich G, Panchal P, Gopal-

an A, Zurita J, Achilefu S, Chiosis G, Ponomarev V, Schwaiger M, Carver BS, Pomper MG and Grimm J. Prostate-specific membrane antigen cleavage of vitamin B9 stimulates oncogenic signaling through metabotropic glutamate receptors. J Exp Med 2018; 215: 159-175.

[80] Dupont WD, Breyer JP, Plummer WD, Chang SS, Cookson MS, Smith JA, Blue EE, Bamshad MJ and Smith JR. 8q24 genetic variation and comprehensive haplotypes altering familial risk of prostate cancer. Nat Commun 2020; 11: 1523.

[81] Ray J, Hoey C, Huang X, Jeon J, Taeb S, Downes MR, Boutros PC and Liu SK. MicroRNA-198 suppresses prostate tumorigenesis by targeting MIB1. Oncol Rep 2019; 42: 1047-1056.

[82] Ye L, Li S, Ye D, Yang D, Yue F, Guo Y, Chen X, Chen F, Zhang J and Song X. Livin expression may be regulated by miR-198 in human prostate cancer cell lines. Eur J Cancer 2013; 49: 734-740.

[83] Li Y, Luo H, Xiao N, Duan J, Wang Z and Wang S. Long noncoding RNA SChLAP1 accelerates the proliferation and metastasis of prostate cancer via targeting miR-198 and promoting the MAPK1 pathway. Oncol Res 2018; 26: 131-143.

[84] Gong TT, Guo Q, Li X, Zhang TN, Liu FH, He XH, Lin B and Wu QJ. Isothiocyanate Iberin inhibits cell proliferation and induces cell apoptosis in the progression of ovarian cancer by mediating ROS accumulation and GPX1 expression. Biomed Pharmacother 2021; 142: 111533.

[85] Xiao H, Zheng Y, Chen J and Shen H. MiR-198 inhibits proliferation, invasion and migration of ovarian cancer cells by regulating the PI3K/Akt signaling pathway. Acta Biochim Pol 2021; 68: 673-677.

[86] Chaisuparat R, Limpiwatana S, Kongpanitkul S, Yodsanga S and Jham BC. The Akt/mTOR pathway is activated in verrucous carcinoma of the oral cavity. J Oral Pathol Med 2016; 45: 581-585.

[87] Zhang LQ, Yang HQ, Yang SQ, Wang Y, Chen XJ, Lu HS and Zhao LP. CNDP2 acts as an activator for human ovarian cancer growth and metastasis via the PI3K/AKT pathway. Technol Cancer Res Treat 2019; 18: 1533033819-874773.

[88] Xu F, Ni M, Li J, Cheng J, Zhao H, Zhao J, Huang S and Wu X. Circ0004390 promotes cell proliferation through sponging miR-198 in ovarian cancer. Biochem Biophys Res Commun 2020; 526: 14-20.

[89] Matsuoka K, Bakiri L, Wolff LI, Linder M, Mikels-Vigdal A, Patiño-García A, Lecanda F, Hartmann C, Sibilia M and Wagner EF. Wnt signaling and Loxl2 promote aggressive osteosarcoma. Cell Res 2020; 30: 885-901.

[90] Rubio R, Abarrategi A, Garcia-Castro J, Martinez-Cruzado L, Suarez C, Tornin J, Santos L, Astudillo A, Colmenero I, Mulero F, Rosu-Myles M, Menendez P and Rodriguez R. Bone environment is essential for osteosarcoma development from transformed mesenchymal stem cells. Stem Cells 2014; 32: 1136-1148.

[91] Casali PG, Bielack S, Abecassis N, Aro HT, Bauer S, Biagini R, Bonvalot S, Boukovinas I, Bovee JVMG, Brennan B, Brodowicz T, Broto JM, Brugières L, Buonadonna A, De Álava E, Dei Tos AP, Del Muro XG, Dileo P, Dhooge C, Eriksson M, Fagioli F, Fedenko A, Ferraresi V, Ferrari A, Ferrari S, Frezza AM, Gaspar N, Gasperoni S, Gelderblom H, Gil T, Grignani G, Gronchi A, Haas RL, Hassan B, Hecker-Nolting S, Hohenberger P, Issels R, Joensuu H, Jones RL, Judson I, Jutte P, Kaal S, Kager L, Kasper B, Kopeckova K, Krákorová DA, Ladenstein R, Le Cesne A, Lugowska I, Merimsky O, Montemurro M, Morland B, Pantaleo MA, Piana R, Picci P, Piperno-Neumann S, Pousa AL, Reichardt P, Robinson MH, Rutkowski P, Safwat AA, Schöffski P, Sleijfer S, Stacchiotti S, Strauss SJ, Sundby Hall K, Unk M, Van Coevorden F, van der Graaf WTA, Whelan J, Wardelmann E, Zaikova O and Blay JY. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29: iv79-iv95.

[92] Georges S, Calleja LR, Jacques C, Lavaud M, Moukengue B, Lecanda F, Quillard T, Gabriel MT, Cartron PF, Baud'huin M, Lamoureux F, Heymann D and Ory B. Loss of miR-198 and -206 during primary tumor progression enables metastatic dissemination in human osteosarcoma. Oncotarget 2018; 9: 35726-35741.

[93] Lu Z, Wang C, Lv X and Dai W. Hsa_circ_0010220 regulates miR-198/Syntaxin 6 axis to promote osteosarcoma progression. J Bone Oncol 2021; 28: 100360.

[94] Thomas D and Radhakrishnan P. Tumor-stromal crosstalk in pancreatic cancer and tissue fibrosis. Mol Cancer 2019; 18: 14.

[95] Ji Y, Liu J, Zhu W and Ji J. circ_0002060 enhances doxorubicin resistance in osteosarcoma by regulating the miR-198/ABCB1 axis. Cancer Biother Radiopharm 2020; [Epub ahead of print].

[96] Eastell R, O'Neill TW, Hofbauer LC, Langdahl B, Reid IR, Gold DT and Cummings SR. Postmenopausal osteoporosis. Nat Rev Dis Primers 2016; 2: 16069.

[97] Pan Y, Shi D, Wang H, Chen T, Cui D, Cheng X and Lu Y. Automatic opportunistic osteoporosis screening using low-dose chest computed tomography scans obtained for lung cancer screening. Eur Radiol 2020; 30: 4107-4116.

[98] Sipilä S, Törmäkangas T, Sillanpää E, Aukee P, Kujala UM, Kovanen V and Laakkonen EK. Muscle and bone mass in middle-aged women: role of menopausal status and physical activity. J Cachexia Sarcopenia Muscle 2020; 11: 698-709.
[99] Chen LR, Ko NY and Chen KH. Medical treatment for osteoporosis: from molecular to clinical opinions. Int J Mol Sci 2019; 20: 2213.
[100] Liu M, Meng Y, He K and Luan C. Hsa_circ_0002060 knockdown ameliorates osteoporosis by targeting MiR-198-5p. Biol Pharm Bull 2021; 44: 88-95.
[101] Lim H, Devesa SS, Sosa JA, Check D and Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974-2013. JAMA 2017; 317: 1338-1348.
[102] Valvo V and Nucera C. Coding molecular determinants of thyroid cancer development and progression. Endocrinol Metab Clin North Am 2019; 48: 37-59.
[103] Huang LL, Wang Z, Cao CJ, Ke ZF, Wang F, Wang R, Luo CQ, Lu X and Wang LT. AEG-1 associates with metastasis in papillary thyroid cancer through upregulation of MMP2/9. Int J Oncol 2017; 51: 812-822.
[104] Fusco A, Chiappetta G, Hui P, Garcia-Rostan G, Golden L, Kinder BK, Dillon DA, Giuliano A, Cirafici AM, Santoro M, Rosai J and Tallini G. Assessment of RET/PTC oncogene activation and clonality in thyroid nodules with incomplete morphological evidence of papillary carcinoma: a search for the early precursors of papillary cancer. Am J Pathol 2002; 160: 2157-2167.
[105] Zhu L, Li XJ, Kalimuthu S, Gangadaran P, Lee HW, Oh JM, Baek SH, Jeong SY, Lee SW, Lee J and Ahn BC. Natural killer cell (NK-92MI)-based therapy for pulmonary metastasis of anaplastic thyroid cancer in a nude mouse model. Front Immunol 2017; 8: 816.
[106] Liu W, Zhao J, Jin M and Zhou M. circRAPGEF5 contributes to papillary thyroid proliferation and metastatis by regulation miR-198/FGFR1. Mol Ther Nucleic Acids 2019; 14: 609-616.
[107] Li S, Yang J, Liu X, Guo R and Zhang R. circITGA7 functions as an oncogene by sponging miR-198 and upregulating FGFR1 expression in thyroid cancer. Biomed Res Int 2020; 2020: 8084028.
[108] Karbownik A, Sobańska K, Płotek W, Grabowski T, Klupczynska A, Plewa S, Grześkowiak E and Szałek E. The influence of the coadministration of the p-glycoprotein modulator elacridar on the pharmacokinetics of lapatinib and its distribution in the brain and cerebrospinal fluid. Invest New Drugs 2020; 38: 574-583.
[109] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.
[110] Zhou SY, Chen W, Yang SJ, Xu ZH, Hu JH, Zhang HD, Zhong SL and Tang JH. The emerging role of circular RNAs in breast cancer. Biosci Rep 2019; 39: BSR20190621.
[111] Niu L, Zhou Y, Zhang W and Ren Y. Long noncoding RNA LINC00473 functions as a competing endogenous RNA to regulate MAPK1 expression by sponging miR-198 in breast cancer. Pathol Res Pract 2019; 215: 152470.
[112] Deng Y, Zhu H, Xiao L, Liu C and Meng X. Circ_0005198 enhances temozolomide resistance of glioma cells through miR-198/TRIM14 axis. Aging (Albany NY) 2020; 13: 2198-2211.
[113] Bian D, Wu Y and Song G. Novel circular RNA, hsa_circ_0025039 promotes cell growth, invasion and glucose metabolism in malignant melanoma via the miR-198/CDK4 axis. Biomed Pharmacother 2018; 108: 165-176.
[114] Wang R, Shen J, Wang Q and Zhang M. Bortezomib inhibited the progression of diffuse large B-cell lymphoma via targeting miR-198. Biomed Pharmacother 2018; 108: 43-49.
[115] Nie E, Jin X, Wu W, Yu T, Zhou X, Shi Z, Zhang J, Liu N and You Y. MiR-198 enhances temozolomide sensitivity in glioblastoma by targeting MGMT. J Neurooncol 2017; 133: 59-68.