Am J Transl Res 2023;15(11):6342-6361
www.ajtr.org /ISSN:1943-8141/AJTR0151752

Review Article

Role of microRNA-494 in tumor progression

Amirhosein Maharati[1], Iman Akhlaghipour[1], Negin Taghehchian[2], Zahra Farshchian Yazdi[3], Meysam Moghbeli[2]

[1]*Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;* [2]*Department of Medical Genetics and Molecular Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;* [3]*Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*

Received June 13, 2023; Accepted October 26, 2023; Epub November 15, 2023; Published November 30, 2023

Abstract: Various progresses in tumor therapy during the recent decades have significantly reduced the cancer related deaths globally. However, there is still a high rate of mortality in these patients. The early stage tumors have no aggressive and clear clinical symptoms in the majority of cancer types, which causes a high rate of therapeutic failure in advanced tumor stages. Therefore, identification of the molecular tumor biology can be promising to introduce the early diagnostic markers. MicroRNAs (miRNAs) are the key regulators of cellular processes that can also be involved in tumor progression as tumor-suppressor or oncogene. Due to the high stability of miRNAs in body fluids, they can be used as the non-invasive diagnostic tumor markers. In the present review, we discussed the role of miR-494 in tumor progression. It has been shown that miR-494 has mainly a tumor suppressor function by regulation of transcriptional and structural factors and signaling pathways such as transforming growth factor-β (TGF-β), WNT, and Janus kinase (JAK)-signal transducer and activator of transcription (STAT). The phosphatase and tensin homolog/phosphoinositide 3-kinase (PTEN/PI3K) axis has been also reported as the main target of miR-494 as an oncogene. These findings suggest that miR-494 is a non-invasive diagnostic marker for the early diagnosis and therapeutic management of cancer patients.

Keywords: MicroRNA-494, cancer, diagnosis, non-invasive, marker

Introduction

Cancer has been considered as one of the leading causes of human deaths worldwide during the recent decades [1]. Various therapeutic and diagnostic strategies have been introduced for the cancer patients [2, 3]. However, there is still a high rate of mortality in cancer patients that is mainly associated with late diagnosis. Therefore, a detailed understanding about the molecular tumor biology can be promising to suggest the efficient diagnostic markers for the early detection of cancer. MicroRNAs (miRNAs) are important post-transcriptional regulators that function through the translational repression or mRNA degradation [4, 5]. A single miRNA simultaneously regulates the expression of dozens of target mRNAs [6]. MiRNAs have regulatory roles in cell proliferation, apoptosis, and migration [7]. Aberrant expression of miRNAs has been frequently reported in various tumor types [8-10]. This highlights the therapeutic and diagnostic values of the miRNAs in cancer patients [11-13]. The sensitivity of detection techniques has improved during the recent years in which the sample types have expanded from formalin-fixed paraffin/fresh frozen tissues to miRNAs in body fluids [14-16]. Circulating miRNAs have a high stability in body fluids by binding with the high-density lipoproteins (HDL) or argonaute proteins that make them the potential non-invasive diagnostic biomarkers for cancer [11, 17, 18]. MiR-494 is located on human chromosome 14q32.31 [19]. Aberrant expression of miR-494 has been observed in different stages of tumor progression [20]. MiR-494 has been introduced as an oncogene [21-23] or tumor suppressor in different tumor types [24-27]. Therefore, the present review aimed to investigate the role of miR-494 during tumor progression to suggest it as a novel reliable non-invasive marker for the diag-

nostic and prognostic purposes among cancer patients (**Table 1**).

PI3K/AKT signaling pathway

PI3K/AKT is a pivotal signaling pathway in modulation of cell survival, differentiation, and apoptosis [28]. MiR-494 has an important role in tumor progression via regulation of PI3K/AKT pathway (**Figure 1**). Phosphatase and tensin homolog (PTEN) is a lipid phosphatase that inhibits tumor progression through the suppression of PI3K/AKT pathway [29]. There were significant miR-494 up regulations in glioblastoma (GBM) cells and tissues. MiR-494-3p promoted GBM cell proliferation and invasion while suppressed apoptosis through PTEN inhibition [30]. There were significant miR-494-3p up regulations in endometrial, colorectal, glioma, cervical, and hepatocellular cancer tissues that contributed to poor prognosis. MiR-494-3p enhanced the cell proliferation and invasion by PTEN targeting [31-35]. Long non-coding RNAs (lncRNAs) have a dual function during tumorigenesis as oncogene or tumor suppressor [36-38]. The reduced MEG3 expression and reverse correlation with VEGF expression implied that MEG3 negatively regulated the proliferation of Hemangioma (HA) cells. MEG3 suppressed cell proliferation, colony formation, and tumorigenesis in HAs xenograft model. MEG3 reduced tumor cell proliferation via VEGF and CCND1 inhibition in HAs cells. MEG3 reduced HA progression by miR-494 sponging and regulation of PTEN/PI3K/AKT axis [39]. There were significant circSLC8A1 down regulations in bladder cancer tissues and cell lines that was positively associated with the clinical stage and grade. CircSLC8A1 reduced the bladder tumor progression by regulation of miR-494/PTEN axis [40]. There was circ-0000317 down regulation in non-small-cell lung cancer (NSCLC) tissues and cells that was correlated with poor prognosis. Circ-0000317 reduced NSCLC growth via miR-494-3p/PTEN pathway [41]. WT1-AS also inhibited NSCLC growth and aggressiveness while promoted the apoptosis via miR-494-3p/PTEN axis [42].

Receptor tyrosine kinases (RTKs) are the important upstream mediators for the PI3K/AKT cascade [43]. The classical PI3K signaling pathway is activated through RTKs following the growth factors binding [44]. Insulin like growth factor 1 receptor (IGF1R) is a RTK that has key roles in tumor progression [45, 46]. CircVAPA promoted the progression of small cell lung cancer (SCLC) via miR-494-3p/IGF1R axis and PI3K/AKT pathway activation [47]. IGF1R is involved in the EGFR-TKIs resistance of NSCLC cells [48]. MiR-494 down regulation has been found in gastric cancer (GC) tissues and cell lines. MiR-494 suppressed GC cell proliferation and migration by IGF1R targeting [48]. HER2 up regulation has been observed in more than 15% of GC patients that was correlated with poor prognosis [49-54]. Lapatinib is a potent ATP-competitive inhibitor that inhibits the tyrosine kinases, including HER2 and EGFR1 [55]. Fibroblast growth factor receptor 2 (FGFR2) is a RTK that is activated in various cancers through gene amplification, translocations, and point mutations [56]. FGFR2 is directly correlated with poor prognosis in GC patients [57, 58]. There were significant FGFR2 up-regulations in GC tumor tissues. FGFR2 increased the p-MET, p-HER3, and p-Stat3 expression in the HER2-positive GC cells. MiR-494 decreased lapatinib resistance GC cells via FGFR2 targeting [59]. MiR-494 inhibited the OC cell proliferation and apoptosis by FGFR2 targeting [60]. There was SBF2-AS1 up regulation in diffuse large B-cell lymphoma (DLBCL) tissues. SBF2-AS1 triggered DLBCL tumorigenesis and cell growth by regulating the miR-494-3p/FGFR2 axis [61]. KIT is also an oncogenic RTK that takes part in the PI3K/AKT, MAPK, and JAK-STAT signaling pathways [62-64]. It has been demonstrated that miR-494 modulated the p-AKT and p-STAT3 expressions via mutant KIT down regulation. Additionally, miR-494 suppressed proliferation of gastrointestinal stromal tumor (GIST) cells through KIT targeting [65].

Epithelial-mesenchymal transition (EMT) induces self-renewal features and tumor cell invasion in several cancers [66, 67]. Chemokine receptors (CXCR) have pivotal roles in tumor biology and progression [68-76]. Stromal cell-derived factor 1 (SDF-1) promotes metastasis and angiogenesis in breast cancer by establishing an immunosuppressive tumor microenvironment through CXCR4 activation [77]. MAPK and PI3K/AKT signaling pathways can be triggered by SDF-1/CXCR4 axis during tumor progression. MiR-494-3p inhibited the prostate tumor cell proliferation and invasion by CXCR4

Table 1. Molecular targets of miR-494 during tumor progressions

Study	Year	Type	Target gene	Samples	Function	Clinical application
PI3K/AKT signaling pathway						
Yuan [26]	2016	Epithelial Ovarian Cancer	C-MYC	15TN* tissues SKOV3 and HO8910 cell lines	Tumor suppressor	Diagnosis
Zhao [27]	2016	Gastric cancer	IGF1R	25TN tissues BGC823 and SGC7901 cell lines	Tumor suppressor	Diagnosis
Li [30]	2015	Glioblastoma	PTEN	72 patients 8 controls U87MG and U251MG cell lines	Oncogene	Diagnosis
Zhu [31]	2019	Endometrial cancer	PTEN	43TN tissues HHUA and JEC cell lines	Oncogene	Diagnosis
Lin [32]	2018	Hepatocellular carcinoma	PTEN	271TN tissues SMMC-7721, Huh7, HCC-LM3, HepG2, Hep3B and THLE-3 cell lines	Oncogene	Diagnosis and Prognosis
Sun [33]	2014	Colorectal cancer	PTEN	247TN tissues SW620, SW480, HCT116 cell lines	Oncogene	Diagnosis and Prognosis
Yang [34]	2015	Cervical cancer	PTEN	89TN tissues HeLa, C33A, Caski and SiHa cell lines	Oncogene	Diagnosis and Prognosis
Han [35]	2019	Glioma cancer	PTEN	58T 28N blood U251 cell line	Oncogene	Diagnosis
Dai [39]	2018	Hemangiomas	PTEN	30T 15N tissues HDEC and CRL-2586 EOMA cell lines	Oncogene	Diagnosis
Lu [40]	2019	Bladder cancer	PTEN	70TN tissues 5637, T24, J82, EJ, UMUC, and RT4 cell lines	Oncogene	Diagnosis and Prognosis
Xia [41]	2022	Non-small cell lung cancer	PTEN	67TN tissues A549, H460, PC9, H1299, and SPC-A1 cell lines	Oncogene	Diagnosis and Prognosis
Wu [42]	2021	Non-Small Cell Lung Cancer	PTEN	A549, NCI-H1975, SK-MES-1 cell lines	Oncogene	Diagnosis
Hua [47]	2022	Small cell lung cancer	IGF1R	6TN tissues 36T 118N serum H69, DMS79, H82, DMS273, H446, H526, HCC827, and PC9 cell lines	Tumor suppressor	Diagnosis
Yu [59]	2018	Gastric cancer	FGFR2	6TN tissues YCC1 and YCC1-F cell lines	Tumor suppressor	Diagnosis
Zhao [60]	2016	Ovarian cancer	FGFR2	25TN tissues ES2, HO8910, OVCAR3, A2780, SKOV3, and HeLa cell lines	Tumor suppressor	Diagnosis
Fu [61]	2021	Diffuse large B-cell lymphoma	FGFR2	50TN tissues OCI-LY-3, OCI-LY-7, OCI-LY-10, SU-DHL-4 and SU-DHL-6 cell lines	Tumor suppressor	Diagnosis
Kim [65]	2011	Gastrointestinal Stromal Tumor	KIT	31TN tissues GIST882, SNU216, SNU638, SNU1, NCI-N87, DLD-1, and HeLa cell lines	Tumor suppressor	Diagnosis

Song [78]	2015	Breast cancer	CXCR4	MDA-MB-231, MCF-7, MDA-MB-468, MDA-MB-435, T47D, BT-474, SK-BR-3, ZR-75-30 cell lines	Tumor suppressor	Diagnosis
MAPK signaling pathway						
Ou-Yang [84]	2018	Glioblastoma	SOCS6	U87MG and U118MG cell lines	Tumor suppressor	Diagnosis
Cheng [85]	2018	Cervical cancer	SOCS6	40TN tissues HeLa cell line	Tumor suppressor	Diagnosis and Prognosis
Yang [87]	2022	Acute lymphoblastic leukemia	NET1	30T 30N tissues Kasumi-1 and KG-1 cell lines	Tumor suppressor	Diagnosis
WNT signaling pathway						
Li [92]	2014	Pancreatic Ductal Adenocarcinoma	FOXM1	10TN tissues AsPC-1 and PANC-1 cell lines	Tumor suppressor	Diagnosis and Prognosis
JAK/STAT and TGF-β signaling pathways						
Jiang [99]	2021	Prostate cancer	STAT3	22TN tissues VCaP, LNCaP, 22RV1, PC3, and DU145 cell lines THP-1 cells	Tumor suppressor	Diagnosis
Yang [108]	2022	Esophageal squamous cell carcinoma	TGIF1	79TN tissues EC9706, Eca109, TE-1, and KYSE-150 cell lines	Tumor suppressor	Diagnosis and Prognosis
Transcription factors						
Libório-Kimura [128]	2015	Oral cancer	HOXA10	17T 3N tissues SCC-25, CAL 27, and FaDu cell lines	Tumor suppressor	Diagnosis
Liu [132]	2015	Pancreatic cancer	SIRT1, C-MYC	86T 41N tissues AsPC-1, BXPC-3, SW1990, MIAPaCa-2, PANC-1	Tumor suppressor	Diagnosis and Prognosis
He [133]	2014	Gastric carcinoma	C-MYC	56TN tissues SGC7901, MKN45 and AGS cell lines	Tumor suppressor	Diagnosis
He [135]	2018	Nasopharyngeal carcinoma	SOX7	30T 13N tissues S18, S26, CNE-1, CNE-2, HONE-1, and 5-8F cell lines	Oncogene	Diagnosis
Li [136]	2015	Chondrosarcoma	SOX9	71T 71 corresponding benign chondroma SW1353, JJ012 cell lines	Tumor suppressor	Diagnosis and Prognosis
Apoptosis and drug response						
Xu [153]	2018	Gastric Cancer	SURVIVIN	30TN tissues BGC-823 and MGC-803 cell lines	Tumor suppressor	Diagnosis
Gao [156]	2020	Osteosarcoma	ASK1	87T 100N blood MG-63 cell line	Tumor suppressor	Diagnosis and Prognosis
Zhang [165]	2019	Non-small cell lung cancer	CASP2	A549 and H460 cell lines	Oncogene	Diagnosis
Zhang [175]	2015	Esophageal Squamous Cell Carcinoma	CLPTM1L	37TN tissues EC9706 and KYSE30 cell lines	Tumor suppressor	Diagnosis

Chang [180]	2022	Esophageal Squamous cell carcinoma	LASP1	60T tissues KYSE150, ECA109, TE1, and KYSE410 cell lines	Tumor suppressor	Diagnosis
Chai [182]	2015	Colon cancer	DPYD	HCT116, HCT15, HCT8, HT-29, LOVO, SW480 and SW620 cell lines	Tumor suppressor	Diagnosis
Wei [189]	2021	Osteosarcoma	TGM2	63TN tissues U2OS and HOS cell lines	Tumor suppressor	Diagnosis
Structural factors						
Nie [193]	2016	Nasopharyngeal carcinoma	GALNT7	CNE2, 6-10B, and 9-4E cell lines	Tumor suppressor	Diagnosis
Yang [209]	2018	Pancreatic cancer	SDC1	42T 42N ASPC-1, SW1990, BXPC-3, CFPAC-1 and PANC-1 cell lines	Tumor suppressor	Diagnosis
Liu [213]	2019	Cholangiocarcinoma	WDHD1	135T 34N tissues QBC939 and RBE cell lines	Tumor suppressor	Diagnosis

* T: tumor tissues; N: normal margins.

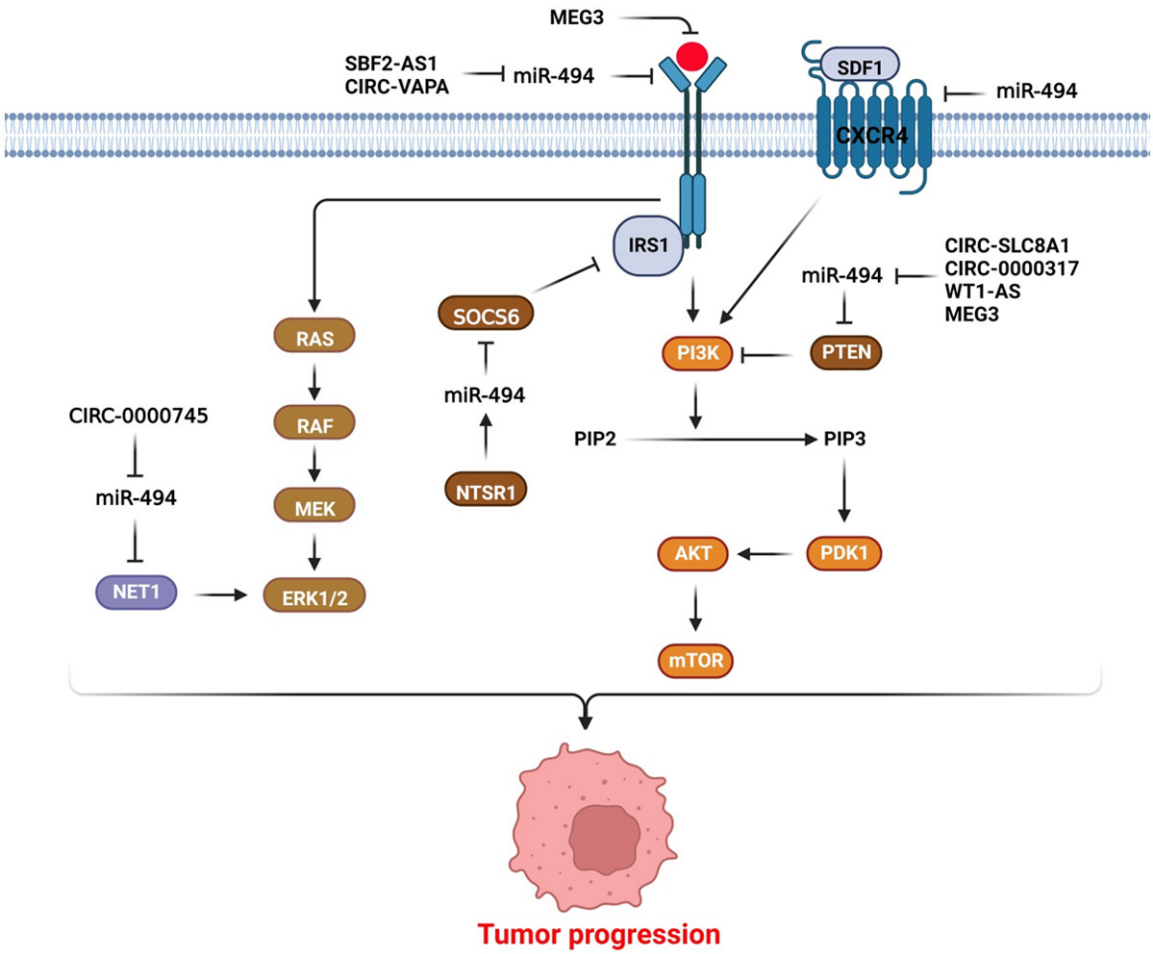

Figure 1. Role of miR-494 during tumor progression by regulation of PI3K/AKT and MAPK signaling pathway (Created with BioRender.com).

targeting [20]. MiR-494 inhibited the EMT by cadherin 1 (CDH1) up regulation, while CDH2, VIM, and α-SMA down regulations in breast tumor cells. It reduced breast tumor progression by CXCR4 targeting [78].

MAPK signaling pathway

Mitogen-activated protein kinase (MAPK) singling pathway can also be one of the miR-494 targets during tumor progression (**Figure 1**). Stimulation of neurotensin receptor 1 (NTSR1) activates extracellular signal-regulated kinase (ERK1/2), Rho GTPases, and focal adhesion kinase, which triggers tumor development [79, 80]. Activation of NTSR1 signaling regulates cell proliferation, apoptosis, and self-renewal of glioma cells [81-83]. It has been shown that inhibition of NTSR1 suppressed glioblastoma invasion. NTSR1 induced miR-494 expression via Jun transcription factor. MiR-494 was a vital regulator of the tumor cell invasion in glioblastoma cells through NTSR1 targeting. NTSR1 down regulated the suppressor of cytokine signaling 6 (SOCS6) by up regulating miR-494. SOCS6 was shown to be involved in the invasion of glioblastoma cells through NTSR1 targeting [84]. There was miR-494 down regulation in cervical cancer tissue that was correlated with prognosis in patients. MiR-494 reduced growth and invasion in cervical cancer cells via SOCS6 targeting [85]. Neuroepithelial cell transforming 1 (NET1) belongs to the Ras homolog family member A (RhoA) that regulates the ERK1/2 and PI3K/Akt1 pathways [86]. There were circ-0000745 up regulations in acute lymphoblastic leukemia (ALL) patients and cell lines. Circ_0000745 promoted cell cycle while suppressing apoptosis in ALL cells via miR-494-3p/NET1 targeting [87].

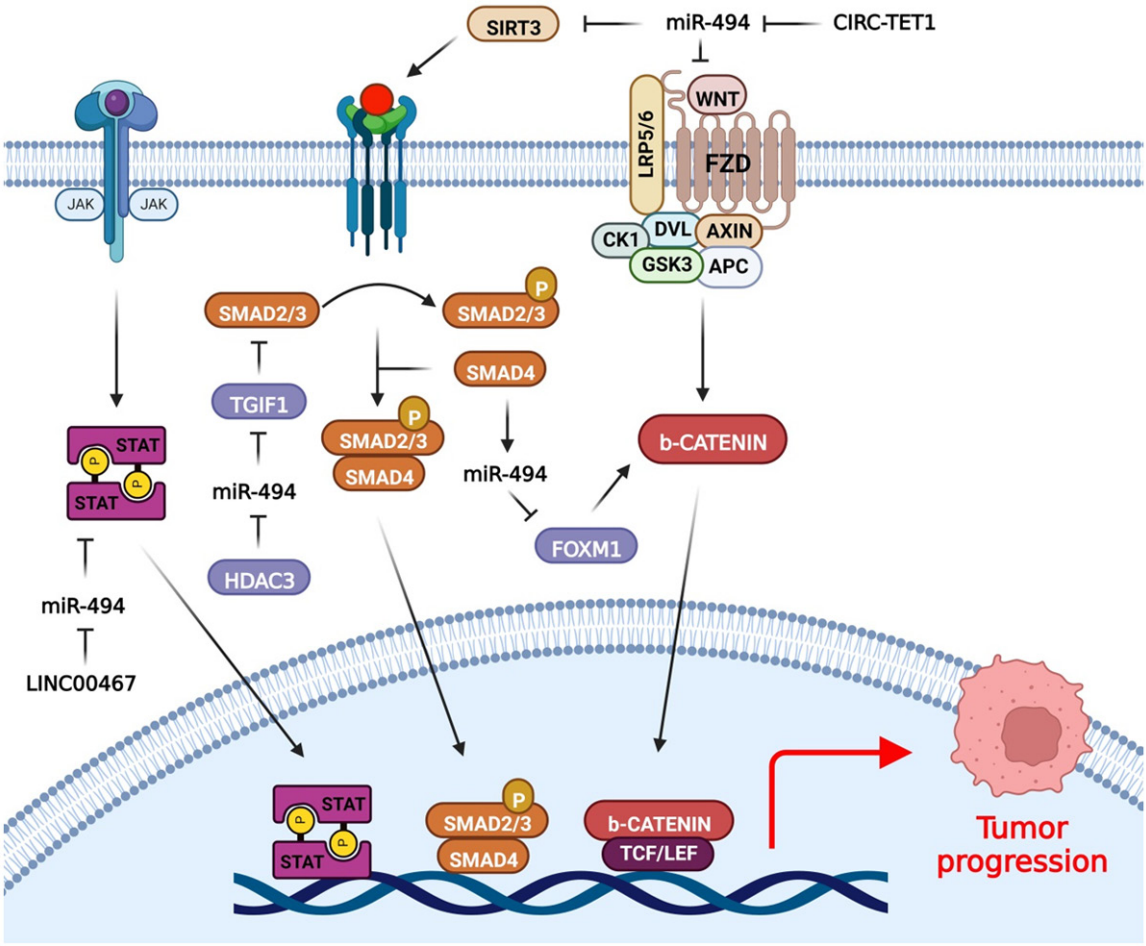

Figure 2. Role of miR-494 during tumor progression by regulation of WNT, TGF-β, and JAK/STAT signaling pathways (Created with BioRender.com).

WNT signaling pathway

Wnt/β-catenin is a key signaling pathway during tumorigenesis [88]. Wnt signaling includes a series of cascades initiating from Wnt ligands binding to the cell surface receptors that leads to cytoplasmic β-catenin stabilization. Subsequently, β-catenin enters the nucleus to regulate the WNT target genes such as cyclin D1 (CCND1) and c-MYC by interaction with T-cell factor/lymphoid enhancer factor (TCF/LEF) transcriptional complex [89, 90]. MiR-494 has pivotal roles in tumor progression by regulation of WNT signaling pathway (**Figure 2**). Forkhead box M1 (FOXM1) regulates stabilization and activation of β-catenin and has a critical role in tumor biology [91]. It has been shown that miR-494 was negatively associated with FOXM1/β-catenin in pancreatic ductal adenocarcinoma (PDAC) cells. MiR-494 was down regulated by the Smad4 knockdown. Therefore, the Smad4/miR-494/FOXM1/β-catenin axis had an important impact on pathogenesis of PDAC. MiR-494 inhibited stemness, metastasis, and progression of PDAC cells and increased gemcitabine sensitivity in PDAC cells. Knockdown of Smad4 down regulated the miR-494, suggesting that TGF-β/Smad signaling is a modulator of the miR-494 expression and FOXM1/β-catenin pathway. MiR-494 negatively regulated β-catenin signaling pathway via FOXM1 down regulation that reduced PDAC cell growth and invasion [92]. The significant up-regulation of miR-494-3p and down-regulation of circTET1 have been reported in retinoblastoma (RB) cells. CircTET1 improved the malignant potential of RB by targeting miR-494-3p and Wnt/β-catenin pathway [93].

JAK/STAT and TGF-β signaling pathways

The canonical JAK/STAT signaling pathway can be activated following the interaction between

the JAK tyrosine kinases and cytokine receptors [94]. Trans-phosphorylation of JAKs is crucial for the recruitment of phosphorylated signal transducer and activator of transcription (STATs) that finally enter the nucleus and regulate the expression of several genes involved in apoptosis, cell proliferation, and metastasis. MiR-494 plays an important role in tumor progression by regulation of JAK/STAT signaling pathway (**Figure 2**). Tumor-associated macrophages (TAMs) are one of the most common immune cells in solid tumors that are associated with tumor progression, drug resistance, and poor prognosis [95]. Macrophages are classified into two phenotypes, M1 (pro-inflammatory) and M2 (anti-inflammatory). TAMs as M2-like macrophages are highly associated with cancer progression [96-98]. There were LINC00467 up regulations in PC tissues and cell lines. The M2-like macrophages had higher LINC00467 expression levels than M1-like or unpolarized macrophages. Silencing of LINC00467 significantly reduced the expression of M2-like macrophage markers. Down regulation of LINC00467 inhibited the STAT3 pathway. LINC00467 induced PCa progression through miR-494-3p/STAT3 axis and M2 macrophage polarization [99]. Cyclin dependent kinase 6 (CDK6) is involved in G1/S transition [100]. There were X-inactive specific transcript (XIST) up regulations in esophageal carcinoma (EC) tissues and cells. XIST inhibition significantly suppressed EC cell proliferation, while stimulated apoptosis. XIST sponged miR-494 that subsequently decreased the invasion of EC cells via CDK6 targeting. CDK6 knockdown also suppressed the JAK2/STAT3 pathway. MiR-494 inhibition increased the level of p-JAK2 and p-STAT3 expression. The p-JAK2 and p-STAT3 expressions were reduced by the suppression of miR-494 and CDK6 co-transfection. Therefore, miR-494/CDK6 enhanced EC progression through JAK2/STAT3 activating [101]. Histone deacetylases (HDACs) are the key proteins in chromatin remodeling that remove the acetyl groups in histone and non-histone proteins [102]. HDAC inhibitors have been reported as epigenetic therapeutic targets for treating various cancers [103-105]. TG-interacting factor 1 (TGIF1) belongs to the TALE superfamily that acts as a component of a ubiquitin ligase complex [106]. It plays a vital role in promoting the degradation of Smad2 in a ubiquitin-dependent manner [107]. Inhibition of HDAC3 up regulated miR-494 and down regulated the TGIF1 to activate the TGF signaling pathway, which reduced the malignant characteristics of ESCC cells [108].

Endothelial to mesenchymal transition (EndMT) is a crucial process that plays a critical role in metastasis and tumor growth. This process increases tumor cell invasion and migration by up regulation of mesenchymal markers while reducing the expression of epithelial markers [109-116]. It involves the loss of endothelial phenotypes and the acquisition of mesenchymal characteristics. In addition, EndMT induces the expression of mesenchymal cell markers (Smad3, α-SMA, and FSP-1) and reduces the endothelial markers (CD31 and VE-cadherin) and cell-cell junctions [117-119]. TGF-β signaling is activated through the interaction of TGF-β to its ser/thr kinase receptors that results in Smad2/3/4 interaction. Subsequently, Smad complex transport into the nucleus to modulate transcription of the TGF-β target genes [120]. MiR-494 is a key regulator of TGF-β signaling pathway during tumor progression (**Figure 2**). Sirtuin3 (SIRT3) is a histone deacetylase that is essential for tumor progression [121]. There was miR-494 up-regulation in hepatocellular carcinoma (HCC) compared with the normal tissues. MiR-494 induced cell proliferation and migration by up regulation of mesenchymal markers, including α-smooth muscle actin (α-SMA), SMAD3, and p-SMAD3 in HCC cells. Suppression of miR-494 also significantly up regulated the SIRT3 and TGF-β, while inhibited mesenchymal cell markers in the animal model. Therefore, miR-494 has a crucial role in regulating EndMT and the progression of HCC cells via SIRT3/TGF-β/SMAD axis [122].

Transcription factors

Homeobox (HOX) is an evolutionarily conserved transcription factor family that has a critical role in progression of normal cells to neoplastic state via regulation of the cellular pathways and apoptosis [123-126]. They have been also implicated in DNA and histone methylation that can be associated with the epigenetic modulation of several cancer-related genes [127]. There were HOXA10 up-regulation and miR-494 down-regulation in oral squamous cell carcinoma (OSCC) cells which were associated with advanced tumor stages. HOXA10 expres-

sion was also associated with tumor size, TNM stage, and aggressiveness of OSCC. MiR-494 significantly inhibited the OSCC cell proliferation by HOXA10 targeting [128]. C-Myc is a transcription factor that is involved in cell proliferation, differentiation, EMT, and angiogenesis [129-131]. There was significant down-regulation of miR-494 in pancreatic cancer (PC) tissues that was correlated with tumor size, age, TNM stage, distant metastasis, and lymphatic invasion. The expression of miR-494 was associated with decreased CCND1 and increased p21, which remarkably induced G1 phase arrest. MiR-494 suppressed migration and invasiveness of pancreatic cancer cells via down regulation of matrix metalloproteinase-2 (MMP-2) and MMP-9. It also inhibited the proliferation and chemo resistance of PC cells by c-Myc and SIRT1 targeting [132]. MiR-494 reduced ovarian tumor cell proliferation by c-Myc targeting [26]. There was also miR-494 down regulation in GC, and miR-494 reduced the GC cell proliferation via c-Myc targeting [133]. SRY-box transcription factor 7 (SOX7) is a transcription factor involved in hematopoiesis and angiogenesis [134]. MiR-494-3p has been found to increase cell proliferation and migration in nasopharyngeal carcinoma (NPC) cells via SOX7 targeting [135]. There were miR-494 down regulations in chondrosarcoma tissues that was correlated with poor survival and prognosis. MiR-494 suppressed the progression and invasion of chondrosarcoma cells by SOX9 targeting [136]. The ubiquitination proteasome system is the crucial process responsible for intracellular protein breakdown [137]. Y-box binding protein 1 (YBX1) is a transcription factor that is involved in regulation of drug resistance and cell proliferation [138]. It has been shown as a crucial regulator of EMT via Snail1 and hypoxia-inducible-factor 1A (HIF1A) up regulations [139]. Activating transcription factor 3 (ATF3) is a negative modulator of cellular antiviral signaling, inflammatory responses, and autophagy in mammalian cells [140]. There was Linc01612 down regulation in HCC tissues in comparison with normal controls that contributed to poor prognosis. Linc01612 sponged the miR-494 to up regulate ATF3 that results in inhibition of p53 ubiquitination by ATF3. Linc01612 also interacted with YBX1 and promoted its ubiquitin-mediated degradation in p53-deficient HCC cells. Moreover, the YBX1 mediated pathway was suppressed in HCC cells expressing p53 [141].

Apoptosis and drug response

Surgery is the most beneficial therapy in the early stages of GC; however, advanced GC patients have fewer therapeutic alternatives. Since the advanced gastric tumors are unresectable, systemic therapy is the only therapeutic choice [142-145]. Tumor cells usually acquire resistance against anti-tumor drugs [146, 147]. TNF-related apoptosis-inducing ligand (TRAIL) interacts with death receptors to activate procaspase-8 to establish the death-inducing signaling complex (DISC). Subsequently, mitochondrial apoptosis occurs as a result of caspase-8 activation [147-149]. Survivin belongs to the inhibitor of apoptosis protein (IAP) family that suppresses the release of mitochondrial cytochrome c and the activation of CASP9 and CASP3 [150-152]. MiR-494 sensitized the GC cells to TRAIL treatment via Survivin targeting [153]. Apoptosis signal-regulating kinase 1 (ASK-1) phosphorylation is a crucial part of TNF-α-induced apoptosis pathway. The interaction of STRAP and 14-3-3 proteins with ASK1 impairs the correlation of TRAF2 and ASK-1 that leads in suppression of TNF-α-induced apoptosis [154, 155]. There were miR-494 down regulations in osteosarcoma (OS) tissues and serums that were inversely associated with TNM stage. MiR-494 triggered the TNF-α/ASK1 mediated apoptosis and inhibited the OS cell proliferation by suppressing the ASK-1/STRAP/14-3-3 axis. A significant higher mortality was also observed in OS patients with miR-494 under expression in both tissues and serum [156]. Protein arginine methyltransferase 1 (PRMT1) is an arginine methyl transferase that is essential for the methylation of Arg3 on H4 tail peptides. It catalyzes the ASK1 methylation that leads to chemo resistance. PRMT1 functions as oncogenes in several cancers [157]. PRMT1 was also known as a suppressive marker for regulating TNFα/NF-κB response through the RelA methylation [158]. In addition, PRMT1 mediates methylation of enhancer of zeste homolog 2 (EZH2) to trigger its stability that stimulates tumor cell metastasis [159]. It has been determined that there was NNT-AS1 up regulation in glioma tissues that was correlated with early tumor stage. The suppression of NNT-AS1 significantly reduced proliferation

and invasion of glioma cells via miR-494-3p/PRMT1 axis [160]. CASP2 belongs to the cysteine protease family that functions as a tumor suppressor [161, 162]. It mediates apoptosis through oxidative stress, cytoskeleton degradation, and heat shock [163]. CASP2 is a negative regulator of autophagy through the modulation of reactive oxygen species (ROS). Down regulation of CASP2 regulates the FOXO3 to down regulate the superoxide dismutase-2 (SOD2) [164]. It has been shown that miR-494 increased the NSCLC cell proliferation while decreased their sensitivity to CDDP-induced apoptosis through CASP2 inhibition [165].

Cisplatin (CDDP) is a first-line medication used to treat several human malignancies [166]. On the other hand, the CDDP resistance significantly affects the therapeutic efficacy of ESCC patients [167]. Cleft lip and palate transmembrane protein 1-like (CLPTM1L) is an inhibitor of mitochondrial related apoptosis via Bcl-xL stimulation. It has also a key role in chemotherapeutic resistance and tumorigenesis via Bcl-xL up regulation [168, 169]. CLPTM1L stimulates apoptosis in DDP-sensitive cells and is contributed with an increased risk of tumor progression in different cancers [170-172]. CLPTM1L conferred resistance to chemotherapeutic mediated apoptosis by Bcl-xL up regulation [173, 174]. MiR-494 reduced the ESCC cell aggressiveness while increased apoptosis through CLPTM1L targeting [175]. LIM and SH3 protein 1 (LASP1) is an actin-binding protein that is deregulated in various cancers [176, 177]. The association between LASP1 and CDDP resistance has also been reported in several human cancers [178, 179]. Circ-0007142 inhibition promoted CDDP sensitivity by miR-494-3p/LASP1 in ESCC cells [180]. Dihydropyrimidine dehydrogenase (DPYD) is a regulatory enzyme in the 5-Fu catabolic pathway. The conventional 5-Fu dosage has a higher risk of fatal effects in patients with poor DPYD function [181]. MiR-494 increased the 5-Fu sensitivity by DPYD targeting in CRC cells [182]. Transglutaminase 2 (TGM2) is involved in the tumor cell growth, apoptosis, metastasis, and chemo resistance [183-186]. It inhibits tumor cell apoptosis through the Bax regulation and cytochrome C release following the hypoxia [187]. Silencing of TGM2 could promote chemo sensitivity in cancer cells by the inhibition of Akt and MAPK pathways [188]. There was circ-0081001 up regulation in osteosarcoma (OS) tissues that was correlated with methotrexate (MTX) resistance. Inhibition of circ-0081001 enhanced MTX sensitivity in MTX-resistant OS cells through modulating miR-494-3p and TGM2 expression [189].

Structural factors

Polypeptide-N-acetyl-galactosaminlytransferase 7 (GALNT7) is a member of the acetyl-galactosaminyl-transferase family that binds through N-acetylgalactosamine to the serine or threonine residues of its target proteins [190]. It catalyzes the O-GlcNAcylation of proteins as a crucial step in many biological processes [191]. Aberrant glycosylation is closely associated with cell growth, division, adhesion, and tumorigenesis [192]. It was also reported that miR-494 suppressed the NPC cell in-vivo growth via GALNT7 targeting [193].

EMT is a cellular process in which epithelial cells obtain mesenchymal characteristics [194-198]. Syndecan-1 (SDC1) is a crucial protein involved in the maintenance of cell morphology and tumor progression [199, 200]. It regulates the intercellular adhesion and activation of growth factor receptors via its heparan sulfate side chains [201]. SDC1 also increases tumor cell invasion via MMP-9 regulation by nuclear factor kappa B (NF-κb) [202]. Down regulation of SDC1 induces the tumor cell proliferation and EMT [203]. Deregulation of SDC1 has been reported in various types of cancer [204-208]. MiR-494 inhibited EMT and pancreatic tumor cell invasion via SDC1 targeting [209].

WD repeat and HMG-box DNA binding protein 1 (WDHD1) is a nuclear ubiquitin ligase that interacts with DNA via the HMG domain [210]. It has a critical role in both pre-replicative complexes assembly and initiation of DNA replication. It also mediates the cellular response to DNA damage and functions as a G1 checkpoint control protein [211]. WDHD1 promotes cisplatin resistance in cancer cells upon inducing the MAPRE2 ubiquitination [212]. It has been demonstrated that miR-494 inhibited cholangiocarcinoma (CCA) progression via EMT process through WDHD1 targeting. MiR-494 up regulated the CDH1, while down regulated WDHD1, CDH2, Vimentin, and MMP-9 [213].

Conclusions

Considering the importance of miRNAs as the non-invasive diagnostic markers in various diseases and cancers, in the present review, we discussed the role of miR-494 during tumor progression. It has been shown that miR-494 mainly exerts its tumor suppressor role by regulation of transcription factors, structural proteins, and signaling pathways including TGF-β, WNT, and JAK/STAT. PTEN/PI3K axis has also been reported as the main target of miR-494 as an oncogene in different cancers. These findings suggest that miR-494 is a non-invasive diagnostic marker and a probable therapeutic target in cancer patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Meysam Moghbeli, Department of Medical Genetics and Molecular Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: moghbelim@mums.ac.ir

References

[1] Siegel RL, Miller KD, Fuchs HE and Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021; 71: 7-33.
[2] Mun EJ, Babiker HM, Weinberg U, Kirson ED and Von Hoff DD. Tumor-treating fields: a fourth modality in cancer treatment. Clin Cancer Res 2018; 24: 266-275.
[3] Shi J, Kantoff PW, Wooster R and Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer 2017; 17: 20-37.
[4] Rahimi HR, Mojarrad M and Moghbeli M. MicroRNA-96: a therapeutic and diagnostic tumor marker. Iran J Basic Med Sci 2022; 25: 3-13.
[5] Moghbeli M. Molecular interactions of miR-338 during tumor progression and metastasis. Cell Mol Biol Lett 2021; 26: 13.
[6] Shin VY and Chu KM. MiRNA as potential biomarkers and therapeutic targets for gastric cancer. World J Gastroenterol 2014; 20: 10432-10439.
[7] Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004; 116: 281-297.
[8] Zangouei AS and Moghbeli M. MicroRNAs as the critical regulators of cisplatin resistance in gastric tumor cells. Genes Environ 2021; 43: 21.
[9] Zangouei AS, Alimardani M and Moghbeli M. MicroRNAs as the critical regulators of Doxorubicin resistance in breast tumor cells. Cancer Cell Int 2021; 21: 213.
[10] Moghbeli M. MicroRNAs as the critical regulators of Cisplatin resistance in ovarian cancer cells. J Ovarian Res 2021; 14: 127.
[11] Bertoli G, Cava C and Castiglioni I. MicroRNAs: new biomarkers for diagnosis, prognosis, therapy prediction and therapeutic tools for breast cancer. Theranostics 2015; 5: 1122-1143.
[12] Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR and Golub TR. MicroRNA expression profiles classify human cancers. Nature 2005; 435: 834-838.
[13] Moghbeli M, Zangouei AS, Nasrpour Navaii Z and Taghehchian N. Molecular mechanisms of the microRNA-132 during tumor progressions. Cancer Cell Int 2021; 21: 439.
[14] Backes C, Meese E and Keller A. Specific miRNA disease biomarkers in blood, serum and plasma: challenges and prospects. Mol Diagn Ther 2016; 20: 509-518.
[15] Kappel A and Keller A. miRNA assays in the clinical laboratory: workflow, detection technologies and automation aspects. Clin Chem Lab Med 2017; 55: 636-647.
[16] Schulte C, Karakas M and Zeller T. microRNAs in cardiovascular disease - clinical application. Clin Chem Lab Med 2017; 55: 687-704.
[17] Mishra S, Yadav T and Rani V. Exploring miRNA based approaches in cancer diagnostics and therapeutics. Crit Rev Oncol Hematol 2016; 98: 12-23.
[18] Shi Y, Liu Z, Lin Q, Luo Q, Cen Y, Li J, Fang X and Gong C. MiRNAs and cancer: key link in diagnosis and therapy. Genes (Basel) 2021; 12: 1289.
[19] Song L, Liu D, Wang B, He J, Zhang S, Dai Z, Ma X and Wang X. miR-494 suppresses the progression of breast cancer in vitro by targeting CXCR4 through the Wnt/beta-catenin signaling pathway. Oncol Rep 2015; 34: 525-531.
[20] Shen PF, Chen XQ, Liao YC, Chen N, Zhou Q, Wei Q, Li X, Wang J and Zeng H. MicroRNA-494-3p targets CXCR4 to suppress the proliferation, invasion, and migration of prostate cancer. Prostate 2014; 74: 756-767.
[21] Faversani A, Amatori S, Augello C, Colombo F, Porretti L, Fanelli M, Ferrero S, Palleschi A, Pelicci PG, Belloni E, Ercoli G, Degrassi A, Baccarin M, Altieri DC, Vaira V and Bosari S. miR-494-3p is a novel tumor driver of lung carcinogenesis. Oncotarget 2017; 8: 7231-7247.
[22] Macedo T, Silva-Oliveira RJ, Silva VAO, Vidal DO, Evangelista AF and Marques MMC. Overexpression of mir-183 and mir-494 promotes

proliferation and migration in human breast cancer cell lines. Oncol Lett 2017; 14: 1054-1060.
[23] Mao G, Liu Y, Fang X, Liu Y, Fang L, Lin L, Liu X and Wang N. Tumor-derived microRNA-494 promotes angiogenesis in non-small cell lung cancer. Angiogenesis 2015; 18: 373-382.
[24] Zhan MN, Yu XT, Tang J, Zhou CX, Wang CL, Yin QQ, Gong XF, He M, He JR, Chen GQ and Zhao Q. MicroRNA-494 inhibits breast cancer progression by directly targeting PAK1. Cell Death Dis 2017; 8: e2529.
[25] Han X, Fang Z, Wang H, Jiao R, Zhou J and Fang N. CUL4A functions as an oncogene in ovarian cancer and is directly regulated by miR-494. Biochem Biophys Res Commun 2016; 480: 675-681.
[26] Yuan J, Wang K and Xi M. MiR-494 inhibits epithelial ovarian cancer growth by targeting c-Myc. Med Sci Monit 2016; 22: 617-624.
[27] Zhao XQ, Liang TJ and Fu JW. miR-494 inhibits invasion and proliferation of gastric cancer by targeting IGF-1R. Eur Rev Med Pharmacol Sci 2016; 20: 3818-3824.
[28] Jafari M, Ghadami E, Dadkhah T and Akhavan-Niaki H. PI3k/AKT signaling pathway: erythropoiesis and beyond. J Cell Physiol 2019; 234: 2373-2385.
[29] Yang F, Yan Y, Yang Y, Hong X, Wang M, Yang Z, Liu B and Ye L. MiR-210 in exosomes derived from CAFs promotes non-small cell lung cancer migration and invasion through PTEN/PI3K/AKT pathway. Cell Signal 2020; 73: 109675.
[30] Li XT, Wang HZ, Wu ZW, Yang TQ, Zhao ZH, Chen GL, Xie XS, Li B, Wei YX, Huang YL, Zhou YX and Du ZW. miR-494-3p regulates cellular proliferation, invasion, migration, and apoptosis by PTEN/AKT signaling in human glioblastoma cells. Cell Mol Neurobiol 2015; 35: 679-687.
[31] Zhu L, Wang X, Wang T, Zhu W and Zhou X. miR-494-3p promotes the progression of endometrial cancer by regulating the PTEN/PI3K/AKT pathway. Mol Med Rep 2019; 19: 581-588.
[32] Lin H, Huang ZP, Liu J, Qiu Y, Tao YP, Wang MC, Yao H, Hou KZ, Gu FM and Xu XF. MiR-494-3p promotes PI3K/AKT pathway hyperactivation and human hepatocellular carcinoma progression by targeting PTEN. Sci Rep 2018; 8: 10461.
[33] Sun HB, Chen X, Ji H, Wu T, Lu HW, Zhang Y, Li H and Li YM. miR-494 is an independent prognostic factor and promotes cell migration and invasion in colorectal cancer by directly targeting PTEN. Int J Oncol 2014; 45: 2486-2494.
[34] Yang YK, Xi WY, Xi RX, Li JY, Li Q and Gao YE. MicroRNA-494 promotes cervical cancer proliferation through the regulation of PTEN. Oncol Rep 2015; 33: 2393-2401.
[35] Han K, Li ZJ and Sun P. MicroRNA-494 promotes the proliferation and migration of human glioma cancer cells through the protein kinase B/mechanistic target of rapamycin pathway by phosphatase and tensin homolog expression. Oncol Rep 2019; 41: 351-360.
[36] Rahmani Z, Mojarrad M and Moghbeli M. Long non-coding RNAs as the critical factors during tumor progressions among Iranian population: an overview. Cell Biosci 2020; 10: 6.
[37] Khalili-Tanha G and Moghbeli M. Long non-coding RNAs as the critical regulators of doxorubicin resistance in tumor cells. Cell Mol Biol Lett 2021; 26: 39.
[38] Hamidi AA, Khalili-Tanha G, Nasrpour Navaei Z and Moghbeli M. Long non-coding RNAs as the critical regulators of epithelial mesenchymal transition in colorectal tumor cells: an overview. Cancer Cell Int 2022; 22: 71.
[39] Dai Y, Wan Y, Qiu M, Wang S, Pan C, Wang Y and Ou J. lncRNA MEG3 suppresses the tumorigenesis of hemangioma by sponging miR-494 and regulating PTEN/PI3K/AKT pathway. Cell Physiol Biochem 2018; 51: 2872-2886.
[40] Lu Q, Liu T, Feng H, Yang R, Zhao X, Chen W, Jiang B, Qin H, Guo X, Liu M, Li L and Guo H. Circular RNA circSLC8A1 acts as a sponge of miR-130b/miR-494 in suppressing bladder cancer progression via regulating PTEN. Mol Cancer 2019; 18: 111.
[41] Xia S and Zhang Z. Circular RNA hsa_circ_0000317 inhibits non-small cell lung cancer progression through regulating microRNA-494-3p/phosphatase and tensin homolog deleted on chromosome 10 axis. Clinics (Sao Paulo) 2022; 77: 100086.
[42] Wu C, Yang J, Li R, Lin X, Wu J and Wu J. LncRNA WT1-AS/miR-494-3p regulates cell proliferation, apoptosis, migration and invasion via PTEN/PI3K/AKT signaling pathway in non-small cell lung cancer. Onco Targets Ther 2021; 14: 891-904.
[43] Jiang W and Ji M. Receptor tyrosine kinases in PI3K signaling: the therapeutic targets in cancer. Semin Cancer Biol 2019: 59: 3-22.
[44] Chandarlapaty S, Sawai A, Scaltriti M, Rodrik-Outmezguine V, Grbovic-Huezo O, Serra V, Majumder PK, Baselga J and Rosen N. AKT inhibition relieves feedback suppression of receptor tyrosine kinase expression and activity. Cancer Cell 2011; 19: 58-71.
[45] Zangouei AS, Barjasteh AH, Rahimi HR, Mojarrad M and Moghbeli M. Role of tyrosine kinases in bladder cancer progression: an overview. Cell Commun Signal 2020; 18: 127.
[46] Maharati A, Zanguei AS, Khalili-Tanha G and Moghbeli M. MicroRNAs as the critical regulators of tyrosine kinase inhibitors resistance in lung tumor cells. Cell Commun Signal 2022; 20: 27.

[47] Hua J, Wang X, Ma L, Li J, Cao G, Zhang S and Lin W. CircVAPA promotes small cell lung cancer progression by modulating the miR-377-3p and miR-494-3p/IGF1R/AKT axis. Mol Cancer 2022; 21: 123.
[48] Zhao FY, Han J, Chen XW, Wang J, Wang XD, Sun JG and Chen ZT. miR-223 enhances the sensitivity of non-small cell lung cancer cells to erlotinib by targeting the insulin-like growth factor-1 receptor. Int J Mol Med 2016; 38: 183-191.
[49] Resende C, Ristimäki A and Machado JC. Genetic and epigenetic alteration in gastric carcinogenesis. Helicobacter 2010; 15 Suppl 1: 34-39.
[50] Nakajima M, Sawada H, Yamada Y, Watanabe A, Tatsumi M, Yamashita J, Matsuda M, Sakaguchi T, Hirao T and Nakano H. The prognostic significance of amplification and overexpression of c-met and c-erb B-2 in human gastric carcinomas. Cancer 1999; 85: 1894-1902.
[51] Chen CT, Kim H, Liska D, Gao S, Christensen JG and Weiser MR. MET activation mediates resistance to lapatinib inhibition of HER2-amplified gastric cancer cells. Mol Cancer Ther 2012; 11: 660-669.
[52] Park DI, Yun JW, Park JH, Oh SJ, Kim HJ, Cho YK, Sohn CI, Jeon WK, Kim BI, Yoo CH, Son BH, Cho EY, Chae SW, Kim EJ, Sohn JH, Ryu SH and Sepulveda AR. HER-2/neu amplification is an independent prognostic factor in gastric cancer. Dig Dis Sci 2006; 51: 1371-1379.
[53] Zhang XL, Yang YS, Xu DP, Qu JH, Guo MZ, Gong Y and Huang J. Comparative study on overexpression of HER2/neu and HER3 in gastric cancer. World J Surg 2009; 33: 2112-2118.
[54] De Vita F, Giuliani F, Silvestris N, Catalano G, Ciardiello F and Orditura M. Human epidermal growth factor receptor 2 (HER2) in gastric cancer: a new therapeutic target. Cancer Treat Rev 2010; 36 Suppl 3: S11-15.
[55] Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, Jagiello-Gruszfeld A, Crown J, Chan A, Kaufman B, Skarlos D, Campone M, Davidson N, Berger M, Oliva C, Rubin SD, Stein S and Cameron D. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355: 2733-2743.
[56] Hierro C, Rodon J and Tabernero J. Fibroblast growth factor (FGF) receptor/FGF inhibitors: novel targets and strategies for optimization of response of solid tumors. Semin Oncol 2015; 42: 801-819.
[57] Deng N, Goh LK, Wang H, Das K, Tao J, Tan IB, Zhang S, Lee M, Wu J, Lim KH, Lei Z, Goh G, Lim QY, Tan AL, Sin Poh DY, Riahi S, Bell S, Shi MM, Linnartz R, Zhu F, Yeoh KG, Toh HC, Yong WP, Cheong HC, Rha SY, Boussioutas A, Grabsch H, Rozen S and Tan P. A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. Gut 2012; 61: 673-684.
[58] Huang T, Wang L, Liu D, Li P, Xiong H, Zhuang L, Sun L, Yuan X and Qiu H. FGF7/FGFR2 signal promotes invasion and migration in human gastric cancer through upregulation of thrombospondin-1. Int J Oncol 2017; 50: 1501-1512.
[59] Yu Y, Yu X, Liu H, Song Q and Yang Y. miR-494 inhibits cancer-initiating cell phenotypes and reverses resistance to lapatinib by downregulating FGFR2 in HER2-positive gastric cancer. Int J Mol Med 2018; 42: 998-1007.
[60] Zhao X, Zhou Y, Chen YU and Yu F. miR-494 inhibits ovarian cancer cell proliferation and promotes apoptosis by targeting FGFR2. Oncol Lett 2016; 11: 4245-4251.
[61] Fu DW and Liu AC. LncRNA SBF2-AS1 promotes diffuse large B-cell lymphoma growth by regulating FGFR2 via sponging miR-494-3p. Cancer Manag Res 2021; 13: 571-578.
[62] Lennartsson J and Rönnstrand L. The stem cell factor receptor/c-Kit as a drug target in cancer. Curr Cancer Drug Targets 2006; 6: 65-75.
[63] Bellone G, Carbone A, Sibona N, Bosco O, Tibaudi D, Smirne C, Martone T, Gramigni C, Camandona M, Emanuelli G and Rodeck U. Aberrant activation of c-kit protects colon carcinoma cells against apoptosis and enhances their invasive potential. Cancer Res 2001; 61: 2200-2206.
[64] Yasuda A, Sawai H, Takahashi H, Ochi N, Matsuo Y, Funahashi H, Sato M, Okada Y, Takeyama H and Manabe T. Stem cell factor/c-kit receptor signaling enhances the proliferation and invasion of colorectal cancer cells through the PI3K/Akt pathway. Dig Dis Sci 2007; 52: 2292-2300.
[65] Kim WK, Park M, Kim YK, Tae YK, Yang HK, Lee JM and Kim H. MicroRNA-494 downregulates KIT and inhibits gastrointestinal stromal tumor cell proliferation. Clin Cancer Res 2011; 17: 7584-7594.
[66] Gomes LR, Terra LF, Sogayar MC and Labriola L. Epithelial-mesenchymal transition: implications in cancer progression and metastasis. Curr Pharm Biotechnol 2011; 12: 1881-1890.
[67] Forghanifard MM, Rad A, Farshchian M, Khaleghizadeh M, Gholamin M, Moghbeli M and Abbaszadegan MR. TWIST1 upregulates the MAGEA4 oncogene. Mol Carcinog 2017; 56: 877-885.
[68] Vandercappellen J, Van Damme J and Struyf S. The role of CXC chemokines and their recep-

tors in cancer. Cancer Lett 2008; 267: 226-244.
[69] Mantovani A, Savino B, Locati M, Zammataro L, Allavena P and Bonecchi R. The chemokine system in cancer biology and therapy. Cytokine Growth Factor Rev 2010; 21: 27-39.
[70] Darash-Yahana M, Pikarsky E, Abramovitch R, Zeira E, Pal B, Karplus R, Beider K, Avniel S, Kasem S, Galun E and Peled A. Role of high expression levels of CXCR4 in tumor growth, vascularization, and metastasis. FASEB J 2004; 18: 1240-1242.
[71] Vindrieux D, Escobar P and Lazennec G. Emerging roles of chemokines in prostate cancer. Endocr Relat Cancer 2009; 16: 663-673.
[72] Hirbe AC, Morgan EA and Weilbaecher KN. The CXCR4/SDF-1 chemokine axis: a potential therapeutic target for bone metastases? Curr Pharm Des 2010; 16: 1284-1290.
[73] Kim J, Yip ML, Shen X, Li H, Hsin LY, Labarge S, Heinrich EL, Lee W, Lu J and Vaidehi N. Identification of anti-malarial compounds as novel antagonists to chemokine receptor CXCR4 in pancreatic cancer cells. PLoS One 2012; 7: e31004.
[74] Chen G, Chen SM, Wang X, Ding XF, Ding J and Meng LH. Inhibition of chemokine (CXC motif) ligand 12/chemokine (CXC motif) receptor 4 axis (CXCL12/CXCR4)-mediated cell migration by targeting mammalian target of rapamycin (mTOR) pathway in human gastric carcinoma cells. J Biol Chem 2012; 287: 12132-12141.
[75] Balestrieri ML, Balestrieri A, Mancini FP and Napoli C. Understanding the immunoangiostatic CXC chemokine network. Cardiovasc Res 2008; 78: 250-256.
[76] Locati M, Bonecchi R and Corsi MM. Chemokines and their receptors: roles in specific clinical conditions and measurement in the clinical laboratory. Am J Clin Pathol 2005; 123 Suppl 1: S82-95.
[77] Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, Carey VJ, Richardson AL and Weinberg RA. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell 2005; 121: 335-348.
[78] Song L, Liu D, Wang B, He J, Zhang S, Dai Z, Ma X and Wang X. miR-494 suppresses the progression of breast cancer in vitro by targeting CXCR4 through the Wnt/β-catenin signaling pathway. Oncol Rep 2015; 34: 525-531.
[79] Ouyang Q, Zhou J, Yang W, Cui H, Xu M and Yi L. Oncogenic role of neurotensin and neurotensin receptors in various cancers. Clin Exp Pharmacol Physiol 2017; 44: 841-846.
[80] Xiao H, Zeng Y, Wang Q, Wei S and Zhu X. A novel positive feedback loop between NTSR1 and Wnt/β-catenin contributes to tumor growth of glioblastoma. Cell Physiol Biochem 2017; 43: 2133-2142.
[81] Ouyang Q, Chen G, Zhou J, Li L, Dong Z, Yang R, Xu L, Cui H, Xu M and Yi L. Neurotensin signaling stimulates glioblastoma cell proliferation by upregulating c-Myc and inhibiting miR-29b-1 and miR-129-3p. Neuro Oncol 2016; 18: 216-226.
[82] Zhou J, Yi L, Ouyang Q, Xu L, Cui H and Xu M. Neurotensin signaling regulates stem-like traits of glioblastoma stem cells through activation of IL-8/CXCR1/STAT3 pathway. Cell Signal 2014; 26: 2896-2902.
[83] Dong Z, Lei Q, Yang R, Zhu S, Ke XX, Yang L, Cui H and Yi L. Inhibition of neurotensin receptor 1 induces intrinsic apoptosis via let-7a-3p/Bcl-w axis in glioblastoma. Br J Cancer 2017; 116: 1572-1584.
[84] Ou-Yang Q, He X, Yang A, Li B and Xu M. Interference with NTSR1 expression exerts an anti-invasion effect via the Jun/miR-494/SOCS6 axis of glioblastoma cells. Cell Physiol Biochem 2018; 49: 2382-2395.
[85] Cheng L, Kong B, Zhao Y and Jiang J. miR-494 inhibits cervical cancer cell proliferation through upregulation of SOCS6 expression. Oncol Lett 2018; 15: 3075-3080.
[86] Zuo Y, Ulu A, Chang JT and Frost JA. Contributions of the RhoA guanine nucleotide exchange factor Net1 to polyoma middle T antigen-mediated mammary gland tumorigenesis and metastasis. Breast Cancer Res 2018; 20: 41.
[87] Yang X, Li Y, Zhang Y and Liu J. Circ_0000745 promotes acute lymphoblastic leukemia progression through mediating miR-494-3p/NET1 axis. Hematology 2022; 27: 11-22.
[88] Rosenbluh J, Wang X and Hahn WC. Genomic insights into WNT/β-catenin signaling. Trends Pharmacol Sci 2014; 35: 103-109.
[89] Takahashi-Yanaga F and Sasaguri T. Drug development targeting the glycogen synthase kinase-3beta (GSK-3beta)-mediated signal transduction pathway: inhibitors of the Wnt/beta-catenin signaling pathway as novel anticancer drugs. J Pharmacol Sci 2009; 109: 179-183.
[90] Karim R, Tse G, Putti T, Scolyer R and Lee S. The significance of the Wnt pathway in the pathology of human cancers. Pathology 2004; 36: 120-128.
[91] Kong X, Li L, Li Z, Le X, Huang C, Jia Z, Cui J, Huang S, Wang L and Xie K. Dysregulated expression of FOXM1 isoforms drives progression of pancreatic cancer. Cancer Res 2013; 73: 3987-3996.
[92] Li L, Li Z, Kong X, Xie D, Jia Z, Jiang W, Cui J, Du Y, Wei D, Huang S and Xie K. Down-regulation of microRNA-494 via loss of SMAD4 increases FOXM1 and β-catenin signaling in pancreatic

ductal adenocarcinoma cells. Gastroenterology 2014; 147: 485-497, e18.
[93] Fu C, Wang S, Jin L, Zhang M and Li M. CircTET1 inhibits retinoblastoma progression via targeting miR-492 and miR-494-3p through Wnt/β-catenin signaling pathway. Curr Eye Res 2021; 46: 978-987.
[94] Banerjee S, Biehl A, Gadina M, Hasni S and Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. Drugs 2017; 77: 521-546.
[95] Tang X, Mo C, Wang Y, Wei D and Xiao H. Anti-tumour strategies aiming to target tumour-associated macrophages. Immunology 2013; 138: 93-104.
[96] Binnemars-Postma K, Storm G and Prakash J. Nanomedicine strategies to target tumor-associated macrophages. Int J Mol Sci 2017; 18: 979.
[97] Anfray C, Ummarino A, Andón FT and Allavena P. Current strategies to target tumor-associated-macrophages to improve anti-tumor immune responses. Cells 2019; 9: 46.
[98] Tian X, Wu Y, Yang Y, Wang J, Niu M, Gao S, Qin T and Bao D. Long noncoding RNA LINC00662 promotes M2 macrophage polarization and hepatocellular carcinoma progression via activating Wnt/β-catenin signaling. Mol Oncol 2020; 14: 462-483.
[99] Jiang H, Deng W, Zhu K, Zeng Z, Hu B, Zhou Z, Xie A, Zhang C, Fu B, Zhou X and Wang G. LINC00467 promotes prostate cancer progression via M2 macrophage polarization and the miR-494-3p/STAT3 axis. Front Oncol 2021; 11: 661431.
[100] Xia B, Yang S, Liu T and Lou G. miR-211 suppresses epithelial ovarian cancer proliferation and cell-cycle progression by targeting Cyclin D1 and CDK6. Mol Cancer 2015; 14: 57.
[101] Chen Z, Hu X, Wu Y, Cong L, He X, Lu J, Feng J and Liu D. Long non-coding RNA XIST promotes the development of esophageal cancer by sponging miR-494 to regulate CDK6 expression. Biomed Pharmacother 2019; 109: 2228-2236.
[102] Seto E and Yoshida M. Erasers of histone acetylation: the histone deacetylase enzymes. Cold Spring Harb Perspect Biol 2014; 6: a018713.
[103] McClure JJ, Li X and Chou CJ. Advances and challenges of hdac inhibitors in cancer therapeutics. Adv Cancer Res 2018; 138: 183-211.
[104] Cao F, Zwinderman MRH and Dekker FJ. The process and strategy for developing selective histone deacetylase 3 inhibitors. Molecules 2018; 23: 551.
[105] Zhang L, Chen Y, Jiang Q, Song W and Zhang L. Therapeutic potential of selective histone deacetylase 3 inhibition. Eur J Med Chem 2019; 162: 534-542.
[106] Razzaque MS and Atfi A. TGIF1-Twist1 axis in pancreatic ductal adenocarcinoma. Comput Struct Biotechnol J 2020; 18: 2568-2572.
[107] Weng CC, Hsieh MJ, Wu CC, Lin YC, Shan YS, Hung WC, Chen LT and Cheng KH. Loss of the transcriptional repressor TGIF1 results in enhanced Kras-driven development of pancreatic cancer. Mol Cancer 2019; 18: 96.
[108] Yang Y, Zhang Y, Lin Z, Wu K, He Z, Zhu D, Zhao J, Zhang C and Fan Y. Silencing of histone deacetylase 3 suppresses the development of esophageal squamous cell carcinoma through regulation of miR-494-mediated TGIF1. Cancer Cell Int 2022; 22: 191.
[109] Lee TK, Poon RT, Yuen AP, Ling MT, Kwok WK, Wang XH, Wong YC, Guan XY, Man K, Chau KL and Fan ST. Twist overexpression correlates with hepatocellular carcinoma metastasis through induction of epithelial-mesenchymal transition. Clin Cancer Res 2006; 12: 5369-5376.
[110] Giannelli G, Bergamini C, Fransvea E, Sgarra C and Antonaci S. Laminin-5 with transforming growth factor-beta1 induces epithelial to mesenchymal transition in hepatocellular carcinoma. Gastroenterology 2005; 129: 1375-1383.
[111] Tang ZY, Ye SL, Liu YK, Qin LX, Sun HC, Ye QH, Wang L, Zhou J, Qiu SJ, Li Y, Ji XN, Liu H, Xia JL, Wu ZQ, Fan J, Ma ZC, Zhou XD, Lin ZY and Liu KD. A decade's studies on metastasis of hepatocellular carcinoma. J Cancer Res Clin Oncol 2004; 130: 187-196.
[112] Huber MA, Kraut N and Beug H. Molecular requirements for epithelial-mesenchymal transition during tumor progression. Curr Opin Cell Biol 2005; 17: 548-558.
[113] Lourenço AR and Coffer PJ. SOX4: joining the master regulators of epithelial-to-mesenchymal transition? Trends Cancer 2017; 3: 571-582.
[114] Yamada S, Fuchs BC, Fujii T, Shimoyama Y, Sugimoto H, Nomoto S, Takeda S, Tanabe KK, Kodera Y and Nakao A. Epithelial-to-mesenchymal transition predicts prognosis of pancreatic cancer. Surgery 2013; 154: 946-954.
[115] Huber MA, Azoitei N, Baumann B, Grünert S, Sommer A, Pehamberger H, Kraut N, Beug H and Wirth T. NF-kappaB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. J Clin Invest 2004; 114: 569-581.
[116] De Craene B and Berx G. Regulatory networks defining EMT during cancer initiation and progression. Nat Rev Cancer 2013; 13: 97-110.
[117] Finak G, Bertos N, Pepin F, Sadekova S, Souleimanova M, Zhao H, Chen H, Omeroglu G, Meterissian S, Omeroglu A, Hallett M and Park M. Stromal gene expression predicts clinical outcome in breast cancer. Nat Med 2008; 14: 518-527.

[118] Sund M and Kalluri R. Tumor stroma derived biomarkers in cancer. Cancer Metastasis Rev 2009; 28: 177-183.
[119] Zeisberg EM, Tarnavski O, Zeisberg M, Dorfman AL, McMullen JR, Gustafsson E, Chandraker A, Yuan X, Pu WT, Roberts AB, Neilson EG, Sayegh MH, Izumo S and Kalluri R. Endothelial-to-mesenchymal transition contributes to cardiac fibrosis. Nat Med 2007; 13: 952-961.
[120] Akhurst RJ and Hata A. Targeting the TGFβ signalling pathway in disease. Nat Rev Drug Discov 2012; 11: 790-811.
[121] Sundaresan NR, Samant SA, Pillai VB, Rajamohan SB and Gupta MP. SIRT3 is a stress-responsive deacetylase in cardiomyocytes that protects cells from stress-mediated cell death by deacetylation of Ku70. Mol Cell Biol 2008; 28: 6384-6401.
[122] Zhang J, Zhu Y, Hu L, Yan F and Chen J. miR-494 induces EndMT and promotes the development of HCC (Hepatocellular Carcinoma) by targeting SIRT3/TGF-β/SMAD signaling pathway. Sci Rep 2019; 9: 7213.
[123] Abate-Shen C. Deregulated homeobox gene expression in cancer: cause or consequence? Nat Rev Cancer 2002; 2: 777-785.
[124] Haria D and Naora H. Homeobox gene deregulation: impact on the hallmarks of cancer. Cancer Hallm 2013; 1: 67-76.
[125] Nunes FD, de Almeida FC, Tucci R and de Sousa SC. Homeobox genes: a molecular link between development and cancer. Pesqui Odontol Bras 2003; 17: 94-98.
[126] Rodini CO, Xavier FC, Paiva KB, De Souza Setúbal Destro MF, Moyses RA, Michaluarte P, Carvalho MB, Fukuyama EE; Head And Neck Genome Project Gencapo, Tajara EH, Okamoto OK and Nunes FD. Homeobox gene expression profile indicates HOXA5 as a candidate prognostic marker in oral squamous cell carcinoma. Int J Oncol 2012; 40: 1180-1188.
[127] Feng Y, Zhang T, Wang Y, Xie M, Ji X, Luo X, Huang W and Xia L. Homeobox genes in cancers: from carcinogenesis to recent therapeutic intervention. Front Oncol 2021; 11: 770428.
[128] Libório-Kimura TN, Jung HM and Chan EK. miR-494 represses HOXA10 expression and inhibits cell proliferation in oral cancer. Oral Oncol 2015; 51: 151-157.
[129] Jackstadt R and Hermeking H. MicroRNAs as regulators and mediators of c-MYC function. Biochim Biophys Acta 2015; 1849: 544-553.
[130] Eilers M and Eisenman RN. Myc's broad reach. Genes Dev 2008; 22: 2755-2766.
[131] Albihn A, Johnsen JI and Henriksson MA. MYC in oncogenesis and as a target for cancer therapies. Adv Cancer Res 2010; 107: 163-224.
[132] Liu Y, Li X, Zhu S, Zhang JG, Yang M, Qin Q, Deng SC, Wang B, Tian K, Liu L, Niu Y, Wang CY and Zhao G. Ectopic expression of miR-494 inhibited the proliferation, invasion and chemoresistance of pancreatic cancer by regulating SIRT1 and c-Myc. Gene Ther 2015; 22: 729-738.
[133] He W, Li Y, Chen X, Lu L, Tang B, Wang Z, Pan Y, Cai S, He Y and Ke Z. miR-494 acts as an anti-oncogene in gastric carcinoma by targeting c-myc. J Gastroenterol Hepatol 2014; 29: 1427-1434.
[134] Stovall DB, Cao P and Sui G. SOX7: from a developmental regulator to an emerging tumor suppressor. Histol Histopathol 2014; 29: 439-445.
[135] He H, Liao X, Yang Q, Liu Y, Peng Y, Zhong H, Yang J, Zhang H, Yu Z, Zuo Y, Guan C and Xu Z. MicroRNA-494-3p promotes cell growth, migration, and invasion of nasopharyngeal carcinoma by targeting Sox7. Technol Cancer Res Treat 2018; 17: 1533033818809993.
[136] Li J, Wang L, Liu Z, Zu C, Xing F, Yang P, Yang Y, Dang X and Wang K. MicroRNA-494 inhibits cell proliferation and invasion of chondrosarcoma cells in vivo and in vitro by directly targeting SOX9. Oncotarget 2015; 6: 26216-26229.
[137] Jiang X, Wang G, Liu Y, Mei C, Yao Y, Wu X, Chen X, Ma W, Li K, Zhang Z and Yuan Y. A novel long non-coding RNA RP11-286H15.1 represses hepatocellular carcinoma progression by promoting ubiquitination of PABPC4. Cancer Lett 2021; 499: 109-121.
[138] Yang XJ, Zhu H, Mu SR, Wei WJ, Yuan X, Wang M, Liu Y, Hui J and Huang Y. Crystal structure of a Y-box binding protein 1 (YB-1)-RNA complex reveals key features and residues interacting with RNA. J Biol Chem 2019; 294: 10998-11010.
[139] Evdokimova V, Tognon C, Ng T, Ruzanov P, Melnyk N, Fink D, Sorokin A, Ovchinnikov LP, Davicioni E, Triche TJ and Sorensen PH. Translational activation of snail1 and other developmentally regulated transcription factors by YB-1 promotes an epithelial-mesenchymal transition. Cancer Cell 2009; 15: 402-415.
[140] Aguirre A, López-Alonso I, González-López A, Amado-Rodríguez L, Batalla-Solís E, Astudillo A, Blázquez-Prieto J, Fernández AF, Galván JA, Dos Santos CC and Albaiceta GM. Defective autophagy impairs ATF3 activity and worsens lung injury during endotoxemia. J Mol Med (Berl) 2014; 92: 665-676.
[141] Liu P, Zhong Q, Song Y, Guo D, Ma D, Chen B, Lan J and Liu Q. Long noncoding RNA Linc01612 represses hepatocellular carcinoma progression by regulating miR-494/ATF3/p53 axis and promoting ubiquitination of YBX1. Int J Biol Sci 2022; 18: 2932-2948.

[142] Bornschein J and Malfertheiner P. Gastric carcinogenesis. Langenbecks Arch Surg 2011; 396: 729-742.
[143] Orditura M, Galizia G, Sforza V, Gambardella V, Fabozzi A, Laterza MM, Andreozzi F, Ventriglia J, Savastano B, Mabilia A, Lieto E, Ciardiello F and De Vita F. Treatment of gastric cancer. World J Gastroenterol 2014; 20: 1635-1649.
[144] Niccolai E, Taddei A, Prisco D and Amedei A. Gastric cancer and the epoch of immunotherapy approaches. World J Gastroenterol 2015; 21: 5778-5793.
[145] Choi AH, Kim J and Chao J. Perioperative chemotherapy for resectable gastric cancer: MAGIC and beyond. World J Gastroenterol 2015; 21: 7343-7348.
[146] Shi WJ and Gao JB. Molecular mechanisms of chemoresistance in gastric cancer. World J Gastrointest Oncol 2016; 8: 673-681.
[147] Joshi P, Jeon YJ, Laganà A, Middleton J, Secchiero P, Garofalo M and Croce CM. MicroRNA-148a reduces tumorigenesis and increases TRAIL-induced apoptosis in NSCLC. Proc Natl Acad Sci U S A 2015; 112: 8650-8655.
[148] Enari M, Talanian RV, Wong WW and Nagata S. Sequential activation of ICE-like and CPP32-like proteases during Fas-mediated apoptosis. Nature 1996; 380: 723-726.
[149] Xu C, Shi L, Chen W, Fang P, Li J, Jin L, Pan Z and Pan C. MiR-106b inhibitors sensitize TRAIL-induced apoptosis in hepatocellular carcinoma through increase of death receptor 4. Oncotarget 2017; 8: 41921-41931.
[150] Salvesen GS and Duckett CS. IAP proteins: blocking the road to death's door. Nat Rev Mol Cell Biol 2002; 3: 401-410.
[151] Shin S, Sung BJ, Cho YS, Kim HJ, Ha NC, Hwang JI, Chung CW, Jung YK and Oh BH. An anti-apoptotic protein human survivin is a direct inhibitor of caspase-3 and -7. Biochemistry 2001; 40: 1117-1123.
[152] Minoda M, Kawamoto T, Ueha T, Kamata E, Morishita M, Harada R, Toda M, Onishi Y, Hara H, Kurosaka M and Akisue T. Antitumor effect of YM155, a novel small-molecule survivin suppressant, via mitochondrial apoptosis in human MFH/UPS. Int J Oncol 2015; 47: 891-899.
[153] Xu S, Li D, Li T, Qiao L, Li K, Guo L and Liu Y. miR-494 sensitizes gastric cancer cells to TRAIL treatment through downregulation of survivin. Cell Physiol Biochem 2018; 51: 2212-2223.
[154] Han SJ, Jung SY, Wu SP, Hawkins SM, Park MJ, Kyo S, Qin J, Lydon JP, Tsai SY, Tsai MJ, DeMayo FJ and O'Malley BW. Estrogen receptor β modulates apoptosis complexes and the inflammasome to drive the pathogenesis of endometriosis. Cell 2015; 163: 960-974.
[155] Hatai T, Matsuzawa A, Inoshita S, Mochida Y, Kuroda T, Sakamaki K, Kuida K, Yonehara S, Ichijo H and Takeda K. Execution of apoptosis signal-regulating kinase 1 (ASK1)-induced apoptosis by the mitochondria-dependent caspase activation. J Biol Chem 2000; 275: 26576-26581.
[156] Gao G and Jian Y. MicroRNA-494 represses osteosarcoma development by modulating ASK-1 related apoptosis complexes. Transl Cancer Res 2020; 9: 4121-4130.
[157] Plotnikov A, Kozer N, Cohen G, Carvalho S, Duberstein S, Almog O, Solmesky LJ, Shurrush KA, Babaev I, Benjamin S, Gilad S, Kupervaser M, Levin Y, Gershovits M, Ben-Avraham D and Barr HM. PRMT1 inhibition induces differentiation of colon cancer cells. Sci Rep 2020; 10: 20030.
[158] Reintjes A, Fuchs JE, Kremser L, Lindner HH, Liedl KR, Huber LA and Valovka T. Asymmetric arginine dimethylation of RelA provides a repressive mark to modulate TNFα/NF-κB response. Proc Natl Acad Sci U S A 2016; 113: 4326-4331.
[159] Li Z, Wang D, Lu J, Huang B, Wang Y, Dong M, Fan D, Li H, Gao Y, Hou P, Li M, Liu H, Pan ZQ, Zheng J and Bai J. Methylation of EZH2 by PRMT1 regulates its stability and promotes breast cancer metastasis. Cell Death Differ 2020; 27: 3226-3242.
[160] Zheng D, Chen D, Lin F, Wang X, Lu L, Luo S, Chen J and Xu X. LncRNA NNT-AS1 promote glioma cell proliferation and metastases through miR-494-3p/PRMT1 axis. Cell Cycle 2020; 19: 1621-1631.
[161] Puccini J, Dorstyn L and Kumar S. Caspase-2 as a tumour suppressor. Cell Death Differ 2013; 20: 1133-1139.
[162] López-García C, Sansregret L, Domingo E, McGranahan N, Hobor S, Birkbak NJ, Horswell S, Grönroos E, Favero F, Rowan AJ, Matthews N, Begum S, Phillimore B, Burrell R, Oukrif D, Spencer-Dene B, Kovac M, Stamp G, Stewart A, Danielsen H, Novelli M, Tomlinson I and Swanton C. BCL9L dysfunction impairs caspase-2 expression permitting aneuploidy tolerance in colorectal cancer. Cancer Cell 2017; 31: 79-93.
[163] Poreba M, Rut W, Groborz K, Snipas SJ, Salvesen GS and Drag M. Potent and selective caspase-2 inhibitor prevents MDM-2 cleavage in reversine-treated colon cancer cells. Cell Death Differ 2019; 26: 2695-2709.
[164] Tiwari M, Sharma LK, Vanegas D, Callaway DA, Bai Y, Lechleiter JD and Herman B. A nonapop-

totic role for CASP2/caspase 2: modulation of autophagy. Autophagy 2014; 10: 1054-1070.
[165] Zhang Q, Li Y, Zhao M, Lin H, Wang W, Li D, Cui W, Zhou C, Zhong J and Huang C. MiR-494 acts as a tumor promoter by targeting CASP2 in non-small cell lung cancer. Sci Rep 2019; 9: 3008.
[166] Darnton SJ, Archer VR, Stocken DD, Mulholland PJ, Casson AG and Ferry DR. Preoperative mitomycin, ifosfamide, and cisplatin followed by esophagectomy in squamous cell carcinoma of the esophagus: pathologic complete response induced by chemotherapy leads to long-term survival. J Clin Oncol 2003; 21: 4009-4015.
[167] Phatak P, Byrnes KA, Mansour D, Liu L, Cao S, Li R, Rao JN, Turner DJ, Wang JY and Donahue JM. Overexpression of miR-214-3p in esophageal squamous cancer cells enhances sensitivity to cisplatin by targeting survivin directly and indirectly through CUG-BP1. Oncogene 2016; 35: 2087-2097.
[168] Li H, Che J, Jiang M, Cui M, Feng G, Dong J, Zhang S, Lu L, Liu W and Fan S. CLPTM1L induces estrogen receptor β signaling-mediated radioresistance in non-small cell lung cancer cells. Cell Commun Signal 2020; 18: 152.
[169] Jia J, Bosley AD, Thompson A, Hoskins JW, Cheuk A, Collins I, Parikh H, Xiao Z, Ylaya K, Dzyadyk M, Cozen W, Hernandez BY, Lynch CF, Loncarek J, Altekruse SF, Zhang L, Westlake CJ, Factor VM, Thorgeirsson S, Bamlet WR, Hewitt SM, Petersen GM, Andresson T and Amundadottir LT. CLPTM1L promotes growth and enhances aneuploidy in pancreatic cancer cells. Cancer Res 2014; 74: 2785-2795.
[170] Prescott J, Wentzensen IM, Savage SA and De Vivo I. Epidemiologic evidence for a role of telomere dysfunction in cancer etiology. Mutat Res 2012; 730: 75-84.
[171] Rafnar T, Sulem P, Stacey SN, Geller F, Gudmundsson J, Sigurdsson A, Jakobsdottir M, Helgadottir H, Thorlacius S, Aben KK, Blöndal T, Thorgeirsson TE, Thorleifsson G, Kristjansson K, Thorisdottir K, Ragnarsson R, Sigurgeirsson B, Skuladottir H, Gudbjartsson T, Isaksson HJ, Einarsson GV, Benediktsdottir KR, Agnarsson BA, Olafsson K, Salvarsdottir A, Bjarnason H, Asgeirsdottir M, Kristinsson KT, Matthiasdottir S, Sveinsdottir SG, Polidoro S, Höiom V, Botella-Estrada R, Hemminki K, Rudnai P, Bishop DT, Campagna M, Kellen E, Zeegers MP, de Verdier P, Ferrer A, Isla D, Vidal MJ, Andres R, Saez B, Juberias P, Banzo J, Navarrete S, Tres A, Kan D, Lindblom A, Gurzau E, Koppova K, de Vegt F, Schalken JA, van der Heijden HF, Smit HJ, Termeer RA, Oosterwijk E, van Hooij O, Nagore E, Porru S, Steineck G, Hansson J, Buntinx F, Catalona WJ, Matullo G, Vineis P, Kiltie AE, Mayordomo JI, Kumar R, Kiemeney LA, Frigge ML, Jonsson T, Saemundsson H, Barkardottir RB, Jonsson E, Jonsson S, Olafsson JH, Gulcher JR, Masson G, Gudbjartsson DF, Kong A, Thorsteinsdottir U and Stefansson K. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet 2009; 41: 221-227.
[172] Yamamoto K, Okamoto A, Isonishi S, Ochiai K and Ohtake Y. A novel gene, CRR9, which was up-regulated in CDDP-resistant ovarian tumor cell line, was associated with apoptosis. Biochem Biophys Res Commun 2001; 280: 1148-1154.
[173] Lu X, Ke J, Luo X, Zhu Y, Zou L, Li H, Zhu B, Xiong Z, Chen W, Deng L, Lou J, Wang X, Zhang Y, Wang Z, Miao X and Cheng L. The SNP rs402710 in 5p15.33 is associated with lung cancer risk: a replication study in Chinese population and a meta-analysis. PLoS One 2013; 8: e76252.
[174] James MA, Wen W, Wang Y, Byers LA, Heymach JV, Coombes KR, Girard L, Minna J and You M. Functional characterization of CLPTM1L as a lung cancer risk candidate gene in the 5p15.33 locus. PLoS One 2012; 7: e36116.
[175] Zhang R, Chen X, Zhang S, Zhang X, Li T, Liu Z, Wang J, Zang W, Wang Y, Du Y and Zhao G. Upregulation of miR-494 inhibits cell growth and invasion and induces cell apoptosis by targeting cleft lip and palate transmembrane 1-like in esophageal squamous cell carcinoma. Dig Dis Sci 2015; 60: 1247-1255.
[176] Chew CS, Chen X, Parente JA Jr, Tarrer S, Okamoto C and Qin HY. Lasp-1 binds to non-muscle F-actin in vitro and is localized within multiple sites of dynamic actin assembly in vivo. J Cell Sci 2002; 115: 4787-4799.
[177] He B, Yin B, Wang B, Chen C, Xia Z, Tang J, Yuan Y, Feng X and Yin N. Overexpression of LASP1 is associated with proliferation, migration and invasion in esophageal squamous cell carcinoma. Oncol Rep 2013; 29: 1115-1123.
[178] Chen K, Quan J, Yang J and Chen Z. The potential markers of endocrine resistance among HR+/HER2+ breast cancer patients. Clin Transl Oncol 2020; 22: 576-584.
[179] Zhong C, Chen Y, Tao B, Peng L, Peng T, Yang X, Xia X and Chen L. LIM and SH3 protein 1 regulates cell growth and chemosensitivity of human glioblastoma via the PI3K/AKT pathway. BMC Cancer 2018; 18: 722.
[180] Chang N, Ge N, Zhao Y, Yang L, Qin W and Cui Y. Hsa_circ_0007142 contributes to cisplatin resistance in esophageal squamous cell carcinoma via miR-494-3p/LASP1 axis. J Clin Lab Anal 2022; 36: e24304.
[181] Panczyk M. Pharmacogenetics research on chemotherapy resistance in colorectal cancer

over the last 20 years. World J Gastroenterol 2014; 20: 9775-9827.
[182] Chai J, Dong W, Xie C, Wang L, Han DL, Wang S, Guo HL and Zhang ZL. MicroRNA-494 sensitizes colon cancer cells to fluorouracil through regulation of DPYD. IUBMB Life 2015; 67: 191-201.
[183] Ai L, Kim WJ, Demircan B, Dyer LM, Bray KJ, Skehan RR, Massoll NA and Brown KD. The transglutaminase 2 gene (TGM2), a potential molecular marker for chemotherapeutic drug sensitivity, is epigenetically silenced in breast cancer. Carcinogenesis 2008; 29: 510-518.
[184] Park MK, Jo SH, Lee HJ, Kang JH, Kim YR, Kim HJ, Lee EJ, Koh JY, Ahn KO, Jung KC, Oh SH, Kim SY and Lee CH. Novel suppressive effects of cardamonin on the activity and expression of transglutaminase-2 lead to blocking the migration and invasion of cancer cells. Life Sci 2013; 92: 154-160.
[185] Li C, Cai J, Ge F and Wang G. TGM2 knockdown reverses cisplatin chemoresistance in osteosarcoma. Int J Mol Med 2018; 42: 1799-1808.
[186] He W, Sun Z and Liu Z. Silencing of TGM2 reverses epithelial to mesenchymal transition and modulates the chemosensitivity of breast cancer to docetaxel. Exp Ther Med 2015; 10: 1413-1418.
[187] Leicht DT, Kausar T, Wang Z, Ferrer-Torres D, Wang TD, Thomas DG, Lin J, Chang AC, Lin L and Beer DG. TGM2: a cell surface marker in esophageal adenocarcinomas. J Thorac Oncol 2014; 9: 872-881.
[188] Li C, Cai J, Ge F and Wang G. TGM2 knockdown reverses cisplatin chemoresistance in osteosarcoma. Int J Mol Med 2018; 42: 1799-1808.
[189] Wei W, Ji L, Duan W and Zhu J. Circular RNA circ_0081001 knockdown enhances methotrexate sensitivity in osteosarcoma cells by regulating miR-494-3p/TGM2 axis. J Orthop Surg Res 2021; 16: 50.
[190] Ten Hagen KG, Fritz TA and Tabak LA. All in the family: the UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferases. Glycobiology 2003; 13: 1R-16R.
[191] Ten Hagen KG, Hagen FK, Balys MM, Beres TM, Van Wuyckhuyse B and Tabak LA. Cloning and expression of a novel, tissue specifically expressed member of the UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase family. J Biol Chem 1998; 273: 27749-27754.
[192] Brockhausen I. Pathways of O-glycan biosynthesis in cancer cells. Biochim Biophys Acta 1999; 1473: 67-95.
[193] Nie GH, Luo L, Duan HF, Li XQ, Yin MJ, Li Z and Zhang W. GALNT7, a target of miR-494, participates in the oncogenesis of nasopharyngeal carcinoma. Tumour Biol 2016; 37: 4559-4567.
[194] Hotz B, Arndt M, Dullat S, Bhargava S, Buhr HJ and Hotz HG. Epithelial to mesenchymal transition: expression of the regulators snail, slug, and twist in pancreatic cancer. Clin Cancer Res 2007; 13: 4769-4776.
[195] Sabbah M, Emami S, Redeuilh G, Julien S, Prévost G, Zimber A, Ouelaa R, Bracke M, De Wever O and Gespach C. Molecular signature and therapeutic perspective of the epithelial-to-mesenchymal transitions in epithelial cancers. Drug Resist Updat 2008; 11: 123-151.
[196] Yang J and Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. Dev Cell 2008; 14: 818-829.
[197] Buck E, Eyzaguirre A, Barr S, Thompson S, Sennello R, Young D, Iwata KK, Gibson NW, Cagnoni P and Haley JD. Loss of homotypic cell adhesion by epithelial-mesenchymal transition or mutation limits sensitivity to epidermal growth factor receptor inhibition. Mol Cancer Ther 2007; 6: 532-541.
[198] Thomson S, Buck E, Petti F, Griffin G, Brown E, Ramnarine N, Iwata KK, Gibson N and Haley JD. Epithelial to mesenchymal transition is a determinant of sensitivity of non-small-cell lung carcinoma cell lines and xenografts to epidermal growth factor receptor inhibition. Cancer Res 2005; 65: 9455-9462.
[199] Gharbaran R. Advances in the molecular functions of syndecan-1 (SDC1/CD138) in the pathogenesis of malignancies. Crit Rev Oncol Hematol 2015; 94: 1-17.
[200] Akl MR, Nagpal P, Ayoub NM, Prabhu SA, Gliksman M, Tai B, Hatipoglu A, Goy A and Suh KS. Molecular and clinical profiles of syndecan-1 in solid and hematological cancer for prognosis and precision medicine. Oncotarget 2015; 6: 28693-28715.
[201] Cui X, Jing X, Yi Q, Long C, Tian J and Zhu J. Clinicopathological and prognostic significance of SDC1 overexpression in breast cancer. Oncotarget 2017; 8: 111444-111455.
[202] Yang N, Mosher R, Seo S, Beebe D and Friedl A. Syndecan-1 in breast cancer stroma fibroblasts regulates extracellular matrix fiber organization and carcinoma cell motility. Am J Pathol 2011; 178: 325-335.
[203] Liu Z, Jin H, Yang S, Cao H, Zhang Z, Wen B and Zhou S. SDC1 knockdown induces epithelial-mesenchymal transition and invasion of gallbladder cancer cells via the ERK/Snail pathway. J Int Med Res 2020; 48: 300060520947883.
[204] Hashimoto Y, Skacel M and Adams JC. Association of loss of epithelial syndecan-1 with stage and local metastasis of colorectal adenocarcinomas: an immunohistochemical study of clinically annotated tumors. BMC Cancer 2008; 8: 185.

[205] Lundin M, Nordling S, Lundin J, Isola J, Wiksten JP and Haglund C. Epithelial syndecan-1 expression is associated with stage and grade in colorectal cancer. Oncology 2005; 68: 306-313.
[206] Lee SH, Choi EJ, Kim MS, Park JW, Lee YS, Kim SY and Kang CS. Prognostic significance of syndecan-1 expression in squamous cell carcinoma of the tonsil. Int J Clin Oncol 2014; 19: 247-253.
[207] Lendorf ME, Manon-Jensen T, Kronqvist P, Multhaupt HA and Couchman JR. Syndecan-1 and syndecan-4 are independent indicators in breast carcinoma. J Histochem Cytochem 2011; 59: 615-629.
[208] Kusumoto T, Kodama J, Seki N, Nakamura K, Hongo A and Hiramatsu Y. Clinical significance of syndecan-1 and versican expression in human epithelial ovarian cancer. Oncol Rep 2010; 23: 917-925.
[209] Yang Y, Tao X, Li CB and Wang CM. MicroRNA-494 acts as a tumor suppressor in pancreatic cancer, inhibiting epithelial-mesenchymal transition, migration and invasion by binding to SDC1. Int J Oncol 2018; 53: 1204-1214.
[210] Guan C, Li J, Sun D, Liu Y and Liang H. The structure and polymerase-recognition mechanism of the crucial adaptor protein AND-1 in the human replisome. J Biol Chem 2017; 292: 9627-9636.
[211] Zhou Y, Pei F, Ji M, Zhang F, Sun Y, Zhao Q, Wang X, Hong Y, Tian J, Wang Y and Chen JJ. WDHD1 facilitates G1 checkpoint abrogation in HPV E7 expressing cells by modulating GCN5. BMC Cancer 2020; 20: 840.
[212] Gong L, Xiao M, He D, Hu Y, Zhu Y, Xiang L, Bao Y, Liu X, Zeng Q, Liu J, Zhou M, Zhou Y, Cheng Y, Zhang Y, Deng L, Zhu R, Lan H and Cao K. WDHD1 leads to cisplatin resistance by promoting MAPRE2 ubiquitination in lung adenocarcinoma. Front Oncol 2020; 10: 461.
[213] Liu B, Hu Y, Qin L, Peng XB and Huang YX. MicroRNA-494-dependent WDHDI inhibition suppresses epithelial-mesenchymal transition, tumor growth and metastasis in cholangiocarcinoma. Dig Liver Dis 2019; 51: 397-411.