REVIEW

Regulatory Networks of LncRNA MALAT-1 in Cancer

Shijian Fu[1]
Yanhong Wang[2]
Hang Li[1]
Leilei Chen[3]
Quanzhong Liu[4]

[1]The First Affiliated Hospital of Harbin Medical University, Harbin 150081, People's Republic of China; [2]Department of Laboratory Medicine, Yuebei People's Hospital of Shaoguan, The Affiliated Hospital of Shantou University, Shaoguan 512025, People's Republic of China; [3]Department of Cardiology, Beijing Anzhen Hospital, Beijing Institute of Heart Lung and Blood Vessel Disease, Capital Medical University, Beijing 100029, People's Republic of China; [4]Department of Medical Genetics, Harbin Medical University, Harbin 150081, People's Republic of China

Abstract: Long noncoding (lnc)RNAs are a group of RNAs with a length greater than 200 nt that do not encode a protein but play an essential role in regulating the expression of target genes in normal biological contexts as well as pathologic processes including tumorigenesis. The lncRNA metastasis-associated lung adenocarcinoma transcript (MALAT)-1 has been widely studied in cancer. In this review, we describe the known functions of MALAT-1; its mechanisms of action; and associated signaling pathways and their clinical significance in different cancers. In most malignancies, including lung, colorectal, thyroid, and other cancers, MALAT-1 functions as an oncogene and is upregulated in tumors and tumor cell lines. MALAT-1 has a distinct mechanism of action in each cancer type and is thus at the center of large gene regulatory networks. Dysregulation of MALAT-1 affects cellular processes such as alternative splicing, epithelial–mesenchymal transition, apoptosis, and autophagy, which ultimately results in the abnormal cell proliferation, invasion, and migration that characterize cancers. In other malignancies, such as glioma and endometrial carcinoma, MALAT-1 functions as a tumor suppressor and thus forms additional regulatory networks. The current evidence indicates that MALAT-1 and its associated signaling pathways can serve as diagnostic or prognostic biomarker or therapeutic target in the treatment of many cancers.

Keywords: long noncoding RNA, tumorigenesis, metastasis-associated lung adenocarcinoma transcript 1, regulatory cascade, oncogene, tumor suppressor

Introduction

It is estimated that just 2% of the human genome is protein-coding.[1,2] Noncoding (nc)RNAs are divided into short ncRNAs, midsize ncRNAs, and long (l)ncRNAs according to their length.[3] LncRNAs range from 200 nt to ~100 kb and are processed by RNA polymerase II;[4,5] they were originally considered as transcriptional noise, and it is only recently that their varied functions have become clear. LncRNAs are now known to act as regulators of transcription and alternative splicing, post-transcriptional regulators, and molecular decoys for micro(mi) RNAs.[6,7]

The interaction between lncRNAs and miRNAs has been the focus of intense research in recent years. MiRNAs usually function as tumor suppressors in cancers; lncRNAs can act as a molecular sponge that releases miRNAs from target mRNAs, leading to derepression of target genes and oncogenic transformation.[8] Accordingly, lncRNAs have been implicated in many pathologic processes such as tumor cell proliferation, invasion, and apoptosis.[9] Moreover, upregulation of some lncRNAs has been linked to shorter disease-free survival and overall survival in cancer

Correspondence: Quanzhong Liu
Email JaneHeather@outlook.com

patients. Thus, lncRNAs are potential diagnostic and prognostic biomarkers as well as therapeutic targets for cancer treatment.[10,11]

MALAT-1

Metastasis-associated lung adenocarcinoma transcript (MALAT)-1 (also known as hepcarcin [HCN], nuclear paraspeckle assembly transcript [NEAT]2, PRO2853, and NCRNA00047) is one of the first lncRNAs to be identified and studied. MALAT-1 is located on chromosome 11q13 and is approximately 8.7 kb in length;[12] it is highly conserved and broadly expressed in mammalian tissue and cancers. MALAT-1 is located on nuclear speckles that may be related to its function in alternative splicing.[13] There is accumulating evidence that MALAT-1 is dysregulated in multiple cancers; in most cases, it functions as an oncogene, with variable effects on tumorigenesis. MALAT-1 was shown to be upregulated like nonsmall cell lung cancer (NSCLC),[14] hepatocellular carcinoma,[15] cervical cancer,[16] osteosarcoma,[17] glioblastoma,[18] colorectal cancer,[19] and other cancers,[20] and contributes to tumorigenesis by regulating epithelial–mesenchymal transition (EMT), autophagy, and apoptosis.

MALAT-1 regulates cancer development via diverse mechanisms, including the MALAT-1/miR-183/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and Wnt/β-catenin signaling pathways (Figure 1). However, the precise mechanisms of action of MALAT-1 in different cancers and the pathways involved are not fully understood. In this review, we summarize what is known of the function of MALAT-1 in various cancers. The existing evidence suggests that knowledge of MALAT-1 and its regulatory networks will be highly useful for cancer diagnosis and treatment.

MALAT-1 in Cancer
Hepatocellular Carcinoma (HCC)

MALAT-1 is overexpressed in HCC tissues and cell lines; its expression level was shown to be negatively correlated with several prognostic variables, and it has been identified as a biomarker of liver damage and HCC development.[21,22] MALAT-1 is upregulated by hypoxia, forming a feedback look with hypoxia-inducible factor (HIF)-2α, Yes-associated oncoprotein (YAP)1, and specificity protein (SP)1 and SP3[23] to inhibit apoptosis and promote the proliferation,[24,25] invasion, and migration[26]

of HCC cells. Additionally, hepatitis B virus X protein (HBx) can induce MALAT-1, leading to upregulation of latent transforming growth factor β-binding proteins (LTBPs) that promote HCC growth and metastasis.[27] Thus, MALAT-1 plays an oncogenic role in HCC. Conversely, downregulation of MALAT-1 via inhibition of autophagy leads to suppression of HCC cell proliferation and tumor growth.[28] Single nucleotide polymorphisms in the *MALAT-1* gene are related to clinical characteristics of HCC: in patients <50 years old, the G allele of the MALAT-1 rs619586 polymorphism was associated with a lower incidence of HCC, while female smokers who were carriers of the CA or AA genotype of rs119433829 had a lower risk of vascular invasion and lower Child-Pugh grade than noncarriers.[29]

Hypoxia, which plays an important role in solid tumor development, can enhance MALAT-1 expression in HCC.[24,30] MALAT-1 was shown to modulate the proliferation, apoptosis, migration, and invasion HCC cells exposed to hypoxia by sponging miR-200a.[24] MALAT-1 indirectly activates Sirt1 deacetylase by competing for binding with Depleted in breast cancer (DBC)1; this ultimately results in the deacetylation of p53, which inhibits proapoptosis gene expression and promotes tumor cell growth.[31] Additionally, MALAT-1 promotes HCC progression by upregulating Serine/arginine-rich protein-specific kinase (SRSF) and activating mTOR.[32] MALAT-1 protects the integrity of mRNAs through competing endogenous (ce)RNA networks, and regulates protein expression at the posttranscriptional level to stimulate tumor progression.[33] MALAT-1 was shown to enhance the expression of vascular endothelial growth factor (VEGF)-A by sponging the miRNA miR-140, thereby promoting angiogenesis and accelerating HCC progression and metastasis.[34] MALAT-1 also increased the expression of Snail family zinc finger (Slug) by binding to miR-124-3p; Slug inhibited the expression of the epithelial marker cadherin 1,[35] thereby stimulating HCC cell migration and metastasis.[36] Upregulated MALAT-1 can sponge miR-30a-5p, leading to increased expression of the mesenchymal marker vimentin; EMT is consequently induced through the migration and invasion of HCC cells.[37] The sponging of miR-125a-3p by MALAT-1[38] enhances the expression of forkhead box (FOX)M1,[39] which promotes HCC proliferation, migration, invasion, and viability. The MALAT-1/miR-143-3p/zinc finger E-box binding homeobox transcription factor (ZEB)1 signaling axis has been implicated in HCC progression.[40] Similarly, the MALAT-1/miR-204/silent information regulator (SIRT)1[28] and MALAT-1/miR-195/
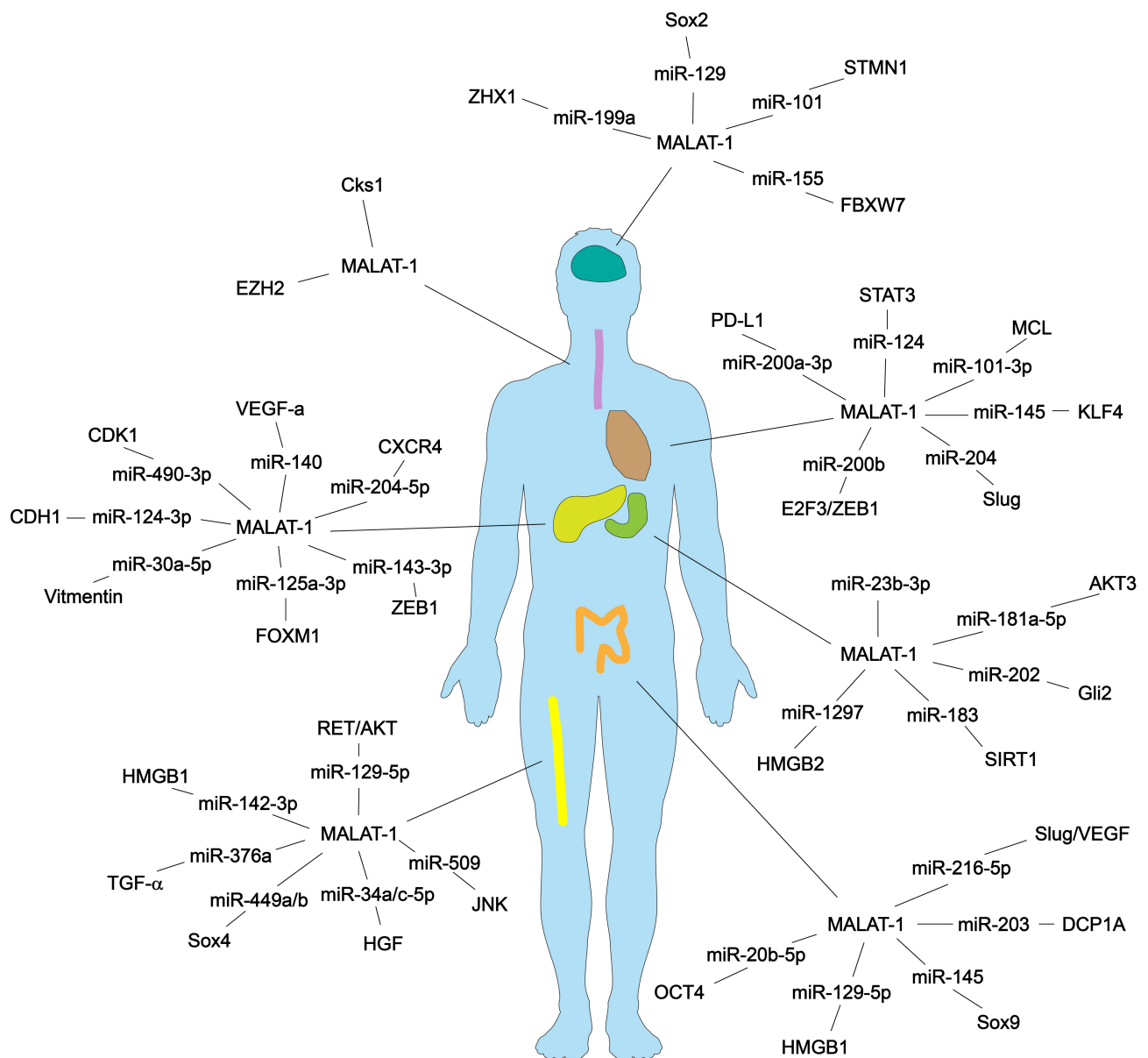
Figure I MALAT1 as ceRNA in different cancers, the figure lists some cancers (hepatocellular carcinoma, lung carcinoma, colorectal cancer, osteosarcoma, brain tumor and esophageal cancer).

epidermal growth factor receptor (EGFR)[33] axes were shown to regulate HCC cell migration and invasion. MALAT-1 negatively regulates miR-146b-5p expression, which in turn regulates HCC growth and metastasis.[41] In human hilar cholangiocarcinoma, MALAT-1 increased the expression of C-X-C chemokine receptor (CXCR)4 by sponging miR-204-5p, which stimulated HCC cell proliferation, invasion, and migration.[42] By interacting with the lncRNA Highly upregulated in liver cancer (HULC), MALAT-1 induces telomere repeat-binding factor (TRF)2, which was shown to promote HCC growth.[43] MALAT-1 also binds Brahma-related gene (BRG)1 to enhance the inflammatory response in HCC

tissues and thus accelerate HCC progression, suggesting that MALAT-1 silencing is a potential therapeutic strategy for the treatment of HCC.[44]

5-Fluorouracil (5-FU) is a broadly used chemotherapeutic agent.[45] However, its clinical effect is limited by various factors.[46] MALAT-1 depletion was shown to inactivate IκB kinase (IKK)α/nuclear factor (NF)-κB signaling, which increased 5-FU sensitivity by inducing cell cycle arrest and apoptosis.[47] Chemoresistance in HCC was shown to be mediated by the HIF-2α/MALAT-1/miR-216b axis.[48] The roles of MALAT-1 and its interaction partners in HCC are summarized in Figure 2 and Table 1.
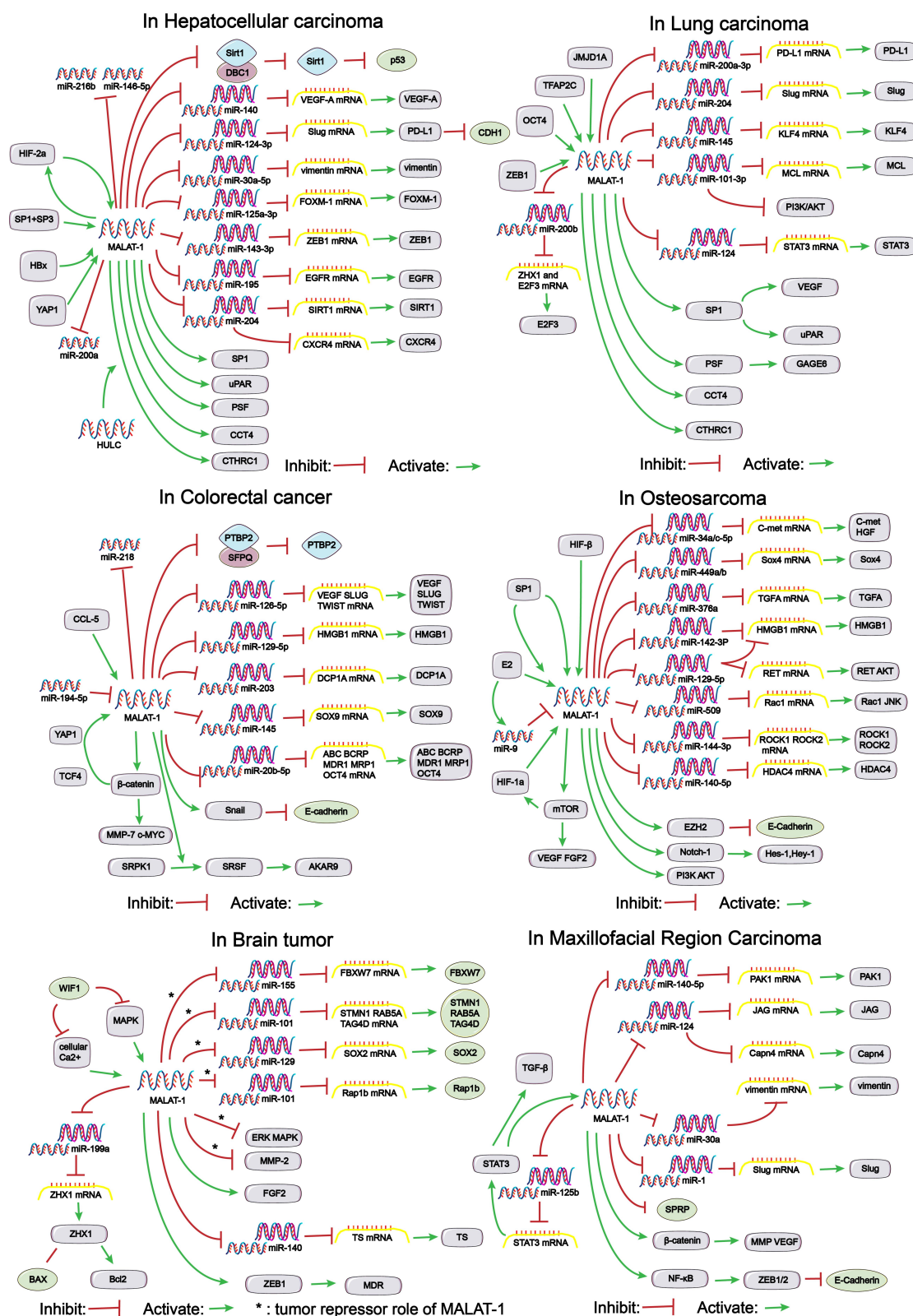
Figure 2 Regulatory networks of the lncRNA MALAT-1 in hepatocellular carcinoma, lung carcinoma, colorectal cancer, osteosarcoma, brain tumors and carcinoma of the maxillofacial region.

Table I MALAT1 May Function as ceRNA in HCC

LncRNA	miRNA	Target	Features	Reference
MALAT-1	miR-204	SIRT1	Migration and invasion	[28]
	miR-195	EGFR	Migration and invasion	[33]
	miR-140	VEGF-a	Promoting angiogenesis and accelerate the progression and metastasis	[34]
	miR-124-3p	CDH1	Promote migration and metastasis	[35]
	miR-30a-5p	Vimentin	Facilitate EMT, migration and invasion	[37]
	miR-125a-3p	FOXM1	Proliferation, migration, invasion and viability	[38]
	miR-143-3p	ZEB1	Regulate migration and invasion	[40]
	miR-204-5p	CXCR4	Proliferation, invasion and migration	[42]
	miR-216b	IGF2BP2	Proliferation, migration and invasion	[48]

Lung Carcinoma

MALAT-1 is dysregulated in NSCLC and its expression level is closely related to metastasis,[14] suggesting that it can serve as biomarker for NSCLC progression.[49] The level of MALAT-1 derived from NSCLC cell exosomes was found to be correlated with tumor stage and lymph node metastasis;[50] and knocking down MALAT-1 inhibited autophagy in NSCLC.[51]

Jumonji C-domain–containing protein (JMJD)1A is a histone demethylase that targets H3 lysine 9 (H3K9) and was shown to enhance MALAT-1 expression in NSCLC by binding to and demethylating the *MALAT-1* promoter.[52] Octamer-binding transcription factor (OCT)4, which contributes to the maintenance of stemness, also modulates MALAT-1 expression by binding to its enhancer, leading to increased tumor cell proliferation, migration, and invasion in NSCLC.[53] An elevated level of MALAT-1 reduced the expression of the tumor suppressor miR-200a-3p while increasing that of Programmed death ligand (PD-L)1,[54] which allowed lung tumor cells to avoid T-cell-mediated death by inhibiting antitumor immune responses.[55] The MALAT-1/miR-124 signaling axis was shown to be involved in the regulation of EMT and apoptosis.[56]

In lung adenocarcinoma, MALAT-1 induced by Transcription factor AP-2 gamma (TFAP2C) and ZEB1 stimulated the expression of E2F transcription factor (E2F)3 and ZEB1 by sponging miR-200b, resulting in docetaxel resistance, cell proliferation and migration, and EMT,[57] while silencing of which impairs tumor cells in migration and form fewer nodules.[58] Under hypoxia, MALAT-1 binds to the RNA-binding domain of polypyrimidine tract-binding (PTB) protein-associated splicing factor protein (PSF), causing it to release its downstream gene Proto-oncogene G antigen (GAGE)6 from repression, leading to proliferation, migration, and invasion of lung cancer cells.[59] MALAT-1 stabilizes SP1 by interacting with the MALAT-1 5′ end fragment M5 and SP1-C protein.[60] Constitutive expression of SP1 resulted in the upregulation of downstream factors such as VEGF and urokinase-type plasminogen activator receptor (uPAR), which was shown to accelerate angiogenesis and promote lung cancer development.[61] MALAT-1 was also found to promote lung tumorigenesis via MALAT-1/miR-204/Slug signaling[62] as well as lung adenocarcinoma progression by modulating the expression of cell motility-related genes such as Collagen triple helix repeat containing (CTHRC)1, Chaperonin-containing TCP1 subunit (CCT)4, and Regulator of differentiation (ROD)1.[63]

Cisplatin is a widely used chemotherapy drug for NSCLC. However, the development of chemoresistance can lead to treatment failure. MALAT-1 has been implicated in cisplatin resistance: MALAT-1 level was found to be elevated in cisplatin-resistant NSCLC.[64] Recent studies have suggested potential mechanisms underlying this effect. MALAT-1 was shown to enhance the expression of Kruppel-like factor (KLF) 4—an oncogene related to chemoresistance[65]–by inhibiting miR-145.[64] MALAT-1 silencing has been linked to cisplatin resensitization. Cisplatin resistance was also found to be correlated with MALAT-1/miR-101-3p/myeloid cell leukemia (MCL) signaling.[66] Interestingly, miR-101-3p inhibits PI3K/AKT signaling by targeting MALAT-1, thereby suppressing NSCLC proliferation, migration, invasion, growth, and metastasis.[67] Additionally, MALAT-1 causes cisplatin resistance by inducing the expression of genes encoding multidrug resistance (MDR) factors such as MDR1 and multidrug resistance-associated protein (MRP)1 via activation of Signal transducer and activator of transcription protein (STAT)3.[68] The MALAT-1/miR-124/STAT3 axis has been linked to lung tumor growth.[69] The regulatory network of MALAT-1 in lung carcinoma is summarized in Figure 2 and Table 2.

Table 2 MALAT1 May Function as ceRNA in Lung Carcinoma

LncRNA	miRNA	Target	Features	Reference
MALAT-1	miR-200a-3p	PD-L1	Anti-tumor immune responses	[54]
	miR-124	STAT3	Regulation of EMT and apoptosis, tumor growth	[56,69]
	miR-200b	E2F3/ZEB1	Docetaxel-resistant, proliferation, migration and EMT	[57]
	miR-204	Slug	Promote tumor development	[62]
	miR-145	KLF4	Cisplatin treatment	[64]
	miR-101-3p	MCL	Proliferation, migration, invasion, growth and metastasis	[66]

Colorectal Cancer (CRC)

Most CRC tissues and cell lines overexpress MALAT-1, which is correlated with CRC cell proliferation and migration in vitro and CRC growth and metastasis in vivo. MALAT-1 expression was found to be correlated with disease-free survival, overall survival, tumor–node–metastasis (TNM) stage, and lymphovascular invasion in CRC patients.[70] The 3′ end motif of MALAT-1 (nt 6918–8441) is important for the malignant transformation of CRC, while nt 5434–6951 are involved in maintaining normal function.[71] The AA and CC genotypes of the *MALAT-1* polymorphisms rs619586 and rs1194338, respectively, are associated with an increased incidence of colorectal cancer.[72] Moreover, the G allele of the rs664589 polymorphism influences the interaction of MALAT-1 with miR-194-5p, which may increase the risk of CRC.[19]

Tumor-associated dendritic cells secrete chemokine (C-C motif) ligand (CCL)5, which stimulates MALAT-1 expression to promote CRC development.[73] YAP1 complexed with β-catenin and T cell factor (TCF)4 was shown to induce MALAT-1 expression by binding to its promoter, leading to decreased miR-126-5p and increased Slug, VEGF-A, and Twist expression and promoting EMT and metastasis in CRC.[74] Resveratrol reduced MALAT-1 level, which inhibited Wnt/β-catenin signaling by preventing β-catenin nuclear localization, leading to decreased matrix metalloproteinase (MMP)7 and c-Myc levels and inhibition of CRC cell proliferation, invasion, and migration.[75]

In CRC cells, MALAT-1 releases PTB protein (PTBP)2 from a complex with PTB-associated splicing factor (SFP) Q by binding to the latter.[76] PTBP2 is highly expressed in cancers and is involved in cancer cell growth,[77] and is normally inhibited by SFPQ.[78] PTBP2 induced by MALAT-1 can promote CRC cell migration and proliferation. By enhancing Serine/arginine-rich splicing factor kinase (SRPK)1-induced SRSF1 phosphorylation, MALAT-1 promoted CRC cell proliferation, invasion, and migration via upregulation of Protein kinase (PRK)A

kinase anchor protein (AKAR)9;[79] and by acting as decoy for miR-203, MALAT-1 induced the expression of mRNA-decapping enzyme (DCP)1A, resulting in increased CRC cell proliferation, invasion, and chemoresistance.[80] Activation of the MALAT-1/miR-145/Sex determining region Y-box (Sox)9 signaling axis promotes proliferation, invasion, and migration and inhibits cell cycle progression and apoptosis in CRC.[81] CRC progression is also influenced by MALAT-1/miR-129-5p/high-mobility group box (HMGB)1 signaling.[82]

MALAT-1 regulates the expression of E-cadherin as well as EMT progression, which requires enhancer of zeste homolog (EZH)2 and is correlated with oxaliplatin resistance in CRC.[83] Furthermore, MALAT-1 was shown to decrease E-cadherin level by inducing the transcriptional repressor Snail. The interaction of MALAT-1 and miR-218 also influenced oxaliplatin sensitivity in CRC cells, while small interfering (si)RNA-mediated knockdown of MALAT-1 restored oxaliplatin sensitivity.[82] It was reported that silencing MALAT-1 reduced the expression of drug resistance genes such as *MDR1, MRP1, breast cancer resistance protein* (*BCRP*), and ATP-binding cassette (ABC) transporters by upregulating miR-20b-5p, which induced apoptosis, inhibited EMT, and enhanced 5-FU sensitivity.[84] Interestingly, the stemness factor OCT4 is another downstream effector of miR-20b-5p;[85] the MALAT-1/miR-20b-5p/OCT4 axis was found to be involved in maintaining a stem cell-like phenotype and metabolic activity, which were correlated in tumorgenesis.[86] Thus, inhibiting the expression of MALAT-1 is a potential strategy for CRC treatment. The molecular interactions of MALAT-1 in CRC are shown in Figure 2, and its functions as a ceRNA in CRC are detailed in Table 3.

Osteosarcoma (OS)

MALAT-1 is upregulated in OS tissue and cell lines, which is correlated with poor overall survival[87] and increased OS cell proliferation, invasion, migration, and growth. SP1

Table 3 MALAT1 May Function as ceRNA in CRC

LncRNA	miRNA	Target	Features	Reference
MALAT-1	miR-126-5p	Slug/VEGF-a/Twist	Promote EMT and metastasis	[74]
	miR-203	DCP1A	Proliferation, invasion and chemoresistance	[80]
	miR-145	Sox9	Proliferation, invasion, migration and inhibition of cell cycle progress, apoptosis	[81]
	miR-129-5p	HMGB1	Progress of tumor	[82]
	miR-20b-5p	OCT4	Tumorgenesis	[86]

enhances MALAT-1 expression in OS cells by binding to its promoter, resulting in increased cell migration and invasion.[88] One study showed that 17-β-estradiol (E2) stimulated MALAT-1 expression through formation of the E2/E2-activated estrogen receptor (ER)α/SP1 complex, which enhanced OS cell proliferation, colony formation, invasion, and migration.[89] However, high concentrations of E2 were shown to induce miR-9, resulting in the degradation of MALAT-1 and estrogen receptor-independent decreases in OS cell proliferation, colony formation, invasion, migration, and apoptosis, and EMT.[17] MALAT-1 induced by transforming growth factor (TGF)-β repressed the expression of E-cadherin via interaction with EZH2, leading to EMT and metastasis in OS.[90]

MALAT-1 promotes OS proliferation and metastasis by sponging miR-34a/c-5p and miR-449a/b and inducing the expression of c-Met and Sox4.[91] c-Met encodes the tyrosine kinase receptor of hepatocyte growth factor (HGF), which regulates OS migration and invasion.[92] Sox4 acts downstream of TGF-β and the Wnt/β-catenin signaling pathway to modulate EMT and cancer metastasis.[93] MALAT-1 competes with TGF-α for binding to miR-376a, resulting in the release of TGF-α from the complex and stimulating OS cell growth.[94] By inhibiting miR-142-3p and miR-129-5p, MALAT-1 enhanced the expression of HMGB1, thereby promoting growth and proliferation and inhibiting apoptosis in OS cells.[95] Activation of the MALAT-1/miR-129-5p/Rearranged during transfection (RET)/AKT axis increased the proportion

of stem-like cells in OS, which ultimately enhanced OS cell proliferation and migration.[96] Additionally, a malignant phenotype in OS (ie, increased cell proliferation and metastasis) was also shown to be mediated by the MALAT-1/miR-509/Rac1/c-Jun N-terminal kinase (JNK)[97] and MALAT-1/miR-144-3p/Rho-associated kinase (ROCK)1/2[87] pathways. MALAT-1/mTOR/HIF-1α forms a positive feedback loop that can alter angiogenesis by inducing VEGF and fibroblast growth factor (FGF)2.[98] Moreover, MALAT-1 enhanced proliferation and suppressed apoptosis in OS cells by sponging miR-140-5p and aberrantly inducing histone deacetylase (HDAC)4 expression,[99] which has been linked to cancer development.[100,101] Suppression of MALAT-1 in OS resulted in the inhibition of PI3K/AKT signaling, which stimulated cell proliferation via dephosphorylation of PI3K p85α and AKT.[102] MALAT-1 functions as a ceRNA in various cellular processes in OS (Table 4).

MALAT-1 is upregulated in chondrosarcoma and promotes chondrosarcoma cell proliferation and viability by inducing the expression of Notch 1—which is frequently downregulated in cancers[103]—and its downstream targets Hairy and enhancer of split (HES)1 and HES-related with YRPW motif protein (HEY)1, among others.[104] The regulatory network of MALAT-1 in OS is depicted in Figure 2.

Brain Tumors

The function of MALAT-1 in brain tumors is controversial. MALAT-1 was shown to be downregulated in glioma,[105] but

Table 4 MALAT1 May Function as ceRNA in OS

LncRNA	miRNA	Target	Features	Reference
MALAT-1	miR-34a/c-5p	C-met/HGF	Migration and invasion	[91]
	miR-449a/b	Sox4	Migration and invasion	[91]
	miR-376a	TGF-α	Cell growth	[94]
	miR-142-3p	HMGB1	Cell growth, proliferation and anti-apoptosis	[95]
	miR-129-5p	RET/AKT	Promotion of proliferation and migration	[96]
	miR-509	JNK	Proliferation and metastasis	[97]
	miR-144-3p	ROCK1/ROCK2	Proliferation and metastasis	[87]
	miR-140-5p	HDAC4	Anti-apoptosis	[99]

glioma stem cells (GSCs) show elevated expression of MALAT-1. *MALAT-1* knockdown increased the proliferation of GSCs and decreased the expression of stemness markers through activation of extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signaling.[106] In glioma, MALAT-1 overexpression enhanced F-box and WD repeat domain-containing (FBXW7) expression by sponging miR-155. FBXW7 functions as a tumor suppressor in glioma by accelerating oncogenic product degradation.[107] Inhibition of MALAT-1 enhanced glioma cell viability and colony formation. MALAT-1 was shown to suppress glioma cell growth via inhibiting ERK/MAPK signaling and MMP2-mediated glioma cell invasion;[108] knocking down MALAT-1 increased cell migration and proliferation.[109] However, there is evidence that MALAT-1 functions as an oncogene in glioma: the MALAT-1/miR-101/stathmin (STMN)1 axis in conjunction with RAB5A and Autophagy-related 4D cysteine peptidase (ATG4D) promoted autophagy and proliferation in glioma cells,[110] and GSC viability, proliferation, and tumorigenesis were increased by MALAT-1/miR-129/Sox2 signaling.[111] By acting as a ceRNA of miR-101, MALAT-1 promotes proliferation and inhibits apoptosis in glioma cells by depressing Rap1b.[112] FGF2 induced by MALAT-1–stimulated vasculogenesis in glioma under hypoxic conditions.[113]

MALAT-1 is upregulated in glioblastoma multiforme (GBM). Wnt inhibitory factor (WIF)1 inhibited MALAT-1 via noncanonical Wnt/Ca^{2+} signaling in GBM cells, thereby blocking metastasis while having little effect on growth and proliferation.[109] MALAT-1 increased the expression of the antiapoptotic protein B cell lymphoma (Bcl)-2 while inhibiting that of the proapoptotic factor Bcl-2–associated X protein (Bax), which enhanced GBM cell proliferation, colony formation, and invasion via the MALAT-1/miR-199a/Zinc fingers and homeoboxes (ZHX)1 axis.[114] Additionally, MALAT-1 was found to promote thymidylate synthase expression by stimulating that of miR-203, which induced temozolomide (TMZ) resistance in GBM cells.[115] Knocking down *MALAT-1* decreased the levels of the multidrug resistance genes *MDR1, MRP5*, and ABC subfamily (ABC)B1 via downregulation of ZEB1, which increased the sensitivity of GBM to TMZ;[18] siRNA-mediated knockdown of *MALAT-1* in GBM stem cells resensitized the cells to TMZ.[116] Thus, strategies targeting MALAT-1 have potential therapeutic value for GBM treatment. Figure 2 shows the signaling pathways regulated by MALAT-1 in brain tumors.

Carcinoma of the Maxillofacial Region

MALAT-1 is upregulated in tongue squamous cell carcinoma (TSCC). MALAT-1 depletion was shown to inhibit TSCC cell proliferation, migration, colony formation, and metastasis[117] via a mechanism that is thought to involve upregulation of small proline-rich protein (SPRP),[118] which has been linked to abnormal epithelial proliferation and malignant progression.[119] By acting as a decoy of miR-140-5p, MALAT-1 promoted TSCC cell proliferation, invasion, and migration via upregulation of p21 (RAC1)-activated kinase (PAK)1,[120] which is implicated in tumorigenesis.[121] Knocking down *MALAT-1* suppressed tongue cancer growth via MALAT-1/miR-124/Jagged (JAG) signaling.[122]

Oral squamous cell carcinoma (OSCC) tissues and cell lines overexpress MALAT-1, which is associated with inhibition of apoptosis via activation of Wnt/β-catenin signaling. Another study demonstrated that MALAT-1 promotes OSCC cell growth and metastasis by activating the β-catenin and NF-κB pathways, leading to EMT.[123] Activated β-catenin induces MMP and VEGF, which are involved in cell invasion and angiogenesis;[124] meanwhile, activated NF-κB regulates the expression of E-cadherin by stimulating ZEB1/2.[125] The MALAT-1/miR-125b/STAT3 axis was shown to promote OSCC development.[126]

In head and neck squamous cell carcinoma (HNSCC), STAT3 induced by TGF-β induces the expression of MALAT-1, facilitating HNSCC invasion and metastasis by sponging miR-30a and upregulating vimentin.[127]

MALAT-1 was found to be overexpressed in nasopharyngeal carcinoma (NPC) cells; this was accompanied by upregulation of calpain small subunit 1 (Capn4) and downregulation of miR-124. MALAT-1 may modulate NPC cell proliferation and invasion and EMT in part by downregulating miR-124 and upregulating Capn4,[125,128] which normally function as a tumor suppressor and oncogene, respectively.[129,130] The MALAT-1/miR-1/Slug axis is associated with resistance to radiotherapy.[131] The role of MALAT-1 in carcinoma of the maxillofacial region is depicted in Figure 2.

Gastric Cancer (GC)

MALAT-1 is highly expressed in GC tissue and cell lines, which is correlated with peritoneal metastasis, local invasion, lymph node metastasis, and TNM stage.[132] Inhibition of MALAT-1 inhibited EMT, decreased the G0/G1 ratio, and induced S phase arrest and apoptosis in GC cells.[133]

Up-frameshift suppressor (UPF)1, a key component of the nonsense-mediated mRNA decay pathway,[134] was shown to inhibit GC cell proliferation, migration, and invasion and induce cell cycle arrest and apoptosis by targeting MALAT-1 for degradation.[135] MALAT-1 is also modulated by the miR-122/insulin-like growth factor 1 receptor (IGF-1R) axis.[136] In gastroblastoma, fusion of the 5′ region of MALAT-1 to glioma-associated oncogene (Gli) leads to an aggressive phenotype through activation of Sonic hedgehog (SHH) signaling.[137]

PI3K/AKT/mTOR signaling has been shown to be aberrantly activated in various cancers; this pathway is a target of MALAT-1.[138] MALAT-1 was found to promote the phosphorylation of PI3K and AKT, resulting in PI3K/AKT pathway activation and inducing GC cell proliferation, invasion, and migration.[139] Meanwhile, MALAT-1 interacted with EZH2 to decrease protocadherin (PCDH) 10 and stimulate the migration and invasion of GC cells.[140] By sponging miR-181a-5p, MALAT-1 enhanced the expression of RAC-γ serine/threonine-specific protein kinase (AKT3),[141] a component of the PI3K signaling pathway, resulting in the growth of gastric adenocarcinoma.[142] Activation of the MALAT-1/miR-202/Gli2 axis is correlated with clinical features of GC,[143] and GC cell viability, apoptosis, and autophagy are partly regulated by MALAT-1/miR-183/SIRT1 and MALAT-1/miR-183/PI3K/AKT/mTOR signaling.[144]

By sponging miR-1297, MALAT-1 promotes GC progression by upregulating High-mobility group box (HMGB) 2, which is involved in chemoresistance in GC.[145,146] The MALAT-1/miR-23b-3p axis confers chemoresistance by inducing prosurvival autophagy.[147] The regulatory network of MALAT-1 in GC is illustrated in Figure 3.

Ovarian Cancer (OC)

MALAT-1 is overexpressed in OC tissue and cell lines, which is associated with increased tumor cell proliferation, migration, and apoptosis. MALAT-1 level in OC is related to International Federation of Gynecology and Obstetrics stage, recurrence, and overall survival; and elevated plasma MALAT-1 has been linked to increased risk of distant metastasis and worse disease-free survival.[148] Knocking down *MALAT-1* impaired OC cell growth, invasion, and migration.[149]

MALAT-1 promotes tumorigenesis via upregulation of MMP13 and downregulation of MMP19 and thrombospondin type-1 motif (ADAMTS1), which are involved in extracellular matrix turnover and cancer progression.[150]

Cytidine monophosphate kinase (CMPK) is critical for OC development;[151] the MALAT-1/miR-143-3p/CMPK axis is linked to OC cell behavior and patient survival.[152] MALAT-1 stimulates proliferation and blocks apoptosis in OC via MALAT-1/miR-503-3p/Janus kinase (JAK)2/STAT3 signaling,[153] while the MALAT-1/miR-506 feedback loop also plays a role in regulating cell growth.[154] Activation of the PI3K/AKT signaling pathway induced by MALAT-1 was found to modulate OC cell proliferation.[155]

Repression of RNA-binding Fox-1 homolog (RBFOX) 2 by MALAT-1 leads to downregulation of kinesin-related protein (KIF)1Bβ, which has proapoptotic and tumor-suppressor functions that induce anoikis resistance.[156,157] Knocking down *MALAT-1* in OC cells resulted in increased sensitivity to cisplatin through repression of Notch-1 signaling—which is involved in tumor cell proliferation and apoptosis and carcinogenesis[158]—and expression of ABC membrane transporters (P-glycoprotein) and resistance-related proteins (ABCC1/MRP1).[159] The MALAT-1/miR-200c axis has also been implicated in chemoresistance.[160] The gene interaction network of MALAT-1 in OC is shown in Figure 3.

Breast Cancer (BC)

MALAT-1 has varied roles in BC. MALAT-1 overexpression was associated with worse outcome in BC patients and was positively correlated with tumor size and stage.[161] MALAT-1 delivered by exosomes—which is an important mode of intracellular communication[162]—was shown to induce BC cell proliferation.[163] Induction of MALAT-1 by Lysine-specific demethylase (KDM)5B enhanced invasion and colony formation in triple-negative BC.[164] Targeting MALAT-1 with antisense oligonucleotide in a mouse mammary tumor virus polyoma middle tumor antigen carcinoma model resulted in inhibition of tumor growth and metastasis and induction of differentiation.[165] In BC, E2 was shown to suppress the expression of MALAT-1 in a concentration-dependent and not an ER receptor-dependent manner.[166] It was demonstrated that MALAT-1 modulates the expression of cell division cycle (CDC)42 by competing for binding with miR-1, thereby facilitating BC cell migration and invasion.[167] Additionally, the MALAT-1/miR-204/ZEB2 axis promoted EMT[168] whereas the MALAT-1/miR-145/VEGF axis stimulated angiogenesis, proliferation, migration, and invasion in BC.[169] Sox2 induced by MALAT-1 was found to induce a stem cell-like phenotype in BC cells.[170]
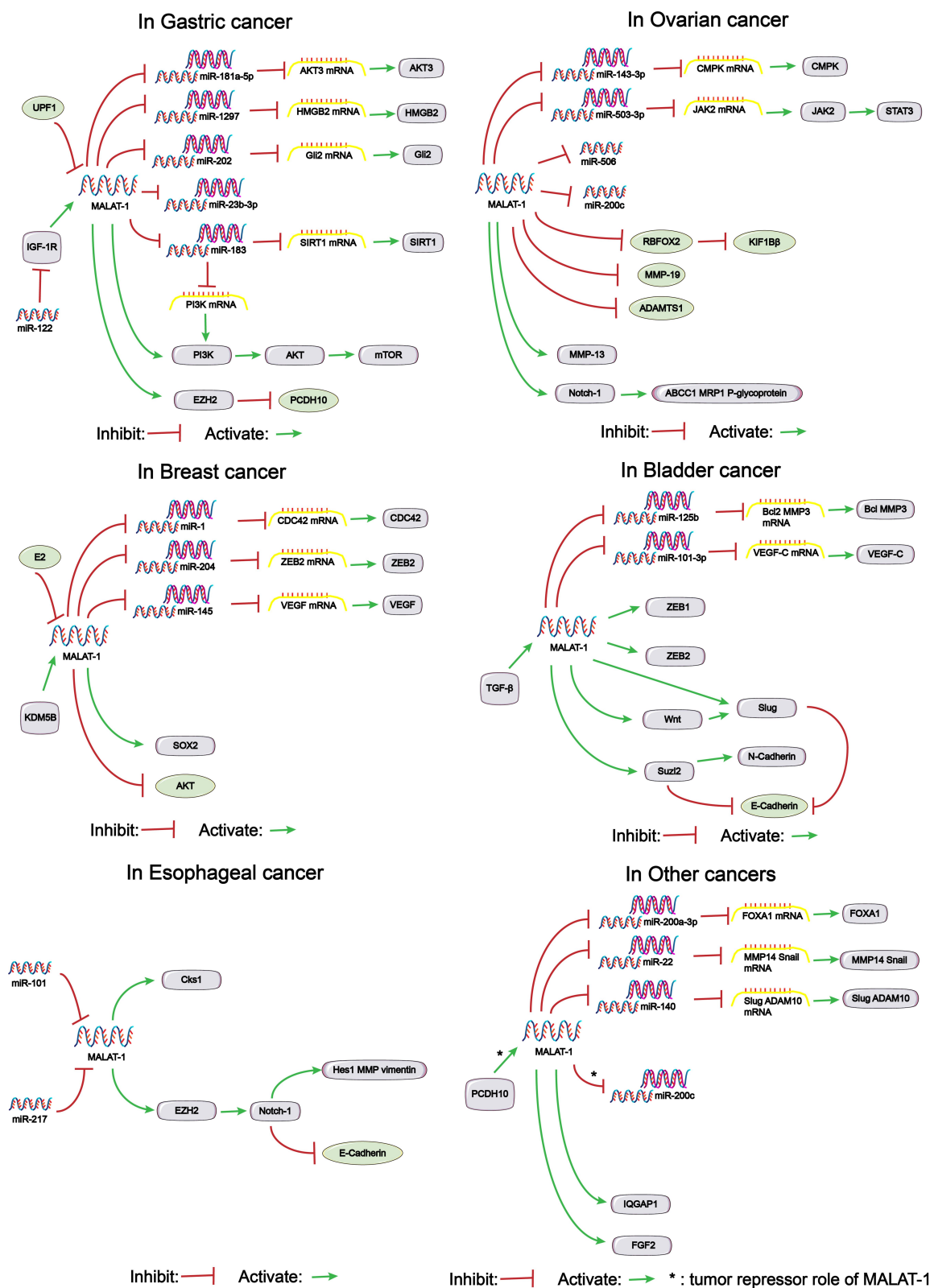
Figure 3 MALAT-1 and its cascade network in gastric cancer, ovarian cancer, breast cancer, bladder cancer, esophageal cancer and other cancers.

On the contrary, MALAT-1 may function as a tumor repressor by inducing Nischarin expression.[171] Downregulation of MALAT-1 in BC tissue and cell lines was correlated with axillary lymph node metastasis and clinical features, and may induce EMT via AKT phosphorylation and activation of PI3K/AKT signaling.[138] The putative regulatory cascade of MALAT-1 in BC is outlined in Figure 3.

Bladder Cancer

Elevated expression of MALAT-1 is considered as a prognostic biomarker in bladder cancer.[172] MALAT-1 induced by TGF-β was shown to increase N-cadherin and decrease E-cadherin expression through interaction with the Polycomb repressive complex (PRC)2 component Suppressor of zeste-like (Suzl)2, which is required for E-cadherin repression;[173] this ultimately promoted EMT, tumor growth, and invasion in bladder cancer.[174] MALAT-1 activates Wnt signaling, which results in activation of Slug and acceleration of EMT.[175] Silencing MALAT-1 reduced ZEB1, ZEB2, and Slug expression and increased that of E-cadherin, which blocked EMT in bladder cancer.[175] By acting as a ceRNA of miR-125b, MALAT-1 enhances the expression of Bcl-2 and MMP-13, thereby suppressing apoptosis and promoting metastasis.[176] The MALAT-1/miR-101-3p/VEGF-C axis mediates cisplatin resistance.[177] Figure 3 shows the regulatory network of MALAT-1 in bladder cancer.

Esophageal Cancer (EC)

MALAT-1 is upregulated in EC tissues and cell lines, which is correlated with tumor stage, lymph node metastasis, and poor outcome. MALAT-1 is considered as a prognostic biomarker in middle thoracic ESCC patients who have undergone radical resection.[178] In esophageal squamous cell carcinoma (ESCC), a C>T mutation in rs3200401 increased the risk of ESCC in a nonalcoholic background, whereas an A>G mutation in rs619586 had the opposite effect in an alcoholic background.[179] Knocking down MALAT-1 inhibited ESCC cell growth, colony formation, invasion, and migration and caused G2/M phase arrest and apoptosis.[180,181]

The miRNAs miR-101 and miR-217 were shown to inhibit MALAT-1 expression in EC.[181] EZH2/Notch1 signaling has been implicated in the development of many cancers;[182] MALAT-1 silencing reduced cancer cell viability, invasion, and migration by inhibiting this pathway.[183] Additionally, the MALAT-1/EZH2/β-catenin axis is dysregulated in EC.[184]

Radiotherapy is commonly used to treat EC,[185] but the development of resistance can lead to treatment failure. Resistance to radiotherapy was found to be correlated with MALAT-1 level;[186] it was also shown that MALAT-1 induced Cyclin-dependent kinases regulatory subunit (Cks)1, which was related to increased radiotherapy resistance.[187] Depletion of MALAT-1 may resensitize EC cells to radiotherapy by inducing G2/M phase arrest. The signaling pathways modulated by MALAT-1 in EC are shown in Figure 3.

Other Cancers

Thyroid cancer (TC) tissue and cell lines express a high level of MALAT-1, which is correlated with cell invasion and proliferation. MALAT-1 can induce expression of IQ motif-containing GTPase activating protein (IQGAP)1,[188] which is involved in cell adhesion and motility;[189] this was correlated with TC growth and invasion.[190] MALAT-1 was also shown to modulate the expression of FGF2 protein secreted by tumor-associated macrophages, leading to enhanced proliferation, migration, and angiogenesis in TC.[191] In anaplastic thyroid carcinoma, knocking down MALAT-1 suppressed cell proliferation, invasion, and migration via MALAT-1/miR-200a-3p/FOXA1 signaling.[192]

MALAT-1 is overexpressed in prostate cancer and melanoma tissues as well as cell lines, which is associated with metastasis. Repression of MALAT-1 inhibited melanoma cell migration, whereas proliferation was less affected,[193] and prostate cancer cell cycle arrest in the G0/G1 phases.[194] It was reported that MALAT-1 promotes melanoma cell proliferation, invasion, and migration via the MALAT-1/miR-22/MMP-14/Snail axis,[195] while the MALAT-1/miR-140/Slug/ADAM10 axis has also been linked to melanoma growth and invasion.

MALAT-1 is downregulated in type 1 endometrial carcinoma[196] and functions downstream of PCDH10, a negative regulator of Wnt/β-catenin signaling.[197] The MALAT-1/miR-200c axis is involved in cell migration and invasion, tumor growth, and EMT in endometrial carcinoma.[198] Figure 3 outlines the molecular interactions of MALAT-1 in other cancers.

Conclusion

LncRNAs have several important functions in cells. (a) Molecular decoy: Through competitive interaction with specific molecules such as miRNAs, lncRNAs derepress target molecules, leading to activation of downstream signaling pathways.[199] (b) Molecular guide: LncRNAs guide

the modification of chromosomes[200] and target molecules.[6] (c) Molecular scaffold: LncRNAs participate in the formation of ribonucleoprotein complexes.[201] (d) Molecular regulator: LncRNAs directly regulate transcription through interaction with transcription factors. The specific functions of lncRNAs are context-dependent and vary according to cancer type, tumor microenvironment, genetic background, and associated signaling pathways.

MALAT-1 plays an important role in cancer development by regulating oncogene as well as its own transcription: it can either interact with a transcription factor that binds to the promoter of a target gene, or function as a sponge to control the inhibitory effect of miRNAs on target transcripts. Epigenetic modifications (eg, demethylation of H3K9 at the *MALAT-1* promoter) can lead to MALAT-1 overexpression.[202] By coordinating gene expression and splicing, MALAT-1 contributes to cell cycle and proliferation disorders and promotes cell migration and metastasis in cancer.[203] MALAT-1 has the merits of a biomarker: it can be detected in body fluids (eg, blood),[204] which can be easily obtained with minimal risk to the patient; technologic advances have enabled the detection of low-abundance RNA transcripts by PCR amplification or RNA sequencing in clinical laboratories. Moreover, MALAT-1 overexpression is observed in a variety of cancers and is related to clinical characteristics as well as drug resistance in patients.

In this review, we summarized the roles and mechanisms of action of MALAT-1 and associated signaling networks in a variety of malignancies. A deeper understanding of MALAT-1 function in cancer can guide the design of targeted therapies for different cancers. Although further research is needed to clarify the contribution of MALAT-1 to different cancers, the existing evidence suggests that MALAT-1, along with related signaling pathways, can serve as a diagnostic or prognostic biomarker or drug target in cancer treatment.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Claverie J-M. Fewer genes, more noncoding RNA. *Science*. 2005;309 (5740):1529–1530. doi:10.1126/science.1116800
2. Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. *Cell*. 2009;136(4):629–641.
3. Core LJ, Waterfall JJ, Lis JT. Nascent RNA sequencing reveals widespread pausing and divergent initiation at human promoters. *Science*. 2008;322(5909):1845–1848.
4. Gutschner T, Hammerle M, Diederichs S. MALAT1 – a paradigm for long noncoding RNA function in cancer. *J Mol Med (Berl)*. 2013;91(7):791–801.
5. Qiu MT, Hu JW, Yin R, Xu L. Long noncoding RNA: an emerging paradigm of cancer research. *Tumour Biol*. 2013;34 (2):613–620.
6. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. *Mol Cell*. 2011;43(6):904–914.
7. Yoon JH, Abdelmohsen K, Srikantan S, et al. LincRNA-p21 suppresses target mRNA translation. *Mol Cell*. 2012;47 (4):648–655.
8. Chan JJ, Noncoding TY. RNA:RNA Regulatory Networks in Cancer. *Int J Mol Sci*. 2018;19:5.
9. Prabhu KS, Raza A, Karedath T, et al. Non-Coding RNAs as Regulators and Markers for Targeting of Breast Cancer and Cancer Stem Cells. *Cancers*. 2020;12:2.
10. Rao A, Rajkumar T, Mani S. Perspectives of long non-coding RNAs in cancer. *Mol Biol Rep*. 2017;44(2):203–218.
11. Malik B, Feng FY. Long noncoding RNAs in prostate cancer: overview and clinical implications. *Asian J Androl*. 2016;18 (4):568–574. doi:10.4103/1008-682X.177123
12. Chakrabarti R, Srivatsan ES, Wood TF, et al. Deletion mapping of endocrine tumors localizes a second tumor suppressor gene on chromosome band 11q13. *Genes Chromosomes Cancer*. 1998;22 (2):130–137.
13. Tripathi V, Ellis JD, Shen Z, et al. The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. *Mol Cell*. 2010;39(6):925–938.
14. Ji P, Diederichs S, Wang W, et al. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene*. 2003;22(39):8031–8041.
15. Guerrieri F. Long non-coding RNAs era in liver cancer. *World J Hepatol*. 2015;7(16):1971–1973.
16. Xu Y, Zhang Q, Lin F, et al. Casiopeina IIgly acts on lncRNA MALAT1 by miR175p to inhibit FZD2 expression via the Wnt signaling pathway during the treatment of cervical carcinoma. *Oncol Rep*. 2019;1.
17. Fang D, Yang H, Lin J, et al. 17beta-estradiol regulates cell proliferation, colony formation, migration, invasion and promotes apoptosis by upregulating miR-9 and thus degrades MALAT-1 in osteosarcoma cell MG-63 in an estrogen receptor-independent manner. *Biochem Biophys Res Commun*. 2015;457(4):500–506.
18. Li H, Yuan X, Yan D, et al. Long Non-Coding RNA MALAT1 Decreases the Sensitivity of Resistant Glioblastoma Cell Lines to Temozolomide. *Cell Physiol Biochem*. 2017;42(3):1192–1201.
19. Wu S, Sun H, Wang Y, et al. MALAT1 rs664589 Polymorphism Inhibits Binding to miR-194-5p, Contributing to Colorectal Cancer Risk, Growth, and Metastasis. *Cancer Res*. 2019;79 (20):5432–5441.
20. Gao D, Lv AE, Li HP, Han DH, Zhang YP. LncRNA MALAT-1 Elevates HMGB1 to Promote Autophagy Resulting in Inhibition of Tumor Cell Apoptosis in Multiple Myeloma. *J Cell Biochem*. 2017;118(10):3341–3348.
21. Lai MC, Yang Z, Zhou L, et al. Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. *Med Oncol*. 2012;29(3):1810–1816.
22. Konishi H, Ichikawa D, Yamamoto Y, et al. Plasma level of metastasis-associated lung adenocarcinoma transcript 1 is associated with liver damage and predicts development of hepatocellular carcinoma. *Cancer Sci*. 2016;107(2):149–154.
23. Huang Z, Huang L, Shen S, et al. Sp1 cooperates with Sp3 to upregulate MALAT1 expression in human hepatocellular carcinoma. *Oncol Rep*. 2015;34(5):2403–2412.

24. Zhao ZB, Chen F, Bai XF. Long Noncoding RNA MALAT1 Regulates Hepatocellular Carcinoma Growth Under Hypoxia via Sponging MicroRNA-200a. *Yonsei Med J*. 2019;60(8):727–734.

25. Wang J, Wang H, Zhang Y, et al. Mutual inhibition between YAP and SRSF1 maintains long non-coding RNA, Malat1-induced tumourigenesis in liver cancer. *Cell Signal*. 2014;26 (5):1048–1059.

26. Luo F, Sun B, Li H, et al. A MALAT1/HIF-2alpha feedback loop contributes to arsenite carcinogenesis. *Oncotarget*. 2016;7 (5):5769–5787.

27. Huang JF, Guo YJ, Zhao CX, et al. Hepatitis B virus X protein (HBx)-related long noncoding RNA (lncRNA) down-regulated expression by HBx (Dreh) inhibits hepatocellular carcinoma metastasis by targeting the intermediate filament protein vimentin. *Hepatology*. 2013;57(5):1882–1892.

28. Hou Z, Xu X, Zhou L, et al. The long non-coding RNA MALAT1 promotes the migration and invasion of hepatocellular carcinoma by sponging miR-204 and releasing SIRT1. *Tumour Biol*. 2017;39 (7):1010428317718135.

29. Yuan LT, Chang JH, Lee HL, et al. Genetic Variants of lncRNA MALAT1 Exert Diverse Impacts on the Risk and Clinicopathologic Characteristics of Patients with Hepatocellular Carcinoma. *J Clin Med*. 2019;8:9.

30. Hockel M, Vaupel P. Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects. *J Natl Cancer Inst*. 2001;93(4):266–276.

31. Chen R, Liu Y, Zhuang H, et al. Quantitative proteomics reveals that long non-coding RNA MALAT1 interacts with DBC1 to regulate p53 acetylation. *Nucleic Acids Res*. 2017;45 (17):9947–9959.

32. Malakar P, Shilo A, Mogilevsky A, et al. Long Noncoding RNA MALAT1 Promotes Hepatocellular Carcinoma Development by SRSF1 Upregulation and mTOR Activation. *Cancer Res*. 2017;77 (5):1155–1167.

33. Liu D, Zhu Y, Pang J, Weng X, Feng X, Guo Y. Knockdown of long non-coding RNA MALAT1 inhibits growth and motility of human hepatoma cells via modulation of miR-195. *J Cell Biochem*. 2018;119(2):1368–1380.

34. Hou ZH, Xu XW, Fu XY, Zhou LD, Liu SP, Tan DM. Long non-coding RNA MALAT1 promotes angiogenesis and immuno-suppressive properties of HCC cells by sponging miR-140. *Am J Physiol Cell Physiol*. 2020;318(3):C649–C663.

35. Qin W, Pan Y, Zheng X, et al. MicroRNA-124 regulates TGF-alpha-induced epithelial-mesenchymal transition in human prostate cancer cells. *Int J Oncol*. 2014;45(3):1225–1231.

36. Wang P, Voronkova M, Luanpitpong S, et al. Induction of Slug by Chronic Exposure to Single-Walled Carbon Nanotubes Promotes Tumor Formation and Metastasis. *Chem Res Toxicol*. 2017;30(7):1396–1405.

37. Pan Y, Tong S, Cui R, et al. Long Non-Coding MALAT1 Functions as a Competing Endogenous RNA to Regulate Vimentin Expression by Sponging miR-30a-5p in Hepatocellular Carcinoma. *Cell Physiol Biochem*. 2018;50(1):108–120.

38. Liu S, Qiu J, He G, et al. LncRNA MALAT1 acts as a miR-125a-3p sponge to regulate FOXM1 expression and promote hepato-cellular carcinoma progression. *J Cancer*. 2019;10 (26):6649–6659.

39. Raychaudhuri P, Park HJ. FoxM1: a master regulator of tumor metastasis. *Cancer Res*. 2011;71(13):4329–4333.

40. Chen L, Yao H, Wang K, Liu X. Long Non-Coding RNA MALAT1 Regulates ZEB1 Expression by Sponging miR-143-3p and Promotes Hepatocellular Carcinoma Progression. *J Cell Biochem*. 2017;118(12):4836–4843.

41. Li C, Miao R, Liu S, et al. Down-regulation of miR-146b-5p by long noncoding RNA MALAT1 in hepatocellular carcinoma pro-motes cancer growth and metastasis. *Oncotarget*. 2017;8 (17):28683–28695.

42. Tan X, Huang Z, Li X. Long Non-Coding RNA MALAT1 Interacts With miR-204 to Modulate Human Hilar Cholangiocarcinoma Proliferation, Migration, and Invasion by Targeting CXCR4. *J Cell Biochem*. 2017;118(11):3643–3653.

43. Wu M, Lin Z, Li X, et al. HULC cooperates with MALAT1 to aggravate liver cancer stem cells growth through telomere repeat-binding factor 2. *Sci Rep*. 2016;6:36045.

44. Huang M, Wang H, Hu X, Cao X. lncRNA MALAT1 binds chromatin remodeling subunit BRG1 to epigenetically promote inflammation-related hepatocellular carcinoma progression. *Oncoimmunology*. 2019;8(1):e1518628.

45. Lee HW, Kim SJ, Choi IJ, Song J, Chun KH. Targeting Notch signaling by gamma-secretase inhibitor I enhances the cytotoxic effect of 5-FU in gastric cancer. *Clin Exp Metastasis*. 2015;32 (6):593–603.

46. Kim SH, Kim SC, Ku JL. Metformin increases chemo-sensitivity via gene downregulation encoding DNA replication proteins in 5-Fu resistant colorectal cancer cells. *Oncotarget*. 2017;8 (34):56546–56557.

47. Ji DG, Guan LY, Luo X, Ma F, Yang B, Liu HY. Inhibition of MALAT1 sensitizes liver cancer cells to 5-fluorouracil by regu-lating apoptosis through IKKalpha/NF-kappaB pathway. *Biochem Biophys Res Commun*. 2018;501(1):33–40.

48. Yuan P, Cao W, Zang Q, Li G, Guo X, Fan J. The HIF-2alpha-MALAT1-miR-216b axis regulates multi-drug resistance of hepa-tocellular carcinoma cells via modulating autophagy. *Biochem Biophys Res Commun*. 2016;478(3):1067–1073.

49. Peng H, Wang J, Li J, et al. A circulating non-coding RNA panel as an early detection predictor of non-small cell lung cancer. *Life Sci*. 2016;151:235–242.

50. Zhang R, Xia Y, Wang Z, et al. Serum long non coding RNA MALAT-1 protected by exosomes is up-regulated and promotes cell proliferation and migration in non-small cell lung cancer. *Biochem Biophys Res Commun*. 2017;490(2):406–414.

51. Ma J, Wu K, Liu K, Miao R. Effects of MALAT1 on proliferation and apo- ptosis of human non-small cell lung cancer A549 cells in vitro and tumor xenograft growth in vivo by modulating autophagy. *Cancer Biomark*. 2018;22(1):63–72.

52. Park SJ, Kim JG, Son TG, et al. The histone demethylase JMJD1A regulates adrenomedullin-mediated cell proliferation in hepatocellular carcinoma under hypoxia. *Biochem Biophys Res Commun*. 2013;434(4):722–727.

53. Jen J, Tang YA, Lu YH, Lin CC, Lai WW, Wang YC. Oct4 transcriptionally regulates the expression of long non-coding RNAs NEAT1 and MALAT1 to promote lung cancer progression. *Mol Cancer*. 2017;16(1):104.

54. Wei S, Wang K, Huang X, Zhao Z, Zhao Z. LncRNA MALAT1 contributes to non-small cell lung cancer progression via modu-lating miR-200a-3p/programmed death-ligand 1 axis. *Int J Immunopathol Pharmacol*. 2019;33:2058738419859699.

55. Chen T, Li Q, Liu Z, Chen Y, Feng F, Sun H. Peptide-based and small synthetic molecule inhibitors on PD-1/PD-L1 pathway: A new choice for immunotherapy? *Eur J Med Chem*. 2019;161:378–398.

56. Wu J, Weng Y, He F, Liang D, Cai L. LncRNA MALAT-1 competi-tively regulates miR-124 to promote EMT and development of non-small-cell lung cancer. *Anticancer Drugs*. 2018;29(7):628–636.

57. Chen J, Liu X, Xu Y, et al. TFAP2C-Activated MALAT1 Modulates the Chemoresistance of Docetaxel-Resistant Lung Adenocarcinoma Cells. *Mol Ther Nucleic Acids*. 2019;14:567–582.

58. Gutschner T, Hammerle M, Eissmann M, et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. *Cancer Res*. 2013;73(3):1180–1189.

59. Hu L, Tang J, Huang X, Zhang T, Feng X. Hypoxia exposure upregulates MALAT-1 and regulates the transcriptional activity of PTB-associated splicing factor in A549 lung adenocarcinoma cells. *Oncol Lett*. 2018;16(1):294–300.

60. Li S, Ma F, Jiang K, Shan H, Shi M, Chen B. Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 promotes lung adenocarcinoma by directly interacting with specificity protein 1. *Cancer Sci*. 2018;109(5):1346–1356.

61. Li X, Song Y, Liu F, et al. Long Non-Coding RNA MALAT1 Promotes Proliferation, Angiogenesis, and Immunosuppressive Properties of Mesenchymal Stem Cells by Inducing VEGF and IDO. *J Cell Biochem*. 2017;118(9):2780–2791.

62. Li J, Wang J, Chen Y, et al. LncRNA MALAT1 exerts oncogenic functions in lung adenocarcinoma by targeting miR-204. *Am J Cancer Res*. 2016;6(5):1099–1107.

63. Tano K, Mizuno R, Okada T, et al. MALAT-1 enhances cell motility of lung adenocarcinoma cells by influencing the expression of motility-related genes. *FEBS Lett*. 2010;584(22):4575–4580.

64. Cui Y, Li G, Zhang X, Dai F, Zhang R. Increased MALAT1 expression contributes to cisplatin resistance in non-small cell lung cancer. *Oncol Lett*. 2018;16(4):4821–4828.

65. Shi M, Cui J, Du J, et al. A novel KLF4/LDHA signaling pathway regulates aerobic glycolysis in and progression of pancreatic cancer. *Clin Cancer Res*. 2014;20(16):4370–4380.

66. Wang H, Wang L, Zhang G, et al. MALAT1/miR-101-3p/MCL1 axis mediates cisplatin resistance in lung cancer. *Oncotarget*. 2018;9(7):7501–7512.

67. Zhang X, He X, Liu Y, et al. MiR-101-3p inhibits the growth and metastasis of non-small cell lung cancer through blocking PI3K/AKT signal pathway by targeting MALAT-1. *Biomed Pharmacother*. 2017;93:1065–1073.

68. Fang Z, Chen W, Yuan Z, Liu X, Jiang H. LncRNA-MALAT1 contributes to the cisplatin-resistance of lung cancer by upregulating MRP1 and MDR1 via STAT3 activation. *Biomed Pharmacother*. 2018;101:536–542.

69. Li S, Mei Z, Hu HB, Zhang X. The lncRNA MALAT1 contributes to non-small cell lung cancer development via modulating miR-124/STAT3 axis. *J Cell Physiol*. 2018;233(9):6679–6688.

70. Qiu G, Zhang XB, Zhang SQ, et al. Dysregulation of MALAT1 and miR-619-5p as a prognostic indicator in advanced colorectal carcinoma. *Oncol Lett*. 2016;12(6):5036–5042.

71. Xu C, Yang M, Tian J, Wang X, Li Z. MALAT-1: a long non-coding RNA and its important 3′ end functional motif in colorectal cancer metastasis. *Int J Oncol*. 2011;39(1):169–175.

72. Zhao K, Jin S, Wei B, Cao S, Xiong Z. Association study of genetic variation of lncRNA MALAT1 with carcinogenesis of colorectal cancer. *Cancer Manag Res*. 2018;10:6257–6261.

73. Kan JY, Wu DC, Yu FJ, et al. Chemokine (C-C Motif) Ligand 5 is Involved in Tumor-Associated Dendritic Cell-Mediated Colon Cancer Progression Through Non-Coding RNA MALAT-1. *J Cell Physiol*. 2015;230(8):1883–1894.

74. Sun Z, Ou C, Liu J, et al. YAP1-induced MALAT1 promotes epithelial-mesenchymal transition and angiogenesis by sponging miR-126-5p in colorectal cancer. *Oncogene*. 2019;38(14):2627–2644.

75. Ji Q, Liu X, Fu X, et al. Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/beta-catenin signal pathway. *PLoS One*. 2013;8(11):e78700.

76. Ji Q, Zhang L, Liu X, et al. Long non-coding RNA MALAT1 promotes tumour growth and metastasis in colorectal cancer through binding to SFPQ and releasing oncogene PTBP2 from SFPQ/PTBP2 complex. *Br J Cancer*. 2014;111(4):736–748.

77. Patton JG, Mayer SA, Tempst P, Nadal-Ginard B. Characterization and molecular cloning of polypyrimidine tract-binding protein: a component of a complex necessary for pre-mRNA splicing. *Genes Dev*. 1991;5(7):1237–1251.

78. Meissner M, Dechat T, Gerner C, Grimm R, Foisner R, Sauermann G. Differential nuclear localization and nuclear matrix association of the splicing factors PSF and PTB. *J Cell Biochem*. 2000;76(4):559–566.

79. Hu ZY, Wang XY, Guo WB, et al. Long non-coding RNA MALAT1 increases AKAP-9 expression by promoting SRPK1-catalyzed SRSF1 phosphorylation in colorectal cancer cells. *Oncotarget*. 2016;7(10):11733–11743.

80. Wu C, Zhu X, Tao K, et al. MALAT1 promotes the colorectal cancer malignancy by increasing DCP1A expression and miR203 downregulation. *Mol Carcinog*. 2018;57(10):1421–1431.

81. Xu Y, Zhang X, Hu X, et al. The effects of lncRNA MALAT1 on proliferation, invasion and migration in colorectal cancer through regulating SOX9. *Mol Med*. 2018;24(1):52.

82. Wu Q, Meng WY, Jie Y, LncRNA ZH. MALAT1 induces colon cancer development by regulating miR-129-5p/HMGB1 axis. *J Cell Physiol*. 2018;233(9):6750–6757.

83. Li P, Zhang X, Wang H, et al. MALAT1 Is Associated with Poor Response to Oxaliplatin-Based Chemotherapy in Colorectal Cancer Patients and Promotes Chemoresistance through EZH2. *Mol Cancer Ther*. 2017;16(4):739–751.

84. Tang D, Yang Z, Long F, et al. Inhibition of MALAT1 reduces tumor growth and metastasis and promotes drug sensitivity in colorectal cancer. *Cell Signal*. 2019;57:21–28.

85. Wang H, Liu B, Wang J, et al. Reduction of NANOG Mediates the Inhibitory Effect of Aspirin on Tumor Growth and Stemness in Colorectal Cancer. *Cell Physiol Biochem*. 2017;44(3):1051–1063.

86. Tang D, Yang Z, Long F, et al. Long noncoding RNA MALAT1 mediates stem cell-like properties in human colorectal cancer cells by regulating miR-20b-5p/Oct4 axis. *J Cell Physiol*. 2019;234(11):20816–20828.

87. Wang Y, Zhang Y, Yang T, et al. Long non-coding RNA MALAT1 for promoting metastasis and proliferation by acting as a ceRNA of miR-144-3p in osteosarcoma cells. *Oncotarget*. 2017;8(35):59417–59434.

88. Li S, Wang Q, Qiang Q, et al. Sp1-mediated transcriptional regulation of MALAT1 plays a critical role in tumor. *J Cancer Res Clin Oncol*. 2015;141(11):1909–1920.

89. Hu Q, Li S, Chen C, Zhu M, Chen Y, Zhao Z. 17betaEstradiol treatment drives Sp1 to upregulate MALAT1 expression and epigenetically affects physiological processes in U2OS cells. *Mol Med Rep*. 2017;15(3):1335–1342.

90. Huo Y, Li Q, Wang X, et al. MALAT1 predicts poor survival in osteosarcoma patients and promotes cell metastasis through associating with EZH2. *Oncotarget*. 2017;8(29):46993–47006.

91. Sun Z, Zhang T, Chen B. Long Non-Coding RNA Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) Promotes Proliferation and Metastasis of Osteosarcoma Cells by Targeting c-Met and SOX4 via miR-34a/c-5p and miR-449a/b. *Med Sci Monit*. 2019;25:1410–1422.

92. Husmann K, Ducommun P, Sabile AA, Pedersen EM, Born W, Fuchs B. Signal transduction and downregulation of C-MET in HGF stimulated low and highly metastatic human osteosarcoma cells. *Biochem Biophys Res Commun*. 2015;464(4):1222–1227.

93. Bu P, Wang L, Chen KY, et al. miR-1269 promotes metastasis and forms a positive feedback loop with TGF-beta. *Nat Commun*. 2015;6:6879.

94. Luo W, He H, Xiao W, et al. MALAT1 promotes osteosarcoma development by targeting TGFA via MIR376A. *Oncotarget*. 2016;7(34):54733–54743.

95. Liu K, Huang J, Ni J, et al. MALAT1 promotes osteosarcoma development by regulation of HMGB1 via miR-142-3p and miR-129-5p. *Cell Cycle*. 2017;16(6):578–587.

96. Chen Y, Huang W, Sun W, et al. LncRNA MALAT1 Promotes Cancer Metastasis in Osteosarcoma via Activation of the PI3K-Akt Signaling Pathway. *Cell Physiol Biochem*. 2018;51(3):1313–1326.

97. Zhang Y, Dai Q, Zeng F, Liu H. MALAT1 Promotes the Proliferation and Metastasis of Osteosarcoma Cells By Activating the Rac1/JNK Pathway Via Targeting MiR-509. *Oncol Res*. 2018;2:124.

98. Zhang ZC, Tang C, Dong Y, et al. Targeting the long noncoding RNA MALAT1 blocks the pro-angiogenic effects of osteosarcoma and suppresses tumour growth. *Int J Biol Sci*. 2017;13 (11):1398–1408.

99. Sun Y, Qin B. Long noncoding RNA MALAT1 regulates HDAC4-mediated proliferation and apoptosis via decoying of miR-140-5p in osteosarcoma cells. *Cancer Med*. 2018;7 (9):4584–4597.

100. Sun L, He Q, Tsai C, et al. HDAC inhibitors suppressed small cell lung cancer cell growth and enhanced the suppressive effects of receptor-targeting cytotoxins via upregulating somatostatin receptor II. *Am J Transl Res*. 2018;10(2):545–553.

101. Marampon F, Megiorni F, Camero S, et al. HDAC4 and HDAC6 sustain DNA double strand break repair and stem-like phenotype by promoting radioresistance in glioblastoma cells. *Cancer Lett*. 2017;397:1–11. doi:10.1016/j.canlet.2017.03.028

102. Dong Y, Liang G, Yuan B, Yang C, Gao R, Zhou X. MALAT1 promotes the proliferation and metastasis of osteosarcoma cells by activating the PI3K/Akt pathway. *Tumour Biol*. 2015;36(3):1477–1486.

103. Bolos V, Grego-Bessa J, de la Pompa JL. Notch signaling in development and cancer. *Endocr Rev*. 2007;28(3):339–363.

104. Xu F, Zhang ZQ, Fang YC, et al. Metastasis-associated lung adenocarcinoma transcript 1 promotes the proliferation of chondrosarcoma cell via activating Notch-1 signaling pathway. *Onco Targets Ther*. 2016;9:2143–2151.

105. Ma K-X, Wang H-J, Li X-R, et al. Long noncoding RNA MALAT1 associates with the malignant status and poor prognosis in glioma. *Tumour Biol*. 2015;36(5):3355–3359. doi:10.1007/s13277-014-2969-7

106. Han Y, Zhou L, Wu T, et al. Downregulation of lncRNA-MALAT1 Affects Proliferation and the Expression of Stemness Markers in Glioma Stem Cell Line SHG139S. *Cell Mol Neurobiol*. 2016;36 (7):1097–1107. doi:10.1007/s10571-015-0303-6

107. Cao S, Wang Y, Li J, Lv M, Niu H, Tian Y. Tumor-suppressive function of long noncoding RNA MALAT1 in glioma cells by suppressing miR-155 expression and activating FBXW7 function. *Am J Cancer Res*. 2016;6(11):2561–2574.

108. Han Y, Wu Z, Wu T, et al. Tumor-suppressive function of long noncoding RNA MALAT1 in glioma cells by downregulation of MMP2 and inactivation of ERK/MAPK signaling. *Cell Death Dis*. 2016;7(3):e2123. doi:10.1038/cddis.2015.407

109. Vassallo I, Zinn P, Lai M, Rajakannu P, Hamou M-F, Hegi ME. WIF1 re-expression in glioblastoma inhibits migration through attenuation of non-canonical WNT signaling by downregulating the lncRNA MALAT1. *Oncogene*. 2016;35(1):12–21. doi:10.1038/onc.2015.61

110. Fu Z, Luo W, Wang J, et al. Malat1 activates autophagy and promotes cell proliferation by sponging miR-101 and upregulating STMN1, RAB5A and ATG4D expression in glioma. *Biochem Biophys Res Commun*. 2017;492(3):480–486. doi:10.1016/j.bbrc.2017.08.070

111. Xiong Z, Wang L, Wang Q, Yuan Y. LncRNA MALAT1/miR-129 axis promotes glioma tumorigenesis by targeting SOX2. *J Cell Mol Med*. 2018;22(8):3929–3940. doi:10.1111/jcmm.13667

112. Li Z, Xu C, Ding B, Gao M, Wei X, Ji N. Long non-coding RNA MALAT1 promotes proliferation and suppresses apoptosis of glioma cells through derepressing Rap1B by sponging miR-101. *J Neurooncol*. 2017;134(1):19–28. doi:10.1007/s11060-017-2498-5

113. Tee AE, Liu B, Song R, et al. The long noncoding RNA MALAT1 promotes tumor-driven angiogenesis by up-regulating pro-angiogenic gene expression. *Oncotarget*. 2016;7 (8):8663–8675. doi:10.18632/oncotarget.6675

114. Liao K, Lin Y, Gao W, et al. Blocking lncRNA MALAT1/miR-199a/ZHX1 Axis Inhibits Glioblastoma Proliferation and Progression. *Mol Ther Nucleic Acids*. 2019;18:388–399.

115. Chen W, Xu X-K, Li J-L, et al. MALAT1 is a prognostic factor in glioblastoma multiforme and induces chemoresistance to temozolomide through suppressing miR-203 and promoting thymidylate synthase expression. *Oncotarget*. 2017;8(14):22783–22799. doi:10.18632/oncotarget.15199

116. Kim -S-S, Harford JB, Moghe M, Rait A, Pirollo KF, Chang EH. Targeted nanocomplex carrying siRNA against MALAT1 sensitizes glioblastoma to temozolomide. *Nucleic Acids Res*. 2016;35 (1):1424–1440. doi:10.1093/nar/gkx1221

117. Han X, Xu Z, Tian G, et al. Suppression of the long non-coding RNA MALAT-1 impairs the growth and migration of human tongue squamous cell carcinoma SCC4 cells. *Arch Med Sci*. 2019;15(4):992–1000.

118. Fang Z, Zhang S, Wang Y, et al. Long non-coding RNA MALAT-1 modulates metastatic potential of tongue squamous cell carcinomas partially through the regulation of small proline rich proteins. *BMC Cancer*. 2016;16:706.

119. Tesfaigzi J, Carlson DM. Expression, regulation, and function of the SPR family of proteins. A review. *Cell Biochem Biophys*. 1999;30(2):243–265.

120. Zhu M, Zhang C, Chen D, Chen S, Zheng H. lncRNA MALAT1 potentiates the progression of tongue squamous cell carcinoma through regulating miR-140-5p-PAK1 pathway. *Onco Targets Ther*. 2019;12:1365–1377.

121. King H, Nicholas NS, Wells CM. Role of p-21-activated kinases in cancer progression. *Int Rev Cell Mol Biol*. 2014;309:347–387.

122. Zhang TH, Liang LZ, Liu XL, et al. Long non-coding RNA MALAT1 interacts with miR-124 and modulates tongue cancer growth by targeting JAG1. *Oncol Rep*. 2017;37(4):2087–2094.

123. Zhou X, Liu S, Cai G, et al. Long Non Coding RNA MALAT1 Promotes Tumor Growth and Metastasis by inducing Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma. *Sci Rep*. 2015;5:15972.

124. Tripathi V, Shen Z, Chakraborty A, et al. Long noncoding RNA MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB. *PLoS Genet*. 2013;9(3):e1003368.

125. Chua HL, Bhat-Nakshatri P, Clare SE, Morimiya A, Badve S, Nakshatri H. NF-kappaB represses E-cadherin expression and enhances epithelial to mesenchymal transition of mammary epithelial cells: potential involvement of ZEB-1 and ZEB-2. *Oncogene*. 2007;26(5):711–724.

126. Chang SM, Hu WW. Long non-coding RNA MALAT1 promotes oral squamous cell carcinoma development via microRNA-125b/STAT3 axis. *J Cell Physiol*. 2018;233(4):3384–3396.

127. Wang Y, Wu C, Zhang C, et al. TGF-beta-induced STAT3 over-expression promotes human head and neck squamous cell carcinoma invasion and metastasis through malat1/miR-30a interactions. *Cancer Lett*. 2018;436:52–62.

128. Shi B, Wang Y, Yin F. MALAT1/miR-124/Capn4 axis regulates proliferation, invasion and EMT in nasopharyngeal carcinoma cells. *Cancer Biol Ther*. 2017;18(10):792–800.

129. Cai JJ, Qi ZX, Chen LC, Yao Y, Gong Y, Mao Y. miR-124 suppresses the migration and invasion of glioma cells in vitro via Capn4. *Oncol Rep*. 2016;35(1):284–290.

130. Furuta M, Kozaki KI, Tanaka S, Arii S, Imoto I, Inazawa J. miR-124 and miR-203 are epigenetically silenced tumor-suppressive microRNAs in hepatocellular carcinoma. *Carcinogenesis*. 2010;31(5):766–776.

131. Jin C, Yan B, Lu Q, Lin Y, Ma L. The role of MALAT1/miR-1/slug axis on radioresistance in nasopharyngeal carcinoma. *Tumour Biol*. 2016;37(3):4025–4033.

132. Okugawa Y, Toiyama Y, Hur K, et al. Metastasis-associated long non-coding RNA drives gastric cancer development and promotes peritoneal metastasis. *Carcinogenesis*. 2014;35(12):2731–2739.

133. Lee NK, Lee JH, Ivan C, et al. MALAT1 promoted invasiveness of gastric adenocarcinoma. *BMC Cancer*. 2017;17(1):46.

134. Kim YK, Furic L, Desgroseillers L, Maquat LE. Mammalian Staufen1 recruits Upf1 to specific mRNA 3′UTRs so as to elicit mRNA decay. *Cell*. 2005;120(2):195–208.

135. Li L, Geng Y, Feng R, et al. The Human RNA Surveillance Factor UPF1 Modulates Gastric Cancer Progression by Targeting Long Non-Coding RNA MALAT1. *Cell Physiol Biochem*. 2017;42 (6):2194–2206.

136. Xia H, Chen Q, Chen Y, et al. The lncRNA MALAT1 is a novel biomarker for gastric cancer metastasis. *Oncotarget*. 2016;7 (35):56209–56218.

137. Graham RP, Nair AA, Davila JI, et al. Gastroblastoma harbors a recurrent somatic MALAT1-GLI1 fusion gene. *Mod Pathol*. 2017;30(10):1443–1452.

138. Xu S, Sui S, Zhang J, et al. Downregulation of long noncoding RNA MALAT1 induces epithelial-to-mesenchymal transition via the PI3K-AKT pathway in breast cancer. *Int J Clin Exp Pathol*. 2015;8(5):4881–4891.

139. Zhu K, Ren Q, Zhao Y. lncRNA MALAT1 overexpression promotes proliferation, migration and invasion of gastric cancer by activating the PI3K/AKT pathway. *Oncol Lett*. 2019;17 (6):5335–5342.

140. Qi Y, Ooi HS, Wu J, et al. MALAT1 long ncRNA promotes gastric cancer metastasis by suppressing PCDH10. *Oncotarget*. 2016;7(11):12693–12703.

141. Lu Z, Luo T, Pang T, et al. MALAT1 promotes gastric adenocarcinoma through the MALAT1/miR-181a-5p/AKT3 axis. *Open Biol*. 2019;9(9):190095.

142. Gai D, Haan E, Scholar M, Nicholl J, Yu S. Phenotypes of AKT3 deletion: a case report and literature review. *Am J Med Genet A*. 2015;167A(1):174–179.

143. Zhang Y, Chen Z, Li MJ, Guo HY, Jing NC. Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 regulates the expression of Gli2 by miR-202 to strengthen gastric cancer progression. *Biomed Pharmacother*. 2017;85:264–271.

144. Li H, He C, Wang X, Wang H, Nan G, Fang L. MicroRNA-183 affects the development of gastric cancer by regulating autophagy via MALAT1-miR-183-SIRT1 axis and PI3K/AKT/mTOR signals. *Artif Cells Nanomed Biotechnol*. 2019;47(1):3163–3171.

145. Li J, Gao J, Tian W, Li Y, Zhang J. Long non-coding RNA MALAT1 drives gastric cancer progression by regulating HMGB2 modulating the miR-1297. *Cancer Cell Int*. 2017;17:44.

146. An Y, Zhang Z, Shang Y, et al. miR-23b-3p regulates the chemoresistance of gastric cancer cells by targeting ATG12 and HMGB2. *Cell Death Dis*. 2015;6:e1766.

147. YiRen H, YingCong Y, Sunwu Y, et al. Long noncoding RNA MALAT1 regulates autophagy associated chemoresistance via miR-23b-3p sequestration in gastric cancer. *Mol Cancer*. 2017;16(1):174.

148. Chen Q, Su Y, He X, et al. Plasma long non-coding RNA MALAT1 is associated with distant metastasis in patients with epithelial ovarian cancer. *Oncol Lett*. 2016;12(2):1361–1366.

149. Liu S, Jiang X, Li W, Cao D, Shen K, Yang J. Inhibition of the long non-coding RNA MALAT1 suppresses tumorigenicity and induces apoptosis in the human ovarian cancer SKOV3 cell line. *Oncol Lett*. 2016;11(6):3686–3692.

150. Zhou Y, Xu X, Lv H, et al. The Long Noncoding RNA MALAT-1 Is Highly Expressed in Ovarian Cancer and Induces Cell Growth and Migration. *PLoS One*. 2016;11(5):e0155250.

151. Zhou D, Zhang L, Sun W, et al. Cytidine monophosphate kinase is inhibited by the TGF-beta signalling pathway through the upregulation of miR-130b-3p in human epithelial ovarian cancer. *Cell Signal*. 2017;35:197–207.

152. Lin Q, Guan W, Ren W, Zhang L, Zhang J, Xu G. MALAT1 affects ovarian cancer cell behavior and patient survival. *Oncol Rep*. 2018;39(6):2644–2652.

153. Sun Q, Li Q, Xie F. LncRNA-MALAT1 regulates proliferation and apoptosis of ovarian cancer cells by targeting miR-503-5p. *Onco Targets Ther*. 2019;12:6297–6307.

154. Lei R, Xue M, Zhang L, Lin Z. Long noncoding RNA MALAT1-regulated microRNA 506 modulates ovarian cancer growth by targeting iASPP. *Onco Targets Ther*. 2017;10:35–46.

155. Jin Y, Feng SJ, Qiu S, Shao N, Zheng JH. LncRNA MALAT1 promotes proliferation and metastasis in epithelial ovarian cancer via the PI3K-AKT pathway. *Eur Rev Med Pharmacol Sci*. 2017;21(14):3176–3184.

156. Gordon MA, Babbs B, Cochrane DR, Bitler BG, Richer JK. The long non-coding RNA MALAT1 promotes ovarian cancer progression by regulating RBFOX2-mediated alternative splicing. *Mol Carcinog*. 2019;58(2):196–205.

157. Yang SZ, Wang JT, Yu WW, Liu Q, Wu YF, Chen SG. Downregulation of KIF1B mRNA in hepatocellular carcinoma tissues correlates with poor prognosis. *World J Gastroenterol*. 2015;21(27):8418–8424.

158. Leong KG, Karsan A. Recent insights into the role of Notch signaling in tumorigenesis. *Blood*. 2006;107(6):2223–2233.

159. Bai L, Wang A, Zhang Y, Xu X, Zhang X. Knockdown of MALAT1 enhances chemosensitivity of ovarian cancer cells to cisplatin through inhibiting the Notch1 signaling pathway. *Exp Cell Res*. 2018;366(2):161–171.

160. Cittelly DM, Dimitrova I, Howe EN, et al. Restoration of miR-200c to ovarian cancer reduces tumor burden and increases sensitivity to paclitaxel. *Mol Cancer Ther*. 2012;11(12):2556–2565.

161. Wang Z, Katsaros D, Biglia N, et al. High expression of long non-coding RNA MALAT1 in breast cancer is associated with poor relapse-free survival. *Breast Cancer Res Treat*. 2018;171 (2):261–271.

162. Zhang P, Zhou H, Lu K, Lu Y, Wang Y, Feng T. Exosome-mediated delivery of MALAT1 induces cell proliferation in breast cancer. *Onco Targets Ther*. 2018;11:291–299.

163. Hoshino A, Costa-Silva B, Shen TL, et al. Tumour exosome integrins determine organotropic metastasis. *Nature*. 2015;527 (7578):329–335.

164. Bamodu OA, Huang WC, Lee WH, et al. Aberrant KDM5B expression promotes aggressive breast cancer through MALAT1 overexpression and downregulation of hsa-miR-448. *BMC Cancer*. 2016;16:160.

165. Arun G, Diermeier S, Akerman M, et al. Differentiation of mammary tumors and reduction in metastasis upon Malat1 lncRNA loss. *Genes Dev*. 2016;30(1):34–51.

166. Zhao Z, Chen C, Liu Y, Wu C. 17beta-Estradiol treatment inhibits breast cell proliferation, migration and invasion by decreasing MALAT-1 RNA level. *Biochem Biophys Res Commun*. 2014;445(2):388–393.

167. Chou J, Wang B, Zheng T, et al. MALAT1 induced migration and invasion of human breast cancer cells by competitively binding miR-1 with cdc42. *Biochem Biophys Res Commun*. 2016;472 (1):262–269.

168. Wang Y, Zhou Y, Yang Z, et al. MiR-204/ZEB2 axis functions as key mediator for MALAT1-induced epithelial-mesenchymal transition in breast cancer. *Tumour Biol*. 2017;39(7):1010428 317690998.

169. Huang XJ, Xia Y, He GF, et al. MALAT1 promotes angiogenesis of breast cancer. *Oncol Rep*. 2018;40(5):2683–2689.

170. Zeng L, Cen Y, Chen J. Long non-coding RNA MALAT-1 contributes to maintenance of stem cell-like phenotypes in breast cancer cells. *Oncol Lett*. 2018;15(2):2117–2122.

171. Eastlack SC, Dong S, Mo YY, Alahari SK. Expression of long noncoding RNA MALAT1 correlates with increased levels of Nischarin and inhibits oncogenic cell functions in breast cancer. *PLoS One*. 2018;13(6):e0198945.

172. Li C, Cui Y, Liu LF, et al. High Expression of Long Noncoding RNA MALAT1 Indicates a Poor Prognosis and Promotes Clinical Progression and Metastasis in Bladder Cancer. *Clin Genitourin Cancer*. 2017;15(5):570–576.

173. Herranz N, Pasini D, Diaz VM, et al. Polycomb complex 2 is required for E-cadherin repression by the Snail1 transcription factor. *Mol Cell Biol*. 2008;28(15):4772–4781.

174. Fan Y, Shen B, Tan M, et al. TGF-beta-induced upregulation of malat1 promotes bladder cancer metastasis by associating with suz12. *Clin Cancer Res*. 2014;20(6):1531–1541.

175. Ying L, Chen Q, Wang Y, Zhou Z, Huang Y, Upregulated QF. MALAT-1 contributes to bladder cancer cell migration by inducing epithelial-to-mesenchymal transition. *Mol Biosyst*. 2012;8(9):2289–2294.

176. Xie H, Liao X, Chen Z, et al. LncRNA MALAT1 Inhibits Apoptosis and Promotes Invasion by Antagonizing miR-125b in Bladder Cancer Cells. *J Cancer*. 2017;8(18):3803–3811.

177. Liu P, Li X, Cui Y, et al. LncRNA-MALAT1 mediates cisplatin resistance via miR-101-3p/VEGF-C pathway in bladder cancer. *Acta Biochim Biophys Sin (Shanghai)*. 2019;51(11):1148–1157.

178. Cao X, Zhao R, Chen Q, et al. MALAT1 might be a predictive marker of poor prognosis in patients who underwent radical resection of middle thoracic esophageal squamous cell carcinoma. *Cancer Biomark*. 2015;15(6):717–723.

179. Qu Y, Shao N, Yang W, Wang J, Cheng Y. Association of polymorphisms in MALAT1 with the risk of esophageal squamous cell carcinoma in a Chinese population. *Onco Targets Ther*. 2019;12:2495–2503.

180. Yao W, Bai Y, Li Y, et al. Upregulation of MALAT-1 and its association with survival rate and the effect on cell cycle and migration in patients with esophageal squamous cell carcinoma. *Tumour Biol*. 2016;37(4):4305–4312.

181. Wang X, Li M, Wang Z, et al. Silencing of long noncoding RNA MALAT1 by miR-101 and miR-217 inhibits proliferation, migration, and invasion of esophageal squamous cell carcinoma cells. *J Biol Chem*. 2015;290(7):3925–3935.

182. Wu GQ, Chai KQ, Zhu XM, et al. Anti-cancer effects of curcumin on lung cancer through the inhibition of EZH2 and NOTCH1. *Oncotarget*. 2016;7(18):26535–26550.

183. Chen M, Xia Z, Chen C, Hu W, LncRNA YY. MALAT1 promotes epithelial-to-mesenchymal transition of esophageal cancer through Ezh2-Notch1 signaling pathway. *Anticancer Drugs*. 2018;29(8):767–773.

184. Wang W, Zhu Y, Li S, et al. Long noncoding RNA MALAT1 promotes malignant development of esophageal squamous cell carcinoma by targeting beta-catenin via Ezh2. *Oncotarget*. 2016;7(18):25668–25682.

185. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet*. 2013;381(9864):400–412.

186. Li Z, Zhou Y, Tu B, Bu Y, Liu A, Kong J. Long noncoding RNA MALAT1 affects the efficacy of radiotherapy for esophageal squamous cell carcinoma by regulating Cks1 expression. *J Oral Pathol Med*. 2017;46(8):583–590.

187. Wang XC, Tian LL, Tian J, et al. Overexpression of Cks1 increases the radiotherapy resistance of esophageal squamous cell carcinoma. *J Radiat Res*. 2012;53(1):72–78.

188. Huang JK, Ma L, Song WH, et al. MALAT1 promotes the proliferation and invasion of thyroid cancer cells via regulating the expression of IQGAP1. *Biomed Pharmacother*. 2016;83:1–7.

189. Noritake J, Watanabe T, Sato K, Wang S, Kaibuchi K. IQGAP1: a key regulator of adhesion and migration. *J Cell Sci*. 2005;118(Pt 10):2085–2092.

190. Liu Z, Liu D, Bojdani E, El-Naggar AK, Vasko V, Xing M. IQGAP1 plays an important role in the invasiveness of thyroid cancer. *Clin Cancer Res*. 2010;16(24):6009–6018.

191. Huang JK, Ma L, Song WH, et al. LncRNA-MALAT1 Promotes Angiogenesis of Thyroid Cancer by Modulating Tumor-Associated Macrophage FGF2 Protein Secretion. *J Cell Biochem*. 2017;118(12):4821–4830.

192. Gou L, Zou H, Li B. Long noncoding RNA MALAT1 knockdown inhibits progression of anaplastic thyroid carcinoma by regulating miR-200a-3p/FOXA1. *Cancer Biol Ther*. 2019;20(11):1355–1365.

193. Tian Y, Zhang X, Hao Y, Fang Z, He Y. Potential roles of abnormally expressed long noncoding RNA UCA1 and Malat-1 in metastasis of melanoma. *Melanoma Res*. 2014;24(4):335–341.

194. Ren S, Liu Y, Xu W, et al. Long noncoding RNA MALAT-1 is a new potential therapeutic target for castration resistant prostate cancer. *J Urol*. 2013;190(6):2278–2287.

195. Luan W, Li L, Shi Y, et al. Long non-coding RNA MALAT1 acts as a competing endogenous RNA to promote malignant melanoma growth and metastasis by sponging miR-22. *Oncotarget*. 2016;7(39):63901–63912.

196. Smolle MA, Bullock MD, Ling H, Pichler M, Long Non-Coding HJ. RNAs in Endometrial Carcinoma. *Int J Mol Sci*. 2015;16(11):26463–26472.

197. Zhao Y, Yang Y, Trovik J, et al. A novel wnt regulatory axis in endometrioid endometrial cancer. *Cancer Res*. 2014;74(18):5103–5117.

198. Li Q, Zhang C, Chen R, et al. Disrupting MALAT1/miR-200c sponge decreases invasion and migration in endometrioid endometrial carcinoma. *Cancer Lett*. 2016;383(1):28–40.

199. Bayoumi AS, Sayed A, Broskova Z, et al. Crosstalk between Long Noncoding RNAs and MicroRNAs in Health and Disease. *Int J Mol Sci*. 2016;17(3):356.

200. Nishikawa K, Kinjo AR. Essential role of long non-coding RNAs in de novo chromatin modifications: the genomic address code hypothesis. *Biophys Rev*. 2017;9(2):73–77.

201. Ribeiro DM, Zanzoni A, Cipriano A, et al. Protein complex scaffolding predicted as a prevalent function of long non-coding RNAs. *Nucleic Acids Res*. 2018;46(2):917–928.

202. Amodio N, Raimondi L, Juli G, et al. MALAT1: a druggable long non-coding RNA for targeted anti-cancer approaches. *J Hematol Oncol*. 2018;11(1):63.

203. Dinescu S, Ignat S, Lazar AD, Constantin C, Neagu M, Costache M. Epitranscriptomic Signatures in lncRNAs and Their Possible Roles in Cancer. *Genes*. 2019;10:1.

204. Li ZX, Zhu QN, Zhang HB, Hu Y, Wang G, Zhu YS. MALAT1: a potential biomarker in cancer. *Cancer Manag Res*. 2018;10:6757–6768.