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REVIEW

Regulatory Networks of LncRNA MALAT-1 in Cancer

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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

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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/

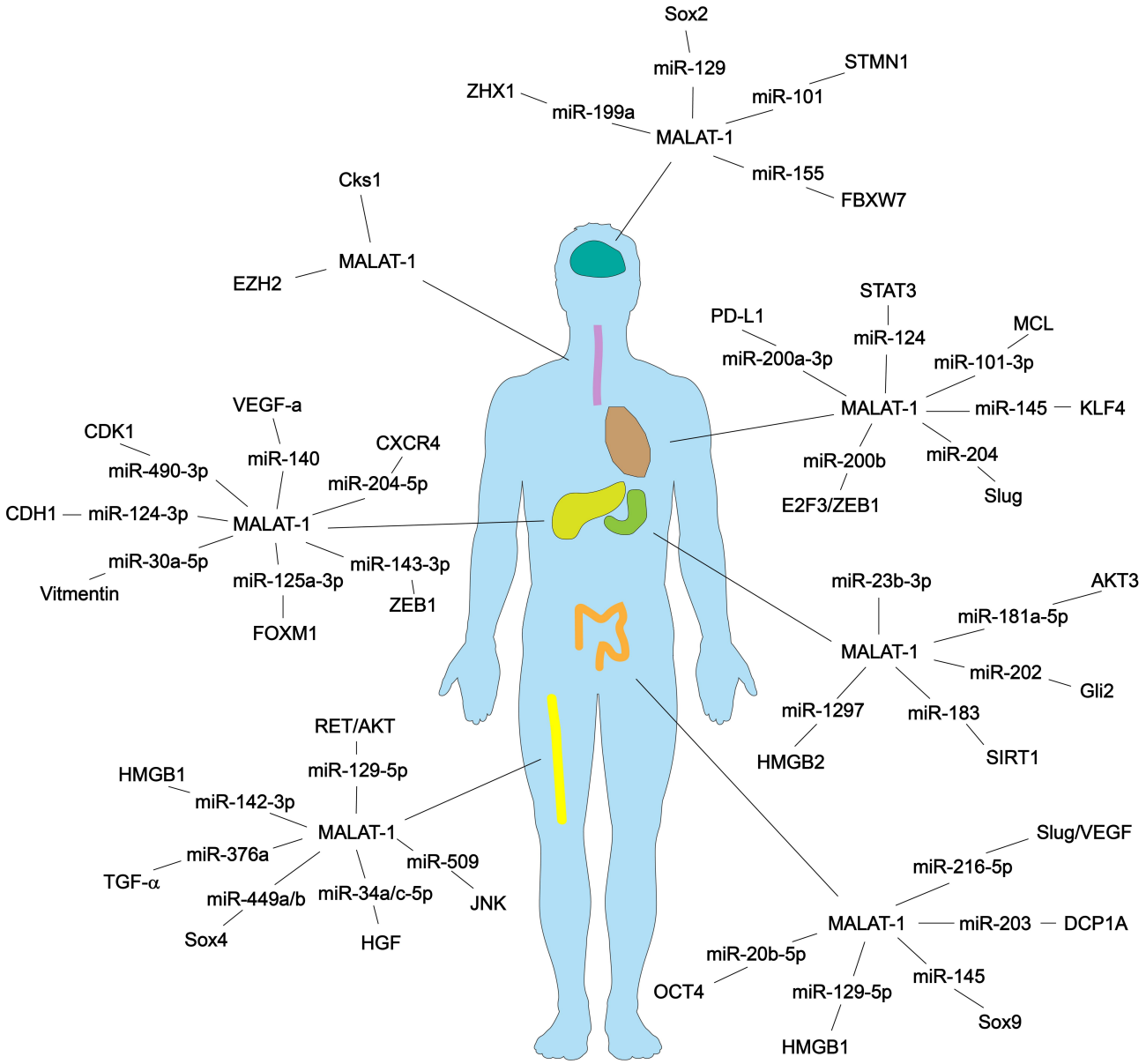

Figure 1 MALAT1 as ceRNA in different cancers, the figure lists some cancers (hepatocellular carcinoma, lung carcinoma, colorectal cancer, osteosarcoma, brain tumor and esophageal cancer).

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.

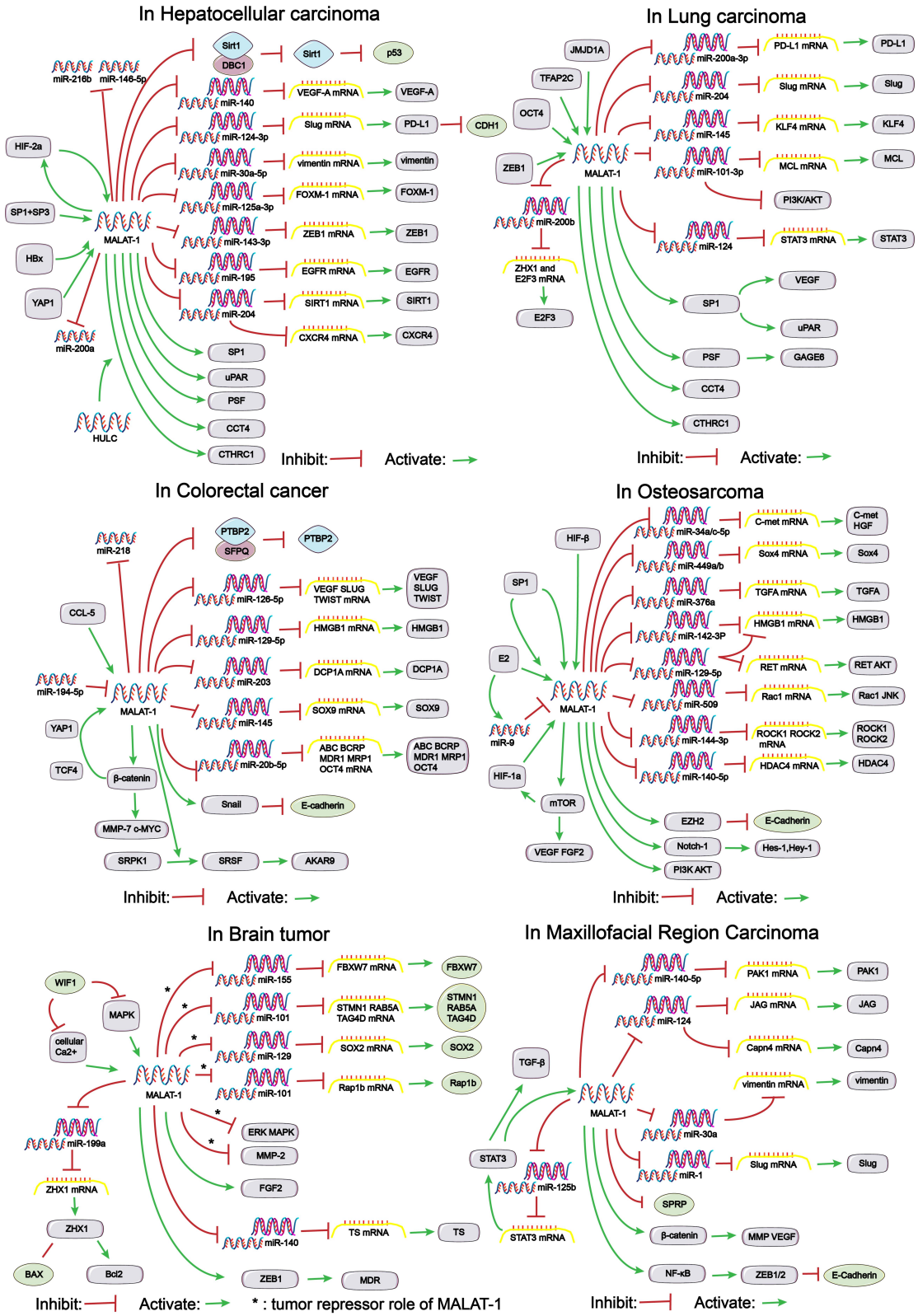

Figure 2 Regulatory networks of the lncRNA MALAT-1 in hepatocellular carcinoma, lung carcinoma, colorectal cancer, osteosarcoma, brain tumors and carcinoma of the maxillofacial region.

Table 1 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 (FBXW)7 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]

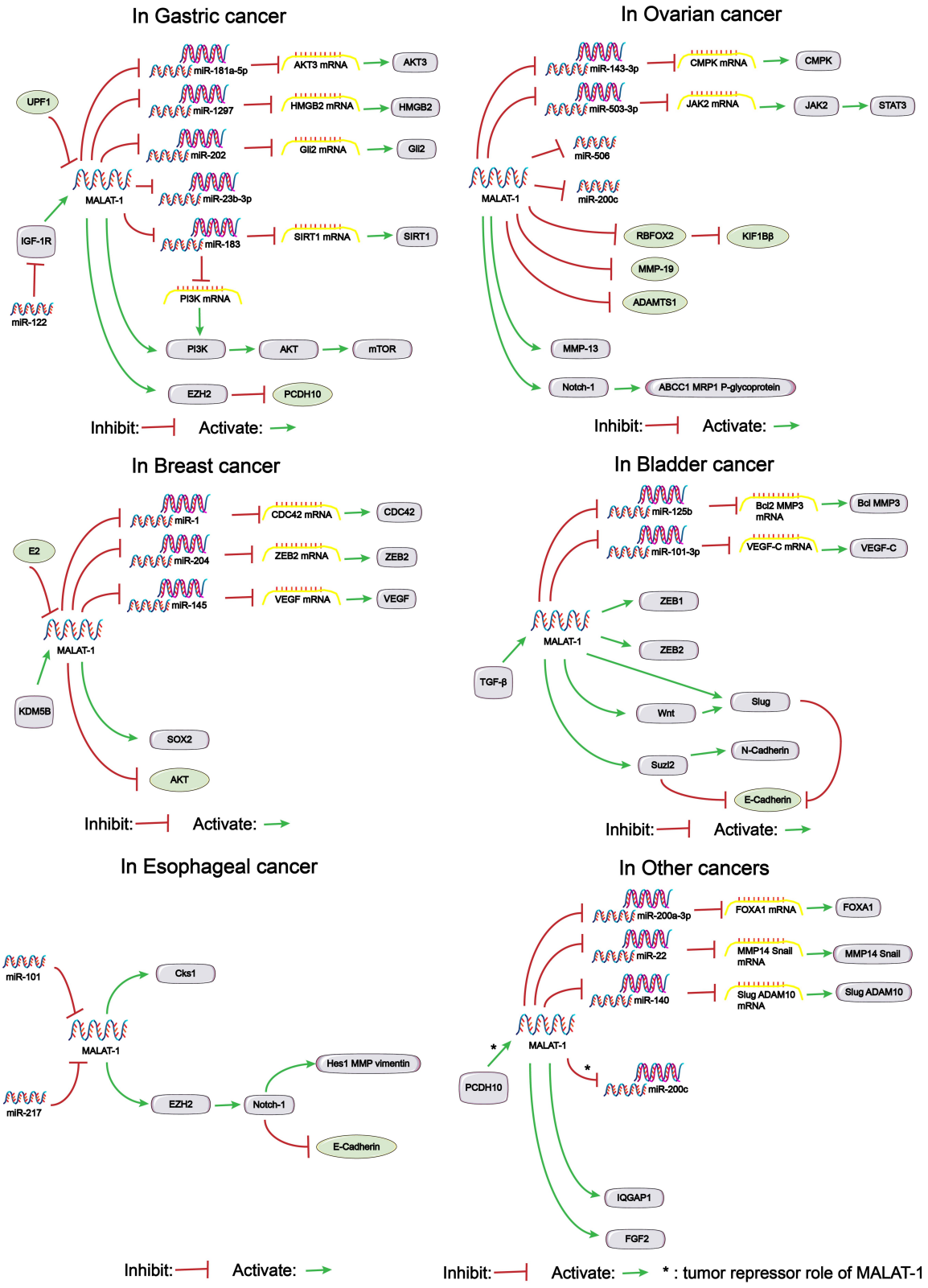

Figure 3 MALAT-1 and its cascade network in gastric cancer, ovarian cancer, breast cancer, bladder cancer, esophageal cancer and other cancers.

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.

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