REVIEW

MALAT1: a potential biomarker in cancer

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Purpose: The research of long non-coding RNAs (lncRNAs) has become a new passion with the discovery of abundant new lncRNAs and extensive investigation of their roles in various diseases, especially in cancers. Metastasis associated in lung adenocarcinoma transcript 1 (MALAT1) emerges as a hotspot, which has been reported to be involved in dysregulation of cell signaling and closely correlated with cancer development, progression, and response to therapy. This review is a brief update of the current knowledge related to the role of MALAT1 in cancer-associated molecular pathways and pathophysiology and possible determinants for MALAT1 to function as a biomarker, aiming to stimulate the basic investigation of lncRNA MALAT1 as well as its translation to clinical applications.

Methods: We have selected vast literature from electronic databases including studies associated with its clinical significance and the pivotal functions in cancer processes such as cell proliferation, apoptosis, metastasis, immunity, angiogenesis, and drug resistance.

Results: Studies have shown that aberrant expression of MALAT1 is related to cancer pathophysiology with the potential to be translated clinically and MALAT1 can regulate cancer processes by interacting with molecules, such as proteins, RNAs and DNAs, and further altering different signal pathways.

Conclusion: MALAT1 lncRNA promises to be a potential biomarker for cancer diagnosis as well as prognosis. Additionally, it might be a therapeutic target for human cancers.

Keywords: MALAT1, lncRNA, cancer therapy, signal pathways, biomarker, chemoresistance, metastasis

Introduction

With the rapid development of high-throughput platforms, the transcriptional landscape of the mammalian genome has been demonstrated. Almost 80% of the genome is transcribed into RNA, while <2% of the genome accounts for protein-coding mRNA.[1] Remarkably, a large part of RNAs are non-coding RNAs (ncRNAs), which were once considered transcriptional noise without any biological function. However, their complex and diverse functions have been gradually identified with the advancement of powerful technologies.

NcRNAs can be categorized into two groups according to their length: small ncRNAs and long ncRNAs. In recent years, long ncRNAs that have >200 nucleotides in length are becoming hotspots, and expanding evidence has indicated their complex roles in the regulation of vital cellular function.[2] XIST, TSIX, H19, AIR, HOTAIR, NRON, and metastasis associated in lung adenocarcinoma transcript 1 (MALAT1) provide examples of some well-characterized long non-coding RNAs (lncRNAs), and

they exert distinctive biological functions through diverse molecular mechanisms. XIST and TSIX mainly function in X-chromosome inactivation.[3,4] H19 and AIR are imprinted genes, and H19 is recently reported to have a dual function as an oncogene and a tumor-suppressor gene.[5–7] HOTAIR participates in transregulation of gene expression and is associated with tumor invasion and metastasis.[8–10] NRON is involved in nuclear trafficking of NFAT.[11] Among all these prevalent lncRNAs, *MALAT1* has attracted a lot of attention over the past few years, and remarkable progress about MALAT1 has been achieved.

MALAT1, an 8.5 kb lncRNA, located at 11q13, was characterized by Ji et al[12] in a study of early-stage non-small-cell lung cancer (NSCLC). MALAT1 (aka α gene) is named due to its clinical significance in predicting metastasis and survival in early-stage NSCLC. A subsequent research study has demonstrated that MALAT1 is widely expressed in normal tissues

and conserved among other mammalian species, hinting at a potentially important function in development and evolution.[13]

Recent research studies have shown that MALAT1 contributes greatly to cancer development and progression. MALAT1 is involved in the modulation of several molecular signaling pathways such as MAPK/ERK,[14,15] PI3K/AKT,[16] WNT/β-catenin,[17] and NF-kB,[18] leading to a modification of proliferation, cell death, cell cycle, migration, invasion, immunity, angiogenesis, and tumorigenicity (Figure 1). It is also associated with clinicopathological features including tumor location, tumor size, differentiation, and cancer stage. Furthermore, growing evidence suggests that the aberrant expression of MALAT1 in tumor tissues and/or body fluids may serve as a biomarker for tumor diagnosis and prognosis.

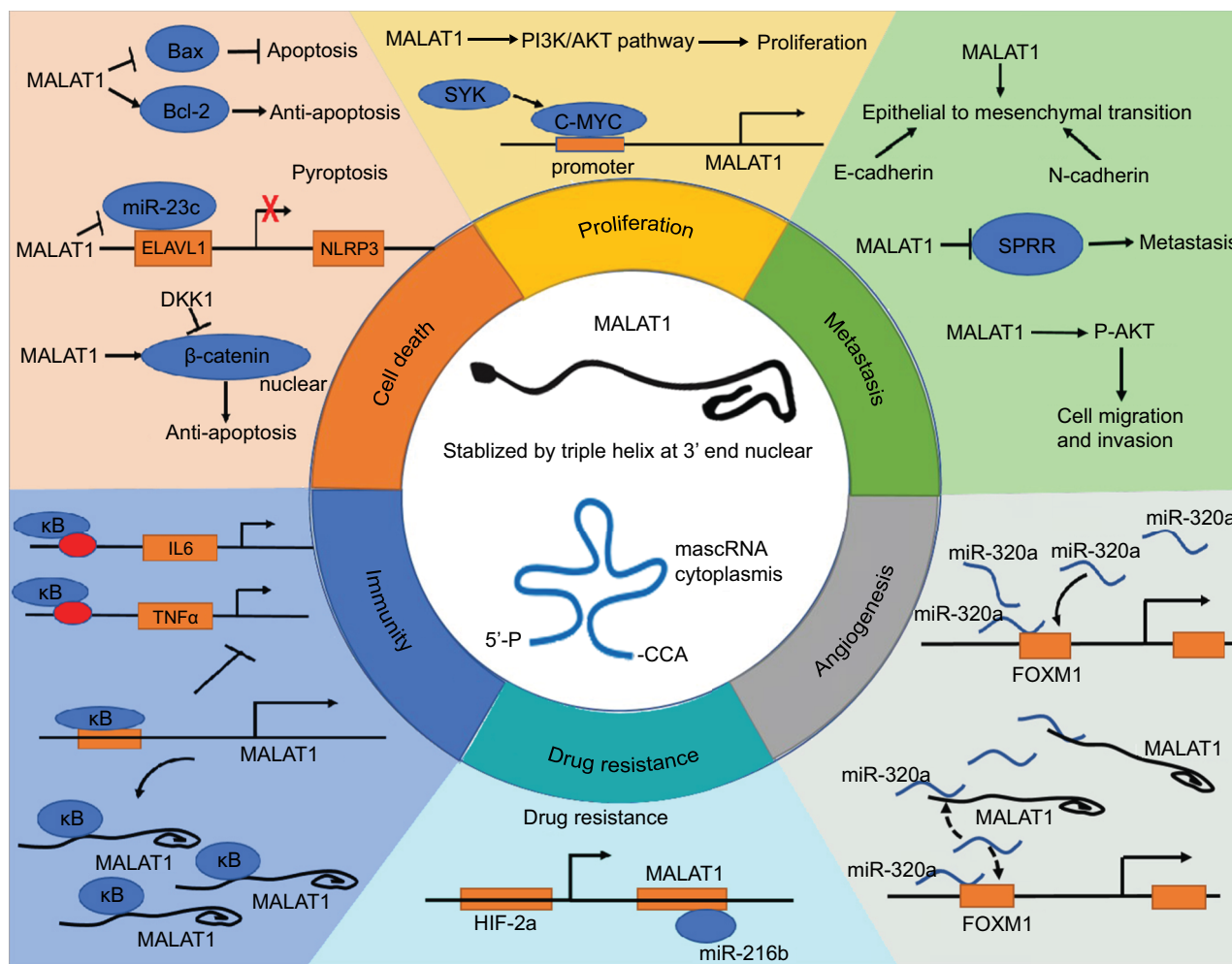In the present review, we mainly summarize the recent advancement of MALAT1 related to cancer

Figure 1 MALAT1 in cancer pathways.
Notes: MALAT1 promotes generation of the six phenotypes of cancer. Diagram partly adapted from Schmitt AM, Chang HY. Long noncoding RNAs in cancer pathways. *Cancer Cell.* 2016; 29(4):452–463).[112] Copyright 2016, with permission from Elsevier. Cancer pathways of MALAT1 involved in metastasis, proliferation, cell death, immunity, angiogenesis, and drug resistance are shown. ELAVL1, ELAV-like protein 1 or HuR (human antigen R); NLRP3, NACHT, LRR and PYD domains-containing protein 3; DKK1, Dickkopf1, a Wnt/β-catenin signaling pathway inhibitor; SYK, Spleen tyrosine kinase, also known as Syk; HIF-2a,hypoxia-inducible factor-2a (HIF-2a); FOXM1, Forkhead box protein M1 (FOXM1).
Abbreviations: MALAT1, metastasis associated in lung adenocarcinoma transcript 1; SPRR, small proline-rich proteins.

clinicopathological features and signaling pathways as well as determinants for MALAT1 to be a biomarker in cancer.

MALAT1 involvement in signaling pathways associated with cancer development and progression

Studies over the years have clearly indicated that cancer can generate several pronounced characteristics during its multistep development and progression, including sustaining cell proliferation, resisting cell death, inducing angiogenesis, activating invasion and metastasis, evading immune destruction,[19,20] and increasing chemotherapeutic resistance. Recently, accumulating evidence suggests that MALAT1 is one of the important factors to drive these phenotypes by regulating signaling pathways related to the deterioration of cancer. We will therefore briefly describe the specific signaling pathways in which MALAT1 is involved in the regulation of cancer characteristics.

MALAT1 in cell proliferation

LncRNA MALAT1 is generally reported to be an upstream regulator of the MAPK/ERK pathway, which is thought to be one of the most classical pathways referring to cell proliferation.[21,22] In retinoblastoma (RB), the MALAT1-induced tumor growth is partly mediated through inhibiting miR-124, then upregulating Slug, a member of MAPK/ERK pathway, leading to an activation of the MAPK/ERK pathway.[14] In a Neuro-2a in vitro differentiation cell model, MALAT1 upregulation has been observed and MALAT1 depletion caused a decrease in neurite outgrowth. Furthermore, Neuro-2a cell neurite outgrowth was blocked by PD98059, an inhibitor of ERK/MAPK pathway, whereas an activation of ERK by phorbol 12-myristate 13-acetate rescued the defect in neurite outgrowth due to MALAT1 depletion,[15] suggesting that MALAT1 promotes neurite outgrowth through activating the MAPK/ERK pathway. In addition, MALAT1 has been reported to affect cell proliferation through other molecular pathways. In osteosarcoma, both cell proliferation and the phosphorylation of main molecules PI3Kp85α and Akt in the PI3K/AKT signaling pathway were suppressed when MALAT1 expression was downregulated.[16] In Ewing's sarcoma (EWS), MALAT1 may serve as a target of c-MYC that induces MALAT1 expression and cell proliferation.[23]

MALAT1 in cell death

The regulation of cell death is mediated by many patterns, including apoptosis, autophagy, pyroptosis, and so on.

Studies over the years have reported that MALAT1 participated in cell death in a variety of cancers. In multiple myeloma, knockdown of MALAT1 induced apoptosis, which was likely to be associated with the activation of mitochondrial-controlled apoptosis through an upregulation of Bax, Caspase-3/-9 expression and a downregulation of Bcl-2.[24] On the other hand, overexpression of MALAT1 inhibited oral tongue squamous cell apoptosis by inducing nuclear β-catenin, whereas the apoptosis is slightly increased when using the Wnt/β-catenin signaling pathway inhibitor DKK1 simultaneously.[17] In hepatocellular carcinoma cells (HCC), knockdown of MALAT1 using small-interfering RNAs (siRNAs) inhibited autophagy through inhibiting p62 degradation and puncta formation.[25] Additionally, when MALAT1 was repressed in diabetic nephropathy, the expression of ELAVL1, NLRP3, Caspase-1, and the proinflammatory cytokine IL-1β, markers of pyroptosis, were downregulated simultaneously,[26] indicating that MALAT1 may participate in pyroptosis.

MALAT1 in cancer metastasis

Metastasis is a typical cause of cancer-associated death. It has been documented that the role of MALAT1 in cancer metastasis is primarily modulated by regulating epithelial-to-mesenchymal transition (EMT), a pro-process of metastasis.[19,20,27] In ovarian tumor, Jin et al[28] have reported that MALAT1 may function as an oncogene, and an inhibition of MALAT1 has significantly impeded EMT with a decrease in matrix metalloproteinase (MMP) and mesenchymal cell markers, including N-cadherin, vimentin, and snail, and an increase in epithelial cell marker, E-cadherin. Furthermore, the PI3K/AKT signaling pathway is verified to be involved in MALAT1 knockdown-mediated reduction of EMT in ovarian cancer cells. In cervical cancer, the expression of MALAT1 was significantly increased in cancer cells and tissues, and the knockdown of MALAT1 in cancer cells inhibited the invasion and metastasis in vitro and in vivo, which may be mediated via attenuating EMT as the epithelial markers, E-cadherin and ZO-1, were upregulated and the mesenchymal markers, β-catenin and vimentin, were downregulated in the MALAT1-knocked-down cells.[29] Apart from EMT, MALAT1 has also been reported to promote metastasis through other mechanisms. For example, in tongue cancer, small proline-rich proteins (SPRR) may be involved in MALAT1-mediated tumor metastasis since MALAT1 knockdown causes an upregulation of certain SPRR that influence the distant metastasis of tongue cancer cells.[30]

MALAT1 in cancer angiogenesis

Basal endothelial sprouting is an indicator of angiogenesis and proliferation.[31] It has been reported that MALAT1 regulates angiogenesis through modulating genes associated with cell cycle in endothelial cells.[32] In various kinds of endothelial cells, an inhibition of MALAT1 expression resulted in an increase in both endothelial sprout length and the expression of p21 and p27Kip1, genes associated with the inhibition of cell cycle, while a decrease in the number of S-phase cells and in the expression of cyclins: CCNA2, CCNB1, and CCNB2.[33] Recently, Li et al[34] have demonstrated that MALAT1 plays an important role in vasculogenic mimicry (VM) and angiogenesis in gastric cancer, and they concluded that MALAT1 can promote tumorigenicity and metastasis in gastric cancer cells by facilitating VM and angiogenesis via the VE-cadherin/β-catenin complex and ERK/MMP and FAK/paxillin signaling pathways based on genetic and pharmacological analyses. Moreover, in human umbilical vein endothelial cells, MALAT1 has been shown to competitively bind to miR-320a, partly block the direct interaction between miR-320a and FOXM1, and lead to endothelial cell proliferation and angiogenesis, suggesting that lncRNA MALAT1 may function as a competing endogenous RNA (ceRNA) to promote angiogenesis.[35]

MALAT1 in cancer immunity

It is now well documented that all tumor lesions have the infiltration of immune cells,[36] which possess significant implications in tumorigenicity, tumor progression, and therapy. Recently, many studies have explored the relationship between lncRNA MALAT1 and tumor immunity.[18,36,37] In lipopolysaccharide-activated macrophages, MALAT1 was found to interact with NF-kB in the nucleus, leading to an inhibition of NF-kB DNA binding to inflammatory cytokine gene promoters and consequently resulting in a decrease in the production of TNF-α and IL-6.[18] In thyroid cancer, it has been shown that the expression of both MALAT1 and FGF2 were enhanced in the tumor tissues and tumor-associated macrophage (TAMs) and that the MALAT1-mediated FGF2 protein secretion from TAMs inhibited inflammatory cytokine release, promoted tumor cell proliferation, migration, and invasion, and induced vasculature formation.[37] Taken together, these data suggest that MALAT1 may be involved in tumor immunity mainly through the modulation of tumor microenvironment, especially cytokine production.

MALAT1 in chemotherapeutics resistance

MALAT1 has been reported to contribute to the chemoresistance and radiation resistance of cancer (Table 1). In HCC, MALAT1 upregulation is associated with multiple drug resistance, mediated through an HIF-2α-MALAT1-miR-216b pathway, as evidenced by the findings that the sensitivity of drug-resistant cells to multiple chemotherapeutic agents, including 5-fluorouracil, adriamycin, and mitomycin C, was elevated when MALAT1 siRNA and miR-216b mimics were used.[25] In studies investigating the resistance of glioblastoma to temozolomide (TMZ), MALAT1 has been shown to modify drug sensitivity through the regulation of MALAT1/ZEB1/MDR pathway as well as the expression of thymidylate synthase (TS) and miR203; besides, the induced miR-101 expression by MALAT1 knockdown can reverse the chemoresistance to TMZ.[38–40] Similarly, in colorectal cancer, MALAT1 overexpression is associated with oxaliplatin resistance and poor patient survival.[41] Furthermore, in lung cancer, Wang et al[42] have found that MALAT1 knockdown in cisplatin-resistant A549/DDP cells resulted in miR-101-3p upregulation and MCL1 downregulation, which consequently increased cisplatin sensitivity; moreover, the polymorphism, rs619586, of MALAT1 has been demonstrated to be notably associated with platinum-based chemotherapeutic response, which may serve as a potential biomarker for the selection of platinum-based chemotherapy response in lung cancer patients.[43] In addition, MALAT1 has been reported to be involved in radiotherapy resistance of nasopharyngeal carcinoma, in which lncRNA MALAT1 was upregulated in tumor tissues and knockdown of MALAT1 potentiated

Table 1 MALAT1 and drug resistance

Cancer	Drug	Dysregulation	Mechanism of action	Reference
Hepatocellular carcinoma cells	5-FU, ADR, or MMC	Upregulation	Regulating miR-216b	25
Glioblastoma	TMZ	Upregulation	Regulating ZEB1/MDR1, MRP5, LRP1 or modulating miR-203/TS pathway	38–40
Colorectal cancer	Oxaliplatin	Upregulation	Modulating miR-218/EZH2 pathway	41
Lung cancer	Platinum	MALAT1 SNP rs619586	Polymorphisms	42,43
Nasopharyngeal carcinoma	Radiotherapy	Upregulation	Modulating miR-1/slug pathway	44

Abbreviations: ADR, adriamycin; 5-FU, 5-fluorouracil; MALAT1, metastasis associated in lung adenocarcinoma transcript 1; MMC, mitomycin C; TMZ, temozolomide.

cell sensitivity to radiotherapy both in vitro and in vivo.[44] These data collectively indicate that MALAT1 may serve as a potential therapeutic target in multiple cancers.

Generally, the hallmarks generated during cancer development and progression are caused by mutations that produce oncogenes and tumor suppressor genes, and the altered expression of these genes can greatly influence fundamental biological processes, such as cell proliferation, cell death, cell metastasis, and so on. The oncogenes and tumor suppressor genes with similar functions can generate a signaling pathway, involving the regulation of multiple biological processes. MALAT1 can interact with these oncogenes and tumor suppressors, thus participating in various signaling pathways and regulating the processes associated with cancer development and progression. Currently, the research studies of MALAT1 mainly focus on cancer metastasis, an indicator of cancer deterioration, which is possibly due to MALAT1 involvement in EMT and the closed correlation with lymph node metastasis. These research studies in cancer collectively indicate that MALAT1 may be an anchor which bridges multiple pathological processes associated with cancer, and it can be a potential biomarker for cancer.

Mechanisms of MALAT1 function

Recent studies have documented that MALAT1 represents a functional molecule that displays vital roles not only in clinical but also in diverse physiological and pathological processes,[1,45,46] such as cell proliferation, cell death, cell cycle, cell migration, invasion, immunity, and angiogenesis via involvement of signaling pathways, making it a possible biomarker and drug target. However, this also raises several questions: how does MALAT1 fulfill its function mechanistically? Human body is a huge factory, which produces millions of proteins, RNAs, and DNAs, and the functions of these molecules are important for its biological processes.

Many studies over the years have revealed that lncRNAs fulfill their functions through directly or indirectly interacting with other molecules such as proteins, RNAs, or DNAs.[47] Although the molecular mechanisms of MALAT1 actions are not fully understood, we will highlight some of the mechanisms associated with MALAT1 actions in diverse cellular processes.

MALAT1 interaction with protein

To date, many proteins have been shown to interact with MALAT1. MALAT1 predominantly is retained in nuclear speckles,[48] eliciting possible functional binding to the serine/arginine-rich (SR) family splicing factors, which locate at nuclear speckles, as well as functioning as modulators of alternative splicing (AS). Tripathi et al[49] conducted a series of computational and biochemical assays and found that MALAT1 can interact with several splicing factors, such as SRSF1 (ASF/SF2), SC35 (SRSF2), and SRSF3. Interestingly, depletion of SR proteins does not change the speckle localization of MALAT1, whereas depletion of MALAT1 influences the speckle distribution and phosphorylation of SR proteins, indicating a functional role of MALAT1 in AS.[49] In hepatocellular carcinoma, MALAT1 induces the expression of oncogenic splicing factor SRSF1, which enhances the production of antiapoptotic splicing isoforms and modulates the AS of S6K1 to activate the mTOR pathway, thus promoting the development of hepatocellular carcinoma.[50] In breast cancer (BC), mutant p53 and ID4 proteins influence the interaction between MALAT1 and SRSF1 and intranuclear localization of MALAT1 to active transcription sites. Further study shows that mutant p53 and ID4 favor the interaction of MALAT1 with VEGFA precursor mRNA, stabilizing binding of SRSF1 to this precursor and modulating the expression of VEGFA isoforms and finally impacting the angiogenesis of BC cells.[51] These results are consistent with the former study that repression of MALAT1 could alter the pattern of AS of particular pre-mRNAs. Recent studies have shown that MALAT1 and TUGA1 play important role in the regulation of proliferation. MALAT1 directly binds to the unmethylated Polycomb 2 (Pc2) on the promoter of E2F1, a critical regulator of cell proliferation, leading to E2F1 SUMOylation and the relocation of the growth control genes from transcriptional repressive Pc2 bodies to a transcriptionally permissive environment of the interchromatin granules. On the contrary, TUGA1 binds to the methylated Pc2, resulting in the growth control gene promoters retaining in Pc2 bodies and thus inhibiting gene expression and cell proliferation.[52] A systematic research delineates that MALAT1 competitively binds to depleted in breast cancer 1 (DBC1) from a sirtuin1 (SIRT1)–DBC1 complex, leading to the release of SIRT1. SIRT1 has an increased deacetylation activity and promotes the acetylation of p53, which subsequently impairs P53 function in promoting cell apoptosis and inhibiting cell growth.[53] Similarly, in colorectal cancer, MALAT1 promotes tumor growth and metastasis by competitively binding to SFPQ, a tumor suppressor, thus releasing proto-oncogene PTBP2 from the SFPQ/PTBP2 complex. Studies conducted by Yang et al[54] have shown that the interaction between MALAT1 and a nuclear protein hnRNP C promotes the translocation of MALAT1 from the nucleus into the cytoplasm, which consequently increases mitosis and promotes the transition

of G2/M phase. RNA–protein interaction studies show that MALAT1 can bind to several other proteins as well as affect the pathophysiology of cancer. These data collectively indicate that the interaction of MALAT1 with some RNA-related proteins is critical for the regulation of cellular biological processes.

MALAT1 interaction with RNA

Except for proteins, MALAT1 can interact with RNAs to achieve its diverse molecular functions. Using RAP-RNA, an assay to detect intermolecular RNA–RNA interactions, Engreitz et al[55] have observed that Malat1 could interact with nascent transcripts indirectly through protein intermediates, which caused Malat1 to localize proximally to chromatin at active genes, suggesting that Malat1 may influence RNA processing through recruitment or modification of other proteins localized to these sites.

The importance of ceRNA network in cancer pathophysiology has become evident in recent years. MicroRNAs are important regulators in the ceRNA network that negatively regulates gene expression of mRNAs. The most commonly observed mechanism is that microRNAs interact with mRNA 3′-UTRs of target gene, leading to deadenylation, decreased mRNA stability, and translation suppression.[56] Recent evidence has shown that other RNAs can compete with mRNAs for shared microRNAs.[57] Among these RNAs, MALAT1 is one of the most studied as a ceRNA to be involved in various molecular processes (Table 2).

The strongest evidence of MALAT1 as a ceRNA comes from studies on cancer. In BC, MALAT1 and cell division cycle 42 (CDC42) compete for the binding of miR-1, consequently reducing CDC42 expression and leading to increased ability of migration and invasion.[58] Another study showed that MALAT1 regulates the EMT of BC through competitively binding to miR-204 with ZEB2, a target gene

of miR-204.[59] In osteosarcoma, upregulation of MALAT1 expression is observed in both human osteosarcoma cell lines and tissues, which promotes osteosarcoma cell growth. Mechanical research studies showed that MIR376A is shared by TGFA and MALAT1, and upregulation of MALAT1 results in decreased binding of MIR376A to TGFA, thus increasing TGFA expression and osteosarcoma cell growth.[60] In gastric cancer, the MALAT1/miR-202/Gli2 regulatory pathway may explain the clinical relevance with tumor size, lymph node metastasis, and TNM stage and the alteration of some molecular processes such as proliferation, cell cycle, and cell apoptosis.[61] In hepatocellular carcinoma, the alteration in regulatory network of two ceRNAs, MALAT1-miR-195-EGFR and MALAT1 miRNA-204-SIRT1, is responsible for the increased ability of migration and invasion.[62,63] In gallbladder cancer, MALAT1 functions as an oncogene with high expression in tumor tissues and cell lines. Recent studies showed that MALAT1 modifies proliferation, apoptosis, cell cycle, and invasion by acting as a molecular sponge to negatively regulate miR-206 or miR-363-3p, thus resulting in the upregulation of ANXA2 and KRAS or MCL-1.[64,65] In glioma, MALAT1 conversely plays a tumor-suppressive function with inhibited cell viability, which is mediated by downregulating miR-155 and upregulating FBXW7 expression. Another study demonstrated that miR-129 can function as a linker, which directly bridges MALAT1 and Sox4, and its expression negatively correlates with the expression of MALAT1 and Sox4, indicating that the disorder of MALAT1/miR-129/Sox4/pathway may account for the enhanced glioma stem cell viability and proliferation abilities and promoted glioma tumorigenesis.[66,67]

In addition, the abnormal interaction between MALAT1 and micro-interfering RNA (miRNA) can be seen in other cancers, such as ovarian cancer,[68,69] cervical cancer,[70] and melanoma.[71]

Table 2 MALAT1 may function as ceRNA in human cancer

LncRNA	MiRNA	Target	Cancer	Features	Reference
MALAT1	miR-1/miR-204	CDC42/ZEB2	Breast cancer	Decrease miR-1/miR-204	58,59
	MIR376A	TGFA	Osteosarcoma	Inhibit miRNA expression	60
	miR-202	Gli2	Gastric cancer	Negatively regulate miR-202	61
	miR-195/miR-204	EGFR/SIRT1	Hepatocellular carcinoma	Modulate miR-195/sponging miR-204	62,63
	miR-363–3 p/miR-206	MCL-1/ANXA2, KRAS	Gallbladder cancer	Molecular sponge	64,65
	miR-155/miR-129	FBXW7/Sox4	Glioma	Reciprocal repression negatively regulating	66,67
	miR-506/miR-211	IASPP/PHF19	Ovarian cancer	Targeting miR-506/miR-211 directly	68,69
	miR-124	RBG2	Cervical cancer	Negatively regulate miR-124	70
	miR-22	MMP14, Snail	Melanoma	Sponging miR-22	71

Abbreviations: CDC42, cell division cycle 42; ceRNA, competing endogenous RNA; lncRNA, long non-coding RNA; MALAT1, metastasis associated in lung adenocarcinoma transcript 1; miRNA, micro-interfering RNA.

MALAT1 interaction with DNA

Considering the intrinsic nature of MALAT1, an RNA, it has an easy access to bind to homologous DNA sequence. West et al[72] applied Capture Hybridization Analysis of RNA Targets (CHART), a technology developed to identify putative *trans* genomic binding sites for endogenous RNAs and to map the genomic binding sites for two highly expressed lncRNAs, NEAT1 and MALAT1. Subsequent analyses demonstrated that NEAT1 and MALAT1 can interact with numerous active genes and NEAT1 and MALAT1 can colocalize to many transcribed gene loci while with different binding patterns, indicating a possible mechanism that MALAT1 may modify transcription through binding to actively transcribed gene loci.[72] In renal tumor cells, the MALAT1 (aka Alpha) gene locus is found to translocate to that of transcription factor EB (TFEB), leading to an Alpha-TFEB fusion. MALAT1 promoter induces the expression of this fusion gene, actually the upregulation of TFEB due to the fact that MALAT1 does not contribute to the ORF. The upregulation of TFEB transcription consequently results in tumorigenesis.[73] We can infer that a mechanism by which MALAT1 regulates transcription is through translocation and fusion of the MALAT1 gene locus to another gene locus.

The clinical significance of MALAT1

Epidemiological study has indicated that cancer is a leading cause of death.[74] Most cancers are hard to be cured due to the limited diagnostic and therapeutic methods. Since MALAT1 was first identified to stratify early-stage NSCLC patients at high risk to develop metastasis,[12] the later research studies paid more attention to its clinical significance (Table 3).[76–83] Herein, we briefly introduce the clinical significance of MALAT1 in commonly diagnosed cancers.

MALAT1 serves as a biomarker for cancer diagnosis

Early cancer detection is crucial for a successful cancer therapy. Although various cancer diagnostic methodologies are available, it is unfortunate that these methods do not fully meet the demand of early cancer diagnosis, and new methods with high specificity and sufficient sensitivity are needed. Studies over the years have indicated that lncRNA MALAT1 may serve as a diagnostic biomarker with sufficient specificity and sensitivity for multiple malignancies (Table 3). The diagnostic value of a biomarker is estimated through the receiver operating characteristic (ROC) curve, which is defined as diagnostic accuracy. The accuracy of tests is based on a rough rule of thumb. If the area under the ROC curve (AUC) is between 0.50 and 0.70, the accuracy is low; if AUCs are over 0.90, the accuracy is high and those between these two are considered moderate.[75]

In a clinical study of NSCLC with a small sample size, different MALAT1 expression levels in human peripheral blood are observed between cancer patients and cancer-free controls, and ROC analysis has demonstrated that MALAT1 might not be an independent diagnostic biomarker due to its relatively low sensitivity, whereas it can be used with other diagnostic biomarkers to improve the entire sensitivity and specificity.[76] However, in a relatively larger clinical trial, the investigators have revealed that the expression of a circulating ncRNA panel consisting of MALAT1, miR-1254, miR-485-5p, and miR-574-5p can distinguish NSCLC patients from controls with sufficient specificity and sensitivity.[77] Moreover, serum exosomal MALAT1 level could be used as a diagnostic biomarker for the metastasis of NSCLC.[78] In BC patients, the serum MALAT1 level is distinguishably increased compared to benign breast tumor patients, which

Table 3 Examples of MALAT1 involvement in cancer diagnosis

Cancer type	Origin	Feature	AUC	95% CI	Diagnostic efficiency	Reference
Non-small-cell lung cancer	Peripheral blood	Single lncRNA	0.79	0.68–0.89	Moderate	76
	Venous blood	NcRNA panel[a]	0.861[b]/0.844[c]	0.771–0.952[b]/0.778–0.910[c]	Moderate	77
	Exosome	Single lncRNA	0.703	Not available	Moderate	78
Breast cancer	Serum	Single lncRNA	0.833	0.756–0.910	Moderate	79
Bladder cancer	Serum	LncRNA panel[a]	0.865[b]/0.828[c]	0.815–0.905[b] 0.768–0.877[c]	Moderate	80
Nasopharyngeal carcinoma	Venous blood	LncRNA panel[a]	0.918	0.886–0.949	High	81
Osteosarcoma	Serum	Single lncRNA	0.834	0.738–0.906	Moderate	82
Epithelial ovarian cancer	Plasma	Single lncRNA	0.820	0.734–0.905	Moderate	83

Notes: [a]Complementary diagnostic biomarker. [b]Training set. [c]Validation set.
Abbreviations: AUC, area under the receiver operating characteristic curve; lncRNA, long non-coding RNAs; ncRNA, non-coding RNAs; MALAT1, metastasis associated in lung adenocarcinoma transcript 1.

is fairly satisfactory to serve as a diagnostic biomarker of BC.[79] A serum circulating lncRNA panel, including MEG3, SNHG16, and MALAT1, has been identified for bladder cancer diagnosis, which has a significantly higher AUC compared to the urinary cytology, indicating a far superior diagnostic performance.[80] Furthermore, MALAT1 has been used for the diagnosis of other types of cancers, such as nasopharyngeal carcinoma,[81] osteosarcoma,[82] and epithelial ovarian cancer.[83]. These data collectively indicate that MALATA1 alone or in combination with other molecules may serve as a useful biomarker for the diagnosis of various cancers.

MALAT1 serves as a biomarker for cancer prognosis

Recently, aberrant expression of MALAT1 has been reported to be associated with cancer prognosis markedly (Table 4). In NSCLC, a higher MALAT1 expression significantly related to female sex (P=0.019), TNM stage (P=0.016), vessel invasion (P=0.032), pathological differentiation (P=0.013), and recurrence (P=0.006).[84] Additionally, cooverexpression of MALAT1, NEAT1, and Oct4 in lung cancer has been shown to be an independent prognostic factor for poor outcome.[85] Further study has indicated that MALAT1 overexpression is significantly related to the prognosis of lung squamous cell carcinoma but not non-squamous cell carcinoma.[86] Genetic variants of MALAT1 are associated with survival outcome in advanced lung adenoma patients, such as the rs3200401 T allele, which is a protective factor, and advanced lung adenoma patients with rs3200401 T allele have a longer median survival time (MST) and better prognosis.[87] In BC, MALAT1 is overexpressed in cancerous tissues, which is dramatically correlated with lymph metastasis, adverse 5-year disease-free survival and poor relapse-free survival in a cancer subtype-dependent manner.[79,88–90] In colorectal cancer, the overexpression of MALAT1 in tumor tissues is related to a relatively shorter survival time.[91,92] In nasopharyngeal carcinoma, MALAT1 overexpression is associated with advanced TNM stage and EBV infection, and an alteration of serum MALAT1 is a predictive biomarker for therapeutic

outcome.[81] In osteosarcoma, patients with higher MALAT1 expression show poor overall survival (OS) and progressive-free survival (PFS) compared to those with lower MALAT1 expression.[82] In bladder cancer, overexpression of MALAT1 in tumor tissues is associated with poor OS, metastatic lymph node, advanced histological grade, and higher tumor stage, indicating that MALAT1 may serve as an independent prognostic biomarker for bladder cancer.[93] Taken together, these studies provide promising data that MALAT1 may be an independent biomarker for the prediction of various cancer outcomes and warrant further clinical investigations with larger sample sizes.

MALAT1 serves as a target for cancer therapy

Advances in gene therapy will contribute to the treatment of a large number of genetic diseases as well as cancers because of the flexibility, efficiency, and reduced off-target effects of the innovative treatments.[94] The current research of MALAT1 in cancer[95] and methodological advances in targeting tumor cells have provided MALAT1 an opportunity to serve as a target for cancer therapy. In osteosarcoma, in vitro knockdown of oncogene MALAT1 leads to the inducement of cell cycle arrest and apoptosis, whereas the decrease in cell proliferation and migration. Besides, the xenograft model verified that MALAT1 silencing inhibits tumorigenesis of osteosarcoma cells, which collectively indicates that MALAT1 lncRNA can be targeted for osteosarcoma treatment.[96] Studies conducted by Gutschner et al[97] have unraveled that lung cancer cells with a 1,000-fold reduction of MALAT1 using Zinc-finger nucleases (ZFNs) showed impaired ability in migration and formed significantly fewer and smaller lung tumor nodules in a xenograft lung cancer mouse model, suggesting that decreasing MALAT1 expression may be a potential therapeutic strategy for metastasizing lung cancer. Additionally, the mouse with luminal B BC can benefit from the defect in Malat1, which facilitates the transformation from aggressive mammary carcinomas with higher possibility of lung metastasis to cystic tumors that are less prone to metastasizing,

Table 4 Examples of MALAT1 involvement in cancer prognosis

Cancer type	Dysregulation	Detection method	Prognostic indicator	Prognosis	Reference
Lung cancer	Upregulated	qRT-PCR/ISH TaqMan assay	OS/recurrence	Poor	84–87
Breast cancer	Upregulated	qRT-PCR	DFS/DSS/RFS[c]	Poor	79,88–90
Colorectal cancer	Upregulated	qRT-PCR	OS/DFS	Poor	91,92
Bladder cancer	Upregulated	qRT-PCR/ISH	OS	Poor	93
Hepatocellular carcinoma	Upregulated	qRT-PCR	Recurrence	Poor	94

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; RFS, recurrence-free survival; ISH, in situ hybridization; MALAT1, metastasis associated in lung adenocarcinoma transcript 1; OS, overall survival; qRT-PCR, quantitative reverse transcription PCR.

giving a strong clue on the further clinical strategy of targeting MALAT1 for the treatment of BC.[98] Similarly, another independent group has also verified that Malat1 deficiency in the MMTV-PyMT mammary carcinoma mouse model significantly influences AS and the expression of molecules in pro-tumorigenic signaling pathways, thus resulting in a better pathological feature with higher differentiation and less metastasis. These data show that MALAT1 may serve as a target for inducing differentiation of primary human breast tumors and significantly reducing the risk of tumor metastasis.[99] Furthermore, Wheeler et al[100] have proved that antisense oligonucleotides (ASOs) based on the RNase H-dependent antisense knockdown are efficient to knockdown the nuclear retained RNAs such as lncRNA MALAT1. Short double-stranded RNA molecules and genome-editing techniques, including siRNAs,[101] miRNAs,[102] ZFNs, transcription activator-like effector nucleases (TALENs) and clustered, regularly interspaced, short palindromic repeat (CRISPR)/ CRISPR associated (Cas)-9 systems,[103] have emerged as powerful strategies for the treatment of various diseases with potential therapeutic value. Together, these data demonstrate that MALAT1 may represent a candidate therapeutic target, and MALAT1 knockdown strategies may represent potential therapies for inhibiting cancer progression.

Characteristics of MALAT1 as a potential biomarker

Generally, an ideal biomarker should possess several typical characteristics. First, it should be easily obtained with minimal risk and discomfort to patients. Second, it should be measurable and/or quantifiable with high sensitivity and specificity, making it easy to be detectable and reproducible in standard clinical laboratories. In addition, it should be of high specificity and its expression should be altered significantly in cancer patients.[104,105]

MALAT1 lncRNA possesses all the features as a biomarker. MALAT1 is expressed not only in tissues but also detectable in body fluids such as blood,[45] a sample source easily obtainable with minimal risk to the patient. The advancement in technology makes it possible to detect low-abundant RNA transcripts through PCR amplification and RNA-seq in clinical laboratories. It is evident that the differential expression of MALAT1 lncRNA in diverse cancers is present, which is associated with clinical characteristics and drug resistance in cancer patients,[38,39] suggesting that MALAT1 lncRNA is a potential biomarker. However, few studies have currently emphasized the cell-type specificity and intratumor heterogeneity of MALAT1 expression in

cancer patients, which might be addressed using fluorescent in situ hybridization (ISH or FISH) and single-cell RNA-seq. Furthermore, MALAT1 lncRNA is a relatively stable RNA transcript with a half-life of 9–12 hours, presumably due to its triple helix structure at the 3′-end.[106–108] This long half-life feature makes it easily detectable in tumor tissues as well as in body fluids. Regrettably, unlike PCA3 lncRNA, a prostate cancer-specific biomarker approved by the US Food and Drug Administration (FDA) in 2012 for prostate cancer diagnosis,[105] MALAT1 is expressed across a broad range of cell types, making it less specific to distinguish the origin of tumors when it is used as a diagnostic biomarker in body fluids. Nevertheless, a hematic detection of MALAT1 may serve as a supplement for the clinical diagnosis of cancer patients to enhance diagnostic sensitivity and accuracy.

Conclusion and prospective

As a prominent lncRNA, MALAT1 has been widely studied in the last several years, especially its roles in cancer development, metastasis, drug resistance, and clinical outcome. However, it is puzzling that knockout of MALAT1 in animals has no robust phenotypes in development, gene expression, and physiological functions.[13,109,110] Studies by Spector's group in Cold Spring Harbor Laboratory have demonstrated in a mouse Malat1 loss-of-function genetic model that lncRNA Malat1 was dispensable for mouse development, but it might play a *cis*-regulatory role in neighboring gene expression in adulthood.[109] This observation is consistent with the findings by other independent groups, who have reported that a loss of MALAT1 was compatible with life and development[13] and had no impact on physiological functions.[110] Taken together, these observations suggest that MALAT1 per se may contribute moderately to normal development and physiological functions in mammals. However, through interacting with other RNAs, proteins, and DNA,[54,55,111] lncRNA MALAT1 may possess significant roles in pathophysiology, especially in cancer development, progression, and response to therapy, presumably mediated via various molecular pathways. In spite of the abovementioned mechanisms, there are still some questions. For example, are there any triggers for the alteration of MALAT1? Why does MALAT1 play different roles in various cell lines? Do the different transcripts of MALAT1 have distinct functions? Elucidation of the molecular pathways and the interacting networks of MALAT1 with other molecules will facilitate the understanding of its roles in the pathogenesis of various diseases and pave the way for in-depth knowledge of MALAT1, leading to clinical applications in the near future.

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Disclosure

The authors report no conflicts of interest in this work.

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