Novel insight into MALAT-1 in cancer: Therapeutic targets and clinical applications (Review)

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Abstract. Long non-protein-coding RNAs (lncRNAs) are emerging as important gene expression regulators that are linked to various biological processes at the post-transcriptional and transcriptional levels. lncRNAs are known to be important in cell proliferation, cell differentiation, apoptosis and metastasis. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1), a novel lncRNA, is highly conserved amongst mammals. In addition, it has been considered to act as an oncogene, depending on the tumor system. An increasing number of studies have indicated that MALAT-1 may be detected in certain types of human tumors, including lung and bladder cancer and hepatocellular carcinoma. MALAT-1 silencing may be an effective therapeutic approach against tumors. The present study reviews the current knowledge on the functional role of MALAT-1 in the control of various cancers.

Contents

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1. Introduction

Previously, studies categorized non-coding (nc)RNAs as short ncRNA, mid-size ncRNA, and long ncRNA (lncRNA) by their lengths (1,2). In addition, lncRNAs are subdivided by function, loci and post-transcriptional modification. lncRNAs have been operationally defined as transcripts that are produced by RNA polymerase II (Pol II), which are broadly classified as transcripts >200 nucleotides in length (3,4). Transcriptome analyses have revealed that 70-90% of the mammalian genome was transcribed, but only 1-2% may encode proteins (5). Additionally, lncRNAs that are localized to the nucleus possess stronger secondary structures. Therefore, knockdown of lncRNAs may not be sufficiently effective at evoking a phenotype and uncovering the physiological function of the lncRNA (5-8). The regulation of mRNA decay in the cytoplasm is crucial for controlling the abundance of cellular transcripts and the levels of protein expression. Therefore, the regulation of lncRNA decay in the nucleus is considered to be important for biological function (9). Overall, lncRNAs are important in the programming and regulation of the mammalian genome. The expression of lncRNAs is associated with numerous human diseases, including cancer (10).

The prevention of 20% of cancers in the United States alone would result in 300,000 fewer new cases annually (11). The growing knowledge of cancer treatment reveals methods to intercept cancers by novel, active approaches. Cancer results in high mortality and morbidity globally, largely due to the complex, heterogeneous nature of the disease and the lack of biomarkers for early diagnosis. A proteomics study of cancer identified functional proteins and drove the transformation of malignancy, identified biomarkers to detect early-stage cancer, determined therapy efficacy, identified novel drug targets and ultimately developed personalized medicine (12). Since tumor formation is a multistep process, normal cells evolve progressively to the neoplastic stage. Therefore, normal cells may acquire particular capacities that enable them to become tumorigenic. Over the last decade, remarkable progress was made in the field of cancer research, which led to a better understanding of cancer therapy (13).

Notably, metastasis associated lung adenocarcinoma transcript-1 (MALAT-1) is reported in numerous studies. For example, MALAT-1 was detected in the cerebellum of human

Table I. The expression of MALAT-1 in cancer. MALAT-1 was expressed in all samples.

Sample	Function in tumorigenesis	References
HeLa, CaSki, SiHa and HCC94 cells	Oncogene	(32,49)
Gallbladder carcinoma tissues	Oncogene	(22)
Bladder cancer tissues	Oncogene	(16,25)
Mesenchymal stem cells	Oncogene	(75)
SGC-7901, MKN-45 and SUN-16 cells	Biomarker	(5)
Human colorectal cancer tissues and LoVo and SW620 cells	Biomarker	(20)
Liver cancer tissues and hepatocellular carcinoma cells	Biomarker	(6,11)
Neuroblastoma SK-N-SH cells	Oncogene	(75)
Non-small cell lung cancer cells	Biomarker	(20,36)
Pancreatic ductal adenocarcinoma tissues	Biomarker	(38)
Melanoma tissues	Oncogene	(76)
Bladder urothelial carcinoma cells	Biomarker	(3)
Brain metastasis lung cancer cells	Biomarker	(10)
Colorectal cancer tissues	Biomarker	(48)
Gastric cancer tissues	Biomarker	(14)

MALAT-1, metastasis associated lung adenocarcinoma transcript-1.

alcoholics (14). However, MALAT-1 is a typical multifunctional gene that is important in a wide array of cancers, including bladder cancer (15,16), gallbladder carcinoma (GBC) (17,18), hepatocellular carcinoma (HCC) (19) and lung (20,21) and gastric cancer (GC) (22). Therefore, understanding the regulation function of MALAT-1 within the context of cancer is of considerable significance. The present study focuses on the recent advances in the role of MALAT-1 in diverse cancers, as MALAT-1 possesses a typical multifunctional lncRNA (Table I).

2. Overview of MALAT-1

MALAT-1 is generally defined as a lncRNA that consists of >8,000 nt and is coded by chromosome 11q13. MALAT-1 transcripts are upregulated in a number of human carcinomas, highly expressed in numerous cancer types, including bladder cancer, gallbladder carcinoma, liver cancer, melanoma, colorectal cancer and gastric cancer, and associated with metastasis. MALAT-1 lacks a significant open reading frame; therefore, it may not translate proteins *in vitro* (23,24). Studies have indicated that MALAT-1 possesses a distinct sequence or secondary structure that directs localization to nuclear speckles in human tumor cells (25,26). Additionally, MALAT-1 expression may be abrogated using zinc finger nucleases (5). Notably, the quantitative loss of MALAT-1 did not affect proliferation, cell cycle progression or nuclear architecture in human lung or liver cancer cells (8). The MALAT-1 mouse model did not reveal any evident phenotype or histological abnormalities compared with wild-type animals. In addition, the loss of abundant nuclear MALAT-1 is compatible with cell viability and normal development (8). Previous studies have demonstrated that MALAT-1 interacts with pre-mRNA splicing factors, including the serine- and arginine-rich (SR) family of proteins (27-29). In detail, MALAT-1 may regulate numerous biological processes, including cancer cell migration, synapse formation, cell cycle progression and response to serum stimulation. However, MALAT-1 function becomes apparent only in specific cell types, such as metastatic cancer cells, and under particular conditions (27). MALAT-1 controls cell cycle progression by modulating the oncogenic transcription factor Myb-related protein B (B-MYB). B-MYB is a transcription factor that is required for the transcription of a large number of genes involved in mitotic progression (30).

Xu *et al* divided MALAT-1 into five fragments. The fragment located in the 3' end (6,918-8,441 nt), was pivotal in the biological processes of cell proliferation, migration and invasion in colorectal cancer (CRC) SW620 and SW480 cells (31). Notably, MALAT-1 exhibited substantially high expression levels in HeLa and MCF-7 cells and was clearly downregulated in a dose-dependent manner. According to the decline, MALAT-1 demonstrates a statistically significant dose-dependent decrease in human melanoma (BLM)-treated HeLa cells, but not in BLM-treated MCF-7 cells or irradiated cells (32). The 3' end of MALAT-1 is transcribed by Pol II and formed by the cleavage of ribonuclease P (RNase P). The 3' ends form a novel triple-helical structure that is essential for stimulating translation, the stability of the RNA and supporting export to the cytoplasm (33). Notably, another study indicated that the 3' end processing mechanism of MALAT-1 may yield a stable nuclear-retained ncRNA with a short poly (A) tail-like moiety and a small tRNA-like cytoplasmic RNA (34). MALAT-1 has been implicated in the regulation of mRNA splicing and expression (35). In addition, MALAT-1 is associated with prostate cancer progression, including castration-resistant prostate cancer (CRPC) (36). Tee *et al* observed that MALAT-1 induced neuroblastoma cell migration and invasion (37). MALAT-1 may also specifically regulate gene expression, but not alternative splicing in lung cancer cells (38). Additionally, MALAT-1 is abundantly expressed in the SK-N-SH cell line under

normal culture conditions and the activation of the oxytocin receptor resulted in a significant increase of MALAT-1 expression (39). The results of an additional study of the 5' end of the MALAT-1 transcript indicated that an alternate transcription initiation site was used in the neuroblastoma cell line, which resulted in a shorter transcript compared with the previously reported transcript in lung cancer cells (39).

Previous studies have demonstrated that MALAT-1 is a highly conserved transcript that regulates the expression of metastasis-associated genes (38,40). Analysis of the nuclear/cytoplasmic distribution of MALAT-1 during the cell cycle reveals a distinct profile, which demonstrates a profound enrichment in the G2/M phase in HeLa cells (28). The heterogeneous nuclear ribonucleoprotein (hnRNP) C protein is of particular interest, due to the RNA-binding capability of the protein and the reported cytoplasmic translocation in the G2/M phase (41). Compared with the insufficient binding capacity at the 5' end of the transcript, strong binding to the hnRNP C protein has been indicated in other regions of MALAT-1 (42). The function of MALAT-1 in the cell cycle may be regulated by facilitating the cytoplasmic translocation of the hnRNP C protein. However, in a previous study, MALAT-1 silencing only compromised the cytoplasmic translocation and not the expression of the hnRNP C protein (42).

3. Molecular targets of MALAT-1

At present, numerous studies have reported the antitumor role of MALAT-1 in cancer development (Table II). In addition, high expression of MALAT-1 has been indicated in cervical (30) and lung cancer (43). MALAT-1 is involved in the pathogenesis of cancers through the regulation of carcinoma-associated signaling pathways, including the mitogen-activated protein kinase (MAPK) signaling pathway (17). Tripathi *et al* showed that the specific deletion of MALAT-1 in human osteosarcoma cells led to the activation of p53 (30). MALAT-1-depleted cells demonstrated cell cycle defects that were sensitive to the p53 levels, which indicates that p53 is a main downstream mediator for MALAT-1 activity. In MALAT-1-depleted cells, replication of the S-phase was decreased and the cell population of G1 and G2/M cells was increased. In addition, MALAT-1 was involved in cervical cancer cell growth, cell cycle progression and invasion. The accumulation of evidence indicated that the downregulation of MALAT-1 may induce the expression of caspase-3, caspase-8 and B-cell lymphoma 2 (Bcl-2)-associated X protein. In addition, MALAT-1 may suppress the expression of Bcl-2 and B-cell lymphoma-extra large. Overall, these results suggested that MALAT-1 may act as a therapeutic target in the prevention of human cervical cancer (44).

The knockdown of MALAT-1 in GBC cell lines may significantly inhibit the proliferation and metastasis of the GBC cells *in vitro* and *in vivo*. In addition, the extracellular signal-regulated kinase/MAPK signaling pathway may be inactivated in the GBC cell lines following MALAT-1 knockdown, which indicates that MALAT-1 may act as an oncogenic lncRNA that promotes the proliferation and metastasis of GBC (17). Other studies indicate that transforming growth factor-β (TGF-β) induces MALAT-1 expression and epithelial-mesenchymal transition (EMT) in bladder cancer cells (15,16,45,46). In addition, the inhibition of MALAT-1 or suppressor of zeste 12 suppressed the migratory and invasive properties induced by TGF-β (15). A previous study revealed that the Wnt signaling pathway demonstrated particularly close links with EMT (47). Immunostaining analysis showed that MALAT-1-siRNA treatment significantly decreased the nuclear accumulation of β-catenin. Therefore, MALAT-1 promotes EMT and sequent cell migration by activating the Wnt/β-catenin signaling pathway in bladder cancer cells (16).

MALAT-1 is recognized as an oncogene, as it regulates the alternative splicing of endogenous target genes that are involved in cancer (40). Taniguchi *et al* indicated that Myc-6 acts as a nuclear sequence-specific transcription factor, which specifically binds to the theoretical target site that is located within the 5'-upstream region of MALAT-1 (48). In addition, Myc-6 exposure led to a dose-dependent decrease in the expression level of MALAT-1 in human osteosarcoma MG63 cells. Multiple serine/arginine-rich splicing factor 1 (SRSF1) proteins bound specifically and directly to the 5' end of MALAT-1. Additionally, MALAT-1 regulated alternative splicing by modulating the levels of active SR proteins (28). Li *et al* considered the potential significance that MALAT-1 promotes the activation effect of the key transcription factor Sp1 on the latent TGF-β-binding protein 3 (LTBP3) promoter by modulating the recruitment of Sp1 to the LTBP3 gene, which regulates the bioavailability of TGF-β, particularly in mesenchymal stem cells from myeloma patients (49). MALAT-1 may promote cell migration and decrease cell proliferation in CaSki cells. Notably, MALAT-1 may increase cell proliferation by upregulating cyclin D1, cyclin E and cluster of differentiation K6 (18). The study conducted by Wang *et al* indicated that MALAT-1 was overexpressed in GC cells (22). Additional studies revealed that MALAT-1 may induce a particularly high expression of SF2/ASF, an important member of the SR protein family, in the nucleolus. The depression of SF2/ASF induced poor cell proliferation in a similar way to MALAT-1 depletion; however, no significant effect on the cell proliferation depression or the loss of nuclear distribution of SF2/ASF was observed with low MALAT-1 expression. Therefore, MALAT-1 promotes cell proliferation in GC cells by recruiting SF2/ASF.

In tumorigenesis studies, MALAT-1 is one of several important splicing factor proline/glutamine-rich (SFPQ)-binding RNAs (50-53). SFPQs may also be termed PTB-associated splicing factors. Additionally, MALAT-1 may competitively bind to SFPQ to release SFPQ from the SFPQ/polypyrimidine tract binding protein 2 (PTBP2) complex in CRC LoVo cells. SFPQs, not PTBP2 proteins, are critical in the regulatory effect (54). In esophageal squamous cell carcinoma, MALAT-1 is suppressed by sex determining region Y (SRY)-box 17 via SRY binding-mediated transcriptional regulation (55).

Cancer metastasis has been indicated as the major cause of cancer recurrence and tumor-associated mortality. In a previous study, antisense oligonucleotides (ASOs) were designed to potently target MALAT-1. The altered ASOs effectively reduced MALAT-1 expression compared with the control ASO (38). A study conducted by Wang *et al* indicated an interaction between the Yes-associated protein (YAP) and SRSF1 by Angiomotin regulated MALAT-1 (19). The MALAT-1-mediated tumorigenesis in HCC provided a novel mechanism for YAP regulation of gene expression at

Table II. Targets of metastasis associated lung adenocarcinoma transcript 1 in cancer.

Cellular system	Modulators	Target molecules	Biological consequences	References
HeLa cells		p53	Cell cycle arrest	(30)
HeLa cells	SRSF1		Alternative splicing	(28)
Human cervical cancer	Caspase-3, caspase-8, Bax, Bcl-2 and Bcl-xL		Cell growth, cell cycle progression and invasion	(44)
Gallbladder carcinoma		ERK/MAPK	Proliferation and metastasis	(17)
Gallbladder carcinoma		Cyclin D1, cyclin E and CDK6	Cell migration and proliferation	(49)
Bladder cancer	TGF-β		Epithelial-mesenchymal transition and tumor metastasis	(15)
Bladder cancer		Wnt/β-catenin	Epithelial-mesenchymal transition and sequent cell migration	(16)
Human osteosarcoma	Myc-6		Cell growth	(48)
Myeloma		Sp1, LTBP3 and TGF-β	Therapeutic target biomarker	(49)
Gastric cancer		SF2/ASF	Cell proliferation	(22)
Colorectal cancer		SFPQ	Tumor metastasis, prognosis and therapeutic target	(54)
Esophageal squamous cell carcinoma	SOX17		Cell growth and migration	(55)
Liver cancer	YAP, SRSF1		Transwell mobility	(19)
Neuroblastoma	CREB		Tumor marker	(39)
Human and mouse lung cancer	ASOs			(38)

SRSF1, serine/arginine-rich splicing factor 1; Bax, Bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; TGF-β, transforming growth factor; YAP, yes-associated protein; CREB, cAMP response element-binding protein; ASO, anti-streptolysin O; p53, tumor protein p53; ERK/MAPK, extracellular signal-regulated kinase/mitogen-activated protein kinase pathway; CDK6, cyclin-dependent kinase 6; Sp1, transcription factor Sp1; LTBP3, latent transforming growth factor β binding protein 3; SF2/ASF, splicing factor 2/alternative splicing factor; SFPQ, splicing factor proline/glutamine rich.

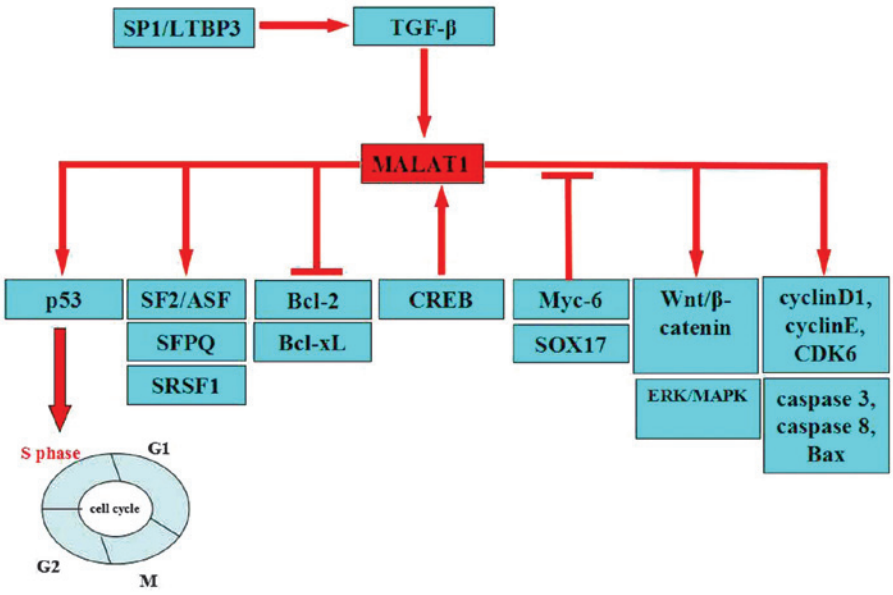

Figure 1. Target function of MALAT-1 in cancer. MALAT-1 acts as an oncogene by targeting significant tumor suppressor genes, including SF2/ASF, SFPQ, SRSF1, cyclin D1, cyclin E and CDK6. Overexpression of MALAT-1 increases cell proliferation through the activation of ERK/MAPK, p53, Wnt/β-catenin, caspase-3, caspase-8, the Bax signaling pathway and the cell cycle. MALAT-1 may suppress the expression of Bcl-2 and Bcl-xL. The expression of MALAT-1 is suppressed by Myc-6 and SOX17. TGF-β induces MALAT-1 expression. CREB binds to the proximal promoter of the MALAT-1. MALAT-1, metastasis associated lung adenocarcinoma transcript 1; SF2/ASF, splicing factor 2/alternative splicing factor; SFPQ, splicing factor proline/glutamine rich; SRSF1, serine/arginine-rich splicing factor 1; CDK6, cyclin-dependent kinase 6; ERK/MAPK, extracellular signal-regulated kinase/mitogen-activated protein kinase pathway; Bax, Bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; TGF-β, transforming growth factor; CREB, cAMP response element-binding protein; Sox17, sex determining region Y-box 17; p53, tumor protein p53; Sp1/LTBP3, transcription factor Sp1/latent transforming growth factor β binding protein 3.

the transcriptional and post-transcriptional stages. The cyclic AMP-responsive element binding protein was indicated to bind to the proximal promoter of MALAT-1 in the human neuroblastoma SK-N-SH cell line (39). These results demonstrated that MALAT-1 expression may be modulated by the extracellular stimulation of tumor cells (Fig. 1).

The identification of MALAT-1 target genes that are involved in tumor development may aid the development of novel therapeutic strategies for tumor intervention.

4. MALAT-1 and epigenetic regulation

As aforementioned, the upregulation of MALAT-1 has been described in several types of human tumors. MALAT-1 silencing or gene therapy may be effective therapeutic approaches for human tumors (10,38,56). At present, epigenetic mechanisms are important in the regulation of gene expression. The role of MALAT-1 is being elucidated in the epigenetic field. For example, post-translational histone modifications and RNA-based mechanisms, including those controlled by microRNAs, are significant mechanisms of the epigenetic regulation of gene expression. Overall, MALAT-1 may affect cancer development (57,58). Notably, Jumonji C-domain-containing protein (JMJD)1A belongs to the JMJD family. Tee *et al* observed that the anti-JMJD1A antibody efficiently immunoprecipitated the MALAT-1 gene core promoter (37). In addtion, JMJD1A increased MALAT1 gene transcription by demethylating histone H3K9. Addtional studies revealed that JMJD1A increased MALAT-1 expression by directly binding to the MALAT-1 gene promoter, which lead to histone H3K9 demethylation by activating JMJD1A gene transcription (59,60). Overall, the findings suggest that the development of more potent JMJD1A/MALAT-1 inhibitors may be used for the prevention of tumor metastasis (37). The methylation/demethylation cycle of Polycomb 2 (Pc2), a component of the polycomb repressive complex 1, is responsible for the physical relocation of growth control genes from Polycomb bodies (PcGs). Methylated Pc2 may demonstrate an antimitogenic signal, but unmethylated Pc2 is essential for physiological growth control, gene expression and cell proliferation. Additionally, a sequence analysis of 94 various clones identified that taurine upregulated 1 (TUG1) repressed cell cycle genes, and was the most enriched RNA that interacted with methylated Pc2 (61). TUG1 localizes to PcGs and interacts with the methylated form of Pc2. However, MALAT-1 resides in nuclear speckles and only interacts with the unmethylated Pc2 protein (62). MALAT-1 silencing has been indicated to inhibit cell growth in HeLa cells, even in the presence of growth signals. The promoters that are associated with MALAT-1 in these domains exhibit high levels of activating the methylation of Lys36 at histone H3 trimethylation (H3K36me3) and H3K4me3 marks. This finding may be facilitated by the interaction of MALAT-1 with lysine demethylase 1 and SET nuclear proto-oncogene (SET) domain-containing 2. Histone methyltransferases and demethylases are associated with transcriptional activation and pre-mRNA splicing factors (63,64). In summary, the results of previous studies may influence the chromatin modifications and accessibility of target gene loci.

Evidently, microRNA-125b (miR-125b), miR-99a and miR-100 are overexpressed in vincristine-resistant acute lymphoblastic leukemia (ALL). Co-expression of these miRNAs resulted in the downregulation of DNA nucleotidylexotransferase,

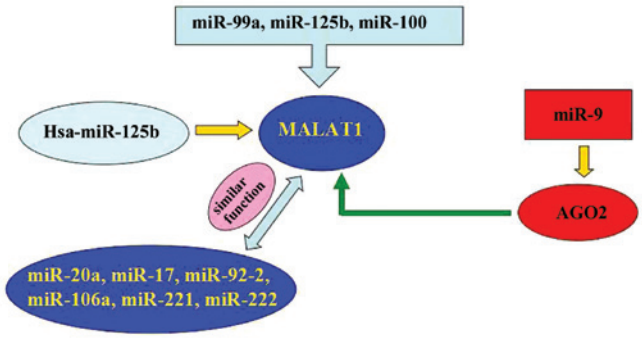

Figure 2. miR regulation of MALAT-1 in cancer. Co-expression of miR-125b, miR-99a, and miR-100 resulted in downregulation of MALAT-1. The function of miR-20a, miR-17, miR-92-2, miR-106a, miR-221 and miR-222 is similar to the function of MALAT-1 in mouse mammary tumors. miR-9 targets AGO2-mediated regulation of MALAT-1 and thus may regulate the expression of MALAT-1. Hsa-miR-125b mimic markedly inhibited MALAT-1 expression levels. MALAT-1, metastasis associated lung adenocarcinoma transcript 1; AGO2, argonaute-2; miR, microRNA.

nuclear casein kinase and cyclin-dependent kinase substrate 1, MALAT-1, small nuclear ribonucleoprotein polypeptide E, PNO1 protein, SET, kinesin-1 heavy chain, phosphoribosyl pyrophosphate synthetase 2, and ribosomal proteins S11, L38 and L23a. One study indicated that 7 of these genes, including MALAT-1, demonstrated decreased expression in the vincristine-resistant ALL cells of children (65). Another study showed that certain miRNAs, including miR-20a, -17, -92-2, -106a, -221 and -222, and chr19 ncRNA, which is similar to MALAT-1, may contribute to c-myc induced mouse mammary tumors (66). miR-9 may regulate the expression of MALAT-1. In addition, miR-9 may target AGO2-mediated regulation of MALAT-1 in the nucleus (67). Han *et al* hypothesized that Hsa-miR-125b is downregulated in bladder cancer compared with matched normal urothelium (68). However, sirtuin (SIRT)7 and MALAT-1 were upregulated in bladder cancer compared with matched normal urothelium. SIRT7 is identified as a crucial regulator of mitochondrial homeostasis. Additionally, high-grade and high-stage carcinomas demonstrated increased expression levels of SIRT7 and MALAT-1. However, additional studies indicated lower Hsa-miR-125b expression levels of SIRT7 and MALAT-1 compared with low-grade and low-stage carcinomas. In addition, Hsa-miR-125b mimics demonstrated markedly inhibited MALAT-1 expression levels in T24 and 5637 cells, whereas hsa-miR-125b inhibitors demonstrated markedly increased MALAT-1 expression levels. Notably, hsa-miR-125b binding sites within MALAT-1 were functional (Fig. 2).

5. Potential clinical applications of MALAT-1

Studies on MALAT-1 are, at present, at an early stage, and no extensive clinical studies on the expression of MALAT-1 in cancer tissues have been reported. In addition, the functional roles and associations of MALAT-1 with cancer are unclear. Therefore, MALAT-1 may be expected to potentially function as novel biomarkers in the diagnosis, prognosis, metastasis and the prediction of responses to therapy in solid tumors.

Numerous studies have assessed the biology of MALAT-1 in cancer (15-22). The role of MALAT-1 in cellular transformation suggests that MALAT-1 has the potential to function as a biomarker and a target for novel therapeutic approaches in multiple myeloma (MM). Previous studies have suggested that MALAT-1 expression in B-cell malignancies is decreased compared with solid tumors (27,69). Another study demonstrated significantly lower MALAT-1 expression levels in the plasma of MM patients (70).

The study conducted by Jiang *et al* identified the correlation between MALAT-1 and human papillomavirus (HPV) (18). In this study, 64 cases of clinical cervical squamous cell carcinoma (SCC) samples were collected. MALAT-1 was identified in 6/18 cases in HPV-positive cervical normal cells and 14/22 cases in HPV-positive cervical lesion specimens. Therefore, these results suggested that HPV was an important factor that led to that activation of MALAT-1 in cervical SCC.

MALAT-1 was previously indicated to demonstrate extremely high expression levels in the established human non-small cell lung cancer (NSCLC) A549 and HTB58 cell lines. In addition, the downregulation of MALAT-1 decreased tumor growth *in vivo*. Human MALAT-1 transcripts increased the migration potential in the mouse fibroblast NIH3T3 cell line, and the downregulation of MALAT-1 decreased the migration potential and tumor growth in human NSCLC A549 cells *in vivo*. Overall, for SCC, increased expression of MALAT-1 may be associated with a poor prognosis (20). Notably, the A549 MALAT-1 wild-type cells and the two knockout (KO) cell lines with the lowest MALAT-1 expression, KO2 and KO3, were injected into the tail vein of nude mice, and the formation of the lung tumor nodules was analyzed 2 months later. The results of this pharmacological study suggested that MALAT-1 is required for effective tumor nodule formation *in vivo*, and therefore affects the metastatic process in lung cancer (38).

In order to identify tumor-associated MALAT-1 and to determine the correlation of the transcript with pancreatic duct adenocarcinoma (PDAC), Weber *et al* identified that MALAT-1 complies with the key characteristics of diagnostic biomarkers, including minimal invasiveness, high specificity and robustness (21). Alternatively, MALAT-1 may be applied as a complementary biomarker within a panel, in order to improve the entire diagnostic performance. The results of the study also showed that MALAT-1 expression levels are upregulated in pancreatic cancer tissues compared with adjacent noncancerous controls. Consistently, a higher expression level of MALAT-1 was identified in all seven pancreatic cancer cell lines relative to the human pancreatic ductal epithelial cell. Function analysis revealed that the downregulation of MALAT-1 may inhibit tumor cell proliferation and decrease cell migration and invasion. The underlying mechanisms are possibly involved in inducing G2/M cell cycle arrest, promoting cell apoptosis, suppressing EMT and reducing cancer stem-like properties. Therefore, the accumulation of evidence indicates that MALAT-1 may act as an oncogenic lncRNA that is involved in the malignant phenotype of pancreatic cancer. Importantly, MALAT-1 may be used as a potential therapeutic target (71). Another study indicated that the overexpression of MALAT-1, the tumor location and nerve invasion were independent predictors of disease-specific survival of PDAC (56).

MALAT-1 overexpression has been reported to predict the recurrence of HCC following liver transplantation (LT). MALAT-1 rs619586 was associated with a decreased HCC

risk, with a borderline significance (P=0.057). Larger studies are required in order to clarify the associations between rs619586 in MALAT-1 and HCC risk (72). Notably, a consistently higher expression level of MALAT-1 was identified in all nine liver cancer cell lines, relative to the normal liver LO2 cell line. The association study indicated that the overexpression of MALAT-1 did not exhibit significant correlations with the pathological features of age, gender, tumor size, histological differentiation or portal vein tumor thrombi (73). More importantly, the multivariate regression analysis revealed that the overexpression of MALAT-1 may be a novel independent predictor of recurrence-free survival in HCC patients following LT. In addition, MALAT-1 silencing in HCC may be a potential anticancer therapy to prevent tumor recurrence following orthotopic liver transplantations (74). However, MALAT-1 is overexpressed in hepatoblastomas (HPBL) compared with HCC, as HCC and HPBL have distinct patterns of gene expression (75). Subsequent studies have provided evidence about the importance of MALAT-1 in liver cell proliferation, which was confirmed by the finding of arrested liver cell proliferation in response to partial MALAT-siRNA mediated knockdown (40,76,77).

The expression level of MALAT-1 was significantly increased in melanoma tissues compared with paired adjacent normal tissues. Although no statistical difference of MALAT-1 expression was observed between melanomas with or without lymph node metastasis, the expression level of MALAT-1 was affected by the metastatic status of the tumor in melanoma. In addition, the migration of A-375 cells transfected with MALAT-1-siRNA was estimated using a Transwell assay. The cells with impaired expression of MALAT-1 migrated less effectively through the Transwell membrane. Therefore, the enhanced expression of MALAT-1 had the potential to affect cancer metastasis in melanomas. In general, these findings indicated that the expression level of MALAT-1 had the potential to be a prognostic indicator for the metastasis of melanoma (78).

17β-Estradiol (E2) treatment to breast cell lines causes MALAT-1 RNA to decrease in an estrogen receptor α independent manner. This effect of E2 treatment is caused by MALAT-1 transcriptional regulation of E2. Zhao *et al* hypothesized that the effects of E2 treatment on breast cells are achieved by regulating MALAT-1 (79). However, MALAT-1 was downregulated in the cell culture, with the cells exhibiting high metastatic potential for ovarian cancer metastasis. The function of MALAT-1 may vary with various cancer types and context (80).

Several reports indicate that MALAT-1 contributes to the complex molecular mechanisms involved in the control of cell growth, differentiation and motility. Therefore, MALAT-1 may be important in the process of cancer metastasis. Han *et al* observed that MALAT-1 is upregulated in bladder urothelial carcinoma compared with the matched normal urothelium (81). A high expression level of MALAT-1 was associated with high-grade and high-stage bladder urothelial carcinoma. MALAT-1 silencing inhibited bladder urothelial carcinoma cell growth, induced apoptosis and decreased cell motility in T24 and 5637 cells. In addition, MALAT-1 knockdown also inhibited tumor metastasis (15). MALAT-1 inhibition may represent a promising therapeutic option for the suppression of bladder cancer progression. MALAT-1 expression levels were significantly upregulated in the majority of bladder cancer tissues compared with normal tissues. These data indicated that the upregulation of MALAT-1 may be associated with the onset of bladder cancer metastasis. In addition, MALAT-1 silencing impaired bladder cancer cell migration (16).

A study conducted by Okugawa *et al* illustrated that the expression levels of both MALAT-1 and HOX transcript antisense RNA were significantly increased in GC tissues compared with matching adjacent normal mucosa (82). Elevated MALAT-1 expression significantly correlated with peritoneal dissemination. Additionally, a difference in the levels of MALAT-1 was not evident in the plasma in a comparison between the healthy controls and GC patients (83).

The expression level of MALAT-1 was significantly increased in brain metastasis samples compared with non-brain metastasis samples. MALAT-1 was increased in a highly invasive subline of brain metastasis lung cancer cells. Functional studies indicated that MALAT-1 silencing inhibits a highly invasive subline of brain metastasis lung cancer cell migration and metastasis by inducing EMT (10).

A recent study indicated that the expression of MALAT-1 was higher in human CRC tissues than adjacent normal tissues (54). MALAT-1 upregulation has been demonstrated in CRC tumors. In addition, the expression levels of MALAT-1 in cancerous tissues were increased compared with noncancerous tissues. Although no associations were identified between MALAT-1 expression and the stages, including stage II and III, in CRC patients, the expression of MALAT-1 was significantly increased in male patients compared with female patients. In particular, patients with a high level of MALAT-1 expression showed significantly shorter disease-free survival (DFS) and overall survival times (OS) compared with patients with low MALAT-1 expression. In addition, patients with perineural invasion demonstrated significantly shorter DFS and OS times compared with those without perineural invasion. Multivariate Cox regression analysis indicated that MALAT-1 expression and perineural invasion were predictors of poor prognosis regarding DFS in CRC patients (84).

Another study investigated that MALAT-1 was upregulated across all 8 CRPC samples, which has been implicated in regulating mRNA splicing. The expression of MALAT-1 was also recently indicated to be associated with prostate cancer progression (36).

6. MALAT-1 and chemoresistance

MALAT-1 has been indicated to promote cell proliferation, migration and inhibit cell apoptosis in numerous cancer cells. The expression of MALAT-1 was reported to dramatically decrease with the increasing concentration of cisplatin and paclitaxel, which lengthened the treatment duration. Cisplatin and paclitaxel target significant lncRNAs in laryngeal squamous cell carcinoma (LSCC), which provides a novel molecular target to treat LSCC patients and sets direction for the development of novel drugs (85). Lung cancer is the top cause of cancer-associated mortality (86). One reason for this is the development of resistance to the chemotherapy treatment. In particular, cancer stem cells (CSCs) may escape treatment

and regenerate the bulk of the tumor. Gene expression analysis showed that MALAT-1 was involved in tumor development and metastasis. In addition, MALAT-1 was similarly induced in CSCs and cisplatin-resistant H460 cells (87).

7. Conclusion and future perspectives

The identification of ncRNAs as important regulators of gene expression improved the understanding of numerous biological processes, including cancer cell migration, synapse formation, cell cycle progression and response to serum stimulation. The findings indicate that MALAT-1 is an important novel modulator in the development of cancers. MALAT-1 may promote cell proliferation, inhibit apoptosis, and enhance tumor growth in numerous cancer cell lines, and therefore, may serve as an excellent candidate for therapeutic intervention. High expression levels of MALAT-1 are widely hypothesized to associate with the prognosis and survival in clinical cancer patients. Notably, single MALAT-1 detection has strong potential as an independent prognostic factor in cancer patients. However, the applicability and epigenetic regulation of MALAT-1 targeted strategies for the clinical treatment of human tumors requires additional studies.

Additional studies are also required to elucidate the mechanism of MALAT-1, the emerging targets in oncology and the possible future directions for clinical applications. Therefore, in-depth studies on the functions of MALAT-1 may lead to novel diagnostic and therapeutic approaches.

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