MALAT1: A long non-coding RNA highly associated with human cancers (Review)

MIAOMIAO ZHAO[1,2], SONGPO WANG[1], QI LI[3], QING JI[3], PIAOTING GUO[1] and XIAOWEI LIU[1]

[1]Department of Traditional Chinese Medicine, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080; [2]Department of Oncology, Zhengzhou Traditional Chinese Medicine Hospital, Zhengzhou 450007; [3]Department of Oncology, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, P.R. China

Abstract. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), a well-known lncRNA associated with numerous diseases, particularly cancer, has received increased attention. The expression of MALAT1 was determined to be upregulated in numerous types of tumors and MALAT1 exhibited effects on tumor cell proliferation, migration, invasion and apoptosis. The abnormal expression of MALAT1 was identified in almost in every organ of the digestive system. MALAT1 performed an important role in the pathological alterations of organs that are associated with sex hormones and several reproductive system cancers. MALAT1 participates in molecular pathways. In the clinical application of MALAT1, MALAT1 was considered as a potential biomarker for the diagnosis and prediction of cancers, and may also serve as therapeutic target for treatment of specific tumors. This review summarizes the abnormal expression of MALAT1 in cancer, its significant effect on the primary features of cancer, as well as the underlying molecular mechanisms of MALAT1 in various cancers. According to studies on MALAT1, we introduce the upstream and downstream substances associated with the function of MALAT1. These reviewed studies promote the clinical application of MALAT1 in the aspect of diagnosis and treatment of different cancers, and may help point out new study directions for MALAT1.

Contents

1. Introduction

For decades, studies have focused on protein-coding genes, as they are significantly involved in the mechanisms of cancer initiation and progression. Mutation or deletion of the TP53 may lead to development of Li-Fraumeni syndrome, a disease that leads to increased likelihood of developing tumors during early adulthood (1). PTEN may suppress the growth of tumor cells by antagonizing protein tyrosine kinases and may regulate the invasion and metastasis of tumor cells through interaction with focal adhesion (2). Completion of the human genome sequencing project (3), enriched the available information regarding genome organization and content. Along with the identification that non-protein coding RNAs (ncRNAs) account for the majority of human genome-transcribed sequences (4), ncRNAs have attracted markedly growing research interest.

Long non-coding RNAs (lncRNAs) are a type of RNA molecule with a length of >200 nucleotides (nt), which are unable to encode proteins (5). Specifically, lncRNAs have been defined as RNA molecules that may function as either primary or spliced transcripts, and do not match with these known classes of small RNAs or structural RNAs (6). lncRNAs regulate gene expression through various processes, including chromatin modification, transcription and post-transcription (6,7). lncRNAs can regulate the transcription processing by interacting with RNA binding proteins, co-activating transcription factors, or repressing the promoters of target genes (8-10). Although these lncRNAs cannot encode proteins, their roles in cellular functions are indispensable as well as complex.

2. Research background of MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), also termed nuclear enriched abundant transcript 2, is a long intergenic non-coding RNA (lincRNA) with >8,000 nts, located on chromosome 11q13 (11). Sequences

Correspondence to: Professor Songpo Wang, Department of Traditional Chinese Medicine, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, 100 Haining Road, Hongkou, Shanghai 200080, P.R. China
E-mail: 13386259791@163.com

of lncRNAs are highly evolutionarily conserved among species, which predicts the potentially important biological functions of MALAT1 (11). In 2003, MALAT1 was firstly identified to be significantly associated with the metastasis of early-stage non-small cell lung cancer (NSCLC), and therefore MALAT1 was proposed to be a prognostic marker for stage I NSCLC (11). Since then, studies about MALAT1 have gradually increased. A search for all the MALAT1-associated publications on PubMed was performed, and the statistical result is shown in Fig. 1. As shown in Fig. 1, between 2003 and December 2014, the amount of relevant studies increased year-by-year, indicating growing interest of researchers in MALAT1. Among all these articles, cancer-associated studies accounted for ~20% of the total. In addition to cancers, several non-cancer diseases, including myocardial infarction and hyperghlycemia, have also been reported to be associated with MALAT1 (12-16). Studies have identified that MALAT1 performs a vital role in regulating the function of endothelial cell and vessel growth (12), and the role was evidenced in the cardiovascular vascular system (13). In addition, the abnormal expression of MALAT1 in patients with myocardial infarction indicated that it performs an important role in cardiovascular diseases (14). Notably, MALAT1 was also involved in hyperglycemia by inducing inflammatory processes (15), and in diabetic retinopathy it was improperly regulated (16). MALAT1 also affected the progression of proliferative vitreoretinopathy (17), hereditary degenerative disease myotonic dystrophy type 1 (18) and keratoacanthoma (19). In addition, the upregulation of MALAT1 was identified in the cerebellum, hippocampus and brain stem of human alcoholics (20) and the progression of microtia (21) were reported to be associated with MALAT1 expression. Therefore, MALAT1 is widely involved in numerous pathological processes.

3. Association of MALAT1 with cancers

Since the association between MALAT1 and NSCLC was identified, its important roles as an lncRNA in cancer have been considered as a paradigm (22). The expression of MALAT1 was found to be upregulated in numerous types of tumor, and MALAT1 exhibited marked effects on tumor cell proliferation, migration, invasion and apoptosis (22). The advances in clinical study about MALAT1 on cancer during recent years are summarized in Table I.

Aberrant expression and multiple biological functions of MALAT1 in different cancers. Following the first identification of MALAT1 in NSCLC(11), a subsequent study on NSCLC about MALAT1 hypothesized that the apparent overexpression of MALAT1 in stage I and II NSCLC primary tumors increased the likelihood to metastasis (23). Furthermore, increased MALAT1 expression contributed to brain metastasis by promoting epithelial-mesenchymal transition (EMT) in NSCLC (24).

Undoubtedly, the action of MALAT1 on digestive system cancer deserves wide attention. It was demonstrated that in esophageal squamous cell carcinoma (ESCC), the overexpression of MALAT1 promoted tumor proliferation and metastasis (25). In gastric cancer, the high-level expression of MALAT1 was reported to promote the development and the peritoneal metastasis of cancer (26). A previous clinical study showed that MALAT1 was associated with colorectal
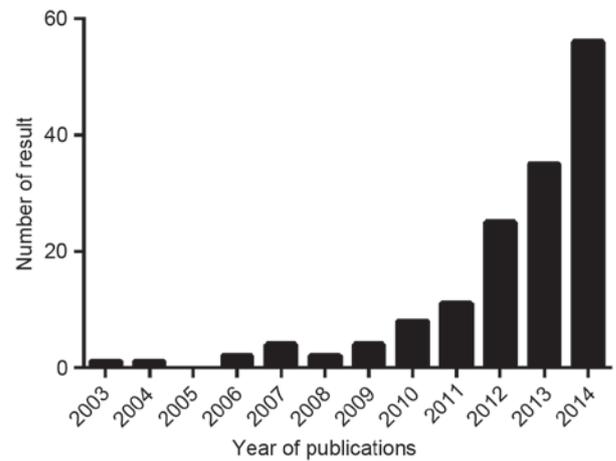

Figure 1. Literature about MALAT1. Articles were searched on PubMed, limited to 'between 2003 and December 2014'.

cancer (CRC), and its elevated expression may be a negative prognostic factor of patients with stage II/III CRC (27). MALAT1 was also revealed to be upregulated in hepatocellular carcinoma, and its overexpression may indicate a higher risk of tumor recurrence following liver transplantation (28). In a clinical study on pancreatic cancer, the abnormal overexpression of MALAT1 was identified as an unfavorable predictor for its clinical progression and prognosis (29). In accordance with the former research, studies on pancreatic cancer *in vitro* using seven associated cell lines confirmed the role of MALAT1 in promoting cell growth, migration and invasion (30).

The situation was similar in clear cell renal carcinoma; patients with higher levels of MALAT1 indicated worse tumor progression and poor prognosis, and exploration revealed that knockdown of MALAT1 could inhibit proliferation, migration and invasion in renal cancer cells (31). A previous study on bladder cancer revealed that MALAT1 promoted EMT-associated cell migration and may be activated via Wnt signaling (32). The upregulated MALAT1 was associated with the ability of proliferation, apoptosis and motility in urothelial carcinoma of bladder cancer cells (33). Therefore, its effect on the urinary system was also noteworthy.

It appeared that MALAT1 performed an important role in the pathological changes of organs that are highly associated with sex hormones and several reproductive system cancers (34-37). The upregulation of MALAT1 was involved in the progression of castration-resistant prostate cancer (CRPC) and was associated with the maintenance of tumorigenicity (34). It was also shown to be one of the 10 most highly-expressed transcripts in CRPC, involving RNA processing and resulting in incomplete splicing (35). In addition, the inhibitory effect of 17β-estradiol treatment on breast tumor cell proliferation, migration and invasion was elucidated to be not ERα-dependent but dose-dependent by downregulating the expression level of MALAT1 (36). Furthermore, in cervical cancer, upregulated MALAT1 was associated with positive human papilloma virus (HPV) in cervical squamous cells (37), and MALAT1 was found effect cervical cancer cell proliferation and invasion(38).

MALAT1 was also studied in several other types of cancers (39-42). Among numerous lncRNAs, MALAT1 was

Table I. Research advances of MALAT1 in cancers.

Cancers	Function of MALAT1	(Refs.)
NSCLC	Associated with metastasis and survival	(4)
	A prognostic parameter for stage I and stage II NSCLC	(4,16)
	Contributes to brain metastasis	(24)
Esophageal Squamous cell carcinoma	Promotes tumor proliferation and metastasis	(25)
Gastric cancer	Promotes the development and peritoneal metastasis of cancer	(26)
	Promotes cell proliferation	(35)
CRC	A negative prognostic factor to patients with stage II/III CRC	(27)
Hepatocellular carcinoma	Predicts a significantly increased risk of tumor recurrence following liver transplantation	(28)
	Modulating cell proliferation	(59)
Pancreatic cancer	Unfavorable predictor for its clinical progression and prognosis	(29)
	Promotes cell growth, migration and invasion	(30)
	Promotes the stem cell-like phenotypes in cancer cells	(70)
Clear cell renal carcinoma	Associated with proliferation, migration and invasion, indicates tumor progression and poor prognosis	(31)
Bladder cancer	Promotes cell migration with the EMT	(32)
	Mediates the TGFβ-induced EMT and promotes tumor metastasis	(75)
Urothelial carcinoma of the bladder	Associated with proliferation, apoptosis and motility	(33)
Castration-resistant prostate cancer	Maintains tumorigenicity	(34)
	Involved in RNA processing and resulting in incomplete splicing	(35)
Breast cancer	Involved in the inhibitory effect of 17β-Estradiol treatment on breast tumor cell proliferation, migration and invasion	(36)
	Regulated EMT	(68)
Cervical cancer	Associated with the positive of human papilloma virus in cervical squamous cells	(37)
	Effected cervical cancer cell proliferation and invasion	(38)
Adrenocortical cancer	The second most upregulated lncRNA	(39)
Multiple myeloma	Predicts early progression	(40)
Melanoma	Associated with the metastasis	(41)
Osteosarcoma	Promotes tumor proliferation and metastasis	(42)
	Involved in drug action in high-grade osteosarcoma	(51)
Neuroblastoma	Involved in neuroblastoma cells migration and invasion	(48)
Glioblastoma	Affects the migration of glioblastoma cells	(81)

MALAT1, metastasis-associated lung adenocarcinoma transcript 1; EMT, epithelial-mesenchymal transition; lncRNA, long non-coding RNA; TGFβ, transforming growth factor β; CRC, colorectal cancer; NSCLC, non-small cell lung cancer.

revealed to be the second most largely upregulated lncRNA in adrenocortical cancer (39). In patients with multiple myeloma, MALAT1 was reported as overexpressed (40). The markedly high expression of MALAT1 was also shown to be associated with melanoma metastasis (41). In the progression of osteosarcoma, MALAT1 was reported to promote tumor proliferation and metastasis via the phosphoinositide 3-kinase (PI3K)/Akt pathway (42).

In conclusion, these studies demonstrated that MALAT1 serves as an oncogenic gene during the progression of diverse cancers, and that the potential functions of MALAT1 are associated with the basic features of cancer, including proliferation, metastasis, invasion and apoptosis.

Preliminary studies on clinical application of MALAT1 in cancers. As aforementioned, MALAT1 serves a vital role in several cancers, and increasing efforts have been devoted to developing MALAT1-based cancer diagnosis and treatment. The deregulation of MALAT1 in certain types of tumor tissues and association with tumor cell proliferation, migration and invasion make it potential diagnostic biomarkers (4,16,27,29,39). One study has already revealed that urine MALAT1 may act as a promising diagnostic biomarker for prostate cancer based on a multicenter evaluation (43). In addition, MALAT1-derived miniRNA in the plasma may be used to detect and diagnose prostate cancer (44). Other applications about MALAT1 on predicting cancer progression, prognosis, recurrence and metastasis have always been important directions in cancer research. A study about the association between the expression of MALAT1 in the peripheral whole blood of patients and lung

cancer progression indicated that its expression level may reflect the host response to lung cancer development (45).

In addition to its advantages as diagnostic or predictive biomarkers, MALAT1 and substances interacting with it may also serve as therapeutic targets in specific tumors (46-48). Several synthetic artificial microRNAs targeting MALAT1 and other genes successfully exhibited anticancer effects on two bladder cancer cell lines (46), which was at the forefront of the application study. The tumor-suppressive ability of Myc-6, a small synthetic chemical pyrrole-imidazole polyamide, on human osteosarcoma MG63 cells was suggested to be partly associated with the specific decrease of MALAT1 (47). In another study about the histone demethylase jumonji domain-containing protein 1A (JMJD1A) and MALAT1, the small molecule JMJD1A inhibitor dimethyloxaloylglycine was demonstrated be able to suppress neuroblastoma cell migration and invasion (48). These studies laid the basis of clinical applications.

Clinical application studies about MALAT1 were not confined to the aforementioned fields. In the study of the genotoxic stress-induced apoptosis, MALAT1 was markedly downregulated in bleomycin-treated HeLa and MCF-7 cells (49). MALAT1 was one of the significant lncRNAs in laryngeal squamous cell carcinoma; the expression of MALAT1 decreased when patients were treated with increasing concentrations of cisplatin and paclitaxel (50). MALAT1 was previously identified to be involved in drug action in high-grade osteosarcoma, suggesting its potential to modulate the drug sensitivity (51). Therefore, the association between MALAT1 and drug action is noteworthy.

4. Molecular mechanisms of MALAT1 in cancers

MALAT1 co-localizes with SC35 splicing domains which were also known as interchromatin granule clusters or nuclear speckles, and the localization of MALAT1 suggests its function in RNA metabolism (52) MALAT1 is a nuclear-retained RNA, and has been shown to be involved in pre-mRNA processing in mammalian cells (53). The 3' end processing of MALAT1 generates the mature MALAT1 transcript and a tRNA-like RNA cytoplasmic RNA (54). Mature MALAT1 lacking a poly (A) tail was protected by the triple helix structure to maintain the stability of its 3' ends, and the triple helix could also serve as a translational enhancer (55). MALAT1 was involved in mRNA processing, splicing and exporting (56), and these findings laid the basis of the MALAT1 function.

MALAT1 is regulated by upstream genes or proteins. The expression of MALAT1 was regulated by numerous genes or proteins during transcription and post-transcriptional processing (Fig. 2). Sp1 and JMJD1A were reported to regulate the expression of MALAT1 by binding to the gene promoter, consequently affecting the transcription processing (48,57). A study revealed that Sp1 may bind to the promoter to activate MALAT1, leading to the upregulation of MALAT1 in lung cancer (57). By binding to the promoter and activating the transcription of MALAT1, the histone demethylase JMJD1A upregulated the expression of MALAT1, facilitating neuroblastoma cell migration and invasion (48). In a study on the sex determining region Y-box (Sox) 17 in esophageal cancer, MALAT1 was confirmed as one
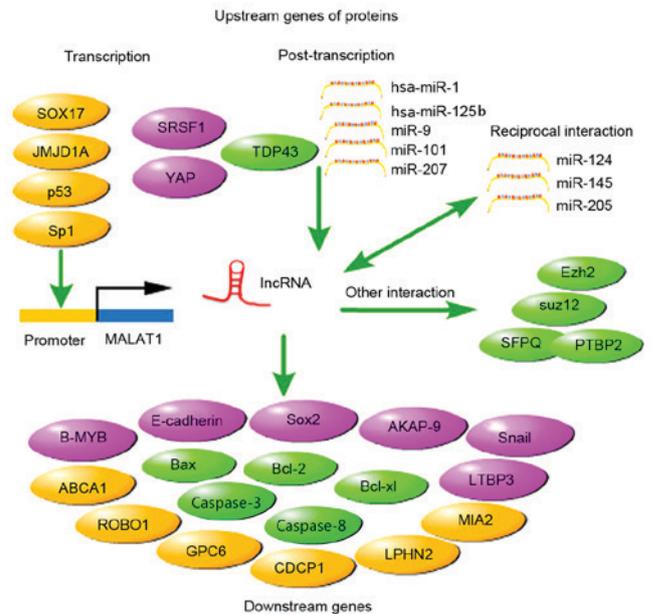

Figure 2. Genes, proteins or miRNAs associated with MALAT1. The upstream regulators during the transcriptional and posttranscriptional procession and the downstream genes modulated by MALAT1 are exhibited. In addition, reciprocal interaction and other associations between MALAT1 and other genes, proteins or miRNAs are shown. MALAT1, metastasis-associated lung adenocarcinoma transcript 1; SOX17, sex-determining region-Y-box 17; SRSF1, serine/arginine-rich splicing factor 1; YAP, yes-associated protein 1; Bcl-2, B-cell lymphoma-2; miR/miRNA, microRNA; ABCA1, ATP-binding cassette transporter member 1; ROBO1, roundabout guidance receptor 1; GPC6, glupican 6; CDCP1, CUB domain-containing protein 1; LPHN2, latrophilin-2, a cell-adhesion G protein-coupled receptor and presumptive α-latrotoxin receptor; MIA2, melanoma inhibitory activity 2; LTBP3, latent transforming growth factor β-binding protein 3; PTBP2, polypyrimidine tract binding protein 2; SFPQ, splicing factor proline-glutamine rich; suz12, suz12 polycomb repressive complex 2 subunit; Ezh2, enhancer of zeste homolog 2; Bax, Bcl-2-associated X protein; Bcl-xl, B-cell lymphoma-extra-large; TDP43, TAR DNA-binding protein 43; lncRNA, long non-coding RNA; AKAP-9, A-kinase anchor protein-9.

of the new suppressive downstream genes in its transcriptional network (58). MALAT1 was reported to perform an important role in modulating proliferation of early-stage hematopoietic cells, and p53 regulated the process of hematopoietic differentiation via changing MALAT1 expression (59).

The post-transcriptional processing of MALAT1 is complex (60). In NSCLC, TDP-43 may regulate the expression of MALAT1 by directly binding to MALAT1 RNA (61). The interactions with nucleic acids, including miRNAs, during post-transcriptional processing significantly affect the expression and functions of MALAT1 (62-65). By downregulating K-ras and MALAT1, hsa-miR-1 was identified to suppress the development of breast cancer (62). Similarly, MALAT1 was suggested as suppressed by hsa-miR-125b in bladder cancer (63). In the study of the posttranscriptional regulation of MALAT1 in ESCC, studies identified that the posttranscriptional silencing of MALAT1 could suppress tumor proliferation, migration and invasion by miR-101 and miR-217 (64). miR-9 was also reported to modulate the degradation of MALAT1 by targeting AGO2-mediated regulation in the nucleus (65).

As the mechanism underlying the expression and function of MALAT1 is complex, the interactions between

upstream regulators and MALAT1 are not simple either. According to a related study, MALAT1 was associated with yes-associated protein (YAP) and serine/arginine-rich splicing factor 1 (SRSF1) at transcriptional and post-transcriptional processing in liver cancer (60), and the associations among MALAT1, YAP and SRSF1 were complicated.

MALAT1 regulates downstream gene expression. Modulation of gene expression is one of the most important functions of lncRNA (6). In lung cancer, the pivotal function of MALAT1 associated with metastasis phenotype was not alternative splicing but regulating the expression of 23 concerning genes, including melanoma inhibitory activity 2, roundabout 1, glypican 6, latrophilin 2, CUB domain containing protein 1 and ATP-binding cassette, subfamily A, member 1 (66). It was previously revealed in NSCLC that the MALAT1 levels affect the expression of B-cell lymphoma (Bcl-2), and Bcl-2 was identified to affect the prognosis (67). Notably, MALAT1 was identified to promote the expression of caspase-3, -8 and Bcl-2-associated X protein, and inhibit the expression of Bcl-2 and Bcl-extra-large, subsequently affecting cervical cancer cells proliferation and invasion (68). PPKA kinase anchor protein 9 was indicated to be the target protein of MALAT1 in colorectal cancer, and the two of them were involved in tumor promotion (69). One study has shown that the promotion of MALAT1 on the stem cell-like phenotypes in pancreatic cancer cells is associated with increased expression of Sox2, a self-renewal associated factor (70). Another study on multiple myeloma revealed that in mesenchymal stem cells, MALAT1 promoted the activation of the promoter of latent transforming growth factor-β binding protein (LTBPS) via regulating recruitment of Sp1 to LTBPS, and the interaction of MALAT1 with Sp1 and LTBP3 promoter increased the expression of LTBPS (71). In terms of its mechanism on regulating the proliferation of cancer cells, MALAT1 modulated the expression level of transcription factor B-MYB, an oncogenic gene involved in cell cycle progression (72). The downstream genes associated with MALAT1 are listed in Fig. 2.

Interaction between MALAT1 and other genes. The underlying mechanism of MALAT1 promoting tumor growth and metastasis in colorectal cancer was revealed to be associated with its competitive binding to the tumor suppressor gene splicing factor proline and glutamine rich (SFPQ) and subsequently releasing SFPQ from the SFPQ/polypyrimidine tract binding protein 2 (PTBP2) complex, which was accompanied by increased SFPQ-detached PTBP2, which served as a proto-oncogene (73). In gastric cancer, MALAT1 promoted cellular proliferation partly by recruiting the splicing factor SF2/alternative splicing factor, a member of the serine/arginine-rich protein family (74). According to a study on bladder cancer, MALAT1 also mediated the TGF-β-induced EMT and was associated with suppressor of zeste12, thus promoting tumor metastasis (75). To investigate the mechanism underlying the promotion of MALAT1, a recent study conducted on renal cell carcinoma showed that the binding of MALAT1 and enhancer of zeste homolog 2 affected the epithelial-mesenchymal transition by affecting the expression of E-cadherin and β-catenin, thus, finally affecting

the tumor progression (76). Furthermore, its reciprocal interaction with miR-205 was also disclosed (76). miR-205 was not the only miRNA involved in the reciprocal interaction with MALAT1; it was demonstrated that MALAT1 could regulate the radiosensitivity of HR-HPV+ cervical cancer by the reciprocal repression between MALAT1 and miR-145 (77). The reciprocal interaction between MALAT1 and miR-124 was also involved in the growth and invasion of HR-HPV-positive cervical cancer cells via the MALAT1-miR-124-RBG2 axis (78). In Fig. 2 we show the interaction.

Signaling pathways involving MALAT1. MALAT1 has been found to be associated with a multitude of molecular pathways, which in turn complicated the mechanism of action (25,68,79-83). It modulated nuclear factor-κB/RelA, which is involved in the process of EMT (79). Furthermore, another study on breast cancer revealed that the expression of MALAT1 could regulate EMT through the PI3K-AKT pathway (68), which was also involved in the progression of osteosarcoma (41). In ESCC, the overexpression of MALAT1 was demonstrated to promote tumor proliferation and metastasis by dephosphorylating the ATM-CHK2 pathway (25). In the study of gallbladder carcinoma, researchers found MALAT1 acted as an oncogenic lncRNA by activating the extracellular-signal regulated kinase/mitogen-activated protein kinase pathway (80). Another study on glioblastoma revealed MALAT1 was the top downregulated gene in the WNT inhibitory factor 1-expressing cells, and identified that knockdown of MALAT1 could reduce the migration of glioblastoma cells (81). Furthermore, this study also suggested the possible association between the non-canonical Wnt signaling and MALAT1 (81). Chemokine (C-C motif) ligand 5, derived from tumor-associated dendritic cell, was revealed to be associated with colon cancer progression through the MALAT1/Snail pathway (82). In addition, the PCDH10-Wnt/β-catenin-MALAT1 regulatory axis was established in a study on endometrioid endometrial cancer (83).

5. Perspectives and challenges

Firstly, MALAT1 is an important lncRNA involved in numerous biological processes. The critical roles of MALAT1 in gene regulation and the noticeable effect on the basic function of cells, particularly on tumor cells, have been confirmed by numerous concerning studies (72,84-86). However, certain results of these studies were inconsistent. A study showed that the quantitative loss of MALAT1 had no effect on the phenotypes of human lung or liver cancer cells, including proliferation and cell cycle progression (87), which disagreed with other studies (11,59,88). Similarly, the expression of MALAT1 also differed significantly from another study on hepatocellular carcinoma, according to the expression profiles of lncRNAs (89). Secondly, since numerous molecular mechanisms underlying the action of MALAT1 remain unclear, multiple experiments are required to explore and verify its functions. Furthermore, certain parts of mechanisms underlying the progression of different cancers appear to be the same. For example, the abnormal expression of MALAT1 was found almost in

every organ of the digestive system (25-30), MALAT1 and PI3K-AKT pathway are involved in osteosarcoma and breast cancer (42,68). It is then important to confirm whether these shared mechanisms are universal. Furthermore, in terms of the diverse types of diseases associated with MALAT1, research fields should be expanded to its associated functions in addition to cancer. Finally, there is no doubt that the application of MALAT1 was diverse. During the development of MALAT1-based cancer diagnosis and treatment, with the expectation of its advantages as a diagnostic biomarker, predictive biomarker or therapeutic targets in specific tumors, its effect on drug action is also a good study direction on its clinical application.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SW made substantial contributions to design. QJ and QL were involved in drafting the manuscript or revising it critically for important intellectual content, XL and PG were involved in acquiring, and analyzing related articles and data. MZ was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interests.

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