Review Article

The Role of MALAT1 in Cancer

Dake Chen[1#], Tao Xu[2#], Howard Hoyon Chang[3#], Qi Song[3], Yu Zhu[4], Yan Han[3*], Shubin Wang[4*], Jian Chen[5*]

[1]Department of Oncology, Tongzhou People's Hospital, Nantong 226300, China

[2]Department of Anesthesiology, Affiliated Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai 200233, China

[3]CuraCloud Corporation, 999 Third Ave, Suite 700, Seattle, WA 98104, Washington, USA

[4]Department of Oncology, Peking University-Shenzhen Hospital, China

[5]Department of Orthopedics, Tongzhou People's Hospital, Nantong 226300, China

[#]These authors contributed equally to this work.

[*]**Corresponding Authors:** Yan Han, CuraCloud Corporation, 999 Third Ave, Suite 700, Seattle, WA 98104, Washington, USA, E-mail: yanh@curacloudcorp.com

Shubin Wang, Department of Oncology, Peking University-Shenzhen Hospital, China, E-mail: wangshubin2013@163.com

Jian Chen, Department of Orthopedics, Tongzhou People's Hospital, Nantong 226300, China, E-mail: jchentz@163.com

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Abstract

Long non-coding RNA (LncRNA) are involved in chromatin remodeling, transcriptional control, and post-transcriptional processing. The LncRNA, Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has been shown to be involved in metastasis for many cancers. In this review, we summarize recent findings of MALAT1 in lung cancer, colorectal cancer, breast cancer, cervical cancer, pancreatic cancer, hepatocellular cancer, gliomas, bladder cancer, esophageal cancer, stomach cancer, gall bladder cancer, nasopharyngeal cancer, osteosarcoma, ovarian cancer, prostate cancer, melanoma, tongue cancer, oral squamous cell carcinoma, and multiple myeloma.

Keywords: Long non-coding RNA; microRNA; Metastasis; Cancer

1. Introduction

Recent studies have showed that only 2% of the human genome transcripts are responsible for protein-coding RNA, and the remaining 98% do not have the protein-coding function. However, they play an important role in cell biology. These types of RNA are collectively referred to as non-coding RNA (ncRNA). The ncRNA in the human genomics is divided into short-chain, non-coding RNAs, and long non-coding RNAs (LncRNAs), which are between 200 bp to 10 kbp in length and account for more than 80% of all ncRNAs [1]. Unlike other LncRNAs, MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is abundantly expressed and evolutionarily conserved in various mammalian species. MALAT1 is actively involved in a variety of physiological processes, including alternative splicing, epigenetic modification of gene expression, synapse formation, and myogenesis. In addition, there is ample evidence suggesting that MALAT1 also plays a key role in a variety of pathological conditions. MALAT1 is also one of the first LncRNAs that have been shown to be associated with human diseases. Numerous studies have shown that MALAT1 plays a key role in the development and metastasis of various cancers [2].

2. Overview

MALAT1, also known as nuclear-enriched autosomal transcript 2 (NEAT2), is 8,708 bp in length (NR_002819.2). The gene is located on chromosome 11q13.1 and is expressed in almost all human and murine tissue cells, but its expression is most prominent in the nervous system [3]. MALAT1 is evolutionarily conserved with high levels of homology amongst species. When the 6,918nt ~ 8,441nt fragment at the 3'-end of MALAT1 is mutated, MALAT1 loses its ability to promote cell proliferation, invasion, and metastasis [4].

MALAT1 was first discovered by Ji et al. [5] in 2003 when observing the metastasis of early stage non-small cell lung cancer (NSCLC). In early NSCLC cell lines, MALAT1 expression was up-regulated in cells that have a tendency of undergoing late metastasis compared to cells that do not have metastasis tendencies [5]. In addition, MALAT1 expression was negatively correlated with the survival rate of patients [5]. Since then, many studies have shown that MALAT1 may serve as transcriptional regulators of many genes, including some involved in cancer metastasis and cell migration. These studies suggest that MALAT1 has a role in cell cycle regulation. MALAT1 upregulation has been shown in a variety of cancerous tissues and in the proliferation and metastasis of tumor cells, which will be discussed later in the review.

MALAT1 localizes to a nuclear spot rich in precursor mRNA splicing factors. It was found that MALAT1 regulates the splicing of precursor RNA by regulating the phosphorylation level of the serine/arginine (SR family) splicing factor, a factor that regulates alternative splicing [6-9]. In addition, MALAT1 participates in transcriptional regulation by interacting with the transcriptional loci to control expression [10-12]. Moreover, LncRNAs, such as MALAT1, have complex post-transcriptional regulatory functions, including maintaining mRNA stability, regulating mRNA translation, acting as a precursor of mRNA splicing, and as a regulator of protein activity [13, 14]. The major mechanisms of post-transcriptional regulation by MALAT1 include regulating alternative splicing, regulating protein activity, and by acting as competing endogenous RNA

(ceRNA) [15]. In addition, studies have shown that MALAT1 is deeply involved in the regulation of cancerous malignant phenotypes of cancer through the interaction and negative regulation between MALAT1 and microRNAs [16-23]. Chen R et al. [24] used RNA pull-down, quantitative proteomics, and bioinformatics to characterize the proteins that interact with MALAT1. One hundred twenty-seven potential MALAT1 interacting proteins were identified, and a highly linked MALAT1 interactome net consisting of 788 connections was established [24]. Analysis shows that MALAT1 is highly involved in regulating five biological processes: RNA processing, gene transcription, ribosomal protein interactions, protein degradation, and metabolic regulation [24].

MALAT1 is involved in many physiological functions, such as neurodevelopment[3, 25-27], skeletal muscle development [28-30], and vascular growth [31]. MALAT1 is also abnormally expressed in other diseases such as myocardial infarction in cardiovascular disease [32, 33], vascular complications [34-36], stroke in neurological disorders [3, 37-39], Alzheimer's disease [40], Parkinson's disease [41, 42], and retinal neurodegeneration [40, 43, 44]. MALAT1 expression in tumorigenesis and metastasis has become a hot research topic in recent years.

3. MALAT1 in Tumors

MALAT1 is one of the first LncRNAs to be identified to be associated with oncogenes, and up-regulation of MALAT1 has been identified as a biomarker of cancer in many studies [45-49]. MALAT1 drives tumorigenesis by promoting tumor cell proliferation [4, 8, 10, 31, 50, 51]. In addition, overexpression of MALAT1 leads to increase *in vitro* cell migration [4, 51, 52]. Furthermore, in cancer mouse models, inactivation of MALAT1 (using antisense oligonucleotides, siRNAs, or knockout strategies) can inhibit *in vitro* cell motility and significantly inhibit tumor metastasis [46, 51, 53-56]. In one experiment, human A549 lung cancer cells were injected into the tail vein of nude mice, and A549 cells lacking MALAT1 exhibited 80-90% less lung metastasis than wild-type A549 cell injections [46]. Recent studies have found that MALAT1 expression is increased in human gliomas and glioma endothelial cells (GECs) [20]. Therefore, MALAT1 is thought to be a potential biomarker of cancer and a potential therapeutic target for limiting metastatic growth. MALAT1 inhibition has the potential to translate into clinical settings from *in vivo* antisense oligonucleotide injection studies demonstrating the ability to knockdown MALAT1 transcripts [46, 56-58].

MALAT1 transcripts are often overexpressed in different types of cancers and it's also commonly found with mutations [56, 59, 60]. Mutations in the MALAT1 gene are common in bladder, head and neck squamous cell carcinomas, and lung adenocarcinomas. In addition, MALAT1 mutations are also present at high frequency in breast cancer [56, 59, 61]. Several studies have shown that the MALAT1 promoter can be fused to the open reading frame (ORF) of transcriptional factor EB (TFEB) in renal cell carcinoma [62-65] through chromosomal translocations. This translocation event leads to changes in MALAT1 expression levels, promoter switching, and approximately 30-fold upregulation of TFEB, which may lead to disruption of key developmental

pathways [63]. Taken together, MALAT1 transcripts may act through different mechanisms in tumors, and the molecular function of MALAT1 inactivation in cancer needs further investigation.

4. MALAT1 and Lung Cancer

Lung cancer is the leading cause of cancer-related death in the world [66]. The expression of MALAT1 is significantly higher in NSCLC than in adjacent normal tissues [67]. MALAT1 expression correlated with the pathological stage, differentiation degree, and lymph node metastasis. There was no statistically significant difference between the gender, age, histological type, tumor diameter, and CEA level in these patients, suggesting that MALAT1 can be used as a biomarker for tumor diagnosis [67].

Guo et al. [68] found that there was a difference in the degree of MALAT1 methylation in lung cancer tissues and normal tissues, indicating that the proto-oncogene function of MALAT1 may be regulated by methylation. Shen et al. [69] found that the expression of MALAT1 in patients with brain metastasis from lung cancer was significantly higher than those without brain metastasis, and the MALAT1 expression was also negatively correlated to the survival rate of patients.

Li et al. [70] found that Sp1 can activate MALAT1 promoter and up-regulate the expression of MALAT1. Knockdown of Sp1 reduces MALAT1 expression and inhibits the growth and invasion of lung cancer A549 cells, suggesting that Sp1 may serve as a therapeutic target for lung cancer. In 2016, Li et al. [71] found that MALAT1 can act as a ceRNA to combine miR-204 on *Slug* protein to form MALAT1/miR-204/Slug pathway to regulate the development of lung cancer. Guo et al. [72] also found that silencing the TDP-43 gene reduced the transcriptional level of MALAT1 RNA, indicating that MALAT1 can control the growth, migration, and invasion of NSCLC cells through the regulation of TDP-43. Wang J et al. [73] studied 538 patients with NSCLC, including 140 early (stage I and II) and 398 advanced (stage III and IV) patients, and found that high expression of MALAT1 was associated with advanced lung adenocarcinoma metastasis, but not with lung squamous cell carcinoma.

Schmidt et al. [51] used *in situ* hybridization in primary NSCLC tissue and found that MALAT1 was expressed in all stages and subtypes of the tumors. Patients with low MALAT1 expression had better prognosis than patients with higher expression, suggesting that the gene may be a potential marker of survival for patients with early stage NSCLC. In xenograft experiments, knockdown of MALAT1 gene in tumor cells showed a significant decrease in distant metastasis; similarly, targeting of MALAT1 with antisense oligonucleotides resulted in inhibition of lung cancer metastasis [46]. The above results suggest that MALAT1 may be an important regulatory factor for lung cancer metastasis.

Guo et al. [74] found that the expression of MALAT1 gene in the whole blood of lung cancer patients was lower than that of the normal control group but significantly increased in patients with metastasis of lung cancer, indicating that MALAT1 could be used as a biomarker to screen for lung cancer, as well as be utilized

as a diagnostic marker of NSCLC. MALAT1 had relatively higher specificity and stability and less traumatic during detection. However, because the difficulty in detecting MALAT1 as a biomarker, precipitated its use as only a supplementary marker for biomarker diagnosis.

To improve the diagnostic value of MALAT1 for NSCLC, Peng et al. [75] constructed a serum miRNA and MALAT1 RNA panel and detected the expression of 11 candidate miRNAs and MALAT1 using quantitatve reverse transcription PCR (qRT-PCR), and obtained receiver operating characteristic (ROC) curves to detect and confirm the diagnostic results of serum of non-coding RNA panels. The results showed that three miRNAs and MALAT1 were significantly different in non-small cell lung cancer and normal controls. Risk analysis showed that ncRNA panels could identify NSCLC from normal controls. The results showed that the four ncRNA risk scores were highly correlated with the proliferation and the diagnosis of stage I/II/III of NSCLC. The three kinds of miRNA and MALAT1 panels could be used as a convenient method to diagnose NSCLC.
Zhang R. et al. [76] demonstrated that exosomal MALAT1 was up-regulated in NSCLC patients. They also found that exosomal MALAT1 was positively correlated with increased TNM (tumor, node, and metastasis) staging and lymph node metastasis. In addition, MALAT1 knockdown inhibits cell proliferation, colony formation, and cell migration, while inducing cell cycle arrest and apoptosis. These results suggest that MALAT1 could be a predictive factor and clinical treatment target for lung cancer prognosis.

5. MALAT1 and Colorectal Cancer (CRC)

Studies below have shown that MALAT1 expression is higher in metastatic CRC tissue than in non-metastatic or low metastatic CRC tissue. Yang et al. [77] found that MALAT1 overexpression can promote CRC cell growth, proliferation, invasion, and metastasis. Furthermore, silencing MALAT1 can inhibit CRC growth and metastasis. A genome-wide cross-section showed that PRKA kinase-9 (AKAP-9) was overexpressed in metastatic potential tissues, and AKAP-9 knockdown prevented MALAT1-mediated proliferation, migration, and invasion of CRC cells. Hu et al. [78] found that AKAP-9 is a target gene regulated by MALAT1. MALAT1 can promote CRC cell invasion and metastasis by SRPK1-catalyzed phosphorylation of SRSF1 and upregulation of AKAP-9 expression. Ji et al. [79] found that MALAT1 can bind to SFPQ and then promote the dissociation of PTBP2 from the SFPQ/PTBP2 complex. Separation of PTBP2 from SFPQ can promote cell proliferation and migration. The expression of MALAT1 and PTBP2 increased in colon cancer tissues, but there was no significant change in MALAT1 and PTBP2 expression in cancer tissue and adjacent tissues. The results indicate that MALAT1 may be a predictor of tumor metastasis and prognosis, and the interaction between MALAT1 and SFPQ may be a therapeutic target for CRC.

Kan et al. [80] found that MALAT1 can promote the expression of Snail. Inhibition of MALAT1 expression can reduce TDAC and CCL5-mediated cell migration and invasion by decreasing the enhancement of Snail, indicating the importance of the MALAT1/Snail pathway in TDAC-mediated colon cancer. Zheng et al. [81] also demonstrated that the expression of MALAT1 in CRC tissues is elevated in stage II/III CRC tissues and can be used as a marker of stage II/III CRC prognosis.

Ji et al. [52] found that resveratrol down-regulated the expression of MALAT1, causing the distribution of β-catenin in the nucleus to decrease, attenuating the Wnt/β-catenin signaling pathway, and inhibiting the invasion and metastasis of CRC. This finding of resveratrol provided the basis for prevention and treatment of CRC. The study found that MALAT1 expression is not only higher than that of adenoma in CRC, but is also positively correlated with the degree of metastasis in colorectal cancer [4]. These results support the potential use of MALAT1 for the identification of colorectal adenoma and CRC.

Studies by Jie et al. [82] demonstrated that MALAT1 is up-regulated in human colon cancer cell lines including LoVo, HCT116, SW480, and HT29 cells compared to normal human intestinal epithelial HIEC cells. Inhibition of MALAT1 can inhibit the proliferation of colon cancer SW480 cells and HCT116 cells. Bioinformatic analysis was used to predict the microRNA of MALAT1 target gene. The miRNA, miR-129-5p, was identified and confirmed as a direct regulator of MALAT1. Furthermore, miR-129-5p mimics inhibited colon cancer cell progression. In addition, high mobility group box 1 (HMGB1) is predicted as a miR-129-5p mRNA target. Moreover, the study also found that MALAT1 regulates the biological function of HMGB1 by in vitro amplification of miR-129-5p. Silencing of MALAT1 greatly suppresses HMGB1 expression and can be reversed by miR-129-5p inhibitors. This suggests that MALAT1 may act as a competitive endogenous LncRNA (ceRNA) that promotes HMGB1 by inhibiting miR-129-5p in colon cancer. These results suggest that MALAT1, miR-129-5p, and HMGB1 could be important prognostic biomarkers for of colon cancer.

Xiong et al. [83] studied the effect of oxymatrine on CRC cells and further investigated the role of MALAT1 in oxymatrine-induced resistance and EMT. It was demonstrated that MALAT1 promoted oxymatrine resistance in CRC and can provide therapeutic and prognostic information for CRC patients. Li Y et al. [84] investigated the relationship between genetic variation in the MALAT1 promoter region and CRC risk. The study conducted a two-phase case-control study to assess whether MALAT1 gene variants are associated with CRC risk. A single nucleotide polymorphism (SNP) rs1194338 was found to be significantly associated with a reduced risk of CRC, with an odds ratio (OR) value of 0.70 [95% confidence interval (CI)=0.49-0.99]. Subsequent stratification analysis showed that the protective effect of rs1194338 was more pronounced in several subgroups. In addition, gene expression profiling showed overexpression of MALAT1 mRNA in CRC tissues as compared to normal controls. Shi et al. [85] showed that MALAT1 may promote tumor growth of choriocarcinoma through miR-218-mediated Fbxw8 regulation. MALAT1 may be an oncogenic LncRNA that promotes the proliferation of choriocarcinoma and may serve as a therapeutic target in human choriocarcinoma.

6. MALAT1 and Breast Cancer

Breast cancer is the most common malignant tumor in women [86]. The incidence of breast cancer is rising every year. Breast cancer is attributed to 15% of all new cases of cancer in women, and is the leading cause of cancer death in women under 45 years of age in China [87]. The recurrence and metastasis of breast cancer is the main cause of death in patients [88]. Abundant expression of MALAT1 was detected in primary breast tumors. In

addition, mutations and deletions of the MALAT1 gene were also detected in breast cancer, particularly in areas that could mediate MALAT1 interaction with the splicing factor SRSF1 [89].

Zidan et al. [90] evaluated the changes in MALAT1 in breast cancer in 80 breast cancer patients and 80 controls. MALAT1 expression was measured by qRT-PCR, and CA15-3 was evaluated using chemiluminescence immunoassay (CLIA). Compared with the control, MALAT1 expression was significantly increased in breast cancer cases ($P < 0.0001$). By performing ROC curve analysis, the combination of the two parameters improves the diagnostic sensitivity of CA15-3 in breast cancer. These data shows that MALAT1 expression levels were positively correlated with lymph node size, estrogen receptor (ER) expression, tumor stage, and histological grade. This suggest that MALAT1 expression can be used as an accurate marker of breast cancer diagnosis and provide a prognostic value of this disease.

Miao et al. [91] studied 78 breast cancer patients undergoing radical resection. The expression of MALAT1 in tissues and serum was detected by qRT-PCR. The ROC curves were constructed to characterize the diagnostic specificity and sensitivity. Lentivirus-mediated RNA interference was used to knock down MALAT1 in the MDA-MB-231 cell line to explore cell proliferation and invasion. The results showed that MALAT1 expression in 85.9% (67/78) of cancerous tissues was significantly upregulated ($P < 0.01$) compared with the normal control group. In addition, elevated MALAT1 expression was associated with lymph node metastasis ($P=0.037$) and 5-year disease-free survival (mean 48.5 months vs 62.7 months, $P=0.012$) in breast cancer tissues. Inhibition of MALAT1 LncRNA significantly inhibited breast cancer cell proliferation, migration, invasion, apoptosis, and cell cycle arrest.
Zhao et al. [92] found that high concentrations of 17β-estradiol significantly decreased the expression level of MALAT1, thereby inhibiting the proliferation and invasion of MALAT1-induced breast cancer cells. This effect was independent of whether the tumor cells expressed ERα. Chou et al. [93] demonstrated that MALAT1 can act as a ceRNA of miRNA-1, which binds the 3'-untranslated region (UTR) of the cell division cycle gene 42 (CDC42) to suppress its expression. Thus, MALAT1 promotes metastasis and invasion of breast cancer cells. Further research is needed to determine the utility of MALAT1 as a biomarker for breast cancer.

Studies by Jadaliha et al. [94] have demonstrated that MALAT1 expression levels do not entirely predict the regulation of aggressive breast cancer. Loss-of-function (LOF) and gain-of-function (GOF) *in vitro* and *in vivo* studies have shown that even though MALAT1 expression is lower in ER- or HER2-positive breast cancer cells, MALAT1 promotes cell proliferation, tumor progression, and metastasis in triple-negative breast cancer (TNBC) cells. Assessment of MALAT1 in human breast cancer (n=1,992) reveals that the increase in MALAT1 expression is associated with a reduced disease-specific survival in ER negative and lymph node negative patients of the HER2 and TNBC subtypes. Multivariable analysis confirmed the independent prognostic significance of MALAT1 in the subgroup of TNBC-negative patients. The studies support the functional significance of MALAT1 as a metastasis driver and its potential uses as a prognostic indicator for ER-negative and node-negative breast cancer patients who might otherwise be miscategorized as having a low risk of recurrence.

Arun et al. [56] knocked out the MALAT1 gene using antisense oligonucleotides (ASOs). The results showed that the growth of breast tumor cells was inhibited, and they differentiated into cystic tumors with markedly reduced metastasis. These results suggest that MALAT1 ASOs may be a therapeutic option for breast cancer. Xu et al. [95] found that MALAT1 regulates cell motility-related genes, and the inhibition of MALAT1 expression induces EMT through the PI3K/Akt pathway. Thus, MALAT1 may be a regulator of breast cancer progression. Jin et al. [96] suggested that MALAT1 may also cause tumor metastasis through the miR-1/Slug pathway. In addition, MALAT1 can also reverse the inhibitory effect of miR-124 on breast cancer cell proliferation [97]. The MALAT1‐dependent miR-124 / CDK4 / E2F1 signaling pathway will provide a new pathway for the study of breast cancer. Bamodu et al. [98] found that silencing KDM5B expression in TNBC can inhibit the expression of MALAT1, reduce the migration, invasion, and clonal proliferation of tumor cells. This indicates that MALAT1 is an important mediator of the proto-oncogenic properties of KDM5B. Huang et al. [78] found that overexpression of MALAT1 was associated with the expression of ER, progesterone receptor (PR), and of ER target genes such as PGR and CCND1. In addition, MALAT1 overexpression was associated with ER positive breast cancer and with poor recurrence-free survival (RFS) after tamoxifen treatment, suggesting that it may serve as a potential biomarker for predicting endocrine therapy sensitivity. This study also confirmed that MALAT1 is the only independent RFS predictor in ER-negative breast cancer patients. Chen R et al. [24] demonstrated that MALAT1 interacts with deleted in breast cancer 1 (DBC1) using RNA pull-down and RNA immunoprecipitation experiments. The studies showed that MALAT1 binding competes with the interaction between sirtuin1 (SIRT1) and DBC1. MALAT1 promotes the release of SIRT1 and enhances the deacetylation activity of SIRT1. Deacetylation of p53 reduces the transcription of p53 downstream target genes, which leads to increased cell proliferation and the inhibition of apoptosis. These data revealed a novel LncRNA-protein interaction in which MALAT1 regulates p53 activity.

Zuo et al. [99] studied the collection of 43 cases of TNBC tissues and their paired adjacent non-tumor tissues. Quantitative RT-PCR detection of MALAT1 expression was performed *in vitro* to determine the MALAT1 TNBC progress. The results showed that the relative expression of MALAT1 is increased in TNBC tissues and cell lines. High MALAT1 expression is associated with advanced clinical features and poor overall survival in TNBC patients. Functional assays show that MALAT1 silencing significantly reduced cell proliferation, migration, and invasion. Flow cytometry showed that MALAT1 inhibition significantly induced cell cycle arrest in the G0 / G1 phase. The role of MALAT1 in TNBC cell development is mediated by miR-129-5p.

Pruszko et al. [100] demonstrated that in breast cancer cells, the oncogenic factor, SRSF1 mediates MALAT1 interaction with mutant p53 and ID4 proteins. Mutant p53 and ID4 interacts with MALAT1 to remove MALAT1 from nuclear spots and supports its association with chromatin. This causes MALAT1 to be abnormally recruited on the VEGFA precursor mRNA and to adjust the expression of the VEGFA subtype. The VEGFA-dependent expression profile is specifically associated with ID4 expression in basal-like breast cancer carrying the TP53 mutation. Latorre et al. [101] showed that the RNA complex, HuR-MALAT1 inhibits CD133 expression and EMT in breast cancer. Findings of Meseure et al. [102] reveal a complex pattern of expression of various MALAT1 transcripts in breast tumors and suggests that this expression pattern should be considered in evaluating MALAT1 as

a predictive biomarker and therapeutic target. Studies by Bamodu et al. [98] demonstrated that KDM5B, MALAT1, and hsa-miR-448 are active components in aggressive breast cancer.

7. MALAT1 and Cervical Cancer

Cervical cancer is the second most common cancer in women worldwide with more than 275,100 deaths each year. Cervical cancer is related to HR-HPV infection. Zhang et al. [103] compared the expression of MALAT1 in 30 cases of cervical cancer and adjacent normal tissues and found that the expression level of MALAT1 was correlated with clinicopathological features. Using qRT-PCR analysis, MALAT1 expression was found to be significantly higher in cervical cancer tissues and in four cervical cancer cell lines. MALAT1 can promote cell proliferation, cell migration, invasiveness, which results in cervical cancer cell growth and metastasis. Yang et al. [104] showed that MALAT1 expression is correlated with tumor size, tumor staging, vascular migration, and lymph node metastasis. Studies have also shown that the high expression of MALAT1 is related to HPV infection and MALAT1 can be an independent prognostic factor for cervical cancer. Silencing MALAT1 can reduce the migration and invasion of cancer cells and increase apoptosis. MALAT1 may be a target of cervical cancer therapy and an important factor in prognosis. Lu et al. [105] showed that in cervical cancer cell lines (CaSki and HeLa), inhibiting MALAT1 expression can reduce the formation of cancer clones by cause a large number of cells in the G2/M phase to arrest and increase cell apoptosis. Through RNA-binding protein immunoprecipitation (RIP) and RNA pull-down assays, they confirmed that MALAT1 and miR-145 associate together in the same Ago2 complex. MALAT1 and miR-145 reduce cancer cell clone formation, regulate the cell cycle, and induce apoptosis effect. Liu et al. [106] also confirmed that MALAT1 can be used as a ceRNA to compete against miR-124. The miRNA, miR-124, can directly bind to the 3'UTR of GRB2 and regulate GRB2 expression, which promotes the growth and invasion of HR-HPV positive cervical cancer cells through the MALAT1/miR-124/GRB2 pathway. Sun et al. [107] found that MALAT1 can promote cervical cancer cell invasion and metastasis through EMT. In summary, MALAT1 will be an important target for the prediction and treatment of cervical cancer.

8. MALAT1 and HCC (Hepatocellular Carcinoma)

HCC, commonly known as liver cancer, is one of the most common malignant tumors in the US. Functional studies have found that MALAT1 expression in both HCC and HCC cell lines are increased. Patients with high expression of MALAT1 had a higher recurrence rate after liver transplantation (especially in patients under Milan standards). Inhibition of MALAT1 expression can effectively reduce cell development, migration, invasion, and increase apoptosis. Konishi et al. [108] found that plasma MALAT1 expression levels were different in HCC patients, liver disease patients, and normal control groups, indicating that plasma MALAT1 levels can be used as a non-invasive method for predicting the progression of liver cancer. Luo et al. [109] found that MALAT1 was overexpressed in the serum of patients exposed to arsenite and closely related to the clinicopathological features of HCC. Arsenite-induced MALAT1 can dissociate the hypoxia-inducible factor 2 (hypoxia- inducible factor-2α, HIFα2α), and relieve the VHL-mediated accumulation of HIFα2α ubiquitination. HIFα2α, in turn, regulates MALAT1 at the transcriptional level to form a circular positive feedback. MALAT1 / HIF-2α feedback loop plays an important role

in arsenite-induced malignant transformation, which not only confirms the mutual regulation between MALAT1 and HIF‑2α, but also expands the understanding of the role of arsenite in promoting cancer. Huang et al. [110] found that the expression of specificity protein 1/3 (Sp1/3) and MALAT1 in HCC tissue were higher than those in control group and were related to α-fetoprotein (AFP) levels. MALAT1 transcription is regulated by the presence of five Sp1/3 binding sites upstream of MALAT1. Silencing of Sp1 and Sp3 can inhibit the expression of MALAT1. Wang et al. [111] found that SRSF1 inhibits MALAT1 by (1) promoting MALAT1 degradation and by (2) inhibiting the Yes-associated protein (YAP) recruitment to the MALAT1 promoter. The overexpression of YAP combined with the knockdown of SRSF1 enhances tumorigenicity by increasing MALAT1. In conclusion, MALAT1 plays an important role in tumor development and can be used as a new biomarker to predict tumor recurrence after liver transplantation.

9. MALAT1 and Pancreatic Cancer

Pancreatic ductal adenocarcinoma has a high degree of malignancy and mortality. The prognosis is poor. In the past 30 years, survival rate for 5 years was only 6%. Pang et al. [112] used qPCR to compare MALAT1 expression in 126 cases of pancreatic cancer tissue and 15 cases of paraneoplastic tissue. The results showed that the expression of MALAT1 was significantly increased in pancreatic cancer tissue. MALAT1 expression also correlated with increased staging of pancreatic cancer, tumor size, and lymph node metastasis. MALAT1 can reduce the proliferation, migration, and invasion of tumor cells. The mechanism may be related to the induction of G2/M arrest in the cell cycle, the promotion of apoptosis, the inhibition of EMT, and the induction of cancer stem cell degeneration. In addition, overexpression of MALAT1 is an adverse prognostic factor for pancreatic cancer and can be used to predict the patient's prognosis. Jiao F et al. [113] used in vitro studies to show that MALAT1 can increase the proportion of pancreatic cancer stem cells in order to maintain its ability to self-renew, accelerate tumor angiogenesis, promote pancreatic cancer growth, and reduce its sensitivity to anti-cancer drugs. Han T et al. [114] used RIP and chromatin-immunoprecipitation (ChIP) experiments and found that MALAT1 can recruit EZH2 to E-cadherin promoter and regulate the expression of E-cadherin, suggesting that EZH2 could be used as a target for the treatment of pancreatic cancer. In a recent study by Li L et al. [115], it was also found that some autophagy-related molecules (LC3, p62 and LAMP-2, etc.) were modulated as expression of MALAT1 was downregulated. In addition, the silencing of MALAT1 expression enhanced the post-transcriptional regulation of TIA-1 and inhibited autophagy. These results suggest the potential anti-cancer therapy by upregulating MALAT1 to activate autophagy in pancreatic cancer.

10. MALAT1 and Glioma

Glioblastoma is the most aggressive brain tumor in adults. Xiang et al. [116] silenced MALAT1 and found glioma cells to have increased apoptosis, decreased motility, and the decreased expression of tumor markers, such as CCND1 and Myc. This suggests that MALAT1 might be a glioma-promoting factor. Han Y et al. [117] found that downregulation of MALAT1 expression inhibits "stem-like" properties by inhibiting Sox2 and Nestin gene expression and can activate ERK / MAPK signaling pathway to promote glioma cell differentiation and proliferation. Vassallo et al. [118] found that Wnt inhibitor 1 (WIF1) promotes the

migration of glioma cells through Wnt5A activation of Wnt/Ca^{2+} and MALAT1, suggesting that the canonical or atypical Wnt pathway plays an important role in glioma cell proliferation and invasion. The blood-tumor barrier (BTB) is a major obstacle in the treatment of brain tumors, which can prevent the transport of antitumor drugs. Ma J et al. [20] found that MALAT1 and miR-140 inhibit each other. In addition, MALAT1 knockdown increased BTB permeability by decreasing the expression of the tight-junction proteins, Zo-1 and claudin-5. These findings suggest that inhibiting MALAT1 may be a potential target for the treatment of glioma.

11. MALAT1 and Bladder Cancer

Bladder cancer is the most common urological tumor in China. Its occurrence and development is a gradual process. Studies have shown that MALAT1 can promote proliferation, invasion, migration of bladder cancer cells, and clonality, which may be related to the regulation of tumor-related genes. Ying L et al. [119] showed that the expression of MALAT1 in bladder cancer by qRT-PCR was higher than that in adjacent normal tissues. MALAT1 silencing can inhibit cell migration and reduce the levels of ZEB1, ZEB2, and Slung, while increasing the expression of E-cadherin. Fan Y et al. [120] found that MALAT1 expression was inversely related to E-cadherin expression. MALAT1, in vitro, can promote EMT through Wnt signaling pathway and enhance the invasion and metastasis of bladder cancer cells. Thus, the inhibition of MALAT1 may be a potential treatment for bladder cancer.

12. MALAT and Esophageal Cancer

Esophageal cancer is a highly lethal malignant tumor. The squamous cell carcinoma sub-type accounts for approximately 90% of the total number of patients with very poor prognosis. Mortality is a problem that needs to be solved urgently. Recent research by Yao W et al. [121] showed that the expression of MALAT1 in esophageal squamous cell carcinoma was higher than in adjacent normal tissues, and that the high expression of MALAT1 was associated with poor prognosis. Knockdown of MALAT1 decreased cell proliferation, increased apoptosis, inhibited migration and invasion, reduced clonogenicity, and arrested the cell cycle at the G2/M phase. Wang W et al. [122] also found that upregulation of MALAT1 is correlated to increasing clinical stage, lymph node metastasis, and poor prognosis. Downregulation of MALAT1 can reduce the expression of β-catenin, Lin28, and EZH2. Hu L et al. [123] used Western blot analysis to show that knockdown of MALAT1 induces the phosphorylation of ATM/CHK2 pathway to promote G2/M phase arrest and regulates the growth of esophageal squamous cell carcinoma. Thus, MALAT1 could be used as a potential target for the treatment of esophageal squamous cell carcinoma.

13. MALAT1 and Stomach Cancer

The incidence of gastric cancer is high and geographical. Deng Q et al. [124] detected higher MALAT1 expression in 25 cases of gastric cancer and 3 different gastric cancer cell lines compared to adjacent normal tissue. Downregulating the expression level of MALAT1 can inhibit tumor metastasis, while the upregulation of MALAT1 expression can promote metastasis. Chromatin immunoprecipitation (ChIP) experiments suggest that the expression of MALAT1 changes the acetylation of H3 histone to affect the EGFL7 promoter. Qi Y et

al. [125] found that MALAT1 can bind EZH2, inhibit the expression of PCDH10, and promote gastric cancer cell migration and invasion. Wang J et al. [126] found that increased expression of MALAT1 can cause high expression of nuclear SF2/ASF and abnormal distribution. Silencing MALAT1 or SF2/ASF can cause cell cycle arrest at the G0/G1 phase and inhibit cell proliferation. These results suggest that MALAT1 could be used as a gastric cancer cell proliferation promoter. MALAT1 is expected to become a potential target for the diagnosis and treatment of gastric cancer.

14. MALAT1 and Other Tumors

14.1 Gallbladder cancer

Wang S et al. [127] studies have shown that MALAT1 was highly expressed in gallbladder cancer tissues and cells. High MALAT1 levels was directly related to tumor size, lymphatic metastasis, and poorer prognosis. MALAT1 was also found to act as a ceRNA of miR-206. The combination of MALAT1 and miR-206 promote the growth of gallbladder cancer tissues and cells. MALAT1 knockdown can inhibit the migration and invasion of gallbladder cancer cells, increase apoptosis, and reduce tumor volume. Wu X et al. [128] also found that MALAT1 can promote the migration and invasion of gallbladder carcinoma cells by activating the ERK/MAKP pathway, suggesting that MALAT1 can be used as a therapeutic target and prognostic indicator of gallbladder cancer.

14.2 Nasopharyngeal cancer

Jin C et al. [129] found that MALAT1 was highly upregulated in nasopharyngeal carcinoma tissue and cell lines. Knockout of MALAT1 in nasopharyngeal carcinoma cells *in vitro* and *in vivo* are more sensitive to radiation. MALAT1 also regulates tumor stem cell activity through miR-1 / Slug to regulate radiation tolerance. Thus, MALAT1 can be used as a target for the treatment of nasopharyngeal carcinoma.

14.3 Osteosarcoma

Cai X et al. [130] used qRT-PCR to study the expression of MALAT1 in human osteosarcoma cell lines. It was found that the expression of MALAT1 in human osteosarcoma tissues and cell lines was upregulated. Inhibiting the expression of MALAT1 *in vitro* can significantly inhibit the proliferation, migration, and EMT progression of cells. It can also induce osteosarcoma cell cycle arrest and apoptosis. Fang X et al. [131] also found that miR-9 plays an important role in the regulation of MALAT1 at the post-transcriptional level. These findings indicate that MALAT1 plays an important proto-oncogenic role in osteosarcoma and may provide a therapeutic target for osteosarcoma patients.

14.4 Ovarian cancer

Ovarian cancer has the highest fatality rate of gynecological malignancies. The lack of effective diagnosis and treatment is the cause of its high mortality. Zhou Y et al. [132] used qRT-PCR to determine that MALAT1 was overexpressed in 45 cases of ovarian cancer tissue when compared to 37 cases of normal ovarian tissue. The knockdown of MALAT1 decreased the expression of MMP-13 protein and increased the expression of MMP-

19 and ADAMTS1, which inhibits the proliferation, migration, and invasion of G0/G1 cells. This results in the arrest of G0/G1 cells and the apoptosis of tumor cells growth. MALAT1 plays an oncogenic role in ovarian cancer and may be able to become a new target for the treatment of ovarian cancer. Lei et al. [133] investigated the role of MALAT1 in human ovarian cancer cell lines and clinical tumor samples and found that MALAT1 LncRNA is specifically up-regulated in ovarian cancer cell lines and promotes ovarian cancer by targeting microRNAs (miR-506). Knockdown of MALAT1 suppresses the proliferation and DNA synthesis of human ovarian cancer cells in vitro. In addition, miR-506-dependent iASPP regulation is required in MALAT1-induced ovarian cancer cell growth, suggesting that MALAT1 may inhibit tumor growth through miR-506-dependent iASPP regulation. MALAT1 may be an oncogenic LncRNA that promotes ovarian cancer proliferation and may be considered as a therapeutic target for human ovarian cancer.

14.5 Prostate cancer

Ren S et al. [134] used qRT-PCR to study the expression of MALAT1 in prostate cancer tissues and their cell lines. Human prostate cancer tissues and cell lines showed increased MALAT1 expression levels. The high expression of MALAT1 is correlated with Gleason score, prostate specific sexual antigens, tumor staging, and castrated-refractory prostate cancer. Silencing MALAT1 can inhibit the growth, migration, invasion of prostate cancer cells, and induce the arrest of cell growth at the G0/G1 phase in castration-refractory prostate cancer cells, indicating that MALAT1 plays an important role in tumorigenesis and may be used for clinical treatment and provide a target for clinical therapy. Wang F et al. [135] evaluated urine MALAT1 as a predictive biomarker for prostate cancer to replace traditional PSA measurements. They concluded that a MALAT1-based test would prevent 30 - 46% of the unnecessary biopsies in patients that have PSA in the 4-10 ng/ml range. ChIP studies by Aiello et al. [136] showed that MALAT1 may have a repressive function on sex steroid hormone receptor genes, such as pS2 and PSA. These genes have been associated with prostate cancer. Thus, these results show that MALAT1 in could be used as a biomarker for predicting prostate cancer.

14.6 Melanoma

Melanoma is a highly aggressive form of skin cancer and its incidence is on the rise throughout the world. Tian Y et al. [137] used qRT-PCR to test 63 cases of MALAT1 expression in melanoma tissue and adjacent normal tissue. The results showed higher expression of MALAT1 and lymph node metastasis in melanoma cells than in normal tissue. The silencing of MALAT1 attenuated the migration of melanoma cells in vitro. The increased expression of MALAT1 was associated with the metastasis of melanoma.

14.7 Tongue cancer

Liang J et al. [138] used qRT-PCR to detect MALAT1 in squamous cell carcinoma of the tongue and cervical lymph node metastasis. In addition, MALAT1 also induces cell migration by regulating the Wnt / β-catenin signaling pathway, promoting invasion, promoting EMT, inhibiting cell apoptosis, and promoting the development and metastasis of tongue cancer.

14.8 Oral squamous cell carcinoma

Patients with advanced oral squamous cell carcinoma have poor outcomes. Zhou X et al. [139] found increased MALAT1 expression in oral squamous cell carcinoma. Inhibiting MALAT1 was shown to be required for EMT-mediated cell migration and invasion. This result suggests that MALAT1 may be an important predictor of oral squamous cell carcinoma and a potential therapeutic target.

14.9 Multiple myeloma

Cho et al. [140] showed that MALAT1 overexpression is closely related to the disease status in newly diagnosed patients when compared to healthy individuals and post-treatment patients, Furthermore, treatment changes the magnitude of MALAT1 expression, and thus, could be used as a prognostic biomarker. Patients with less MALAT1 expression tend to have longer survival rates than those with more MALAT1 expression. MALAT1 may serve as a molecular predictor of early stages of multiple myeloma (MM). Li B et al. [141] showed that MALAT1 interacted with Sp1 to activate the LTBP3 gene. LTBP3 regulates TGF-B that is important for MM cell growth. Thus, high levels of MALAT1 may regulate TGF-B to inhibit the growth of cancer. These results suggest the potential use of MALAT1 as a biomarker and a novel therapeutic target for MM.

15 Future Prospect

Studies have shown that LncMALAT1 is upregulated in a variety of tumor tissues, including NSCLC, breast cancer, bladder cancer, cervical cancer, pancreatic cancer, gastric cancer, and HCC. Overexpression of MALAT1 can play an oncogenic role in promoting the growth, proliferation, invasion, and metastasis of tumor cells by acting as a ceRNA or by regulating EMT and the cell cycle. MALAT1 also plays an important role in tumor genesis and development. This suggests that MALAT1 can be used as an important biomarker for early diagnosis, treatment-tracking, and prognosis of various tumors. Suppressing MALAT1 may be a novel target to treat cancer, and it may become an important clinical treatment tool in the future.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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