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ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Qiang Lin, MD, PhD, Professor, Department of Oncology, North China Petroleum Bureau General Hospital, Hebei Medical University, Renqiu 062552, Hebei Province, China. billhappy001@163.com

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Metastasis-associated lung adenocarcinoma transcript 1 molecular mechanisms in gastric cancer progression

Daniel Mateus de Oliveira Batista, Jéssica Manoelli Costa da Silva, Carolina de Oliveira Gigek, Marília de Arruda Cardoso Smith, Paulo Pimentel de Assumpção, Danielle Queiroz Calcagno

Daniel Mateus de Oliveira Batista, Jéssica Manoelli Costa da Silva, Paulo Pimentel de Assumpção, Danielle Queiroz Calcagno, Núcleo de Pesquisas em Oncologia, Universidade Federal do Pará, Belém 66073-000, Pará, Brazil

Carolina de Oliveira Gigek, Departamento de Patologia, Universidade Federal de São Paulo, São Paulo 04023-062, São Paulo, Brazil

Marília de Arruda Cardoso Smith, Disciplina de Genética,Departamento de Morfologia e Genética, Universidade Federal de São Paulo, São Paulo 04023-900, São Paulo, Brazil

Corresponding author: Danielle Queiroz Calcagno, PhD, Núcleo de Pesquisas em Oncologia, Universidade Federal do Pará, R. dos Mundurucus, 4487-Guamá, Belém-PA, Belém 66073-000, Pará, Brazil. danicalcagno@gmail.com

Abstract

Gastric cancer (GC) remains among the most common cancers worldwide with a high mortality-to-incidence ratio. Accumulated evidence suggests that long non-coding RNAs (lncRNAs) are involved in gastric carcinogenesis. These transcripts are longer than 200 nucleotides and modulate gene expression at multiple molecular levels, inducing or inhibiting biological processes and diseases. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is one of the best-studied lncRNAs with comprehensive actions contributing to cancer progression. This lncRNA regulates gene expression at the transcriptional and posttranscriptional levels through interactions with microRNAs and proteins. In the present review, we discussed the molecular mechanism of MALAT1 and summarized the current knowledge of its expression in GC. Moreover, we highlighted the potential use of MALAT1 as a biomarker, including liquid biopsy.

Key Words: Long noncoding RNA; Gastric carcinogenesis; Transcriptional levels; Posttranscriptional levels; Prognostic biomarker; Liquid biopsy

Core Tip: Gastric cancer (GC) is one of the leading causes of cancer-related deaths globally, highlighting the need for novel biomarker for improved evaluation. The long noncoding RNAs metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) plays a crucial role in many cellular processes associated with GC progression, including proliferation, invasion, metastasis, and drug response. The current review summarizes the present knowledge of MALAT1 in GC, elucidating its molecular mechanisms of action and potential as a biomarker for the clinical management of GC.

INTRODUCTION

Gastric cancer (GC) is the fifth most prevalent neoplasm and the fourth leading cause of cancer-related deaths worldwide. Despite advancements in treatment modalities, the prognosis for advanced GC remains poor. Therefore, one of the main factors related to the high incidence and mortality of GC is complex tumor heterogeneity at the molecular level, which poses a major challenge to comprehensively understanding the mechanisms underlying gastric tumorigenesis[1]. As such, identifying molecular biomarkers is critical for improving the clinical outcomes of GC patients.

Advanced RNA-sequencing techniques have allowed the discovery of novel contributors to tumor development, as noncoding RNAs (ncRNAs)[2]. NcRNAs are essential regulators of gene expression that play a vital role in the progression of GC, including mainly microRNAs (miRNAs) and long ncRNAs (lncRNAs)[3-5].

MiRNAs are a class of small RNAs with an average 22 nucleotides in length that modulate negatively the expression of target mRNAs by base-pairing complementarity. This interaction between the two nuclei acids is dynamic and dependent on many factors, such as subcellular location of miRNAs, the abundance of miRNAs and target mRNAs, and the affinity of miRNA-mRNA interactions. Interestingly, these ncRNAs may play an essential role in intercellular signaling. Mature miRNAs transported to the cytoplasm may cross gap junctions (intercellular channels present in the plasma membrane of solid tissues, allowing communication between adjacent cell) and target mRNAs in neighboring cells[6-8].

In contrast, lncRNAs are transcripts highly heterogeneous with more than 200 nucleotides[9] that play a crucial role as master regulators by interacting with DNA, RNA, or proteins to regulate gene expression[10,11].

Due to their complex characteristics, lncRNAs can be classificafied based on their genomic location relative to the nearest protein-coding genes. These classifications include: (1) Long intergenic ncRNAs, which do not overlap or are close to protein-coding genes; (2) Sense lncRNAs, which are on the same strand and transcribed in the same direction; (3) Antisense lncRNAs, which are situated on the opposite strand and overlap protein-coding genes; (4) Intronic lncRNAs, whose sequence is within the boundaries of introns; and (5) Bidirectional lncRNAs, positioned on the antisense strand and having their transcription start site (TSS) near the TSS of protein-coding genes, with transcription occurring in the opposite direction[12-14].

In addition, lncRNAs exhibit archetypes that distinguish them based on molecular functions: (1) Signals are stimuli expressed lncRNAs that interact with transcription factors or chromatin modifiers; (2) Decoy lncRNAs bind to regulatory factors, turning off their activity; (3) Guide lncRNAs recruit and direct chromatin modifiers or transcription factors to specific target genomic locations, either in cis (neighboring-genes) or in trans (distantly-located genes); and (4) Scaffold lncRNAs function as structural elements in the assembly and organization of ribonucleoprotein complexes[15].

Over recent years, evidence has suggested that lncRNAs are key players in the initiation, progression, and response to therapy in GC[16,17]. Regarding their role in cancer, lncRNAs participate in different biological processes, including cell proliferation, angiogenesis, autophagy, apoptosis, differentiation, and immune responses. Consequently, they may be potential targets for clinical applications[18].

Among the lncRNAs involved in GC, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has gained attention as a promoter of cancer progression and an inhibitor of cell sensitivity to therapies[19]. Here, we summarized the current knowledge regarding MALAT1 function and its putative role in biological processes, including GC. Furthermore, we explored the association of MALAT1 overexpression with the clinicopathological features of GC patients and highlighted its potential as a biomarker for diagnosis, prognosis, and prediction of response to therapy.

MALAT1

MALAT1, also known as nuclear enriched abundant transcript 2, is a transcript > 8.7 kbp encoded on human chromosome 11q13.1 widely expressed in normal tissues, especially in the lung and pancreas. Compared to other lncRNAs, MALAT1 exhibits a distinctive triple helix structure at its 3' end. This unique structural feature has been demonstrated to provide protection against exonucleases, contributing to the enhanced stability of MALAT1[20,21]. The subcellular localization determines the molecular functions of MALAT1. Generally, this lncRNA resides in nuclear speckles and specific nuclear bodies enriched with epigenetic regulators, splicing, and transcription factors. Within these nuclear bodies, MALAT1 can interact with various proteins, enabling it to exert regulatory control over alternative

splicing (AS) and transcription processes[22] (Figure 1).

MALAT1 has been shown modulate recruitment of pre-mRNA splicing factors, such as serine/arginine-rich (SR) proteins, acting as a sponge of these components. As illustrated in Figure 1, MALAT1 can influence endogenous pre-mRNA AS through the regulation of SR protein phosphorylation and dephosphorylation. This process leads to modifications in mRNA expression and subsequent alterations in cellular function[22,23].

Furthermore, MALAT1 plays a significant role in modulating gene expression through its interactions with transcription factors, such as members of the polycomb2 protein family and transcriptional enhanced factors with TEA/ATTS domain (TEAD). The crosstalk between MALAT1 and TEAD blocks their association with the coactivator Yes-associated protein, resulting in a negative modulation of gene transcription[24].

In addition to influencing splicing and transcription, MALAT1 also can act as a competitive endogenous RNA (ceRNA) or miRNA sponge to sequester miRNAs under various conditions. CeRNAs are genetic components that control gene expression at a posttranscriptional level. They share miRNA response elements and compete with mRNAs for miRNA binding[25]. Consequently, binding of ceRNAs to miRNAs releases the target mRNA, allowing their translation[21,26,27]. Accumulating evidence supports the regulatory role of MALAT1 in endothelial cell function and vascular growth. A study conducted by Michalik *et al*[28] reported that inhibiting MALAT1 has an antiproliferative and promigratory effect on endothelial cells. Moreover, this transcript differentiates bone marrow-derived mesenchymal stem cells from endothelial cells, contributing to endothelial repair[29]. However, further research is required to understand the role of MALAT1 in physiological processes.

Several studies have shown the involvement of MALAT1 in the molecular mechanisms of various complex diseases, including cardiovascular and neurodegenerative disorders, as well as solid tumors such as lung cancer, pancreatic cancer, breast cancer, and GC[30,31].

MALAT1 IN GC

MALAT1 overexpression has been linked with the clinical characteristics of GC patients, including histological subtype, tumor node metastasis stage, overall survival (OS), and drug resistance (Table 1).

Notably, drug resistance a major challenge in the clinical management of GC[32-36]. For instance, Zhang *et al*[36] showed that MALAT1 expression was noticeably higher in tissue samples from 24 GC patients with oxaliplatin (OXA) resistance than in GC patients without chemoresistance.

Recently, new avenues have opened in the complex field of GC-related lncRNAs. Circulating lncRNAs have attracted considerable attention as potential minimally invasive diagnostic, prognostic, and predictive biomarkers. Even in unfavorable circumstances such as severe potential of hydrogen and numerous freeze-thaw cycles, ncRNAs in body fluids are resistant to exonucleases and highly stable[16,36,37].

Notably, circulating MALAT1 levels in body fluids and clinicopathological traits of GC patients were related to in three studies. For example, Xia *et al*[38] identified that circulating MALAT1 expression in plasma from GC patients was significantly higher at later stages of tumor development and in tumors that had undergone extensive metastasis. In contrast, circulating MALAT1 levels in GC patients without metastasis showed no significant difference compared to healthy controls. Taken together, these results suggest that circulating MALAT1 expression is linked to widespread metastasis and tumor stage, indicating its potential as a prognostic biomarker for GC.

Moreover, in their study, Lu *et al*[39] observed higher circulating MALAT1 expression in sera from GC patients without metastasis than healthy controls. They also found that GC patients with advanced stage had higher levels of MALAT1 expression than GC patients within early stages, indicating the potential of MALAT1 as both a prognostic and diagnostic tool.

Similarly, Zhu *et al*[33] conducted research with plasma samples from 64 GC patients. Circulating MALAT1 was overexpressed in plasma samples from GC patients compared to healthy controls. An estimated area under the curve value of 0.898 from receiver operating characteristic analyses indicates that MALAT1 may effectively discriminate against GC patients from healthy controls. These findings support the utilization of lncRNAs as valuable tools for improving the clinical management of GC.

Overall, the collective results of these studies consistently indicate that MALAT1 overexpression in plasma and serum is correlated with patients clinicopathological characteristics, highlighting its importance as a valuable prognostic and diagnostic biomarker in GC.

MOLECULAR MECHANISMS OF MALAT1 IN GC

Several studies have also explored the molecular mechanism of MALAT1 using GC cell lines, highlighting that MALAT1 plays putative role in chemoresistance, metastasis, and angiogenesis (Table 2).

CHEMORESISTANCE

Cisplatin and OXA are platinum compounds and alkylating agents widely used in cancer treatment, and the latter is more commonly used in gastrointestinal malignancies. These molecules form metal adducts through their interaction

Table 1 MALAT1 overexpression and clinical characteristics in GC patients

Samples	Sample	Clinical implications	Ref.
61 GC/DM, 50 GC/NDM, 36 C	Plasma, tissue	Staging, Metastasis	Xia *et al*[38]
150 GC, 15 peritumoral paraffin-embedded	Tissue	OS, PFS	Li *et al*[49]
78 GC, 78 NTAT	Tissue	Staging, LNM	Li *et al*[52]
60 GC, 60 NTAT	Tissue	Staging, LNM, Tumor size	Zhang *et al*[53]
20 GC, 20 NTAT	Tissue	Metastasis	Chen *et al*[54]
70 GC, 70 C	Serum	Staging	Lu *et al*[39]
89 GC, 89 NTAT	Tissue	LNM, Tumor size	Yan *et al*[32]
64 GC, 64 NTAT, 64 C	Tissue, plasma	Metastasis	Zhu *et al*[33]
30 GC, 30 NTAT	Tissue	Vascular invasion, Lymphatic invasion	Esfandi *et al*[30]
37 GC, 37 NTAT	Tissue	Staging	Li *et al*[34]
30 GC, 30 NTAT	Tissue	OS	Dai *et al*[35]
24 GC, 24 NTAT, 24 GC/OXA	Tissue	Chemoresistance	Zhang *et al*[36]

C: control samples without cancer; GC: gastric cancer patients; GC/OXA: gastric cancer patients treated with oxaliplatin; GC/DM: gastric cancer patients with distant metastasis; CG/NDM: gastric cancer patients withoutmetastasis; LNM: lymph node metastasis; OS: overall survival; NTAT: nontumoral adjacent tissues of GC patients; PFS: progression-free survival.

with DNA, forming interstrand or intrastrand DNA crosslinks that disrupt DNA replication and transcriptional processes [40,41].

Among the observed miRNAs, miR-22-3p was the sole miRNA observed in more than one study. In GC, miR-22-3p acts as a tumor suppressor, effectively inhibiting cell proliferation and cell sensitivity to therapy[34,36]. In the context of OXA resistance, MALAT1 functions as a ceRNA for miR-22-3p, exerting control over ZPF91 expression and increasing GC cell resistance to OXA. Notably, overexpression of MALAT1 enhances cell proliferation, confers resistance to OXA, and inhibits cell death mechanisms[36]. Consistent with these findings, Zhang *et al*[36] also reported the relationship between MALAT1 and cellular sensitivity to OXA in GC cell lines. Knockdown of MALAT1 using small interfering RNA MALAT1 (siMALAT1) reduced the level of ZPF91 protein and increased miR-22-3p expression. Furthermore, transfection of miR-22-3p in OXA-resistant cell lines yielded similar results.

Additionally, MALAT1 regulates phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/ serine/threonine-protein kinase (AKT) pathway promoting GC cell resistance to cisplatin. Knockdown of MALAT1 using siMALAT1 decreased PI3K and AKT activity, reducing GC cell proliferation, migration, and invasion. In contrast, GC cell lines treated with plasmid cloning DNA-MALAT1 (pcDNA-MALAT1) did not impact on the expression of PI3K, AKT, and signal transducer and activator of transcription 3[35].

These findings highlight the multifaceted involvement of MALAT1 in modulating drug resistance in GC, provide insights into the underlying mechanisms through which it influences cellular responses to therapy, and show the untapped potential of MALAT1 as a therapeutic target for GC treatment.

METASTASIS

From the data of several studies described in this review, epithelial-mesenchymal transition (EMT) markers were the most frequently reported proteins associated with MALAT1 overexpression in GC cell lines. Specifically, Vimentin and E-cadherin emerged as the most reported proteins linked to MALAT1 dysregulation in GC. EMT is a crucial stage in the metastatic process, characterized by losing epithelial properties and acquiring of mesenchymal characteristics[42].
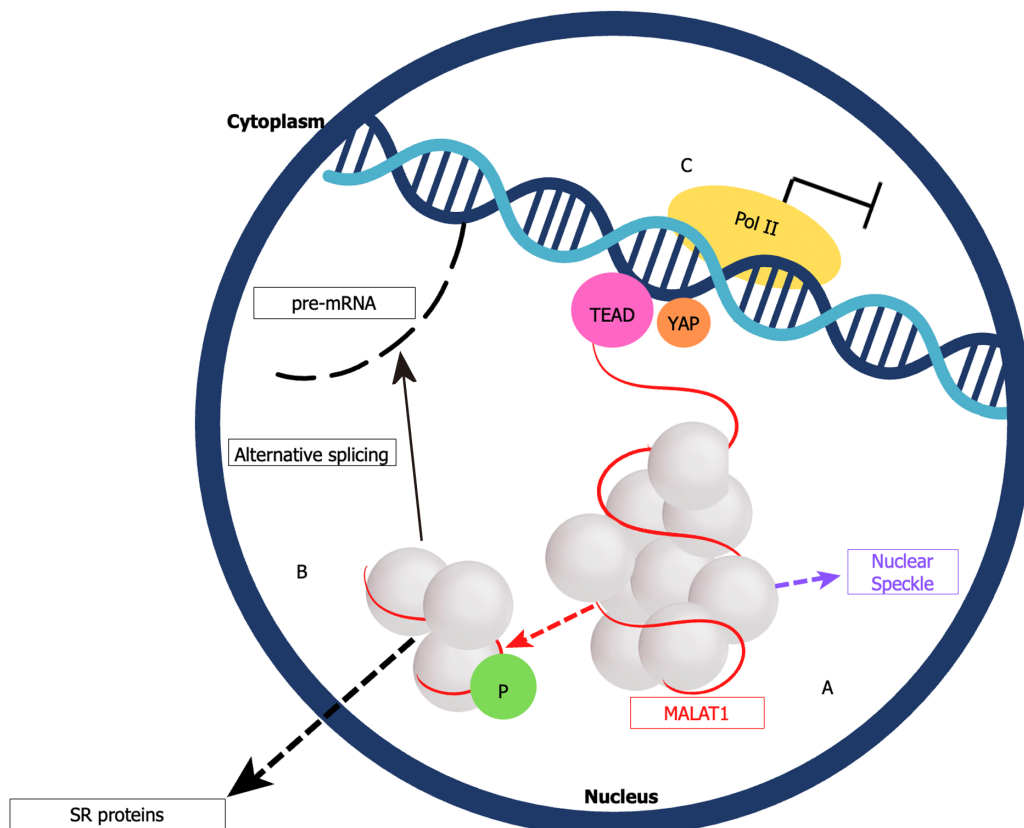
MALAT1 upregulation led to a reduction in E-cadherin expression and an increase in vimentin. In GC, E-cadherin acts as a tumor suppressor by preserving cell adhesion and inhibiting cell migration and invasion, while vimentin enhances GC cell migration and invasion[43,44].

Moreover, chemokine ligand 21 may upregulate MALAT1, promoting the expression of serine and arginine-rich splicing factor 1 (SRSF1) and the activation of the mammalian target of rapamycin (mTOR) pathway, consequently facilitating EMT[45]. Transfection assays using overexpression vectors and siMALAT1 demonstrated that the upregulation of MALAT1 increased the expression of SRSF1 protein and the phosphorylation of the mTOR pathway, leading to the downregulation of E-cadherin and overexpression of vimentin, slug, snail, and twist. Furthermore, the role of MALAT1 as a ceRNA for miR-202-3p contributes to the positive regulation of SRSF1, enhancing EMT processes (Figure 2).

Table 2 MALAT1 molecular mechanism in GC

Cell line	Molecular interactions	Main discoveries	Ref.
MKN28, SGC7901, BCG823, GES1	EGFL7	MALAT1/EGFL7 axis promotes metastasis and cell invasion	Deng *et al*[46]
MKN45, AGS, GES1	EZH2/PCDH10	MALAT1 recruits EZH2 to inhibit the synthesis of cadherin PCDH10, promoting metastasis	Qi *et al*[55]
SGC7901, MKN 45, BGC823, CTC141, CTC105, GES1	miR-122/IGF1R	miR-122/IGF1R axis causes dysregulation of MALAT1, increasing cell invasion and migration of cells	Xia *et al*[38]
SGC7901, MKN45, BGC823, AGS, SGC7901NM, SGC7901M, GES1	E-cadherin, vimentin, SLUG, SNAIL, TWIST	MALAT1 contributes to cell migration, invasion, and proliferation by upregulating EMT markers and downregulating E-cadherin	Chen *et al*[54]
MKN28, MKN74, AGS	RASSF6, β-catenin	Dysregulation of MALAT1 improves the expression of β-catenin and other EMT markers, promoting metastasis	Lee *et al*[56]
BGC823, SGC7901, HEK293T, GES1	UPF1	Overexpression of MALAT1 causes hypermethylation of the UPF1 promoter, increasing cell migration, invasion, and proliferation	Li *et al*[57]
BGC823, SGC7901, MKN45, AGS, BGC803, MGC803, GES1	VE-cadherin/β-catenin, ERK/MMP, FAK/paxillin	MALAT1 promotes angiogenesis by through vasculogenic mimicry	Li *et al*[49]
BGC823, SGC7901, MKN45, MKN28, GES1	miR-1297/HMGB2	MALAT1/miR-1297 increases HMGB2 protein, promoting cell invasion and proliferation of cells	Li *et al*[52]
SGC7901, SGC7901/VCR, BGC823	miR-23b-3p/ATG12	MALAT1/miR-23b-3p, promotes drug resistance *via* the ATG12 protein	YiRen *et al*[37]
SGC7901, MKN45, MKN28, GES1	miR-202/GLI2	MALAT1/miR-202, increases GLI2 expression, inducing tumor progression and cell proliferation	Zhang *et al*[53]
BGC823, SGC7901, GES1	Vimentin, E-cadherin	MALAT1 decreases E-cadherin and increases vimentin expression, promoting EMT	Yang *et al*[58]
BGC823, HGC27, SGC7901, GES1	miR-183/SIRT1, PI3KCA/AKT/mTOR	MALAT1/miR-183 increases SIRT1 protein expression, increasing cell viability, and inhibiting cell apoptosis	Li *et al*[59]
MGC803, GES1	miR-181a-5p/AKT3	MALAT1/miR-181a-5p increases AKT3 protein expression, promoting cell proliferation and inhibiting cell apoptosis	Lu *et al*[39]
MKN45, SGC7901, GES1	Vimentin, E-cadherin, SOX2	MALAT1 increases cell stemness *via* the SOX2 protein, and promotes metastasis	Xiao *et al*[60]
BGC823, HGC27, MKN45, AGS, GES1	IL-21R/miR-125a	MALAT1/miR-125a increases IL-21R expression, increasing cell invasion	Yan *et al*[32]
AGS, SNU1	PI3KCA/AKT	MALAT1 contributes to cell proliferation, invasion, and migration through the PI3KCA/AKT pathway	Zhu *et al*[33]
MKN45, MKN28, MGC803, MGC803/CDDP, HGC27, NCIN87, AGS, GES1	PI3KCA/AKT	MALAT1 increases PI3KCA, AKT and STAT3 activity, promoting resistance to cisplatin	Dai *et al*[35]
SGC7901, BGC823, GES1	miR-22-3p/ErbB3	MALAT1/miR22-3p inhibits cell apoptosis	Li *et al*[34]
CTC141, CTC105, MKN45, GES1	miR-204/MAP1LC3B/TRPM3	MALAT1/miR-204 increases the expression of LC3B and TRPM3, promoting autophagy	Shao *et al*[18]
SGC7901, BGC823, SGC7901/OXA, BGC823/OXA	miR22-3p/ZFP91	MALAT1 increases resistance to OXA	Zhang *et al*[36]
SGC7901, SGC7901/CDDP	miR-30e/ATG5	MALAT1 acts as a ceRNA to miR-30e, raising cisplatin resistance and autophagy *via* the miR-30e/AGT5 axis	Zhang *et al*[61]

| SGC7901, MGC803, HEK293T | CCL21, miR-202-3p/SRSF1, SRSF1/mTOR | MALAT1 promotes EMT through miR-202-3p/SRSF1/ mTOR | Fu *et al*[45] |

AKT: erine/threonine-protein kinase; ATG5: Autophagy related 5; ATG12: autophagy related 12; CCL21: C-C Motif Chemokine Ligand 21; ceRNA: Competitive endogenous RNA; EGFL7: Epidermal growth factor-like domain-containing protein 7; ERBB3: Erb-b2 receptor tyrosine kinase 3; ERK: Extracellular signal-regulated kinase; EMT: Epithelial-mesenchymal transition; EZH2: Enhancer of zeste 2 polycomb repressive complex 2 subunit; FAK: Focal adhesion kinase; GLI2: GLI family zinc finger 2; HMGB2: High mobility group box 2; IGF1R: insulin like growth factor 1 receptor; IL-21R: Interleukin 21 receptor; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; MAP1LC3B: Microtubule Associated Protein 1 Light Chain 3 Beta; mTOR: Mammalian target of rapamycin; MMP: Matrix metalloproteinases; OXA: Oxaliplatin; PCDH10: Protocadherin 10; PI3KCA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RASSF6: Ras association domain family member 6; SIRT1: Sirtuin 1; SOX2: SRY-box transcription factor 2; SRSF1: Serine and arginine-rich splicing factor 1; STAT3: Signal transducer and activator of transcription 3; TRPM3: Transient receptor potential cation channel subfamily M member 3; UPF1: UPF1 RNA helicase and ATPase; ZFP91: Zinc finger protein 91.

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Figure 1 Metastasis-associated lung adenocarcinoma transcript 1 subcellular location. A: Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is the red strand around the nuclear spots (white spheres), MALAT1 can interact with proteins present in nuclear speckles; B: MALAT1 can interact with serine/arginine proteins to modulate alternative splicing of pre-mRNAs; C: MALAT1 binds with transcriptional enhancer factor transcriptional enhanced factors with TEA/ATTS domain, blocking Yes-associated protein, inhibiting gene transcription. MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; SR: Serine/arginine-rich; TEAD: Transcriptional enhanced factors with TEA/ATTS domain; YAP: Yes-associated protein.

Additionally, MALAT1 overexpression significantly impacts themetastasis, invasion, and migration of GC cells through epidermal growth factor-like domain-containing protein 7 (EGFL7). Transfection assays with siMALAT1 in BGC823 cells demonstrated a reduction in acetylation of the promoter region EGFL7 located in histone H3, decreasing the EGFL7 protein level. Conversely, the injection of pcDNA-MALAT1 into MKN28 cells increased EGFL7 acetylation and EGFL7 protein concentration[46] (Figure 3).

Therefore, MALAT1 plays a pivotal role in promoting EMT, invasion, and migration of GC cells, suggesting its potential as a therapeutic target for metastasis and EMT. These compelling findings underscore the need for further research in this area, warranting exploration to understand its potential as a therapeutic target and assess its clinical significance.
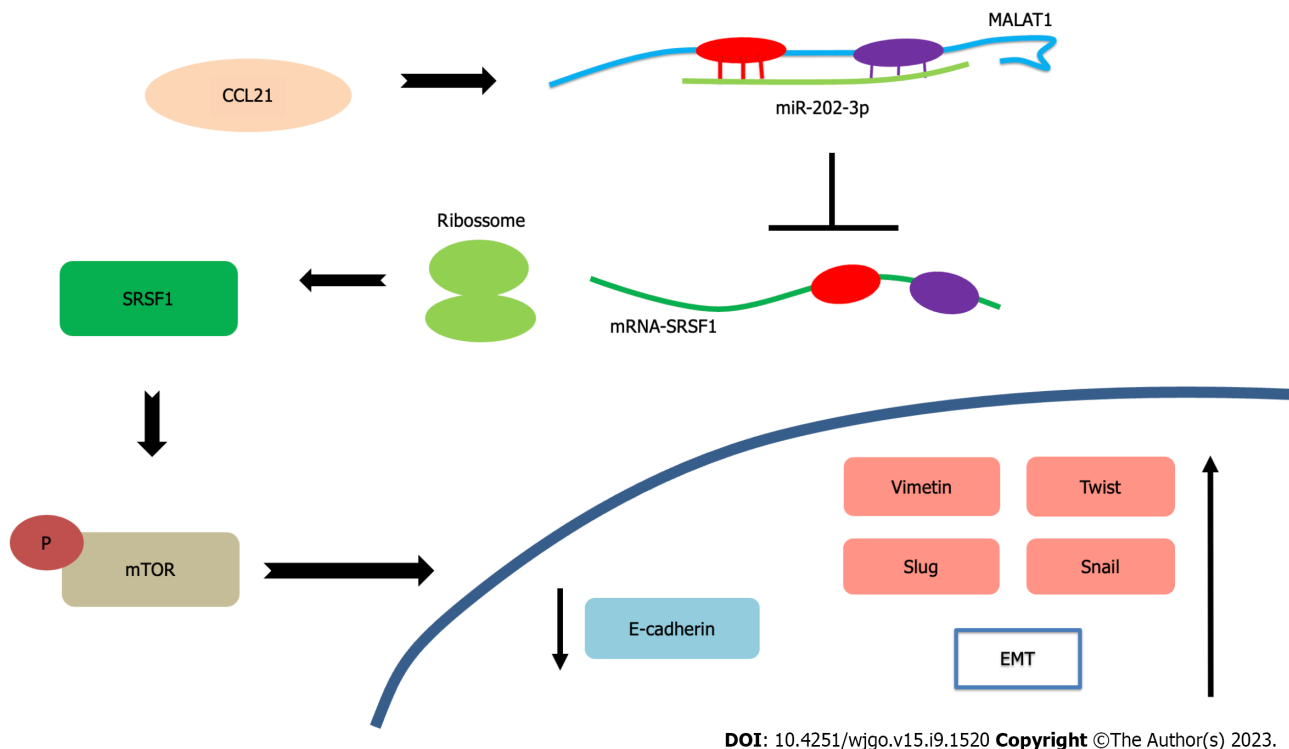
DOI: 10.4251/wjgo.v15.i9.1520 **Copyright** ©The Author(s) 2023.

Figure 2 Metastasis-associated lung adenocarcinoma transcript 1 expression is influenced by protein CCL21. Metastasis-associated lung adenocarcinoma transcript 1 sponges miR-202-3p, then SRSF1 mRNA (serine and arginine-rich splicing factor 1) is translated in protein and activates mammalian target of rapamycin pathway improving epithelial-mesenchymal transition (EMT) factors and decreasing E-cadherin expression. EMT: epithelial-mesenchymal transition; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; SRSF1: serine and arginine-rich splicing factor 1; mTOR: Mammalian target of rapamycin.

ANGIOGENESIS

Angiogenesis comprises the growth of new blood vessels from preexisting vasculature, providing tissues with oxygen and nutrients essential to tumor progression[47,48]. Vasculogenic mimicry (VM) is a phenomenon observed in highly aggressive tumors, where malignant cells imitate endothelial cells, contributing to the formation of microvascular channels that supply blood to cancer cells[49]. A key player in this process is CDH5 or vascular endothelial-cadherin, a transmembrane protein commonly expressed in the endothelium that acts to form and maintain adherent junctions between endothelial cells [50,51].

Furthermore, Li *et al*[49] revealed that MALAT1 overexpression regulates the expression of CDH5 and β-catenin. Interestingly, the knockdown of MALAT1 *in vitro* showed a significant decrease in the expression of the CDH5/β-catenin complex. When upregulated, MALAT1 influenced the CDH5/β-catenin complex to initiate VM and increase vascular permeability.

MALAT1 expression was also associated with the extracellular signal-regulated kinase (ERK)/matrix metalloproteinase (MMP) and focal adhesion kinase (FAK)/paxillin complexes. Upregulation of MALAT1 increased the activity of ERK, FAK, and paxillin; and increased the expression of MMPs, enhancing VM.
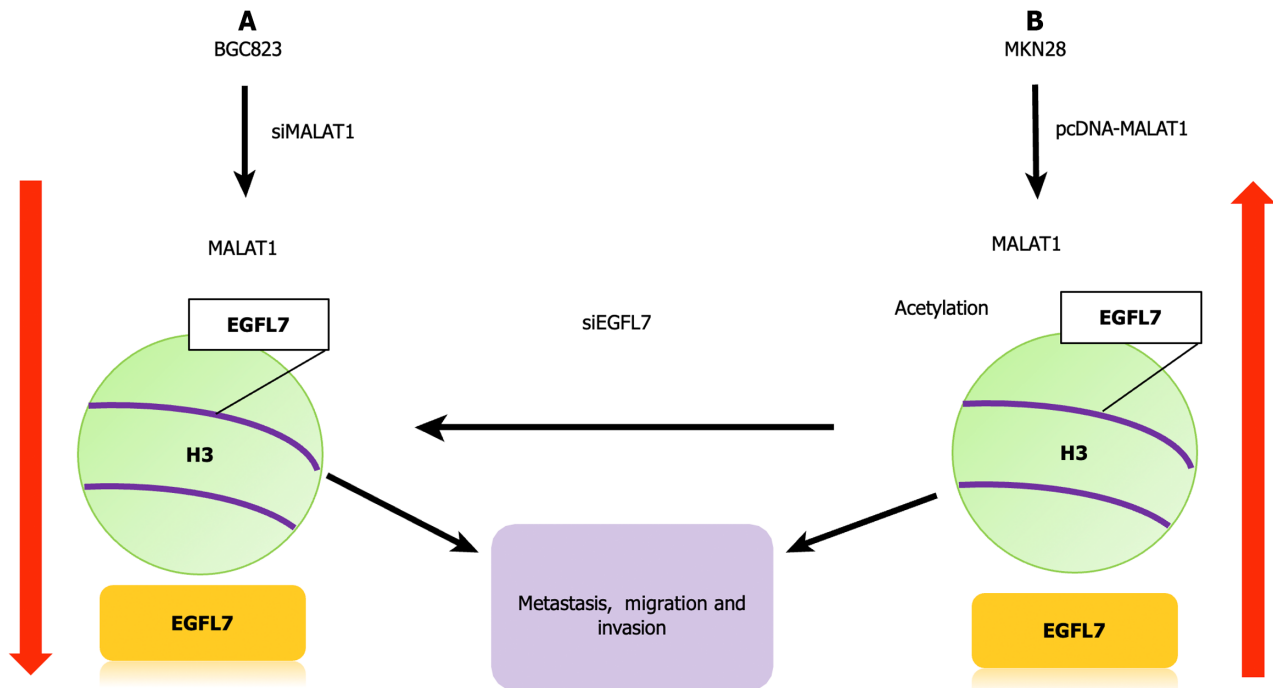
These insights provide valuable evidence for the involvement of MALAT1 in the modulation of these processes. However, further studies are warranted to clarify the intricate mechanism on how MALAT1 exerts influence over CDH5, which may offer potential avenues for targeted therapeutic interventions against VM and angiogenesis in GC.

CONCLUSION

In summary**,** MALAT1 is an antisense lncRNA that acts as a fundamental regulator of gene expression through interactions with proteins or miRNAs. In GC, MALAT1 has the potential to be a pivotal contributor to various molecular mechanisms, including EMT, apoptosis, proliferation, cell migration, and invasion.

Accumulating evidence has demonstrated a significant tumor suppressor role of miR-22-3p and its interaction with MALAT1 in GC, inhibiting cell apoptosis and increasing GC cell resistance to OXA.

Moreover, studies have correlated MALAT1 overexpression in the tissues and liquid biopsy samples of GC patients with metastasis, staging, worse OS, tumor size, and chemoresistance. The presence of MALAT1 in plasma and serum samples allows the use of minimally invasive collection methods. Although additional validations are needed, these findings show the potential of MALAT1 as a prognostic biomarker and therapeutic target. Further research to elucidate MALAT1 mechanisms of action may identify a new target of interest for translation into clinical applications, thereby

Figure 3 MALAT1 modulates acetylation in promoter region epidermal growth factor-like domain-containing protein 7 located in histone H3. A: Transfection of small interfering MALAT1 reduces acetylation on promoter region of *EGFL7* gene (Epidermal growth factor-like domain-containing protein 7), decreasing metastasis, cell invasion and migration; B: Plasmid cloning DNA-MALAT1 transfection increases *EGFL7* acetylation and protein expression, promoting migration, invasion, and metastasis of GC cells. EGFL7: Epidermal growth factor-like domain-containing protein 7; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; siMALAT1: Small interfering RNA MALAT1; pcDNA-MALAT1: Plasmid cloning DNA-MALAT1; siEGFL7: Small interfering RNA EGFL7.

improving the personalized clinical management of GC.

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FOOTNOTES

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