Review Article

Involvement of long non-coding RNA LOXL1-AS1 in the tumourigenesis and development of malignant tumours: a narrative review

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Background and Objective: Long noncoding RNAs (lncRNAs) are involved in a wide variety of physiological and pathological processes in organisms. LncRNAs play a significant role as oncogenic or tumour-suppressing factors in various biological processes associated with malignant tumours and are closely linked to the occurrence and development of malignancies. Lysyl oxidase like 1 antisense RNA 1 (LOXL1-AS1) is a recently discovered lncRNA. It is upregulated in various malignant tumours and is associated with pathological characteristics such as tumour size, tumour node metastasis (TNM) staging, lymph node metastasis, and tumour prognosis. LOXL1-AS1 exerts its oncogenic role by competitively binding with multiple microRNAs (miRs), thereby regulating the expression of downstream target genes and controlling relevant signalling pathways. This article aims to explore the structure and the function of LOXL1-AS1, and the relationship between LOXL1-AS1 and the occurrence and development of human malignant tumours to provide a reference for further clinical research.

Methods: English literature on LOXL1-AS1 in the occurrence and development of various malignant tumours was searched in PubMed. The main search terms were "LOXL1-AS1", "tumour".

Key Content and Findings: This article mainly summarizes the biological processes in which LOXL1-AS1 is involved in various human malignant tumours and the ways in which this lncRNA affects malignant biological behaviours such as proliferation, metastasis, invasion, and apoptosis of tumour cells through different molecular regulatory mechanisms. This article also explores the potential clinical significance and application prospects of LOXL1-AS1, aiming to provide a theoretical basis and reference for the clinical diagnosis, treatment, and screening of prognostic markers for malignant tumours.

Conclusions: LOXL1-AS1 acts as a competing endogenous RNA (ceRNA), binding to miRs to regulate downstream target genes and exert its oncogenic effects. LOXL1-AS1 may become a novel molecular biomarker for cancer diagnosis and treatment in humans, and it may also serve as an independent prognostic indicator.

Keywords: Long noncoding RNA (lncRNA); lysyl oxidase like 1 antisense RNA 1 (LOXL1-AS1); microRNA (miR); malignant tumours

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Introduction

Cancer is a malignant disease that seriously threatens human health and has consistently been one of the main causes of noncommunicable disease-related deaths worldwide. It has been reported that the global cancer burden is predicted to increase by 47% from 2020 to 2040, reaching 28.4 million cases (1). With the development of foundational disciplines such as genomics and molecular biology, the molecular mechanisms related to the occurrence and development of cancer have been extensively researched. Research has found that long noncoding RNAs (lncRNAs) serve as primary regulatory factors in a spectrum of biological behaviours and diseases (2). Dysfunction of lncRNAs is considered to be one of the major factors contributing to the occurrence of various diseases, such as cancer, cardiovascular disease, fibrosis, and obesity.

Approximately 93% of human genomic DNA can be transcribed into RNA, of which only 2% are mRNAs that encode proteins, while the remaining 98% are noncoding RNAs that do not code for proteins. More than 200 bases of noncoding RNAs are categorized as lncRNAs (3). Although lncRNAs rarely encode proteins, they can regulate gene expression and participate in various molecular biological processes through mechanisms such as RNA interference, gene co-repression, gene silencing, gene imprinting and DNA demethylation (4). The classification of lncRNAs is currently not standardized and is typically classified according to adjacent protein-coding genes: sense strand lncRNAs, antisense strand lncRNAs, intronic lncRNAs, bidirectional lncRNAs, long intergenic noncoding RNAs, and enhancer-associated lncRNAs. Additionally, a study has classified lncRNAs into four categories based on their functions: signalling molecules, scaffolding molecules, guidance molecules, and decoy molecules (5). LncRNAs can act as signal molecules participating in signal transduction pathways and regulate the expression of downstream target genes. Then, lncRNAs can also act as scaffolding molecules, serving as structural components of proteins and binding with various proteins to form stable nucleic acid-protein complexes and mediate chromatin histone modification. Moreover, lncRNAs can act as guidance molecules, recruiting chromatin modification-related enzymes to regulate target genes. As bait molecules, lncRNAs can recruit related proteins or transcription factors to regulate the expression of target genes by binding to miRNAs (miRNA sponges). Abnormal expression of lncRNAs is associated with the occurrence and progression of various cancers (6,7). For example, the lncRNA lymph node metastasis-associated transcript 1 (LNMAT1) recruits heterogeneous nuclear ribonucleoprotein L (hnRNPL) to the C-C motif chemokine ligand 2 (CCL2) promoter, activating CCL2 expression to promote lymphatic vessel formation and lymphatic metastasis in bladder cancer (8). LncRNA SPRY4-IT1 promotes the proliferation and metastasis of bladder cancer cells through the upregulation of enhancer of zeste homologue 2 (EZH2) by sponging miR-101-3p (9). Actin filament-associated protein 1 antisense RNA 1 (AFAP1-AS1) was initially discovered in oesophageal adenocarcinoma in 2013. Research over the past decade has indicated that a crucial oncogenic lncRNA, i.e., human lysyl oxidase like 1 antisense RNA 1 (LOXL1-AS1), is upregulated in various cancers and can enhance different processes in multiple cancers. The high expression of LOXL1-AS1 in human cancers is closely associated with adverse clinical outcomes, such as lymph node metastasis and distant metastasis.

Therefore, this article aims to elucidate the functions and mechanisms of LOXL1-AS1 in cancer, in order to further assist clinical professionals in exploring new strategies for the prevention or treatment of malignant tumors. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2282/rc).

Methods

We searched literature in PubMed database to find relevant studies on LOXL1-AS1 in the occurrence and development of various malignant tumours. The keywords used were "LOXL1-AS1", "tumour". Only English literature was selected, and relevant references cited in the obtained articles were also retrieved. The search strategy is listed in *Table 1*.

Table 1 The search strategy summary

Items	Specification
Date of search	13-Nov-2023
Databases and other sources searched	PubMed
Search terms used	(LOXL1-AS1) AND (tumour)
Timeframe	2018–2023
Inclusion and exclusion criteria	Inclusion criteria: all study types and reviews, written in English; exclusion criteria: articles with no search terms used
Selection process	X.W. and R.L. independently screened data sources. J.L. mediated the process when disagreements occurred

LOXL1-AS1, lysyl oxidase like 1 antisense RNA 1.

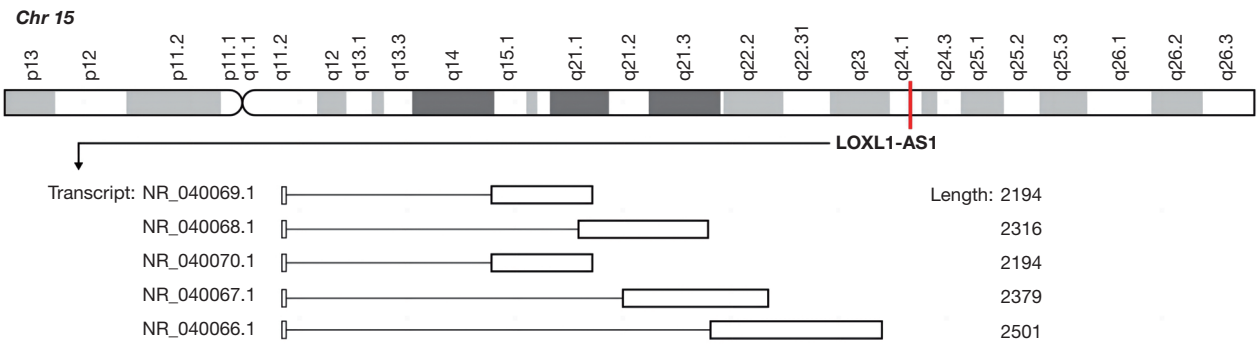

Figure 1 The position of LOXL1-AS1 on human chromosome 15 (sourced from the GeneCards database, database website: https://www.genecards.org). Information collected from the online database shows that LOXL1-AS1 is an antisense lncRNA of the *LOXL1* gene, which is located at 15q24.1. LOXL1-AS1, lysyl oxidase like 1 antisense RNA 1.

Structure and function of LOXL1-AS1

LOXL1-AS1 is an antisense lncRNA transcribed from the lysyl oxidase like 1 (*LOXL1*) gene. The *LOXL1* gene encodes a lysyl oxidase-like protein and belongs to the lysyl oxidase (LOX) protein family (5,6). According to information from the GeneCards online database, LOXL1-AS1 is an antisense lncRNA located in the 15q24.1 region of human chromosome 15 (*Figure 1*, data sourced from the website: https://www.genecards.org). The total length of LOXL1-AS1 is 2,501 base pairs, which includes five exons and comprises five different transcripts (extracted from the NCBI database) labelled NR_040069.1, NR_040068.1, NR_040070.1, NR_040067.1, and NR_040066.1. Recent research has shown that LOXL1-AS1 exhibits high expression in various cell lines, including gastric cancer (GC) MKN-45 cells and SGC7901 cells (10), liver cancer Hep-G2 and SK-HEP1 cells (11), lung cancer (LUNG) SPC-A1 and A549 cells (12), and triple-negative breast cancer (BC) MDA-MB-231 and MDA-MB-468 cells (13). LOXL1-AS1 primarily localizes to the cytoplasm. Sequence analysis of the *LOXL1-AS1* gene using the lncLocator database also confirms its primary cytoplasmic localization (*Table 2*). Increasing evidence indicates that LOXL1-AS1 is highly expressed in various human malignancies, such as oesophageal squamous cell carcinoma (OSCC) (14), GC (10), LUNG (12), renal cell carcinoma (RCC) (15), and BC (13), and is closely associated with the clinical pathological features of cancer patients (*Figure 2*, *Table 3*). Additionally, LOXL1-AS1 is involved in regulating various biological processes in these cancers, such as cell proliferation, invasion, migration, and apoptosis (*Table 3*). The role of the lncRNA LOXL1-AS1 in different biological processes primarily arises from its competitive binding with miRs

Table 2 Subcellular localization analysis of LOXL1-AS1 (sourced from the lncLocator database: www.csbio.sjtu.edu.cn/bioinfo/lnclocator)

Subcellular localization	Score
Cytoplasm	0.107860004284
Nucleus	0.0149309109124
Ribosome	0.301013575702
Cytosol	0.484305103525
Exosome	0.0918904055762

LOXL1-AS1, lysyl oxidase like 1 antisense RNA 1.

or through complex interactions with proteins, including those actively participating in cell proliferation, invasion, migration, and apoptosis.

LOXL1-AS1 and digestive system tumours

OSCC

OSCC is the seventh most prevalent malignant tumour globally and ranks as the sixth most prevalent cause of cancer-related mortality (1). Li *et al.* (14) demonstrated that LOXL1-AS1 exhibits significantly elevated expression

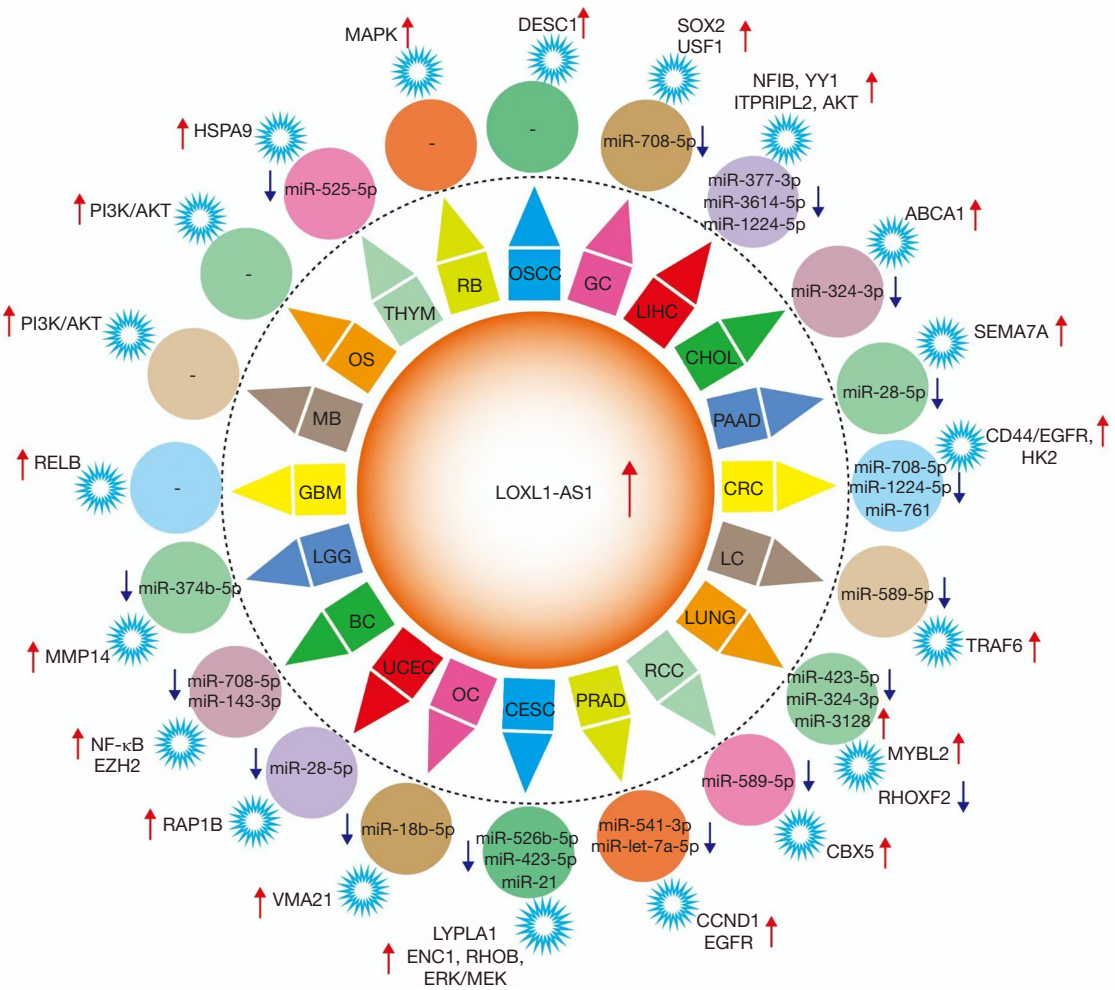

Figure 2 Role of LOXL1-AS1 as a ceRNA in multiple human cancers and its potential molecular mechanism. LOXL1-AS1 inhibits microRNA expression and regulates downstream molecules. Red arrows: upregulated; blue arrows: downregulated. LOXL1-AS1, lysyl oxidase like 1 antisense RNA 1; ceRNA, competing endogenous RNA.

Table 3 Clinical pathological correlations of LOXL1-AS1 overexpression in different types of tumours

Cancer types	Expression	miRNA	Related gene	Biological function	Clinical-pathological correlation	References
OSCC	Upregulated	–	*DESC1*	Proliferation, migration, invasion, cell apoptosis	Lymph node metastasis, poor prognosis	(1,14)
GC	Upregulated	miR-708-5p	*USF1, SOX2*	Proliferation, migration, EMT, stemness	Tumour enlargement, poor prognosis	(10)
LIHC	Upregulated	miR-377-3p; miR-3614-5p; miR-1224-5p	*NFIB; YY1; ITPRIPL2; AKT*	Proliferation, migration, invasion, cell apoptosis, glucose metabolism, EMT	Lower overall survival rate	(11,16-19)
CHOL	Upregulated	miR-324-3p	*ABCA1*	Proliferation, migration, invasion, cell apoptosis	Lymph node metastasis, increasing TNM stage, poor prognosis	(20)
PAAD	Upregulated	miR-28-5p	*SEMA7A*	Proliferation, migration	–	(21)
CRC	Upregulated	miR-708-5p; miR-1224-5p; miR-761	*CD44/EGFR; HK2*	Proliferation, migration, invasion, glycolysis, cell apoptosis	Tumour size, differentiation grade, TNM staging, liver metastasis, MSI staging	(1,22,23)
LC	Upregulated	miR-589-5p	*TRAF6*	Proliferation, migration, EMT	–	(24)
LUNG	Upregulated	miR-423-5p; miR-324-3p; miR-3128	*MYBL2; RHOXF2*	Proliferation, migration, invasion, EMT, cell apoptosis	Late-stage tumour, metastasis	(1,12,25,26)
RCC	Upregulated	miR-589-5p	*CBX5*	Proliferation, migration	–	(15)
PRAD	Upregulated	miR-541-3p; miR-let-7a-5p	*CCND1; EGFR*	Proliferation, migration, cell apoptosis	–	(27,28)
CESC	Upregulated	miR-526b-5p; miR-423-5p; miR-21	*LYPLA1; ENC1; ERK/MEK; RHOB*	Proliferation, migration, invasion, angiogenesis	–	(1,29-31)
OC	Upregulated	miR-18b-5p	*VMA21*	Proliferation, colony formation, migration, invasion	FIGO staging, distant metastasis, decreased overall survival, poor prognosis	(32,33)
UCEC	Upregulated	miR-28-5p	*RAP1B*	Proliferation, migration, invasion, cell apoptosis	–	(34)
BC	Upregulated	miR-708-5p; miR-143-3p	*NF-κB, EZH2*	Proliferation, migration, invasion, cell apoptosis	Tumour staging, lymph node metastasis	(1,13,35)
LGG	Upregulated	miR-374b-5p	*MMP14*	Proliferation, migration, invasion, vascular mimicry	Decreased overall survival, grade	(36-38)
GBM	Upregulated	–	*RELB*	Proliferation	Decreased overall survival, poor prognosis	(39,40)
MB	Upregulated	–	*PI3K/AKT*	Proliferation, migration, cell apoptosis, cell viability and colony forming ability	–	(41)
OS	Upregulated	–	*PI3K/AKT*	Proliferation, migration, invasion	Enneking staging, tumour size, distant metastasis, histological grading, decreased overall survival	(42,43)
THYM	Upregulated	miR-525-5p	*HSPA9*	Proliferation, invasion, cell apoptosis	Poor prognosis	(44)
RB	Upregulated	–	*MAPK*	Proliferation, invasion, cell apoptosis	–	(45)

LOXL1-AS1, lysyl oxidase like 1 antisense RNA 1; EMT, epithelial-mesenchymal transition; TNM, tumour node metastasis; MSI, microsatellite instability; FIGO, International Federation of Gynecology and Obstetrics.

in OSCC tissue compared to adjacent non-tumour tissue. High LOXL1-AS1 expression is closely related to lymph node metastasis and poor prognosis in OSCC patients. Knockdown of the *LOXL1-AS1* gene *in vitro* can suppress OSCC cell proliferation, migration, and invasion, leading to cell cycle arrest and induction of apoptosis. High-throughput RNA sequencing (RNA-seq) analysis reveals DESC1 to be a pivotal downstream target of LOXL1-AS1. LOXL1-AS1 promotes OSCC progression by modulating *DESC1* gene expression. In conclusion, LOXL1-AS1 has the potential to serve as a novel diagnostic marker and therapeutic target for OSCC.

GC

GC exhibits a relatively low rate of early diagnosis, with most patients being diagnosed in the advanced or metastatic stages, resulting in poorer treatment outcomes. Consequently, research on GC-related genes plays a key role in the treatment and prognostic assessment of GC.

Sun *et al.* (10) demonstrated that LOXL1-AS1 is highly expressed in GC tissue and cells. Upregulation of LOXL1-AS1 is indicative of poor prognosis in GC patients. Additionally, LOXL1-AS1 accelerates the deterioration of GC by inducing cell proliferation, migration, epithelial-mesenchymal transition (EMT), and stemness. Furthermore, the expression of the *USF1* gene is higher in GC cells than in normal control cells, and LOXL1-AS1 negatively regulates the expression of the *USF1* gene. LOXL1-AS1 functions as a competing endogenous RNA (ceRNA) and upregulates the expression of the *USF1* gene through interaction with miR-708-5p. In turn, USF1 can promote the transcription of the stem cell marker *SOX2* gene. These studies confirm the role of the LOXL1-AS1/miR-708-5p/USF1 pathway in promoting GC progression.

These studies collectively suggest that LOXL1-AS1 may be involved in the onset and progression of GC and function as an oncogene, holding the potential to serve as one of the indicators for predicting and evaluating the prognosis of GC patients.

Liver hepatocellular carcinoma (LIHC)

LIHC is a primary liver cancer characterized by an increasing incidence and mortality rate, making it one of the most prevalent malignancies worldwide (16). Liu *et al.* (11) revealed that LOXL1-AS1 expression is significantly elevated in LIHC tissue compared with adjacent non-tumour liver tissue and is highly expressed in three different LIHC cell lines compared with normal liver cells. Moreover, knockdown of the *LOXL1-AS1* gene *in vitro* effectively inhibited the proliferation, migration, and invasion of HepG2 liver cancer cells. Yu *et al.* (17) indicated that LOXL1-AS1 is significantly upregulated in LIHC tissue and cells. High LOXL1-AS1 expression is associated with poorer clinical outcomes in LIHC patients. Additionally, knockdown of the *LOXL1-AS1* gene suppresses glucose metabolism, proliferation, migration, and EMT in LIHC cells. Silencing LOXL1-AS1 upregulates the expression of miR-377-3p, and nuclear factor I B (NFIB) shows a positive correlation with LOXL1-AS1 expression. Further research has shown that LOXL1-AS1 upregulates *NFIB* gene expression in LIHC cells by competitively binding with miR-377-3p and then promoting glucose metabolism, proliferation, migration, and EMT in LIHC cells. These studies may offer new insights into the treatment of LIHC.

Feng *et al.* (18) found that LOXL1-AS1 is significantly upregulated in various LIHC tissues and cells. Overexpression of LOXL1-AS1 promotes the proliferation, migration, and invasion of LIHC cells while inhibiting cell apoptosis. In addition, LOXL1-AS1 competes with miR-3614-5p, leading to the upregulation of the transcription factor YY1, which enhances the malignant behaviour of LIHC cells. YY1 can transcriptionally activate LOXL1-AS1 expression, thereby forming a positive feedback loop in LIHC cells. Chen *et al.* (19) demonstrated that LOXL1-AS1 induces cell proliferation and suppresses cell apoptosis in primary LIHC by activating the AKT pathway, sponging miR-1224-5p and upregulating ITPRIPL2. The aforementioned findings may contribute to the identification of more effective therapeutic targets for LIHC in the future.

Cholangiocarcinoma (CHOL)

CHOL is one of the most common malignant tumours in the hepatobiliary system. Current treatment approaches for inhibiting CHOL progression are far from ideal. Timely diagnosis and effective treatment are crucial for improving the prognosis of CHOL. Zhang *et al.* (20) discovered a significant upregulation of LOXL1-AS1 expression in CHOL tissues and cells through The Cancer Genome Atlas (TCGA) data mining and quantitative real-time polymerase chain reaction (qRT-PCR) analysis. This upregulation is closely associated with lymph node metastasis, higher tumour node metastasis (TNM) staging,

and poorer prognosis in CHOL patients. Furthermore, LOXL1-AS1 promotes cell proliferation, migration, and invasion while inhibiting apoptosis. Additionally, acting as a ceRNA for miR-324-3p, LOXL1-AS1 significantly elevates the expression of ABCA1 and displays a malignant phenotype in CHOL cells, thereby exerting an oncogenic effect in CHOL. In summary, LOXL1-AS1 holds potential as a candidate biomarker and therapeutic target for clinical applications in CHOL.

Pancreatic adenocarcinoma (PAAD)

PAAD is one of the most aggressive and deadly malignancies in humans. Despite continuous advances in treatment strategies, the prognosis remains poor. Liu *et al.* (21) discovered an upregulation of LOXL1-AS1 expression in PAAD cells. Silencing LOXL1-AS1 was found to inhibit cell proliferation and migration in PAAD. Additionally, the *SEMA7A* gene was upregulated in PAAD cells and negatively regulated by miR-28-5p, while it was positively regulated by LOXL1-AS1. These studies have suggested that miR-28-5p may serve as a molecular sponge for LOXL1-AS1 and that the LOXL1-AS1/miR-28-5p/SEMA7A axis promotes PAAD progression, potentially providing a new molecular target for PAAD treatment.

Colorectal cancer (CRC)

CRC is ranked as the third most common cancer (1). Wu *et al.* (22) observed that LOXL1-AS1 was highly expressed in CRC tissues and cell lines, and this upregulation was significantly associated with tumour size, differentiation degree, TNM stage, liver metastasis, and microsatellite instability (MSI) stage. Furthermore, *LOXL1-AS1* gene knockout and miR-708-5p overexpression inhibited CRC cell proliferation, migration, and invasion. Mechanistically, LOXL1-AS1 acted as a molecular sponge for miR-708-5p, activating the CD44-EGFR signalling pathway in CRC cells and thereby promoting the proliferation, migration, invasion, and progression of CRC.

Guo *et al.* (23) revealed that the levels of LOXL1-AS1 and HK2 were elevated in CRC tissues and cells, while the levels of miR-1224-5p and miR-761 were reduced. Additionally, knocking down LOXL1-AS1 inhibited the proliferation, invasion, migration, and glycolysis of CRC cells and induced apoptosis. Silencing LOXL1-AS1 *in vivo* blocked tumour growth. Furthermore, LOXL1-AS1 accelerated the progression of CRC cells by sequestering miR-1224-5p/miR-761. Additionally, miR-1224-5p and miR-761 suppressed the progression of CRC cells by targeting HK2. In conclusion, LOXL1-AS1 promotes the progression of CRC by modulating the miR-1224-5p/miR-761/HK2 pathway. These findings provide a theoretical basis for further research on CRC treatment strategies.

LOXL1-AS1 and respiratory system tumours

Laryngeal cancer (LC)

LC is a common malignancy of the upper respiratory tract. He *et al.* (24) found that LOXL1-AS1 is primarily expressed in the cytoplasm of LC cells and is significantly upregulated in these cells. Additionally, silencing the *LOXL1-AS1* gene inhibits the proliferation, migration, and EMT of LC cells. Furthermore, miR-589-5p plays a tumour-suppressive role in LC, while TRAF6 plays a tumour-promoting role. Functional rescue experiments *in vivo* and *in vitro* confirm that LOXL1-AS1 enhances the malignancy of LC by targeting the miR-589-5p/TRAF6 pathway, promoting the proliferation and migration of LC cells. These studies establish that the LOXL1-AS1/miR-589-5p/TRAF6 signalling pathway contributes to LC development, potentially providing a novel biomarker and therapeutic target for LC treatment.

Lung cancer (LUNG)

LUNG is the second most prevalent malignancy globally, and recently, it has exhibited the highest fatality rate (1). Li *et al.* (12) discovered that LOXL1-AS1 is predominantly localized in the cytoplasm of lung adenocarcinoma (LUAD) cells, with significantly elevated expression in both LUAD tissues and cells. Furthermore, the deletion of LOXL1-AS1 suppresses the proliferation and migration of LUAD cells while promoting apoptosis. Mechanistically, miR-423-5p negatively regulates MYBL2. LOXL1-AS1 functions as a molecular sponge for miR-423-5p, upregulating MYBL2 to expedite the progression of LUAD. These findings elucidate the oncogenic role of LOXL1-AS1 and the feedback loop involving LOXL1-AS1/miR-423-5p/MYBL2 in LUAD.

Xie *et al.* (25) revealed that LOXL1-AS1 exhibits significant upregulation in non-small cell lung cancer (NSCLC) tissues and cells, with a negative correlation between miR-324-3p and *LOXL1-AS1* gene expression. LOXL1-AS1 overexpression enhances the proliferation, invasion, and EMT induction of NSCLC cells by regulating

miR-324-3p. These results suggest that LOXL1-AS1 acts as a molecular sponge for miR-324-3p and promotes the proliferation and invasion of NSCLC cells. Zhao *et al.* (26) discovered that lncRNA LOXL1-AS1 was higher expressed in NSCLC tissues and cells. Moreover, LOXL1-AS1 expression was upregulated in tumour tissues with advanced stages and metastasis. After knocking down LOXL1-AS1, proliferation, invasion and migration of NSCLC H1299 and A549 cells were inhibited. Interestingly, miR-3128 negatively regulates RHOXF2, while lncRNA LOXL1-AS1 negatively regulates miR-3128, thus promoting the expression of RHOXF2. In summary, LOXL1-AS1 promotes the progression of NSCLC by regulating miR-3128/RHOXF2 axis, which might be a new potential target for the diagnosis and treatment of NSCLC.

These research findings provide new insights into the potential of LOXL1-AS1 as a diagnostic and therapeutic target in LUNG.

LOXL1-AS1 and urological system tumours

RCC

RCC is a common malignant tumour of the urological system that poses a serious threat to human health. Wu *et al.* (15) discovered that LOXL1-AS1 is highly expressed in RCC tissues and cells. Knocking down LOXL1-AS1 *in vitro* inhibits the proliferation and migration of RCC cells. Furthermore, miR-589-5p is downregulated in RCC cells, and CBX5 is a target of miR-589-5p. Its deficiency can suppress the malignant phenotype of RCC cells. In addition, overexpression of CBX5 or inhibition of miR-589-5p expression can reverse the inhibitory effect of silenced LOXL1-AS1 on the malignant phenotype of RCC. Therefore, LOXL1-AS1 promotes the malignant biological behaviour of RCC by regulating the expression of the miR-589-5p and *CBX5* gene, which may provide a useful theoretical basis for exploring new effective treatment strategies for RCC.

Prostate adenocarcinoma (PRAD)

PRAD is one of the most common malignant tumours in men, posing a significant threat to their health. Long *et al.* (27) discovered that knockdown of the *LOXL1-AS1* gene *in vitro* can significantly inhibit PRAD cell proliferation and induce cell cycle G1/S phase arrest. LOXL1-AS1 is primarily located in the cytoplasm and acts as a molecular sponge to negatively regulate the expression of miR-541-3p. The *CCND1* gene is the target of miR-541-3p, and miR-541-3p suppresses the expression of the *CCND1* gene by binding to its 3' untranslated region (3'UTR). Therefore, LOXL1-AS1 regulates PRAD cell proliferation and cell cycle progression through miR-541-3p and CCND1, offering a potential therapeutic avenue for PRAD.

Furthermore, doxorubicin (DOX) is used to treat PRAD, but its effectiveness is limited due to side effects and strong multidrug resistance after repeated administration. Consequently, drug resistance remains a major issue in the late-stage treatment of PRAD. Bai *et al.* (28) discovered that in DOX-resistant PRAD DU-145 cells, the expression of *LOXL1-AS1* and *EGFR* genes is downregulated, while miR-let-7a-5p expression is upregulated. Upregulation of LOXL1-AS1 promotes cell proliferation and migration while inhibiting apoptosis. *In vitro* experiments further validated that upregulated LOXL1-AS1 expression enhances the proliferation of DOX/DU-145 cells. Xenograft experiments confirmed that silencing the *LOXL1-AS1* gene significantly inhibits the *in vivo* growth of PRAD cells. These studies suggest that the LOXL1-AS1/miR-let-7a-5p/EGFR axis significantly influences the proliferation, migration, and apoptosis of DOX-resistant PRAD DU-145 cells, providing a potential treatment strategy for drug-resistant PRAD patients.

LOXL1-AS1 and the female reproductive system and breast tumours

Cervical cancer (CESC)

CESC is a common malignant tumour in gynaecology, ranking fourth in both mortality and morbidity among female cancers (1). Zhang *et al.* (29) demonstrated that LOXL1-AS1 is significantly upregulated in CESC tissues and cells. In CESC samples, the expression of miR-526b-5p is negatively correlated with LYPLA1 and LOXL1-AS1 expression. Additionally, *LOXL1-AS1* gene knockdown can inhibit the proliferation, migration, invasion, and angiogenesis of CESC cells *in vivo*. Furthermore, functional rescue experiments *in vitro* showed that the overexpression of LYPLA1 reversed the inhibitory effect of *LOXL1-AS1* gene silencing on the malignant phenotype of CESC cells. These results suggest that LOXL1-AS1 promotes CESC development by acting as a molecular sponge for miR-526b-5p, providing a potential theoretical basis for CESC treatment.

Zhang *et al.* (30) showed that *LOXL1-AS1* and *ENC1* genes are upregulated in CESC cells and tissues, while miR-423-5p expression is downregulated. Downregulation of LOXL1-AS1 inhibits CESC tumour growth, cell migration and proliferation. Furthermore, knocking down the *ENC1* gene inhibits the activation of the ERK/MEK pathway. Importantly, LOXL1-AS1 can bind to miR-423-5p to reduce its regulation of ENC1, thereby promoting CESC progression through the activation of the ERK/MEK pathway.

Bai *et al.* (31) found that LOXL1-AS1 is downregulated in cervical squamous cell carcinoma (CSCC) tissues compared to non-tumour tissues. Moreover, overexpression of LOXL1-AS1 leads to the upregulation of *RHOB* gene expression. RHOB is a direct target of miR-21, and overexpression of miR-21 leads to downregulation of RHOB expression in CSCC cells. Overexpression of LOXL1-AS1 and RHOB reduces the invasion and migration of CSCC cells. Therefore, LOXL1-AS1 may up-regulate RHOB by modulating miR-21, thereby promoting the invasion and migration of CSCC cells. LOXL1-AS1 is downregulated in CSCC and may inhibit the invasion and migration of CSCC cells by regulating miR-21/RHOB, providing a theoretical basis for CSCC treatment.

Ovarian cancer (OC)

OC is a common tumour of the female reproductive organs. Epithelial ovarian cancer (EOC) constitutes 50–70% of ovarian tumours and has been on the rise in China. Liu *et al.* (32) discovered that EOC patients exhibited significantly higher LOXL1-AS1 expression compared to the normal adjacent group. Additionally, LOXL1-AS1 expression was positively correlated with advanced International Federation of Gynecology and Obstetrics (FIGO) stage and distant metastasis, with patients with high LOXL1-AS1 expression experiencing shorter overall survival. Therefore, LOXL1-AS1 expression is associated with adverse clinical outcomes in EOC patients and may serve as an independent prognostic indicator and a novel diagnostic biomarker.

Xue *et al.* (33) found that LOXL1-AS1 was significantly upregulated in OC tissues and cells. Downregulation of LOXL1-AS1 inhibited OC cell proliferation, colony formation, migration, and invasion and reduced the capacity for distant metastatic growth in OC cells. miR-18b-5p was identified as a target of LOXL1-AS1, which exhibited a negative regulatory effect on miR-18b-5p. VMA21 is a direct target gene of miR-18b-5p and is highly expressed in OC tissues. MiR-18b-5p inhibited OC cell proliferation and migration by targeting VMA21. Furthermore, LOXL1-AS1 expression was positively correlated with VMA21 expression, while miR-18b-5p expression was negatively correlated with VMA21 expression. Mechanistically, LOXL1-AS1 interacted with miR-18b-5p to regulate OC cell growth and migration. These findings indicate that LOXL1-AS1 promotes OC cell growth, migration, and invasion through the regulation of the miR-18b-5p/VMA21 axis.

Uterine corpus endometrial carcinoma (UCEC)

UCEC originates in the uterus and is one of the most common gynaecological tumours, with an increasing incidence. Yang *et al.* (34) found that LOXL1-AS1 was significantly upregulated in UCEC tissues and cell lines. Moreover, knockdown of LOXL1-AS1 *in vitro* significantly inhibited cell proliferation, migration, and invasion and promoted apoptosis. Furthermore, the regulatory effects induced by LOXL1-AS1 in UCEC cells could be partially reversed by a miR-28-5p inhibitor. Mechanistically, LOXL1-AS1 acted as a ceRNA targeting miR-28-5p and upregulating the expression of the *RAP1B* gene in UCEC cells, thereby promoting UCEC progression. These studies confirm that LOXL1-AS1 has the potential to serve as a diagnostic and therapeutic biomarker for UCEC.

BC

BC is one of the most common cancers among women, and it ranks as the second leading cause of cancer-related deaths (1). Dong *et al.* (13) conducted a study and found that LOXL1-AS1 is upregulated in BC tissues and cells. Furthermore, high expression of LOXL1-AS1 is associated with tumour staging and lymph node metastasis in BC patients. *in vitro* research indicates that overexpression of the *LOXL1-AS1* gene enhances the migration and invasion abilities of BC cells, whereas knocking down the *LOXL1-AS1* gene reduces the migratory and invasive capacities of BC cells. *In vivo* research has demonstrated that knocking out the *LOXL1-AS1* gene inhibits BC metastasis.

Regarding the underlying mechanism, LOXL1-AS1 functions as a molecular sponge for miR-708-5p, significantly increasing NF-κB activity. LOXL1-AS1 can also interact with EZH2 protein, enhancing EZH2's transcriptional repression of miR-708-5p. LOXL1-AS1 and miR-708-5p exhibit a negative correlation in BC specimens.

Upregulation of LOXL1-AS1 induces NF-κB activation via miR-708-5p, promoting BC invasion and metastasis.

Li *et al.* (35) discovered that LOXL1-AS1 is highly expressed in BC tissues and cells, whereas miR-143-3p expression is downregulated. *in vitro* studies have shown that knocking down the *LOXL1-AS1* gene inhibits BC cell proliferation, promotes apoptosis, and reduces cell migration and invasion capabilities. LOXL1-AS1 modulates BC cell proliferation, migration, invasion, and apoptosis through the regulation of miR-143-3p, offering a novel therapeutic target for BC patients.

LOXL1-AS1 and brain lower grade glioma (LGG)

LGG are the most prevalent primary brain tumours, representing 81% of malignant brain tumours (36). Despite the development of various surgeries and medicines over the years, the prognosis of LGG patients remains poor. Krusnauskas *et al.* (37) found that LOXL1-AS1 is significantly associated with LGG grade and survival. Yi *et al.* (38) revealed that the T-cell intracellular antigen 1-related protein (*TIAR*) gene is downregulated in LGG cells and tissues, while LOXL1-AS1 is up-regulated. Furthermore, TIAR downregulates the expression of LOXL1-AS1 by destabilizing it. LOXL1-AS1 acts as a miRNA sponge for miR-374b-5p, and the downregulation of LOXL1-AS1 inhibits cell proliferation, migration, invasion, and vasculogenic mimicry (VM). Additionally, overexpressed miR-374b-5p suppresses malignant biological behaviours and VM in LGG cells by modifying MMP14. The study demonstrates that TIAR, in conjunction with LOXL1-AS1, regulates VM in LGG through the miR-374b-5p/MMP14 axis, providing new therapeutic targets for LGG treatment.

Wang *et al.* (39) found that LOXL1-AS1 is upregulated in glioblastoma multiforme (GBM). Silencing LOXL1-AS1 directly downregulates expression of the NF-κB transcription factor family member RELB and inhibits cell proliferation. Moreover, patients with high LOXL1-AS1 expression have shorter overall survival. Liu *et al.* (40) demonstrated that LOXL1-AS1 is prominently associated with GBM prognosis. Therefore, LOXL1-AS1 can serve as an adverse prognostic indicator for GBM patients in a clinical context and may offer more insight into lncRNA-based LGG treatment.

Moreover, Gao *et al.* (41) discovered that LOXL1-AS1 is significantly upregulated in medulloblastoma (MB) tissues and cells compared to non-tumour tissues and cells. Knocking down the *LOXL1-AS1* gene can significantly inhibit the viability and colony-forming ability of D283 cells and D341 cells, induce G2/M phase arrest in the cell cycle, and lead to apoptosis. Similarly, knocking down LOXL1-AS1 in a human MB xenograft model significantly inhibits tumour growth and promotes tumour cell apoptosis. These results suggest that LOXL1-AS1 promotes the proliferation of MB cells and facilitates tumour metastasis by activating the PI3K-AKT pathway, and knocking down *LOXL1-AS1* gene expression could be a potential therapeutic strategy for MB.

LOXL1-AS1 and osteosarcoma (OS)

OS is one of the most common malignant bone tumours in children and young adults. Some studies found that LOXL1-AS1 expression levels in OS tissues and cell lines were significantly higher than those in normal bone tissues and normal osteoblast cell lines (42,43). Furthermore, high expression of LOXL1-AS1 was associated with Enneking stage, tumour size, distant metastasis, histological grade, and overall survival time of OS patients. High expression of LOXL1-AS1 was identified as an independent prognostic factor for poor overall survival in OS patients. Functional gene loss studies have shown that knocking down the *LOXL1-AS1* gene *in vitro* significantly inhibits the proliferation, migration, and invasion of OS cells by suppressing the PI3K-AKT pathway. In summary, LOXL1-AS1 is a novel biomarker for predicting clinical progression and poor prognosis in OS, functioning as an oncogenic lncRNA that regulates cell proliferation, cell cycle, migration, and invasion.

Other tumours

Thymomas (THYMs) often lack specific symptoms in the early stages, leading to late-stage diagnosis in many patients. Wang *et al.* (44) discovered that LOXL1-AS1 and HSPA9 are highly expressed in THYMs. Elevated expression of the *LOXL1-AS1* and *HSPA9* genes is significantly associated with poor prognosis in thymic epithelial tumour patients. Additionally, miR-525-5p exhibits low expression in THYMs. MiR-525-5p inhibits *HSPA9* gene expression by targeting the 3'UTR of the *HSPA9* gene. In summary, LOXL1-AS1 acts as a molecular sponge, targeting miR-525-5p to promote *HSPA9* gene expression, thereby facilitating the growth and invasion of THYMs while suppressing apoptosis. This suggests that LOXL1-AS1/miR-525-5p/HSPA9 may serve as early diagnostic

biomarkers for THYMs and potentially become new targets for their treatment. Additionally, retinoblastoma (RB) is a blinding and potentially fatal disease that is the most common eye cancer of childhood. Wu *et al.* (45) discovered that LOXL1-AS1 is overexpressed in RB tissues and cells. Moreover, the lncRNA LOXL1-AS1 promotes the proliferation and invasion and inhibits the apoptosis of RB by regulating the MAPK signalling pathway and might be expected to be a novel basis for clinical diagnosis and treatment. In addition, choriocarcinoma (CC), as a type of gestational trophoblastic disease, is a malignant and aggressive cancer of trophoblastic cells in uterus. Zhang *et al.* (46) found that the low expression of LOXL1-AS1 inhibits the proliferation and migration of human CC cells, which might be related to miR-515-5p and NF-κB signaling pathways.

Conclusions

LOXL1-AS1 is a newly discovered lncRNA in recent years, and it is overexpressed as an oncogene in various human cancers. High expression of LOXL1-AS1 in various cancers predicts poorer overall survival, distant metastasis, and lymph node metastasis. LOXL1-AS1 is closely associated with the clinical pathological features and prognosis of cancer patients. These findings suggest that LOXL1-AS1 could serve as a novel biomarker for clinical cancer diagnosis and prognosis evaluation. Previous research indicates that LOXL1-AS1 acts as a ceRNA, binding to microRNAs (miRs) to regulate downstream target genes and exert its oncogenic effects. Moreover, downregulation of LOXL1-AS1 can inhibit cancer cell proliferation and migration, promote apoptosis, and reduce chemotherapy resistance. Therefore, LOXL1-AS1 holds promise as a new therapeutic target for cancer. However, the precise molecular regulatory mechanisms upstream and downstream of LOXL1-AS1 in different human cancer types remain to be fully elucidated. Additionally, the expression levels and stability of LOXL1-AS1 in human whole blood, serum, plasma, or other bodily fluid samples have not been revealed.

Furthermore, the biological activities of LOXL1-AS1 may indeed be relevant to its functional role in cancer biology. Schmitt *et al.* (47) demonstrated that LOXL1-AS1 can selectively bind to the mRNA processing protein, hnRNPL. Both components of this complex are crucial for the regulation of global gene expression in ocular cells, making LOXL1-AS1 a primary target in the study of pseudoexfoliation (PEX) syndrome and glaucoma. Therefore, this suggests that LOXL1-AS1 can also directly influence transcription by recruiting proteins and transcription factors, rather than solely functioning as a miRNA sponge. Wu *et al.* have indicated that LncRNA LOXL1-AS1 promotes proliferation, invasion, and inhibits apoptosis of RB by regulating the MAPK signaling pathway, potentially providing a novel basis for clinical diagnosis and treatment (45). He *et al.* (48) investigated the role of LOXL1-AS1 as a key epigenetic regulator in cardiomyocyte pyroptosis during myocardial ischemia and reperfusion injury (MIRI), proposing the LOXL1-AS1/miR-761/PTEN pathway as a novel signaling pathway affecting pyroptosis in MIRI. Therefore, LOXL1-AS1 also plays a crucial role in other systems, and this function may be related to its role in cancer, although not yet clearly understood. Future research can further explore the relationship between the biological activities of LOXL1-AS1 in other systems and its functional role in cancer, providing a reference basis for clinical diagnosis and treatment.

In conclusion, these limitations pose challenges to its clinical application and highlight the need for further in-depth exploration to reveal more potential biological functions of LOXL1-AS1. LOXL1-AS1 may emerge as a novel molecular biomarker for cancer diagnosis and treatment in humans, and it may also serve as an independent prognostic indicator.

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Footnote

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