Review Article

Potential role of lncRNA LOXL1-AS1 in human cancer development: a narrative review

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Background and Objective: Long non-coding RNAs (lncRNAs) are a group of non-coding RNAs consisting of more than 200 nucleotides that are widely involved in various physiological and pathobiological processes in the body. LncRNA plays a crucial role in tumorigenesis and development with its unique functions, such as playing a role in a variety of biological processes of malignant tumors as a cancer-promoting factor or a cancer-suppressor factor. Lysyl oxidase-like protein 1-antisense RNA1 (LOXL1-AS1) is a novel functional lncRNA recently reported. This article reviews the current findings on the role of LOXL1-AS1 in cancer, and discusses the potential clinical significance and application prospects, in order to provide a theoretical basis and reference for the clinical diagnosis, treatment and screening of prognostic markers for malignant tumors.

Methods: The PubMed and Embase databases were searched using the keywords "cancer" or "tumor" or "neoplasm" and "LOXL1-AS1" for publications from 2018 to the present. The English literature was searched, with a focus on relevant articles. These articles validated the role and mechanism of LOXL1-AS1 in different cancers.

Key Content and Findings: LOXL1-AS1 is a recently reported novel lncRNA, which is abnormally expressed and upregulated in more than ten cancers, and is positively correlated with adverse clinical features and poor prognosis in cancer patients. LOXL1-AS1 competently binds to a variety of microRNAs to regulate the expression of downstream target genes and regulate related signaling pathways, including proliferation, migration, invasion and inhibition of malignant biological behaviors such as apoptosis.

Conclusions: LOXL1-AS1 is expected to become a novel biomarker for cancer diagnosis and treatment, with great potential as an independent prognostic indicator.

Keywords: Lysyl oxidase-like protein 1-antisense RNA1 (LOXL1-AS1); long non-coding RNA (lncRNA); cancer; biomarker; therapeutic target

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Introduction

Cancer is one of the most intractable public health problems threatening human health worldwide, and despite ongoing efforts to find the most effective cancer treatment, cancer remains the second leading cause of death worldwide (1). This is associated with a variety of causes, including complex inheritance of the genome, mutations in cancer-promoting or cancer-suppressor genes, and tumor microenvironment (TME) instability (2,3). Cancer is a highly heterogeneous disease, which is reflected in different decision-making phenotypes at the transcription and translation levels, such as abnormal proliferation and high aggressiveness (4,5). Compared with timely diagnosis and treatment of cancer, the prolongation of its course is the main reason for the high mortality rate of cancer patients (6,7). Therefore, it is particularly important to find novel potential diagnostic and prognostic biomarkers for early identification of cancer in order to develop cancer treatment strategies and reduce patient mortality (8).

Extensive human genome analysis shows that 90% of eukaryotic genomic DNA is actively transcribed into RNA, but only 2% is actually mRNA that can be encoded for subsequent biological functions of proteins (9-11). This suggests that the entire genome transcription process consists mostly of non-coding RNA (ncRNA) (12). Early studies believed that ncRNAs did not have biological functions, but with the development of high-throughput technology, people's understanding of ncRNAs has gradually deepened, and more and more evidence shows that ncRNAs are by no means unnecessary or functional (8,13,14). Long non-coding RNA (lncRNA) is the most dominant type of ncRNA, named as it is because it is usually of more than 200 nt in length (15). In addition, the amount of lncRNA is huge, and its intracellular content exceeds 70% of the total RNA (16). In recent years, there has been continuous evidence that lncRNA can participate in the regulation of tumor biological development, which is inseparable from lncRNA's ability to mediate a variety of cancer-promoting mechanisms and signaling pathways (17,18). LncRNA can affect chromatin remodeling, gene transcription, protein translation, post-translational processing and modification, thereby changing cell structure, functional status, and participating in tumor cell proliferation, invasion, migration and recurrence (19). Some lncRNAs are known to play a key role in cancer development. Hypoxia is associated with different stages of cancer development, and lncRNA DACT3-AS1 can be induced by HIF-1α in a hypoxic environment to promote hepatocellular carcinoma (HCC) metastasis (20). MCM3AP-AS1 has been identified as a novel oncogenic lncRNA with abnormal expression that accelerates cancer growth levels in cancers such as non-small cell lung cancer (NSCLC), inhibits apoptosis, and accelerates epithelial-mesenchymal transition (EMT) (21). NNT-AS1 is a novel cytoplasmic lncRNA that upregulates expression in most tumors, NNT-AS1 can affect the development of malignant phenotypes such as proliferation, invasion and migration of a variety of tumors, and is associated with chemotherapy resistance (22).

Recently, a multifunctional lncRNA called lysyl oxidase-like protein 1-antisense RNA1 (LOXL1-AS1) has come into the limelight. LOXL1-AS1 has been found to be overexpressed in a wide variety of cancers, in HCC, breast cancer (BC), lung cancer (LC), glioma, renal cell carcinoma (RCC), prostate cancer (PCa), cervical cancer, endometrial cancer, ovarian cancer (OC), pancreatic cancer (PC), gastric cancer (GC), osteosarcoma (OS), colorectal cancer (CRC), esophageal squamous cell carcinoma (ESCC), cholangiocarcinoma (CCA), thymic cancer. In these cancers, abnormally expressed LOXL1-AS1 is often associated with different clinicopathological features and poor survival prognosis. Many *in vivo* and *in vitro* experimental studies have shown that LOXL1-AS1 can bind to miRNA as competitive endogenous RNAs (ceRNAs), that is, the regulatory mechanism of miRNA sponge, targeting a variety of specific genes or signaling pathways, regulating the malignant biological behavior of tumor cells, and promoting tumor growth (23-25) (*Figure 1*). Therefore, LOXL1-AS1 is considered a cancer-promoting molecule with the ability to become a marker for cancer diagnosis and prognosis.

The expression profile, cell function experiments, clinicopathological features and prognosis, and molecular regulatory mechanism of LOXL1-AS1 in tumor clinical samples and cell lines were reviewed to elucidate the regulatory effect and mechanism of LOXL1-AS1 in carcinogenesis. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1450/rc).

Methods

Relevant literature was searched in PubMed and Embase databases using the keywords "cancer" or "tumor" or "neoplasm" and "LOXL1-AS1", and screening criteria were

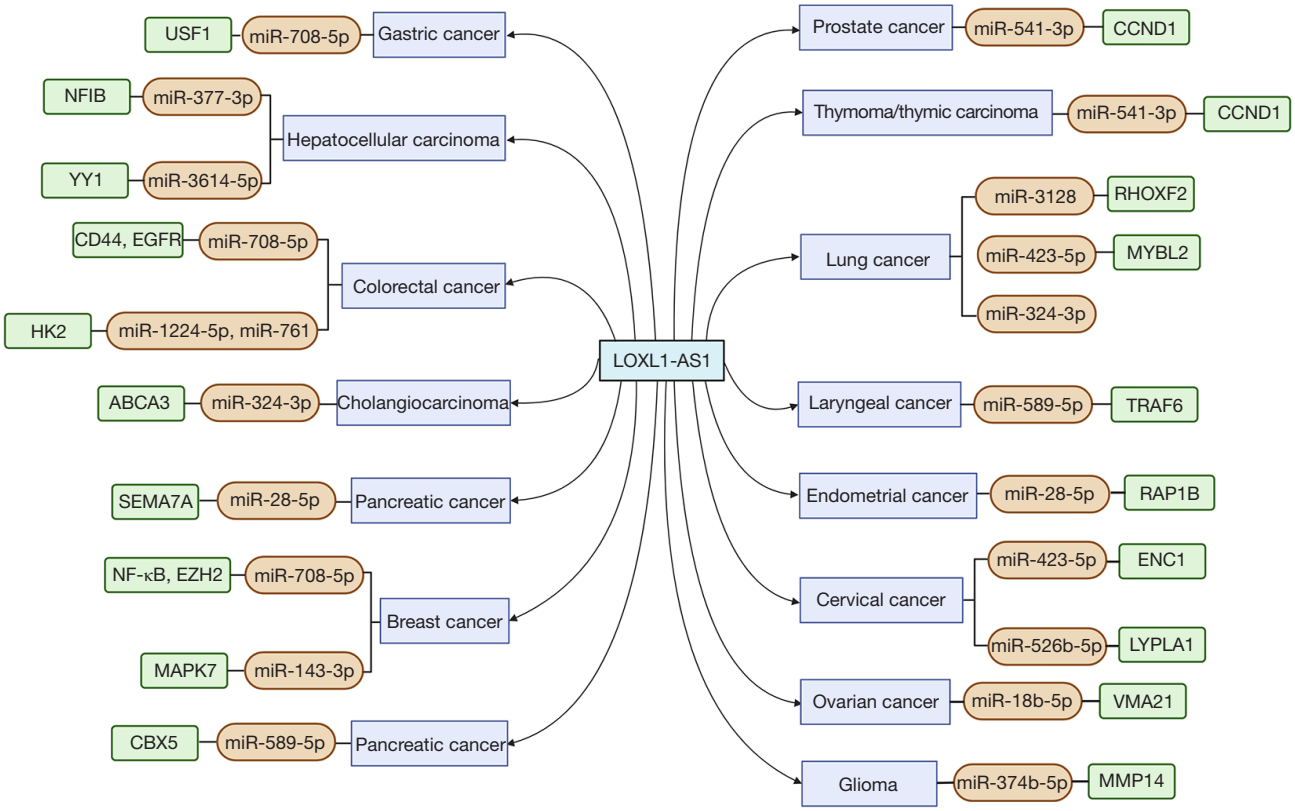

Figure 1 The ceRNA regulatory network of lncRNA LOXL1-AS1. LOXL1-AS1, lysyl oxidase-like protein 1-antisense RNA1.

English-language literature from 2018 to 2023, with a focus on the inclusion of research-based literature on LOXL1-AS1 in different cancers and the exclusion of irrelevant review articles. Details of the search are shown in *Table 1*.

Overview of findings

Role of LOXL1-AS1 in different cancers

Several studies have reported abnormal expression of LOXL1-AS1 in a variety of human cancers, such as HCC, BC, NSCLC, glioma, RCC, PCa, OC, GC, CRC, ESCC. In addition, studies have shown that high LOXL1-AS1 expression levels are associated with late clinicopathological features (*Table 2*). The various regulatory functions and potential mechanisms of LOXL1-AS1 in the process of tumor progression are shown in *Table 3*.

LOXL1-AS1 in carcinomas

BC

BC is one of the most common malignancies today, and drug resistance, metastasis and recurrence are the main influences that exacerbate the development of a malignant prognosis in BC patients (49,50). Numerous studies have shown that LOXL1-AS1 is overexpressed in various BC cell lines and BC tissues such as MCF7, T47D, MDA-MB-231, MDA-MB-468, BT549 and SKBR-3, the overexpression level of LOXL1-AS1 is positively correlated with Tumor Node Metastasis (TNM) stage and lymph node metastasis of BC patients (26,27). Moreover, LOXL1-AS1 overexpression is able to regulate the phenotype of BC cells, including cell proliferation, migration, invasion, apoptosis and cell cycle (26,27).

GC

GC is the fourth leading cause of cancer deaths, it has become an important global public health security issue (51). Sun *et al.* (28) detected the expression level of LOXL1-AS1 in 84 GC pathological tissues, respectively, and the expression level of LOXL1-AS1 was increased compared with that in normal tissues. LOXL1-AS1 expression levels are also upregulated in MKN-45, AGS, SGC7901, MGC-803 cells. It is worth noting that overexpressed LOXL1-AS1 was significantly associated with poor survival prognosis

Table 1 The search strategy summary

Items	Specification
Date of search	May 1st–June 1st 2023
Databases and other sources searched	PubMed/Embase
Search terms used	((LOXL1-AS1) AND ((cancer) OR (tumor) OR (neoplasm)))
Timeframe	2018–2023
Inclusion and exclusion criteria	Inclusion criteria: Original Articles
	Exclusion criteria: non-English language; Meta-Analyses; non-relevant Review Articles
Selection process	Selection was made by M.T. and Y.R., who screened separately and individually, then pooled and selected the common selected studies

LOXL1-AS1, lysyl oxidase-like protein 1-antisense RNA1.

Table 2 LOXL1-AS1 expression and clinicopathological features in cancers

Type of disease	Expression	Clinical features	Ref
Breast cancer	Upregulate	TNM stage, lymph node metastasis	(26,27)
Gastric cancer	Upregulate	Overall survival, poor prognosis	(28)
Endometrial cancer	Upregulate	Menstruation, pathologic stage, lymph node metastasis, FIGO stage, overall survival, poor prognosis	(23)
Ovarian cancer	Upregulate	FIGO stage, distant metastasis, overall survival, poor prognosis	(29,30)
Liver cancer	Upregulate		(24,31)
Cervical cancer	Upregulate	TNM stage, distant metastasis, lymph node metastasis, overall survival, poor prognosis	(32,33)
Laryngocarcinoma	Upregulate		(34)
Glioma	Upregulate	Tumor pathological stage, overall survival, poor prognosis	(35-37)
Prostate cancer	Upregulate		(38)
Lung cancer	Upregulate	Tumor pathological stage	(39-41)
Osteosarcoma	Upregulate	Enneking stage, tumor size, distant metastasis, histological grade	(42)
Colorectal cancer	Upregulate	Tumor size, differentiation, TNM stage, lymph node metastasis, liver metastasis, MSI status	(43,44)
Pancreatic cancer	Upregulate		(45)
Esophageal squamous cell carcinoma	Upregulate	Lymph node metastasis	(46)
Renal cancer	Upregulate		(25)
Cholangiocarcinoma	Upregulate	Lymph node infiltration, TNM stage, overall survival, poor prognosis	(47)
Thymoma/thymic carcinoma	Upregulate		(48)

LOXL1-AS1, lysyl oxidase-like protein 1-antisense RNA1; TNM, Tumor Node Metastasis; FIGO, Federation International of Gynecology and Obstetrics; MSI, microsatellite instability.

Table 3 Functions and mechanisms of LOXL1-AS1 in cancers

Disease type	Cell lines	Targets	Pathway	Functions	Ref
Breast cancer	MCF42, MDA-MB-7, MCF7, T47D, MCF65, MDA-MB-231, BT549, and SKBR-3	Mir-708-5p, mir-143-3p, EZH2, MAPK7, and H3K27	NF-κB	Cell proliferation, migration, invasion, apoptosis, and cell cycle	(26,27)
Gastric cancer	MKN-45, SGC7901, MGC-803, AGS	Mir-708-5p, USF1, and SOX2		Cell proliferation, migration, epithelial-mesenchymal transformation, and stemness	(28)
Endometrial cancer	HAC-1A, KLE, Ishikawa, and RL-95-2	Mir-28-5p and RAP1B		Cell proliferation, colony formation, apoptosis, invasion, and migration	(23)
Ovarian cancer	A2780, SKOV3, Caov-3, and OVCAR3	Mir-18b-5p, DOCK4, and VMA21		Cell proliferation, colony formation, invasion, and migration	(29,30)
Liver cancer	Hep-G2, SMMC7721, HCCLM3, Huh-7, and SK-HEP-1	Mir-3614-5p, mir-377-3p, YY1, and NFIB		Cell proliferation, migration, invasion, apoptosis, epithelial-mesenchymal transformation and cell cycle	(24,31)
Cervical cancer	HeLa, SiHa, CaSki, and ME-180	Mir-423-5p, mir-526b-5p, ENC1, LYPLA1, and Ki-67	MEK/ERK	Cell proliferation, migration, invasion, and angiogenesis	(32,33)
Laryngocarcinoma	Tu-177, M4E, SNU-899, SNU-46, and AMC-HN-8	Mir-589-5p and mir-589-5p		Cell proliferation, migration, epithelial-mesenchymal transformation	(34)
Glioma	HEK293T, U87, U251, Daoy, D283, D425, D341, and D458	Mir-374b-5p, MMP14, and RELB	NF-κB, PI3K/AKT, MAPK	Cell proliferation, migration, colony formation, cell cycle, apoptosis, and angiogenesis	(35-37)
Prostate cancer	PC3, DU145, VCap, and 22RV1	Mir-541-3p, and CCND1		Cell proliferation and cell cycle	(38)
Lung cancer	H549, A1299, H1, SPC-A16, H1299, A549, H520, H596, H1975, and SPC-A1	Mir-324-3p, mir-3128, RHOXF2, mir-423-5p, and MYBL2		Cell proliferation, invasion, and epithelial-mesenchymal transformation	(39-41)
Osteosarcoma	MG63, U-2 OS, Saos-2, and HOS			Cell proliferation and invasion	(42)
Colorectal cancer	HCT8, LoVo, SW620, Caco2, and SW1463	Mir-708-5p, mir-1224-5p, mir-761, and HK2	PI3K/AKT	Cell proliferation, migration, invasion, apoptosis, and glycolysis	(43,44)
Pancreatic cancer	SW1990, BXPC-3, PANC-1, and PaCa-2	Mir-28-5p and SEMA7A	CD44/EGFR	Cell proliferation and migration	(45)
Esophageal squamous cell carcinoma	KYSE30 and EC109	Desc1		Cell proliferation, migration, invasion, apoptosis, and cell cycle	(46)
Renal cancer	786-O, A-498, and 769-P	Mir-589-5p and CBX5		Cell proliferation and migration	(25)
Cholangiocarcinoma	RBE, HuCCT1, QBC939, Huh-28, and CCLP1	Mir-324-3p and ABCA3		Cell proliferation, migration and invasion and apoptosis	(47)
Thymoma/thymic carcinoma	Thy0517, Ty-82	Mir-525-5p and HSPA9		Cell migration and apoptosis	(48)

LOXL1-AS1, lysyl oxidase-like protein 1-antisense RNA1.

in GC patients. This study confirmed that LOXL1-AS1 can regulate the proliferation and migration ability of GC cells, promote the process of EMT and upregulate the stem expression of GC cancer stem cells (CSCs) (28).

Endometrial cancer

Endometrial cancer is a malignant tumor originating from the uterus and is one of the most common gynaecological cancers (52). Despite the many clinical treatments currently available for endometrial cancer, patient survival rates are not yet satisfactory (53). One study reported that LOXL1-AS1 expression was upregulated in both pathological tissues and cells (HAC-1A, KLE, Ishikawa, RL-95-2) of endometrial cancer patients (23). In addition, that study showed that overexpression of LOXL1-AS1 was significantly associated with menstruation, pathological stage, lymph node metastasis and Federation International of Gynecology and Obstetrics (FIGO) stage in endometrial cancer patients. Patients with high LOXL1-AS1 expression tend to have a poorer prognosis. LOXL1-AS1 has also been shown to play a role in promoting proliferation, invasion, migration, colony formation and apoptosis of endometrial cancer cells.

OC

OC is the most deadly malignancy of the gynaecological system (54). Xue *et al.* (29) selected tissue samples from 45 OC patients and 4 OC cells for LOXL1-AS1 expression verification, and the results showed that the expression level of LOXL1-AS1 was increased. Prognostic analysis of LOXL1-AS1 showed that patients with high LOXL1-AS1 expression were significantly associated with poorer overall survival. *In vitro* experiments showed that the proliferation, migration and invasion of OC cells such as A2780, SKOV3, Caov-3 and OVCAR3 could be significantly inhibited when LOXL1-AS1 expression was downregulated. Another study showed that patients with epithelial OC had higher levels of LOXL1-AS1 expression and shorter overall survival compared to healthy groups, and that overexpressed LOXL1-AS1 was significantly associated with advanced FIGO staging and positive distant metastasis in OC patients (29).

Liver cancer

Liver cancer is the third leading cause of cancer death worldwide and is a highly aggressive cancer, with HCC being the most common type of primary liver cancer (55). Feng *et al.* and Yu and Dai (24,31) examined the expression levels of LOXL1-AS1 in normal and HCC tissues by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) and showed that LOXL1-AS1 was highly expressed in HCC tissues and was significantly and positively correlated with poor patient prognosis. In addition, the experimenters focused on the regulatory role of LOXL1-AS1 on the malignant phenotype of HCC cells, such as LOXL1-AS1 could promote the proliferation, migration and invasion ability of HCCLM1 and SK-HEP-3 cells, and inhibit the apoptotic process. Similarly, Liu *et al.* (56) showed that the expression level of LOXL1-AS1 was upregulated in HCC tissues and HCC cells. When LOXL1-AS1 expression was inhibited, the expression levels of cell cycle-related proteins CDC2, CDC25A, and Cyclin B1 were also inhibited, suggesting that LOXL1-AS1 can also regulate the cell cycle progression of HCC cells by inhibiting cell cycle proteins. In addition, *in vivo* experiments showed that knockdown of LOXL1-AS1 significantly suppressed the tumor growth trend in nude mice.

Cervical cancer

As the fourth largest type of malignant tumor in women, cervical cancer has a huge potential threat to women's health (57). LOXL1-AS1 has been shown to be overexpressed in a variety of cervical cancer cells and cervical cancer tissues, acting as a cancer-promoting gene and predicting poor prognosis (32). However, LOXL1-AS1 has also been reported to have low expression levels in cervical squamous cell carcinoma (CSCC) tissues (58). Overexpression of LOXL1-AS1 is strongly associated with proliferation, invasion, migration, and tumor-associated angiogenesis of cervical cancer cells (33). Therefore, LOXL1-AS1 is a novel disease and prognostic marker for cervical cancer.

Laryngocarcinoma

Laryngocarcinoma is a common malignancy of the head and neck. Although there are various clinical treatments for early laryngeal cancer, including surgery, radiotherapy, chemotherapy, etc., the prognosis of patients with advanced laryngeal cancer is still worrying, and the 5-year survival rate is less than 50% (59). A study showed that LOXL1-AS1 expression is upregulated in laryngeal cancer cells such as Tu-177, M4E, SNU-899, SNU-46, and AMC-HN-8, and it is proved that LOXL1-AS1 can enhance the proliferation and migration ability of laryngeal cancer cells and promote the EMT process (34). At the same time, *in vivo* experiments have also shown that overexpressed LOXL1-AS1 can accelerate the tumor formation rate of laryngeal cancer and promote tumor development (34).

PCa

PCa is a malignant tumor that seriously threatens men's health (60). Studies have reported that LOXL1-AS1 can be overexpressed in a variety of PCa cells, including PC3,

DU145, VCap, and 22RV1 (61). *In vitro* experiments have shown that when LOXL1-AS1 expression is inhibited, its cell proliferation ability is also inhibited. And cell cycle-related protein expression is downregulated, thereby inhibiting cell cycle progression (38).

LC

LC remains the leading cause of cancer-related death worldwide, with about 20,000 new patients diagnosed with LC each year and dying within 75 years (62,63). Several studies have shown that the expression level of LOXL1-AS1 in various LC cell lines and LC tissues is upregulated, and this expression degree is more correlated with tumor advanced and metastasis (39,40). In addition, the results of experiments involving cell function showed that LOXL1-AS1 has the function of a cancer-promoting gene, which can enhance the proliferation and aggressiveness of LC cells and induce the process of EMT (41). When LOXL1-AS1 expression is inhibited, LC cells are more likely to undergo apoptosis (40). Therefore, LOXL1-AS1 can accelerate the tumor progression of LC.

CRC

CRC is one of the most common gastrointestinal malignancies in humans, accounting for approximately 10% of global cancer incidence and mortality (64). In recent years, studies have shown that LOXL1-AS1 is highly expressed in HCT8, LoVo, SW620, Caco2, SW1468, SW480 CRC cells. It is also overexpressed in CRC tissues and is associated with adverse clinicopathological features such as tumor size, differentiation, TNM stage, and lymph node metastasis. Further functional experiments showed that LOXL1-AS1 could promote the progression of CRC by enhancing the biological behaviors of CRC cells such as proliferation, migration, invasion, colony formation, and inhibition of apoptosis (43,44). The cancer-promoting effect of LOXL1-AS1 has also been verified *in vivo* experiments, and the tumorigenesis rate of xenograft models slows down after LOXL1-AS1 is inhibited (44).

PC

PC is one of the deadliest cancers in the world, with a lack of early symptoms, high metastasis and complex drug resistance as the reasons for its high level of malignancy (65). LOXL1-AS1 is a novel cancer-promoting functional molecule found to be highly expressed in PC tissues and PC cells (SW1990, BXPC-3, PANC-1, PaCa-2). LOXL1-AS1 promotes the proliferation and migration of PC cells through a series of complex regulatory mechanisms (45).

Esophageal cancer (EC)

EC is one of the diseases that threatens the health and safety of people around the world. ESCC and esophageal adenocarcinoma (EAC) are its two main types, of which ESCC is the main type of death from EC (66). Li *et al.* (46) obtained 45 pairs of ESCC and normal paracancerous tissue samples to detect LOXL1-AS1 expression levels. The results showed that LOXL1-AS1 was expressed at a high level, especially in ESCC samples with lymph node metastasis, and was also associated with poor survival in patients. In addition, LOXL1-AS1 has been shown to have a positive effect on the development of ESCC.

RCC

RCC is a malignant tumor that originates in the renal parenchymal urinary tubular epithelial system, and is the most common and highly malignant tumor of the urinary system (67). LOXL1-AS1 has been shown to be a cancer-promoting molecule with high expression in RCC species, significantly more expressed in RCC tissues and RCC cells such as 786-O, A-498 and 769-P (25). When LOXL1-AS1 is silenced, the proliferation and migration ability of RCC cells is significantly inhibited, so LOXL1-AS1 has strong carcinogenicity for RCC (25).

CCA

As one of the hepatobiliary malignant tumors, CCA has a health threat that should not be underestimated, and the 5-year prognosis is still not ideal (68). LOXL1-AS1 expression has been found to be upregulated in CCA cells. Overexpression of LOXL1-AS1 was strongly associated with shorter survival, advanced TNM stage, and lymph node metastasis. Cell experiments on RBE, HuCCT1, QBC939, Huh-28 and CCLP1 showed that overexpression of LOXL1-AS1 was also associated with enhancing tumor cell proliferation, migration and invasion, and weakening the apoptosis process (47).

Thymoma/thymic carcinoma

Thymic epithelial tumors (TETs) mainly refer to thymomas that originate from thymic epithelial cells, with the most malignant subtype being thymic carcinoma. Tissue expression verification from 42 cases of thymoma and 28 cases of thymic carcinoma found that LOXL1-AS1 was highly expressed in thymoma/thymic carcinoma, and its expression level was positively correlated with the poor prognosis of patients, and LOXL1-AS1 could accelerate the malignant development of thymoma/thymic carcinoma (48).

LOXL1-AS1 in sarcomas

OS

OS is a primary bone tumor that tends to occur in adolescents and children, accounting for 1/5 of all primary

bone tumors (69). Chen *et al.* (42) used a multicenter research method to obtain different bone tumor tissue samples from two regions to detect the expression trend of LOXL1-AS1 in OS. The expression level and functional role of LOXL1-AS1 in several OS cells were observed *in vitro* experiments. The above results showed that the expression of LOXL1-AS1 was upregulated in OS and could promote malignant functions such as proliferation and migration. Overexpression of LOXL1-AS1 was significantly positively correlated with poor OS levels, and also significantly correlated with clinicopathological features such as enneking stage, tumor size, distant metastasis, and histological grade.

LOXL1-AS1 in other solid tumors

Glioma

Glioma is one of the most common malignancies of the nervous system, and glioblastoma is the most lethal and recurrent of these, accounting for 57% of all gliomas (70). There are currently limited effective treatments for gliomas, so finding effective glioma biomarkers is a potential treatment (71). Yi *et al.* (35) showed that LOXL1-AS1 is highly expressed in glioma tissue and a variety of glioma cells. LOXL1-AS1 acts as a prognostic marker for gliomas and functions as a cancer-promoting gene (72). Notably, LOXL1-AS1 has been shown to regulate angiogenesis in gliomas (35). Medulloblastoma is the most malignant glioma in the skull, mainly in children under 14 years of age (73). It has been noted that LOXL1-AS1 is also overexpressed in medulloblastoma tissues and is associated with the degree of advanced malignancy of tumors (37). LOXL1-AS1 is also a key mediator to mobilize medulloblastoma proliferation and migration, while affecting apoptosis and cell cycle progression. When LOXL1-AS1 in the medulloblastoma xenograft model was silenced, tumor growth was also significantly restricted (37). Retinoblasts are intraocular malignancies that originate from glial cells and occur much more in children than in adults (74). Wu *et al.* (36) confirmed that LOXL1-AS1 is highly expressed in retinoblast tissues and cells, has significant carcinogenicity, can promote the proliferation and migration of retinoblasts and inhibit apoptosis.

Mechanism of LOXL1-AS1 regulation of tumor development

As a newly discovered oncogene, LOXL1-AS1 has been reported to be widely involved in the mediation of key biological processes such as proliferation, invasion, migration, and apoptosis of various types of cancer cells. Here, we mainly provide current understanding of the main biological functions and corresponding molecular mechanisms of LOXL1-AS1. *Figure 2* shows the mechanism by which LOXL1-AS1 mediates different signaling pathways to accelerate the development of multiple cancers.

LOXL1-AS1 regulates the proliferation and apoptosis of tumor cells

A variety of malignant behaviors such as abnormal proliferation, migration and invasion of tumor cells are the main causes of death. LOXL1-AS1 has been shown to modulate the biological phenotypes of different tumors through multiple mechanisms. There is multiple evidence showing that LOXL1-AS1 can participate in the regulation of proliferation and apoptosis during the development of a variety of cancers. In GC cells, miR-708-5p activates the proproliferative effect of lncRNA LOXL1-AS1 by upregulating USF1 (28). Another study showed that overexpression of LOXL1-AS1 could enhance the proliferation of MCF-7 and MDA-MB-231, while inhibiting apoptosis by upregulating the expression of Bax and caspase-3 and downregulating the expression of Bcl-2 (27). A study showed that compared with ordinary PCa cells, LOXL1-AS1 can be underexpressed in doxorubicin-resistant PCa cell line DU-145, and epidermal growth factor receptor (EGFR) expression is down-regulated, while miR-let-7a-5p expression is up-regulated. Further experiments showed that upregulation of LOXL1-AS1 could promote the proliferation of DOX/DU-145 cells, and silence of LOXL1-AS1 gene significantly inhibited the growth level of PCa cells *in vivo*. The LOXL1-AS1/miR-let-7a-5p/EGFR axis significantly affected the proliferation and apoptosis of the drug-resistant strain DU-145 in PCa, which provides a potential treatment strategy for patients with drug-resistant PCa (61). In HCC cells, LOXL1-AS1 can upregulate YY1 expression through sponge miR-3614-5p, exacerbating the malignant behavior of HCC. Specifically, overexpressed YY1 transcription factor (YY1 TF) can completely reverse the weakening of cell proliferation capacity and apoptosis activity caused by LOXL1-AS1 inhibition (24). One study showed that overexpressed LOXL1-AS1 is an important cancer-promoting factor in CRC, and LOXL1-AS1 can promote tumor cell proliferation and inhibit apoptosis by regulating the miR-1224-5p/miR-761/HK2 signaling axis (24). Similarly, there is evidence showing that LOXL1-AS1 can

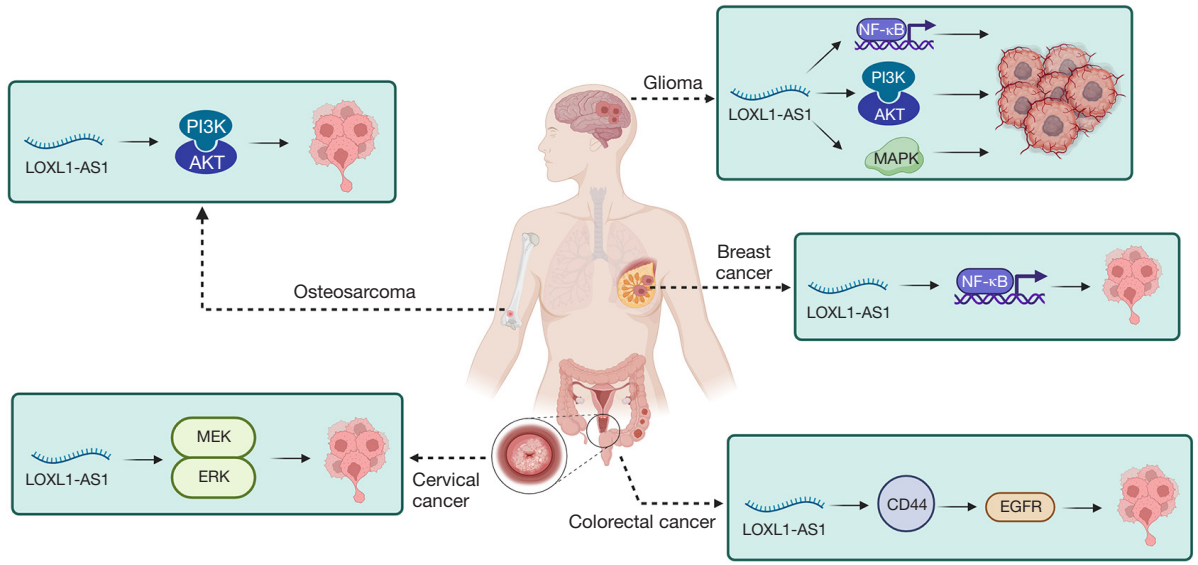

Figure 2 Relevant molecular mechanisms of LOXL1-AS1 during proliferation, invasion, and migration of cancer cells. In gliomas, LOXL1-AS1 enhances tumor cell proliferation, migration, and invasion by regulating NF-κB, PI3K-AKT, and MAPK pathways. In breast cancer, LOXL1-AS1 mediates the NF-κB pathway to enhance tumor cell proliferation and invasion. In colorectal cancer, LOXL1-AS1 enhances tumor cell proliferation, migration and invasion by upregulating the CD44/EGFR pathway. In colorectal cancer, LOXL1-AS1 mediates the MEK/ERK pathway to exacerbate the proliferation and migration capacity of tumor cells. LOXL1-AS1 enhances the proliferation, invasion and migration capacity of osteosarcoma cells by upregulating PI3K/AKT pathway expression. LOXL1-AS1, lysyl oxidase-like protein 1-antisense RNA1.

act as ceRNA of miR-324-3p to upregulate the expression of ATP binding cassette subfamily A member 3 (ABCA3) by spongylating miR-324-3p, thereby promoting the proliferation of CCA cells such as RBE and CCLP1 and attenuating apoptosis (47). In addition, Li *et al.* (46) found that in ESCC cells, the expression level of LOXL1-AS1 had a strong positive correlation with the proliferation ability of ESCC cells, and further studies showed that when LOXL1-AS1 was silenced, the apoptosis program of ESCC cells was significantly induced. One previous study showed that LOXL1-AS1 expression is upregulated in glioblastoma, and silence LOXL1-AS1 directly downregulates the expression of RELB, a member of the nuclear factor kappa-B (NF-κB) TF family, and can inhibit tumor cell proliferation (72). At the same time, another study has also proposed that when LOXL1-AS1 expression is down-regulated, it can significantly inhibit the viability and colony formation ability of D283 and D341 cells, causing G2/M phase blockade and inducing apoptosis with blastoma cells (37). For thymoma/thymic carcinoma, LOXL1-AS1 has been shown to inhibit the apoptosis process of thymoma and thymic carcinoma by targeting miR-525-5p (48).

LOXL1-AS1 regulates invasion and migration of tumor cells

The spread of tumor cells is the most dangerous process in the development of tumors. When tumor cells form clones in distant organs, they often cause serious damage to the body (75,76). Therefore, the invasion and migration of tumor cells is still one of the key targets of cancer treatment (77). Dong *et al.* (26) found through *in vitro* research that overexpression of LOXL1-AS1 can enhance the migration and invasion ability of BC cells, while knockdown LOXL1-AS1 reduces the migration and invasion ability of BC cells. Further *in vivo* studies have shown that knocking out the LOXL1-AS1 gene inhibits BC cell metastasis. Zhang *et al.* (32) showed that overexpression of LOXL1-AS1 in cell carcinoma (CC) tissues and cells can promote its malignant phenotype of invasion and migration. Another study pointed out that the expression level of LOXL1-AS1 in CSCC is down-regulated, which leads to the downregulation of Ras homologous family member B (*RHOB*) gene expression, and RHOB can be used as a direct target for miR-21, and RHOB expression in CSCC cells is immediately downregulated after miR-21 overexpression.

Therefore, LOXL1-AS1 may upregulate RHOB by modulating miR-21, thereby promoting invasion and migration of CSCC cells (58). In addition, LOXL1-AS1 has also been observed to be overexpressed in OS tissues and cell lines, which enhances the invasion and migration capacity of OS cells by activating the PI3K-AKT pathway (42). Similarly, LOXLI-AS1 can also promote the invasion and migration of cells of various types of cancer including pancreatic, HCC, RCC, CC, etc. (24,25,33,42).

LOXL1-AS1 regulates EMT progression and cell cycle in tumor cells

EMT is recognized as an important link affecting tumorigenesis and development (78,79). Its progression is closely related to the activation and expression of many regulatory factors or signaling pathways, such as transforming growth factor-β (TGF-β), induced EMT TFs, WNT/β-catenin, etc. This process weakens the epithelial characteristics of tumor cells, and tends to the expression of mesenchymal cell phenotypic genes, reconstructs the cytoskeleton and cell shape, and ultimately enhances the migration and invasion ability of tumor cells (80-83). The cell cycle is a highly regulated process that promotes cell growth, replication of genetic material, and cell division, but when overactivated, its mechanisms are often a trigger for tumor development (84-86). In recent years, LOXL1-AS1 has been found to play an important role in regulating EMT and cell cycle processes in a variety of cancers. In GC, when LOXL1-AS1 expression is downregulated, the EMT process is inhibited, and the western blot results show up-regulation of E-cadherin expression and down-regulation of Vimentin expression (28). Yu and Dai (31) found that low-expression LOXL1-AS1 could upregulate E-cadherin expression and down-regulate N-cadherin in SK-HEP-1 and Hep3B hepatoma cells, so overexpressed LOXL1-AS1 could promote the EMT process of hepatoma cells. In another study on hepatoma cell cycle analysis, LOXL1-AS1 was found to significantly induce G1/G2 phase arrest in hepatoma cells at low levels, which is attributed to inhibition of CDC25, CDC1A, and cyclin B expression (56). In NSCLC, overexpressed LOXL1-AS1 upregulates N-cadherin and Vimentin expression by regulating miR-324-3p, inducing EMT occurrence in NSCLC cells. At the same time, it increases cyclin D1 expression levels (41). LOXL1-AS1 has also been shown to promote the progression of EMT in laryngeal cancer cells (34). In addition, when LOXL1-AS1 expression in PCa cells is inhibited, it will lead to a decrease in the expression of CCND1 and a hindered cell cycle progression (38). A study has shown that knocking down the expression level of LOXL1-AS1 in ESCC cells can increase the percentage of G1 phase in the ESCC cell cycle, while reducing the proportion of S phase, causing cell cycle arrest (46). In addition, LOXL1-AS1 has been shown to have the ability to regulate cell cycle progression in BC and reticuloblastoma (27,36).

LOLX1-AS1 as a novel cancer diagnostic and prognostic marker

Cancer markers are of high clinical value for understanding and controlling the development of tumor malignancy, they are key to the discovery and development of novel cancer therapies, and they are a key element in clinical practice (87-89). Cancer markers can be categorized as predictive, diagnostic, and prognostic depending on the application. Accurate diagnostic and prognostic markers are not only clinically important for the detection of early-stage tumors, but also for predicting tumor recurrence or progression (90,91). Numerous tumor-related studies have pointed out that LOXL1-AS1 is generally overexpressed in cancer tissues, which can distinguish tumor tissues from normal tissues more specifically, making it have obvious advantages in early diagnosis of tumors (26,28,30).

In addition, overexpression of LOXL1-AS1 is strongly associated with more advanced tumor stage or grade, early lymph node metastasis, tumor size, and adverse overall survival, which provides strong evidence for the prognostic predictive power of LOXL1-AS1 in a variety of cancers, such as GC, endometrial cancer, RCC, glioma, and CCA (23,28,32,47). Therefore, LOXL1-AS1 combined with related clinicopathological features can be used as independent prognostic indicators for multiple cancer types.

LOXL1-AS1 as a potential cancer therapeutic target

LncRNAs have been pointed out in the important role of lncRNAs in the development of cancer, and they can be used as biomarkers of cancer. Recently, lncRNAs called LOXL1-AS1 have been active in the field of view of targeted cancer therapy, which is involved in the growth and development of a variety of cancers by regulating multiple mechanisms, including promoting tumor cell proliferation, invasion, migration, colony formation, EMT progression, cell cycle, stemness characteristics, tumor-associated angiogenesis, and inhibition of apoptosis. In addition, a series of studies exploring the molecular mechanism of LOXL1-AS1 have

confirmed that LOXL1-AS1 acts as a tumor promoter and cancer-promoting functional molecule by regulating the activity of key target genes and influencing multiple important signaling pathways, which makes it a potential therapeutic target for many cancers, including PCa, HCC, BC, CRC and NSCLC (24,27,38,39,43). Therefore, given the multiple biological functions of LOXL1-AS1, it is necessary to further explore its cancer-promoting mechanism to better move towards the new stage of tumor targeted therapy.

Discussion

LOXL1-AS1 is a novel lncRNA discovered in recent years, which is overexpressed as a cancer-promoting gene in many types of human tumors. LOXL1-AS1 affects a variety of tumor biological functions and is closely related to the clinicopathological features and poor prognosis of cancer patients, suggesting that LOXL1-AS1 can be used as a new marker for clinical diagnosis and prognosis assessment of cancer. First, LOXL1-AS1 can be used as ceRNA to bind to a variety of miRNAs to regulate downstream target genes, thereby exerting cancer-promoting effects *in vitro* and *in vivo*. LOXL1-AS1 is involved in a number of biological processes and plays a vital role, including promoting tumor cell proliferation, invasion, migration, cell cycle, EMT, stem characteristics, angiogenesis and inhibition of tumor cell apoptosis, and enhancing chemotherapy resistance, which suggest that targeted inhibition of LOXL1-AS1 may be an effective cancer treatment. Second, overexpressed LOXL1-AS1 is significantly associated with adverse clinicopathological features and poor survival prognosis in a variety of cancers, including tumor stage and grade, tumor size, lymph node metastasis, and poor prognostic outcomes. These associations reveal the potential of LOXL1-AS1 as a prognostic biomarker, and its predictive prognostic ability will confer more positive guidance on novel tumor treatments. Although the biological function of lncRNAs, including LOXL1-AS1, has made some progress, it is still in the pre-clinical application stage and has limitations for clinical practice. Therefore, there is an urgent need to further explore the underlying molecular mechanism by which LOXL1-AS1 regulates malignant biological behavior in tumor cells and is used in cancer treatment. It is worth noting that this study also has some limitations, this study mainly provides information about the role of lncRNA LOXL1-AS1 in different types of cancers, and lacks further expansion by exploring the progression of LOXL1-AS1-targeted miRNAs and genes in a variety of cancers and the correlation with them, which will be our next step.

Conclusions

In conclusion, LOXL1-AS1 is a multifunctional cancer-promoting molecule that holds promise as a novel biomarker for the diagnosis and treatment of cancer and has great potential as an independent prognostic indicator.

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Footnote

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