Review Article

The dual role of LOXL4 in the pathogenesis and development of human malignant tumors: a narrative review

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Background and Objective: Lysyl oxidase-like protein 4 (LOXL4) is a secreted copper-dependent amine oxidase involved in the assembly and maintenance of extracellular matrix (ECM), playing a critical role in ECM formation and repair. Tumor-stroma interactions and ECM dysregulation are closely associated with the mechanisms underlying tumor initiation and progression. LOXL4 is the latest identified member of the lysyl oxidase (LOX) protein family. Currently, there is limited and controversial research on the role of LOXL4 in human malignancies. Its specific regulatory pathways, mechanisms, and roles in the occurrence, development, and treatment of malignancies remain incompletely understood. This article aims to illustrate the primary protein structure and the function of LOXL4 protein, and the relationship between LOXL4 protein and the occurrence and development of human malignant tumors to provide a reference for further clinical research.

Methods: We searched the English literature on LOXL4 in the occurrence and development of various malignant tumors in PubMed and Web of Science. The search keywords include "cancer" "LOXL4" "malignant tumor" "tumorigenesis and development", etc.

Key Content and Findings: LOXL4 is up-regulated in human gastric cancer, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, esophageal carcinoma and colorectal cancer, but down-regulated in human bladder cancer and lung cancer and inhibits tumor growth. There are two conflicting reports of both upregulation and downregulation in hepatocellular carcinoma, suggesting that LOXL4 has a bidirectional effect of promoting or inhibiting cancer in different types of human malignant tumors. We further explore the application prospect of LOXL4 protein in the study of malignant tumors, laying a theoretical foundation for the clinical diagnosis, treatment and screening of prognostic markers of malignant tumors.

Conclusions: LOXL4 exerts a bidirectional regulatory role, either inhibiting or promoting tumors depending on the type of cancer. We still need more research to further confirm the molecular mechanism of LOXL4 in cancer progression.

Keywords: Lysyl oxidase-like protein 4 (LOXL4); extracellular matrix (ECM); malignant tumor; tumorigenesis and development

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Introduction

Lysyl oxidase (LOX) is a secreted copper-dependent amine oxidase that catalyzes the covalent cross-linking of elastin and collagen within the extracellular matrix (ECM) (1). LOX catalyzes the oxidative deamination of lysine and hydroxylysine residues in ECM elastin and collagen proteins, resulting in the formation of cross-linked products through both intra- and intermolecular reactions (2). Intermolecular cross-linking converts soluble monomers of elastin or collagen proteins into insoluble fibers within the ECM. These fibers can resist nonspecific proteinases, preventing the degradation of elastin and the dissolution of collagen proteins and stabilizing the ECM (2,3). The LOX family has five members: LOX and lysyl oxidase-like protein 1–4 (LOXL1–4). LOXL4 is the most recently discovered member. Currently, abnormal expression of LOX family members has been observed in various human malignant tumors (4). Elevated levels of LOX can lead to excessive cross-linking of collagen and elastin in the ECM and may be associated with tumor proliferation, invasion and metastasis. Furthermore, the expression levels of LOXL4 are closely associated with the occurrence and development of various human malignant tumors. LOXL4 exerts a bidirectional regulatory role, either inhibiting or promoting tumors depending on the type of cancer. This article reviews the primary protein structure and function of LOXL4 and its relationship with the development of human malignant tumors and explores the potential application prospects of LOXL4 protein in malignant tumor research. We aim to provide a theoretical foundation and reference for the early diagnosis, treatment, and selection of prognostic markers for cancer patients and populations at high risk 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-23-2003/rc).

Methods

We searched and studied relevant studies on the role of LOXL4 in the occurrence and development of various malignant tumors in the PubMed and Web of Science databases. The keywords used were “cancer”, “LOXL4”, “malignant tumor” and “tumorigenesis and development”. We only screened the English references in the search results for subsequent research. References cited in the literature were retrieved and analyzed from the PubMed database. The information such as search strategy and keywords is described in *Table 1*.

LOXL4: gene and protein structure

The *LOXL4* gene, also known as LOXC, is located on chromosome 10q24.2 and consists of 17 exons. The full-length cDNA of the *LOXL4* gene is 3,597 bp and encodes an open reading frame (ORF) of 2,271 bp (*Figure 1A*). In tumors involving the serosal cavities, LOXL4 is alternatively spliced in an anatomic site-specific manner, producing two splice variants (splv-1 and splv-2) (5). According to Sebban *et al.*’s analysis of the LOXL4 messenger RNA (mRNA) sequence, exons 8 and 9 are translated together to form a functional unit, resulting in the formation of scavenger receptor cysteine-rich 4 (SRCR4) (5) *(Figure 1A)*. The splice variants lack exon 9 (splv-1) or both exon 8 and exon 9 (splv-2), leading to structural changes in SRCR4 and transforming the function of *LOXL4* gene expression products from tumor suppressors to oncogenic factors.

The *LOXL4* gene encodes a protein of 756 amino acids, including a signal peptide of 24 residues with a molecular mass of 84.5 kDa (5). LOXL4 is secreted by vascular smooth muscle cells (VSMCs) and targeted to the ECM by N-terminal signaling peptides. The C-terminal region of the LOXL4 protein contains the LOX domain common to all LOX family proteins, which includes copper-binding sites, lysine tyrosylquinone (LTQ) residue and cytokine receptor-like (CRL) domains, all of which are associated with LOX catalytic activity. In this structural domain of LOXL4, the tyrosine residue (Tyr693) and the lysine residue (Lys638) together form the LTQ cofactor. The CRL domain exhibits a C-X9-C-X-W-X34-C-X13-C motif found in the cytokine receptors of class I (6). No function has been associated with this domain so far. The N-terminal region of LOXL4 contains four SRCR domains rich in cysteine residues (7) (*Figure 1B*). LOXL4, LOXL2 and LOXL3 collectively constitute a subfamily of the LOX protein family characterized by the presence of four SRCR

Table 1 The search strategy summary

Items	Specification
Date of search	September 20th 2022—September 20th 2023
Databases and other sources searched	PubMed, Web of Science
Search terms used	"LOXL4" and ("cancer" or "malignant tumor" or "tumorigenesis and development")
Timeframe	2001–2023
Inclusion criteria	Restricted to articles published in English; without predefined restriction as to the study type
Selection process	Selection process conducted by the author of this study: R.L.

LOXL4, lysyl oxidase-like protein 4.

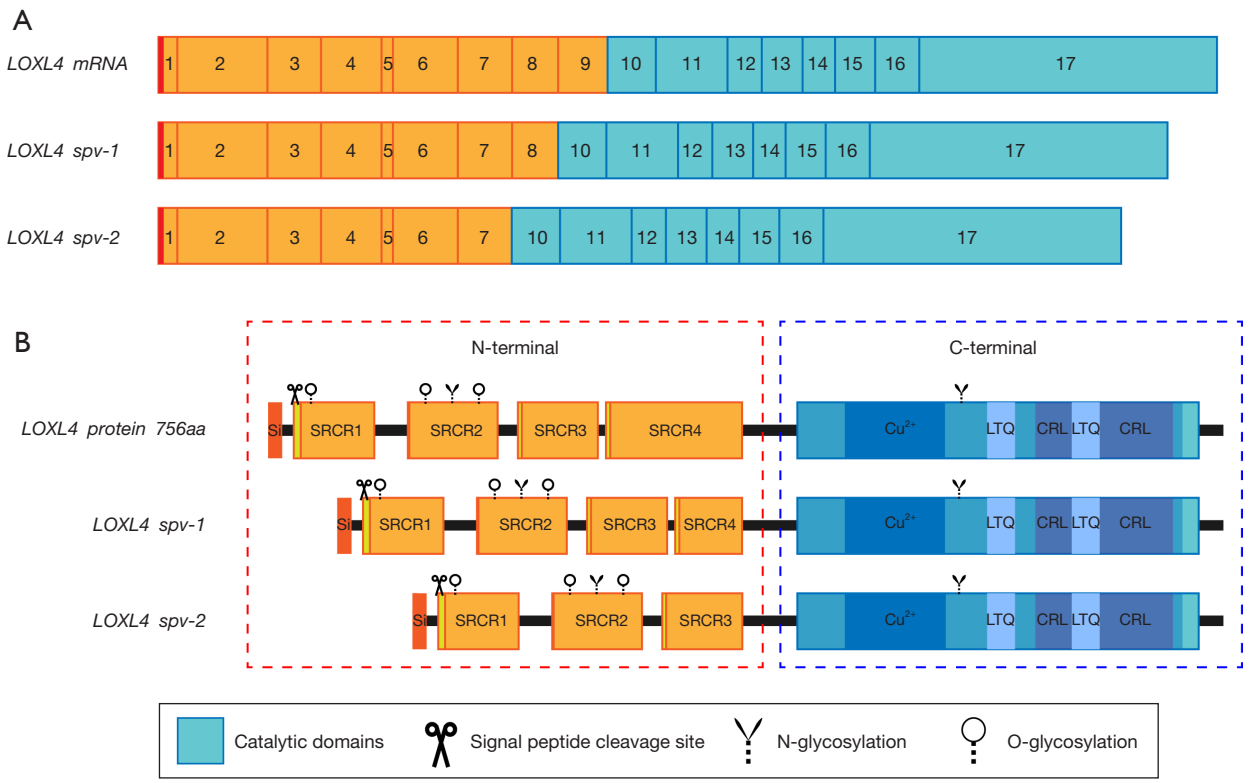

Figure 1 Schematic diagram of the exon structure and open reading frame of the *LOXL4* gene. (A) *LOXL4* exon structure. (B) The primary protein structure of LOXL4. LOXL4, lysyl oxidase-like protein 4; mRNA, messenger RNA; spv-1, splice variants-1; spv-2, splice variants-2; 1-17, exon 1-exon 17; SRCR, scavenger receptor cysteine-rich; LTQ, lysine tyrosylquinone residue; CRL, cytokine receptor-like domain.

domains, whereas LOX and LOXL1 lack SRCR domains but have pro-peptides. SRCR domains are found in various secreted and cell-surface proteins, which appear to regulate cell adhesion and intercellular signaling by participating in protein-protein interactions and also have been suggested to be a catalytic domain that regulates protein deacetylation or deacetylimination (8-10) (*Figure 1B*).

Localization

Tissue-specific expression of LOXL4

As a protein with low expression abundance, the levels of LOXL4 are significantly lower than levels of other LOX-like proteins (LOXLs) in various normal tissues. Northern blot analysis revealed that *LOXL4* mRNA is highly

expressed in the skeletal muscle, pancreas and testes (11). *LOXL4* mRNA is also present in the placenta, lungs, liver, spleen, prostate, ovaries and small intestine, with lower expression levels in the heart, brain, thymus and colon (11,12).

Data on *LOXL4* expression in various human cancers from The Cancer Genome Atlas (TCGA) database were analyzed and presented using the Browser (https://portal.gdc.cancer.gov) (*Figure 2*). Overexpression of *LOXL4* transcripts has been detected in cholangiocarcinoma, skin cutaneous melanoma, pancreatic adenocarcinoma, thyroid carcinoma, uterine carcinosarcoma, lung squamous cell carcinoma, liver hepatocellular carcinoma (LIHC), ovarian serous cystadenocarcinoma, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, lung adenocarcinoma and sarcoma (*Figure 2A*). Furthermore, the cBioPortal database (https://www.cbioportal.org/) indicated that the *LOXL4* gene frequently exhibits mutations and deletions in tumors, with different frequencies of gene mutation, amplification, and deep deletion observed across various cancers. Among them, the *LOXL4* mutation frequency is highest in undifferentiated stomach adenocarcinoma, and the deep deletion frequency is highest in miscellaneous neuroepithelial tumors (*Figure 2B*).

Subcellular localization

In 2001, Maki and Asuncion independently reported the complete complementary DNA (cDNA) sequence of the *LOXL4* gene and demonstrated that LOXL4 is a secreted ECM protein (12). LOXL4 is primarily localized in the cytoplasm and ECM but can also be found in the cell nucleus (11). Recombinant LOXL4 protein can be detected in the culture medium of HT-1080 human fibrosarcoma cells in vitro, indicating that it has not undergone significant protein degradation. LOXL4 was expected to be glycosylated, and three O-glycosylation sites and two N-glycosylation sites are predicted to be located immediately after the signal peptide cleavage site (11). Immunofluorescence experiments have shown that LOXL4 is primarily localized in the cytoplasm but is also found in the nucleus (13). Additionally, LOXL4 was detected in the cell membrane and within the cytoplasm of cultured primary hypopharyngeal HTB-43 carcinoma cells, but no nuclear localization was observed. The SRCR domains of LOXL4 can serve as interaction sites for proteins on the cell membrane, indicating a close association between LOXL4 and the maintenance of cellular membrane function (14). Therefore, the SRCR domains of LOXL4 may be specifically expressed and combined with tumor cell surface, and its catalytic activity may perform multiple functions in tumor cell adhesion and interaction with the ECM (15).

Roles of LOXL4 in the occurrence and progression of human malignant tumors

Selective splicing of the *LOXL4* gene is an indicator of tumor development and progression. The *LOXL4* gene splice mutants splv-1 and splv-2 can promote the metastasis and progression of tumor (5,13). In contrast, the full-length LOXL4 may act as a tumor suppressor. Moreover, Sebban *et al.* (5) suggested that LOXL4 is a splicing target for two oncogenic splicing factors, serine/arginine-rich splicing factor 1 (SRSF1) and heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1). LOXL4 regulates signal transduction pathways through multiple mechanisms and participates in the occurrence and development of various tumors.

At present, there are conflicting findings on the effects of LOXL4 in cancer. These discrepancies might be attributed to differences in tumor cell types and developmental stages, influencing the role of LOXL4 in various cancers and determining whether it acts as a tumor suppressor or a promoter of metastasis. Northern blot hybridization analysis revealed that *LOXL4* mRNA is expressed in various normal tissues, but its expression varies among different malignant tumor cell lines and tumor tissues (11). LOXL4 protein expression is upregulated in stomach cancer, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, esophageal cancer and colorectal cancer (CRC) (16). Conversely, it is downregulated and inhibits tumor growth in human bladder cancer (BCa) and lung cancer, and there are two conflicting reports of both upregulation and downregulation in hepatocellular carcinoma (HCC) (17). Therefore, LOXL4 plays a dual role by promoting or suppressing cancer in different types of human malignant tumors (*Table 2*).

The role of LOXL4 in the occurrence and progression of HCC

HCC is one of the most common human malignancies worldwide and is characterized by high malignancy, rapid progression, and recalcitrance to treatment (18). HCC treatment has long been a significant medical challenge, and its incidence and mortality are expected to rise by 2030 (19). Li *et al.* found that LOXL4 is upregulated in HCC tissues

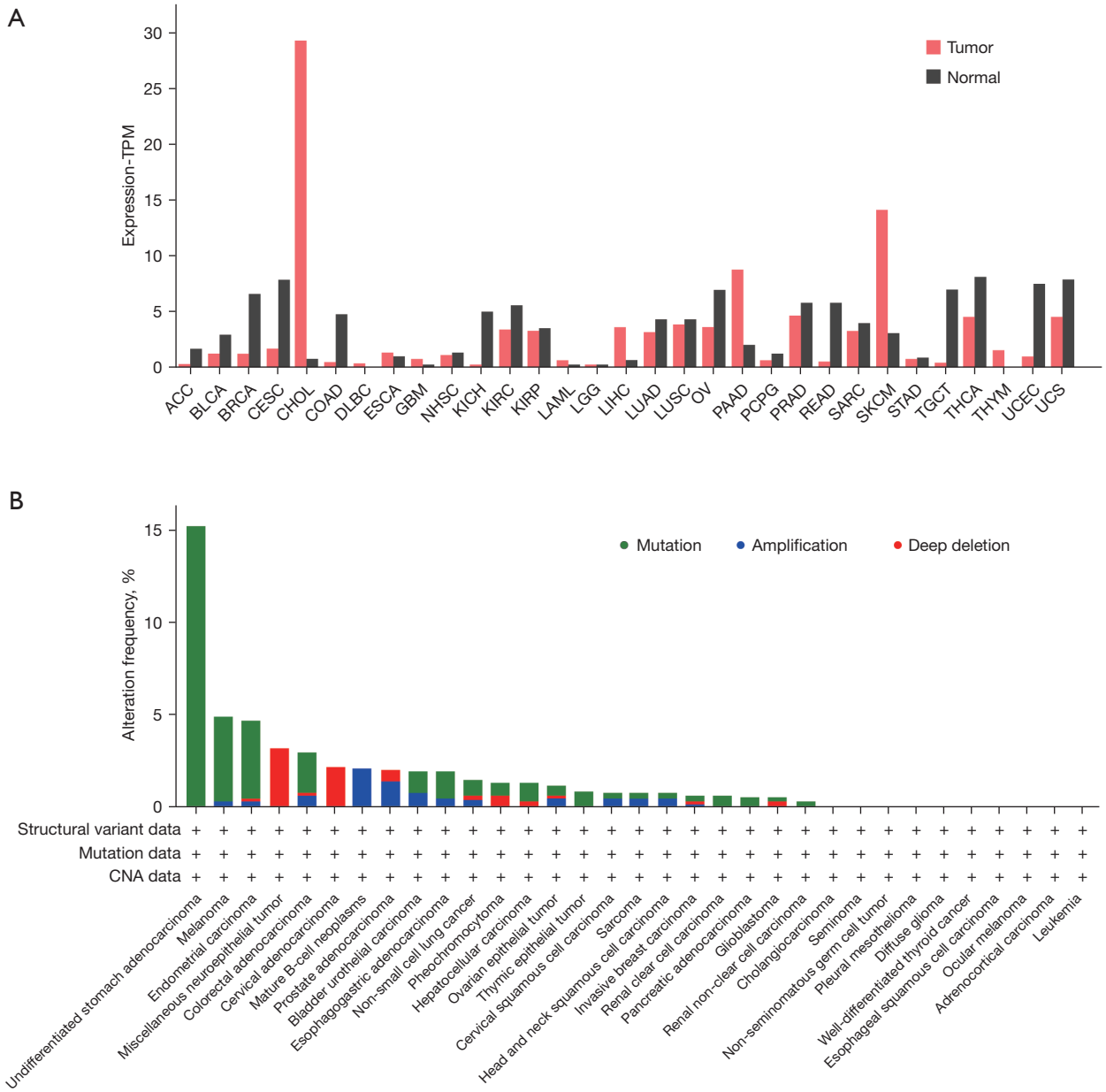

Figure 2 Tissue-specific expression analysis of *LOXL4*. (A) Expression of *LOXL4* in diverse human cancers (including tumor and normal samples). Expression levels are shown in TPM. (B) Differences in the frequency of mutation, amplification and deep deletion of the *LOXL4* gene in human cancers. LOXL4, lysyl oxidase-like protein 4; TPM, transcripts per million; ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; NHSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; CNA, copy number alterations.

Table 2 The dual role of LOXL4 in various types of human cancers

Cancer types	Expression levels of LOXL4	Functions	miRNA	Target	References
Hepatocellular carcinoma	Up regulated	Involves in prognosis; promotes migration, metastasis and invasion; promotes cancer cell death; involves in poor prognosis and recurrence	N/A	FAK/Src, PD-L1	(18-22)
	Down regulated	Tumor suppressor, low LOXL4 expression involves in poor prognosis and recurrence	N/A	P53, TGF-β1	(23-27)
Lung cancer	Down regulated	Tumor suppressor: knockout of *LOXL4* promotes proliferation, migration and invasion	miR-328-5p, miR-183-5p, miR-210, miR-135a-5p	N/A	(28-37)
Gastric cancer	Up regulated	Oncoprotein; promotes proliferation, migration, invasion; involves in poor prognosis	N/A	FAK/Src	(38-43)
Bladder cancer	Down regulated	Tumor suppressor; epigenetic modification, methylation	miR-193a-3p	Ras/ERK	(44-49)
Breast cancer	Up regulated	Promotes migration, metastasis and invasion; and correlated with prognosis; involves in diagnosis and chemotherapeutics	miR-29b, miR-30d	N/A	(50-60)
Ovarian cancer	Up regulated	Oncoprotein; promotes tumor metastatic potential and progression; correlated with poor prognosis and chemotherapy	N/A	N/A	(61-64)
Head and neck cancer	Up regulated	Oncoprotein; relates with the local lymph nodes, metastases and higher tumor stages; promotes the angiogenesis	N/A	N/A	(65-74)
Esophageal squamous cell carcinoma	Up regulated	Promotes proliferation, migration, invasion; involves in poor prognosis	miR-193a-3p	N/A	(75-82)
Colorectal cancer	Up regulated	Promotes metastasis and resistance to radiotherapy and chemotherapy	N/A	N/A	(83-88)

LOXL4, lysyl oxidase-like protein 4; miRNA, microRNA; FAK, focal adhesion kinase; Src, steroid receptor coactivator; PD-L1, programmed death ligand 1; TGF-β1, transforming growth factor β1; Ras, rat sarcoma virus; ERK, extracellular signal-regulated kinase; N/A, not available.

and predicts poor prognosis (20). The high expression of LOXL4 is significantly associated with tumor differentiation status, degree of vascular invasion, and tumor-node-metastasis (TNM) stage but is not correlated with sex, age, cirrhosis, tumor volume, pathological grade or clinical stage. Furthermore, LOXL4 overexpression significantly promotes HCC cell migration and invasion, as well as intrahepatic and pulmonary metastases in patients, whereas *LOXL4* knockdown inhibits the malignant biological behavior of tumor cells (20). LOXL4 catalyzes the oxidative deamination of peptidyl lysine and hydroxylysine in collagen and peptidyl lysine in elastin to produce hydrogen peroxide (H_2O_2) and peptidyl aldehydes. Peptidyl aldehydes can spontaneously condense and undergo oxidation reactions to generate the covalent crosslinkages which stabilize and insolubilize polymeric collagen or elastin fibers in the ECM. H_2O_2 promotes the phosphorylation of focal adhesion kinase (FAK) and steroid receptor coactivator (Src) and directly activates the FAK/Src pathway (20). Therefore, LOXL4 promotes cell-matrix adhesion and cell migration dependent on its catalytic activity through a H_2O_2-mediated mechanism. Additionally, LOXL4 was shown to be present in exosomes through analysis of the ExoCarta database (http://www.exocarta.org/),

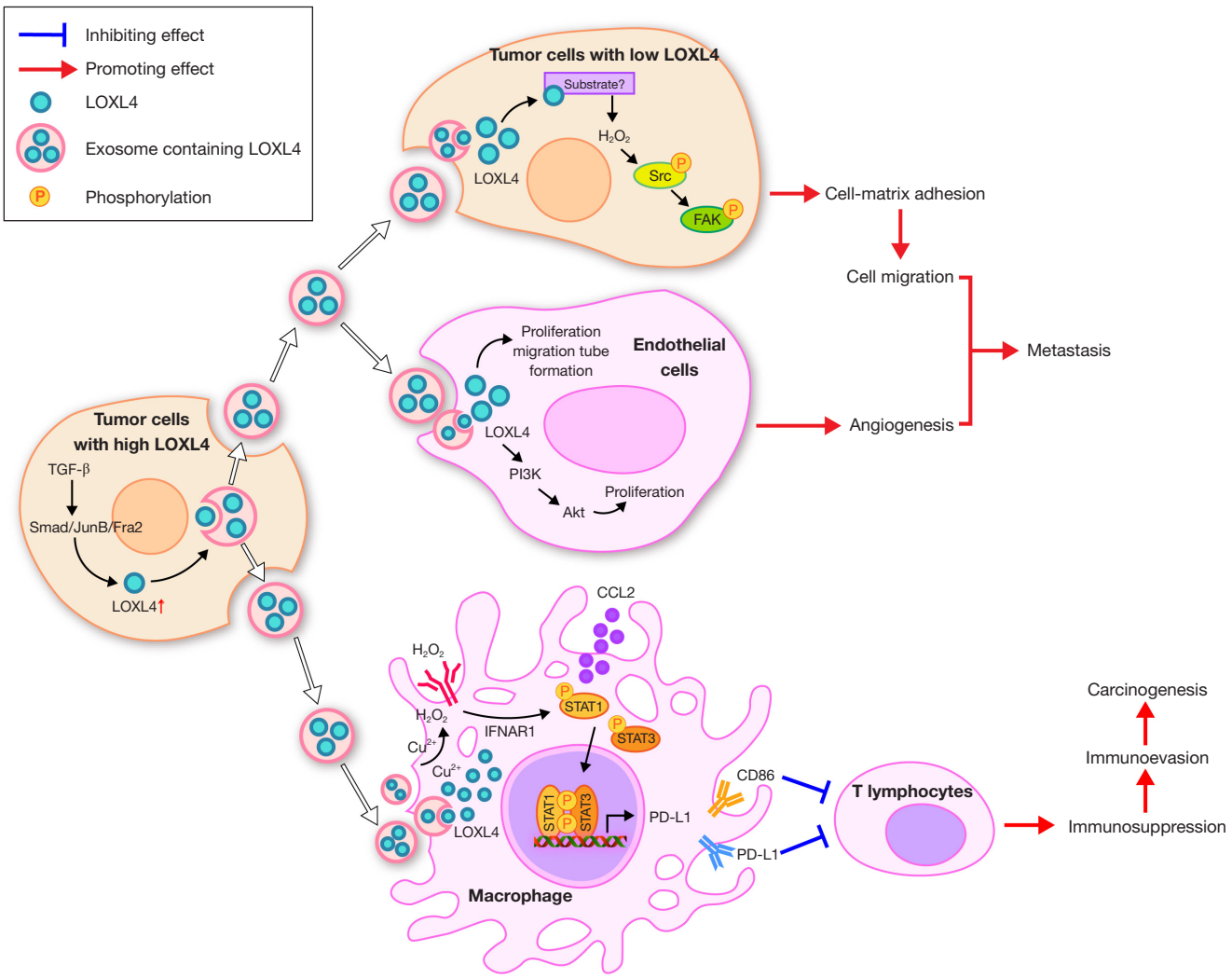

Figure 3 The possible mechanism by which LOXL4 promotes the pathogenesis and development of human malignant tumors. LOXL4, lysyl oxidase-like protein 4; TGF-β, transforming growth factor β; IFNAR1, interferon alpha/beta receptor 1; STAT1–3, signal transducer and activator of transcription 1–3; PD-L1, programmed death ligand 1; CCL2, C-C motif chemokine ligand 2.

cell immunofluorescence, scanning electron microscopy and western blotting. Exosomes secreted by HCC cells transfer LOXL4 to human umbilical vein endothelial cells (HUVECs) through a paracrine mechanism to promote angiogenesis, leading to tumor invasion and metastasis (20). Tan *et al.* indicated that LOXL4 plays an important role in fostering the immunosuppressive microenvironment that facilitates subsequent hepatic tumors (21). HCC-derived exosomes transfer LOXL4 between HCC cells or macrophages, shaping immunosuppressive macrophages by inducing programmed death ligand 1 (PD-L1) presentation. LOXL4-induced PD-L1 expression in macrophages is STAT1- and STAT3 dependent and leads to immune escape and the development of malignant tumors (22) (*Figure 3*).

However, several studies offer different perspectives. 5-aza-CR upregulates LOXL4, and the interaction between LOXL4 and P53 enhances the phosphorylation of P53 at serine 15, thereby reactivating compromised P53 and promoting the death and regression of tumor cells (23). LOXL2, LOXL3 and LOXL4 are reported to be induced by TGF-β1 in HCC cells (24-26). Kim *et al.* demonstrated that *LOXL4* is a novel target gene that can inhibit TGF-β1 signaling to negatively regulate TGF-β1-reduced cell motility and inhibit the activity of ECM-related genes

and matrix metalloproteinase-2 (MMP2) in PLC/PRF/5 hepatoma cells (26). This suggests that LOXL4 functions as a tumor suppressor in HCC through heterozygote loss and methylation inactivation. To further assess the prognosis and diagnostic value of LOXL4, Tian *et al.* analyzed the mRNA expression levels of LOXL4 in 28 pairs of HCC specimens and performed LOXL4 immunohistochemical staining analysis of tissue microarrays of 298 HCC patients (27). LOXL4 mRNA or protein expression was significantly lower in HCC tissues than in adjacent normal tissues ($P<0.01$) (27). Contrary to previous studies, lower LOXL4 expression indicates higher cumulative recurrence rates and poorer overall survival (OS) rates after radical resection. In recent years, multiple lines of evidence have suggested that epigenetic changes are important molecular mechanisms leading to the inactivation of tumor suppressor genes in tumors. However, the role and specific mechanism of LOXL4 in HCC, whether promoting or inhibiting, remains to be defined. In summary, LOXL4 contributes to the activation of P53 in HCC and promotes microenvironment suppression in the development of HCC, thereby playing an important role in the invasion and metastasis of HCC. These studies suggest that LOXL4 may be a novel diagnostic biomarker and therapeutic target for HCC patients with a higher risk of recurrence.

The role of LOXL4 in the occurrence and development of lung cancer

Lung cancer is the most common neoplasm and has a high incidence rate (28). Internationally, lung cancer is the leading cause of cancer-related deaths in men and women, representing a global burden to public health (29,30). LOXL4 is the main driver of pathological collagen cross-linking and fibrosis in the lung and thus is a compelling drug target (31). Accumulating evidence indicates a crucial regulatory effect of microRNAs (miRNAs) and LOXL4 on lung cancer progression. Zhang *et al.* revealed that miR-135a-5p expression was significantly elevated in lung cancer cells, and knockdown of miR-135a-5p inhibited the progression of lung cancer (32). *LOXL4* is one of the target genes of miR-135a-5p. In nude mouse xenograft tumor models, miR-135a-5p promotes the progression of lung cancer by inhibiting the expression of the *LOXL4* gene (32).

Non-small cell lung cancer (NSCLC) is a commonly encountered cancer in clinical practice, estimated to constitute approximately 84% of lung cancer patients in the world (33,34). miR-183-5p expression is decreased in NSCLC and is negatively correlated with elevated LOXL4 expression. miR-183-5p represses NSCLC cell proliferation, migration, invasion, ECM formation, and epithelial-mesenchymal transition (EMT) and promotes apoptosis by targeting LOXL4 expression (35). Moreover, overexpression of miR-328-5p enhances cell growth and migration to promote NSCLC progression by targeting LOXL4 (36). Xie *et al.* confirmed that LOXL4 is a downstream target of miR-210 and that miR-210 promotes lung cancer progression by targeting LOXL4 (37). Compared with BEAS-2B human normal lung epithelial cells, miR-210 is significantly upregulated in A549 and H1650 lung adenocarcinoma cells and promotes cell proliferation, migration and invasion (37). In A549 and H1650 cells, small interfering RNA (siRNA)-mediated knockdown of *LOXL4* reverses the inhibitory effect of miR-210 on lung adenocarcinoma. Taken together, these studies indicate that several miRNAs are potential targets for lung cancer treatment via effects on LOXL4.

The role of LOXL4 in the occurrence and development of gastric cancer (GC)

GC is a malignant solid tumor arising from the gastric mucosal epithelium and is the fifth most common tumor and third leading cause of cancer-related deaths worldwide (38). Upregulation of LOXL4 expression is a frequent event in GC progression and contributes to tumor cell proliferation and metastasis (39). This overexpression is positively correlated with tumor size, depth of tumor invasion, lymph node metastasis, TNM classification and poor OS in GC patients. Furthermore, recombinant human LOXL4 protein promotes GC cell proliferation and migration and enhances cell-ECM adhesion by activating the FAK/Src pathway (39). The expression of LOXL1, LOXL3 and LOXL4 proteins is associated with tumor infiltration, lymph node metastasis, lymphatic invasion, and venous invasion (40). The OS of patients who are positive for LOXL1, LOXL3 or LOXL4 expression is lower than that of patients who are negative for LOXL4 expression. *LOXL3* and *LOXL4* mRNA are significantly upregulated in highly invasive diffuse-type GC cells. TGF-β can reduce the expression of LOXL1 and increase the expression of LOXL3 and LOXL4 (41). A large-sample, multicenter retrospective analysis revealed that LOXL4 can effectively access and categorize the prognostic risk for GC patients (42). Among them, the high-risk group exhibited a poorer prognosis and was accompanied by extensive immune infiltration of

macrophages and regulator T-cells (43). Therefore, LOXL4 and other LOX family members may be biomarkers for predicting tumor prognosis and potential targets for tumor therapy.

The role of LOXL4 in the occurrence and development of BCa

BCa is one of the most common malignant tumors in the urinary system, ranking as the fourth most prevalent malignancy in men (44,45). Due to its chemotherapy resistance and high recurrence rates after surgery, BCa is one of the most expensive and challenging cancers to manage. LOX, LOXL1 and LOXL4 expressions suppress BCa growth (46). *LOXL4* gene methylation and loss of expression are commonly observed in primary BCa cells, and overexpression of LOXL4 in human BCa cells reduces colony formation (47). Methylation is the primary cause of *LOXL4* expression loss in BCa. In BCa, somatic mutations and polymorphisms of the *LOXL4* gene are clustered in exon 8, which encodes the SRCR4 domain. Overexpression of the *LOXL4* gene can serve as a tumor suppressor gene by inhibiting the rat sarcoma virus (Ras)-mediated extracellular signal-regulated kinase (ERK) signaling pathway in human BCa (47) (*Figure 4*). Chemoresistance is a major obstacle to curative BCa chemotherapy (48). Deng *et al.* demonstrated that miR-193a-3p promotes multidrug resistance in BCa by inhibiting the *LOXL4* gene (a direct target of miR-193a-3p) (49). LOXL4 primarily mediates the chemoresistance of miR-193a-3p in BCa through negative regulation of the oxidative stress pathway. In summary, the miR-193a-3p axis may be a new target for anti-BCa chemotherapeutics. In addition, methylation of the *LOXL4* gene may be a potential DNA marker for the early detection and diagnosis of BCa.

The role of LOXL4 in the occurrence and development of breast cancer

In recent years, the incidence of breast cancer has continued to rise annually, ranking as the leading malignancy in women and a primary cause of cancer-related deaths (50,51). The stage at diagnosis and biological features determine breast cancer prognosis. LOXL4 splice variants play a significant role in tumor progression, these variants are predominantly present in the effusions of breast and ovarian cancer patients, rather than in primary tumor tissues (52). Komalasari *et al.* (53) demonstrated that LOXL4 exhibits high expression in triple-negative breast cancer (TNBC) cells. LOXL4 inhibits integrin β-1 internalization and promotes tumor cell growth and proliferation by cross-linking and inducing the polymerization of annexin A2 via. Consistent with these findings, Yin *et al.* (54) found that the EZH2-miR-29b/miR-30d-LOXL4 signaling pathway is involved in the progression of breast cancer metastases by regulating macrophage immune infiltration and collagen remodeling. The high expression of miR-29b and miR-30d inhibits LOXL4, thereby negatively regulating the proliferation and migration of breast cancer cells and inhibiting tumorigenesis and metastasis (54). These studies indicate that it is promising to treat breast cancer by targeting the LOXL4 signaling pathway and epigenetic modulation to control macrophage activation. EMT is tightly regulated by the action of several EMT core transcription factors, particularly ZEB1 (55,56). LOXL4 can enhance the invasive processes of TNBC cells by binding to the Zn^{2+} reign of ZEB1 (57). Recent research indicated that among LOXLs, only LOXL4 exhibits higher expression in TNBC patient tissues than in those from estrogen receptor-positive breast cancer patients (58). Semenza *et al.* (59) reported that LOXL4 is also highly expressed in various types of primary human breast cancer tissues compared to paired adjacent normal tissues. In hypoxic MDA-MB-231 cells, knockout of the hypoxia-inducible factor-1α (HIF-1α) and HIF-2α genes or simultaneous blockage of hypoxia inhibits lung collagen remodeling and recruitment of bone marrow-derived dendritic cells (BMDCs) in tumor-bearing small mice, similar to the effects of inhibiting LOX or LOXL4 expression (59). This suggests that LOXL4 is expressed in different types of human metastatic breast cancer cell lines in a HIF-dependent manner. Hypoxia is a major regulator of the LOX protein family.

The role and specific mechanisms of LOXL4 in the occurrence and development of breast cancer remain a topic of ongoing debate. Choi *et al.* (60) demonstrated that LOXL4 is expressed at the highest level in MDA-MB-231 cells compared with other breast cancer cell lines, and knockdown of *LOXL4* promoted primary tumor growth and lung metastasis of the MDA-MB-231 cells. In addition, low expression of LOXL4 indicates a poor prognosis for breast cancer patients, this correlation is strongest in TNBC patients (60). These results suggest that low LOXL4 expression leads to ECM remodeling by inducing collagen synthesis, deposition and structural changes. In turn, these changes promote tumor initiation and progression, correlating with adverse patient outcomes. These findings

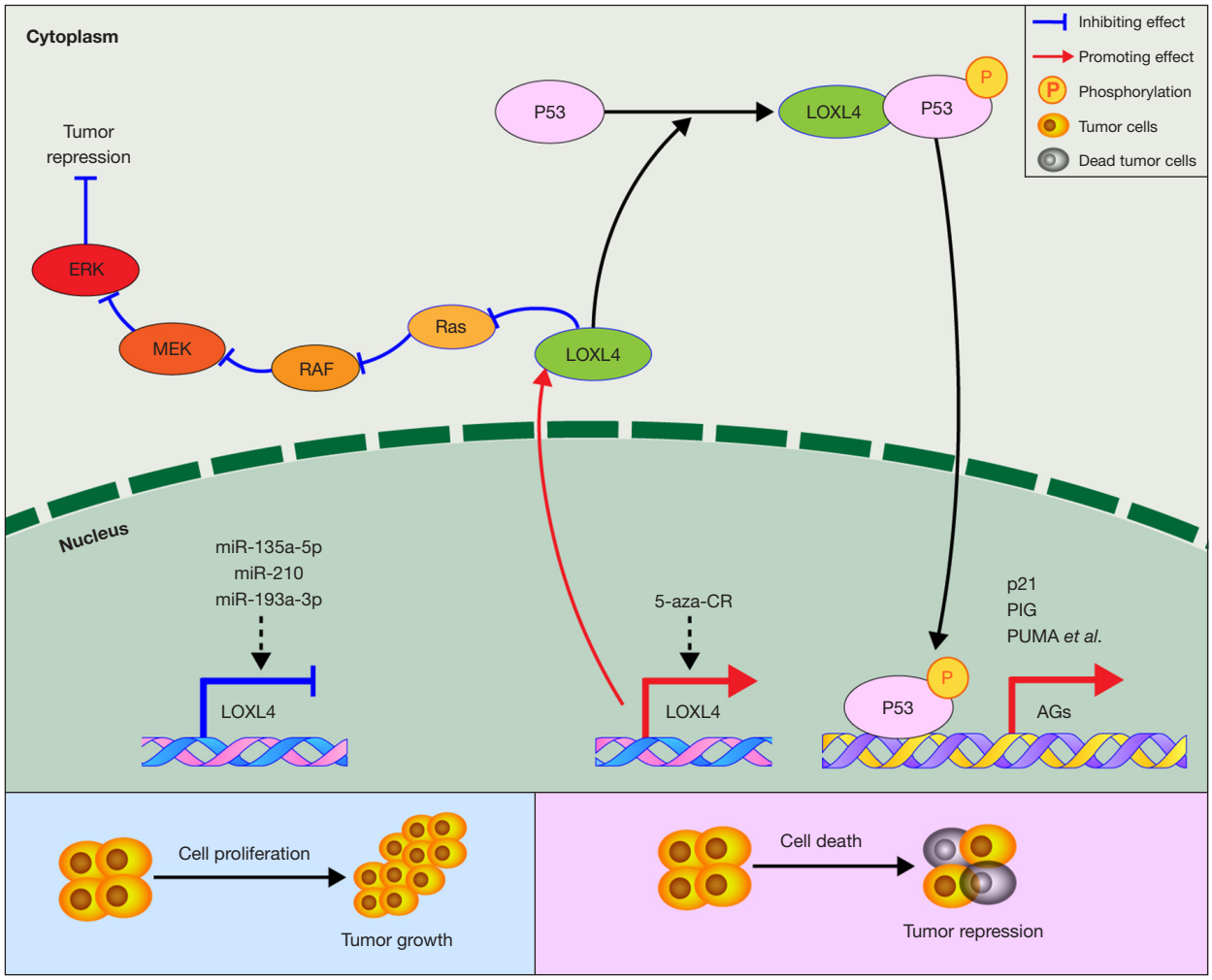

Figure 4 The possible mechanism by which LOXL4 inhibits tumorigenesis and the development of human malignant tumors. LOXL4 exerts a tumor-suppressing function by activating P53 and inhibiting the Ras/ERK signal transduction pathway. LOXL4, lysyl oxidase-like protein 4; Ras, rat sarcoma virus; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; 5-aza-CR, 5-azacytidine; PIG, P53-inducible gene; PUMA, P53-upregulated mediator of apoptosis; AGs, activator of G-protein signaling.

are inconsistent with previous reports that high LOXL4 expression promotes breast cancer tumorigenesis. Currently, there are still no satisfactory studies to clarify the conflicting results obtained in cell lines and xenograft models. These discrepancies may be attributable to differences in lung metastasis models and the tumor microenvironments of the host mice. The role of LOXL4 in breast cancer may depend on the heterogeneous characteristics of different cancer tissues. Further research is needed to clarify the function of LOXL4 in different subtypes of breast cancer.

The role of LOXL4 in the occurrence and development of ovarian cancer

Ovarian cancer is a global challenge for medicine. It is the 8th most common cause of cancer-related mortality in females and the deadliest malignant gynecological carcinoma (61,62). Molecular features are promising biomarkers in ovarian cancer. Low oxygen tension activates the HIF pathway in the ovarian cancer tumor microenvironment, subsequently increasing LOX expression to promote collagen remodeling, tumor invasion and progression (63).

Ye *et al.* (64) demonstrated that overexpression of *LOXL4* mRNA is associated with poor progression-free survival (PFS) in ovarian cancer patients. Furthermore, overexpression of *LOX*, *LOXL3*, and *LOXL4* mRNA suggests a poorer clinical prognosis of ovarian cancer patients after receiving platinum and Taxol chemotherapy. The LOXL4 splicing variants are overexpressed in ES-2 ovarian cancer cells, promoting the migration and tumor progression of ovarian cancer cells. In conclusion, selective splicing of LOXL4 plays a crucial role in ovarian cancer progression. LOXL4 and other LOX family members may serve as novel molecular biomarkers for assessing disease progression and chemotherapy efficacy in ovarian cancer patients. However, reports on the relationship between LOXL4 and ovarian cancer are limited, and the correlation and specific mechanism remain to be further investigated.

The role of LOXL4 in the occurrence and development of head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) is one of the most common cancers worldwide (65). Most head and neck cancers originate from the mucosal epithelium in the oral cavity, pharynx and larynx and are collectively known as HNSCC (66). Studies have shown that LOXL4 can serve as a molecular marker for both primary and metastatic head and neck cancer (67,68). LOXL4 is transcribed in HNSCC but not in normal squamous epithelial cells. Görögh *et al.* (66). demonstrated that high LOXL4 expression is significantly correlated with local lymph node metastasis, primary tumor type, and higher tumor stage. Functional analysis of the 5' flanking domain of the *LOXL4* gene in HNSCC cells indicates an increased binding activity to TATA (–25) and SP1 (–181) sites compared to normal epithelial cells, suggesting that these transcription factors are involved in the upregulation of *LOXL4* gene expression in HNSCC (69). Fluorescence *in situ* hybridization (FISH) analysis indicated a significant increase in the copy number of the *LOXL4* gene on chromosome 10q24 in HNSCC cell lines. In addition to gene amplification in HNSCC, LOXL4 may be upregulated through demethylation of CpG islands in its promoter (66).

LOXL4 is both a tumor marker and a therapeutic target in the diagnosis and treatment of HNSCC. The increased number of lymph node metastases in HNSCC is associated with high LOXL4 expression. Lymph node metastasis is a major determinant of the clinical progression of HNSCC. LOXL4 also has potential prognostic significance. In xenograft experiments, tumor regression mediated by LOXL4 monoclonal antibodies (mAbs) was analyzed in 41 severe combined immunodeficiency disease (SCID) mice. The results indicated that LOXL4 mAbs had potent antitumor activity, suggesting their potential as therapeutic immunomodulators for HNSCC with LOXL4 upregulation (70). It is worth noting that, dendritic cells expressing LOXL4 can stimulate T cells and increase the secretion of the antitumor cytokine interferon-γ (IFN-γ). These dendritic cells can be used as a vaccination strategy for treating HNSCC patients and are particularly suitable for those with tumor-specific upregulation of LOXL4.

Laryngeal squamous cell carcinoma (LSCC) is the most common type of HNSCC and is an aggressive malignancy with a high mortality rate (71). LOXL4 is significantly overexpressed in LSCC tumor tissues compared to adjacent normal tissues ($P<0.001$) (72). However, LOXL4 expression is not significantly correlated with the metastatic potential or T stage of tumor samples. Altuntaş *et al.* (73) revealed that LOXL4 is associated with tumor stage and differentiation degree, but not tumor size. Increased LOXL4 expression suggests a longer 2-year OS for LSCC patients. The expression of LOXL4 appears with tumor progression and disappears with worsening differentiation, suggesting a potential tumor-suppressive role in laryngeal cancer (73). Additionally, knockdown of the long noncoding RNA (lncRNA) AGAP2-AS1 inhibits the proliferation and invasion of LSCC cells by regulating the miR-193a-3p/LOXL4 axis (74). Therefore, LOXL4 and AGAP2-AS1 might be therapeutic targets for LSCC treatment. The exact role of LOXL4 in LSCC tumorigenesis requires further clarification, which may lead to novel treatment methods, such as LOXL4-targeted immunotherapy.

The role of LOXL4 in the occurrence and development of esophageal squamous cell carcinoma (ESCC)

Esophageal cancer is the sixth leading cause of cancer-related deaths but a lesser-known cancer (75-77). Approximately 90% of esophageal cancer is ESCC (78,79). ESCC has an inferior prognosis and a high mortality rate (80). Du *et al.* (81) demonstrated that LOXL4 is upregulated in ESCC. Kaplan-Meier analysis confirmed that high LOXL4 expression is related to lower survival rates in patients. Moreover, protein-protein interaction network analysis suggested that LOXL4 and its associated proteins, including collagen type II alpha 1 (COL2A1) and suppressor of variegation 3-9 homolog 1 (SUV39H1),

are potential biomarkers for ESCC patients (82). High expression levels of these genes are related to tumor progression and poor clinical outcomes in ESCC even after curative surgery. Therefore, LOXL4 may play an oncogenic role in the progression and prognosis of ESCC through interactions with multiple proteins. However, research on the specific mechanisms and expression of LOXL4 in ESCC is limited.

The role of LOXL4 in the occurrence and development of CRC

CRC, which includes rectal cancer and colon cancer, is the third most common cancer globally and the second leading cause of death in tumor patients (83). Barker *et al.* demonstrated that *LOXL4* gene upregulation in CRC significantly increases sensitivity to radiotherapy and chemotherapy in CRC (84). Furthermore, real-time quantitative polymerase chain reaction (qPCR) analysis of tumor tissues and paired adjacent normal tissue specimens from 104 CRC patients indicated that there is no statistical correlation between the expression of the *LOXL4* gene and tumor location, stage, growth type or differentiation status (85). However, upregulation of LOXL4 expression in CRC is significantly associated with lymphovascular invasion. The oxygen tension in or around the tumors may be an important regulator of the differential expression of LOXL4 in CRC (85). Therefore, the upregulation of *LOXL4* gene expression may be related to the increased invasiveness and metastatic potential of CRC.

Tumor metastasis and recurrence are the primary cause of mortality in CRC patients, and the liver is the most common site of metastasis (86). Currently, there is still a lack of effective strategies for the control and treatment of CRC liver metastasis (CRCLM) in clinical practice (87). RNA sequencing showed that LOXL4 transcription is upregulated in replacement histopathological growth pattern (HGP) CRCLM compared with desmoplastic HGP CRCLM and adjacent normal liver (88). LOXL4 protein is expressed by neutrophils in the tumor microenvironment. This study was the first to reveal that LOXL4-expressing neutrophils support the replacement HGP phenotype and can serve as a surrogate biomarker of this subtype of CRCLM. These studies have revealed the important role of LOXL4 in tumor progression and the tumor immune microenvironment. Therefore, targeting LOXL4 may be a new option for CRC therapeutics.

Conclusions

LOXLs are responsible for maintaining the stability of the ECM and play a role in maintaining connective tissue function, embryonic development, and wound healing (89). In recent years, a growing body of research has demonstrated that LOXLs play a crucial role in promoting tumor cell migration and invasion by inducing EMT, activating the FAK signaling pathway, and participating in the formation of the pre-metastatic microenvironment (90). The LOX family may serve as a novel molecular marker for cancer treatment and prevention of metastasis. As a new member of the LOX protein family, LOXL4 participates in the occurrence and development of human malignant tumors. LOXL4 is highly expressed in multiple malignant tumors. Interestingly, LOXL4 plays a dual role, as it inhibits or promotes tumor development in different types of human malignancies. Tumor cells secrete exosomes that transfer LOXL4 between cells, activating the Src/FAK signaling pathway, promoting tumor cell invasion and metastasis, and leading to poor prognosis of malignant tumors. Methylation of the *LOXL4* gene in primary tumor cells is associated with expression loss. The methylated *LOXL4* gene is a potential tumor suppressor and a novel target for gene therapy or early detection. The *LOXL4* gene can be used as an adjunctive diagnostic or predictive marker for cancer staging, grading and recurrence. It is also a potential indicator for monitoring cancer radioresistance and sensitivity. LOXL4 inhibitors may benefit cancer patients with high LOXL4 expression. Molecular therapy targeting the *LOXL4* gene may improve the prognosis of cancer patients.

miRNAs have been identified as essential players in the processes of tumor initiation and progression, such as the regulation of the EMT pathway (91). In recent years, serval studies have revealed the crucial role of the interaction between LOXL4 and miRNA in various cancers, impacting ECM remodeling and the progression of EMT. For instance, LOXL4 serves as the target for various miRNAs in the progression of lung cancer, such as miR-183-5p, miR-135a-5p, miR-210 and miR-328-5p (32,35-37). These miRNAs inhibit the malignant biological behaviors of lung cancer cells, as well as ECM formation and EMT processes and promote tumor cell apoptosis by targeting LOXL4. For instance, the epigenetic silencing of miR-29/miR-30 targets LOXL4 and promotes the initiation, progression and immune microenvironment remodeling in breast cancer (54). Moreover, miR-193a-3p/LOXL4 axis

promotes cell proliferation and invasion in LSCC (74). In addition, miR-193a-3p promotes multidrug resistance in BCa by activating the oxidative stress pathway through the inhibition of LOXL4 expression (49). In conclusion, LOXL4 may play a significant role in the development and progression of cancer through its interaction with miRNAs, serving as a diagnostic target to guide anti-tumor chemotherapy. Currently, the research on the miRNAs interacting with LOXL4 is limited. Further studies are needed to identify various miRNAs interacting with LOXL4 in different types of cancers and to elucidate the underlying mechanisms regulating tumor progression.

Intratumoral hypoxia, a frequent finding in metastatic cancer, results in the activation of the HIFs, which promotes tumor cell invasion and migration (92). Since HIF-1 serves as a crucial regulator of oxygen homeostasis, targeting it directly for the development of anticancer drugs poses significant challenges. Therefore, it is necessary to explore the upstream or downstream effectors of HIF-1. LOXLs were proven to regulate hypoxia-induced metastases through a HIF-1-dependent mechanism and promote the progression of various tumors, including CRC, HCC, NSCLC, TNBC, etc. (93-96). Altuntaş *et al.* demonstrated that LOXL4 is an enzyme activated under hypoxia conditions and is expressed more strongly in advanced stages of LSCC tumor cells (73). Moreover, hypoxia can induce the overexpression of LOXL4 in breast cancer cells in a HIF-dependent manner (59). Knockdown of HIF-1α and HIF-2α blocked hypoxia-induced expression of LOX and LOXL4 and collagen remodeling and BMDC recruitment in the lungs of tumor bearing mice. At present, the significance of LOXL4 in hypoxic stress and tumorigenesis, along with its mode of action and underlying mechanisms related to HIFs are undeniably interesting.

Knowledge of the precise molecular function of LOXL4 in tumors is minimal, although links to tumor progression have been established. To obtain a comprehensive understanding of the role of LOXL4 in tumor initiation and progression, several questions remain to be answered. Firstly, most studies have analyzed downstream targets of the *LOXL4* gene in tumor cell lines, and how LOXL4 is regulated by upstream genes and its degradation process remains unclear. To further clarify the role of the *LOXL4* gene in tumorigenesis and progression, mouse models, such as gene knock-in mice and gene knockout mice, must be established, and extensive *in vivo* studies using experimental animal models are needed. Finally, further development of mAbs targeting LOXL4 and high-throughput screening of small-molecule inhibitors for LOXL4 protein are needed to find specific inhibitors for the treatment of human malignant tumors with high *LOXL4* gene expression. A novel ECM-targeting nanotherapeutic may be designed and engineered using a lipid-based nanoparticle chemically linked to an inhibitor of the LOXL4, which inhibits the crosslinking of elastin and collagen fibers (97). This therapy holds the potential to enhance tumor growth inhibition and reduce toxicity, thereby offering significant therapeutic advantages for cancer patients.

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Footnote

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