Role of LMO7 in cancer (Review)

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Abstract. Cancer constitutes a multifaceted ailment characterized by the dysregulation of numerous genes and pathways. Among these, LIM domain only 7 (LMO7) has emerged as a significant player in various cancer types, garnering substantial attention for its involvement in tumorigenesis and cancer progression. This review endeavors to furnish a comprehensive discourse on the functional intricacies and mechanisms of LMO7 in cancer, with a particular emphasis on its potential as both a therapeutic target and prognostic indicator. It delves into the molecular attributes of LMO7, its implications in cancer etiology and the underlying mechanisms propelling its oncogenic properties. Furthermore, it underscores the extant challenges and forthcoming prospects in targeting LMO7 for combating cancer.

Contents

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1. Introduction

Cancer is a complex group of diseases characterized by the uncontrolled growth and spread of abnormal cells in the body. With the capacity to afflict any anatomical site and propagate to adjacent tissues or distant organs, cancer poses a formidable global health challenge (1,2). The World Health Organization estimates that cancer accounted for nearly 10 million deaths worldwide in 2020. Notably, the incidence of several cancer types continues to increase, imposing an onerous burden on healthcare systems and affected individuals (3). Research efforts have been instrumental in advancing our understanding of cancer biology, thereby facilitating the development of targeted therapeutic modalities and innovative treatment paradigms. Breakthroughs in precision medicine, immunotherapy and genetic manipulation have shown promising results in improving patient outcomes and prolonging survival rates.

Early detection and screening programs play a crucial role in cancer management by enabling the timely identification of cancerous cells through regular screenings, such as mammograms, colonoscopies and pap smears, ultimately leading to better treatment outcomes (3).

Given the increasing prevalence of cancer and its impact on individuals, families and societies, the importance of current cancer research and treatment cannot be overstated. Continued investments in scientific advancements and access to quality care are essential to drive further progress and improve the lives of cancer patients worldwide. Overall, the importance of cancer lies in its severe impact on physical, emotional and socioeconomic aspects of individuals and society, emphasizing the need for sustained research, prevention efforts and improved access to quality care (4).

Oncogenes, tumor suppressor gene and DNA repair genes play pivotal roles in tumorigenesis, which is the process wherein normal cells undergo malignant transformation (5-7). Oncogenes, when activated or mutated, harbor the potential to instigate cancer by fostering uncontrolled cellular proliferation and aberrant signaling cascades (5). Conversely, tumor suppressor genes act as guardians of cellular homeostasis, curtailing aberrant growth and facilitating DNA repair mechanisms (6). DNA repair genes, as the name suggests, are responsible for repairing DNA damage that occurs naturally or

due to external factors such as exposure to radiation or harmful chemicals. The intricate interplay among these genes and their functions is contingent upon the specific cancer type and implicated genetic aberrations (7). Understanding these mechanisms is indispensable for identifying potential therapeutic targets and devising efficacious cancer interventions (7,8).

The present review centers on elucidating the pivotal role of LIM domain only 7 (LMO7) in tumorigenesis, encompassing its molecular attributes, oncogenic functions, clinical relevance and therapeutic implications. Of note, LMO7, a multifunctional protein encoded by the LMO7 gene, has garnered attention for its involvement in diverse physiological processes, including neuronal development, cardiovascular health (9,10), and notably, cancer pathogenesis (11,12). Dysregulation of LMO7 has been implicated in various malignancies, underscoring its potential as a prognostic marker and therapeutic target. This review delineates the intricate molecular characteristics and biological functions of LMO7, elucidates its implications in cancer development across different organ systems, and elaborates on the mechanistic underpinnings of its oncogenic effects. Furthermore, it delineates the challenges inherent in targeting LMO7 for therapeutic intervention and suggests avenues for future research aimed at unraveling the complexities of LMO7-mediated carcinogenesis.

2. Molecular characteristics and biological functions of LMO7

The LMO7 gene encodes a protein called LMO7, which is found in humans and is located on chromosome 13q14.11. The LMO7 protein is predominantly expressed in cardiac and skeletal muscle tissues (13). LMO7 protein encompasses multiple LIM domains, serving as protein-protein interaction motifs implicated in cell growth, differentiation and cytoskeletal organization (14-16). In addition, LMO7 contains PDZ domains, facilitating interaction modules that typically bind to specific protein sequences, and which are involved in protein localization, signal transduction and the assembly of protein complexes within cells (17,18). LMO7 protein also contains CH domains, an actin-binding motif, which may exist as a single copy or in tandem repeats, either functioning autonomously or serving a regulatory role. CH domains are found in cytoskeletal and signal transduction proteins, including actin-binding proteins like spectrin, α-actinin, dystrophin, utrophin and fimbrin, as well as proteins essential for the regulation of cell shape (cortexillins) and signaling proteins (Vav), and are crucial for regulating cell shape and signaling (19,20). It has one CH domain at its N-terminus, a PDZ domain in the middle region and two DUF4757 domains of unknown function (Fig. 1A). The human LMO7 protein shares a high degree of homology with LMO7 proteins in other species, particularly in the CH, PDZ and LIM domains (Fig. 1B).

It has been observed that LMO7 gathers at cell-cell adhesion sites subsequent to the assembly of nectin-afadin and E-cadherin-catenin complexes, thereby influencing cell migration, intercellular communication and tissue organization (21). In *Drosophila*, the vertebrate homolog of LMO7, Smash, interacts with Bazooka/Par-3, canoe/afadin, and the tyrosine kinase Src42A, localizing to the zonula adherens in a plane-polarized manner. Deletion of smash leads to severe defects in the morphogenesis of embryonic epithelial tissues and organs (22). In muscle cells, LMO7 functions as a transcription factor, regulating the expression of various muscle genes, including paired box gene 3 (Pax3), Pax7, myogenic differentiation antigen (MyoD) and myogenic factor 5, thereby controlling myogenesis (11-13). LMO7-null mice exhibit growth retardation, reduced fiber size, and impaired skeletal muscle and cardiac function (11). Knockdown of chicken LMO7 diminishes the number and width of myotubes and the number of MyoD-positive myoblasts, a phenotype rescued by Wnt/β-catenin activation, suggesting a role for LMO7 in the initial events of chick skeletal muscle formation, particularly in myoblast survival (12).

As a critical adapter and scaffolding protein, LMO7 interacts directly or indirectly with ~20 proteins through its three domains, thereby having vital biological functions (Fig. 1C). Using the Search Tool for the Retrieval of Interacting Genes and Proteins (STRING) database (string-db.org) to predict protein interactions of LMO7 revealed its association with various proteins, such as enamel matrix derivatives, Afadin (AFDN), actinin α 1/4 and COMM domain-containing protein 6/9, among others, to exert its functions in different tumors (Table I). With these predicted interactions, future investigations could explore the specific proteins with which LMO7 interacts to regulate tumorigenesis in various tumor tissues.

3. LMO7 gene in cancer development

LMO7 is a protein that has a role in cell adhesion, cytoskeletal organization and cellular signaling pathways (23-25). While extensive research is still needed to fully understand the precise role of LMO7 in cancer, LMO7 has been implicated as an oncogene in several types of cancer (11,12).

In breast cancer, elevated LMO7 levels correlate with aggressive phenotypes characterized by enhanced cell migration and invasiveness and are positively regulated by CUGBP Elav-like family member 1 (26,27). Higher levels of LMO7 expression have been associated with more aggressive breast cancer phenotypes, including increased cell migration and invasion (26,28). Serum response factor (SRF) regulates specific functions such as muscle development and breast cancer metastasis. LMO7 orchestrates the myocardin-related transcription factors (MRTFs) as coactivators promoting cytoskeletal rearrangements conducive to cancer cell motility (26,29). LMO7 is a specific regulator of MRTFs and plays a vital role in breast cancer cell migration (26,30). LMO7 activates MRTFs by relieving actin-mediated inhibition in cooperation with Rho GTPase. Disruption of actin-RPEL interactions eliminates Rho dependency, allowing strong Rho-independent activation of LMO7 (30,31). LMO7 reduces the G-actin/F-actin ratio by colocalizing with F-actin. Knockdown of LMO7 compromises MRTF activities and impairs breast cancer cell migration (26,31). LMO7 is upregulated in invasive breast carcinoma and correlates with increased expression of SRF target genes regulating muscle and actin cytoskeleton functions (23,32), suggesting a cell-specific mechanism regulating Rho-MRTF-SRF signaling and breast cancer cell migration (26).

A novel fusion gene, LMO7-BRAF, was identified in thyroid cancer (33). Enhanced expression of the LMO7-BRAF fusion protein stimulates endogenous ERK1/2 phosphorylation

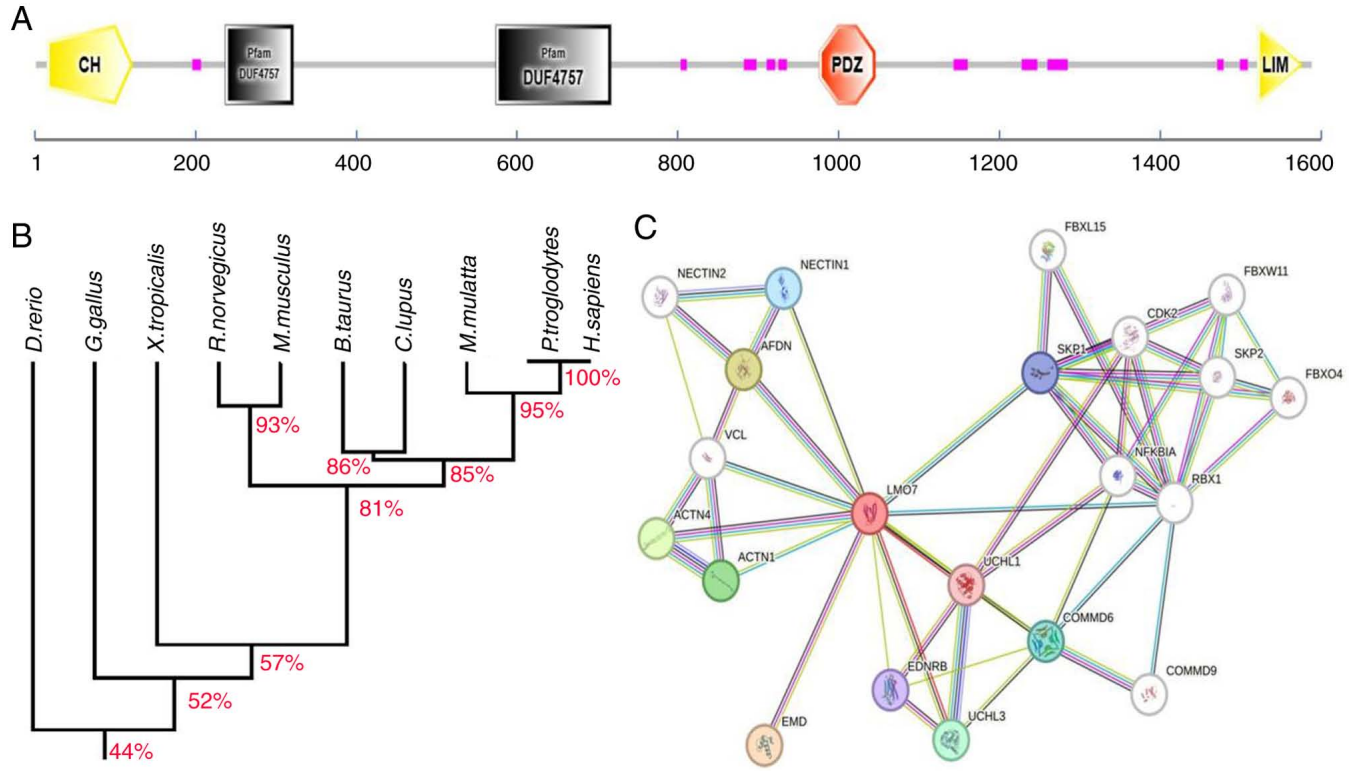

Figure 1. Bioinformatics analysis of *H. sapiens* LOM7. (A) LMO7 contains LIM domain at its C-terminus, one CH domain at its N-terminus, a PDZ domain in the middle region and two DUF4757 domains of unknown function. (B) Homology tree: The amino acid sequence of *H. sapiens* LOM7 was compared with known LMO7 proteins of other species. (C) Protein-protein interaction network of LMO7. LMO7 (LIM domain only 7). NECTIN1/2, nectin cell adhesion molecule 1/2; AFDN, afadin; VCL, vinculin; ACTIN1/4, cytoplasmic 1/4; EMD, enamel matrix derivatives; EDNRB, endothelin receptor type B; UCHL1/3, ubiquitin carboxyl-terminal hydrolase isozyme L1/3; COMMD6/9, COMM domain-containing protein 6/9; FBXL15, F-box/LRR-repeat protein 15; FBXW11, F-box and WD-40 domain protein 11; SKP1/2, S-phase kinase associated protein 1/2; CDK2, cyclin-dependent kinase 2; FBXO4, F-box protein 4; NFKBIA, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; RBX1, ring box protein 1.

and promotes anchorage-independent cell growth. The LMO7-BRAF fusion is a recurrent somatic alteration that occurred in 2% of thyroid cancer and presented as an oncogenic alteration (33).

Transcription factor krüppel-like factor 4 binds to methylated CpGs at the enhancer regions of LMO7 and activates LMO7 expression via 3D chromatin loop formation with its promoter regions, influencing cellular functions in human glioblastoma cells (34).

LMO7 has been suggested to act as a tumor suppressor for murine lung adenocarcinoma. LMO7-deficient mice develop irregular and prominent epithelial lesions in terminal and respiratory bronchioles at a young age, whereas these mice tend to develop lung adenocarcinoma at an old age (28,35). Leucine-rich repeats and immunoglobulin-like domains proteins 3 (LRIG3) interacts with LMO7 and LIM and calponin homology domains 1 (LIMCH1), with co-localization and co-immunoprecipitation observed between LRIG1/3 and LMO7/LIMCH1 (36). LMO7 and LIMCH1 are highly expressed in normal lung tissue but reduced in malignant tissue. LMO7 immunoreactivity predicts poor prognosis in LRIG1-positive tumors (36). MicroRNA (miR)-96, as a serum biomarker for lung cancer, inhibits the expression of LMO7 by binding to its 3'-UTR, ultimately regulating lung carcinogenesis through the miR-96-LMO7 axis (37).

LMO7 has been found to be overexpressed in pancreatic cancer (PC), with recent studies identifying LMO7 as a potential prognostic marker for PC (38,39). Its overexpression is associated with tumor progression and poor patient survival. Studies have shown that knockdown or knockout of LMO7 in mouse PC cells leads to PC cell cycle arrest and apoptosis, significantly inhibiting PC cell proliferation, anchorage-free colony formation, migration *in vitro*, and slowing down the growth and metastasis of pancreatic carcinoma *in vivo* (28,40).

In inflammatory hepatocellular adenomas (IHCA), among the five IHCA cases with fyn related Src family tyrosine kinase (FRK) gene rearrangements, LMO7 was identified to be fused to the exon 3-8 region of FRK (39). In tumor cells, human genes use alternative transcription start sites (TSS) to control mRNA levels and expand transcriptional output, thereby promoting carcinogenesis (41,42). A study analyzing 108 colorectal cancer samples using exome arrays identified multiple genes, including *LMO7*, relative to normal mucosa, showing tumor-specific alternative TSS use in both adenoma and cancer samples (28,43).

LMO7 is upregulated in human malignancies, including colorectal cancer, with no transcriptional upregulation of the LMO7 observed in adenomas compared with normal mucosa (28,44,45). However, upregulation of LMO7 transcription was observed in cancer. LMO7 expression in primary tumors with p53 mutation was significantly higher than that in tumors without p53 mutation (45,46).

While LMO7 is not commonly discussed as a well-established oncogene, emerging evidence suggests its potential oncogenic

Table I. Proteins that interact with LIM domain only 7.

Protein	Full name	Functions	(Refs.)
EMD	Enamel matrix derivatives	Stabilizes and promotes the formation of a nuclear actin cortical network	(70,71)
AFDN	Afadin	Plays a role in the organization of homotypic, interneuronal and heterotypic cell-cell adherens junctions	(72-74)
ACTN1	Actinin α 1	Anchors actin to a variety of intracellular structures	(75,76)
ACTN4	Actinin α 4	Involved in vesicular trafficking via its association with the CART complex	(77,78)
COMMD6	COMM domain-containing protein 6	Modulates activity of cullin-RING E3 ubiquitin ligase complexes. Inhibits TNF-induced NF-κB1 activation	(79,80)
COMMD9	COMM domain-containing protein 9	Modulates Na(+) transport; downregulates activation of NF-κB	(81,82)
Nectin-1	Nectin cell adhesion molecule 1	Promotes cell-cell contacts by forming homophilic or heterophilic trans-dimers	(83,84)
Nectin-2	Nectin cell adhesion molecule 2	Modulator of T-cell signaling	(85,86)
EDNRB	Endothelin receptor type B	Mediates its action by association with G proteins that activate a phosphatidylinositol-calcium second messenger system	(87,88)
UCHL1	Ubiquitin carboxyl-terminal hydrolase isozyme L1	Has ATP-independent ubiquitin ligase activity	(89,90)
UCHL3	Ubiquitin carboxyl-terminal hydrolase isozyme L3	Controls levels of cellular ubiquitin through processing of ubiquitin precursors and ubiquitinated protein	(91,92)
SKP1	S-phase kinase associated protein 1	Mediates the ubiquitination of proteins involved in cell cycle progression, signal transduction and transcription	(93,94)
SKP2	S-phase kinase associated protein 2	Specifically recognizes phosphorylated CDKN1B/p27kip and is involved in the regulation of G1/S transition	(95,96)
RBX1	Ring box protein 1	Mediates ubiquitination of target proteins	(97,98)
VCL	Vinculin	Involved in cell-matrix adhesion and cell-cell adhesion	(99,100)
NFKBIA	Nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor, α	Inhibits the activity of dimeric NF-κB/REL complexes	(101,102)
FBXO4	F-box protein 4	Promotes ubiquitination of cyclin D1 and its subsequent proteasomal degradation	(103,104)
FBXW11	F-box and WD-40 domain protein 11	Mediates the ubiquitination of phosphorylated β-catenin and participates in Wnt signaling	(105,106)
FBXL15	F-box/LRR-repeat protein 15	Acts as a positive regulator of the bone morphogenetic protein signaling pathway	(107,108)
CDK2	Cyclin-dependent kinase 2	Control of the cell cycle; essential for meiosis	(109,110)

role in certain cancers; LMO7 was upregulated in most tumors, but downregulated in certain other tumors (Fig. 2) (28); data were from GEPIA 2 (http://gepia2.cancer-pku.cn/). It is important to note that more research is needed to fully understand the molecular mechanisms by which LMO7 functions as an oncogene in cancer. This will help determine its potential as a therapeutic target and develop strategies to inhibit its activity for the treatment of specific cancers.

4. Mechanisms underlying the oncogenic effects of LMO7

LMO7 has been found to play a role in promoting cell proliferation (37). Studies have elucidated LMO7's role in promoting cell proliferation by fostering dysregulated cell cycle progression and mitigating apoptotic signaling pathways (11,26-31). Furthermore, LMO7 facilitates cancer cell migration and invasion by modulating the dynamics of actin cytoskeleton and focal adhesion complexes, thereby augmenting cellular motility and tissue invasiveness (34-39) (Table I). LMO7 may affect the dynamics of actin filaments and focal adhesions, thereby enhancing cell motility and invasion into surrounding tissues (34-39).

LMO7 has been implicated in promoting epithelial-mesenchymal transition (EMT) (47), potentially regulating EMT-related genes and signaling pathways, leading to the loss of cell-cell adhesion and the acquisition of invasive properties by cancer cells (Fig. 3). LMO7 may modulate the activity of these signaling pathways, consequently promoting oncogenic

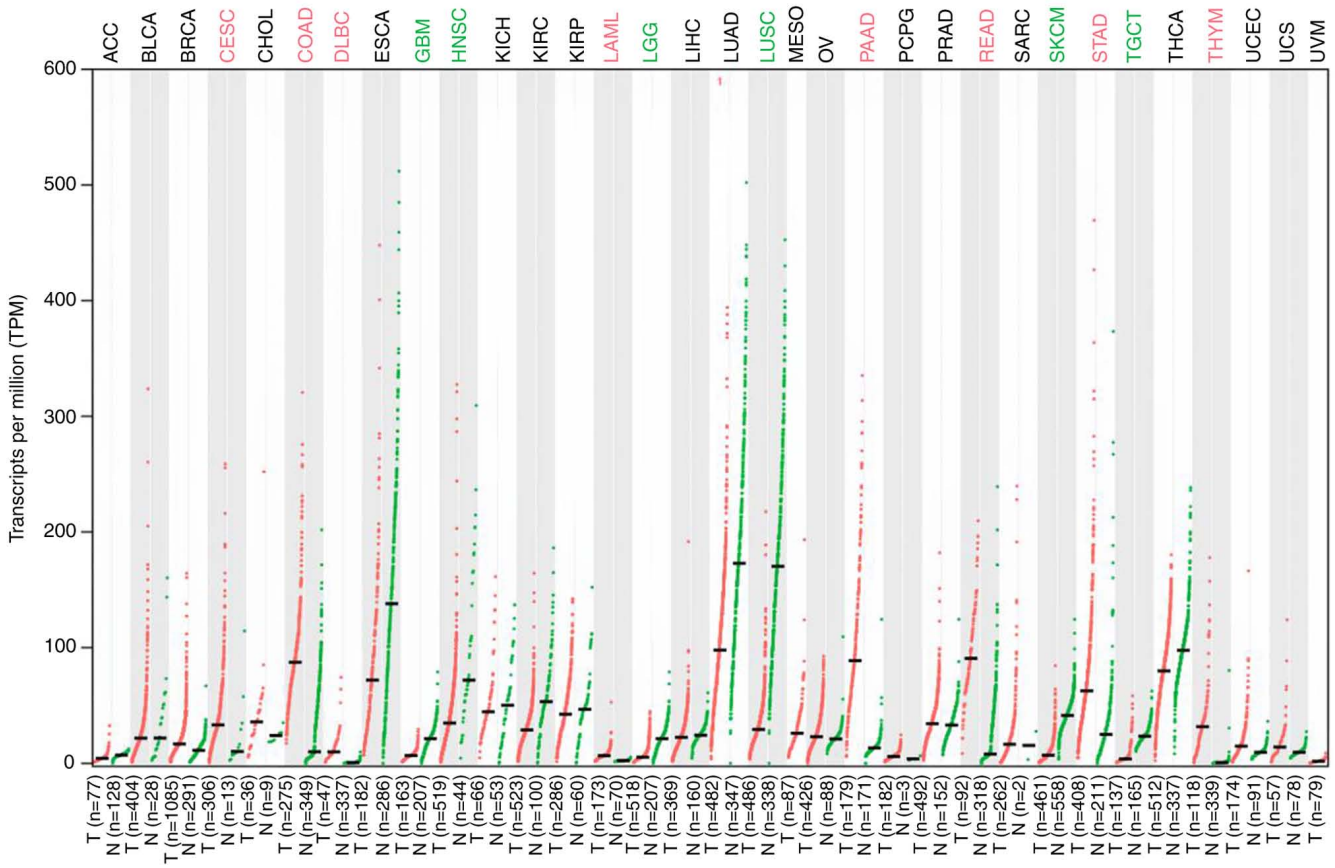

Figure 2. Gene expression profile across all T and N samples. Each dot represents the expression in a sample. The red font indicates that the TPM of LMO7 is significantly upregulated in this tumor type, the green font indicates that the TPM of LMO7 is significantly downregulated in this tumor type and the black font indicates that there is no significant difference between T and N samples. The data were obtained from GEPIA 2. LMO7, LIM domain only 7; T, tumor; N, paired normal tissues; ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal cancer; GBM, glioblastoma multiforme; HNSC, 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; MESO, mesothelioma; 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; UVM, uveal melanoma.

effects such as enhanced cell survival, proliferation and metastasis (37). Specifically, LMO7 has been shown to promote EMT by regulating the activity of transcription factors such as snail, slug and ZEB1, which have pivotal roles in EMT (Fig. 3) (48). Through activation of these transcription factors, LMO7 facilitates the reprogramming of target genes involved in the EMT process, leading to the loss of epithelial characteristics and the acquisition of mesenchymal traits (47,48), facilitating cell invasion and migration, crucial for processes such as tissue repair and wound healing.

LMO7 interacts with AKT, a downstream effector of PI3K, potentially contributing to the activation of AKT signaling (49). This interaction suggests that LMO7 may promote cell survival and growth by enhancing the activity of the PI3K/AKT/mTOR pathway (49). Furthermore, LMO7 may modulate Rho-GTPase activity, impacting cellular processes involved in cancer progression, such as cell migration and invasion (Fig. 3) (50). In addition, LMO7 has been shown to bind to and modulate the activity of MEK1, a kinase upstream of ERK, potentially influencing cell proliferation and survival through the regulation of the ERK/MAPK pathway (Fig. 3) (49). Further research is necessary to fully understand the precise mechanisms and consequences of LMO7's interactions with these pathways in cancer development and progression.

Epigenetic modifications play a critical role in regulating gene expression and can contribute to cancer development and progression (51). Evidence suggests that epigenetic alterations may influence LMO7 expression in different cancer types (29). For instance, in breast cancer, LMO7 has been found to undergo hypermethylation, resulting in reduced gene expression (47). Hypermethylation of the LMO7 promoter region has been associated with tumor progression and poor patient prognosis (52). Further investigation into LMO7-associated epigenetic alterations may offer insight into potential diagnostic, prognostic and therapeutic strategies for cancer patients.

Furthermore, LMO7 has been identified as a TGF-β1 target gene in hepatoma cells, functioning in vascular physiology and fibrosis (53). It is triggered by injury and TGF-β in vascular smooth muscle cells *in vitro* (53). Loss of LMO7 enhanced TGF-β signaling by upregulating TGF-β1 mRNA, TGF-β protein, integrin-αvβ3, latent TGF-β activation, downstream effectors Smad3 phosphorylation and connective tissue growth

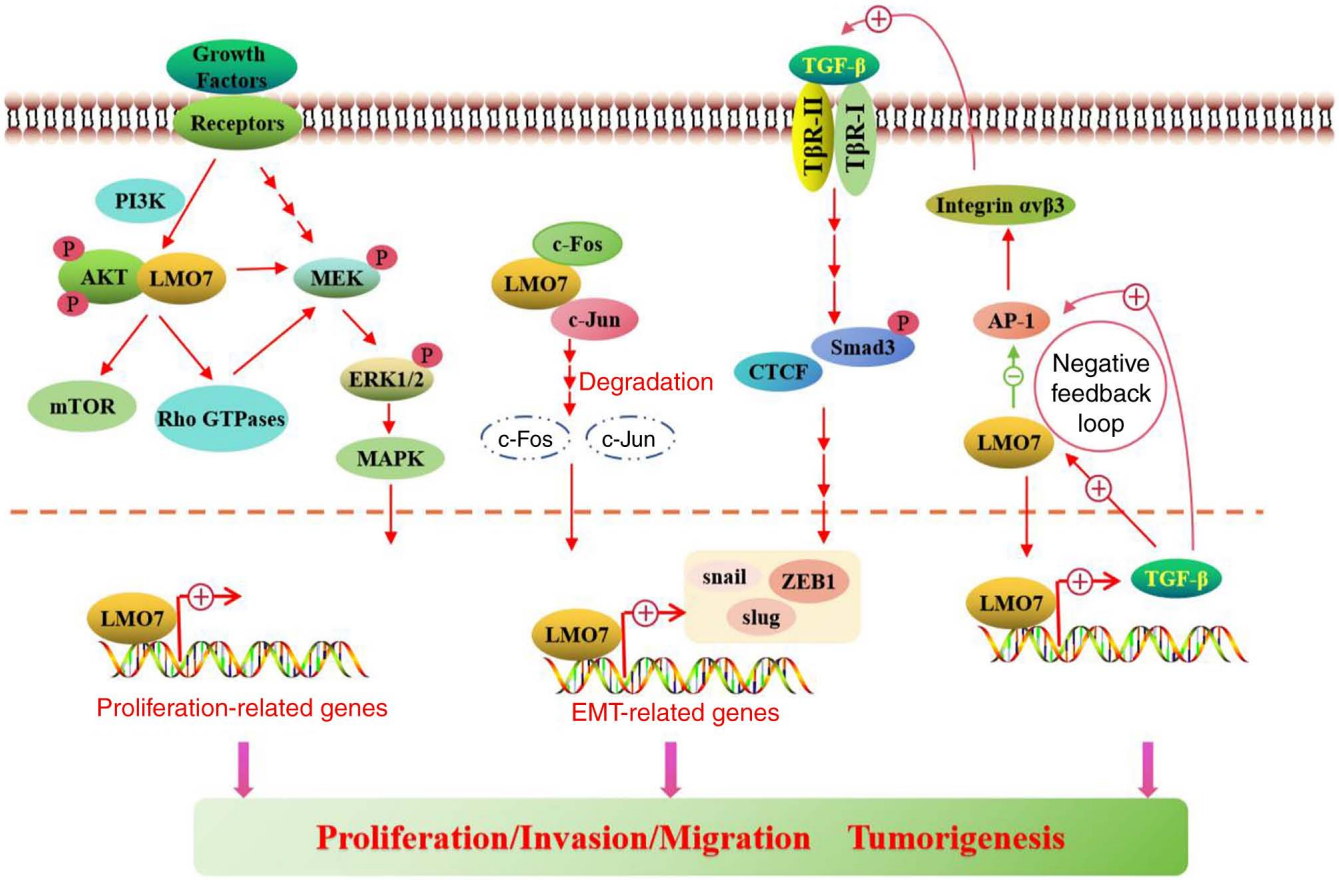

Figure 3. Molecular pathways regulated by LMO7 in tumorigenesis. LMO7 mediates signal transduction pathways and controls the expression of target genes by interacting with different proteins. LMO7 interacts with AKT to enhance the activity of the PI3K/AKT/mTOR pathway and Rho-GTPase. LMO7 interacts with c-Fos and c-Jun, promoting their degradation and interrupting activator protein 1-dependent TGF-β autoinduction. LMO7 and TGF-β form a negative feedback loop to regulate cell proliferation, invasion and migration, leading to tumorigenesis. LMO7, LIM domain only 7; EMT, epithelial to mesenchymal transition; PI3K, phosphoinositide3-kinase; AKT, serine/threonine-protein kinase; mTOR, mechanistic target of rapamycin; Rho-GTPase, rhodopsin-guanosine triphosphatase; MEK1/2, MAP kinase kinase 1/2; MAPK, mitogen-activated protein kinase; c-Fos, Fos proto-oncogene; c-Jun, Jun proto-oncogene; Snail, snail family transcriptional repressor 1; ZEB1, zinc finger E-box binding homeobox 1; Slug, snail family transcriptional repressor 2; CTCF, CCCTC-binding factor; Smad3, SMAD family member 3; TGF-β, transforming growth factor β; TβR-I/II, transforming growth factor beta receptor I/II; integrin-αvβ3, integrin subunit αVβ3; AP-1, activator protein 1.

factor (53). Mechanistically, LMO7's LIM domain interacts with activator protein 1 transcription factors c-Fos and c-Jun, promoting their degradation and interrupting activator protein 1-dependent TGF-β autoinduction (53). A study has shown that the increase in LMO7 mRNA expression synchronizes with TGF-β1-induced invasion, with higher LMO7 expression in high metastatic cells compared to low metastatic cells (36). Induced by TGF-β, LMO7 may limit vascular fibrosis by negative feedback regulation of the TGF-β pathway (Fig. 3), suggesting implications for intimal hyperplasia, wound healing and fibrotic diseases and potentially impacting tumor angiogenesis.

Researchers have found that the curcumin analogue CA-5f {(3E,5E)-3-(3,4-dimethoxybenzylidene)-5-[(1H-indol-3-yl)methylene]-1-methylpiperidin-4-one}, as an anticancer therapeutic agent (54), reduced LMO7 protein levels, which induced the accumulation of microtubule-associated protein 1 light chain 3β and sequestosome 1, increased mitochondrial reactive oxygen species levels and then inhibited autophagosome-lysosome fusion and induced cell death (55). It may thus be suggested that LMO7 may be the target of CA-5f, and related antisense RNA can be designed from LMO7 to interfere with the expression of LMO7 and inhibit the growth of tumor cells.

LMO7 also has a role in inflammation. In the mouse model of autoimmune hepatitis (AIH), injection of bone marrow mesenchymal stem cells (BMSCs) upregulated the levels of LMO7 and downregulated the levels of AP-1 and TGF-β, while the expression of AP-1 and TGF-β was upregulated in the LMO7 interference group. BMSCs can significantly reduce liver injury in the mouse AIH model by regulating the LMO7/AP-1/TGF-β signaling pathway to alleviate liver fibrosis of autoimmune hepatitis (56). The expression of the LMO7 gene was found to be upregulated in gastric epithelial AGS cells (a gastric cancer cell line) infected with *Helicobacter pylori*, which is involved in the adhesion, invasion and possibly proliferation of gastric epithelial cells (57). The expression of LMO7 in *H. pylori* may be involved in the carcinogenesis or differentiation of gastric epithelial cells through direct interactions with other proteins. The proteins that bind to LMO7 and the functional role of protein interactions in cell adhesion should be investigated in gastric epithelial cells stimulated by *H. pylori*. AFDN, vinculin and other proteins that were mentioned in Table I play a role in cell-cell adherens junctions (Table I).

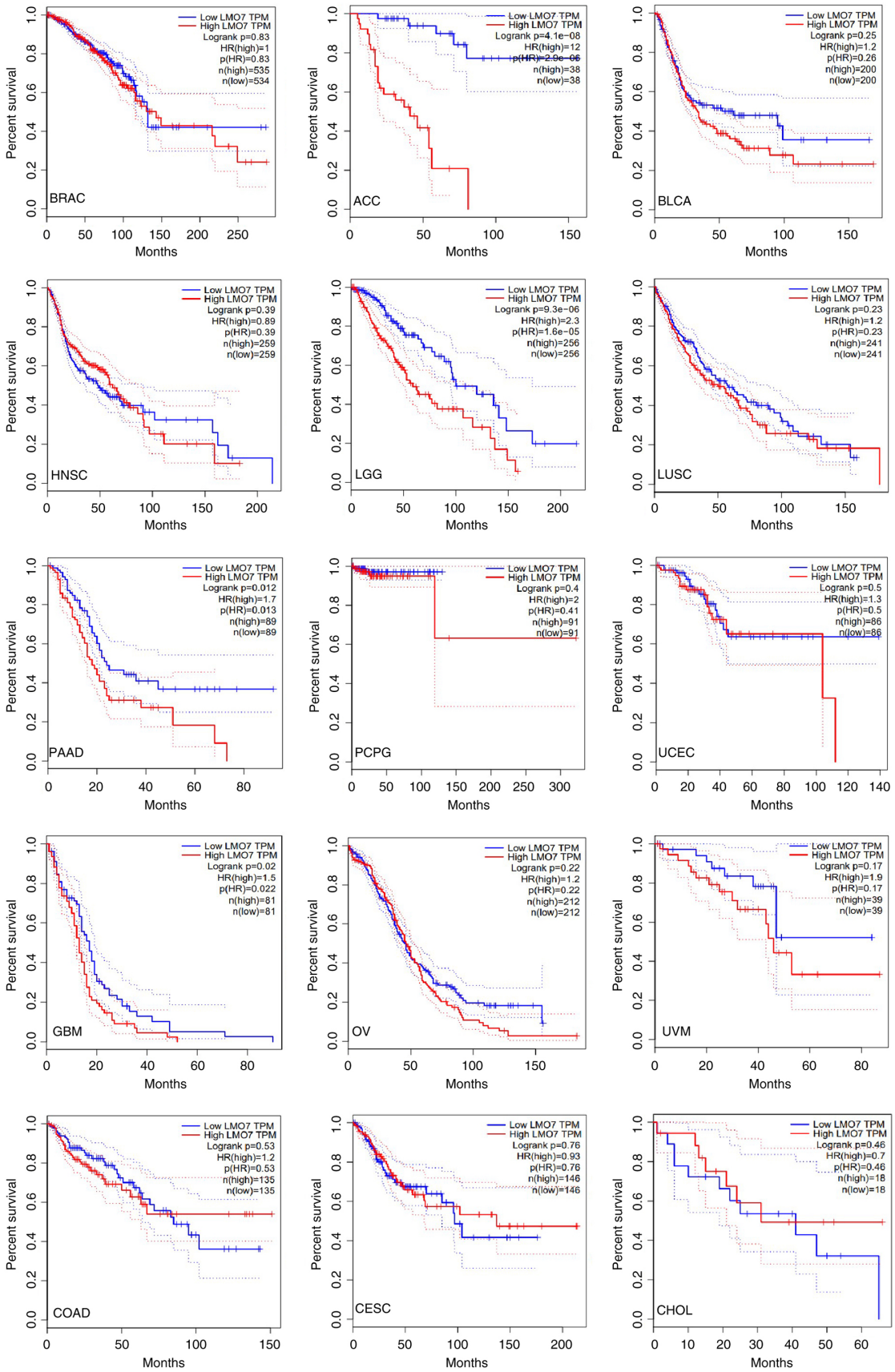

Figure 4. Overall survival analysis based on LMO7 expression. Correlation between high LMO7 TPM and decreased overall survival in BRCA, ACC, BLCA, HNSC, LGG, LUSC, PAAD, PCPG, GBM, UCEC, OV and UVM. Correlation between low LMO7 (TPM) and decreased overall survival in COAD, CESC and CHOL. Data were obtained from GEPIA 2. LMO7, LIM domain only 7; TPM, transcripts per million; HR, hazard ratio; BRCA, breast invasive carcinoma; ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; HNSC, head and neck squamous cell carcinoma; LGG, brain lower grade glioma; LUSC, lung squamous cell carcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; GBM, glioblastoma multiforme; UCEC, uterine corpus endometrial carcinoma; OV, ovarian serous cystadenocarcinoma; UVM, uveal melanoma; COAD, colon adenocarcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma.

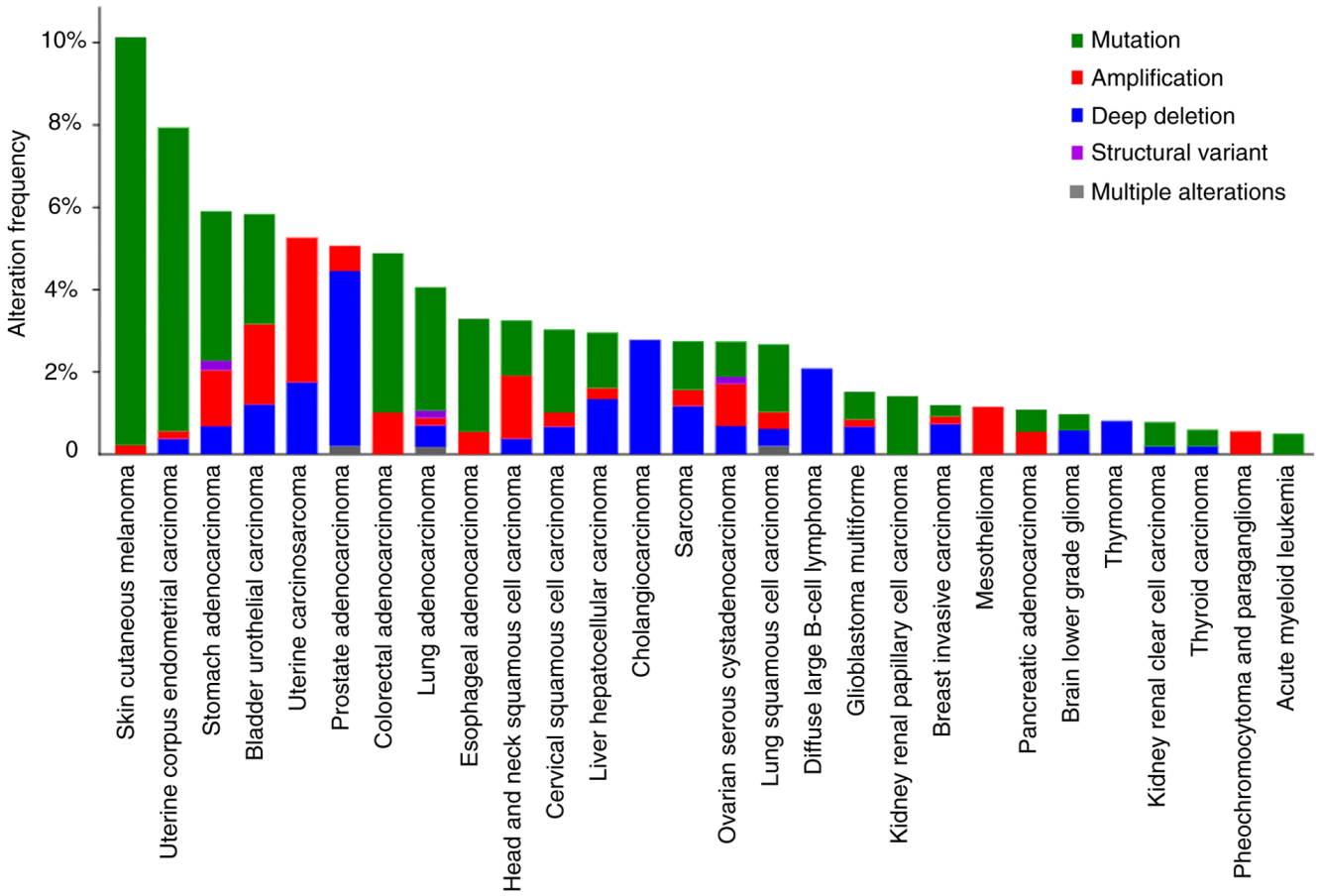

Figure 5. The genomic alterations of LMO7 in different tumors were divided into four categories: Mutation, amplification, deep deletion and structural variant. Among them, mutation and amplification were the most frequent alterations. Data were obtained from the cBioPortal for Cancer Genomics.

5. Prognostic relevance of LMO7 in cancer

The clinical relevance of LMO7 in cancer extends beyond its prognostic value to encompass its potential as a therapeutic target for precision medicine approaches. Of note, elevated LMO7 expression correlates with adverse clinical outcomes and poor patient prognosis across various cancer types, thereby underscoring its utility as a prognostic biomarker (37,47). However, it is important to note that the prognostic relevance of LMO7 may vary across different cancer types and stages (Fig. 4) (28); data were from GEPIA 2.

Compared with human papillomavirus (HPV)-dependent disease, patients with HPV-independent vulvar squamous cell carcinoma (VSCC) have a survival deficit and data suggest that leucine rich repeats and immunoglobulin like domains 2 (LRIG2) and LMO7 are positive prognostic factors in HPV-independent cases; LMO7 is a positive prognostic factor in the most advanced tumors. Therefore, these markers may provide tools for individual treatment strategy selection in patients with VSCC. However, more studies are needed to further elucidate the functional and prognostic value of the molecular markers studied in VSCC (58). High expression of LMO7 antisense RNA 1 was associated with poor survival in kidney cancer (59).

LMO7, along with aminopeptidase like 1, von Willebrand factor, aldehyde dehydrogenase 2 family member, NUAK family kinase 1 and tumor protein, translationally-controlled 1, named the castration-resistant PC-derived prognosis signature, is considered an important molecular signature for predicting progression-free survival (PFS) of patients with castration-resistant PC for therapeutic decision-making (60).

In breast cancer, elevated LMO7 expression correlates with an unfavorable patient prognosis (46,47). Similarly, in colorectal cancer, LMO7 expression serves as a potential prognostic marker, with higher levels associated with adverse patient outcomes, including reduced overall survival and disease-free survival (46,47,50). In addition, increased LMO7 expression correlates with advanced tumor stages, lymph node metastasis and poor tumor differentiation in colorectal cancer cases (44,45). In lung cancer, multiple studies consistently link increased LMO7 expression with unfavorable patient outcomes, including diminished overall survival and disease-free survival rates (Fig. 4) (28,34-36). However, contradictory evidence suggests that elevated LMO7 levels may paradoxically be associated with improved overall survival (Fig. 4) (28). The association between LMO7 expression and prognosis in other cancer types remains to be elucidated. Further research, considering additional factors, is essential to establish LMO7 as a reliable and independent prognostic biomarker in specific cancer contexts.

6. Genomic alteration types

LMO7 mutations have been identified within tumor tissues, implicating their role in cancer development and progression.

These mutations encompass various types, broadly categorized as mutation, structural variant, amplification, deep deletion and multiple alterations (Fig. 5) (61,62); data were from cBioPortal for Cancer Genomics (http://www.cbioportal.org). An analysis in cBioPortal revealed the presence of two missense mutations (P928Q and S1259R) in LMO7 among cancer patients. In addition, LMO7 demonstrated high-level amplification in lung adenocarcinoma, leading to LMO7-ITGBL1 fusion and a Q1334* nonsense mutation (61,62). Deep deletion of LMO7 has been observed in prostate adenocarcinoma and lung squamous cell carcinoma genomes, resulting in TPTE2P5-LMO7 fusion and an I774V missense mutation, respectively (62). It is important to note that the specific consequences of LMO7 mutations in tumor tissues can vary based on the mutation and cancer context. Further research is imperative to comprehensively understand the impact of LMO7 mutations on tumorigenesis and potentially identify novel therapeutic targets.

7. Challenges and future perspectives

Although the expression pattern of LMO7 has been explored across various cancer types, its precise molecular functions in tumorigenesis and cancer progression remain largely elusive. Further research is imperative to identify the specific mechanisms through which LMO7 promotes cancer development and metastasis. Numerous studies investigating LMO7 and cancer have relied on relatively small sample sizes, potentially constraining the generalizability and statistical power of their findings (61,62). Robust larger-scale studies are necessary to corroborate the significance of LMO7 across different cancer types (63-65). The heterogeneity observed within cancer samples, including variations in tumor stage, grade and molecular subtypes, complicates the interpretation of the role of LMO7. Investigating LMO7 expression and its correlation with patient outcomes across large, well-characterized cohorts is necessary to better understand its clinical relevance. Standardized methodologies for studying LMO7 in cancer research are lacking, with studies employing diverse experimental approaches like immunohistochemistry, gene expression profiling and functional assays, posing challenges for comparison and integration of findings across studies. The functional characterization of LMO7 in cancer has mainly relied on *in vitro* cell culture experiments and xenograft models (28-30). The development of more sophisticated preclinical models is crucial for validating its role in cancer progression, as these models fail to fully replicate the complex tumor microenvironment and organismal interactions.

Targeting LMO7 for cancer treatment shows promise due to its involvement in various cellular processes contributing to tumorigenesis (26-31,66,67). However, several challenges need to be addressed before LMO7-based therapies can be effectively developed. These include the complexity of LMO7 function, its context-dependent roles in different cancer types and the absence of specific inhibitors or modulators targeting LMO7. The diverse functions of LMO7 in cell adhesion, cytoskeletal organization, signal transduction and gene regulation make it difficult to selectively target its activity without interfering with important cellular processes (23-25). Interfering with LMO7 function may lead to unintended consequences, undesirable side effects or the limitation of therapeutic efficacy. The role and expression levels of LMO7 may vary among different cancer types and even among subtypes of the same cancer, posing challenges for targeted therapies. Further studies are needed to understand the precise mechanism by which LMO7 is involved in the genesis of different cancer types and to identify reliable biomarkers for patient stratification. Currently, there is a lack of specific inhibitors or modulators selectively targeting LMO7. High-throughput screening and rational drug design methods can be utilized to identify small molecules or peptides interfering with LMO7 interactions or functional domains.

To overcome the challenges in understanding the role of LMO7 in various cancer types, continued research is essential. This includes conducting comprehensive studies to investigate the molecular mechanisms by which LMO7 promotes tumor progression and metastasis. Additional experiments using cellular and animal models can provide valuable insight into its specific contributions to cancer development.

In PC, prediction of PFS and castration resistance molecular characteristics is crucial for making treatment decisions, but current methods lack reliability. Researchers have applied the Robust Rank Aggregation method to analyze the transcriptome profile of PC to identify 287 differentially expressed genes, including LMO7 (68,69). However, this work has yet to be validated and clinically applied.

Further research is needed to elucidate the role of LMO7 as a diagnostic and prognostic biomarker. If LMO7 is confirmed as an oncogene, strategies for therapeutic targeting can be explored, such as developing small-molecule inhibitors specific to LMO7 or gene therapy approaches to suppress its expression. In-depth molecular characterization of LMO7 and its associated signaling pathways can help identify potential drug targets and combination therapies to overcome challenges such as drug resistance and metastasis. Analyzing LMO7 expression levels in patient samples through techniques such as immunohistochemistry can establish correlations between LMO7 expression and clinical outcomes, including patient survival and response to therapy. Longitudinal studies can also provide information about dynamic changes in LMO7 expression during disease progression and its potential as a predictive biomarker or therapeutic target. In addition, the development of reliable biomarkers associated with LMO7 may aid in monitoring treatment response and disease progression.

The present review delved into the intricate role of LMO7 in cancer development, elucidating the molecular mechanisms underlying its oncogenic effects. With its involvement across various cancer types and potential as a prognostic marker and therapeutic target, understanding the function of LMO7 offers valuable insight into cancer biology and paves the way for precision medicine. However, further research is imperative to overcome current limitations and fully harness the potential of targeting LMO7 in cancer therapy. By unraveling the mysteries surrounding LMO7, we can advance towards personalized and effective cancer treatments.

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Availability of data and materials

The experimental data and the simulation results that support the findings of this review are available from the STRING database (string-db.org), GEPIA 2 (http://gepia2.cancer-pku.cn/) and cBioPortal (http://www.cbioportal.org).

Authors' contributions

QZ and TJ: Substantial contributions to conception and design of the work, acquisition, analysis and interpretation of data for the study; drafting the manuscript or reviewing it critically for important intellectual content. JW: Conception and design, revising the manuscript, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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