Advances in the molecular mechanisms and clinical applications of LEMD1 in tumor development and progression (Review)

XIAO-BO WANG[1-3], XIAN-FEI WANG[1,3] and SAIRAH BINTI ABDUL KARIM[4]

[1]Department of Gastroenterology, Digestive Endoscopy Center, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan 637000, P.R. China; [2]School of Graduate Studies, Post Graduate Centre, Management and Science University, Shah Alam, Selangor 40100, Malaysia; [3]Sichuan Branch of National Clinical Research Center for Digestive Diseases, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan 637000, P.R. China; [4]Faculty of Health and Life Sciences, Management and Science University, Shah Alam, Selangor 40100, Malaysia

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Abstract. LAP2-emerin-MAN1 (LEM) domain-containing protein 1 (LEMD1), first identified in colorectal cancer in 2004, is a gene that is specifically expressed in the testis. The expression of LEMD1 is minimal in normal somatic cells but high in various types of malignant tumor (such as gastric, prostate, pancreatic and colorectal cancer as well as oral squamous cell carcinoma) due to abnormal promoter demethylation. LEMD1 promotes cell proliferation, invasion and metastasis during tumor progression, making it a potential diagnostic marker and therapeutic target. The present review summarized the research progress of LEMD1 as a cancer-testis antigen in tumor biology. Furthermore, the present review investigated the molecular structure and biological functions of LEMD1, its expression patterns, clinical relevance in various types of tumor, and highlighted current research challenges and future directions.

Correspondence to: Dr Xian-Fei Wang, Department of Gastroenterology, Digestive Endoscopy Center, Affiliated Hospital of North Sichuan Medical College, 1 Maoyuan South Road, Shunqing, Nanchong, Sichuan 637000, P.R. China
E-mail: 2750853458@qq.com

Dr Sairah Binti Abdul Karim, Faculty of Health and Life Sciences, Management and Science University, University Drive, Section 13, Shah Alam, Selangor 40100, Malaysia
E-mail: sairah@msu.edu.my

Abbreviations: LEMD1, LEM domain-containing protein 1; CTA, cancer-testis antigen; EMT, epithelial-mesenchymal transition; OS, overall survival; DFS, disease-free survival; NSCLC, non-small-cell lung cancer; TNBC, triple-negative breast cancer; ALCL, anaplastic large cell lymphoma

Key words: LEMD1, CTA, tumor, nuclear inner membrane protein, molecular mechanisms, prognostic biomarker

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1. Introduction

LAP2-emerin-MAN1 (LEM) domain-containing protein 1 (LEMD1; also referred to as LEMP-1 and testes-specific protease 50) is a cancer-testis antigen (CTA) that was first identified in 2004 as a novel testis-specific gene expressed in colorectal cancer tissues (1,2). As a CTA, LEMD1 has a low expression level in normal somatic cells and is only expressed in immune-privileged tissues such as the testis (3). However, in tumors, abnormal demethylation and activation of the gene promoter leads to high expression levels of LEMD1 in various tumor tissues, including gastric, pancreatic, colorectal and prostate cancer as well as oral squamous cell carcinoma (OSCC) (4-6). Consistent with the broader CTA paradigm, prototypical CTAs such as New York esophageal squamous cell carcinoma 1 and melanoma-associated antigen 4 exhibit testis restricted expression yet are aberrantly activated across diverse malignancies (7). An increasing number of studies suggest that LEMD1 serves an oncogenic role in the development and progression of tumors in which its overexpression can promote malignant phenotypes such as tumor cell proliferation, invasion and metastasis (2,8). Therefore, LEMD1 has received widespread attention in the field of tumor biology and is considered a potential diagnostic marker and therapeutic target.

The present review summarized the molecular structure and biological functions of LEMD1, its expression patterns and clinical relevance across diverse tumors, mechanistic insights

into its tumor-promoting actions, and emerging therapeutic approaches. Unlike previous reports that investigate LEMD1 in a single type of tumor or along a single pathway, the present review provided two distinct advances. Firstly, it provided, to the best of our knowledge, the first comprehensive integration of the nuclear-inner-membrane localization of LEMD1 with five convergent cytoplasmic signaling cascades, namely PI3K/Akt, ERK/MAPK, Wnt/β-catenin, Ras homolog family member A (RhoA)/Rho-associated coiled-coil-containing protein kinase (ROCK) and p53/mTORC1, each of which were previously only examined in isolation (2,9-11). Secondly, the present review offered a systematic synthesis of 'expression-signaling-clinical relevance' data for LEMD1 across >10 tumor entities, allowing for the construction of a cross-cancer landscape, which has not been addressed in previous LEMD1-related studies (12,13) and highlighted its diagnostic and therapeutic potential.

2. Molecular structure and biological functions of LEMD1

LEMD1 gene and protein structure. Located in the q32.1 region of human chromosome 1, the LEMD1 gene contains 9 exons, encoding multiple splice variants. At present, five transcript variants have been reported, with V1-3 mainly expressed in testis and colorectal cancer stem cells, while V4 and 5 are expressed at low levels in normal tissues (14). The LEMD1 protein belongs to the LEM domain protein family. The full-length protein consists of 181 amino acids with a molecular weight of ~20 kDa. It contains an N-terminal LEM domain and a C-terminal transmembrane region, making it a single-pass membrane protein (15,16) localized to the inner nuclear membrane, as presented in Fig. 1. The LEM domain is a conserved structure composed of ~40 amino acids that binds to the barrier-to-autointegration factor (BAF) (17). In classic LEM family proteins [such as lamina-associated polypeptide 2β (LAP2β), emerin and MAN1 (also known as LEMD3)], the LEM domain is located on the nucleoplasmic side and can anchor chromatin to the nuclear membrane by binding to BAF or BAF-DNA complexes (14,18). As a member of the aforementioned family, the LEMD1 protein is hypothesized to have similar structural features and interaction interfaces, potentially participating in nuclear membrane-chromatin connections (14,19,20).

Biological functions of LEMD1 in cell biology. Under normal physiological conditions, research on the normal biological functions of LEMD1 is limited due to its low expression levels in the majority of normal tissues. Previous studies suggest that LEMD1 may serve roles in cell cycle regulation, chromatin conformation maintenance and nuclear membrane homeostasis in specific cell types (such as germ cells) (15,21).

Typically, chromatin anchored to the nuclear periphery is associated with deacetylated histones, for example H3K9 and H3K27, and heterochromatin-associated markers (such as H3K9me2 and H3K9me3) (22), which maintains a relatively transcriptionally silent state (16). LEMD1 may anchor specific chromatin regions to the nuclear periphery through its LEM domain binding with BAF, potentially influencing the epigenetic state and transcriptional activity of these genes (16). Therefore, it is hypothesized that LEMD1 may participate in the regulation of gene expression. Other studies demonstrate potential associations between LEMD1 and gene splicing and epigenetic regulation processes (14,19,20,23). For example, a study by Li *et al* (11) suggests that the methylation state of the LEMD1 gene promoter region maintains high methylation in normal cells, resulting in silencing, while demethylation occurs in tumor cells leading to gene activation.

Additionally, during human spermatogenesis, LEMD1 transcripts are highly enriched in post-meiotic germ cells, with single-cell analyses showing maximal expression levels in late spermatids (24,25). This testis-specific pattern suggests a specialized role during spermatogenesis. Furthermore, as developing spermatids undergo chromatin remodeling and nuclear reshaping, a number of canonical nuclear envelope proteins (such as emerin and LEMD3) are absent; however, LEMD1 is one of the small number of LEM-domain factors expressed in these cells (24). Notably, LEMD1 is not detected at the nuclear periphery in spermatids but instead localizes within the nucleoplasm, and slowly localizes toward the posterior pole of the nucleus as spermatids elongate (24). This dynamic localization suggests that LEMD1 may help tether chromatin to the remaining nuclear scaffold or otherwise contribute to nucleus remodeling during the histone-to-protamine transition. Consistent with this hypothesis, in human spermiogenesis, LEMD1 (along with LAP2β and lamin B1) is suggested to substitute for the lamin B receptor (which is absent in spermatids) as an anchoring interface between chromatin and the nuclear envelope (26). As LEMD1 can bind to BAF, its presence in spermatids may possibly maintain transient chromatin-nuclear envelope connections at a stage when the lamina is being dismantled (24). These observations point to a physiological role for LEMD1 in orchestrating spermatid nuclear organization and stability, which may be critical for proper spermatogenesis and subsequent sperm function. These phenomena are consistent with the regulatory patterns of the majority of CTA genes, suggesting that LEMD1 has limited function in normal cell biology, while its abnormal expression primarily occurs in the context of tumorigenesis.

3. Expression of LEMD1 and clinical relevance in different types of tumor

LEMD1 expression levels in different types of tumor. The present analyses using the Tumor Immune Estimation Resource 2.0 database (https://compbio.cn/timer2/) indicated that LEMD1 mRNA was highly expressed across ~20 types of cancer, whereas its expression level was low or undetectable in the majority of normal tissues, as illustrated in Fig. 2. In 2004, a study by Yuki *et al* (1) first reported a high expression of LEMD1 in colorectal cancer. Subsequently, in a study by Li *et al* (4), which analyses The Cancer Genome Atlas database and patient samples, reports that LEMD1 is notably upregulated in tissues and cell lines of gastric cancer compared with normal gastric mucosa and normal gastric epithelial cells. In addition to the digestive system, upregulated LEMD1 expression levels are reported in various solid tumors. For example, a study by Ghafouri-Fard *et al* (23) examines 30 prostate cancer cases and reports LEMD1 transcripts in 23% of them, while none are detected in 25 cases of benign prostatic hyperplasia. In OSCC, ~35% of patient

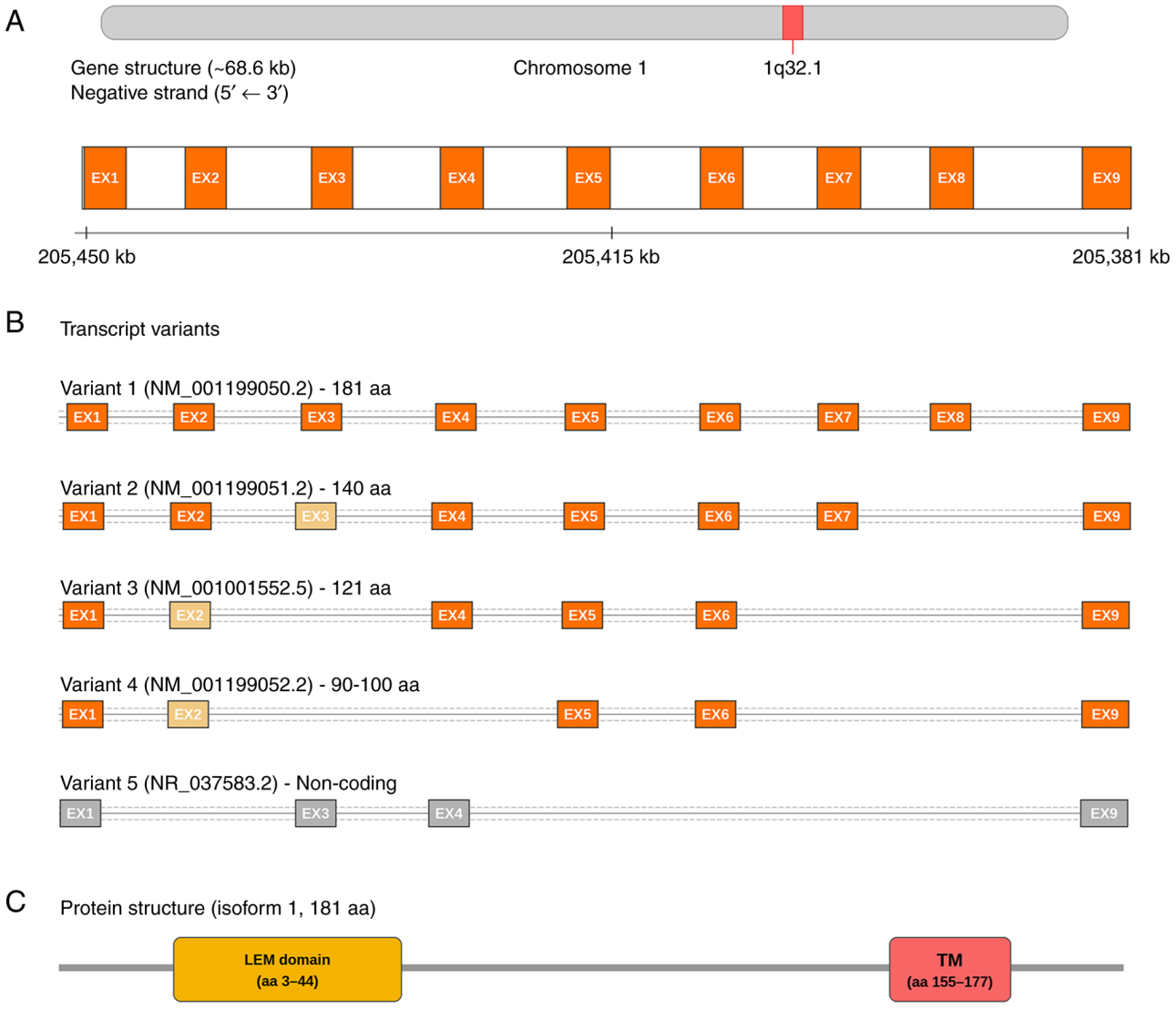

Figure 1. Schematic diagram of the LEMD1 gene and protein structure. (A) An illustration of the genomic organization of LEMD1 on chromosome 1q32.1, including exons 1-9. (B) Five transcript variants generated by alternative splicing. Coding exons are shown in orange, alternatively spliced exons in light orange, non-coding exons in gray and introns as connecting lines. (C) The domain architecture of isoform 1, which contains a LEM domain and a TM domain. The schematic is not drawn to scale. The figure was created using Microsoft PowerPoint 365 (version 2602; build 16.0.19725.20126; Microsoft Corporation). LEM, LAP2-emerin-MAN1; TM, transmembrane; NM, NCBI RefSeq mRNA accession prefix; NR, NCBI RefSeq non-coding RNA accession prefix; LEMD1, LEM domain-containing protein 1.

tumors showed positive immunohistochemistry for LEMD1, with elevated LEMD1 protein expression levels in positive tumors (9). Both sequencing analysis and quantitative PCR validation of LEMD1 mRNA reveal notably increased transcription levels in papillary thyroid cancer tissues compared with adjacent normal thyroid tissues (27). Triple-negative breast cancer (TNBC), a type of breast cancer with a poor prognosis, reveals higher LEMD1 expression levels in tissues compared with other subtypes of breast cancer (11). Pancreatic cancer tissues also exhibit abnormally high LEMD1 expression levels, with reports indicating higher mRNA and protein levels compared with normal pancreatic tissues (2). Additionally, elevated LEMD1 expression levels are confirmed in non-small cell lung cancer (NSCLC) and are associated with malignant tumor behaviors. For example, higher LEMD1 levels are associated with poorer differentiation, advanced TNM stage and lymph node metastasis, and it predicts a shorter overall survival in patients with NSCLC (28). Furthermore, LEMD1 is also implicated in anaplastic large cell lymphoma (ALCL), with nucleophosmin-anaplastic lymphoma kinase/STAT3 signaling reported to upregulate LEMD1 expression levels (29). Overall, as a CTA, LEMD1 shows cancer tissue-specific high expression levels in multiple types of tumor, providing a basis for its potential use as a universal tumor marker.

Association between LEMD1 and clinicopathological features. Abnormal expression of LEMD1 not only has tumor specificity but is also notably associated with adverse clinicopathological features in multiple types of tumor, such as OSCC, thyroid cancer and TNBC (9,11,27), including more advanced TNM staging, lymph node metastasis, distant metastasis, increased tumor volume and vascular or lymphatic invasion (9,21,30). Previous studies suggest that

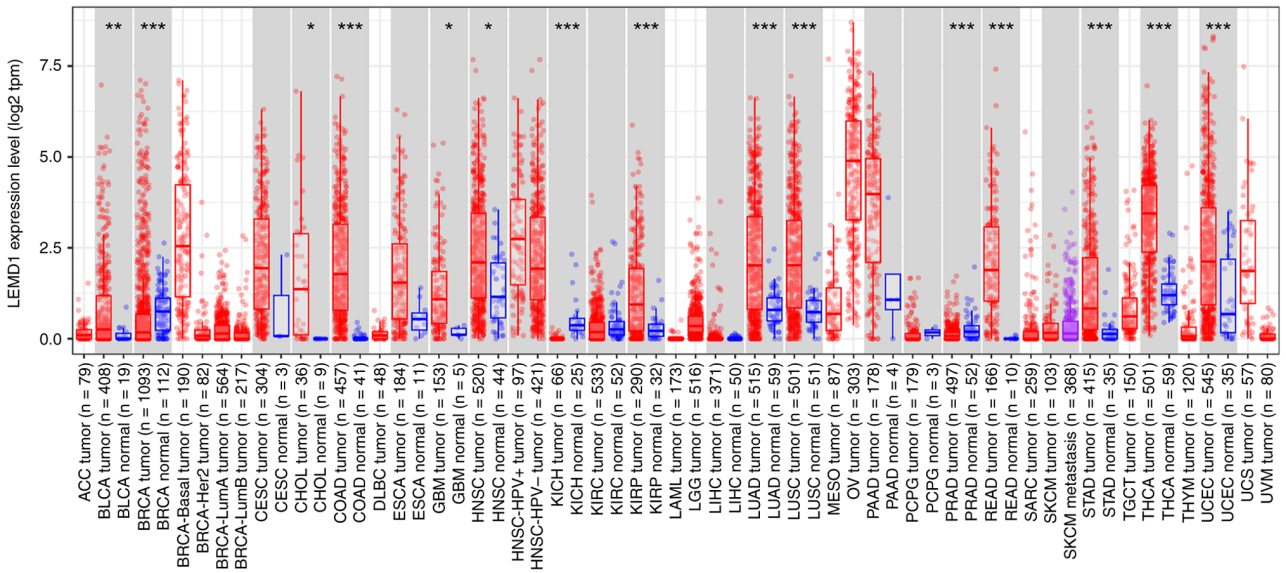

Figure 2. Expression profile of LEMD1 across different types of tumors. Box plots showing the mRNA expression levels of LEMD1 in tumor (red) and matched normal (blue) tissues across multiple types of cancer, presented as log2 tpm. The sample size for each group is indicated in parentheses on the x-axis. Normal data are shonw only when available; therefore, a number of types of cancer do not have corresponding normal tissue expression levels. Differential expression analysis was carried out using edgeR (version 4.4.2; https://bioconductor.org/packages/edgeR) based on RNA sequencing raw counts. *P<0.05, **P<0.01 and ***P<0.001. The figure was generated using the Tumor Immune Estimation Resource, version 2 database (https://compbio.cn/timer2/). LEMD1, LAP2-emerin-MAN1 domain containing 1; 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, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; 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, 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 tumor; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

in colorectal cancer, high expression of LEMD1 is positively correlated not only with lymph node metastasis and liver metastasis but also with tumor staging (1,14,21,31). A study by Sasahira *et al* (9) analyzed 289 patients with OSCC and found that LEMD1 expression levels were notably associated with tumor progression (T factor and clinical stage), nodal metastasis and poor prognosis. Furthermore, immunostaining for cytoplasmic LEMD1 is positive more frequently in patients with nodal metastasis compared with those without nodal metastasis [65.7% (46/70 patients) vs. 25.1% (55/219 patients)]. Multivariate analysis further identifies LEMD1 expression levels as an independent predictor of disease-free survival (DFS) in patients with OSCC (9). In patients with papillary thyroid cancer, high LEMD1 expression levels are also notably associated with a higher risk of lymph node metastasis (27). Additionally, in patients with TNBC, high LEMD1 expression levels are notably associated with a higher histological grade and shorter overall survival (OS) compared with those with low LEMD1 expression levels (11). A study on NSCLC reports that high LEMD1 expression levels are associated with later TNM staging, poorer tumor differentiation and an increased likelihood of lymph node metastasis, as well as increased cancer stem cell-like phenotypes and invasiveness (28). Additionally, a study by Cao *et al* (2) reports that LEMD1 is upregulated in pancreatic cancer tissue, and patients with high LEMD1 expression levels are more likely to develop distant metastasis, suggesting that LEMD1 may promote the metastatic ability of pancreatic cancer. These results indicate that high LEMD1 expression levels often suggest a more aggressive tumor biological behavior and worse clinical outcomes. By contrast, in normal tissues or benign/early stages of tumors, LEMD1 typically remains silent or at low levels, corresponding to an improved prognosis.

Potential diagnostic and prognostic value of LEMD1 in tumors. Due to the absence of LEMD1 in the majority of normal tissues and its abnormal appearance in tumors, its detection has potential value for tumor diagnosis and prognosis assessment. Multiple studies based on Kaplan-Meier survival analyses and multivariate Cox regression analyses report that LEMD1 can serve as an adverse prognostic factor for various types of tumor (9,11,21). In cohorts with colorectal or pancreatic cancer, patients with high LEMD1 expression levels have a notably reduced OS and DFS (2,32). A previous study on colorectal cancer constructed a three-gene model including LEMD1 to predict postoperative recurrence risk, with results showing that this model can effectively identify patients at high risk of recurrence (21). Several studies provide performance indicators for the diagnostic utility of LEMD1 (9,23,27). In papillary thyroid carcinoma, LEMD1 overexpression distinguishes tumor from normal tissue with high accuracy (receiver operating characteristic analysis yielding ~80% sensitivity and ~90% specificity) (27). Furthermore, in pancreatic cancer, an autoantibody biomarker panel incorporating LEMD1 achieved an area under the

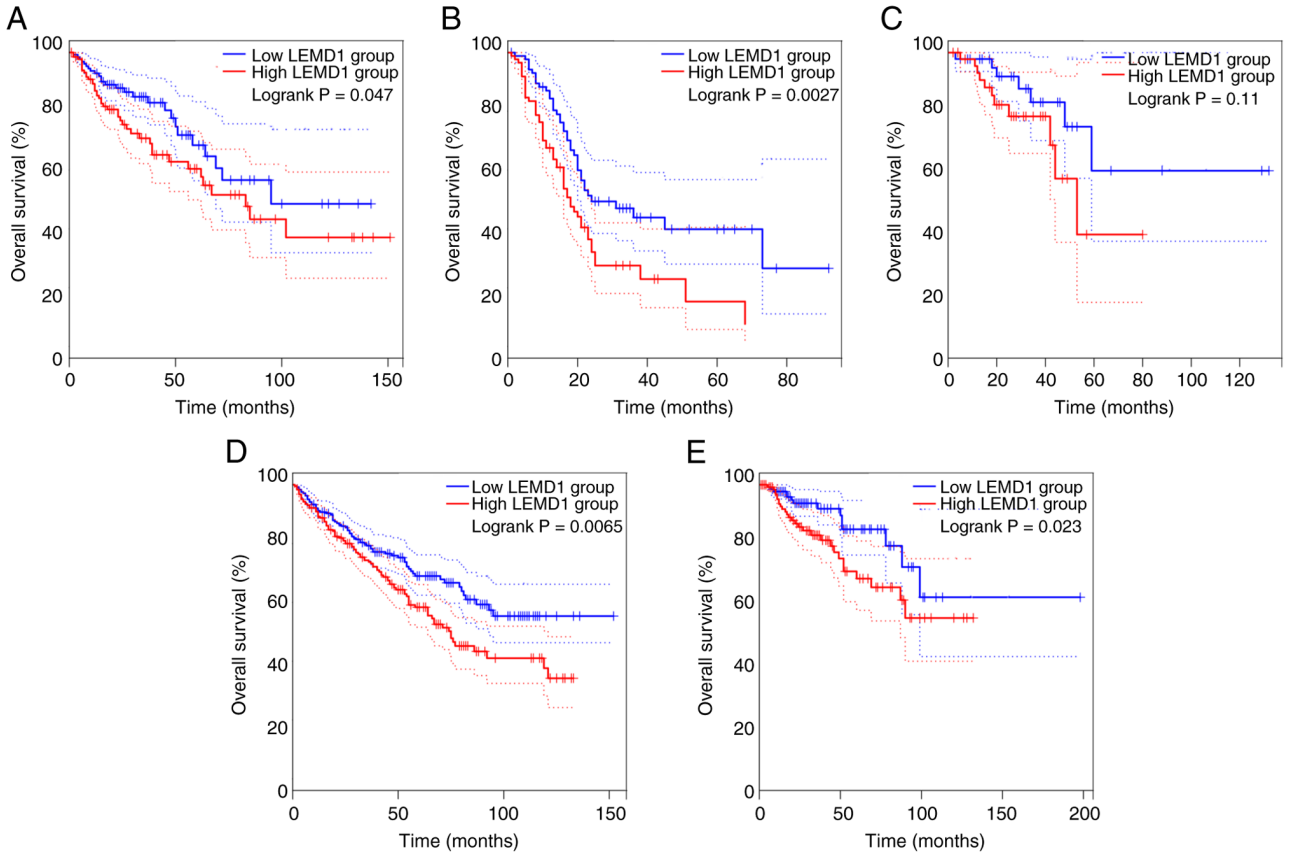

Figure 3. Kaplan-Meier overall survival curves according to LEMD1 expression levels in five types of cancer. Patients were divided into high and low LEMD1 expression level groups based on the median expression level values. The blue solid lines represent the low LEMD1 expression level groups and the red solid lines represent the high LEMD1 expression level groups, with dotted lines indicating the 95% confidence intervals. The log-rank test P-values are shown in each panel. (A) Colon adenocarcinoma (high LEMD1 group, n=135; low LEMD1 group, n=135; HR=1.6; P=0.048; log-rank P=0.047). (B) Pancreatic adenocarcinoma (high LEMD1 group, n=89; low LEMD1 group, n=89; HR=1.9; P=0.0031; log-rank P=0.0027). (C) Rectum adenocarcinoma (high LEMD1 group, n=46; low LEMD1 group, n=46; HR=2.2; P=0.11; log-rank P=0.11). (D) Kidney renal clear cell carcinoma (high LEMD1 group, n=253; low LEMD1 group, n=250; HR=1.5; P=0.0069; log-rank P=0.0065). (E) Kidney renal papillary cell carcinoma (high LEMD1 group, n=140; low LEMD1 group, n=141; HR=2.1; P=0.026; log-rank P=0.023). The figure was generated using the GEPIA2 database (http://gepia2.cancer-pku.cn). The survival data were derived from The Cancer Genome Atlas (database of Genotypes and Phenotypes accession no. phs000178; https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000178) using the following search parameters in the GEPIA2 database: Gene symbol, LEMD1; type of cancer, esophageal carcinoma; analysis method, overall survival; group cutoff, median; HR based on Cox proportional hazards model; and 95% confidence interval. LEMD1, LAP2-emerin-MAN1 domain-containing protein 1; HR, hazard ratio; GEPIA2, Gene Expression Profiling Interactive Analysis 2.

curve of 0.906 (93.3% sensitivity and 76.7% specificity) (33), highlighting the diagnostic potential of LEMD1 in oncology. Furthermore, as a CTA, LEMD1 also has potential immunogenicity that can be used for serological detection, such as the elevated LEMD1 autoantibodies detected in the blood of patients with pancreatic cancer (33), suggesting its research value in early diagnosis and recurrence monitoring. Whether similar anti-LEMD1 autoantibodies are present in other types of cancer is yet to be elucidated; however, given the status of LEMD1 as a CTA, this is a plausible possibility that warrants further investigation.

The survival analysis of the present review used the Gene Expression Profiling Interactive Analysis 2 (http://GEPIA2.cancer-pku.cn/) database and revealed that high LEMD1 expression levels were associated with a poor prognosis in colon, rectal, pancreatic and kidney cancer, as presented in Fig. 3. The aforementioned evidence suggests that detecting LEMD1 expression levels in tumor samples has the potential to provide useful prognostic information for clinical practice and guide subsequent treatment strategies.

4. Molecular mechanisms of LEMD1 in tumor development and progression

Association between LEMD1 and cell proliferation, apoptosis and migration. Several functional experiments (2,4,9,21,27) reveal that LEMD1 promotes tumor progression in multiple types of cancer. For example, knocking down LEMD1 suppresses invasion and endothelial transmigration in OSCC; in gastric cancer, it promotes proliferation through effects on the cell cycle and apoptosis; in colorectal cancer, it enhances proliferation, migration, invasion and the epithelial-mesenchymal transition (EMT); and in thyroid and pancreatic cancer, gain- and loss-of-function experiments show effects on proliferation, migration/invasion and apoptosis (Table I) (2,4,10,11,21,27-31,34). A study by Li *et al* (4) demonstrates in gastric cancer cells that the overexpression of LEMD1 accelerates the G1/S phase transition and inhibits the expression of the apoptosis-related protein Bax, which increases tumor cell proliferation rates and promotes clone formation. By contrast, LEMD1 knockdown inhibits cell proliferation and induces

Table I. Functions and potential mechanisms of LEMD1 in different types of tumors.

First author, year	Type of tumor	Expression of LEMD1	Functional impact	Associated genes or signaling pathways	(Refs.)
Zhang *et al*, 2022	Colorectal cancer	Highly expressed	Promotes cell proliferation, migration, invasion and the EMT	RhoA/ROCK1 signaling pathway	(21)
Luo *et al*, 2021	Colorectal cancer	Highly expressed	Promotes cell proliferation, migration, invasion and angiogenesis	PI3K/AKT signaling pathway	(31)
Li *et al*, 2022	Colorectal cancer	Highly expressed	Promotes cell proliferation, migration, invasion and angiogenesis	PI3K/AKT pathway and upstream regulation by SOX4	(30)
Li *et al*, 2022	Oral squamous cell carcinoma	Highly expressed	Promotes cell migration and invasion	PI3K-AKT signaling pathway, which may be activated via the LEMD1-AS1/LEMD1 axis	(34)
Sasahira *et al*, 2020	Oral squamous cell carcinoma	Highly expressed	Promotes cell invasion, adhesion to endothelial cells and transendothelial migration	SRPX2-uPAR/HGF pathway	(10)
Li and Zhang, 2023	Non-small cell lung cancer	Highly expressed	Promotes cell proliferation, invasion, stem cell characteristics and inhibits apoptosis	PI3K/AKT pathway	(28)
Cao *et al*, 2022	Pancreatic cancer	Highly expressed	Promotes cell proliferation, migration, invasion and inhibits apoptosis	p53 and mTORC1 signaling pathways	(2)
Li *et al*, 2019	Gastric cancer	Highly expressed	Promotes cell proliferation, cell cycle progression and inhibits apoptosis	PI3K/Akt signaling pathway	(4)
Xu *et al*, 2021	Papillary thyroid cancer	Highly expressed	Promotes cell proliferation, migration, invasion, the EMT and inhibits apoptosis	Wnt/β-catenin signaling pathway	(27)
Li *et al*, 2023	Triple-negative breast cancer	Highly expressed	Promotes cell proliferation, migration, invasion, the EMT and inhibits apoptosis	ERK signaling pathway	(11)
Matsuyama *et al*, 2011	Anaplastic large cell lymphoma	Highly expressed	Reduces chemotherapy sensitivity, promotes cell proliferation and inhibits apoptosis	NPM-ALK/STAT3 pathway	(29)

LEMD1, LEM domain containing 1; EMT, epithelial-mesenchymal transition; RhoA, ras homolog family member A; ROCK1, Rho-associated coiled-coil-containing protein kinase 1; AS1, antisense RNA 1; SRPX2-uPAR, sushi repeat containing protein X-linked 2-urokinase plasminogen activator receptor; HGF, hepatocyte growth factor; NPM-ALK, nucleophosmin-anaplastic lymphoma kinase.

cell cycle arrest and increases apoptosis. *In vivo* experiments also demonstrate that reduced LEMD1 levels slows the growth of transplanted tumors (4). In colon cancer, knockdown of LEMD1 notably reduces the proliferative activity of tumor cells (30). A study by Li and Zhang (28) on NSCLC cells reveals that upregulation of LEMD1 confers 'stem cell-like' phenotypes to tumors, including enhanced spherical clone formation and self-renewal capacity. A study by Cao *et al* (2) hypothesizes that LEMD1 knockdown notably enhances p53 pathway-mediated apoptosis. This finding suggests that, under normal conditions, LEMD1 helps restrain the pro-apoptotic activation of p53, likely by upregulating survival signals or pathways that keep p53 in check. Collectively, these studies indicate that LEMD1 promotes tumor cell proliferation and survival across multiple types of cancer, likely by facilitating cell-cycle progression and suppressing apoptosis, which contributes to tumor growth.

The presence of LEMD1 notably increases the invasive and metastatic potential of cancer cells. Previous studies suggest that LEMD1 is involved in metastatic progression in OSCC; high LEMD1 expression levels are associated with lymph node metastasis, and metastatic tumors have higher LEMD1 expression levels compared with non-metastatic tumors (9,10,34). *In vitro* functional experiments confirm that

LEMD1 knockdown inhibits the invasive ability of oral cancer cells and reduces the ability of cancer cells to migrate through endothelial cell monolayers (9). Furthermore, in colorectal and pancreatic cancer models, LEMD1 silencing results in decreased tumor cell invasion and migration abilities, while overexpression made tumors more invasive (2,30). A study by Li *et al* (11) knocked down LEMD1 in TNBC cells, and the results reveal that these tumors not only reduced their *in vitro* migration ability but also reduced their tumorigenicity and metastatic ability *in vivo*. LEMD1 is also associated with the regulation of the EMT. For example, in thyroid cancer cells, LEMD1 overexpression decreases the levels of the epithelial marker E-cadherin and increases the expression of mesenchymal markers N-cadherin and Vimentin, promoting cells to acquire a spindle-shaped, migratory phenotype (27). Additionally, in OSCC (9) and TNBC, LEMD1 promotes transmembrane migration of vascular or lymphatic endothelial cells, enhancing metastatic capacity (11).

Therefore, evidence suggests that LEMD1 promotes the malignant phenotypes of tumors in multiple ways such as by accelerating cell proliferation and inhibiting apoptosis to promote tumor growth, while also enhancing cell migration and invasion characteristics to facilitate tumor metastasis. In summary, LEMD1 promotes metastasis by inducing the EMT and cytoskeletal reorganization (for example, via RhoA/ROCK signaling), which increases cancer cell motility and invasive capability.

Interactions between LEMD1 and signal transduction pathways. LEMD1 can regulate multiple signaling pathways associated with tumor progression, including the PI3K/AKT, Wnt/β-catenin and RhoA/ROCK1 pathways, which exert tumor-promoting effects (4,21,27,30) (Fig. 4). The PI3K/Akt signaling pathway is important for regulating cell proliferation and survival, and LEMD1 is associated with the abnormal activation of this pathway in various tumors. For example, in gastric cancer research, overexpression of LEMD1 can promote the activation of the PI3K/Akt pathway and increase the phosphorylation levels of Akt (4). Additionally, silencing LEMD1 decreases p-PI3K and p-AKT, whereas LEMD1 overexpression increases p-PI3K and p-AKT (4). A study by Li *et al* (30) reports that the expression of LEMD1 is upregulated by the transcription factor SOX4, enhancing the activity of PI3K/Akt signaling and promoting the proliferation and invasion of colon cancer cells. Functional tests in NSCLC also show that LEMD1-mediated malignant phenotypes are reversed by the PI3K activator 740 Y-P, suggesting that the action of LEMD1 depends on the activation of the PI3K/Akt pathway (28). Taken together, these findings indicate that aberrant activation of the PI3K/Akt pathway is a possible primary downstream mechanism that mediates the tumor-promoting effects of LEMD1, as this pathway is consistently implicated in LEMD1-associated oncogenic processes across multiple types of cancer (4,28,30).

The Wnt/β-catenin pathway is also associated with LEMD1. Using gene set enrichment analyses on thyroid cancer, a study by Xu *et al* (27) reveals that the Wnt/β-catenin pathway is notably enriched in samples with high LEMD1 expression levels, downregulated E-cadherin and upregulated N-cadherin and Vimentin, suggesting the occurrence of the EMT. Further experiments confirm that knocking down LEMD1 reverses these changes, indicating that LEMD1 promotes proliferation and migration of thyroid cancer cells by activating the Wnt pathway to induce the EMT (27). Additionally, LEMD1 can influence the activity of the MAPK signaling pathway. In TNBC, LEMD1 overexpression leads to the excessive activation of the ERK1/2 pathway, while silencing LEMD1 reduces downstream ERK signal transduction, inhibiting tumor cell proliferation and migration (11). Furthermore, the interaction between LEMD1 and the p53/mTORC1 pathway is evident in pancreatic cancer, in which excessive LEMD1 can inhibit the function of the tumor suppressor protein p53 and activate mTORC1 signaling, promoting pancreatic cancer cell proliferation and metastasis (2). Although the precise mechanism is yet to be elucidated, LEMD1 activates pro-survival pathways upstream of p53, including the PI3K/Akt/mTOR pathway, which contributes to p53 inhibition and its reduced pro-apoptotic function. LEMD1 also affects cytoskeleton rearrangement-related pathways, such as the activation of RhoA/ROCK1 signaling, which promotes stress fiber formation and cell migration. A previous study investigating colorectal cancer shows that overexpression of LEMD1 can increase RhoA activity and enhance tumor cell migration, while interfering with LEMD1 has the opposite effect (21). In summary, LEMD1 may promote malignant tumor phenotypes through multi-target signaling pathway interactions, including but not limited to PI3K/Akt, Wnt/β-catenin, ERK/MAPK, p53/mTOR and RhoA/ROCK. Among these pathways the PI3K/Akt axis appears to be a central downstream node for the oncogenic effect of LEMD1, which supports its broad involvement in several types of cancer.

LEMD1 appears to activate different downstream signaling pathways depending on the type of tumor. For example, in colorectal cancer, SOX4-induced transcriptional upregulation of LEMD1 is linked to increased RhoA-GTP levels and enhanced cell migration via activation of the RhoA/ROCK signaling cascade (21). By contrast, in TNBC, LEMD1 overexpression downregulates ERK-inhibitory phosphatases such as dual specificity phosphatases 5 and 6, sustaining ERK/MAPK pathway activity, which in turn promotes tumor cell proliferation and the EMT (11). This tissue-specific signaling divergence may be attributed to differences in chromatin accessibility, transcription factor repertoires or regulatory cofactors. For example, in OSCC, particularly metastatic OSCC, the long non-coding (lnc)RNA LEMD1-antisense RNA 1 (AS1) stabilizes LEMD1 mRNA, which increases LEMD1 expression levels and activates the PI3K-AKT signaling pathway (34). Additionally, the expression of specific LEMD1 isoforms depending on the type of cancer, may influence partner protein interactions, therefore mediating distinct functional outcomes across tumor entities. These findings explain the extensive biological effects of LEMD1 and indicates a potential for further therapeutic interventions targeting associated pathways.

Effects of LEMD1 on gene expression levels and epigenetic regulation. As a nuclear membrane-associated protein, LEMD1 may participate in tumorigenesis by influencing chromatin state and gene expression levels. Firstly, expression of LEMD1 is subject to epigenetic regulation. In normal

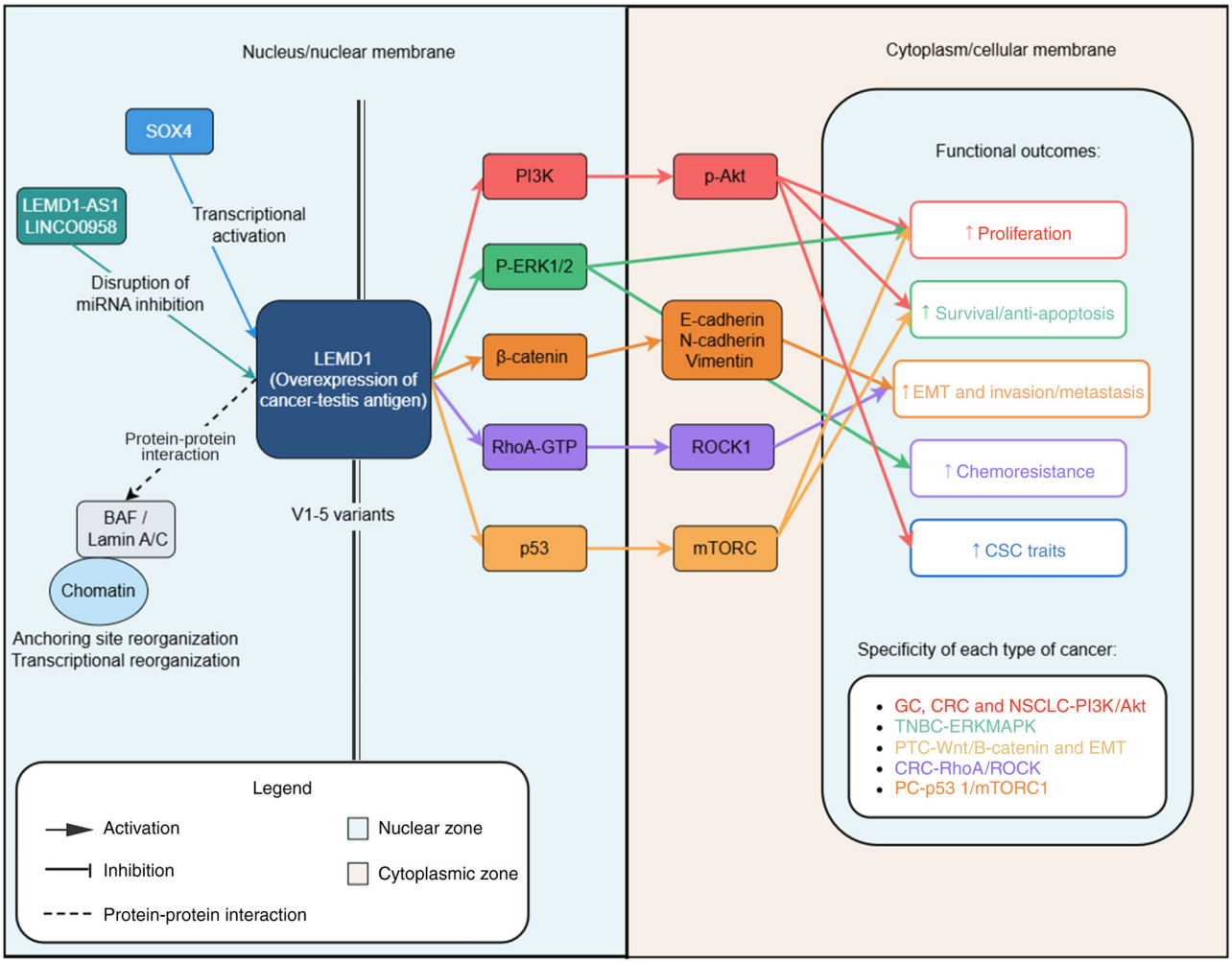

Figure 4. Schematic summary of the oncogenic roles and signaling networks of LEMD1 in different types of tumors. An integrated overview of the upstream regulators, downstream signaling pathways and functional consequences associated with LEMD1 overexpression across multiple types of cancer. In the nucleus/nuclear membrane, SOX4 and LEMD1-AS1/LINC00958 are upstream regulators of LEMD1, which contribute to transcriptional activation and disruption of microRNA-mediated inhibition, respectively. LEMD1 overexpression activates multiple downstream signaling pathways, including PI3K/p-Akt, ERK1/2, β-catenin, RhoA/ROCK and p53/mTORC1-related pathways, and is associated with altered expression of E-cadherin, N-cadherin and vimentin. These downstream events are associated with increased proliferation, survival/anti-apoptosis, the EMT and invasion/metastasis, chemoresistance, and CSC traits (such as an enhanced sphere formation ability, elevated expression of stemness markers and an increased tumor-initiating potential). The tumor-type-specific pathway associations reported in GC, CRC and NSCLC, as well as in TNBC, PTC and PC are summarized. Arrowheads indicate activation, T-shaped lines indicate inhibition, and dashed lines indicate protein-protein interaction. The present figure was produced using Adobe Illustrator 2024 (version 28; Adobe Systems, Inc.). BAF, barrier-to-autointegration factor; CSC, cancer stem cell; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; GC, gastric cancer; LEMD1, LAP2-emerin-MAN1 domain-containing protein 1; LEMD1-AS1, LEMD1 antisense RNA 1; LINC00958, long intergenic non-protein coding RNA 958; mTORC1, mechanistic target of rapamycin complex 1; NSCLC, non-small cell lung cancer; p-Akt, phosphorylated Akt; PC, pancreatic cancer; PTC, papillary thyroid cancer; ROCK, Rho-associated coiled-coil containing protein kinase; RhoA, Ras homolog family member A; SOX4, SRY-box transcription factor 4; TNBC, triple-negative breast cancer.

cells, high methylation of the LEMD1 promoter leads to transcriptional silencing, while in tumors such as breast cancer, this promoter undergoes notable demethylation, resulting in abnormally high LEMD1 expression levels. This promoter demethylation positively correlates with poor patient prognosis (11), indicating that epigenetic activation of LEMD1 is linked to tumor progression. Additionally, the 1q32 region, where the LEMD1 gene is located, frequently undergoes copy number increases in certain types of cancer (such as breast, endometrial and ovarian clear cell carcinomas) (35-37), which may further enhance LEMD1 expression levels (38). Besides DNA methylation and gene amplification, transcription factors and non-coding RNAs also participate in the regulatory network of the expression of LEMD1. The SOX4 transcription factor can directly bind to the LEMD1 promoter and upregulate its transcription, thereby promoting the activation of the LEMD1/PI3K/Akt axis in colon cancer cells (30). In anaplastic lymphoma kinase fusion-positive ALCL, the oncogene nucleophosmin-ALK induces upregulation of microRNA (miR)-135b through the STAT3 pathway, and miR-135b is located in the first intron of the LEMD1 gene. With the upregulation of miR-135b, LEMD1 transcription is also co-activated (38). This reveals that inflammation-associated transcription factors or cytokine pathways (such as the IL-3/STAT3 pathway) can indirectly upregulate LEMD1 through miR-135b in ALCL, suggesting a mechanistic link between inflammatory signaling and LEMD1 expression levels.

Beyond ALCL, an associated inflammation linked mechanism is described in epithelial tumors. In NSCLC, LEMD1 intronic miR-135b enhances NF-κB signaling by repressing cylindromatosis tumor suppressor protein, which is a negative regulator of the NF-κB pathway, with the expression of miR-135b induced by IL-6/STAT3 (39). As miR-135b resides within the first intron of LEMD1, these observations support a mechanistic connection between inflammatory cytokine pathways and the LEMD1 locus in solid tumors, potentially coupling IL-6/STAT3 input to NF-κB activation through an IL-6/STAT3 to miR-135b to NF-κB axis (39). This reveals that inflammatory/cytokine signaling can promote the expression of LEMD1 through epigenetic pathways. This connects stimulation of the tumor microenvironment with the expression of oncogenes.

Furthermore, lncRNAs also serve roles in regulating LEMD1. In OSCC, LEMD1-AS1 binds to LEMD1 mRNA, stabilizing its transcript level. This increases the LEMD1 expression levels and activates the PI3K/Akt pathway to promote tumor metastasis (34). Similarly, LINC00958 lncRNA indirectly enhances the expression of LEMD1 by absorbing miR-3064-5p (which can target and downregulate LEMD1). This enhances the malignant behavior of tumor cells (31). LEMD1-AS1, as a cuproptosis-related tumor suppressor, not only facilitates molecular subtyping and prognostic evaluation of ovarian cancer, but is also a potential biomarker for guiding personalized treatment strategies (40). These findings indicate that LEMD1 is involved in a complex gene regulatory network, with its expression levels subject to multi-level regulation including DNA methylation status, copy number variations, transcription factors (such as SOX4 and STAT3) and ncRNAs. These mechanisms not only determine the expression level of LEMD1 itself but may also influence the expression patterns of a number of downstream genes through LEMD1, which warrants additional in-depth research in the future.

In addition to LEMD1 expression levels, its location at the inner nuclear membrane suggests it may have direct effects on gene regulation. As with other LEM-domain proteins, LEMD1 may anchor chromatin to the nuclear periphery through interactions with BAF or the nuclear lamina, potentially silencing or activating specific gene regions (41). Although direct evidence is still lacking, such a mechanism may explain how LEMD1 influences a broad range of cellular behaviors. If LEMD1 tethers genomic regions associated with tumor suppressor genes or differentiation genes to the nuclear periphery, this may repress their expression levels, contributing to the maintenance of a proliferative, undifferentiated state in cancer cells. However, detachment of chromatin from the repressive nuclear periphery due to LEMD1 loss may activate tumor suppressor networks, which is consistent with observations of increased p53 pathway activity upon LEMD1 knockdown (2). These hypotheses require further validation, but they highlight that the pro-oncogenic effects of LEMD1 may stem from a combination of signaling pathway activation and higher-order genome organization changes.

5. Therapeutic potential of LEMD1 in cancer

Prospects of LEMD1 as a therapeutic target. Highly specific expression and tumor-promoting effects of LEMD1 in tumors make it an attractive therapeutic target. Traditional molecular targeting approaches may consider inhibiting the function (via small molecules) or expression [via small interfering (si)RNA and short hairpin RNA gene-silencing strategies] of LEMD1 to inhibit tumor progression. However, as LEMD1 is an intracellular nuclear envelope protein, designing small-molecule drugs that act on its transmembrane region or LEM domain is challenging. Gene-level interventions, such as via siRNA or antisense oligonucleotides, demonstrates notable antitumor effects *in vivo* (11). For example, in mouse models of TNBC, the silencing of LEMD1 inhibits tumor growth and metastasis (11), suggesting that therapies targeting LEMD1 may potentially reduce tumor malignancy. While monoclonal antibody or immunoconjugate approaches may be theoretically considered, the predominant inner nuclear membrane localization of LEMD1 prevents the accessibility of extracellular epitopes, rendering such strategies impractical for direct targeting.

A more feasible approach is the possible use of the classification of LEMD1 as a CTA for immunotherapeutic intervention (11). Under physiological conditions, LEMD1 expression levels are mostly restricted to immune-privileged germ cells, which minimizes central immune tolerance and potentially facilitates tumor-specific immune responses (3). Nevertheless, developing effective LEMD1-targeted immunotherapies poses several challenges. Firstly, intratumoral heterogeneity in LEMD1 expression levels presents a risk of immune escape through antigen downregulation, although this risk may be mitigated if LEMD1 is functionally indispensable for tumor cell survival. Secondly, for vaccine development, a critical prerequisite is the identification of immunogenic LEMD1-derived epitopes that can be presented by common HLA class I molecules (42). The robust activation of cytotoxic T lymphocytes against these epitopes would be essential to overcome any residual immune tolerances and mount effective tumor-specific immune responses. However, previous CTA-targeted cancer vaccines, such as recombinant melanoma-associated antigen A3 protein vaccines and New York esophageal squamous cell carcinoma-1 (NY-ESO-1) protein vaccines formulated with immune-stimulating complex matrix adjuvant, only had modest clinical efficacy, with objective response rates of ~13% in trials (43-46), highlighting the necessity for potent adjuvants or combination immunotherapies (such as immune checkpoint inhibitors) to enhance the antitumor immunity. Additionally, innovative delivery systems capable of targeting intracellular LEMD1 warrant further investigation. In terms of immunotherapy, LEMD1, as a CTA, is a possible target for tumor vaccines or T-cell therapies. Since expression of LEMD1 is limited in normal tissues (occurring mainly in the testis), immune responses against it would be tumor-specific and spare normal cells (21). It may be considered to use LEMD1 peptide vaccines to activate the T cells of patients, or to expand cytotoxic T lymphocytes that recognize LEMD1 *ex vivo* and reinfuse them to target LEMD1-positive tumors. Additionally, chimeric antigen receptor T-cell therapy may be adapted to recognize LEMD1-derived peptides presented on tumor cell MHC molecules, provided suitable epitopes and HLA restrictions are identified. Furthermore, advanced drug delivery systems could possibly be used to overcome the challenge of

the intranuclear location (inner nuclear membrane) of LEMD1. For example, nanoparticle-based carriers or ligand-directed vehicles could potentially deliver LEMD1-targeted siRNA or protein-degrading agents specifically into tumor cells. In summary, LEMD1 has potential promising prospects as a therapeutic target, and these strategies (from CTA-targeted immunotherapies to gene silencing with innovative delivery mechanisms) warrant further investigation.

Role of LEMD1 in anticancer drug resistance. Tumor resistance is one of the key challenges affecting treatment efficacy, and increasing evidence suggests tumor-promoting genes such as LEMD1 serve a role in this process. LEMD1 enhances tumor cell tolerance to adverse environments by activating survival pathways such as PI3K/Akt and ERK, which may also include tolerance to stress induced by chemotherapeutic drugs. TNBC research reveals that knocking down LEMD1 not only inhibits tumor proliferation but also notably increases the sensitivity of tumor cells to paclitaxel chemotherapy (11). By contrast, TNBC cells with high LEMD1 expression levels are relatively resistant to paclitaxel, requiring higher drug doses to achieve the same inhibitory effect (11). This finding suggests that the presence of LEMD1 may confer a degree of chemotherapy resistance to tumor cells.

The mechanism of chemotherapy resistance may be associated with the antiapoptotic capacity that is promoted by LEMD1 (4) chemotherapeutic drugs typically kill cancer cells by inducing DNA damage and apoptosis, while the inhibition of apoptosis by LEMD1 would reduce the effect of the drug. Additionally, the cancer cell stemness and the EMT state maintained by LEMD1 are also hypothesized to be associated with resistant phenotypes. Stem cell-like tumor cells often have an increased tolerance to radio- and chemotherapy, which may explain why LEMD1-enhanced stemness in NSCLC leads to more stubborn tumors that are difficult to eliminate (28). At the same time, the EMT process is often accompanied by increased chemotherapy resistance, and the LEMD1-induced EMT (27) may render tumor cells insensitive to certain drugs.

LEMD1 appears to mediate chemotherapy resistance through multiple, reinforcing mechanisms. One major mechanism is the activation of pro-survival signaling pathways such as PI3K/Akt. LEMD1 overexpression activates the PI3K/Akt cascade in cancer cells (4), which is notable because PI3K/Akt signaling confers broad chemoresistance by upregulating antiapoptotic effectors (such as Bcl-2 and X-linked inhibitor of apoptosis protein) and suppressing proapoptotic factors (such as Bax) (47). Consistently, LEMD1 knockdown sensitizes tumor cells to paclitaxel. For example, *in vitro*, silencing LEMD1 in paclitaxel-treated MDA-MB-231 TNBC cells downregulates Bcl-2 and increases Bax expression levels, which enhances apoptosis and chemosensitivity, compared with those with paclitaxel treatment alone (11).

Another mechanism is through inducing the EMT and enriching cancer stem-like properties, which are well-known inducers of drug resistance. LEMD1 silencing increases E-cadherin and decreases N-cadherin/vimentin (mesenchymal markers) (11), indicating that LEMD1 normally promotes a mesenchymal, migratory cell state. This shift is notable as the EMT not only facilitates invasion but also often coincides with the upregulation of drug efflux transporters, such as ATP-binding cassette (ABC) sub-family B member 1/P-glycoprotein (multidrug resistance protein 1), ABC sub-family C member 1/multidrug resistance-associated protein 1 and ABC sub-family G member 2/breast cancer resistance protein (48-50), as well as other adaptive mechanisms, including enhanced resistance to apoptosis, increased DNA damage repair capacity and acquisition of cancer stem cell-like properties (51-53), that allow cells to evade chemotherapeutics (54). In addition, the EMT is frequently linked to the emergence of cancer stem-like cells, which is a subpopulation of tumor cells that are intrinsically more chemo-resistant, partly due to their quiescent nature and ability to survive drug-induced stress (54). By supporting a mesenchymal phenotype and potentially maintaining a pool of stem-like cells, LEMD1 endows tumor cells with a capacity to withstand chemotherapy, which may explain why LEMD1-enhanced stemness in NSCLC leads to more stubborn tumors that are difficult to eliminate (28). In summary, high LEMD1 expression levels can protect cancer cells from chemotherapy-induced apoptosis (via survival pathways such as PI3K/Akt) while promoting cellular traits (such as the EMT and stemness) that undermine drug efficacy. Clinically, this suggests that tumors with elevated LEMD1 expression levels may be predisposed to chemoresistance, and conversely that targeting LEMD1 or its downstream signals may help overcome resistance and improve the response to treatment (11).

Therefore, it can be hypothesized that inhibiting LEMD1 in tumors may synergistically enhance the efficacy of conventional treatments. Although current direct research on LEMD1 and drug resistance is limited, the aforementioned indications suggest its potential importance. Future research is needed to further investigate the effects of LEMD1 on the sensitivity to various treatments (such as chemotherapy, targeted drugs and radiotherapy) in different tumor contexts. If the resistance spectrum corresponding to high LEMD1 expression levels can be clarified, it may help formulate more optimized personalized treatment plans.

6. Current research challenges and future directions

Shortcomings and challenges in current research. Despite notable progress in research on LEMD1 in tumors, there are still a number of shortcomings and challenges to overcome. Current basic research on the molecular biological functions of LEMD1 is not in depth enough, with the majority of studies focusing on observing the effects of LEMD1 up- or downregulation on tumor phenotypes and signaling pathways, lacking direct evidence for its specific role in nuclear structure and gene regulation as a nuclear inner membrane protein. For example, it is still unclear whether LEMD1 reshapes chromatin structure through interactions with BAF or nuclear lamina proteins to affect gene expression levels. There are also challenges regarding the 'druggability' of LEMD1 as a drug target. Since LEMD1 has no enzymatic active site and is located on the inner nuclear membrane, the use of traditional small molecule drugs to directly target it is difficult. Therefore, innovative drug delivery systems or new types of molecules are needed to achieve effective intervention.

The heterogeneity of LEMD1 expression levels and the functional differences across different types of tumor are yet

to be fully elucidated. Although the majority of studies consistently suggest the cancer-promoting effects of LEMD1, there may be exceptions in certain types of cancer. For example, in multiple myeloma, a large-scale study involving 2,546 patients identifies LEMD1 as a favorable prognostic marker in which patients with high LEMD1 expression levels exhibit notably prolonged survival compared with those with low expression (55). In prostatic adenocarcinoma, LEMD1 is frequently upregulated in tumor tissues; however, a comprehensive study failed to demonstrate a notable prognostic impact of LEMD1 in prostate cancer (unlike other LEM family proteins associated with clinical outcomes) (6). By contrast, in ovarian cancer, elevated LEMD1 expression levels are associated with improved patient survival. An integrative genomics study reveals that patients with ovarian tumors and high LEMD1 expression levels have a markedly longer OS compared with the low-expression level group (55,56). This outlier implies that the oncogenic role of LEMD1 is not universal and might be modulated by tissue-specific contexts. One hypothesis is that the immune microenvironment in ovarian cancer may respond uniquely to LEMD1. As an immunogenic CTA, high LEMD1 expression levels in ovarian tumors might stimulate stronger anti-tumor immune responses, making the tumor more immunologically 'hot' and contributing to improved patient outcomes (57,58). In support of this, a number of CTAs are associated with an inflamed tumor microenvironment and favorable clinical outcomes in specific types of cancer. For example, NY-ESO-1 expression levels in TNBC are linked to higher tumor-infiltrating lymphocyte levels, favorable disease-free survival and higher $CD8^+$ T-cell counts; Hemogen expression levels in lung adenocarcinoma are associated with $CD8^+$ T-cell infiltration and an improved prognosis; and CTA-high seminomas, including preferentially expressed antigen in melanoma-enriched tumors, demonstrate activated T-cell infiltration, with CTA and $CD8^+$/regulatory T-cell signatures correlating with recurrence-free survival (57,59-62). Alternatively, ovarian tumors might harbor unique co-factors or signaling contexts (such as hormone-related factors or distinct co-regulated pathways) that alter the downstream effects of LEMD1. In gynecological cells, LEMD1 may interact with tissue-specific partners or regulatory networks, potentially dampening its tumor-promoting activities or even associating its high expression levels with a more differentiated, less aggressive tumor phenotype. In summary, LEMD1 may serve different biological roles in ovarian cancer compared with other malignancies, highlighting the importance of context-dependent research into its functions. Furthermore, immunotherapy targeting LEMD1 is yet to be clinically implemented, and its feasibility and safety are yet to be verified. Additionally, as a member of the CTA family, the potential immunogenicity of LEMD1 is both an advantage and a challenge as it may promote the immune clearance of tumors but it might also be limited by tumor immune evasion mechanisms or even trigger autoimmune responses. Therefore, all of these issues require further investigation.

Future research directions. To address the aforementioned shortcomings, several directions may be worth investigating in the future. At the fundamental level, the molecular mechanism of LEMD1 should be analyzed in depth. Proteomics and biochemical methods could be used to identify LEMD1-interacting proteins and clarify whether they directly bind BAF, chromatin or nuclear lamina components. Techniques such as chromatin immunoprecipitation sequencing could be used to identify genomic regions affected by LEMD1 and investigate its regulatory role in genome-wide transcription and epigenetic modifications. This may possibly reveal the fundamental mechanisms of the cancer-promoting effects of LEMD1. Additionally, the function of LEMD1 should be further evaluated in cellular and animal models. For example, LEMD1 gene knockout mouse models could potentially be constructed to observe possible phenotypic changes in normal development and tumor susceptibility, in order to determine whether LEMD1 is a necessary factor for tumorigenesis.

Furthermore, larger-scale correlation studies should be conducted in clinical samples. This includes detecting LEMD1 expression profiles in different types of cancer and at different stages, combined with patient treatment and survival data, to assess the reliability and independence of LEMD1 as a prognostic or predictive marker. Investigating LEMD1-related immunotherapy should also be advanced. For example, by identifying the T cell epitopes of LEMD1, the presence of natural anti-LEMD1 immune responses in the peripheral blood of patients with cancer could be evaluated. Once its immunogenicity is proven, attempts can be made to develop LEMD1 vaccines or CAR-T cells, testing their anti-tumor effects in animal models. Through these multi-faceted research efforts, a foundation will be laid for LEMD1 to progress from laboratory to clinical application.

7. Conclusion

As a CTA, LEMD1 demonstrates consistent tumor-promoting effects and notable clinical relevance across multiple tumor types. Its unique expression profile and molecular functions make it a focal point in tumor biology research and a possible novel opportunity for tumor therapy. Current research preliminarily reveals various mechanisms by which LEMD1 promotes tumor development, including activating proliferation signaling pathways, inducing the EMT and maintaining cancer stem cell characteristics. Furthermore, the clinicopathological importance of LEMD1 has become clear, serving as a marker of poor prognosis in several tumor types. Considering this, continuing in-depth research investigating the mechanisms of action of LEMD1 and evaluating its possible value as a diagnostic and therapeutic target has scientific importance and potential clinical translation prospects. Therefore, as the understanding of LEMD1 increases, this molecule may potentially be incorporated into the landscape of precision oncology, which may possibly provide patients with more effective individualized diagnostic and treatment options. It may be anticipated that multidisciplinary research investigating LEMD1 could potentially advance the understanding of the complex network of tumor development and progression, which may potentially offer novel treatments for refractory tumors.

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Authors' contributions

XiaoW conceived the review, conducted the literature search, verified all source literature and the publicly available data retrieved from the Gene Expression Omnibus for Fig. 1, and drafted the initial manuscript. XianW revised the manuscript for important intellectual content and provided supervisory guidance. SK critically revised the manuscript for important intellectual content, verified all raw data and source literature, and provided supervisory guidance. All authors 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.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Yuki D, Lin YM, Fujii Y, Nakamura Y and Furukawa Y: Isolation of LEM domain-containing 1, a novel testis-specific gene expressed in colorectal cancers. Oncol Rep 12: 275-280, 2004.
2. Cao X, Yao N, Zhao Z, Fu Y, Hu Y, Zhu P, Shi W and Tang L: LEM domain containing 1 promotes pancreatic cancer growth and metastasis by p53 and mTORC1 signaling pathway. Bioengineered 13: 7771-7784, 2022.
3. Gjerstorff MF, Andersen MH and Ditzel HJ: Oncogenic cancer/testis antigens: Prime candidates for immunotherapy. Oncotarget 6: 15772-15787, 2015.
4. Li Q, Ge Y, Chen X, Wang L, Xia Y, Xu Z, Li Z, Wang W, Yang L, Zhang D and Xu Z: LEM domain containing 1 promotes proliferation via activating the PI3K/Akt signaling pathway in gastric cancer. J Cell Biochem 120: 15190-15201, 2019.
5. Sasahira T and Kirita T: Hallmarks of cancer-related newly prognostic factors of oral squamous cell carcinoma. Int J Mol Sci 19: 2413, 2018.
6. He T, Zhang Y, Li X, Liu C, Zhu G, Yin X, Zhang Z, Zhao K, Wang Z, Zhao P and Wang K: Collective analysis of the expression and prognosis for LEM-domain proteins in prostate cancer. World J Surg Oncol 20: 174, 2022.
7. Hashimoto K, Nishimura S, Ito T, Oka N, Kakinoki R and Akagi M: Clinicopathological assessment of cancer/testis antigens NY-ESO-1 and MAGE-A4 in osteosarcoma. Eur J Histochem 66: 3377, 2022.
8. Wang H, Liu J, Yang J, Wang Z, Zhang Z, Peng J, Wang Y and Hong L: A novel tumor mutational burden-based risk model predicts prognosis and correlates with immune infiltration in ovarian cancer. Front. Immunol 13: 943389, 2022.
9. Sasahira T, Kurihara M, Nakashima C, Kirita T and Kuniyasu H: LEM domain containing 1 promotes oral squamous cell carcinoma invasion and endothelial transmigration. Br J Cancer 115: 52-58, 2016.
10. Sasahira T, Kurihara-Shimomura M, Nishiguchi Y, Shimomura H and Kirita T: Sushi repeat containing protein X-linked 2 is a downstream signal of LEM domain containing 1 and acts as a tumor-promoting factor in oral squamous cell carcinoma. Int J Mol Sci 21: 3655, 2020.
11. Li X, Jiang S, Jiang T, Sun X, Guan Y, Fan S and Cheng Y: LEM domain containing 1 acts as a novel oncogene and therapeutic target for triple-negative breast cancer. Cancers (Basel) 15: 2924, 2023.
12. Wang Y, Chen Z, Yang G and Yuan G: Unveiling the roles of LEMD proteins in cellular processes. Life Sci 357: 123116, 2024.
13. Rose M, Burgess JT, O'Byrne K, Richard DJ and Bolderson E: The role of inner nuclear membrane proteins in tumourigenesis and as potential targets for cancer therapy. Cancer Metastasis Rev 41: 953-963, 2022.
14. Takeda R, Hirohashi Y, Shen M, Wang L, Ogawa T, Murai A, Yamamoto E, Kubo T, Nakatsugawa M, Kanaseki T, *et al*: Identification and functional analysis of variants of a cancer/testis antigen LEMD1 in colorectal cancer stem-like cells. Biochem Biophys Res Commun 485: 651-657, 2017.
15. Barton LJ, Soshnev AA and Geyer PK: Networking in the nucleus: a spotlight on LEM-domain proteins. Curr Opin Cell Biol 34: 1-8, 2015.
16. Brachner A and Foisner R: Evolvement of LEM proteins as chromatin tethers at the nuclear periphery. Biochem Soc Trans 39: 1735-1741, 2011.
17. Wagner N, Krohne G: LEM-Domain proteins: New insights into lamin-interacting proteins. Int Rev Cytol 261: 1-26, 2007.
18. Herrada I, Bourgeois B, Samson C, Buendia B, Worman HJ and Zinn-Justin S: Purification and structural analysis of LEM-Domain proteins. Methods Enzymol 569: 43-61, 2016.
19. Ai H, Yang H, Li L, Ma J, Liu K and Li Z: Cancer/testis antigens: Promising immunotherapy targets for digestive tract cancers. Front Immunol 14: 1190883, 2023.
20. Li H, Chiappinelli KB, Guzzetta AA, Easwaran H, Yen RW, Vatapalli R, Topper MJ, Luo J, Connolly RM, Azad NS, *et al*: Immune regulation by low doses of the DNA methyltransferase inhibitor 5-azacitidine in common human epithelial cancers. Oncotarget 5: 587-598, 2014.
21. Zhang H, Xu C, Jiang F and Feng J: A three-genes signature predicting colorectal cancer relapse reveals LEMD1 promoting CRC cells migration by RhoA/ROCK1 signaling pathway. Front Oncol 12: 823696, 2022.
22. Martin CJ, Oser EA, Nagarajan P, Popova LV, Sunkel BD, Stanton BZ and Parthun MR: Distinct classes of lamina-associated domains are defined by differential patterns of repressive histone methylation. Genome Res 35: 1959-1974, 2025.
23. Ghafouri-Fard S, Ousati Ashtiani Z, Sabah Golian B, Hasheminasab SM and Modarressi MH: Expression of two testis-specific genes, SPATA19 and LEMD1, in prostate cancer. Arch Med Res 41: 195-200, 2010.
24. Elkhatib RA, Paci M, Boissier R, Longepied G, Auguste Y, Achard V, Bourgeois P, Levy N, Branger N, Mitchell MJ and Metzler-Guillemain C: LEM-domain proteins are lost during human spermiogenesis but BAF and BAF-L persist. Reproduction 154: 387-401, 2017.
25. Karlsson M, Zhang C, Méar L, Zhong W, Digre A, Katona B, Sjöstedt E, Butler L, Odeberg J, Dusart P, *et al*: A single-cell type transcriptomics map of human tissues. Sci Adv 7: eabh2169, 2021.
26. Okada Y: Sperm chromatin condensation: Epigenetic mechanisms to compact the genome and spatiotemporal regulation from inside and outside the nucleus. Genes Genet Syst 97: 41-53, 2022.
27. Xu M, Lin B, Zheng D, Wen J, Hu W, Li C, Zhang X, Zhang X and Qu J: LEM domain containing 1 promotes thyroid cancer cell proliferation and migration by activating the Wnt/β-catenin signaling pathway and epithelial-mesenchymal transition. Oncol. Lett 21: 442, 2021.

28. Li L and Zhang P: Elevation of LEM domain containing 1 predicts poor prognosis of NSCLC patients and triggers malignant stemness and invasion of NSCLC cells by stimulating PI3K/AKT pathway. Curr Mol Med 24: 366-378, 2024.
29. Matsuyama H, Suzuki HI, Nishimori H, Noguchi M, Yao T, Komatsu N, Mano H, Sugimoto K and Miyazono K: miR-135b mediates NPM-ALK-driven oncogenicity and renders IL-17-producing immunophenotype to anaplastic large cell lymphoma. Blood 118: 6881-6892, 2011.
30. Li D, Wang D, Liu H, Jiang X: LEM domain containing 1 (LEMD1) transcriptionally activated by SRY-related high-mobility-group box 4 (SOX4) accelerates the progression of colon cancer by upregulating phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway. Bioengineered 13: 8087-8100, 2022.
31. Luo Z, Hao S, Yuan J, Zhu K, Liu S, Zhang J and Yao L: Long non-coding RNA LINC00958 promotes colorectal cancer progression by enhancing the expression of LEM domain containing 1 via microRNA miR-3064-5p. Bioengineered 12: 8100-8115, 2021.
32. Martinez-Romero J, Bueno-Fortes S, Martín-Merino M, Ramirez de Molina A and De Las Rivas J: Survival marker genes of colorectal cancer derived from consistent transcriptomic profiling. BMC Genomics 19 (Suppl 8): S857, 2018.
33. Maimela PWM, Smith M, Nel AJM, Bernam SDP, Jonas EG and Blackburn JM: Humoral immunoprofiling identifies novel biomarkers and an immune suppressive autoantibody phenotype at the site of disease in pancreatic ductal adenocarcinoma. Front Oncol 14: 1330419, 2024.
34. Li Z, Wang J, Wu J, Li N and Jiang C: Long Noncoding RNA LEMD1-AS1 increases LEMD1 expression and activates PI3K-AKT pathway to promote metastasis in oral squamous cell carcinoma. Biomed Res Int 2022: 3543948, 2022.
35. Mesquita B, Lopes P, Rodrigues A, Pereira D, Afonso M, Leal C, Henrique R, Lind GE, Jerónimo C, Lothe RA and Teixeira MR: Frequent copy number gains at 1q21 and 1q32 are associated with overexpression of the ETS transcription factors ETV3 and ELF3 in breast cancer irrespective of molecular subtypes. Breast Cancer Res Treat 138: 37-45, 2013.
36. Depreeuw J, Stelloo E, Osse EM, Creutzberg CL, Nout RA, Moisse M, Garcia-Dios DA, Dewaele M, Willekens K, Marine JC, *et al*: Amplification of 1q32.1 refines the molecular classification of endometrial carcinoma. Clin Cancer Res 23: 7232-7241, 2017.
37. Tan DS, Lambros MB, Rayter S, Natrajan R, Vatcheva R, Gao Q, Marchiò C, Geyer FC, Savage K, Parry S, *et al*: PPM1D is a potential therapeutic target in ovarian clear cell carcinomas. Clin Cancer Res 15: 2269-2280, 2009.
38. Khatri R and Subramanian S: MicroRNA-135b and its circuitry networks as potential therapeutic targets in colon cancer. Front Oncol 3: 268, 2013.
39. Zhao J, Wang X, Mi Z, Jiang X, Sun L, Zheng B, Wang J, Meng M, Zhang L, Wang Z, *et al*: STAT3/miR-135b/NF-κB axis confers aggressiveness and unfavorable prognosis in non-small-cell lung cancer. Cell Death Dis 12: 493, 2021.
40. Li N, Yu K, Huang D, Li S, Zeng D, Li J and Fan L: Molecular characterization of cuproptosis-related lncRNAs: Defining molecular subtypes and a prognostic signature of ovarian cancer. Biol Trace Elem Res 202: 1428-1445, 2024.
41. Shevelyov YY: Interactions of chromatin with the nuclear lamina and nuclear pore complexes. Int J Mol Sci 24: 15771, 2023.
42. Akiyama Y, Komiyama M, Miyata H, Yagoto M, Ashizawa T, Iizuka A, Oshita C, Kume A, Nogami M, Ito I, *et al*: Novel cancer-testis antigen expression on glioma cell lines derived from high-grade glioma patients. Oncol Rep 31: 1683-1690, 2014.
43. Kruit WH, Suciu S, Dreno B, Mortier L, Robert C, Chiarion-Sileni V, Maio M, Testori A, Dorval T, Grob JJ, *et al*: Selection of immunostimulant AS15 for active immunization with MAGE-A3 protein: Results of a randomized phase II study of the European organisation for research and treatment of cancer melanoma group in metastatic melanoma. J Clin Oncol 31: 2413-2420, 2013.
44. Kruit WH, Van Ojik HH, Brichard VG, Escudier B, Dorval T, Dréno B, Patel P, Van Baren N, Avril MF, Piperno S, *et al*: Phase 1/2 study of subcutaneous and intradermal immunization with a recombinant MAGE-3 protein in patients with detectable metastatic melanoma. Int J Cancer 117: 596-604, 2005.
45. Nicholaou T, Ebert LM, Davis ID, McArthur GA, Jackson H, Dimopoulos N, Tan B, Maraskovsky E, Miloradovic L, Hopkins W, *et al*: Regulatory T-Cell-mediated attenuation of T-Cell responses to the NY-ESO-1ISCOMATRIX vaccine in patients with advanced malignant melanoma. Clin Cancer Res 15: 2166-2173, 2009.
46. Jiang J, Li L, Yu Z, Wang K, Ma J, Li D, Guo Z, Wang L, Zhang H, Xu L and Zhang M: Clinical efficacy and challenges of cancer-testis antigen vaccines in advanced solid tumors: A systematic review and meta-analysis. Crit Rev Oncol Hematol 216: 104981, 2025.
47. Liu R, Chen Y, Liu G, Li C, Song Y, Cao Z, Li W, Hu J, Lu C and Liu Y: PI3K/AKT pathway as a key link modulates the multidrug resistance of cancers. Cell Death Dis 11: 797, 2020.
48. Saxena M, Stephens MA, Pathak H and Rangarajan A: Transcription factors that mediate epithelial-mesenchymal transition lead to multidrug resistance by upregulating ABC transporters. Cell Death Dis 2: e179, 2011.
49. Liu YR, Liang L, Zhao JM, Zhang Y, Zhang M, Zhong WL, Zhang Q, Wei JJ, Li M, Yuan J, *et al*: Twist1 confers multidrug resistance in colon cancer through upregulation of ATP-binding cassette transporters. Oncotarget 8: 52901-52912, 2017.
50. Wang H, Li JM, Wei W, Yang R, Chen D, Ma XD, Jiang GM and Wang BL: Regulation of ATP-binding cassette subfamily B member 1 by Snail contributes to chemoresistance in colorectal cancer. Cancer Sci 111: 84-97, 2020.
51. Debaugnies M, Rodríguez-Acebes S, Blondeau J, Parent MA, Zocco M, Song Y, de Maertelaer V, Moers V, Latil M, Dubois C, *et al*: RHOJ controls EMT-associated resistance to chemotherapy. Nature 616: 168-175, 2023.
52. Hu J, Wang J, Guo X, Fan Q, Li X, Li K, Wang Z, Liang S, Amin B, Zhang N, *et al*: MSLN induced EMT, cancer stem cell traits and chemotherapy resistance of pancreatic cancer cells. Heliyon 10: e29210, 2024.
53. Nie F, Sun X, Sun J, Zhang J and Wang Y: Epithelial-mesenchymal transition in colorectal cancer metastasis and progression: Molecular mechanisms and therapeutic strategies. Cell Death Discov 11: 336, 2025.
54. Błaszczak E, Miziak P, Odrzywolski A, Baran M, Gumbarewicz E and Stepulak A: Triple-Negative breast cancer progression and drug resistance in the context of epithelial-mesenchymal transition. Cancers (Basel) 17: 228, 2025.
55. Park J, Chiu B, Delaney J, Paschal C, Roche D, Shima J, Umesh A, Wisotzkey R, Shekar M and Kupershmidt I: Abstract 5151: Integrative genomic analysis identifies cancer-testis antigen LEMD1 as a prognostic biomarker. Cancer Res 73 (Suppl 8): 5151, 2013.
56. Taherian-Esfahani Z, Abedin-Do A, Nikpayam E, Tasharofi B, Ghahghaei Nezamabadi A and Ghafouri-Fard S: Cancer-Testis Antigens: A Novel Group of Tumor Biomarkers in Ovarian Cancers. Int J Cancer Manag 9: e4993, 2016.
57. da Silva VL, Fonseca AF, Fonseca M, da Silva TE, Coelho AC, Kroll JE, de Souza JES, Stransky B, de Souza GA and de Souza SJ: Genome-wide identification of cancer/testis genes and their association with prognosis in a pan-cancer analysis. Oncotarget 8: 92966-92977, 2017.
58. Lin L, Zou X, Nong W, Ge Y, Li F, Luo B, Zhang Q and Xie X: The potential value of cancer-testis antigens in ovarian cancer: Prognostic markers and targets for immunotherapy. Immun. Inflamm. Dis 12: e1284, 2024.
59. Ademuyiwa FO, Bshara W, Attwood K, Morrison C, Edge SB, Karpf AR, James SA, Ambrosone CB, O'Connor TL, Levine EG, *et al*: NY-ESO-1 cancer testis antigen demonstrates high immunogenicity in triple negative breast cancer. PLoS One 7: e38783, 2012.
60. Lee HJ, Kim JY, Song IH, Park IA, Yu JH and Gong G: Expression of NY-ESO-1 in triple-negative breast cancer is associated with tumor-infiltrating lymphocytes and a good prognosis. Oncology 89: 337-344, 2015.
61. Jiang Y, Yu L, Hu Q, Kang Y, You J, Huang C, Xu X and Chen L: Cancer/testis antigen HEMGN correlated with immune infiltration serves as a prognostic biomarker in lung adenocarcinoma. Mol Immunol 153: 226-237, 2023.
62. Siska PJ, Johnpulle RAN, Zhou A, Bordeaux J, Kim JY, Dabbas B, Dakappagari N, Rathmell JC, Rathmell WK, Morgans AK, *et al*: Deep exploration of the immune infiltrate and outcome prediction in testicular cancer by quantitative multiplexed immunohistochemistry and gene expression profiling. Oncoimmunology 6: e1305535, 2017.