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REVIEW ARTICLE

LINC00941: a novel player involved in the progression of human cancers

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Abstract

LINC00941, also known as lncRNA-MUF, is an intergenic non-coding RNA located on chromosome 12p11.21. It actively participates in a complex competing endogenous RNA network, regulating the expression of microRNA and its downstream proteins. Through transcriptional and post-transcriptional regulation, LINC00941 plays a vital role in multiple signaling pathways, influencing cell behaviors such as tumor cell proliferation, epithelial–mesenchymal transition, migration, and invasion. Noteworthy is its consistently high expression in various tumor types, closely correlating with clinicopathological features and cancer prognoses. Elevated LINC00941 levels are associated with adverse clinical outcomes, including increased tumor size, extensive lymphatic metastasis, and distant metastasis, leading to poorer survival rates across different cancers. Additionally, LINC00941 and its associated genes are linked to various targeted drugs available in the market. In this comprehensive review, we systematically summarize existing studies, detailing LINC00941's differential expression, clinicopathological and prognostic implications, regulatory mechanisms, and associated therapeutic drugs. Our analysis includes relevant charts and incorporates bioinformatics analyses to verify LINC00941's differential expression in pan-cancer and explore potential transcriptional regulation patterns of downstream targets. This work not only establishes a robust data foundation but also guides future research directions. Given its potential as a significant cancer biomarker and therapeutic target, further investigation into LINC00941's differential expression and regulatory mechanisms is essential.

Keywords LINC00941 · LncRNA-MUF · Cancer · CeRNA · Signaling pathway · Prognosis

Abbreviations

ACC	Adrenocortical carcinoma
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BLCA	Bladder urothelial carcinoma
BRCA	Breast invasive carcinoma
ceRNA	Competing endogenous RNA
CESC	Cervical esophageal squamous cell carcinoma
CHOL	Cholangiocarcinoma
COAD	Colon adenocarcinoma
CRC	Colorectal cancer
DFS	Disease-free survival
EMT	Epithelial–mesenchymal transition
ESCA	Esophageal carcinoma
ESCC	Esophageal squamous cell carcinoma
FAK	Focal adhesion kinase
GBM	Glioblastoma multiforme
GC	Gastric cancer
HCC	Hepatocellular carcinoma
HNSC	Head and neck squamous cell carcinoma

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KICH	Kidney chromophobe
KIRC	Kidney renal clear cell carcinoma
KIRP	Kidney papillary cell carcinoma
LATS1/2	Large tumor suppressor 1/2
LC	Laryngocarcinoma
LGG	Lower grade glioma
LIHC	Liver hepatocellular carcinoma
LncRNA	Long non-coding RNA
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
miRNA	MicroRNA
miRNA-RISC	MiRNA-containing RNA-induced silencing complex
MREs	MicroRNA response elements
MST1/2	Mammalian sterile20-like kinase 1/2
NBL	Neuroblastoma
NSCLC	Non-small cell lung cancerr
OV	Ovarian cancer
OS	Overall survival
OSCC	Oral squamous cell carcinoma
PAAD	Pancreatic adenocarcinoma
PC	Pancreatic cancer
PCPG	Pheochromocytoma and paraganglioma cancer
PDAC	Pancreatic ductal adenocarcinoma
PP2A	Protein phosphatase 2A
PRAD	Prostate adenocarcinoma
PTC	Primes papillary thyroid cancer
READ	Rectum adenocarcinoma
SARC	Sarcoma
SKCM	Skin cutaneous melanoma
SPP	Signaling pathways project
STAD	Stomach adenocarcinoma
TGCT	Testicular germ cell tumors
TGF- β	Transforming growth factor-β
THCA	Thyroid carcinoma
THYM	Thymoma
TNM	Tumor node metastasis
TSS	Transcription start site
UCEC	Endometrioid cancer
UCS	Uterine carcinosarcoma
UCSC Genome Browser	http://genome.ucsc.edu/
CADDIE database	https://exbio.wzw.tum.de/caddie/
ChIP-Atlas	https://chip-atlas.org/
JASPAR 2022 database	https://jaspar.genereg.net/
SPP database	http://signalingpathways.org/index.jsf
TCGA database	https://portal.gdc.cancer.gov/

Background

Long non-coding RNA (lncRNA) are RNA transcripts synthesized by RNA polymerase II that exceed 200 nucleotides in length and do not encode proteins [1, 2]. They have been demonstrated to play crucial roles in various biological processes, including inflammation, cell growth, and differentiation [2]. In tumor cells, lncRNAs exert significant influence on cellular processes such as differentiation, proliferation, metastasis, invasion, and apoptosis [3, 4]. Furthermore, current studies have revealed the potential of lncRNAs as biomarkers for cancer diagnosis and prognosis [5–7].

LINC00941, also known as lncRNA-MUF (MSC up-regulatory factor), is an intergenic non-coding RNA located on chromosome 12p11.21 in humans, with a length of 1895nt [8]. LINC00941 exhibits distinct distributions within cells: predominantly in the cytoplasm, it primarily influences post-transcriptional regulation, whereas its presence in the nucleus is associated with gene regulation [9]. It exhibits abnormally high expression levels in 12 different cancers and is closely associated with poor prognosis and clinical features in cancer patients, including degree of tumor–node–metastasis (TNM) stage and clinical stage.

Competing endogenous RNA (ceRNA) refers to a class of RNA molecules that competitively bind to microRNA (miRNA) and regulate the expression of downstream mRNA targets [10]. Increasing evidence suggests that lncRNAs can function as important ceRNAs, exerting regulatory effects [1]. LINC00941 serves as a ceRNA for five miRNAs, including miR-205-5p, miR-873-3p, miR-877-3p, miR-335-5p, and miR-34a-5p, promoting cancer cell proliferation, metastasis, invasion, and apoptosis. Additionally, LINC00941 is involved in five signaling pathways: PI3K/AKT [11, 12], TGF-β/SMAD [13, 14], Wnt/β-catenin [3, 8, 15], LIMK1/Cofilin-1 [16], and Hippo signaling pathways [17]. Moreover, LINC00941 can up-regulate the expression of downstream proteins, such as SOX2 [18], ANXA2 [8, 11], PKM [12], CAPRIN2 [3], hnRNPK [15], and YAP1 [17], by recruiting transcription factors.

This article comprehensively explores the aberrant expression, molecular mechanisms, and prognostic relevance of LINC00941 across various documented tumor types. It delves into the ceRNA regulatory network involving LINC00941 and its profound influence on the biological behavior of cancer cells. Additionally, we have broadened the scope of possible regulatory mechanisms and potential targeted drugs associated with LINC00941 by consulting online databases and conducting bioinformatics analysis. Our manuscript serves as a foundational reference, offering valuable insights for future research endeavors into the role of LINC00941 in tumor development.

Abnormal expression of LINC00941 in cancers

As depicted in Table 1, our analysis revealed the up-regulation of LINC00941 in various digestive system tumor tissues and cell lines. Specifically, elevated expression was observed in gastric cancer (GC) [19, 20], laryngocarcinoma (LC) [12, 21], and colorectal cancer (CRC) [14, 22]. Furthermore, LINC00941 exhibited high expression in cell lines of oral squamous cell carcinoma (OSCC) [3, 15] and esophageal squamous cell carcinoma (ESCC) [7]. In respiratory tumors, such as non-small cell lung cancer (NSCLC) [23] and pancreatic adenocarcinoma (PAAD) [24], LINC00941 displayed elevated expression in both corresponding tumor tissues and cell lines. Aberrantly high expression of LINC00941 was also identified in endocrine system cancer cell lines and tissues, including pancreatic ductal adenocarcinoma (PDAC) [17] and pancreatic cancer (PC) [16]. Additionally, current evidence indicates high expression of LINC00941 in a glioblastoma multiforme (GBM) cell line [13].

To explore the expression patterns of LINC00941 in cancer, we obtained the expression profile data of LINC00941 from the TCGA database (https://portal.gdc.cancer.gov/) (Fig. 1). We downloaded the TPM expression data of LINC00941 for 32 cancer types from the UCSC Xena database and performed a $\log_2^{(TPM+1)}$ transformation on them. We calculated the median expression of all lncRNAs and the rank percentage of LINC00941 among all lncRNAs with non-zero expression in these 32 cancer types. As shown in Fig. 1A, LINC00941 was highly expressed in 13 tumors (0.75–1.0 quantile, Q4) including cholangiocarcinoma (CHOL), head and neck squamous cell carcinoma (HNSC), PAAD, esophageal carcinoma (ESCA), stomach adenocarcinoma (STAD), adrenocortical carcinoma (ACC), lung squamous cell carcinoma (LUSC), bladder urothelial carcinoma (BLCA), sarcoma (SARC), colon adenocarcinoma (COAD), GBM, skin cutaneous melanoma (SKCM) and pheochromocytoma and paraganglioma cancer (PCPG); highly expressed in 14 types of tumors (0.5–0.75 quantile, Q3) including testicular germ cell tumors (TGCT), ovarian cancer (OV), rectum adenocarcinoma (READ), cervical esophageal squamous cell carcinoma (CESC), thyroid carcinoma (THCA), kidney renal clear cell carcinoma (KIRC), lung adenocarcinoma (LUAD), breast invasive carcinoma (BRCA), prostate Adenocarcinoma (PRAD), neuroblastoma (NBL), endometrioid cancer (UCEC), kidney papillary cell carcinoma (KIRP), uterine carcinosarcoma (UCS) and liver hepatocellular carcinoma (LIHC); and moderately expressed (0.25–0.5 quantile, Q2) in 5 types of tumors including lower grade glioma (LGG), kidney chromophobe (KICH), acute myeloid leukemia (AML), thymoma (THYM) and acute lymphoblastic leukemia (ALL). These suggest the value of LINC00941 in pan-cancer. We compared the expression difference of LINC00941 between normal and tumor samples in each cancer type. As shown in Fig. 1B, we found that LINC00941 was significantly upregulated in 18 tumor types including ALL, AML, BLCA, CHOL, COAD, ESCA, GBM, HNSC, KIRC, LIHC, LUSC, PAAD, READ, SARC, SKCM, STAD, TGCT, and THCA; significantly down-regulated in 9 tumors including ACC, BRCA, KICH, LGG, NBL, PCPG, PRAD, UCEC and UCS; and showed no significant difference in 5 tumors including CESC, KIRP, LUAD, OV and THYM. After comparing the reported tumor information, it was found that the results of 7 TCGA tumors (COAD, ESCA, GBM, LIHC, LUSC, PAAD, and THCA) were consistent with existing reports (Table S1). However, some TCGA results differ from the existing reports such as TGCA-HNSC and TGCA-LUAD. Previous studies have shown that LINC00941 is highly expressed in OSCC [7], LC [12] and NSCLC [23]. The reason for this discrepancy may be due to differences in cancer subtypes in the TCGA database, detection methods and small sample size.

Furthermore, we performed a correlation analysis between the expression of LINC00941 and three types of RNA modification genes using the TCGA database. These included 10 m1A modification genes, 13 m5C modification genes, and 21 m6A modifying genes. The results revealed significant associations between LINC00941 and RNA-modifying genes in various cancers, although the specific correlations varied (Figure S2).

In conclusion, the dysregulation of LINC00941 in cancer has been broadly established. However, further investigation is required to explore its differential expression in specific cancer types by expanding the sample size and including different sample types. Additionally, it is worth noting that although a certain correlation exists, the relationship between LINC00941 and common epigenetic modifications has not been extensively studied, underscoring the need for further experimental verification.

Molecular mechanism of LINC00941 affecting cancer development

Currently, an increasing number of studies have provided evidence that lncRNAs participate in intricate regulatory networks and play a significant role in cancer pathogenesis [25]. Among them, LINC00941 has been shown to recruit transcription factors, thereby regulating the expression of six downstream factors (CTCF, YBX1, ILF2, ANXA2, PKM, and HNRNPK) at the transcriptional level. Moreover, LINC00941 functions as a ceRNA for six miRNAs, enabling

Table 1 Regulatory mechanism of LINC00941 in various cancers

Cancers	Assessed cell lines	LINC00941 expression	Effects in vivo	Effects in vitro	Regulatory mechanism	Signaling pathway	References
CRC	HT-29, HCT-116, SW480, SW620, and LoVo versus FHC	Up-regulated	Tumor invasion↓ and migratory ↓(LINC00941 knockdown)	EMT↓, invasion↓, and migration↓	–	TGF-β1/SMAD	[14]
	LS174T, HCT116, CT26, HCT8, HCT29, SW480, and LoVo versus NCM460	Up-regulated	Tumor growth↓ and metastasis↓(LINC00941 knockdown)	Proliferation↓, invasion↓, and migration↓	LINC00941/miR-205-5p/MYC	–	[22]
ESCC	KYSE-30, Eca-109, and KYSE-510 versus HEEC	Up-regulated	Tumor growth↓(LINC00941 knockdown)	Proliferation↓, EMT↓, invasion↓, and migration↓	LINC00941/ miR-877-3p/PMEPA1	–	[7]
	KYSE-170, KYSE-150, TE-1,and YES-2 versus HEEC	Up-regulated	Tumor growth↑ and metastasis↑ (LINC00941 overexpression)	Proliferation↓, invasion↓, and migration↓	LINC00941/ILF2/YBX1/SOX2	–	[18]
GBM	U87-MG, LN229, 293 T, and LN18 versus T98G	Up-regulated	Tumor growth↓(LINC00941 knockdown)	Proliferation↓, invasion↓, migration↓, and apoptosis↑	LINC00941/miR-34a-5p/Snail1	TGF-β/SMAD2/3	[13]
GBMLGG	U87, U21 and SNB19 versus NHAS	Up-regulated	–	Proliferation↓, invasion↓, and apoptosis↑	–	–	[71]
GC	MKN45, and AGS	Up-regulated	Tumor growth↓ (LINC00941 knockdown)	Proliferation↓, invasion↓, and migration↓	–	–	[69]
HCC	MHCC-97L, HCC-LM3, SMMC-7721, Hep3B, PLC, Huh7, and HepG2, versus 293 T	Up-regulated	Tumor growth↓ (LINC00941 knockdown)	Proliferation↓, EMT↓, invasion↓, and migration↓	LINC00941/ANXA2/GSK-3β; LINC00941/miR-34a-5p/Snail1	Wnt/β-catenin	[8]
KIRC	786-O, Caki-1, Caki-2, and versus HK-2	Up-regulated	–	Proliferation↓, invasion↓, and migration↓	–	–	[72]
LC	SNU-46, AMC-HN-8, SNU-899, and SNU-1076 versus HuLa-PC	Up-regulated	Tumor migratory↓(LINC00941 knockdown)	Cell cycle↓, viability↓, proliferation↓, invasion↓, migration↓, and apoptosis↑	LINC00941/PKM	PI3K/AKT/mTOR	[12]
NSCLC	A549, and NCI-1299	Up-regulated	Tumor development↓(LINC00941 knockdown)	Proliferation↓ and migration↓	LINC00941/miR-877-3p/VEGFA	–	[23]
OSCC	SCC9, OSC19, HSU3, CAL-27 and versus hNOK	Up-regulated	–	Proliferation↓, EMT↓, migration↓, and invasion↓	LINC00941/hnRNPK	Wnt/β-catenin	[15]
	HSC-3, SCC-9, CAL-27, and OSC-19 versus HOK	Up-regulated	Tumor growth↓ (LINC00941 knockdown)	Proliferation↓, invasion↓, and migration↓	LINC00941/CTCF/CAPRIN2	Wnt/β-catenin	[3]
PAAD	PANC-1, PK-9, BXPC-3, and SW1990 versus HPDE6-C7	Up-regulated	–	Proliferation↓, invasion↓, and migration↓	LINC00941/miR-873-3p/ATXN2	–	[24]

Table 1 (continued)

Cancers	Assessed cell lines	LINC00941 expression	Effects in vivo	Effects in vitro	Regulatory mechanism	Signaling pathway	References
PC	AsPC-1, BxPC-3, PANC-1, MIA PaCa-2, and Capan-2 versus HPDE	Up-regulated	Tumor growth↓ and metastasis↓ (LINC00941 knockdown)	Proliferation↓, EMT↓, migration↓, and invasion↓	LINC00941/miR-335-5p/ROCK1	LIMK1/Cofilin-1	[16]
	AsPC-1, BxPC-3, and Capan-2 versus HPDE	Up-regulated	Tumor growth ↓ and metastasis↓ (LINC00941 knockdown)	Proliferation↓, invasion↓, and migration↓	LINC00941/ANXA2	FAK/PI3K/AKT	[11]
	PANC-1, MIAPaCa-2, SW1990, AsPC-1, and BxPC-3 versus HPDE6-c7	Up-regulated	–	Migration↓, and invasion↓	–	–	[31]
PDAC	PANC-1, SW1990, BxPC-3, and CFPAC-1 versus HPDE and HPAC	Up-regulated	Glycolysis↓ and tumor growth↓ (LINC00941 knockdown)	Proliferation↓	LINC00941/MST1/YAP1	Hippo	[17]
PTC	B-CPAP, TPC1, Cal62, 8505c, FTC133, and SW579	Up-regulated	–	Proliferation↓ and invasion↓	–	–	[66]

CRC, colorectal cancer; *ESCC*, esophageal squamous cell carcinoma; *GBM*, glioblastoma; *GC*, gastric cancer; *HCC*, hepatocellular carcinoma; *LC*, laryngocarcinoma; *NSCLC*, non-small cell lung cancer; *OSCC*, oral squamous cell carcinoma; *PAAD*, pancreatic adenocarcinoma; *PDAC*, pancreatic ductal adenocarcinoma; *PTC*, primes papillary thyroid cancer

the regulation of six downstream factors (including MYC, PMEPA, Snail1, VEGFA, ATXN2, and ROCK1) at the post-transcriptional level. Additionally, LINC00941 is involved in six key signaling pathways, namely the focal adhesion kinase (FAK)/AKT signaling pathway, PI3K/AKT signaling pathway, TGF-β/SMAD signaling pathway, Wnt/β-catenin signaling pathway, LIMK1/Cofilin-1 signaling pathway, and Hippo signaling pathway.

LINC00941 regulates gene expression at the transcriptional level

LncRNAs exert their influence on cancer progression by recruiting various molecular complexes, including transcription factors, RNA-binding proteins, DNA-binding proteins, or histone modification complexes, thereby modulating gene expression [26] In OSCC, the acetylation activity of EP300 is facilitated by its interaction with HAT, leading to the formation of the EP300-HAT domain. This, in turn, promotes H3K27ac modification on the LINC00941 promoter and enhances LINC00941 expression. Upregulation of LINC00941 occurs through the recruitment of the transcription factor CTCF, which induces DNA circularization via homodimerization, ultimately upregulating the expression of its downstream gene, CAPRIN2. The upregulated CAPRIN2 protein phosphorylates the WNT co-receptor LRP6, resulting in increased activity of the canonical Wnt/β-catenin signaling pathway and ultimately contributing to the development of OSCC [3, 27–30]. In ESCC, LINC00941 plays a role in promoting disease progression by directly recruiting YBX1 and the transcription factor ILF2 to the SOX2 promoter. This interaction activates the expression of SOX2 and enhances its mRNA stability, contributing to ESCC progression [18]. Similarly, in hepatocellular carcinoma (HCC), LINC00941 forms a complex with ANXA2 and disrupts the formation of the GSK-3β/β-catenin complex. This activation of the Wnt/β-catenin signaling pathway promotes HCC progression [8]. Additionally, in PC, LINC00941 competes with NEDD4L for binding to ANXA2, preventing the ubiquitination and degradation of ANXA2. This, in turn, activates the FAK/AKT signaling pathway and contributes to the progression of PC [11]. Importantly, a study demonstrated that METTL14 upregulated the m6A modification of LINC00941, leading to enhanced recognition of LINC00941 by IGF2BP2. This interaction subsequently stabilized LINC00941 and facilitated the progression of PC [31].

LINC00941 is primarily localized in the nucleus, although it can also be found in the cytoplasm [14, 18]. Within the nucleus, lncRNAs are known to recruit transcriptional regulators to target gene promoters, thereby modulating gene transcription [32]. Hence, it is plausible that LINC00941 regulates the transcription levels of ANXA2 [8], PKM [12], and HNRNPK [15] by recruiting

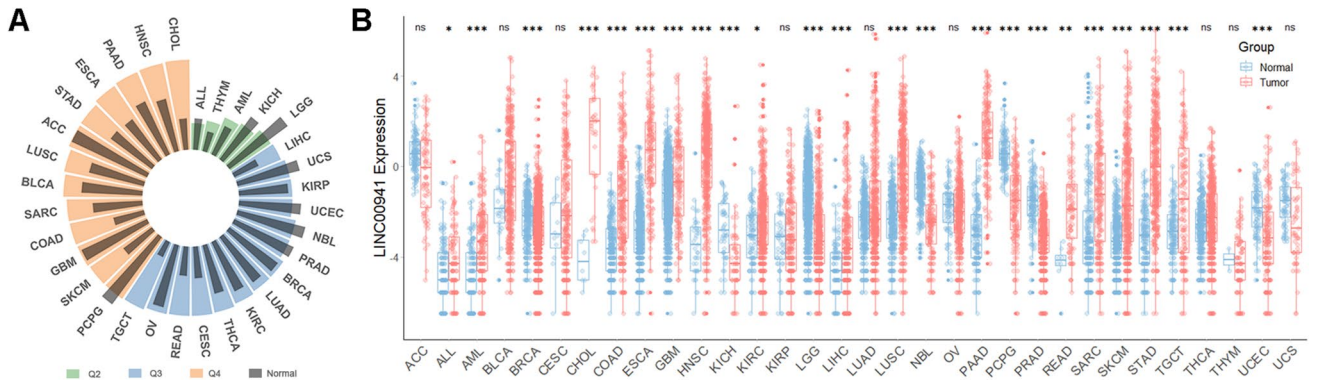

Fig. 1 A pan-cancer analysis of LINC00941 **A** quantile expression of LINC00941 in 32 cancer types; **B** LINC00941 is dysregulated in 32 cancer types. (*** means $p<0.001$, ** means $p<0.01$, * means $p<0.05$, ns means no significant difference). Please check GDC (https://gdc.cancer.gov/resources-tcga-users/tcga-code-tables/tcga-study-abbreviations) for the full name of the TCGA abbreviations and OCG (https://ocg.cancer.gov/programs/target/data-matrix) for the full name of the TARGET abbreviations

transcription factors. To identify potential transcription factors recruited by LINC00941, we employed the Signaling Pathways Project (SPP) database [33] and the ChIP-Atlas database [34] (Fig. 2). These databases were utilized to predict regulatory transcription factors within the 2000 bp upstream regions of ANXA2, PKM, and HNRNPK. Through screening and applying certain criteria (Fold Enrichment > 50, $p<0.05$ for ChIP-Atlas database, and $p<0.05$ for SPP database), we identified JUN as a potential candidate for ANXA2 and PKM. To further validate the role of JUN in regulating these downstream factors, we retrieved the DNA sequences of the 2000 bp upstream of ANXA2 and PKM from the UCSC Genome Browser, with the transcription start site (TSS) as the reference point. These sequences were then analyzed using the JASPAR 2022 database [35] with a relative profile score threshold set at 80%, leading to the prediction of nine binding sites on ANXA2 and six binding sites on PKM. In summary, it is likely that LINC00941 regulates downstream gene transcription by recruiting JUN, although the specific mechanism remains to be elucidated. Further experimental verification is warranted to confirm the transcriptional regulatory role of LINC00941.

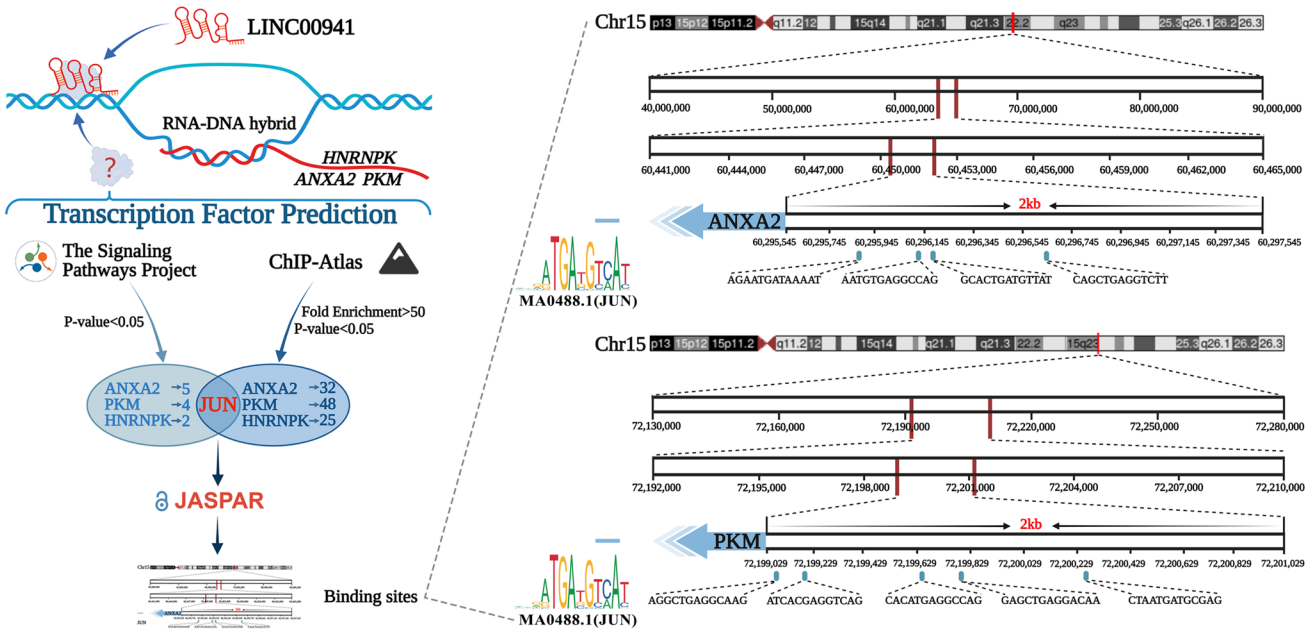

Fig. 2 Exploration of potential upstream transcription factors of ARNT, HF1A, and TBP Utilizing data from SPP, ChIP-Atlas, and JASPAR databases, LINC00941 is predicted to regulate the expression of ANXA2 and PKM by recruiting JUN

Regulation of gene expression by LINC00941 at the post-transcriptional level

CeRNA encompasses RNA transcripts containing microRNA response elements (MREs), such as mRNAs, transcribed pseudogenes, and lncRNAs [36]. CeRNAs possess the capability to modulate the expression of downstream targets by sequestering miRNAs that share the same MRE as the downstream targets [37]. When lncRNAs function as ceRNAs, they bind to miRNA-containing RNA-induced silencing complexes (miRNA-RISC), thereby diminishing the inhibitory effect of miRNAs on mRNA expression and leading to an elevation in mRNA expression levels [37].

As depicted in Fig. 3A, Table 1, and Table S2, LINC00941 exerts its regulatory role by engaging in six ceRNA axes involving five miRNAs, consequently promoting cancer progression. These axes encompass the LINC00941/miR-205-5p/MYC axis in CRC [22], the LINC00941/miR-877-3p/PMEPA axis in ESCC [22], the LINC00941/miR-34a-5p/Snail1 axis in GBM and HCC [8, 23], the LINC00941/miR-877-3p/VEGFA axis in NSCLC [23], the LINC00941/miR-873-3p/ATXN2 axis in PAAD [24], and the LINC00941/miR-335-5p/ROCK1 axis in PC [16].

Involvement of LINC00941 in multiple signaling pathways

LncRNAs play a crucial role in regulating various cellular signals in cancer, thereby influencing cancer progression [38]. As depicted in Fig. 3B, LINC00941 participates in five signaling pathways to facilitate the occurrence and advancement of cancer.

The PI3K/AKT signaling pathway is a vital pathway involved in normal cellular processes, regulating cellular glycolysis and influencing diverse cellular functions [39, 40]. Within the PI3K/AKT signaling, the PI3K/AKT/mTOR pathway plays a significant role by responding to upstream signals in cancer and regulating cell survival, metabolism, growth, and protein synthesis [41]. In LC, LINC00941 activates the PI3K/AKT/mTOR pathway, leading to upregulation of PKM expression. This activation enhances glucose uptake and conversion of glucose to pyruvate, thereby promoting glycolysis in LC cells and facilitating cancer progression [12]. FAK is a non-receptor tyrosine kinase and adapter protein that predominantly regulates adhesion signal transduction and cell migration [42]. FAK influences various physiological functions of cancer cells through its kinase and scaffold functions. It is often overexpressed in cancer and is considered a promising therapeutic target [43]. In PC, LINC00941 upregulates ANXA2 expression and activates the FAK/PI3K/

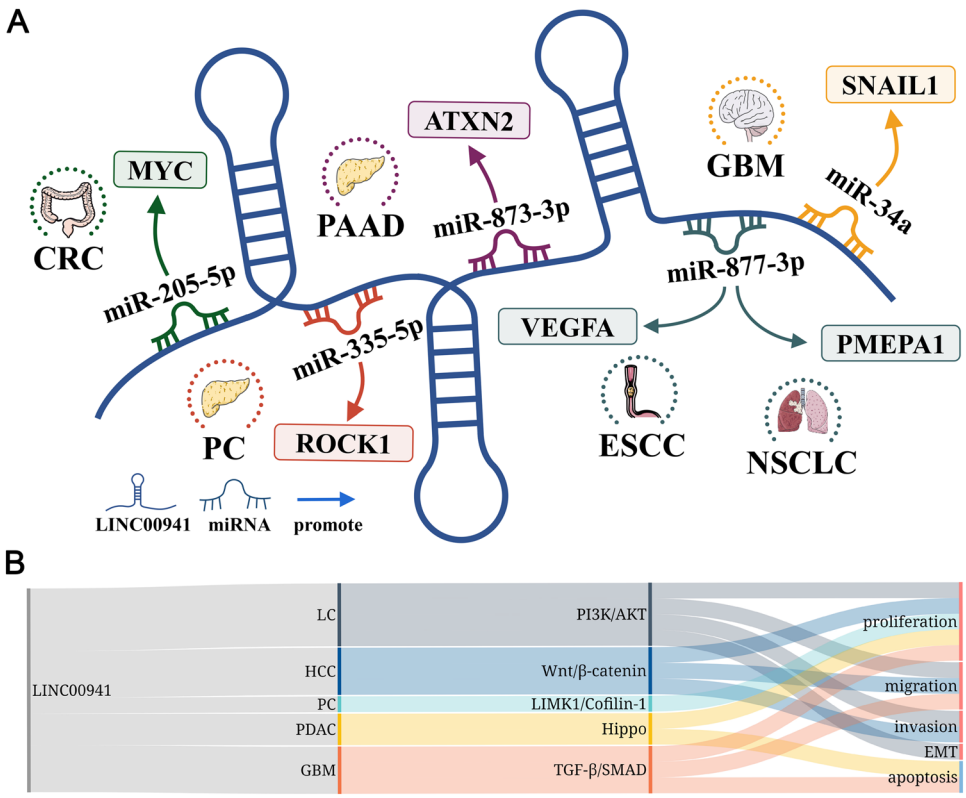

Fig. 3 Regulatory mechanism of LINC00941 in human cancers **A** LINC00941 functions as a ceRNA by binding to miRNAs and participating in the regulation of transcriptional levels. **B** LINC00941 is involved in five signaling pathways that regulate the biological behavior of cells in five different cancers

AKT signaling, promoting the proliferation, invasion, and metastasis of PC cells [11].

The TGF-β/SMAD signaling pathway represents a classic SMAD-dependent pathway in TGF-β signaling. Transforming growth factor β (TGF-β) is a pleiotropic cytokine that modulates multiple cellular responses, influences the immune system and the tumor microenvironment, and promotes tumor cell invasion and metastasis [44, 45]. SMAD proteins serve as downstream signal transduction molecules of TGF-β family receptors and consist of two globular domains (MH1 and MH2 domains) connected by an unstructured linker [45, 46]. SMAD4, a shared component among all SMAD proteins, plays a crucial role in cancer metastasis and acts as an essential effector of TGF-β-induced epithelial–mesenchymal transition (EMT) [47, 48]. Phosphorylation of the two C-terminal Ser residues of SMADs by receptor-mediated targeting enables them to bind to the MH2 domain of SMAD4 or the cognate MH2 structure [48]. In CRC, nucleotides 1465 to 1895 of LINC00941 compete with β-TrCP for binding to the MH2 domain of both SMAD4 and full-length SMAD4. This interaction regulates the ubiquitination and degradation of SMAD4, stabilizes SMAD4, activates the TGF-β/SMAD signaling pathway, accelerates the EMT process in CRC cells, and promotes CRC cell metastasis [14].

Wnt/β-catenin signaling pathway plays a crucial role in the proliferation, metastasis, and invasion of cancer cells [49–51]. In HCC, nucleotides 800 to 1600 of LINC00941 specifically bind to ANXA2. Additionally, ANXA2 interacts with GSK-3β and disrupts the formation of the GSK-3β/β-catenin complex. Consequently, β-catenin accumulates continuously and translocates into the nucleus, activating the Wnt/β-catenin signaling pathway. This activation promotes the expression of downstream genes, facilitates the EMT process, and ultimately contributes to the progression of HCC in vivo [8]. In OSCC, hnRNPK directly enhances the expression of LINC00941 [15]. Furthermore, hnRNPK overexpression inhibits the phosphorylation of β-catenin, leading to its degradation through the ubiquitin–proteasome system. This results in the activation of the Wnt/β-catenin signaling pathway, promoting cell proliferation and metastasis [15].

The LIMK1/Cofilin-1 signaling pathway plays a significant role in the growth, invasion, and metastasis of cancer cells [52]. LIMK1, a serine/threonine protein kinase, phosphorylates and inactivates the downstream actin regulator, Cofilin-1. This affects the formation of actin stress fibers and adhesion plaques, thereby modulating the cytoskeleton system and influencing tumor cell metastasis [53, 54]. In PC, LINC00941 acts as a molecular sponge for miR-335-5p, leading to upregulation of ROCK1 and activation of the LIMK1/Cofilin-1 pathway. Consequently, the growth, EMT, and metastasis of PC cells are promoted [16].

The Hippo signaling pathway, a highly conserved pathway, is involved in various biological processes such as cell growth, apoptosis, and cancer development [55]. The core of the mammalian Hippo pathway consists of a kinase cascade involving mammalian sterile20-like kinase 1/2 (MST1/2) and large tumor suppressor 1/2 (LATS1/2), along with downstream effectors YAP and TAZ, which function as transcriptional coactivators. These core components govern cell proliferation, survival, metastasis, stemness, and differentiation [56]. In PDAC, LINC00941 interacts with mammalian MST1, promoting protein phosphatase 2A (PP2A)-mediated dephosphorylation of MST1 and activating the Hippo signaling pathway. This leads to the nuclear translocation of the transcriptional coactivator YAP, initiation of downstream target gene transcription, and promotion of the glycolysis process in PDAC cell lines, thereby enhancing cell proliferation [17].

LINC00941 drives tumor progression by modulating the diverse biological behaviors of cancer cells.

LncRNA plays a pivotal role in regulating the occurrence and development of cancer by influencing multiple cellular processes [57]. Figure 4 and Table 1 provide a comprehensive overview of the impact of LINC00941 on cancer progression, highlighting its modulation of downstream genes involved in pivotal cellular functions such as cell proliferation, apoptosis, EMT, invasion, and migration.

Upregulation of LINC00941 promotes cell proliferation while inhibiting apoptosis

Cell proliferation refers to the intricate process by which cells absorb nutrients, undergo growth, and divide, ultimately leading to an increase in cell population. Uncontrolled cell proliferation is a hallmark of cancer [58]. LINC00941 engages in various regulatory axes, exerting transcriptional and post-transcriptional control to facilitate cell proliferation. In CRC, LINC00941 is implicated in the LINC00941/miR-205-5p/MYC axis [22]. In ESCC, it participates in the LINC00941/miR-877-3p/PMEPA1 axis [7] as well as the LINC00941/ILF2/YBX1/SOX2 axis [18]. The LINC00941/miR-34a-5p/Snail1 axis has been identified in GBM [13], while the LINC00941/ANXA2/GSK-3β axis and LINC00941/miR-34a-5p/Snail1 axis are involved in HCC [8]. Additionally, LINC00941 contributes to cell proliferation in LC through the LINC00941/PKM axis [12], in NSCLC through the LINC00941/miR-877-3p/VEGFA axis [23], in OSCC through the LINC00941/hnRNPK axis [15] and the LINC00941/CTCF/CAPRIN2 axis [3], in PAAD through the LINC00941/miR-873-3p/ATXN2 axis [24], in

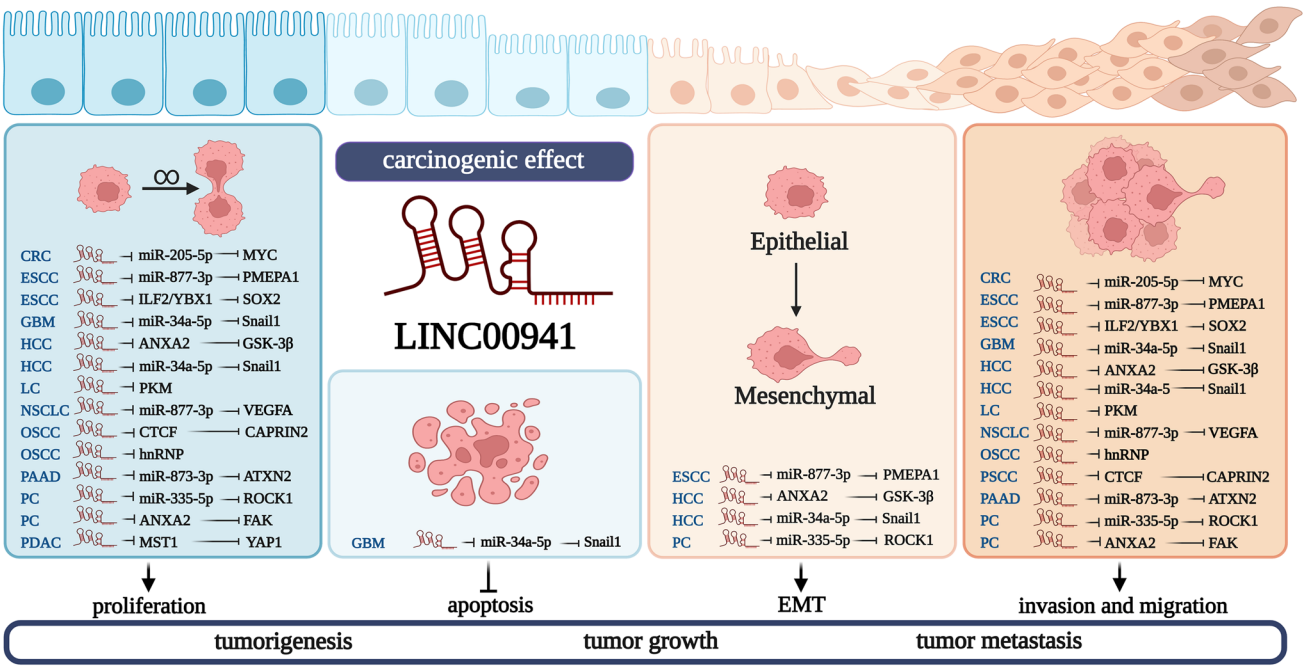

Fig. 4 LINC00941's involvement in the regulation of various cellular behaviors LINC00941 plays a role in regulating cellular proliferation, apoptosis, EMT, invasion, and migration

PC through the LINC00941/miR-335-5p/ROCK1 axis and the LINC00941/ANXA2 axis [11, 16], and in PDAC through the LINC00941/MST1/YAP1 axis [17].

Apoptosis, a programmed cell death mechanism regulated by specific genes, represents a normal physiological response of cells [59]. However, in the context of cancer, apoptosis is frequently suppressed, leading to uncontrolled proliferation of cancer cells [60]. In GBM, LINC00941 activates the TGF-β/SMAD2/3 signaling pathway via the LINC00941/miR-34a-5p/Snail1 axis, thereby suppressing apoptosis [13].

Upregulation of LINC00941 promotes EMT, invasion, and migration

EMT is a pivotal process through which epithelial cells acquire mesenchymal characteristics, playing a significant role in cancer cell metastasis [61]. In HCC, LINC00941 upregulation triggers the EMT process by activating the Wnt/β-catenin signaling pathway via its interaction with ANXA2 [8]. Moreover, LINC00941 contributes to EMT promotion in various tumor cells through its involvement in the ceRNA axes. Notably, it participates in the LINC00941/miR-877-3p/PMEPA1 axis in ESCC [7], the LINC00941/miR-34a-5p/Snail1 axis in HCC [8], and the LINC00941/miR-335-5p/ROCK1 axis in PC [16].

Invasion and migration characterize the active motility and infiltration of malignant cells into surrounding tissues from the primary tumor site [62]. LINC00941 actively engages in multiple regulatory axes, promoting cell invasion and migration at both transcriptional and post-transcriptional levels. For example, in CRC, LINC00941 is implicated in the LINC00941/miR-205-5p/MYC axis [22]. In ESCC, it participates in the LINC00941/miR-877-3p/PMEPA1 axis [7] and the LINC00941/ILF2/YBX1/SOX2 axis [18]. In GBM, the LINC00941/miR-34a-5p/Snail1 axis comes into play [13], while in HCC, LINC00941 contributes to cell invasion and migration through the LINC00941/ANXA2/GSK-3β axis and the LINC00941/miR-34a-5p/Snail1 axis [8]. Additionally, LINC00941 is involved in the LINC00941/PKM axis in LC [12], the LINC00941/miR-877-3p/VEGFA axis in NSCLC [23], the LINC00941/hnRNPK axis and the LINC00941/CTCF/CAPRIN2 axis in OSCC [3, 15], the LINC00941/miR-873-3p/ATXN2 axis in PAAD [24], and the LINC00941/miR-335-5p/ROCK1 axis and the LINC00941/ANXA2 axis in PC [11, 16].

The potential implications of LINC00941 in clinical diagnosis and treatment

Given their substantial differential expression and extensive regulatory roles, lncRNAs hold tremendous promise as emerging biomarkers and therapeutic targets, thus playing a significant role in clinical diagnosis and treatment [63]. High expression of LINC00941 has been correlated with poorer

prognosis, including overall survival (OS) and disease-free survival (DFS), as well as various clinicopathological characteristics such as tumor size, degree of metastasis, and clinical stage. Notably, several downstream targets of LINC00941 have demonstrated drug-targetable properties.

The association between LINC00941 and prognostic value and clinicopathological features of cancer patients

Table 2 highlights the close link between aberrant LINC00941 expression and the prognosis and clinicopathological features of different tumor types. In ten cancer types, elevated levels of LINC00941 were consistently associated with worse overall survival of patients. These cancer types include CRC [14], GC [19, 20], HCC [8, 21], LC [12], LUAD [64, 65], NSCLC [23], PAAD [24], PC [11, 16], PDAC [17], and papillary thyroid cancer (PTC) [66]. Furthermore, in PAAD [24] and PC [11, 16, 31], high LINC00941 expression was associated with reduced disease-free survival.

In LC, increased LINC00941 expression correlated with advanced tumor stage, deeper tumor invasion depth, and higher lymph node metastasis [12]. Similarly, in CRC, high LINC00941 expression was typically linked to a higher rate of lymph node metastasis, larger tumor size, more distant tumor metastasis [14, 22]. In GC, elevated LINC00941 expression was associated with advanced clinical stage and more advanced TNM stage [67, 68]. However, some studies have also reported that increased LINC00941 expression is related to more advanced tumor depth and a higher rate of distant metastasis [69]. In HCC, increased LINC00941 expression was significantly correlated with a higher rate of lymph node metastasis, and larger tumor size [8, 21]. Similarly, in PC, increased LINC00941 expression was significantly correlated with distant metastasis and higher lymph node metastasis [16]. In PDAC, elevated LINC00941 expression was significantly associated with larger tumor size and a higher tumor stage [17]. Lastly, in PTC, increased LINC00941 expression was significantly associated with a more advanced TNM stage [66].

Table 2 Clinicopathological and prognostic values of LINC00941 in cancers

Cancers	LINC00941 expression	Clinical sample	Clinicopathological characteristics	Prognosis	References
CRC	Up-regulated	90 CRC patients	Higher rate of lymph node metastasis; larger tumor size; more advanced AJCC stage	Poor OS	[14]
	Up-regulated	42 CRC patients	Further distant metastasis; higher lymph node metastasis	–	[22]
GC	–	–	More advanced clinical stage; higher rate of lymphatic metastasis; more advanced invasion depth	Poor OS	[20]
	Up-regulated	82 GC patients	More advanced invasion depth; higher rate of lymphoma metastasis	Poor OS	[19]
	Up-regulated	358 GC patients from TCGA	More advanced tumor depth; higher rate of distant metastasis	–	[69]
HCC	Up-regulated	351 HCC patients	Higher clinical stage	Poor OS	[8]
	Up-regulated	370 HCC patients from TCGA	Higher rate of lymphoma metastasis; larger tumor size	Poor OS	[21]
LC	Up-regulated	56 LC patients	Higher lymph node metastasis; more advanced tumor stage and tumor depth	Poor OS	[12]
LUAD	Up-regulated	20 LUAD patients	–	Poor OS	[64]
	Up-regulated	468 LUAD patients	More advanced TNM stage	Poor OS	[65]
NSCLC	Up-regulated	40 NSCLC patients	–	Poor OS	[23]
PAAD	Up-regulated	50 PAAD patients	–	Poor OS and DFS	[24]
PC	Up-regulated	54 PC patients	Further distant metastasis; more advanced pathological grading; higher lymph node metastasis	Poor OS and DFS	[16]
	Up-regulated	178 PC patients from TCGA	Higher lymph node metastasis, larger tumor size and higher tumor stage	Poor OS and DFS	[11]
PDAC	Up-regulated	10 PDACC patients	Larger tumor size and higher tumor stage	Poor OS	[17]
PTC	Up-regulated	568 PTC patients	More advanced TNM stage	Poor OS	[66]

CRC, colorectal cancer; *GC*, gastric cancer; *HCC*, hepatocellular carcinoma; *LC*, laryngocarcinoma; *LUAD*, lung adenocarcinoma; *NSCLC*, non-small cell lung cancer; *PAAD*, pancreatic adenocarcinoma; *PC*, pancreatic cancer; *PDAC*, pancreatic ductal adenocarcinoma; *PTC*, primes papillary thyroid cancer

Drugs targeting downstream effectors of LINC00941

LINC00941 and its downstream targets hold substantial potential as therapeutic targets for drug intervention. Figure 5 illustrates that a search in the CADDIE database (https://exbio.wzw.tum.de/caddie/) [70] has identified numerous approved drugs that target the downstream effectors of LINC00941. These include marketed drugs such as warfarin, acetylsalicylic acid, nadroparin, and resveratrol, which target MYC. Drugs targeting ATXN2 encompass raloxifene, nadroparin, nicardipine, amsacrine, and maprotiline. Marketed drugs targeting VEGFA include celecoxib, denibulin, enalapril, and carvedilol. Lastly, drugs targeting ROCK1 consist of midostaurin, lapatinib, bosutinib, imatinib, salicylamide, adenine, ruxolitinib, vandetanib, imatinib, and pazopanib.

Conclusions and future prospects

LINC00941, recently identified as an oncogenic factor, exhibits widespread upregulation in various types of cancers. Current research reveals the abnormal overexpression of LINC00941 in cancer cells or tissues across 12 different cancer types. However, the existing studies suffer from limitations such as small sample sizes and a narrow range of cancer types. Furthermore, there is a lack of differential research focusing on clinically relevant detection carriers suchas serum and cerebrospinal fluid. Moving forward, it is imperative to expand the sample size and include diverse sample types to gain further insights into the potential value of LINC00941 in non-invasive cancer diagnosis.

LINC00941 plays a pivotal role in extensive regulatory networks within cancer, exerting its influence through multiple mechanisms. It acts as a miRNA sponge, indirectly modulating the translation of five downstream mRNAs, and facilitates the transcription of downstream effector genes by recruiting transcription factors. Additionally, LINC00941 is involved in five important signaling pathways. However, the current understanding of the molecular mechanisms underlying LINC00941's actions remains limited and incomplete. Further research is necessary to unveil a more comprehensive and detailed regulatory network associated with LINC00941, providing a solid foundation for future studies focused on clinical treatment.

The clinical potential of LINC00941 has been observed across various cancer types. Elevated expression of LINC00941 shows a strong correlation with the prognosis and clinicopathological features of ten different cancers, making it a promising biomarker for prognostic evaluation

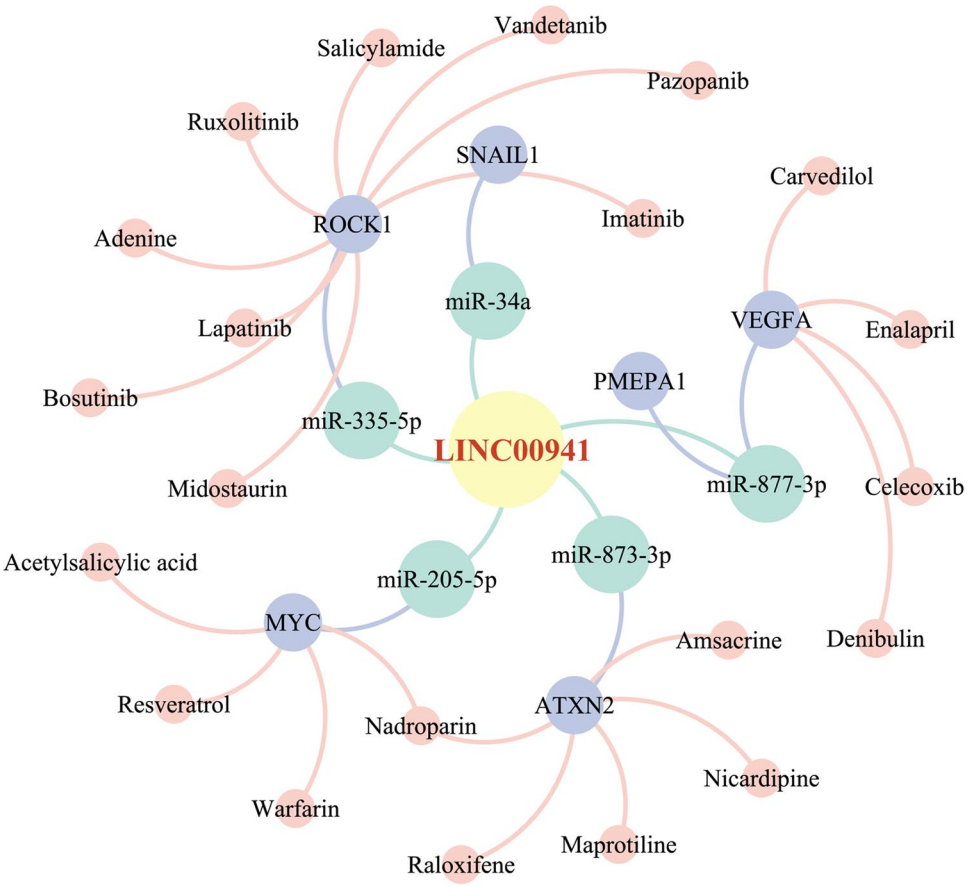

Fig. 5 Therapeutic drugs targeting genes regulated by LINC00941 The CADDIE database provides information on the ceRNA axes involving LINC00941 and the therapeutic drugs associated with its downstream targets

in diverse malignancies. However, the current research faces challenges due to small sample sizes and a limited range of cancer types investigated. To validate the prognostic value of LINC00941, larger and more diverse sample sizes, including multi-center clinical studies, are needed in the future. It is worth noting that research on drugs targeting LINC00941 is currently scarce, and no drugs directly targeting LINC00941 have been reported. Although drugs targeting downstream effectors exist, their correlation with LINC00941 remains unexplored. Therefore, further exploration and experimental validation of LINC00941 and the drugs within its regulatory network are crucial to uncover the potential therapeutic value of LINC00941 in cancer treatment. Enhancing our understanding of the prognosis and drug interactions involving LINC00941 will contribute to a better grasp of its pivotal role in cancer treatment and facilitate its clinical translation.

This work presents a comprehensive review of the differential expression, molecular mechanisms, and clinical significance of LINC00941. LINC00941 emerges as a critical oncogene with the potential to serve as a biomarker and therapeutic target in various cancers. However, further research on LINC00941 is imperative to unravel its specific molecular mechanisms in different cancer types and uncover its diagnostic and therapeutic value in cancer management.

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Data availability Not applicable.

Declarations

Conflict of interest All authors declare no competing interests.

Ethical approval Not applicable.

Consent to participate Not applicable.

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