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LINC00467: A key oncogenic long non-coding RNA

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ABSTRACT

The significance of long non-coding RNAs (lncRNAs) in the development and progression of human cancers has attracted increasing attention in recent years of investigations. Having versatile interactions and diverse functions, lncRNAs can act as oncogenes or tumor-suppressors to actively regulate cell proliferation, survival, stemness, drug resistance, invasion and metastasis. LINC00467, an oncogenic member of long intergenic non-coding RNAs, is upregulated in numerous malignancies and its high expression is often related to poor clinicopathological features. LINC00467 facilitates the progression of cancer via sponging tumor-suppressive microRNAs, inhibiting cell death cascade, modulating cell cycle controllers, and regulating signalling pathways including AKT, STAT3, NF-κB and Wnt/β-catenin. A growing number of studies have revealed that LINC00467 may serve as a novel prognostic biomarker and its inhibitory targeting has a valuable therapeutic potential to suppress the malignant phenotypes of cancer cells. In the present review, we discuss the importance of LINC00467 and provide a comprehensive collection of its functions and molecular mechanisms in a variety of cancer types.

1. Introduction

Non-coding RNAs (ncRNAs) have significantly expanded our viewpoint on the human genome and principles of molecular biology. Among the diverse types of ncRNAs, long non-coding RNAs (lncRNAs) are distinguished by two characteristics: longer length (more than 200 nucleotides) and a wider range of functions [1,2]. In comparison to mRNAs, lncRNAs indicate more cell type- or tissue-specificity and less quantitative abundance. LncRNAs are classified into intergenic, sense, antisense, bidirectional and intronic categories, according to their genomic structure (Fig. 1). Functionally, lncRNAs classes include scaffolds, *ribo*-repressors (decoys), *ribo*-activators, guides, competing endogenous RNAs (ceRNAs) and precursors of small ncRNAs [3,4]. They are mostly transcribed by RNA polymerase II and can function at transcriptional or post-transcriptional levels to regulate gene expression. With the ability to interact with other macromolecules, lncRNAs are involved in a variety of biological activities such as epigenetic modulation, splicing, imprinting, X-inactivation, development, differentiation and tumorigenesis [5–7].

Accumulating evidence indicates lncRNA deregulation in various cancer types and its implication in all hallmarks of cancer by diverse molecular mechanisms [8–10]. As a notable mode of action, it has frequently been reported that a lncRNA can sponge and sequester multiple microRNAs (miRNAs), thereby indirectly upregulating miRNA target expression [6,11–13]. LncRNAs may act as oncogenes or tumor suppressors and their aberrant expression results in cancer cell proliferation, stemness, survival, metabolic reprogramming, drug resistance, invasion and metastasis [14–18]. ANRIL, H19, HOTAIR and XIST are examples of the oncogenic lncRNAs and BGL3, GAS5, MEG3 and TERRA exert tumor-suppressive effects [19,20]. Due to the importance and cancer type-specific expression of the lncRNAs, they have a remarkable potential to be effectively served as the diagnostic biomarkers, prognostic factors and therapeutic targets in cancer [21–23].

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2. Considerable features of long intergenic ncRNAs (lincRNAs)

Modulating chromatin topology, scaffolding, acting as decoys, regulating neighbouring genes transcription and encoding micropeptides are the known functions of lincRNAs. They affect chromatin topology to enforce transcriptional activation or repression in *cis* by chromatin looping as well as in *trans* by chromosomal looping or by binding transcription factors and chromatin-modifying complexes [24–26]. In most cases, protein/RNA scaffolding is the defining factor for the lincRNA function. Sequence complementarity and RNA structural elements enable lincRNAs to interact with nucleic acids and proteins [27,28]. Another feature of the lincRNAs is the inhibitory sequestration of proteins, mRNAs and miRNAs. In the proposed mechanism of ceRNA function, circular RNAs and pseudogene transcripts also participate in the process of miRNA sequestering by a lincRNA to prevent the binding of RISC complexes and mRNA degradation [29,30]. The transcription of lincRNA may influence the neighbouring coding loci by modifying the epigenetic state. Without overlap with coding genes, many enhancer RNAs (eRNAs) assemble the mediator complex to coordinate enhancer-directed chromatin looping [31,32]. Besides, micropeptides of less than 100 codons encoded from small open reading frames (smORFs) of non-coding loci have been identified. The expression levels of lincRNAs harbouring smORFs are higher than lincRNAs lacking smORFs [33,34].

Long intergenic non-coding RNA 00467 (LINC00467) has been recognized as a tumor-promoting lncRNA that actively partakes in the pathological process of multiple types of cancer. The gene encoding LINC00467, located in chr1q32.3, has 6 exons and the full length of the transcripts is 3508 nucleotides. LINC00467 normally exhibits a testis-specific expression and its deregulation leads to cancer progression by affecting varied processes and regulatory targets. In this review, we aim to discuss the significance, clinical value and molecular mechanisms of LINC00467 in human malignancies.

3. Expression pattern and clinical potential of LINC00467 in cancers

The absolute majority of the studies demonstrate that LINC00467 is significantly upregulated in numerous cancers (Table 1). The downregulation of LINC00467 in testicular germ cell tumors can be attributed to its normal high testis-specific expression. Either by analysing patients' specimens or bioinformatics databases, the prognostic value of LINC00467 aberrant expression and its correlation with clinicopathological features have been reported for several cancer types. As summarized in Table 1, the upregulation of LINC00467 is associated with poor overall/disease-free survival and/or advanced pathological grades/stages in lung adenocarcinoma, colorectal cancer, glioma, bladder cancer, osteosarcoma, cervical cancer, non-small cell lung cancer, breast cancer, testicular germ cell tumor and gastric cancer. Furthermore, LINC00467 has been introduced as a potential diagnostic biomarker in prostate cancer (area under the ROC curve = 0.802). Taken together, LINC00467 seems a novel efficient prognostic/diagnostic biomarker in a variety of human neoplastic conditions.

4. Subcellular localization of LINC00467

The elementary determinant of a lncRNA function is its subcellular localization. The fate of a lncRNA is finely regulated to be localized in specific compartments inside or outside the nucleus. Interestingly, the subcellular localization of lncRNAs can be dynamically changed to respond to diverse cellular states. The most common techniques for subcellular RNA mapping are biochemical fractionation coupled to RNA quantification, and oligonucleotide hybridization coupled to imaging [35,36]. Several studies have reported the localization of LINC00467 in cancer cell lines (Table 2). Most of the studies elucidate that LINC00467 is found in both the nucleus and cytoplasm of cancer cells, majorly located in the cytoplasm. However, there are also some investigations indicating a predominantly nuclear localization for LINC00467. Altogether, a wide range of pan-cancer functions and interactions can be inferred from LINC00467 subcellular localization.

5. Functions and molecular mechanisms of LINC00467

The functions and effects of LINC00467 overexpression in different types of cancer at the levels of cell lines and animal models have been collected in Tables 3 and 4, respectively, and will be explained in the next sections.

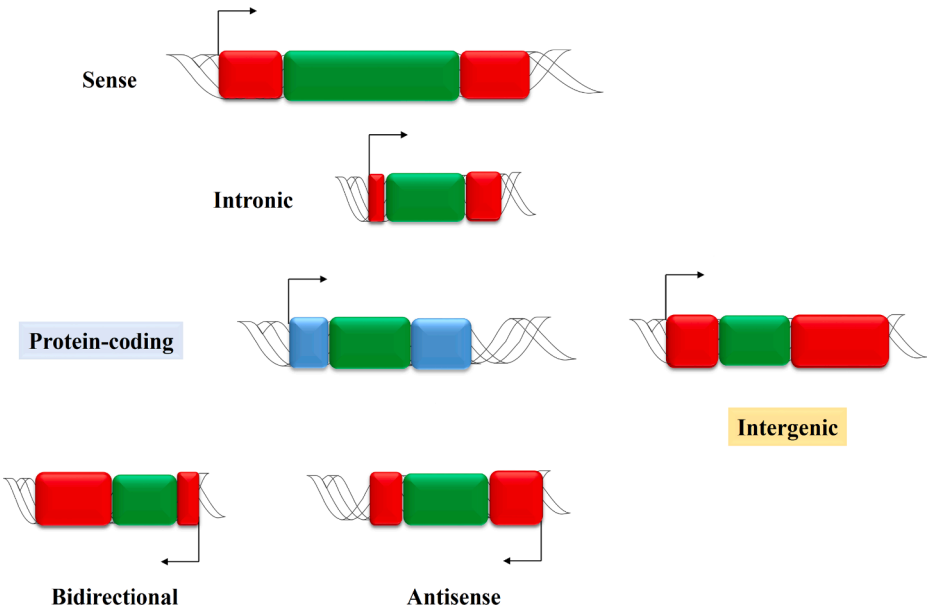

Fig. 1. Genomic structure (intragenic or intergenic) of the lncRNAs relative to a hypothetical protein-coding gene (PCG). Intragenic class includes sense, antisense, intronic and bidirectional types. LINC00467 belongs to the intergenic class. Located on the same strand as the PCGs, intergenic lncRNAs usually do not overlap with them and exert a unique set of functional, structural and regulatory activities. Red and blue boxes represent exons.

Table 1
Expression and clinical significance of LINC00467 in human cancers.

Cancer types	Samples (Tumor vs Normal)	Expression (Tumor vs Normal)	Clinicopathological features	Refs
Acute myeloid leukemia	134:40	Up	–	[74]
Lung adenocarcinoma	33:33	Up	-	[434344444245]
	TCGA	Up	Poor OS	
	38:38	Up	Poor OS	
	TCGA	Up	Poor OS	
	TCGA	Up	Poor OS	
	TCGA	Up	Poor OS, association with distant metastasis, correlation with immune cells infiltration	
Colorectal cancer	45:45	Up	-	[474747474849]
	GEO	Up	Correlation with distant metastasis	
	CRN	Up	Correlation with advanced pathological stages	
	TCGA	Up	Poor OS and DFS	
	50:10	Up	Poor OS	
	50:50	Up	Poor OS	
Glioma	TCGA	Up	-	[5252535454]
	30:30	Up	Correlation with advanced tumor grades	
	TCGA	Up	-	
	TCGA	Up	-	
	30:30	Up	-	
Osteosarcoma	36:36	Up	Poor OS	[5758]
	44:44	Up	Poor OS	
Hepatocellular carcinoma	TCGA	Up	-	[60616164626363]
	GEO	Up	-	
	56:56	Up	-	
	65:31	Down	Negative correlation with metastasis	
	TCGA	Up	-	
	20:20	Up	-	
	TCGA	Up	-	
Bladder cancer	TCGA	Up	Poor DFS	[787878]
	GEO	Up	-	
	6:6	Up	-	
Cervical cancer	GEO	Up	-	[8080]
	54:54	Up	Poor DFS	
Esophageal squamous cell carcinoma	TCGA	Up	–	[8282]
	44:44	Up	-	
Non-small cell lung cancer	GEO	Up	-	[404040]
	TCGA	Up	Poor OS and DFS, association with advanced clinical stages	
	lnCAR	Up	-	
Gastric cancer	52:52	Up	–	[7269]
	TCGA	Up	-	
	31:31	Up	Positive correlation with tumor size, differentiation, N stage and T stage	[69]
	TCGA	Up	–	[70]
	52:52	Up	Poor survival, implicaton in pathological stage, lymph node metastasis and tumor differentiation	[71]
Head and neck squamous cell carcinoma	35:35	Up	–	[66]
Breast cancer	TCGA	Up	-	[7676]
	70:70	Up	Poor OS	
Prostate cancer	GTEx, TCGA	Up	-	[8484]
	24:24	Up	Diagnosis biomarker	
Testicular germ cell tumor	14:9	Down	-	[868686]
	TCGA	Down	Association with advanced pathological grades, negative correlation with immune cells infiltration and response to anti-PD-1 immunotherapy	
	KMplotter	-	Poor OS and DFS	

Abbreviations: OS: overall survival, DFS: disease-free survival, TCGA: the cancer genome atlas, GEO: gene expression omnibus, CRN: cancer RNA-seq nexus, lnCAR: lncRNAs from cancer arrays, GTEx: genotype-tissue expression, KMplotter: Kaplan-Meier plotter, PD-1: programmed cell death protein 1.

5.1. *Neuroblastoma*

Almost 15% of all cancer-related deaths in children are attributed to neuroblastoma (NB) [37]. The first study to investigate the role and underlying molecular mechanism of LINC00467 was conducted by Atmadibrata et al. using BE(2)-C and Kelly NB cell lines. They showed that siRNA-mediated knockdown of LINC00467 could increase apoptosis and reduce the survival of NB cells. Downregulation of RD3 and DKK1 by LINC00467 and suppressive impact of *n*-Myc on *LINC00467* gene promoter were demonstrated using chromatin immunoprecipitation, luciferase assays and RT-PCR. *RD3* is the protein-coding gene located downstream of the *LINC00467* gene. Co-transfection of LINC00467 siRNA with DKK1 siRNA reversed the effects of LINC00467 on the survival and apoptosis of NB cells [38].

5.2. *Non-small cell lung cancer*

Approximately 85% of lung cancers, the first leading cause of cancer deaths, are non-small cell lung cancer (NSCLC) including lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) as the

Table 2
Subcellular localization of LINC00467 in cancer cell lines.

Validated localization	Cancer cell type	Refs
Mainly in cytoplasm	LUAD, CRC, GB, OS, HCC, GC, CC, ESCC, PC	[44,47,54,57,58,61,62,69,80,82,84]
Both nucleus and cytoplasm	NSCLC, glioma, BLCA	[40,55,78]
Cytoplasm	CRC, HNSCC	[49,66]
Mainly in nucleus	Glioma, HNSCC	[53,67]
Nucleus	LUAD	[42]

Abbreviations: LUAD: lung adenocarcinoma, CRC: colorectal cancer, GB: glioblastoma, OS: osteosarcoma, HCC: hepatocellular carcinoma, GC: gastric cancer, CC: cervical cancer, ESCC: esophageal squamous cell carcinoma, PC: prostate cancer, NSCLC: non-small cell lung cancer, BLCA: bladder cancer, HNSCC: head and neck squamous cell carcinoma.

most frequent subtypes [39]. Zhu et al. verified the stimulatory impact of LINC00467 on cell proliferation, migration and invasion of H1299 and A549 NSCLC cell lines via regulating the AKT signalling pathway. LINC00467 was upregulated by TDG-mediated H3K27 acetylation at its promoter with direct binding between TDG and EP300. The inhibition of LINC00467 increased AZGP1 expression but reduced the level of phosphorylated AKT (p-AKT) in NSCLC cells. As *in vivo* experiments confirmed, LINC00467 overexpression significantly incremented tumor growth and metastasis in nude mice [40].

5.3. Lung adenocarcinoma

LUAD is the most common type of lung cancer, having high aggression and fatality [41]. Yang et al. reported that STAT1 could act as a transcription regulator of *LINC00467* to induce its promoter activity in H1299, SPC-A1 and A549 LUAD cell lines. Upregulated LINC00467 activated Wnt/β-catenin signalling pathway through epigenetically silencing DKK1 (inhibitor of the pathway) by recruiting enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) to DKK1 promoter and also upregulating β-catenin, c-Myc and Cyclin D1 expression, leading to LUAD cells proliferation and migration [42].

Knocking down LINC00467 by Ding et al. led to inhibition of H1299 and A549 lung cancer cells proliferation and G_0/G_1 cell cycle arrest via decreasing CCND1 (Cyclin D1) level and its downstream target phosphorylated pRB. LINC00467 knockdown resulted in a significant reduction of tumor weight and volume in nude mice as well as decreased levels of CCND1 and phosphorylated pRB, consistent with *in vitro* experiments. Further analyses demonstrated that LINC00467 acts as a molecular sponge of miR-20b-5p to promote CCND1 expression in lung cancer cells [43].

Chang and Yang illustrated elevated proliferation of A549 and SPC-A1 cells by LINC00467 and introduced three groups of its downstream regulatory targets. First, LINC00467 promoted cancer cell stemness through upregulating Oct4, CD44 and CD133. Second, LINC00467 exhibited an anti-apoptotic effect via decreasing the protein level of Cleaved Caspase3 and Bax while inducing Bcl-2. Third, LINC00467 negatively regulated miR-4779 and miR-7978 previously reported antitumor miRNAs. Additionally, tumor growth in immunodeficient mice was observed as a result of LINC00467 expression [44] (Fig. 2).

In another study based on TCGA data mining, Wang et al. discovered the positive correlation of DNA copy number amplification and hypomethylation with the expression of LINC00467. After the knockdown of LINC00467 in the A549 LUAD cell line and microarray analysis, they constructed a ceRNA network specific to LINC00467 including miR-575, miR-1225-5p and five mRNAs (TMEM182, BCL9, KCNK1, BARX2, KIAA1324) in LUAD [45].

5.4. Colorectal cancer

Colorectal cancer (CRC) is considered the second cause of cancer mortality worldwide [46]. siRNA-mediated knockdown of LINC00467 contributed to suppressing proliferation, invasion and epithelial-mesenchymal transition (EMT) of HT29 CRC cell line through an enhanced expression of E-cadherin and reduced expression of Cyclin A1, Cyclin D1, CDK2, CDK4 and Twist1, reported by He et al. [47].

Li et al. found that LINC00467 and Ferritin Light Chain (FTL) enhanced HCT116 and SW480 CRC cells' capabilities to migrate, invade and resist 5-fluor-ouracil (5-Fu). miR-133b interacted with both the oncogenes and LINC00467/miR-133b axis upregulated FTL expression, leading to CRC cells survival, invasion and chemoresistance. The elevated expression of LINC00467 and FTL in HCT116 CRC cells injected into nude mice resulted in lung metastasis *in vivo* [48].

As mentioned in section 2, lincRNAs may encode functional micropeptides from their smORFs. This feature has been perpended in a study by Ge et al. They identified and characterized a 94 residue-length micropeptide produced by LINC00467 in HCT116 and RKO CRC cell lines. This micropeptide could interact with the subunits α and γ of ATP synthase (ATP5A, ATP5C) to enhance the complex activity and oxygen consumption rate. The peptide termed ATP synthase–associated peptide (ASAP), promoted CRC cell proliferation. In addition, silencing ASAP gave rise to attenuated mitochondrial ATP production and prohibited growth in patient-derived xenograft (PDX) [49].

5.5. Glioma

Gliomas include one-third of total brain tumor cases and their most lethal type is glioblastoma (GB) [50]. Gao et al. stated that the viability, migration and invasion of U87 glioma cells were inhibited by LINC00467 knockdown. Mechanistically, LINC00467 negatively regulated miR-200a to promote the expression of E2F3. LINC00467/miR-200a/E2F3 axis was also observed to regulate glioma tumor growth *in vivo*. Co-transfection of LINC00467 shRNA with miR-200a inhibitors reversed the negative effect of LINC00467 shRNA on the weight and volume of athymic nude mice xenograft models. Moreover, co-transfection of LINC00467 shRNA with miR-200a inhibitors significantly reduced the inducing impact of LINC00467 shRNA on the rate of apoptosis. Other results of the mentioned co-transfection were upregulated expression of E2F3 protein and increased Ki67-positive cells in tumor tissues of the mouse models [51].

As Jiang and Liu revealed, silencing LINC00467 intensified apoptosis and attenuated the proliferation and invasion of glioma cell lines. In mechanism, LINC00467 could bind and sponge miR-485-5p to aggravate the malignant phenotypes of U87 and U251 glioma cells [52].

Zhang et al. discovered epigenetically silencing of p53 by LINC00467 in glioma. They primarily found upregulation of LINC00467 in U87 and LN229 glioma cell lines led to G_0/G_1 cell cycle acceleration, inhibition of apoptosis and promotion of proliferation and invasion. LINC00467 bound to DNA methyltransferase1 (DNMT1) to suppress p53 expression, demonstrated by the results of RNA immunoprecipitation (RIP) and Chromatin immunoprecipitation (ChIP) assays. Overexpressing p53 partially reversed the influence of LINC00467 on glioma cells [53].

In another study, Liang and Tang showed that LINC00467 stimulated cell proliferation but repressed apoptosis via miR-339-3p/IP6K2 axis, upregulating Bcl-2 and downregulating Cleaved Caspase3, Cleaved PARP and Bax in A172 and U373 GB cell lines [54]. The LINC00467/miR-339-3p/IP6K2 oncogenic regulatory axis has been also validated by Zhang et al. in U87 and U251 GB cells [55] (Fig. 3).

5.6. Osteosarcoma

The most prevalent primary bone cancer is osteosarcoma (OS) [56]. According to Yan et al., LINC00467 was able to facilitate U2OS and HOS cells proliferation, migration, invasion and EMT by serving as a

Table 3
Functional characterization of LINC00467 in cancer cell lines.

Cancer types	Cell lines	Role	Function	Targets/regulators/related signalling pathways	Refs
Acute myeloid leukemia	HL-60, THP-1	Oncogene	Proliferation, cell cycle progression, migration, invasion, anti-apoptosis	Cleaved Caspase3, Cleaved Caspase9, miR-339, SKI	[74]
Lung adenocarcinoma	H1299, SPC-A1, A549	Oncogene	Proliferation, migration	STAT1, DKK1, EZH2, β-catenin, c-Myc, Cyclin D1, Wnt/β-catenin pathway	[424344]
		Oncogene	Proliferation, cell cycle progression	miR-20b-5p, Cyclin D1, pRB	
	H1299, A549			miR-4779, miR-7978, Bcl-2, Bax, Cleaved	
		Oncogene	Proliferation, anti-apoptosis, stemness	Caspase3, CD44, CD133, Oct4	
	A549, SPC-A1				
Colorectal cancer	HT29	Oncogene	Proliferation, cell cycle progression, invasion, EMT	Cyclin D1, Cyclin A1, CDK2, CDK4, Twist1, E-cadherin	[474849]
	HCT116, SW480	Oncogene	Viability, migration, invasion, anti-apoptosis, 5-fluor-ouracil resistance	miR-133b, FTL	
		Oncogene	Encoding micropeptide, modulating mitochondrial metabolism, cell proliferation	ATP5A, ATP5C	
	HCT116, RKO				
Glioma	U87	Oncogene	Viability, migration, invasion, anti-apoptosis	miR-200a, E2F3	[5152535455]
	U87, U251	Oncogene	Viability, proliferation, anti-apoptosis, invasion	miR-485-5p	
	U87, LN229	Oncogene	Viability, proliferation, cell cycle progression, anti-apoptosis, invasion	DNMT1, p53	
	A172, U373	Oncogene	Proliferation, anti-apoptosis	Cleaved PARP, Cleaved Caspase3, Bcl-2, Bax, miR-339-3p, IP6K2	
	U87, U251	Oncogene	Proliferation, migration, invasion	miR-339-3p, IP6K2	
Osteosarcoma	U2OS, HOS	Oncogene	Viability, proliferation, migration, invasion, EMT	miR-217, KPNA4, Vimentin, Slug, Twist, E-cadherin, *N*-cadherin	[5758]
	HOS, MG63	Oncogene	Proliferation, anti-apoptosis, migration, invasion, EMT	Bcl-2, Bax, Cleaved Caspase3, Vimentin, E-cadherin, *N*-cadherin, miR-217, HMGA1	
Hepatocellular carcinoma	Huh7, HepG2	Oncogene	Proliferation, anti-apoptosis, invasion, Axitinib resistance	miR-509-3p, PDGFRA	[6061646362]
	SK-HEP-1, Huh7	Oncogene	Proliferation, anti-apoptosis, migration	NR4A3	
		Tumor suppressor	Suppressing viability, proliferation, migration and invasion	miR-9-5p, PPARA	
	SMMC-7721, HepG2				
		Oncogene	Proliferation, migration, invasion, anti-apoptosis	Bcl-2, Bax, Cleaved Caspase3, Cleaved Caspase9, p-AKT, p-mTOR, Cyclin D1, miR-18a-5p, NEDD9, AKT pathway	
	SMMC-7721, HepG2				
		Oncogene	Proliferation, migration, invasion, anti-apoptosis	MMP2, MMP9, TRAF5, IGF2BP3	
	Huh7, HepG2				
Bladder cancer	RT4, T24	Oncogene	Proliferation, migration, invasion	NF-kb-p65, p-NF-kb-p65, IκBα, NF-κB pathway	[78]
Cervical cancer	HeLa	Oncogene	Proliferation, migration, invasion, EMT	miR-107, KIF23, MMP2, MMP9	[80]
Esophageal squamous cell carcinoma	TE-5, KYSE510	Oncogene	Proliferation, anti-apoptosis	miR-485-5p, DPAGT1, Bcl-2, Bax, Cleaved Caspase3, Cleaved Caspase9	[82]
Non-small cell lung cancer	H1299, A549	Oncogene	Proliferation, migration, invasion	p-AKT, AZGP1, TDG, EP300, AKT pathway Reprimo, DNMT1	[4072697071]
Gastric cancer	OCUM-1	Oncogene	Proliferation, migration, invasion, anti-apoptosis	ITGB3, PCNA, Cleaved Caspase3, Cleaved PARP1	
	SNU-16, HGC27	Oncogene	Viability, proliferation, anti-apoptosis	miR-7-5p, EGFR	
		Oncogene	Proliferation, migration, invasion	miR-27b-3p, STAT3	
	AGS, MKN28				
		Oncogene	Proliferation, migration, invasion, anti-apoptosis		
	BGC-823, AGS				
Head and neck squamous cell carcinoma	SCC-9	Oncogene	Invasion, anti-apoptosis	miR-1285-3p, TFAP2A	[6667]
	NH4, Cal27	Oncogene	Proliferation, migration, invasion, EMT	E-cadherin, *N*-cadherin, MMP2, MMP7, miR-299-5p, USP48	
Breast cancer	MCF-7, MDA-MB-231	Oncogene	Proliferation, migration, invasion, EMT	E-cadherin, *N*-cadherin, MMP9, Vimentin, miR-138-5p, LIN28B	[76]
Prostate cancer	DU145, 22RV1	Oncogene	Proliferation, cell cycle progression, M2 macrophage polarization, migration, invasion, EMT	miR-494-3p, STAT3, p-STAT3, E-cadherin, *N*-cadherin, Vimentin, STAT3 pathway	[84]
Neuroblastoma	BE(2)-C, Kelly	Oncogene	Viability, anti-apoptosis, cell cycle progression	*n*-Myc, RD3, DKK1	[38]
Testicular germ cell tumor	NCCIT, Tcam-2	Oncogene	Migration, invasion	AKT3, p-AKT, AKT pathway	[86]

Table 4
Oncogenic effects of LINC00467 in animal models.

Cancer types	Animal models	Effects	Refs
Acute myeloid leukemia	Immunodeficient (NOD/SCID) mice	Poor survival, increasing the percentage of GFP^+ cells in bone marrow and spleen	[74]
Lung adenocarcinoma	Female nude mice	Tumor growth, upregulating CCND1 and phosphorylated pRB	[4344]
	Immunodeficient mice	Tumor growth	
Colorectal cancer	Male BALB/c nude mice	Lung metastasis	[4849]
	Female nude mice	Tumor growth, cell proliferation	
Glioma	Male athymic BALB/c nude mice	Tumor growth, cell proliferation, anti-apoptosis, downregulating miR-200a, upregulating E2F3	[51]
Hepatocellular carcinoma	BALB/c nude mice	Tumor growth, Axitinib resistance, downregulating miR-509-3p, upregulating PDGFRA	[6061]
		Tumor growth, cell proliferation, anti-apoptosis	
Bladder cancer	Male BALB/c nude mice		
	Female nude mice	Tumor growth, cell proliferation, upregulating NF-kb-p65	[78]
Cervical cancer	Male BALB/c nude mice	Tumor growth	[80]
Esophageal squamous cell carcinoma	Female BALB/c nude mice	Tumor growth	[82407172]
Non-small cell lung cancer	Male BALB/c nude mice	Tumor growth and metastasis	
Gastric cancer	BALB/c nude mice	Tumor growth	
	Female BALB/c nude mice	Tumor growth, cell proliferation, anti-apoptosis, liver metastasis	
Breast cancer	Female BALB/c nude mice	Tumor growth, cell proliferation, lung metastasis	[76]
Prostate cancer	Male BALB/c nude mice	Tumor growth, cell proliferation, downregulating miR-494-3p, upregulating STAT3	[84]

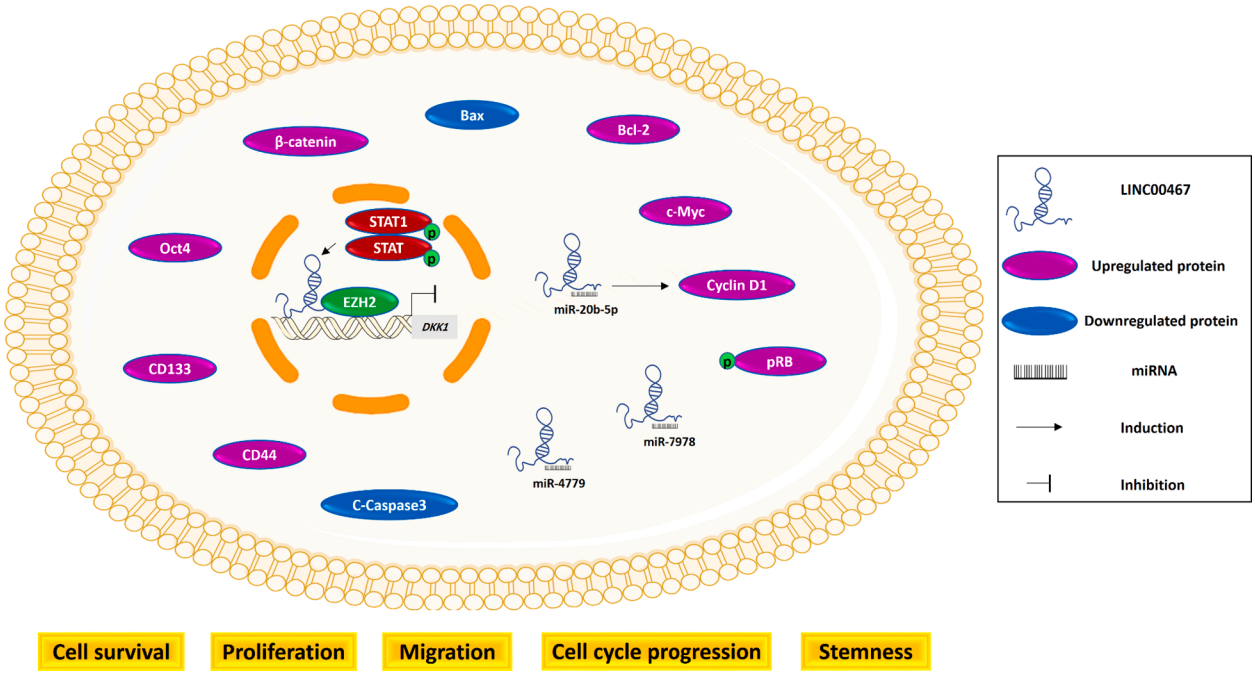

Fig. 2. The mechanisms and oncogenic functions of LINC00467 in lung adenocarcinoma.

molecular sponge for miR-217 to positively regulate karyopherin subunit α4 (KPNA4). Additionally, LINC00467 decreased the protein level of E-cadherin and increased the levels of *N*-cadherin, Vimentin, Twist and Slug to exert its oncogenic function in OS [57].

In a study by Ma et al., the miR-217/HMGA1 axis was identified as a regulatory mechanism for LINC00467 in OS. *N*-cadherin, Vimentin and Bcl-2 were upregulated by LINC00467 while E-cadherin, Cleaved Caspase3 and Bax were downregulated to promote cell proliferation, migration, invasion and EMT, and suppress apoptosis in HOS and MG63 cells [58].

5.7. *Hepatocellular carcinoma*

The fourth cause of cancer mortality is hepatocellular carcinoma

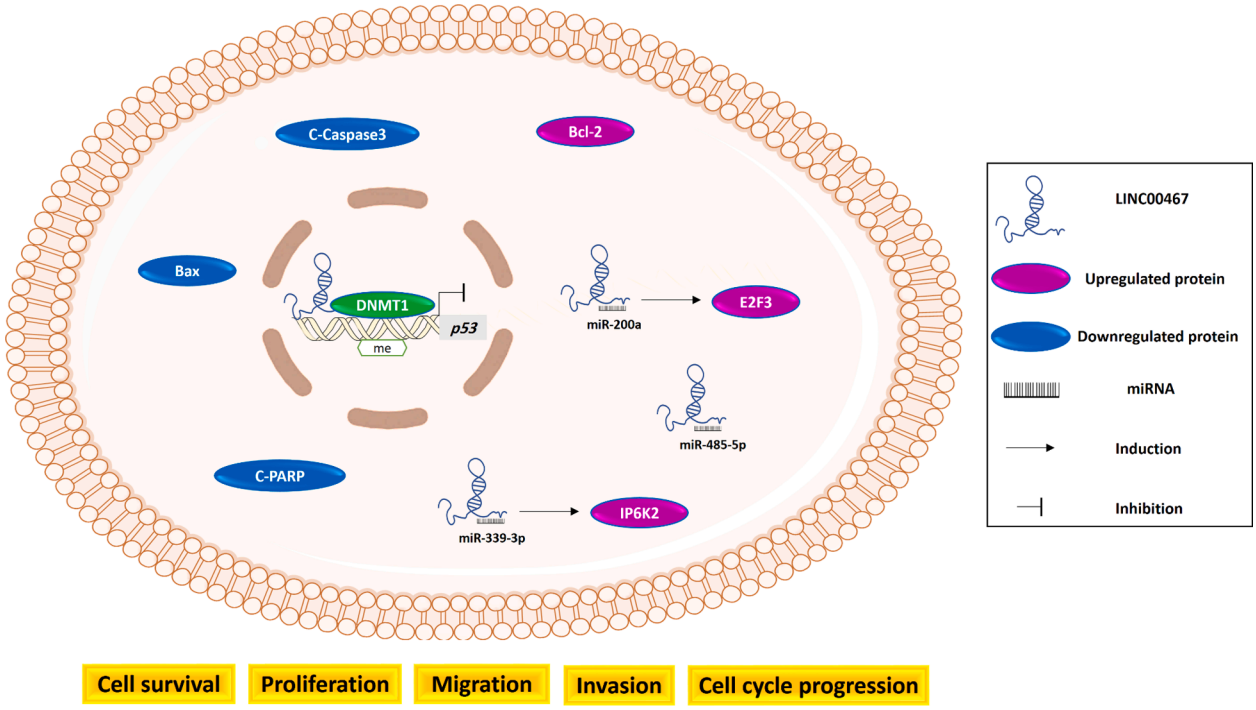

Fig. 3. The mechanisms and oncogenic functions of LINC00467 in glioma.

(HCC), comprising more than 80% of primary liver cancers [59]. As reported by Li et al., LINC00467 could stimulate platelet-derived growth factor receptor alpha (PDGFRA) expression via sponging miR-509-3p to induce Axitinib resistance, promote proliferation and invasion, and impede apoptosis in Huh7 and HepG2 HCC cells. *In vivo* experiments also showed that LINC00467 overexpression contributed to tumor growth, Axitinib resistance, reduced level of miR-509-3p and elevated level of PDGFRA in xenograft nude mice [60].

Wang et al. revealed that LINC00467 interacted with NR4A3 mRNA and post-transcriptionally repressed NR4A3 expression in a Dicer-dependent manner. LINC00467 reduced apoptosis and intensified the proliferation and migration of SK-HEP-1 and Huh7 cells. Moreover, LINC00467 caused tumor growth, cell survival and cell proliferation *in vivo* [61].

As discovered by Jiang et al., LINC00467 positively modulated the expression of tumor necrosis factor receptor-associated factor 5 (TRAF5), MMP2 and MMP9 in Huh7 and HepG2 cells, resulting in cell survival, proliferation and metastasis. LINC00467 could bind with insulin-like growth factor-2 messenger RNA-binding protein 3 (IGF2BP3) to promote the mRNA stability of TRAF5 in HCC cells. Silencing TRAF5

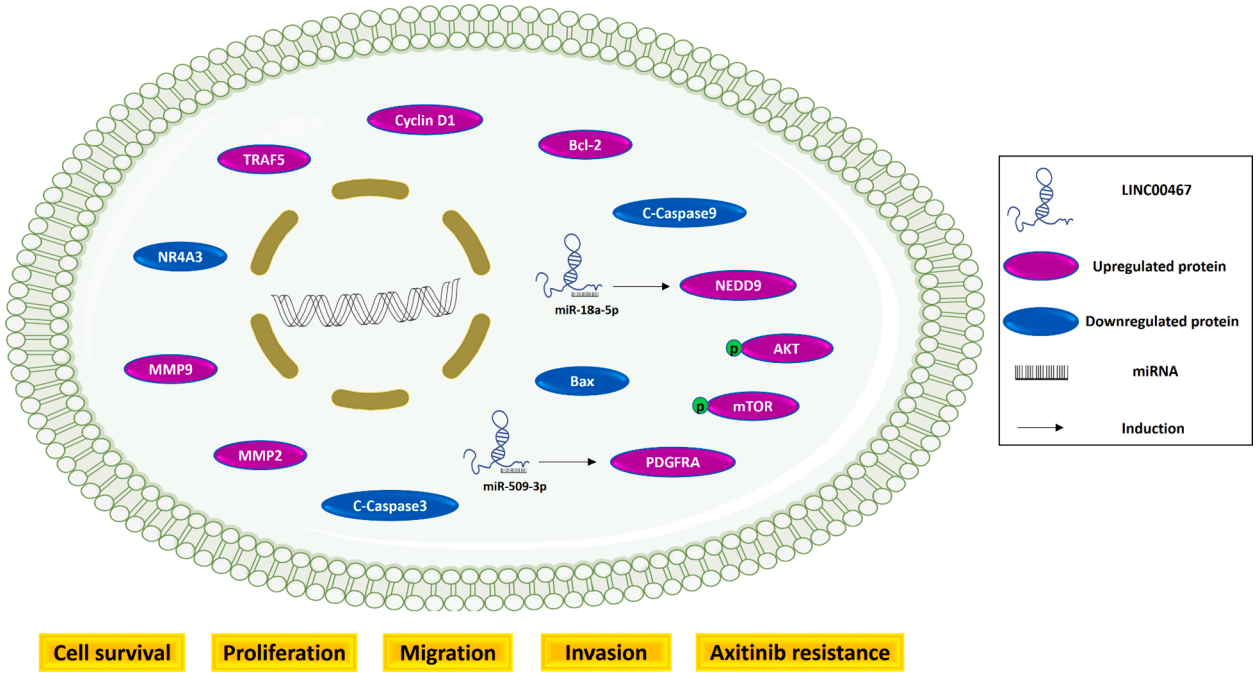

Fig. 4. The mechanisms and oncogenic functions of LINC00467 in hepatocellular carcinoma.

or IGF2BP3 blocked the stimulating influence of LINC00467 on HCC progression [62].

Sponging miR-18a-5p, inducing NEDD9 expression, regulating caspase cascade and the Bcl-2/Bax axis, and activating the AKT-mTOR signalling pathway were the mechanisms of LINC00467 functions to promote growth and motility and inhibit apoptosis in SMMC-7721 and HepG2 cells, reported by Zheng et al. [63] (Fig. 4).

In the only study indicating a tumor-suppressive function of LINC00467 in cancer, Cai et al. introduced modulating miR-9-5p/peroxisome proliferator-activated receptor alpha (PPARA) axis as a mechanism employed by LINC00467 to suppress cell viability, proliferation, migration and invasion of SMMC-7721 and HepG2 cell lines [64].

5.8. Head and neck squamous cell carcinoma

Head and neck squamous cell carcinomas (HNSCCs), originating from mucosal epithelial cells, are the most frequent cancers developing in the head and neck [65]. Mechanistically, LINC00467 acts as a ceRNA and adsorb miR-1285-3p to upregulate TFAP2A in HNSCC. This axis contributes to a decreased apoptosis rate and elevated invasion of the SCC-9 cell line. The oncogenic effects of LINC00467 were partially rescued by overexpressing miR-1285-3p in HNSCC cells, as indicated by Liang et al. [66].

Chen and Ding reported that LINC00467 promoted the expression of *N*-cadherin, MMP2 and MMP7 and suppressed E-cadherin in NH4 and Cal27 cell lines. Furthermore, sponging miR-299-5p by LINC00467 gave rise to the upregulation of ubiquitin-specific protease 48 (USP48). The absence of LINC00467 inhibited cell proliferation, migration, invasion and EMT, compensated by overexpressing USP48 in HNSCC cells [67].

5.9. Gastric cancer

Gastric cancer (GC) is enumerated as the second cause of cancer death worldwide [68]. Xu et al. studied the functional role and modulatory mechanism of LINC00467 in HGC27 and SNU-16 GC cell lines. The promotion of cell viability and proliferation as well as the suppression of apoptosis were observed under the action of overexpressed LINC00467. shLINC00467 abated levels of integrin subunit beta 3 (ITGB3) and proliferating cell nuclear antigen (PCNA) while enhancing Cleaved Caspase3 and Cleaved PARP1 levels. Overexpression of ITGB3 partially reversed the cellular and molecular effects of shLINC00467 in GC cells [69].

Based on a study by Deng et al., LINC00467 acts as a tumor-promotive player to augment the proliferation, migration and invasion of AGS and MKN28 GC cells by direct negative regulation of miR-7-5p and indirect positive regulation of epidermal growth factor receptor (EGFR) [70].

It has been reported by Lu et al. that the binding relationships among LINC00467, miR-27b-3p, and signal transducer and activator of transcription 3 (STAT3) affect BGC-823 and AGS cell malignancy. The reduction of LINC00467 upregulated miR-27b-3p and inhibited STAT3 to suppress GC cell proliferation, migration and invasion, and accent the rate of apoptosis. GC tumor growth was attenuated by knocking-down LINC00467 or elevating miR-27b-3p *in vivo* [71].

Wu and Du have also alluded to a functional mechanism for LINC00467 in the OCUM-1 GC cell line. Overexpression of LINC00467 downregulated Reprimo protein (a cell cycle depressor manipulated by p53) by recruiting DNMT1 and inducing Reprimo promoter methylation. The positive impact of LINC00467 on GC cell proliferation, migration and invasion, as well as a negative effect on apoptosis rate was established. LINC00467 overexpression eventuated in tumor growth, liver metastasis and diminished apoptosis in nude mice [72].

5.10. Other types of cancer

Acute myeloid leukemia

Acute myeloid leukemia (AML) has the highest percentage of mortality among all subtypes of leukemia [73]. Lu et al. investigated the role of LINC00467 in the progression of HL-60 and THP-1 AML cell lines. Knocking down LINC00467 inhibited the proliferation, migration and invasion of AML cells and caused an arrest in the cell cycle. Moreover, an increased level of some pro-apoptotic proteins like Cleaved Caspase3 and Cleaved Caspase9 was observed as a result of LINC00467 knockdown. The mechanism of LINC00467 was related to miR-339/SKI axis. Competing with miR-339, LINC00467 was able to bind to it and overexpression of LINC00467 could decrease the level of miR-339 and upregulate SKI proto-oncogene. Consistent with *in vitro* results, silencing LINC00467 prolonged the survival time of immunodeficient mice and notably reduced the percentage of GFP^+ cells in their bone marrow and spleen [74].

Breast cancer

The second leading cause of cancer-related mortality in women is breast cancer (BC) [75]. In a study by Zhang et al. to determine the role of LINC00467 in malignant phenotypes of BC, the impacts of LINC00467 knockdown and overexpression were investigated in MCF-7 and MDA-MB-231 cell lines. Methyl thiazolyl tetrazolium (MTT) and colony formation assays revealed the inhibition of cell viability and colony formation capacity as a result of silencing LINC00467 and their enhancement in LINC00467-overexpressing cells. Besides, cell proliferation was repressed and increased in depleted LINC00467 expression and LINC00467-overexpressing cells, respectively. Wound healing and Transwell assays were used to evaluate cell migration and invasion. In addition, the function of LINC00467 as a putative mediator in EMT progression was investigated. The results evinced that LINC00467 significantly promoted migration, invasion and EMT by upregulating MMP9, *N*-cadherin and Vimentin, and downregulating E-cadherin in BC cells. The direct interaction of LINC00467 and tumor suppressor miR-138-5p was validated by luciferase reporter and biotin RNA pull-down assays, demonstrating LINC00467 action as a miRNA sponge which results to repress miR-138-5p expression. The RIP assay manifested the direct interaction of LINC00467 and lin-28 homolog B (LIN28B), a critical oncogene in BC, leading to the enhancement of the LIN28B protein level. However, how this interaction increases the LIN28B protein level needs further investigation. Finally, forced expression of LINC00467 in nude mice contributed to lung metastasis and larger tumors compared to corresponding controls [76].

Bladder cancer

Bladder cancer (BLCA) is responsible for 2.1% of all cancer-related deaths throughout the world [77]. Xiao et al. suggested that LINC00467 regulates the NF-κB signalling pathway in BLCA cells. In mechanism, LINC00467 overexpression significantly upregulated NF-kb-p65 and p-NF-kb-p65, reduced the binding of IκBα to NF-kb-p65 to dissociate IκBα from the NF-kb-p65/ IκBα complex, and induce the translocation of NF-kb-p65 to the nucleus. These events activated the NF-kB signalling pathway and promoted proliferation, migration and invasion of T24 and RT4 BLCA cell lines. Silencing LINC00467 had the contrary influence. *In vivo* experiments were accomplished using nude mice and the results pointed out that knockdown of LINC00467 not only caused tumor cells to grow slower and smaller but also decreased the expression of NF-kb-p65 in tumor tissue. Overexpressing LINC00467 indicated the opposite effect in mouse models [78].

Cervical cancer

The fourth most prevalent cancer in women is cervical cancer (CC) [79]. Li et al. aimed to identify the functional role, molecular mechanism and tumorigenic capability of LINC00467 in cervical cancer. Lentiviral-mediated LINC00467 silencing suppressed cell proliferation, migration, invasion and EMT in HeLa cervical cancer cells. Acting as a ceRNA against miR-107, LINC00467 enhanced the protein level of kinesin family member 23 (KIF23). Additionally, the knockdown of LINC00467 led to a decreased level of MMP2 and MMP9 in HeLa cells. LINC00467 silencing or miR-107 overexpression could repress tumor growth in xenograft nude mice [80].

Esophageal squamous cell carcinoma

Esophageal squamous cell carcinoma (ESCC) constitutes about 90% of esophageal cancer cases [81]. Liu et al. explored the molecular mechanism of LINC00467 in TE-5 and KYSE510 ESCC cell lines. They found that LINC00467 upregulation inhibits apoptosis but improves cell proliferation. Positive regulation of Bcl-2, and reduced protein levels of Bax, Cleaved Caspase3 and Cleaved Caspase9 were validated under the influence of LINC00467. With lower expression in ESCC, miR-485-5p was shown to interact with LINC00467. In addition, miR-485-5P could directly target and negatively regulate DPAGT1. Overexpression of DPAGT1 compensated for the consequences of LINC00467 cellular deficiency on apoptosis and cell proliferation, based on rescue assays. Finally, silencing LINC00467 attenuated tumor growth *in vivo* [82].

Prostate cancer

Prostate cancer (PC) is the second most common cancer in men throughout the world [83]. Silencing LINC00467 by Jiang et al. suppressed the proliferation, migration, invasion and infiltration abilities of DU145 and 22RV1 PC cell lines and contributed to the cell cycle arrest through congesting cells in G0/G1 and decreasing cell count in S and G2/M phases. Knockdown of LINC00467 decreased M2 macrophage polarization to inhibit PC cell migration. Bioinformatics analysis and rescue experiments manifested that LINC00467 acts as an oncogene in PC via the miR-494-3p/STAT3 regulatory axis. Overexpressing LINC00467 negatively regulated the expression of miR-494-3p and elevated the protein level of total STAT3 and phosphorylated STAT3 (p-STAT3) to activate the STAT3 pathway. Moreover, upregulated LINC00467 could induce EMT by inhibiting E-cadherin, and positively regulating Vimentin and *N*-cadherin in PC cells. For *in vivo* analysis, DU145 cells with knocked-down LINC00467 were transplanted subcutaneously into nude mice. The observations confirmed the *in vitro* results as it inhibited tumor growth and cell proliferation, elevated the level of miR-494-3p and decreased STAT3 protein level [84].

Testicular germ cell tumor

Although testicular germ cell tumors (TGCTs) are rare in the population, they are considered the most common tumors in adolescents and young men [85]. Bo et al. evaluated the function of LINC00467 in Tcam-2 for seminoma type and NCCIT for non-seminoma type TGCT cells. Silencing LINC00467 prohibited migration and invasion in both cell lines. Measuring the expression level of AKT and AKT3 demonstrated that the mechanism of LINC00467 in TGCT is related to the AKT signalling pathway, as upregulating LINC00467 enhanced AKT phosphorylation and reduced expression of AKT3 was detected in LINC00467-silenced NCCIT cells. Analyzing TCGA data exhibited that LINC00467 plays an inhibitory role in the infiltration of neutrophils, macrophages, B cells, dendritic cells, and $CD4^+$ T cells in the tumor microenvironment and causes resistance to anti-PD-1 tumor immunotherapy. Furthermore, the positive correlation of LINC00467 with TNFSF4, TNFRSF9, CD70, and CD200, and its negative correlation with CD274, CTLA4, and CD40 were revealed [86].

6. LINC00467, other onco-lncRNAs and signalling pathways

Signal transduction is a key factor in a variety of cellular processes such as carcinogenesis. Increasing evidence illustrates the lncRNA-pathway interplay in various malignant conditions. As mentioned in the previous sections, the oncogenicity of LINC00467 accompanies the regulation of some cell signalling pathways including AKT, NF-κB, STAT3 and Wnt/β-catenin. Therewithal, STAT1 acts as an upstream transducer to upregulate LINC00467 and launch its tumor-promoting functions.

AKT or protein kinase B (PKB), a serine/threonine kinase, acts as a central mediator of multiple cascade pathways like phosphoinositide 3-kinase (PI3K) and it is dysregulated in cancers with a high frequency [87]. Triggered by tyrosine kinases or other types of receptors, PI3K converts PIP2 to PIP3 which leads to membrane recruitment and succedent phosphorylation and activation of AKT [88]. The downstream targets of activated AKT participate in the modulation of cell survival, glucose metabolism, autophagy, angiogenesis, proliferation and migration [89]. LINC00467 deregulation triggers the AKT signalling pathway via upregulating AKT, phosphorylated AKT and phosphorylated mTOR in HCC, NSCLC and TGCT. Several carcinogenic lncRNAs have been identified to activate the PI3K/AKT pathway with some mechanistic differences. HOXA-AS2 increases phosphorylation of PI3K and AKT in AML, HCP5 upregulates PDK1 (a membrane kinase which phosphorylates AKT) via sponging miR-216a-3p in esophageal carcinoma, and CASC11 downregulates phosphatase and tensin homolog (PTEN, the negative regulator of the PI3K/AKT signalling) through binding with EZH2 in HCC [90–93].

Nuclear factor-kappa B (NF-κB) is a pro-inflammatory transcription factor involved in immune responses, cell death, proliferation and differentiation. NF-κB subunits include NF-κB1 (p105/p50), NF-κB2 (p100/p52), c-Rel, RelA (p65), and RelB [94]. The inhibitors of κB (IκBs) repress NF-κB stimulation. A stimulus, e.g. a cytokine, triggers the IκB kinase (IKK) complex to phosphorylate IκB at serine residue and subsequently, p50/65 heterodimer translocates to the nucleus as the transcription factor of the canonical NF-κB signalling [95]. Constitutive activation of the NF-κB pathway induces the hallmarks of tumorigenesis [96]. Upregulating RelA and phosphorylated RelA, attenuating binding of IκBα to RelA, as well as inducing translocation of RelA to the nucleus are the known mechanisms exploited by LINC00467 to activate the NF-κB pathway in BLCA cells. In comparison, lncRNA TUG1 induces RelA and negatively affects IκBα expression to promote the NF-κB route in pituitary adenoma [97]. LOXL1-AS1 launches NF-κB signalling by suppression of miR-708-5p via recruiting EZH2 to its promoter in BC cells [98]. Therewithal, lncRNA CamK-A induces phosphorylation of IκBα by upregulating PNCK (a Ca^{2+}/calmodulin-dependent kinase) leading to NF-κB activation [99].

STAT3 oncoprotein belongs to the signal transducer and activator of transcription (STAT) seven-member family with critical roles in cell survival, proliferation, invasion, immune response and angiogenesis [100,101]. In the canonical STAT3 pathway, binding of a ligand (hormone, cytokine or growth factor) to the cell surface receptor activates STAT3 through phosphorylation by Janus kinase (JAK) and hetero- or homo-dimerization, followed by translocation into the nucleus and affecting the target genes [102]. LINC00467 increases the protein levels of STAT3 and phosphorylated STAT3 in GC and PC cells, thereby actuating the pertaining pathway. In addition to elevating STAT3 and p-STAT3 protein levels, lncRNA KCNQ1OT1 positively regulates JAK2 and phosphorylated JAK2 in small cell lung cancer [103]. Interacting with STAT3 in the nucleus of GC cells, PVT1 inhibits polyubiquitination and proteasome-dependent degradation of STAT3 to elevate its stability [104]. Furthermore, BHLHE40-AS1 binds to interleukin enhancer-binding factor 3 in IL-3 to stimulate IL-6/STAT3 signalling in BC cells [105].

Embryonic development, normal homeostasis of adult tissues and cell fate are controlled by Wnt signalling, and dysfunctions of the

pathway demonstrate a strong connection with different kinds of cancer [106]. The binding of the Wnt ligand to cell surface receptors initiates the Wnt/β-catenin (canonical) pathway, and a chain of events separates β-catenin from the degradation complex and stabilizes it in the cytoplasm. Subsequently, accumulated β-catenin is imported to the nucleus to interact with TCF/LEF transcription factors and transcribe the target genes, including c-Myc and Cyclin D1 [107]. LINC00467 upregulates β-catenin, c-Myc and Cyclin D1, and epigenetically silences DKK1 to operate the Wnt/β-catenin signalling in LUAD. LncTCF7 positively regulates TCF7 expression and activates the Wnt pathway in CRC [108]. RBM5-AS1 prevents β-catenin degradation and organizes the β-catenin-TCF4 transcriptional complex in BC [109]. Moreover, SNHG16 launches the Wnt signalling pathway by the mediation of upregulating nuclear factor of activated *T*-cells 5 (NFAT5) in laryngeal squamous cell carcinoma [110] (Fig. 5).

STAT1 transcription factor is the first discovered member of the STAT family and is less-studied compared to STAT3. The cytoplasmic inactive form of STAT1 is phosphorylated by an interferon-stimulated kinase such as JAK and forms a homo- or hetero-dimer. The activated STAT1 translocates to the nucleus to regulate its target genes including lncRNAs and affect cancer cell behavior [111]. STAT1-upregulated LINC00467 induces the Wnt/β-catenin pathway and LUAD progression. ZFPM2-AS1 transcriptionally mediated by STAT1 weakens the inhibition of miR-515-5p on TUSC3 and promotes thyroid cancer cell growth, migration and invasion [112]. Activated by STAT1, LINC01806 enhances NOTCH2 expression to drive the Notch signalling pathway via sponging miR-4428, thereby developing cell proliferation, migration, invasion, and stemness in NSCLC [113]. For another example, STAT1-overexpressed LINC00504 stabilizes the expression of cytoplasmic polyadenylation element-binding protein 2 (CPEB2) via binding to TATA-box binding protein associated factor 15 (TAF15) and negatively influences the radiosensitivity of BC cells [114] (Fig. 6).

7. Conclusions

LncRNAs have been introduced as novel key players in the regulation of gene expression and modulation of cancer progression. The structural dynamics and versatility in interactions have endowed a functional diversity with them, comparable to proteins. An increasing number of studies have revealed the potent oncogenic functions of LINC00467 in a variety of malignancies. LINC00467 is highly expressed in the majority of cancer types and exhibits a meaningful association with some clinicopathological features like advanced clinical stages, pathological grades and poor survival. Hence, it can be regarded as a potential prognostic biomarker in cancer. Besides, LINC00467 regulates multiple miRNAs, proteins (Fig. 7), and signalling pathways including AKT, Wnt/β-catenin, NF-κB and STAT3 to promote cancer progression *in vitro* and *in vivo*. Therefore, targeting LINC00467 may be a novel efficient therapeutic intervention for improving patient prognosis. However, more studies are still needed to identify other mechanisms and molecular interactors of LINC00467, especially upstream pathways, and to complete our delineation of its regulatory network.

Author Contributions

MC designed and organized the study; MC, FN, VH, MP and ZB performed the study and wrote the manuscript; MMB supervised the study. All authors critically revised and gave final approval of the manuscript.

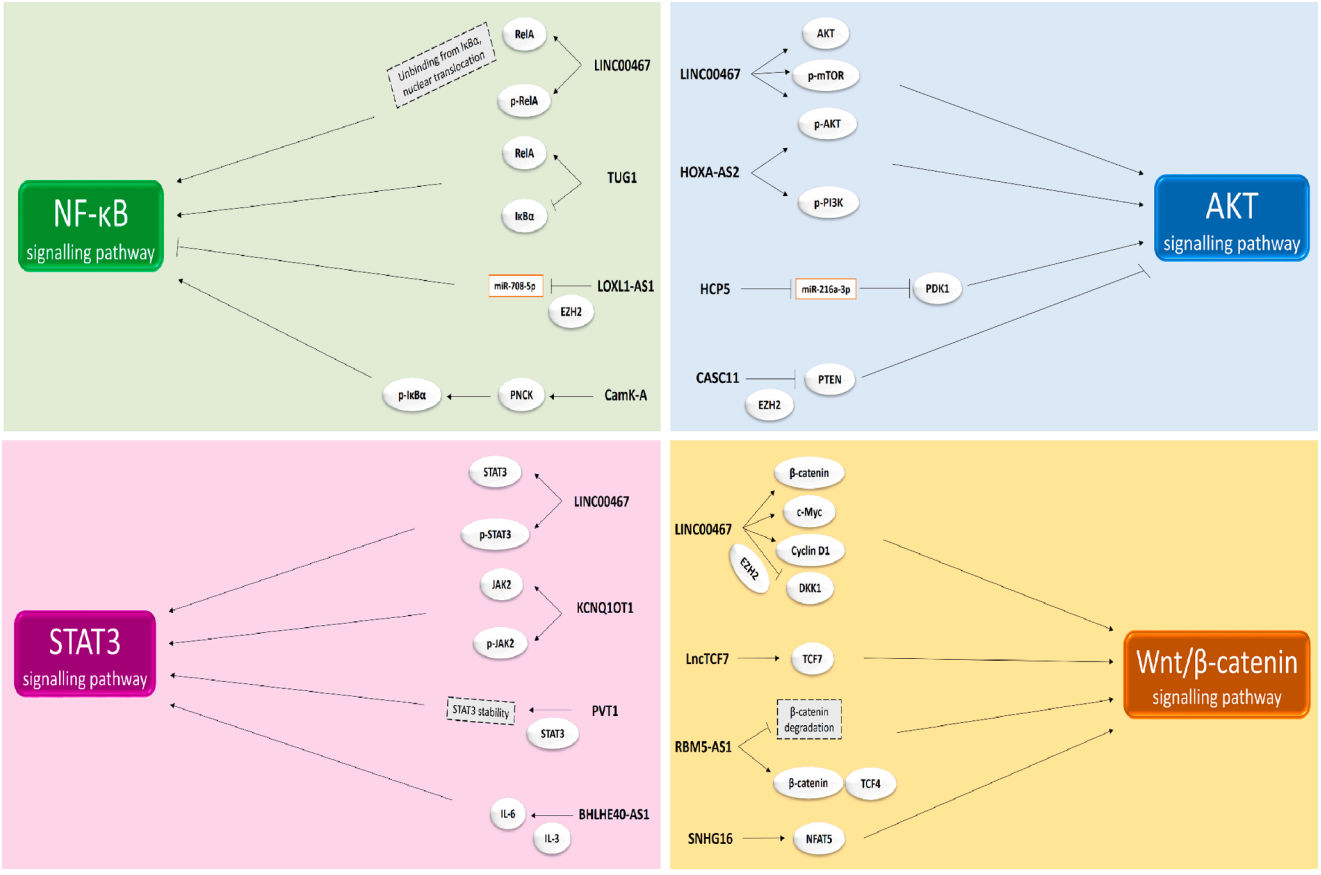

Fig. 5. Activation of tumor-promoting cell signalling pathways by deregulated onco-lncRNAs, leading to cancer progression. Arrows and 'T'-shaped signs indicate induction and inhibition, respectively.

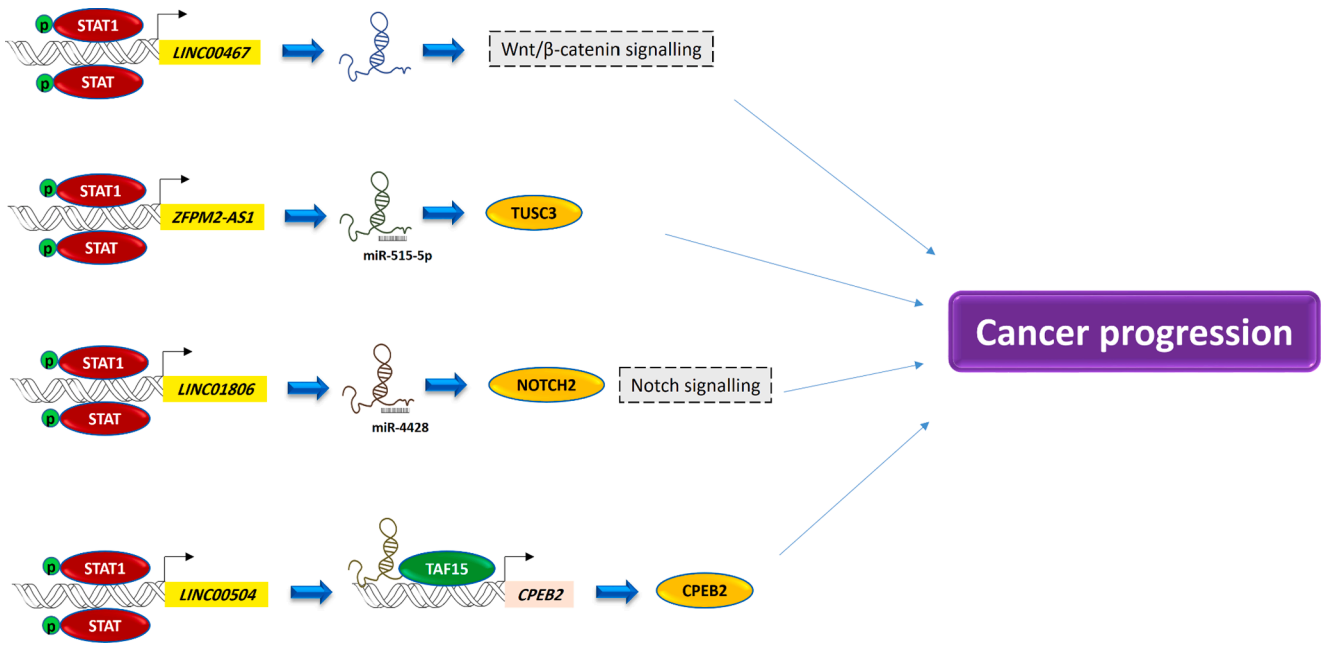

Fig. 6. STAT1-mediated upregulation of onco-lncRNAs induces cancer cell progression.

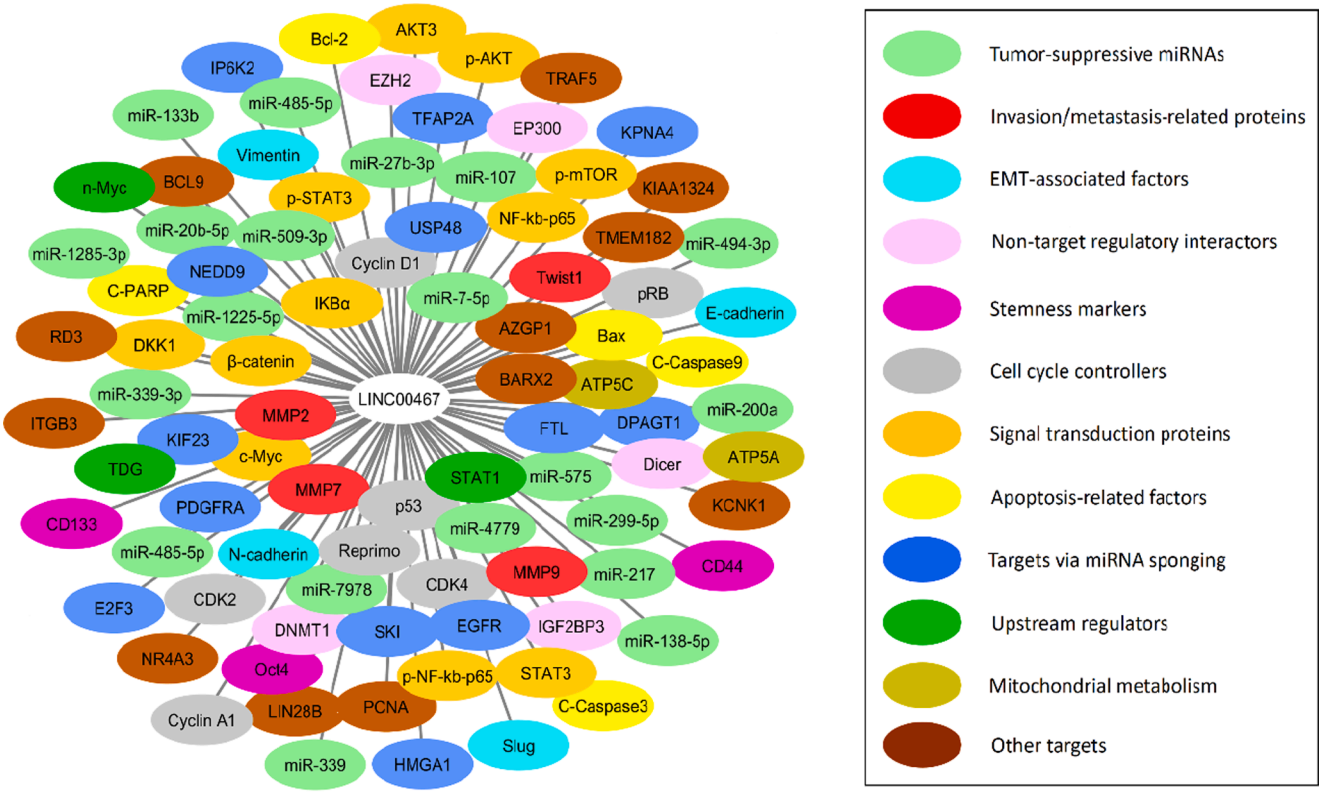

Fig. 7. Pan-cancer regulatory targets and interactors of LINC00467. They have been categorized into 12 functional groups.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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