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REVIEW

Cell Cycle-Related lncRNAs as Innovative Targets to Advance Cancer Management

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Abstract: Long non-coding RNAs (lncRNAs) are non-coding RNAs (ncRNAs) longer than 200nt. They have complex biological functions and take part in multiple fundamental biological processes, such as cell proliferation, differentiation, survival and apoptosis. Recent studies suggest that lncRNAs modulate critical regulatory proteins involved in cancer cell cycle, such as cyclin, cell cycle protein-dependent kinases (CDK) and cell cycle protein-dependent kinase inhibitors (CKI) through different mechanisms. To clarify the role of lncRNAs in the regulation of cell cycle will provide new ideas for design of antitumor therapies which intervene with the cell cycle progression. In this paper, we review the recent studies about the controlling of lncRNAs on cell cycle related proteins such as cyclin, CDK and CKI in different cancers. We further outline the different mechanisms involved in this regulation and describe the emerging role of cell cycle-related lncRNAs in cancer diagnosis and therapy.

Keywords: cyclin, cyclin-CDK, CDK inhibitors, lncRNA

Introduction

The cell cycle means the process that a cell undergoes from the end of one mitosis to the completion of the next mitosis, including two periods, interphase and cytokinesis (M phase).[1] Interphase is further divided into prophase of DNA synthesis (G1 phase), S phase of DNA synthesis (S phase) and late phase of DNA synthesis (G2 phase).[1,2] Mammalian cell cycle is controlled by cyclin-dependent kinases (CDKs) and their related pathways.[3] Activation of CDK4 and CDK6 can affect G1 phase progression at an early stage. They bind to cyclin D (CCND) to phosphorylate the retinoblastoma protein pRb, prevent its binding, and inhibit E2F transcription factors to promote cells to the next phase.[4,5] However, recent studies have found that cyclin D-CDK is not involved in the initial inactivation of Rb, but rather "primes" cells to enter the cell cycle by preventing them from exiting or facilitating their entry into the G1 phase.[2] CDK associates with its regulatory proteins to control the different cell cycle phases.[6] Cyclin E (CCNE) binds to CDK2 and regulates the progression of S phase, while cyclin B (CCNB) binds to CDK1 and regulates the G2/M phase transition.[7] The cyclin dependent kinase inhibitors (CKIs) inhibit the activity of CDK and cyclin, and block cells cycle at different stages.[4] Apart from its roles in cell cycle regulation, cell cycle regulators are involved in cell invasion, migration, apoptosis and DNA repairing. Thus, the abnormal expression or deletion of cyclin, CDK and CKI will cause the cell cycle disorder and closely related to the occurrence and development of cancers.

Some evidence points to the important role of long non-coding RNAs (lncRNAs) in the regulation of the aforesaid proteins' expression or activity. Several studies have indicated that these regulators of cell cycle are targets of lncRNAs. LncRNAs are transcripts more than 200 nucleotides and commonly not involved in encoding proteins.[8] Previous studies have reported aberrant lncRNA expression in various cancers where they function as oncogenes or tumor suppressors

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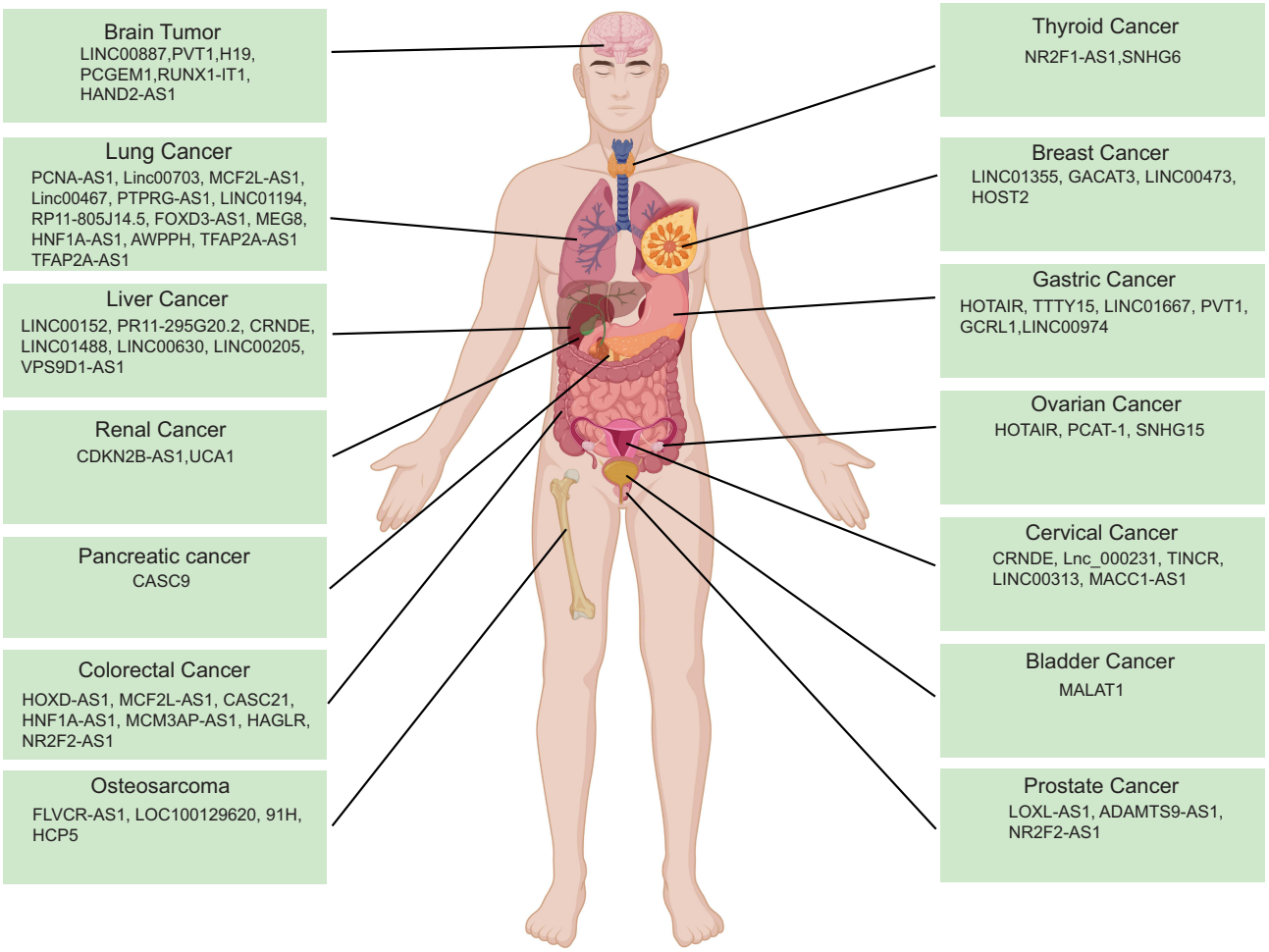

Figure 1 LncRNAs associated with various types of cancer.

(Figure 1). LncRNAs influence cancer progression through multiple mechanisms including epigenetic regulation, DNA damage, cell cycle and chromosomal instability.[3,9–11] The interaction between lncRNAs and cell cycle regulators can affect cell cycle progression in many tumor cells. Therefore, to clarify the mechanisms of cell cycle controlling by lncRNAs will provide a new perspective for early diagnosis and treatment of tumors. In this review, we summarize the regulatory function and mechanism of lncRNAs on multiple malignant behaviors by modulating cell cycle regulators, such as cyclins, CDKs and CKIs, in different cancers and point out the emerging role of cell cycle-related lncRNAs in the diagnosis and treatment of tumors.

LncRNAs are Involved in Cancer Cell Cycle

Cell cycle is regulated by cycle-related proteins and cycle aberrancy can cause many diseases including cancers. Recent studies have suggested that some lncRNAs are involved in cancer cell cycle regulation. Understanding the role of lncRNAs in regulating cell cycle factors will not only provide new insights into the regulation of fundamental cellular processes, but reveal new pathogenic mechanisms and develop rational anti-cancer therapeutic targets in the future.

Cyclin-Targeted Cell Malignancy Regulation Mediated by lncRNAs in Tumors

Cyclin is an important regulator and plays a crucial role in cell cycle of cancers. The cyclin family mainly contains four members, that is cyclin A, B, C and D. Cyclin D, a proto-oncogene in cancer cells, is a key regulator of the G1/S phase.[12] Cyclin A plays an established role in S phase and promotes specific cell cycle events and transitions.[13] Cyclin B is an

important regulator of G2 to M phase transition.[14] Cyclin E, G1-S phase transition regulator, has a crucial role especially in the early stages of cancer.[15] Recently, some lncRNAs are reported to interact with cyclins and influence various malignant behaviors of cancer cells. Here, we describe the regulatory roles involved in lncRNA mediating cyclin in different types of tumors (Table 1).

Table 1 The Regulation of lncRNAs on Cyclin in Tumors

LncRNA	Cancer types	Expression	Functions	Related gene	Reference
HOTAIR	GC	Upregulated	Promoted the proliferation of cancer cells	miR-454-3p, CCND1, STAT3	[16]
TTTY15	GC	Upregulated	Promoted cancer progression	miR-98-5p, CCND2	[17]
PVT1	GC	Upregulated	Promoted cancer cell proliferation, invasion, and cell cycle progression	miR-16, CCND1	[18]
LINC01667	GC	Upregulated	Promoted the proliferation of cancer cells	miR-138-5p, CCNE1	[19]
LINC00152	HCC	Upregulated	Promoted cancer cell proliferation	miR-193a-3p, CCND1	[20]
PR11-295G20.2	HCC	Upregulated	Promoted cancer cell proliferation, invasion, and migration	miR-6884-3p, CCNB1	[21]
LINC01488	HCC	Downregulated	Inhibited metastasis and tumorigenesis	miR-124-3p, miR-138-5p, CCNE	[22]
CASC9	Pancreatic Cancer	Upregulated	Promoted cancer progression	miR-497-5p, CCND1	[23]
XIST	ESCC	Upregulated	Promoted cell cycle progression, proliferation, migration, invasion, and inhibited cell apoptosis	miR-129-5p, CCND1	[24]
LINC01234	EC	Upregulated	Promoted cancer cell proliferation and inhibited apoptosis	miR-193a-5p, CCNE1	[25]
HOXD-AS1	CRC	Upregulated	Promoted the proliferation, invasion and migration of cancer cells	miR-526b-3p, CCND1	[26]
MCF2L-AS1	CRC	Upregulated	Promoted the proliferation of cancer cells	miR-874-3p, CCNE1	[27]
HNF1A-AS1	CRC	Upregulated	Promoted the proliferation, migration and angiogenesis, accelerated cell cycle and reduced apoptosis	miR-93-5p, PDCD4, CCND1	[28]
CDKN2B-AS1	RCC	Upregulated	Promoted cancer cell invasion	miR-141, CCND1, CCND2	[29]
LOXL1-AS1	PC	Upregulated	Regulated cancer cell proliferation and cell cycle progression	miR-541-3p, CCND1	[30]
ADAMTS9-AS1	PC	Downregulated	Inhibited cancer progression	miR-142-5p, CCND1	[31]
MALAT1	Bladder cancer	Upregulated	Promoted cancer cell proliferation and migration	miR-34a, CCND1	[32]
LINC01355	BC	Downregulated	Inhibited cancer progression	CCND1	[33]
GACAT3	BC	Upregulated	Promoted cancer progression	miR-497, CCND2	[34]
LINC00473	BC	Upregulated	Promoted cancer progression	miR-424-5p, CCNE1	[35]
HOTAIR	OC	Upregulated	Promoted cancer cell proliferation, cell cycle progression, migration and invasion	miR-206, CCND1, CCND2	[36]
PCAT-1	EOC	Upregulated	Regulated the proliferation, migration and invasion of cancer cells	CCND1, CDK4	[37]
CRNDE	CC	Upregulated	Regulated the proliferation, migration and invasion of cancer cells.	miR-183, CCNB1	[38]
Lnc_000231	CC	Upregulated	Promoted cancer cell proliferation and tumor formation	miR-497-5p, CCNE1	[39]
TINCR	CSCC	Upregulated	Promoted cancer cell proliferation	miR-302, CCND1	[40]

(*Continued*)

Table 1 (Continued).

LncRNA	Cancer types	Expression	Functions	Related gene	Reference
PCNA-AS1	NSCLC	Upregulated	Promoted cancer cell proliferation	CCND1	[41]
Linc00703	NSCLC	Downregulated	Inhibited cancer cell proliferation	CCND1, CDK4	[42]
MCF2L-AS1	NSCLC	Upregulated	Promoted cancer progression	ELAVL1, CCND1	[43]
Linc00467	LUAD	Upregulated	Promoted cancer cell proliferation	miR-20b-5p, CCND1	[44]
PTPRG-AS1	LUAD	Upregulated	Promoted cancer cell proliferation and cell cycle progression	miR-124-3p, CCND1	[45]
RP11-805J14.5	LUAD	Downregulated	Inhibited cancer progression	miR-139-5p, miR-34b-3p, CCND2	[46]
FLVCR-AS1	OS	Upregulated	Promoted cancer cell proliferation	miR-381-3p, CCND1	[47]
NR2F1-AS1	TC	Upregulated	Promoted the proliferation and migration of cancer cells	miR-338-3p, CCND1	[48]
LINC00887	Glioma	Upregulated	Promoted malignant progression of cancer	CCND1	[49]
RUNX1-IT1	GBM	Upregulated	Promoted cancer cell proliferation	miR-195, CCND1	[50]
HCP5	MM	Upregulated	Promoted cancer progression	miR-128-3p, PLAGL2, CCND1	[51]
PVT1	Pituitary adenoma	Upregulated	Promoted the proliferation and migration of cancer cells	CCND1	[52]

Abbreviations: GC, Gastric Cancer; HCC, Hepatocellular Carcinoma; ESCC, Esophageal Squamous Cell Carcinoma; EC, Esophageal Carcinoma; CRC, Colorectal Cancer; RCC, Renal Cell Carcinoma; PC, Prostate Cancer; BC, Breast Cancer; OC, Ovarian cancer; EOC, Epithelial ovarian cancer; CC, Cervical cancer; CSCC, Cervical Squamous Cell Carcinoma; NSCLC, Non-Small Cell Lung Cancer; LUAD, Lung Adenocarcinoma; OS, Osteosarcoma; TC, Thyroid Cancer; GBM, Glioblastoma; MM, Multiple Myeloma.

Digestive System Tumors

HOTAIR knockdown increased miR-454-3p expression, thereby inhibiting gastric cancer (GC) cell proliferation through downregulation of STAT3/cyclin D1 (CCND1) activity.[16] Inhibition of lncRNA TTTY15 could reduce GC progression by competitively binding miR-98-5p to suppress CCND2 expression, and TTTY15 might become a new target for GC therapy.[17] PVT1 positively regulated GC cell proliferation, migration and cell cycle progression through the regulation of miR-16 and CCND1.[18] The downregulation of LINC01667 was involved in the inhibition of GC cell proliferation through miR-138-5p/cyclin E1 (CCNE1) axis.[19]

In hepatocellular carcinoma (HCC), LINC00152 facilitated HCC cell proliferation by controlling cell cycle progression through regulation of CCND1, thus, it was identified as a potential therapeutic target for HCC.[20] The knockdown of PR11-295G20.2 partially inhibited HCC cell proliferation, invasion and migration through the miR-6884-3p/cyclin B1 (CCNB1) pathway.[21] LINC01488 actively promoted miR-124-3p and miR-138-5p biogenesis to reduce vimentin expression and negatively regulated CCNE, thereby inhibiting the progression of G1 phase and suppressing the entry of S phase.[22]

LncRNA CASC9 was found to be upregulated in pancreatic tissues and it could upregulate CCND1 expression by targeting miR-497-5p, then contribute to pancreatic cancer (PC) progression.[23] LncRNA XIST promoted CCND1 expression by competitively binding with miR-129-5p in esophageal squamous cell carcinoma (ESCC).[24] In esophageal carcinoma (EC), LINC01234 bound to miR-193a-5p to induce CCNE1, thus promoted EC cell proliferation and inhibited cell apoptosis.[25]

Similarly, HOXD-AS1 upregulated CCND1 by targeting miR-526b-3p and MCF2L-AS1 partially modulated the expression of CCNE1 by targeting miR-874-3p to promote colorectal cancer (CRC) cell proliferation, migration and invasion, providing a theoretical basis for developing anticancer therapy for CRC.[26,27] In addition, HNF1A-AS1 might also be a promising target for CRC due to its interaction with CCND1, including stabilizing CCND1 mRNA by interacting with IGF2BP2 through m6A modification, regulating CCND1 expression by targeting miR-93-5p or suppressing PDCD4 to activate the PI3K/AKT pathway.[28]

Urogenital Tumors

In renal cell carcinoma (RCC), CDKN2B-AS1 promoted the expression of CCND1 and CCND2 and enhanced the invasion of RCC.[29] Similarly, both LOXL1-AS1/miR-541-3p and ADAMTS9-AS1/miR-142-5p targeted CCND1, and

aberrant expression of CCND1 eventually led to cell cycle progression and carcinogenesis in prostate cancer (PC).[30,31] Upregulation of MALAT1 promoted the proliferation of bladder cancer cells through the miR-34a/CCND1 axis.[32]

In breast cancer (BC), LINC01355 blocked BC cells in G0/G1 phase and inhibited BC growth through FOXO3-mediated CCND1 transcriptional repression.[33] GACAT3 competitively bound to miR-497 and enhanced CCND2 expression to promote BC progression.[34] The knockdown of LINC00473 inhibited the expression of CCNE1, while the inhibition of miR-424-5p eliminated the inhibitory effect of LINC00473 knockdown on CCNE1 protein expression. The ceRNA network formed by LINC00473, miR-424-5p, and CCNE1 provided a new clue for cancer diagnosis and treatment.[35] In ovarian cancer (OC), HOTAIR stimulated CCND1 and CCND2 expression by negatively regulating miR-206 expression, thereby promoting OC cell proliferation, migration and invasion.[36] Knockdown of PCAT-1 suppressed cell proliferation, invasion and migration, and also reduced cyclin D1/CDK4 expression to arrest the cell cycle in G0/G1 phase.[37] CRNDE controlled CCNB1 expression through miR-183 to affect cervical cancer (CC) cell proliferation, migration and invasion.[38] Lnc_000231 promoted CC cell proliferation and tumor formation by interacting with miR-497-5p and maintaining CCNE1 expression.[39] In addition, TINCR upregulated CCND1 expression by uptake of miR-302 to promote cervical squamous cell carcinoma (CSCC) cell proliferation.[40]

Respiratory System Tumors

In non-small cell lung cancer (NSCLC), PCNA-AS1 upregulated CCND1 to promote cell proliferation.[41] Reduced CCND1 and CDK4 expression after overexpression of Linc00703 inhibited NSCLC progression.[42] MCF2L-AS1 and CCND1 expression was upregulated in gefitinib-resistant NSCLC patients. MCF2L-AS1 promoted CCND1 mRNA stability by combining with ELAVL1, thereby facilitating NSCLC cell growth and gefitinib resistance.[43] In lung adenocarcinoma (LUAD), Linc00467 and PTPRG-AS1, respectively, bound to miR-20b-5p and miR-124-3p, to promote CCND1 expression and proliferation of LUAD cells.[44,45] RP11-805J14.5 suppressed the growth, invasion and migration of LUAD cells by sponging miR-34b-3p and miR-139-5p and down-regulating CCND2, which made RP11805J14.5 a potential target for LUAD therapy.[46]

Other Tumors

In osteosarcoma (OS), FLVCR-AS1 bound to miR-381-3p to promote CCND1 expression and OS cell proliferation.[47] Similarly, NR2F1-AS1 competitively bound to miR-338-3p to facilitate CCND1 expression and promote thyroid cancer (TC) cell proliferation and migration.[48] LINC00887 also interacted with CCND1 to regulate cell cycle progression and exacerbate the malignant progression of glioma.[49] RUNX1-IT1 competitively bound to miR-195 to upregulate CCND1 expression, thereby contributing to the proliferation of glioblastoma (GBM) cells.[50] In multiple myeloma (MM), competitive inhibition of miR-128-3p by lncRNA HCP5 promoted PLAGL2 activation of wnt/β-catenin/CCND1 signaling.[51] Moreover, PVT1 activated the expression of β-catenin, c-myc and CCND1 to promote the proliferation and migration of pituitary adenoma cells.[52]

CDK-Targeted Cell Malignancy Regulation Mediated by lncRNAs in Tumors

Different CDKs are involved in the regulation of different cell cycle phases. For example, CDK4, CDK6 mainly acts in G1 phase and CDK2 mainly acts in S phase.[53] CDK4, CDK6 and CDK2 are often overexpressed and promotes cancer cell cycle progression, which in turn accelerates cell division and tumor growth.[54] Recent studies have shown that CDK expression could be regulated by certain lncRNAs and further affect tumorigenesis and progression (Table 2). Therefore, to clarify the interaction between lncRNAs and CDKs is essential for developing targeted strategy in the future.

Digestive System Tumors

LncRNA GCRL1 promoted GC cells proliferation and metastasis by targeting CDK4 and LINC00974 upregulated CDK6 to accelerate the G1-S phase transition to promote GC cell proliferation, indicating their oncogenic roles and promising blocking targets for GC.[55,56]

LINC00630 could recruit E2F1 to the promoter region of CDK2 to promote CDK2 transcription, thereby promoting HCC cell proliferation, inhibiting apoptosis and accelerating the cell cycle.[57] VPS9D-AS1 was found to bind with HuR protein, thus affecting the post-transcriptional expression of CDK4 mRNA and driving HCC cell proliferation.[58]

Table 2 The Regulation of lncRNAs on CDK in Tumors

LncRNA	Cancer Types	Expression	Functions	Related Gene	Reference
GCRL1	GC	Upregulated	Promoted cancer cell proliferation and migration	CDK4, miR-885-3p	[55]
LINC00974	GC	Upregulated	Promoted the proliferation of cancer cells	CDK6	[56]
LINC00630	HCC	Upregulated	Promoted the malignant progression of cancer	CDK2, E2F1	[57]
VPS9D1-AS1	HCC	Upregulated	Regulated the proliferation of cancer cells	CDK4, HuR protein	[58]
LINC00205	HCC	Upregulated	Promoted the proliferation of cancer cells	CDK6, YY1, miR-26a-5p	[59]
CRNDE	HCC	Upregulated	Promoted proliferation, invasion and migration	CDK6, miR-33a-5p	[60]
MCM3AP-AS1	CRC	Upregulated	Promoted cell cycle progression	CDK4, miR-545	[61]
NR2F2-AS1	Colon Cancer	Upregulated	Promoted the proliferation of cancer cells	CDK6	[62]
CASC21	CRC	Upregulated	Promoted the proliferation of cancer cells	CDK6, miR-539-5p	[63]
HAGLR	CRC	Upregulated	Promoted cancer progression	CDK4/6, miR-185-5p	[64]
UCA1	ACC	Upregulated	Promoted cancer cell growth	CDK6, miR-298	[65]
HOST2	TNBC	Upregulated	Promoted the proliferation of cancer cells	CDK6, let-7b	[66]
SNHG15	OC	Upregulated	Promoted the proliferation of cancer cells	CDK6, miR-370-3p	[67]
LINC00313	CC	Upregulated	Promoted cancer cell proliferation and migration	CDK6, miR-4677-3p	[68]
MACC1-AS1	CSCC	Upregulated	Promoted proliferation and cell cycle	CDK6, miR-34a	[69]
NR2F2-AS1	PC	Upregulated	Promoted the proliferation of cancer cells	CDK4	[70]
LINC01194	NSCLC	Upregulated	Promoted the proliferation of cancer cells	CDK4, miR-486-5p	[71]
FOXD3-AS1	NSCLC	Upregulated	Promoted proliferation, inhibited apoptosis	CDK6, miR-135a-5p	[72]
HNF1A-AS1	NSCLC	Upregulated	Promoted proliferation, invasion and migration	CDK6, miR-149-5p	[73,74]
MEG8	NSCLC	Upregulated	Promoted proliferation, invasion and migration	CDK6, miR-107	[75]
AWPPH	NSCLC	Upregulated	Promoted malignant progression of cancer	CDK6, miRNA-204	[76]
TFAP2A-AS1	NSCLC	Upregulated	Promoted cancer progression	miR-584-3p, CDK4	[77]
91H	OS	Upregulated	Promoted cancer progression	CDK4	[78]
LOC100129620	OS	Upregulated	Promoted proliferation, invasion and migration	CDK6, miR-335-3p	[79]
SNHG6	PTC	Upregulated	Promoted the proliferation of cancer cells	CDK6, miR-186	[80]
PCGEM1	Glioma	Upregulated	Promoted cancer progression	CDK6, miR-539-5p	[81]
H19	Glioma	Upregulated	Promoted growth, invasion and migration	CDK6, miR-200a, ZEB1	[82]
HAND2-AS1	Glioma	Upregulated	Regulated the proliferation, invasion and migration of cancer cells	CDK6	[83]
LINC00704	NPC	Upregulated	Promoted growth and cell cycle	CDK6, ETS1	[84]

Abbreviations: GC, Gastric Cancer; HCC, Hepatocellular Carcinoma; CRC, Colorectal Cancer; ACC, Adrenocortical Carcinoma; TNBC, Triple Negative Breast Cancer; OC, Ovarian cancer; CC, Cervical cancer; CSCC, Cervical Squamous Cell Carcinoma; PC, Prostate Cancer; NSCLC, Non-Small Cell Lung Cancer; OS, Osteosarcoma; PTC, Papillary Thyroid Cancer; NPC, Nasopharyngeal Carcinoma.

Transcription factor YY1 triggered transcription of LINC00205, and YY1-regulated LINC00205 promoted cell cycle and cancer cell proliferation via miR-26a-5p/CDK6-mediated ceRNA axis.[59] Knockdown of CRNDE could inhibit CDK6 expression by targeting miR-33a-5p, blocking the cell cycle at G0/G1 phase. These oncogenic lncRNAs provide potential therapeutic targets for HCC cancer treatment despite their variable actions.[60]

In CRC, MCM3AP-AS1 facilitated cell cycle progression by targeting miR-545/CDK4 and NR2F2-AS1 knockdown induced cell cycle block by downregulating CDK6.[61,62] Transcription factor FOXP1 provoked transcription of CASC21, which interacted with miR-539-5p and increased CDK6 expression to promote cancer cell proliferation.[63] HAGLR promoted CRC progression through miR-185-5p/CDK4/CDK6 axis.[64] These lncRNAs could be promising targets for CRC diagnosis due to their abnormal expression in CRC tissues and blocking targets for treatment due to their significant carcinogenic effect.

Urogenital Tumors

In adrenocortical carcinoma (ACC), UCA1 promoted ACC growth by regulating the miR-298/CDK6 axis.[65] LncRNA HOST2/let-7b/CDK6 axis was involved in the regulation of triple-negative breast cancer (TNBC) cell proliferation.[66] SNHG15 promoted cancer cell proliferation by inhibiting miR-370-3p to upregulate CDK6, which provide a new

theoretical basis for new clinical treatment strategies.[67] In CC, LINC00313 promoted CDK6 expression through competitive binding of miR-4677-3p, thus promoting cancer progression.[68] Similarly, MACC1-AS1 promoted cell cycle progression and cell proliferation by competitively inhibiting miR-34a to enhance CDK6.[69] LncRNA NR2F2-AS1 positively regulated CDK4 expression to promote PC cell proliferation.[70]

Respiratory System Tumors

LINC01194 and FOXD3-AS1 were both highly expressed in NSCLC tissues and cell lines. LINC01194 regulated the miR-486-5p/CDK4 axis and FOXD3-AS1 interacted with miR-135a-5p/CDK6 to promote the proliferation of NSCLC cells.[71,72] As an oncogenic lncRNA, HNF1A-AS1 was notably correlated with advanced TNM stage, tumor size and lymph node metastasis.[73] Mechanically, HNF1A-AS1 upregulated CDK6 expression by targeting miR-149-5p and provided new evidence for NSCLC potential therapeutic target.[74] Similarly, MEG8 had a great potential to facilitate proliferation, invasion and migration of NSCLC by sponging miR-107 and targeting CDK6 to regulate the Rb/E2F3 signaling pathway.[75] In addition, the level of AWPPH was negatively correlated with the overall survival rate of NSCLC patients and AWPPH/miRNA-204/CDK6 regulatory loop was identified to aggravate the malignant progression of NSCLC.[76] Similarly, TFAP2A-AS1 contributed to cancer progression by regulating the miR-584-3p/CDK4 axis[77] (Figure 2).

Other Tumors

In OS, 91H could serve as new targets for cancer therapy due to their influence on cell proliferation, through inducing CDK4 promoter methylation, or LOC100129620/miR-335-3p/CDK6 signaling pathway.[78,79] In papillary thyroid cancer (PTC), SNHG6 promoted CDK6 expression by regulating miR-186.[80] Similarly, PCGEM1 and H19 promoted or inhibited glioma development by competitively binding the corresponding miRNAs to regulate CDK development.[81,82] On the contrary, HAND2-AS1 was lowly expressed in glioma cells and tissues, and CDK was negatively correlated with

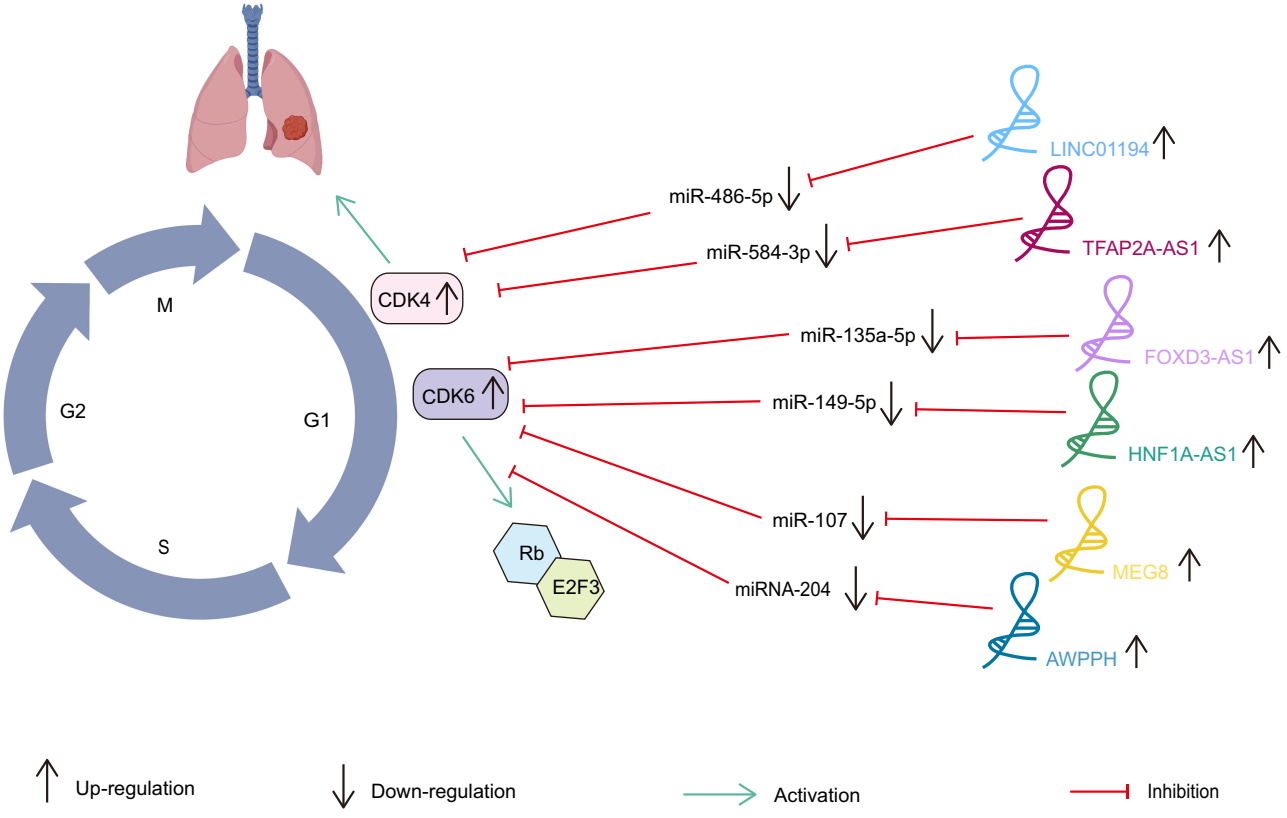

Figure 2 CDK-targeted cell cycle regulation in NSCLC mediated by lncRNA. LINC01194 regulated the miR-486-5p/CDK4 axis and FOXD3-AS1 interacted with miR-135a-5p/CDK6 to promote the proliferation of NSCLC cells. HNF1A-AS1 regulated the miR-149-5p/CDK6 axis and MEG8 interacted with miR-107/CDK6 to facilitate proliferation, invasion and migration of NSCLC. AWPPH/miRNA-204/CDK6 regulatory loop was identified to aggravate the malignant progression of NSCLC and TFAP2A-AS1 contributed to cancer progression by regulating the miR-584-3p/CDK4 axis.[71–77]

HAND2-AS1. HAND2-AS1 regulated cell proliferation, invasion and migration through regulation of CDK6 and provided new insights into the diagnosis and treatment of cancer.[83] In nasopharyngeal carcinoma (NPC), LINC00704 could recruit ETS1 to the promoter region of CDK6 to promote CDK6 transcription, facilitating cell cycle progression and promising as a diagnostic marker and molecular therapeutic target for cancer.[84]

CDK Inhibitor-Targeted Cell Malignancy Regulation Mediated by lncRNAs in Tumors

Many lncRNAs regulate cell cycle by participating in the regulation of CDK inhibitors that delay or stop the cell cycle progression. There are two families of CKI proteins, including inhibitors of INK4 and CDK interacting protein/kinase inhibitory protein (CIP/KIP).[10]

INK4 Family Inhibitors

The INK4 family members contain $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$ (hereafter referred to as p16, p15, p18, p19),[85] among which, p16, p15 and p19 bind to CDK4 and CDK6, preventing them from binding to cyclin D, thereby inhibiting CDK4/6-mediated phosphorylation of pRb and exiting G1 phase.[86] The INK4 locus encodes three important genes: p15 (CDKN2B), p16 (CDKN2A) genes and ARF, which are tumor suppressor genes.[87]

LncRNA ANRIL binds to the INK4 locus and interacts specifically with SUZ12 in the PRC2 complex and with CBX7 in the PRC1 complex. ANRIL suppresses the INK4 locus by recognizing H3K27me3 and CBX7, and inhibits p15 transcription with SUZ12.[88] E2F1 transcriptionally activates ANRIL in an ATM-dependent manner and participates in DNA repair.[89] After DNA repair, ANRIL promotes cell growth and re-enters the cell cycle by repressing the INK4 locus (Figure 3). In addition, knockdown of lncRNA ANROC increases p16, p15 and ARF levels and ANROC acts as a negative regulator of cell cycle progression by suppressing CCNB1 expression, thereby inhibiting cell proliferation.[87] LINC01012 has also been found to be negatively correlated with p19. LINC01012 expression is upregulated in CC and stimulates the proliferation and migration of cancer cells, thereby promoting CC progression by downregulating p19.[90]

Cip/Kip Family Inhibitors

Cip/Kip family inhibitors include $p21^{cip1}$, $p27^{kip1}$, and $p57^{kip2}$, which are involved in cell cycle regulation, transcriptional regulation, and cell migration.[91] ZXF1 mediates cancer cell cycle progression by competitively binding to miR-378-3p to regulate the expression of PCDHA3. ZXF1 binds directly to p21 and blocks CDC20 (E3 ligase of p21) mediated ubiquitin degradation. Thus, ZXF1 becomes a promising diagnostic and prognostic indicator.[92] HCG11 exerts tumor

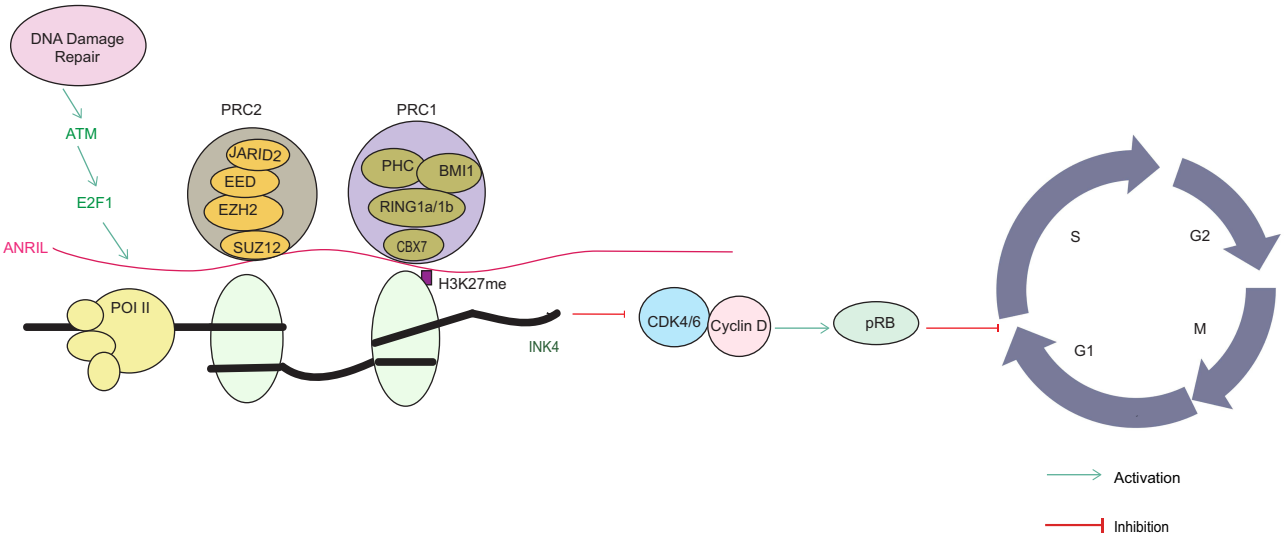

Figure 3 Mechanism of lncRNA ANRIL-mediated regulation of the INK4 locus. LncRNA ANRIL binds to the INK4 locus and interacts specifically with SUZ12 in the PRC2 complex and with CBX7 in the PRC1 complex. ANRIL suppresses the INK4 locus by recognizing H3K27me3 and CBX7, and inhibits p15 transcription with SUZ12. E2F1 transcriptionally activates ANRIL in an ATM-dependent manner and participates in DNA repair. After DNA repair, ANRIL promoted cell growth and re-enters the cell cycle by repressing the INK4 locus.[88,89]

suppressive effects by increasing the expression of p27. On the one hand, HCG11 increases p27 expression by inhibiting the activity of miR-942-5p, thereby inhibiting cancer progression. On the other hand, HCG11 stabilizes p27 mRNA by recruiting IGF2BP2 (an RNA-binding protein).[93] SNHG17 is involved in GC genesis and development as a member of PRC2-mediated epigenetic regulation. P15 and p57 are downstream regulators involved in SNHG17-mediated GC cell cycle and proliferation processes. SNHG17 regulates p15 and p57 by binding to EZH2 to mediate epigenetic p15 and p57 transcriptional inhibition. Activation of PRC2 and induction of GC cell proliferation by SNHG17 suggest that SNHG17 can directly bind to EZH2 and repress p15 and p57 expression in GC.[94]

Emerging evidences about lncRNAs on cell cycle regulatory proteins indicate that lncRNAs can influence various malignant behaviors of cancer cells including not only cell proliferation but apoptosis, migration and invasion, even drug resistance. To further clarify the interaction mechanisms between aforesaid regulators will surely pave the way for design of anticancer therapies which intervene with the cell malignancy progression.

The Regulatory Mechanism of lncRNAs Involved in Cancer Cell Cycle

The regulatory roles of lncRNAs on cancer cell cycle involve different mechanisms, including sponging by the ceRNA network, epigenetic modifications, transcription regulations and other regulatory pathways (Figure 4).

The ceRNA Network

LncRNAs can regulate gene expression by acting as endogenous target mimics, which compete with miRNAs. This mode of action is called "miRNA sponge", and lncRNAs with this function are called competitive endogenous RNAs

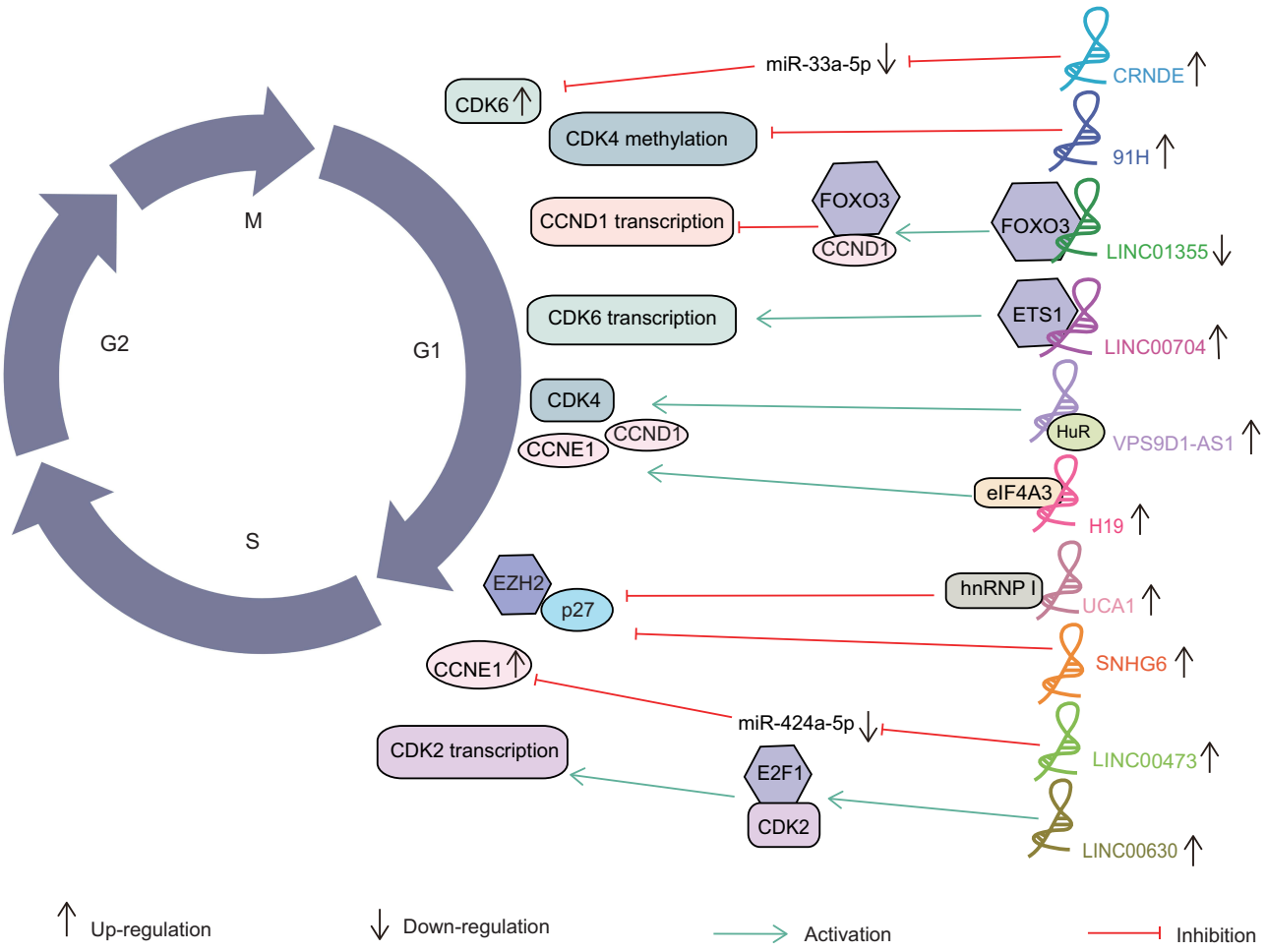

Figure 4 The regulatory mechanism of lncRNAs involved in cancer cell cycle. The regulatory roles of lncRNAs on cancer cell cycle involve different mechanisms, including sponging by the ceRNA network, epigenetic modifications, transcription regulations and other regulatory pathways.

(ceRNAs).[8] Several lncRNAs are involved in the regulation of cancer cell cycle by this way. For instance, knockdown of LINC00473 inhibited CCNE1 expression, while inhibition of miR-424-5P eliminated the inhibitory effect of LINC00473 knockdown on CCNE1 protein expression.[35] Inhibition of CRNDE enhanced the level of miR-33a-5p to suppress CDK6 expression thereby blocking the G0/G1 phase of colorectal cancer.[60]

The Epigenetic Modifications

Epigenetics refers to genetic alterations in gene expression without alterations in DNA sequence. The molecular mechanisms mainly include DNA methylation, histone modifications, chromatin remodeling and non-coding RNA.[8] LncRNAs, as epigenetic regulators, could adjust epigenetic modifications in the nucleus and regulate gene transcription by regulating histone or DNA modifications, mainly methylation and acetylation. For example, knockdown of lncRNA 91H suppressed the progression of osteosarcoma and inhibited tumorigenesis by inducing methylation of the CDK4 promoter.[78] SNHG6 could modulate the G1-S phase transition by recruiting EZH2 to the p27 promoter region, and increase the enrichment of H3K27Me3, inhibit the expression of p27, ultimately regulate the cell cycle, and promote cancer progression. Thus, it provided a new target for NSCLC treatment.[95]

The Transcription Regulations

Certain lncRNAs also modulate the cancer cell cycle via the transcription regulations. This process occurs mainly in the nucleus. LncRNAs bind directly to DNA sequences and repress gene transcription. In addition, they interacted directly with proteins (mainly transcription factors) to repress or activate the expression of downstream genes.[8] For example, overexpression of LINC01355 selectively enhanced the binding of the CCND1 promoter region to FOXO3 protein that was a transcriptional repressor of CCND1. The FOXO3/CCND1 axis plays an important role in LINC01355-mediated tumor suppression.[33] LINC00704 promoted CDK6 transcription by recruiting ETS1 to the promoter region of CDK6, promoting the cancer cell cycle progression.[84] LINC00630 was a novel regulator of E2F1 transcriptional activity. Overexpression of LINC00630 promoted the binding of E2F1 to the CDK2 promoter region, which in turn promoted CDK2 expression and finally led to HCC cell proliferation, inhibition of apoptosis and acceleration of the cell cycle.[57]

Other Regulatory Mechanisms

LncRNA VPS9D1-AS1 could directly bind to the HuR protein and thus impact the stability and expression of the CDK4 mRNA, thereby impacting HCC cell proliferation.[58] H19 was able to bind to eIF4A3, a core exon junction complex (EJC) component that was loaded onto mRNAs by pre-mRNA splicing, thus modulating the expression of CCND1, CCNE1 and CDK4, finally promoting CRC cell proliferation.[96] UCA1 could suppress the tumor suppressor p27 through interaction with heterogeneous nuclear ribonucleoprotein I (hnRNP I). UCA1 mediated tumor growth by interaction with hnRNP I, thus leading to the suppression of p27 protein expression and causing G1 phase cell cycle arrest.[97]

Although lncRNAs play a crucial role in cancer development and progression through complex interaction with cycle regulatory proteins, the molecular mechanisms underlying their function are not fully understood partly due to the tissue-specific modes of action of lncRNAs. Further insight into the biological significance and function of lncRNAs and cycle regulators requires additional studies, which may not only reveal additional mechanisms of action but develop promising anticancer strategies.

Emerging Role of Cell Cycle-Related lncRNAs in Cancer Diagnosis and Therapy

More and more studies have shown that lncRNAs can be used as new tools for early diagnosis and treatment of cancer. Their abnormal expression is related to different cancer types and has obvious specificity. The specific expression of lncRNAs and their detection in patients' serum, plasma, saliva or urine make them effective diagnostic markers for different cancers.[98–100] LncRNA DRAIR is low expressed, and the plasma DRAIR level of patients is decreased. The downregulation of DRAIR is sufficient to distinguish stage I and II patients from healthy controls and thus can be used as an early diagnostic marker for cancer.[101] Another example is that the expression levels of LNCR565 and LNCR641 in the

serum of glioblastoma multiforme patients are significantly higher than those of healthy controls. LNCR565 and LNCR641 can be used as diagnostic markers in BC patients.[102] In addition, one lncRNA can also be abnormally expressed in a variety of cancers, which is called non-specific. For example, the expression level of LUCAT1 is increased in GC, lung cancer, CC and other cancers.[103–105] The non-specificity of lncRNA enables them to diagnose different cancers, and can also make one cancer to be associated with multiple lncRNAs. For example, elevated HULC, H19, HOTAIR, GACAT2 in a patient's serum can be used as a diagnostic marker for GC.[106] Tantai et al reported that XIST and HIF1A-AS1 in serum are elevated, which can be used as diagnostic markers of non-small cell lung cancer, and that the combined detection of XIST and HIF1A-AS1 has a higher diagnostic rate for NSCLC than the detection of a single marker.[107] In addition, some lncRNAs can be used to predict cancer prognosis. For example, LINC01488 is associated with the prognosis of HCC, and HOXD-AS1 is associated with the prognosis of CRC.[22,26]

Chemotherapy, radiotherapy and surgical resection of tumors are the traditional treatment methods of cancer, which can lead to cancer recurrence in many cases. Studies have shown that interfering with the dysregulated lncRNA level can effectively normalize cancer-related cellular changes. Zhang et al found that LINC00628 interacts with EZH2 and regulates gene expression by regulating H3K27me3. In this study, LINC00628 inhibits the proliferation, migration and colony formation of GC cells and acts as an inhibitor of GC.[108] Similarly, it has been reported that lncRNAs HULC and AK126698 act as tumor suppressors by inhibiting cell proliferation and migration.[109,110] These studies indicate that lncRNA can be a new therapeutic target for cancer therapy.

Conclusion and Future Perspective

LncRNAs were aberrantly expressed in many types of cancer and their dysregulation plays an important role in cancer cell development, progression and survival. LncRNAs are related to a variety of clinicopathological features, such as tumor TNM staging, lymph node metastasis, distant metastasis and short overall survival time and involved in various cellular processes including cell proliferation, apoptosis, invasion and migration. In this review, we pay close attention to the regulation of the lncRNAs on the cell cycle regulators of cancers. LncRNAs regulate the cell cycle factors, such as CDK and CDK inhibitors through various mechanisms, including sponging by the ceRNA network, epigenetic modifications, transcription regulations and other regulatory pathways. Although the regulation of cell cycle by lncRNAs was closely related to tumorigenesis and development, many lncRNAs with functional roles and the mechanisms by which they regulate the tumor cell malignancy have not been fully clarified due to the complex regulatory relationships among molecules. Therefore, an in-depth understanding of the roles and ways of lncRNAs in cell cycle regulation will be helpful for clarifying the interaction between lncRNAs and the cell cycle molecules of cancers.

The differential expression of cell cycle-related lncRNAs in normal and cancer tissues and cell lines makes them a promising and powerful selection tool for use in cancer diagnosis and provide new insights into drug candidates for cancer therapy. However, the expression of lncRNAs in certain cancers remains unclear due to limited research. Therefore, further studies are needed to confirm the exact expression of lncRNAs in various cancers. In addition, lncRNAs were currently less studied in human plasma, serum, urine and other body fluids, which hinders the application of lncRNAs in diagnosis. More studies on the expression and stability of lncRNAs in non-invasive body fluids are needed to make lncRNAs an ideal tool for disease diagnosis. Also, there is limited information on the use of lncRNAs for therapeutic applications, and further preclinical and clinical studies on the efficacy, stability, and safety of lncRNAs-targeted drugs are needed. In addition to the efficacy, stability, and safety of lncRNAs-targeted drugs for cancer therapy, further studies are needed to investigate the expression and stability of lncRNAs in non-invasive body fluids used for cancer diagnosis.

In conclusion, we highlight the regulation of lncRNAs-modulated cancer progression through various cell cycle regulators in tumors. LncRNAs can be used as diagnostic biomarkers and therapeutic targets for cancers, but this part of the research is still under-developed and needs to be further explored to provide new insights in the mechanisms of action and the development of new biomarkers and therapeutic targets.

Author Contributions

All authors made significant contributions to the reported work, including the conceptualization, literature collection, figure, and tabulation, or in all of these areas; participated in drafting, revising, or critically reviewing the article; gave final approval to the version to be published; have agreed on the journal to which the article has been submitted; and have agreed to take responsibility for all aspects of the work.

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Disclosure

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