The role of lncRNA binding to RNA-binding proteins to regulate mRNA stability in cancer progression and drug resistance mechanisms (Review)

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Abstract. Cancer is a disease that poses a serious threat to human health, the occurrence and development of which involves complex molecular mechanisms. Long non-coding RNAs (lncRNAs) and RNA-binding proteins (RBPs) are important regulatory molecules within cells, which have garnered extensive attention in cancer research in recent years. The binding of lncRNAs and RBPs plays a crucial role in the post-transcriptional regulation of mRNA, affecting the synthesis of proteins related to cancer by regulating the stability of mRNA. This, in turn, regulates the malignant biological behaviors of tumor cells, such as proliferation and metastasis, and serves an important role in therapeutic resistance. The present study reviewed the role of lncRNA-RBP interactions in the regulation of mRNA stability in various malignant tumors, with a focus on the molecular mechanisms underlying this regulatory interaction. The aim of the present review was to gain a deeper understanding of these molecular mechanisms to provide new strategies and insights for the precise treatment of cancer.

Contents

1. Introduction

Cancer is a complex disease involving multiple aspects at the genetic, molecular and cellular levels, which is characterized by unlimited cell proliferation, invasion and metastasis (1-3). With global population aging and lifestyle changes, the incidence and mortality rates of cancer are continuously rising, posing significant challenges to the global public health system (4-7). The complexity of cancer treatment lies in its high heterogeneity and adaptability to therapies, and even the most advanced treatments face issues of resistance and relapse (8-10). Therefore, understanding and studying the fundamental biological characteristics and pathogenesis of cancer is crucial for developing new therapeutic strategies.

mRNA is a single-stranded ribonucleic acid transcribed from DNA. Its function is to transfer genetic information from DNA in the nucleus to ribosomes in the cytoplasm, directing the synthesis of proteins to execute various functions. This process is influenced by numerous factors, and the stability of mRNA can ultimately affect its protein expression levels, thereby impacting its functional performance (11). The stability of mRNA is related to the integrity of its structure, which includes the 5' cap, the 5' untranslated region (UTR), the open reading frame, the 3' UTR and the polyadenylated tail [Poly(A) tail] at the 3' end (12,13). The 5' cap and Poly(A) tail are crucial for maintaining mRNA stability. When the 5' cap and Poly(A) tail are present, mRNA is protected from degradation by

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exonucleases and can continue to be translated into proteins. However, when they are removed, mRNA is degraded by exonucleases, leading to a reduction in the synthesis of its encoded protein products (14,15). Some proteins bind to the 5' UTR or 3' UTR of mRNA and can maintain or remove the 5' cap and Poly(A) tail, thereby affecting whether the mRNA is degraded; this is a key mechanism for regulating mRNA stability.

RNA-binding proteins (RBPs) are important regulatory molecules within cells that bind to RNA to regulate its splicing, transport, translation and degradation, thereby maintaining normal cellular physiological functions (16-18). Studies have found that RBPs can influence mRNA stability through post-transcriptional regulation, playing a regulatory role in the occurrence, development and therapeutic resistance of malignant tumors (19,20). In addition to binding to mRNA, RBPs can bind to long non-coding RNA (lncRNA). lncRNAs are RNA molecules longer than 200 nucleotides that do not encode proteins; however, they maintain normal cellular functions and homeostasis by regulating gene expression, participating in chromatin remodeling, and modulating RNA splicing and translation (21-23). Abnormal expression of lncRNAs and RBPs can significantly affect the biological behavior of cancer (24,25). Studies have found that lncRNAs regulate mRNA stability through interactions with RBPs, which is an important mechanism in cancer progression and drug resistance (26-28).

For the present review, a systematic literature search was conducted using the PubMed platform (https://pubmed.ncbi.nlm.nih.gov/) with key words including 'lncRNA', 'RBP', 'mRNA', 'RNA stability', 'RNA degradation' and 'cancer'. Subsequently, articles on how lncRNAs regulate mRNA stability in cancer through interactions with RBPs were screened and analyzed. The present study focused on reviewing the impact of lncRNA-RBP interactions on mRNA stability in cancer, and their roles in cancer occurrence, development and drug resistance, exploring the potential of targeting this mechanism as a new therapeutic strategy for cancer.

2. lncRNA acts as a molecular scaffold, promoting the binding of RBPs to mRNA, thereby regulating mRNA stability

Molecular scaffolds refer to RNA, proteins or other macromolecules that, during normal cellular physiological processes and signal transduction, provide binding sites and interact with multiple molecules. This promotes interactions among these molecules, ensuring appropriate transmission of signals by kinases, receptors and other signaling molecules, thus fulfilling biological functions (29-31). Molecular scaffolds not only speed up the transmission and efficiency of signals but also ensure that signals are accurately transmitted to specific cellular locations, finely regulating cell proliferation, differentiation, metabolism and other important functions (32,33). In cancer, some lncRNAs also act as molecular scaffolds, promoting the binding of RBPs to mRNA, enhancing or weakening mRNA stability, and regulating the synthesis of related proteins (Fig. 1A); this ultimately affects the malignant biological behavior of tumors and therapeutic resistance (34-37).

Enhanced mRNA stability. lncRNA acts as a molecular scaffold to promote the binding of RBPs to the 5' UTR or 3' UTR of mRNA, further regulating mRNA stability (38-40). The regulatory effect depends on the function of the RBP. When the RBP stabilizes the 5' cap or Poly(A) tail of mRNA, it can prevent mRNA from being degraded by exonucleases, enhancing mRNA stability, increasing the synthesis of its encoded protein and thus its corresponding biological functions.

As a molecular scaffold, lncRNA promotes the binding of RBPs to the mRNA of oncogenes or tumor suppressor genes, enhancing their stability and exerting oncogenic or tumor-suppressing effects. Wang *et al* (41) reported that the lncRNA EGFR-AS1 was highly expressed in renal cancer. After EGFR-AS1 binds with HuR, it promotes the binding of human antigen R (HuR) to the ARE sequence in the 3' UTR of EGFR mRNA, forming a stable complex that maintains the stability of the Poly(A) tail at the 3' end of EGFR mRNA, preventing its degradation by exonucleases, thereby increasing its stability. This, in turn, increases EGFR protein synthesis, promoting renal cancer cell proliferation (41). In a study by Wu *et al* (42), the lncRNA small nucleolar RNA host gene 12 was shown to recruit insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2) and promote its binding to the 3' UTR of catenin beta 1 (CTNNB1) mRNA, forming a complex that prevents CTNNB1 mRNA degradation and increases CTNNB1 protein synthesis. The CTNNB1 protein further activates the Wnt/β-catenin signaling pathway, promoting the invasion and metastasis of esophageal cancer (42). Chen *et al* (43) demonstrated that LINC00659 was lowly expressed in hepatocellular carcinoma (HCC), and its overexpression significantly inhibited HCC proliferation and metastasis. Mechanistic studies have indicated that LINC00659 acts as a molecular scaffold to promote the binding of FUS to SLC10A1 mRNA, preventing its degradation and increasing SLC10A1 protein synthesis. The SLC10A1 protein can block aerobic glycolysis in liver cancer cells, thereby significantly inhibiting HCC proliferation and metastasis (43). Similar mechanisms have also been observed in numerous other types of cancer (Table I) (44-55).

The regulation of mRNA stability by lncRNA as a molecular scaffold promoting RBP binding to mRNA not only influences the malignant biological behavior of cancer, but also plays a role in regulating cancer treatment resistance (56). Ferroptosis is closely related to cancer drug resistance. Unlike classical forms of cell death, such as apoptosis, necrosis or autophagy, ferroptosis is a form of cell death induced by iron-catalyzed lipid peroxidation, primarily involving the peroxidative damage of polyunsaturated fatty acids in cell membranes. Excess iron ions promote the generation of reactive oxygen species (ROS), disrupt cell membrane integrity, lead to cellular dysfunction and ultimately trigger cell death (57-59). Studies have shown that cancer cells develop drug resistance by evading ferroptosis (60-62), while inducing ferroptosis in cancer cells can reverse their drug resistance (63,64). Temozolomide (TMZ) is a primary drug for the treatment of glioma; however, drug resistance is a major challenge in its treatment. Luo *et al* (65) found that the lncRNA ataxin-8 opposite strand (ATXN8OS) was lowly expressed in glioma, and overexpression of ATXN8OS could inhibit glioma resistance to TMZ. Mechanistic studies indicated that ATXN8OS

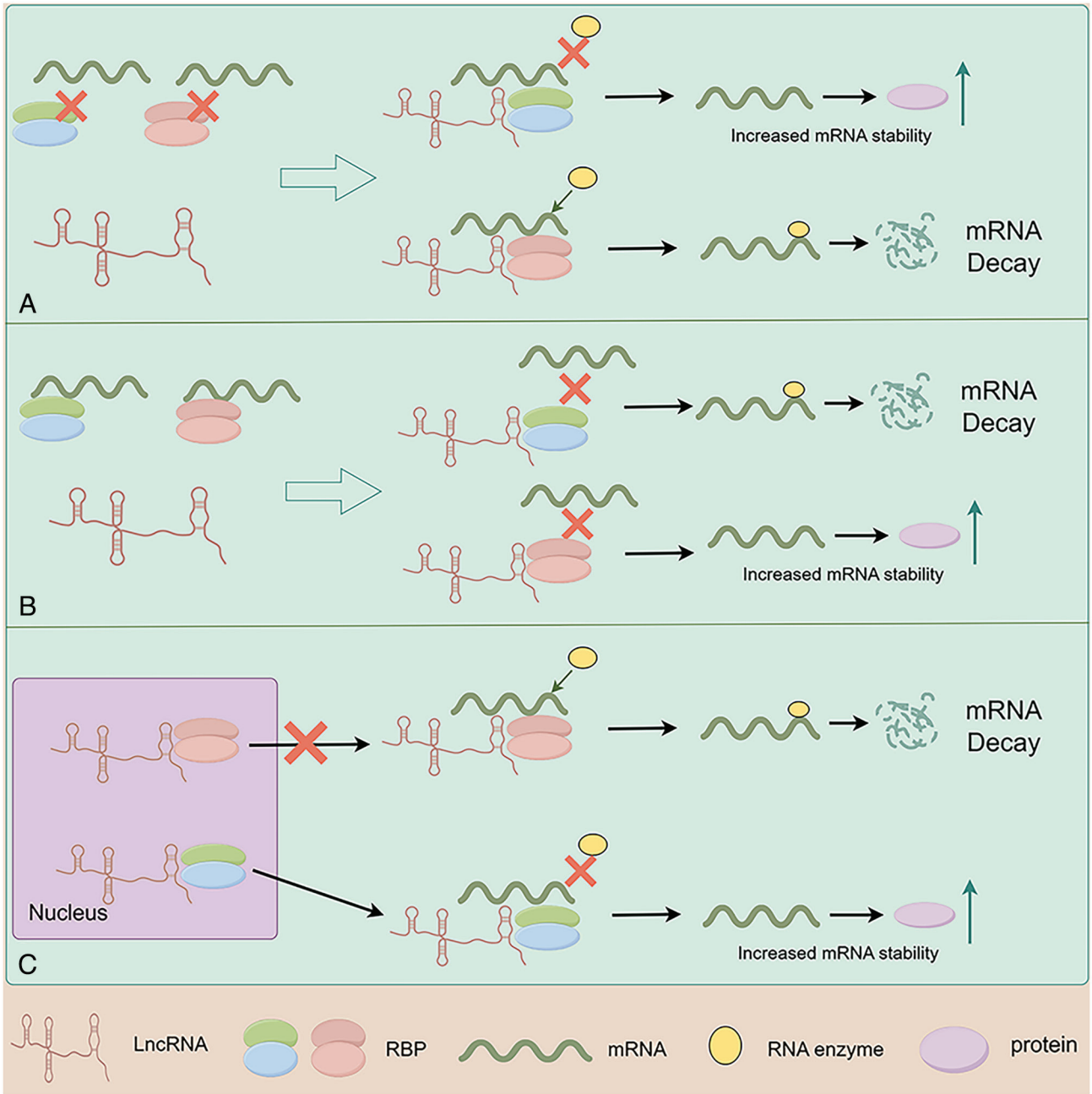

Figure 1. Mechanisms by which lncRNA acts as a molecular scaffold to promote RBP-mRNA binding, competitively binds RBPs, and influences the nuclear-cytoplasmic localization of RBPs to regulate mRNA stability. (A) lncRNA acts as a molecular scaffold for RBP-mRNA binding, promoting RBP-mRNA interactions to prevent or promote mRNA degradation. (B) lncRNA competitively binds different functional RBPs, blocking RBP-mRNA binding, thereby increasing or decreasing mRNA stability. (C) lncRNA regulates the subcellular localization of RBPs to control mRNA stability. In the nucleus, lncRNA binds to RBPs, preventing RBPs that promote mRNA degradation from entering the cytoplasm and transporting RBPs that increase mRNA stability to the cytoplasm, thereby reducing mRNA degradation and increasing mRNA stability. lncRNA, long non-coding RNA; RBP, RNA-binding protein. The image was drawn using Figdraw (www.figdraw.com).

recruits adenosine deaminase acting on RNA and promotes its binding to glutaminase 2 (GLS2) mRNA, enhancing GLS2 mRNA stability and increasing intracellular GLS2 protein synthesis. GLS2 increases iron ion and ROS levels, promoting ferroptosis in glioma, ultimately enhancing the sensitivity of glioma to TMZ (65).

Decreased mRNA stability. When lncRNA functions as a molecular scaffold to bind RBPs that remove the 5' cap or Poly(A) tail of mRNA, it leads to mRNA degradation, reducing its stability and the synthesis of its encoded protein, thereby exerting oncogenic or tumor-suppressive effects.

Staufen (STAU)-mediated mRNA decay (SMD) is a post-transcriptional regulatory mechanism of gene expression, which involves the role of STAU in recognizing and promoting the degradation of specific mRNA molecules (66,67). Lu *et al* (68) found that in breast cancer, the lncRNA TINCR could act as a molecular scaffold to bind STAU1, a member of the Staufen protein family, thus promoting the degradation of oligoadenylate synthetase 1 (OAS1) mRNA through the

Table I. LncRNAs acts as a molecular scaffold for RBPs to bind mRNAs, thereby increasing mRNAs stability.

First author/s, year	LncRNAs	RBPs	mRNAs	Mechanism	Effect	(Refs.)
Wang *et al*, 2019; Tuo *et al*, 2023; Tian *et al*, 2021; Ren *et al*, 2022; Yang and Hu, 2020; Zhu *et al*, 2022; Yang *et al*, 2014	EGFR-AS1, MRVI1-AS1, Linc-ROR, SNHG16, HOXC-AS3, LINC01232, GHET1	HuR, CELF2, HNRNPK, EIF4A3, FUS, IGF2BP2, IGF2BP1	EGFR, SKA1, DEPDC1, RhoU, FOXM1, TGFBR1, c-Myc	LncRNA acts as a molecular scaffold for binding RBP to mRNA	Increase mRNA stability and promote cancer proliferation	(41,44-49)
Wu *et al*, 2020; Luo *et al*, 2020; Ning *et al*, 2022; Wen *et al*, 2020; Wang *et al*, 2022; Chen *et al*, 2020; Lu *et al*, 2020	SNHG12, ZEB1-AS1, NUTM2A-AS1, LINC02535, ZFAS1, HOXB-AS1, LEF1-AS1	IGF2BP2, ELAVL1, SRSF1, PCBP2, U2AF2, ELAVL1, HNRNPL	CTNNB1, ZEB1, Trim37, RRM1, HMGCR, FUT4, LEF1	LncRNA acts as a molecular scaffold for binding RBP to mRNA	Increase mRNA stability and promote cancer metastasis	(42,50-55)
Chen *et al*, 2023	LINC00659	FUS	SLC10A1	LncRNA acts as a molecular scaffold for binding RBP to mRNA	Increase mRNA stability and inhibit cancer progression	(43)
Luo *et al*, 2022	ATXN8OS	ADAR	GLS2	LncRNA acts as a molecular scaffold for binding RBP to mRNA	Increase mRNA stability and inhibit cancer resistance	(65)
Lu *et al*, 2021; Zhao *et al*, 2021	TINCR, SPRY4-IT1	STAU1	OAS1, TCEB1	LncRNA acts as a molecular scaffold to promote mRNA degradation through SMD pathway	It reduces mRNA stability and promotes cancer proliferation.	(68,69)
Liu *et al*, 2022	FIRRE	PTBP1	Smurf2	LncRNA acts as a molecular scaffold for binding RBP to mRNA	It reduces mRNA stability and promotes cancer proliferation.	(72)

LncRNAs, long non-coding RNAs; RBPs, RNA-binding proteins; EGFR-AS1, epidermal growth factor receptor antisense RNA 1; MRVI1-AS1, MRVI1 antisense RNA 1; Linc-ROR, long intergenic non-protein coding RNA, regulator of reprogramming; SNHG16, small nucleolar RNA host gene 16; HOXC-AS3, HOXC cluster antisense RNA 3; LINC01232, long intergenic nonprotein coding RNA 1232; GHET1, gastric carcinoma high expressed transcript 1; HuR, human antigen R; CELF2, CUGBP Elav-like family member 2; HNRNPK, heterogeneous nuclear ribonucleoprotein K; EIF4A3, eukaryotic translation initiation factor 4A3; FUS, fused in sarcoma; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; IGF2BP1, insulin-like growth factor 2 mRNA binding protein 1; EGFR, epidermal growth factor receptor; SKA1, spindle and kinetochore associated complex subunit 1; DEPDC1, DEP domain containing 1; RhoU, Ras homolog family member U; FOXM1, forkhead box M1; TGFBR1, transforming growth factor beta receptor 1; SNHG12, small nucleolar RNA host gene 12; ZEB1-AS1, zinc finger E-box binding homeobox 1 antisense RNA 1; NUTM2A-AS1, NUTM2A antisense RNA 1; LINC02535, long intergenic non-protein coding RNA 2535; ZFAS1, ZNFX1 antisense RNA 1; HOXB-AS1, Homeobox antisense RNA 1; LEF1-AS1:LEF1 antisense RNA 1; ELAVL1, embryonic lethal, abnormal vision, *Drosophila*-Like 1; SRSF1, serine and arginine rich splicing factor 1; PCBP2, Poly (rC) binding protein 2; U2AF2, U2 small nuclear RNA auxiliary factor 2; HNRNPL, heterogeneous nuclear ribonucleoprotein L; CTNNB1, catenin beta 1; ZEB1, zinc finger E-box binding homeobox 1; RRM1, ribonucleotide reductase M1; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; FUT4, fucosyl-transferase 4; LEF1, lymphoid enhancer-binding factor 1; LINC00659, long intergenic non-protein coding RNA 659; SLC10A1, solute carrier family 10 member 1; ATXN8OS, ataxin-8 opposite strand; ADAR, adenosine deaminase acting on RNA; GLS2, glutaminase 2; TINCR, terminal differentiation-induced ncRNA; SPRY4-IT1, Sprouty RTK signaling antagonist 4 intronic transcript 1; FIRRE, functional intergenic repeating RNA element; STAU1, Staufen double-stranded RNA binding protein 1; PTBP1, polypyrimidine tract-binding protein 1; OAS1, oligoadenylate synthetase 1; TCEB1, transcription elongation factor B polypeptide 1; Smurf2, SMAD specific E3 ubiquitin protein ligase 2.

SMD pathway. Mechanistically, STAU1 binds to the 3' UTR region of OAS1 mRNA and removes its Poly(A) tail at the 3' end, ultimately leading to degradation by exonucleases and reducing OAS1 mRNA stability. OAS1 is a tumor suppressor gene, and reduced protein synthesis of OAS1 can promote breast cancer cell proliferation and metastasis (68). Similarly, in ovarian cancer, the lncRNA SPRY4-IT1 (69) has been revealed to promote mRNA degradation through a similar mechanism, reducing the synthesis of tumor suppressor gene-encoded proteins, thereby promoting tumor proliferation and metastasis.

Additionally, as a molecular scaffold, lncRNA promotes the binding of RBPs to mRNA encoding ubiquitination-related proteins, regulating the synthesis of ubiquitin ligases, and thus the ubiquitin-mediated degradation of cancer-related proteins, which is another mechanism influencing the malignant biological behavior of cancer. The BCR protein complex is a major signaling molecule on the surface of B cells, which is involved in regulating B-cell activation, proliferation and differentiation. Aberrant activation of BCR signaling is a key factor in the proliferation of diffuse large B-cell lymphoma (DLBCL) cells (70,71). Polypyrimidine tract-binding protein 1 (PTBP1) is a multifunctional RBP that can promote the degradation of certain mRNAs by recruiting degradation complexes, or can prevent mRNA degradation by stabilizing its structure; the specific function depends on the binding site and other regulatory factors within the cell. Liu *et al* (72) identified that the lncRNA functional intergenic repeating RNA element (FIRRE) was highly expressed in DLBCL. After FIRRE binds to PTBP1, it promotes the binding of PTBP1 to the 3' UTR of SMAD specific E3 ubiquitin protein ligase 2 (Smurf2) mRNA, possibly leading to Smurf2 mRNA degradation by recruiting degradation complexes. Smurf2 is a ubiquitin ligase that promotes the ubiquitin-mediated degradation of BCR proteins. After Smurf2 mRNA is degraded, the synthesis of Smurf2 decreases, reducing the ubiquitin-mediated degradation of BCR proteins. This further maintains the abnormal activation of BCR signaling, ultimately promoting DLBCL proliferation (72).

lncRNA acting as a molecular scaffold to promote the binding of RBPs to mRNA is the most frequently reported mechanism of lncRNA-RBP interactions regulating mRNA stability in cancer research (Table I). In this mechanism, lncRNAs exert oncogenic or tumor-suppressive effects, or regulate chemotherapy sensitivity, by directly modulating the stability of mRNAs that have cancer-promoting, cancer-suppressing and chemotherapy sensitivity-influencing roles. On the other hand, it can regulate the stability of ubiquitin ligase genes, influencing the expression of tumor-suppressive or oncogenic genes, thus controlling the malignant biological behavior of tumors.

3. lncRNA competitively binds to RBPs, inhibiting the binding of RBPs to mRNA, thereby regulating mRNA stability

Competitive binding refers to the phenomenon where different molecules compete for the same binding site in biological systems, playing a key role in various biological processes, including enzyme activity regulation, receptor-ligand interactions, transcription factor-DNA binding and RBP-RNA interactions (73,74). In cancer, some lncRNAs bind to RBPs with different functions, blocking the binding of RBPs to mRNA. This competitive action is one of the mechanisms that regulates mRNA stability (Fig. 1B).

Competitive binding to RBPs that promote mRNA degradation. In cancer, after lncRNA binds to RBPs that promote mRNA degradation, it blocks the binding of RBPs to mRNA, preventing mRNA degradation, increasing mRNA stability and the synthesis of its encoded protein, thus affecting the malignant biological behavior of cancer. Zhou *et al* (75) found that the lncRNA six-transmembrane epithelial antigen of prostate 3 antisense RNA 1 (STEAP3-AS1) was highly expressed in colorectal cancer (CRC), and promoted CRC proliferation and metastasis. Mechanistically, STEAP3-AS1 competitively binds to YTHDF2, blocking its binding to STEAP3 mRNA, further inhibiting the YTHDF2-mediated degradation of STEAP3 mRNA (75); this increases STEAP3 mRNA stability, enhances STEAP3 protein synthesis, activates the Wnt/β-catenin signaling pathway, and promotes CRC cell proliferation, migration and invasion. In breast cancer studies, Tao *et al* (76) demonstrated that the lncRNA SCAMP1-TV2 could also promote tumor proliferation and metastasis through a similar mechanism (76).

Competitive binding to RBPs that prevent mRNA degradation. On the other hand, certain lncRNAs bind to RBPs that prevent mRNA degradation, blocking the binding of RBPs to mRNA, leading to mRNA degradation and reduced stability, playing an important role in regulating the malignant biological behavior of cancer. Heterogeneous nuclear ribonucleoprotein L (HNRNPL) is an RBP belonging to the heterogeneous nuclear ribonucleoprotein family, which can bind to the 3' UTR of mRNA, forming a stable complex and preventing its degradation. In HCC studies, Wang *et al* (77) found that the lncRNA small nucleolar RNA host gene 6 could competitively bind to HNRNPL, blocking its binding to SET domain containing 7 (SETD7) mRNA, inhibiting the protective effect of HNRNPL on SETD7 mRNA, and promoting SETD7 mRNA degradation. The SETD7 protein has a tumor-suppressive role in HCC, and its reduced synthesis can enhance HCC migration and invasion, playing an important role in HCC progression (77). He *et al* (78) reported that the lncRNA LINC01093 was significantly downregulated in HCC, and its overexpression could significantly inhibit HCC progression. Mechanistically, LINC01093 competitively binds to IGF2BP1, blocking its binding to GLI1 mRNA, leading to the degradation of GLI1 mRNA without the protective effect of IGF2BP1. The GLI1 protein can upregulate cell cycle-related genes, promote cell transition from the G_1 phase to the S phase, and enhance tumor cell proliferation; therefore, its reduced synthesis can significantly inhibit HCC proliferation and metastasis (78).

These studies revealed that lncRNAs, through competitive binding with different functional RBPs, can inhibit the binding of RBPs to mRNA, regulating mRNA stability and the synthesis of its encoded protein, thereby exerting oncogenic or tumor-suppressive effects in cancer (Table II).

Table II. Mechanism by which LncRNAs competitively binds RBPs to mRNA and regulates mRNAs stability by affecting nucleoplasmic localization of RBPs.

First author/s, year	LncRNAs	RBPs	mRNAs	Mechanism	Effect	(Refs.)
Zhou *et al*, 2022	STEAP3-AS1	YTHDF2	STEAP3	STEAP3-AS1 competitively binds to YTHDF2 and prevents YTHDF2 from binding to STEAP3 mRNA	Prevent degradation of STEAP3 mRNA	(75)
Tao *et al*, 2020	SCAMP1-TV2	PUM2	INSM1	SCAMP1-TV2 binds to PUM2 and prevents PUM2 from binding to INSM1 mRNA	Prevent degradation of INSM1 mRNA	(76)
Wang *et al*, 2021	SNHG6	HNRNPL	SETD7	SNHG6 competitively binds to HNRNPL and disrupts HNRNPL binding to SETD7 mRNA	Reduce the stability of SETD7 mRNA	(77)
He *et al*, 2019	LINC01093	IGF2BP1	GLI1	LINC01093 competitively binds to IGF2BP1 and disrupts IGF2BP1 binding to GLI1 mRNA	Reduce the stability of GLI1 mRNA	(78)
Chen *et al*, 2016	ASNR	AUF1	Bcl-2	Lnc-ASNR binds to AUF1 and prevents it from entering the cytoplasm, reducing its degradation of Bcl-2 mRNA	Increase the stability of Bcl-2 mRNA	(81)
Wang *et al*, 2022	FIRRE	PTBP1	BECN1	The combination of FIRRE and PTBP1 promotes the transfer of PTBP1 to the cytoplasm and increases the binding of PTBP1 to BECN1 mRNA	Increase the stability of BECN1 mRNA	(82)

LncRNAs, long non-coding RNAs; RBPs, RNA-binding proteins; YTHDF2, YTH N6-methyladenosine RNA binding protein 2; STEAP3, six-transmembrane epithelial antigen of prostate 3; STEAP3-AS1, STEAP3 antisense RNA 1; SCAMP1-TV2, synaptic vesicle membrane protein 1 transcripts variant 2; PUM2, Pumilio RNA-binding family member 2; INSM1, insulinoma-associated 1; SNHG6, small nucleolar RNA host gene 6; HNRNPL, heterogeneous nuclear ribonucleoprotein L; SETD7, SET domain containing 7; LINC01093, long intergenic non-protein coding RNA 1093; IGF2BP1, insulin-like growth factor 2 mRNA binding protein 1; GLI1, glioma-associated oncogene 1; ASNR, antisense non-coding RNA in the INSR locus; AUF1, ARE/poly (U)-binding/degradation factor 1; Bcl-2, B-cell lymphoma 2; FIRRE, functional intergenic repeating RNA element; PTBP1, polypyrimidine tract-binding protein 1; BECN1, Beclin 1.

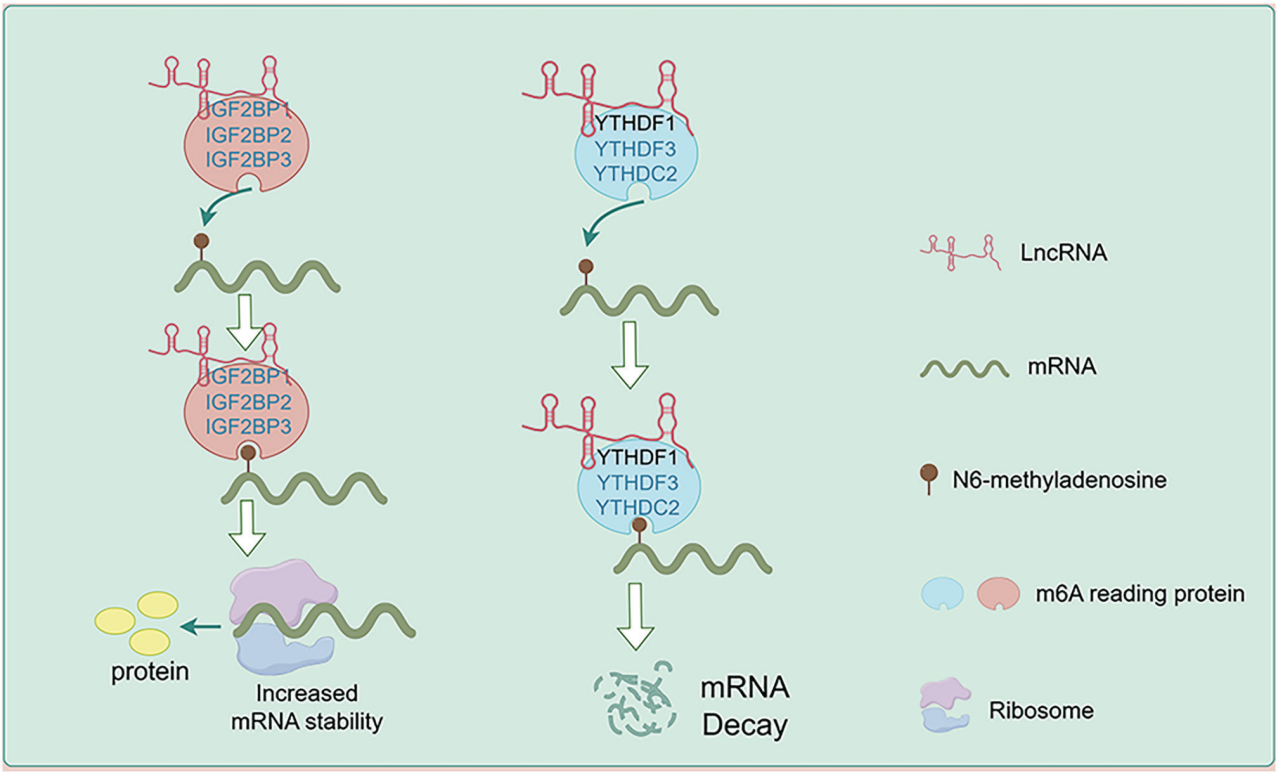

Figure 2. Mechanism by which lncRNA regulates mRNA stability after binding to m6A reader RBPs. Some lncRNAs bind to IGF2BP family proteins, further recognizing and binding to m6A-modified mRNA to prevent its degradation and increase mRNA stability; on the other hand, some lncRNAs bind to YTH family proteins, recognizing and binding to m6A-modified mRNA, promoting its degradation and decreasing mRNA stability. lncRNA, long non-coding RNA; RBP, RNA-binding protein. The image was drawn using Figdraw (www.figdraw.com).

4. lncRNA affects the nuclear-cytoplasmic localization of RBPs, influencing the amount of RBP bound to mRNA, thereby regulating mRNA stability

The normal distribution of proteins, RNA and other biological macromolecules between the nucleus and cytoplasm plays an important regulatory role in biological processes. When the nuclear-cytoplasmic distribution of these macromolecules is abnormal, it can lead to cellular dysfunction (79,80). In cancer, the abnormal nuclear-cytoplasmic distribution of lncRNAs and RBPs can affect mRNA stability, thereby influencing tumor progression. Chen *et al* (81) found that the lncRNA ASNR may have anti-apoptotic functions. The RBP AUF1 binds to the 3' UTR region of Bcl-2 mRNA, promoting Bcl-2 mRNA degradation. Bcl-2 is an anti-apoptotic protein that serves a key role in apoptosis; however, when ASNR binds to AUF1 in the nucleus to form a complex, it prevents AUF1 from entering the cytoplasm, significantly altering its nuclear-cytoplasmic distribution, reducing Bcl-2 mRNA degradation and increasing Bcl-2 protein synthesis, thereby inhibiting tumor cell apoptosis (81). Conversely, Wang *et al* (82) demonstrated that after the lncRNA FIRRE binds to PTBP1 in the nucleus, it can promote the transfer of PTBP1 from the nucleus to the cytoplasm, forming a stable complex with Beclin 1 (BECN1) mRNA in the cytoplasm, preventing BECN1 mRNA degradation by enzymes, increasing its stability and enhancing BECN1 protein synthesis, thereby further promoting CRC proliferation and metastasis. This finding contrasts with that of Liu *et al* (72), but confirms that PTBP1, as a multifunctional RBP, affects mRNA stability differently depending on the binding site and intracellular regulatory factors. Through the aforementioned mechanisms, lncRNA alters the nuclear-cytoplasmic distribution of RBPs, thereby increasing or decreasing the binding of RBPs to mRNA, further regulating mRNA stability and affecting the malignant biological behavior of cancer (Fig. 1C; Table II).

5. lncRNA binds to RBPs that recognize m6A modifications, which then further identify and bind to m6A-modified mRNA, thereby regulating mRNA stability

RNA modification is an important mechanism of post-transcriptional regulation, with m6A modification being the most common type of RNA modification (83,84). m6A modification serves a crucial role in regulating mRNA stability and is an important mechanism for regulating gene expression (85,86). m6A reader proteins are a special class of RBPs that can recognize and bind m6A-modified mRNA, enhancing or reducing mRNA stability, and further influencing cellular functions (87). The main m6A reader proteins include the IGF2BP (88) family proteins (including IGF2BP1, IGF2BP2 and IGF2BP3) and the YTH (89,90) family proteins (including YTHDF1, YTHDF2 and YTHDF3). In cancer, lncRNAs bind to these m6A reader proteins, further recognizing and binding to m6A-modified mRNA, thereby regulating mRNA stability and influencing the malignant biological behavior and drug resistance of tumors. This is another mechanism for regulating mRNA stability (Fig. 2; Table III).

Table III. Mechanisms by which LncRNAs interact with RBPs that recognize m6A modifications to regulate mRNAs stability.

First author/s, year	LncRNAs	RBPs	mRNAs	Mechanism	Effect	(Refs.)
Yang *et al*, 2022	LCAT1	IGF2BP2	CDC6	m6A methylation of CDC6 mRNA is maintained	Increase the stability of CDC6 mRNA	(91)
Zhu *et al*, 2021	KB-1980E6.3	IGF2BP1	c-Myc	m6A methylation of c-Myc mRNA is maintained	Increase the stability of c-Myc mRNA	(92)
Wang and Chen, 2022	UBA6-AS1	IGF2BP1	UBA6	m6A methylation of UBA6 mRNA is maintained	Increase the stability of UBA6 mRNA	(93)
Yang *et al*, 2021	CBSLR	YTHDF2	CBS	Recognize and bind m6A-methylated CBS mRNA	Promote the degradation of CBS mRNA	(94)

LncRNAs, long non-coding RNAs; RBPs, RNA-binding proteins; LCAT1, long-chain acyl-CoA synthetase 1; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; CDC6, cell division cycle 6 homolog; KB-1980E6.3, also named AP002852.1; IGF2BP1, insulin-like growth factor 2 mRNA binding protein 1; UBA6-AS1, UBA6 antisense RNA 1; UBA6, ubiquitin-like modifier activating enzyme 6; CBSLR, cystathionine-beta-synthase long non-coding RNA; YTHDF2, YTH N6-methyladenosine RNA binding protein 2; CBS, cystathionine-beta-synthase.

Yang *et al* found that the lncRNA LCAT1 was upregulated in lung cancer. After binding to IGF2BP2, LCAT1 further recognizes and binds to m6A-modified CDC6 mRNA, forming a stable complex that prevents CDC6 mRNA degradation, increasing its stability and the synthesis of its encoded protein. The CDC6 protein promotes cancer cell migration and invasion by affecting cytoskeleton reorganization, cell adhesion and matrix degradation, thereby promoting lung cancer cell proliferation and metastasis (91). Similarly, in breast cancer, the lncRNA KB-1980E6.3 may promote tumor proliferation and metastasis through a similar mechanism (92). Wang *et al* (93) demonstrated that the lncRNA UBA6-AS1 was downregulated in ovarian cancer, and its overexpression could inhibit tumor proliferation and metastasis. Mechanistically, UBA6-AS1 recruits IGF2BP1, and recognizes and binds to m6A-modified UBA6 mRNA, preventing its degradation, thus increasing UBA6 mRNA stability and the synthesis of its encoded protein. UBA6 promotes the ubiquitin-mediated degradation of cell cycle proteins and anti-apoptotic proteins, inhibiting ovarian cancer cell proliferation and metastasis (93).

Yang *et al* (94) reported that the lncRNA CBSLR, cystathionine-beta-synthase long non-coding RNA (CBSLR) could protect gastric cancer cells from ferroptosis, leading to chemotherapy resistance. Mechanistically, after CBSLR binds to the m6A reader protein YTHDF2, it promotes the recognition and binding of YTHDF2 to m6A-modified CBS mRNA. YTHDF2 further recruits the CCR4-NOT complex, leading to CBS mRNA degradation, reducing CBS protein synthesis and subsequently decreasing ACSL4 protein methylation, which leads to its degradation via the ubiquitin-proteasome pathway. This ultimately protects gastric cancer cells from ferroptosis, promoting chemotherapy resistance (94).

6. Potential therapeutic strategies targeting the molecular mechanisms by which lncRNA binding to RBPs regulates mRNA stability

In cancer, lncRNAs and RBPs regulate mRNA stability through the four aforementioned mechanisms. These findings not only improve the understanding of cancer progression and drug resistance mechanisms, but also provide a theoretical basis for developing new therapeutic strategies. In recent years, small molecule inhibitors, RNA interference technology and gene editing technology have been widely applied in molecular biology. By precisely regulating specific genes and protein functions, these technologies have advanced biomedical research (95-97). In addition, these technologies may have potential in cancer treatment. For example, small molecule inhibitors or RNA interference technology may be used to target lncRNAs, inhibit their binding to RBPs, or specifically inhibit RBPs to block their interactions with lncRNAs and mRNAs. This ultimately reduces the synthesis of oncogenic proteins or increases the synthesis of tumor-suppressive proteins, inhibiting tumor growth and metastasis, thereby playing a role in cancer treatment.

In a preclinical study by Wang *et al* (98), a small interfering (si)RNA targeting the lncRNA MALAT1 showed some efficacy in treating enzalutamide-resistant prostate cancer. In addition, in a breast cancer xenograft model, Wu *et al* (99) used the small molecule inhibitor 1c to bind to

the RNA-binding domain of HuR, inhibiting the binding of HuR to TGFB2 and THBS1 mRNAs, which further inhibited breast cancer growth. Additionally, m6A reader proteins are key mechanisms in regulating mRNA stability. Inhibitors targeting m6A reader proteins, such as IGF2BP2 and YTHDF2, may significantly alter the biological behavior of cancer cells, inhibiting tumor growth and metastasis (100,101). Gene editing technology is also a potential means of treating cancer; for example, CRISPR/Cas9, which uses guide RNA and Cas9 protein complexes to precisely cut and edit DNA sequences. This can be used to knock out oncogenic lncRNA genes or repair mutated RBP genes, blocking the abnormal regulation of mRNA stability with high specificity and efficiency. Katsushima *et al* (102) found that knocking out the lnc-HLX-2-7 gene using CRISPR/Cas9 significantly inhibited tumor growth and prolonged the survival time of mice (102).

Although small molecule inhibitors, RNA interference technology and gene editing technology show great potential in cancer treatment and may provide novel options for precision cancer therapy, most research remains at the cellular and animal model stage, with only a few methods entering preclinical studies. These technologies face a series of challenges and limitations in practical application. Small molecule inhibitors lack selectivity, and the bioavailability and cellular delivery efficiency of drugs are key obstacles. The main challenge of RNA interference technology is to develop delivery systems that ensure siRNA or short hairpin RNA reaches target cells safely and effectively, and functions stably. Although gene editing technology can precisely modify genes, off-target effects, editing efficiency and long-term genetic impacts remain major challenges, and ethical issues also limit its clinical application. Therefore, these technologies have provided potential new areas for cancer treatment, but overcoming the aforementioned issues is necessary for them to be translated into safe and effective therapeutic approaches.

7. Conclusion and prospects

The interaction between lncRNAs and RBPs serves an important role in regulating gene expression, maintaining genome stability and participating in cell signal transduction, and it has a key role in cancer progression and drug resistance. In-depth analysis of lncRNA-RBP interactions is of great significance for revealing cancer molecular mechanisms, discovering new biomarkers and developing new therapeutic strategies. The present study reviewed the various mechanisms by which lncRNA regulates mRNA stability, including acting as a molecular scaffold to promote RBP binding to mRNA, competitively binding RBPs, affecting the nuclear-cytoplasmic localization of RBPs, and binding to m6A reader RBPs to regulate mRNA stability. These mechanisms affect the malignant biological behavior of cancer cells and drug resistance, highlighting their importance in cancer biology. Targeting these mechanisms via small molecule inhibitors, RNA interference technology and gene editing technology may provide new therapeutic options, but these still face challenges and limitations, such as the precise delivery of interfering molecules within cells, avoiding non-specific binding and reducing immune responses. This requires continuous optimization of existing technologies, development of more efficient delivery systems, and strengthening of ethical and safety regulations. Additionally, research on the impact of lncRNA-RBP interactions on mRNA stability in cancer remains limited in both scope and the range of cancers investigated, which constitutes a limitation of the present review. Future research should focus on large-scale screening methods, such as high-throughput sequencing or single-cell sequencing technologies, to more comprehensively reveal the network of lncRNA-RBP interactions and their specific roles in different types of cancer.

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Authors' contributions

NJZ and KW conceived the study. NJZ conducted the literature search and data analysis for inclusion in the review, drafted the manuscript and produced figures. KW edited and revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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