Non-coding RNA Research 9 (2024) 964–969

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Review Article

Biochemical targets of the micropeptides encoded by lncRNAs

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ARTICLE INFO

Keywords:
LncRNA
Micropeptide
Microprotein
Biochemical target

ABSTRACT

Long non-coding RNAs (lncRNAs) are a group of transcripts longer than 200 nucleotides, which play important roles in regulating various cellular activities by the action of the RNA itself. However, about 40% of lncRNAs in human cells are potentially translated into micropeptides (also referred to as microproteins) usually shorter than 100 amino acids. Thus, these lncRNAs may function by both RNAs directly and their encoded micropeptides. The micropeptides encoded by lncRNAs may regulate transcription, translation, protein phosphorylation or degradation, or subcellular membrane functions. This review attempts to summarize the biochemical targets of the micropeptides-encoded by lncRNAs, which function by both RNAs and micropeptides, and discuss their associations with various diseases and their potentials as drug targets.

1. Introduction

The human genome is remarkably transcriptionally active, with at least 87% undergoing transcription. However, only less than 2% was thought to encode proteins [1]. The RNAs that cannot encode any proteins are called non-coding RNAs (ncRNAs). In addition to well-known rRNA and tRNA, ncRNAs encompass small non-coding RNAs (sncRNAs), circular RNA (circRNA), and long non-coding RNAs (lncRNAs) with more than 200 nucleotides [2–4]. However, short open reading frames (sORFs) have been found to be generated by lncRNAs, intergenic regions, pseudogenes, circRNAs, pre-microRNA or ribosomal RNAs (rRNA) [5,6].

To date, a large number of lncRNAs have been identified by high-throughput RNA sequencing and computational analyses. LncRNAs play critical roles in a wide variety of important biological processes, and are involved in the development of many human diseases, such as cancer, inflammation, metabolic disorders and heart diseases [7–9]. LncRNAs can act as *cis*- or *trans*-regulators, directly inhibiting the expression of downstream target genes. They can also function as competitive endogenous RNAs (ceRNAs) by sponging miRNAs, thereby modulating the expression of downstream target genes (Fig. 1).

Similar to mRNAs, lncRNAs are predominantly transcribed by RNA polymerase II and are post-transcriptionally processed by splicing, capping, and polyadenylation, hinting that lncRNAs might harbor translational potentials [10]. Indeed, certain lncRNAs also possess short open reading frames (sORFs) and the potential to encode micropeptides (also referred to as microproteins) usually shorter than 100 amino acids [11]. These micropeptides actively participate in the regulation of various cellular processes by multiple mechanisms, such as regulating mRNA/protein stability and protein kinase activity. Although 40% of lncRNAs and pseudogene RNAs in human cells are potentially translated [12], this review aims to summarize the biochemical targets of the experimentally validated micropeptides encoded by lncRNAs, which function by both RNAs and micropeptides (Fig. 2), and discuss their potential implications in diseases and drug design.

2. Regulation of protein phosphorylation by micropeptides

Protein phosphorylation plays critical roles in regulating almost all cellular activities. Among the micropeptides identified so far, one of their functions is to regulate protein kinase or phosphatase activity to influence the levels of protein phosphorylation. The micropeptide ASRPS encoded by LINC00908, via its coiled coil domain, directly binds the downstream factor STAT3 and inhibits STAT3 phosphorylation. This regulatory mechanism leads to elevated levels of LINC00908. This cascade results in reduced levels of vascular endothelial growth factor

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https://doi.org/10.1016/j.ncrna.2024.04.005
Received 6 March 2024; Received in revised form 16 April 2024; Accepted 24 April 2024
Available online 25 April 2024

(VEGF), ultimately restraining the growth of Triple-negative breast cancer (TNBCs) [13]. The micropeptide CIP2A-BP, encoded by LINC00665, directly interacts with CIP2A, leading to the release of protein phosphatase 2A (PP2A), an inhibitor of the PI3K/AKT/NF-κB pathway [14]. SMIM30, encoded by LINC00998, mediates the membrane anchoring of the non-receptor tyrosine kinase SRC and then activates downstream Mitogen-activated protein kinase (MAPK) signaling pathway, thus promoting hepatocellular carcinoma (HCC) tumorigenesis [15]. SMIM26, encoded by LINC00493 that inhibits cell proliferation as a transcript [16], forms a complex with acylglycerol kinase (AGK) and the glutathione transport regulator Solute Carrier Family 25 Member 11 (SLC25A11), leading to an increase in mitochondrial-resident AGK and subsequent inhibition of AGK-mediated AKT phosphorylation [17].

It is noteworthy that the roles of these micropeptides are all different from those of their counterpart lncRNAs (Table 1). For example, the micropeptide CIP2A-BP inhibits the PI3K/AKT/NF-κB pathway by releasing PP2A [14], whereas its counterpart lncRNA LINC00665 promotes the expression of the oncogenic RNA-binding protein Lin-28 Homolog B (LIN28B) as a competitive endogenous RNA by sponging miR-379–5p [18]. LIN28B represents a potential therapeutic target for cancer treatment. Upregulation of LINC00665 expression and inhibition of miR-379-5p were observed in breast cancer compared to normal cells. The LINC00665/miR-379-5p/LIN28B axis may be a crucial player in breast cancer development. Even though the micropeptide CIP2A-BP and its encoding LINC00665 regulate different components or pathways in cellular signaling, they both promote tumorigenesis. In certain cases, micropeptides and their encoding lncRNAs may function oppositely. For example, SMIM30 activates the MAPK signaling pathway to promote HCC tumorigenesis [15], whereas LINC00998 inhibits the c-Met/AKT/mTOR signaling pathway to suppress tumorigenesis by functioning as an RNA [19]. So far, most micropeptides seem to more specifically regulate their downstream targets, whereas lncRNAs usually target multiple downstream effectors by means of RNAs directly. For example, LINC00908 that encodes the micropeptide ASRPS also functions as a competitive endogenous RNA (ceRNA) to target multiple miRNAs. Its binding to the downstream miR-483–5p elevates TSPY-Like 5 (TSPYL5) expression and impedes the progression of prostate cancer [20]. In colorectal cancer, LINC00908 sponges miR-143-3p, resulting in an increased level of the downstream target gene KLF Transcription Factor 5 (KLF5), which plays pivotal roles in proliferation and anti-apoptosis [21]. Thus, both LINC00908 and its micropeptide ASRPS emerge as pivotal players in carcinogenesis [13].

3. Regulation of mRNA and the related transcription or translation by micropeptides

N6-methyladenosine (m^6A) modification stands out as one of the most extensively studied modifications in eukaryotic RNAs. This modification is recognized by m^6A readers, which play a crucial role in determining the fate and function of mRNA [22]. LINC00266-1 encodes a micropeptide named "RNA-binding regulatory peptide" (RBRP) [23], which regulates mRNA stability by interacting with the m^6A reader IGF2BP1. This interaction promotes the IGFBP1-mediated m^6A recognition on mRNAs, such as c-Myc. As a result, the stability and levels of c-Myc mRNA are increased, ultimately promoting the occurrence of colorectal tumors. The transcript of LINC00266-1 has been implicated in the regulation of cancer development in distinct contexts. In osteosarcoma cells, LINC00266-1 expression was significantly up-regulated compared to normal tissues. LINC00266-1 positively regulates the expression of SMAD Family Member 2 (SMAD2) by acting as a sponge for miR-548c-3p [24].

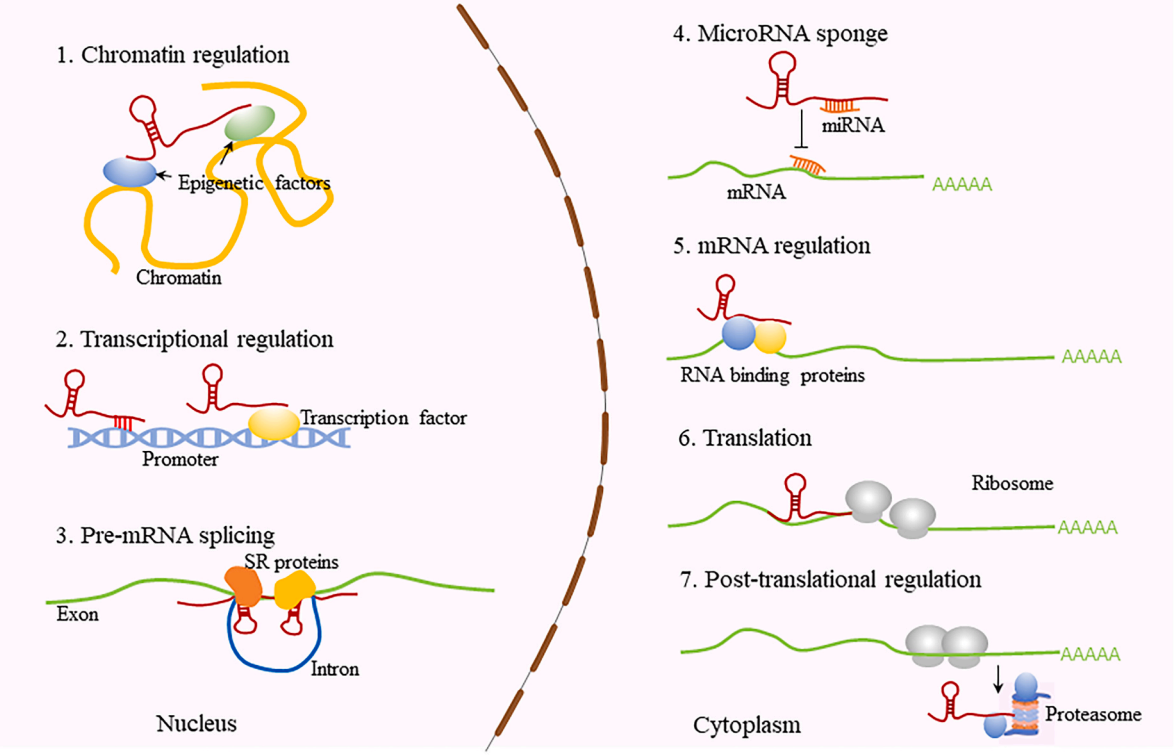

Fig. 1. Functions of lncRNAs by RNAs themselves. 1) Chromatin regulation. LncRNAs regulate chromatin conformation by recruiting epigenetic factors. **2)** Transcriptional regulation. LncRNAs modulate gene transcription through interacting with DNA sequences or binding with transcription factors on certain gene promoters. **3)** Pre-mRNA splicing. LncRNAs regulate pre-mRNA splicing by interacting with serine and arginine-rich (SR) proteins. **4)** MicroRNA sponging. LncRNA act as ceRNAs by sponging miRNAs to reduce the inhibitory effects of miRNAs on their target mRNAs. **5)** mRNA regulation. LncRNAs modulate mRNA stability through interacting with RNA binding proteins involved in mRNA degradation. **6)** Translation regulation. LncRNAs change translation of targets by regulating the association between ribosomes and certain mRNAs. **7)** Post-translational regulation. LncRNAs bind proteins directly and alter post-translational processes.

Similarly, the 87-aa micropeptide PINT87aa encoded by the lncRNA LINC-PINT interacts with the RNA polymerase II-associated factor 1 (PAF1) to inhibit the transcription of tumorigenic genes downstream of the PAF1 [25]. LINC-PINT was initially identified as a tumor suppressor in colon cancer due to its association with p53. In gastric cancer, LINC-PINT serves as an upstream inhibitor of Hypoxia Inducible Factor 1 Subunit Alpha (HIF-1α), resulting in downregulation of HIF-1α and the subsequent inhibition of gastric cancer cell proliferation [26]. Additionally, LINC-PINT plays a role in gastric cancer by recruiting Enhancer of Zeste Homolog 2 (EZH2) to the Autophagy Related 5 (ATG5) promoter. This recruitment leads to increased levels of H3K27me3, facilitating epigenetic silencing [27].

LINC01420 encodes a 7 kDa micropeptide named "Non-annotated P-body dissociating polypeptide" (NoBody) [28]. NoBody interacts with mRNA decapping proteins, promoting the removal of the 5′ cap from mRNAs. The levels of NoBody are negatively correlated with the levels of the mRNA decay-associated RNA-protein granules. LINC01420, as an RNA, inhibited cell migration in the human melanoma cell line A375 without significantly affecting cell viability [29].

LINC00689 encodes a 50-aa peptide called STORM. Phosphorylation of the translation initiation factor eIF4E induces STORM to compete with the signal recognition particle 19 kDa protein (SRP19) for 7SL RNA interaction, thereby suppressing translation [30]. LINC00689 is highly expressed in gliomas compared to normal brain tissues.s as a competing endogenous RNA (ceRNA) to sponge miR-338-3p. This action, in turn, amplifies the expression of pyruvate kinase M2 (PKM2) [31].

In summary, lncRNAs described above all encode various micropeptides that participate in transcription, modification, stability, or translation of mRNAs. In addition to encoding micropeptides, these lncRNAs also function as RNAs to regulate directly signaling pathways involved in regulation of cell proliferation or migration and cancer development (Table 1).

4. Membrane regulation by micropeptides

In addition to being present in the cytoplasm, many micropeptides are localized in membranes of various subcellular compartments [32], and are involved in metabolism, electron transfer or Ca^{2+} transport processes. LINC00961,which impairs cancer invasion and migration [33], encodes a 90-aa peptide termed “small regulatory polypeptide of amino acid response” (SPAR) [34] in the late endosome/lysosome by interacting with v-ATPase. SPAR inhibits the activation of Mechanistic Target of Rapamycin Complex 1 (mTORC1) induced by amino acid stimulation, thus restraining muscle regeneration.

LncRNA TUNAR encodes a 48-aa micropeptide BNLN, which is localized on the endoplasmic reticulum (ER) of the pancreatic β cells [35]. Interaction of BNLN with Sarcoplasmic Endoplasmic Reticulum Ca^{2+}-ATPase 3 (SERCA3) regulates endoplasmic reticulum Ca^{2+} levels in β cells, ensuring ER stability and inducing insulin secretion.

The micropeptide Mtln encoded by lncRNA LINC00116 is localized on the mitochondrial membrane and is required for oxygen consumption and lipid metabolism [36]. Mtln interacts with cytochrome *b*5 reductase (Cyb5r3) in the electron transport chain. Cyb5r3 is involved in desaturation of Δ9 fatty acid and biosynthesis of cholesterol, which is associated with the cristae structure of the mitochondrial inner membrane [36].

In addition, the 53-aa micropeptide Kastor and the 40-aa micropeptide Polluks encoded by lncRNA GM9999 are able to interact with the mitochondrial pore protein VDAC and co-localize to the outer mitochondrial membrane. These micropeptides are involved in the middle and late stages of spermatocyte development probably by regulating mitochondrial morphology [37].

LINC00948 (also known as LINC-RAM) has recently been revealed to encode a conserved 46-aa micropeptide, MLN [38]. MLN directly interacts with SERCA, the protein responsible for the reuptake of Ca^{2+} into the sarcoplasmic reticulum. This interaction leads to the inhibition of

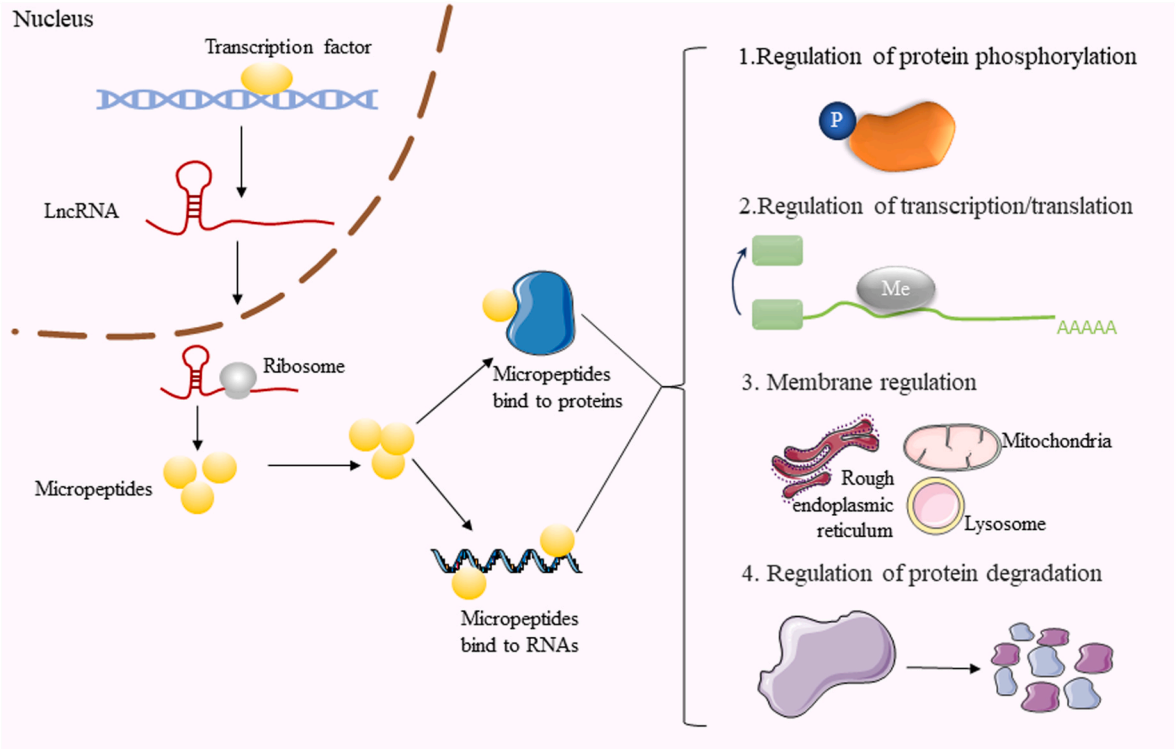

Fig. 2. Functions of lncRNA-encoded micropeptides. The micropeptides encoded by lncRNAs are involved at different levels by binding to different proteins or nucleic acids: **1)** Regulation of protein phosphorylation by interacting with kinases or binding to related proteins; **2)** Regulation of transcription by interacting with the RNA polymerase II associated factor 1 (PAF1) or translation by mRNA decapping or mRNA methylation; **3)** Regulation of mitochondria/endoplasmic reticulum and other membrane functions; **4)** Regulation of protein cleavage or degradation.

Table 1
Summary of targets of the selected bifunctional-lncRNAs.

Bifunctional-lncRNA	Functions of lncRNA	Reference	LncRNA-encoded peptides	Biochemical targets of micropeptide	Reference
LINC00908	MicroRNA sponge	20,21	ASRPS	Protein phosphorylation	13
LINC00665	MicroRNA sponge	18	CIP2A-BP	Protein phosphorylation	14
LINC00998	Post-translational regulation	19	SMIM30	Protein phosphorylation	15
LINC00493	Regulate cell proliferation	16	SMIM26	Protein phosphorylation	17
LINC-PINT	mRNA regulation/Chromatin regulation	26,27	PINT87aa	Protein phosphorylation	25
LINC00266-1	MicroRNA sponge	24	RBRP	mRNA regulation	23
LINC01420	Regulate cell proliferation	29	NoBody	mRNA regulation	28
LINC00689	MicroRNA sponge	31	STORM	Translation regulation	30
LINC00961	Regulate cell proliferation	33	SPAR	Membrane regulation	34
TUNAR	Chromatin regulation	42	BNLN	Membrane regulation	35
LINC00116	MicroRNA sponge	40	Mtln	Membrane regulation	36
LINC00948	Transcription regulation	41	MLN	Membrane regulation	37
LINC00278	Transcriptional regulation	39	YY1BM	Membrane regulation	38
HOXB-AS3	MicroRNA sponge	44	HOXB-AS3	Protein cleavage	43
TINCR	MicroRNA sponge	48,49	TUBL	Protein degradation	45–47

SERCA's pump activity, resulting in enhanced Ca^{2+} handling and improved muscle contractility.

The 21-aa micropeptide YY1BM encoded by LINC00278 plays an oncogenic role in esophageal squamous cell carcinoma (ESCC) by impeding the binding of YY1 to the membrane-bound androgen receptor (AR) and down-regulating the expression of eukaryotic elongation factor 2 kinase (eEF2K), ultimately contributing to ESCC apoptosis [39]. M^6A modification of LINC00278 and YY1BM translation can be down-regulated by cigarette smoking [39]. In addition to encoding the micropeptide YY1BM, LINC00278 directly inhibits phosphorylation of the transcription factor ETS Proto-Oncogene 1 (ETS1) and suppresses downstream Collagen Type IV Alpha 1/2 Chain (COL4A1/2) mRNA levels, thus restraining laryngeal squamous cell carcinoma (LSCC) cell proliferation, migration and invasion [40].

Taken together, these micropeptides regulate the functions of proteins on different membranes, such as endosome/lysosome, ER, sarcoplasmic reticulum and mitochondrial inner membrane. Meanwhile, their lncRNAs also function as RNAs themselves as summarized in Table 1 by serving as either a ceRNA that binds to miRNAs (e.g., LINC00116) [41], a direct regulator of transcriptional regulatory factors (e.g., LINC00948) [42] or a cascade inhibitor of WNT signaling pathway (e.g., TUNAR) [43].

5. Regulation of protein degradation by micropeptides

Micropeptides are also involved in the regulation of protein degradation/cleavage. LncRNA HOXB-AS3 encodes a 53-aa peptide, which suppresses pyruvate kinase M2 (PKM2) production and subsequent metabolic reprogramming [44]. HOXB-AS3 peptide binds to the RGG motif of hnRNP family protein hnRNP A1 and blocks hnRNP A1-dependent PKM splicing and PKM2 formation, thus suppressing cell metabolic reprogramming in colon cancer cells. Colon cancer patients with downregulated expression of HOXB-AS3 have poorer overall survival. Therefore, HOXB-AS3 functions as a switch for PKM2 splicing and cancer metabolism reprogramming. As an RNA, lncRNA HOXB-AS3 located in the cytoplasm is able to competitively bind to miR-378a-3p, thus enhancing the expression of lactate dehydrogenase (LDHA) and promoting glycolysis in epithelial ovarian cancer cells [45].

The terminal differentiation-induced ncRNA (TINCR) encodes an 87-aa micropeptide, the TINCR-encoded ubiquitin-like protein (TUBL) [46]. TUBL co-precipitates with proteasomal subunits [47]. Radiation sensitive protein 23 (RAD23) and Ubiquilin 2 (UBQLN2/DSK2) contain a Ubiquitin-associated (Uba) domain that interacts with ubiquitinated proteins in addition to a type 2 Ubiquitin-like (Ubl) domain that associates with the proteasome. Unlike RAD23 and DSK2 that facilitate the recruitment of ubiquitinated proteins to the proteasome [48], TUBL is a type 2-only Ubl protein and thus might function as a negative regulator for the interaction between authentic Ubl-Uba proteins and the proteasome [47]. As an RNA, TINCR is involved in the development of various cancers, including HCC and LSCC by competitively inhibiting related miRNAs and their downstream signaling pathways [49,50].

6. Conclusions and future perspectives

About 40% of lncRNAs in human cells are potentially translated into micropeptides [12], suggesting that these lncRNAs would have dual functions by both RNAs and micropeptides. Despite that most of them are still putative, this review has collected a part of the experimentally validated dual-functional lncRNAs and found that the roles of these micropeptides are all different from those for their counterpart lncRNAs (Fig. 2). Particularly, LINC00998 and its micropeptide SMIM30 play opposite roles in tumorigenesis. Due to their relatively small sizes, it is tempting to speculate whether their intracellular functions different from the proteins with regular sizes. Notably, biochemical targets of almost all validated micropeptides encoded by lncRNAs can be categorized into the following 4 groups: 1) regulation of protein phosphorylation; 2) regulation of transcription, modification, decapping, stability or translation of mRNA; 3) association with different membranes, such as endosome/lysosome, endoplasmic reticulum, sarcoplasmic reticulum and mitochondrial inner membrane; 4) involvement in protein degradation or cleavage (Fig. 2). With more bifunctional lncRNAs to be validated, additional biochemical targets would surely be identified. Discovery of these biochemical targets for lncRNA-encoded micropeptides should be important for understanding the pathogeneses of various diseases and designing the drugs to treat these diseases.

Micropeptides such as RBRP, Nobody, and CIP2A-BP are involved in the tumorigenesis, and the correlation with cancer prognosis has been demonstrated in a wide range of tumor cells. However, it remains unknown whether oncogenic micropeptides can be secreted into serum or whether they can enter tumor cells via transporter proteins on the cell membrane. However, the half-life of micropeptides as drugs can be prolonged by improving the affinity and specificity of micropeptides and by adopting different delivery methods [6]. Like other non-coding RNAs, off-target effects of the micropeptides-encoded lncRNAs may still occur due to the limited effective sequences and structure of these sequences of lncRNAs. Certain approaches, such as computer modeling, are still important for analyzing and avoiding the off-target effects.

Funding

This study was supported by the National Key R & D Program of China (2019YFA0802100, 2022YFC2303200), the National Science Foundation of China (32330027 and 82350006), and Jiangsu Province Funds (BK20231011).

CRediT authorship contribution statement

Bi-Ying Wang: Writing – original draft. **Qi Gao:** Writing – review & editing, Writing – original draft. **Yan Sun:** Writing – review & editing. **Xiao-Bo Qiu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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.

List of abbreviations

AKT	AKT Serine/Threonine Kinase
ATG5	Autophagy Related 5
COL4A1/COL4A2	Collagen Type IV Alpha 1 Chain/Collagen Type IV Alpha 2 Chain
DSK2(UBQLN2)	Ubiquilin 2
eIF4E	Eukaryotic Translation Initiation Factor 4E
ETS1	ETS Proto-Oncogene 1
HIF-1α	Hypoxia Inducible Factor 1 Subunit Alpha
hnRNP	Heterogeneous Nuclear Ribonucleoprotein
KLF5	KLF Transcription Factor 5
LIN28B	Lin-28 Homolog B
mTORC1	Mechanistic Target of Rapamycin Complex 1
NF-κB	Nuclear Factor Kappa B
PI3K	Phosphoinositide 3-kinase
RAD23	Radiation sensitive protein 23
SLC25A11	Solute Carrier Family 25 Member 11
SMAD2	SMAD Family Member 2
STAT3	Signal Transducer and Activator of Transcription 3
TSPYL5	TSPY Like 5

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