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# CircRNA and lncRNA-encoded peptide in diseases, an update review

Qian Yi[1†], Jianguo Feng[2*†], Weiwu Lan[3], Houyin shi[4], Wei Sun[3*] and Weichao Sun[3*]

**Abstract**

Non-coding RNAs (ncRNAs), including circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs), are unique RNA molecules widely identified in the eukaryotic genome. Their dysregulation has been discovered and played key roles in the pathogenesis of numerous diseases, including various cancers. Previously considered devoid of protein-coding ability, recent research has revealed that a small number of open reading frames (ORFs) within these ncRNAs endow them with the potential for protein coding. These ncRNAs-derived peptides or proteins have been proven to regulate various physiological and pathological processes through diverse mechanisms. Their emerging roles in disease diagnosis and targeted therapy underscore their potential utility in clinical settings. This comprehensive review aims to provide a systematic overview of proteins or peptides encoded by lncRNAs and circRNAs, elucidate their production and functional mechanisms, and explore their promising applications in cancer diagnosis, disease prediction, and targeted therapy.

**Keywords** Non-coding RNAs, Peptide encoding, Tumorigenesis, Diagnosis, Targeted therapy, Molecular mechanisms

## Introduction

Many non-coding transcripts are generated alongside the protein-coding ones during mammalian genome transcription. Non-coding transcripts, including long non-coding RNAs (lncRNAs), circular RNAs (circRNAs) and microRNAs, account for approximately 98% of the total transcripts in the human transcriptome [1]. LncRNAs are commonly defined as long RNA molecules (>200 nucleotides[nt]) that do not encode proteins. MicroRNAs are small non-coding RNAs typically 18–22 nt long, while circRNAs are characterized by a covalently closed, uninterrupted loop [2–4]. In the traditional perspective, these non-coding RNAs (ncRNAs) do not translate into proteins, they significantly regulate gene expression during physiological and developmental processes by influencing gene transcription, RNA stability, and protein function [5–8]. However, recent advancements have challenged this view.

Recently, a significant number of peptides or proteins encoded by ncRNAs have been validated. Deep

†Qian Yi and Jianguo Feng contributed equally to this work.

*Correspondence:
Jianguo Feng
fengjianguo@swmu.edu.cn
Wei Sun
414464705@qq.com
Weichao Sun
weichaosunshine@163.com
[1]Department of Physiology, School of Basic Medical Sciences, Southwest Medical University, Luzhou, Sichuan 646099, China
[2]Department of Anesthesiology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China
[3]Department of Orthopedics, Shenzhen Second People's Hospital/First Affiliated Hospital of Shenzhen University Health Science Center, Shenzhen, Guangdong 518035, China
[4]Department of Orthopedics, The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, Luzhou 646000, China

sequencing has revealed that lncRNAs harbor translatable short open reading frames (sORFs) that facilitate lncRNA translation. Extensive identification and analysis reveal that these translatable lncRNAs possess richer protein-coding related sequence features and more stable secondary structures compared to untranslatable lncRNAs [9]. It has also been proven that the pervasive translation of circular RNAs can be driven by short internal ribosome entry site (IRES)-like elements [10]. Despite using various bioinformatics tools and mass spectrometry to predict the coding potential of ncRNAs and detect their peptides, only a fraction has been extensively studied.

Significantly, these peptides have been shown to play important roles in various biological and pathological processes, including neuronal maturation, muscle regeneration, and tumorigenesis [11–13]. For example, a novel 113-amino acid protein encoded by circ-CUX1 enhances lipid metabolic reprogramming, mitochondrial activity, and the proliferation, invasion, and metastasis of neuroblastoma cells [14]. Moreover, recent research highlights the potential of circRNA- or lncRNA-encoded peptides in disease diagnosis and targeted therapies [15, 16]. Sajib et al. revealed a substantial upregulation of five lncRNA-encoded polypeptides in tumor tissues, emphasizing their potential as valuable cancer biomarkers [17]. Furthermore, Humberto et al. identified 54 unique circRNA-derived peptides in the immunopeptidome of melanoma and lung cancer samples, indicating their potential in immunotherapy [18].

This review summarizes the current research on ncRNAs-encoded peptides involved in tumorigenesis and other diseases. It further discussed their production, functions, underlying mechanisms, and potential values in cancer diagnosis, disease prediction, vaccine development, and targeted therapies. The review also addressed existing challenges and gaps in identifying and applying these peptides.

## Biogenesis of lncRNAs and circRNAs

Like typical RNA molecules, lncRNAs possess a 5′ methyl-cytosine cap and a 3′ poly(A) tail and are transcribed by RNA polymerase II through a canonical pathway [19]. Some other RNA polymerases have also been reported to be involved in the biogenesis of lncRNAs [20]. In non-canonical pathways, lncRNAs may be cleaved by ribonuclease P, or recognized by snoRNA-protein complexes and other enzymes, to produce mature 3′ ends, or capping structures, or circular structures [21]. lncRNAs can be divided into sense, antisense, bidirectional, intronic, and intergenic classes according to their distinct genomic origins [22]. Sequence motifs in cis and factors in trans coordinately, RNA binding proteins contribute to the splicing or nuclear localization of lncRNAs, leading to their categorization into nuclear, cytoplasmic, and mitochondrial lncRNAs [20, 23].

Circular RNAs are another significant class of ncRNAs, characterized by their covalently closed loop structures with neither 5' to 3' polarity nor polyadenylated tail and produced by precursor mRNA back-splicing of genes in eukaryotes [24]. The biogenesis of circRNAs involves two main steps: first, the transcription of circRNA-producing pre-mRNA by RNA polymerase II. Second, the back-splicing of this pre-mRNA by the spliceosome to form circRNAs. During back-splicing step, cis regulatory elements such as intronic complementary sequences around exons, and trans-regulatory factors, including core spliceosomal components, and other regulatory RNA binding proteins cooperated to influence the biogenesis of circRNAs [25, 26]. According to their origins, circRNAs can be divided into three types: exonic circRNAs (EcRNAs), exon-intron circRNA (ElciRNAs), and circular intronic RNAs (CiRNAs). There are two widely accepted models of circRNAs formations: lariat-driven circularization and intron-pairing-driven circularization [27]. In the lariat-driven model, a splicing donor covalently binds to a splicing acceptor, creating an exon-containing lariat, then spliced to form a circRNA. This process can result in circRNAs composed of a signal, or multiple exons, or multiple exons and introns [28, 29]. In the intron-pairing-driven model, complementary base pairing between introns mediated circularization [30, 31]. These models primarily account for the formation of EcRNAs and ElciRNAs. Moreover, the interconnections of introns cause the formation of CiRNAs after the lariat structure undergoes internal reverse splicing. Furthermore, CiRNA formation is also influenced by specific sequence elements, including a 7nt GU-rich motif near the 5′ splice site, and the 11 nt C-rich component close to the branch-point site [32].

The human genome is estimated to encode approximately 100,000 LncRNAs [33, 34]. Recent studies have identified more than 180,000 circRNAs in human transcriptomes [35, 36]. These ncRNAs are involved in both normal cellular functions and disease processes via acting as sponges of other RNAs or proteins, or encoding functional peptides.

## Mechanisms regulating ncRNA translation

ORFs are continuous nt sequences that begin with an initiation codon and end with one of the termination codons [37]. In conventional protein translation process, mRNA transcripts with a start codon and a classic ORF can be translated into functional proteins. The regulatory elements upstream of these ORFs are instrumental in controlling the translation [38, 39]. On such regulatory element is the internal ribosome entry site (IRES), which recruits ribosomes, assembles them, and directly initiates

protein translation independently of the 5′ cap [40, 41]. Another critical regulatory mechanism is N6-methyladenosine (m6A) modification, where m6A readers such as YTHDF3, recognize m6A sites on RNA molecules and promote translation of m6A-enriched gene transcripts [42]. The mechanisms governing ncRNAs translation are illustrated in Fig. 1.

### IRES-dependent ncRNAs translation

Typically, IRES elements are located in the 5′ -UTRs of their corresponding ORFs. However, recent advances in next-generation sequencing have revealed the presence of certain IRESs located between or within ORFs [43, 44]. Consequently, endogenous ncRNAs containing IRES elements can facilitate the translation of long polypeptide chains along a continuous ORF [45, 46].

The circ-EPS15 was identified as containing a spanning junction ORF driven by an IRES, leading to the production of a novel protein that modulates tumor metastasis in hepatocellular carcinoma (HCC) [47]. Similarly, circ-SHPRH contains an IRES-driven ORF that translates a functional peptide, which protects the full-length SHPRH from degradation and inhibits glioma tumorigenesis [48]. Yang et al. reported that circ-EIF6 contains a 675nt ORF with a 150-bp IRES sequence, mediating the translation of circ-EIF6 into the EIF6-224-amino acid(aa) protein [49]. Moreover, an IRES within circ-HGF, mediates the translation of its cross-junctional ORF into C-HGF, an HGF protein variant with 119amino acids in length [50]. The spanning junction ORF in circGSPT1, driven by an IRES, encodes a functional peptide named GSPT1-238aa [51]. Shan et al. reported that circ_0036176 contains an IRES element, and a 627 nt ORF, translating into a 208-aa protein [52]. In clear cell renal cell carcinoma, CircP-DHK1 contains a functional IRES, encoding the novel peptide PDHK1-241aa [53]. Furthermore, circATRNL1 contains an IRES and an ORF encoding a 131 aa protein in ovarian cancer [54].

IRES-dependent translation is not limited to circRNAs. Li et al. discovered that DNA damage provokes the association of ribosomes with the IRES region in lncRNA CTBP1-DT, eliciting the translation of a novel micro-protein [55]. And hnRNPA1 promotes the IRES-dependent translation of the long noncoding RNA-meloe in melanoma cells [56, 57]. But the current reports about IRES-dependent translation of lncRNAs are few, more studies were needed to explore their existence.

### m6A-dependent ncRNAs translation

N6-methyladenosine (m6A) methylation, is a reversible and dynamic post-transcriptional modification involving adding a methyl group to the N6 position of adenosine in mRNA [58]. This modification is regulated by three primary classes of enzymes and proteins: writers, erasers, and readers. Among these, m6A readers are RNA-binding proteins that specifically recognize and

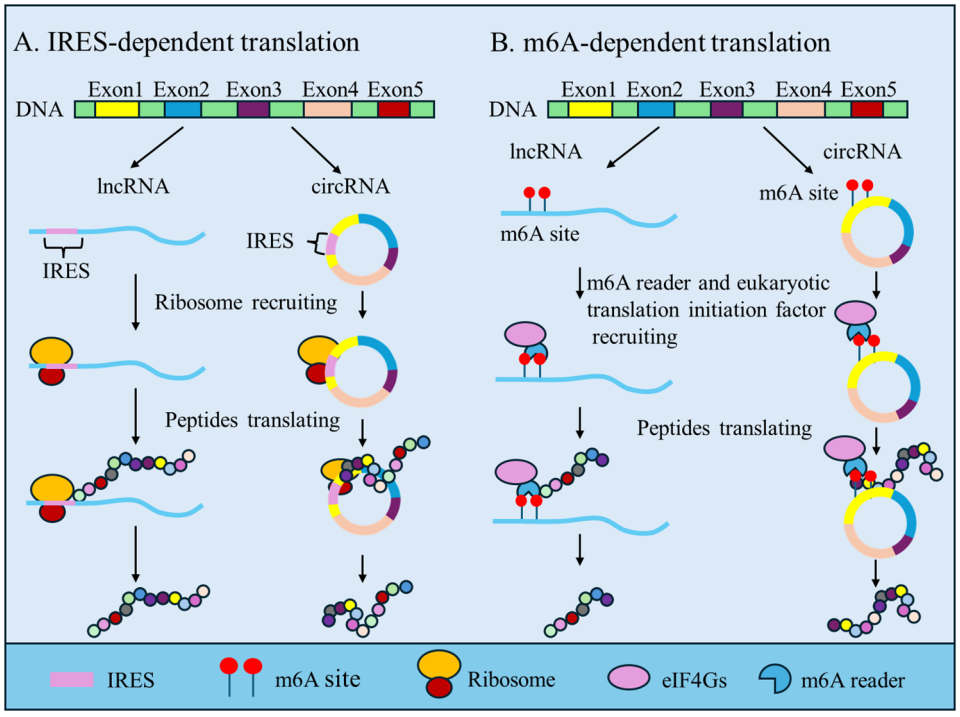


**Fig. 1** Translation mechanism of lncRNAs and circRNAs. (**A**) Certain non-coding RNAs possess open reading frames and internal ribosome entry site sequences that recruit ribosomes, induce ribosomal assembly, and directly initiate protein translation; (**B**) Some non-coding RNAs undergo m6A modification, where m6A readers recognize the site. These readers recruit eukaryotic translation initiation factors, thereby promoting peptide translation

bind to m6A-modified sites on RNA. Critical m6A readers include YT521-B homology domain family proteins, heterogeneous nuclear ribonucleoproteins, insulin-like growth factor 2 mRNA-binding proteins, and ELAVL1. As one of the most prevalent modifications of mRNA and lncRNA in mammals, m6A is integral to various aspects of RNA metabolism, including splicing, transport, localization, and degradation [59, 60]. Recent research has also highlighted the significant role of m6A in influencing the translation of ncRNAs [61]. It has been shown that m6A readers recognize m6A sites on ncRNA, recruit eukaryotic translation initiation factors, and facilitate the assembly of the initiation complex, thereby promoting the translation of ncRNAs [62, 63].

It has been discovered that circ-YAP encodes a novel truncated protein, termed YAP-220aa, relies on m6A modification, involving the m6A reader YTHDF3 and the eIF4G2 translation initiation complex [64]. Similarly, circ-MIB2 harbors m6A sites that recruit YTHDF1 and YTHDF3, facilitating its translation into the MIB2-134aa peptide [65]. In a related case, YTHDF1 and YTHDF3 bind to the m6A sites of circ-Ythdc2, promoting its translation into Ythdc2-170aa [66]. Furthermore, the m6A modification on circ-MAP3K4 is recognized by IGF2BP1, enhancing its translation into circMAP3K4-455aa [67]. Similarly, circ-MET encodes a 404-aa MET variant facilitated by the m6A reader YTHDF2 [68]. Tang et al. demonstrated that several male germ cell circ-RNAs possess large ORFs with m6A-modified start codons in their junctions, a feature recently associated with protein-coding potential [69].

The m6A modification also contributes to the translation of lncRNAs. For instance, YTHDF1 recognizes m6A modification sites on lncRNA-METTL4-2 and facilitates the translation of METTL4-2 [70]. The m6A methylation at the 1313 adenine locus of lncRNA-AFAP1-AS1 regulates the translation of the 90-aa functional peptide, ATMLP [71]. Wu et al. identified a novel micro-peptide encoded by Y-Linked LINC00278, with reduced m6A modification leading to decreased translation of YY1BM [72]. Due to the development of m6A sequencing, various lncRNAs were reported undergone m6A modification, indicating there may exist amount lncRNAs-encoded proteins.

#### Other non-coding RNAs translation mechanisms

Recently, Gunter et al. found that some circ-RNAs contain ORFs that could be translated. However, the translation of circ-ZNF609 occurs independently of m6A modification or IRESs [73]. Moreover, some lncRNAs feature capping or polyadenylated tail structures similar to traditional mRNAs [62], which may enable them to encode proteins. For instance, the Kaposi's sarcoma-associated herpesvirus produces a noncoding polyadenylated nuclear RNA that, associates with translating ribosomes to generate viral peptides [74]. Meng et al. reported that LINC00493 is recognized by the RNA-binding protein PABPC4 and subsequently transported to ribosomes for the translation of a 95-aa protein, SMIM26 [75]. Furthermore, Kyung-Won Min et al. discovered that phosphorylation of eIF4E inhibits its binding to 5′-cap, leading to a closer association of active polyribosomes with lncRNAs, such as LINC00689 and enhances their translation [76].

Ribosomal profiling has recently revealed that many lncRNAs contain small ORFs (smORFs). Patraquim et al. found that approximately 30% of lncRNAs harbor smORFs engaged by ribosomes, resulting in the regulated translation of micro-peptides [77]. Yang et al. identified three novel lincRNAs with ORFs that produce peptides conserved across mice, rats, and human [78]. Notably, LINC01013 has been reported to harbor an ORF that encodes a fibroblast-activating micro-peptide [79]. Wang et al. revealed that the ORF in lncRNA-HCP5 encodes a 132aa protein, termed HCP5-132aa, which is associated with triple-negative breast cancer [80]. Ahmed et al. described how LincRNA-2099 could be translated into a 24-aa micro-peptide featuring a non-canonical leucine start codon [81]. Moreover, Leopold Eckhart et al. identified an evolutionarily conserved ORF within the terminal differentiation-induced non-coding RNA (TINCR) and characterized peptides derived from this ORF [82].

### LncRNA-encoded peptides and diseases

The lncRNA refers to RNA sequences longer than 200-nt that do not code for proteins [2]. However, their role in pathological conditions including cancer has been documented [83, 84]. Historically, lncRNAs were considered incapable of encoding proteins and were primarily thought to function by acting as RNA sponges [85]. However, recent studies have revealed that some lncRNAs can encode peptides, including sense, antisense, intergenic, and overlapping lncRNAs. For example, a peptide encoded by lncRNA-MIR7-3HG alleviates dexamethasone-induced pancreatic β-cells dysfunction by activating the PI3K/AKT pathway [86]. The micropeptide SMIM30, derived from LINC00998, facilitates the G1/S transition of the cell cycle by enhancing SERCA activity and reducing cytosolic calcium levels [87]. Moreover, LncRNA-PSR regulates vascular remodeling by encoding a novel protein that, directly interacts with YBX1 and influencing its nuclear translocation [88]. Bernardo et al. identified 35 smORFs within 15 lncRNAs that likely encode functional microproteins in human adipose-derived stem cells [89]. Furthermore, TP53-regulated lncRNAs, TP53LC02 and TP53LC04 produce peptides that inhibit cell proliferation [90]. Conversely, a peptide encoded by lncRNA DLX6-AS1 promotes tumorigenesis by activating the Wnt/β-Catenin signaling

[91]. Additionally, lnc-NDRG1-OT1 encoded peptide enhances the malignancy of breast cancer cells [92]. These findings collectively underscore the diverse roles of lncRNAs in cancer biology, highlighting their potential as both oncogenic and tumor-suppressive factors. As research continues to uncover the functional significance of lncRNA-encoded peptides, they may emerge as valuable targets for therapeutic intervention.

### LncRNA-encoded peptides and cancer

Several lncRNAs encode peptides or proteins with oncogenic functions. For instance, a 51-aa peptide encoded by HNF4A-AS1 promotes the self-renewal and malignancy of neuroblastoma stem cells by repressing SMAD4 transactivation through eEF1A1, illustrating how lncRNA-encoded peptides can influence critical signaling pathways in cancer [93]. Similarly, LINC00511-133aa, a 133aa peptide encoded by LINC00511, regulates breast cancer cell invasion and stemness by facilitating the nuclear entry of β-catenin protein [94]. Zhang et al. identified RASON, a novel protein encoded by LINC00673, as a positive regulator of oncogenic RAS signaling. Deprivation of RASON sensitizes KRAS mutant pancreatic cancer cells and patient-derived organoids to EGFR inhibitors, highlighting its potential as a therapeutic target [95]. Furthermore, lncRNA AFAP1-AS1 encodes a conserved 90-aa peptide located in the mitochondria, facilitating the tumorigenesis of non-small cell lung cancer (NSCLC) [71]. In gastric cancer, LncAKR1C2 encodes a microprotein in lymphatic endothelial cells that enhances CPT1A expression by regulating YAP phosphorylation and contributes to gastric cancer lymph node metastasis [96]. In colorectal cancer, lncRNA BVES-AS1 encodes a 50-aa micro-peptide that enhances cell viability and promotes the migratory and invasive capacities of cancer cells by activating the SRC/mTOR signaling pathway [97]. These findings underscore the oncogenic roles of lncRNAs-derived peptides.

Conversely, some of these novel peptides have demonstrated significant tumor-suppressive effects. Li et al. reported that RNF217-AS1 translates into a short peptide in stomach cancer that inhibits THP-1 cell migration, reduces pro-inflammatory responses, inactivates the TLR4/NF-κB/STAT1 signaling pathways, and inhibits tumorigenesis [98]. In breast cancer, the polypeptide encoded by the lncRNA MAGI2-AS3 restrained the proliferation and migration of cancer cells by binding to extracellular matrix-related proteins [99]. Moreover, lncRNA AF127577.4 encodes an endogenous micro-peptide that downregulates p-ERK levels, thereby suppressing glioblastoma cell proliferation [100]. Additionally, in pulmonary adenocarcinoma, LINC00954 was confirmed to encode a novel polypeptide that enhances pemetrexed sensitivity and suppresses cancer cell growth [101]. Moreover, in esophageal squamous cell carcinoma, a peptide encoded by KDM4A-AS1 inhibits the expression of stearoyl-CoA desaturase and fatty acid synthase, increases ROS levels, and weakens cell viability and migration [102]. In renal cell carcinoma and head and neck squamous cell, lncRNA AC025154.2 encodes the micro-peptide MIAC, which inhibits tumor progression [103, 104].

Current research indicates that lncRNA-encoded peptides can exhibit either promoting or inhibiting effects on tumorigenesis. These contrasting effects may be attributed to variations in tumor types or the cellular sources of ncRNAs. Further research is needed to clarify this phenomenon, with additional reports summarized in Table 1.

### LncRNA-encoded peptides and other diseases

Endometrial receptivity (ER) is a pivotal event for successful embryo implantation. Song et al. revealed that

**Table 1** LncRNA-encoded peptide in tumorigenesis

| Cancer | LncRNAs | Peptides | Functions | Mechanisms | Reference |
|---|---|---|---|---|---|
| HCC | LINC-PINT | PINT87aa | Tumor suppressor | Induced growth inhibition, cellular senescence, and decreased mitophagy | [105] |
| HCC | lncRNA- HB-VPTPAP | - | Tumor suppressor | Modulated JAK/STAT signaling pathways | [106] |
| Breast cancer | LINC00908 | ASRPS | Tumor suppressor | Down-regulated p-STAT3, reduced expression of VEGF | [107] |
| Epithelial cancer | lncRNA- TINCR | pTINCR | Tumor suppressor | Promoted epithelial differentiation and CDC42 SUMOylation | [108] |
| Neuroblastoma | FAM201A | NBASP | Tumor suppressor | Suppresses the MAPK pathway | [103] |
| Osteosarcoma | LINC00665 | LINC00665_18aa | Tumor suppressor | Suppressed the proliferation and migration | [109] |
| Colorectal cancer | LINC00467 | ASAP | Tumor promotor | Directly modulate ATP synthase activity | [110] |
| OSCC | HOXB-AS3 | - | Tumor promotor | Directly bind with IGF2BP2 to stabilize c-Myc | [111] |
| HCC | LINC00998 | SMIM30 | Tumor promotor | Induced SRC/YES1 membrane anchoring and MAPK pathway activation | [112] |
| colorectal cancer | lncRNA LOC90024 | SRSP | Tumor promotor | Regulated mRNA splicing | [113] |

LINC00339 exhibits substantial ribosomal binding and encodes a 49-aa peptide, that regulates ER by promoting the attachment of trophoblasts to endometrial cells via the MAPK and PI3K-Akt signaling pathways [114]. Additionally, a short peptide encoded by lncRNA SNHG6 promotes cell migration and epithelial-mesenchymal transition by activating the TGF-b/SMAD signaling pathway in human endometrial cells. This peptide plays an important role in the development of endometrial stromal and epithelial cells and in various related gynecological disorders [115]. Furthermore, Helen et al. identified a micro-peptide encoded by LINC00961 that modulates endothelial cell function [116].

Retinal ischemia/reperfusion (IR) triggers inflammation and microglia activation that led to irreversible retinal damage. LncRNA 1810058I24Rik encodes a mitochondrially localized micro-peptide, Stmp1, which activates Nlrp3 inflammasome, exacerbating microglia-mediated neuroinflammation in retinal IR injury [117]. The function of Stmp1 in Nlrp3 inflammation activation has also been demonstrated in mouse macrophages [118]. Furthermore, Stmp1 is reported to promote retinal cell differentiation [119]. Another mitochondrially localized micro-peptide, encoded by LINC01013, has been identified as a novel fibroblast-activating micro-peptide that supports the activation of human cardiac atrial fibroblasts [79]. Furthermore, LINC00116 encodes a highly conserved 56-aa micro-protein, known as mitoregulin. This protein localizes to the inner mitochondrial membrane, supporting mitochondrial super-complexes and enhancing respiratory efficiency [120].

The differentiation of bone marrow mesenchymal stem cells (BMSCs) affects the progression of steroid-induced osteonecrosis of the femoral head (SONFH). Zhang et al. discovered that RIP, a 102-aa polypeptide encoded by the lncRNA DGCR5, aggravates SONFH by repressing the nuclear localization of β-catenin in BMSCs [121]. The peptide RPS4XL, encoded by lncRPS4L, regulates RPS6 phosphorylation and inhibits the proliferation of pulmonary artery smooth muscle cells under hypoxic conditions [122]. Moreover, lncRNA-MyolncR4 encodes a 56-aa micro-peptide, which fosters muscle formation and regeneration [123]. LncRNA-MFRL encodes a novel micro-peptide, MFRLP, which regulates the phenotypic transitions of vascular smooth muscle cells to attenuate arterial remodeling [124]. Sabikunnahar et al. demonstrated that activated myeloid cells release a protein encoded by lnc-U90926, which protects against endotoxic shock [125].

Moreover, lncRNA-TUNAR encodes a micro-protein that regulates neural differentiation and neurite formation by modulating calcium dynamics [126]. Similarly, Linc-mipep and Linc-wrb encode micro-peptides that regulate chromatin accessibility in vertebrate-specific neural cells, which has significant implications for neurodevelopmental disorders and diseases [127]. Excessive immune responses to self-antigens characterize autoimmune diseases. A 17-aa micro-peptide encoded by lncRNA Dleu2 alleviates autoimmunity and maintains immune homeostasis by facilitating Smad3-mediated regulatory T cell (Treg) induction [128]. Furthermore, lncRNA-LOUP contains three smORFs capable of being translated into peptides, which regulate macrophage differentiation and inflammatory signaling by suppressing the TLR4/NF-κB signaling pathway [129].

#### Mechanisms of lncRNA-encoded peptides

In mRNA metabolism, lncRNAs and circRNAs play critical roles as sponges for miRNAs and in modulating processes such as splicing, mRNA stability, and translation. They also interact with various proteins, facilitating the assembly of protein complexes, or disrupting protein-protein interactions [4, 130]. The discovery of lncRNA-encoded peptides has expanded this regulatory scope, introducing a novel layer of complexity and expanding our understanding of how mRNA and protein metabolism are regulated.

Firstly, a micro-peptide encoded by HOXB-AS3 has been shown to promote the proliferation and viability of oral squamous cell carcinoma cell lines by binding to IGF2BP2 and stabilizing c-Myc mRNA [111]. Secondly, this peptide antagonizes hnRNPA1-mediated regulation of pyruvate kinase M splicing, thereby suppressing glucose metabolism reprogramming and favoring the formation of lower PKM2 via interaction with hnRNPA1 [131]. Thirdly, lncRNA-encoded peptides have emerged as modulators of gene transcription. LncRNA-PSR encodes a protein called arteridin, which interacts with the transcription factor YBX1 and modulates its nuclear translocation, thereby affecting gene transcription [132].

Moreover, these peptides could regulate protein phosphorylation or degradation through various mechanisms. For instance, LINC00908 encodes a 60-aa polypeptide, which directly interacts with STAT3 through its coiled coil domain, downregulating its phosphorylation [107]. Similarly, lncRNA DGCR5 encodes a polypeptide, which binds to the N-terminal motif of RAC1, inactivating the RAC1/PAK1 signaling cascade and reducing Ser675 phosphorylation of b-catenin [121]. LINC00998 encodes a small peptide, termed SMIM30, involved in membrane anchoring and phosphorylation of the non-receptor tyrosine kinases SRC/YES1 [112]. Furthermore, the peptide SP0495, encoded by lncRNA KIAA0495, inhibits AKT phosphorylation/activation [133]. The peptide derived from lncRNA BVES-AS1 activates the Src/mTOR signaling pathway [97]. The Linc-PINT-encoded peptide obstructs FOXM1-mediated transcription of PHB2, leading to reduced PHB2-mediated mitophagy [105].

Moreover, specifics lncRNA-encoded peptides are localized to mitochondria and crucial for mitochondrial function. For instance, LINC00467 encodes the 94-aa micro-peptide, which enhances ATP synthase assembly by interacting with ATP5A/P5C, thereby increasing ATP synthase activity and mitochondrial oxygen consumption [110]. Additionally, the mitochondrial peptide Stmp1, encoded by lncRNA-1810058I24Rik, exacerbates microglia-mediated neuroinflammation in retinal ischemia/reperfusion injury [117].

Current research highlights the diverse and significant role of lncRNA-encoded peptides in biological processes, including mRNA stability regulation, alternative splicing, gene transcription modulation, and influencing protein phosphorylation or degradation. These highlights are illustrated in Fig. 2.

## CircRNA-encoded peptides and diseases

CircRNAs are a class of ncRNA characterized by their covalently closed, uninterrupted loops [4]. These RNAs have been confirmed to play diverse roles in biological processes by functioning as sponges for RNAs or proteins, thereby influencing gene expression, transcription, and alternative splicing [134, 135]. Beyond their known RNA-based regulatory functions, circRNAs have also been identified as capable of encoding proteins or peptides, expanding their functional repertoire. For instance, Jiang et al. identified circPPP1R12A-73aa, a novel protein encoded by circPPP1R12A, which enhances promoted tumor pathogenesis and metastasis in colon cancer [136]. This finding highlights the potential of circRNAs to contribute directly to cancer progression through peptide production. Furthermore, Zhang et al. discovered an 87-aa peptide encoded by the circular form of LINC-PINT and demonstrated its role as a tumor suppressor in GBM [137]. This underscores the importance of circRNA-derived peptides in regulating tumorigenesis. Furthermore, Zhang et al. reported that circ-FBXW7 could encode FBXW7-185aa, which shortens the half-life of c-Myc by antagonizing USP28-induced stabilization of c-Myc, illustrating how circRNAs can modulate key oncogenic pathways [138]. Moreover, Juergen et al.

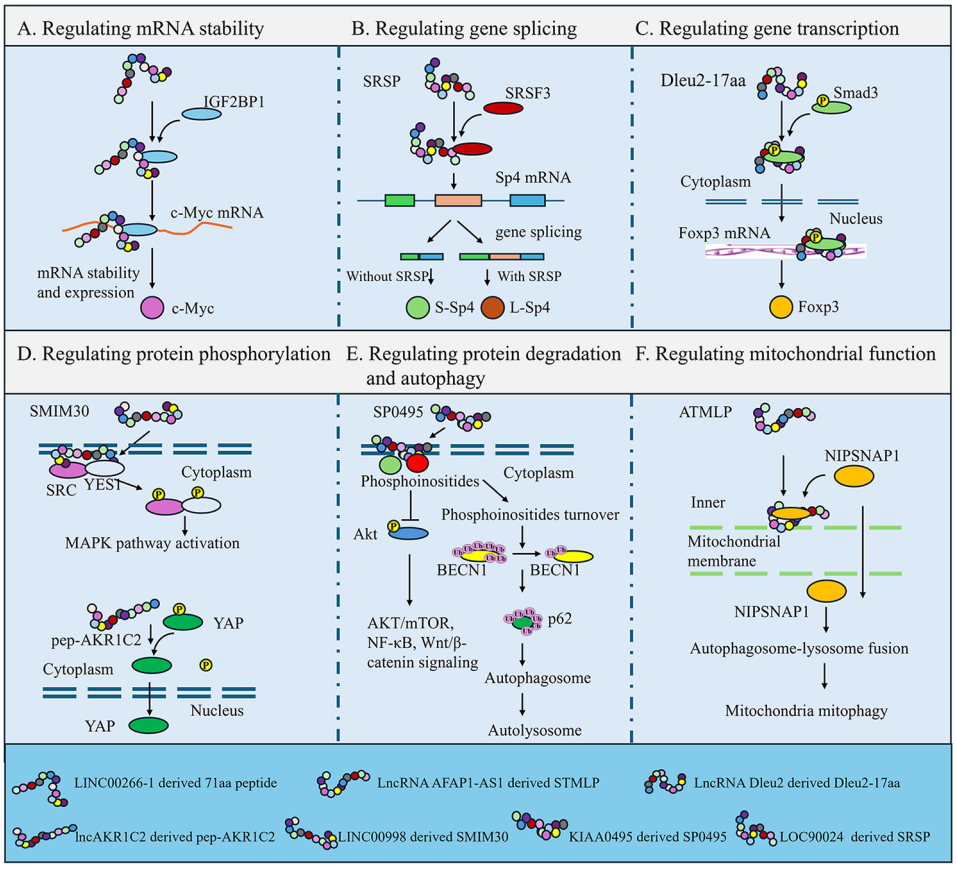


**Fig. 2** Mechanisms and functions of lncRNA-encoded peptides. (**A**) The lncRNA-encoded peptides interact with RNA binding proteins, stabilizing their target mRNA molecules; (**B**) lncRNA-encoded peptides bind target mRNAs, recruit splicing factors, and facilitate the splicing of target genes; (**C**) lncRNA-encoded peptides bind to transcription factors, promoting their nuclear translocation and regulating the RNA transcription; **D**, **E**. lncRNA-encoded peptides influence protein interactions, thereby modulating phosphorylation, ubiquitination, and degradation; **F**. The lncRNA-encoded peptides localize to mitochondria, impacting mitochondrial function

demonstrated that circAb-a is translated into a novel Ab-containing polypeptide, Ab175, in cultured cells and human brain tissue, further emphasizing the functional diversity of circRNAs [139]. Moreover, circRNA-vSP27 encodes a viral peptide, vSP27, which induces the generation of ROS, activates the NF-κB signaling pathway, and promotes the expression of antimicrobial proteins [140]. Zhu et al. revealed that circFAM188B encodes a peptide, circFAM188B-103aa, which regulates the proliferation and differentiation of skeletal muscle satellite cells, highlighting the involvement of circRNAs in muscle biology [141]. These findings collectively illustrate the multifaceted roles of circRNAs, not only as regulators of gene expression but also as sources of functional peptides that can influence various biological processes.

#### CircRNA-encoded peptides and cancer

The circRNA-encoded peptides or proteins contribute to tumorigenesis. Xiao et al. identified a novel peptide, PDHK1-241aa, from circPDHK1, which enhances cancer cell proliferation, migration, and invasion by interacting with PPP1CA. This interaction inhibits AKT dephosphorylation and activates the AKT-mTOR signaling pathway in clear cell renal cell carcinoma [53]. Jacquelyn et al. found that circHGF encodes an HGF protein, secreted by GBM cells, which promotes GBM growth by stimulating c-MET [50]. Furthermore, circTRIM1 encodes a 269aa peptide, TRIM1, contributing to chemoresistance and metastasis in TNBC [142]. Similarly, circCOL6A3_030 encodes a small peptide that promotes metastasis aiding distant lymph node metastasis in gastric cancer [143]. Circ-E-Cad encodes a protein that promotes proliferation and migration in gastric cancer through the TGF-β/Smad/C-E-Cad/PI3K/AKT pathway [144]. Furthermore, cGGNBP2 encodes a protein that enhances cell growth and metastasis in intrahepatic cholangiocarcinoma by inducing Stat3 phosphorylation [145].

Some circRNA-encoded peptides or proteins have demonstrated potential in tumor suppression. For instance, Tian et al. identified a 188-aa peptide encoded by hsa_circRNA_103820, which reduced cell viability, facilitated apoptosis, and inhibited cell migration and invasion by deactivating the AKT pathway in lung cancer [146]. Similarly, the peptide KEAP1-259aa, encoded by circKEAP1, was found to decrease cell proliferation, invasion, and tumorsphere formation in osteosarcoma cells [147]. The CM-248aa peptide, derived from circMTHFD2L, also suppressed cancer cell proliferation and metastasis, thereby inhibiting gastric cancer progression [148]. Furthermore, the SHPRH-146aa, peptide encoded by the circular form of the SHPRH gene, inhibited migration and invasion while inducing apoptosis in neuroblastoma cells [149]. Huang et al. found that circCCDC7-180aa, encoded by circCCDC7, inhibits prostate cancer progression by upregulating FLRT3 [150]. Moreover, circNFIB encodes a 56-aa protein that reduces arachidonic acid synthesis, inhibiting breast tumor growth and metastasis [151]. Another peptide, CORO1C-47aa, encoded by circ-0000437, was reported to reduce VEGF expression and act as a negative regulator of endometrial tumor angiogenesis [152].

Table 2 summarizes other circRNAs-encoded peptides involved in tumorigenesis, including tumor promoters and suppressors. These findings collectively illustrate the dual roles of circRNA-encoded peptides in cancer biology, emphasizing their potential as therapeutic targets.

#### CircRNA-encoded peptides and other diseases

Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory disorder. Ding et al. identified that circ-0008833 contains an ORF encoding a functional protein, circ-0008833-57aa. This peptide has been implicated in advancing COPD by triggering pyroptosis in bronchial epithelial cells [166]. Moreover, the circRNA-encoded peptide, CDC42-165aa, also induces pyroptosis by hyperactivating pyrin inflammasomes, thereby worsening pyroptosis in Klebsiella pneumoniae-infected alveolar macrophages [167]. Furthermore, circ-NEB, a circular RNA derived from Nebulin, encodes a 907-aa muscle-specific peptide, which enhances myoblast proliferation through its role in ubiquitination and activation of the PI3K-AKTpathway, thereby regulating cell differentiation [168]. Sun et al. identified a novel protein encoded by circ-KANSL1L that modulates skeletal myogenesis via the Akt-FoxO3 signaling axis [169]. Moreover, circ-LARP1B encodes the circ-LARP1B-243aa protein, which promotes the proliferation and migration of vascular smooth muscle cells by suppressing cAMP signaling [170]. Furthermore, circ-Tmeff1 encodes the TMEFF1-339aa protein, which contributes to the progression of muscle atrophy [171].

Xu et al. discovered a novel circRNA, circ-Ythdc2, which translates into a 170-aa polypeptide that undermines the host's antiviral innate immunity by promoting the degradation of STING [66]. Moreover, circRNA-000010 encodes a 39aa viral peptide, vSP39, which facilitates viral replication [172]. Another newly identified circular RNA-encoded protein, BIRC6-236aa, mitigates mitochondrial dysfunction induced by the transmissible gastroenteritis virus [173]. Wang et al. reported that circMORC3 encodes a novel protein, MORC3-84aa, which suppresses antiviral immunity by interacting with the host gene MORC3 [174].

It has been reported that circGlis3 contributes to b-cell dysfunction by binding to hnRNPF and encoding a protein, Glis3-348aa, which interacts with GLIS3 to inhibit its transcriptional activity [175]. Moreover, circZNF609 plays a crucial role in fibroblast activation

**Table 2** CircRNA-encoded peptide in tumorigenesis

| Cancer | circRNAs | Peptides | Functions | Mechanisms | Reference |
|---|---|---|---|---|---|
| TNBC | circCAPG | CAPG-171aa | Tumor promotor | Activating MEKK2-MEK1/2-ERK1/2 pathway | [153] |
| colorectal cancer | circINSIG1 | circINSIG1-121aa | Tumor promotor | Promoted proliferation and metastasis | [154] |
| breast cancer | circ-β-TrCP | β-TrCP-343aa | Tumor promotor | Conferred trastuzumab resistance | [155] |
| esophageal squamous cell carcinoma | circUBE4B | circUBE4B-173aa | Tumor promotor | Promoted phosphorylation of MAPK1, activated MAPK/ERK signaling pathway | [156] |
| HCC | circMRCKα | circMRCKα-227aa | Tumor promotor | Promotes glycolysis and progression | [150] |
| GBM | circ-SHPRH | SHPRH-146aa | Tumor suppressor | Suppresses tumorigenesis | [141] |
| neuroblastoma | circ-SHPRH | SHPRH-146aa | Tumor suppressor | Upregulated P21, inhibited CDKs | [157] |
| colon cancer | circFNDC3B | circFNDC3B-218aa | Tumor suppressor | Inhibits the proliferation, invasion and migration | [158] |
| HCC | circZKSCAN1 | circZKSaa | Tumor suppressor | Inhibiting the PI3K/AKT/mTOR pathway | [159] |
| NSCLC | cIGF1R | C-IGF1R | Tumor suppressor | Restricted mitophagy of drug-tolerant persister tumour cells | [160] |
| gastric cancer | circ0003692 | FNDC3B-267aa | Tumor suppressor | Inhibits metastasis via promoting proteasomal degradation of c-Myc | [161] |
| gastric cancer | circAXIN1 | AXIN1-295aa | Tumor suppressor | Activates the Wnt/β-catenin signaling pathway | [162] |
| gastric cancer | CircDIDO1 | DIDO1-529aa | Tumor suppressor | Interacte with poly ADP-ribose polymerase 1 and inhibited its activity | [163] |
| glioblastoma | circHEATR5B | HEATR5B-881aa | Tumor suppressor | Suppressed aerobic glycolysis | [164] |
| endometrial cancer | hsa-circ-0000437 | CORO1C-47aa | Tumor suppressor | Anti-angiogenic activity | [165] |

through peptide encoding [70]. Furthermore, circRsrc1 encodes a novel protein, Rsrc1-161aa, which is involved in mitochondrial ribosome assembly and translation during spermatogenesis [176]. Furthermore, the protein encoded by circ-ZNF609, ZNF609-250aa, induces acute kidney injury via activation of the AKT/mTOR-autophagy pathway [177].

#### Mechanism of circRNA-encoded peptides

Firstly, circRNA-encoded peptides have been reported to play roles in regulating gene transcription and mRNA stability. For instance, Hsa_circ_0006401 encodes a novel 198-aa peptide that regulates the stability of the host gene col6a3 mRNA, thereby promoting colorectal cancer proliferation and metastasis [178]. This peptide also enhances the metastasis of gastric cancer [143]. Huang et al. discovered that circ-ARHGAP35 encodes a peptide that interacts with the TFII-I protein, facilitating its nuclear translocation and subsequent regulation of gene transcription [179]. Moreover, the peptide derived from Circ-GGNBP2, cGGNBP2-184aa, directly interacts with STAT3, leading to STAT3 phosphorylation and nuclear translocation, which in turn regulates target gene transcription [145]. The PINT-87aa peptide directly binds to the PAF1c, enhancing its binding to gene promoters and influencing the transcriptional process [137]. Moreover, the peptide encoded by circPPP1R12A, circPPP1R12A-73aa, inhibits MST1/2-LATS1/2-induced phosphorylation and nuclear translocation of YAP, and thereby promoting the transcription of downstream oncogenes [180].

Secondly, various studies highlight the significant role of circRNA-encoded peptides in regulating protein ubiquitination and degradation. In osteosarcoma, the tumor suppressor circ-KEAP1 encodes a truncated protein, KEAP1-259aa, which binds to vimentin in the cytoplasm, promotes the proteasomal degradation of vimentin by engaging with the E3 ligase ARIH1 [147]. The peptide, CAPG-171aa, facilitates tumor growth by disrupting the interaction between serine/threonine 38 and SMAD-specific E3 ubiquitin protein ligase 1, thereby preventing MEKK2 ubiquitination and subsequent degradation [153]. The circ-EIF6 encodes a novel peptide, EIF6-224aa, which directly interacts with MYH9, reducing MYH9 degradation by inhibiting the ubiquitin-proteasome pathway [49]. Furthermore, circ-FBXW7 produces short polypeptides, circFBXW7-185aa, which interact with β-catenin, decreasing its stability of β-catenin through induced ubiquitination [181]. The circMYBL2-encoded p185 protein counteracts UCH3-mediated deubiquitination of phosphoglycerate dehydrogenase (PHGDH) by competitively binding to the C1 domain of UCHL3, leading to PHGDH degradation [182]. Lastly, PDE5A-500aa, encoded by circPDE5A, interacts with PIK3IP1 and promotes USP14-mediated deubiquitination of the K48-linked polyubiqu chain at its K198 residue, thereby attenuating the PI3K/AKT pathway [183].

Thirdly, some circRNA-encoded peptides interact with proteins or receptors on the cell membrane, thereby activating downstream pathways. For instance, TRIMI-269aa, encoded by circ-TRIMI, enhances the interaction between MARCKS and CALM2, leading

to MARCKS release from PIP2 on the cell membrane, thereby initiating the activation of the PI3K/AKT/mTOR pathway [142]. C-E-Cad, a circ-E-cadherin encoded functional peptide, binds to the EGFR CR2 domain via a unique14-aa carboxy terminus, activating EGFR signaling independently of EGF and promotes glioma stem cell tumorigenicity [184]. Additionally, circ-MET encodes a 404-aa MET variant, MET404, which interacts directly with the MET β-subunit to form a constitutively activated MET receptor, bypassing the need for HGF stimulation [68].

Notably, circRNA-encoded peptides can regulate the activity of proteins from their parent genes. Zhang et al. reported that a novel protein encoded by circ-SMO, SMO-193aa, interacts with SMO to enhance SMO cholesterol modification. This modification releases SMO from inhibition by patched transmembrane receptors, leading to SMO activation, hedgehog signaling activation, and GBM tumorigenicity [185]. Furthermore, circ-β-catenin identified as encoding a novel peptide, Circβ-catenin-370aa, which binds to GSK3β. This interaction inhibits the phosphorylation and subsequent degradation of β-catenin by GSK3β, thereby activating the β-catenin signaling pathway in NSCLC [186]. Similarly, circINSIG1 encodes a 121-aa protein, circINSIG1-121, which binds to INSIG1 and promotes its K48-linked ubiquitination [154]. Furthermore, MAPK1-109aa, encoded by circMAPK1, which competitively binds to MERK1 to inhibit the MAPK1 phosphorylation, thereby suppressing the activation of MAPK pathway [187]. The mechanisms by which circRNA-encoded peptides regulate RNA or protein metabolism are illustrated in Fig. 3.

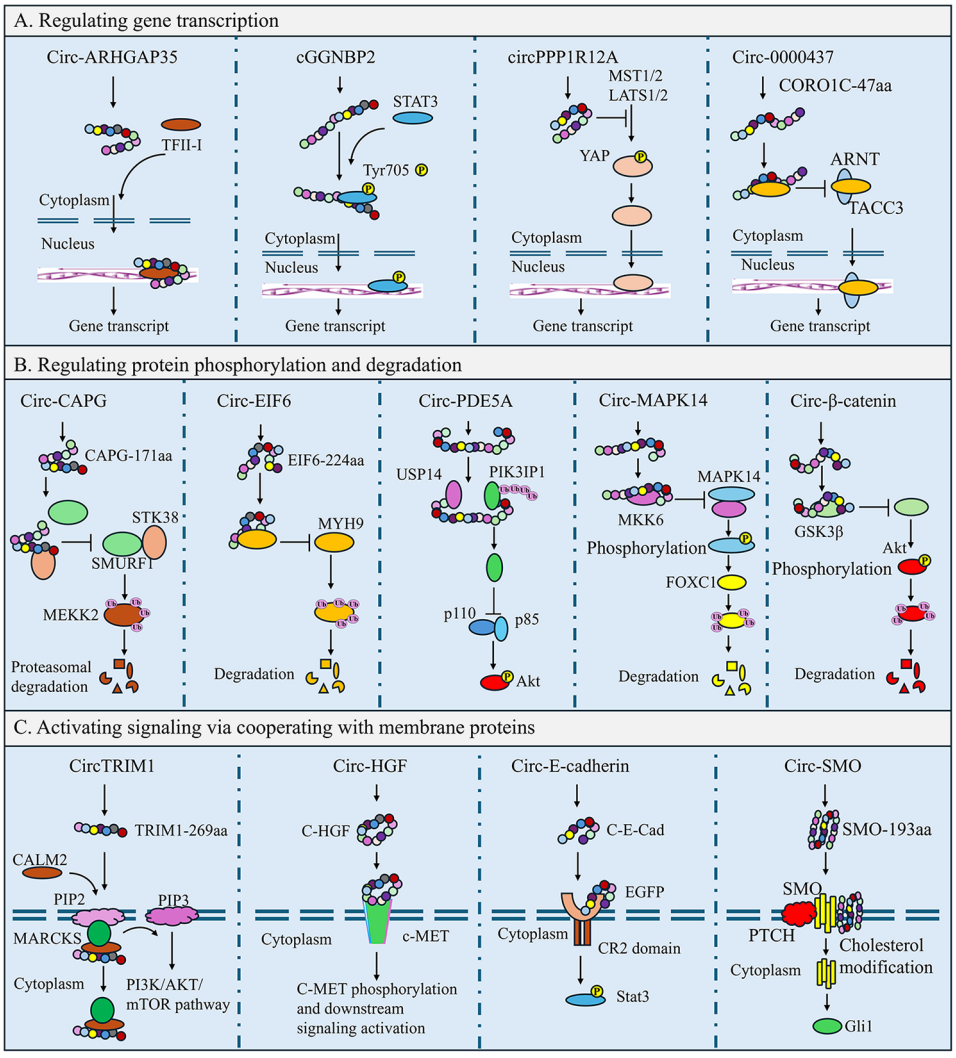


**Fig. 3** Mechanisms and functions of circRNA-encoded peptides. (**A**) The circRNA-encoded peptides regulate transcription factors activation, thereby controlling the transcription of target genes; (**B**) These circRNA-encoded peptides bind directly at or competitively inhibit target proteins, affecting their phosphorylation, ubiquitination, and degradation; (**C**) The circRNA-encoded peptides influence the function of membrane proteins (such as cytokine receptors), thereby modulating downstream signaling pathways

## Prediction and detection of ncRNA-encoded peptides

Advancements in technology have enabled several methods for predicting and validating the peptide-coding potential of ncRNAs with small ORFs. Bioinformatics tools such as RNAsamba, Small Open Reading Frame Prediction (sORFPred), and Phylogenetic Codon Substitution Frequencies (PhyloCSF) are designed to predict the coding potential of sORFs systematically [188]. Furthermore, tools such as CircCode, CircPro and Circular RNA Database (CircRNADb) compile information on IRES and ORFs of circRNAs, aiding in the prediction of their coding potential [189–191]. Moreover, tools such as IRESite (University of California, Berkeley, California, USA), DeepM6ASeq (University of California, Los Angeles, California, USA), and M6APred-EL (National Institute of Biological Sciences, Beijing, China) can predict the IRES and m6A modifications, which contribute to the IRES/m6A dependent translations of ncRNAs [192, 193]. These resources have significantly expanded our understanding of the coding potential of ncRNAs, while it's just prediction and need be proven by experimental methods.

Compared to bioinformatic tools for prediction, experimental techniques are used to detect the translation of ncRNAs. Ribosome profiling sequencing, ribosome immunoprecipitation, and ribosome affinity purification can identify ncRNAs with encoding functions [194, 195]. However, these techniques face challenges, including tissue specificity of sORFs, potential sequencing false positive, and the required massive material for sequencing. Furthermore, the coding potential of sORFs derived from ncRNAs can be evaluated by fusing them with reporter tags or incorporating recognizable epitope tags and subsequently detecting the expression levels of these tags by western blotting, fluorescence microscopy or immunofluorescence [72, 107, 196, 197]. These methods have some drawbacks, internal tag insertion may disrupt the native structure and function of micro-peptides, and the efficiency of tag insertion also requires careful consideration.

Mass spectrometry provides direct evidence of the translation of ncRNAs contain sORFs into sORF-encoded polypeptides (SEPs) [198, 199]. Combined with high-resolution liquid chromatography, it has revealed peptides encoded by ncRNAs [78, 200]. However, it struggles with identifying short-length micro-peptides and low-abundance samples [201]. Future efforts should enhance peptide separation and concentration, and integrate large-scale bioinformatics with mass spectrometry to improve the detection and validation of small peptides translated by ncRNAs.

## Future perspectives and discussions

With the unique expression patterns of these novel non-coding RNA-encoded peptides and proteins, they offer considerable potential for molecular diagnostics. For instance, Circ-MRPS35 encodes a novel 168-aa peptide significantly induced by chemotherapeutic drugs, contributing to cisplatin resistance. This peptide has the potential as a novel biomarker for diagnosing and predicting the prognosis of HCC [202]. Similarly, CM-248aa, encoded by circ-MTHFD2L, is notably downregulated in GC tissues, with its reduced expression associated with advanced tumor-node-metastasis stages and higher histopathological grades [148]. Francesca et al. identified 183 circRNAs encoding proteins with differential expression in cancer, with eight linked explicitly to prognosis in acute myeloid leukemia [203]. Moreover, the expression of the onco-peptide MBOP, encoded by LINC01234, is significantly upregulated in colorectal cancer tissues [204]. A small 130-aa protein encoded by LOC90024 is upregulated and correlates positively with malignant phenotypes and poor prognosis in patients with colorectal cancer [113]. Furthermore, the downregulation of CIP2A-BP, a peptide encoded by LINC00665, is significantly associated with metastasis and poor overall survival in TNBC [205]. However, the use of ncRNAs encoded peptides for disease diagnosis is limited by challenges such as the difficulty of tissue acquisition and the rapid degradation of these peptides [10]. Interestingly, Yang et al. observed that the expression profile of lncRNA-encoded microproteins in extracellular vesicles from patients with glioma differs from that in healthy donors [206]. Therefore, future research should explore the ncRNAs-encoded peptides in various biofluids, such as urine and blood.

Furthermore, recent studies highlighted the therapeutic potential of ncRNA-derived peptides or proteins. While mRNA therapy is already established for various diseases, emerging research indicates that circRNAs with stable RNA structures can encode proteins, thereby expanding the scope of mRNA therapy [207]. A novel circ-MIB2-encoded peptide significantly reduced the degradation of TRAF6 by its host gene MIB2, thereby inducing the innate immune response [65]. Peptides derived from lncRNAs have demonstrated the ability to provoke a potent antigen-specific CD8 T lymphocyte response, leading to significant delays in tumor growth and holding potential as cancer vaccines [208]. Specifically, a peptide encoded by the lncRNA-PVT1 was found to be highly enriched in multiple colorectal cancer tissues. It could be recognized by CD8+tumor-infiltrating lymphocytes and peripheral blood mononuclear cells from patients, suggesting its potential for immune therapy [209]. Furthermore, a short peptide, pep-AP, encoded by lnc-AP, sensitizes colorectal cancer cells to Oxaliplatin [210].

Therefore, developing precise tools that specifically overexpress tumor-suppressing ncRNAs holds great promise for gene therapy applications.

Antisense oligonucleotides (ASOs) are short nucleic acids designed to bind to specific RNA sequences, such as the back-splice junctions of circRNAs, leading to their degradation through RNase H-mediated cleavage. Similar outcomes can be achieved using RNA interference (RNAi) strategies [211, 212]. Significantly, ASOs can target disease-associated transcripts transcribed by host genes if the circRNA-coded peptides prove beneficial, as reported by Zhang et al. [137]. Besides RNAi strategies and ASOs, Li et al. demonstrated that the RNA-directed CRISPR-Cas13 system exhibits exceptional efficiency and specificity in targeting circRNAs and lncRNAs [213, 214]. For instance, by using guide RNAs that target sequences spanning distinctive back-splicing junction sites, the CRISPR-Cas13 system can effectively discriminates circRNAs from mRNAs and degrade circRNAs [213]. The advancement of such innovative tools is vital for developing effective treatments for diseases-associated with peptides or RNAs though further research is needed.

Some findings present conflicting results. For instance, Xu et al. reported that the peptide CIP2A-BP, encoded by LINC00665, markedly increased the proliferation, invasion, and migration of HCC cells [215]. Conversely, Zhou et al. found that the same micro-peptide reduced lung metastases and inhibited the progression of TNBC [205]. Moreover, a short 18-aa peptide derived from LINC00665 was reported to suppress the proliferation and migration of osteosarcoma cells [109]. Furthermore, the micro-peptide encoded by HOXB-AS3 acts as a tumor promoter in oral squamous cell carcinoma [111], it functions as a tumor suppressor in colon cancer [131]. Although many ncRNA-encoded peptides have demonstrated tumor-suppressing properties, numerous questions remain unresolved before clinical applications can be realized. Whether these cancer-suppressive micro-peptides can be easily mass-produced in vitro, or effectively target tumor cells following injection remains uncertain. Future research should focus on understanding the mechanisms governing their expression and elucidating how they suppress tumors.

In addition, research on peptides encoded by ncRNAs is still in its early stages and presents several challenges. Firstly, while many ncRNAs are predicted to encode short peptides, only a few have been experimentally validated. Moreover, the mechanisms ncRNA translation are still insufficient and not been well illustrated and require further investigation. It is essential to clarify how these ncRNA-encoded peptides function and are internalized by the cells. Extracellular vesicles may serve as an effective delivery system for these peptides due to their low immunogenicity and ease of cellular absorption [216]. Lastly, some studies report contrasting results regarding the tissue- or disease-specific effects of these peptides, necessitating further research.

## Conclusion

In summary, this review provides a thorough overview of the current knowledge regarding proteins encoded by lncRNAs and circRNAs in tumorigenesis and other diseases. It examines their production mechanisms, focusing on IRES-ORFs and m6A-ORFs dependent manner, and introduces the prediction and identification of peptides derived from these ncRNAs. This study discusses their varied functions in tumorigenesis, summarizes their roles in regulating RNA and protein metabolism, and highlights their potential for cancer diagnosis, disease prediction, and targeted therapy. This review aims to offer new insights and perspectives to advance research in this field.

### Abbreviations

| | |
|---|---|
| ncRNAs | Non-coding RNAs |
| ORFs | Open reading frames |
| lncRNAs | Long non-coding RNA |
| circRNAs | Circular RNA |
| sORFs | Short open reading frames |
| MALAT1 | Metastasis-Associated Lung Adenocarcinoma Transcript 1 |
| HLA | Human leukocyte antigen |
| IRES | Internal ribosome entry site |
| m6A | N6-methyladenosine |
| hnRNPs | Heterogeneous nuclear ribonucleoproteins |
| IGF2BPs | Insulin-like growth factor 2 mRNA-binding proteins |
| smORFs | Small open reading frames |
| TNBC | Triple-negative breast cancer |
| TINCR | Terminal differentiation-induced non-coding RNA |
| NSCLC | Non-small cell lung cancer |
| GBM | Glioblastoma |
| ESCC | Esophageal squamous cell carcinoma |
| HNSCC | Head and neck squamous cell carcinoma |
| ER | Endometrial receptivity |
| IR | Ischemia/reperfusion |
| Mtln | Mitoregulin |
| BMSCs | Bone marrow mesenchymal stem cells |
| SONFH | Steroid-induced osteonecrosis of the femoral head |
| PKM | Pyruvate kinase M |
| CCD | Coiled coil domain |
| COPD | Chronic obstructive pulmonary disease |
| STK38 | Serine/threonine 38 |
| SMURF1 | SMAD-specific E3 ubiquitin protein ligase 1 |
| PHGDH | Phosphoglycerate dehydrogenase |
| EVs | Extracellular vesicles |
| AML | Acute myeloid leukemia |

### Author contributions

Q. Y. and WW. L. performed the literature search; Q. Y. and WC. S. prepared the first draft of the manuscript; WC. S. wrote and edited the manuscript; JG. F. and HY. S. draw the figures; W. S. polished the manuscript. All authors reviewed the manuscript.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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**References**

1. Inzulza-Tapia A, Alarcón M. Role of non-coding RNA of human platelet in Cardiovascular Disease. Curr Med Chem. 2022;29(19):3420–44.
2. Huang Y, Yi Q, Feng J, et al. The role of lincRNA-p21 in regulating the biology of cancer cells. Hum Cell. 2022;35(6):1640–9.
3. Yi Q, Xie W, Sun W, et al. A concise review of MicroRNA-383: exploring the insights of its function in Tumorigenesis. J Cancer. 2022;13(1):313–24.
4. Yi Q, Yue J, Liu Y, et al. Recent advances of exosomal circRNAs in cancer and their potential clinical applications. J Transl Med. 2023;21(1):516.
5. Ali Syeda Z, Langden SSS, Munkhzul C et al. Regulatory mechanism of MicroRNA expression in Cancer. Int J Mol Sci, 2020. 21(5).
6. Hansen TB, Jensen TI, Clausen BH, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495(7441):384–8.
7. Xu L, Feng X, Hao X, et al. CircSETD3 (Hsa_circ_0000567) acts as a sponge for microRNA-421 inhibiting hepatocellular carcinoma growth. J Exp Clin Cancer Res. 2019;38(1):98.
8. Xue ST, Zheng B, Cao SQ, et al. Long non-coding RNA LINC00680 functions as a ceRNA to promote esophageal squamous cell carcinoma progression through the miR-423-5p/PAK6 axis. Mol Cancer. 2022;21(1):69.
9. Zhang M, Zhao J, Wu J, et al. In-depth characterization and identification of translatable lncRNAs. Comput Biol Med. 2023;164:107243.
10. Fan X, Yang Y, Chen C, et al. Pervasive translation of circular RNAs driven by short IRES-like elements. Nat Commun. 2022;13(1):3751.
11. Xiao W, Halabi R, Lin CH, et al. The lncRNA Malat1 is trafficked to the cytoplasm as a localized mRNA encoding a small peptide in neurons. Genes Dev. 2024;38(7–8):294–307.
12. Matsumoto A, Clohessy JG, Pandolfi PP. SPAR, a lncRNA encoded mTORC1 inhibitor. Cell Cycle. 2017;16(9):815–6.
13. Matsumoto A, Pasut A, Matsumoto M, et al. mTORC1 and muscle regeneration are regulated by the LINC00961-encoded SPAR polypeptide. Nature. 2017;541(7636):228–32.
14. Yang F, Hu A, Guo Y, et al. 113 isoform encoded by CUX1 circular RNA drives tumor progression via facilitating ZRF1/BRD4 transactivation. Mol Cancer. 2021;20(1):123.
15. Zhu S, Wang JZ, Chen D, et al. An oncopeptide regulates m(6)a recognition by the m(6)a reader IGF2BP1 and tumorigenesis. Nat Commun. 2020;11(1):1685.
16. Huang D, Zhu X, Ye S, et al. Tumour circular RNAs elicit anti-tumour immunity by encoding cryptic peptides. Nature. 2024;625(7995):593–602.
17. Chakraborty S, Andrieux G, Hasan AMM, et al. Harnessing the tissue and plasma lncRNA-peptidome to discover peptide-based cancer biomarkers. Sci Rep. 2019;9(1):12322.
18. Ferreira HJ, Stevenson BJ, Pak H, et al. Immunopeptidomics-based identification of naturally presented non-canonical circRNA-derived peptides. Nat Commun. 2024;15(1):2357.
19. Zhang X, Hong R, Chen W, et al. The role of long noncoding RNA in major human disease. Bioorg Chem. 2019;92:103214.
20. Statello L, Guo CJ, Chen LL, et al. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021;22(2):96–118.
21. Wu H, Yang L, Chen LL. The diversity of long noncoding RNAs and their generation. Trends Genet. 2017;33(8):540–52.
22. Liu Y, Ding W, Yu W, et al. Long non-coding RNAs: Biogenesis, functions, and clinical significance in gastric cancer. Mol Ther Oncolytics. 2021;23:458–76.
23. Alessio E, Bonadio RS, Buson L et al. A single cell but many different transcripts: a journey into the World of Long non-coding RNAs. Int J Mol Sci, 2020. 21(1).
24. Li X, Yang L, Chen LL. The Biogenesis, functions, and challenges of Circular RNAs. Mol Cell. 2018;71(3):428–42.
25. Ma S, Kong S, Wang F, et al. CircRNAs: biogenesis, functions, and role in drug-resistant tumours. Mol Cancer. 2020;19(1):119.
26. Shan C, Zhang Y, Hao X, et al. Biogenesis, functions and clinical significance of circRNAs in gastric cancer. Mol Cancer. 2019;18(1):136.
27. Jeck WR, Sorrentino JA, Wang K, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA. 2013;19(2):141–57.
28. Memczak S, Jens M, Elefsinioti A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013;495(7441):333–8.
29. Li Z, Huang C, Bao C, et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol. 2015;22(3):256–64.
30. Liu CX, Li X, Nan F, et al. Structure and degradation of circular RNAs regulate PKR activation in Innate Immunity. Cell. 2019;177(4):865–e88021.
31. Tang L, Jiang B, Zhu H, et al. The Biogenesis and functions of circRNAs and their roles in breast Cancer. Front Oncol. 2021;11:605988.
32. Zhang Y, Zhang XO, Chen T, et al. Circular intronic long noncoding RNAs. Mol Cell. 2013;51(6):792–806.
33. Uszczynska-Ratajczak B, Lagarde J, Frankish A, et al. Towards a complete map of the human long non-coding RNA transcriptome. Nat Rev Genet. 2018;19(9):535–48.
34. Fang S, Zhang L, Guo J, et al. NONCODEV5: a comprehensive annotation database for long non-coding RNAs. Nucleic Acids Res. 2018;46(D1):D308–14.
35. Dong R, Ma XK, Li GW, et al. CIRCpedia v2: an updated database for Comprehensive Circular RNA annotation and expression comparison. Genomics Proteom Bioinf. 2018;16(4):226–33.
36. Arnaiz E, Sole C, Manterola L, et al. CircRNAs and cancer: biomarkers and master regulators. Semin Cancer Biol. 2019;58:90–9.
37. Mo Y, Wang Y, Xiong F, et al. Proteomic analysis of the molecular mechanism of Lovastatin inhibiting the growth of Nasopharyngeal Carcinoma Cells. J Cancer. 2019;10(10):2342–9.
38. Jackson R, Kroehling L, Khitun A, et al. The translation of non-canonical open reading frames controls mucosal immunity. Nature. 2018;564(7736):434–8.
39. Hinnebusch AG, Ivanov IP, Sonenberg N. Translational control by 5′-untranslated regions of eukaryotic mRNAs. Science. 2016;352(6292):1413–6.
40. King HA, Cobbold LC, Willis AE. The role of IRES trans-acting factors in regulating translation initiation. Biochem Soc Trans. 2010;38(6):1581–6.
41. Stoneley M, Willis AE. Cellular internal ribosome entry segments: structures, trans-acting factors and regulation of gene expression. Oncogene. 2004;23(18):3200–7.
42. Chang G, Shi L, Ye Y, et al. YTHDF3 induces the translation of m(6)A-Enriched gene transcripts to promote breast Cancer brain metastasis. Cancer Cell. 2020;38(6):857–e8717.
43. Plaza S, Menschaert G, Payre F. Search of lost small peptides. Annu Rev Cell Dev Biol. 2017;33:391–416.
44. Wu Y, Wei F, Tang L, et al. Herpesvirus acts with the cytoskeleton and promotes cancer progression. J Cancer. 2019;10(10):2185–93.
45. Dudekula DB, Panda AC, Grammatikakis I, et al. CircInteractome: a web tool for exploring circular RNAs and their interacting proteins and microRNAs. RNA Biol. 2016;13(1):34–42.
46. Meganck RM, Borchardt EK, Castellanos Rivera RM, et al. Tissue-dependent expression and translation of circular RNAs with recombinant AAV vectors in vivo. Mol Ther Nucleic Acids. 2018;13:89–98.
47. Jiang B, Tian M, Li G, et al. circEPS15 overexpression in Hepatocellular Carcinoma modulates Tumor Invasion and Migration. Front Genet. 2022;13:804848.
48. Zhang M, Huang N, Yang X, et al. A novel protein encoded by the circular form of the SHPRH gene suppresses glioma tumorigenesis. Oncogene. 2018;37(13):1805–14.
49. Li Y, Wang Z, Su P, et al. circ-EIF6 encodes EIF6-224aa to promote TNBC progression via stabilizing MYH9 and activating the Wnt/beta-catenin pathway. Mol Ther. 2022;30(1):415–30.
50. Saunders JT, Kumar S, Benavides-Serrato A, et al. Translation of circHGF RNA encodes an HGF protein variant promoting glioblastoma growth through stimulation of c-MET. J Neurooncol. 2023;163(1):207–18.

51. Hu F, Peng Y, Chang S, et al. Vimentin binds to a novel tumor suppressor protein, GSPT1-238aa, encoded by circGSPT1 with a selective encoding priority to halt autophagy in gastric carcinoma. Cancer Lett. 2022;545:215826.
52. Guo J, Chen LW, Huang ZQ, et al. Suppression of the Inhibitory Effect of circ_0036176-Translated Myo9a-208 on Cardiac Fibroblast Proliferation by miR-218-5p. J Cardiovasc Transl Res. 2022;15(3):548–59.
53. Huang B, Ren J, Ma Q, et al. A novel peptide PDHK1-241aa encoded by circPDHK1 promotes ccRCC progression via interacting with PPP1CA to inhibit AKT dephosphorylation and activate the AKT-mTOR signaling pathway. Mol Cancer. 2024;23(1):34.
54. Lyu M, Li X, Shen Y, et al. CircATRNL1 and circZNF608 inhibit ovarian Cancer by sequestering mir-152-5p and encoding protein. Front Genet. 2022;13:784089.
55. Yu R, Hu Y, Zhang S, et al. LncRNA CTBP1-DT-encoded microprotein DDUP sustains DNA damage response signalling to trigger dual DNA repair mechanisms. Nucleic Acids Res. 2022;50(14):8060–79.
56. Charpentier M, Croyal M, Carbonnelle D, et al. IRES-dependent translation of the long non coding RNA meloe in melanoma cells produces the most immunogenic MELOE antigens. Oncotarget. 2016;7(37):59704–13.
57. Charpentier M, Dupré E, Fortun A, et al. hnRNP-A1 binds to the IRES of MELOE-1 antigen to promote MELOE-1 translation in stressed melanoma cells. Mol Oncol. 2022;16(3):594–606.
58. Liang J, Yi Q, Liu Y, et al. Recent advances of m6A methylation in skeletal system disease. J Transl Med. 2024;22(1):153.
59. An Y, Duan H. The role of m6A RNA methylation in cancer metabolism. Mol Cancer. 2022;21(1):14.
60. Zhang Q, Xu K. The role of regulators of RNA m(6)a methylation in lung cancer. Genes Dis. 2023;10(2):495–504.
61. Meyer KD, Patil DP, Zhou J, et al. 5′UTR m(6)a promotes Cap-Independent translation. Cell. 2015;163(4):999–1010.
62. Yang Y, Fan X, Mao M, et al. Extensive translation of circular RNAs driven by N(6)-methyladenosine. Cell Res. 2017;27(5):626–41.
63. Shi H, Wang X, Lu Z, et al. YTHDF3 facilitates translation and decay of N(6)-methyladenosine-modified RNA. Cell Res. 2017;27(3):315–28.
64. Zeng K, Peng J, Xing Y, et al. A positive feedback circuit driven by m(6)A-modified circular RNA facilitates colorectal cancer liver metastasis. Mol Cancer. 2023;22(1):202.
65. Zheng W, Wang L, Geng S, et al. CircMIB2 therapy can effectively treat pathogenic infection by encoding a novel protein. Cell Death Dis. 2023;14(8):578.
66. Zheng W, Wang L, Geng S, et al. CircYthdc2 generates polypeptides through two translation strategies to facilitate virus escape. Cell Mol Life Sci. 2024;81(1):91.
67. Duan JL, Chen W, Xie JJ, et al. A novel peptide encoded by N6-methyladenosine modified circMAP3K4 prevents apoptosis in hepatocellular carcinoma. Mol Cancer. 2022;21(1):93.
68. Zhong J, Wu X, Gao Y, et al. Circular RNA encoded MET variant promotes glioblastoma tumorigenesis. Nat Commun. 2023;14(1):4467.
69. Tang C, Xie Y, Yu T, et al. M(6)A-dependent biogenesis of circular RNAs in male germ cells. Cell Res. 2020;30(3):211–28.
70. Shen G, Li F, Wang Y, et al. New insights on the interaction between m(6)a modification and non-coding RNA in cervical squamous cell carcinoma. World J Surg Oncol. 2023;21(1):25.
71. Pei H, Dai Y, Yu Y, et al. The Tumorigenic Effect of lncRNA AFAP1-AS1 is mediated by translated peptide ATMLP under the control of m(6) a methylation. Adv Sci (Weinh). 2023;10(13):e2300314.
72. Wu S, Zhang L, Deng J, et al. A Novel Micropeptide encoded by Y-Linked LINC00278 links cigarette smoking and AR Signaling in male esophageal squamous cell carcinoma. Cancer Res. 2020;80(13):2790–803.
73. Ho-Xuan H, Glažar P, Latini C, et al. Comprehensive analysis of translation from overexpressed circular RNAs reveals pervasive translation from linear transcripts. Nucleic Acids Res. 2020;48(18):10368–82.
74. Conrad NK. New insights into the expression and functions of the Kaposi's sarcoma-associated herpesvirus long noncoding PAN RNA. Virus Res. 2016;212:53–63.
75. Meng K, Lu S, Li YY, et al. LINC00493-encoded microprotein SMIM26 exerts anti-metastatic activity in renal cell carcinoma. EMBO Rep. 2023;24(6):e56282.
76. Min KW, Davila S, Zealy RW, et al. eIF4E phosphorylation by MST1 reduces translation of a subset of mRNAs, but increases lncRNA translation. Biochim Biophys Acta Gene Regul Mech. 2017;1860(7):761–72.
77. Patraquim P, Magny EG, Pueyo JI, et al. Translation and natural selection of micropeptides from long non-canonical RNAs. Nat Commun. 2022;13(1):6515.
78. Flower CT, Chen L, Jung HJ, et al. An integrative proteogenomics approach reveals peptides encoded by annotated lincRNA in the mouse kidney inner medulla. Physiol Genomics. 2020;52(10):485–91.
79. Quaife NM, Chothani S, Schulz JF, et al. LINC01013 is a determinant of fibroblast activation and encodes a Novel fibroblast-activating Micropeptide. J Cardiovasc Transl Res. 2023;16(1):77–85.
80. Tong X, Yu Z, Xing J et al. LncRNA HCP5-Encoded protein regulates ferroptosis to promote the progression of Triple-negative breast Cancer. Cancers (Basel), 2023. 15(6).
81. Ibrahim AGE, Ciullo A, Yamaguchi S et al. A novel micropeptide, Slitharin, exerts cardioprotective effects in myocardial infarction. Proteom Clin Appl, 2024: p. e2300128.
82. Eckhart L, Lachner J, Tschachler E, et al. TINCR is not a non-coding RNA but encodes a protein component of cornified epidermal keratinocytes. Exp Dermatol. 2020;29(4):376–9.
83. Song W, Xie J, Li J, et al. The emerging roles of long noncoding RNAs in bone homeostasis and their potential application in bone-related diseases. DNA Cell Biol. 2020;39(6):926–37.
84. Bhan A, Soleimani M, Mandal SS. Long noncoding RNA and Cancer: a New Paradigm. Cancer Res. 2017;77(15):3965–81.
85. Zhou Y, Shao Y, Hu W et al. A novel long noncoding RNA SP100-AS1 induces radioresistance of colorectal cancer via sponging miR-622 and stabilizing ATG3. Cell Death Differ, 2023. 30(1): pp. 111–124.
86. Mao X, Zhou J, Kong L, et al. A peptide encoded by lncRNA MIR7-3 host gene (MIR7-3HG) alleviates dexamethasone-induced dysfunction in pancreatic β-cells through the PI3K/AKT signaling pathway. Biochem Biophys Res Commun. 2023;647:62–71.
87. Yang JE, Zhong WJ, Li JF, et al. LINC00998-encoded micropeptide SMIM30 promotes the G1/S transition of cell cycle by regulating cytosolic calcium level. Mol Oncol. 2023;17(5):901–16.
88. Yu J, Wang W, Yang J, et al. LncRNA PSR regulates vascular remodeling through encoding a Novel protein arteridin. Circ Res. 2022;131(9):768–87.
89. Bonilauri B, Holetz FB, Dallagiovanna B. Long non-coding RNAs Associated with ribosomes in Human adipose-derived stem cells: from RNAs to Microproteins. Biomolecules, 2021. 11(11).
90. Xu W, Liu C, Deng B, et al. TP53-inducible putative long noncoding RNAs encode functional polypeptides that suppress cell proliferation. Genome Res. 2022;32(6):1026–41.
91. Xu X, Zhang Y, Wang M, et al. A peptide encoded by a long non-coding RNA DLX6-AS1 facilitates cell proliferation, Migration, and Invasion by activating the wnt/β-Catenin signaling pathway in Non-small-cell Lung Cancer Cell. Crit Rev Eukaryot Gene Expr. 2022;32(8):43–53.
92. Chao HH, Luo JL, Hsu MH, et al. Regulatory mechanisms and function of hypoxia-induced long noncoding RNA NDRG1-OT1 in breast cancer cells. Cell Death Dis. 2022;13(9):807.
93. Song H, Wang J, Wang X, et al. HNF4A-AS1-encoded small peptide promotes self-renewal and aggressiveness of neuroblastoma stem cells via eEF1A1-repressed SMAD4 transactivation. Oncogene. 2022;41(17):2505–19.
94. Tan Z, Zhao L, Huang S, et al. Small peptide LINC00511-133aa encoded by LINC00511 regulates breast cancer cell invasion and stemness through the Wnt/β-catenin pathway. Mol Cell Probes. 2023;69:101913.
95. Cheng R, Li F, Zhang M, et al. A novel protein RASON encoded by a lncRNA controls oncogenic RAS signaling in KRAS mutant cancers. Cell Res. 2023;33(1):30–45.
96. Zhu KG, Yang J, Zhu Y, et al. The microprotein encoded by exosomal lncAKR1C2 promotes gastric cancer lymph node metastasis by regulating fatty acid metabolism. Cell Death Dis. 2023;14(10):708.
97. Zheng W, Guo Y, Zhang G, et al. Peptide encoded by lncRNA BVES-AS1 promotes cell viability, migration, and invasion in colorectal cancer cells via the SRC/mTOR signaling pathway. PLoS ONE. 2023;18(6):e0287133.
98. Ma Q, Ma F, Zhang B, et al. The short peptide encoded by long non-coding RNA RNF217-AS1 inhibits stomach cancer tumorigenesis, macrophage recruitment, and pro-inflammatory responses. Amino Acids. 2024;56(1):45.
99. Zhang Z, Yi Y, Wang Z, et al. LncRNA MAGI2-AS3-Encoded polypeptide restrains the Proliferation and Migration of breast Cancer cells. Mol Biotechnol. 2024;66(6):1409–23.
100. Du B, Zhang Z, Jia L, et al. Micropeptide AF127577.4-ORF hidden in a lncRNA diminishes glioblastoma cell proliferation via the modulation of ERK2/METTL3 interaction. Sci Rep. 2024;14(1):12090.
101. Han X, Chen L, Sun P, et al. A novel lncRNA-hidden polypeptide regulates malignant phenotypes and pemetrexed sensitivity in A549 pulmonary adenocarcinoma cells. Amino Acids. 2024;56(1):15.

102. Zhou B, Wu Y, Cheng P, et al. Long noncoding RNAs with peptide-encoding potential identified in esophageal squamous cell carcinoma: KDM4A-AS1-encoded peptide weakens cancer cell viability and migratory capacity. Mol Oncol. 2023;17(7):1419–36.
103. Li M, Liu G, Jin X, et al. Micropeptide MIAC inhibits the tumor progression by interacting with AQP2 and inhibiting EREG/EGFR signaling in renal cell carcinoma. Mol Cancer. 2022;21(1):181.
104. Li M, Li X, Zhang Y, et al. Micropeptide MIAC inhibits HNSCC progression by interacting with Aquaporin 2. J Am Chem Soc. 2020;142(14):6708–16.
105. Xiang X, Fu Y, Zhao K, et al. Cellular senescence in hepatocellular carcinoma induced by a long non-coding RNA-encoded peptide PINT87aa by blocking FOXM1-mediated PHB2. Theranostics. 2021;11(10):4929–44.
106. Lun YZ, Pan ZP, Liu SA, et al. The peptide encoded by a novel putative lncRNA HBVPTPAP inducing the apoptosis of hepatocellular carcinoma cells by modulating JAK/STAT signaling pathways. Virus Res. 2020;287:198104.
107. Wang Y, Wu S, Zhu X et al. LncRNA-encoded polypeptide ASRPS inhibits triple-negative breast cancer angiogenesis. J Exp Med, 2020. 217(3).
108. Boix O, Martinez M, Vidal S, et al. pTINCR microprotein promotes epithelial differentiation and suppresses tumor growth through CDC42 SUMOylation and activation. Nat Commun. 2022;13(1):6840.
109. Pan J, Liu M, Duan X, et al. A short peptide LINC00665_18aa encoded by lncRNA LINC00665 suppresses the proliferation and migration of osteosarcoma cells through the regulation of the CREB1/RPS6KA3 interaction. PLoS ONE. 2023;18(6):e0286422.
110. Ge Q, Jia D, Cen D et al. Micropeptide ASAP encoded by LINC00467 promotes colorectal cancer progression by directly modulating ATP synthase activity. J Clin Invest, 2021. 131(22).
111. Leng F, Miu YY, Zhang Y, et al. A micro-peptide encoded by HOXB-AS3 promotes the proliferation and viability of oral squamous cell carcinoma cell lines by directly binding with IGF2BP2 to stabilize c-Myc. Oncol Lett. 2021;22(4):697.
112. Pang Y, Liu Z, Han H, et al. Peptide SMIM30 promotes HCC development by inducing SRC/YES1 membrane anchoring and MAPK pathway activation. J Hepatol. 2020;73(5):1155–69.
113. Meng N, Chen M, Chen D, et al. Small protein hidden in lncRNA LOC90024 promotes cancerous RNA splicing and Tumorigenesis. Adv Sci (Weinh). 2020;7(10):1903233.
114. Zhou B, Yu G, Zhao M, et al. The lncRNA LINC00339-encoded peptide promotes trophoblast adhesion to endometrial cells via MAPK and PI3K-Akt signaling pathways. J Assist Reprod Genet. 2024;41(2):493–504.
115. Zou Q, Du X, Zhou L, et al. A short peptide encoded by long non-coding RNA small nucleolar RNA host gene 6 promotes cell migration and epithelial-mesenchymal transition by activating transforming growth factor-beta/SMAD signaling pathway in human endometrial cells. J Obstet Gynaecol Res. 2023;49(1):232–42.
116. Spencer HL, Sanders R, Boulberdaa M, et al. The LINC00961 transcript and its encoded micropeptide, small regulatory polypeptide of amino acid response, regulate endothelial cell function. Cardiovasc Res. 2020;116(12):1981–94.
117. Zheng X, Wang M, Liu S, et al. A lncRNA-encoded mitochondrial micropeptide exacerbates microglia-mediated neuroinflammation in retinal ischemia/reperfusion injury. Cell Death Dis. 2023;14(2):126.
118. Bhatta A, Atianand M, Jiang Z, et al. A mitochondrial micropeptide is required for activation of the Nlrp3 inflammasome. J Immunol. 2020;204(2):428–37.
119. Zheng X, Guo Y, Zhang R, et al. The mitochondrial micropeptide Stmp1 promotes retinal cell differentiation. Biochem Biophys Res Commun. 2022;636(Pt 2):79–86.
120. Stein CS, Jadiya P, Zhang X, et al. Mitoregulin: a lncRNA-Encoded microprotein that supports mitochondrial supercomplexes and respiratory efficiency. Cell Rep. 2018;23(13):3710–e37208.
121. Jiang W, Chen Y, Sun M, et al. LncRNA DGCR5-encoded polypeptide RIP aggravates SONFH by repressing nuclear localization of β-catenin in BMSCs. Cell Rep. 2023;42(8):112969.
122. Li Y, Zhang J, Sun H et al. lnc-Rps4l-encoded peptide RPS4XL regulates RPS6 phosphorylation and inhibits the proliferation of PASMCs caused by hypoxia. Mol Ther, 2024; 29(4):1411–1424
123. Wang L, Fan J, Han L, et al. The micropeptide LEMP plays an evolutionarily conserved role in myogenesis. Cell Death Dis. 2020;11(5):357.
124. Liu X, Chen S, Luo W, et al. LncRNA MFRL regulates the phenotypic switch of vascular smooth muscle cells to attenuate arterial remodeling by encoding a novel micropeptide MFRLP. Transl Res. 2024;272:54–67.
125. Sabikunnahar B, Caldwell S, Varnum S, et al. Long noncoding RNA U90926 is Induced in activated macrophages, is protective in endotoxic shock, and encodes a Novel secreted protein. J Immunol. 2023;210(6):807–19.
126. Senís E, Esgleas M, Najas S, et al. TUNAR lncRNA encodes a Microprotein that regulates neural differentiation and neurite formation by modulating Calcium dynamics. Front Cell Dev Biol. 2021;9:747667.
127. Tornini VA, Miao L, Lee HJ et al. linc-mipep and linc-wrb encode micropeptides that regulate chromatin accessibility in vertebrate-specific neural cells. Elife, 2023. 12.
128. Tang S, Zhang J, Lou F, et al. A lncRNA Dleu2-encoded peptide relieves autoimmunity by facilitating Smad3-mediated Treg induction. EMBO Rep. 2024;25(3):1208–32.
129. Halasz H, Malekos E, Covarrubias S, et al. CRISPRi screens identify the lncRNA, LOUP, as a multifunctional locus regulating macrophage differentiation and inflammatory signaling. Proc Natl Acad Sci U S A. 2024;121(22):e2322524121.
130. Liu SJ, Dang HX, Lim DA, et al. Long noncoding RNAs in cancer metastasis. Nat Rev Cancer. 2021;21(7):446–60.
131. Huang JZ, Chen M, Chen D, et al. A peptide encoded by a putative lncRNA HOXB-AS3 suppresses Colon cancer growth. Mol Cell. 2017;68(1):171–e1846.
132. Correction to: LncRNA PSR regulates vascular remodeling through encoding a Novel protein arteridin. Circ Res, 2023. 133(1): p. e17.
133. Li L, Shu XS, Geng H, et al. A novel tumor suppressor encoded by a 1p36.3 lncRNA functions as a phosphoinositide-binding protein repressing AKT phosphorylation/activation and promoting autophagy. Cell Death Differ. 2023;30(5):1166–83.
134. Yi Q, Feng J, Liao Y, et al. Circular RNAs in chemotherapy resistance of lung cancer and their potential therapeutic application. IUBMB Life. 2023;75(3):225–37.
135. Wang C, Tan S, Li J, et al. CircRNAs in lung cancer - Biogenesis, function and clinical implication. Cancer Lett. 2020;492:106–15.
136. Zheng X, Chen L, Zhou Y, et al. A novel protein encoded by a circular RNA circPPP1R12A promotes tumor pathogenesis and metastasis of colon cancer via Hippo-YAP signaling. Mol Cancer. 2019;18(1):47.
137. Zhang M, Zhao K, Xu X, et al. A peptide encoded by circular form of LINC-PINT suppresses oncogenic transcriptional elongation in glioblastoma. Nat Commun. 2018;9(1):4475.
138. Yang Y, Gao X, Zhang M, et al. Novel role of FBXW7 circular RNA in repressing Glioma Tumorigenesis. J Natl Cancer Inst. 2018;110(3):304–15.
139. Mo D, Li X, Raabe CA et al. Circular RNA Encoded Amyloid Beta peptides-A Novel Putative Player in Alzheimer's Disease. Cells, 2020. 9(10).
140. Zhang Y, Zhang X, Dai K, et al. Bombyx mori akirin hijacks a viral peptide vSP27 encoded by BmCPV circRNA and activates the ROS-NF-κB pathway against viral infection. Int J Biol Macromol. 2022;194:223–32.
141. Yin H, Shen X, Zhao J, et al. Circular RNA CircFAM188B encodes a protein that regulates proliferation and differentiation of chicken skeletal muscle Satellite cells. Front Cell Dev Biol. 2020;8:522588.
142. Li Y, Wang Z, Yang J, et al. CircTRIM1 encodes TRIM1-269aa to promote chemoresistance and metastasis of TNBC via enhancing CaM-dependent MARCKS translocation and PI3K/AKT/mTOR activation. Mol Cancer. 2024;23(1):102.
143. Geng X, Wang J, Zhang C, et al. Circular RNA circCOL6A3_030 is involved in the metastasis of gastric cancer by encoding polypeptide. Bioengineered. 2021;12(1):8202–16.
144. Li F, Tang H, Zhao S et al. Circ-E-Cad encodes a protein that promotes the proliferation and migration of gastric cancer via the TGF-β/Smad/C-E-Cad/PI3K/AKT pathway. Mol Carcinog, 2023. 62(3): pp. 360–368.
145. Li H, Lan T, Liu H, et al. IL-6-induced cGGNBP2 encodes a protein to promote cell growth and metastasis in intrahepatic cholangiocarcinoma. Hepatology. 2022;75(6):1402–19.
146. Zhou J, Yao L, Su Y, et al. IGF2BP3 loss inhibits cell progression by upregulating has_circRNA_103820, and hsa_circRNA_103820-encoded peptide inhibits cell progression by inactivating the AKT pathway in lung cancer. Chem Biol Drug Des. 2024;103(2):e14473.
147. Zhang Y, Liu Z, Zhong Z, et al. A tumor suppressor protein encoded by circKEAP1 inhibits osteosarcoma cell stemness and metastasis by promoting vimentin proteasome degradation and activating anti-tumor immunity. J Exp Clin Cancer Res. 2024;43(1):52.
148. Liu H, Fang D, Zhang C, et al. Circular MTHFD2L RNA-encoded CM-248aa inhibits gastric cancer progression by targeting the SET-PP2A interaction. Mol Ther. 2023;31(6):1739–55.
149. Gao J, Pan H, Li J, et al. A peptide encoded by the circular form of the SHPRH gene induces apoptosis in neuroblastoma cells. PeerJ. 2024;12:e16806.

150. Wang Q, Cheng B, Singh S, et al. A protein-encoding CCDC7 circular RNA inhibits the progression of prostate cancer by up-regulating FLRT3. NPJ Precis Oncol. 2024;8(1):11.
151. Zhong S, Xu H, Wang D, et al. circNFIB decreases synthesis of arachidonic acid and inhibits breast tumor growth and metastasis. Eur J Pharmacol. 2024;963:176221.
152. Li F, Cai Y, Deng S, et al. A peptide CORO1C-47aa encoded by the circular noncoding RNA circ-0000437 functions as a negative regulator in endometrium tumor angiogenesis. J Biol Chem. 2021;297(5):101182.
153. Song R, Guo P, Ren X, et al. A novel polypeptide CAPG-171aa encoded by circCAPG plays a critical role in triple-negative breast cancer. Mol Cancer. 2023;22(1):104.
154. Xiong L, Liu HS, Zhou C, et al. A novel protein encoded by circINSIG1 reprograms cholesterol metabolism by promoting the ubiquitin-dependent degradation of INSIG1 in colorectal cancer. Mol Cancer. 2023;22(1):72.
155. Wang S, Wang Y, Li Q, et al. The novel β-TrCP protein isoform hidden in circular RNA confers trastuzumab resistance in HER2-positive breast cancer. Redox Biol. 2023;67:102896.
156. Lyu Y, Tan B, Li L, et al. A novel protein encoded by circUBE4B promotes progression of esophageal squamous cell carcinoma by augmenting MAPK/ERK signaling. Cell Death Dis. 2023;14(6):346.
157. Chang S, Ren D, Zhang L, et al. Therapeutic SHPRH-146aa encoded by circ-SHPRH dynamically upregulates P21 to inhibit CDKs in neuroblastoma. Cancer Lett. 2024;598:217120.
158. Pan Z, Cai J, Lin J, et al. A novel protein encoded by circFNDC3B inhibits tumor progression and EMT through regulating snail in colon cancer. Mol Cancer. 2020;19(1):71.
159. Song R, Ma S, Xu J, et al. A novel polypeptide encoded by the circular RNA ZKSCAN1 suppresses HCC via degradation of mTOR. Mol Cancer. 2023;22(1):16.
160. Wang H, Liang Y, Zhang T, et al. C-IGF1R encoded by cIGF1R acts as a molecular switch to restrict mitophagy of drug-tolerant persister tumour cells in non-small cell lung cancer. Cell Death Differ. 2023;30(11):2365–81.
161. Liu YY, Zhang YY, Ran LY, et al. A novel protein FNDC3B-267aa encoded by circ0003692 inhibits gastric cancer metastasis via promoting proteasomal degradation of c-Myc. J Transl Med. 2024;22(1):507.
162. Peng Y, Xu Y, Zhang X, et al. A novel protein AXIN1-295aa encoded by circAXIN1 activates the Wnt/β-catenin signaling pathway to promote gastric cancer progression. Mol Cancer. 2021;20(1):158.
163. Zhang Y, Jiang J, Zhang J, et al. CircDIDO1 inhibits gastric cancer progression by encoding a novel DIDO1-529aa protein and regulating PRDX2 protein stability. Mol Cancer. 2021;20(1):101.
164. Song J, Zheng J, Liu X, et al. A novel protein encoded by ZCRB1-induced circHEATR5B suppresses aerobic glycolysis of GBM through phosphorylation of JMJD5. J Exp Clin Cancer Res. 2022;41(1):171.
165. Biswas S, Bhagat GK, Guha D, et al. Molecular characterization of the unusual peptide CORO1C-47aa encoded by the circular RNA and docking simulations with its binding partner. Gene. 2023;877:147546.
166. Xie T, Yang Z, Xian S, et al. Hsa_circ_0008833 promotes COPD progression via inducing pyroptosis in bronchial epithelial cells. Exp Lung Res. 2024;50(1):1–14.
167. Xu N, Jiang J, Jiang F, et al. CircCDC42-encoded CDC42-165aa regulates macrophage pyroptosis in Klebsiella pneumoniae infection through pyrin inflammasome activation. Nat Commun. 2024;15(1):5730.
168. Huang K, Li Z, Zhong D, et al. A circular RNA generated from Nebulin (NEB) gene splicing promotes skeletal muscle myogenesis in cattle as detected by a Multi-omics Approach. Adv Sci (Weinh). 2024;11(3):e2300702.
169. Lin Z, Xie F, He X, et al. A novel protein encoded by circKANSL1L regulates skeletal myogenesis via the Akt-FoxO3 signaling axis. Int J Biol Macromol. 2024;257(Pt 1):128609.
170. Lu P, Fan J, Li B, et al. A novel protein encoded by circLARP1B promotes the proliferation and migration of vascular smooth muscle cells by suppressing cAMP signaling. Atherosclerosis. 2024;395:117575.
171. Chen R, Yang T, Jin B, et al. CircTmeff1 promotes muscle atrophy by interacting with TDP-43 and Encoding A Novel TMEFF1-339aa protein. Adv Sci (Weinh). 2023;10(17):e2206732.
172. Zhang Y, Zhang X, Shen Z, et al. BmNPV circular RNA-encoded peptide VSP39 promotes viral replication. Int J Biol Macromol. 2023;228:299–310.
173. Zhao X, Guo J, Wang X, et al. A new circular RNA-encoded protein BIRC6-236aa inhibits transmissible gastroenteritis virus (TGEV)-induced mitochondrial dysfunction. J Biol Chem. 2022;298(9):102280.
174. Wang L, Zheng W, Lv X, et al. circMORC3-encoded novel protein negatively regulates antiviral immunity through synergizing with host gene MORC3. PLoS Pathog. 2023;19(12):e1011894.
175. Xiong L, Gong Y, Liu H, et al. circGlis3 promotes β-cell dysfunction by binding to heterogeneous nuclear ribonucleoprotein F and encoding Glis3-348aa protein. iScience. 2024;27(1):108680.
176. Zhang S, Wang C, Wang Y, et al. A novel protein encoded by circRsrc1 regulates mitochondrial ribosome assembly and translation during spermatogenesis. BMC Biol. 2023;21(1):94.
177. Ouyang X, He Z, Fang H, et al. A protein encoded by circular ZNF609 RNA induces acute kidney injury by activating the AKT/mTOR-autophagy pathway. Mol Ther. 2023;31(6):1722–38.
178. Zhang C, Zhou X, Geng X, et al. Circular RNA hsa_circ_0006401 promotes proliferation and metastasis in colorectal carcinoma. Cell Death Dis. 2021;12(5):443.
179. Li Y, Chen B, Zhao J, et al. HNRNPL Circularizes ARHGAP35 to produce an oncogenic protein. Adv Sci (Weinh). 2021;8(13):2001701.
180. Zheng X, Chen L, Zhou Y, et al. Correction to: a novel protein encoded by a circular RNA circPPP1R12A promotes tumor pathogenesis and metastasis of colon cancer via Hippo-YAP signaling. Mol Cancer. 2021;20(1):42.
181. Li K, Peng ZY, Wang R, et al. Enhancement of TKI sensitivity in lung adenocarcinoma through m6A-dependent translational repression of wnt signaling by circ-FBXW7. Mol Cancer. 2023;22(1):103.
182. Zhao N, Cao Y, Tao R et al. The circMYBL2-encoded p185 protein suppresses colorectal cancer progression by inhibiting serine biosynthesis. Cancer Res, 2024; 84(13):2155–2168
183. Lei K, Liang R, Liang J, et al. CircPDE5A-encoded novel regulator of the PI3K/AKT pathway inhibits esophageal squamous cell carcinoma progression by promoting USP14-mediated de-ubiquitination of PIK3IP1. J Exp Clin Cancer Res. 2024;43(1):124.
184. Gao X, Xia X, Li F, et al. Circular RNA-encoded oncogenic E-cadherin variant promotes glioblastoma tumorigenicity through activation of EGFR-STAT3 signalling. Nat Cell Biol. 2021;23(3):278–91.
185. Wu X, Xiao S, Zhang M, et al. A novel protein encoded by circular SMO RNA is essential for hedgehog signaling activation and glioblastoma tumorigenicity. Genome Biol. 2021;22(1):33.
186. Zhao W, Zhang Y, Zhu Y. Circular RNA circβ-catenin aggravates the malignant phenotype of non-small-cell lung cancer via encoding a peptide. J Clin Lab Anal. 2021;35(9):e23900.
187. Jiang T, Xia Y, Lv J, et al. A novel protein encoded by circMAPK1 inhibits progression of gastric cancer by suppressing activation of MAPK signaling. Mol Cancer. 2021;20(1):66.
188. Zhang Y. LncRNA-encoded peptides in cancer. J Hematol Oncol. 2024;17(1):66.
189. Chen X, Han P, Zhou T, et al. circRNADb: a comprehensive database for human circular RNAs with protein-coding annotations. Sci Rep. 2016;6:34985.
190. Meng X, Chen Q, Zhang P, et al. CircPro: an integrated tool for the identification of circRNAs with protein-coding potential. Bioinformatics. 2017;33(20):3314–6.
191. Sun P, Li G. CircCode: a powerful Tool for identifying circRNA coding ability. Front Genet. 2019;10:981.
192. Zhang L, Gao H, Li X et al. The important regulatory roles of circRNA–encoded proteins or peptides in cancer pathogenesis (review). Int J Oncol, 2024. 64(2).
193. Wei L, Chen H, Su R. M6APred-EL: a sequence-based predictor for identifying N6-methyladenosine sites using ensemble learning. Mol Ther Nucleic Acids. 2018;12:635–44.
194. Erhard F, Halenius A, Zimmermann C, et al. Improved ribo-seq enables identification of cryptic translation events. Nat Methods. 2018;15(5):363–6.
195. Menschaert G, Van Criekinge W, Notelaers T, et al. Deep proteome coverage based on ribosome profiling aids mass spectrometry-based protein and peptide discovery and provides evidence of alternative translation products and near-cognate translation initiation events. Mol Cell Proteom. 2013;12(7):1780–90.
196. Pan J, Wang R, Shang F, et al. Functional micropeptides encoded by long non-coding RNAs: a Comprehensive Review. Front Mol Biosci. 2022;9:817517.
197. Lobbestael E, Reumers V, Ibrahimi A, et al. Immunohistochemical detection of transgene expression in the brain using small epitope tags. BMC Biotechnol. 2010;10:16.
198. Li S, Peng D, Pan N, et al. Identification and analysis of short open reading frame-encoded peptides in different regions of mouse brain. iScience. 2023;26(4):106427.

199. Peng M, Zhou Y, Wan C. Identification of phosphorylated small ORF-encoded peptides in Hep3B cells by LC/MS/MS. J Proteom. 2024;303:105214.
200. Chen Z, Qi Z, He D, et al. Strategy for scanning peptide-coding circular RNAs in Colorectal Cancer based on Bioinformatics Analysis and experimental assays. Front Cell Dev Biol. 2021;9:815895.
201. Peeters MKR, Menschaert G. The hunt for sORFs: a multidisciplinary strategy. Exp Cell Res. 2020;391(1):111923.
202. Li P, Song R, Yin F, et al. circMRPS35 promotes malignant progression and cisplatin resistance in hepatocellular carcinoma. Mol Ther. 2022;30(1):431–47.
203. Crudele F, Bianchi N, Terrazzan A et al. Circular RNAs Could Encode Unique Proteins Affect Cancer Pathways Biology (Basel), 2023. 12(4).
204. Tang C, Zhou Y, Sun W et al. Oncopeptide MBOP encoded by LINC01234 promotes colorectal Cancer through MAPK signaling pathway. Cancers (Basel), 2022. 14(9).
205. Guo B, Wu S, Zhu X, et al. Micropeptide CIP2A-BP encoded by LINC00665 inhibits triple-negative breast cancer progression. Embo j. 2020;39(1):e102190.
206. Cai T, Zhang Q, Wu B, et al. LncRNA-encoded microproteins: a new form of cargo in cell culture-derived and circulating extracellular vesicles. J Extracell Vesicles. 2021;10(9):e12123.
207. Yang J, Zhu J, Sun J, et al. Intratumoral delivered novel circular mRNA encoding cytokines for immune modulation and cancer therapy. Mol Ther Nucleic Acids. 2022;30:184–97.
208. Barczak W, Carr SM, Liu G, et al. Long non-coding RNA-derived peptides are immunogenic and drive a potent anti-tumour response. Nat Commun. 2023;14(1):1078.
209. Kikuchi Y, Tokita S, Hirama T, et al. CD8(+) T-cell Immune Surveillance against a Tumor Antigen encoded by the oncogenic long noncoding RNA PVT1. Cancer Immunol Res. 2021;9(11):1342–53.
210. Wang X, Zhang H, Yin S, et al. lncRNA-encoded pep-AP attenuates the pentose phosphate pathway and sensitizes colorectal cancer cells to Oxaliplatin. EMBO Rep. 2022;23(1):e53140.
211. Løvendorf MB, Holm A, Petri A, et al. Knockdown of circular RNAs using LNA-Modified antisense oligonucleotides. Nucleic Acid Ther. 2023;33(1):45–57.
212. Holdt LM, Kohlmaier A, Teupser D. Circular RNAs as therapeutic agents and targets. Front Physiol. 2018;9:1262.
213. Li S, Li X, Xue W, et al. Screening for functional circular RNAs using the CRISPR-Cas13 system. Nat Methods. 2021;18(1):51–9.
214. Xu D, Cai Y, Tang L, et al. A CRISPR/Cas13-based approach demonstrates biological relevance of vlinc class of long non-coding RNAs in anticancer drug response. Sci Rep. 2020;10(1):1794.
215. Li YR, Zong RQ, Zhang HY, et al. Mechanism analysis of LINC00665 and its peptides CIP2A-BP in Hepatocellular Carcinoma. Front Genet. 2022;13:861096.
216. You Q, Wang F, Du R, et al. M(6) a reader YTHDF1-Targeting Engineered Small Extracellular vesicles for gastric Cancer Therapy via Epigenetic and Immune Regulation. Adv Mater. 2023;35(8):e2204910.

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