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REVIEW

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Noncoding RNA-encoded peptides in cancer: biological functions, posttranslational modifications and therapeutic potential

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Abstract

In the present era, noncoding RNAs (ncRNAs) have become a subject of considerable scientific interest, with peptides encoded by ncRNAs representing a particularly promising avenue of investigation. The identification of ncRNA-encoded peptides in human cancers is increasing. These peptides regulate cancer progression through multiple molecular mechanisms. Here, we delineate the patterns of diverse ncRNA-encoded peptides and provide a synopsis of the methodologies employed for the identification of ncRNAs that possess the capacity to encode these peptides. Furthermore, we discuss the impacts of ncRNA-encoded peptides on the biological behavior of cancer cells and the underlying molecular mechanisms. In conclusion, we describe the prospects of ncRNA-encoded peptides in cancer and the challenges that need to be overcome.

Introduction

Previously, ncRNAs were assumed to be incapable of encoding proteins. However, recent discoveries have challenged this view, with the identification of a significant number of small open reading frames (sORFs) in noncoding regions of the genome [1]. These sORFs are known to produce peptides through translation [2]. Some peptides are conserved, stabilized within the cell, and perform crucial functions independently of their parental RNAs [3]. NcRNA-encoded peptides diverge from the category of "traditional" small bioactive peptides (comprising natural peptides, neuropeptides, peptide hormones, and antimicrobial peptides) in that the majority of the former are encoded by long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and precursor microRNAs (pri-miRNAs), whereas the latter are derived from messenger RNAs (mRNAs) [4, 5]. In this review, we focus on the description of biologically active peptides or proteins encoded by ncRNAs in tumors and collectively refer to these peptides as ncRNA-encoded peptides. Typically, peptides encoded by lncRNAs and pri-miRNAs are less than 100 amino acids (aa) in length, and studies refer to them as peptides, micropeptides, polypeptides, short peptides or miRNA-encoded peptides (miPEPs). Peptides

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encoded by circRNAs are longer than 100 aa, and studies refer to them as peptides, proteins, or microproteins. Here, we refer to the coding products of these ncRNAs uniformly as ncRNA-encoded peptides, and summarize the expression, subcellular localization, function, mechanism, and application of these peptides in cancer (Figs. 1 and 2).

Initially, RNAs transcribed from the genome that could not be translated into proteins but were capable of performing their biological functions at the RNA level were classified as ncRNAs. In the early twentieth century, some researchers proposed that the traditional approach of simply classifying transcripts into coding and non-coding categories was too one-sided and limited [6–8]. With the advancement of technologies such as ribosome sequencing, it has been increasingly recognized that ncRNAs contain sORFs capable of translating into bioactive peptides [9, 10]. Certain ncRNA-encoded peptides have also been gradually discovered and given specific names. For example, in 2002, researchers studying Alzheimer's disease and tumors discovered that an ORF located in the mitochondrial 16S rRNA gene encodes a functional peptide named Humanin (24 aa) [11]. This discovery was the first to overturn the conventional wisdom that ncRNAs have no coding function. Subsequently, lncRNA-encoded peptides and pri-miRNA-encoded peptides were sequentially discovered in 2015. The ORF (138 nt) present in an lncRNA (LINC00948 in humans and AK009351 in mice) can encode a highly conserved peptide (46 aa) named myoregulin (MLN) [12]. Researchers have identified a 63 nt ORF in pri-miR171b from alfalfa and a 57 nt ORF in pri-miR165a from *Arabidopsis thaliana* encoding miPEP171b (20 aa) and miPEP165a (18 aa), respectively [13]. These results indicate that the nascent field of ncRNA-encoded peptide research is on the rise. Subsequent studies reported examples of other types of ncRNA-encoded peptides. For example, circ-ZNF609 contains an ORF beginning with a start codon identical to a linear transcript and ending with an in-frame stop codon that is translated into a protein in a splice-dependent and cap-dependent manner [14]. In another study, a database of *E. coli* tRNA-encoded peptides was constructed and screened for a tREP-18 molecule with antiparasitic activity [15]. These findings contradict

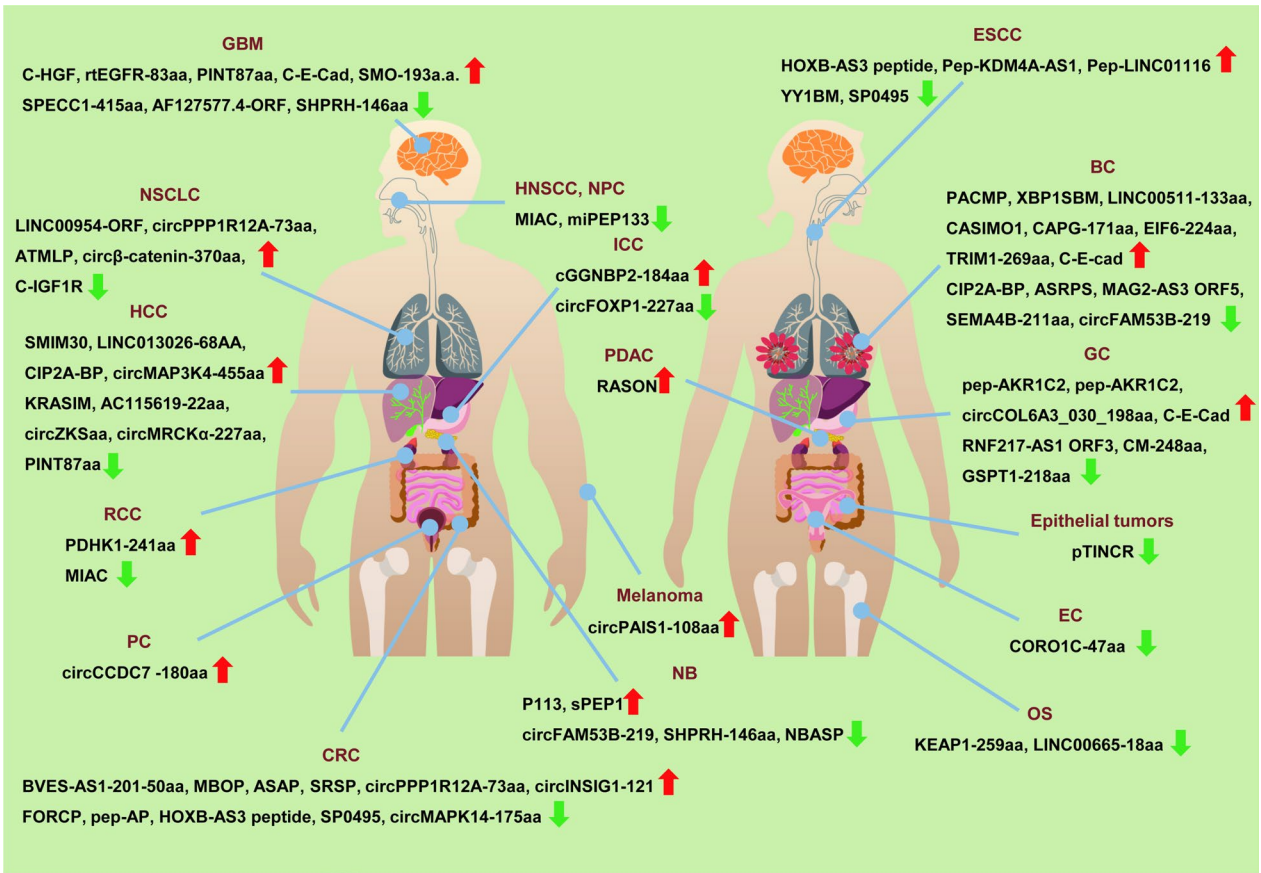

Fig. 1 Identification of ncRNA-encoded peptides and their aberrant expression in various types of human primary tumors. Red arrows: Up-regulated. Green arrows: Down-regulated

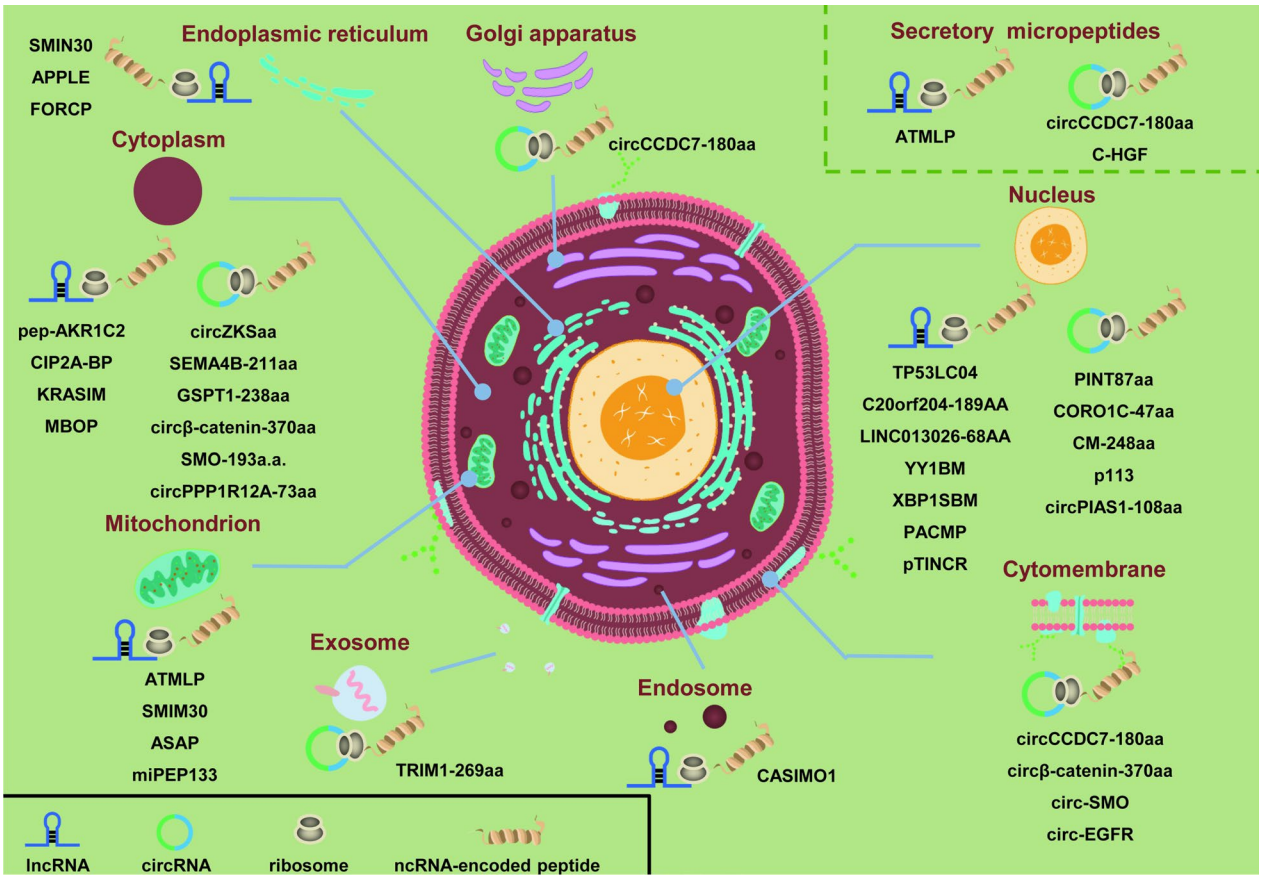

Fig. 2 Identification of ncRNA-encoded peptides in various organelles. A subset of studies have reported on the subcellular localization of ncRNA-encoded peptides, which are mainly localized to the nucleus, cytoplasm, plasma membrane, mitochondria, Golgi apparatus, and endoplasmic reticulum. Some ncRNA-encoded peptides can be sorted to endosomes and exosomes. In addition, a small number of ncrna-encoded peptides can be secreted extracellularly

traditional concepts, and more attention has been given to ncRNA-encoded peptides, which also implies that new technological methods are urgently needed to characterize ncRNA-encoded peptides (Fig. 3).

Currently, several technical tools can be used to predict the coding capacity of ncRNAs. Bioinformatics tools are convenient for predictions, and several databases (CPC2 [16], CPAT [17], sORFfinder [18], and PhyloCSF [19]) can be used to evaluate the coding capacity of ncRNAs based on the transcript sequences and structural features. Several databases (FuncPEP [20] and ncEP [21]) contain experimentally validated ncRNA-encoded peptides. In addition, databases are available for condition-specific searches: LncPEP [22] for lncRNA-encoded peptides, circRNADb [23] for circRNA-encoded peptides, and SPENCER [24] for ncRNA-encoded peptides in cancer. Mass spectrometry screens and ribosomal profiling techniques provide important technical support for the study of ncRNA-encoded peptides [25–27]. sORFs are often easily missed in traditional gene annotation, and mass spectrometry screens are able to detect peptides that are actually present. An affinity-based algorithm for chemical proteomics enables the enrichment and identification of cysteine-containing human sORF-encoded polypeptides (ccSEPs) derived from uncharacterized sORFs in cells [27]. In addition, MicroID, a novel technology, facilitates the discovery of entirely new microproteins in specific organelles [28]. Ribosomal profiling, which is based on the behavior of ribosomes during translation, is able to detect the presence of specific regions enriched for ribosome-protected fragments on ncRNAs, indicating the translational capacity of ncRNAs. Another study showed that ribosome occupancy alone is not sufficient to categorize transcripts as coding or noncoding [29]. In addition, validating the existence of ncRNA-encoded peptides is now feasible through a combination of methodologies, including sucrose density gradient centrifugation, reporter gene systems, gene editing technologies, specific antibody verification, and mass spectrometry. In the future, the development and maturation of technologies

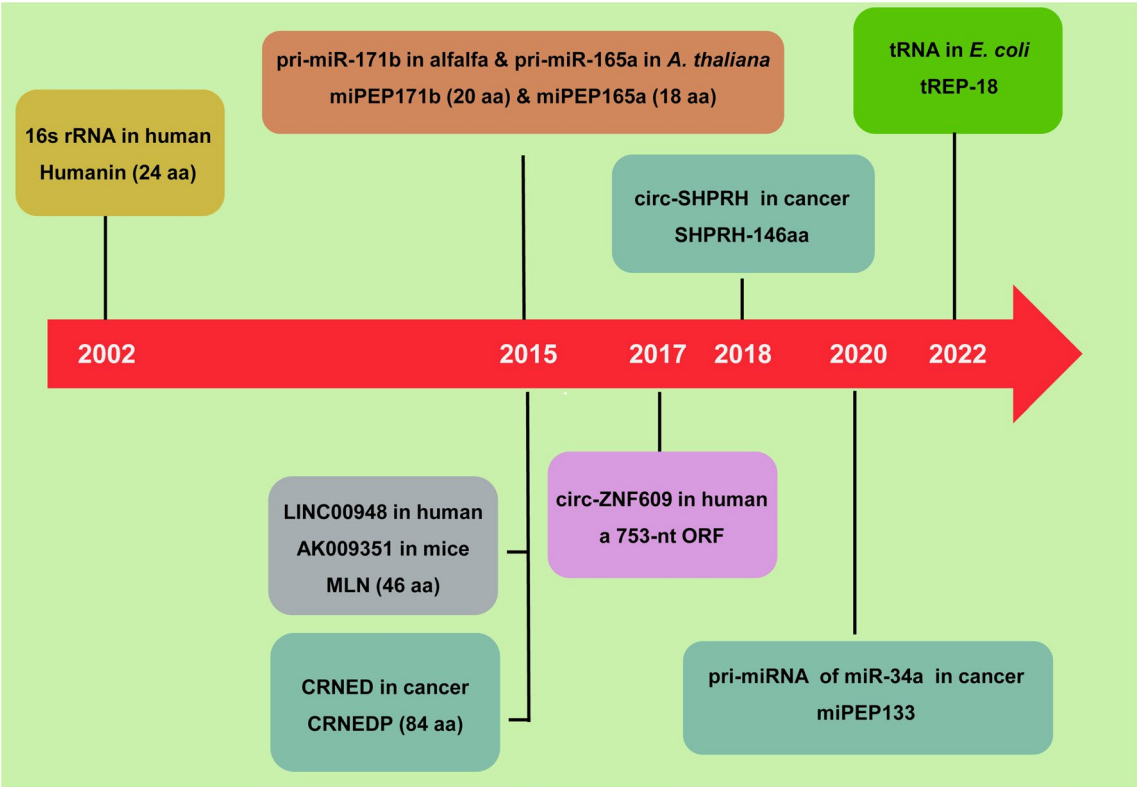

Fig. 3 Timeline of the discoveries in ncRNA-encoded peptides. Timeline of first reports of different types of ncRNA-encoded peptides and first reports of different types of ncRNA-encoded peptides in cancer

such as NAP-seq [30], NERD-seq [31] and nBAT [32] are expected to further aid in the characterization of ncRNA coding ability (Fig. 4).

Types of ncRNA-encoded peptides

Approximately 93% of the nucleotide sequence of human genomic DNA can be transcribed into RNA [33]. Among the transcribed products, only 2% are translated into proteins, whereas the remaining 98% are ncRNAs [34, 35]. Indeed, ncRNAs are primarily classified into several categories, including lncRNAs, circRNAs, miRNAs, rRNAs, tRNAs, piRNAs, snRNAs, and snoRNAs, based on their lengths and biological functions [36, 37]. To date, more attention has been given to peptides encoded by lncRNAs, circRNAs and pri-miRNAs [38–40]. Additionally, a limited number of rRNAs and tRNAs have also been identified as potential peptide-encoding molecules, although their functional roles remain largely uncharacterized [41, 42].

LncRNA-encoded peptides

LncRNAs are a common type of ncRNA with coding capacity [43]. LncRNAs are typically more than 200 nt in length and are transcribed by RNA polymerase II (Pol II) or other RNA polymerases [44, 45]. Their biogenesis occurs via capping at the 5' end (7-methylguanosine (m7G)) and polyadenylation at the 3' end (polyA), in a process that is similar to the biogenesis of mRNAs. The analogous physiological configuration results in the capacity of ribosomes to recognize these lncRNA transcripts in a manner analogous to that of mRNAs [46]. In addition, ribosome profiling revealed that, on average, 39.17% of human lncRNAs and 48.16% of mouse lncRNAs interact with ribosomes [47]. These findings suggest that lncRNAs have coding potential. However, the ability of lncRNAs to bind to ribosomes does not mean that they can encode peptides [29]. Another study suggested that the binding of lncRNAs to ribosomes may affect the stability of lncRNAs [48]. Despite the poor overall sequence conservation of lncRNAs, some locally conserved sequences may be present in these transcripts and contain coding-competent sORFs. Notably, although AUG is the most common start codon, the sORF of an lncRNA does not use the common AUG as a start codon but uses other codons, such as CUG and GUG, to initiate translation, which makes its translation mechanism relatively complex [49, 50].

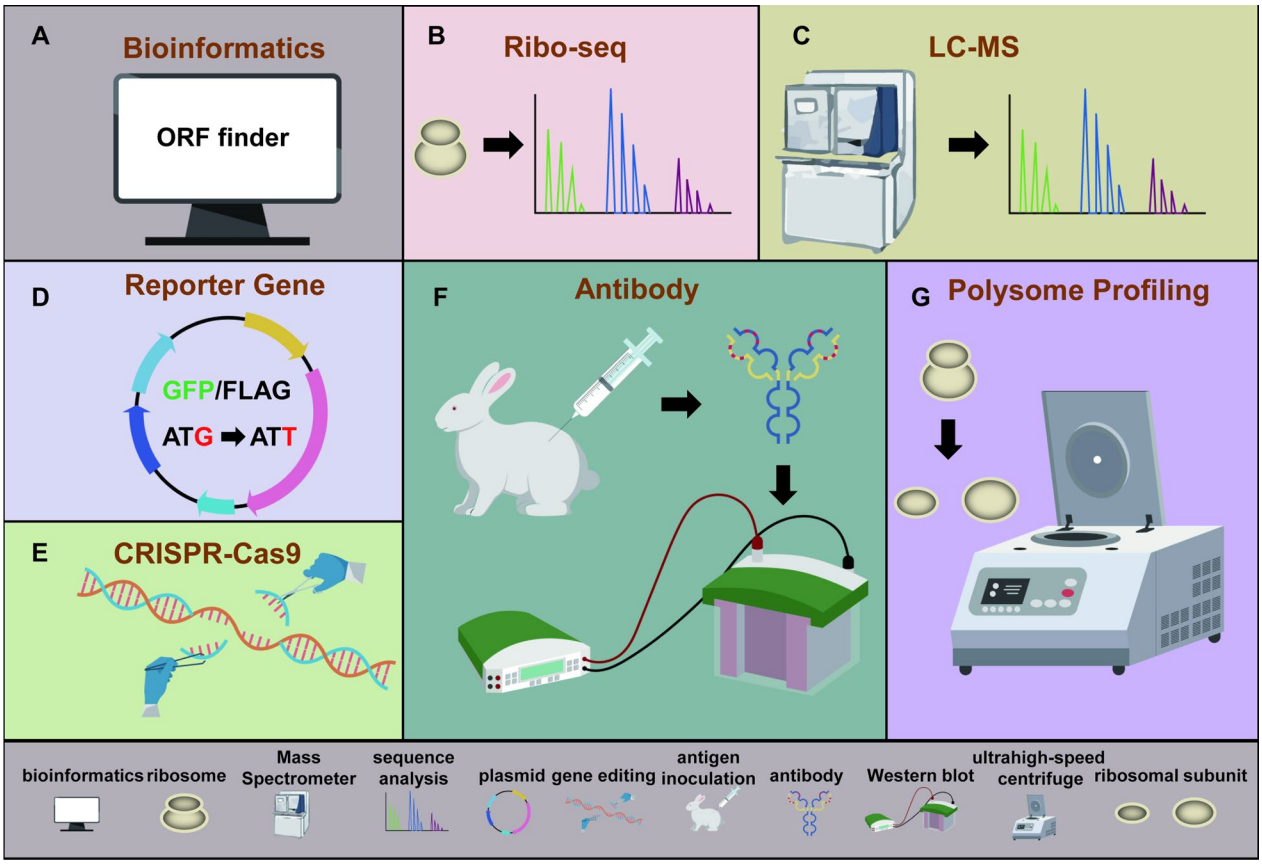

Fig. 4 Methods for prediction and characterization of ncRNA-encoded peptides. **A** Bioinformatics prediction of sORF. **B** Ribo-seq screening of ncRNAs with coding potential. **C** Mass spectrometry identification of peptide sequences. **D** Detection of TAG for mutated start codon fusions in ncRNA sORFs. **E** CRISPR/Cas9 knock-in TAG to detect endogenous expression of ncRNA-encoded peptides. **F** Generation of target antibodies to detect endogenous expression of ncRNA-encoded peptides. **G** Sucrose density gradient separation to detect ribosomal enrichment on ncRNAs

Tumor-associated lncRNA-encoded peptides were initially identified in 2015, when researchers identified an lncRNA, CRNDE, encoding a conserved 84-aa peptide, CRNDEP. CRNDEP has been observed in the HeLa cell line and in a range of human tissues (epithelial ovarian cancer, normal proliferative endometrium, tonsils, parabasal squamous epithelium and intestinal crypts) [51]. In 2017, a study revealed that the lncRNA HOXB-AS3 can encode a 53-aa peptide and described the function and molecular mechanism of this peptide in colorectal cancer (CRC) [38]. This finding highlights the important roles that lncRNA-encoded peptides play in tumorigenesis. Subsequently, additional tumor-associated lncRNA-encoded peptides that regulate tumor development through multiple pathways have been identified.

CircRNA-encoded peptides

Recently, circRNAs have been widely reported to have coding ability. During gene transcription, introns form lasso structures as linear precursor mRNAs are spliced. Specifically, the 3′ end of the upstream exon is covalently linked to the 5' end of the downstream exon, "looping out" the intron to form a circRNA consisting of the exon alone [52]. Therefore, if circRNAs are formed by the cyclization of the same exonic regions as linear RNAs, they are likely to contain the same open reading frames, leading to the possibility that circRNA-encoded peptides may have amino acid sequences similar to those of proteins encoded by linear RNAs. CircRNAs are covalently closed circular RNAs that lack a 5′ cap [53]. Some circRNAs possess internal ribosome entry sites (IRESs), which are RNA secondary or tertiary structures that recruit the 40S subunit to the 5′ untranslated region (UTR), thereby facilitating mRNA translation through a cap structure-independent mechanism [54, 55]. The m6A modification and the eIF4 or exon junction complex (EJC) play important roles in regulating the translation of circRNAs [56–59]. Notably, one study constructed unmodified and m6A-modified circRNAs separately to evaluate the effect of m6A on circRNA translation and reported that unmodified circRNAs and circRNAs containing 5% m6A exhibited comparable translation [60]. Thus, revealing

the process by which circRNAs encode peptides is challenging.

In contrast to linear RNAs, the coding products of circRNAs may have identical, analogous, or chimeric amino acid sequences [61]. This phenomenon can be attributed to the intrinsic characteristics of the sORFs present in circular RNAs. The production of chimeric proteins may occur when the stop codon is situated three nucleotides upstream of the start codon and three nucleotides downstream of the back-splicing junction (BSJ) [62]. In addition, in-frame termination codons that are solely present following the second round of translation may also result in the generation of chimeric proteins [63]. One of the characteristics of circRNA-encoded proteins is rolling translation. In normal linear mRNA translation, the ribosome recognizes the start codon at the 5′ end of the mRNA, moves along the mRNA for translation, and terminates when it encounters the stop codon. In the absence of well-defined 5′ and 3′ ends, multiple rounds of translation occur when a ribosome binds to an IRES or other translation initiation element on the circRNA and begins translation along the circRNA, which involves multiple rounds of translation when the start codon and stop codon in the sORF of a circRNA overlap [64]. Furthermore, in the absence of a termination codon within the sORF, the loaded ribosome continues to synthesize proteins in the unterminated ORF, a process known as rolling circle translation [65]. Notably, rolling circle translation results in significantly larger proteins, but due to the limited number of studies on these proteins, we still use peptides to refer to the circRNA-encoded products in this review.

In 2018, researchers identified the first circRNA-encoded peptide in tumors. This peptide, named SHPRH-146aa, is encoded by circ-SHPRH [66, 67]. A variety of circRNA-encoded peptides have subsequently been identified in tumors. Due to the distinctive characteristics of circRNA-encoded peptides (rolling translation), these peptides typically possess extended amino acid sequences, leading to their classification as circRNA-encoded peptides or circRNA-encoded proteins.

Pri-miRNA-encoded peptides

Pri-miRNAs are primary transcripts of miRNAs [68]. In addition to being cleaved by nucleases to yield mature miRNAs, specific pri-miRNAs are capable of encoding peptides, thereby acquiring functional properties [69]. Pri-miRNAs can be described as a special class of lncRNAs because they have similar secondary structures with lengths ranging from several hundred to one thousand nucleotides [70, 71]. These molecules contain short open reading frames (sORFs) that encode functional peptides. To date, the mirEX database has included only the complete sequences of pri-miRNAs from a limited number of plant species [72]. However, the vast majority of pri-miRNAs lack complete sequence information. DMS-MaPseq and RACE assays can be employed to amplify and identify the complete sequences of pri-miRNAs and secondary structures in both plants and animals [73, 74]. In light of technological and financial constraints, every pri-miRNA is unlikely to be subjected to the aforementioned characterization methods. In most cases, the sequence of the pri-miRNA can be obtained by extending the pre-miRNA sequence by hundreds to thousands of base pairs toward each of the 5′ and 3′ ends. The sequences of some pri-miRNAs overlap with the sequences of a specific class of lncRNAs, often called miRNA host genes [75]. Consequently, the peptides encoded by the sORFs of these lncRNAs can be regarded as analogous to those encoded by the sORFs of pri-miRNAs [76].

Typically, pri-miRNA-encoded peptides are referred to as miPEPs [77]. Currently, research on miPEPs has been largely confined to the field of plant biology [78]. However, a small number of miPEPs have also been identified in human cells and are associated with human diseases [75, 79]. The significance of miPEPs in the context of tumors cannot be overlooked. MIR22HG and pri-miR-497 can encode peptides in human-derived tumor cell lines, including A549 and HeLa cells [71, 80]. The expression of miPEP133, a peptide encoded by pri-miR-34a, is downregulated in NPC [40]. miPEP133 has been shown to inhibit tumor growth and metastasis by regulating mitochondrial function and enhancing the transcriptional activity of p53 [40]. Although only a limited number of miPEPs have been documented in tumors, given the evolutionary conservation of miRNAs, the hypothesis that additional pri-miRNAs could encode functional peptides is reasonable, but their existence remains to be confirmed, along with their associated functions.

Other types of ncRNA-encoded peptides

rRNA is a type of RNA that is integral to the ribosome and is regarded as the molecular machine that catalyzes protein synthesis [81]. The number of studies on rRNA-encoded peptides is relatively limited, with the majority of research concentrating on 12S rRNA, 16S rRNA, and 23S rRNA [41, 82, 83]. As early as 1996, a pentapeptide open reading frame, which encodes a peptide that mediates resistance to erythromycin, was identified in the 23S rRNA of *Escherichia coli* [84]. Furthermore, the mitochondrial 16S rRNA gene encodes a functional peptide, humanin, which is a potential drug for the treatment of Alzheimer's disease [11, 85]. Additionally, humanin has the ability to modulate the endoplasmic reticulum and

oxidative stress within the retinal pigment epithelium, and these factors might be potential therapeutic molecules for age-related macular degeneration [86]. Another functional peptide, SHLP, is encoded by 16S rRNA and includes six isoforms, designated SHLP1-6 [87, 88]. The mitochondrial open reading frame of the 12S rRNA-C type (MOTS-c) is a mitochondria-derived peptide encoded by the 12S rRNA region of the mitochondrial genome [89–91]. It consists of 16 amino acids with metabolic functions.

rRNA-encoded peptides are anticipated to play a growing role in the diagnosis and prognosis of tumors. The study revealed that the serum levels of MOTS-c were markedly elevated in lung cancer patients who had undergone radiotherapy, whereas the serum levels of Humanin were significantly decreased in breast cancer patients who had undergone radiotherapy [92]. Another study revealed that a reduction in serum SHLP2 levels was linked to an elevated risk of prostate cancer in white males [93, 94]. Additionally, a study of adrenal tumors revealed elevated serum MOTS-c protein levels in adrenocortical adenoma and pheochromocytoma patients but not in adrenocortical carcinoma patients. Intriguingly, the results of tissue biopsies indicated that the expression of MOTS-c protein decreased with the progression of adrenocortical carcinoma (stages III and IV). The distinct patterns of serum MOTS-c and tissue MOTS-c levels might be associated with the posttranslational modification of the MOTS-c protein [95]. These results indicate that rRNA-encoded peptides can be secreted into serum, exhibit robust biological stability, and possess the potential to serve as tumor biomarkers.

The prevailing view is that transfer RNA (tRNA) molecules are housekeeping molecules whose primary function is to transport amino acids into the ribosome [96]. tRNA typically comprises 73 to 90 nucleotides and assumes a cloverleaf-like configuration through a folding process that incorporates four structural elements: the anticodon arm, D arm, TψC arm, and amino acid receptor arm [97, 98]. tRNA is capable of forming hydrogen bonds with messenger RNA (mRNA) and ester bonds with amino acids [99]. In this way, tRNA acts as a "bridge" between nucleotide and amino acid sequences during the process of translation [100]. Notably, sORFs are also present in transfer RNAs (tRNAs) and these molecules have the potential to translate their own sequences [15]. Despite the absence of direct evidence indicating that tRNAs in the human genome are capable of encoding peptides, tRNA-encoded peptides derived from bacterial tRNA sequences designed to encode peptides may be widely utilized in the future. The tREP-18 molecule, which has been designed against the tRNA sequence of *Escherichia coli*, is anticipated to be a potential antiparasitic peptide [15]. In addition, the extraction of epitope vaccines from tRNA-encoded peptides (tREPs) may provide a solution to the safety and specificity issues that arise during the development of vaccines [42]. The tREP anticancer therapeutic modality, which targets the estrogen receptor (ER) and peroxisome proliferator-activated receptor alpha (PPAR) in breast cancer, represents a novel approach in this field of research [101].

Tumor-associated ncRNA-encoded peptides

It is crucial to acknowledge that in the study of ncRNA-encoded peptides and their relationship with tumors, researchers predominantly concentrate on the biological behavior of cancer cells and delve into their molecular mechanisms. However, not all studies encompass interacting proteins, downstream molecules, or signaling pathways associated with ncRNA-encoded peptides, nor do they all consider the subcellular localization of these peptides. Therefore, we have systematically summarized the cancer-related ncRNA-encoded peptides discovered to date, categorizing them based on the biological behavior of cancer cells (Fig. 5 and Table 1).

NcRNA-encoded peptides regulate proliferation and metastasis

Unregulated cellular proliferation, tissue invasion, and distant metastasis are fundamental characteristics of tumors. In studies of ncRNA-encoded peptides associated with tumors, researchers typically test the effects of ncRNA-encoded peptides on cancer cell proliferation and invasion at the same time to assess whether these peptides have oncogenic or tumor-suppressing functions. Notably, these peptides have different characteristics and molecular mechanisms; therefore, these studies should be generalized from multiple perspectives.

A systematic summary of the impacts of ncRNA-encoded peptides on the proliferation and metastasis of cancer cells by categorizing them according to distinct signal transduction pathways is beneficial. Certain ncRNA-encoded peptides can modulate multiple signaling pathways, such as CM-248aa, a novel peptide encoded by circMTHFD2L that can compete with PP2A2 for binding to the acidic domain of SET, thereby inhibiting the AKT/ERK/P65 pathway and gastric carcinoma (GC) cell growth and metastasis [102]. In glioblastoma (GBM), upregulated circ-HGF can encode C-HGF, which promotes GBM cell growth and metastasis by binding to c-MET to activate the STAT3/AKT/MAPK signaling axis [103]. Most often, studies of ncRNA-encoded peptides focus on a particular signaling pathway.

MAPK signaling. NcRNA-encoded peptides can regulate cancer cell proliferation and metastasis by activating or inhibiting MAPK signaling. A novel peptide, SMIM30,

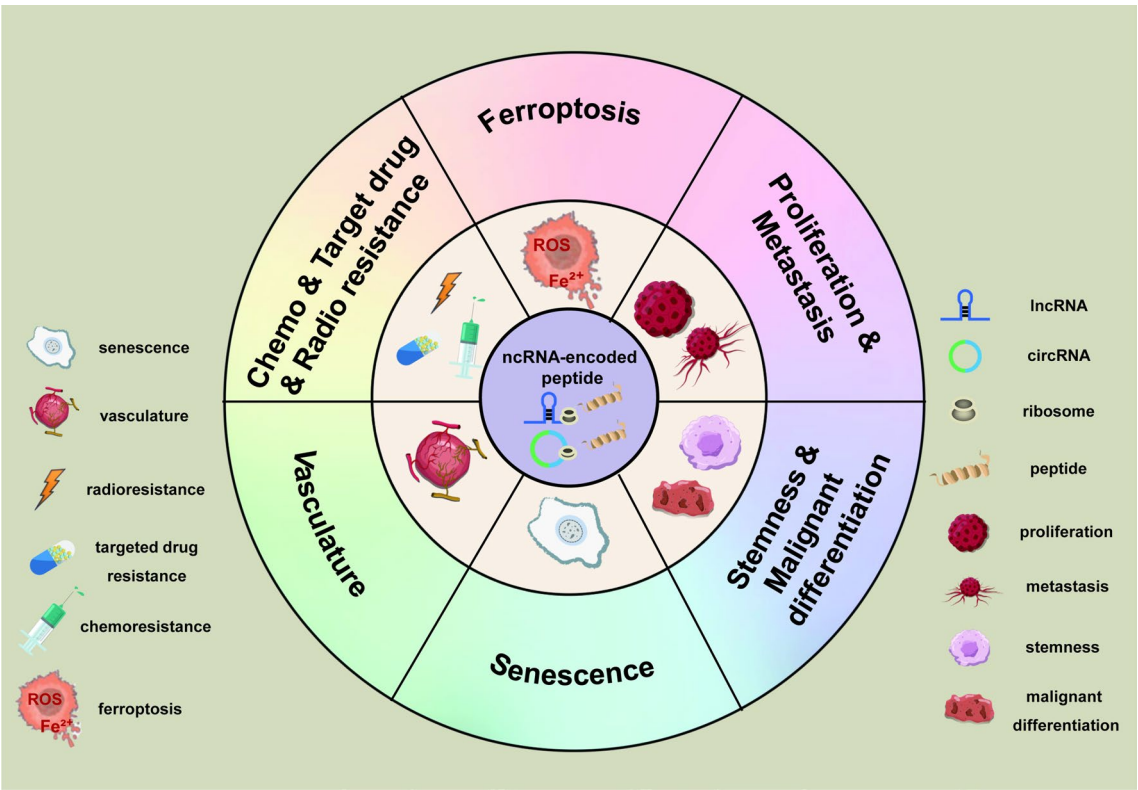

Fig. 5 Effects of ncRNA-encoded peptides on the biological behavior of cancer cells. NcRNA-encoded peptides can affect cancer cell proliferation, metastasis, the tumor vasculature, stemness, malignant differentiation, senescence, ferroptosis, chemoresistance, target drug resistance and radioresistance

encoded by LINC00998 promotes hepatocellular carcinoma (HCC) cell growth and metastasis by driving the membrane-anchored activation of the MAPK pathway by Src/YES1 [104]. CAPG-171aa (encoded by circCAPG) binds to STK38 and activates the MEKK2-MEK1/2-ERK1/2 pathway to promote breast cancer (BC) cell growth and metastasis [105]. The FAM201A-encoded peptide NBASP inhibits the MAPK pathway by interacting with FABP5, thereby inhibiting the proliferation and metastasis of neuroblastoma (NB) cells [106]. The ncRNA-encoded peptide may also regulate MAPK signaling through a direct interaction with key molecules in the MAPK pathway. LINC01234 encodes a peptide called MBOP, which interacts with MEK1 to upregulate the MEK1/p-ERK/MMP2/MMP9 axis and promotes the growth and metastasis of CRC cells [107]. CircMAPK14-175aa, encoded by circMAPK14, downregulates FOXC1 protein expression by competing with MAPK14 to bind MKK6, thus inhibiting the proliferation and invasion of CRC cells [108].

PI3K/AKT/mTOR signaling. The ncRNA-encoded peptides capable of activating PI3K/AKT/mTOR signaling are relatively more numerous. GSPT1-218aa, encoded by circGSPT1, directly binds to vimentin and forms complexes with Beclin1 and 14-3-3, thereby inhibiting the PI3K/AKT/mTOR pathway and GC cell growth and metastasis [109]. A study of CRC revealed that BVES-AS1 can encode a 50-aa peptide and named it BVES-AS1-201-50aa [110]. This peptide can interact with Src, thereby activating the Src/mTOR pathway and promoting the proliferation and invasion of cancer cells [110]. C-E-Cad, which is encoded by Circ-E-Cad, can promote the proliferation and metastasis of GC cells by activating the PI3K/AKT pathway [111]. CircPPP1R12A-73aa has a procarcinogenic effect on non-small cell lung cancer (NSCLC) through the activation of the AKT signaling pathway [112]. CircPDHK1-encoded PDHK1-241aa is capable of interacting with PPP1CA, thereby leading to the nuclear translocation of PPP1CA, activation of the AKT/mTOR pathway, and facilitation of the proliferation and invasion of clear cell renal cell carcinoma (ccRCC) cells [113].

Wnt/β-catenin signaling. In NSCLC, circβ-catenin-370aa, which is encoded by circβ-catenin, is localized to the cell membrane and cytoplasm. It can prevent the interaction between GSK3β and β-catenin and facilitate

Table 1 Effects of ncRNA-encoded peptides on the biological behaviors of tumors and their molecular mechanisms

Cancer	Peptide	NcRNA	Interacting protein	Downstream pathways/molecules	Function	Biological behavior	References
GC	CM-248aa	circMTHFD2L	SET	AKT/ERK/P65	Tumor suppressor	Proliferation and metastasis	[102]
GBM	C-HGF	circ-HGF	c-MET	STAT3/AKT/MAPK	Tumor promotor	Proliferation and metastasis	[103]
HCC	SMIM30	LINC00998	Src/YES1	MAPK	Tumor promotor	Proliferation and metastasis	[104]
TNBC	CAPG-171aa	circCAPG	STK38	MEKK2-MEK1/2-ERK1/2	Tumor promotor	Proliferation and metastasis	[105]
NB	NBASP	FAM201A	FABP5	MAPK	Tumor suppressor	Proliferation and metastasis	[106]
CRC	MBOP	LINC01234	MEK1	MEK1/p-ERK/MMP2/MMP9	Tumor promotor	Proliferation and metastasis	[107]
CRC	circMAPK14-175aa	circMAPK14	MKK6	FOXC1	Tumor suppressor	Proliferation and metastasis	[108]
GC	GSPT1-218aa	circGSPT1	Vimentin	PI3K/AKT/mTOR	Tumor suppressor	Proliferation and metastasis	[109]
CRC	BVES-AS1-201-50aa	BVES-AS1	Src	Src/mTOR	Tumor promotor	Proliferation and metastasis	[110]
GC	C-E-Cad	circ-E-Cad		PI3K/AKT	Tumor promotor	Proliferation and metastasis	[111]
NSCLC	circPPP1R12A-73aa	circPPP1R12A		AKT	Tumor promotor	Proliferation and metastasis	[112]
ccRCC	PDHK1-241aa	circPDHK1	PPP1CA	AKT/mTOR	Tumor promotor	Proliferation and metastasis	[113]
NSCLC	circβ-catenin-370aa	circβ-catenin	GSK3β	β-catenin	Tumor promotor	Proliferation and metastasis	[114]
TNBC	EIF6-224aa	circ-EIF6	MYH9	Wnt/β-catenin	Tumor promotor	Proliferation and metastasis	[115]
ICC	cGGNBP2-184aa	circGGNBP2	STAT3		Tumor promotor	Proliferation and metastasis	[116]
GC	RNF217-AS1 ORF3	RNF217-AS1		TLR4/NF-κB/STAT1	Tumor suppressor	Proliferation and metastasis	[117]
Colon cancer	circPPP1R12A-73aa	circPPP1R12A		Hippo-YAP	Tumor promotor	Proliferation and metastasis	[118]
GBM	rtEGFR-83aa	circ-EGFR	EGFR		Tumor promotor	Proliferation and metastasis	[119]
RCC	MIAC	RP11-469H8.6	AQP2	EREG/EGFR	Tumor suppressor	Proliferation and metastasis	[120]
HCC	SMIM30	LINC00998		CDK4/cyclinE2/p-Rb/E2F1	Tumor promotor	Proliferation	[121]
NB	SHPRH-146aa	circ-SHPRH	RUNX1	NFKBIA	Tumor suppressor	Proliferation and metastasis	[122]
NB	SHPRH-146aa	circ-SHPRH		P21-CDK pathway	Tumor suppressor	Proliferation	122
BC	MAG2-AS3 ORF5	MAG2-AS3	ECM-related proteins		Tumor suppressor	Proliferation and metastasis	[124]
HCC	circMRCKα-227aa	circMRCKα	USP22	HIF-1α	Tumor suppressor	Proliferation and metastasis	[130]
Colon cancer	HOXB-AS3 peptide	HOXB-AS3	hnRNPA1	PKM2	Tumor suppressor	Proliferation and metastasis	[38]
ESCC	HOXB-AS3 peptide	HOXB-AS3	IGF2BP2	c-Myc	Tumor promotor	Proliferation and metastasis	[224]
ESCC	Pep-KDM4A-AS1	KDM4A-AS1		SDC/FASN	Tumor suppressor	Proliferation and metastasis	[134]

Table 1 (continued)

Cancer	Peptide	NcRNA	Interacting protein	Downstream pathways/ molecules	Function	Biological behavior	References
BC	CASIMO1	NR_029453	SQLE		Tumor promotor	Proliferation	[135]
CRC	circINSIG1-121	circINSIG1	CUL5-ASB	INSIG	Tumor promotor	Proliferation and metastasis	[136]
CRC	ASAP	LINC00467	ATP5A/ATP5C		Tumor promotor	Proliferation	[137]
NB	p113	circRNA of CUX1	ZRF1/ BRD4		Tumor promotor	Proliferation and metastasis	[138]
NPC	miPEP133	pri-miR-34	HSAP9	TOM20/DRP1/ MFN1/OPA1	Tumor suppressor	Proliferation and metastasis	[40]
HCC	LINC013026-68AA	LINC013026			Tumor promotor	Proliferation	[140]
HCC	C20orf204-189AA	LINC00176			Tumor promotor	Proliferation	[141]
HCC	TP53LC04	lncAC022075.1			Tumor promotor	Proliferation	[142]
ESCC	YY1BM	LINC00278	YY1	eEF2K	Tumor suppressor	Proliferation	[143]
TNBC	CIP2A-BP	LINC00665	CIP2A	P13K/AKT/NF-KB	Tumor suppressor	Proliferation and metastasis	[144]
HCC	CIP2A-BP	LINC00665			Tumor promotor	Proliferation and metastasis	[223]
HCC	KRASIM	NCBP2-AS2	KRAS	KARS/ERK	Tumor suppressor	Proliferation and metastasis	[145]
CRC	FORCP	LINC00675	BRI3BP		Tumor suppressor	Proliferation and metastasis	[146]
PC	circCCDC7-180aa	circCCDC7		FLRT3	Tumor suppressor	Proliferation and metastasis	[147]
CRC	SRSP	LOC90024	SRSF3	L-Sp4 protein	Tumor promotor	Proliferation and metastasis	[148]
HCC	AC115619-22aa	AC115619	WTAP	WTAP/METTL3/ METTL14	Tumor suppressor	Proliferation and metastasis	[149]
HNSCC	MIAC	RP11-469H8.6	AQP2	SEPT2/ITGB4	Tumor suppressor	Proliferation and metastasis	[150]
OS	LINC00665-18aa	LINC00665	CREB1	RSK2	Tumor suppressor	Proliferation	[151]
GC	circCOL6A3_030_198aa	circCOL6A3_030			Tumor promotor	Proliferation and metastasis	[152]
BC	SEMA4B-211aa	circSEMA4B	p110	AKT	Tumor suppressor	Proliferation and metastasis	[153]
GBM	SHPRH-146aa	circ-SHPRH	SHPRH	PCNA	Tumor suppressor	Proliferation	[66]
GC	pep-AKR1C2	lncRKR1C2		FAO/ CPT1A	Tumor promotor	Lymph-angiogenesis	[156]
TNBC	XBP1SBM	MLLT4-AS1	XBP1s/XBP1a	XBP1/VEGF	Tumor promotor	Angiogenesis	[158]
TNBC	ASRPS	LINC00908	STAT3	VEGF	Tumor suppressor	Angiogenesis	[159]
EC	CORO1C-47aa	circ-0000437	ANRT	TACC3/VEGF/ VEGFR	Tumor suppressor	Angiogenesis	[160, 161]
BC	LINC00511-133aa	LINC00511		Wnt/β-catenin	Tumor promotor	Stemness	[162]
NB	sPEP1	HNFF4A-AS1	eEF1A1	SMAD4	Tumor promotor	Stemness	[163]
GBM	C-E-Cad	circ-E-Cad	EGFR	EGFR/STAT3	Tumor promotor	Stemness	[164]
GBM	SMO-193a.a	circ-SMO	SMO	Hedgehog	Tumor promotor	Stemness	[165]
OS	KEAP1-259aa	circKEAP	ARIH1	Vimentin	Tumor suppressor	Stemness	[166]
NSCLC	ATMLP	AFAP1-AS1	NIPSNAP1		Tumor promotor	Malignant differentiation	[167]
Epithelial tumors	pTINCR	TINCR	SUMO/CDC42	p53	Tumor suppressor	Malignant differentiation	[168]

Table 1 (continued)

Cancer	Peptide	NcRNA	Interacting protein	Downstream pathways/ molecules	Function	Biological behavior	References
CRC/ESCC	SP0495	KIAA0495	phospho-inositides	BECN1/p62/AKT	Tumor suppressor	Senecence	[169]
HCC	PINT87aa	circPINTexon2	FOXM1	PHB2	Tumor suppressor	Senecence	[170]
ICC	circFOXP1-231aa	circFOXP1	OTUD4	NCOA4	Tumor suppressor	Ferroptosis	[173]
Melanoma	circPIAS1-108aa	circPIAS1	Ranbp2	STAT1/ SLC7A11/ GPX4	Tumor promotor	Ferroptosis	[174]
NSCLC	LINC00954-ORF	LINC00954			Tumor promotor	Chemoresistance	[175]
HCC	circMAP3K4-455aa	circMAP3K4	AIF		Tumor promotor	Chemoresistance	[176]
CRC	pep-AP	lnc-AP	TALDO1		Tumor suppressor	Chemoresistance	[177]
GBM	SPECC1-415aa	circSPECC1	ANAX2	EGFR/AKT	Tumor suppressor	Chemoresistance	[178]
TNBC	TRIM1-269aa	circTRIM1	MARCKS	PI3K/AKT/mTOR	Tumor promotor	Chemoresistance	[179]
BC	C-E-cad	circ-E-Cad		CXCL8/EGFR	Tumor promotor	Targeted drug resistance	[180]
PDAC	RASON	LINC00673	KRASG12D/V	KRAS	Tumor promotor	Targeted drug resistance	[181]
NSCLC	C-IGF1R	cIGF1R	VDAC1	Parkin	Tumor suppressor	Targeted drug resistance	[182]
HCC	circZKSaa	circZKSCAN1	FBXW7	mTOR	Tumor suppressor	Targeted drug resistance	[183]
GBM	PINT87aa	circPINTexon2	PAF1	CPEB1	Tumor promotor	Radioresistance	[184]
BC	PACMP	CTD-2256P15.2	KLHL15	CtIP	Tumor promotor	Chemoresistance, targeted drug resistance and, radioresistance	[185]

the growth and metastasis of cancer cells [114]. In triple-negative breast cancer (TNBC), EIF6-224aa, encoded by circ-EIF6, can bind to the MYH9 protein and activate the Wnt/β-catenin pathway to promote cancer cell growth and metastasis [115].

STAT signaling. cGGNBP2-184aa, a peptide encoded by circGGNBP2, promotes the proliferation and invasion of intrahepatic cholangiocarcinoma (ICC) cells through an interaction with STAT3 [116].

NF-κB signaling. A study showed that peptides encoded by ORF3 of RNF217-AS1 attenuate the proliferation and invasion of GC cells by inhibiting the TLR4/NF-κB/STAT1 pathway [117].

Hippo signaling. CircPPP1R12A-73aa, encoded by circPPP1R12A, activates the Hippo–YAP pathway and promotes the growth and metastasis of colon cancer cells [118].

Several key proteins, while not integral components of the signaling pathway, nonetheless exert significant regulatory influences on tumor progression. The role of EGFR in tumors is self-evident. The membrane peptide rtEGFR-83aa, which is encoded by circ-EGFR, promotes GBM progression by reducing the degradation of ubiquitinated EGFR through interactions with EGFR [119]. MIAC, a peptide encoded by RP11-469H.6, can directly interact with AQP2 and inhibit the growth and metastasis of renal cancer cells by regulating the EREG/EGFR axis [120]. Abnormal expression of cyclins is closely linked to the proliferation of cancer cells. SMIM30 promotes the G1/S transition of the cell cycle by decreasing cytoplasmic Ca2+ levels and upregulating the CDK4/cyclinE2/p-Rb/E2F1 axis in HCC cells [121]. SHPRH-146aa, encoded by circ-SHPRH, not only upregulates the expression of p21 while downregulating the levels of CDK4, CDK6, Cyclin D, and CDK1 but also interacts with the transcription factor RUNX1 to increase the expression of NFKBIA [122, 123]. Notably, the physicochemical properties of the extracellular matrix (ECM) are important for the survival

and metastasis of cancer cells. A study conducted on BC cells revealed that ORF5 of MAG2-AS3 has the potential to encode an unreported peptide that can interact with ECM-related proteins, resulting in the inhibition of cancer cell proliferation and invasion [124].

Metabolic reprogramming represents a fundamental hallmark of tumors [125–127]. NcRNA-encoded peptides can regulate cancer cell proliferation and metastasis by reprogramming metabolic pathways.

Glucose metabolism. One of the most prevalent metabolic alterations observed in tumor cells is abnormally active glycolysis [128, 129]. CircMRCKα encodes a 227-aa peptide, circMRCKα-227aa, which enhances glycolysis to promote HCC progression [130]. Researchers discovered that HOXB-AS3 encodes a 53-aa peptide that competitively binds to pro-nucleotide residues in the RGG motif of hnRNPA1, thereby blocking its binding to sequences in PKM exon 9. This process results in the downregulation of PKM2 expression, the inhibition of glucose metabolism and the suppression of CRC cell proliferation and invasion [38].

Lipid metabolism. The reprogramming of lipid metabolism in cancer predominantly involves lipid uptake, lipid synthesis, fatty acid oxidation (FAO), and lipid storage [131–133]. KDM4A-AS1 and LINC01116 have been identified as the factors encoding Pep-KDM4A-AS1 and Pep-LINC01116, respectively, in esophageal squamous cell carcinoma (ESCC) cells [134]. Pep-KDM4A-AS1 has been found to downregulate stearoyl coenzyme A desaturase (SCD) and fatty acid synthase (FASN), inhibiting cancer cell viability and migration [134]. In BC, the peptide CASIMO1, which is localized to endosomes, is encoded by the lncRNA NR_029453 [135]. CASIMO1 interacts with SQLE, a key enzyme involved in cholesterol synthesis, leading to the aggregation of lipid droplets, which promotes cancer cell proliferation [135]. circINSIG1-121, encoded by circINSIG1, induces cholesterol synthesis and promotes CRC cell proliferation and invasion [136].

Mitochondrial metabolism. Mitochondrial metabolism is an extremely important physiological process within the cell that involves energy and material metabolism. ASAP is a mitochondria-distributed peptide encoded by LINC00467 [137]. ASAP can interact with ATP5A and ATP5C, resulting in increased ATP synthase activity and mitochondrial oxygen consumption, which in turn promote CRC cell proliferation [137]. A novel 113-aa nuclear peptide, p113, is encoded by a circRNA of CUX1 [138]. p113 is upregulated and facilitates fatty acid oxidation and mitochondrial activity through the formation of a trimeric complex with ZRF1 and BRD4. This complex contributes to NB cell proliferation and metastasis [138]. Furthermore, a novel tumor-suppressor peptide, miPEP133, which is encoded by pri-miR-34, is distributed in the cytoplasm and mitochondria [40]. The function of miPEP133 in mitochondria is to interact with HSAP9, thereby regulating mitochondrial function (e.g., reducing ATP production) [40].

A number of ncRNA-encoded peptides have been identified as being present and able to influence cancer cell proliferation and metastasis, but the relevant molecular mechanisms have not been described in detail; for this reason, we describe them based on their subcellular localization. Indeed, the subcellular localization of ncRNA-encoded peptides is intricately linked to their functional roles and underlying mechanisms [139]. Notably, not all studies of ncRNA-encoded peptides have described their subcellular localization, and we call for studies to refine their subcellular localization.

Nucleus. LINC013026-68AA is a peptide encoded by LINC013026 that is localized in the perinuclear region and is capable of promoting the proliferation of HCC cells [140]. C20orf204-189AA, which is localized in the nucleus and encoded by LINC00176, has been shown to bind to nucleolin and rRNA, forming a trimeric complex that promotes HCC cell proliferation [141]. Furthermore, a novel peptide, TP53LC04, which is encoded by lncAC022075.1 in the HepG2 cell line and is localized in the nucleus, promotes the proliferation of HepG2 cells [142]. YY1BM, encoded by LINC00278, is located in the nucleus, binds to YY1, inhibits the interaction between YY1 and AR, and promotes the apoptosis of ESCC cells [143].

Cytoplasm. Both CIP2A-BP and KRASIM are cytoplasmic peptides, the former encoded by LINC00665 and the latter by NCBP2-AS2 [144, 145]. CIP2A-BP interacts with CIP2A to inhibit the PI3K/AKT/NF-κB pathway and exert antitumor effects [144]. KRASIM interacts with KRAS to inhibit the KARS/ERK pathway and suppress the growth and metastasis of HCC cells [145].

Endoplasmic reticulum. FORCP, encoded by LINC00675, is localized in the endoplasmic reticulum (ER) and interacts with BRI3BP to impede the progression of CRC [146].

Cell membrane. CircCCDC7-180aa, encoded by circCCDC7, is a secreted peptide localized to the Golgi apparatus and cell membranes that can inhibit the proliferation and invasion of prostate cancer (PC) cells [147].

Furthermore, ncRNA-encoded peptides can influence cancer cell proliferation and metastasis through alternative mechanisms. The lncRNA LOC90024 encodes a peptide that interacts with SRSF3, thus earning the name SRSP. SRSP increases the binding of SRSF3 to exon 3 of the transcription factor Sp4, thereby facilitating the formation of the "cancerous" long Sp4 heterodimer (L-Sp4 protein) and promoting CRC progression

[148]. AC115619-22aa, encoded by AC115619, inhibits the proliferation and metastasis of HCC cells by decreasing global m6A levels [149]. MIAC directly interacts with AQP2 to inhibit the growth and metastasis of HNSCC cells by regulating the SEPT2/ITGB4 pathway [150]. LINC00665 encodes LINC00665-18aa, a peptide that weakens the interaction between CREB1 and RSK2 by blocking the nuclear localization of CREB1, thus inhibiting the growth of osteosarcoma (OS) cells [151]. In addition, circCOL6A3_030_198aa and SEMA4B-211aa can affect the proliferation and metastasis of cancer cells [152, 153] (Fig. 6).

NcRNA-encoded peptides regulate the tumor vasculature

Tumor growth and metastasis are intimately associated with the tumor vasculature [154]. The vasculature furnishes oxygen and nutrients to tumor cells, and the novel vasculature might offer pathways for tumor cells to metastasize [155]. The tumor vasculature system is primarily composed of blood vessels and lymphatic vessels [126]. NcRNA-encoded peptides have been established as regulators of the tumor vasculature.

One study revealed that CM-248aa levels are correlated with lymphatic metastasis in GC patients, suggesting a relationship between circRNA-encoded peptides and tumor lymphatics [102]. Another study revealed that the exosomal lncAKR1C2, which is highly expressed in GC cells, can be secreted into HLEC cells, where it encodes pep-AKR1C2 [156]. This peptide interacts with and inhibits the phosphorylation of YAP, promotes the expression of FAO and CPT1A, and potentially induces lymphangiogenesis through fatty acid metabolism [156].

In addition to the encouraging results observed in anticancer therapy with antiangiogenic drugs such as bevacizumab, the targeting of ncRNA-encoded peptides may also prove to be an effective method of inhibiting tumor angiogenesis [157]. A novel molecular target for antiangiogenic therapy in TNBC, XBP1SBM, is encoded

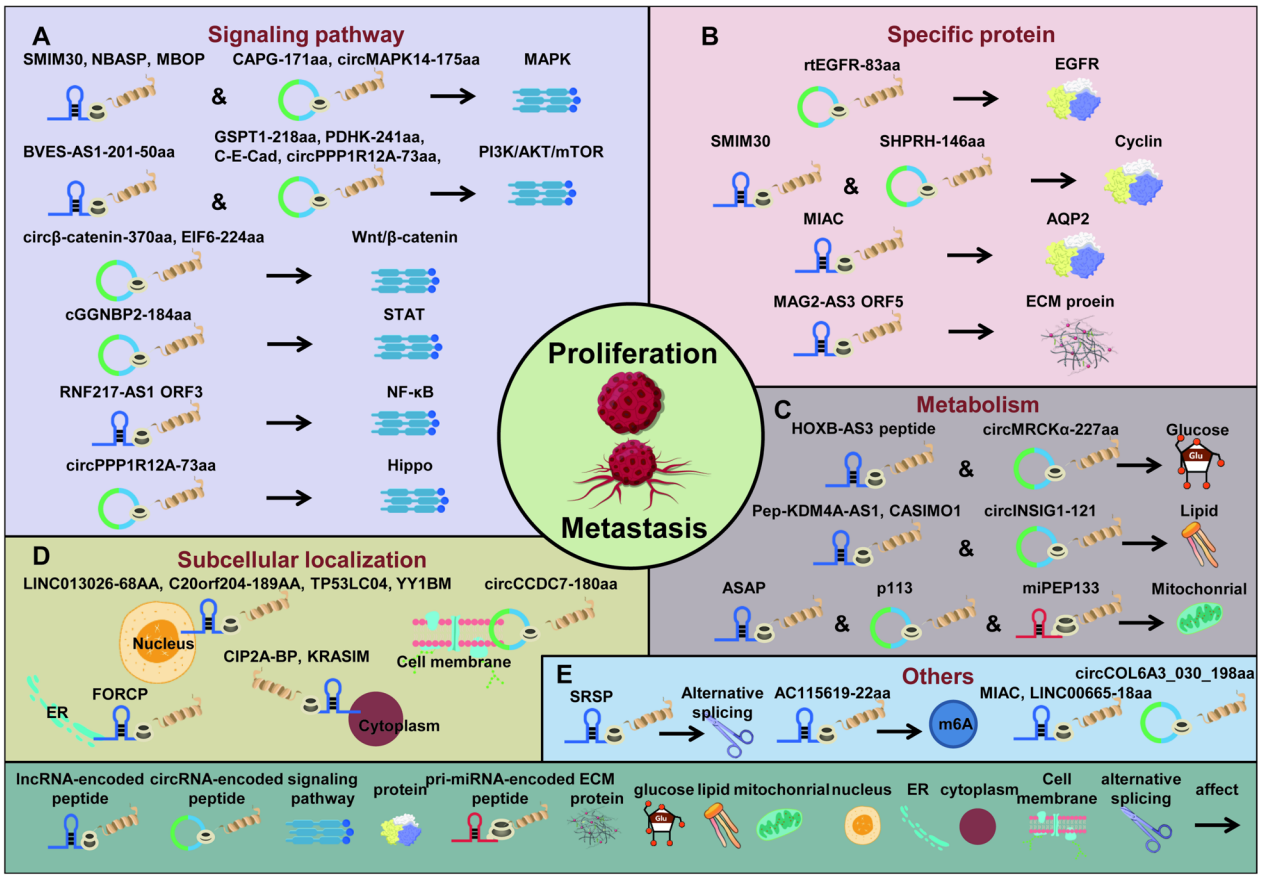

Fig. 6 Different perspectives summarize ncRNA-encoded peptides associated with proliferation and metastasis. **A** NcRNA-encoded peptides regulate cancer cell proliferation and metastasis through multiple signaling pathways. **B** NcRNA-encoded peptides regulate cancer cell proliferation and metastasis by affecting specific proteins. **C** NcRNA-encoded peptides regulate cancer cell proliferation and metastasis through metabolic reprogramming. **D** NcRNA-encoded peptides in different organelles can influence cancer cell proliferation and metastasis. **E** NcRNA-encoded peptides regulate cancer cell proliferation and metastasis through other mechanisms

by MLLT4-AS1. XBP1SBM has the capacity to inhibit the interaction of XBP1s and XBP1a while simultaneously upregulating VEGF, thereby promoting angiogenesis [158]. Conceivably, certain endogenously expressed ncRNA-encoded peptides may serve as novel antiangiogenic drugs. ASRPS is a tumor suppressor gene in TNBC with low endogenous expression. ASRPS, which is encoded by LINC00908, inhibits the phosphorylation of STAT3 by interacting with the coiled-coil domain of STAT3 [159]. This process results in the downregulation of VEGF expression and the inhibition of angiogenesis [159]. CORO1C-47aa, encoded by circ-0000437 in endometrial cancer (EC), is a secreted peptide that is localized within the nucleus. CORO1C-47aa competitively interacts with ARNT and TACC3, leading to the downregulation of VEGF expression and the inhibition of angiogenesis [160, 161].

NcRNA-encoded peptides regulate stemness and malignant differentiation

The majority of studies indicate that ncRNA-encoded peptides play roles in the maintenance of stemness in cancer cells and in the malignant transformation of epithelial cells. Researchers discovered that LINC00511-133aa, which is encoded by LINC00511, plays a role in the nuclear translocation of β-catenin and the subsequent activation of the Wnt/β-catenin pathway, leading to an increase in the stemness of BC cells [162]. In NB, HNFF4A-AS1 encodes a peptide designated sPEP1 that interacts with eEF1A1 and facilitates its binding to SMAD4 [163]. This complex ultimately contributes to the promotion of cancer cell stemness and invasion. In GBM, circ-E-Cad encodes a secreted peptide, C-E-Cad, which promotes glioma stem cell tumorigenicity through the activation of EGFR/STAT3 signaling [164]. A further study of GBM revealed that circ-SMO encodes a peptide, SMO-193a.a., which is localized in the cytoplasm and cell membrane. The interaction between SMO-193a.a. and SMO activates the downstream Hedgehog signaling pathway, contributing to the self-renewal ability of cancer stem cells [165]. At present, only one circRNA-encoding peptide that has the capacity to inhibit cancer cell stemness has been identified. KEAP1-259aa, encoded by circKEAP, is able to bind to the E3 ligase ARIH1, leading to the ubiquitination and degradation of vimentin and inhibition of stemness in OS cells [166].

The role of the ncRNA-encoded peptide-mediated malignant transformation of epithelial cells in tumor evolution must be acknowledged. ATMLP is a peptide that is localized to mitochondria and is encoded by AFAP1-AS [167]. In NSCLC, ATMLP binds to NIPSNAP1 and traps it in the inner mitochondrial membrane, thereby antagonizing NIPSNAP1-mediated autophagic lysosome formation and promoting the malignant transformation of epithelial cells [167]. In epithelial histiocytocarcinoma, pTINCR is a ubiquitin-like protein encoded by TINCR that is localized to the nucleus [168]. pTINCR interacts with SUMO to promote the SUMOylation of CDC42, which in turn promotes epithelial cell differentiation [168] (Fig. 7).

NcRNA-encoded peptides regulate senescence

Two studies have shown that ncRNA-encoded peptides can induce the senescence of tumor cells. The lncRNA KIAA0495 is downregulated in a variety of cancers, and it can encode the peptide SP0495, which induces senescence in cancer cells [169]. Mechanistically, SP0495 functions as a lipid-binding protein that interacts with phosphoinositides, thereby inhibiting AKT phosphorylation and its downstream signaling pathways [169]. Additionally, SP0495 plays a role in regulating the stability of BECN1 and p62, which in turn induces cellular autophagy [169]. PINT87aa was initially identified in GBM, and subsequent investigations revealed that PINT87aa expression was diminished in HCC. PINT87aa binds to the DNA-binding domain of FOXM1, blocking FOXM1-mediated PHB2 transcription, inducing cellular senescence and reducing mitochondrial autophagy [170].

NcRNA-encoded peptides regulate ferroptosis

Ferroptosis is a form of programmed cell death that depends on iron [171, 172]. In ICC, circFOXP1-227aa, which is encoded by circFOXP1, interacts with OTUD4 to promote the expression of the NCOA4 protein and induce ferroptosis [173]. The circPIAS1 gene encodes the oncogenic peptide circPIAS1-108aa. This peptide has been shown to bind to the SUMO E3 ligase Ranbp2 in the nucleus, thereby enhancing the SUMOylation of STAT1 at Lys703 and Glu705. Consequently, STAT1 phosphorylation (Tyr701) is inhibited, the SLC7A11/GPX4 signaling pathway is activated, and IFNγ-induced ferroptosis in melanoma cells is hindered [174] (Fig. 8).

NcRNA-encoded peptides regulate chemoresistance, targeted drug resistance and radioresistance

Drug resistance and radioresistance are critical factors contributing to the failure of tumor treatment. Enhancing the sensitivity of tumors to chemotherapy, targeted therapy, and radiotherapy remains a critical scientific challenge that requires innovative solutions. NcRNA-encoded peptides are expected to solve this problem from a completely new perspective.

Chemotherapy is one of the most widely used forms of tumor treatment. Several studies have reported the relationship between ncRNA-encoded peptides and chemotherapy. The LINC00954-ORF encoded by LINC00954

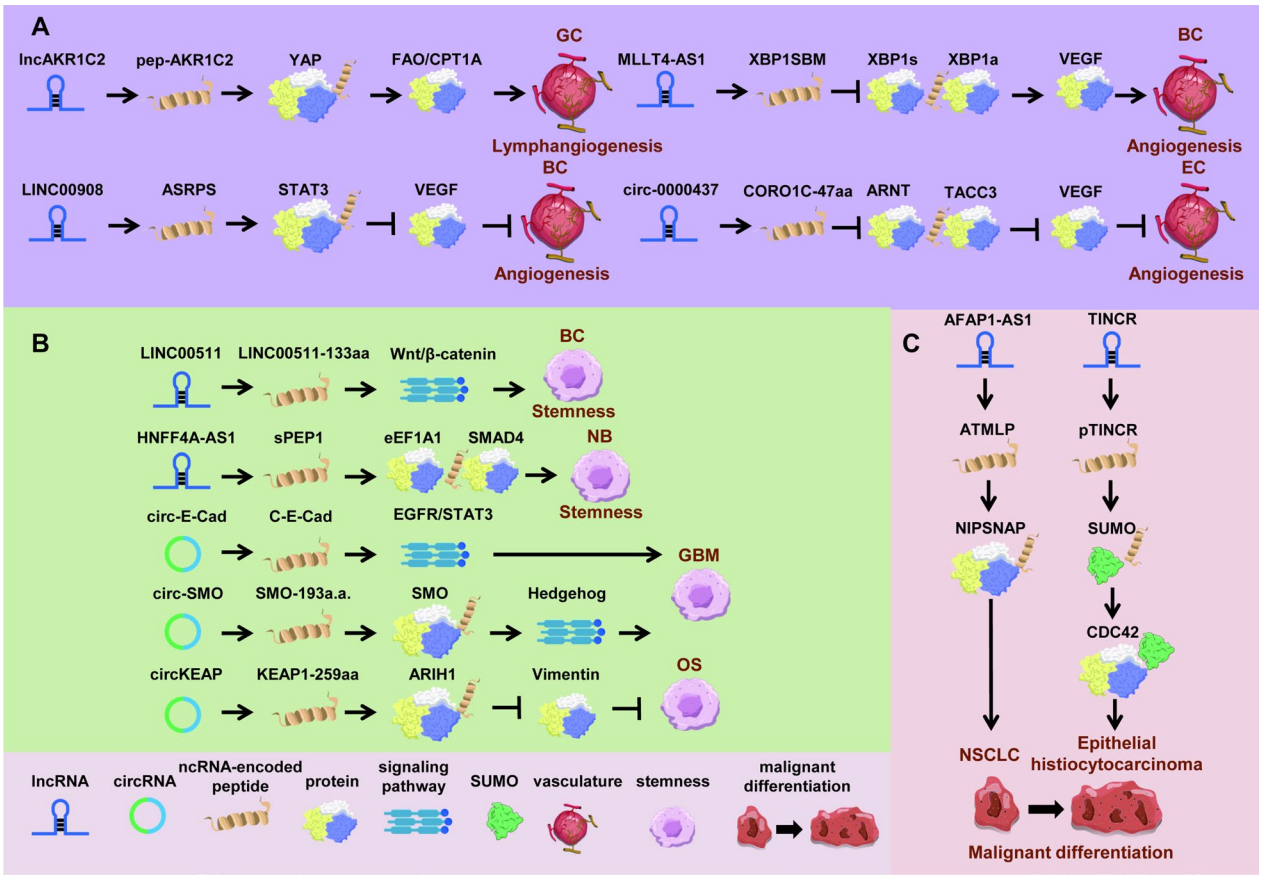

Fig. 7 The role of ncRNA-encoded peptides in vasculature, stemness and malignant differentiation. **A** NcRNA-encoded peptides regulate lymphangiogenesis and angiogenesis through various molecular mechanisms. **B** NcRNA-encoded peptides regulate stemness through various molecular mechanisms. **C** NcRNA-encoded peptides regulate malignant differentiation through various molecular mechanisms

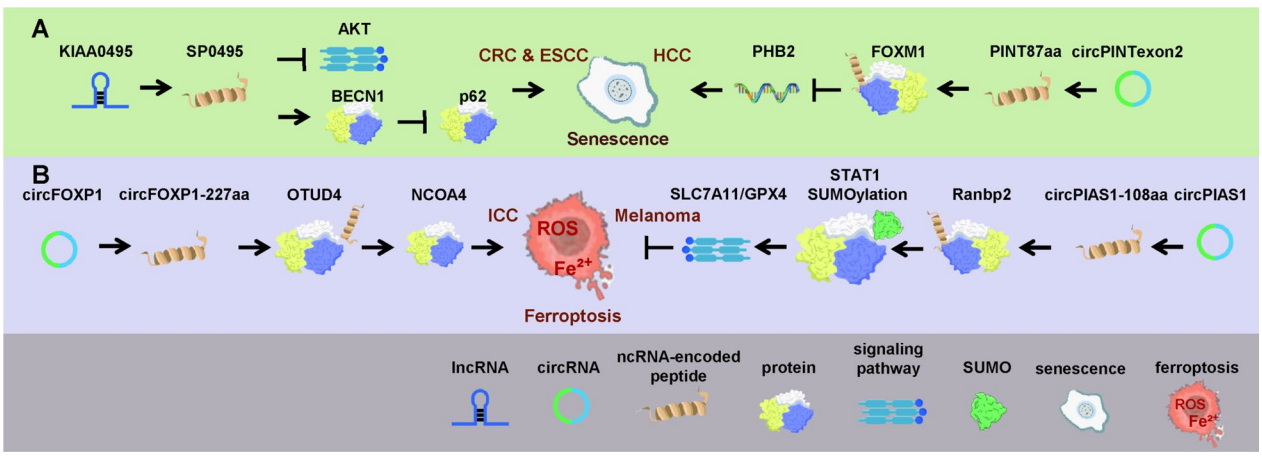

Fig. 8 The role of ncRNA-encoded peptides in senescence and ferroptosis. **A** NcRNA-encoded peptides regulate senescence through various molecular mechanisms. **B** NcRNA-encoded peptides regulate ferroptosis through various molecular mechanisms

increases pemetrexed resistance in A549 cells [175]. However, the molecular mechanism has not been elucidated. NcRNA-encoded peptides can also influence the efficacy of platinum compounds. CircMAP3K4-455aa, encoded by circMAP3K4, interacts with AIF, thereby reducing the N-terminal cleavage and nuclear distribution of AIF and inhibiting the cisplatin-induced apoptosis of HCC cells [176]. Pep-AP, which is encoded by lnc-AP, binds to TALDO1 and downregulates TALDO1 expression. Mechanistically, pep-AP can attenuate the pentose phosphate pathway (PPP), decrease NADPH/NADP+ and GSH levels, and increase ROS levels, increasing oxaliplatin sensitivity in CRC [177]. Furthermore, ncRNA-encoded peptides can influence the efficacy of two categories of chemotherapy agents: alkylating agents and antitumor antibiotics. In GBM, circSPECC1 encodes the SPECC1-415aa protein, which precludes the binding of ANAX2 to EGFR, inhibits EGFR/AKT signaling, and increases the sensitivity of GBM cells to temozolomide (TMZ) [178]. The circTRIM1-encoded TRIM1-269aa peptide interacts with MARCKS, resulting in the translocation of MARCKS from the cell membrane to the cytoplasm [179]. This process activates the PI3K/AKT/mTOR pathway and induces DOX resistance in TNBC cells [179]. A common feature of these chemotherapeutic agents is that they can disrupt DNA structure; therefore, whether these ncRNA-encoding peptides can directly alter the spatial conformation of DNA remains to be determined.

Molecularly targeted agents are more selective and effective than traditional chemotherapeutics and cause less damage to normal cells. The objective of anti-PD-1 therapy is to target PD-1 on the surface of T cells, thereby activating these cells to increase their ability to eliminate tumor cells. C-E-cad can impede the functionality of CD4+ and CD8+ T cells by recruiting myeloid-derived suppressor cells (MDSCs), particularly PMN-MDSCs. Based on this phenomenon, researchers have shown that combined therapy with anti-C-E-cad and anti-PD-1 could increase anti-PD-1 antibody efficacy [180]. These findings suggest that treatments targeting ncRNA-encoded peptides could help to enhance the effects of targeted drugs. The majority of studies on the effects of ncRNA-encoded peptides on targeted drug sensitivity have focused on EGFR-TKIs. Researchers have reported increased expression of RASON, which is encoded by LINC00673, in pancreatic ductal adenocarcinoma (PDAC). The direct binding of RASON to KRASG12D/V facilitates the maintenance of KRASG12D/V in a highly active GTP-bound state. The deprivation of RASON has been shown to sensitize KRAS-mutant pancreatic cancer cells and patient-derived organoids to EGFR-TKIs [181]. cIGF1R encodes the antitumor peptide C-IGF1R that interacts with VDAC1, resulting in reduced ubiquitination of VDAC1 and limiting mitosis in NSCLC cells in the EGFR-TKI drug-tolerant persister (DTP) state [182]. Sorafenib is a multikinase inhibitor. One study suggested that circZKSaa, which is encoded by circZKSCAN1, can form a trimeric complex with FBXW7 and mTOR [183]. This complex promotes the degradation of ubiquitinated mTOR and increases sorafenib sensitivity in HCC [183]. Since some other ncRNA-encoded peptides (e.g., rtEGFR-83aa) can also directly or indirectly regulate the expression of these target proteins, further investigations of whether these ncRNA-encoded peptides can also affect the sensitivity of targeted drugs are worthwhile.

The effect of ncRNA-encoded peptides on the radiosensitivity of tumor cells was initially reported in GBM. The peptide PINT87aa encoded by circPINTexon2 is located in the nucleus, and PINT87aa increases the affinity of PAF1 for the CPEB1 promoter by interacting with the 150–300 aa sequence of PAF1, thereby increasing the radiosensitivity of cancer cells [184]. The DNA damage response is associated with anticancer therapeutic benefits. A study of BC indicated that PACMP, a novel peptide encoded by CTD-2256P15.2, may represent a promising target for anticancer therapy. The dual function of PACMP is to maintain the CtIP abundance and promote poly(ADP-ribosyl)ation. Targeting PACMP alone has been shown to inhibit tumor growth through a synthetic lethal interaction between CtIP and PARP inhibition and to confer sensitivity to PARP/ATR/CDK4/6 inhibitors, ionizing radiation, epirubicin, and camptothecin [185] (Fig. 9).

NcRNA-encoded peptides regulate biological behaviors of cancer cells through PTMs

Researchers have generally accepted that ncRNA-encoded peptides perform their biological functions by binding to a specific protein and affecting the expression or activity of that protein. This finding raises the question of how ncRNA-encoded peptides regulate the expression or activity of their interacting proteins. Posttranslational modifications (PTMs) likely play a significant role in this process and warrant further investigation. Compared with proteins, ncRNA-encoded peptides have a smaller three-dimensional structure, which is reflected in the fact that ncRNA-encoded peptides typically interact with only certain amino acids or regions of a protein. This spatial conformational binding can expose or mask modification sites on the protein. Even if the ncRNA-encoded peptide binds to the modifying enzyme, it may affect the interaction between the modifying enzyme and the substrate protein, thereby affecting the PTM. NcRNA-encoded peptides are attracting attention for

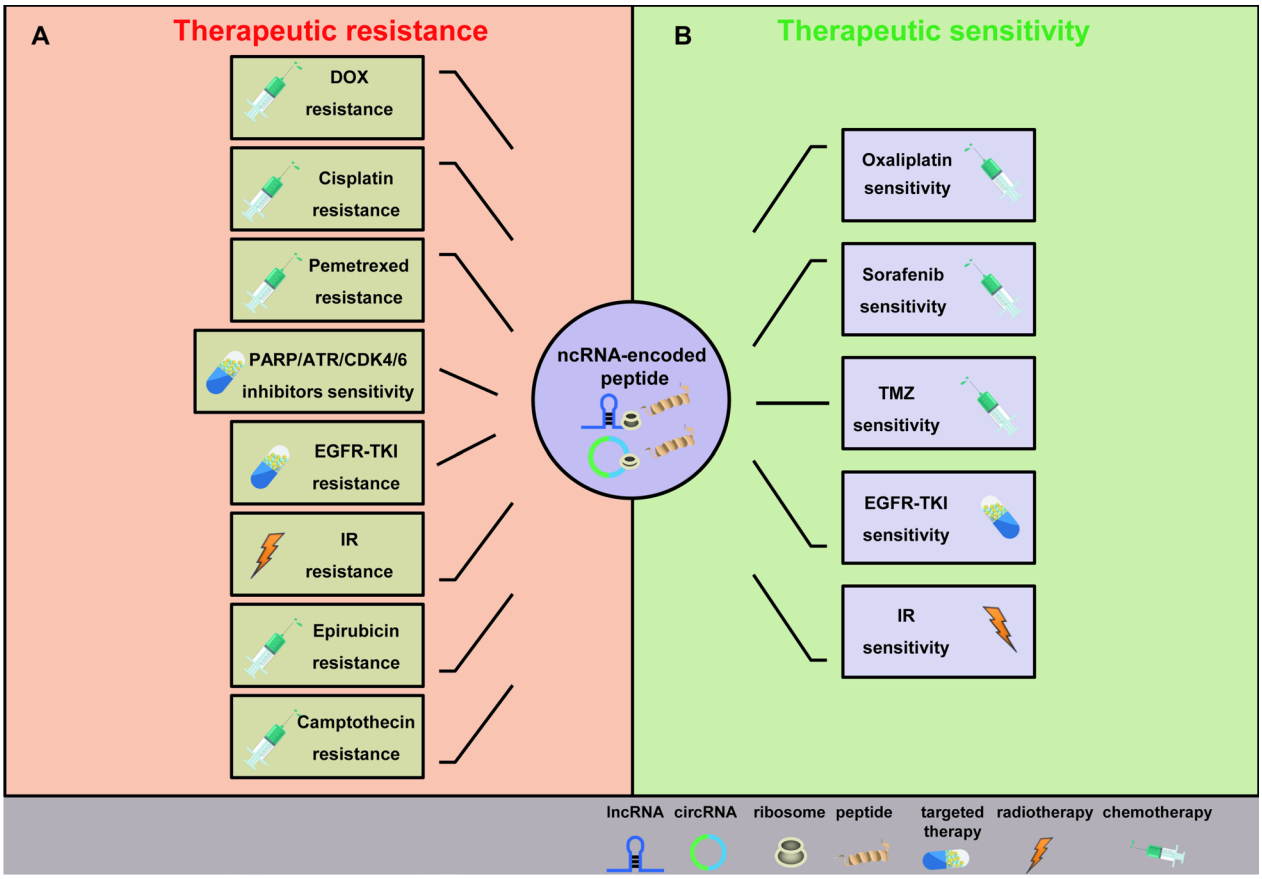

Fig. 9 The role of ncRNA-encoded peptides in therapeutic resistance and therapeutic sensitivity. **A** NcRNA-encoded peptides act as oncogenes that promote DOX, cisplatin, pemetrexed, PARP/ATR/CDK4/6 inhibitors, EGFR-TKI, IR, epirubicin and camptothecin resistance in cancer cells. **B** NcRNA-encoded peptides act as tumor suppressor genes that promote oxaliplatin, sorafenib, TMZ, EGFR-TKI and IR sensitivity in cancer cells

their ability to regulate the biological behavior of cancer through PTMs (Table 2).

NcRNA-encoded peptides regulate phosphorylation

Protein phosphorylation is a process that is catalyzed by a protein kinase (PK) to transfer the phosphate group at the γ-site of ATP or GTP to the amino acid residues of a substrate protein [186, 187]. The reverse of this process is the removal of the corresponding phosphate group by a protein phosphatase [188, 189]. Protein phosphorylation is capable of influencing protein activity, protein subcellular localization, and the activation of numerous signaling pathways [190–193].

NcRNA-encoded peptides can interact with protein kinases or protein phosphatases to indirectly regulate protein phosphorylation in an enzyme-mediated manner and affect the proliferation and metastasis of cancer cells. The peptide SMIM30 serves as an adapter for the membrane anchoring and activation status of SEC/YES1 [104]. SRC/YES1 is a member of the nonreceptor tyrosine kinase family [194, 195]. SMIM30 binds to the N-terminal membrane association domain of SRC/YES1, leading to increased phosphorylation at site P-416 and decreased expression at site P-527 of SRC/YES1, thereby activating MAPK signaling and promoting HCC cell growth and metastasis [104]. The peptide PDHK1-241aa can induce the phosphorylation of AKT at Thr308 to promote the proliferation and invasion of ccRCC cells. However, PDHK1-241aa does not directly bind to AKT. Instead, the H-ATPase domain of PDHK1-241aa interacts with PPP1CA (serine/threonine protein phosphatase), facilitating the nuclear translocation of PPP1CA and inhibiting the dephosphorylation of AKT [113].

NcRNA-encoded peptides have the capacity to bind directly to protein phosphorylation sites, which can impede the attachment of the phosphate group to the protein. One study revealed that the 62–122 aa region of cGGNBP2-184aa is capable of interacting with the DNA-binding domain of STAT3 to induce phosphorylation at the Tyr705 site of STAT3 and promote the proliferation and invasion of ICC cells [116]. The peptide ASRPS

Table 2 Effects of ncRNA-encoded peptides on PTMs and their functions

Cancer	Peptide	PTM of protein	Site and influence	Function	Biological behavior	References
HCC	SMIM30	SRC/YES1 phosphorylation	Promotion at P-416 Inhibition at P-527	Tumor promotor	Proliferation and metastasis	[104]
ccRCC	PDHK1-241aa	AKT phosphorylation	Promotion at Thr-308	Tumor promotor	Proliferation and metastasis	[113]
ICC	cGGNBP2-184aa	STAT3 phosphorylation	Promotion at Tyr-705	Tumor promotor	Proliferation and metastasis	[116]
BC	ASRPS	STAT3 phosphorylation	Promotion	Tumor suppressor	Angiogenesis	[159]
GBM	C-E-Cad	EGFR phosphorylation	Promotion	Tumor promotor	Stemness	[164]
BC	SEMA4B-211aa	AKT phosphorylation	Inhibition at Thr-308	Tumor suppressor	Proliferation and metastasis	[153]
NB	NBASP	FABP5 ubiquitination	Promotion	Tumor suppressor	Proliferation and metastasis	[106]
BC	EIF6-224aa	MYH9 ubiquitination	Inhibition	Tumor suppressor	Proliferation and metastasis	[115]
BC	PACMP	CtIP K48-ubiquitination	Inhibition	Tumor promotor	Chemoresistance, targeted drug resistance and, radioresistance	[185]
CRC	circINSIG1-121	INSIG1 K48-ubiquitination	Promotion at K-156 and K-158	Tumor promotor	Proliferation and metastasis	[136]
HCC	circMRCKα-227aa	HIF-1α ubiquitination	Inhibition	Tumor promotor	Proliferation and metastasis	[130]
ICC	circFOXP1-231aa	NCOA4 ubiquitination	Inhibition	Tumor suppressor	Ferroptosis	[173]
NSCLC	C-IGF1R	VADC ubiquitination	Inhibition at K-110	Tumor suppressor	Targeted drug resistance	[182]
HCC	circZKSaa	mTOR ubiquitination	Promotion at K-631 and K-635	Tumor suppressor	Targeted drug resistance	[183]
GBM	SHPRH-146aa	SHPRH and PCNA ubiquitination	Inhibition of SHPRH and promotion of PCNA	Tumor suppressor	Proliferation	[66]
BC	CAPG-171aa	MEKK2 ubiquitination	Inhibition	Tumor promotor	Proliferation and metastasis	[105]
NSCLC	circβ-catenin-370aa	β-catenin phosphorylation and ubiquitination	Inhibition	Tumor promotor	Proliferation and metastasis	[114]
BC	PACMP	PARylation	Promotion	Tumor promotor	Chemoresistance, targeted drug resistance and, radioresistance	[185]
GBM	SMO-193a.a	SMO phosphorylation and cholesterol modification	Promotion	Tumor promotor	Malignant differentiation	[165]
Melanoma	circPIAS1-108aa	STAT1 SUMOylation and phosphorylation	Promote SUMOylation at Lys-703 and Glu-705 Inhibit phosphorylation at Tyr-701	Tumor promotor	Ferroptosis	[174]
Epithelial tumors	pTINCR	CDC42 SUMOylation	Promotion	Tumor promotor	Malignant differentiation	[168]

inhibits angiogenesis by blocking the phosphorylation of STAT3 at Tyr705 [159]. On the one hand, ASRPS inhibits STAT3 phosphorylation by blocking the interaction between JAK2 (a typical kinase of STAT3) and STAT3 [159]. On the other hand, ASRPS binds to the STAT3 coiled-coil domain, a structural domain that is also the region where R116 (a STAT3 allosteric inhibitor) interacts with STAT3, suggesting that ASRPS may directly mask the phosphorylation site of STAT3 [159].

Intriguingly, ncRNA-encoded peptides can regulate protein phosphorylation either through receptor–ligand binding or by influencing second messengers. The peptide C-E-Cad is associated with the CR2 domain of EGFR via the specific 144-amino-acid carboxyl terminus, which activates EGFR independently of EGF and promotes EGFR phosphorylation. This process helps to increase the tumorigenicity of glioma stem cells [63]. SEMA4B-211aa, a cytoplasmic peptide, competitively interacts with p85

to p110, reducing the generation of the second messenger PIP3 and thereby suppressing the phosphorylation of AKT at Thr308 and the proliferation and metastasis of BC cells [153].

NcRNA-encoded peptides regulate ubiquitination

The primary function of ubiquitination is to induce the degradation of substrate proteins by the 26S proteasome [196, 197]. The ubiquitin-activating enzyme E1, ubiquitin-conjugating enzyme E2, ubiquitin-ligase E3 and deubiquitinating enzymes are involved in the process of protein ubiquitination [198–201]. In addition, according to the quantity of ubiquitin bound to the substrate, ubiquitination can be divided into monoubiquitination and polyubiquitination, among which the polyubiquitination of K48-linked chains and K63-linked chains is of particular interest [202–204].

Recent research has indicated that ncRNA-encoded peptides may regulate tumor progression by modulating protein ubiquitination. The peptide NBASP can interact with FABP5, promoting its ubiquitination, thereby inhibiting the proliferation and metastasis of neuroblastoma (NB) cells [106]. Conversely, the peptide EIF6-224aa interacts with the regions 1–500 aa and 1461–1960 aa of MYH9, inhibiting the ubiquitination of MYH9 and thereby inhibiting the proliferation and metastasis of TNBC cells [115]. However, these two studies did not identify the relevant ubiquitination sites or modifying enzymes. Notably, a study revealed that SHPRH-146aa can safeguard SHPRH from degradation by the ubiquitin–proteasome system. Consequently, stabilized SHPRH functions as an E3 ligase to promote the ubiquitination of PCNA, thereby inhibiting the proliferation and tumorigenicity of GBM [66].

The majority of studies have shown that the ubiquitination of ncRNA-encoded peptide regulatory proteins is achieved by E3 ligases or deubiquitinating enzymes (DUBs). The peptide PACMP can inhibit the K48 polyubiquitination of CtIP by blocking the binding of CtIP to KLHL15 [185]. Mechanistically, KLHL15 is a substrate-specific adapter for the CUL3 E3 ligase [205, 206]. The kelch domain of KLHL15 and the PACMP compete for binding to the C-terminal domain of CtIP, resulting in a reduction in CtIP ubiquitination. This process can cause cancer cells to become resistant to multiple treatment modalities [185]. The peptide circINSIG1-121 promotes the K48-linked ubiquitination of the key cholesterol metabolism regulator INSIG1 at the K156 and K158 sites by recruiting the CUL5-ASB6 complex. This process contributes to the proliferation and metastasis of CRC cells [136]. The USP family of proteins is a common class of DUBs [207]. The 1–113 aa region of the peptide circMRCKα-227aa can interact with the 1–160 aa region of USP22, which contains a zinc finger structural domain, to increase the protein level of USP22 and mediate the deubiquitination of HIF-1α. This process enhances glycolysis to promote HCC progression [130]. The peptide circFOXP1-231aa induces ferroptosis, and mechanistically, circFOXP1-231aa interacts with the 1–976 aa region of OTUD4, resulting in the deubiquitination of NCOA4 [173].

NcRNA-encoded peptides can directly bind to lysine residues on proteins, thereby influencing their ubiquitination. A study revealed that the peptide C-IGF1R can interact with the 91–136 aa region of VADC. Moreover, K110 plays a pivotal role in the regulation of VADC1 ubiquitination by C-IGF1R [182]. The interaction of C-IGF1R with VADC1 impedes the accessibility of this ubiquitination site, which in turn inhibits the ubiquitination of VADC. Additionally, C-IGF1R disrupts the interaction of VADC1 with Parkin, thereby preventing the Parkin-mediated ubiquitination of VADC1 and increasing EGFR-TKIs sensitivity in NSCLC [182]. The peptide circZKSaa increases sorafenib sensitivity in HCC cells. Mechanistically, K631 and K635 of mTOR are key sites recognized by the E3 ligase FBXW7. circZKSaa can bind directly to the K631 and K635 sites of mTOR and amplify the FBXW7-mediated ubiquitination of mTOR [183].

NcRNA-encoded peptides regulate phosphorylation-mediated ubiquitination

Phosphorylation is a critical component of the ubiquitinated protein degradation signaling pathway [208, 209]. A considerable number of ubiquitinated substrate proteins are initially subjected to phosphorylation before being recognized by the corresponding ubiquitin ligases, which then induce the degradation of the ubiquitinated protein [210, 211]. Currently, studies of ncRNA-encoded peptides that affect phosphorylation-mediated ubiquitination are related mainly to cancer cell proliferation and metastasis. SMURF1 is a SMAD-specific E3 ligase that regulates the ubiquitination of MEKK2 [212]. The peptide CAPG-171aa can inhibit MEKK2 ubiquitination by weakening the interaction between STK38 (a member of a subfamily of the AGC kinase family) and SMURF1, which promote proliferation and metastasis in BC [105]. Researchers have hypothesized that the stability of β-catenin depends on its phosphorylation status [213, 214]. β-catenin phosphorylated by GSK-3β (a serine/threonine kinase) can be ubiquitinated by β-TrCP and then degraded by the proteasome [215]. The interaction between circβ-catenin-370aa and GSK-3β inhibits the phosphorylation of β-catenin by GSK-3β, consequently reducing the ubiquitination and degradation of β-catenin. This process facilitates proliferation and metastasis of NSCLC cells [114].

Phosphorylation-mediated ubiquitination is a complex process. For example, when cells are exposed to external stimuli (e.g., radiotherapy, photodynamic therapy, thermotherapy, etc.), protein phosphorylation can occur, which in turn triggers ubiquitination modifications that lead to protein degradation or functional changes at specific times and in specific locations. Therefore, exploring the relationship between ncRNA-encoded peptides and phosphorylation-mediated ubiquitination may provide new insights to improve the efficacy of antitumor therapy.

NcRNA-encoded peptides regulate other PTMs

Poly(ADP-ribosyl)ation (PARylation), the earliest PTM occurring during double-strand break (DSB) repair and lasting for only approximately 15 min, significantly contributes to the repair of damaged DNA [216–218]. The peptide PACMP may regulate cancer progression and drug resistance by regulating the DNA damage response (DDR). As mentioned previously, PACMP can orchestrate the ubiquitination of CtIP. Notably, PACMP can also directly bind DNA damage-induced poly(ADP-ribose) chains to facilitate PARP1-dependent PARylation following DNA damage [185].

The SMO protein serves as a crucial signal transmitter within the Hedgehog signaling pathway [219, 220]. The peptide SMO-193a.a. is capable of binding directly to the N-terminus of SMO and increasing SMO phosphorylation and cholesterol modification through unknown mechanisms that are independent of GRK2 and CKIα [165]. This process can increase the stemness of GBM cells [165]. The peptide circPIAS1-108aa, which binds to the SUMO E3 ligase Ranbp2 in the nucleus, increases STAT1 SUMOylation (Lys703 and Glu705)) and thus blocks STAT1 phosphorylation (Tyr701) [174]. This peptide can inhibit the ferroptosis of melanoma cells [174].

The peptide pTINCR is a ubiquitin-like protein, and the C-terminal part of pTINCR contains two well-conserved and overlapping SUMO-interacting motifs (SIMs). The binding of pTINCR and SUMO facilitates the interaction with CDC42 and increases the SUMOylation and activity of CDC42. This process promotes the malignant differentiation of epithelial cells [168].

Notably, the types of PTMs are not limited to those mentioned above, and ncRNA-encoded peptides may regulate tumor progression through other types of PTMs that are yet to be discovered (Fig. 10).

Perspectives and conclusions

NcRNA-encoded peptides have garnered significant attention because of their observed biological functions in tumors. Notably, a minority of lncRNA-encoded peptides exhibit opposing functions to those of their parental lncRNAs. A previous study revealed that AF127577.4 is associated with a higher GBM grade and shorter patient survival, whereas the peptide AF127577.4-ORF encoded by AF127577.4 is negatively correlated with the GBM grade [221]. Furthermore, AF127577.4-ORF has the capacity to form a complex with ERK2 and METTL3, thereby reducing the interaction between ERK2 and METTL3 and inhibiting the growth of GBM cells [221]. The peptide CIP2A-BP encoded by LINC00665 is a potential tumor suppressor gene for BC [144], but another study showed that LINC00665 promotes BC progression via the miR-379-5p/LIN28B axis [222]. Importantly, identical peptides can exert contrasting effects across different tumor types. For example, CIP2A-BP functions as a tumor suppressor gene in TNBC but acts as an oncogene in HCC [144, 223]. Similarly, the 53-aa peptide encoded by HOXB-AS3 has opposite effects on CRC and ESCC [38, 224]. This phenomenon underscores the importance of precision medicine.

In recent years, the development of cancer vaccines based on ncRNA-encoded peptides has been impressive [225]. Peptides derived from noncanonical ORFs, particularly those of lncRNAs, are highly specific to hepatocellular carcinoma (HCC) [226]. Some peptides are capable of participating in the process of tumorigenesis or of activating T-cell responses following vaccination or blockade by checkpoint inhibitors [226]. A study of CRC revealed that lncRNA PVT1-encoded peptides presented by HLA-1 molecules were recognized by patients' CD8+ tumor-infiltrating lymphocytes and peripheral blood mononuclear cells, indicating immune surveillance in patients [227]. Another study used proteogenomics to identify lncRNA-encoded peptides that are presented by class I HLA from melanoma and EGFR-mutated lung adenocarcinomas [228]. Similarly, circRNA-derived peptides have been identified in the immunopeptidome of melanoma and lung cancer samples [229]. The results of these studies collectively indicate that ncRNAs may encode peptides that bind to human leukocyte antigens (HLAs) and function as cryptic antigens, thereby stimulating adaptive immunity [229]. A recent study identified a specific cryptic antigen. By employing HLA-1 immunoprecipitation and mass spectrometry, whole-exome sequencing, Ribo-seq, and RNA-seq, the researchers were able to ascertain that circFAM53B is capable of encoding circFAM53B-219, a peptide whose expression in BC and melanoma enhances adaptive immunity and improves the prognosis of patients with tumors [39, 230].

NcRNA-encoded peptides with anticancer effects may represent a novel modality for anticancer therapy [231, 232]. Given that ncRNA-encoded peptides that act as tumor suppressor genes are typically endogenous, this finding suggests a reduced risk of rejection and side effects, with the added benefit of high biosafety.

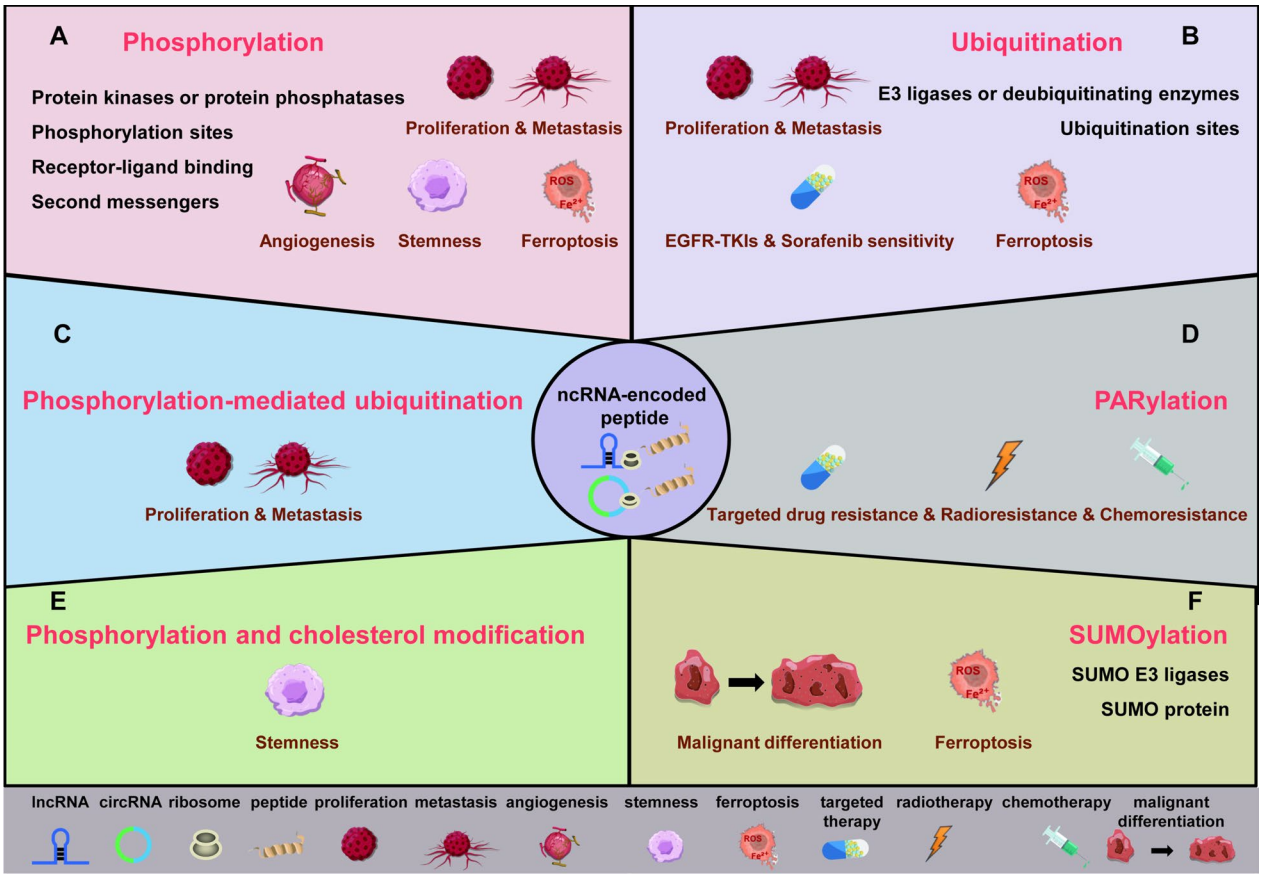

Fig. 10 NcRNA-encoded peptides regulate the biological behavior of cancer cells through PTMs. **A** NcRNA-encoded peptides can regulate protein phosphorylation by affecting protein kinases or protein phosphatases, binding to protein phosphorylation sites, affecting receptor-ligand binding, and affecting second messengers, which in turn modulates cancer cell proliferation, metastasis, angiogenesis, stemness, and ferroptosis. **B** NcRNA-encoded peptides can regulate protein ubiquitination by affecting E3 ligases or deubiquitinating enzymes and binding to protein ubiquitination sites, which in turn modulates cancer cell proliferation, metastasis, EGFR-TKI sensitivity, sorafenib sensitivity and ferroptosis. **C** NcRNA-encoded peptides can regulate cancer cell proliferation and metastasis by affecting phosphorylation-mediated ubiquitination. **D** NcRNA-encoded peptides can regulate cancer cell targeted drug resistance, radioresistance and chemoresistance by affecting PARylation. **E** NcRNA-encoded peptides can regulate cancer cell stemness by affecting phosphorylation and cholesterol modification. **F** NcRNA-encoded peptides can regulate protein SUMOylation by affecting SUMO E3 ligases and binding to SUMO protein, which in turn modulate cancer cell malignant differentiation and ferroptosis

The administration of peptides (such as CIP2A-BP and MIAC) to animals has shown the potential for significant inhibitory effects on cancerous tissue growth [120, 144]. Direct incorporation of the anticancer peptide AC115619-22aa (500 mg/ml) into the culture medium inhibits the proliferation and invasion of hepatocellular carcinoma (HCC) cells. Furthermore, the administration of AC115619-22aa via a physical hydrogel is anticipated to represent an efficacious approach for the treatment of cancer with ncRNA-encoded peptides [149]. Fortunately, the combination of targeted ncRNA-encoded peptides and targeted drugs has improved the efficacy of the latter. Notably, the combination of an anti-C-E-cad antibody targeting the oncogene C-E-cad and an anti-PD-1 antibody has the potential to increase the efficacy of the anti-PD-1 antibody [180]. The utilization of ASOs that are specifically designed to target and reduce the levels of circPIAS1 (which is equivalent to reducing circPIAS1-108aa levels) in conjunction with PD-1 inhibitors significantly improves the efficacy of immunotherapy [174]. Combination therapy with cetuximab and RASON shRNA increases cetuximab sensitivity in KRAS-mutant PDAC cells [181]. However, the development and clinical application of such peptides remain challenging and ongoing processes. A more detailed understanding of their toxicity and side effects is necessary (Fig. 11).

NcRNA-encoded peptides may serve as biomarkers for the early diagnosis and prognosis of tumors. For example,

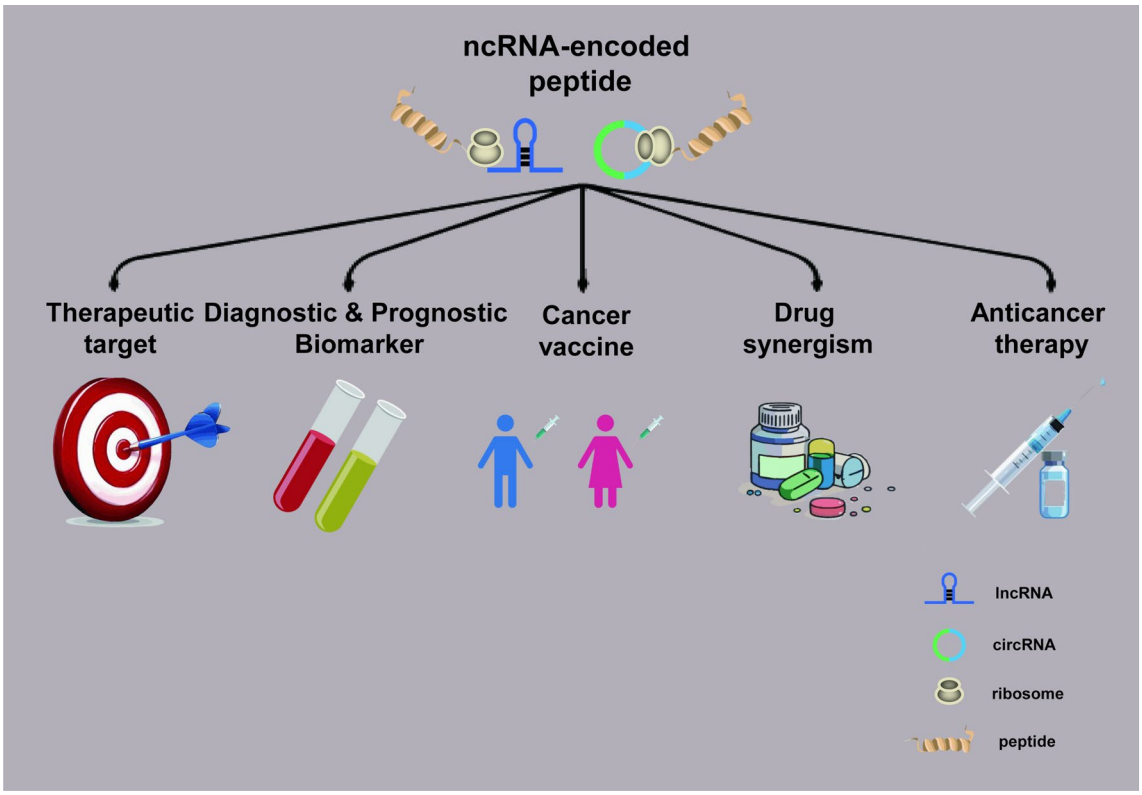

Fig. 11 Potential applications of ncRNA-encoded peptides. The prospective role of ncRNA-encoded peptides in cancer clinical treatment: therapeutic targets, diagnostic and prognostic biomarkers, cancer vaccines, drug synergism, and anticancer therapy

the peptide CRNDEP, which is encoded by the lncRNA CRNDE, is overexpressed in highly aggressive ovarian cancers compared with benign tumors. CRNDEP is a negative, independent, prognostic, and predictive factor in patients with high-grade ovarian cancer (hgOvCa) [233, 234]. In addition, some ncRNA-encoded peptides (e.g., circCCDC7-180aa and C-HGF) can be detected in conditioned media [103, 147]. Although the relevant secretion mechanism remains unclear, these findings are encouraging and suggest that ncRNA-encoded peptides in body fluids may be novel biomarkers. Indeed, a study established a computational–proteogenomic workflow and observed upregulated expression of five lncRNA-encoded polypeptides in COAD tissues [235]. Furthermore, COAD patients were classified by clinical stratification. Moreover, researchers have identified disparities in the concentrations of these polypeptides in the plasma of prostate cancer patients, underscoring their potential as plasma biomarkers [235]. Another study employed an ELISA to detect markedly elevated levels of ATMLP in the serum of NSCLC patients compared with healthy individuals [167]. In the future, the development of kits to monitor the levels of specific ncRNA-encoded peptides in the body fluids of cancer patients will facilitate early diagnosis and prognostic judgments (Table 3).

Importantly, ncRNA-encoded peptides may result in false-positive or false-negative outcomes because of their low molecular weight, low abundance, and unstable half-life. Additionally, this review explores the impacts of ncRNA-encoded peptides on PTMs of interacting proteins, a regulatory process that researchers now frequently investigate using AI-simulated molecular docking. However, the simulated peptide structures inevitably deviate from their real structures. In future studies, the use of cryo-electron microscopy, X-ray crystal diffraction, and nuclear magnetic resonance analyses to obtain detailed structural information on ncRNA-encoded peptides is crucial for research on ncRNA-encoded peptides [236, 237]. Importantly, the PTMs of ncRNA-encoded peptides are likely pivotal for their structural integrity and biological functions. In a previous study, the peptide LINC013026-68AA was identified as a factor that promotes the proliferation of HCC cells. LINC013026-68AA has five potential serine phosphorylation sites, two threonine phosphorylation sites, and one tyrosine phosphorylation site. The researchers observed two additional bands on

Table 3 The applications of ncRNA-encoded peptides

Cancer	Peptide	NcRNA	Application	References
CRC	lncRNA PVT1-encoded peptides	lncRNA PVT1	Cancer vaccines	[227]
BC and melanoma	circFAM53B-219	circFAM53B	Cancer vaccines	[39, 230]
TNBC	CIP2A-BP	LINC00665	Anticancer therapy	[144]
RCC	MIAC	RP11-469H8.6	Anticancer therapy	[120]
HCC	AC115619-22aa	AC115619	Anticancer therapy	[149]
BC	C-E-cad	circ-E-Cad	Therapeutic target and drug synergism	[180]
Melanoma	circPIAS1-108aa	circPIAS1	Therapeutic target and drug synergism	[174]
PDAC	RASON	LINC00673	Therapeutic target and drug synergism	[181]
hgOvCa	CRNDEP	CRNDE	Prognostic biomarker	[233, 234]
PC	circCCDC7-180aa	circCCDC7	Biomarker	[147]
GBM	C-HGF	circ-HGF	Biomarker	[103]
COAD and prostate cancer	five lncRNA-encoding polypeptides		Biomarker	[235]
NSCLC	ATMLP	AFAP1-AS1	Diagnostic biomarker	[167]

SDS–PAGE gels after the cell lysates with proteins containing phosphorylated tyrosine, serine, and threonine residues were dephosphorylated by lambda protein phosphatase (Lambda PP), which may indicate the possible phosphorylation of LINC013026-68AA [140]. Like proteins, ncRNA-encoded peptides may undergo extensive PTMs, which are crucial for maintaining the structural and biological functions of these peptides. However, this area remains largely unexplored. In the future, the development of ncRNA-encoded peptides as therapeutic agents for tumor treatment, along with engineering modifications such as glycosylation and lactylation of ncRNA-encoded peptides, may increase their stability and targeting capabilities, thereby improving both biosafety and efficacy.

In conclusion, this review systematically summarizes the latest research advancements regarding ncRNA-encoded peptides in oncology. We present the impacts of ncRNA-encoded peptides on the biological functions of cancer cells and describe their molecular mechanisms. Particular emphasis is placed on the effects of these peptides on PTMs and their promising application prospects. These findings not only enrich our understanding of ncRNA-encoded peptides but also provide novel insights for the early diagnosis, precise treatment, and prognostic monitoring of cancer.

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Author contributions
S.T. and Y.W. drafted the manuscript and prepared the figures. Z.R., Q.P., X.X., X.J., Z.W., L.O., X.L., J.L., L.X., M.P., N.W. and Y.T. helped collect the related studies and participated in discussions. Y.H., Q.L. and Y.Z. designed the review and revised the manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare that they have no competing interests.

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References

1. Poliseno L, Lanza M, Pandolfi PP. Coding, or non-coding, that is the question. Cell Res. 2024;34(9):609–29.
2. Wu P, Mo Y, Peng M, Tang T, Zhong Y, Deng X, et al. Emerging role of tumor-related functional peptides encoded by lncRNA and circRNA. Mol Cancer. 2020;19(1):22.
3. Zhou H, Wu Y, Cai J, Zhang D, Lan D, Dai X, et al. Micropeptides: potential treatment strategies for cancer. Cancer Cell Int. 2024;24(1):134.
4. Wang J, Zhu S, Meng N, He Y, Lu R, Yan GR. ncRNA-encoded peptides or proteins and cancer. Mol Ther. 2019;27(10):1718–25.
5. Huang J, Yang P, Pan W, Wu F, Qiu J, Ma Z. The role of polypeptides encoded by ncRNAs in cancer. Gene. 2024;928: 148817.

6. Mattick JS, Makunin IV. Non-coding RNA. Hum Mol Genet. 2006;15:R17-29.
7. Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. Annu Rev Biochem. 2012;81:145–66.
8. Mattick JS. A new paradigm for developmental biology. J Exp Biol. 2007;210(Pt 9):1526–47.
9. Magny EG, Pueyo JI, Pearl FM, Cespedes MA, Niven JE, Bishop SA, et al. Conserved regulation of cardiac calcium uptake by peptides encoded in small open reading frames. Science. 2013;341(6150):1116–20.
10. Kondo T, Plaza S, Zanet J, Benrabah E, Valenti P, Hashimoto Y, et al. Small peptides switch the transcriptional activity of Shavenbaby during Drosophila embryogenesis. Science. 2010;329(5989):336–9.
11. Maximov V, Martynenko A, Hunsmann G, Tarantul V. Mitochondrial 16S rRNA gene encodes a functional peptide, a potential drug for Alzheimer's disease and target for cancer therapy. Med Hypotheses. 2002;59(6):670–3.
12. Anderson DM, Anderson KM, Chang CL, Makarewich CA, Nelson BR, McAnally JR, et al. A micropeptide encoded by a putative long noncoding RNA regulates muscle performance. Cell. 2015;160(4):595–606.
13. Lauressergues D, Couzigou JM, Clemente HS, Martinez Y, Dunand C, Becard G, et al. Primary transcripts of microRNAs encode regulatory peptides. Nature. 2015;520(7545):90–3.
14. Legnini I, Di Timoteo G, Rossi F, Morlando M, Briganti F, Sthandier O, et al. Circ-ZNF609 is a circular RNA that can be translated and functions in myogenesis. Mol Cell. 2017;66(1):22–37.
15. Chakrabarti A, Kaushik M, Khan J, Soota D, Ponnusamy K, Saini S, et al. tREPs-a new class of functional tRNA-encoded peptides. ACS Omega. 2022;7(22):18361–73.
16. Kang YJ, Yang DC, Kong L, Hou M, Meng YQ, Wei L, et al. CPC2: a fast and accurate coding potential calculator based on sequence intrinsic features. Nucleic Acids Res. 2017;45(W1):W12–6.
17. Wang L, Park HJ, Dasari S, Wang S, Kocher JP, Li W. CPAT: coding-potential assessment tool using an alignment-free logistic regression model. Nucleic Acids Res. 2013;41(6): e74.
18. Hanada K, Akiyama K, Sakurai T, Toyoda T, Shinozaki K, Shiu SH. sORF finder: a program package to identify small open reading frames with high coding potential. Bioinformatics. 2010;26(3):399–400.
19. Lin MF, Jungreis I, Kellis M. PhyloCSF: a comparative genomics method to distinguish protein coding and non-coding regions. Bioinformatics. 2011;27(13):i275–82.
20. Dragomir MP, Manyam GC, Ott LF, Berland L, Knutsen E, Ivan C, et al. FuncPEP: a database of functional peptides encoded by non-coding RNAs. Noncoding RNA. 2020;6(4):41.
21. Liu H, Zhou X, Yuan M, Zhou S, Huang YE, Hou F, et al. ncEP: a manually curated database for experimentally validated ncRNA-encoded proteins or peptides. J Mol Biol. 2020;432(11):3364–8.
22. Liu T, Wu J, Wu Y, Hu W, Fang Z, Wang Z, et al. LncPep: a resource of translational evidences for lncRNAs. Front Cell Dev Biol. 2022;10: 795084.
23. Chen X, Han P, Zhou T, Guo X, Song X, Li Y. circRNADb: a comprehensive database for human circular RNAs with protein-coding annotations. Sci Rep. 2016;6:34985.
24. Luo X, Huang Y, Li H, Luo Y, Zuo Z, Ren J, et al. SPENCER: a comprehensive database for small peptides encoded by noncoding RNAs in cancer patients. Nucleic Acids Res. 2022;50(D1):D1373–81.
25. Ingolia NT, Lareau LF, Weissman JS. Ribosome profiling of mouse embryonic stem cells reveals the complexity and dynamics of mammalian proteomes. Cell. 2011;147(4):789–802.
26. Ingolia NT, Brar GA, Rouskin S, McGeachy AM, Weissman JS. The ribosome profiling strategy for monitoring translation in vivo by deep sequencing of ribosome-protected mRNA fragments. Nat Protoc. 2012;7(8):1534–50.
27. Schwaid AG, Shannon DA, Ma J, Slavoff SA, Levin JZ, Weerapana E, et al. Chemoproteomic discovery of cysteine-containing human short open reading frames. J Am Chem Soc. 2013;135(45):16750–3.
28. Na Z, Dai X, Zheng SJ, Bryant CJ, Loh KH, Su H, et al. Mapping subcellular localizations of unannotated microproteins and alternative proteins with MicroID. Mol Cell. 2022;82(15):2900–11.
29. Guttman M, Russell P, Ingolia NT, Weissman JS, Lander ES. Ribosome profiling provides evidence that large noncoding RNAs do not encode proteins. Cell. 2013;154(1):240–51.
30. Liu S, Huang J, Zhou J, Chen S, Zheng W, Liu C, et al. NAP-seq reveals multiple classes of structured noncoding RNAs with regulatory functions. Nat Commun. 2024;15(1):2425.
31. Saville L, Wu L, Habtewold J, Cheng Y, Gollen B, Mitchell L, et al. NERD-seq: a novel approach of Nanopore direct RNA sequencing that expands representation of non-coding RNAs. Genome Biol. 2024;25(1):233.
32. Zhang J, Lu H, Jiang Y, Ma Y, Deng L. ncRNA coding potential prediction using BiLSTM and transformer encoder-based model. J Chem Inf Model. 2024;64(16):6712–22.
33. Consortium EP, Birney E, Stamatoyannopoulos JA, Dutta A, Guigo R, Gingeras TR, et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature. 2007;447(7146):799–816.
34. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. Nature. 2001;409(6822):860–921.
35. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. Science. 2001;291(5507):1304–51.
36. Luo Y, Wang H, Wang L, Wu W, Zhao J, Li X, et al. LncRNA MEG3: targeting the molecular mechanisms and pathogenic causes of metabolic diseases. Curr Med Chem. 2024;31(37):6140–53.
37. Koffler-Brill T, Noy Y, Avraham KB. The long and short: Non-coding RNAs in the mammalian inner ear. Hear Res. 2023;428: 108666.
38. Huang JZ, Chen M, Chen D, Gao XC, Zhu S, Huang H, et al. A peptide encoded by a putative lncRNA HOXB-AS3 suppresses colon cancer growth. Mol Cell. 2017;68(1):171–84.
39. Huang D, Zhu X, Ye S, Zhang J, Liao J, Zhang N, et al. Tumour circular RNAs elicit anti-tumour immunity by encoding cryptic peptides. Nature. 2024;625(7995):593–602.
40. Kang M, Tang B, Li J, Zhou Z, Liu K, Wang R, et al. Identification of miPEP133 as a novel tumor-suppressor microprotein encoded by miR-34a pri-miRNA. Mol Cancer. 2020;19(1):143.
41. Zhou Q, Yin S, Lei X, Tian Y, Lin D, Wang L, et al. The correlation between mitochondrial derived peptide (MDP) and metabolic states: a systematic review and meta-analysis. Diabetol Metab Syndr. 2024;16(1):200.
42. Shanthappa PM, Suravajhala R, Kumar G, Melethadathil N. Computational exploration of novel antimicrobial modalities targeting fucose-binding lectins and ribosomes in *Mycobacterium smegmatis* using tRNA-encoded peptides. J Biomol Struct Dyn. 2024. https://doi.org/10.1080/07391102.2024.2335555.
43. Zhang Y. LncRNA-encoded peptides in cancer. J Hematol Oncol. 2024;17(1):66.
44. Qin S, Liu Y, Zhang X, Huang P, Xia L, Leng W, et al. lncRNA FGD5-AS1 is required for gastric cancer proliferation by inhibiting cell senescence and ROS production via stabilizing YBX1. J Exp Clin Cancer Res. 2024;43(1):188.
45. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021;22(2):96–118.
46. Tian H, Tang L, Yang Z, Xiang Y, Min Q, Yin M, et al. Current understanding of functional peptides encoded by lncRNA in cancer. Cancer Cell Int. 2024;24(1):252.
47. Zeng C, Fukunaga T, Hamada M. Identification and analysis of ribosome-associated lncRNAs using ribosome profiling data. BMC Genomics. 2018;19(1):414.
48. Carlevaro-Fita J, Rahim A, Guigo R, Vardy LA, Johnson R. Cytoplasmic long noncoding RNAs are frequently bound to and degraded at ribosomes in human cells. RNA. 2016;22(6):867–82.
49. Duffy EE, Finander B, Choi G, Carter AC, Pritisanac I, Alam A, et al. Developmental dynamics of RNA translation in the human brain. Nat Neurosci. 2022;25(10):1353–65.
50. Zhang Q, Wu E, Tang Y, Cai T, Zhang L, Wang J, et al. Deeply mining a universe of peptides encoded by long noncoding RNAs. Mol Cell Proteomics. 2021;20: 100109.
51. Szafron LM, Balcerak A, Grzybowska EA, Pienkowska-Grela B, Felisiak-Golabek A, Podgorska A, et al. The novel gene CRNDE encodes a nuclear peptide (CRNDEP) which is overexpressed in highly proliferating tissues. PLoS ONE. 2015;10(5): e0127475.
52. Liu CX, Chen LL. Circular RNAs: characterization, cellular roles, and applications. Cell. 2022;185(12):2016–34.

53. Zhang W, Xu C, Yang Z, Zhou J, Peng W, Zhang X, et al. Circular RNAs in tumor immunity and immunotherapy. Mol Cancer. 2024;23(1):171.
54. Zheng W, Wang L, Geng S, Xu T. CircYthdc2 generates polypeptides through two translation strategies to facilitate virus escape. Cell Mol Life Sci. 2024;81(1):91.
55. Zhang L, Gao H, Li X, Yu F, Li P. The important regulatory roles of circRNA-encoded proteins or peptides in cancer pathogenesis (Review). Int J Oncol. 2024;64(2):19.
56. Deng X, Yu YV, Jin YN. Non-canonical translation in cancer: significance and therapeutic potential of non-canonical ORFs, m(6)A-modification, and circular RNAs. Cell Death Discov. 2024;10(1):412.
57. Song J, Ge Y, Dong M, Guan Q, Ju M, Song X, et al. Molecular interplay between EIF4 family and circular RNAs in cancer: mechanisms and therapeutics. Eur J Pharmacol. 2023;954: 175867.
58. Lin HH, Chang CY, Huang YR, Shen CH, Wu YC, Chang KL, et al. Exon junction complex mediates the cap-independent translation of circular RNA. Mol Cancer Res. 2023;21(11):1220–33.
59. Zeng K, Peng J, Xing Y, Zhang L, Zeng P, Li W, 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.
60. Chen R, Wang SK, Belk JA, Amaya L, Li Z, Cardenas A, et al. Engineering circular RNA for enhanced protein production. Nat Biotechnol. 2023;41(2):262–72.
61. Hwang HJ, Kim YK. Molecular mechanisms of circular RNA translation. Exp Mol Med. 2024;56(6):1272–80.
62. Jiang Y, Chen X, Zhang W. Overexpression-based detection of translatable circular RNAs is vulnerable to coexistent linear RNA byproducts. Biochem Biophys Res Commun. 2021;558:189–95.
63. Gao X, Xia X, Li F, Zhang M, Zhou H, Wu X, 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.
64. Welden JR, Margvelani G, Arizaca Maquera KA, Gudlavalleti B, Miranda Sardon SC, Campos AR, et al. RNA editing of microtubule-associated protein tau circular RNAs promotes their translation and tau tangle formation. Nucleic Acids Res. 2022;50(22):12979–96.
65. Nakamoto K, Abe H. Chemical synthesis of circular RNAs with phosphoramidate linkages for rolling-circle translation. Curr Protoc. 2021;1(3):e43.
66. Zhang M, Huang N, Yang X, Luo J, Yan S, Xiao F, et al. A novel protein encoded by the circular form of the SHPRH gene suppresses glioma tumorigenesis. Oncogene. 2018;37(13):1805–14.
67. Begum S, Yiu A, Stebbing J, Castellano L. Novel tumour suppressive protein encoded by circular RNA, circ-SHPRH, in glioblastomas. Oncogene. 2018;37(30):4055–7.
68. Shang R, Lee S, Senavirathne G, Lai EC. microRNAs in action: biogenesis, function and regulation. Nat Rev Genet. 2023;24(12):816–33.
69. Li X, Zhou H, Lu P, Fang Z, Shi G, Tong X, et al. miPEP31 alleviates Ang II-induced hypertension in mice by occupying Cebpalpha binding sites in the pri-miR-31 promoter. Cardiovasc Diabetol. 2024;23(1):249.
70. Mao X, Zhou J, Kong L, Zhu L, Yang D, Zhang Z. A peptide encoded by lncRNA MIR7-3 host gene (MIR7-3HG) alleviates dexamethasone-induced dysfunction in pancreatic beta-cells through the PI3K/AKT signaling pathway. Biochem Biophys Res Commun. 2023;647:62–71.
71. Dozier C, Montigny A, Viladrich M, Culerrier R, Combier JP, Besson A, et al. Small ORFs as new regulators of Pri-miRNAs and miRNAs expression in human and Drosophila. Int J Mol Sci. 2022;23(10):5764.
72. Bielewicz D, Dolata J, Zielezinski A, Alaba S, Szarzynska B, Szczesniak MW, et al. mirEX: a platform for comparative exploration of plant pri-miRNA expression data. Nucleic Acids Res. 2012;40(Database issue):D191-7.
73. Lin Y, Chen Y, Zeng Y, Zhang S, Zhang Z, Chen Y, et al. Molecular characterization of miRNA genes and their expression in *Dimocarpus longan* Lour. Planta. 2021;253(2):41.
74. Li X, Zhong S, Li C, Yan X, Zhu J, Li Y, et al. RNA helicase Brr2a promotes miRNA biogenesis by properly remodelling secondary structure of pri-miRNAs. Nat Plants. 2024;10:1532–47.
75. Ormancey M, Thuleau P, Combier JP, Plaza S. The essentials on microRNA-encoded peptides from plants to animals. Biomolecules. 2023;13(2):206.
76. Erokhina TN, Ryazantsev DY, Zavriev SK, Morozov SY. Regulatory miPEP open reading frames contained in the primary transcripts of microRNAs. Int J Mol Sci. 2023;24(3):2114.
77. Yadav A, Sanyal I, Rai SP, Lata C. An overview on miRNA-encoded peptides in plant biology research. Genomics. 2021;113(4):2385–91.
78. Gautam H, Sharma A, Trivedi PK. Plant microProteins and miPEPs: small molecules with much bigger roles. Plant Sci. 2023;326: 111519.
79. Prel A, Dozier C, Combier JP, Plaza S, Besson A. Evidence that regulation of Pri-miRNA/miRNA expression is not a general rule of miPEPs function in humans. Int J Mol Sci. 2021;22(7):3432.
80. Razooky BS, Obermayer B, O'May JB, Tarakhovsky A. Viral Infection identifies micropeptides differentially regulated in smORF-containing lncRNAs. Genes (Basel). 2017;8(8):206.
81. Cui L, Zheng J, Lin Y, Lin P, Lu Y, Zheng Y, et al. Decoding the ribosome's hidden language: rRNA modifications as key players in cancer dynamics and targeted therapies. Clin Transl Med. 2024;14(5): e1705.
82. Warrier I, Walter MC, Frangoulidis D, Raghavan R, Hicks LD, Minnick MF. The intervening sequence of *Coxiella burnetii*: characterization and evolution. Front Cell Infect Microbiol. 2016;6:83.
83. Paharkova V, Alvarez G, Nakamura H, Cohen P, Lee KW. Rat Humanin is encoded and translated in mitochondria and is localized to the mitochondrial compartment where it regulates ROS production. Mol Cell Endocrinol. 2015;413:96–100.
84. Tenson T, DeBlasio A, Mankin A. A functional peptide encoded in the *Escherichia coli* 23S rRNA. Proc Natl Acad Sci U S A. 1996;93(11):5641–6.
85. Maximov VV, Martynenko AV, Arman IP, Tarantul VZ. Humanin binds MPP8: mapping interaction sites of the peptide and protein. J Pept Sci. 2013;19(5):301–7.
86. Minasyan L, Sreekumar PG, Hinton DR, Kannan R. Protective mechanisms of the mitochondrial-derived peptide humanin in oxidative and endoplasmic reticulum stress in RPE cells. Oxid Med Cell Longev. 2017;2017:1675230.
87. Gruschus JM, Morris DL, Tjandra N. Evidence of natural selection in the mitochondrial-derived peptides humanin and SHLP6. Sci Rep. 2023;13(1):14110.
88. Cobb LJ, Lee C, Xiao J, Yen K, Wong RG, Nakamura HK, et al. Naturally occurring mitochondrial-derived peptides are age-dependent regulators of apoptosis, insulin sensitivity, and inflammatory markers. Aging (Albany NY). 2016;8(4):796–809.
89. Yin Y, Li Y, Ma B, Ren C, Zhao S, Li J, et al. Mitochondrial-derived peptide MOTS-c suppresses ovarian cancer progression by attenuating USP7-mediated LARS1 deubiquitination. Adv Sci (Weinh). 2024;11:e2405620.
90. Zhang Z, Chen D, Du K, Huang Y, Li X, Li Q, et al. MOTS-c: a potential anti-pulmonary fibrosis factor derived by mitochondria. Mitochondrion. 2023;71:76–82.
91. Domin R, Pytka M, Zolynski M, Nizinski J, Rucinski M, Guzik P, et al. MOTS-c serum concentration positively correlates with lower-body muscle strength and is not related to maximal oxygen uptake-a preliminary study. Int J Mol Sci. 2023;24(19):14951.
92. Kavak AG, Karslioglu I, Saracaloglu A, Demiryurek S, Demiryurek AT. Impact of radiation therapy on serum humanin and MOTS-c levels in patients with lung or breast cancer. Curr Radiopharm. 2024;17(3):229–37.
93. Xiao J, Howard L, Wan J, Wiggins E, Vidal A, Cohen P, et al. Low circulating levels of the mitochondrial-peptide hormone SHLP2: novel biomarker for prostate cancer risk. Oncotarget. 2017;8(55):94900–9.
94. Ramirez-Torres A, Reagan AL, Howard LE, Wiggins E, Vidal AC, Wan J, et al. Racial differences in circulating mitochondria-derived peptides may contribute to prostate cancer health disparities. Prostate. 2022;82(13):1248–57.
95. Kaminski K, Blatkiewicz M, Szyszka M, Olechnowicz A, Komarowska H, Klimont A, et al. Expression patterns of MOTS-c in adrenal tumors: results from a preliminary study. Int J Mol Sci. 2024;25(16):8721.
96. Kuhle B, Chen Q, Schimmel P. tRNA renovatio: rebirth through fragmentation. Mol Cell. 2023;83(22):3953–71.
97. Biela A, Hammermeister A, Kaczmarczyk I, Walczak M, Koziej L, Lin TY, et al. The diverse structural modes of tRNA binding and recognition. J Biol Chem. 2023;299(8): 104966.
98. Sharp SJ, Schaack J, Cooley L, Burke DJ, Soll D. Structure and transcription of eukaryotic tRNA genes. CRC Crit Rev Biochem. 1985;19(2):107–44.

99. Pinzaru AM, Tavazoie SF. Transfer RNAs as dynamic and critical regulators of cancer progression. Nat Rev Cancer. 2023;23(11):746–61.
100. Santos FB, Del-Bem LE. The evolution of tRNA copy number and repertoire in cellular life. Genes (Basel). 2022;14(1):27.
101. Shanthappa PM, Verma N, George A, Dhar PK, Athri P. Computational prediction of potential vaccine candidates from tRNA encoded peptides (tREP) using a bioinformatic workflow and molecular dynamics validations. IEEE/ACM Trans Comput Biol Bioinform. 2024;21(3):439–49.
102. Liu H, Fang D, Zhang C, Zhao Z, Liu Y, Zhao S, 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.
103. Saunders JT, Kumar S, Benavides-Serrato A, Holmes B, Benavides KE, Bashir MT, 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.
104. Pang Y, Liu Z, Han H, Wang B, Li W, Mao C, et al. Peptide SMIM30 promotes HCC development by inducing SRC/YES1 membrane anchoring and MAPK pathway activation. J Hepatol. 2020;73(5):1155–69.
105. Song R, Guo P, Ren X, Zhou L, Li P, Rahman NA, 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.
106. Ye M, Gao R, Chen S, Bai J, Chen J, Lu F, et al. FAM201A encodes small protein NBASP to inhibit neuroblastoma progression via inactivating MAPK pathway mediated by FABP5. Commun Biol. 2023;6(1):714.
107. Tang C, Zhou Y, Sun W, Hu H, Liu Y, Chen L, et al. Oncopeptide MBOP encoded by LINC01234 promotes colorectal cancer through MAPK signaling pathway. Cancers (Basel). 2022;14(9):2338.
108. Wang L, Zhou J, Zhang C, Chen R, Sun Q, Yang P, et al. A novel tumour suppressor protein encoded by circMAPK14 inhibits progression and metastasis of colorectal cancer by competitively binding to MKK6. Clin Transl Med. 2021;11(10): e613.
109. Hu F, Peng Y, Chang S, Luo X, Yuan Y, Zhu X, 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.
110. Zheng W, Guo Y, Zhang G, Bai J, Song Y, Song X, 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.
111. Li F, Tang H, Zhao S, Gao X, Yang L, Xu J. Circ-E-Cad encodes a protein that promotes the proliferation and migration of gastric cancer via the TGF-beta/Smad/C-E-Cad/PI3K/AKT pathway. Mol Carcinog. 2023;62(3):360–8.
112. Zhao W, Xue Y, Zhang Y, Zhu Y, Chen Z, Zhao X. A peptide translated from circPPP1R12A promotes the malignancy of non-small cell lung cancer cells through AKT signaling pathway. J Clin Lab Anal. 2022;36(10): e24644.
113. Huang B, Ren J, Ma Q, Yang F, Pan X, Zhang Y, 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.
114. Zhao W, Zhang Y, Zhu Y. Circular RNA circbeta-catenin aggravates the malignant phenotype of non-small-cell lung cancer via encoding a peptide. J Clin Lab Anal. 2021;35(9): e23900.
115. Li Y, Wang Z, Su P, Liang Y, Li Z, Zhang H, 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.
116. Li H, Lan T, Liu H, Liu C, Dai J, Xu L, et al. IL-6-induced cGGNBP2 encodes a protein to promote cell growth and metastasis in intrahepatic cholangiocarcinoma. Hepatology. 2022;75(6):1402–19.
117. Ma Q, Ma F, Zhang B, Zhang Y, Peng L, Li X. 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.
118. Zheng X, Chen L, Zhou Y, Wang Q, Zheng Z, Xu B, 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.
119. Liu Y, Li Z, Zhang M, Zhou H, Wu X, Zhong J, et al. Rolling-translated EGFR variants sustain EGFR signaling and promote glioblastoma tumorigenicity. Neuro Oncol. 2021;23(5):743–56.
120. Li M, Liu G, Jin X, Guo H, Setrerrahmane S, Xu 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.
121. Yang JE, Zhong WJ, Li JF, Lin YY, Liu FT, Tian H, 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.
122. Gao J, Pan H, Li J, Jiang J, Wang W. A peptide encoded by the circular form of the SHPRH gene induces apoptosis in neuroblastoma cells. PeerJ. 2024;12: e16806.
123. Chang S, Ren D, Zhang L, Liu S, Yang W, Cheng H, et al. Therapeutic SHPRH-146aa encoded by circ-SHPRH dynamically upregulates P21 to inhibit CDKs in neuroblastoma. Cancer Lett. 2024;598: 217120.
124. Zhang Z, Yi Y, Wang Z, Zhang H, Zhao Y, He R, et al. LncRNA MAGI2-AS3-encoded polypeptide restrains the proliferation and migration of breast cancer cells. Mol Biotechnol. 2024;66(6):1409–23.
125. Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discov. 2022;12(1):31–46.
126. Tan S, Yang Y, Yang W, Han Y, Huang L, Yang R, et al. Exosomal cargos-mediated metabolic reprogramming in tumor microenvironment. J Exp Clin Cancer Res. 2023;42(1):59.
127. Tufail M, Jiang CH, Li N. Altered metabolism in cancer: insights into energy pathways and therapeutic targets. Mol Cancer. 2024;23(1):203.
128. Peng X, Li S, Zeng A, Song L. Regulatory function of glycolysis-related lncRNAs in tumor progression: Mechanism, facts, and perspectives. Biochem Pharmacol. 2024;229: 116511.
129. Kooshan Z, Cardenas-Piedra L, Clements J, Batra J. Glycolysis, the sweet appetite of the tumor microenvironment. Cancer Lett. 2024;600: 217156.
130. Yu S, Su S, Wang P, Li J, Chen C, Xin H, et al. Tumor-associated macrophage-induced circMRCKalpha encodes a peptide to promote glycolysis and progression in hepatocellular carcinoma. Cancer Lett. 2024;591: 216872.
131. Lin Z, Hua G, Hu X. Lipid metabolism associated crosstalk: the bidirectional interaction between cancer cells and immune/stromal cells within the tumor microenvironment for prognostic insight. Cancer Cell Int. 2024;24(1):295.
132. Jin HR, Wang J, Wang ZJ, Xi MJ, Xia BH, Deng K, et al. Lipid metabolic reprogramming in tumor microenvironment: from mechanisms to therapeutics. J Hematol Oncol. 2023;16(1):103.
133. Yang K, Wang X, Song C, He Z, Wang R, Xu Y, et al. The role of lipid metabolic reprogramming in tumor microenvironment. Theranostics. 2023;13(6):1774–808.
134. Zhou B, Wu Y, Cheng P, Wu C. 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.
135. Polycarpou-Schwarz M, Gross M, Mestdagh P, Schott J, Grund SE, Hildenbrand C, et al. The cancer-associated microprotein CASIMO1 controls cell proliferation and interacts with squalene epoxidase modulating lipid droplet formation. Oncogene. 2018;37(34):4750–68.
136. Xiong L, Liu HS, Zhou C, Yang X, Huang L, Jie HQ, 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.
137. Ge Q, Jia D, Cen D, Qi Y, Shi C, Li J, et al. Micropeptide ASAP encoded by LINC00467 promotes colorectal cancer progression by directly modulating ATP synthase activity. J Clin Invest. 2021;131(22):e152911.
138. Yang F, Hu A, Guo Y, Wang J, Li D, Wang X, et al. p113 isoform encoded by CUX1 circular RNA drives tumor progression via facilitating ZRF1/BRD4 transactivation. Mol Cancer. 2021;20(1):123.
139. Deng J, Xu W, Jie Y, Chong Y. Subcellular localization and relevant mechanisms of human cancer-related micropeptides. FASEB J. 2023;37(12): e23270.
140. Polenkowski M, Burbano de Lara S, Allister AB, Nguyen TNQ, Tamura T, Tran DDH. Identification of novel micropeptides derived from hepatocellular carcinoma-specific long noncoding RNA. Int J Mol Sci. 2021;23(1): 58.
141. Burbano De Lara S, Tran DDH, Allister AB, Polenkowski M, Nashan B, Koch M, et al. C20orf204, a hepatocellular carcinoma-specific protein

interacts with nucleolin and promotes cell proliferation. Oncogenesis. 2021;10(3): 31.
142. Xu W, Liu C, Deng B, Lin P, Sun Z, Liu A, et al. TP53-inducible putative long noncoding RNAs encode functional polypeptides that suppress cell proliferation. Genome Res. 2022;32(6):1026–41.
143. Wu S, Zhang L, Deng J, Guo B, Li F, Wang Y, 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.
144. Guo B, Wu S, Zhu X, Zhang L, Deng J, Li F, et al. Micropeptide CIP2A-BP encoded by LINC00665 inhibits triple-negative breast cancer progression. EMBO J. 2020;39(1): e102190.
145. Xu W, Deng B, Lin P, Liu C, Li B, Huang Q, et al. Ribosome profiling analysis identified a KRAS-interacting microprotein that represses oncogenic signaling in hepatocellular carcinoma cells. Sci China Life Sci. 2020;63(4):529–42.
146. Li XL, Pongor L, Tang W, Das S, Muys BR, Jones MF, et al. A small protein encoded by a putative lncRNA regulates apoptosis and tumorigenicity in human colorectal cancer cells. Elife. 2020;9:e53734.
147. Wang Q, Cheng B, Singh S, Tao Y, Xie Z, Qin F, et al. A protein-encoding CCDC7 circular RNA inhibits the progression of prostate cancer by upregulating FLRT3. NPJ Precis Oncol. 2024;8(1):11.
148. Meng N, Chen M, Chen D, Chen XH, Wang JZ, Zhu S, et al. Small protein hidden in lncRNA LOC90024 promotes "cancerous" RNA splicing and tumorigenesis. Adv Sci (Weinh). 2020;7(10):1903233.
149. Zhang Q, Wei T, Yan L, Zhu S, Jin W, Bai Y, et al. Hypoxia-responsive lncRNA AC115619 encodes a micropeptide that suppresses m6A modifications and hepatocellular carcinoma progression. Cancer Res. 2023;83(15):2496–512.
150. Li M, Li X, Zhang Y, Wu H, Zhou H, Ding X, et al. Micropeptide MIAC Inhibits HNSCC progression by interacting with aquaporin 2. J Am Chem Soc. 2020;142(14):6708–16.
151. Pan J, Liu M, Duan X, Wang D. 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.
152. Geng X, Wang J, Zhang C, Zhou X, Jing J, Pan W. Circular RNA circCOL6A3_030 is involved in the metastasis of gastric cancer by encoding polypeptide. Bioengineered. 2021;12(1):8202–16.
153. Wang X, Jian W, Luo Q, Fang L. CircSEMA4B inhibits the progression of breast cancer by encoding a novel protein SEMA4B-211aa and regulating AKT phosphorylation. Cell Death Dis. 2022;13(9):794.
154. Harris AL, Kerr DJ, Pezzella F, Ribatti D. Accessing the vasculature in cancer: revising an old hallmark. Trends Cancer. 2024;10:1038–51.
155. Nowosad A, Marine JC, Karras P. Perivascular niches: critical hubs in cancer evolution. Trends Cancer. 2023;9(11):897–910.
156. Zhu KG, Yang J, Zhu Y, Zhu Q, Pan W, Deng S, 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.
157. Bakhti SZ, Latifi-Navid S. Non-coding RNA-encoded peptides/proteins in human cancer: the future for cancer therapy. Curr Med Chem. 2022;29(22):3819–35.
158. Wu S, Guo B, Zhang L, Zhu X, Zhao P, Deng J, et al. A micropeptide XBP1SBM encoded by lncRNA promotes angiogenesis and metastasis of TNBC via XBP1s pathway. Oncogene. 2022;41(15):2163–72.
159. Wang Y, Wu S, Zhu X, Zhang L, Deng J, Li F, et al. LncRNA-encoded polypeptide ASRPS inhibits triple-negative breast cancer angiogenesis. J Exp Med. 2020. https://doi.org/10.1084/jem.20190950.
160. Li F, Cai Y, Deng S, Yang L, Liu N, Chang X, 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.
161. Biswas S, Bhagat GK, Guha D, Bagchi A. Molecular characterization of the unusual peptide CORO1C-47aa encoded by the circular RNA and docking simulations with its binding partner. Gene. 2023;877: 147546.
162. Tan Z, Zhao L, Huang S, Jiang Q, Wei Y, Wu JL, et al. Small peptide LINC00511-133aa encoded by LINC00511 regulates breast cancer cell invasion and stemness through the Wnt/beta-catenin pathway. Mol Cell Probes. 2023;69: 101913.
163. Song H, Wang J, Wang X, Yuan B, Li D, Hu A, 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.
164. Lee KC, Ng WF, Chan JK. Epithelioid haemangioendothelioma presenting as a gastric polyp. Histopathology. 1988;12(3):335–7.
165. Wu X, Xiao S, Zhang M, Yang L, Zhong J, Li B, 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.
166. Zhang Y, Liu Z, Zhong Z, Ji Y, Guo H, Wang W, 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.
167. Pei H, Dai Y, Yu Y, Tang J, Cao Z, Zhang 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.
168. Boix O, Martinez M, Vidal S, Gimenez-Alejandre M, Palenzuela L, Lorenzo-Sanz L, et al. pTINCR microprotein promotes epithelial differentiation and suppresses tumor growth through CDC42 SUMOylation and activation. Nat Commun. 2022;13(1):6840.
169. Li L, Shu XS, Geng H, Ying J, Guo L, Luo J, 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.
170. Xiang X, Fu Y, Zhao K, Miao R, Zhang X, Ma X, 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.
171. Dixon SJ, Olzmann JA. The cell biology of ferroptosis. Nat Rev Mol Cell Biol. 2024;25(6):424–42.
172. Newton K, Strasser A, Kayagaki N, Dixit VM. Cell death. Cell. 2024;187(2):235–56.
173. Wang P, Hu Z, Yu S, Su S, Wu R, Chen C, et al. A novel protein encoded by circFOXP1 enhances ferroptosis and inhibits tumor recurrence in intrahepatic cholangiocarcinoma. Cancer Lett. 2024;598: 217092.
174. Zang X, He XY, Xiao CM, Lin Q, Wang MY, Liu CY, et al. Circular RNA-encoded oncogenic PIAS1 variant blocks immunogenic ferroptosis by modulating the balance between SUMOylation and phosphorylation of STAT1. Mol Cancer. 2024;23(1):207.
175. Han X, Chen L, Sun P, Wang X, Zhao Q, Liao L, et al. A novel lncRNA-hidden polypeptide regulates malignant phenotypes and pemetrexed sensitivity in A549 pulmonary adenocarcinoma cells. Amino Acids. 2024;56(1):15.
176. Duan JL, Chen W, Xie JJ, Zhang ML, Nie RC, Liang H, et al. A novel peptide encoded by N6-methyladenosine modified circMAP3K4 prevents apoptosis in hepatocellular carcinoma. Mol Cancer. 2022;21(1):93.
177. Wang X, Zhang H, Yin S, Yang Y, Yang H, Yang J, et al. lncRNA-encoded pep-AP attenuates the pentose phosphate pathway and sensitizes colorectal cancer cells to Oxaliplatin. EMBO Rep. 2022;23(1): e53140.
178. Wei C, Peng D, Jing B, Wang B, Li Z, Yu R, et al. A novel protein SPECC1-415aa encoded by N6-methyladenosine modified circSPECC1 regulates the sensitivity of glioblastoma to TMZ. Cell Mol Biol Lett. 2024;29(1):127.
179. Li Y, Wang Z, Yang J, Sun Y, He Y, Wang Y, 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.
180. Zhou J, Xu H, Li X, Liu H, Sun Z, Li J, et al. Targeting tumorous Circ-E-Cadherinencoded C-E-Cad inhibits the recruitment and function of breast cancer-associated myeloid-derived suppressor cells. Pharmacol Res. 2024;204: 107204.
181. Cheng R, Li F, Zhang M, Xia X, Wu J, Gao X, 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.
182. Wang H, Liang Y, Zhang T, Yu X, Song X, Chen Y, 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.
183. Song R, Ma S, Xu J, Ren X, Guo P, Liu H, et al. A novel polypeptide encoded by the circular RNA ZKSCAN1 suppresses HCC via degradation of mTOR. Mol Cancer. 2023;22(1):16.

184. Zhang M, Zhao K, Xu X, Yang Y, Yan S, Wei P, et al. A peptide encoded by circular form of LINC-PINT suppresses oncogenic transcriptional elongation in glioblastoma. Nat Commun. 2018;9(1):4475.
185. Zhang C, Zhou B, Gu F, Liu H, Wu H, Yao F, et al. Micropeptide PACMP inhibition elicits synthetic lethal effects by decreasing CtIP and poly(ADP-ribosyl)ation. Mol Cell. 2022;82(7):1297-312.e8.
186. Houles T, Yoon SO, Roux PP. The expanding landscape of canonical and non-canonical protein phosphorylation. Trends Biochem Sci. 2024;49:986–99.
187. Nguyen H, Kettenbach AN. Substrate and phosphorylation site selection by phosphoprotein phosphatases. Trends Biochem Sci. 2023;48(8):713–25.
188. Yu Y, Zhang L, Li B, Fu Z, Brohawn SG, Isacoff EY. Coupling sensor to enzyme in the voltage sensing phosphatase. Nat Commun. 2024;15(1):6409.
189. Kieft R, Zhang Y, Yan H, Schmitz RJ, Sabatini R. Protein phosphatase PP1 regulation of RNA polymerase II transcription termination and allelic exclusion of VSG genes in trypanosomes. Nucleic Acids Res. 2024;52(12):6866–85.
190. Ge J, Wang Y, Li X, Lu Q, Yu H, Liu H, et al. Phosphorylation of caspases by a bacterial kinase inhibits host programmed cell death. Nat Commun. 2024;15(1):8464.
191. Shen Y, Yan J, Li L, Sun H, Zhang L, Li G, et al. LOXL2-induced PEAR1 Ser891 phosphorylation suppresses CD44 degradation and promotes triple-negative breast cancer metastasis. J Clin Invest. 2024;134(16):e177357.
192. Nie L, Fei C, Fan Y, Dang F, Zhao Z, Zhu T, et al. Consecutive palmitoylation and phosphorylation orchestrates NLRP3 membrane trafficking and inflammasome activation. Mol Cell. 2024;84(17):3336-53.e7.
193. Li W, Guo F, Zeng R, Liang H, Wang Y, Xiong W, et al. CDK4/6 alters TBK1 phosphorylation to inhibit the STING signaling pathway in prostate cancer. Cancer Res. 2024;84(16):2588–606.
194. Zhu C, Fan F, Li CY, Xiong Y, Liu X. Caspase-3 promotes oncogene-induced malignant transformation via EndoG-dependent Src-STAT3 phosphorylation. Cell Death Dis. 2024;15(7):486.
195. Kook E, Chun KS, Kim DH. Emerging roles of YES1 in cancer: the putative target in drug resistance. Int J Mol Sci. 2024;25(3):1450.
196. Arkinson C, Dong KC, Gee CL, Martin A. Mechanisms and regulation of substrate degradation by the 26S proteasome. Nat Rev Mol Cell Biol. 2024;26:104–22.
197. Sun L, Liu Z, Wu Z, Wu Z, Qiu B, Liu S, et al. PSMD11 promotes the proliferation of hepatocellular carcinoma by regulating the ubiquitination degradation of CDK4. Cell Signal. 2024;121: 111279.
198. Magnati S, Alladio E, Bracco E. A survey on the expression of the ubiquitin proteasome system components HECT- and RBR-E3 ubiquitin ligases and E2 ubiquitin-conjugating and E1 ubiquitin-activating enzymes during human brain development. Int J Mol Sci. 2024;25(4):2361.
199. Li H, Sun Y, Yao Y, Ke S, Zhang N, Xiong W, et al. USP8-governed GPX4 homeostasis orchestrates ferroptosis and cancer immunotherapy. Proc Natl Acad Sci U S A. 2024;121(16): e2315541121.
200. Taylor JD, Barrett N, Martinez Cuesta S, Cassidy K, Pachl F, Dodgson J, et al. Targeted protein degradation using chimeric human E2 ubiquitin-conjugating enzymes. Commun Biol. 2024;7(1):1179.
201. Zhao L, Yuan H, Wang Y, Hou C, Lv P, Zhang H, et al. p-STAT3-elevated E3 ubiquitin ligase DTX4 confers the stability of HBV cccDNA by ubiquitinating APOBEC3B in liver. Theranostics. 2024;14(15):6036–52.
202. Lange SM, McFarland MR, Lamoliatte F, Carroll T, Krshnan L, Perez-Rafols A, et al. VCP/p97-associated proteins are binders and debranching enzymes of K48–K63-branched ubiquitin chains. Nat Struct Mol Biol. 2024;31:1872–87.
203. Liu W, Wang Y, Liu S, Zhang X, Cao X, Jiang M. E3 ubiquitin ligase RNF13 suppresses TLR lysosomal degradation by promoting LAMP-1 proteasomal degradation. Adv Sci (Weinh). 2024;11(32): e2309560.
204. Rho H, Kim S, Kim SU, Kim JW, Lee SH, Park SH, et al. CHIP ameliorates nonalcoholic fatty liver disease via promoting K63- and K27-linked STX17 ubiquitination to facilitate autophagosome-lysosome fusion. Nat Commun. 2024;15(1):8519.
205. Timms RT, Mena EL, Leng Y, Li MZ, Tchasovnikarova IA, Koren I, et al. Defining E3 ligase-substrate relationships through multiplex CRISPR screening. Nat Cell Biol. 2023;25(10):1535–45.
206. Ferretti LP, Himmels SF, Trenner A, Walker C, von Aesch C, Eggenschwiler A, et al. Cullin3-KLHL15 ubiquitin ligase mediates CtIP protein turnover to fine-tune DNA-end resection. Nat Commun. 2016;7:12628.
207. Gao H, Yin J, Ji C, Yu X, Xue J, Guan X, et al. Targeting ubiquitin specific proteases (USPs) in cancer immunotherapy: from basic research to preclinical application. J Exp Clin Cancer Res. 2023;42(1):225.
208. Zhang HL, Hu BX, Ye ZP, Li ZL, Liu S, Zhong WQ, et al. TRPML1 triggers ferroptosis defense and is a potential therapeutic target in AKT-hyperactivated cancer. Sci Transl Med. 2024;16(753):eadk0330.
209. Yan Y, Zhou S, Chen X, Yi Q, Feng S, Zhao Z, et al. Suppression of ITPKB degradation by Trim25 confers TMZ resistance in glioblastoma through ROS homeostasis. Signal Transduct Target Ther. 2024;9(1):58.
210. Wu L, Zhou Z, Yu Y, Cheng C, Zhou S, Yan Y, et al. Phosphorylation-dependent deubiquitinase OTUD3 regulates YY1 stability and promotes colorectal cancer progression. Cell Death Dis. 2024;15(2):137.
211. Berkane R, Ho-Xuan H, Glogger M, Sanz-Martinez P, Brunello L, Glaesner T, et al. The function of ER-phagy receptors is regulated through phosphorylation-dependent ubiquitination pathways. Nat Commun. 2023;14(1):8364.
212. Ma X, Wang D, Li N, Gao P, Zhang M, Zhang Y. Hippo kinase NDR2 inhibits IL-17 signaling by promoting Smurf1-mediated MEKK2 ubiquitination and degradation. Mol Immunol. 2019;105:131–6.
213. Xuan Z, Chen C, Sun H, Yang K, Li J, Fu M, et al. NDR1/FBXO11 promotes phosphorylation-mediated ubiquitination of beta-catenin to suppress metastasis in prostate cancer. Int J Biol Sci. 2024;20(12):4957–77.
214. Ilhan M, Hastar N, Kampfrath B, Spierling DN, Jatzlau J, Knaus P. BMP stimulation differentially affects phosphorylation and protein stability of beta-catenin in breast cancer cell lines. Int J Mol Sci. 2024;25(9):4593.
215. Yang MH, Basappa B, Deveshegowda SN, Ravish A, Mohan A, Nagaraja O, et al. A novel drug prejudice scaffold-imidazopyridine-conjugate can promote cell death in a colorectal cancer model by binding to beta-catenin and suppressing the Wnt signaling pathway. J Adv Res. 2024. https://doi.org/10.1016/j.jare.2024.07.022.
216. Zhang J, Chen Y, Gong X, Yang Y, Gu Y, Huang L, et al. GATA factor TRPS1, a new DNA repair protein, cooperates with reversible PARylation to promote chemoresistance in patients with breast cancer. J Biol Chem. 2024;300(10): 107780.
217. Das PK, Matada GSP, Pal R, Maji L, Dhiwar PS, Manjushree BV, et al. Poly (ADP-ribose) polymerase (PARP) inhibitors as anticancer agents: an outlook on clinical progress, synthetic strategies, biological activity, and structure-activity relationship. Eur J Med Chem. 2024;274: 116535.
218. Zhang Z, Samsa WE, Gong Z. NUDT16 regulates CtIP PARylation to dictate homologous recombination repair. Nucleic Acids Res. 2024;52(7):3761–77.
219. Wang S, Wang Y, Hao L, Chen B, Zhang J, Li X, et al. BOC targets SMO to regulate the Hedgehog pathway and promote proliferation, migration, and invasion of glioma cells. Brain Res Bull. 2024;216: 111037.
220. Zhu Q, Yang X, Lv Y. HERC4 modulates ovarian cancer cell proliferation by regulating SMO-elicited hedgehog signaling. Biochim Biophys Acta Gen Subj. 2024;1868(4): 130557.
221. Du B, Zhang Z, Jia L, Zhang H, Zhang S, Wang H, 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.
222. Ji W, Diao YL, Qiu YR, Ge J, Cao XC, Yu Y. LINC00665 promotes breast cancer progression through regulation of the miR-379-5p/LIN28B axis. Cell Death Dis. 2020;11(1):16.
223. Li YR, Zong RQ, Zhang HY, Meng XY, Wu FX. Mechanism analysis of LINC00665 and its peptides CIP2A-BP in hepatocellular carcinoma. Front Genet. 2022;13: 861096.
224. Leng F, Miu YY, Zhang Y, Luo H, Lu XL, Cheng H, 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.
225. Barczak W, Carr SM, Liu G, Munro S, Nicastri A, Lee LN, et al. Long non-coding RNA-derived peptides are immunogenic and drive a potent anti-tumour response. Nat Commun. 2023;14(1):1078.
226. Camarena ME, Theunissen P, Ruiz M, Ruiz-Orera J, Calvo-Serra B, Castelo R, et al. Microproteins encoded by noncanonical ORFs are a major source of tumor-specific antigens in a liver cancer patient meta-cohort. Sci Adv. 2024;10(28):eadn3628.

227. Kikuchi Y, Tokita S, Hirama T, Kochin V, Nakatsugawa M, Shinkawa 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.
228. Qi YA, Maity TK, Cultraro CM, Misra V, Zhang X, Ade C, et al. Proteogenomic analysis unveils the HLA class I-presented immunopeptidome in melanoma and EGFR-mutant lung adenocarcinoma. Mol Cell Proteomics. 2021;20: 100136.
229. Ferreira HJ, Stevenson BJ, Pak H, Yu F, Almeida Oliveira J, Huber F, et al. Immunopeptidomics-based identification of naturally presented non-canonical circRNA-derived peptides. Nat Commun. 2024;15(1):2357.
230. Feng J, Wu H, Li S. Noncanonical translation of circRNAs drive antitumor immunity. Trends Cancer. 2024;10(2):100–2.
231. Setrerrahmane S, Li M, Zoghbi A, Lv X, Zhang S, Zhao W, et al. Cancer-related micropeptides encoded by ncRNAs: Promising drug targets and prognostic biomarkers. Cancer Lett. 2022;547: 215723.
232. Wen K, Chen X, Gu J, Chen Z, Wang Z. Beyond traditional translation: ncRNA derived peptides as modulators of tumor behaviors. J Biomed Sci. 2024;31(1):63.
233. Szafron LA, Iwanicka-Nowicka R, Podgorska A, Bonna AM, Sobiczewski P, Kupryjanczyk J, et al. The clinical significance of CRNDE gene methylation, polymorphisms, and CRNDEP micropeptide expression in ovarian tumors. Int J Mol Sci. 2024;25(14):7531.
234. Balcerak A, Szafron LA, Rubel T, Swiderska B, Bonna AM, Konarzewska M, et al. A multi-faceted analysis showing CRNDE transcripts and a recently confirmed micropeptide as important players in ovarian carcinogenesis. Int J Mol Sci. 2024;25(8):4381.
235. Chakraborty S, Andrieux G, Hasan AMM, Ahmed M, Hosen MI, Rahman T, et al. Harnessing the tissue and plasma lncRNA-peptidome to discover peptide-based cancer biomarkers. Sci Rep. 2019;9(1):12322.
236. Mohammed ASA, Soloviov D, Jeffries CM. Perspectives on solution-based small angle X-ray scattering for protein and biological macromolecule structural biology. Phys Chem Chem Phys. 2024;26(39):25268–86.
237. Doyen C, Larquet E, Coureux PD, Frances O, Herman F, Sable S, et al. Nuclear magnetic resonance spectroscopy: a multifaceted toolbox to probe structure, dynamics, interactions, and real-time in situ release kinetics in peptide-liposome formulations. Mol Pharm. 2021;18(7):2521–39.

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