

m6A modification of non-coding RNA: Mechanisms, functions and potential values in human diseases (Review)

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Abstract. N6-methyladenosine (m6A) RNA modification represents a pivotal and novel post-transcriptional modification in eukaryotic RNAs. Initially identified in messenger RNAs (mRNAs), m6A modification on these transcripts regulates a spectrum of essential cellular processes, including mRNA splicing, subcellular localization, stability and translation. Recent studies have highlighted the involvement of m6A methylation in both biological and pathological processes, particularly in cancer. Non-coding RNAs (ncRNAs), a diverse class of RNA molecules that do not encode proteins, encompass microRNAs, long ncRNAs and circular RNAs. Notably, m6A has been recognized as a reversible epigenetic modification

within ncRNAs, a discovery that has garnered considerable attention. This modification not only influences the stability of ncRNAs but also endows them with the novel capacity for peptide translation. The differential and specific expression pattern in diseases give these m6A-modified ncRNAs potential as biomarkers for molecular diagnostics and targeted therapy, and using ncRNA-encoded peptides as a target for immunotherapy has also been attempted. This review synthesizes the current understanding of m6A modifications in ncRNAs, explores the effects of m6A on ncRNA function and presents the latest insights into the role of ncRNA m6A modifications in disease progression.

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Abbreviations: m6A, N6-methyladenosine; METTL3, methyltransferase-like 3; WTAP, Wilms' tumor 1-associated protein; lncRNA, long non-coding RNA; circRNA, circular RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; hnRNP, heterogeneous nuclear ribonucleoprotein; IGF2BP, insulin-like growth factor 2 mRNA-binding protein; NSCLC, non-small cell lung cancer; GBM, glioblastoma; HCC, hepatocellular carcinoma; CRC, colorectal cancer; HNSCC, hypopharyngeal squamous cell carcinoma; VSMC, vascular smooth muscle cell; LSCC, laryngeal squamous cell carcinoma; RBM, RNA-binding motif; SNHG1, small nucleolar RNA host gene 1; FTO, fat mass and obesity-associated protein; ALKBH5, α -ketoglutarate-dependent dioxygenase alk B homolog 5; ESCC, esophageal squamous cell carcinoma; TAM, tumour-associated macrophage; OC, ovarian cancer; BC, breast cancer; GC, gastric cancer; I/R, ischemia/reperfusion; EV, extracellular vesicle; AGO2, Argonaute 2; LPS, lipopolysaccharide

Key words: m6A modification, lncRNAs, circRNAs, peptides

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1. Introduction

RNA methylation is a key epigenetic modification that regulates gene transcription without altering the underlying gene sequence. Key types of RNA methylation include N6-methyladenosine (m6A), 5-methylcytosine, m1A, N7-methylguanosine and 3-methylcytidine (1,2). Among these, m6A is the most prevalent and extensively studied RNA modification. As the name suggests, m6A occurs at the N6 position of adenosine, with two predominant motifs-RRACH and DRACH-where H represents U, A or C; R denotes A or G; and D refers to U, A or G (3). This modification plays a pivotal role in various aspects of RNA metabolism, including splicing, transport, localization, translation and degradation (4,5). Numerous studies have demonstrated that m6A is critical for physiological processes, such as embryonic development (6), and it has also been implicated in various pathological processes, including cancer (7,8).

In eukaryotic cells, non-coding RNAs (ncRNAs) are a class of endogenous RNA molecules that do not encode proteins (9). These ncRNAs can be categorized into several types, including transfer RNAs, microRNAs (miRNAs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs) (10,11). Although ncRNAs do not directly translate into proteins, they perform vital biological functions at the RNA level. They can interact with DNA, mRNA and proteins, playing specialized roles in the regulation of gene expression, mRNA stability and protein function (12-14). Dysregulation of ncRNAs has been strongly linked to the progression of various diseases and malignancies.

Recent studies have expanded the understanding of m6A modifications in ncRNAs (15,16). m6A methylation regulates the transcription, structural stability, localization and translation of ncRNAs. Importantly, the abnormal changes induced by m6A modification enable ncRNAs to participate in diverse biological and pathological processes, including cancer. For instance, peptides derived from m6A-modified ncRNAs have been reported to exhibit both oncogenic and tumor-suppressive functions (17,18). Therefore, the roles of m6A modification in ncRNAs and their underlying mechanisms warrant further investigation, with the potential to uncover novel biomarkers for disease diagnosis, prognostic indicators and therapeutic strategies.

The present review synthesizes recent findings on m6A modifications in ncRNAs, focusing on their impact on the stability, localization and translation of ncRNAs. Additionally, it discusses the involvement of m6A-modified ncRNAs in disease progression and tumorigenesis, providing new insights into the role of m6A modification in ncRNA biology and facilitating further research in this area.

2. m6A modification

After transcription, RNA nucleosides, including adenosine, guanosine, cytidine and uridine, can undergo additional chemical modifications, adding complexity to their function. One such modification is m6A, where a methyl group is added to the N6 position of adenosine. Since its discovery in 1974, m6A has been recognized as a prevalent and abundant modification in mRNAs, and it remains one of the most extensively studied RNA modifications to date (19,20). Extensive research has demonstrated that m6A modifications play a pivotal role in various physiological processes and are implicated in numerous diseases, including obesity, diabetes, gastrointestinal disorders, Alzheimer's disease (AD) and cancers (21,22).

m6A methylation is a dynamic and reversible post-transcriptional modification that sets it apart from other forms of epigenetic regulation (Fig. 1). This reversible process is mediated by enzymes and proteins involved in the m6A modification, including 'writers' and 'erasers' (4). The m6A writers, or methyltransferases, include methyltransferase-like 3 (METTL3), METTL5, METTL14, METTL16, Wilms' tumor 1-associated protein (WTAP), RNA binding motif protein 15/15B (RBM15/15B), zinc finger CCCH-type containing 13 and KIAA1429 (also known as vir-like m6A methyltransferase associated protein). These enzymes form a methyltransferase complex that catalyzes the addition of m6A to RNA molecules (23-25). Conversely, m6A erasers,

or demethylases, such as fat mass and obesity-associated protein (FTO) and α -ketoglutarate-dependent dioxygenase alk B homolog 5 (ALKBH5), are responsible for removing m6A modifications from target RNA molecules (2,26,27). The m6A readers are the key enzymes, as they recognize the m6A sites on RNA molecules and mediate the influence of m6A on the fate of mRNA. The YTH domain family (YTHDF) represents the most common group of m6A readers. YTHDF1 enhances mRNA translation, while YTHDF2 promotes mRNA degradation, and YTHDF3 works in concert with YTHDF1 and YTHDF2 to regulate mRNA metabolism. YTHDC1 and YTHDC2, other key m6A readers, are involved in RNA splicing, cytoplasmic-nuclear shuttling and stability (28-30). The insulin-like growth factor 2 mRNA-binding protein (IGF2BP) family, comprising IGF2BP1, IGF2BP2 and IGF2BP3, protects m6A-modified mRNAs from degradation within P-bodies and stress granules (31-33). Other m6A readers, such as heterogeneous nuclear ribonucleoprotein A2B1 (hnRNP A2B1) and serine and arginine rich splicing factor 9, have been shown to regulate mRNA stability, localization and translation (34,35). While the majority of studies on m6A focus on mRNA molecules, emerging evidence indicates that ncRNAs can also undergo m6A modification, which regulates their stability, localization and translation.

The m6A modification can be detected along with the development of detection technologies. Single-molecule epitranscriptomic analysis and single-molecule sequencing could detect and reveal functional roles of site-specific m6As (36,37). However, high-throughput sequencing or *in vitro* assays are not reflected in the dynamic changes of m6A modification, and current *in situ* imaging techniques for site-specific m6A are constrained. Recently, Song *et al* (38) presented a method, termed proximity hybridization followed by primer exchange amplification, which could image m6A methylation sites concurrently in multiple cell types, revealing cell-to-cell variability in expression levels. Furthermore, Zhang *et al* (39) introduced the Tada8.20-assisted N6-methyladenosine RNA imaging at single-base resolution method for precise visualization and quantification of both A and m6A forms at specific RNA sites within single cells. With the development of detection technology, detecting dynamic changes in m6A modification can provide a more accurate basis for molecular diagnosis and targeted therapy of diseases.

3. ncRNAs

ncRNAs are a diverse group of endogenous RNA molecules that typically do not encode proteins (10). These ncRNAs can be categorized into several classes: lncRNAs, which are longer than 200 nucleotides (nt); small ncRNAs, including miRNAs and small nuclear RNAs, which are shorter than 200 nt; circRNAs; small interfering RNAs; piwi-interacting RNAs; and ribosomal RNAs.

MiRNAs are a well-conserved class of endogenous ncRNAs ~22 nucleotides in length (40). They interact with mRNAs, regulating their degradation, translational repression or direct cleavage in a post-transcriptional manner (41,42). >2,600 miRNAs have been identified in the human genome and are known to regulate the expression of 30-50% of functional genes. Small nuclear RNAs, averaging 150 nucleotides, are

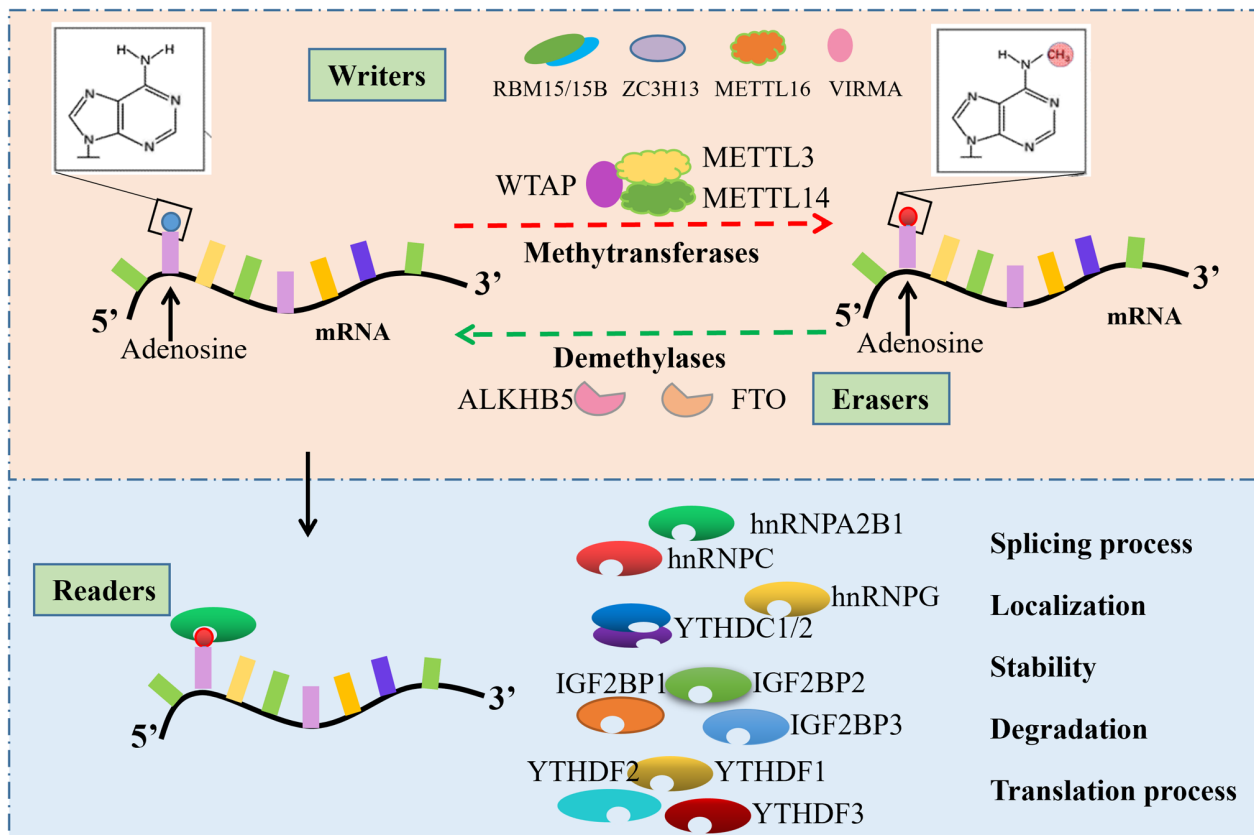


Figure 1. Structural schematic representation of the reversible and dynamic post-transcriptional m6A modification of RNA. In the nucleus, methyltransferases and demethylases regulate the m6A modifications of target mRNAs. m6A readers modulate the splicing and transport of target mRNAs. In the cytoplasm, different m6A readers control the stability, degradation, localization and translation of mRNAs through distinct mechanisms. WTAP, Wilms' tumor 1-associated protein; ZC3H13, zinc finger CCCH-type containing 13; METTL3/14/16, methyltransferase-like 3/14/16; VIRMA, vir like m6A methyltransferase associated protein; FTO, fat mass and obesity-associated protein; ALKBH5, α -ketoglutarate-dependent dioxygenase alk B homolog 5; hnRNP C/hnRNP G/hnRNP A2B1, heterogeneous nuclear ribonucleoprotein C/G/A2B1; IGF2BP1/2/3, insulin-like growth factor 2 mRNA-binding protein 1/2/3; YTHDF1/2/3, YTHDC1/2, YTH N6-methyladenosine RNA binding protein F1/2/3, C1/2.

primarily located in the nucleus and are core components of small nuclear ribonucleoproteins, which are essential for RNA splicing (43,44).

Like typical RNA molecules, lncRNAs possess a 5'-methyl-cytosine cap and a 3'-poly(A) tail (45). In the canonical pathway, lncRNAs are transcribed by RNA polymerase II. They may be cleaved by ribonuclease P or recognized by small nucleolar RNA-protein complexes and other enzymes to produce mature 3' ends, capping structures or circular forms in non-canonical pathways (46,47). Based on their genomic origins, lncRNAs can be classified into five categories: Sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intronic lncRNAs and intergenic lncRNAs (48). Initially, lncRNAs were thought to be non-coding and to primarily act as RNA sponges or sponges for RNA-binding proteins (RBPs) (49,50).

CircRNAs are a distinct class of ncRNA characterized by a covalently closed loop structure (51). They are generated through back-splicing, where a downstream splice donor site is joined with an upstream splice acceptor site (52). CircRNAs can be further classified into three major groups based on their genomic origins: Circular intronic RNAs, exon-intron circRNAs and exonic circRNAs (53). CircRNAs have been shown to regulate transcription, RNA stability, localization and protein function by binding to DNA, RNA molecules or proteins (54,55).

The dysregulation of miRNAs, lncRNAs and circRNAs has been implicated in various biological processes, primarily through their ability to sponge RNA molecules or proteins (56,57). Recently, it has been discovered that lncRNAs and circRNAs containing internal ribosome entry sites or m6A modification sites can be translated into micro-peptides (58,59). These novel findings provide critical insights for further research.

4. m6A modification of ncRNAs

m6A modification of miRNAs. In the case of miRNAs, m6A modification has been shown to impact their biogenesis and subsequently alter the functionality of mature miRNAs. Garbo *et al* (16) demonstrated that m6A modification on specific miRNAs affects argonaute 2 (AGO2)/miRNA and RBP/miRNA interactions, impairing their ability to regulate target mRNAs and influencing extracellular vesicle (EV) loading. Alarcón *et al* (60) highlighted m6A methylation as a critical mechanism in miRNA biogenesis. METTL3-mediated m6A methylation promotes the maturation of pri-miR-BART3-3p by interacting with DGCR8, thereby facilitating Natural killer/T cell lymphoma progression (25). Similarly, METTL14 modulates pri-miR-100 processing to mature miR-100-3p in an m6A-dependent

manner through DGCR8 microprocessor complex subunit (DGCR8) during ultraviolet B-induced human dermal fibroblast photoaging (61). In addition, ALKBH5 demethylates pri-miR-194-2, suppressing miR-194-2 biogenesis via an m6A/DGCR8-dependent pathway (62), while FTO inhibits DGCR8 binding to pri-miR-138-5p through m6A modification, thereby limiting miR-138-5p processing (63). Furthermore, YTHDF2 recognizes m6A sites in pre-miR-126 and recruits AGO2 to enhance the maturation of pre-miR-126 into mature miR-126 (51). YTHDC1 promotes the biogenesis of mature miR-30d through m6A-mediated regulation of mRNA stability (64).

m6A modification of lncRNAs. Numerous studies have reported the m6A modification of lncRNAs. Bian *et al* (65) found that METTL3 mediates the m6A modification of lncRNA ABHD11-antisense 1 (AS1), which inhibits ferroptosis and promotes colorectal cancer (CRC) progression. Likewise, Zhao *et al* (66) identified METTL3 as a key factor in enhancing the m6A modification of homeobox (HOX)A10-AS, thereby increasing its RNA stability. METTL14-mediated m6A modification stabilizes lncRNA THRIL (TNF and HNRNPL related immunoregulatory lncRNA), accelerating lipopolysaccharide (LPS)-induced acute injury in alveolar epithelial cells (67). Furthermore, WTAP-mediated m6A modification enhances the stability of lnc-OXAR, which contributes to oxaliplatin resistance in non-alcoholic steatohepatitis-related hepatocellular carcinoma (HCC) (68). Additionally, FTO has been shown to suppress the m6A modification of lncRNA small nucleolar RNA host gene 1 (SNHG14), attenuating LPS-induced acute kidney injury by inhibiting autophagy (69). ALKBH5 decreases m6A-modified sites on DNA damage inducible transcript 4 (DDIT4)-AS1, inhibiting the recruitment of ELAV-like RNA binding protein 1 and stabilizing DDIT4-AS1 (70).

m6A modification of circRNAs. CircRNAs are also subject to m6A modification. Chen *et al* (71) demonstrated that METTL3 promotes the m6A modification of circ-CTTN, thereby enhancing osteogenic differentiation of human umbilical cord mesenchymal stem cells (MSCs). Fan *et al* (72) uncovered that METTL14 mediates m6A modification of circORC5, which suppresses gastric cancer (GC) progression. Additionally, WTAP-mediated m6A modification of circ_0056856 promotes proliferation, migration and invasion of interleukin-22-stimulated human keratinocytes (73). ALKBH5 has also been reported to regulate the demethylation of circCPSF6, influencing its recognition and stabilization by YTHDF2 (74). The ALKBH5/insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2) axis mediates the m6A modification of circXPO1, which accelerates CRC progression (75). Furthermore, Wu *et al* (76) found that FTO binds to circFAM192A at specific sites, removing the m6A modification and protecting it from degradation.

5. Function of m6A modification on ncRNAs

For mRNAs, the roles of m6A modification are well-established, encompassing various aspects of RNA metabolism, including splicing, transportation, translation and

degradation. For ncRNAs, m6A modification plays a critical role in regulating their biogenesis, stability, localization and even translation (Fig. 2).

Regulating the biogenesis and expression of ncRNAs. As widely recognized, m6A modification impacts the biogenesis and functionality of mature miRNAs. In addition, m6A modulates RNA splicing, which is essential for the biogenesis of circRNAs. For instance, circDDIT4 is generated by back-splicing at the 3'-UTR using a 5' splice acceptor site in exon 2 of linear DDIT4 mRNA. The WTAP/METTL3/METTL14 methyltransferase complex mediates m6A modification in both the circDDIT4-5' flanking and circDDIT4-3'-UTR regions, promoting circDDIT4 circularization (77). METTL3/YTHDC1-mediated m6A modification regulates the biogenesis of circRBM33, generated from exon 3 to exon 5 of RBM33 mRNA (78). Similarly, METTL3/YTHDC1-mediated m6A modification and back-splicing events contribute to the biogenesis of circCDYL (79). METTL3 increases m6A modification of circARL3, with YTHDC1 binding to modified sites and facilitating reverse splicing and circularization (80). METTL3 also mediates the m6A modification of circIGF2BP3, promoting its circularization in an m6A-dependent manner through YTHDC1 (81). The m6A reader YTHDC1, along with the RNA helicase DEAD-box helicase 5 (DDX5), regulates the production of circRNAs enriched in rhabdomyosarcoma (82). Furthermore, the upregulation of lncRNA CHASERR in response to m6A modification is facilitated by METTL3/YTHDF1-mediated RNA transcripts (83). Silencing METTL14 suppresses DHRS4-AS1 expression by reducing the m6A modification of DHRS4-AS1 transcripts (84). Additionally, Chen *et al* (85) reported that suppressing METTL3 inhibits the expression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). ALKBH5 promotes the upregulation of lncRMRP expression through demethylation (86) and enhances the expression of the lncRNA DIO3OS via m6A modification (87).

Regulating the stability of ncRNAs. m6A modification has been demonstrated to play a pivotal role in regulating the stability of lncRNAs and circRNAs. For instance, m6A modification is significantly enriched in lncRNA RMRP, enhancing its RNA stability (88). In addition, METTL14-induced m6A modification stabilizes lncRNA-PLCB1, thereby inhibiting GC progression through the destabilization of DDX21 (89). Xie *et al* (90) demonstrated that IGF2BP3 binds to m6A-modified sites on lncRNA OIP5-AS1, stabilizing its expression. Similarly, Luo *et al* (91) highlighted the critical role of m6A modification in maintaining the stability of lncRNA FAM83H-AS1, facilitated by METTL3 and the readers IGF2BP2/IGF2BP3. Furthermore, ALKBH5 demethylates lncRNA-CARMN, reducing its m6A modification, while YTHDF2/YTHDF3 recognizes and degrades m6A-modified lncRNA-CARMN (92). The demethylation of lncRNA SNHG15 by ALKBH5 enhances its stability (93). The abundance of m6A modification sites on lncRNA TP53TG1 is countered by ALKBH5, which reduces its stability and down-regulates its expression (94). hnRNP A2B1 interacts with and stabilizes lncRNA NEAT1 in an m6A-dependent manner (95). Yi *et al* (96) identified the m6A modification of circPSMA7,

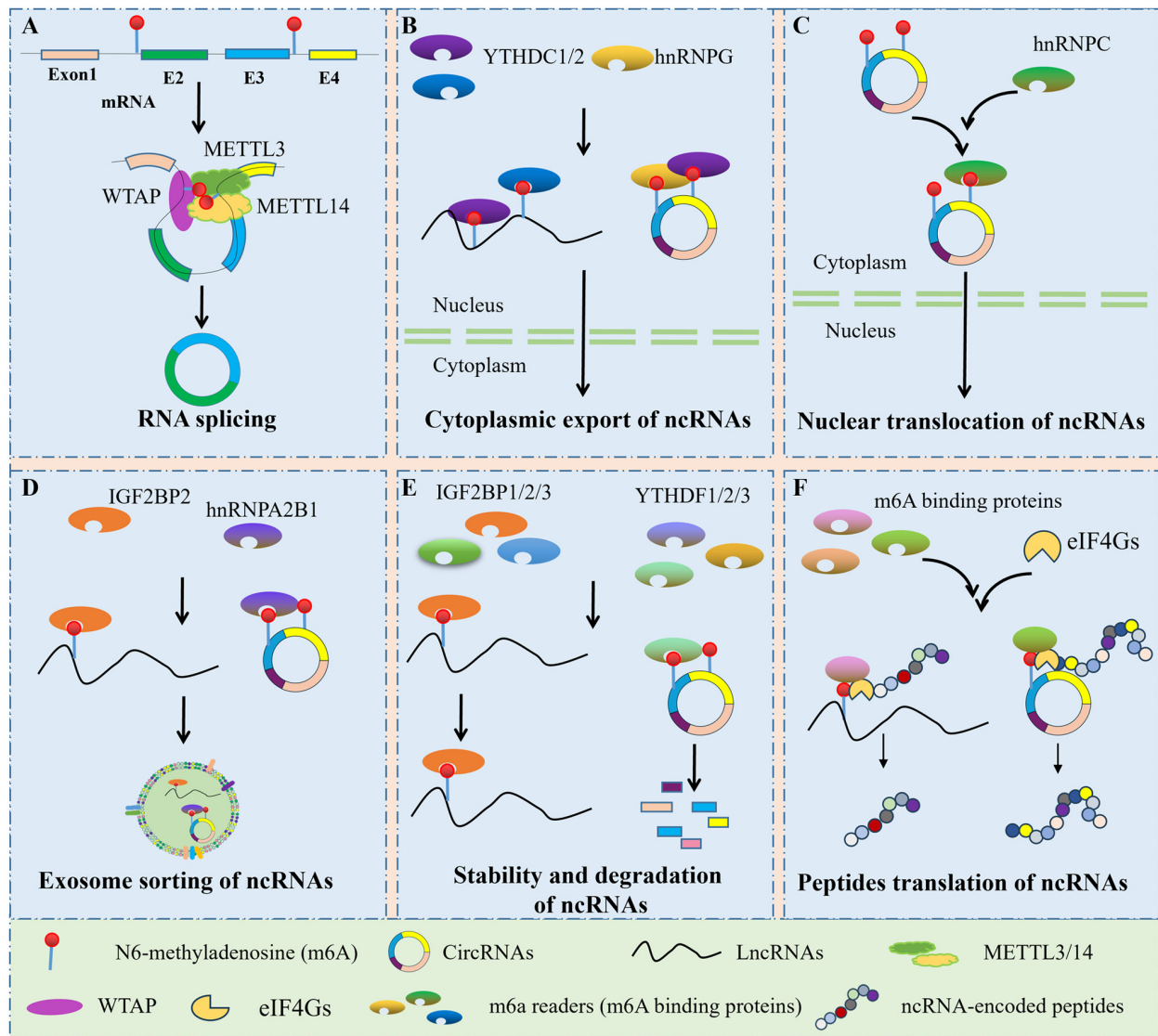


Figure 2. Effects and functions of m6A modification on ncRNAs (lncRNAs and circRNAs). (A) m6A modification facilitates the biogenesis of ncRNAs. (B) m6A readers promote the cytoplasmic export of ncRNAs. (C) m6A readers mediate the nuclear retention or translocation of ncRNAs. (D) m6A readers regulate the sorting of ncRNAs into exosomes. (E) m6A readers control the stability or degradation of ncRNAs. (F) m6A-dependent translation of ncRNAs. WTAP, Wilms' tumor 1-associated protein; lncRNA, long noncoding RNA; METTL3/14, methyltransferase-like 3/14; hnRNPC/ hnRNPA2B1, heterogeneous nuclear ribonucleoprotein C/A2B1; IGF2BP1/2/3, insulin-like growth factor 2 mRNA-binding protein 1/2/3; YTHDF1/2/3, YTH N6-methyladenosine RNA binding protein F1/2/3, C1/2; eIF4Gs, eukaryotic translation initiation factor 4 gamma.

noting that IGF2BP3 recognizes these sites and stabilizes circPSMA7, thereby enhancing its expression. Furthermore, the upregulation of circ_104797 in cisplatin-resistant bladder cancer is attributed to increased stability driven by elevated m6A levels in its sequence (97). Similarly, the increased stability of circPLPP4 in cisplatin-resistant ovarian cancer is mediated by heightened m6A modification (98). The elevated level of circ_0000337 in bortezomib-resistant multiple myeloma cells results from augmented m6A levels, leading to enhanced RNA stability (99). METTL3-mediated m6A methylation of circSLCO1B3 stabilizes its expression, with m6A-modified circSLCO1B3 promoting intrahepatic cholangiocarcinoma progression via regulation of HOXC8 and programmed cell death ligand 1 (100). Finally, FTO acts as an eraser, increasing the stability and expression of circBRCA1 by demethylating its m6A modification, thereby alleviating oxidative stress-induced granulosa cell damage (101).

Table I summarizes additional studies on the role of m6A modification in regulating ncRNA stability and the functional implications of these ncRNAs in various diseases (102-142).

Regulating the localization of ncRNAs. m6A modification also plays a pivotal role in the localization of ncRNAs, influencing their shuttling between the cytoplasm and nucleus. The m6A modification of circNSUN2 facilitates its export to the cytoplasm, enhancing the stability of HMGA2 mRNA and promoting CRC metastasis (143). Similarly, circPAK2 undergoes m6A modification, which is recognized by YTHDC1, enabling its nuclear export to the cytoplasm and subsequently promoting lymph node metastasis in GC (144). In parallel, YTHDC1 directly binds to the m6A sites on various circRNAs, including hsa_circ_0102678 (145), circFNDC3B (146), circPOLR2B (147), circRNA3634 (148) and circHPS5 (149), promoting their export to the cytoplasm. Furthermore, METTL3 mediates the m6A

Table I. Effects of m6A modification on ncRNA stability.

ncRNAs	m6A regulator	Stability	Function	(Refs.)
LncRNA PVT1	ALKBH5	Decreased	Regulates OC growth and lung cancer metastasis	(102,103)
LncRNA MEG3	HNRNPA2B1	Decreased	Facilitates tumorigenesis of NSCLC	(104)
LncRNA NEAT1	ALKBH5, METTL3	Enhanced	Facilitates immunosuppression and cerebral I/R injury	(105,106)
LncRNA MALAT1	METTL3/HuR, METTL3, IGF2BP2	Enhanced	Promotes the malignant progression of glioma, OS and NSCLC	(107-109)
LncRNA ZFAS1	IGF2BP2, METTL3	Enhanced	Promotes mitochondrial energy metabolism and affects autophagy and progression of NPC	(110,111)
LncRNA DANCR	METTL3, IGF2BP2	Enhanced	Contributes to OS, pancreatic cancer and acute myeloid leukemia progression	(112-114)
LINC00958	METTL3, KIAA1429	Enhanced	Promotes BC tumorigenesis, HCC lipogenesis and progression, and accelerates GC aerobic glycolysis	(115-117)
KCNQ1OT1	IGF2BP1, MELL3, ALKBH5	Enhanced	Promotes cardiomyocyte ferroptosis, doxorubicin resistance in BC and the development of LSCC	(118-120)
FOXD2-AS1	METTL3, WTAP	Enhanced	Accelerates cervical cancer and OS progression	(121,122)
LncRNA PCAT6	METTL3/IGF2BP2	Enhanced	Promotes bone metastasis in prostate cancer	(123)
THAP7-AS1	METTL3/IGF2BP1	Enhanced	Promotes GC growth, invasion and metastasis	(124)
LncRNA PTTG3P	METTL3/IGF2BP2	Enhanced	Contributes to CRC proliferation	(125)
DLGAP1-AS1	WTAP	Enhanced	Enhances the resistance of BC to adriamycin	(126)
LncRNA CASC9	IGF2BP2	Enhanced	Accelerates glioblastoma aerobic glycolysis	(127)
ABHD11-AS1	METTL3	Enhanced	Enhances the Warburg effect of NSCLC	(128)
CircCUX1	METTL3	Enhanced	Confers radioresistance of hypopharyngeal squamous cell carcinoma	(129)
CircARHGAP12	IGF2BP2	Enhanced	Promotes cervical cancer progression	(130)
CircGLIS3	METTL3	Enhanced	Promotes cell proliferation and invasion.	(131)
CircDLC1	METTL3	Enhanced	Suppresses the proliferation of glioma	(132)
CircRPS6KC1	METTL3/ YTHDF1	Enhanced	Regulate cellular senescence	(133)
CircASXL1	METTL3/IGF2BP1	Enhanced	Promotes proliferation and migration of OC	(134)
Circ_0006168	METTL3/IGF2BP2	Enhanced	Promotes EMT process in ESCC	(135)
CircPAPPA2	METTL14/IGF2BP3	Decreased	Regulates the pathogenesis of preeclampsia	(136)
CircCCDC134	ALKBH5	Decreased	Facilitates cervical cancer metastasis	(137)
CircHIPK2	YTHDF2	Decreased	Alleviates microglia activation	(138)
CircAFF2	ALKBH5/YTHDF2	Decreased	Enhances radiosensitivity of colorectal cancer	(139)
CircMPP1	YTHDC1	Decreased	Maintains trophoblasts function	(140)
Circ_0003979	RBM15/ YTHDF2	Decreased	Inhibits HCC tumorigenesis	(141)
CircIRF2	YTHDF2	Decreased	Suppresses liver fibrosis	(142)

OS, osteosarcoma; OC, ovarian cancer; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; BC, breast cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; LSCC, laryngeal squamous cell carcinoma; CRC, colorectal cancer; ALKBH5, α -ketoglutarate-dependent dioxygenase alk B homolog 5; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1; METTL3/14, methyltransferase 3/14; HuR, also known as Elavl1, ELAV like RNA binding protein 1; IGF2BP1/2/3, insulin-like growth factor 2 mRNA binding protein 1/2/3; KIAA1429, also known as vir-like m6A methyltransferase associated protein; WTAP, Wilms' tumor 1-associated protein; YTHDF1/2, YTH N6-methyladenosine RNA binding protein F1/2, YTHDC1, YTH N6-methyladenosine RNA binding protein C1; RBM15, RNA binding motif protein 15.

modification of LINC00294, with YTHDC1 recognizing the m6A sites and promoting its cytoplasmic localization (150). Similarly, YTHDF1 interacts with the m6A site of lncRNA FOXD1-AS1, facilitated by METTL3, thereby promoting its cytoplasmic localization (151). In addition, hnRNPC mediates the cytoplasmic export of m6A-modified circMARK2 (152). METTL3-induced m6A modification also facilitates the export of circTEAD1 to the cytoplasm (153).

Beyond localization, m6A modification of ncRNAs also regulates nuclear retention or translocation, impacting gene transcription. For instance, circPPAP2B harbors m6A sites that recruit hnRNPC in an m6A-dependent manner, facilitating the nuclear translocation of hnRNPC, which subsequently regulates alternative splicing of pre-mRNA (154). The m6A modification of circCCDC134 by ALKBH5/YTHDF2 recruits p65 in the nucleus, ultimately stimulating HIF1A transcription

Table II. Effects of m6A modification on ncRNA localization.

ncRNAs	m6A regulator	Localization	(Refs.)
CircTET2	YTHDC1	Transport of circTET2 out of the nucleus	(168)
CircRNA388	YTHDC1/CRM1	Facilitates m6A-modified circRNA388 nuclear export	(169)
CircCSDE1	METTL3	Enhances its cyclization efficiency and nuclear export	(170)
hsa_circ_0058493	YTHDC1	Promotes its localization from the nucleus to the cytoplasm	(171)
CircMET	YTHDC1	Delivery to cytosol	(172)
hsa_circ_0001599	hnRNP A2/B1	Translocation from the nucleus to the cytoplasm	(173)
CircEHD2	hnRNP A2/B1	Regulates the package of circEHD2 into EVs	(174)
CircTLCD4-RWDD3	hnRNP A2/B1	Facilitates the sorting into NSCLC cell-derived EVs	(175)
CircATP9A	hnRNP A2/B1	Mediates the incorporation of circATP9A into EVs	(176)
CircNEIL3	hnRNP A2/B1	Packaging into exosomes and transmission to infiltrated TAMs	(177)
Lnc668	YTHDC1	Promotion of the nuclear export of m6A-modified Lnc668	(178)
LncRNA TUC338	METTL3/YTHDF1	Delivery to EVs	(179)

EV, extracellular vesicle; YTHDC1, YTH N6-methyladenosine RNA binding protein C1; METTL3, methyltransferase 3; TAMs, tumor-associated macrophages; HNRNP A2/B1, heterogeneous nuclear ribonucleoprotein A2/B1; NSCLC, non-small cell lung cancer; YTHDF1, YTH N6-methyladenosine RNA binding protein F1.

and facilitating cancer cell growth and metastasis (137). In addition, circMMP9 is stabilized by IGF2BP2 in an m6A-dependent manner, with circMMP9 recruiting ETS1 to promote tripartite motif containing 59 (TRIM59) transcription (155). Furthermore, DNA damage has been shown to increase m6A levels on NEAT1, promoting structural alterations and the accumulation of hypermethylated NEAT1 at promoter-associated double-strand breaks (156). METTL3-induced m6A modification upregulates POU6F2-AS1, tethering Y-box binding protein 1 to the fatty acid synthase promoter and activating transcription (157). Allele-specific m6A methylation affects YTHDC1-mediated protein binding affinity, with the LOC339803-YTHDC1 interaction determining chromatin localization of LOC339803, inducing the expression of NF- κ B-mediated proinflammatory cytokines (158). Additionally, Vaid *et al* (159) reported that m6A-mediated recruitment of hnRNP A2/B1 to lncRNA-TERRA is essential for R-loop formation and telomere localization.

m6A modification plays a pivotal role in sorting ncRNAs into exosomes through interactions with m6A-binding proteins. For instance, the m6A reader hnRNP A2/B1 contributes to the progression of multiple myeloma osteolytic bone disease by modulating the expression and exosomal transport of miRNAs to recipient monocytes or MSCs (160). Wei *et al* (79) demonstrated that m6A modification of circCDYL promotes its active sorting into exosomes via hnRNP A2/B1. Similarly, the m6A modification of circCCAR1, mediated by WTAP, facilitates its secretion by HCC cells into exosomes in a hnRNP A2/B1-dependent manner (161). Exosomal encapsulation of circHIF1 α is also governed by hnRNP A2/B1 (162). Furthermore, multiple myeloma cells enhance the packaging of lncRNA into adipocyte-derived exosomes through METTL7A-mediated m6A methylation (163). Additionally, m6A modification drives the sorting of LINC00657 into exosomes, promoting breast cancer progression by inducing macrophage M2 polarization (164). He *et al* (165) reported that m6A modification, recognized by

IGF2BP2, stabilizes TRPM2-AS and enhances its exosomal sorting. Other m6A readers, such as RNA binding motif protein X-linked (RBMX), may also play significant roles in exosome cargo loading (166), with RBMX being a newly identified m6A reader involved in this process (167). Table II summarizes other studies on the role of m6A modification in regulating ncRNA localization (168-179).

m6A-dependent peptides translation of ncRNAs. Traditionally, ncRNAs were considered non-coding and incapable of serving as a template for producing proteins or peptides. However, recent research has challenged this notion, revealing that ncRNAs can indeed be translated into micro-peptides in an m6A modification-dependent manner. It has been reported that circSLC9A6 encodes a novel peptide, SLC9A6-126 amino-acid (aa), through m6A modification, involving the m6A reader YTHDF2 (180). Similarly, circYAP encodes a truncated protein, YAP-220aa, through m6A modification, facilitated by YTHDF3 and the eIF4G2 translation initiation complex (181). YTHDF1 and YTHDF3 bind to m6A sites on circYthdc2, promoting its translation into the Ythdc2-170aa peptide (182). Li *et al* (183) discovered that circFBXW7 can be translated into the short polypeptide circFBXW7-185aa, involving the m6A reader YTHDF3. In a related study, circ-MIB2 harbors m6A sites that recruit YTHDF1 and YTHDF3, facilitating its translation into the MIB2-134aa (184). Tang *et al* (185) demonstrated that several male germ cell circRNAs contain large open reading frames with m6A-modified start codons in their junctions, a characteristic recently associated with protein-coding potential. Additionally, circFNDC3B, modified by m6A, is translocated to the cytoplasm, and Pan *et al* (186) found that circFNDC3B encodes a novel protein, circFNDC3B-218aa. METTL3-mediated m6A-modified circGLIS3 contributes to β -cell dysfunction by encoding the protein Glis3-348aa (187). The stability of circ-ZNF609 is regulated by m6A methylation and circ-ZNF609 plays a pivotal role in fibroblast activation through peptide encoding (188).

Table III. m6A-related circRNA and lncRNA translation.

ncRNAs	Peptide name	Disease	Functions and mechanisms	(Refs.)
Circ-MET	MET404	GBM	Oncogenic; directly interacts with the MET β subunit and forms a constitutively activated MET receptor	(197)
CircASK1	ASK1-272aa	Lung cancer	Oncogenic; ameliorates gefitinib resistance in lung adenocarcinoma	(198)
CircSTX6	CircSTX6-144aa	HCC	Oncogenic; promotes HCC proliferation, migration and invasion	(199)
CircARHGAP35	P190-A	HCC	Oncogenic; circARHGAP35 protein interacts with TFII-I in the nucleus	(200)
CircPETH	CircPETH-147aa	HCC	Regulates metabolic reprogramming and remodels the immunosuppressive microenvironment	(201)
CircNFIB	CircNFIB-56aa	Breast tumor	Tumor suppressor; decreases synthesis of arachidonic acid and inhibits breast tumor growth and metastasis	(202)
CircSPECC1	SPECC1-415aa	GBM	Tumor suppressor; restores the sensitivity of TMZ-resistant GBM cells to TMZ.	(203)
CircKEAP1	KEAP1-259aa	OS	Tumor suppressor; reduces cell proliferation, invasion and tumorsphere formation of OS cells	(204)
CircCDYL	tCDYL-100aa	Cardiac hypertrophys	Exacerbates cardiac hypertrophy	(205)
LINC00339	LINC00339-205-49aa	Endometrial receptivity	Promotes trophoblast adhesion to endometrial cells	(206,207)
MALAT1	-	Neurons	Modulates synaptic function	(208,209)
lncRNA BVES-AS1	BVES-AS1-201-50aa	CRC	Promotes cell viability, migration and invasion in colorectal cancer	(210,211)

TMZ, temozolomide; MET, MET proto-oncogene, receptor tyrosine kinase; HCC, hepatocellular carcinoma; TFII-I (also known as GTF2I), general transcription factor Iii; TMZ, temozolomide; OS, osteosarcoma; CRC, colorectal cancer.

The m6A modification also plays a critical role in the translation of lncRNAs. Wu *et al* (189) identified a novel micro-peptide, YY1BM, encoded by the Y-linked LINC00278, where reduced m6A modification led to decreased translation. Additionally, the translation of AFAP1-AS1 translated mitochondrial-localized peptide (ATMLP) peptides from lncRNA AFAP1-AS1 was found to be regulated by m6A methylation at the adenine locus 1,313 of AFAP1-AS1 (190). Furthermore, METTL3 catalyzed the installation of m6A modification, enhancing the stability of the METTL4-2 transcript and thereby increasing its expression. In parallel, YTHDF1 recognized these m6A sites, facilitating the translation of METTL4-2 (191). Moreover, m6A modification regulates the expression of various lncRNAs, some of which have been reported to encode micro-peptides. For instance, YTHDC1 was found to upregulate the expression of HOXB-AS3 through m6A modification of its precursor RNA (192), and a micro-peptide encoded by HOXB-AS3 was reported to promote the proliferation and viability of oral squamous cell carcinoma cells (193). Another novel peptide, HOXB-AS3-32aa encoded by lncRNA HOXB-AS3, was found to promote cigarette smoke-induced inflammation and apoptosis (194). Additionally, the micro-peptide ATP synthase-associated peptide encoded by LINC00467 has been shown to promote CRC progression (195), although Zhang *et al* (196) recently reported the negative

impact of m6A methylation on LINC00467 translation. The development of m6A sequencing technologies has led to the identification of numerous lncRNAs undergoing m6A modification, suggesting the potential for a significant number of lncRNA-encoded proteins. Table III summarizes other studies on m6A-related circRNA and lncRNA translation (197-211).

6. m6A modification of ncRNAs in other diseases

m6A modification of ncRNAs in cardiovascular disorders. Atherosclerosis (AS), myocardial infarction injury, myocardial ischemia-reperfusion injury and cardiac hypertrophy are the most common cardiovascular diseases. It has been reported that m6A modification of ncRNAs participates in the pathological processes of cardiovascular diseases (Fig. 3). METTL14-mediated m6A modification upregulated circARHGAP12 and aspartate beta-hydroxylase to aggravate overload-induced lipid peroxidative damage and facilitate AS progression (212). Shen *et al* (213) reported that hypoxia triggers cardiomyocyte apoptosis via regulating the m6A methylation-mediated lncMIAT/miR-708-5p/p53 axis. ALKBH5 decreased the N6-methylation and promoted the destabilization of circPan3, and circPan3 could attenuate cardiomyocyte hypertrophy by targeting the miR-320-3p/HSP20 axis (214). METTL3 mediated the

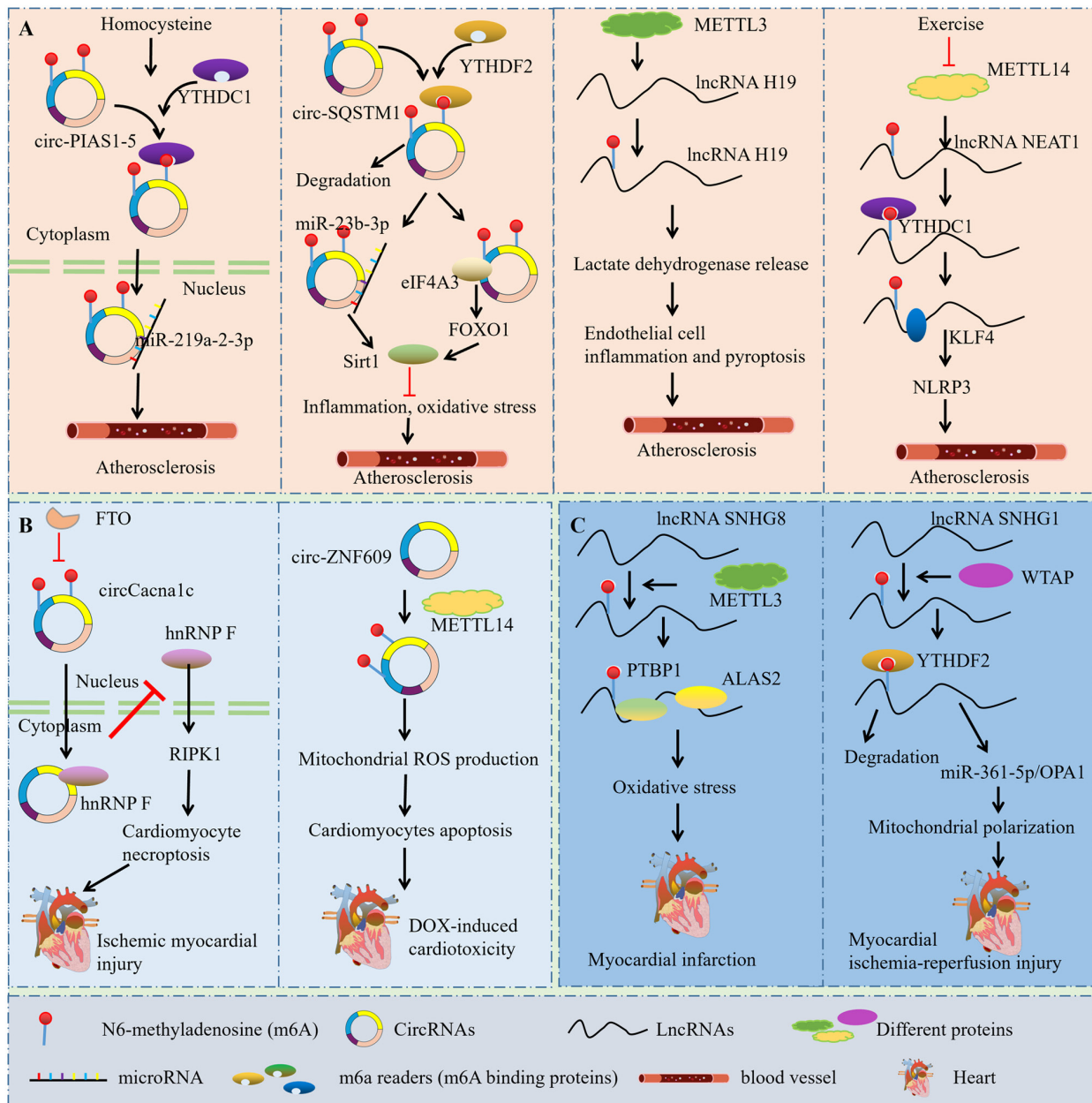


Figure 3. Effects of m6A-modified ncRNAs in the pathological processes of cardiovascular diseases. (A) m6A-modified ncRNAs facilitate the progression of atherosclerosis. (B) Role of m6A-modified ncRNAs in regulating the viability of cardiomyocytes. (C) m6A-modified ncRNAs facilitate the progression of myocardial ischemia-reperfusion injury. WTAP, Wilms' tumor 1-associated protein; METTL3/14, methyltransferase-like 3/14; YTHDF2/C1, YTH N6-methyladenosine RNA binding protein F2/C1; hnRNP F, heterogeneous nuclear ribonucleoprotein F; EIF4A3, eukaryotic translation initiation factor 4A3; Sirt1, sirtuin 1; FOXO1, forkhead box O1; NEAT1, nuclear paraspeckle assembly transcript 1; FTO, fat mass and obesity-associated protein; KLF4, KLF transcription factor 4; NLRP3, NLR family pyrin domain containing 3; RIPK1, receptor interacting serine/threonine kinase 1, ROS, reactive oxygen species; DOX, doxorubicin; SNHG1/8, small nucleolar RNA host gene 1/8; PTBP1, polypyrimidine tract binding protein 1; ALAS2, 5'-aminolevulinate synthase 2; OPA1, OPA1 mitochondrial dynamin like GTPase.

m6A modification of lncRNA H19 to alleviate cerebral ischemia-reperfusion injury by regulating the sphingosine-1-phosphate receptor 2/Toll-like receptor 4/NLR family pyrin domain containing 3 (NLRP3) signaling pathway (215). METTL14 mediated m6A-modified circZNF609, which regulated doxorubicin-induced cardiotoxicity by upregulating FTO (216).

m6A modification of ncRNAs in metabolic diseases. Diabetes-related diseases, obesity and nonalcoholic fatty liver disease are the most common metabolic diseases (Fig. 4). It has been

reported that YTHDC2 mediated the m6A modification of circYTHDC2, which promoted dysfunction of vascular SMCs (VSMCs) and is an important target of metformin in preventing the progression of VSMC dysfunction in type 2 diabetes (217). METTL3 ameliorated diabetes-induced testicular damage by upregulating lncRNA TUG1/clusterin signaling (218). Diabetic retinopathy (DR) and diabetic nephropathy are common complications of diabetes. Fu *et al* (219) found that METTL3/YTHDC1 mediates the m6A modification and upregulation of lncRNA OGRU, which led to oxidative stress, inflammation and DR progression. Macrophage M1 regulatory

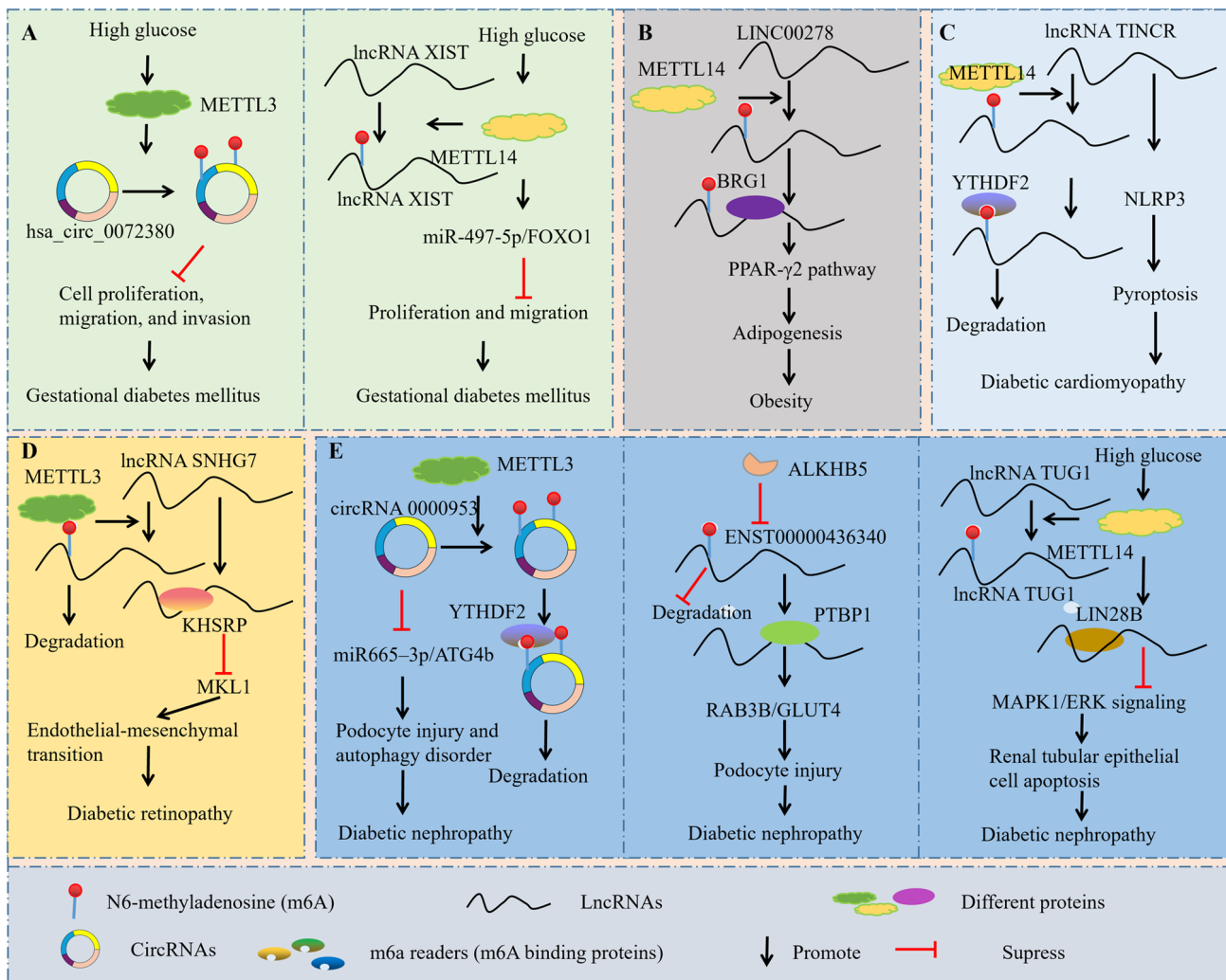


Figure 4. Effects of m6A-modified ncRNAs in the pathological processes of metabolic diseases. (A) m6A-modified ncRNAs facilitate the progression of gestational diabetes mellitus. (B) Role of m6A-modified ncRNAs in regulating obesity. (C) m6A-modified ncRNAs facilitate the progression of diabetic cardiomyopathy. (D) m6A-modified ncRNAs facilitate the progression of diabetic retinopathy. (E) m6A-modified ncRNAs facilitate the progression of diabetic nephropathy. METTL3/14, methyltransferase-like 3/14; lncRNA, long noncoding RNA; FOXO1, forkhead box O1; XIST, X inactive specific transcript; BRG1, SBP (S-ribonuclease binding protein) family protein; TINCR, TINCR ubiquitin domain containing; NLRP3, NLR family pyrin domain containing 3; SNHG7, small nucleolar RNA host gene 7; KHSRP, KH-type splicing regulatory protein; MKL1, kinase MKL1 MAPK-like protein; ALKBH5, α -ketoglutarate-dependent dioxygenase alk B homolog 5; PTBP1, polypyrimidine tract binding protein 1; RAB3B, member RAS oncogene family; GLUT4, solute carrier family 2 (facilitated glucose transporter), member 4; TUG1, taurine up-regulated 1; LIN28B, lin-28 homolog B; MAPK1, mitogen-activated protein kinase 1.

DR is mediated by FTO-regulated m6A modification of LINC00342, LINC00667 and LINC00963 expression (220). WTAP mediated the m6A methylation of NEAT1, and subsequently NLRP3 inflammasome activation and dry eye disease in diabetes mellitus (221). In addition, Zheng *et al* (222) reported recently that dysregulated expression of circRNAs may be influenced by m6A modifications, and these circRNAs play significant roles in metabolism-associated fatty liver disease.

m6A modification of ncRNAs in neurological diseases. It has been reported that abnormal expression of m6A-related proteins also occurs in the nervous system, thereby affecting the development of neuroinflammation, AD, spinal cord injury (SCI) and cerebral ischemia-reperfusion injury (Fig. 5). For instance, Zhang *et al* (223) recently reported that m6A modification is enriched in circRNAs of neurons,

and the m6A modification of circRNAs was reduced under oxygen-glucose deprivation and reoxygenation (OGD/R) injury conditions. Furthermore, through high-throughput sequencing, Zhang *et al* (224) identified eight m6A-modified circRNA that may be associated with the pathogenesis of AD. Furthermore, Liu *et al* (225) examined m6A modifications in SCI, revealing that 738 lncRNAs were differentially methylated (488 hypermethylated and 250 hypomethylated). In addition, Atrian *et al* (226) reported that tau-induced m6A methylation is a mechanistic driver of circMbl formation, and circMbl contributed to neurotoxicity and neurodegeneration. Electroacupuncture serum [serum was obtained from rats that were received electroacupuncture treatment 3 times at 'Renzhong' (GV26) and 'Baihui' (GV20) acupoints] alleviates OGD/R-induced astrocyte damage by regulating aquaporin 4 via m6A methylation of lncRNA MALAT1 (227).

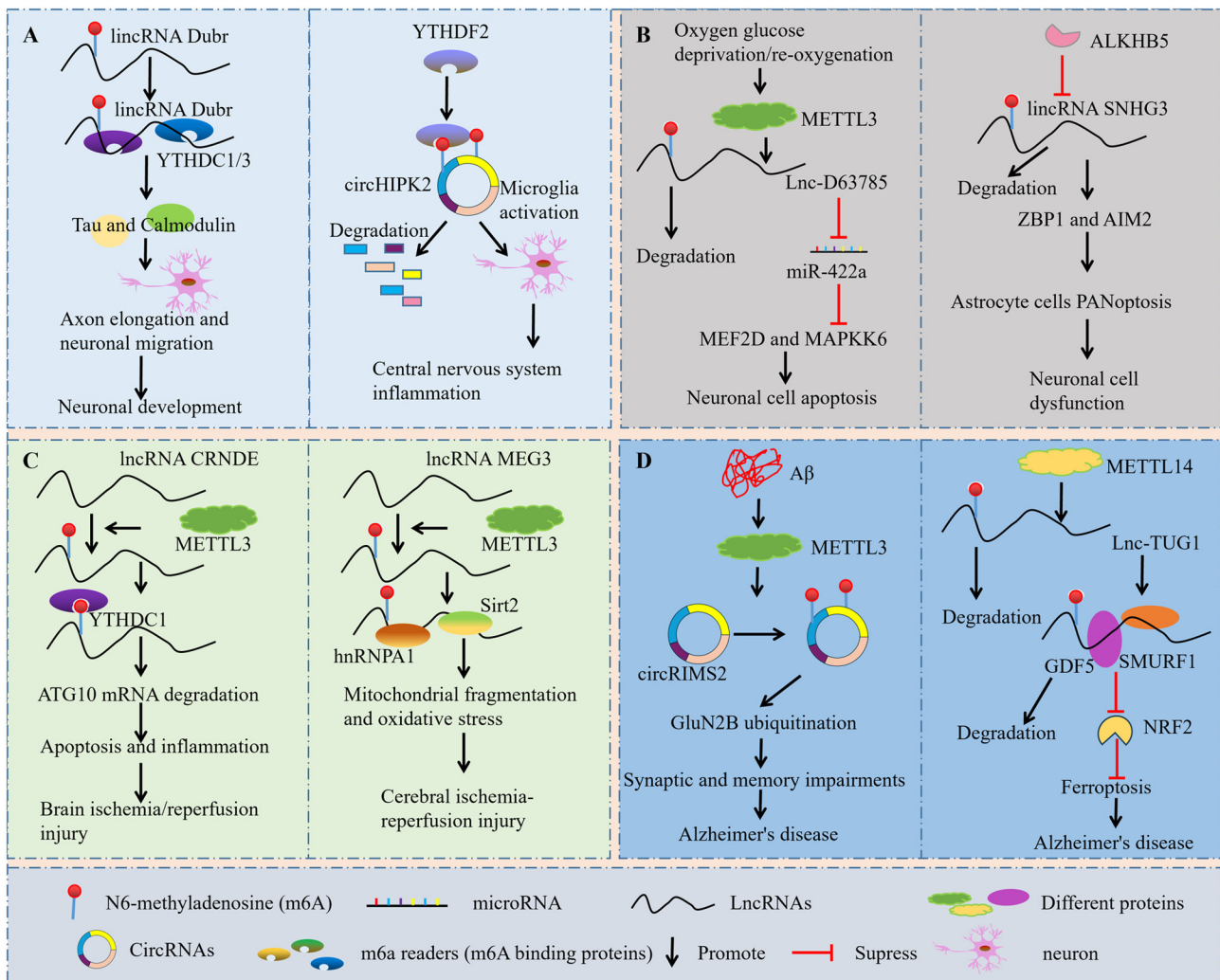


Figure 5. Effects of m6A-modified ncRNAs in the pathological processes of neurological diseases. (A) m6A-modified ncRNAs regulate the development and inflammation of the central nervous system. (B) m6A-modified ncRNAs regulate the viability and function of neuronal cells. (C) m6A-modified ncRNAs facilitate the progression of cerebral ischemia-reperfusion injury. (D) m6A-modified ncRNAs facilitate the progression of Alzheimer's disease.

7. Discussion

Various studies have shown the potential clinical value of m6A-modified ncRNAs as diagnostic biomarkers and prognostic indicators. It has been reported that the expression of m6A-modified circCUX1 was significantly upregulated in hypopharyngeal squamous cell carcinoma, and correlated with primary tumor size, lymph node metastasis, distant metastasis and tumor node metastasis stage, and its high expression indicated poor overall survival and poor disease-free survival (129). Furthermore, m6A-modified ABHD11-AS1 was found to be upregulated in human CRC tissues and related to poor prognosis (65). In addition, m6A-modified circCDYL existed in a stable form in HCC-derived exosomes, and was indicated to be a promising early diagnostic biomarker with an area under the curve of 0.896 (79). The distinct expression patterns of these novel ncRNA-derived peptides and proteins also offer considerable diagnostic potential. For instance, the serum levels of m6A-modified lincRNA AFAP1-AS1-encoded lincRNA AFAP1-AS1 translated mitochondrial-localized peptide were elevated in patients with non-small cell lung cancer (NSCLC) and associated with a poorer prognosis (190).

The expression profiles of lincRNA-encoded microproteins in extracellular vesicles from patients with glioma differ from those in healthy donors (225). The high expression of circMAP3K4-455aa, a novel peptide encoded by m6A-modified circMAP3K4, predicts a worse prognosis for patients with HCC (17). Similarly, circMET encodes a 404-aa MET variant (MET404), and high MET404 expression was associated with poor prognosis in patients with glioblastoma (197).

The recent studies on m6A regulators and ncRNA-derived peptides render them promising therapeutic targets for numerous diseases, including malignant cancers. In esophageal squamous cell carcinoma, increasing m6A modification of circCREBBP could enhance the radiosensitivity of tumor cells (228). In CRC, ALKBH5 directly demethylates lincRNA CARMN, thereby suppressing the degradation of lincRNA CARMN and preserving lincRNA CARMN expression, and upregulated CARMN promoted tumor progression (92). Furthermore, Xinfeng capsule inhibited the progression of rheumatoid arthritis by modulating FTO-mediated m6A modification of lincRNA ENST00000619282 (229). These results indicated that modulating the activity of m6A-related enzymes, thereby regulating the m6A modification of target

genes, has a critical role in disease treatment. A phase II study of bisantrene (a FTO inhibitor) in patients with relapsed/refractory acute myeloid leukemia showed that it achieved a partial remission, resulting in an overall response rate of 40% (230). Preclinical studies about METTL3 and METTL14 show promise in inhibiting tumor growth via direct anti-tumor effects and anti-cancer immune responses (231–233), and STC-15, a small-molecule inhibitor of METTL3, now has entered Phase I clinical trials (234). On the other hand, certain ncRNA-derived peptides have been reported to have special roles in disease treatment. For instance, a 188-aa peptide encoded by hsa_circRNA_103820 suppresses cell viability, induces apoptosis and inhibits cell migration and invasion in lung cancer (18). In addition, a tumor suppressor protein encoded by circKEAP1 inhibited stemness and metastasis by promoting vimentin proteasomal degradation and activating anti-tumor immunity in osteosarcoma (204). SPECC1-415aa, encoded by circSPECC1, inhibits the binding of annexin A1 (ANXA1) to EGFR by competitively binding to ANXA2, thereby preventing EGFR and AKT phosphorylation and restoring the sensitivity of temozolomide (TMZ)-resistant glioblastoma cells to TMZ (203). Although several ncRNA-encoded peptides have demonstrated tumor-suppressive functions, critical questions remain regarding their clinical applications. These include concerns about the feasibility of large-scale *in vitro* production and whether these cancer-suppressive micro-peptides can effectively target tumor cells upon injection. Future research should focus on unraveling the regulatory mechanisms underlying their expression and investigating how they exert their tumor-suppressing effects.

However, the use of ncRNAs or ncRNA-derived peptides for disease diagnosis or target therapy remains constrained by challenges. First, the roles of certain m6A-modified ncRNAs are conflicting. For instance, m6A-modified lncRNA MEG3 has been reported to suppress the proliferation, migration and invasion of HCC (235), while it promoted tumorigenesis and metastasis of NSCLC (104). Furthermore, it is difficult to detect m6A-modified ncRNAs or their encoded peptides in clinical samples. However, certain studies reported the existence of these ncRNAs or peptides in biofluids, such as blood and urine, indicating it is accessibility that using ncRNAs for testing diagnostic. For instance, m6A-modified circSLC38A1 was identified in serum exosomes of patients with bladder cancer and could distinguish patients with bladder cancer from healthy individuals with a diagnostic accuracy of 0.878 (236). Furthermore, Li *et al* (59) reported that circTRIM1 encoded TRIM1-269aa, which can be detected in exosomes from patients with triple-negative breast cancer. In addition, standard hybridization-based techniques cannot be applied for sensing m6A in RNAs and the development of new methods for accurate and sensitive profiling of locus-specific m6A in RNAs remains a great challenge. Liu *et al* (237) recently constructed a hierarchical DNA circuit for single-molecule profiling of locus-specific m6a-MALAT1 in clinical tissues. Finally, the dynamic nature of m6A modification makes it difficult to establish causal relationships *in vivo*. However, it has been reported that the transcriptome-wide m6A methylome was dynamically altered during initial diagnosis and relapse and can be monitored by methylated RNA immunoprecipitation next-generation

sequencing (238). Recently, Song *et al* (38) presented a method termed proximity hybridization followed by primer exchange amplification, which could image m6A methylation sites concurrently in multiple cell types, revealing cell-to-cell variability in expression levels.

8. Conclusions

In conclusion, this review provided a comprehensive overview of the current understanding of m6A modification in ncRNAs, including miRNAs, lncRNAs and circRNAs. It explored how m6A modification regulates their biogenesis, maturation, localization and stability. Importantly, this review introduced the identification of peptides derived from m6A-modified ncRNAs. Furthermore, the diverse roles of m6A-modified ncRNAs and their encoded peptides in tumorigenesis, cardiovascular disorders, metabolic diseases and neurological diseases were discussed. It also highlights their potential clinical applications in cancer diagnosis, disease prediction and targeted therapy, offering new insights and perspectives to advance research in this field.

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Authors' contributions

QY performed the literature search. QY and YL prepared the first draft of the manuscript. WS wrote and edited the manuscript. JL and DY drew the figures. WS and HS prepared the tables and were responsible for revising the manuscript. QY, WS and WC obtained funding support. All authors reviewed the manuscript, and have read and approved of the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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