Molecular Therapy
Nucleic Acids
Review

The role of M^{6}A modification in the regulation of tumor-related lncRNAs

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N^6-methyladenosine (m^{6}A) is the most abundant modification in eukaryotic cells, and it regulates RNA transcription, processing, splicing, degradation, and translation. Long non-coding RNAs (lncRNAs), as transcriptional products with no or limited protein coding ability more than 200 nt in length, play an important role in epigenetic modification, mRNA transcription, splicing, stability, translation, and other biological functions. Extensive studies have shown that both m^{6}A modification and lncRNAs are involved in the pathogenesis of various diseases, such as kinds of cancers, heart failure, Alzheimer's disease, periodontitis, human abdominal aortic aneurysm, and obesity. To date, m^{6}A modification has been identified as an important biological function in enrichment and regulation of lncRNAs. In this review, we summarize the role of m^{6}A modification in the regulation and function of tumor-related lncRNAs. Moreover, we discuss the potential applications and possible future directions in the field.

BACKGROUND

Long non-coding RNAs (lncRNAs) are novel ncRNAs longer than 200 nt and generally transcribed in the human genome.[1] It is now confirmed that lncRNAs play a significant role in biological functions such as epigenetic modification, mRNA transcription, splicing, stability, and translation.[2] Specifically, it has been demonstrated that lncRNA is involved in the occurrence, development, and prognosis of various diseases, including carcinomas,[3–5] neuropsychiatric disorders,[6,7] immune molecular mechanism,[8–10] and cardiac gene programs.[11] lncRNAs can interact with proteins, RNA, DNA, and can mediate their function.[10] However, there are limited studies to show how lncRNAs are regulated.

Thus far, numerous studies on methylation modification in eukaryotic cells have shown that many methylation modifications can regulate RNA in eukaryotic cells, including 7-methylguanine (m^{7}G), 5-methylcytosine (m^{5}C), *N*6,2′-*O*-dimethyladenosine (m^{6}Am), N^1-methyladenosine (m^{1}A), 5-hydroxymethylcytosine (5hmC), and *N*6-methyladenosine, among others.[12] One of the most abundant modification methods in RNAs has been shown to be m^{6}A. Studies have demonstrated that the m^{6}A modification is dynamic and reversible, and it can influence the metabolism of mRNA and regulate RNA transcription, export, splicing, degradation, and translation.[13] The m^{6}A methylation level is related to the occurrence and progression of many diseases, such as tumors,[14–17] heart failure,[18] Alzheimer's disease,[19] periodontitis,[20] human abdominal aortic aneurysm,[21] and obesity.[22] However, the mechanism of how cell-specific m^{6}A methylomes are established is poorly described.[23]

There are many mechanisms of both m^{6}A modification and lncRNA that have not been elucidated. In this review, we summarize the role of m^{6}A modification in the regulation of tumor-related lncRNAs. We also discuss the potential applications and possible future directions in this field.

m^{6}A WRITERS, READERS, AND ERASERS

m^{6}A has modifications and effects on RNA through the dynamic interaction between three homologous factors, writers (methyltransferases), readers (binding proteins), and erasers (demethylases)[24] (Figure 1).

Writers

An m^{6}A writer is a protein complex with a high molecular weight of around 1 MDa,[25] which consists of the following core subunits: methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), and their cofactors; Wilms' tumor 1-associating protein (WTAP); Vir like m^{6}A methyltransferase associated (VIRMA); zinc finger CCCH-type containing 13 (ZC3H13); CBLL1 (also known as HAKAI); RNA-binding motif protein 15/15B (RBM15/15B); and the complex methylate mRNAs in a sequence context of RRACH (R = A or G; H = A, C, or U),[26] often in 30 UTRs.[27] Methyltransferase-like 16 (METTL16) is a novel m^{6}A writer protein when we exclude the above-mentioned complex, m^{6}A methyltransferase complex (MTC).[28] METTL3, as a significant catalytic subunit of MTC that

https://doi.org/10.1016/j.omtn.2021.04.002.

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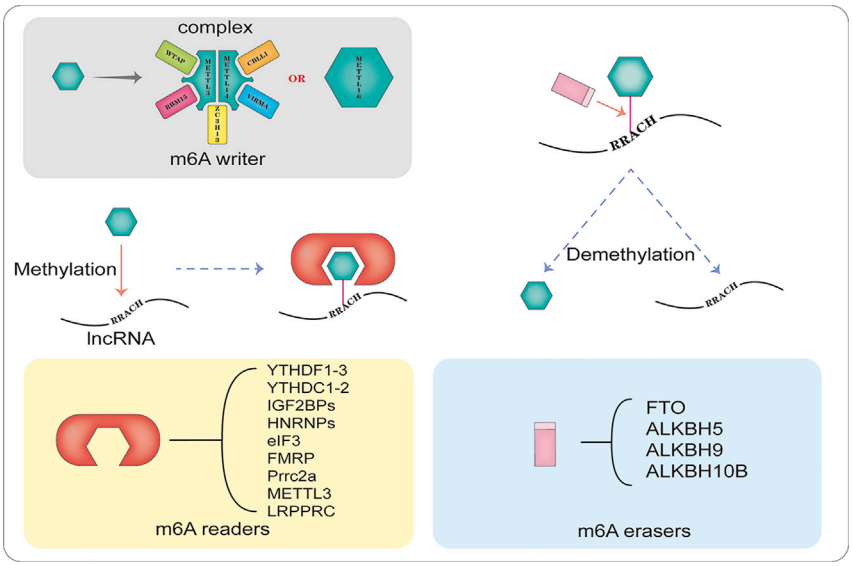

Figure 1. m^{6}A writer complex is conducted by METTL3, METTL14, WTAP, RBM15, ZC3H13, VIRMA, and CBLL1

Additionally, METTL16 is another novel independent RNA methyltransferase. Readers such as YTHDF1–3, YTHDC1–2, IGF2BPs, HNRNPs, eIF3, FMRP, Prrc2a, METTL3, and LRPPRC could recognize the m^{6}A writer and then have different functions on mRNA. Erasers are proteins that can regulate the process of demethylation, including FTO, ALKBH5, ALKBH9, and ALKBH10B.

belongs to the class I MTase family,[29] is the earliest known and key enzyme of m^{6}A methylation modification.[30] Previous studies have shown that knockdown of METTL3 directly leads to m^{6}A decreases in mammalian embryonic stem cells (ESCs), HeLa cells, and HepG2 cells.[31] Additionally, METTL3 can be detected in both the nucleus and cytoplasm,[32] which means that mRNA methylation could occur in both the nucleus and cytoplasm.[31] Hence, we can conclude that METTL3 plays an important role in m^{6}A regulation. As a great adaptor needed to assist METTL3 activity, METTL14 has homology to methyltransferases.[33] METTL14 could form a stable heterodimer core complex with METTL3.[34] At the same time, METTL14 plays a key role in β cell survival, insulin secretion, and glucose homeostasis.[35] Knockdown of METTL14 could downregulate the m^{6}A level of X-inactive specific transcript (XIST) and augment XIST expression.[36] We can regard METTL14 as the second methyltransferase enzyme. WTAP is also a pivotal component of MTC, associated with the tumor suppressor gene Wilms' tumor 1, recruiting METTL3 and METTL14 to be localized in mRNA targets to catalyze m6A's formation together.[37] Depletion of WTAP could induce a loss of nuclear speckle localization for METTL3 and METTL14.[38] VIRMA was originally known as KIAA1429, a recently identified component of MTC, which has been proven to mediate the deposition of preferential m^{6}A in the 3′ UTR and near stop codon and is associated with selective polyadenylation (APA) in HeLa cells.[39] ZC3H13 is also a novel component of MTC that stabilizes the interaction between WTAP and RBM15.[40] CBLLI (HAKAI) was confirmed as an E3 ubiquitin-ligase that interacts with the tyrosine phosphorylated substrates to induce their ubiquitination and degradation.[41] Just as for the other components of MTC, the downregulation of HAKAI will decrease the level of m^{6}A and fault in embryonic development.[42] RBM15 and RBM15B are paralogs and bind the MTC and recruit it to specific loci in RNAs.[43] In addition to MTC, METTL16 is an independent methyltransferase that targets U6 small nuclear RNA (snRNA) and MAT2A mRNA.[27]

Readers

m^{6}A readers are a type of binding proteins that can specifically decode the m^{6}A mark and affect methylated mRNAs. In addition, different m^{6}A readers have different functions on mRNA.[44] One class of abundant m^{6}A readers belongs to the YT521-B homology (YTH) domain family, including YTH domain family 1–3 (YTHDF1–3) and YTH domain containing 1–2 (YTHDC1–2).[26] YTHDF1 was reported to enhance translational efficiency via interacting with initiation factors,[45] while Liu et al.[46] validated the vital oncogenic roles of YTHDF1 in tumor progression. YTHDF2 has the function to modulate mRNA instability by identifying and distributing m^{6}A-modified mRNA as well as degrading both tumor promoter and suppressor gene mRNAs.[33,47] YTHDF3 could accelerate protein synthesis with YTHDF1 and mediate the decay of methylated mRNA through YTHDF2.[48] Recent research elucidated that YTHDF3 proteins could limit HIV infection of new target cells at the period of reverse transcription.[49] YTHDC1 localizes to the nucleus in cultured mammalian somatic cells, while YTHDC2 is meiotic spermatocytes' cytoplasmic.[50] YTHDC1 was confirmed to modulate mRNA splice site selection in a concentration-dependent manner through minigene reporter assays.[51] As the largest member of the YTH family, YTHDC2 also binds m^{6}A preferentially within the consensus motif, and it can enhance the translation efficiency while decreasing the abundance of its target mRNAs.[24] Huang et al.[52] reported that insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs; including IGF2BP1/2/3) are another species of m^{6}A readers in post-transcriptional gene regulation and cancer biology. IGF2BPs have the function of stabilizing target mRNA and promoting their translation level in an m^{6}A-dependent manner and can then affect gene expression.[53] Several heterogeneous nuclear ribonucleoproteins (HNRNPs), including HNRNPC, HNRNPG, and HNRNPA2/B1, regulate alternative splicing (AS) or processing of target transcripts.[26] HNRNPC could affect precursor (pre-)mRNA stability, splicing, export, and translation via binding to nascent RNA transcripts.[54] Zhou et al.[55] showed that HNRNPG could regulate AS through interacting with m^{6}A-modified embryonic pre-mRNA and the phosphorylated C-terminal domain of RNA polymerase II. Moreover, through bioinformatics analysis, Wu et al.[56] suggested that HNRNPA2/B1 may mediate the effects of m^{6}A via an "m^{6}A switch" mechanism, rather than acting as a direct m^{6}A reader. Eukaryotic initiation factor 3

(eIF3) also serves as a reader of m^{6}A and binds a single 5′ UTR m^{6}A directly rather than 5′ cap to promote translation under cellular stresses.[57] Fragile X mental retardation protein (FMRP) could directly bind YTHDF2 and indirectly maintain m^{6}A-containing mRNAs instead of recruiting RNA-binding proteins (RBPs).[58] Hsu et al.[59] concluded that FMRP might affect the nuclear export of m^{6}A-modified RNA targets. Recently, Wu et al.[60] identified proline rich coiled-coil 2A (Prrc2a) as a novel m^{6}A reader regulating oligodendrocytes expression. Apart from the above readers, METTL3 can act as an m^{6}A reader as well, enhancing translation by binding a small part of cytoplasmic m^{6}A-modified mRNA.[58,61] In addition, researchers have identified leucine-rich pentatricopeptide repeat-containing protein (LRPPRC) as a potential reader.[62]

Erasers

m^{6}A regulation depends on the erasers, including fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5), to catalyze the demethylation of m^{6}A. FTO, also known as AlkB homolog 9 (ALKBH9), was discovered as the first m^{6}A eraser that established the dynastic and reversible m^{6}A modification.[63] FTO localizes largely in the nucleus and mediates 5%–10% of total mRNA m^{6}A demethylation; however, FTO is also highly abundant in the cytoplasm of certain leukemia cells and can mediate up to 40% of all mRNA m^{6}A.[26] Yang et al.[64] suggested that knockdown of FTO increases m^{6}A methylation in the key pro-tumorigenic melanoma cell-intrinsic genes, which resulted in the increase of RNA decay through the m^{6}A reader YTHDF2. Nevertheless, whether FTO recognizes and removes m^{6}A from the internal m^{6}A motifs is still an essential problem.[65] Unlike FTO, ALKBH5 catalyzes m^{6}A progression directly by removing the methyl group from m^{6}A-methylated adenosine instead of oxidative demethylation.[66] ALKBH5 inhibits the binding of reader protein YTHDF2 in plasmacytoma variant translocation 1 (PVT1) by down-regulating the m^{6}A modification of PVT1.[67] Additionally, ALKBH5 deficiency boosts PDAC cell proliferation, migration, and invasion both *in vivo* and *in vitro*.[68] ALKBH5 was also involved in glioblastoma, and it plays a key role in spermatogenesis and male fertility.[69] ALKBH5 is an FTO homolog that ensures the equilibrium of m^{6}A modification in the transcriptome.[70] In addition to the two erasers, *Arabidopsis* is an m^{6}A demethylase of mRNA, which affects the transformation of *Arabidopsis thaliana* from vegetative growth to reproductive growth and its mRNA stability.[71]

CHARACTERISTICS, REGULATORY MECHANISMS, AND BIOLOGICAL FUNCTIONS OF lncRNAs

lncRNAs are defined as a class of non-coding RNAs greater than 200 nt in length, which lack an open reading frame (ORF) and are unable to encode protein. lncRNAs have been detected in all species at the genomic level, including animals, plants, fungi, prokaryotes, and even viruses.[72] Interestingly, only less than 2% of the genomic sequence is transcribed into mRNA,[73] which suggests that the precise function of ncRNAs needs greater in-depth exploration. Many lncRNAs undergo the same RNA processing steps as mRNAs, including splicing and polyadenylation,[74] while they are also transcribed by RNA polymerase II (RNA Pol II).[75] Compared with protein-coding genes, the proportion of conserved specificity is apparently lower in lncRNAs.[76] Similar to microRNAs (miRNAs), a type of small ncRNAs, lncRNAs have been calculated to have a high degree of tissue specificity in humans.[77] Testis differs from other tissues in that it has great tissue-specific lncRNAs. Different levels of expression in different tissues suggest that specific lncRNAs can serve as biomarkers for diseases, especially cancer (Table 1).

The growing ranks of lncRNAs have attracted adequate attention on the regulatory mechanisms. Regulation of chromatin structure by histone modification and chromatin remodeling is the most classic mode. Second chromosome locus associated with prostate-1 (SChLAP1) can repress the modulation of the SWI/SNF chromatin remodeling complex to promote invasiveness in human prostate cancer.[107] Additionally, lncRNAs are associated with imprinted gene clusters that can mediate the transcriptional silencing.[108] The writers give an example of how Kcnq1ot1 accumulates on the chromatin of the promoter of the silenced alleles. At the same time, it also plays an inhibitory role in histone modification in mouse placenta, similar to XIST, which is representative of the field in which m^{6}A functions.[109] Zhang et al.[110] concluded that UPK1A antisense RNA 1 (UPK1A-AS1) accelerated the cell cycle process and promoted the development of hepatocellular carcinoma (HCC) by interacting with EZH2 and sponging miR-138-5p. lncRNAs are also related to the activation of transcription factors to facilitate gene expression, such as lncKdm2b, and can promote ESC self-renewal via activating Zbtb3.[111] Activation of Zpf292 to maintain the intestinal group 3 innate lymphoid cells (ILC3s) was also a positive effort.[112] Furthermore, studies have shown that enhancer lncRNAs (eRNAs) can upregulate gene expression by interacting with the proximal promoter.[113] lncRNAs also perform specific physiological functions as "miRNA sponges" to bind with miRNAs to protect mRNAs from degradation, suggesting that this posttranscriptional regulation could be a popular therapeutic target for many diseases in the future.[114] For instance, muscle anabolic regulator 1 (MAR1), as a miRNA sponge, decoys miR-487b to form a complementary sequence and release inhibitory effects on Wnt5a.[115] Given that m^{6}A is the most abundant modification in mammalian RNA, it has become a research hotspot recently.

Moving forward with research on regulatory mechanisms, several scientists are focusing on the cellular physiologic functions of lncRNAs, including cellular differentiation and development.[35,115,116] lncRNAs play critical roles in the disease process, such as different cancers, heart diseases, diabetes, muscle disease, and Alzheimer's disease, among others. Since lncRNAs are involved in almost all of our lives, more attention to modulation, especially m^{6}A, is reasonable.

ROLE OF m^{6}A METHYLATION IN THE REGULATION OF TUMOR-RELATED lncRNAs

To date, especially in the last 5 years, studies on m^{6}A methylation modification keep emerging, and great progress has been made. Although recent studies have shown that abnormal regulation of m^{6}A can lead to various diseases, especially in some tumors, the

Table 1. lncRNA biomarkers in cancers

Cancer	lncRNA biomarker	Expression	References
Breast cancer	HOTAIR	up	78
	H19	up	79
	LSINCT5	up	79
	NEAT1	up	79
Lung cancer	SOX2-OT	up	80
	ENSG0000245648	up	80
	MALAT1	up	80
	HOTAIR	up	81
	TUG1	down	81
	GAS5	down	82
	PVT1	up	83
Hepatocellular carcinoma	HOTAIR	up	84
	UCA1	up	85
	lncRNA-URHC	up	86
Gastric cancer	LINC00470	up	87
	UCA1	up	88
	H19	up	89
	LINC00659	up	90
Pancreatic cancer	H19	up	91
	BX111	up	92
	GLS-AS	down	93
Colorectal cancer	UCA1	up	94
	MALAT1	up	95
	PVT1	up	96
	CRNDE	up	97
Prostate cancer	PCA3	up	98
	HOTAIR	up	98
	DRAIC	down	98
	MALAT-1	up	99
Bladder cancer	UCA1	up	100
	HOTAIR	up	101
	GAS5	up	101
Glioma	HOXA11-AS	up	102
	FOXD1-AS1	up	103
	NEAT1	up	104
	ANCR	up	105
	PCED1B-AS1	up	106
	PCED1B	up	106

role of m^{6}A modification in tumorigenesis and tumor suppression is being gradually explored by scientists. m^{6}A methylation could regulate almost all RNA metabolism steps by certain factors and proteins, including writers, readers, and erasers. Despite the advances made, m6A-modified ncRNAs remain to be further investigated. Our research group mainly focuses on m^{6}A methylation modification and lncRNAs; hence, we summarize the role of m^{6}A modification in the regulation and function of lncRNAs (Figure 2).

m^{6}A modification regulates lncRNAs

m^{6}A modification may affect lncRNA function through a variety of regulatory mechanisms (Figure 3).

On the one hand, m^{6}A modification acts on the RNA-DNA triple helix structure to regulate the relationship between lncRNAs and specific DNA sites. On the other hand, m^{6}A modification provides binding sites for readers or regulates the structure of local RNA, and then induces the binding of RBPs to regulate the function of lncRNAs.[117]

m^{6}A writers could modulate lncRNAs; for instance, XIST is a target of RBM15/15B-directed methylation,[72] which interacts with the m^{6}A machinery directly via ZC3H13.[118] Proteomic analysis showed that WTAP is an XIST-related protein, and RBM15/RBM15B also bind to METTL3 in a WTAP-dependent manner to act on XIST as an m^{6}A methylase complex, thereby affecting its function.[37] Both METTL16 and METTL3 are also recruited to lncRNAs, including the well-studied MALAT1 and XIST.[119] Deleting the m^{6}A domain in XIST and analysis of these genes will immediately have affects downstream, suggesting that m^{6}A's role in XIST is far less significant than when the cell-scope system is destroyed and the entire cellular transcription level used to analyze gene expression is analyzed.[109] Xue et al.[120] identified that m^{6}A modification was installed on METTL3 to enhance the stability of the ABHD11-AS1 transcript, thereby increasing its expression, which emphasizes the function and mechanism of METTL3-induced ABHD11-AS1 in non-small cell lung cancer (NSCLC). As a critical factor sustaining m^{6}A levels in prostate cancer cells, VIRMA downregulation reduces the stability and abundance of oncogenic lncRNAs and the invasive phenotype of prostate cancer by attenuating the overall level of m^{6}A.[121]

m^{6}A readers also have such a functional role in lncRNAs. YTHDC2 is located in the nucleus and cytoplasm and has been shown to bind to the selective m^{6}A sites in lncRNAs.[72] HNRNPC and HNRNPA2/B1 are proteins that bind to m^{6}A sites after local and secondary structural changes of lncRNA.[122] A novel lncRNA (DMDRMR) that regulates DNA methylation and cooperates with an RNA m^{6}A reader promotes tumor growth and metastasis in clear cell renal cell carcinoma (ccRCC). Gao et al.[123] elucidated that DMDRMR interacted with IGF2BP3 to regulate target genes in an m^{6}A-dependent manner and might be a potential diagnostic, prognostic, and therapeutic target for ccRCC. As a nuclear m^{6}A reader, YTHDC1 could regulate RNA splicing, and in gynecologic tumor cell lines, hypoxia leads to a decrease in YTHDC1 protein levels by altering splicing to produce meaninglessly mediated decay of targeted mRNA subtypes.[124] At the same time, Hu et al.[125] indicated that IGF2BP2 could promote pancreatic cancer cell proliferation and stemness-like properties as a m^{6}A reader through regulating its novel target lncRNA DANCR stability. Yoneda et al.[126] suggested that under the m^{6}A modification, promoter-associated ncRNA (pncRNA)-D, an irradiation-induced

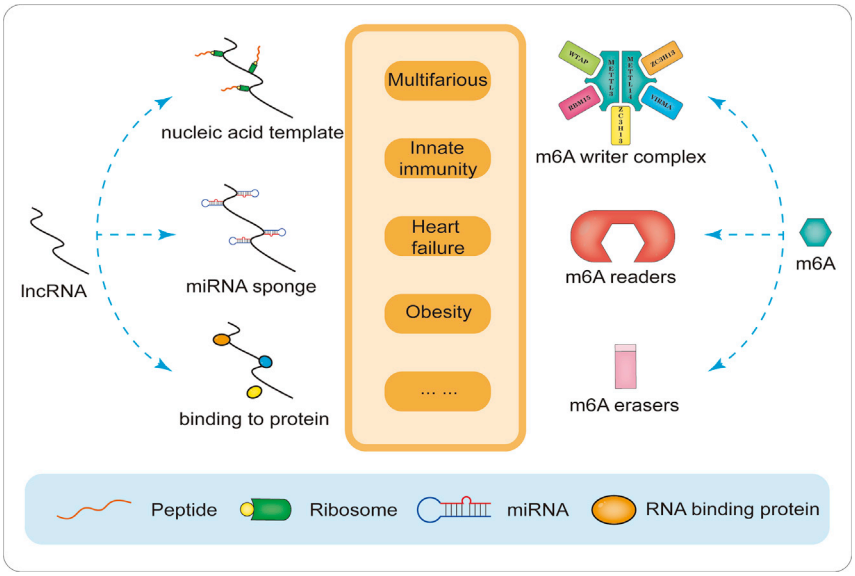

Figure 2. Role of lncRNA and m^{6}A modification in different diseases

Three major biological functions of lncRNAs are shown on the left, and three essential components of m^{6}A modification are listed on the right.

602-nt lncRNA transcribed from the promoter region of the cyclin D1 (CCND1) gene, influences the regulation of CCND1 gene expression and cell cycle progression. As an additional regulatory post-transcriptional process for gene expression, AS could be regulated by m^{6}A modification and subsequently generate lncRNAs from one primary transcript.[127] Olfr29-ps1, a lncRNA pseudogene expressed in myeloid-derived suppressor cells (MDSCs), can be regulated by the inflammatory factor interleukin-6 (IL-6), and it relies mainly on the m^{6}A-modified Olfr29-ps1/mir-214-3-p/MyD88 regulatory pathway to regulate MDSC immune inhibition and differentiation.[128] Zhu et al.[129] discovered that LINC00266-1, a previously annotated lncRNA, could encode an uncharacterized peptide, named RNA-binding regulatory peptide (RBRP), which has the ability to combine IGF2BP1 and enhance its ability to recognize m^{6}A on RNAs, and subsequently plays a carcinogenic role in tumorigenesis. The combination of METTL3/14 and WATP as a writer, ALKBH5 as an eraser, and YTHDF1 as a reader all influenced the translation of LINC00278 into YY1BM.[130] Zhang et al.[131] found that AKLBH5 could regulate the expression of H19, which is a lncRNA, and dexmedetomidine posttreatment could reduce the hypoxia-reoxygenation-induced senile myocardial cell injury by ALKBH5. Highly enriched m^{6}A could enhance the RNA stability of LINC00857, and m^{6}A-modified LINC00857 upregulation promotes tumorigenesis in pancreatic cancer by regulating the miR-150-5p/E2F3 axis.[132]

m^{6}A-modified lncRNAs in tumors

The phenotype observed on teratoma assays indicated that lack of m^{6}A could also play an important role in tumor progression; undeniably, many studies have elucidated that both m^{6}A writers and erasers are related with cancer.[124] However, most studies have focused on mRNA, and little is known about the functional correlation of RNA modification in lncRNAs. Much evidence suggests that both m^{6}A and lncRNA play a certain role in developing and evolving tumors (Figure 4).

Therefore, we can combine the two to explore the role and function of m^{6}A-modified lncRNA in tumors. Next, we briefly review the relevant research results in this field in recent years.

Analysis of datasets from The Cancer Genome Atlas (TCGA) Research Network acute myeloid leukemia (AML) study showed a solid association between mutations and copy number variation of m^{6}A regulatory genes and TP53 in AML patients. Additionally, changes in the m^{6}A regulatory gene lead to poor survival in AML patients.[124] Importantly, the treated MALAT1 transcript contains a 3′-triple helical RNA stabilization element consisting of a U-rich inner ring associated with a downstream A-rich channel to protect the MALAT1 transcript from degradation. METTL16, one novel m^{6}A writer, recognizes and combines this triple helix, which increases the possibility that the m^{6}A modification exists in this triple helix.[133] Only a small part of MALAT1 molecules (about 2%–3%) carried the m^{6}A modification at the other predicted sites (A2674/2684/2698) in two out of four cell lines.[134] MALAT1 could also regulate the output of chimeric mRNA in an m^{6}A-dependent manner, including YTHDC1 and METTL14, thereby controlling the differentiation of hematopoietic cells.[135] Wang et al.[136] further revealed that YTHDC1 recognition of MALAT1-m^{6}A plays a key role in maintaining the composition of nuclear spots and genomic binding sites, thereby regulating the expression of several key oncogenes, and artificial tethering of YTHDC1 to m^{6}A-deficient MALAT1 largely saved the metastatic potential of cancer cells. The Hox transcript antisense intergenic RNA (HOTAIR) is a lncRNA of about 2.2 kb that is transcribed from the antisense strand of the developmental the HOXC gene cluster on chromosome 12, and Meyer et al.[137] used methylated RNA immunoprecipitation followed by sequencing (MeRIP-seq) in HEK293T cells and found a single m^{6}A peak region (126nt) in the front half of HOTAIR, which did not overlap with m^{5}C. Dominissini et al.[138] mapped m^{6}A to the lncRNAs, for instance, PVT1 and NEAT1 and uncharacterized lncRNA transcripts. Only a few studies have carefully mapped the locations of modified residues in a single transcript, such as m^{6}A in lncRNA taurine upregulation 1 (TUG1).[134]

In addition, m^{6}A-modified lncRNA can induce the proliferation, migration, and apoptosis of tumor cells, including pancreatic carcinoma, oophoroma, and hepatoma.[139] Wu et al.[140] characterized a Y-linked lncRNA, LINC00278, which is downregulated in male ESCC, and smoking could downregulate m^{6}A modification of LINC00278 translation. Moreover, their data suggested that METTL3, METTL14, and WTAP work as writers, ALKBH5 works

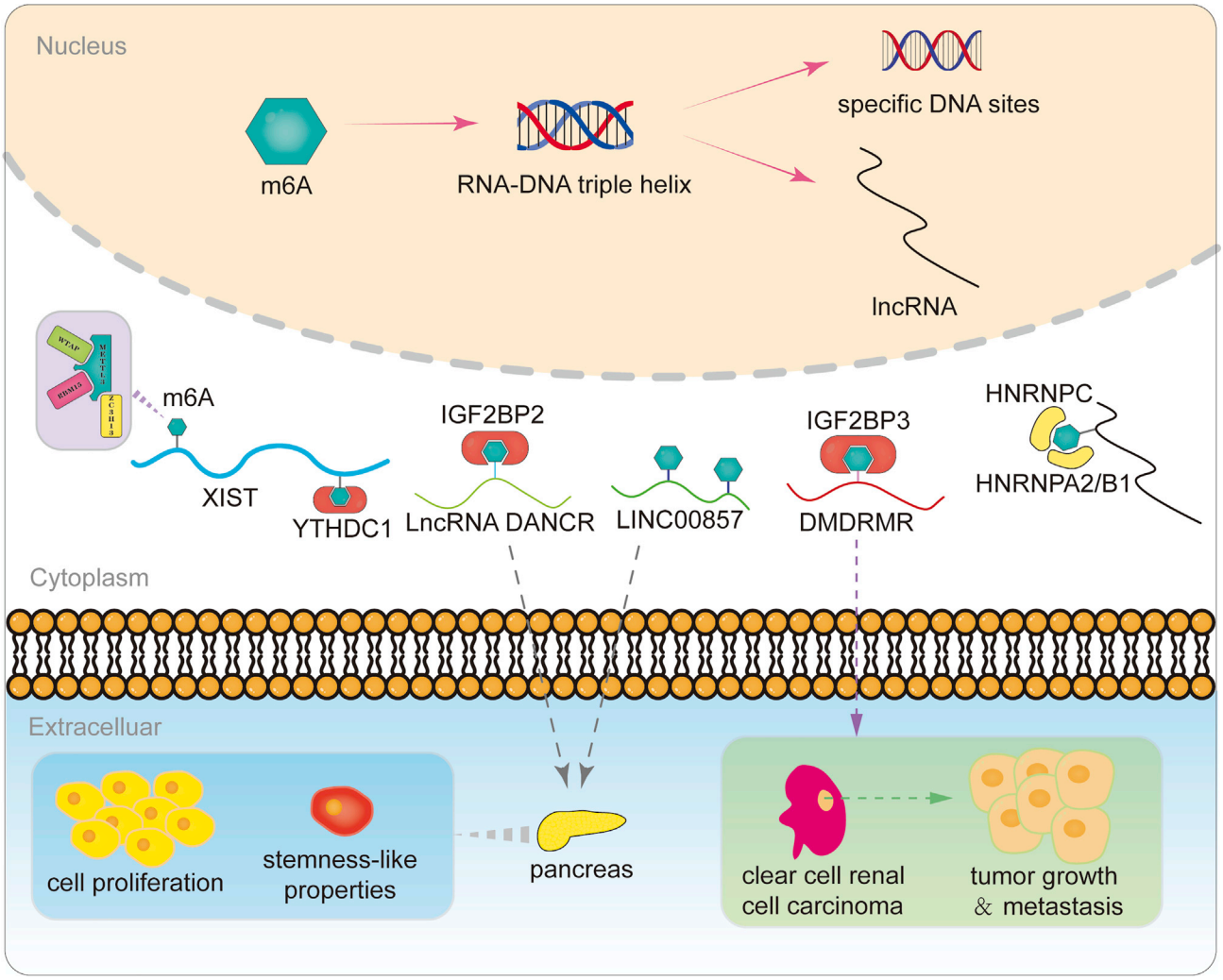

Figure 3. m^{6}A modification regulates lncRNA through various regulatory mechanisms, and it plays different roles in the nucleus, cytoplasm, and extracellular cells

as an eraser, and YTHDF1 work as a reader for LINC00278 m^{6}A modification. Sun et al.[141] revealed a novel LNC942-METTL14-CXCR4/CYP1B1 signaling axis, which provides a novel target for the prevention and treatment of breast cancer (BRCA) and a mechanism of crosstalk m^{6}A epigenetic modification. Clinically, Ni et al.[16] suggested that the expression of lncRNA GAS5 in the tumor of colorectal cancer (CRC) patients is negatively correlated with the protein levels of YAP and YTHDF3. Yang et al.[36] identified a "METTL14-YTHDF2-lncRNA" regulating axis in CRC cells that could mediate the degradation of XIST, significantly enhancing the proliferation and invasion ability of CRC cells *in vitro* and promoting the occurrence and metastasis of tumor *in vivo*. In clinical research, lncRNA RP11-139J23.1 is highly expressed in CRC, which is controlled by m^{6}A methylation, Wu et al.[142] elucidated that m^{6}A-induced lncRNA RP11 could trigger the metastasis and proliferation of CRC cells by upregulation of Zeb1. Zhu et al.[143] demonstrated that lncRNA KB-1980E6.3 maintains the stemness of breast cancer stem cells through the lncRNA KB-1980E6.3/IGF2BP1/c-Myc axis and suggested that disruption of this axis may provide a new therapeutic target for refractory hypoxic tumors. In addition, Hou et al.[144] suggested that LINC00460 interacts with IGF2BP2 and DHX9 to promote mRNA stability of the high mobility group A1 (HMGA1), a member of non-histone chromatin protein, leading to a biological response to malignant proliferation and widespread metastasis of CRC, and HMGA1 is enhanced by METTL3, while LINC00460 relies on METTL3 to regulate HMGA1 expression. In HCC, METTL3-mediated m^{6}A modification results in the upregulation of LINC00958 by stabilizing its mRNA, and LINC00958 sponges miR-3619-5p to increase the expression of hepatocellular carcinoma-derived growth factor, so as to promote HCC progression and lipogenesis.[145] By regulating lncRNA DANCR expression, IGF2BP2 could work together with DANCR on pancreatic cancer cell proliferation and

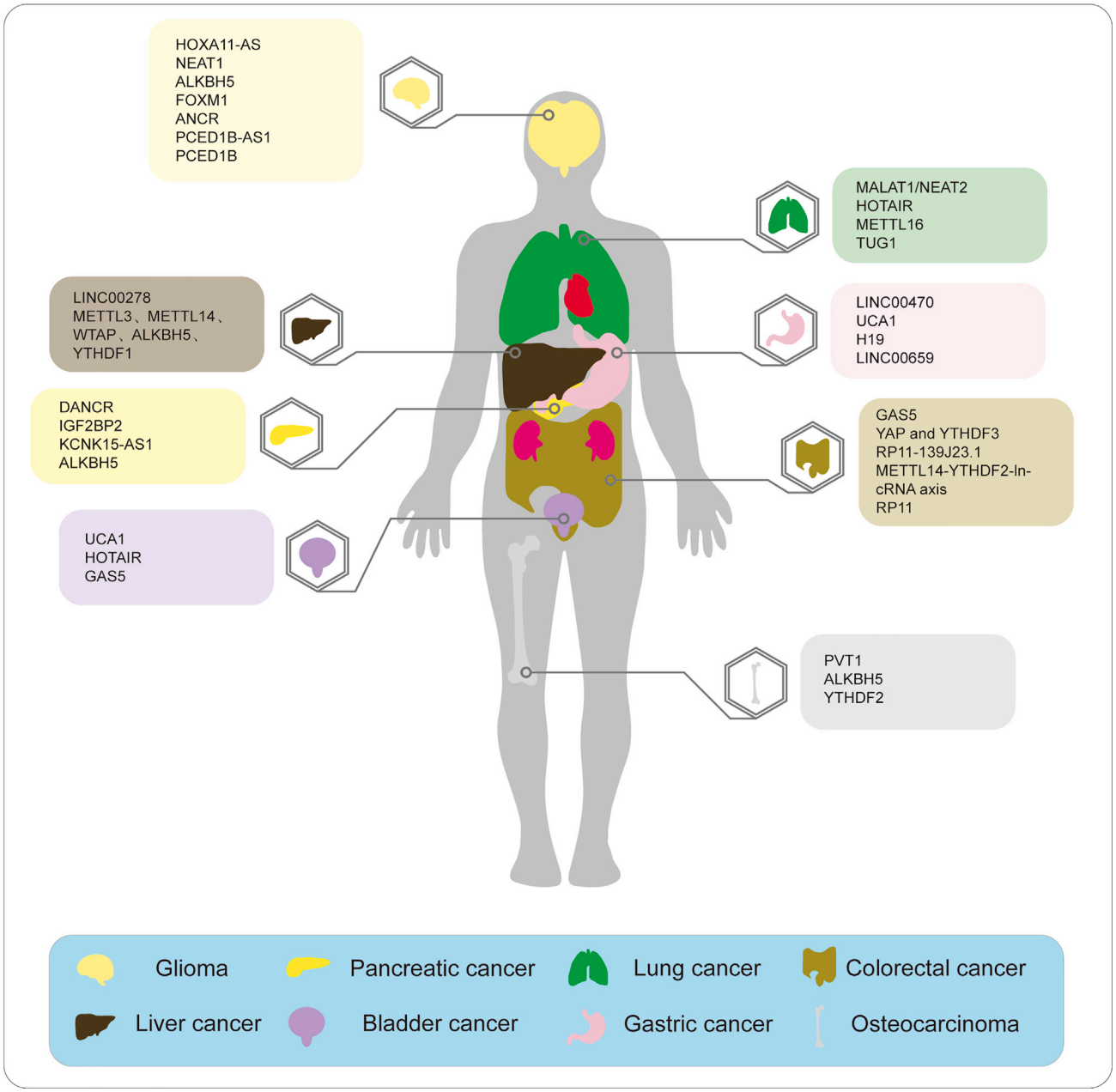

Figure 4. m^{6}A-modified lncRNAs and m^{6}A elements that play a role in tumors in different parts of the body

tumorigenesis.[125] He et al.[146] revealed that ALKBH5 could inhibit pancreatic cancer by demethylation of lncRNA KCNK15-AS1 and regulating its expression, and this new mechanism identified a potential pancreatic cancer therapeutic target. Furthermore, Chen et al.[67] found that ALKBH5 can decrease the m^{6}A modification of PVT1. Thus, the binding of YTHDF2 in PVT1 is inhibited, which promotes the proliferation of osteosarcoma cells and tumor growth. FAM225A is one of the most highly upregulated lncRNAs in nasopharyngeal carcinogenesis (NPC); Zheng et al.[147] found that m^{6}A modification in FAM225A improves its transcripts stability, which may be partly responsible for the significant upregulation of FAM225A in NPC. Ban et al.[148] indicated that LNCAROD, which is overexpressed in head and neck squamous cell carcinoma (HNSCC), is stabilized by m^{6}A methylation and promotes cancer progression via forming a ternary complex with HSPA1A and YBX1 in HNSCC. Wen et al.[149] found that m^{6}A on ncRNA NEAT1-1 plays a key role in regulating RNA Pol II Ser2 phosphorylation and may be a new specific target for the treatment and diagnosis of bone metastatic cancer, and they

think that the novel complex cyclin L1/CDK19/NEAT1-1 may provide new insights into the underlying mechanism of the pathogenesis and progression of bone metastatic prostate cancer. Wang et al.[150] investigated that m^{6}A enhances the stability of RHPN1-AS1 methylated transcript by reducing RNA degradation, leading to upregulation of RHPN1-AS1 in epithelial ovarian cancer. Shen et al.[151] had a conclusion that YTHDF2-mediated degradation of lncRNA FENDRR promotes cell proliferation by increasing SOX4 expression in endometrioid endometrial carcinoma.

APPLICATIONS AND FUTURE DIRECTIONS

Detailed studies of the distribution and function of chemical modifications in lncRNAs, as well as their association with related proteins, will contribute to a comprehensive understanding of the multi-layer gene expression control mechanisms active in mammalian cells.

Recent technological breakthroughs have rekindled enthusiasm for the study of m^{6}A methylation with some ground-breaking discoveries. These allowed for scientists to designate *in vivo* m^{6}A modification events and their association with disease status as functional associations. Recent investigations have emphasized that m^{6}A modification has strong and fine-grained control over cell development programs and can facilitate appropriate, rapid, and complex responses to developmental cues.[152]

Many lncRNAs are gradually recognized as key factors of virus-host interaction mainly through antiviral response-dependent and antiviral response-independent approaches. In contrast, the role of lncRNA in viral infection and innate antiviral response is still unclear.[19] Li and Meng[9] concluded that the identification of immune-related lncRNAs may provide a new direction for the study of the molecular mechanism and treatment of low-grade glioma. Just because of the role of lncRNAs, we can deduce that m^{6}A-modified lncRNAs can act on immunity. Nevertheless, the biological functions of m^{6}A modification in immune-related lncRNAs are still unknown, and thus there is a need for future studies addressing lncRNAs and immunity.

Although we have made great progress in understanding the function and regulation of m^{6}A modification, there is still much more research to be done, such as how m^{6}A precisely regulates gene expression. The potential role of m^{6}A and lncRNA modifications in chromatin state formation may provide additional mechanisms to explain how these modifications are involved in gene regulation during development.[44] By continuously improving m^{6}A's detection methods, identifying more readers, writers, and erasers, and discovering the potential functions of m^{6}A, with the joint efforts of many researchers, we will undoubtedly expand our understanding of m^{6}A's biological characteristics and of human health and disease. Exploring the role of m^{6}A-modified lncRNAs in tumors will provide a broad prospect for early detection, prevention, and tumor treatment. For a long time, scholars have devoted more efforts to elucidate the downstream mechanisms of lncRNAs differentially expressed in tumors, while their upstream regulation mechanisms have not attracted much attention. For lncRNAs regulated by m^{6}A modification, m^{6}A modification may be one of the upstream regulatory mechanisms. For the different expressed lncRNAs regulated by m^{6}A in tumors, we may try to intervene in the expression level of lncRNAs by using m^{6}A inhibitors or activators except small interering RNA (siRNA) or CRISPR-CAS9 RNA editing, which may be a novel way to regulate different expressed lncRNAs to even treat tumors.

Further studies on m^{6}A methylated lncRNAs will help us to better understand their roles in hepatic diseases or other diseases, especially in tumors.[139] m^{6}A methylated lncRNAs serve as potent prognostic biomarkers and provide useful individual treatments.

CONCLUSIONS

Two novel developed high-throughput deep-sequencing techniques, MeRIP-seq and m^{6}A sequencing, played a key role in revealing the functional significance of m^{6}A modification.[152] With scientific technological development, increasing numbers of m^{6}A-modified lncRNAs will be found and tested.

Additionally, the study of m^{6}A-related proteins and their inhibitors provides new opportunities for early diagnosis, effective treatment, and even disease prognosis of cancer, especially when applied in combination with rising immunotherapies. Therefore, further molecular interactions and mechanisms need to be explored. By continuously improving detection methods, identifying more m^{6}A readers, writers, and erasers, and discovering m^{6}A-modified lncRNA potential functions, we will undoubtedly expand our knowledge of the contribution of m^{6}A to human health and disease and its role of in the regulation of lncRNAs, including molecular pathways and tumorigenesis.

ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of Guangdong Province (2017A030308001), the National Natural Science Foundation of China (81874079 and 82073193), and by the Guangdong Provincial Clinical Medical Centre for Neurosurgery (2013B020400005).

AUTHOR CONTRIBUTIONS

Y.L. wrote the manuscript and created the figures. B.L. and H.G. reviewed and made significant revisions to the manuscript. Y.L. collected and prepared the related papers. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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