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REVIEW

N6-methyladenosine RNA modification and its interaction with regulatory non-coding RNAs in colorectal cancer

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ABSTRACT

As one of the most common forms of RNA modification, N6-methyladenosine (m6A) RNA modification has attracted increasing research interest in recent years. This reversible RNA modification added a new dimension to the post-transcriptional regulation of gene expression. In colorectal cancer (CRC), the role of m6A modification has been extensively studied, not only on mRNAs but also on non-coding RNAs (ncRNAs). In the present review, we depicted the role of m6A modification in CRC, systematically elaborate the interaction between m6A modification and regulatory ncRNAs in function and mechanism. Moreover, we discussed the potential applications in clinical.

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1. Introduction

As the most abundant RNA modification in eukaryotic cells [1], N6-methyadenosine (m6A) RNA modification played a vital role in cancer onset and development [2], which has been well studied [3]. m6A modification was first discovered in the 1970s [4], related research has become a new hot spot in the epigenetic study since the new understanding of the reversibility and dynamic process of m6A modification in 2011 [5]. With the rapid advancement of sequencing technology, m6 A modification was found not only on messenger RNAs (mRNAs) but also on non-coding RNAs (ncRNAs), especially regulatory ncRNAs [6–10]. Until now, it has been shown that more than 7000 coding RNAs and 300 ncRNAs contain m6A sites [3,11]. ncRNAs were a group of endogenous RNA molecules that were not translated into proteins but played an important role in regulating gene expression and disease progress [12,13]. ncRNAs could be divided into two categories, housekeeping ncRNAs and regulatory ncRNAs. Regulatory ncRNAs were usually considered as key regulatory RNA molecules in the cancer process, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) [13,14].

Colorectal cancer (CRC) was one of the most common malignant tumours, caused a vast medical burden with its increasing mortality (the second leading cause of cancer-related death) [15–17]. The occurrence and metastasis of CRC were considered a multi-factor, multi-step process, in which aberrant regulation of m6A modification was widely involved [18–20]. While previous studies have reported dysregulated m6A modification in CRC tumorigenesis [18–20], few reviews focused on the association between m6A modification and regulatory ncRNAs in CRC. To better understand the roles of m6A modification in CRC, the present study systematically reviewed the up-to-date research progress of m6A modification and its interaction with regulatory ncRNAs in CRC.

2. Regulation of m6A modification

m6A sites had a typical consensus sequence 'RRACH' (R = G or A; H = A, C, or U), and were enriched in 3′ untranslated regions (UTRs) and around stop codons in mRNAs or near the last exon in ncRNAs [3,11]. The effect of m6A modification was determined by m6A regulatory proteins, which consisted of m6A methyltransferases 'writers', m6A demethylases 'erasers', and m6A-binding proteins 'readers' [21].

m6A modification was installed by a methyltransferase complex (MTC), consisting of Methyltransferase-like 3 (METTL3), Methyltransferase-like 14 (METTL14), and Vir-like m6A methyltransferase-associated (KIAA1429/VIRMA), RNA-binding motif protein 15/15B (RBM15/15B), zinc finger CCCH domain-containing protein 13 (ZC3H13) and other wirters [22]. Among them, METTL3 acted as the primary catalytic subunit bound to the methyl donor S-adenosylmethionine (SAM) and catalysed methyl group transfer, and METTL14 was required for stabilizing METTL3 conformation and substrate RNA binding [23–25]. In addition, it was reported that Methyltransferase-like 16 (METTL16) was a novel m6A methyltransferase to control

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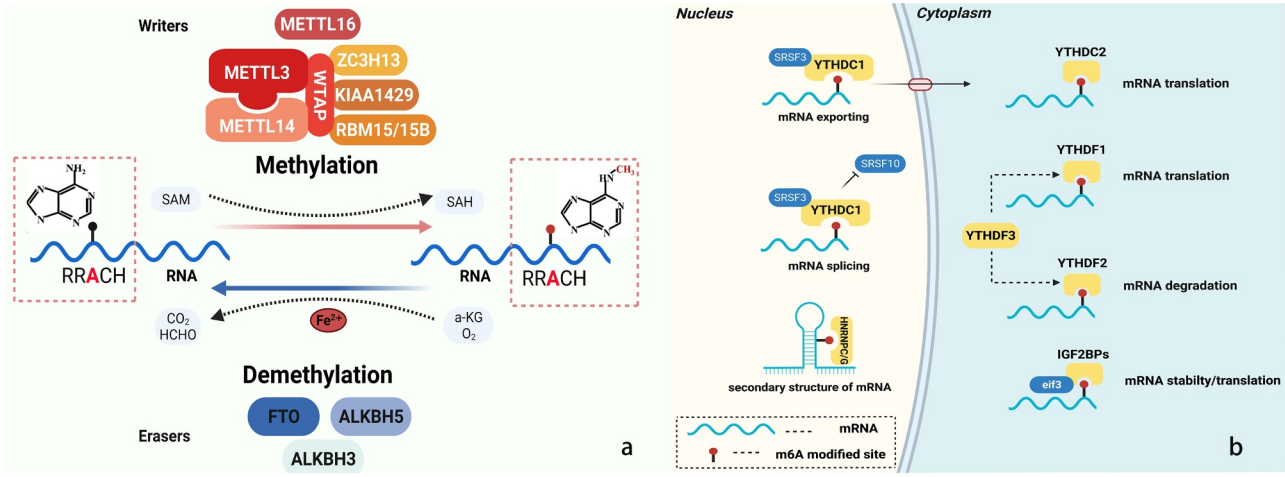

Figure 1. Reversible m6A modification on Eukaryotic RNAs. a. reversible m6A modification; b. the function of m6A modification.

cellular SAM level and installed m6A marks onto the U6 small nuclear RNA [7,26].

As shown in (Figure 1), RNA m6A modification could be reversibly removed, and the demethylation process required erasers, a-ketoglutaric acid (a-KG) and molecular oxygen (O_2) as cosubstrates and ferrous iron (Fe^{2+}) as a cofactor [27]. Alpha-ketoglutarate dependent dioxygenase (FTO) was the first demethylase of m6A modification [5], catalysed the oxidative demethylation of m6A on mRNA. alkB homolog 5 (ALKBH5) one of the two identified m6A demethylases, showed a preference for target transcripts that had a consensus sequence [28]. And alkB homolog 3 (ALKBH3) was a recently discovered demethylase that preferred mitochondrial transfer RNAs (tRNAs) [29].

m6A modifications exerted different biological functions by recruiting specific reader proteins, including the YTH domain family (YTHDF1–3, YTHDC1, and YTHDC2), IGF2BPs (IGF2BP1/2/3), Heterogeneous nuclear ribonucleoprotein C/G (HNRNPC/G), Heterogeneous nuclear ribonucleoprotein A2B1 (HNRNPA2B1), and other proteins. These readers played different roles in the nucleus and cytoplasm (Figure 1(b)). In addition, it was reported that METTL3 could also serve as an m6A reader to promote the translation of target RNAs [30].

3. m6A modification on mRNAs in CRC

Maintaining proper m6A modification levels on mRNAs was essential for normal bioprocesses and development, dysregulation of m6A modification was usually associated with cancers [2,3,31–33]. Herein, we sorted out related articles in CRC and classified them into different parts by m6A regulators.

3.1. Aberrant m6A Writers

As the earliest identified m6A methyltransferase [34], METTL3 had been deeply studied in recent years. In CRC, previous articles reported that METTL3 was highly expressed [35–37] and acted as an oncogene. Li et al. [31] found that METTL3 was highly expressed in metastatic CRC and was associated with a poor prognosis. Mechanistically, METTL3 led to methylation of SRY-box transcription factor 2 (SOX2) transcripts, which were subsequently recognized by IGF2BP2 to prevent the degradation of SOX2 mRNA. Xiang et al. [38] demonstrated that METTL3 was upregulated in CRC and promoted cancer proliferation, with MYC being identified as a target downstream that could be enhanced by IGF2BP1. Zhou et al [39] indicated that METTL3 epigenetically repressed Yippee-like 5 (YPEL5) in an m6A-YTHDF2-dependent manner by targeting the m6A site in the coding sequence region of the YPEL5 transcript. Liu and Sun et al. [40] found that Sec62 homolog, preprotein translocation factor (Sec62) upregulated by the METTL3-mediated m6A modification promotes the stemness and chemoresistance of CRC by binding to β-catenin and enhancing Wnt signalling. Furthermore, the oncogenic function of METTL3-mediated m6A modification was reported in other related articles [41–47], as shown in (Table 1). However, Deng et al. [48] concluded that METTL3 might play a tumour-suppressive role in CRC cell proliferation, migration, and invasion. They demonstrated that METTL3 inhibited CRC progression by modulating the p38/ extracellular-signal-regulated kinase (ERK) pathway.

As another critical component of MTC, recent studies suggested that METTL14 played an inhibitory role in CRC progression. Chen and Xu et al. [32] unveiled that decreased METTL14 could enhance the expression of SRY-related high-mobility-group box 4 (SOX4) through an m6A YTHDF2-dependent way, then promoted SOX4-mediated Epithelial-mesenchymal transition (EMT) process and PI3K /AKT signalling pathway. And Wang et al. [49] demonstrated that METTL14 enhanced tumour suppressor Kruppel-like factor 4 (KLF4) mRNA stability in an m6A IGF2BP2-dependent way. In addition, other writers like WTAP, METTL16 were up-regulated in CRC [50,51].

Table 1. The roles of m6A modification on coding RNAs in CRC.

Regulator	Role	Target mRNA	Function	Mechanism	Ref
Writer					
METTL3	Oncogene	SOX2	promoted CRC metastasis	maintained SOX2 expression through an m6A-IGF2BP2-dependent way.	[31]
		MYC	promoted CRC proliferation and tumorigenesis	enhance MYC expression in an m6A IGF2BP1-dependent manner.	[38]
		YPEL5	promoted CRC tumorigenesis	repressed YPEL5 by targeting the m6A site in the coding sequence region of the YPEL5 transcript.	[39]
		Sec62	promoted stemness and chemoresistance of CRC	enhanced Sec62 mRNA stability by controlling its m6A modification.	[40]
		HSF1	promoted CRC development	promoted HSF1 mRNA translation.	[46]
		HK2 and SLC2A1/ GLUT1	promoted CRC tumorigenesis	stabilized HK2 and SLC2A1/GLUT1 expression.	[41]
		GLUT1	promoted CRC tumorigenesis	promoted GLUT1 translation and glucose metabolism.	[47]
		SOCS2	promoted CRC tumorigenesis	regulated SOCS2 RNA stability with m6A modification.	[42]
		CCNE1	promoted CRC proliferation	stabilized CCNE1 mRNA.	[43]
		CBX8	associated with stemness properties in CRC	induced aberrant overexpression of CBX8.	[44]
		HMGA1	promoted CRC metastasis	regulated HMGA1 expression through an m6A-dependent mechanism.	[45]
	Anti-oncogene	-	suppressed CRC proliferation migration and invasion	modulated the p38/ERK pathways through an m6A-dependent way.	[48]
METTL14	Anti-oncogene	SOX4	suppressed CRC progress	inhibited SOX4-mediated EMT process and PI3K/AKT signalling pathway.	[32]
		KLF4	suppressed CRC metastasis	regulated the expression of tumour suppressor KLF4 through changing m6A modification level.	[49]
Eraser					
FTO	Oncogene	MZF1	promoted CRC proliferation	activated MZF1/c-Myc axis to promote CRC cell proliferation.	[52]
		MYC	promoted CRC progress	activated MYC by reducing the m6A modification of MYC.	[53]
	Anti-oncogene	MTA1	suppressed CRC metastasis	Regulated the MTA1 expression in an m6A-dependent manner	[55]
Reader					
YTHDF1	Oncogene	FZD9/WNT6	promoted CRC tumorigenesis	recognized and promoted the translation of m6A-modified FZD9 and Wnt6 mRNA	[58]
YTHDF2	Anti-oncogene	SOX4	inhibited CRC progress	modulated m6A-dependent SOX4 mRNA degradation.	[32]
	Oncogene	YPEL5	promoted CRC progress	suppressed the expression of YPEL5	[34]
YTHDC2	Oncogene	HIF-1α	promoted CRC proliferation	stabilize HIF-1α mRNA	[62]
IGF2BP1	Oncogene	MYC	promoted CRC progress	recognized the m6A modification sites on MYC to enhance its mRNA stability and translation.	[38,79]
		Sec62	promoted stemness and chemoresistance of CRC	bound to the m6A-modified Sec62 mRNA to maintain the Sec62 mRNA stability.	[40]
IGF2BP2	Oncogene	SOX2	promoted CRC progress	prevented SOX2 mRNA degradation in a m6A-dependent manner.	[31]
		HMGA1	promoted CRC progress	regulated HMGA1 mRNA stability in a m6A-dependent manner.	[45]
		HMGA2	promoted CRC progress	regulated HMGA2 mRNA stability	[63]
		MYC	promoted CRC progress	recognized the m6A modification sites on MYC to enhance its mRNA stability	[82]
IGF2BP2/ 3	Oncogene	HK2 and SLC2A1/ GLUT1	promoted CRC tumorigenesis	stabilized HK2 and SLC2A1/GLUT1 expression.	[41]

3.2. Aberrant m6A Erasers

In CRC, the expression of FTO was increased [51,52]. Yue et al. [53] indicated that FTO activated MYC by reducing the m6A modification of MYC. Zhang and Gao et al. [52] raised that FTO activated the MZF1/c- Myc axis to promote CRC cell proliferation. FTO increased MZF1 expression by demethylating MZF1 mRNA to play its oncogenic role, which was mentioned in lung cancer [54]. However, Liu et al [55] found that reduced FTO protein expression was correlated with a high recurrence rate and poor prognosis in resectable CRC patients. Mechanistically, FTO exerted a tumour-suppressive role by inhibiting the expression of metastasis-associated protein 1 (MTA1) in an m6A-IGF2BP2 dependent way, Demethylation decreased its mRNA stability. In addition, ALKBH5 was down-expressed in CRC [56,57].

3.3. Aberrant m6A Readers

The YTH domain family were overexpressed and extensively involved in CRC progress. Bai and Yang et al. [58] found that overexpressed YTHDF1 played a vital oncogenic role in CRC, and they proposed that YTHDF1 recognized and promoted the translation of m6A-modified FZD9 and Wnt6 mRNA. Nishizawa et al. [59] discovered that YTHDF1 was overexpressed in CRC, which was transcriptionally regulated by MYC. YTHDF2, YTHDF3, and YTHDC2 et al. have also been mentioned [37,51,57,60–62] in CRC-related studies (Table 1).

IGF2BPs were newly reported m6A readers. In CRC, Xiang et al. [38] indicated that MYC mRNA expression might be regulated in an m6A-IGF2BP1 dependent manner. IGF2BP2 and IGF2BP3 were reported to regulate target mRNAs stability in CRC cells [31,41,45,63].

Table 2. The role of m6A modification on regulatory ncRNAs in CRC.

Regulator	Role	Target ncRNA	Function	Mechanism	Ref
Writer/Eraeser					
METTL3	Oncogene	miR-1246	promoted CRC metastasis	promoted the transition from pri-miR-1246 to mature.	[67]
		lncRNA RP11	triggered the dissemination of CRC cells	increased RP11 nuclear accumulation and increased binding between hnRNPA2B1 and RP11.	[72]
		circNSUN2	promoted CRC progression and liver metastasis	increased the nuclear content of circNSUN2 (vague).	[63]
		circ1662	promoted CRC invasion and migration	induced circ1662 expression by marking m6A sites in flanking reverse sequences.	[77]
METTL14	Anti-oncogene	miR-375	inhibited CRC tumour process	modulated DGCR8 binding to pri-miR375.	[68]
		lncRNA XIST	inhibited CRC cell growth, migration, and invasion	knockdown of METTL14 abolished m6A level of XIST to augment XIST expression.	[73]
Nsun2	Oncogene	miR-125b	promoted CRC cell migration	inhibiting the mature process of miR-125b	[69]
ALKBH5	Anti-oncogene	lncRNA RP11	inhibited CRC tumour process	Increased RP11 nuclear accumulation	[72]
Reader					
YTHDF2	Anti-oncogene	lncRNA XIST	inhibited CRC cell growth, migration, and invasion	mediated the recognition and degradation of m6A-modified XIST	[73]
YTHDF3	Oncogene	lncRNA GAS5	promoted CRC progression	facilitated m6A-modified lncRNA GAS5 degradation.	[81]
YTHDC1	Oncogene	circNSUN2	promoted CRC progression and liver metastasis	mediated the nuclear export of circNSUN2.	[63]

4. m6A modification on regulatory ncRNAs in CRC

In addition to mRNAs, ncRNAs could also be regulated by m6A modification [6–10]. An increasing number of studies have reported that m6A modification on ncRNAs was closely related to the occurrence and development of CRC (Table 2), the results were followed.

4.1. m6A on miRNAs

miRNAs were short non-coding RNAs around 22 nucleotides, they could endogenously express and regulate mRNA post-transcriptional gene expression [64]. Perious studies have verified that either METTL3 or METTL14 was required for the engagement of primiRNAs by DiGeorge Syndrome Crisis Area Gene 8 (DGCR8) [65,66]. In CRC, Peng et al. [67] indicated that overexpression of METTL3 increased the level of miR-1246 by promoting the maturation of miR-1246 from pri-miR-1246, which further enhanced the metastatic capacity of CRC. The result of the m6A RNA immunoprecipitation (MeRIP) assay showed that m6A modification was enriched with pri-miR-1246 sequence, and the expression level of pri-miR-1246 was upregulated while miR-1246 level was decreased in METTL3-knockdown CRC cells. Similarly, Chen and Xu et al. [68] found METTL14 was downregulated in CRC, which inhibited the pri-miR-126 processes in an m6A-dependent manner. They immunoprecipitated DGCR8 and detected pri-miR-375 bound to DGCR8, the result shown that the expression levels of pri-miR-375 bound to DGCR8 were significantly increased in METTL14-overexpressing CRC cells. Yang et al. [69] revealed that NOP2/Sun RNA methyltransferase 2 (Nsun2) contributed to the down-regulation of miR-125b via the m6A-dependent way in CRC, interfering with the mature of miR-125b. Mature miR-125b came from pri-miR-125b1 and pri-miR-125b2, they revealed that the RNA methyltransferase NSun2 interfered with the mature processing of miR-125b by activating m6A modificaition on pre-miR-125b2, but not pri-miR-125b2.

4.2. m6A on lncRNAs

LncRNAs referred to those ncRNAs that are longer than 200 nucleotides [70], previous studies have shown that m6A modification on lncRNAs was involved in the CRC progression [70]. Zuo and Su et al. [71] found that m6A levels of lncRNAs in CRC tissues were significantly up-regulated. Wu et al. [72] revealed that m6A modification was involved in the upregulation of lncRNA RP11 via increasing its nuclear accumulation in CRC cells. The m6A RNA-immunoprecipitation (RIP) qPCR showed the m6A sites were enriched in RP11, and they found overexpression of METTL3 increased RP11 expression while ALKBH5 decreased RP11 expression. Moreover, they indicated that overexpressed METTL3 promoted the binding between HNRNPA2B1 and RP11. Yang et al. [73] identified that METTL14 inhibited oncogenic lncRNA X inactivate-specific transcript (XIST) through an m6A dependent pathway. They found that m6A modification on XIST promoting YTHDF2- induced RNA degradation in CRC.

4.3. m6A on circRNAs

CircRNAs belonged to a new class of ncRNAs formed by covalently closed loops through back splicing, played important roles in various biological functions [74]. The existence of m6A modification in circRNAs was confirmed by the interaction between circRNAs and YTHDF1/YTHDF2. Meanwhile, knockdown of METTL3 significantly affected m6A level on circRNAs [75,76]. Chen and Yuan et al. [77] reported that METTL3-induced circ1662 promoted CRC cell invasion and migration. Mechanistically, METTL3 induced circ1662 expression by marking m6A sites in flanking reverse complementary sequences. Meanwihle, Chen et al. [63] found that YTHDC1 could bind to circNSUN2 to facilitate its export from the nucleus to the cytoplasm in an m6A dependent manner, the latter was upregulated in CRC patients with liver metastasis (LM) and predicted poorer patient survival.

In addition, Guo et al. [78] found that m6A modification was involved in regulating the degradation of circ3823, which was highly expressed in CRC. While the mechanism of m6A modification on circRNAs was still vague, these studies proved that m6A modification existed in the ring structure of circRNAs, suggesting that m6A modification could be a regulator to affect circRNA.

5. Regulation of m6A modification by ncRNAs

5.1 ncRNAs regulated the process of m6A modification

As explained above, m6A modification had regulatory effects on ncRNAs, including their mature, accumulation, transport, and degradation. Interestingly, regulatory ncRNAs mediated the process of m6A modification conversely (Figure 3).

A previous study reported that m6A peaks were enriched at miRNA target sites on mRNAs, revealing a solid link between m6A modification and miRNAs. In CRC, Song and Feng et al. [46] reported that miR455-3p inhibited m6A modification on heat shock transcription factor 1 (HSF1) mRNA, thus repressing HSF1 translation. The m6A site on the 3′UTR region of HSF1 was completely complementary to the seed sequence of miR455-3p, thus formed a competitive inhibition between miR455-3p and METTL3. Besides, lncRNAs could also regulate the interaction between m6A regulators and their target mRNAs. Zhu et al. [79] discovered the lncRNA LINC00266-1 encoded a 71-amino acid peptide, which mainly interacted with the RNA-binding proteins (RBP) including IGF2BP1, thus named RNA binding regulatory peptide (RBRP). RBRP bound to IGF2BP1 and strengthened m6A recognition by IGF2BP1 to increase the mRNA stability and expression of c-Myc [79]. Hou et al. [45] demonstrated that LINC00460 enhanced interaction between IGF2BP2 and HMGA1 (High Mobility Group A1), thereby regulating mRNA stability and expression of HMGA1. Moreover, Chen et al. [63] reported that YTHDF1-induced circNSUN2 promoted the interactions between IGF2BP2 and HMGA2, and enhanced the mRNA stability of HMGA2 through the formation of a circNSUN2/IGF2BP2/HMGA2 RNA–protein ternary complex.

5.2 ncRNAs regulated the expression of m6A regulators

m6A regulators themselves as protein-coding genes could be modified by methylation or acetylation or other transcriptional or post-transcription regulations, including the regulation of ncRNAs.

ncRNAs could regulate m6A modification by targeting the mRNAs of m6A regulators. In CRC, Yue et al. [53] found that miR-96 mediated m6A modification by regulating AMP-activated alpha 2 (AMPKα2), which led to overexpression of FTO. And low expressed miR-1266 was reported to promote the occurrence and progression of CRC by directly targeting FTO [80]. Wen et al. [81] uncovered a negative feedback loop between lncRNA GAS5 and m6A reader YTHDF3: In normal, lncRNA GAS5 bound with Yes1 associated transcriptional regulator (YAP) to attenuate YAP-mediated transcription of YTHDF3; In tumour process, YTHDF3 could conversely bind with m6A-modified GAS5 to trigger its decay (Supplementary Figure S1). Moreover, Wang et al [82] also found that lncRNA LINRIS bound to a site of IGF2BP2 and blocked its degradation through the ubiquitination-autophagic pathway, thereby maintaining the MYC-mediated glycolysis and the proliferation of CRC cells.

6. Therapeutic Implications of m6A modification

6.1. m6A modification as biomarkers and therapeutic targets

Given that dysregulation of m6A level and aberrant expression of m6A regulators were widely participated in the cancer progression, m6A modification and its regulatory proteins seemed to be potential biomarkers and therapeutic targets in CRC.

Most m6A related-genes were upregulated in CRC, while METTL14, YTHDF3, and ALKBH5 were downregulated [37,83]. Wang et al. [50] discovered that the differentiation of CRC was closely relevant to m6A modification: high total m6A and high expression of METTL3, METTL16, WTAP were relevant to poor prognosis. Liu et al. [83] found that the expression pattern of m6A regulators including METTL3, METTL14, METTL16, FTO and, ALKBH5 were associated with the clinical outcomes of CRC patients. Li et al. [31] revealed that METTL3 was highly expressed in metastatic CRC tissues and associated with a poor prognosis. Low expression of METTL14 in CRC tissues associated with poor overall survival was revealed in Chen's study [32], and the discovery of the METTL14/SOX4 axis on CRC metastasis would aid in exploring efficient therapeutic target. And Bai et al. [58] revealed that overexpressed YTHDF1 was associated with tumour depth and tumour size in CRC, silencing YTHDF1 could significantly inhibit the Wnt/β-catenin pathway activity in CRC cells, which provided a potential therapeutic target for CRC.

Drug resistance was responsible for treatment failure and/or cancer recurrence. Lan et al. [84] discovered that the total m6A level and the METTL3 expression were increased in CRC tissues from Oxaliplatin (OX) -resistant patients, targeting METTL3-mediated m6A modification might be a promising adjuvant therapeutic strategy for OX-resistant CRC patients. Mohammad B. Uddin et al. [36] found that silencing METTL3 with neplanocin A to suppressing m6A formation in p53 pre-mRNA could re-sensitize CRC cells to anticancer drugs. Moreover, YTHDF1 mediated cisplatin through the GLS1-glutamine metabolism axis was validated by an in vivo xenograft mouse model [85], which revealed a novel sight contributing to overcoming chemo-resistant CRC.

Li et al. suggested [56] that m6A erasers contributed to the efficacy of immunotherapy and identified that ALKBH5 regulated anti-PD-1 therapy response. Wang et al. [35] uncovered that METTL3/14 regulated immune responses to anti-PD-1 therapy in CRC.

6.2. Potential application of the interaction between m6A modification and ncRNAs

The discovery of potent and selective inhibitors for m6A modification was urgent important in cancer treatment. Niu et al. [86] found inhibitors targeting 2-oxoglutarate (2OG) and iron-dependent oxygenases, and DAA (3-deazaadenosine) was shown to block the introduction of m6A into mRNA substrates by inhibiting the hydrolysis of SAH [87]. In addition, inhibitors of FTO including rhein, meclofenamic acid (MA), and MA2 have been mentioned in Acute myeloid leukaemia (AML) treatment [88,89].

However, the effect of these m6A inhibitors was not specific, and not targeted for particular m6A regulators or processes. It was speculated that the ncRNA regulatory mechanisms mentioned above could be used as breakthrough points in targeted therapy. Based on upstream regulation of m6A regulators by ncRNAs, we proposed a novel strategy for the CRC patients' treatments: targeting unique ncRNAs to regulate their downstream m6A regulators and m6A processes (Supplementary Figure S2). For example, using small molecule that specifically acted on the consensus sequences of ncRNAs, the levels of m6A modification were changed, which affected the expression of downstream genes and thereby regulating the biological functions on CRC cells. And the clinical application of ncRNAs in cancer therapy has been widely studied, such as delivering ncRNA mimics or antisense oligonucleotide of ncRNAs and small molecular compounds [90], which provided the possibility for the novel strategy.

However, effective therapeutic clinical application of ncRNAs and m6A modification has been faced lots of challenges, the specific mechanism of ncRNAs for use in targeted therapy needed to be further warranted.

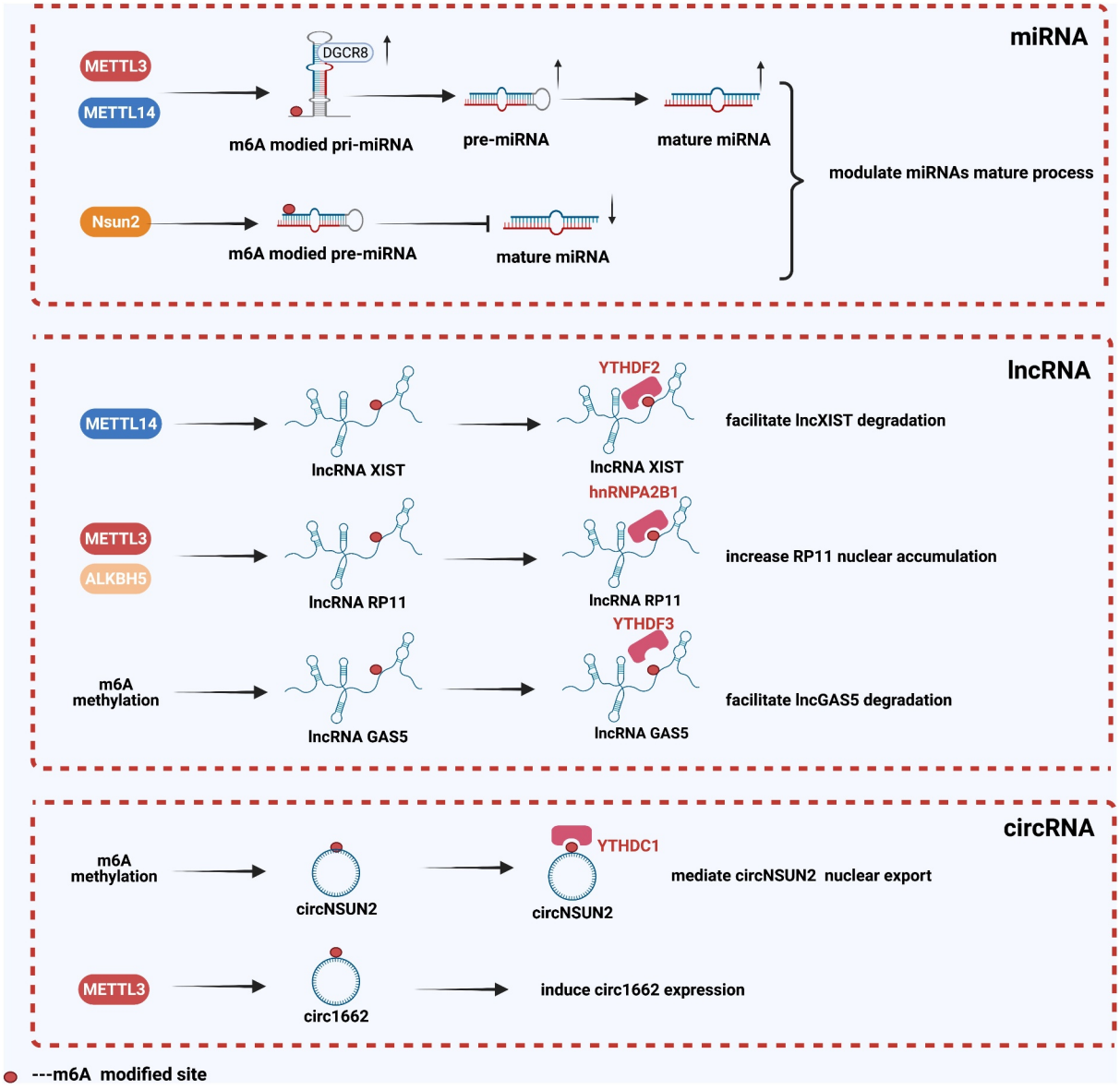

Figure 2. The function of m6A modification on ncRNAs in CRC.

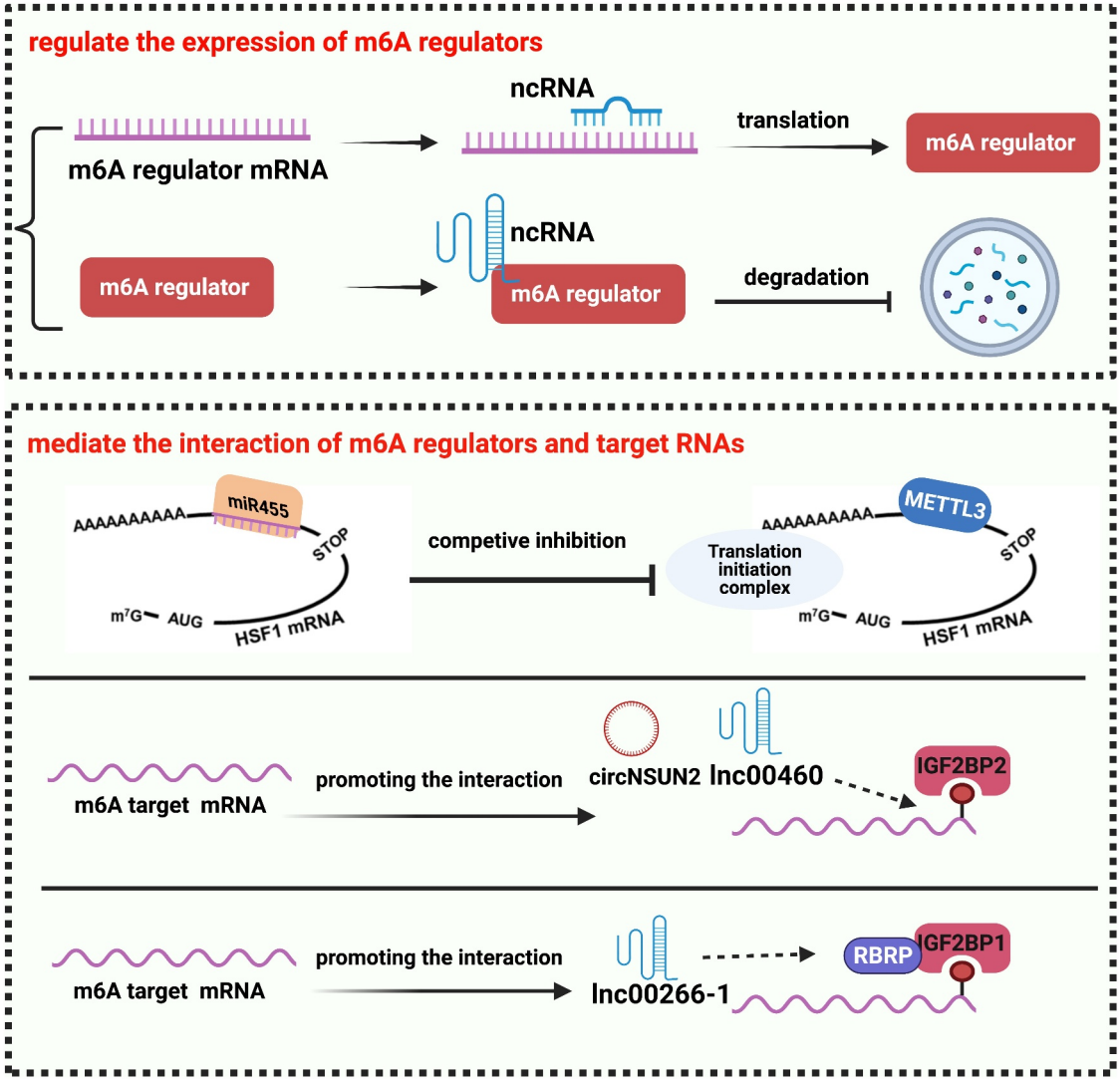

Figure 3. The regulation of m6A modification by ncRNAs in CRC.

7. Discussion

In the past few years, serval reviews about m6A modification in CRC have been published [18–20]. In contrast, the present review especially focused on the interaction of m6A modification with regulatory ncRNAs in CRC, which included m6A modification on regulatory ncRNAs and the regulation of m6A modification by ncRNAs.

In CRC, the m6A modification on regulatory ncRNA regulated the maturation, transportation, stability, and degradation of the target ncRNAs (Figure 2). While m6A modification on ncRNAs had the same reversible process, the function of m6A modification on ncRNAs mainly depended on types of its target ncRNAs: m6A modification on miRNAs mainly regulated the mature process of

Table 3. m6A regulators modulated by regulatory ncRNAs in CRC.

ncRNA	Target m6A regulator	Function	Mechanism	Ref
miR455-3p	METTL3	inhibited CRC development	competed with METTL3 for the m6A modification of HSF1 mRNA.	[46]
miR-96	FTO	stimulated CRC malignancy and aggressiveness	down-regulated AMPKα2 to increased expression of FTO.	[53]
miR-1266	FTO	inhibited CRC progression	down-regulated FTO directly.	[80]
lncRNA GAS5	YTHDF3	inhibited CRC progression	directly bind with YAP to attenuate YAP-mediated transcription of YTHDF3.	[81]
LINC00266-1	IGF2BP1	promoted CRC progression	strengthened IGF2BP1 m6A recognition on the target RNAs	[79]
LINC00460	IGF2BP2	promoted CRC metastasis	enhanced interactions between IGF2BP2 and HMGA1.	[45]
lncRNA LINRIS	IGF2BP2	promoted CRC progression	blocked K139 ubiquitination of IGF2BP2 to prevent its degradation.	[82]

miRNAs, m6A modification on lncRNAs regulated their translation and degradation. Meanwhile, ncRNAs also regulated the m6A modification in the process of post-transcriptional regulation (Table 3). We summarized that ncRNAs could regulate m6A modification in two ways: mediating the expression of m6A regulators; participating in the interaction of m6A regulators with their target RNAs (Figure 3). For example, miR455-3p competitively inhibited the binding of METTL3 to the target site on HSF1 mRNA; The expression of FTO was regulated by miR-96 and miR-1266 [53,80], IGF2BPs were habitually regulated by lncRNAs [45,79,82]. Furthermore, m6A-modified circNSUN2 enhanced HMGA2 mRNA stability through the m6A-IGF2BP2 dependent way [63], and there was a negative feedback loop between lncRNA GAS5 and m6A reader YTHDF3 [81]. The above researches all proved the interplay between m6A modification and regulatory ncRNAs, which was helpful to explain lots of paradoxes in cancer progression.

In CRC, METTL3 was the most studied m6A regulator. Highly expressed METTL3 served as an oncogene in cancer progression through targeting different downstream, such as SOX2, MYC, HMGA1, and YPEL5. However, it was controversial that Deng et al. [48] pointed out METTL3 was low expressed and played a tumour-suppressive role through p38/ERK pathways in CRC. Similarly, the inconsistent conclusions of METTL3 in different cancer types have been mentioned in other articles. We supposed that the dual role of METTL3 might be attributed to background differences of target genes. He et al. [91] revealed that the functional effects of m6A on downstream processes might be heterogeneous greatly and depended on binding target sites of RBP. Besides, the heterogeneity of the tissue samples might partly explain the different expressions of METTL3, Liu et al. [92] indicated that the expression level of METTL3 was related to tumour stage and grade. And noteworthily, METTL3 was also mentioned as a reader in the cytoplasm, promoting the mRNA translation independent of its methyltransferase activity [30].

Contrary to METTL3, METTL14 acted as a tumour suppressor in CRC, which was contradictory for two core components of MTC demonstrated opposite effects on cancer progression. It seemed that METTL3 or METTL14 possessed methylation activity alone under certain conditions, while the METTL3-METTL14 complex displayed much higher catalytic activity [24,93], and with targets specificity. Moreover, Wang et al. [49] found that overexpressed methyl CpG binding protein 2 (MeCP2) occupied reciprocity between METTL3 and METTL14, which indicated that there was a competitive relationship between MeCP2 and METTL3 with METTL14. We speculated that the overexpression of METTL3 and the depletion of METTL14 had some feedback in the MTC. However, the exact mechanism of the MTC functions awaited structural investigation.

As one of the most vital proto-oncogenic transcription factors in tumorigenesis, MYC controlled the transcription of at least 15% of the human genes [94]. Though lack of knowledge the accurate m6A sites on MYC mRNA, MYC was reported as one of the primiary target genes of m6A modification in CRC [38,52,53,82], directly or indirectly. Xiang and Liang et al. [38] pointed out that METTL3 methylated MYC mRNA to enhance its expression, while Yue et al. [53] found that FTO might demethylate MYC mRNA to enhance expression. We speculated that FTO regulated MYC expression in an indirected way as we noticed that FTO modulated MYC expression through the FTO-m6A-MZF1 axis [52]. Besides, Nishizawa et al. [59] discovered that YTHDF1 was overexpressed in CRC, which was transcriptionally regulated by MYC.

Given that m6A modification played significant roles in the regulation of metabolism, stemness, metastasis and, drug resistance in CRC, key m6A modification regulators might be identified as the potential targets in the diagnosis and treatment of CRC. Moreover, we believed that upstream regulation of m6A regulators by ncRNAs provided a new insight for the treatment. Application of unique ncRNAs to regulate downstream m6A regulators might be more accurate and personalized for CRC patients.

8. Conclusions

In this review, we systematically summarized the biological functions of m6A regulators, investigated the interaction between m6A modification and regulatory ncRNAs in CRC. As two critical parts of post-transcriptional regulation, it was vital to figuring out the m6A-mediated post-transcriptional regulation on regulatory ncRNAs and the way regulatory ncRNAs modulated m6A regulators. In the present review, we first deeply investigated the interaction between m6A modification and regulatory ncRNAs in CRC, while other published reviews only mentioned about. Mechanistically, we summarized in detail the way ncRNAs regulated the process of m6A modification. In function, we concluded that the m6A modification on miRNA mainly regulates its maturation process, and the m6A modification on lncRNA regulates its translation and degradation. More importantly, uniquely proposed a novel strategy for CRC patients' treatments based on the regulation of m6A modification by ncRNAs.

Abbreviations

(m6A)	N6-methyladenosine
(CRC)	colorectal cancer
(ncRNAs)	non-coding RNAs
(mRNAs)	messenger RNAs
(UTRs)	the Untranslated Regions
(MTC)	methyltransferase complex
(METTL3)	Methyltransferase-like 3
(METTL14)	Methyltransferase-like 14
(WTAP)	Wilms tumor suppressor-1-associated protein
(RBM15)	RNA Binding Motif Protein 15
(ZC3H13)	Zinc finger CCCH domain-containing protein 13
(SAM)	Sadenosylmethionine
(SAH)	Sahnehaeubchen
(METTL16)	Methyltransferase-like 16
(a-KG)	a-ketoglutaric acid;
(FTO)	Alpha-ketoglutarate dependent dioxygenase
(hm6A)	N6-hydroxymethyladenosine
(f6A)	N6-formyladenosine
(ALKBH5)	AlkB homolog 5
(ALKBH3)	AlkB homologue 3
(tRNAs)	mitochondrial transfer RNAs
(YTHDC1)	YTH domain-containing 1
(YTHDC2)	YTH domain-containing 2
(YTHDF1)	YTH N6-methyladenosine RNA binding protein 1
(YTHDF2)	YTH N6-methyladenosine RNA binding protein 2
(YTHDF3)	YTH N6-methyladenosine RNA binding protein 3
(IGF2BPs)	Insulin-like growth factor 2 mRNA-binding proteins
(IGF2BP1)	Insulin like growth factor 2 mRNA binding protein 1
(IGF2BP2)	Insulin like growth factor 2 mRNA binding protein 2
(IGF2BP3)	Insulin like growth factor 2 mRNA binding protein 3
(HNRNPC)	Heterogeneous nuclear ribonucleoprotein C
(HNRNPG)	Heterogeneous nuclear ribonucleoprotein G
(HNRNPA2B1)	Heterogeneous nuclear ribonucleoprotein A2B1
(SRSF3)	Serine and arginine rich splicing factor 3
(SRSF10)	Serine and arginine rich splicing factor 10
(DGCR8)	DiGeorge Syndrome Crisis Area Gene 8
(SOX2)	SRY-box transcription factor 2
(CSC)	cancer stem cell
(MYC/c-Myc)	MYC proto-oncogene, bHLH transcription factor
(SOCS2)	Suppressor of cytokine signaling
(LGR5)	Leucine-rich repeat-containing G protein-coupled receptor 5
(Sec62)	Sec62 homolog, preprotein translocation factor
(HK2)	exokinase 2
(GLUT1)	Glucose transporter 1;
(CCNE1)	Cyclin E1;
(CBX8)	Chromobox 8
(HMGA1)	High Mobility Group A1
(ERK)	extracellular-signal-regulated kinase
(OS)	Overall survival
(KDM5C)	Lysine-specific histone demethylase 5C
(H3K4me3)	Histone H3 lysine 4 tri-methylation
(SOX4)	SRY-related high-mobility-group box 4
(EMT)	Epithelial-mesenchymal transition
(PI3K)	phosphatidylinositol 3-kinase
(AKT)	AKT serine/threonine kinase 1
(MZF1)	myeloid zinc finger 1
(MTA1)	metastasis-associated protein 1
(YPEL5)	Yippee like 5
(RIP)	m6A RNA-immunoprecipitation
(HMGA2)	High Mobility Group A2
(lncRNAs)	long-non-coding RNAs
(miRNAs)	microRNAs
(circRNAs)	circular RNAs
(XIST)	X inactivate-specific transcript
(YAP)	Yes1 associated transcriptional regulator
(SPRED2)	Sprouty-related, EVH1 domain-containing protein 2
(SP1)	Sp1 transcription factor
(Nsun2)	NOP2/Sun RNA methyltransferase 2
(Gab2)	GRB2 associated binding protein 2
(AMPKα2)	AMP-activated alpha 2
(PAR2)	proteinase activated receptor 2
(HSF1)	heat shock transcription factor 1
(LM)	liver metastasis
(ICB)	immune checkpoint blockade
(DAA)	3-deazaadenosine
(MA)	meclofenamic acid
(RBP)	RNA-binding proteins
(MeCP2)	methyl CpG binding protein 2

Disclosure statement

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