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REVIEW ARTICLE

Molecular targets for therapy

RNA methylation in hematological malignancies and its interactions with other epigenetic modifications

Lan Yao[1] · Hua Yin[1] · Mei Hong[1,2] · Yajun Wang[1] · Tingting Yu[1] · Yao Teng[1] · Tingting Li[1] · Qiuling Wu[1]

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Abstract

Hematological malignancies are a class of malignant neoplasms attributed to abnormal differentiation of hematopoietic stem cells (HSCs). The systemic involvement, poor prognosis, chemotherapy resistance, and recurrence common in hematological malignancies urge researchers to look for novel treatment targets and mechanisms. In recent years, epigenetic abnormalities have been shown to play a vital role in tumorigenesis and progression in hematological malignancies. In addition to DNA methylation and histone modifications, which are most studied, RNA methylation has become increasingly significant. In this review, we elaborate recent advances in the understanding of RNA modification in the pathogenesis, diagnosis and molecular targeted therapies of hematological malignancies and discuss its intricate interactions with other epigenetic modifications, including DNA methylation, histone modifications and noncoding RNAs.

Introduction

Hematological malignancies are a class of malignant neoplasms initiated from aberrant self-renewal, blocked differentiation, clonal expansion, and biological dysfunction of hematopoietic cells. Many aspects contribute to hematological malignancies, such as DNA damage response [1], epigenetic alteration [2], and dysregulation of the bone marrow niches [3]. Among them, epigenetics focuses on heritable variations in gene expression or cell phenotype that occur without altering the actual DNA sequence. Compared with genetic mechanisms, epigenetic pathways exhibit much greater flexibility, and tumors probably rely more on epigenetic alterations to escape immune surveillance and develop drug resistance [4]. Recently, protein drugs targeting epigenetic modifiers such as DNA methyltransferase inhibitors and histone deacetylase inhibitors have achieved significant therapeutic effects in hematological malignancies, which has made epigenetics a hot topic of research [5].

Epigenetics is divided into three levels of modifications and alterations: transcriptional, posttranscriptional, and posttranslational. Epigenetic transcriptional regulation mainly involves DNA methylation, histone modification and chromatin remodeling. Posttranscriptional regulation involves RNA modification and ncRNAs. Posttranslational modifications are covalent modifications of proteins during or after translation.

To date, more than 170 kinds of RNA modifications have been identified [6]. With the discovery of RNA demethylases and the application of methylated RNA immunoprecipitation sequencing (MeRIP-seq), the latest studies on methylation at N-6 adenosine (m6A) in RNA have attracted widespread interest due to the identification of m6A as the most abundant internal modification in higher eukaryotes [7]. M6A RNA regulates mRNA posttranscriptionally by affecting splicing [8, 9], export [10], stability [8, 11], and translation of transcripts [11]. M6A RNA is strongly associated with cancer initiation and progression, and m6A regulators are potential targets in cancer therapy [12].

Here, we elaborate recent discoveries of m6A RNA modification in the pathogenesis, diagnosis and molecular targeted therapies of hematological malignancies and discuss its intricate interplay with DNA methylation, histone modifications, and ncRNAs.

These authors contributed equally: Lan Yao, Hua Yin, Mei Hong

✉ Qiuling Wu
wuqiuling927@qq.com

[1] Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[2] Collaborative Innovation Center of Hematology, Soochow University, Suzhou, China

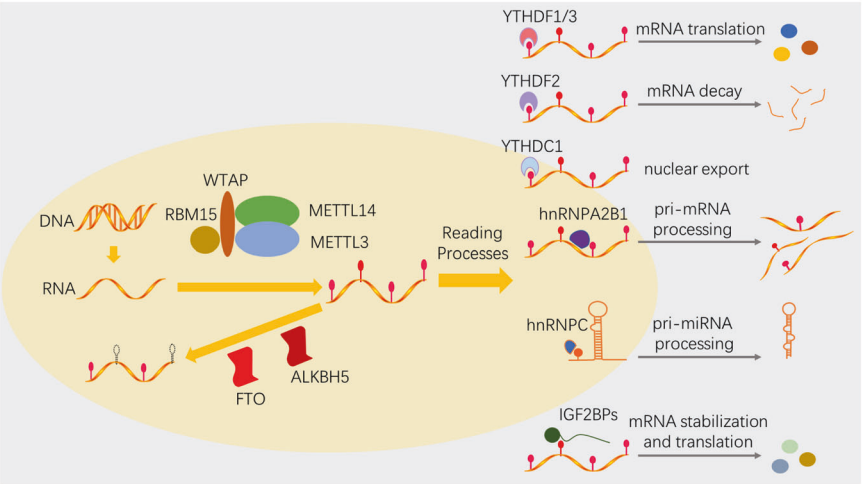

Fig. 1 The mechanism of m6A RNA methylation. The dynamic and reversible m6A formation is realized through different m6A regulators: the "writers" install m6A marks, the "erasers" selectively remove m6A marks, and the "readers" specifically recognize m6A marks.

The mechanism of m6A RNA methylation

MeRIP-seq has been used to identify mRNAs with m6A modification from more than 7000 mammalian genes, and m6A peaks with the consensus motif RRACH (R = A/G, H = A/C/U) were enriched in the 5′ UTR, 3′ UTR, and near coding regions [13, 14]. A group of m6A regulators modulate m6A modification dynamically and reversibly: the "writers" install the m6A marks, the "erasers" selectively remove m6A marks, and the "readers" specifically recognize the m6A marks [7]. S-adenosylmethionine (SAM) serves as the methyl donor [7, 15] (Fig. 1).

m6A Writers

Methyltransferase-like 3 (METTL3), initially named MT-A70, was the first reported m6A RNA writer and has been acknowledged as the core m6A catalytic enzyme [16, 17]. Liu et al. found that methyltransferase-like 14 (METTL14) formed a stable heterodimer core complex with METTL3 and mediated mammalian nuclear RNA m6A methylation [18]. However, studies on the crystal structure of the METTL3/METTL14 complex suggested that METTL14 was not the catalytic core but played a structural role in facilitating RNA substrate recognition and binding [17, 19]. It is now generally considered that METTL14 works as a coregulator of the m6A methyltransferase complex (MTC) and assists m6A RNA methylation.

Other coregulators of MTC are still under investigation. WTAP (Wilms tumor 1-associated protein), which interacts with the N-terminal leader helix of METTL3, is required for METTL3/METTL14 localization to nuclear speckles [20, 21]. RNA-binding motif protein 15 (RBM15) and its paralog RBM15B bind to the MTC and recruit it to U-rich regions of RNA [22]. RBM15/15B mediates m6A formation on the long noncoding RNA X-inactive specific transcript (XIST) to regulate the transcriptional silencing of genes on the X chromosome [22, 23]. Methyltransferase-like 16 (METTL16) modulates the homeostasis of SAM by binding to a vertebrate-conserved hairpin in the 3′ UTR of the SAM synthetase MAT2A and regulating splicing and stability of MAT2A mRNA in a m6A-dependent manner [24]. In addition, Mettl16 is responsible for m6A methylation of human pre-mRNAs and various ncRNAs [25]. VIRMA (Vir-like m6A methyltransferase associated), also known as KIAA1429, regulates preferential mRNA methylation in the 3′ UTR and near the stop codon by recruiting an active METTL3/METTL14/WTAP MTC complex [26]. In eukaryotes, ZC3H13 [27] and HAKAI [28] also participate in m6A RNA formation.

m6A Erasers

The fat mass and obesity-associated (FTO) protein was the first discovered m6A RNA demethylase [29]. Another m6A demethylase, alkB homologue 5 human protein (ALKBH5), was subsequently found by the same team and associated with sperm infertility [30]. They are both homologues of the Fe^{2+} and alpha-ketoglutarate (α-KG)-dependent (AlkB) human dioxygenase family [31, 32].

However, the substrate preference of FTO remains debatable. Mauer et al. considered that FTO's physiologic target was not m6A but N6,2′-O-dimethyladenosine (m6Am), one of the most prevalent and reversible modifications at the 5′ ends of capped mRNAs [33]. They discovered that in vitro, FTO demethylated nearly all m6Am marks on RNA substrates at low concentrations (100 nM), but m6A demethylation was readily detected only at higher FTO concentrations (200 nM) [33, 34]. Zhang et al. found that FTO displayed the same demethylation activity toward m6A and m6Am in the same RNA sequence, suggesting that the substrate specificity of FTO resulted from the

interaction between residues in the FTO catalytic pocket and the nucleobases of RNA substrates [31]. They claimed that m6A was still the most favorable substrate of FTO because the total amount of m6A was tenfold higher than that of m6Am in mRNAs [31].

m6A Readers

Different m6A readers elicit distinct or even opposite effects by recruiting different functional enzymes. There are three m6A reader families: the YT521-B homologue (YTH) protein family, the heterogeneous nuclear ribonucleoprotein (hnRNP) family, and the common m6A RNA-binding protein family. YTH protein family members, including YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2, directly bind to m6A marks with their YTH domain and mediate mRNA alternative splicing [35], nuclear export [10], degradation [36], and translation [37]. The hnRNP family contains hnRNPC, hnRNPG, and hnRNPA2B1. They modulate pre-mRNA processing via an "m6A-switch mechanism": m6A-dependent RNA structural alterations decrease the stability of Watson-Crick base pairing and thereby allow hnRNPs to bind m6A-modified RNAs but not direct m6A marks [9, 38, 39]. Common m6A RNA-binding protein family members, mainly insulin-like growth factor 2 mRNA-binding proteins (IGF2BP1, IGF2BP2, and IGF2BP3), utilize specific KH domains and their flanking regions to selectively bind m6A-containing RNAs in an RNA structure-independent manner, fortify targeted mRNA stability, and promote targeted mRNA translation, but the exact mechanisms have yet to be elucidated [11].

m6A RNA methylation in hematological malignancies

To date, m6A RNA modifications have been shown to govern normal hematopoiesis and leukemogenesis. Most m6A regulators have been affirmed to be dysregulated and play a critical role in hematological tumorigenesis, which holds great therapeutic potential.

m6A Writers

The role of METTL3 as an oncogene or tumor suppressor in human solid malignancies is still controversial [40]. In normal hematopoiesis, the expression of METTL3 in hematopoietic stem and progenitor cells (HSPCs) was higher than that in mature differentiated myeloid cells [41]. Mechanistically, Mettl3 blocked hematopoietic stem cell (HSC) differentiation by enhancing the mRNA stability of MYC [42, 43], which is involved in regulating the self-renewal and differentiation of HSCs [44]. HSCs from the bone marrow of METTL3-null adult mice showed increased cell counts, reduced self-renewal capacity and lower long-term reconstituting activity than controls [42, 45]. In summary, Mettl3 maintained HSCs in a quiescent state.

In hematological malignancies, METTL3 plays a vital role in acute myeloid leukemia (AML) pathogenesis. METTL3 was significantly more abundant in AML cells than in HSPCs [41]. Depletion of METTL3 in vitro resulted in cell cycle arrest, blocked cell growth, differentiation of leukemic cells, and cell apoptosis [41, 46]. METTL3 was found to enhance the translation of many oncogenic mRNAs by interacting with eIF3h [47]. It promoted the translation of the MYC and BCL-2 mRNAs in human AML MOLM13 cells, which are critical for regulating apoptosis and differentiation [41]. In addition, METTL3 is recruited by the CAATT-box binding protein CEBPZ to the promoters of leukemic active genes, such as the transcription factor SP1, and METTL3 at the associated mRNA transcripts induced m6A modification and enhanced translation by relieving ribosome stalling [46]. Recently, a promising small molecule inhibitor targeting METTL3 in the bone marrow and spleen of AML patients was identified, which is likely the first discovered in vivo RNA methyltransferase inhibitor [48].

METTL14, implicated as an adverse prognosis factor, has been shown to be expressed at low levels in several solid cancers, such as hepatocellular carcinoma (HCC) [49], bladder cancer (BCa) [50], and colorectal cancer (CRC) [51]. METTL14 was also highly expressed in normal HSPCs [45]. Silencing of METTL14 promoted terminal myeloid differentiation, but the functions of Mettl14 in m6A formation and HSC regulation were dependent on Mettl3 [45]. Another study uncovered that in AML carrying t(11q23), t(15;17), or t(8;21), upregulated Mettl14 acted as an oncogene via the SPI1-Mettl14-MYB/MYC signaling axis [52]. However, Mettl3 and Mettl14 have been found to be expressed at lower levels in ETV6/RUNX (E/R)1-positive acute lymphoblastic leukemia (ALL) children than in controls, and their expression in relapsed patients was lower than that in nonrelapsed patients [53].

In this decade, researchers have begun to focus on the oncogenic role of WTAP in leukemogenesis. The overexpression of WTAP led to abnormal proliferation and arrested differentiation of leukemic cells [54]. The expression of WTAP was positively correlated with the levels of various cell proliferation-related proteins (cyclins and HSP90), antiapoptotic proteins (BCL-2 and BAX), oncoproteins (FLI1), and proteins important for stem cell functions (MYC and Ash2L) [54]. WTAP knockdown markedly increased apoptosis following etoposide treatment, which suggests an association between the increased expression of WTAP and chemoresistance in AML [54]. Sorci et al. substantiated that the function of WTAP in cell proliferation

was impaired if METTL3 was knocked down in HeLa cells and K562 cells, reconfirming WTAP as a coregulator in MTC [55].

RBM15 has exhibited specific functions in acute megakaryoblastic leukemia (AMKL), a rare type of AML that is more common in children and infants. The fusion of the RBM15 gene and megakaryoblastic leukemia-1 gene by the t(1;22)(p13.3;q13.1) translocation in AMKL was found to be related to recurrent aberrations [56]. RBM15 has been reported to modulate the homeostasis of long-term HSCs, and RBM15-deleted HSCs display decreased self-renewal and aspects associated with ageing through NF-κB activation and DNA damage [57, 58]. RBM15 also plays an important role in megakaryocytic differentiation [58, 59]. RBM15 knockdown in mice produces defective megakaryopoiesis [59]. At the molecular level, RBM15 promoted megakaryocyte terminal differentiation by binding to pre-mRNA intronic regions of genes important for megakaryopoiesis in MEG-01 cells, such as GATA1, RUNX1, TAL1, and c-MPL, and to the 3′ UTRs of genes involved in RNA splicing and metabolic regulation [60]. This process could be enhanced by antisense AS-RBM15 RNA, a lncRNA overlapped with the 5′ UTR of RBM15 [61].

m6A Erasers

Single-nucleotide polymorphisms (SNPs) of FTO are strongly associated with an increased risk of various cancers, including leukemia, myeloma, and lymphoma [62]. FTO plays an oncogenic role in the occurrence, progression and prognosis of many types of cancers in a m6A-dependent manner, especially AML [63], glioblastoma (GBM) [64], and breast cancer (BC) [65]. It is critical for regulating cancer stem cell function and promotes the growth, self-renewal, and metastasis of cancer cells [66].

FTO was found to be aberrantly overexpressed in certain AML subtypes carrying t(11q23)/MLL, t(15;17)/PML-RARA, FLT3-ITD, and NPM1 mutations and was associated with decreased global m6A levels [63]. Further experiments discovered that FTO promoted leukemogenesis and inhibited all-trans-retinoic acid (ATRA)-induced AML cell differentiation by regulating ankyrin repeat and SOCS box protein 2 (ASB2) and retinoic acid receptor alpha (RARα) by reducing their m6A levels [63]. In mice, xenografted leukemic cells with mRNA m6A hypomethylation induced by upregulated FTO had more tyrosine kinase inhibitor (TKI) tolerance and higher growth rates than control cells [67]. Hence, in leukemia, alteration of m6A levels by FTO might be a driver of drug resistance and is a promising target for diagnosis and treatment. In multiple myeloma, FTO was aberrantly upregulated in extramedullary myeloma and enhanced heat shock transcription factor 1 (HSF1) expression by reducing the m6A levels of its transcripts and inhibiting the degradation effect of YTHDF2 [68].

FTO inhibitors are currently under development for the treatment of hematological malignancies. Rhein, the first identified competitive inhibitor for FTO in vitro and in vivo, reversibly bound to the FTO catalytic domain and competitively prevented its recognition of m6A [69]. Meclofenamic acid (MA) is a highly selective inhibitor of FTO on single-stranded nucleic acids over ALKBH5 [70]. A recent study declared that R-2-hydroxyglutarate (R-2HG), an oncometabolite of mutant isocitrate dehydrogenases 1/2 (IDH1/2), downregulated FTO in R-2HG-sensitive leukemia cells, which in turn lessened the mRNA stability of MYC and CEBPA, exerting broad and intrinsic antitumor activity in leukemia [71]. In addition, a novel FTO inhibitor, FB23, designed based on the principle of MA selectivity, was reported to significantly suppress the progression of human leukemia cells and mouse AML models [72]. Su et al. developed two potent small molecule FTO inhibitors, CS1 and CS2, which efficiently suppressed the m6A demethylase activity of FTO with IC50 values in the nanomolar range and exhibited strong antitumor effects in multiple types of cancers, including AML [73]. These FTO inhibitors increase the likelihood of success in developing new therapeutic strategies for hematological malignancies.

Overexpressed ALKBH5 plays an oncogenic role in many solid tumors, such as BC [74], GBM [75], and pancreatic cancer (PC) [76], and is associated with poor outcomes. However, there have been only a few studies on ALKBH5 in hematological malignancies. Two recent studies simultaneously uncovered that ALKBH5 selectively promoted leukemogenesis and modulated self-renewal of leukemia stem cells (LSCs) but had little effect on normal hematopoiesis, suggesting ALKBH5 as a pivotal biotarget of AML [77, 78]. Increased expression of ALKBH5 was correlated with poor prognosis in AML patients, and it exerted tumor-promoting effects in AML via post-transcriptional modulation of TACC3 [77], a prognosis-associated oncogene in various cancers [79–81]. Currently, inhibitors specific to ALKBH5 are under development [82, 83].

m6A Readers

A remote study showed that low IGF2BP1/3 and high IGF2BP2 levels were observed in healthy donor bone marrow and peripheral blood [84], opening the avenue for exploring the oncofetal role of IGF2BPs in normal and malignant hematopoiesis.

IGF2BP1 was upregulated in many types of leukemia and other hematological malignancies. Lower IGF2BP1 expression in AML patients was associated with better survival [85], and depletion of IGPF2BP1 led to a reduction

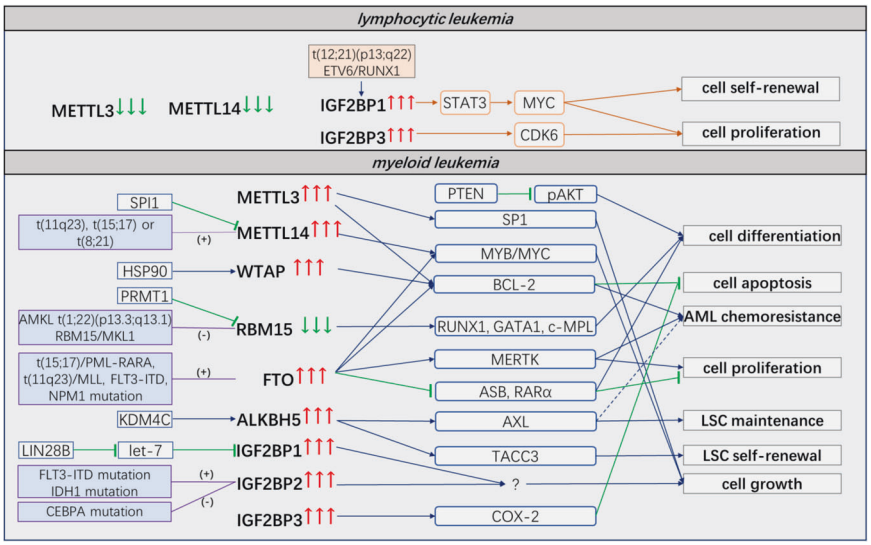

Fig. 2 The functions of m6A regulators in leukemia. Most m6A regulators are dysregulated and play a critical role in leukemia. They modulate leukemogenesis through different pathways and downstream targets.

in proliferation of AML cell lines [86]. In ALL, excessive IGF2BP1 is associated with genetic alterations. IGF2BP1 was significantly overexpressed in t(12;21)(p13;q22) ALL carrying the E/R fusion gene compared with other ALL subtypes, and a meta-analysis identified risk SNPs in the IGF2BP1 gene for E/R-positive ALL [84, 87]. Some B-ALL patients carry recurrent t(14;17)(q32;q21) translocations resulting in an IGH-IGF2BP1 fusion, which probably has prognostic significance in B-ALL [88, 89]. In B-ALL REH cells, downregulation of IGF2BP1 reduces many key mRNAs (ETV6/RUNX1, ACTB, CTNNB1, and MYC) by impairing their stability, thus regulating the cell cycle, migration and an aggressive phenotype [90]. Depletion of IGF2BP1 in REH cells also lessens STAT3 mRNA, an attractive therapeutic outcome in leukemia and lymphoma, and augments the sensitivity of STAT3 to its selective inhibitor S3I-201 [90, 91].

IGF2BP2, overexpressed in AML patients, was not only positively associated with poor prognostic factors (FLT3-ITD mutation and IDH1 mutation) but also negatively correlated with a good prognosis indicator (CEBPA mutation status) [92]. IGF2BP2 knockdown significantly inhibited cell growth in AML cell lines, but the mechanism still requires investigation [92].

IGF2BP3 overexpression leads to an increase in the numbers of bone marrow hematopoietic progenitors and the proliferation rate, providing hematopoietic progenitors with a survival advantage [93]. In CML K562 cells, overexpressed IGF2BP3 promoted cell proliferation and survival through the IGF-II pathway [94]. In AML THP-1 cells, IGF2BP3 bound to the 3′ UTR of COX-2 mRNA and affected its stability [95], which had an antiapoptotic role in AML cells [96]. IGF2BP3 is specifically overexpressed in MLL-rearranged B-ALL, and knockdown of IGF2BP3 disrupted cell growth and accelerated apoptosis [93]. Mechanistically, IGF2BP3 positively targeted mRNAs of the quintessential oncogenes CDK6 and MYC in B-ALL RS4;11 cells and REH cells [93]. Additionally, IGF2BP3 was overexpressed in Hodgkin lymphoma cells against a nearly negative background by immunohistochemical staining and showed a relationship with cytoplasmic immunoreactivity to both CD15 and CD30, indicating IGF2BP3 as a novel biomarker in the diagnosis of Hodgkin lymphoma [97].

YTHDF2-mediated m6A mRNA decay regulates HSC protection, self-renewal and regeneration by targeting multiple critical genes, such as Wnt target genes (CyclinD1, C-MYC, and AXIN2), pro-survival genes (BCL-2 and MCL-1), anti-apoptosis genes (BAX, BAD, and BIM), and the key transcription factor TAL1 [98, 99]. Depletion of YTHDF2 in mouse HPSCs and human umbilical cord blood HSCs boosted HSC expansion without marked lineage bias or leukemic potential [98, 99]. However, long-term hematopoiesis-specific YTHDF2 deficiency in young mice led to a progressive myeloid bias, a loss of lymphoid potential, an expansion of HSCs and the failure of multilineage reconstitution and activated proinflammatory pathways by elevating key genes such as STAT1, IL6RA and GADD45G [100]. In addition, YTHDF2 was upregulated in AML, inhibition of which enhanced myeloid reconstitution in HSCs and specifically compromised the propagation of LSCs, suggesting YTHDF2 as a unique therapeutic AML target [101].

It seems contradictory that both m6A readers and erasers are overexpressed in AML. In fact, they modulate leukemogenesis through different pathways and downstream targets (Fig. 2). METTL3 and METTL14 appear to affect myeloid differentiation and regulate critical genes, such as MYC and MYB, which are essential for the initiation of leukemogenesis [41, 52]. FTO preferentially impacts cell

proliferation and modulates drug resistance via RARα and ASB2 [63]. ALKBH5 promotes leukemogenesis and controls the self-renewal of LSCs via TACC3 [77]. Alternatively, m6A readers and erasers act on different m6A sites of the same downstream transcript, leading to identical results. For instance, METTL14 and FTO have both been reported to promote MYC gene expression in AML. The former mainly facilitates m6A formation on the 3′-terminal exon of MYC mRNA [52], and the latter removes m6A marks on the 5′-terminal and internal exons [71]. More importantly, the outcomes of methylation and demethylation, which promote or repress gene expression, are ultimately implemented through distinct reading processes. High expression levels of leukemic oncogenes are ascribed to either the IGF2BP1/2/3-mediated promotion of mRNA stabilization and translation after MTC deposition of m6A marks or the inhibition of YTHDF2/3-mediated mRNA decay by FTO/ALKBH5-induced m6A mark removal. Therefore, we speculate that it is the site where m6A marks are specifically located that enables the removal by m6A eraser and determines what kind of reader it appeals to.

The internal epigenetic modification network

The internal interactions among different epigenetic modifications are realized via various epigenetic modifiers. Taking DNA methylation and histone modification as examples, DNA and histones intertwine to form nucleosomes, and diverse epigenetic marks deposited on DNA/histones synergistically or antagonistically alter the regional chromatin structure and then enfold or expose double-stranded DNA buried by nucleosomes to control gene transcription. The crosstalk between DNA methylation and histone modifications has been extensively stated in the last two decades [102]. In hematological malignancies, the integration of AML DNA methylation profiles and HSPCs ChIP-seq data revealed that hypermethylated CpG islands in AML were related to a significant reduction in H3K4me3 with a concomitant increase in H3K4me0 levels, suggesting that H3K4me3 levels are strongly associated with DNA methylation patterns in AML [103].

Recently, increasing evidence has highlighted the interaction of RNA modification with other epigenetic modifications: histone modifications, DNA methylation, and ncRNAs.

Interaction of RNA methylation with histone modifications

RNA methylation selectively acts on the transcripts encoding epigenetic modifiers of histone modifications. Chen et al. discovered m6A modifications on the transcripts of the histone methyltransferase EZH2 in adult neural stem cells (NSCs) by MeRIP-seq, and knockdown of METTL3 resulted in both EZH2 protein reduction and a subsequent global H3K27me3 decrease [104]. In Mettl14-knockout NSCs, the stability of the mRNA transcripts of the H3K27 acetyltransferases CBP and P300 was distinctly strengthened compared to that in controls [105]. Increased m6A RNA methylation on mRNA transcripts of the H3K9me3 methyltransferase Suv39H1 after baicalin hydrate treatment was detected in nasopharyngeal carcinoma (NPC) [106]. In mouse embryonic stem cells and HEK293 cells, loss of METTL3 or METTL14 increased global H3K9me2 levels without altering the expression of H3K9me2-related epigenetic modifiers, and loss of FTO or ALKBH5 decreased H3K9me2 levels [107]. The mechanism involved YTHDC1 recruiting the H3K9me2 demethylase KDM3B to m6A-associated chromatin regions to regulate local H3K9me2 levels and gene expression [107]. In AML THP-1 cells, YTHDF2 increased the H3K27me3 marks on the promoters of proinflammatory cytokines by degrading transcripts of the H3K27me3 demethylase KDM6B in an m6A-dependent manner during bacterial infection [108]. In addition, m6A modification also regulates histone modifiers indirectly. ALKBH5 has been found to regulate EZH2 at the protein level rather than the mRNA level by depleting m6A modifications on the lncRNA NEAT1, which recognizes EZH2 as a downstream target, thus affecting the invasion and metastasis of gastric cancer [109].

In contrast, histone modifications guide m6A function. Suppressed Mettl14 was triggered through the H3K36me3 loss induced by methyltransferase SETD2 knockdown or demethylase KDM4A overexpression, resulting in global m6A demethylation [110]. Mechanistic research has implied that Mettl14 serves as a novel H3K36me3 reader and connects the MTC complex to RNAP II, thereby depositing m6A modifications on nascent RNAs during transcriptional elongation [110]. Wang et al. found that the H3K9me3 demethylase KDM4C was accumulated in the ALKBH5 genetic coding area, eliminating the repressive effect of H3K9me3 and recruiting transcription factors MYB and Pol II to upregulate the expression of ALKBH5 in AML [78].

In summary, m6A marks on transcripts encoding epigenetic modifiers of histone modifications regulate histone modifications, and histone modifications dynamically and specifically mediate m6A RNA methylation at both the posttranscriptional and transcriptional levels.

Interaction of RNA methylation with DNA methylation

DNA methylation directly controls the genetic expression of m6A regulators. For instance, in pancreatic duct epithelial cells, cigarette smoke condensate causes hypomethylation of the METTL3 promoter, induces METTL3 expression and promotes the development and progression of PC [111].

Although there is little direct evidence that RNA methylation modulates DNA methylation, they share the same

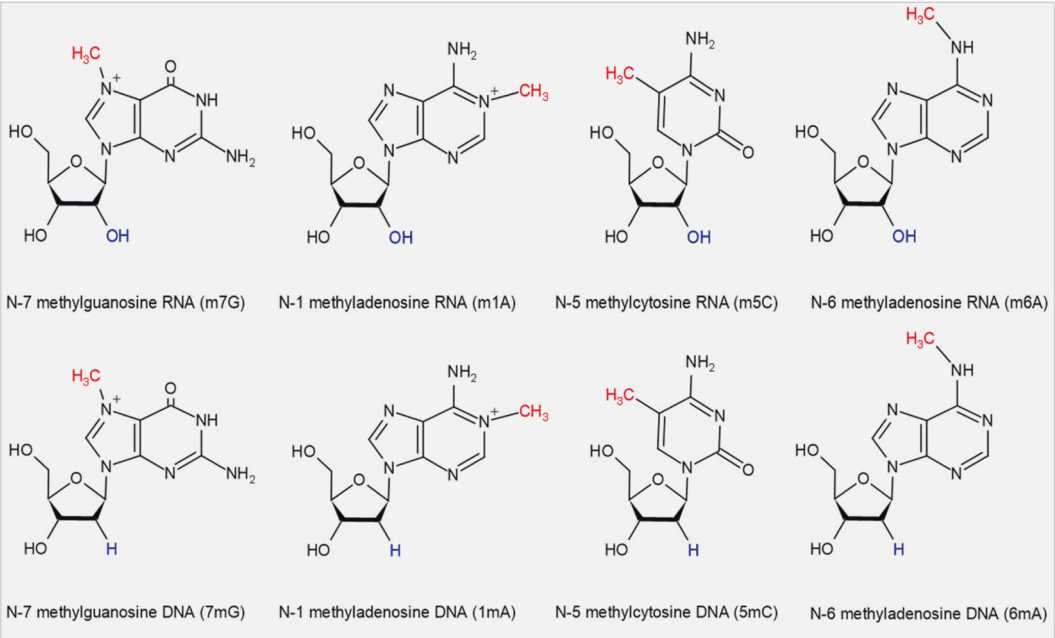

Fig. 3 The identical methyl marks of DNA and RNA methylation. DNA and RNA possess many identical epigenetic marks, such as N-7 methylguanosine, N-1 methyladenosine, N-5 methylcytosine, and N-6 methyladenosine.

methyl donor and identical epigenetic marks. Methyl marks on nucleic acids and histones are installed when the active methyl-group donor SAM turns into S-adenosylhomocysteine (SAH) after donating its methyl-group under the catalysis of relevant methyltransferases [15, 112]. Owing to their chemical structural similarities, DNA and RNA possess many identical epigenetic marks (Fig. 3).

Furthermore, in eukaryotes, most writers and erasers of these identical methyl marks are homologues with the same domain or region. The core RNA m6A methyltransferase METTL3 and the DNA 6 mA methyltransferase METTL4 [113] belong to the eukaryotic methyltransferase-like (METTL) protein family. METTLs deposit methylation modification through their SAM binding region largely onto RNAs, including mRNAs, tRNAs, rRNAs, and even ncRNAs, and less onto DNA and proteins (Table 1). The RNA m6A demethylase FTO and the DNA 6 mA demethylase ALKBH1 [134] are homologues of the AlkB dioxygenase superfamily with the same Fe2OG dioxygenase domain and α-KG binding region that recruits Fe^{2+}/α-KG, and they serve to transfer methyl groups from methylated nucleobases to formaldehyde. Another m6A RNA demethylase, ALKBH5, is also an alkB homologue with the same α-KG binding region [135]. Here, we list the known epigenetic functions of the alkB homologues (Table 2).

Interaction of RNA methylation with ncRNAs

Noncoding RNAs, previously called the "dark matter" of the genome, lack coding capacity but constitute more than 90% of the RNA from the human genome [146]. In recent decades, many ncRNAs, such as long noncoding RNAs (lncRNAs), miRNAs, PIWI-interacting RNAs (piRNAs), pseudogenes and circular RNAs (circRNAs), have been found to play crucial roles in both normal cellular function and diseases, including cancer. Recently, ncRNAs have also been reported to be m6A-modified.

lncRNAs

LncRNAs, composed of more than 200 nt in length, induce chromatin remodeling and histone modifications in the nucleus, modulate alternative splicing patterns and generate endo-siRNAs (miRNAs and piRNAs) at the transcriptional level, and alter the activity and localization of specific proteins directly or indirectly in the cytoplasm [147]. lncRNAs contribute to the aging, malfunction, and malignant transformation of blood cells by various mechanisms during normal and malignant hematopoiesis [148], and their aberrant expression in hematological malignancies has been proposed as a diagnostic biomarker, novel therapeutic target, and predictor of clinical outcomes [149].

The majority of lncRNAs are 5′-capped, polyadenylated and spliced like mRNAs. They can be N-6 adenosine-methylated reversibly by different RNA m6A regulators. In most cancers, METTL3 promotes tumorigenesis, progression and chemoresistance by augmenting oncogenic lncRNA expression and stabilizing the respective transcripts [150–153]. M6A modification triggered by overexpression of METTL3 and YTHDF3 in non-small cell lung cancer

Table 1 The interacted epigenetic function of mammalian METTL protein family.

METTLs	Function
METTL1	tRNA, mRNA, and miRNA 7-methylguanosine (m7G) methyltransferase [114, 115]
METTL2	tRNA 3-methylcytidine (m3C) methyltransferase [116]
METTL3	mRNA 6-methyladenosine (m6A) methyltransferase[17]
METTL4	DNA 6-methyladenosine (6 mA) methyltransferase [117] snRNA N6 2′-O-dimethyladenosine (m6Am) methyltransferase [118]
METTL5	18S rRNA m6A methyltransferase [119]
METTL6	tRNA m3C methyltransferase [116]
METTL8	mRNA m3C methyltransferase [116]
METTL10	Nonhistone lysine methyltransferase [120]
METTL11A	Histone lysine methyltransferase [121]
METTL11B	Proteins N-terminal mono-methytransferase [122]
METTL12	Mitochondrial protein (citrate synthase) lysine methyltransferase [123]
METTL13	Protein (eEF1A) lysine methyltransferase [124]
METTL14	mRNA m6A methyltransferase [17, 18]
METTL15	Mitochondrial 12S rRNA N4-methylcytidine (m4C) methyltransferase [125]
METTL16	snRNA, lncRNA and pre-mRNA m6A methyltransferase [24, 25]
METTL17	Mitochondrial 12S rRNA m4C and 5-methylcytidine (m5C) methyltransferase [126]
METTL20	Mitochondrial lysine methyltransferase [127]
METTL21B	Nonhistone lysine methyltransferase [128]
METTL21C	Nonhistone lysine methyltransferase [129, 130]
METTL21D	Nonhistone lysine methyltransferase [131]
METTL22	Nonhistone lysine methyltransferase [132]
METTL23	Histone arginine methyltransferase (H3R17me2a) [133]

Table 2 The interacted epigenetic function of mammalian AlkB proteins.

Enzymes	Function
ALKBH1	DNA 6 mA demethylase [134]
	tRNA N1-methyladenosine (m1A) demethylase [136]
	Mitochondrial DNA 3-methylcytidine (3mC) and RNA m3C demethylase [137]
	Mitochondrial tRNA m5C demethylase [138]
ALKBH2	DNA 3mC or 1 mA demethylase [139]
	DNA and N4-ethenocytosine dioxygenase [140]
	DNA N3-ethylthymidine decarboxymethylase [141]
ALKBH2/3	DNA m5C and m3C demethylase [142]
ALKBH3	tRNA m1A and m3C demethylase [143]
ALKBH5	RNA m6A demethylase [30]
ALKBH8	tRNA 5-methoxycarbonylmethyluridine (mcm5U) methyltransferase [144]
ALKBH9 (FTO)	RNA m6A demethylase [29]
(FTO)	DNA 6 mA demethylase [145]
	Single-stranded DNA 3-methylthymine and single-stranded RNA 3-methyluracil demethylase [34]

(NSCLC) increased lncRNA MALAT1 mRNA and enhanced its stability, inducing the invasion, metastasis and drug resistance of NSCLC via the MALAT1-miR-1914-3p-YAP axis [154]. In NSCLC H1299 cells, the lncRNA THOR was m6A-methylated by METTL3, which could be read and stabilized by YTHDF1 [155]. However, in HeLa cells, the m6A modification added by METTL3 to the lncRNA pncRNA-D shortened its half-life, and METTL3 together with YTHDC1 impaired the interaction of pncRNA-D with the RNA-binding protein TLS, thus relieving their inhibitory function on cyclinD1 gene expression and cell cycle progression [156].

METTL14 has been confirmed to be downregulated in CRC, and depletion of METTL14 abolished the m6A level of lncRNA XIST and augmented its expression by reducing the degradation function of YTHDF2, resulting in increased CRC cell growth and invasion [51]. In addition, m6A downregulation by VIRMA depletion suppressed oncogenic lncRNA CCAT1 expression, and higher VIRMA and lncRNA CCAT1 expression predicted poor prognosis in prostate cancer (PCa) patients [157]. In PC, upregulated IGF2BP2 served as an m6A reader for the lncRNA DANCR and stabilized its RNA; DANCR interacted with IGF2BP2 to promote cell proliferation and stemness-like properties [158].

ALKBH5 has been reported to positively control the expression of lncRNAs in tumor cells. Overexpressed ALKBH5 in gastric cancer (GC) upregulated the lncRNA NEAT1 by demethylating its transcripts, thus promoting invasion and metastasis of GC cells via targeting of downstream EZH2 [109]. ALKBH5 also promoted osteosarcoma cell proliferation in vitro and tumor growth in vivo by demethylating the lncRNA PVT1 and enhancing its transcripts by inhibiting the recruitment of the degradation-promoting reader YTHDF2 [159]. ALKBH5 and the lncRNA KCNK15-AS1 were both downregulated in PC. Overexpression of ALKBH5 decreased the m6A marks on KCNK15-AS1 but stabilized its mRNA. These outcomes might jointly inhibit the epithelial–mesenchymal transition of PC cells [160].

On the other hand, lncRNAs alter m6A modification of mRNAs by interacting with m6A RNA regulators. In GC, the oncogenic lncRNA LINC00470 binds to the mRNA of the classical tumor suppressor PTEN and recruits METTL3 to it to form m6A marks, eventually mediating PTEN mRNA degradation via the LINC00470-METTL3-YTHDF2 axis [161]. In BC cells, METTL14 is directly recruited by LNC942, promoting the stability and expression of its downstream targets, such as CXCR4 and CYP1B1 (mediated by m6A methylation levels), and subsequently accelerates cell proliferation and colony formation and reduces cell apoptosis in vitro and in vivo [162]. The antisense lncRNA GATA3-AS functions as a cis-acting element for the preferential interaction of KIAA1429 with the pre-mRNA of the tumor suppressor gene GATA3, promotes m6A modification on the 3′ UTR of GATA3 pre-mRNA, and mediates tumor growth and metastasis in HCC [163].

In addition to m6A writers, overexpressed lncRNAs also interact with m6A erasers to control target mRNA expression and cell fate. In glioblastoma stem-like cells (GSCs), the antisense lncRNA FOXM1-AS promotes the interaction of ALKBH5 with nascent transcripts of the FOXM1 gene, increasing FOXM1 expression. Depletion of ALKBH5 and FOXM1-AS disrupts GSC tumorigenesis through the FOXM1 axis [75]. In GBM, the lncRNA SOX2OT upregulates SOX2 expression by recruiting ALKBH5 to its mRNA, inhibits cell apoptosis, and promotes cell proliferation and temozolomide resistance via the Wnt5a/β-catenin signaling pathway [164]. In addition, the antisense lncRNA GAS5-AS1 was found to be markedly decreased in cervical cancer. GAS5-AS1 bound to the tumor suppressor GAS5 and enhanced its stability by interacting with ALKBH5, while this process was inhibited by the YTHDF2-dependent degradation pathway [165].

miRNAs

MiRNAs, with lengths less than 22 nt, are highly conserved in evolution and act in transcriptional repression, mRNA cleavage and degradation. M6A RNA modification regulates miRNA synthesis, processing, and maturation, which are important in tumorigenesis and cancer progression.

METTL3 has been reported to play a vital role in pri-miRNA processing and miRNA maturation in a global and non-cell-type-specific manner by recognizing DGCR8 of the microprocessor complex and binding it with pri-miRNAs [166]. In BCa cells, METTL3 interacted with DGCR8 to accelerate the maturation of pri-miR-221/222, resulting in a reduction in PTEN, which ultimately led to the growth of BCa [167]. In pancreatic cells, overexpressed METTL3 increased m6A formation on pri-miR-25 and facilitated the interaction of pri-miR-25 with DGCR8 by recruiting the RNA-binding protein NKAP, promoting the maturation of oncogenic miR-25-3p [111]. Excessive miR-25-3p targeted PHLPP2 mRNA and promoted the initiation and progression of pancreatic ductal adenocarcinoma via the METTL3-miR-25-3p-PHLPP2-AKT axis [111]. In CRC, METTL3 methylated pri-miR-1246 and promoted the maturation of the metastasis-related RNA miR-1246, which downregulated the anti-oncogenic protein SPRED2 and further inactivated the Raf/MEK/ERK pathway [168]. In addition, Mettl3 increased the splicing of precursor miR-143-3p and enhanced mature miR-143-3p in lung cancer cells, while miR-143-3p overexpression fostered brain metastasis, angiogenesis and tubulin depolymerization in lung cancer cells by repressing VASH1 [169].

Other m6A regulators participate in cancer bioprocesses by targeting miRNAs as well. MiRNA profiling in BC cells showed that METTL14 affected the migration and invasion of BC cells by regulating m6A modification of miRNAs such as miR-146a-5p [170]. However, the underlying mechanism remains to be explored. HNRNPA2B1 reads m6A marks on pri-miRNAs and interacts with DGCR8 to promote pri-miRNA processing [38]. In tamoxifen-sensitive MCF-7 BC cells, overexpression of HNRNPA2B1 reduced tamoxifen and fulvestrant responses via TGFβ signaling and other pathways, which resulted from alterations in miRNA expression (downregulation of miR-29a-3p, miR-29b-3p, and miR-222 and upregulation of miR-1266-5p, miR-1268a, and miR-671-3p) [171]. ALKBH5 inhibited the expression of miR-7 by interacting with HuR to regulate miR-7 processing in epithelial ovarian cancer cells, which promoted EGFR expression [172].

In contrast, miRNAs regulate m6A RNA abundance. The transcriptome-wide distribution of m6A modification in mouse ESCs and HeLa cells revealed that 75% of the m6A peaks with RRACH motifs were identified as potential targets of miRNAs [173]. Further experiments validated that miRNAs induced de novo m6A methylation in a sequence-dependent manner and miRNAs regulated the m6A methyltransferase activity of METTL3 by modulating its binding to mRNAs [173].

A novel mechanism is that miRNAs bind to the 3′ UTR of transcripts encoding m6A regulators and inhibit their expression. Mammalian hepatitis B X-interacting protein (HBXIP) increased METTL3 expression via decreased let-7g miRNA levels, which targeted the 3′ UTR of METTL3 and inhibited its expression, and METTL3 enhanced HBXIP through m6A modification. This HBXIP/let-7g/METTL3/HBXIP loop drove the aggressiveness of BC [174]. In hepatoblastoma, METTL3 was identified to be a direct target of miR-186, and the miR-186/METTL3 axis contributed to the progression of hepatoblastoma via the Wnt/β-catenin pathway [175]. The tumor-suppressive microRNA-1266 in CRC promoted the occurrence and progression of CRC by directly targeting FTO [176]. Fluorescent enzyme reporter gene experiments validated that miR-346 bound to the 3′ UTR of YTHDF1, which has an essential function in glioma diagnosis, treatment and prognosis [177]. MiR-145 decreased the luciferase activities of the 3′ UTR of YTHDF2 mRNA in HCC, and miR-145 inhibition strongly reduced m6A levels by targeting the 3′ UTR of YTHDF2 mRNA in HCC cells [178].

Other ncRNAs

NcRNAs containing the consensus motif RRACH could theoretically be m6A-modified. In addition to their effects on lncRNAs and miRNAs, many METTLs and AlkB homologues have been reported to install methyl marks on rRNAs, tRNAs and other ncRNAs.

CircRNAs, a class of covalently closed ncRNAs without the 5′ cap structure, have recently shown potential to encode

proteins via m6A-mediated initiation of translation [179]. m6A modification was also found to regulate circRNA metabolism by guiding the back-splicing reaction, increasing export to the cytoplasm and facilitating degradation by m6A RNA regulators [180–182].

Discussion

Unlike DNA methylation and histone modifications that chiefly act on the chromatin structure, m6A RNA broadly targets nearly all transcripts [13, 14] and widely modulates their location, processing, stability, and translation [7], playing a critical role in normal hemopoiesis and hematological malignancies [45, 63, 77, 78].

As research continues, the actions of m6A readers gradually become explicit. The seemingly contradictory fact that some m6A writers and erasers are synchronously abundant in certain cancers, such as AML, may be further realized through distinct reading processes. More emphasis should be placed on the deeper investigation of mechanisms through which m6A writers and erasers selectively recruit or hinder m6A readers to or from specific m6A sites of downstream transcripts.

RNA epigenetic drugs targeting m6A regulators have caused immense concern. One METTL3 inhibitor is currently being developed [48] and is in sharp contrast to inhibitors targeting m6A erasers, especially FTO [69–72, 82, 83]. FTO acts on <10% of m6A-containing transcripts but dominates leukemogenesis and drug tolerance to ATRA and TKI treatment [63, 67], which partly explains why FTO inhibitors are expected to have a superior clinical future. However, the role of FTO in normal hemopoiesis remains unclear. On the other hand, ALKBH5 should be investigated as much as FTO, given that it is the only present prognosis-related biotarget among m6A writers and erasers in AML and has no or slight effects on normal hematopoiesis [77, 78]. Considering the few overlapping downstream transcripts of FTO and ALKBH5 (fewer than 10%) [78] and their identical effect on leukemogenesis, the combined application of FTO inhibitors and ALKBH5 inhibitors may hold great therapeutic potential in the future.

The emerging phenomenon of the interplay between m6A and histone modifications [78, 107] prompted us to review to previous related studies. The data that we have summarized powerfully demonstrates that RNA methylation strongly interacts with other epigenetic modifications, including DNA methylation, histone modifications and ncRNAs. Even though there is no direct evidence that RNA methylation guides DNA methylation, the intricate function of METTLs and ALKBHs may provide us answers in the future. Our presentation may enlighten researchers who are interested in RNA modifications on m6A-centered epigenetic interactions and future therapeutic development for all cancers that are not restricted to hematological malignancies.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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