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Review Article

N6-methyladenosine (m6A) RNA Modification's Regulatory Role in Acute and Chronic Leukemia

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Abstract

Hematological malignancies present a complex challenge within oncology, necessitating a thorough understanding of genetic factors for effective detection and management. As we delved into the forefront of cancer research, our focus turned to the emerging field of N6-methyladenosine (m6A) epigenetic approaches. Among RNA modifications, m6A is the most common and thoroughly investigated post-transcriptional alteration in messenger RNA. The m6A modification involves the addition of a methyl group to the adenosine at the N6 position within RNA molecules, a process mediated by proteins collectively referred to as m6A writers, erasers, and readers. The dynamic nature of m6A modifications on RNA molecules presents a promising avenue for enhancing our understanding of gene expression regulation in hematological malignancies. This review explores the potential breakthroughs that m6A epigenetic tools offer in cancer diagnostics and treatment, highlighting their role in enabling more precise interventions. By acknowledging the importance of genetic insights and integrating advancements in m6A epigenetics, this article advocates for a comprehensive approach to managing hematological malignancies.

Introduction

Today, epigenetics, which entails the modification of chromosomes without altering DNA sequences, serves as a crucial regulatory mechanism for gene expression. Hence, "epigenetic" modifications extend to various RNA types, including ribosomal RNA, transfer RNA, small nuclear RNA, and messenger RNA (mRNA), collectively referred to as "epitranscriptomics".[1] Since the discovery of the first RNA pseudouridine modification, referred to as the "fifth nucleotide", in 1957, over 170 distinct chemical modifications have been identified in both protein-coding and non-protein-coding RNA transcripts.[2] Among these modifications, N6-methyladenosine (m6A) is the most common and well-studied post-transcriptional modification in mRNA. m6A RNA modification involves the methylation of adenosine at the N6 position within RNA molecules. This process is facilitated by a group of proteins known as m6A writers, erasers, and readers (Fig. 1), which collectively coordinate a precisely regulated network.[3] Recent investigations into various RNA modifications reveal their dynamic involvement across a wide range of pathological and physiological contexts, including normal development and malignant transformation. Specifically, evidence indicates that RNA modifications play an important role in normal hematopoiesis, especially myelopoiesis, and in the onset and progression of leukemia.[4,5] Additionally, other modifications such as 5-hydroxymethylcytosine, 5-methylcytosine, adenosine to inosine editing, and pseudouridine also play roles in normal hematopoiesis and/or leukemogenesis.[6,7]

A diverse set of chemical modifications found in RNA are necessary for regulating gene expression. These modifications contribute to pre-mRNA processing and expression in the nucleus, as well as to mRNA translation and processing, highlighting their broad impact on RNA biology. The m6A modification acts as a key post-transcriptional regulatory mechanism that influences RNA metabolism and various cellular functions. It modulates processes such as splicing, stability, and translation efficiency, thereby exerting significant control over gene expression. Understanding the complex regulatory mechanisms of m6A is essential to unravel the intricacies of gene regulation in health and disease.[8,9]

In the context of cancer, including leukemia, RNA modifications such as m6A, 5-methylcytosine, and pseudouridine (Ψ) are recognized as critical post-transcriptional regulators influencing gene activity patterns. The association between m6A modification and cancers further emphasizes its significance in understanding disease mechanisms. Over time, it has been recognized that the development of tumors involves several stages driven by numer-

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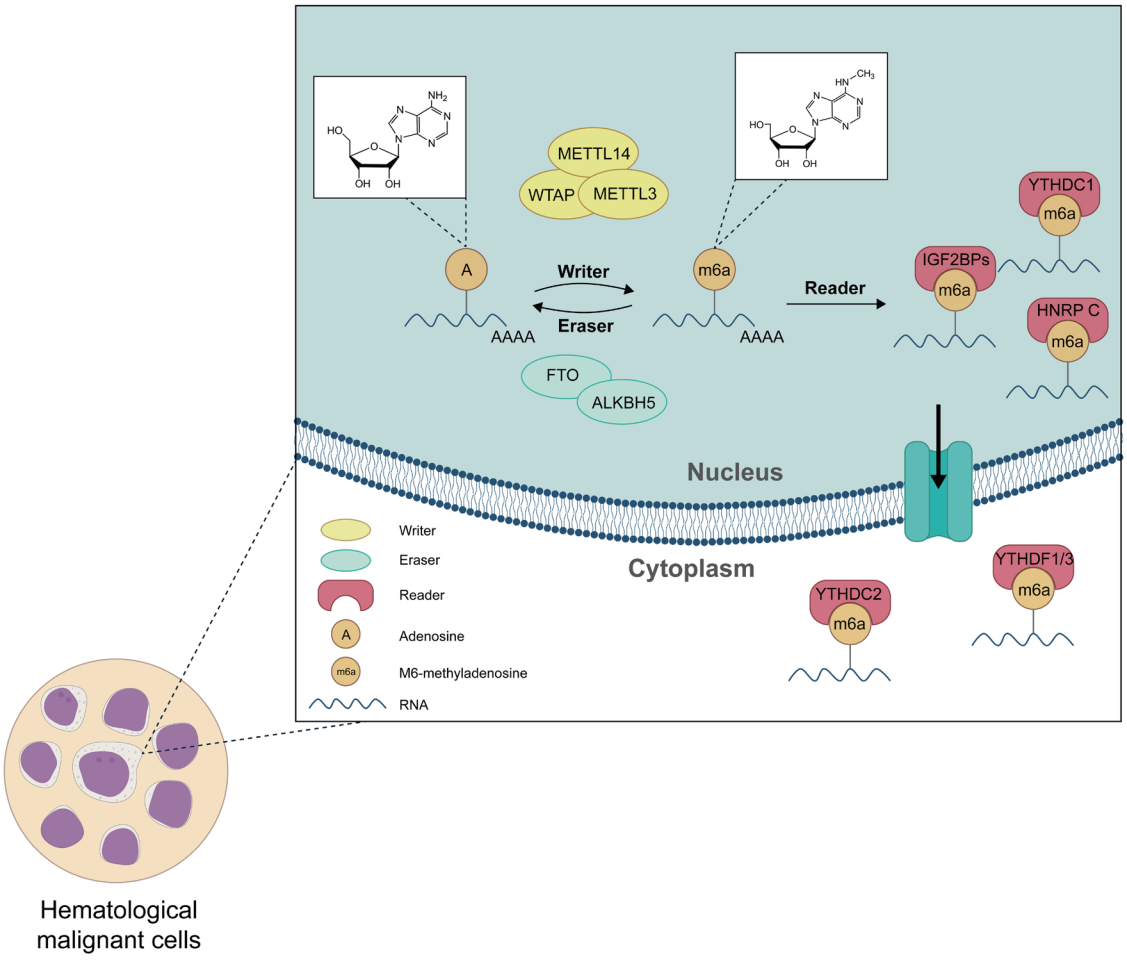

Fig. 1. The roles of m6A RNA modification in leukemia. The m6A RNA modification involves three key actors: writers, erasers, and readers. Writers, including m6A methyltransferases such as *METTL3*, *METTL14*, and *WTAP*, add methyl groups to RNA. Erasers, such as *ALKBH5* and *FTO*, are responsible for removing methyl groups from RNA molecules. Readers, which are proteins that recognize m6A sites, play various roles including RNA splicing, microRNA processing, translation, and RNA degradation. Some of these readers include *YTHDC1*, *IGF2BPs* and *HNRP C* are usually found in the nucleus while *YTHDF1, 2, 3*, and *YTHDC2* are cytoplasmic. Dysregulation of these proteins and m6A levels can contribute to hematological malignancies. A, adenosine; *ALKBH5,* AlkB homolog 5; *FTO,* fat mass and obesity-associated; *HNRP*, heterogeneous nuclear ribonucleoprotein; *IGF2BPs*, insulin-like growth factor-2 mRNA-binding protein; m6A, N6-methyladenosine; *METTL3*, methyltransferase-like 3; *WTAP,* Wilms' tumor 1-associated protein; *YTHDC1*, YTH domain-containing protein 1; *YTHDF1*, YTH N6-methyladenosine RNA binding protein 1.

ous genetic changes, some of which contribute to the progressive transformation of normal cells into a malignant state. In addition to genetic alterations, mounting evidence indicates that epigenetic mechanisms play a significant role in cancer development. Recent studies, particularly in the realm of leukemia, have emphasized the crucial role of the m6A variant as an epigenetic modification in the advancement and progression of both acute and chronic forms of the disease.[10–12] The dysregulation of m6A has been implicated in leukemogenesis, influencing the behavior of leukemic stem cells (LSCs) and playing a role in the pathogenesis of leukemia.[13,14] Hematologic malignancies are a significant global concern, ranking sixth in cancer incidence worldwide and holding the top position in cancer-related mortality among adolescents.[15] It is crucial to explore factors affecting these malignancies through genetic and epigenetic approaches. The future importance of hematologic malignancies is related to several key factors. First, these malignancies, which include various forms of blood cancers such as leukemia, lymphoma, and myeloma, impose a significant burden on global health care. The evolution of our understanding of the molecular and genetic basis of these diseases has led to the development of targeted therapies that improve outcomes. Second, hematological malignancies are often used as models for cancer research. Insights gained from studying these diseases often have broader applications for understanding carcinogenesis, the function of the immune system, and therapeutic strategies applicable to other types of cancers. Additionally, the incidence of hematological malignancies is expected to increase along with the aging of the world population.[16,17] Addressing the challenges posed by these diseases requires continuous research, innovative treatments, and a multidisciplinary approach to patient care. In summary, the future importance of hematologic malignancies is multifaceted, including their role in advancing cancer research, their impact on health care, and their increasing significance in an aging population. Epigenetics plays a crucial role in the assessment, prognosis, and management of hematological malignancies, especially in the context of early detection and personalized approaches. Abnormal

epigenetic patterns serve as specific markers for various blood cancers, enhancing diagnostic precision and allowing rapid intervention. The potential of epigenetics in predicting disease progression and response to therapy highlights its essential role in improving diagnostic accuracy and treatment efficacy in hematological malignancies.[18,19]

The primary purpose of this review was to comprehensively elucidate the crucial role of m6A RNA modification in gene expression regulation in both acute and chronic leukemia. This review synthesizes current findings on how m6A modifications impact hematopoiesis and leukemogenesis, detailing the dynamic interactions among m6A writers, erasers, and readers in leukemia. The significance of this review lies in advancing our molecular understanding of leukemia, highlighting the scientific value of targeting m6A-related pathways for therapeutic interventions. Given the mounting evidence linking m6A dysregulation to leukemia progression and resistance to conventional therapies, this review underscores the necessity for ongoing research in this field. Furthermore, the insights provided can pave the way for developing novel diagnostic markers and targeted therapies, addressing the urgent need for more effective and personalized treatments for leukemia patients. By exploring the current landscape and future prospects of m6A RNA modification research, this review contributes to the broader goal of enhancing cancer diagnostics and therapeutic outcomes.

m6A methylation modifications

As we explore the intricate molecular dynamics of epigenetic modification, it becomes evident that m6A methylation plays a multifaceted role in the regulation of gene expression, thereby exerting significant effects on diverse pathological and physiological processes. m6A, or N6-methyladenosine, is a common RNA modification that involves the addition of a methyl group to the adenosine base at the nitrogen-6 position. This modification occurs mainly in mRNA molecules but is also present in various other RNA types, including long non-coding RNA (lncRNA) and microRNA. Writers are enzymes responsible for m6A modifications, erasers are tasked with removing these modifications, and readers are responsible for interpreting the modified RNA.[20,21]

The core constituents of the m6A methyltransferase complex, referred to as the writers, include Wilm's tumor 1-associated protein (*WTAP*), methyltransferase-like 3 (*METTL3*), and methyltransferase-like 14 (*METTL14*). These enzymes collaborate to perform m6A modifications on RNA transcripts, marking them for subsequent regulatory processes. The Fat mass and obesity-associated (*FTO*) and AlkB homolog 5 (*ALKBH5*) serve as demethylases, tasked with removing m6A modifications. This reversible characteristic of m6A marks provides a dynamic regulatory mechanism for gene expression. Proteins that identify and attach to m6A-modified RNA serve as readers, influencing various aspects of RNA metabolism. The *YT521-B* homology (*YTH*) domain family encompasses key components, namely *YTH* domain family proteins 1/2/3 (*YTHDF1/2/3*) and *YTH* domain-containing proteins 1/2 (*YTHDC1/2*), positioning them as pivotal m6A reader proteins. Notably, *YTHDC1* stands out as the only m6A-binding protein in the nucleus, whereas *YTHDC2* and *YTHDF1-3* are primarily located in the cytoplasm. The *YTH* domain-containing proteins and eIF3 are prominent examples of m6A readers, participating in processes such as RNA splicing, export, translation, and decay.[22–25]

The significance of m6A methylation's functionality can be described as follows: regulation of translation (m6A modifications affect mRNA translation efficiency, impacting the production of specific proteins that are critical for cellular functions); RNA splicing and processing (m6A changes participate in alternative splicing, influencing the variety of mRNA isoforms and contributing to the complexity of the human transcriptome); cellular differentiation and development (m6A methylation is involved in regulating stem cell fate determinations, embryonic development, and tissue-specific gene expression); and disease associations (the disruption of m6A modifications has been associated with various human disorders, including cancer, neurodegenerative conditions, and metabolic disorders).[26–31]

m6A modification in normal hematopoiesis

The blood system is formed through a process termed hematopoiesis, which follows a cellular hierarchy. Hematopoietic stem cells (HSCs) play a crucial role in this process, distinguished by their ability to self-renew and differentiate into various blood cell types. These HSCs give rise to diverse progenitor cells capable of generating multiple lineages, which then differentiate into lineage-specific precursors and, ultimately, mature blood cells.[32] Studies suggest that the function of HSCs is influenced by epigenetic mechanisms, including DNA methylation and histone modification.[33] Additionally, the significance of m6A RNA methylation in regulating the functionality of HSCs and the hematopoietic process has also been emphasized.

In the developmental hematopoietic process, m6A plays a role at various stages, including the early phase of hematopoietic stem and progenitor cell (HSPC) formation during embryonic development.[34,35] HSPCs originate from hemogenic endothelial (HE) cells through the endothelial-to-hematopoietic transition (EHT).[36] Notably, studies conducted by Zhang *et al*.[35] revealed the regulatory role of m6A in the differentiation of HSPCs in zebrafish blood and vascular tissues. The findings showed that m6A influences the gene expression equilibrium of HE cells during EHT. Mechanistically, m6A modification mediates the *YTHDF2*-dependent degradation of Notch receptor 1α (*Notch1α*) mRNA, thereby modulating the activity of the *Notch* signaling pathway. Recent findings suggest that the deletion of *METTL3* in vascular endothelial cells significantly suppresses EHT by reducing the m6A methylation modification level of Notch1α mRNA, thus inhibiting HSPC generation. Consequently, m6A is essential for regulating HSPC generation during the hematopoietic process, particularly in the early stages of zebrafish embryogenesis. A comparable phenotype was observed in mouse models with *METTL3* knockdown.[32,35] Vu *et al*.[37] used short hairpin RNAs to suppress *METTL3* levels in HSPCs, resulting in reduced cell growth and increased myeloid differentiation. Conversely, the enhancement of wild-type *METTL3*, but not the catalytically-dead form, led to increased proliferation and colony formation while inhibiting myeloid differentiation. Like *METTL3*, *METTL14* is a crucial element of the m6A methyltransferase complex (writers) with elevated expression in Lin^- $Sca\text{-}1^+c\text{-}kit^+$ cells and murine HSPCs. However, its expression decreases during myelopoiesis, particularly in granulocyte-macrophage progenitors, common myeloid progenitors, and mature myeloid cells. Reducing *METTL14* levels in human HSPCs through short hairpin RNAs promotes myeloid differentiation *in vitro*. Additionally, using a conditional knockout of *METTL14* in mice demonstrated that its removal hinders the self-renewal capacity of HSCs.

Recent research employed *METTL14* and *METTL3* conditional knockout mice to investigate the influence of these m6A writer proteins on the regulation of HSC self-renewal in the bone marrow

of adult mice. The study revealed that deleting *METTL3* alone or in combination with *METTL14* in the hematopoietic system significantly elevates the frequency of HSCs in the bone marrow. However, the deletion of *METTL14* alone exerts minimal impact. Notably, the conditional deletion of *METTL14*, particularly *METTL3*, impairs HSC self-renewal activity in recipient mice. Furthermore, while the deletion of either *METTL3* or *METTL14* results in a significant decline in donor-derived myeloid cells in the peripheral blood, only the deletion of *METTL3* leads to a significant decrease in B- and T-cell lineages.[38]

RNA-binding motif protein 15, identified within the m6A methyltransferase complex, contributes to normal hematopoiesis.[39–41] It exhibits high expression in murine HSCs but is moderately expressed at other stages of hematopoietic development. Conditional knockout of *Rbm15* in mice impedes pro/pre-B differentiation and promotes the expansion of megakaryocytic and myeloid cells. Depletion of *Rbm15* leads to a bias toward granulocytic maturation.[41] A separate investigation revealed expression of *Rbm15* in lineage-depleted bone marrow cells, contrasting with its reduced expression in differentiated megakaryocytes and macrophages. Enforced expression of *Rbm15* suppresses myeloid differentiation, indicating that enforced expression refers to the artificial overexpression of *Rbm15* in experimental models, leading to the suppression of myeloid differentiation. *Rbm15* triggers Notch-induced HES1 transcription in hematopoietic cells, leading to the inhibition of myeloid differentiation.[40] Additionally, conditional knockout of *Rbm15* hinders the differentiation of long-term HSCs into short-term HSCs and leads to an abnormal increase in megakaryocyte development in mice.[39]

Studies on *YTHDF2* highlight the significance of m6A readers in regulating myelopoiesis. *YTHDF2*, an m6A reader protein, facilitates the decay of mRNA in its designated transcripts.[42] Lack of *YTHDF2* in mice leads to the growth of functional HSCs under hematopoietic stress and physiological situations, without inducing abnormal differentiation within cell lineages or hematopoietic malignancies.[43,44] Conditional knockout of *YTHDF2* in murine HSPCs does not display functional impairments; instead, it enhances repopulating and regenerative capabilities due to the activation of Wnt signaling following *YTHDF2* deletion.[43]

m6A modification in acute leukemia

Acute myeloid leukemia (AML)

AML is an extremely aggressive blood cancer that poses a life-threatening risk without adequate treatment. Despite advancements in risk assessment and therapeutic approaches, the 5-year survival rate for AML patients remains below 30%. There is a critical need for deeper comprehension of the underlying mechanisms of AML progression to develop potential treatments. AML represents the most prevalent form of leukemia in adults, comprising approximately 80% of cases. In the United States, the AML patient population reached 73,168 in 2020, with a yearly age-adjusted incidence rate of 4.3 cases per 100,000 individuals. The incidence of AML increases with age, and the median age at diagnosis is a crucial factor in understanding its prevalence. AML is responsible for about 2% of all cancer-related deaths in the UK, accounting for approximately 2,700 deaths annually.[45,46]

Recent studies underscore the significance of m6A RNA modification in cancer, particularly in AML progression. This modification profoundly influences the behavior of LSCs and extends beyond AML to various cancers, promoting tumor progression and drug resistance. For example, overexpression of m6A demethylase in relapse samples increases drug resistance in AML cells. Additionally, m6A readers play a role in promoting AML. The m6A methylase participates in various biological processes such as mammalian development, tumor generation, immunity, metastasis, stem cell renewal, and fat differentiation.[47–49] Understanding the intricate relationship between m6A and AML offers valuable insights into potential therapeutic targets and prognostic indicators for this hematopoietic malignancy. Identifying the principal regulators of m6A modifications in AML could lead to enhanced therapeutic approaches for patients with this disease.

Recent research has explored the complex connection between m6A writers and the development of AML. *METTL3* and *METTL14*, acting as key "writers", assume pivotal roles in governing RNA epigenetics. In AML, these writers exert significant influence over various stages of leukemia development.[50,51] Enhanced m6A modification, mediated by *METTL3*, disrupts key genes involved in AML initiation and progression. Additionally, *METTL14* and *WTAP*, another essential m6A writer, show similar implications in AML pathogenesis (Table 1).[37,40,52–86] Dysregulation of m6A writers in AML not only reveals molecular mechanisms but also presents potential therapeutic targets. Targeting these m6A writers may provide novel strategies for AML treatment by modulating RNA epigenetic landscapes. As our understanding of the intricate interplay between m6A writers and AML deepens, it opens avenues for developing targeted therapies aimed at disrupting aberrant RNA modifications associated with leukemia. Recent research highlights *METTL3*'s dual role in cancer. Traditionally known as a methyltransferase contributing to cancer progression through its methyltransferase activity, there is emerging evidence of an additional methyltransferase-independent function of cytoplasmic *METTL3*. This alternative mechanism is linked to promoting cancer advancement. Notably, *METTL3*'s cytoplasmic expression, regardless of its methyltransferase activity, plays a significant role in various facets of tumor progression, facilitating tumorigenesis, cell proliferation, invasion, migration, and accelerating the cell cycle. The use of KH12, a potent *METTL3* degrader, has shown promise in reducing m6A levels in MOLM-13 cells, leading to anti-AML effects by lowering c-MYC protein levels.[87] *METTL3* contributes to tumor progression by stabilizing lncRNA PSMA3-AS1, a recognized promoter of tumor advancement. PSMA3-AS1 influences FLT3-ITD+ AML by targeting miR-20a-5p, which regulates the expression of ATG16L1, a down-regulated mRNA in AML that impacts disease progression. This study integrates bioinformatics analysis, *in vitro*, and *in vivo* experiments to confirm *METTL3* and *PSMA3-AS1*'s regulatory roles in the disease process. Furthermore, *METTL3*'s role in stabilizing *PSMA3-AS1* suggests a potential cause for its increased expression. These findings offer valuable insights, serving as a foundation for tailoring targeted drugs to address FLT3-ITD AML.[52] *METTL3*, a methyltransferase-like 3, significantly influences the progression and chemoresistance of AML by impacting bone marrow mesenchymal stem cells (BMMSCs). Research has revealed diminished *METTL3* expression in AML BMMSCs. *In vivo* experiments using mice with *METTL3* depletion in BMMSCs showed elevated bone marrow adiposity, accelerated AML advancement, and increased resistance to cytarabine chemotherapy. *METTL3* deletion in BMMSCs significantly increased adipogenesis of BMMSCs, linked to m6A-dependent decrease in AKT1 expression, a serine/threonine kinase 1 within the AKT pathway. This process promotes chemoresistance in AML. Targeting *METTL3*-mediated BMMSC adipogenesis could serve as a therapeutic approach for AML.[53] Aberrant expression

Table 1. m6A modification in acute leukemia (AML & ALL)

Cancer type	m6A modifiers	Regulation/ Role in cancer	Biological functions	Mechanisms	Potential clinical application	Ref
AML	*METTL3*	Oncogene	*METTL3* has the potential to enhance the stability of PSMA3-AS1 RNA. PSMA3-AS1 might contribute to the progression of FLT3-ITD$^+$ AML by regulating autophagy levels through the miR-20a-5p/ATG16L1 pathway.	*METTL3*/PSMA3-AS1/ miR-20a-5p/FLT3-ITD+ PSMA3-AS1/FLT3-ITD+ miR-20a-5p/ATG16L1	Prompt screening and tailored therapy of FLT3-ITD+ AML	52
AML	*METTL3*	Oncogene	The downregulation of AKT1 expression in BMMSCs leads to a significant increase in adipogenesis. This downregulation occurs in an m6A-dependent manner, highlighting the role of m6A modification in modulating AKT1 levels.	*METTL3*/AKT1	Targeting *METTL3* modification as a therapeutic strategy in AML patient	53
AML	*METTL3*	Oncogene	Circ_0001187 diminishes mRNA m6A modification levels in AML cells by degrading the METTL3 protein.	miR-499a-5p/ RNF113A/*METTL3*	Potential therapeutic targeting of Circ _0001187 as a tumor suppressor in AML patient	54
AML	*METTL3*	Oncogene	*METTL3* was increased in AML cells, leading to induction of cell proliferation and inhibition of cell differentiation.	*METTL3*/c-MYC/ BCL2/PTEN	Therapeutic targeting of *METTL3* in AML	37
AML	*METTL3*	Oncogene	*METTL3* induces proliferation and suppresses differentiation in AML cells. Downregulation of *METTL3* leads to cell cycle arrest and causes leukemia cells to differentiate.	CEBPZ/*METTL3*/SP1	Potential therapeutic target for AML	77
AML	*METTL14*	Oncogene	*METTL14* can suppress the differentiation of normal myeloid cells and is essential for the progress and maintenance of AML via m6A modifications.	SPI1-*METTL14*-MYB/MYC	Targeting *METTL14* as an effective therapeutic method to treat *METTL14*-high AMLs	78
AML	*WTAP*	Oncogene	The expression of *WTAP* is increased in AML patients and its overexpression can be correlated with poor prognosis.	*WTAP*/SUCLG2-AS1/ miR-17-5p/JAK1	Novel therapeutic target for AML treatment	55
AML	*WTAP*	Oncogene	HIF1α promotes the expression of *WTAP* which markedly alters the transcriptome-wide m6A distribution and enhances cell proliferation in AML. *WTAP* is overexpressed and predicts poor prognosis in AML patients.	HIF1α/*WTAP*	–	56
AML	*WTAP*	Oncogene	*WTAP* promotes cell proliferation, tumorigenesis, and chemoresistance of AML.	*WTAP*/MYC	Novel prognostic marker and new treatment target for AML patient	79
AML	*WTAP*	Oncogene	miR-550-1 can suppress tumor progression that is downregulated in AML. miR-550-1 reduces the WWTR1 stability by the reduction in m6A levels through targeting *WTAP*.	miR-550-1/*WTAP*/ WWTR1/BCL-2 miR-550-1/*WTAP*/ WWTR1/CDK6/Rb/E2F1	Upregulation of miR-550-1 can be used as a valuable therapeutic strategy in AML	80
AML	*WTAP*	Oncogene	*WTAP* is upregulated in AML cells due to both decrease and increase of *METTL3*, which has oncogenic function only in the presence of *METTL3*.	*METTL3*/*WTAP*	–	81
AML	*WTAP*	Oncogene	*WTAP* promotes cell proliferation and chemoresistance and inhibits differentiation	Not available	A promising therapeutic target in AML	82
AML	*FTO*	Oncogene	Elevated *FTO* expression in relapse samples contributes to drug resistance in AML cells both *in vivo* and *in vitro*	*FTO*/FOXO3	Potential therapeutic target of the FTO-m6A-FOXO3 axis in AML patients	63

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Table 1. *(continued)*

Cancer type	m6A modifiers	Regulation/ Role in cancer	Biological functions	Mechanisms	Potential clinical application	Ref
AML	*FTO*	Oncogene	*FTO* is overexpressed in t(8;21) AML, which is positively linked with AML1-ETO. Furthermore, *FTO* induces the expression of AML1-ETO by suppressing *YTHDF2*-mediated AML1-ETO mRNA decay. Deletion of *FTO* significantly inhibits cell proliferation, enhances cell differentiation, and contributes to chemoresistance.	AML1-ETO/*FTO*/*IGFBP2*	Therapeutic target of AML1-ETO/*FTO*/*IGFBP2* pathway in t(8;21) patients with resistance to Ara-C	64
AML	*FTO*	Oncogene	BM-MSCs-isolated exosomes transport *FTO*, thereby enhancing the cancer aggressiveness, stem cell characteristics, and resistance to Cytosine arabinoside (Ara-C) chemotherapy in AML cells.	BM-MSCs-derived *FTO*-exo/lncRNA GLCC1/ IGF2BP1/c-Myc	Potential biomarkers for the diagnosis and therapy of AML patients	65
AML	*FTO*	Oncogene	SsD suppresses AML cell proliferation and induces apoptosis and cell cycle arrest by targeting *FTO*/m6A signaling.	Not available	Therapeutic targeting of *FTO*/ m6A and the clinical potential of Saikosaponin in AML patients	57
AML	*FTO*	Oncogene	*FTO* is highly expressed in AML and reduces m6A levels in ASB2 and RARA mRNA, thereby promoting leukemic oncogene-mediated cell transformation and leukemogenesis, and suppressing all-trans-retinoic acid (ATRA)-induced AML cell differentiation.	*FTO*/ASB2, RARA	A promising therapeutic strategy by targeting *FTO* to treat leukemia	58
AML	*FTO*	Oncogene	R-2HG disrupted the post-transcriptional enhancement of *PFKP* and *LDHB* expression (two vital glycolytic genes), mediated by *FTO*/m6A/YTHDF2, thus reducing aerobic glycolysis in leukemia.	FTO/m6A/PFKP/LDHB	Clinical application of potent FTO inhibitors for cancer therapy	59
AML	*FTO*	Oncogene	*FTO* promotes leukemogenesis. *FTO* inhibitors namely *FB23* and *FB23-2*, suppress proliferation, induce differentiation, and promote apoptosis in human AML cells.	Not available	Therapeutic targeting *FTO* by small-molecule inhibitors for potential treatment of AML	60
AML	*ALKBH5*	Oncogene	*ALKBH5* is regulated by chromatin state alteration during leukemogenesis of AML and is required for maintaining LSC function and tumor development.	KDM4C, MYB, Pol II/*ALKBH5*/AXL	The therapeutic target of *ALKBH5* for specific targeting LSCs	61
AML	*ALKBH5*	Oncogene	The expression of *ALKBH5* is increased in AML which correlates with poor prognosis. *ALKBH5* is essential for the progression and maintenance of AML and self-renewal of leukemia stem/initiating cells (LSCs/LICs).	*ALKBH5*/TACC3	The therapeutic potential of targeting *ALKBH5*/m^{6}A axis for the treatment of AML	62
AML	*YTHDC1*	Oncogene	*YTHDC1* interacted with HOXB-AS3, controlling its expression. Elevated levels of either *YTHDC1* or HOXB-AS3 stimulated the growth of THP-1 cells and LSCs while hindering their apoptosis leading to an escalation in the count of LSCs in the blood and bone marrow of AML mice.	*YTHDC1*/HOXB-AS3	Novel perspective for treatment of AML patients	72
AML	*YTHDC1*	Oncogene	*YTHDC1* is overexpressed in AML and is involved in the proliferation and survival of AML cells, as well as the self-renewal of leukemia stem cells (LSCs) in mice	*YTHDC1*/MCM4	Therapeutic potential of targeting *YTHDC1* for the treatment of AML patients	83

(continued)

Table 1. *(continued)*

Cancer type	m6A modifiers	Regulation/ Role in cancer	Biological functions	Mechanisms	Potential clinical application	Ref
AML	*YTHDC1*	Oncogene	nYACs prevent m6A-mRNA degradation by PAXT complex and exosome-related RNAs and also induce mRNA stability, AML cell survival, and undifferentiated state.	*YTHDC1*-m6A condensates (nYACs)	–	84
AML	*YTHDF1*	Oncogene	The expression of *YTHDF1* is increased in human AML samples, particularly in LSC. *YTHDF1* facilitates the translation of cyclin E2. Knockdown of *YTHDF1* diminishes the self-renewal ability and proliferation of AML cells.	YTHDC1/cyclin E2	A potential therapeutic target of *YTHDF1* for the treatment of patients with AML	69
AML	*YTHDF2*	Oncogene	The level of *YTHDF2* is overexpressed in AML patients, particularly in relapsed patients, and has a tumorigenic function in AML.	*YTHDF2*/miR-126	reduction of *YTHDF2* enhances HSC expansion and this makes it an ideal candidate for AML treatment	66
AML	*YTHDF2*	Oncogene	*YTHDF2* expression is increased in t (8; 21)-type AML patients, and knockdown of *YTHDF2* inhibits tumor cell proliferation *in vitro* and *in vivo*.	AML1/ETO-HIF1α loop/*YTHDF2*/TNFRSF1b	–	68
AML	*YTHDF2*	Oncogene	*YTHDF2* is overexpressed in AML patients which contributes to the disease initiation and progression. In addition, *YTHDF2* participates in the general integrity of LSCs function.	*YTHDF2*/TNFR2	Inhibition of *YTHDF2* as a unique therapeutic target to target LSCs and augment HSCs	67
AML	*IGF2BP1*	Oncogene	*IGF2BP1* promotes cell proliferation and chemoresistance and inhibits differentiation in AML cells.	*IGF2BP1*/ALDH1A1, HOXB4, MYB	Therapeutic potential of targeting *IGF2BP1* for the treatment of AML patients	85
AML	*IGF2BP2*	Oncogene	level of *IGF2BP2* is increased in AML, which correlates with a poor prognosis. *IGF2BP2* facilitates the progression of AML and enhances the self-renewal capacity of leukemia stem or initiation cells by controlling the expression of crucial targets such as MYC, GPT2, and SLC1A5 involved in glutamine metabolism pathways.	*IGF2BP2*/MYC, GPT2, and SLC1A5	The potential of targeting *IGF2BP2* as a novel strategy for the treatment of AML patients	70
AML	*IGF2BP3*	Oncogene	*IGF2BP3* is increased in AML and required for the survival of AML cells. Deletion of *IGF2BP3* inhibits apoptosis and decreases the proliferation of AML cells *in vitro* and *in vivo*.	*IGF2BP3*/RCC2	Therapeutic potential of targeting *IGF2BP3* for the treatment of AML patients	71
AML	*YBX1/ IGF2BPs*	Oncogene	*YBX1* expression level is upregulated in myeloid leukemia cells, which maintains AML cell survival. YBX1 deficiency promotes apoptosis and induces differentiation while decreasing the proliferation of AML cells *in vitro* and *in vivo*. Furthermore, *YBX1* through interacting with *IGF2BPs* maintains m6A-modified RNA.	*YBX1/MYC/BCL2* (mRNA)	The therapeutic targeting of *YBX1* in myeloid leukemia	86
ALL	*METTL3/ METTL14*	–	*METTL3* and *METTL14* reduction indicate a possible role in the pathogenesis and development of E/R-positive pediatric ALL.	Not available	New prognostic factors and targeted therapy in E/R-positive ALL relapse patients	73

(continued)

Table 1. *(continued)*

Cancer type	m6A modifiers	Regulation/ Role in cancer	Biological functions	Mechanisms	Potential clinical application	Ref
ALL	Writers/ Erasers	Oncogene	Elevated mRNA expression level of m6A writers (like *METTL3*, *METTL14*, *WTAP*) and m6A erasers (like *FTO* and *ALKBH5*) led to increased disease burden in patients with ALL.	Not available	–	74
ALL	*ALKBH5*	Oncogene	ALKBH5 increased USP1 mRNA stability and decreased m6A levels, which led to upregulation of USP1 and further promoted T-ALL development and chemoresistance.	ALKBH5/USP1/Aurora B	Potential biomarker for the chemoresistance treatment of T-ALL	40
ALL	*FTO*	Oncogene	FTO bound IRF8 mRNA and leading mRNA degradation, and reduced level of IRF8 accelerates the advancement T-ALL.	FTO/IRF8	Targeted therapy for T-ALL patients	75
ALL	*IGF2BP2*	Oncogene	IGF2BP2 is necessary to T-ALL cell proliferation via binding to T-ALL oncogene NOTCH1.	*IGF2BP2*/NOTCH1	Targeted therapy for T-ALL patients	76

AKT1, protein kinase b alpha; *ALDH1A1*, aldehyde dehydrogenase 1a1; *ALKBH5*, human AlkB homolog 5; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; ASB2, ankyrin repeat and SOCS box containing 2; ATG16L1, autophagy related 16-like 1; BCL2, B-cell leukemia/lymphoma 2 protein; BM-MSCs, bone marrow mesenchymal stem cells; FOXO3, forkhead box O3; *FTO*, fat mass and obesity-associated; GPT2, generative pre-trained transformer 2; HIF1α, hypoxia-inducible factor 1-alpha; IGF2BP, insulin-like growth factor-2 mRNA-binding protein; *IRF8*, interferon regulatory factor 8; JAK1, Janus-activated kinase 1; KDM4C, lysine (K)-specific demethylase 4C; *LDHB*, lactate dehydrogenase-B; MCM4, minichromosome maintenance complex component 4; *METTL3*, methyltransferase-like 3; mTOR, mammalian target of rapamycin; MYB, myeloblastosis oncogene; *MYC*, myelocytomatosis oncogene; NOTCH1, neurogenic locus notch homolog protein 1; PFKP, phosphofructokinase platelet; PSMA3, proteasome subunit alpha type-3; PTEN, phosphatase and tensin homologue deleted on chromosome 10; RARA, retinoic acid receptor alpha gene; RCC2, regulator of chromosome condensation 2; TACC3, transforming acidic coiled-coil containing protein 3; USP1, ubiquitin-specific protease 1; *WTAP*, Wilms' tumor 1-associated protein; WWTR1, WW domain-containing transcription regulator 1; YBX1, Y-box binding protein-1; *YTHDC1*, YTH domain-containing protein 1; *YTHDF1*, YTH N6-methyladenosine RNA binding protein 1.

of circular RNAs (circRNAs) has been shown to influence AML progression. The novel circRNA, Circ_0001187, contributes to poor prognosis by being downregulated in AML patients. Knockdown of Circ_0001187 promotes AML cell proliferation and inhibits apoptosis, while overexpression has the opposite effect. Circ_0001187 reduces mRNA m6A modification by promoting the degradation of *METTL3* protein. It acts as a competitive endogenous RNA, sequestering miR-499a-5p to upregulate RNF113A expression, which mediates *METTL3* ubiquitin/proteasome-dependent degradation. Additionally, low Circ_0001187 expression is influenced by histone acetylation and promoter DNA methylation. These results indicate that Circ_0001187 acts as a crucial tumor suppressor in AML via the miR-499a-5p/RNF113A/METTL3 axis.[54] In one study, the WTAP-SUCLG2-AS1-miR-17-5p-JAK1 pathway was identified as a crucial regulatory mechanism in AML development. Overexpressing SUCLG2-AS1 inhibited AML cell growth, migration, and invasion while enhancing apoptosis. SUCLG2-AS1 acts as a competitive endogenous RNA by sponging miR-17-5p, resulting in underexpression of JAK1. Additionally, *WTAP* was found to regulate m6A RNA methylation on SUCLG2-AS1 within AML cells, with increased *WTAP* levels linked to poor prognosis.[55] Another study focused on hypoxia-inducible factor 1α (HIF1α) in t(8;21) AML. They found that HIF1α, known for its abnormal overexpression in this type of leukemia, acts as an oncogene by stimulating the expression of *WTAP*. *WTAP* overexpression alters the distribution of m6A on a transcriptome-wide scale, contributing to enhanced cell proliferation in this leukemia subtype. Research also revealed that elevated *WTAP* expression is linked to adverse prognosis in t(8;21) AML patients. Silencing *WTAP* hindered leukemia cell proliferation, triggered apoptosis, and facilitated cell differentiation. Mechanistically, HIF1α was found to activate *WTAP* transcription by directly binding to the hypoxia-response element in the gene's promoter region. Targeting the HIF1α-WTAP axis, either pharmacologically or genetically, led to a reduction in m6A levels within the transcript of lysine demethylase 4B (KDM4B). This resulted in enhanced degradation of KDM4B, associated with reduced KDM4B expression and elevated levels of trimethylation of histone H3 at lysine 9. Suppression of KDM4B inhibited the growth of leukemia cells both in cell cultures and in murine models. In summary, the study emphasizes that HIF1α-mediated elevation of *WTAP* amplifies the malignant characteristics of leukemia cells. Moreover, it establishes a connection between m6A RNA methylation and histone methylation, demonstrating how the HIF1α-WTAP pathway influences the translation of m6A-dependent KDM4B, thereby affecting the overall development of t(8;21) AML.[56]

Reversible m6A modifications involve demethylases, specifically *FTO* and *ALKBH5*, known as "eraser" complexes. These complexes have been extensively studied in leukemia, particularly in AML. Inhibiting *ALKBH5*, an m6A eraser, effectively hampers AML development and curtails leukemia stem cell self-renewal.[57–62] The challenge of high relapse rates in AML, often attributed to chemotherapy resistance, was investigated using MeRIP-seq analysis on complete remission and relapse samples. The findings reveal dysregulated m6A methylation as a key factor in this process, with hypomethylated RNAs associated with altered cell differentiation. Notably, the m6A demethylase *FTO* exhibited heightened expression in relapse samples, contributing to increased drug resistance observed both *in vivo* and *in vitro* experiments. Knockdown of *FTO* resulted in enhanced cellular differentiation, particularly towards granulocytic and myeloid lineages, following treatment with cytarabine (Ara-C). The research identified *FOXO3* as a downstream target of *FTO*, and decreased hypomethylation

of *FOXO3* mRNA resulted in reduced expression, hindering cell differentiation. The *FTO*-m6A-*FOXO3* axis emerged as a central regulatory pathway influencing chemotherapy resistance in AML, emphasizing *FTO* as a promising therapeutic target.[63] A separate investigation delved into the chromosomal abnormality t(8;21)(q22;q22) in AML, leading to the formation of the AML1-ETO fusion protein. Despite the favorable prognosis associated with t(8;21) AML, 30–50% of patients experience relapse and drug resistance. The role of m6A in AML development and its connection with AML1-ETO and m6A-related enzymes remains unclear. The research aimed to investigate the interplay between *FTO* and AML1-ETO, an enzyme responsible for m6A demethylation. In t(8;21) AML, *FTO* exhibits heightened expression, particularly among individuals with primary refractory disease. An affirmative regulatory loop has been identified between AML1-ETO and *FTO*. AML1-ETO enhances the expression of *FTO* by PU.1-mediated suppression of *FTO* transcription. Concurrently, *FTO* augments AML1-ETO expression while impeding *YTHDF2*-mediated degradation of AML1-ETO mRNA. Suppressing *FTO* activity inhibited cellular growth, enhanced cellular differentiation, and rendered t(8;21) AML cells sensitive to Ara-C. *FTO* operates through the regulation of its mRNA targets, particularly insulin-like growth factor binding protein 2 (*IGFBP2*), via an m6A-mediated mechanism. Targeting the AML1-ETO/*FTO*/*IGFBP2* circuitry offers therapeutic potential for addressing resistance to Ara-C in patients with t(8;21) AML.[64] Another study investigated the effects of exosomes isolated from mesenchymal stem cells in the bone marrow (BM-MSCs) containing *FTO* on AML. Previous research associated AML progression and chemotherapy resistance with exosomes derived from BM-MSCs, but the specific functions and molecular mechanisms remained unclear. The study aimed to explore the impact of *FTO*-carrying exosomes derived from BM-MSCs on the characteristics of AML cells. Findings indicated that exosomes originating from BM-MSCs and containing *FTO* enhanced cancer aggressiveness, stem cell properties, and resistance to the chemotherapy drug Ara-C in AML cells. This study identified that *FTO*-exosome-mediated demethylation of m6A modifications occurred in an lncRNA known as Glycolysis-associated lncRNA of colorectal cancer (GLCC1), leading to increased stability and expression. Conversely, GLCC1 functions as a driver oncogene, promoting cellular expansion and bolstering resistance to Ara-C in AML cells. Additional investigations revealed that demethylated GLCC1 served as a scaffold, facilitating the assembly of the *IGF2BP1*-c-Myc complex and activating subsequent *c-Myc*-associated signaling pathways that promote tumor growth. Silencing experiments validated that the enhancing effects of *FTO*-exosomes derived from BM-MSCs on cancer aggressiveness and drug resistance in AML cells depended on the presence of GLCC1 and c-Myc. In conclusion, the study provided insights into the molecular mechanisms of AML aggressiveness and chemoresistance enhanced by *FTO*-exosomes derived from BM-MSCs, highlighting the potential of targeting the GLCC1-*IGF2BP1*-c-Myc axis for AML diagnosis and therapy in clinical settings.[65] In a study addressing chemotherapy challenges in AML patients, researchers investigated *FTO*'s role and the influence of the inhibitor Rhein on multidrug-resistant AML. They employed the Cell Counting Kit-8 reagent to evaluate Rhein's impact on cell growth, migration, and apoptosis in AML cells, including those resistant to multiple drugs. Results revealed *FTO* overexpression in multidrug-resistant AML. Rhein demonstrated significant dose- and time-dependent inhibitory effects on proliferation and migration, induced apoptosis, and inhibited the *AKT/mTOR* pathways, even in resistant cells. Combining low doses of Rhein with azacitidine sensitized certain AML cells to chemotherapy. Overall, Rhein appears promising for treating multidrug-resistant AML by suppressing growth, inducing apoptosis, and enhancing chemotherapy sensitivity, offering a potential therapeutic option for such challenging cases.[88]

Numerous investigations have highlighted the pivotal role of m6A-associated genes in regulating AML initiation, progression, and drug resistance, while also demonstrating their significance in normal hematopoiesis. The involvement of m6A in interacting with "reader" proteins, including *YTHDC1*, *HNRNPA2B1*, and *HNRNPC* in the nucleus, and *YTHDF1*-3, *IGF2BP1-3*, and *EIF3b* in the cytoplasm, regulates processes such as splicing, translation, nuclear retention, and mRNA stability. Several of these readers, notably *IGF2BP2*, *YTHDF2*, and *YTHDC1*, exhibit oncogenic characteristics in AML. In continuation of this discussion, these findings are depicted in Table 1. Subsequently, we delved into elucidating these studies. For instance, *YTHDF2* contributes to AML progression by enhancing miR-126 expression, a promoter of AML advancement and LSC self-renewal. Enhancing *YTHDF2* inhibition promotes the expansion of HSCs, rendering it a promising candidate for AML treatment.[66] In addition, *YTHDF2* is responsible for reducing the lifespan of different m6A transcripts, contributing to the functionality of LSCs. This includes transcripts such as the tumor necrosis factor receptor *TNFRSF2*, whose increased expression in *YTHDF2*-deficient LSCs primes the cells for apoptosis. Interestingly, *YTHDF2* does not play a critical role in normal HSC function; instead, its absence augments HSC activity. Consequently, *YTHDF2* is recognized as an exceptional therapeutic target, where its inhibition selectively targets LSCs while fostering the proliferation of HSCs.[67] The subtype of AML characterized by the t(8;21)(q22;q22.1) translocation, accounting for 4 to 8% of cases, represents a predominant category within AML and is characterized by frequent genetic abnormalities. *YTHDF2* demonstrates overexpression in patients with t(8;21) AML, which correlates with an increased risk of relapse and inferior relapse-free survival.[68] *YTHDF1*, recognized as an oncogene in AML, affects AML through the translation of Cyclin E2, and Tegaserod can block its oncogenic activity.[69] *IGF2BP2*, highly expressed in AML, especially in LSCs, regulates glutamine metabolism as an m6A reader, making it a potential therapeutic target.[70] *IGF2BP3*, specifically overexpressed in AML, plays a critical role in cell survival through interaction with regulator of chromosome condensation 2 mRNA and maintenance of m6A-modified RNA expression.[71] *YTHDC1*, which enhances LSC self-renewal in AML, increases the expression of HOXB-AS3 spliceosome NR_033205.1 via m6A modification, offering new insights for AML treatment.[72]

Acute lymphoid leukemia (ALL)

ALL, a specific type of acute leukemia, entails widespread growth, extensive infiltration, and suppression of regular hematopoiesis.[89] ALL is the most prevalent cancer in children under 15 years of age, amounting to 25% of such diagnoses.[90] There are two primary classifications of ALL based on the immune cell phenotype: B-cell ALL, the predominant type, and T-cell ALL, which is generally known for its heightened aggressiveness.[91] About 20–30% of ALL cases in adults and approximately 3–5% in children are characterized by the BCR-ABL fusion gene (BCR-ABL+ ALL). This subtype shows limited responsiveness to conventional chemotherapy, increases the risk of relapse, and is linked to an exceptionally poor outlook.[92]

Recent research uncovered the involvement of m6A modifications in the development of pediatric ALL harboring the ETV6/

RUNX1 (E/R)-positive fusion gene, which is detected in approximately 25% of pediatric B-cell ALL cases. Sun *et al*.[73] conducted a comparative analysis of *METTL3* and *METTL14* levels using RT-PCR (reverse transcription polymerase chain reaction) in a cohort of 37 pediatric patients with E/R-positive ALL, alongside six control subjects. They discovered a significant reduction in the expression levels of *METTL3* and *METTL14* in E/R-positive ALL compared to the control group, suggesting a potential contribution to both the onset and advancement of E/R-positive ALL. Another study found upregulation of m6A-modified methylases (*METTL3*, *METTL14*, and *WTAP*) and demethylases (*ALKBH5* and *FTO*) in pediatric patients with E/R-positive ALL, based on an investigation into the expression levels of m6A catalytic enzyme genes in 33 such patients.[74] Delving into various ALL subtypes is imperative to acquire a comprehensive understanding of the complete mechanism underlying m6A epigenetic modification in ALL.

Recent research indicated that ubiquitin-specific proteases (USPs) are implicated in T-cell ALL development and resistance to chemotherapy. Increased USP1 expression has been observed in glucocorticoid-resistant T-cell ALL patients and glucocorticoid-resistant cell line (CEM-C1) cells, correlating with a poor prognosis in T-cell ALL cases. Knockdown of USP1 heightened the sensitivity of CEM-C1 cells to dexamethasone, leading to decreased cell invasion, augmented apoptosis, and enhanced glucocorticoid receptor expression. USP1 modulates T-cell ALL chemoresistance through its interaction with and deubiquitination of Aurora B. *ALKBH5*, an m6A eraser, upregulated USP1 expression by reducing m6A levels and increasing mRNA stability in the USP1 transcript. The investigation confirmed that *ALKBH5* downregulation decreased USP1 and Aurora B expression, thus promoting dexamethasone sensitivity, apoptosis, glucocorticoid receptor expression, and inhibiting cell invasion in CEM-C1 cells. Furthermore, experiments conducted *in vivo* using mice demonstrated that the intravenous injection of sh-USP1 notably suppressed tumor growth, resulting in prolonged survival. These findings offer valuable insights for clinical research on tumor treatment.[93] Another study revealed that *FTO*, an m6A demethylase, plays a role in the progression of T-cell ALL by binding to m6A sites in the 3′ untranslated region of interferon regulatory factor 8 (*IRF8*) mRNA, leading to mRNA degradation through m6A modification. *IRF8*, a crucial transcription factor in determining hematological lineage commitment and capable of inhibiting T-cell ALL, is abnormally suppressed in T-cell ALL. Targeting the *FTO-IRF8* axis in therapy, by inhibiting *FTO*'s demethylase activity, significantly reduces leukemic cell proliferation and extends the survival of mice with T-cell ALL by restoring *IRF8* expression.[75]

In a related investigation, Feng *et al*.[76] explored the function of the m6A reader *IGF2BP2* in T-cell ALL. Their research provided evidence indicating that the increased expression of *IGF2BP2* plays a critical role in promoting tumor cell proliferation in T-cell ALL, facilitated by its interaction with the *NOTCH1* oncogene. A decrease in the expression level of *IGF2BP2* resulted in extended survival in a human T-cell ALL xenograft model. Moreover, the development of the *IGF2BP2* inhibitor *JX5* effectively suppressed *NOTCH1* activation and the progression of T-cell ALL, suggesting potential therapeutic benefits for T-cell ALL treatment.

m6A modification in chronic leukemia

Chronic myeloid leukemia (CML)

CML arises from the abnormal proliferation of multipotent hematopoietic stem cells in the bone marrow. Presently, CML has an annual incidence ranging from 0.7 to 1.8 per 100,000 individuals, making it the third most prevalent leukemia subtype.[94,95] CML is marked by a translocation event involving chromosomes 9 and 22, culminating in the creation of the oncogenic BCR-ABL1 fusion gene.[96,97] The resulting activation of the ABL1 protein tyrosine kinase induces modifications in various signaling pathways that regulate gene expression. Consequently, ABL1 tyrosine kinase inhibitors (TKIs) are extensively utilized for the clinical management and treatment of CML. Nonetheless, around 20% of CML patients develop resistance to TKIs.[98]

Recent reports suggest that *METTL3*, an RNA m6A modifier, plays a regulatory role in CML development (Table 2).[98–104] Ianniello *et al*.[98] discovered elevated expression of the m6A methyltransferase complex, composed of *METTL3* and *METTL14*, in CML patients. This complex is crucial for sustaining the growth of both primary CML cells and CML cell lines, whether they are responsive or resistant to TKIs such as imatinib. The study revealed *METTL3*'s direct regulation of the oncogenic pescadillo ribosomal biogenesis factor 1 (PES1) protein, affecting genes linked to various tumors. *METTL3* is crucial for activating genes involved in ribosome biogenesis and translation, and its depletion significantly hampers translation efficiency. Conversely, a deficiency in *METTL3* severely impairs the efficiency of mRNA translation for genes related to metabolism in organisms. Utilizing inhibitors targeting the *METTL3*/*METTL14* complex could serve as an effective therapeutic approach for eliminating TKI-resistant CML cells. Consequently, these findings suggest that *METTL3* functions as a new oncogene in the progression of CML and could serve as a promising therapeutic focus for TKI-resistant CML. Another study revealed that *METTL3* influences lncRNA nuclear-enriched transcript 1 (*NEAT1*) expression by regulating the miR-766-5p/CDKN1A axis. The elevated expression of NEAT1 reduced cell viability and triggered apoptosis in CML cells. The absence of *METTL3* led to *NEAT1* downregulation in both CML cell lines and peripheral blood mononuclear cells (PBMCs) of CML patients. Moreover, the direct binding of miR-766-5p with NEAT1 resulted in its upregulation in CML PBMCs, consequently counteracting the regulatory effects of *NEAT1* on the survival and programmed cell death of CML cells. The results also revealed that *CDKN1A*, the gene targeted by miR-766-5p, exhibited downregulation in CML PBMCs, and suppressing it reversed the effects of *NEAT1*. This mechanism enables *METTL3* to impact the advancement of CML and undertake a role conducive to oncogenesis.[99] Additionally, Lai *et al*.[100] found that *METTL3* dysregulation could lead to chemotherapy resistance and proliferation of CML cells. The findings reveal an oncogenic role for LINC00470, positively regulating *METTL3*, which in turn inhibits *PTEN* mRNA expression. Furthermore, dysregulation of the LINC00470/*METTL3* signaling pathway decreased the stability of *PTEN* and activated *AKT*, thereby promoting chemoresistance and suppressing autophagy in CML.

Other m6A modifiers also participate in CML progression. An inquiry has shown that KIAA1429, an m6A regulator, is significantly upregulated in patients in the blast phase of CML. This m6A regulator controls the overall extent of RNA m6A modification and amplifies adverse biological traits in CML cells, including migration, growth, and resilience to imatinib. Elevated levels of *KIAA1429* during the accelerated phase of CML enhance the stability of *RAB27B* mRNA through the m6A/*YTHDF1* axis, resulting in upregulated *RAB27B* expression and further advancement of CML. Rucaparib, a novel anti-cancer medication, suppresses

Table 2. m6A modification in chronic leukemia (CML & CLL)

Cancer type	m6A modifiers	Role in cancer	Biological functions	Mechanisms	Potential clinical application	Ref
CML	*METTL3*	Oncogene	*METTL3* regulates the PES1 level and ribosome biogenesis and translation-related genes, thereby leading to the proliferation of CML cells	*METTL3*/PES1 protein pathway	Promising therapeutic target for TKI-resistant CML	98
CML	*METTL3*	–	The deficiency of *METTL3* causes *NEAT1* downregulation in CML which abrogates the effects of *NEAT1* on cell viability and apoptosis of the CML cells	*METTL3*/NEAT1/ miR-766-5p/ CDKN1A pathway	Potential diagnostic indicator or therapeutical target for CML	99
CML	*METTL3*	Oncogene	Dysregulation of *METTL3*-induced chemoresistance and suppressed autophagy in CML cells	LINC00470/*METTL3*/ PTEN mRNA pathway	–	100
CML	*KIAA1429*/ *YTHDF1*	Oncogene	*KIAA1429* regulated the total level of RNA m6A modification, promoted proliferation and migration, and imatinib resistance in the CML cells	*KIAA1429*/ m6A/*YTHDF1*/*RAB27B* mRNA	New anti-cancer agents and potential treatment for the imatinib-resistant CML cells	101
CLL	*METTL3*	Oncogene	*METTL3* can regulate the levels of splicing factors through the translational control of m6A-modified mRNA, contribute to abnormalities in RNA splicing, and lead to disease progression in CLL	Not available	A promising treatment target for aggressive CLL	102
CLL	*HNRNPC, YTHDC1* and *RBMX*	Oncogene	*RBMX* and *YTHDC1* affect the biogenesis and modulation of circTET2/circTET2 interacting with *HNRNPC* contribute to lipid metabolism and CLL progression	CP028/*RBMX* and *YTHDC1*/circTET2 circTET2/*HNRNPC*/FAO and mTORC1pathways	Prognostic indicator and targeting treatment of CLL	103
CLL	*FTO*	Oncogene	*FTO* displays a regulatory role in tumorigenesis and progression of CLL and is linked to a poor prognosis in CLL patients.	Not available	Targeted treatment in progressed CLL	104

CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; FAO, fatty acid oxidation; FTO, fat mass and obesity-associated; HNRNPC, heterogeneous nuclear ribonucleoprotein C; *METTL3,* methyltransferase-like 3; mTOR, mammalian target of rapamycin; *NEAT1*, nuclear enriched abundant transcript 1; PES1, *pescadillo ribosomal biogenesis factor 1*; PTEN, phosphatase and tensin homologue deleted on chromosome 10; *YTHDC1*, YTH domain-containing protein 1; *YTHDF1*, YTH N6-methyladenosine RNA binding protein 1.

KIAA1429 expression, thereby decreasing CML cell proliferation and facilitating apoptosis. Indeed, inhibiting *KIAA1429* destabilizes *RAB27B*, suppressing CML proliferation and drug resistance, and enhancing sensitivity to imatinib.[101] LSCs in CML, which are often insensitive to TKIs, contribute to disease relapse.[105] A study revealed that RNA-binding proteins (RBPs) *YBX1* regulates the survival of CML LSCs via modulating m6A-mediated *YWHAZ* stability.[106] RBPs exert substantial regulatory influence on transcripts by regulating diverse processes such as RNA synthesis, alternative splicing, post-transcriptional adjustments, translation, and transport.[107] *YBX1* expression rises in CML cells and is essential for LSC survival. *YBX1* collaborates with RNA m6A reader *IGF2BPs* to augment the durability of the *YWHAZ* transcript in an m6A-associated manner. Therefore, targeting *YBX1* can provide a new potential method for CML treatment.[106]

Chronic lymphocytic leukemia (CLL)

CLL is a common hematological disorder worldwide, with a global incidence of 42 cases per 100,000, particularly affecting individuals over 80 years old at a rate of 30/100,000/year.[108] m6A modifications play crucial roles in the progression and viability of CLL patients, highlighting the potential for targeted interventions focusing on m6A modifications as a new treatment approach for advanced CLL.[109,110] RNA splicing defects are pervasive across the CLL transcriptome, underscoring the crucial involvement of RNA splicing dysregulation in the pathogenesis of the disease. Integrative transcriptomic and proteomic examinations have revealed an elevation in post-transcriptional RNA splicing proteins within CLL cells, with a heightened prevalence of splicing complexes identified as a standalone predictor of unfavorable prognosis. Dysregulation of RNA splicing may arise from mutations in splicing factors or irregular expression of upstream regulators such as *METTL3*, an m6A writer (Table 2). *METTL3* abundance is closely associated with increased splicing factor expression, as it controls the translation of mRNAs encoding splicing factors through m6A methylation-triggered ribosome pausing and recycling. This process results in dysregulated splicing, contributing to disease progression. Hence, *METTL3* emerges as a potential therapeutic target in aggressive CLL.[102] A distinct study explored the prognostic relevance of m6A modifications in CLL patients, particularly through the regulation of circRNAs, which play a crucial role in cancer metabolism. Wu and colleagues conducted an in-depth analysis of transcriptional sequencing data from 53 CLL patients to establish a prognostic signature based on m6A-modified circRNAs. Their research underscores the importance of m6A-modified circTET2 as a

prognostic marker for CLL patients. *BMX* and *YTHDC1*, identified as m6A regulators, function as RBPs and are modulated by CP028. This study reveals that the formation and control of circTET2, which is elevated in CLL, are influenced by the RBPs *RBMX* and *YTHDC1*. Furthermore, circTET2, interacting with HNRNPC, plays a role in modulating fatty acid oxidation and the *mTORC1* signaling axis, thus fulfilling energy requirements and promoting the growth of CLL cells. The concurrent inhibition of fatty acid oxidation and mTOR demonstrated increased efficacy, suggesting novel avenues for therapeutic intervention in CLL treatment.[103] Accumulating evidence suggests that *FTO* plays a critical role in cancer development. *FB23-2*, a newly developed inhibitor, specifically targets the demethylase activity of *FTO* m6A and has exhibited notable efficacy in the context of AML. Zhang *et al*.[104] explored the impact of *FTO* and *FB23-2* on CLL tumor development and progression. The study revealed the carcinogenic role of *FTO* in CLL progression and elucidated how the *FTO* inhibitor *FB23-2* regulates CLL cells. Increased *FTO* expression correlates with an unfavorable prognosis among CLL patients. *FB23-2* exhibited notable therapeutic promise by efficiently inhibiting cellular viability and inducing cell cycle stasis via methylation of m6A. The study provides a foundation for evaluating *FTO*-targeted interventions and introduces an innovative treatment strategy for advanced CLL.

Conclusions

The intricate world of epitranscriptomics, particularly the impact of m6A modification, has unveiled a new frontier in understanding and combating hematological malignancies. The regulatory network involving m6A modifiers, such as writers, erasers, and readers, is crucial in shaping gene expression, thereby influencing critical cellular functions in both normal hematopoiesis and the pathogenesis of leukemia. Hematological malignancies present significant challenges in healthcare, necessitating constant research and innovative therapeutic strategies. Exploring m6A modifications in these cancers has provided crucial insights into the dysregulation of gene expression, offering potential avenues for targeted interventions. The dynamic landscape of m6A modifications in normal hematopoiesis highlights their importance in maintaining the delicate balance of blood cell development. As we delve deeper into the molecular mechanisms underlying AML, ALL, CML, and CLL, it becomes evident that m6A modifications are key players in disease progression. The identification of specific writers, erasers, and readers associated with each leukemia subtype opens doors to novel therapeutic targets and personalized treatment approaches. The role of genes in the detection and management of cancer cannot be overstated. The dysregulation of m6A modifiers underscores the potential of targeted therapies in mitigating leukemia progression. The m6A RNA methylation landscape provides not only diagnostic and prognostic markers but also novel therapeutic avenues for overcoming treatment challenges and improving patient outcomes. Furthermore, the emerging field of epigenetic approaches, particularly focusing on m6A modifications, holds great promise. Targeting specific m6A regulators, utilizing advanced technologies to modulate RNA methylation patterns, and exploring epigenetic therapies present exciting prospects for the future of leukemia treatment. In conclusion, the importance of hematological malignancies cannot be underestimated, and understanding the intricate roles of genes and epigenetic modifications, especially m6A RNA methylation, is crucial for advancing cancer research and improving patient care. The ongoing exploration of these molecular landscapes provides hope for more effective and personalized therapeutic interventions in the challenging realm of hematological cancers.

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Conflict of interest

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Author contributions

Material preparation, data collection and analysis (ZM, PM, ZKK, SA), writing the first draft of the manuscript (ZM, PM). All authors contributed to the conception and design of the study. They commented on previous versions of the manuscript, read, and approved the final manuscript.

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