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Review

N6-Methyladenosine Role in Cancer: Learning from AML

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Abstract: We are currently assisting at the explosion of the epitranscriptomics, which studies the functional role of chemical modifications into RNA molecules. Among more than 100 RNA modifications, the N6-methyladenosine (m^6A), in particular, has attracted the interest of researchers all around the world. m^6A is the most abundant internal chemical modification in mRNA and it can control any aspect of mRNA post-transcriptional regulation. m^6A is installed by "writers", removed by "erasers", and recognized by "readers", thus, it can be compared to the reversible and dynamic epigenetic modifications in histones and DNA. Given its fundamental role in determining the way mRNAs are expressed, it comes as no surprise that alterations to m^6A modifications have a deep impact in cell differentiation, normal development and human diseases. Here, we review the proteins involved in m^6A modification in mammals, m^6A role in gene expression and its contribution to cancer development. In particular, we will focus on AML that, among first, has indicated how alteration in m^6A modification can disrupt normal cellular differentiation and lead to cancer.

Keywords: m^6A; RNA; AML; leukaemia; epitranscriptomics;

1. Introduction

Leukaemogenesis is caused by gene mutations and chromosomal aberrations resulting in changes of gene expression and, eventually, alteration of cell growth/differentiation programs [1]. Over the past decades, epigenetic modifications (e.g. DNA methylation and histone modifications) have been shown to play a significant role in this process and are now recognized as targets of therapy for different types of leukaemia and other haematological malignancies [2]. More recently, researchers have identified a new layer of gene expression regulation at the RNA levels that consists of reversible chemical modification of messenger RNAs (mRNAs), which led to the birth of the emerging field of "epitranscriptomics" [3,4]. Among more than 100 chemical modifications that can occur within various type of RNA molecules, N6-methyladenosine (m^6A) is the most abundant internal chemical modification of mRNA and is the one with the greatest impact on its dynamic regulation. The m^6A modification is installed by "writers" and removed by "erasers", in addition, it can recruit specific "reader" proteins. m^6A modification and the associated regulatory proteins play a critical role in gene expression by affecting different steps of the mRNA life, including splicing, nuclear export, stability and translation [4,5]. The reversible and dynamic nature of m^6A modification and its ability to fine-tune and coordinate gene expression programs has attracted the interest of many research groups in order to define its contribution to cell differentiation, normal development and human diseases [4]. In particular, it has been shown that deregulation of m^6A modification alters embryonic stem cell maintenance and differentiation [4]. As acquisition of stem cell properties and

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defects in cell differentiation are common features of many cancers, this indicates that alterations of m^{6}A levels might have an important role in cancer development.

In this review, we describe the mammalian proteins involved in m^{6}A modification and its effect on mRNA expression, with more emphasis on the m^{6}A role in acute myeloid leukaemia (AML), which, among first, has indicated how alteration in m^{6}A levels can disrupt normal cellular differentiation and contribute to carcinogenesis.

2. m^{6}A writers, erasers and readers

In mammalian cells, about 0.4% of adenosines inside mRNAs are m^{6}A modified (1–5 m^{6}A sites per transcript) [4,5]. m^{6}A modifications into mRNAs are catalysed by a heterodimeric core complex comprised of *methyltransferase-like protein 3* (METTL3) and *methyltransferase-like protein 14* (METTL14), which specifically methylates the adenosine within the DRACH motif (where D =A/G/U, R=A/G; H=A/C/U). METTL3 is the sole catalytic component of the complex while METTL14 functions in structural stabilization and RNA substrate recognition [6-8]. *In vivo*, the activity of METTL3/METTL14 is regulated by an additional complex (referred to as MACOM, m^{6}A-METTL-associated complex) composed of *Wilms tumour 1-associated protein* (WTAP), *Vir-like m^{6}A methyltransferase-associated* (VIRMA, also known as KIAA1429), *Cbl proto-oncogene like 1* (CBLL1, also known as Hakai), *RNA-binding motif 15* (RBM15), and *zinc finger CCCH-type containing 13* (ZC3H13) proteins [5] (Figure 1). Notably, the percentage of m^{6}A sites is less than the occurrence of the consensus motif, indicating that the core methylation complex is specifically recruited by the MACOM complex on specific sites within mRNAs. In particular, modified adenosines are specifically enriched in regions adjacent to the stop codon, 3′-UTR and within long internal exons [9,10]. It is very likely that additional cell-specific regulators of m^{6}A modification still need to be identified.

m^{6}A modification is essential for embryonic development. Deletion of METTL3 in mice is embryonic lethal. In particular, complete ablation of METTL3 and METTL14 in mESCs impairs the transition of naïve mESCs into the primed state and blocks the subsequent differentiation [11,12]. Similarly, deletion in mice of the regulatory MACOM complex components, WTAP and RBM15, produced embryonic lethality [13-15].

More recently, the U6 snRNA m^{6}A methyltransferase-like protein 16 (METTL16) has been shown to target intronic regions of pre-mRNAs and lncRNAs [16-18]. METTL16 binding sites do not overlap with that one of the METTL3/METTL14 methylation complex, indicating independent functions in m^{6}A modification. However, METTL16 plays an important role in regulating the cellular homeostasis of the methyl donor SAM [16-18], therein, indirectly contributing to global cellular methylation.

m^{6}A modification is a dynamic and reversible process. Removal of m^{6}A marks from transcripts occurs predominantly in the nucleus and requires the activity of the *alkB homologue 5* (ALKBH5) and *fat mass and obesity-associated* (FTO) proteins (Figure 1). FTO has an additional role in demethylating the N6-2′-O-dimethyladenosine (m^{6}Am) modification close to the mRNA CAP. This modification is installed by a still unknown modifying enzyme and has an independent role from m^{6}A in mRNA stability [19]. In mouse, these two enzymes have different tissue distribution with FTO enriched in brain and ALKBH5 in testes, suggesting that they can have diverse biological function and potentially affect different subsets of target mRNAs. Consistent with their different *in vivo* expression, ALKBH5 KO mice show impaired male fertility [20], while FTO KO mice exhibit increased postnatal death and reduced body mass [21].

The biological function of m^{6}A is largely mediated by m^{6}A reader proteins. The YT521-B homology (YTH) domain family of proteins (YTHDF1, YTHDF2, YTHDF3, YTHDC1 and YTHDC2), which contain an aromatic cage for specifically accommodating the m^{6}A, were among the first to be identified [22]. In addition, m^{6}A modification can induce structural alterations in transcripts, which either favour or abolish the interaction of specific RNA binding proteins [23].

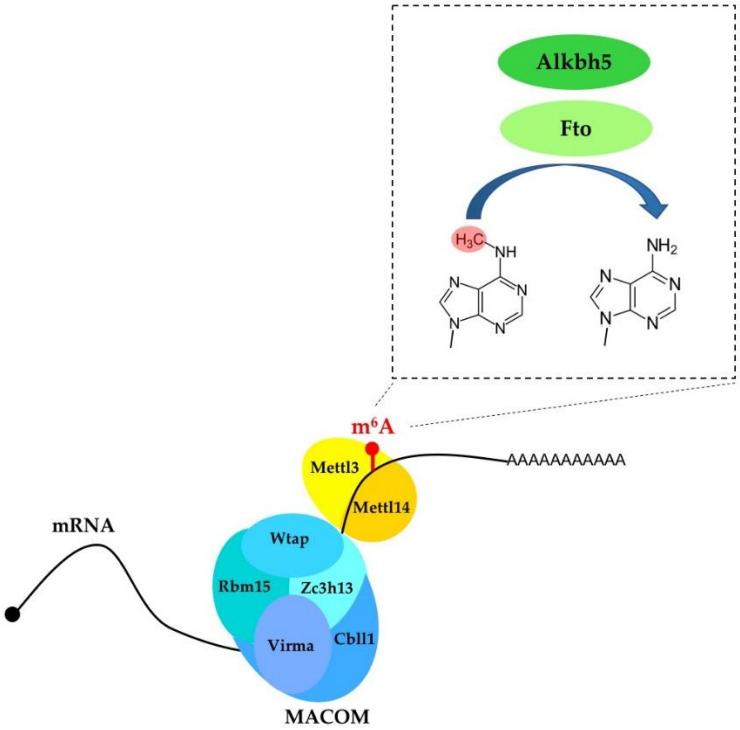

Figure 1. m⁶A modification is installed by the core Mettl3/Mettl14 catalytic complex and erased by the two demethylases Fto and Alkbh5. The MACOM complex, compose of Wtap, Rbm15, Virma, Zc3h13 and Cbll1, guides the core complex on specific mRNAs and contributes to select specific sites within single mRNA.

3. m⁶A effects on gene expression

m⁶A mediates its biological effects by influencing mRNA synthesis and function (Figure 2). Different biological functions of m⁶A modification are carried out by readers. During transcription, m⁶A is deposited on nascent RNA near splice junctions and within intronic regions [24,25]. The co-transcriptional nature of the m⁶A modification was also confirmed by CLIP experiments in which METTL3 and METTL4 were found associated with intronic regions [26]. Due to its dynamic feature, the distribution of m⁶A peaks is cell type specific and, eventually, also depends on developmental stages and changes in the environment. The core m⁶A methylation complex and the regulatory MACOM complex localize predominantly in nuclear speckles, where the mRNA splicing reaction occurs. Indeed, m⁶A levels modulate alternative splicing by direct and indirect mechanisms. The nuclear reader YTHDC1 directly binds to m⁶A modified pre-mRNAs and regulates splicing by recruiting the SR protein SRSF3 (*Serine and arginine-rich splicing factor 3*). By contrast, the splicing regulator SRSF10 is repelled by m⁶A modified regions [27]. The hnRNP protein HNRNPA2B1 also mediates alternative splicing by directly binding m⁶A modified pre-mRNA [28]. HNRNPA2B1 binding also stimulates the processing of microRNAs from host pre-mRNA introns [28,29]. In addition, m⁶A modified regions can undergo conformational changes, referred to as "m⁶A switch", which favour the interaction with RNA binding proteins, as in the case of the splicing regulator HNRNPC [30].

Another crucial step of gene expression that is regulated by m^{6}A is mRNA nuclear export. Silencing of METTL3 delayed mRNA export while downregulation of ALKBH5 has the opposite effect and accelerate export [20,31]. The nuclear reader YTHDC1 plays a role in this process recruiting the mRNA export receptor NXF1 through SRSF3 [32]. Once in the cytoplasm, m^{6}A modified mRNA are mainly regulated by the YTH reader proteins. In particular, YTHDF1 promotes translation while YTHDF2 stimulates mRNA decay by recruiting the translation initiation factor eIF3 and the CCR4-NOT deadenylase complex, respectively [33,34]. Interestingly, YTHDF1 and YTHDF2 share a large set of common target mRNAs. This apparently contradictory effects of the two readers may be required for the expression of transcripts that require rapid and transient control, such as in the case of gene expression programs that are activated upon responses to stress and during cellular differentiation. The YTHDF3 reader can cooperate with both YTHDF1 and YTFDF2 thereby promoting both translation and mRNA decay [35,36]. It has been suggested that YTHDF3 contributes to the RNA binding specificity of YTHDF1 and YTHDF2, which eventually bind m^{6}A methylated mRNAs as heterodimers [35,36]. Strikingly, YTHDF2 KO mice are embryonic lethal [37]. while deletion of YTHDF1 does not affect embryo development and it is compatible with life [38].

YTHDC2 has a dual role in controlling the expression of m^{6}A modified mRNAs, it both enhances their translation and accelerates their decay [39-41]. In contrast to the other YTH proteins, YTHDC2 contains other functional regions in addition to the YTH domain, including an ATP-dependent RNA helicases domain interspersed with two Ankyrin repeats, a known protein-protein interaction module that is responsible for the recruiting of the Xrn1 exoribonuclease [39-41]. In mouse, the protein is highly expressed in germ cells and is essential for male and female fertility. It has been suggested that the binding of YTHDC2 can accelerate protein synthesis as well as rapid mRNA decay to timely regulate gene expression during cell differentiation and developmental programs [39-41].

Additional direct m^{6}A cytoplasmic readers, which lack the YTH domain, are the translation initiation factor eIF3 and the ABCF1 proteins, which stimulate CAP independent translation of mRNA m^{6}A-modified in the 5′-UTR [42-44], and the IGF2BPs (IGFBP1, 2 and 3) oncogenic proteins [45], which increase the stability of modified mRNAs. Thus, the latter have an opposite role to the YTH reader proteins. Moreover, binding sites for IGF2BPs present a different pattern compared to the YTH proteins because are enriched in the 3′-UTR. Finally, the negative regulators of translation FMR1, and its paralogues FXR1 and FXR2, are indirect readers of m^{6}A modified transcripts. Conversely, the G3BP1, G3BP2 and ELAVL1 (also known as HuR) RNA binding proteins, which stabilize mRNA upon binding, are indirectly repelled by the m^{6}A modification [23,46]. Altogether, these data show the existence of a complex network of interactions between m^{6}A modification and RNA-binding proteins that can regulate mRNA expression at multiple levels.

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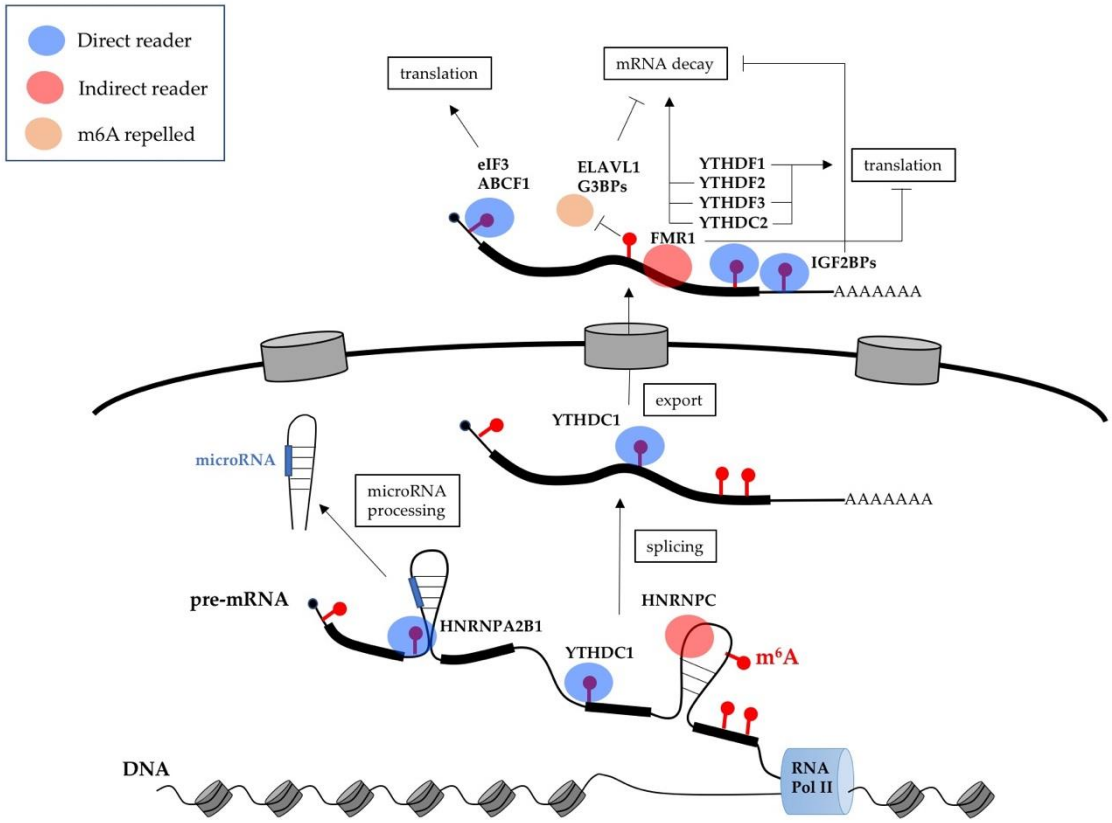

Figure 2. Functional roles of m⁶A modification on mRNA expression. Most of m⁶A effects on mRNA metabolism are mediated by reader proteins whose binding can be directly or indirectly affected by m⁶A (see main text for details).

4. m⁶A roles in AML and normal haematopoiesis

Defects in cell differentiation and uncontrolled proliferation are a hallmark of several cancers. AML represents a remarkable example of malignancy with these features [1]. It is characterized by an accumulation of immature leukemic cells (also referred to as blasts) in the bone marrow and blood. This accumulation arises from a failure of myeloid progenitors to mature and respond to normal regulators of proliferation. Chromosome aberrations, such as translocations, inversions and deletions, are detectable in about half of AML patients and are utilized for the classification and as prognostic factors of the disease. Moreover, a number of gene mutations as well as deregulated expression of genes have been identified and has provided insights into the mechanisms of leukaemogenesis [1]. Noteworthy, cells derived from different AML subtypes can be induced to differentiate by specific agents into cells that resemble normal counterparts. Therein, AML cells are a remarkable experimental system for studying the functional interactions between genes that control the correct balance between cell proliferation and differentiation; and how their deregulated expression may contribute to leukaemogenesis.

First clue of the involvement of the m⁶A modification in cancer was the identification of WTAP protein as specific interactor of the *Wilms' tumour* gene (WT1) [47], even if at that time the complex responsible for the m⁶A modification and its role in mRNA metabolism were still unknown. WT1 was initially discovered as a tumour suppressor gene but in leukaemia, where is generally overexpressed and associated with poor prognosis, it acts as an oncogene [48]. Later on, WTAP

protein was found up-regulated in AML and its downregulation in AML cell lines decreased proliferation, induced apoptosis and delays leukaemia progression in recipient mice [49]. At the same time, WTAP was identified as a regulatory factor for the m^{6}A methylation complex [50], therein m^{6}A modification comes into focus of AML studies.

Notably, AML is one of the cancers with the highest levels of both METTL3 and METTL14 expression (data from the Cancer Genome Atlas, TCGA) and, more importantly, METTL3 and METTL14 were found overexpressed in AML cells compared to normal hematopoietic progenitors [51-54]. Consistent with METTL3 and METTL14 playing an oncogenic role in AML, overexpression of both genes in AML cell lines and primary blasts increased proliferation, while their downregulation impaired proliferation and resulted in a strong induction of apoptosis [51-53]. The oncogenic function of m^{6}A was also demonstrated in primary cells derived from an AML mouse model carrying the MLL-AF9 fusion gene and the FLT3 internal tandem duplication (FLT3-ITD), which characterized aggressive AML subtypes. In this case, a genome-wide CRISPR/Cas9 screening identified METTL3, METTL14 and METTL16 as critical genes for AML survival [52]. More importantly, the METTL3/METTL14 methylation complex was found to promote the development of AML and maintain leukaemia-initiating cells in transplantation mouse models [51-53]. These effects of METTL3 and METTL14 in human and mouse AML cells are abolished by catalytic inactive METTL3 or METTL14 mutant impaired in target recognition of the methyltransferase complex, therein, they depend on the deposition of m^{6}A modification. In AML cells, METTL3 and METTL14 bound predominantly to TSS, even if METTL3 binding did not always correlate with METTL14, and early m^{6}A co-transcriptional deposition promoted translation of mRNAs relevant for AML proliferation, such as c-MYC, BCL2, PTEN, SP1 and MYB [51-53]. The transcription factor CEBPZ, which as an important role in hematopoietic differentiation, was shown to recruit METTL3 on gene promoters [52]. CEBPZ was identified as a novel recurrently mutated gene in AML [55,56], suggesting that in this leukaemia might be lost the co-transcriptional recruitment of METTL3.

Interestingly, even if aberrant alternative splicing plays a relevant role in AML [57] and m^{6}A modification has an established role in regulating alternative splicing, mRNA translation has been identified as the main regulatory step deregulated by m^{6}A in AML [51-53]. Therein, the YTHDF1 reader should mediate most of the observed phenotype in AML. However, in view of the pleiotropic nature of the m^{6}A modification, it is very likely that additional functions for the other m^{6}A readers will be soon characterized in AML.

In AML, METTL3 has been also shown to be mis localized to the cytoplasm and to associate with translating ribosomes [54]. Similar results were also found in lung cancer [58]. It was also demonstrated that cytoplasmic METTL3 can promote translation of specific mRNAs independently from its catalytic activity [54,58]. Moreover, higher levels of cytoplasmic METTL3 results in concomitant increase of WTAP protein expression [54]. As WTAP mRNA expression is not elevated in AML [54], this latter mechanism might be relevant to increase WTAP protein levels concomitantly to the METTL3/METTL14 core complex and sustain its oncogenic role in AML.

Another link between m^{6}A and AML comes from RMB15, a component of the MACOM complex. Some forms of Acute Megakaryoblastic Leukaemia (AMKL), a subtype of paediatric AML characterized by abnormal megakaryoblasts, carry a chromosomal translocation between RBM15 and MKL1 [59], a transcription coactivator that regulates the expression of genes involved in cell growth. Notably, RBM15 directly binds to and controls the alternative splicing of transcripts encoding for key hematopoietic differentiation genes such as GATA1, RUNX1, c-MPL and TAL1 [60]. Therein, it is possible to speculate that the RBM15 fusion protein might also affect MACOM function and produce a deregulation of the m^{6}A modification within transcriptome that will eventually results in aberrant splicing regulation. Conditional-knockout mice of RBM15 in the hematopoietic compartment have been generated. Deletion of RBM15 caused a block in B cell differentiation and myeloid and megakaryocytic expansion [15], indicating that mis regulation of m^{6}A deposition may affect hematopoietic differentiation *in vivo*. However, the relationship between RBM15 depletion and m^{6}A modification in mouse models has not yet been assessed.

m^{6}A levels depend also on the activity of erasers and readers. Elevated expression of FTO has been reported in AML subtypes carrying MLL-AF9, PML-RARA and FTL3-ITD translocation, respectively [61]. Downregulation of FTO in cell models carrying these fusion products decreased their proliferation capacity. Moreover, it was shown that R-2HG, an anti-leukemic compound that inhibits a series of Fe(II)/a-KG-dependent dioxygenases [62], targets also the FTO demethylase [63]. In particular, FTO inhibition by R-2HG resulted in decreased expression of the MYC oncogene and the transcription factor CEBPA. These results are in sharp contrast with the pro-leukemic roles of METTL3 and METTL14 demonstrated by independent groups, in many cases by using cells with the same mutations in which the oncogenic role of FTO was demonstrated [51-53]. Moreover, it was shown that the depletion of FTO by CRISPR/cas9 has no effect on AML growth [51] and the Project DRIVE, a large-scale knockdown screening in cancer cell lines, detected no general FTO-dependency of leukaemia cells [64]. These discrepancies may be due to the conditions used in that studies, rather than a specific oncogenic effect of FTO in AML. It should be also pointed out that there is currently a great debate on the effective contribution of FTO as specific m^{6}A demethylases [65].

METTL3 and METTL14 are also highly expressed in mouse and human HSCs and their expression decrease during myeloid differentiation [51-53]. As observed in AML cell lines, METTL3 and METTL14 silencing in human and mouse HSCs reduced proliferation capacity and stimulated myeloid differentiation [51-53]. Moreover, overexpression of a catalytic active METTL3 or METLL14 in HSCs promoted proliferation and inhibited myeloid differentiation [51-53], indicating that increased m^{6}A levels might alter the normal differentiation pathway in HSC, resulting in accumulation of progenitor cells.

Downregulation of METTL3 in zebrafish embryos and in the mouse aorta-gonad-mesonephros (AGM), the region of the primary origins of the definitive HSC in vertebrates, strongly affect HSC production by repressing Notch signalling [66]. It was also shown that the embryonic METTL3 function in the hematopoietic system is mediated by the YTHDF2 dependent decay of Notch encoding mRNA [66]. Similar results were obtained upon conditional METTL3 KO in the mouse AGM region [67], therein, indicating an evolutionally conserved function of METTL3 in HSPC specification in vertebrates. Conditional KO mice of METTL3 and METTL14 in the adult hematopoietic system have been also produced [53,68]. Strikingly, deletion of METTL3 expands the HSCs in adult bone marrow [68], contrary to what occurred in isolate HSCs, indicating a crucial role for METTL3 in regulating the quiescence of HSCs *in vivo*. Surprisingly, this phenotype was not detected upon conditional deletion of METTL14 [68], which is required for METTL3-mediated m^{6}A modification on target RNAs. However, in transplantation experiments, mouse HSCs deleted for METTL3 or METTL14 showed reduced repopulation ability and the deletion of METTL14 from primary leukaemia blasts significantly delayed leukaemia onset in recipient mice (Weng 2018; Yao 2018). Notably, the downregulation of the m^{6}A methylation complex in normal HSCs did not induce massive apoptosis as observed in AML [51,53,66,68], even if the molecular mechanism responsible for this different behaviour is still not completely clear. In view of this, it is tempting to speculate that AML cells will show higher sensitivity to future chemical inhibitors of the m^{6}A writing complex than normal HSCs providing new therapeutic options for AML treatment.

5. Conclusions

Advances in the understanding of AML pathogenesis have been remarkable in these years, but treatment has changed little in the paste decades and is mainly based on chemotherapy. Moreover, in AML patients, relapse is frequent and generally accompanied by very poor prognosis. For this reason, many studies are now focusing on the development of new treatments that may flank, replace or follow standard therapy. Epigenetic modifications to histones and DNA have established roles in normal haematopoietic development and leukaemia. More importantly, epigenetics drugs that specifically target these modifications are currently in clinical trials for the treatment of AML. Until

recently, little attention has been given to understanding the role of RNA chemical modifications and its contribution to human cancer, even if their presence within different RNA species have been known for decades. The explosion of the epitranscriptomics is deeply changing our approaches to cancer biology studies. In the last year, we have assisted to many acclaimed revolutions in the RNA field that have deeply transformed our understanding of how gene expression is regulated, however, none of these has led to major innovations in tumour therapies. Even if the road ahead is still long, it appears to be different this time with the epitranscriptomics. Currently, alteration of m^6A levels has been found closely associated with various kinds of cancers and to play important roles in metastasis and drug resistance [69,70]. AML, in the first place, have indicated how alteration of m^6A modification can disrupt normal cellular differentiation and contribute to cancer development. In analogy with epigenetic modifications, it is predictable that the activity of the m^6A modifying enzymes might be easily targetable by chemical compounds and, eventually, provide major innovations in future cancer therapies. In this regard, AML is paving the way.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ABCF1	ATP binding cassette subfamily F member 1
AML	Acute myeloid leukaemia
CEBP	CCAAT enhancer binding protein
CLIP	Cross-linked Immunoprecipitation
ELAVL1	ELAV like RNA binding protein 1
G3BP	G3BP stress granule assembly factor
hnRNP	Heterogeneous nuclear ribonucleoprotein
HSC	Hematopoietic stem cell
HSPC	Haematopoietic stem/ progenitor cells
IGF2BP	Insulin-like growth factor 2 mRNA-binding protein
KO	Knock-out
LncRNA	Long non-coding RNA
mESC	Mouse embryonic stem cells
R-2HG	R-2-hydroxyglutarate
SAM	S-adenosylmethionine
TSS	Transcription start site
UTR	Untranslated region

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