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REVIEW

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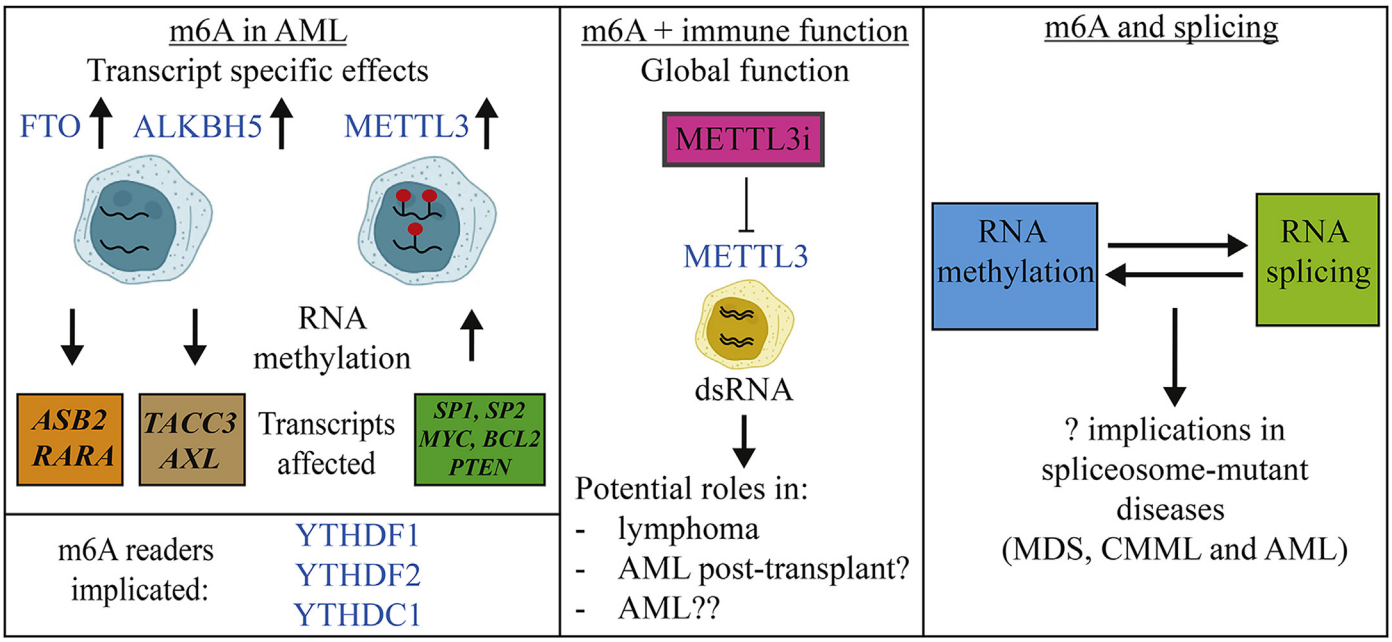
RNA methylation: where to from here for hematologic malignancies?



RNA methylation: where to from here for hematologic malignancies?

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RNA methylation and the machinery that regulates or "reads" its expression has recently been implicated in the pathogenesis of acute myeloid leukemia (AML) and other hematologic malignancies. Modulation of these epigenetic marks has started to become a reality as several companies around the world seek to leverage this knowledge therapeutically in the clinic. Although the bases of observed activity in AML have been described by numerous groups, the exact context in which these therapies will ultimately be used remains to be properly determined. While context is likely to be of great importance here, a more "global" mechanism of action might allow for more widespread applicability to multiple disease subtypes. In other areas such as the myelodysplastic and other preleukemic syndromes, data remain sparse. Ongoing work is needed to determine whether therapeutic modulation of RNA modifications is a viable and biologically plausible approach in these cases. Regardless of the outcomes, this is an exciting era for "epitranscriptomics" as we navigate a pathway forward. Here, I describe the current knowledge around RNA methylation and hematologic malignancies at the end of 2024 including some of the relevant questions that are yet to be answered.

HIGHLIGHTS

- Modulating RNA methylation is a viable therapeutic option in acute myeloid leukemia (AML). Context likely matters.
- A global effect of modulating RNA methylation may be relevant in AML.
- The m6A modification and mRNA splicing bidirectionally impact each other.
- RNA methylation's role in the myelodysplastic syndromes is yet to be determined.
- RNA modifications m7G and 5mC are also implicated in the pathogenesis of AML

Although RNA modifications were first described numerous decades ago [1,2], the significance of these modifications has remained somewhat unclear until recently. This is likely in part due to the sheer number of modifications identified to date [3] and our inability to therapeutically modulate them until recently.

Of all modifications, RNA methylation is by far the most abundant and m6A is the most well-characterized - representing methylation of adenosine at position 6 [3]. Dynamic regulation of m6A is mediated by the methyltransferase (METTL3) complex [4], which cotranscriptionally "writes" m6A [5] and the demethylase enzymes ALKBH5 and FTO, which act to remove or "erase" this modification [6,7] Various "reader" enzymes are also capable of mediating downstream functions, which include effects on RNA stability, splicing, and mRNA translation to protein [8–10] The subsequent discovery that some of these related proteins are overexpressed or essential for the survival of various malignancies [11–15], has driven a wave of global interest from which the field of "epitranscriptomics" or RNA epigenetics [16] has been born.

On this basis, a new therapeutic dimension has emerged [17–21] operating on the premise that modulating the activity of these enzymes might ultimately prove efficacious in the treatment of cancer [18,22], cardiovascular disease [23], viral infections [24,25], and even Alzheimer disease [26]. Within the writer complex, METTL3 is the catalytic component with capacity to bind S-adenosylmethionine (SAM). Its binding partners include METTL14 [4], which functions as an RNA scaffold platform and is important in substrate recognition through its binding to H3K36me3 [5]; and WTAP [27] – which likely plays a role in the cellular localization of the complex [21].

This review focused on the role of RNA methylation across various hematologic malignancies in 2024 with a predominant focus on m6A. From this, potential questions of relevance in each of these areas are highlighted. Although yet to be rigorously peer-reviewed, an update on therapeutic developments across various RNA modifications will also be presented.

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0301-472X/

https://doi.org/10.1016/j.exphem.2024.104694

m6A IN AML: A TRANSCRIPT-SPECIFIC BASIS OF ACTIVITY

Based on the Cancer Genome Atlas (TCGA) data [28], METTL3 expression is often increased in AML at both the mRNA and protein levels [11]. Furthermore, CRISPR-based screening approaches have shown it to be differentially essential (alongside METTL16) for leukemic growth both in vitro and in vivo [12,29]. In this context, it is likely that METTL3 acts to preserve the undifferentiated phenotype associated with AML. On this basis, targeting of METTL3 induces differentiation and apoptosis of leukemic cells [18] delaying disease progression in vivo in recipient mice [30]. Several studies have hypothesized that the basis of METTL3's oncogenic function in AML relates to enhanced translation of specific proteins including SP1 and SP2 driving MYC expression [11,12] and BCL2 and PTEN [11] (Figure 1). This is potentially the result of reduced ribosome stalling [12]. Loss of METTL3 likely leads to transcript stabilization and reduced translational efficiency driving differentiation and apoptosis.

In contrast, it warrants mentioning that machinery with seemingly opposing function to METTL3 has also been implicated in leukemogenesis (e.g., ALKBH5 [15,31] and FTO [32–34]) (Figure 1). ALKBH5 is overexpressed in a subset of AML where it is required for both initiation and maintenance of leukemia stem cells and associates with a poor prognosis [15]. It is believed to signal through MYC and p21 by way of its posttranscriptional regulation of the oncogene, *TACC3*. Alternative groups have postulated that ALKBH5 in AML serves to regulate mRNA stability of the receptor tyrosine kinase *AXL* [31]. For FTO, some might argue the "opposing function" dichotomy can be explained by a slight difference in substrate specificity (i.e., FTO demethylates the dimethylated form of m6A → m6Am [35]), however, the overall level of m6Am in a cell is much less than m6A. This suggests that the main substrate of FTO in AML cells is still m6A [36]. In this case, the specific transcripts impacted are almost certainly different as well. The requirement for FTO in AML has been highlighted by some [34] and is potentially mediated by targeting of transcripts that are important for differentiation including *ASB2* and *RARA*. Specific subtypes of AML that overexpress FTO are more likely to demonstrate greater dependence on it including MLL-rearranged AML [34].

METTL14, by virtue of its association with the METTL3–writer complex has also been implicated as an oncogene in AML [30]. Studies indicate that METTL14 is negatively regulated by *SPI1*, which encodes for the PU.1 transcription factor [30]. Although the loss of METTL14 generates a similar phenotype to that of METTL3, this tends to be more subtle in nature. It is also unclear whether this is functionally the same, because the two proteins bind different stretches of chromatin.

In other studies, readers of m6A have also been implicated in leukemogenesis. YTHDF2 has been shown to be important for AML initiation and propagation, but not steady-state hematopoiesis [37,38]. Similarly, although YTHDF1 is dispensable for normal hematopoiesis, it is necessary for the ongoing self-renewal, proliferation, and leukemic capacity of certain AML cells [39]. Meanwhile, YTHDC1 appears to promote sequestration of AML-promoting m6A mRNAs through nuclear condensate formation preventing their degradation by the exosome [40]. As indicated above, it is likely these effects are context dependent – an area not fully explored as yet. Although other RNA-binding proteins have also been implicated in leukemogenesis, in-depth discussion of these is beyond the scope of this current review. A summary of modifiers and readers of m6A and their

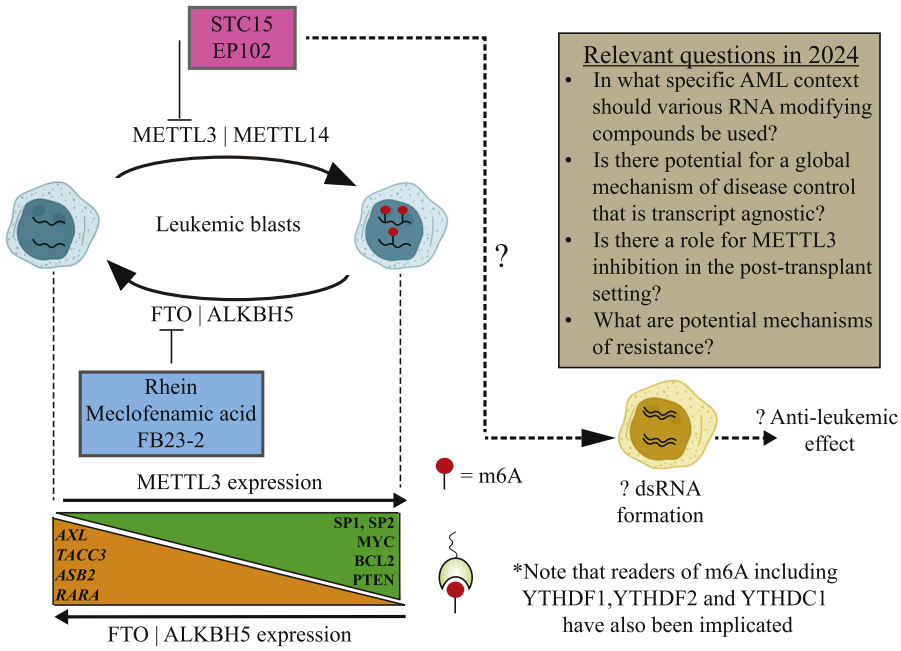

Figure 1 The postulated role of m6A in the pathogenesis of AML. Denoted are the key methylase and demethylase enzymes with their most recently described therapeutics. Relevant targets that are likely affected are shown in the bottom triangles and how these relate to protein expression and methylation state. The potential for a transcript-agnostic mechanism of action is highlighted in the bottom right. Current questions that are relevant in this context are shown in the box. *AML* = Acute myeloid leukemia.

Table 1 Proposed role of m6A modifiers and readers in normal hematopoiesis and in AML

Target of interest	Phenotype in normal hematopoiesis	Potential role in AML
METTL3	– Essential for normal embryonic development [42–44] – Loss of METTL3 is associated with hematopoietic failure = perinatally lethal [41]	– Overexpressed in AML at mRNA + protein levels – Preserves undifferentiated phenotype associated with AML – Likely mediates effects by enhancing translation of SP1, SP2, BCL2, and PTEN [11,12]
METTL14	– Inhibits differentiation of hematopoietic stem and progenitor cells (HSPCs) [30]	– Oncogene implicated in AML – phenotype more subtle and less of a dependency compared with METTL3 [30]
YTHDF1	– Dispensable for normal hematopoiesis	– Necessary for AML progression – an important role in self-renewal and proliferation of leukemic cells [39]
YTHDF2	– Not important for steady-state hematopoiesis [38]	– Role in the initiation and propagation of AML [37]
YTHDC1	– Regulator of microRNA maturation; required for HSC maintenance and self-renewal [45]	– Acts to sequester AML-promoting m6A mRNAs [40]
FTO	– Not common essential unlike METTL3	– Potential oncogene in AML through its impact on *ASB2* and *RARA* [32–34]
ALKBH5	– Not essential for normal hematopoiesis [31]; levels are inversely correlated with degree of "stemness" [15] – likely plays an important role in stress-induced hematopoiesis	– Overexpressed in a subset of AML; necessary for leukemia initiation and maintenance; effects likely mediated through its posttranscriptional regulation of the oncogene, *TACC3* [15] or the receptor tyrosine kinase *AXL* [31]

AML = Acute myeloid leukemia.

role in normal hematopoiesis and leukemogenesis is provided in Table 1 [11,12,15,30–34,37–45].

In sum, the above findings speak to the biology of RNA-modifying enzymes and how these are implicated in leukemogenesis. Additionally, however, m6A machinery may also bear prognostic significance. Analysis of TCGA data indicates that mutations or copy number variations of m6A machinery have a strong association with TP53-mutant mutations in AML predicting for worse outcomes (worse overall survival (OS) and event-free survival (EFS)) [46]. Moreover, mutations within METTL3, METTL14, YTHDF1, FTO, and ALKBH5 also associated with poorer cytogenetic risk disease. This review suggests that molecular analyses of m6A regulatory genes could be useful to risk stratify those with worse outcomes – in the absence of FLT3 or TP53 mutations. In the case of ALKBH5, these findings have also been verified by independent groups [15,31].

TRANSCRIPT-SPECIFIC EFFECTS VS. GLOBAL IMPACT OF RNA METHYLATION

That opposing RNA-modifying machinery can drive leukemogenesis is explained to some degree by the transcript-specific basis of activity. This suggests that context matters. More recently, however, we and others have described a more global impact associated with modulating RNA methylation in the areas of normal hematopoiesis and antitumor immunity. These effects appear to be context-agnostic and may, therefore, have wider-ranging applicability. Key to these effects is that loss of RNA methylation associates with the formation of dsRNA [22,41,47] inducing an inflammatory "milieu" that has further downstream effects.

Studies in hematopoiesis have highlighted a key role for METTL3 in hematopoietic development. In zebrafish, loss of Mettl3 associates with profound hematopoietic failure resulting from impaired endothelial to hematopoietic transition [42]. Subsequently, a number of Mx-Cre–based models suggested similar findings [43,44,48], but the requirement for pIpC (polyinosine-polycytidylic acid) for induction made it difficult to tease out whether the phenotype related directly to METTL3 or whether it was the result of an immune response to the pIpC. More recently, the most convincing study by Gao et al. [41], confirms that early loss of METTL3 (mediated by Vav-Cre) does indeed cause an arrest in hematopoietic differentiation. Although LSK (lineage-negative, Sca-1 positive, Kit-positive) cells were increased in this model, they appeared to be functionally deficient and there was significant failure to thrive perinatally.

In the context of malignancy, we have also demonstrated that catalytic inhibition of METTL3 can be used to co-opt the immune system to mediate antitumor activity [22]. This appears to have broad applicability beyond a single tumor type – as we initially demonstrated in breast cancer, melanoma, and lymphoma models. Some preliminary data in mice also suggest this treatment can induce a durable immune memory at the time of antigen rechallenge [49]. Alternative models of tumor surveillance have also been postulated. Han et al. [50] report the impact of YTHDF2 deficiency (an m6A reader) on lysosomal cathepsins resulting in increased neoantigen presentation by antigen-presenting cells. These antigens are detected by dendritic cells and result in improved tumor clearance. In both cases, the effects mediated appear to be transcript agnostic.

At this time, it still remains to be determined whether an immune basis for activity might be relevant in driving an antileukemic effect (Figure 1). This is exemplified by the marked success of allogeneic transplant in the treatment of AML where a graft-vs.-leukemia effect plays an essential role in disease control [51]. Studies of immunotherapy use in AML have otherwise demonstrated little or modest benefit at best [52]. As such, the context in which these modifiers and readers of RNA methylation are manipulated will be highly important moving forward. Unless a global impact of modulating RNA methylation in AML can be demonstrated, the "one-size-fits-all" approach is unlikely to yield significant benefits. Here lies the challenge – as an example, in what context should a METTL3 inhibitor be used versus an FTO

inhibitor? Which subtypes of AML are likely to be more responsive to which of these therapies based on their gene and protein expression levels at baseline? As an example, an FTO inhibitor may prove to be more efficacious in APML (acute promyelocytic leukemia) due to its dependence on RARA fusions and higher expression of FTO, along with MLL-rearranged leukemias and those associated with *FLT3* and/or *NPM1* mutations [34]. Moving forward, understanding the biological basis of activity in these cases will be of great importance.

Another consideration relates to how these therapies might be combined with other agents already used in AML such as venetoclax and/or azacitidine [53] with the goal of maximizing efficacy while reducing further toxicity [53]. Regardless of the outcome of these studies, whichever therapy is used will need to demonstrate a degree of differential impact on leukemic stem cells versus normal hematopoietic stem cells. To a certain degree, it appears that normal hematopoiesis can be spared in the setting of METTL3 [11,12,18,54] and perhaps even FTO inhibition – however, this may prove challenging as combination of therapies will most likely lead to more widespread toxicity.

m6A AND ALL THINGS "SPLICE"

The cotranscriptional deposition of m6A means it is intricately involved with processes that impact mRNA maturation such as splicing. The impact on splicing is dependent on where m6A is deposited and on its interaction with various reader proteins (Figure 2). Initial work revealed that m6A impacts splicing through YTHDC1 (a reader of m6A) interacting with SRSF3 and SRSF10 [10,55]. YTHDC1 facilitates exon inclusion through recruitment of exon inclusion factor SRSF3 while concurrently blocking SRSF10 mRNA binding. In the absence of YTHDC1, SRSF10 binds mRNA and facilitates exon exclusion. As SRSF3 is often more abundant, exon inclusion is usually favored at baseline. There is additionally some evidence that the writing of m6A can dictate the dynamics of subsequent splicing. Deposition of m6A at splice sites is associated with faster and more constitutive splicing in contrast to m6A within introns, which leads to slow processing and alternative splicing [56]. Intron length also contributes to the determination of alternative splicing.

More recently, it has become clear that splicing and its associated machinery can also impact the deposition of m6A indicating that the relationship between these two processes is in fact bidirectional (Figure 2). Several recent articles demonstrate that formation of exon–junction complexes at exon–exon junctions can act to suppress m6A deposition by excluding m6A machinery from docking to and accessing the RNA [57–60]. This may in fact explain why m6A is more often distributed on longer transcripts and closer to the stop codon. In this way, transcript stability and accessibility can be more closely regulated. Similarly, transcript termination machinery and polyadenylation at the 3′ end of transcripts may also impact deposition of m6A in these areas [58]. Mehravar and Wong [61] provided a recent in-depth review regarding the interaction between RNA methylation and the various impacts on splicing.

A recent body of work suggests that a core component of the spliceosome, SF3B1 in its wild-type form, functions to counteract genotoxic stress associated with the progression of myelodysplastic syndrome (MDS) to AML [62]. In this setting, ALKBH5-induced demethylation drives the translation of SF3B1 in the face of oncogenic stress impacting the splicing of central DNA repair and epigenetic regulators. Authors of this work demonstrate that wild-type SF3B1 plays a protective role in the presence of an oncogene such as MYC. As MDS progresses to AML, wild-type SF3B1 levels fall and are subsequently associated with reduced survival in murine models. These data may explain why SF3B1 is commonly mutated in various hematologic malignancies including MDS and AML [63].

m6A AND THE MYELODYSPLASTIC SYNDROMES

The therapeutic implications if any, of modulating RNA methylation in the myelodysplastic syndromes are yet to be determined. In some

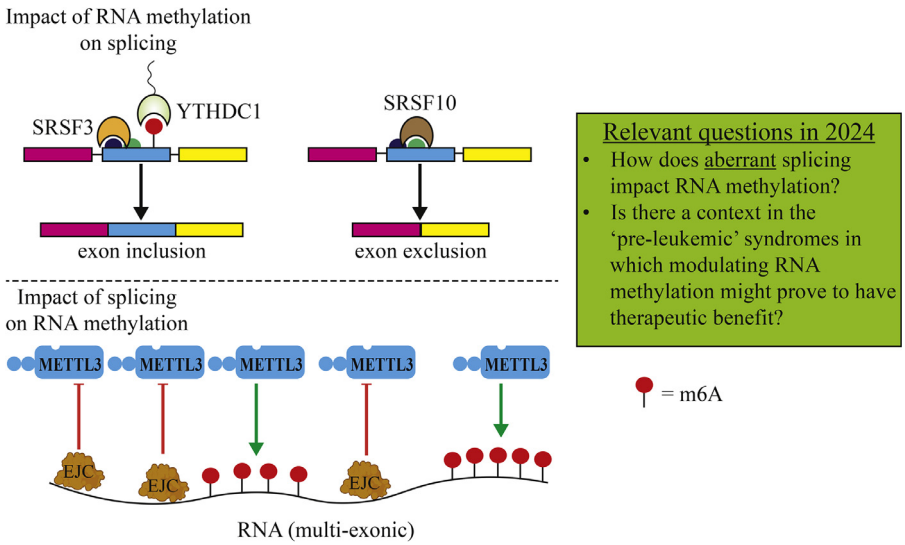

Figure 2 The bidirectional interaction between m6A modifications and splicing. M6A modifications can impact splicing by allowing for the binding or exclusion of other splicing-related factors (top panel). In contrast, splicing and its related machinery can also impact where m6A is deposited on various mRNA transcripts. Relevant questions in this area are shown in the box on the right.

cases, as it is in AML, METTL3 expression is increased in MDS at the protein level — but the evidence for this is not as robust [11]. One recent study indicates an association between DDX41 — which predisposes patients to familial MDS — and R-loop-induced DNA damage by way of an interaction between the METTL3 complex and the reader protein, YTHDC1 [64].

Aberrant splicing associated with splicing mutations has commonly been described in hematologic malignancies [63,65], including the myelodysplastic syndromes and AML. Here it appears to associate with variable prognoses depending on the actual protein mutated. SF3B1 mutations also associate with early clonal disorders such as clonal hematopoiesis [66]. However, at this stage, it remains to be determined how aberrant splicing impacts RNA methylation and vice versa. Additionally, whether there might be a biological rationale on which RNA-modifying agents prove to be of therapeutic benefit in this area of unmet need, remains unchartered territory. Future studies are required to yield insights into this exciting interaction.

m6A AND LYMPHOPROLIFERATIVE DISEASES

Unlike the myelodysplastic syndromes, some data support a basis for modulating RNA methylation in the context of lymphoproliferative diseases such as diffuse large B-cell lymphoma (DLBCL). Similar to AML, TCGA data reveal that DLBCL is associated with some of the highest expression levels of METTL3 [12]. Our recent work demonstrating enhanced antitumor activity in the context of METTL3 inhibition [22] was also applicable to a lymphoid model in vivo (A20 cell line). Additionally, unpublished work shows that following initial treatment with a METTL3 inhibitor, subsequent antigen challenge leads to a resurgence of antitumor activity, indicating the persistence of some sort of "memory" following treatment. Importantly, the effects here are virus agnostic. Although not announced to date, the potential for RNA modulating therapy (such as a METTL3 inhibitor) to be combined with the already successful immunotherapeutic armamentarium in lymphoma is hopefully not too far from being realized [67].

An alternative basis of activity that warrants consideration here is that some single-stranded RNA viruses also associate with lymphoma including HTLV1 and HIV. The loss of RNA methylation in these contexts may allow for enhanced antiviral surveillance by driving the formation of dsRNA. This will likely have a dual benefit of reducing viral titers while also preventing associated complications such as the development of lymphoma [24].

Although EBV (Epstein-Barr virus - the virus associated with glandular fever) is a DNA virus, recent evidence suggests that EBV exploits m6A modifications to support the survival of the host cell and allow for viral production during the so-called "lytic phase." Targeting METTL3 has been shown to reduce the expression of viral lytic proteins and reduce virion production. Concomitantly, the growth and viability of host cells was reduced in association with the induction of apoptosis. This supports a potential antiviral role that may be of particular benefit in suppressing EBV-driven lymphomas — such as Burkitt's, Hodgkin, or posttransplant lymphomas.

RNA MODIFICATION THERAPEUTICS

In 2021, Yankova et al. [18] published data on the world's first catalytic inhibitor of METTL3 (STM2457 by STORM Therapeutics) with demonstrated differential efficacy in AML cells and minimal effect on normal hematopoietic stem cells. This study confirmed that catalytic activity of METTL3 is essential for the survival of AML. Treatment was shown to associate with reduced self-renewal and leukemia-propagating activity. Unsurprisingly, the key proteins thought to be relevant here included SP1, BRD4, and MYC.

Since this study was published, STORM Therapeutics, a UK-based RNA epigenetics company has launched the first clinical METTL3 inhibitor (STC-15) Phase I dose-escalation study in the world for patients with solid organ malignancies (clinicaltrials.gov — Study number: NCT05584111). Administered as an oral formulation, this will no doubt be of benefit with respect to accessibility moving forward. It is important to note that although reported data in the METTL3 inhibitor space are the most mature, this remains to be formally peer-reviewed and is only available in abstract form at the time of writing. To date, the study has accrued a total of 42 patients across 5 dose-escalation cohorts. Initial reports suggest that the drug is well tolerated with expected activity observed across the active dose range. Key adverse events have included thrombocytopenia, rash, pruritus, and gastrointestinal side effects. One patient is reported to have G3 pneumonitis. Sustained partial remissions have been reported in a very small number of patients bearing in mind this would be a heavily pretreated population. Based on these data and our work last year, a phase 2 study is likely to follow. This will combine METTL3 inhibitor with immunotherapeutic modalities for lung, endometrial, and head and neck cancers as well as melanoma. STORM Therapeutics have also indicated other disease areas as part of their drug development pipeline — including Alzheimer disease, inflammation, viral infection, and other oncologic targets.

EPICS therapeutics have also previewed some early preclinical data at ASH 2023 with their newly derived METTL3 inhibitor, EP102. Efficacy has been demonstrated across multiple AML cell lines with evidence of synergy with venetoclax [68,69]. In a similar manner to STC-15, this drug is also orally dosed.

At this stage, it remains somewhat unclear how these RNA-modifying agents will be advanced in the hematologic space. One obvious area for development is in the treatment of lymphoma — alongside some of the current immunotherapeutic agents — either as part of combination therapy or in the face of immunotherapy resistance. Although efficacy has been demonstrated in AML in vitro and in murine in vivo models, it remains to be determined whether these benefits will extend to all-comers in the clinical trial space — which perhaps seems somewhat unlikely — or whether benefits will be limited to AML associated with specific mutations or gene-expression patterns. Additionally, is there a premise for limited duration of therapy or will this need to be ongoing? In the preleukemic setting, data supporting a potential benefit is incredibly sparse at this stage. As is the case for any new therapeutic that enters the public arena, the potential for resistance is yet to be demonstrated, but invariably this may be a problem that will also need to be addressed at some stage.

On the opposite side, several FTO inhibitors have also been described including Rhein [70], meclofenamic acid [71] (an anti-inflammatory agent), and subsequent derivatives of this such as FB23-2 [33]. These are likely to increase *ASB2* and *RARA* mRNA levels while concomitantly reducing MYC and CEBPA. In a similar manner to the inhibition of METTL3, benefits have been demonstrated in vitro by way of increased differentiation and apoptosis and reduced cell cycling. It has been suggested that FTO inhibitors are

Table 2 Key pharmaceutical companies in the RNA modification therapeutics space

Company	Target	Development phase	Disease context
STORM Therapeutics	METTL3 (STC15)	Phase 1 (near completion) Phase 1b|2	Solid organ tumors Lung, endometrial, head and neck cancers + melanoma
	METTL1	Preclinical	Advanced cancer
	ADAR1	Preclinical	
	RNA helicase	Preclinical	
	Viral methyltransferase	Preclinical	
EPICS Therapeutics	METTL3 (EP102)	Preclinical	AML
Accent Therapeutics	DHX9 (RNA helicase)	Preclinical	Breast cancer
	ADAR1	Preclinical	Solid organ cancer
	XRN1 (RNA exonuclease)		
858 Therapeutics (acquired Gotham Therapeutics)	METTL3 ADAR1	Preclinical Preclinical	

AML = Acute myeloid leukemia.

likely to be of relevance in AML subtypes that overexpress FTO (such as APML and MLL fusions) and in other tumor subtypes as well. We await further maturation of data in this space.

Unsurprisingly, protein degraders have also begun to make an appearance in this space aimed at degrading the METTL3 | METTL14 complex or FTO [19,20]. Results have been somewhat modest so far — perhaps relating to issues with cell penetration and permeability — a known problem with PROTACs that must be overcome due to their size and hydrophobicity. However, with further refinement, protein degraders may prove to be beneficial in the setting of resistance to catalytic inhibitors given their mechanism of action.

Several other companies have also shown interest in this therapeutic space with different targets and diseases in mind (Table 2).

METTL1: THE NEW KID ON THE BLOCK. . .OR THE OG

Unlike METTL3, which predominantly methylates mRNA species, *METTL1* encodes a tRNA methyltransferase that methylates guanine at position 46 in tRNA molecules. Inhibition of METTL1 appears to reduce methylation and stabilize various tRNAs impairing cell proliferation and cell cycle progression. To date, this has been implicated in the pathogenesis of a number of solid organ tumors [72–74]. Although data indicate that this could be another dependency in AML, it appears to have less-negative selection compared with METTL3 and METTL16 [12]. At ESMO 2024, STORM presented results from a first-in-class small molecule study specifically targeting METTL1 with potential for antitumor efficacy at low nanomolar concentrations. It will be exciting to see how drug development in this space proceeds and the likely biological applications of this approach in the future.

5mC OF RNA

Commonly mutated in clonal hematopoiesis (CHIP) [66] and other myeloid malignancies [75–78] TET2's role in the posttranslational modification of DNA is well described. Acting as a methylcytosine dioxygenase, TET2 catalyzes the conversion of methylcytosine to 5-hydroxymethylcytosine on DNA [79] Very recently, TET2 has also been shown to play a role in the methylation of RNA [80]. As a result of this latter mechanism, TET2 deficiency (as occurs in TET2-mutant leukemia) promotes an open chromatin state leading to gene activation and a novel dependency associated with aberrant stem cell renewal mediated by the RNA-binding protein MBD6. In this setting, *MBD6* KD associates with complete proliferation block in *TET2*-mutant AML cell lines and decelerated leukemogenesis in vivo. Other groups have also suggested the 5mC modification and expression of its regulators in the tumor microenvironment of AML patients may be of prognostic importance [81]. In addition, the expression and activity of particular RNA methyltransferases may predict for drug response and resistance in leukemia [82]. It remains to be determined how this knowledge might best be used for the future treatment of AML.

CONCLUSIONS

Although RNA modifications have been extensively described over the decades, their recent association with various diseases alongside the machinery that regulates them has sparked significant global interest. For RNA methylation in the hematologic space, targeting m6A has already demonstrated benefit in diseases such as AML and lymphoma, although the specific clinical context in which these novel therapeutics should be used remains to be fully ascertained. We and others have also demonstrated how modulation of m6A can be leveraged to augment antitumor responses in a transcript-agnostic manner

and how these modifications are relevant for normal hematopoiesis. In the "preleukemic" space including the myelodysplastic syndromes, the data are less mature. Beyond m6A, therapeutic targeting of other RNA modifications is still in its infancy, as discoveries are slowly made linking disease pathogenesis to specific modifications. These are no doubt exciting times as the research world works to develop novel therapeutics in this space and determine how best they should be used. We eagerly await the publishing of mature results over the upcoming months in this field of RNA biology.

Conflict of Interest Disclosure

The author does not have any conflicts of interest to declare in relation to this work.

Acknowledgments

I would like to thank mRNA Victoria Research Acceleration Fund for previous grant support associated with our work. Acknowledgment is also made of STORM Therapeutics for their previous collaboration and thanks is offered for my previous time spent in the Cancer Epigenetics Laboratory at Peter MacCallum Cancer Institute (Professor Mark Dawson).

Author Contributions

AAG has contributed significantly to the research described in the paper and has read and approved the final manuscript.

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