Epitranscriptomics in Hematopoiesis and Hematologic Malignancies

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ABSTRACT

Since the 1960s, a large number of chemical modifications have been identified in RNA molecules, establishing the RNA epigenetics field named “epitranscriptomics.” These chemical marks participate in several RNA metabolic processes; however, the biological relevance of many of these modifications and the many enzymes involved in their function is not completely understood. Emerging knowledge of the epitranscriptome (pseudouridine, N⁶-methyladenosine, and A-to-I editing) in hematopoiesis and hematologic malignancies reveals the requirement of these modifications in normal development and their alteration in disorders, leading to the development of new molecules and strategies to target the epitranscriptome as a novel therapeutic approach. RNA modifications are required for the correct development of hematopoietic cells, and their alteration can promote the development of malignancies or the transition from a low-grade to an aggressive disease. While we are expanding our understanding of the epitranscriptome of normal and malignant hematopoiesis, the number of potential new therapeutic interventions is rising.

INTRODUCTION

Chemical modifications of RNA nucleosides were first reported in the 1960s. Such modifications include pseudouridine (ψ), N⁶-methyladenosine (m⁶A), or A-to-I editing. However, the lack of adequate methodology meant their role in development and disease remained elusive. With the emergence of new high-throughput detection methods, previously known modifications have been thoroughly profiled and many more RNA modifications have been discovered. In fact, more than 150 modifications have been described in coding and noncoding RNA molecules, forming the epitranscriptome of the cell (1). Alongside the discovery of RNA modifications, a group of RNA-binding proteins involved in the deposition, recognition, and removal of these modifications have also been identified, known as writers, readers, and erasers of the epitranscriptome, respectively (ref. 1; Fig. 1A).

Pseudouridine was the first epitranscriptomic mark that was discovered. It results from the isomerization of uridine catalyzed by pseudouridine synthase proteins, such as DKC1 or PUS7. Overall, pseudouridine is the most abundant RNA modification in the cell, especially in tRNA and rRNA, where it plays important roles in structure stabilization and folding as well as in translation. It is also found, to a lesser extent, in mRNA where it is shown to affect translation efficiency and accuracy (2).

m⁶A is the most abundant modification in mRNA. It is deposited by a RNA methyltransferase writer complex that consists of a catalytic subunit, METTL3, accompanied by assistant proteins, including METTL14, WTAP, RBM15, KIAA1429, and ZC3H13, that contribute to stabilizing the complex and recruiting it to the target mRNA. m⁶A is a reversible mark and can be erased by the RNA demethylases ALKBH5 and FTO. m⁶A is recognized by a number of m⁶A-binding proteins, the readers, including YTH family (YTHDF1-3 and YTHDC1-2), IGF2BP1-3 proteins, and some heterogeneous nuclear ribonucleoproteins (hnRNP), among others. These proteins mediate the wide-ranging effects of m⁶A in RNA structure, stability, splicing, nuclear export, or translation efficiency (3).

Another commonly studied RNA modification is the irreversible deamination of adenosine to inosine, known as A-to-I editing. This reaction is catalyzed by the ADAR family of enzymes, with ADAR3 acting as a negative regulator of the catalytically active proteins ADAR1 and ADAR2. A-to-I editing occurs in double-stranded RNA (dsRNA), like pri-miRNA and pre-miRNA or in mRNA secondary structures such as...
Figure 1. Regulation of m6A, A-to-I editing, and pseudouridine by writers, readers, and erasers of the epitranscriptome and their role in normal and malignant hematopoiesis. 

A. The m6A writer complex composed by METTL3, METTL14, WTAP, RBM15, KIAA1429, and ZC3H13 acts on the nascent mRNA during transcription. In the nucleus, m6A is recognized by YTHDC1 and some hnRNP to affect mRNA stabilization, regulate splicing events, and facilitate its nuclear export. In the cytosol, YTHDF1-3 and IGF2BP1-3 proteins mediate different functions of m6A on translational control. m6A can be removed from mRNA in the cytosol by RNA demethylases ALKBH5 and FTO. A-to-I editing of mRNA can occur either by ADAR1 or ADAR2. The resulting inosine is resolved as a guanine, leading to alternative splicing patterns, protein recoding, alterations in miRNA and RNA-binding proteins (RBP) binding sequences, or dsRNA unwinding. Pseudouridine is generated by pseudouridine synthases, like DKC1 or PUS7, acting on different RNA molecules. In mRNA, pseudouridine modulates transcription efficiency and accuracy.

B. m6A is very important in HSC biology and leukemia development. During embryogenesis, METTL3 deposits m6A on Notch1a mRNA, and YTHDF2 induces its decay. Notch1a diminish allows HSC differentiation. High expression of METTL3 is observed in AML cells. RNA methylation on target genes, including MYC, PTEN and BCL2, increases their translation and augments cell survival. In CML, signals from the bone marrow microenvironment through JAK2 together signals from the fusion protein BCR-ABL induce the increase of ADAR1. A-to-I RNA editing is associated with several alterations inducing malignant reprogramming of myeloid progenitors and LSC self-renewal. These alterations include editing of pri-lent-7, blocking its biogenesis and inhibiting suppression of LIN28B expression; the increased stability of RNA of transcripts of MDM2, APOBEC3D, GLI1 and AZIN1; and the alteration in the splicing of GSK3β.

C. MDS cells present alteration in chromosome 7, such as 7q deletion or chromosome 7 monosomy. In this region can be found PUS7, a pseudouridine writer, which modifies and activates tRNA-derived small fragments containing 5′ terminal oligoguanine (mTOG) targeting the translation. Alteration of this regulatory circuitry impairs HSC commitment and promotes an aggressive subtype of MDS with a higher chance to transform into an AML.
Alu elements located in the 3’-UTR. The resulting inosine is interpreted as a guanine. Consequently, site-selective A-to-I editing can directly result in alternative splicing patterns, transcriptional recoding of mRNA, defects in miRNA biogenesis, and alterations of miRNA or RNA-binding protein-binding sites. Another form of A-to-I editing is hyperediting, which occurs in many adenosines within a short sequence and has inhibitory effects on IFN signaling by unwinding dsRNA structures (4).

A number of studies have revealed that the correct regulation of the epitranscriptome is crucial for many normal biological processes and in disease (1). Recently, the role of RNA modifications and their cognate enzymes in hematopoiesis has begun to be uncovered, revealing their importance in blood cell production and differentiation. Herein, we will summarize the major contributions of epitranscriptomics in normal and malignant hematopoiesis and how its deregulation can be exploited as a therapeutic target in hematologic malignancies.

**EPITRANSCRIPTOMICS DURING HEMATOPOIESIS**

Hematopoiesis is a delicately orchestrated process that corresponds to the maturation of hematopoietic stem cells (HSC) into a variety of terminal differentiated cells of the blood and immune system. Over the last few decades, key hematopoietic regulators have been identified, including cytokines and chemokines, transcription factors, and epigenetic regulators (5). In addition, the number of observations describing the involvement of RNA modifications in several steps of this process has risen in recent years, adding a new layer of complexity to the posttranscriptional regulation of HSC activity and hematopoiesis (Table 1).

The importance of RNA methylation in hematopoiesis was first depicted in the development of adult hematopoietic stem/progenitor cells (HSPC) during zebrafish embryogenesis (6). In this scenario, the loss of mettl3 impaired the rise of HSPCs by reducing m6A/YTHDF2-mediated effects on notch1a mRNA decay, because continuous Notch1 signaling represses HSPC formation (6). Moreover, the expression levels of m6A writers mettl3 and mettl14 are higher in HSPCs in comparison with differentiated cells from mouse bone marrow (7). Two independent studies revealed that mettl3 depletion in the murine hematopoietic system leads to HSC accumulation in the bone marrow with a concomitant failure of symmetrical differentiation and a reduction of reconstitution potential (8, 9). From a mechanistic perspective, this situation is caused by defects in MYC upregulation, driven by a breakdown in m6A-dependent mRNA stabilization and translation (8, 9). In line with this, m6A reduction in humans by METTL3 depletion in cord blood-derived CD34+ HSPCs is associated with a drop in proliferation and an increase in myeloid differentiation in vitro (ref. 10; Fig. 1B). Similar results have been observed with METTL14, RBM15, and YTHDF2 silencing (7, 11–13), suggesting that m6A machinery is an important regulator of homeostasis and quiescence control of HSC and HSPC. Most m6A studies have focused on the initial steps of hematopoiesis, and its role in adult cells is not well characterized. In this regard, m6A has been found to play an important role in the capacity of naïve T cells to proliferate and differentiate into effector cells. IL7 is an important T-cell regulator, and mettl3-deficient T cells upregulate IL7-negative regulators Socs1, Socs3, and Cish, thus impacting naïve T-cell differentiation (14). RMB15 is also required for the development of mature B cells, because its deletion promotes a block in pro/pre-B differentiation (15).

A-to-I RNA editing is also involved in hematopoiesis. It has been reported that ADAR1 depletion impacts most of the mature lineages except myeloid (16). This study also revealed that ADAR1 loss in the erythroid lineage is embryonic lethal and is associated with a failure of fetal liver hematopoiesis, especially impacting the erythroid lineage–specific KLF1 transcript (16). Moreover, ADAR1 silencing in HSCs promotes a loss in multilineage reconstitution associated with IFN signaling, most likely by the abnormal activation of cytosolic nucleic acid sensors by self-dsRNA, thereby impacting final differentiation of B cells (17). ADAR1-mediated RNA editing is also crucial in more advanced stages of hematopoiesis, as adult hematopoietic progenitor cells fail to differentiate after ADAR1 depletion (18). Interestingly, T-cell–specific deletion of ADAR1 promotes an abnormal thymic T-cell maturation and an impaired negative selection, causing autoimmune events due to a failure in IFN signaling attenuation (19). ADAR1 and ADAR2 are modulated during myeloid differentiation, a process in which they act differently as they target different transcripts. ADAR2 is absent in undifferentiated cells but is strongly upregulated at the end of the differentiation process, concomitantly increasing RNA-editing rates (20).

HSPCs are also particularly sensitive to alterations in pseudouridine and protein synthesis. In this regard, silencing of PUS7 promotes a reduction of a particular type of tRNA-derived small fragments containing 5′ terminal oligoguanine (mTOG), thereby leading to increased protein synthesis and severely blocking HSPC differentiation (21). In another scenario, DKC1-dependent increase in telomerase activity is essential for erythroid lineage commitment (22).

The epitranscriptome is key in normal hematopoiesis from the first generation of embryonic hematopoietic cells to the mature cells. Different enzymes and proteins described above shape RNA stability, translation and interaction capacities to regulate cellular quiescence, differentiation, and proliferation. The effect of RNA modifications has distinct impacts in different cell types or differentiation stages as one would anticipate, because their effects are context dependent based on the abundance of RNAs and their readers. This new level of regulation adds an additional degree of complexity to the already intricately controlled hematopoiesis.

**EPITRANSCRIPTOMICS IN HEMATOLOGIC MALIGNANCIES**

Hematologic malignancies are characterized by the aberrant proliferation of hematopoietic cells accompanied with a block in differentiation and anomalous self-renewal. They can originate in either lymphoid (lymphomas, lymphoerythroid leukemias, and myeloma) or myeloid lineages [acute (AML) and chronic myeloid leukemia (CML), myelodysplastic syndromes (MDS), and myeloproliferative diseases]. Because RNA
Epitranscriptomics in Hematopoiesis and Related Malignancies

These effects are mediated by m\textsubscript{6}A demethylation of METTL3 and other m\textsubscript{6}A writer complex members were reported to be essential genes involved in leukemia cell survival, METTL3 (8). By using a high-throughput strategy with CRISPR to find members, in particular METTL3, are highly expressed in AML in global m\textsubscript{6}A levels, promoting cell growth and inhibiting MLL rear- cells in a context-dependent manner. FTO is overexpressed appears to be advantageous or detrimental for the leukemic requirement in malignant growth is more controversial and complex in AML. However, RNA demethylation and FTO in malignant hematopoiesis, especially in leukemias origi- nate from hematopoietic stem/progenitor cell; LSC, leukemia stem cell; MDS, myelodysplastic syndrome; MM, multiple myeloma; TCR, T-cell receptor.

### Summary of RNA modifiers and RNA modifications contributing to normal and malignant hematopoiesis

| Mark | Tissue | Function | Reference |
|------|--------|----------|-----------|
| m\textsubscript{6}A | HSBC/HSC | notch1a mRNA decay required for HSBC formation | (6) |
| m\textsubscript{6}A | HSBC/HSC | MYC transcript and protein upregulation for symmetrical differentiation | (7-10, 12) |
| m\textsubscript{6}A | HSBC/HSC | m\textsubscript{6}A transcript and protein upregulation factors like TAL1 and GATA2 | (13) |
| T cell | socs1, socs3 and cish mRNA degradation in response to IL7 | (14) |
| B cell | m\textsubscript{6}A requirement for pre/pro-B-cell differentiation | (15) |

### Normal hematopoiesis

| Mark | Tumor | Protein | Alteration | Reference |
|------|-------|--------|------------|-----------|
| m\textsubscript{6}A | AML | ↑ METTL3 | MYC, BCL2, and PTEN translation regulation | (10) |
| m\textsubscript{6}A (MLL translocation) | AML | ↑ FTO | Demethylation of ASB2 and RARA mRNA enhances leukemogenesis | (25) |
| m\textsubscript{6}A (IDH1/2 mutation) | AML | J FTO | Increased m\textsubscript{6}A content contributes to leukemogenesis | (26) |

### Malignant hematopoiesis

| Mark | Tumor | Protein | Alteration | Reference |
|------|-------|--------|------------|-----------|
| m\textsubscript{6}A | CML | ↑ ADAR1 | Impaired pri-let-7 biogenesis contributes to cancer progression | (27) |
| m\textsubscript{6}A | CML | ↑ ADAR1 | GSK3\textsubscript{b} splicing and upregulation of PU.1 connected to LSC renewal | (28) |
| AML | CML | ↑ ADAR1 | MDM2 stabilization increases blast crisis progression | (29) |
| AML | ↓ ADAR1 | Increased expression of Wnt effectors and cell-cycle progression | (32) |
| AML | ↑ ADAR1 | Alternative PTPN6 splicing associated with leukemogenesis | (33) |
| MM | ↑ ADAR1 | Increased GLI1 activity contributes to drug resistance and poor outcome | (34) |
| Ψ | MDS | ↓ PUS7 | Altered protein synthesis and transformation to aggressive leukemia | (21) |
| Ψ | CLL | ↓ DKC1 | Associated with ribosome imbalance and poor outcome | (35, 36) |

**Abbreviations:** AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HSBC, hematopoietic stem/progenitor cell; LSC, leukemia stem cell; MDS, myelodysplastic syndrome; MM, multiple myeloma; TCR, T-cell receptor.

Modifications are critical during the early steps of hematopoiesis, it is not unexpected that they play an important role in malignant hematopoiesis, especially in leukemias originated from immature stages (Table 1).

Currently, AML is the malignance where RNA modifications have been better characterized. m\textsubscript{6}A writer complex members, in particular METTL3, are highly expressed in AML (8). By using a high-throughput strategy with CRISPR to find essential genes involved in leukemia cell survival, METTL3 and other m\textsubscript{6}A writer complex members were reported to be indispensable in AML cell lines and primary mouse leukemia cells (23, 24). Mechanistically, METTL3 regulates the translation of MYC, BCL2, and PTEN, key genes involved in the control of cell survival and differentiation (ref. 10; Fig. 1B). These studies clearly establish the oncogenicity of the m\textsubscript{6}A writer complex in AML. However, RNA demethylation and FTO requirement in malignant growth is more controversial and appears to be advantageous or detrimental for the leukemic cells in a context-dependent manner. FTO is overexpressed in some AML subtypes, especially in cases carrying MLL rearrangements. This overexpression is associated with a decrease in global m\textsubscript{6}A levels, promoting cell growth and inhibiting apoptosis in vitro and enhancing leukemogenesis in vivo (25). These effects are mediated by m\textsubscript{6}A demethylation of ASB2 and RARA mRNAs (25). Conversely, in some IDH1/2-mutant AML patient samples, the production of the oncometabolite R-2-hydroxylutarate inhibits FTO activity, leading to an increase in m\textsubscript{6}A content that contributes to leukemia development (26).

In CML, activation of RNA-editing activity of ADAR1 via JAK2 and BCR–ABL1 inflammatory signals promotes cancer progression and therapeutic resistance, as well as malignant reprogramming of myeloid progenitors and leukemia stem cell (LSC) self-renewal (27). In this context, ADAR1 drives LSCs by impairing pri-let-7 biogenesis, causing unopposed LIN28B expression and enhanced self-renewal (27). In addition, ADAR1 is also associated with misspliced GSK3\textsubscript{b}, likewise connected to LSC renewal, and with upregulation of myeloid transcription factor PU.1 (28). ADAR1 has been reported to stabilize MDM2 transcripts, thereby increasing blast crisis progenitor propagation (29). MDM2, together with APOBEC3D, GLI1, and AZIN1, was identified in a cancer stem cell–specific ADAR1 RNA-editing fingerprint of CML transformation (30). ADAR1 deletion in conditional mouse models restores blood and spleen basal levels and preferentially eliminates LSCs (31). Thus, ADAR1 inhibition could represent a target to prevent relapse in CML without affecting HSC populations (Fig. 1C). ADAR1 is also...
overexpressed in AML and related to leukemia cell proliferation. ADAR1 silencing promotes AML cell-cycle arrest and decreases expression of Wnt effectors (32). An additional example of the effect of RNA editing in AML is the alteration in the splicing pattern of PTPN6 and its association with leukemogenesis (33). In 30% to 50% of multiple myeloma patients, an amplification of the genomic region containing ADAR1 occurs. ADAR1 expression correlates with worse patient outcomes, transcriptional activity of GLI1, immunomodulatory drug resistance, and serial transplantability (34).

In MDS, the loss of PUS7 in conjunction with chromosome 7 abnormalities is frequent. Dysfunction of PUS7 and mTOGs perturbs protein synthesis in patients with MDS, characterized by high rates of transformation to aggressive leukemia (ref. 21; Fig. 1D). In chronic lymphocytic leukemia (CLL), there is a decrease in the expression of DKC1 and its associated proteins (35). An independent study showed a correlation between reduced DKC1 expression with poor survival in CLL (36). Disruption of pseudouridine-driven regulatory circuitry impacts hematologic malignancies.

As described in normal hematopoiesis, the epitranscriptome is involved in malignances of different origins and several kinds of dysregulations have been described above. It is still too early to consider any of these alterations as drivers, but it is clear that in some instances, RNA modifications are required for the maintenance and transformation of the malignant cell. Although the global effect of an altered modification is bound to be type or subtype specific (e.g., patients with MLL vs. IDH1/2-mutant AML), common alterations in transcripts such as MYC and BCL2 can share the same regulation in several malignances. Therefore, the study of normal and malignant hematopoiesis is complementary, and the characterization of one may help to understand and to identify critical points of the other that could be exploited therapeutically.

**CLINICAL IMPLICATIONS**

As described above, epitranscriptomics plays a critical role in hematopoiesis, and its alterations are fundamental in many hematologic malignancies. These alterations may act as a double-edged sword, as they can be advantageous for tumor generation, progression, and resistance to pharmacologic intervention, but at the same time, they can be used to better classify patients and can be targeted therapeutically. Therefore, direct modulation of epitranscriptome writers, readers, and erasers can be potential targets of new drug design efforts. In this regard, FTO inhibitors have been reported to have antitumor effects in AML by increasing m^6^A content (37, 38). So far, there are no molecules known to target the m^6^A writer complex or reader proteins. However, the structure of these proteins resembles the structure of proteins implied in DNA and histone methylation, for which compounds are available, a fact that can potentially facilitate the rational design of RNA methyltransferase inhibitors (39). The efforts in the identification of METTL3 inhibitors can lead to a promising new clinical approach against AML and other hematologic malignancies. Alterations in the epitranscriptome have also been related to the efficiency of other therapies. One example comes from evidence that low m^6^A abundance in specific transcripts confers tolerance against tyrosine kinase inhibitors (TKI) in leukemia, as FTO is upregulated in TKI-resistant cells (40). This reinforces the importance of targeting FTO to increase m^6^A content and eradicate TKI-tolerant cells to improve therapy outcome (40).

However, because epitranscriptomics is implicated in many biological processes, it is important to prove that interference with their function would not cause major side effects and in that case, methodologies to increase target cell efficiency will be required.

**CONCLUSIONS AND PERSPECTIVES**

RNA modifications participate in the fine-tuning of many essential biological processes and have been reported to be altered in cancer (41). Understanding the role of RNA modifications, their cooperative interactions and their associated enzymes in normal and pathologic processes may contribute to the design of new therapeutic strategies to fight diseases. In parallel, increasing our understanding of the epitranscriptomic regulation of gene expression may shed light on novel molecular mechanisms and networks that contribute to the malignant transformation of cells and their responses to specific therapeutic interventions. At the moment, epitranscriptomic alterations appear to have cell type–specific signatures and consequences. Thus, we need to expand our knowledge on this field to better understand the mechanisms underlying tumor development and progression that are governed by RNA modifications. To achieve this goal, researchers have introduced modifications to the technology generated for the study of DNA and RNA, developing high-throughput detection and sequencing methods for RNA modifications and enabling the mapping and characterization of epitranscriptomic marks. New sequencing approaches, such as Oxford Nanopore Technologies, are promising tools for revolutionizing epitranscriptomics, as they will be capable of directly sequencing RNA transcripts for the identification of the less abundant RNA modifications in high resolution (1, 42). All these new data are promoting the generation of new bioinformatic tools that will eventually be used to improve present researchers’ mainstream bioinformatics resources. Therefore, we expect a substantial increase in the understanding of the epitranscriptome in the coming years that may provide a good starting point for new pharmaceutical approaches to target RNA modifications and RNA modifiers. Although this discipline is still in its early stages, the targeting of RNA modifier proteins to modulate the epitranscriptome seems to be a promising strategy to better understand hematopoiesis and fight hematologic malignancies.

**Disclosure of Potential Conflicts of Interest**

M. Esteller is a consultant for Quimatryx and Ferrer International. No potential conflicts of interest were disclosed by the other authors.

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