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RBPs in Hematopoietic Stem Cell Maintenance and Leukemia Initiation: Critical Gaps

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Abstract

Contex: RNA-binding proteins (RBPs) are key regulators of post-transcriptional gene expression and play essential roles in hematopoietic stem cell (HSC) function. Although major advances have been made in understanding transcriptional regulation in hematopoiesis, the contribution of RBPs to HSC maintenance and leukemia development remains incompletely defined.

Evidence Acquisition: Relevant literature was collected from major scientific databases and high-impact journals, including PubMed, Web of Science, Google Scholar, Nature Portfolio, Elsevier, and related peer-reviewed sources. This systematic review summarizes current findings on the roles of major RBPs and RNA-modifying factors in normal and malignant hematopoiesis, with particular focus on MUSASHI2, IGF2BP family proteins, Lin28b, METTL3, METTL14, ALKBH5, and FTO.

Results: Available studies demonstrate that RBPs regulate RNA processing, stability, translation, and modification, thereby influencing stem cell self-renewal, differentiation, and leukemic transformation. Dysregulation of these factors contributes to leukemia progression, maintenance of leukemia stem cells, and treatment resistance. Emerging evidence also highlights RBP-associated pathways as potential therapeutic targets.

Conclusion: RBPs represent a critical regulatory layer in hematopoietic stem cell biology and leukemia. An improved understanding of these post-transcriptional mechanisms may support the development of more effective therapies that target leukemia stem cells while preserving normal hematopoiesis.

Keywords: RNA Binding Proteins; hematopoietic oncogenesis; molecular regulation; M6A modifiers

1. Contex

The Hidden Layer of Hematopoietic Gene Regulation (HSCs)

For decades, research on HSCs and leukemia has focused predominantly on transcription factors and chromatin remodeling. This emphasis has generated substantial insights into how genes are turned on or off. However, this represents only part of the story. Once an mRNA molecule is transcribed, it embarks on a journey through the cell, where its fate –including localization, stability, translation, and splicing – is controlled by a sophisticated network of RNA-binding proteins (1).

Consider the following scenario: two cells express similar levels of a critical mRNA, yet one proliferates aggressively while the other differentiates normally. Such differences can arise from post-transcriptional regulation by RBPs. These proteins act as molecular switches, determining whether an mRNA is translated into protein, how long it survives in the cell, and where it localizes. In HSCs, where the balance between self-renewal and differentiation must be tightly controlled, RBPs serve as critical gatekeepers (2).

1.1 Why RBPs Matter in Hematopoiesis

Normal hematopoiesis depends on the small population of HSCs residing in the bone marrow. These cells face a fundamental choice between self-renewal, which maintains the stem cell pool, and differentiation, which produces billions of blood cells daily. This decision cannot be determined solely at the

transcriptional level. Instead, cells require dynamic and reversible control mechanisms that enable rapid responses to environmental signals. RBPs provide this flexibility (3).

When hematopoiesis is impaired, the consequences can be severe. Acute myeloid leukemia (AML), for instance, develops when HSCs or progenitor cells acquire mutations that lock them into a perpetual state of self-renewal while blocking differentiation. Increasing evidence suggests that dysregulated RBP networks drive and maintain this malignant state. Understanding these networks opens new therapeutic avenues for diseases that remain difficult to cure (4).

1.2 Current Gaps in Knowledge

Despite growing recognition of the importance of RBP, several critical gaps persist:

1. **Mechanistic precision**: While we know that certain RBPs affect HSC function, the precise molecular mechanisms by which they select specific mRNA targets and coordinate with other regulatory layers remain unclear.
2. **Context-dependent functions**: Many RBPs show opposite effects in different cell types or disease contexts. For example, METTL3 promotes leukemia in some AML subtypes but may play different roles in others. The molecular basis underlying these context-dependent functions remains poorly understood.
3. **Integration with metabolism**: Emerging evidence links RNA modifications (particularly m6A) to cellular metabolism, but these connections remain poorly understood in HSCs and leukemia stem cells (LSCs).
4. **Therapeutic targeting**: While RBPs represent attractive therapeutic targets, the development of specific inhibitors has proven challenging. Identifying RBPs that can be safely targeted without disrupting normal hematopoiesis remains a major challenge.
5. **Compensatory mechanisms**: The extent to which other RBPs compensate for the inhibition of a specific RBP remains unclear. Understanding these networks is essential for developing effective therapies.

This review addresses these gaps by examining key RBP families, their molecular mechanisms, their role in pathway regulation, and their therapeutic potential.

2. The MUSASHI Family: Master Regulators of Stem Cell Identity

2.1 MUSASHI2 in Normal Hematopoiesis

MUSASHI2 (MSI2) emerged as one of the first RBPs conclusively linked to both normal HSC function and leukemia. The protein belongs to an evolutionarily conserved family originally discovered in *Drosophila*, where it controls the asymmetric cell division of neural progenitors. In mammals, MSI2 is the predominant family member expressed in HSCs, while MSI1 shows a broader tissue distribution (5). Notably, MSI1 is not essential for steady-state hematopoiesis under normal conditions. Mice lacking MSI2 maintain relatively normal blood cell production in the absence of stress. However, under the conditions of bone marrow transplantation, regenerative stress, or competitive repopulation, MSI2-deficient HSCs fail to function properly. These cells cannot adequately self-renew or compete with normal HSCs (6).

This reveals that MSI2 functions as a stress-response protein maintaining HSC "stemness" when it matters most. Thus, MSI2 appears to serve as an emergency reserve system that acts when HSCs need to expand rapidly.

2.2 Molecular Mechanism: Translation Control of Self-Renewal Programs

MSI2 contains two RNA recognition motifs (RRMs) that bind to specific sequences in mRNA 3' untranslated regions (UTRs). Using techniques such as high-throughput sequencing and crosslinking immunoprecipitation (HITS-CLIP), researchers mapped MSI2's direct RNA targets. The results revealed several functionally important MSI2 targets (6).

MSI2 binds and enhances the translation of key self-renewal factors including, **HOXA9**, a homeobox transcription factor critical for HSC expansion. HOXA9 is normally downregulated during differentiation, but MSI2 maintains its translation even when transcription decreases. CLIP-seq and polysome profiling studies demonstrated MSI2 occupancy on HOXA9 and MYC transcripts. MSI2 depletion reduces their association with heavy polysomes, indicating impaired translational efficiency. Whether MSI2 additionally affects transcript stability may depend on cellular context and remains under active investigation (6-8)

MYC is a well-known oncogene that drives cell growth and proliferation. MSI2 binding to MYC mRNA stabilizes it and enhances translation, particularly during cell cycle entry. **IKZF2,** A zinc finger transcription factor, maintains the undifferentiated state. When MSI2 is depleted, IKZF2 protein levels plummet, even though mRNA levels remain stable, indicating that MSI2 controls translation rather than transcription.

The mechanism involves MSI2 binding to the 3' UTRs of these mRNAs, recruiting the translation machinery, and simultaneously protecting the mRNA from

degradation. The proteins produced from these MSI2-target mRNAs then activate transcription of genes that further promote self-renewal.

2.3 MSI2 in Leukemia: From Driver to Dependency

In acute myeloid leukemia (AML), particularly in cases with mixed lineage leukemia (MLL) rearrangements, MSI2 becomes highly expressed. MLL-rearranged leukemias are among the most aggressive AML subtypes, with poor responses to therapy and dismal outcomes (6). MSI2 plays a critical role in maintaining the MLL-driven gene expression program. MLL fusion proteins aberrantly activate HOXA9 and other HOX genes at the transcriptional level. MSI2 then ensures that these mRNAs are efficiently translated into protein. Without MSI2, MLL leukemia cells lose their self-renewal capacity, differentiate, and undergo apoptosis.

Importantly, MSI2 expression levels correlate with patient outcomes across multiple leukemia types. In chronic myeloid leukemia blast crisis (CML-BC), high MSI2 predicts poor prognosis (9). In B-cell acute lymphoblastic leukemia (B-ALL), elevated MSI2 is associated with worse survival (10). In de novo AML, patients with above-median MSI2 expression have significantly shorter overall survival (median 405 days versus 845 days) (11). These findins establish MSI2 as an independent adverse prognostic marker.

2.4 The MSI2-NUMB Signaling Axis

MSI2 doesn't work alone. It regulates NUMB, a protein that inhibits Notch signaling. In normal stem cells, MSI2 binds to NUMB mRNA and inhibits its translation (10). This keeps Notch signaling active thereby promoting self-renewal. In leukemia, this regulatory circuit becomes dysregulated. Excessive MSI2 suppresses NUMB, leading to constitutive Notch activation and uncontrolled self-renewal (9). This creates a potential therapeutic opportunity. Inhibition of MSI2 could increase NUMB levels, reduce Notch signaling, and probably promoting leukemia cells differentiation. Indeed, the small-molecule inhibitor Ro 08-2750, which disrupts MSI2 RNA binding, showed promising anti-leukemia effects in preclinical models (5).

2.5 MSI2 Interactions with Other RBPs

Recent proteomic studies have revealed that MSI2 forms complexes with other RBPs. One key partner is SYNCRIP (also called hnRNPQ1). SYNCRIP and MSI2 bind many of the same mRNAs, including HOXA9. This co-binding creates a highly stable RNA-protein complex that enhances mRNA translation. When either MSI2 or SYNCRIP is depleted, the complex falls apart and target mRNAs become degraded (4). SYNCRIP also has independent functions in maintaining proteostasis (protein homeostasis) in HSCs. SYNCRIP-deficient HSCs accumulate misfolded proteins, activate the unfolded protein response, and lose their regenerative capacity during stress. This occurs because SYNCRIP regulates translation of CDC42, a small GTPase that controls cell polarity and asymmetric division (12). Without adequate CDC42 levels, HSCs cannot properly segregate damaged proteins and organelles into daughter cells during division (2).

2.6 Therapeutic Implications and Current Limitations

The MSI2 story highlights both the promise and challenges of targeting RBPs in leukemia. On the positive side, MSI2 is clearly druggable, small-molecule inhibitors exist, and MSI2 depletion impairs leukemia without severely disrupting normal hematopoiesis in animal models (5).

However, several challenges remain. For instance, Current MSI2 inhibitors also affect MSI1, which has a different tissue distribution and distinct functions. Leukemia cells might upregulate compensatory RBPs when MSI2 is inhibited. Getting inhibitors into bone marrow HSCs and LSCs in patients requires sophisticated delivery systems(13). Furthermore, not all AML patients have elevated MSI2. Identifying patients who would benefit requires reliable biomarkers.

3. The IGF2BP Family: Oncofetal Proteins in Leukemia Stem Cells

3.1 IGF2BP1: Maintaining Leukemia Stem Cell Properties

The insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) represents a fascinating class of oncofetal RBPs that are expressed during development but silenced in most adult tissues, only to be reactivated in cancer (14).

IGF2BP1 contains six RNA-binding domains: two RRMs at the N-terminus and four hnRNP-K homology (KH) domains at the C-terminus (15). These domains work cooperatively to bind specific mRNA sequences, particularly in the 3' UTR and coding regions (16). In leukemia, IGF2BP1 expression correlates strongly with leukemia stem cell (LSC) properties**.** IGF2BP1-high cells exhibit enhanced colony formation in methylcellulose assays, which measure stem cell self-renewal, forming significantly more and larger colonies than IGF2BP1-low cells. In addition, IGF2BP1-high leukemia cells display increased tumor-initiating capacity. When transplanted into immunodeficient mice, these cells engraft more rapidly and at lower cell numbers, indicating a greater stem cell frequency. Furthermore, IGF2BP1 is enriched in ALDH+ populations. Aldehyde

dehydrogenase (ALDH) activity is a marker of cancer stem cells across many tumor types, and in leukemia, IGF2BP1 is preferentially expressed in the ALDH+ fraction (16).

2. Evidence Acquisition

Relevant literature was collected from major scientific databases and high-impact journals, including PubMed, Web of Science, Google Scholar, Nature Portfolio, Elsevier, and related peer-reviewed sources. This systematic review summarizes current findings on the roles of major RBPs and RNA-modifying factors in normal and malignant hematopoiesis, with particular focus on MUSASHI2, IGF2BP family proteins, Lin28b, METTL3, METTL14, ALKBH5, and FTO.

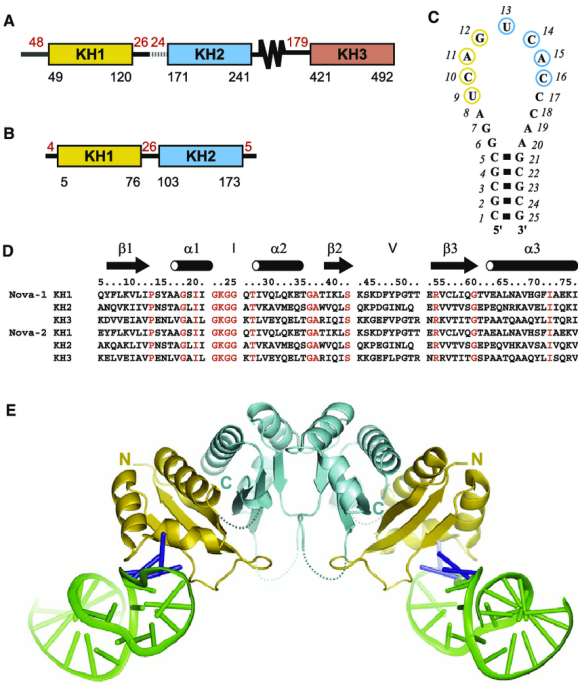

Figure 1. IGF2BP1 contains two RNA recognition motifs and four KH domains that cooperatively bind target mRNAs at coding regions and 3' untranslated regions, enabling selective post-transcriptional regulation.

3.2 Target mRNAs: HOXB4, MYB, and ALDH1A1

Using photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP), researchers identified IGF2BP1's direct mRNA targets. Among them, three targets appear to be particularly important (16):

HOXB4: A hematopoiesis-specific transcription factor that promotes HSC self-renewal without causing leukemia when expressed alone. In leukemia, IGF2BP1 stabilizes HOXB4 mRNA and enhances its translation. When HOXB4 is overexpressed in IGF2BP1-depleted cells, it partially rescues their proliferation defect, demonstrating that it's a functional downstream target.

MYB: A proto-oncogene encoding a transcription factor essential for all hematopoietic development. In AML, many leukemias become "MYB-addicted," requiring constant high MYB levels for survival. By binding to MYB mRNA, IGF2BP1 protects it from degradation; hence, maintaining elevated MYB protein level even when transcription is reduced.

ALDH1A1: An enzyme that converts retinaldehyde to retinoic acid, which normally promotes myeloid differentiation. However, ALDH1A1 also marks cancer stem cells. IGF2BP1 regulates ALDH1A1 mRNA stability, although the functional consequences of it remain unclear. High ALDH activity may help LSCs detoxify chemotherapy drugs or regulate their oxidative state.

3.3 IGF2BP1 and Drug Resistance

IGF2BP1 not only maintains LSCs but also contributes to their resistance to therapy. When IGF2BP1-expressing leukemia cells are treated with chemotherapy drugs, they show greater resistance than IGF2BP1-low cells(12).

Several mechanisms may lead to this effect. In antiapoptotic signaling, IGF2BP1 stabilizes BCL2 family member mRNAs, which prevents programmed cell death. In drug efflux, IGF2BP1 may regulate ABC transporter mRNAs that pump drugs out of cells (although this mechanism requires further investigation). In DNA repair, some IGF2BP1 targets are involved in DNA damage response, potentially helping cells survive genotoxic chemotherapy. These mechanisms may explain the clinical observation that patients with high IGF2BP1 expression exhibit not only poorer overall survival but also lower rates of complete remission following induction chemotherapy.

3.4 IGF2BP2 and IGF2BP3: Distinct but Related Functions

While IGF2BP1 has been most studied in leukemia, its family members IGF2BP2 and IGF2BP3 also play important roles (17).

IGF2BP2 shows more restricted expression than IGF2BP1, primarily in certain AML subtypes. Recent work identified IGF2BP2 as an m6A reader protein (discussed in the m6A section). IGF2BP2 recognizes m6A-modified mRNAs and enhances their stability and translation. In AML, IGF2BP2 regulates glutamine metabolism by controlling the expression of MYC, GPT2 (glutamic-pyruvate transaminase 2), and SLC1A5 (a glutamine transporter). When IGF2BP2 is depleted, leukemia cells show reduced glutamine consumption and impaired energy production (18). As an m6A reader, IGF2BP2 recognizes methylated

transcripts and protects them from degradation. In AML, transcripts involved in glutamine metabolism, such as SLC1A5, MYC, and GPT2, are stabilized through m6A-dependent IGF2BP2 binding, thereby sustaining glutamine utilization and metabolic fitness (19-21)

IGF2BP3 is particularly interesting because it is specifically overexpressed in mixed-lineage leukemia-rearranged (MLL-r) B-cell acute lymphoblastic leukemia (B-ALL) but not in other ALL subtypes. IGF2BP3 promotes the proliferation of hematopoietic stem and progenitor cells. In the context of fetal hematopoiesis, IGF2BP3 cooperates with Lin28b (discussed in section 5) to maintain fetal HSC properties (22).

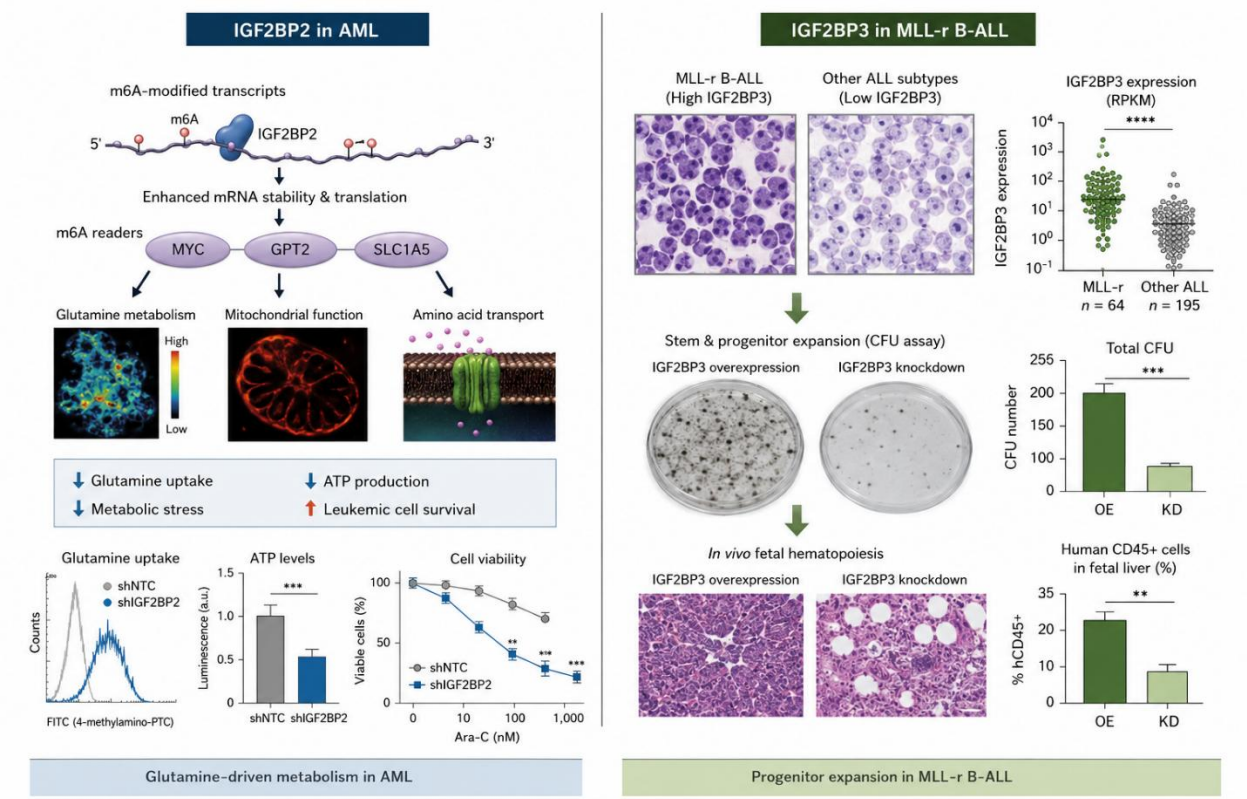

Figure 2. Subtype-specific functions of IGF2BP2 and IGF2BP3 in leukemia metabolism and stem cell programs.

3. Results

3.5 IGF2BP1 Inhibitors

Given IGF2BP1's clear oncogenic role, developing inhibitors became a priority. The first IGF2BP1 inhibitor, BTYNB, showed promising results in preclinical models of melanoma and ovarian cancer. It works by disrupting IGF2BP1 binding to its target mRNAs, leading to decreased expression of MYC and other oncogenes (16).

However, applying this to leukemia faces challenges. BTYNB has limited bioavailability and doesn't efficiently reach bone marrow cells. Newer compounds with improved pharmacological properties are under development. An alternative approach uses antisense oligonucleotides to degrade IGF2BP1 mRNA itself, although this requires sophisticated delivery systems to reach LSCs within their bone marrow niche.

4. m6A Modification: The Methylation Code in Hematopoiesis

4.1 N6-Methyladenosine: The Most Abundant mRNA Modification

N6-methyladenosine (m6A) represents the most prevalent epi-transcriptomic mark in eukaryotic mRNAs. Although discovered in the 1970s, its functional importance only became clear in the past decade, when technologies emerged to map m6A sites transcriptome-wide (23). m6A affects virtually every aspect of mRNA fate. Modified mRNAs can be, spliced differently (m6A near splice sites recruits splicing factors), exported from the nucleus more rapidly (m6A promotes export factor binding), translated more efficiently (some m6A readers enhance ribosome recruitment), or degraded more rapidly (other m6A readers target mRNAs for destruction)

The outcome depends on which "reader" protein recognizes the m6A mark. This creates an extraordinarily flexible regulatory system.

4.2 The m6A Writers: METTL3 and METTL14

m6A is installed by a methyltransferase complex centered on METTL3 and METTL14. METTL3 is the catalytic enzyme that transfers a methyl group from S-adenosylmethionine (SAM) to adenosine. METTL14 doesn't have catalytic activity but serves as a structural platform that helps recognize and bind mRNA substrates (24). WTAP (Wilms tumor 1-associated protein) helps localize the complex to nuclear speckles, where mRNA processing occurs. VIRMA/KIAA1429 directs the complex to preferentially methylate near stop codons and within 3' UTRs. RBM15 and RBM15B recruit the complex to U-rich sequences and help the methylation of long non-coding RNAs such as XIST. Together, these form the methyltransferase complex (MTC) that installs m6A at consensus RRACH motifs (R = A or G; H = A, C, or U) throughout the transcriptome.

4.3 METTL3 in Normal HSC Differentiation

In normal hematopoiesis, METTL3 plays a fascinating stage-specific role. It's not required or the maintenance of quiescent HSCs under steady-state conditions. However, when HSCs receive differentiation signals, METTL3 becomes essential (23).

MYC mRNA contains multiple m6A sites. METTL3-deposited m6A is recognized by reader proteins that enhance MYC translation. The resulting surge in the MYC protein drives cells to enter the cell cycle, commit to differentiation, and progress through lineage specification (25). Since METTL3 lacks intrinsic DNA-binding activity, its recruitment to promoters is mediated by transcription factors such as CEBPZ and associated transcriptional regulatory complexes, which tether METTL3 to chromatin and enable the co-transcriptional methylation of nascent transcripts (26).

When METTL3 is deleted from adult HSCs, the cells accumulate in the bone marrow. At first glance, this looks like an HSC expansion. However, these are not functional HSCs. They are trapped in an intermediate state, unable to properly differentiate and unable to self-renew effectively. In competitive transplantation experiments (in which METTL3-deficient and normal HSCs are transplanted together), the METTL3-deficient cells fail to contribute to long-term hematopoiesis. Although METTL3 serves as the catalytic component of the methyltransferase complex, METTL14 and additional RNA methyltransferases may partially compensate in specific cellular contexts. On the other hand, current evidence suggests that such compensation is insufficient to fully restore m6A deposition during HSC differentiation (27-29).

4.4 METTL3/METTL14 in Leukemia: Oncogenes or Tumor Suppressors?

In acute myeloid leukemia, METTL3 and METTL14 function as oncogenes, promoting leukemia development and maintenance. Yet, they are also required for normal HSC differentiation.

How can the same proteins be both essential for normal differentiation and drivers of leukemia? The answer lies in context-dependent function . In normal HSCs, METTL3-mediated m6A modification promotes differentiation (loss of stemness). However, in AML cells carrying oncogenic mutations, METTL3 is recruited to different genomic locations[31]. Instead of promoting differentiation, it helps maintain the leukemic state.

Unlike its role in normal cells, where it primarily modifies mature mRNAs, METTL3 in AML is recruited to gene promoters. There, it methylates nascent transcripts, enhancing their translation before they even leave the nucleus. This process is called "co-transcriptional methylation" (30,31). In AML, METTL3 preferentially methylates oncogenic mRNAs, such as SP1 (a transcription factor) and BCL2 (an antiapoptotic protein). This promotes leukemia cells survival and proliferation. METTL3 directly binds to eIF3h (a translation initiation factor), creating a "translation bridge" that enhances ribosome recruitment to methylated mRNAs. Clinical data support METTL3/14's oncogenic role in AML. Patients with high METTL3 or METTL14 expression have significantly shorter survival. When METTL3 is depleted from human AML cell lines, the cells stop proliferating, undergo differentiation, and become sensitive to chemotherapy (32).

4.5 METTL14-Specific Functions

While METTL3 has received more attention, METTL14 has distinct functions beyond its role in the MTC. METTL14 acts as a "scaffold" that organizes other m6A regulators. In AML, METTL14 promotes leukemogenesis through the m6A-dependent regulation of MYB, MYC, and targets in the PI3K/AKT signaling pathway (33).

Interestingly, METTL14 shows different effects in different disease contexts. In juvenile myelomonocytic leukemia (JMML), a rare pediatric disorder driven by RAS mutations, METTL14 knockout suppresses disease progression. This occurs through the regulation of autophagy genes. METTL14 normally enhances autophagy in RAS-mutant cells, and autophagy helps these cells survive under stress. Without METTL14, autophagy decreases, and RAS-mutant HSPCs become vulnerable (34).

This illustrates a key principle that RBP functions must be understood within specific disease contexts. What works in one disease subtype may not work in another (35).

4.6 m6A Erasers: FTO and ALKBH5

If m6A can be added, it can also be removed. Two enzymes, FTO (fat mass and obesity-associated protein) and ALKBH5 (AlkB homolog 5), function as m6A demethylases or "erasers." Both belong to the AlkB family of Fe (II)/α-ketoglutarate-dependent dioxygenases.

FTO was the first m6A demethylase to be discovered. Despite its name (derived from its initial discovery in obesity genetics), FTO plays crucial roles in cancer. In AML, FTO is overexpressed and promotes leukemia

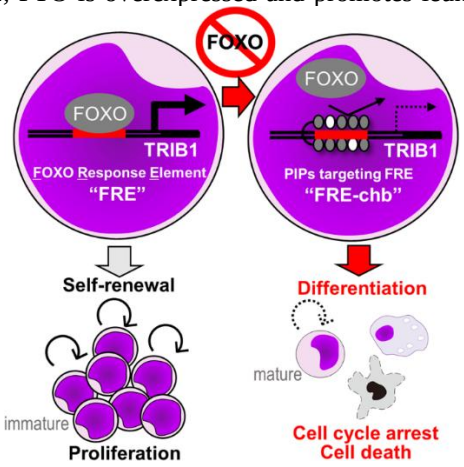

Figure 3. FTO-mediated regulation of FOXO3/TRIB1 signaling that contributes to AML self-renewal and differentiation blockade.

Early reports suggested that ALKBH5 was frequently deleted in AML, implying a tumor-suppressive function. However, comprehensive analyses revealed the opposite. ALKBH5 is overexpressed in most AML cases and correlates with poor prognosis. ALKBH5 selectively promotes leukemia stem cell self-renewal without being essential for normal hematopoiesis. How does it achieve this selectivity? The answer lies in its target specificity. ALKBH5 demethylates TACC3 mRNA (transforming acidic coiled-coil-containing protein 3), an oncogene involved in mitotic spindle organization and cell cycle progression. Demethylation by ALKBH5 stabilizes TACC3 mRNA, increasing TACC3 protein levels. High TACC3 promotes LSC proliferation and survival (24,37).

Importantly, ALKBH5 depletion impairs LSC function in serial transplantation assays (the gold standard test for stem cell function) but doesn't significantly affect normal HSC function. This creates a therapeutic window.

by demethylating ASB2 and RARA mRNAs. Demethylation stabilizes these mRNAs, leading to increased protein production. ASB2 degrades retinoic acid receptors, thereby blocking differentiation. Thus, FTO activity maintains AML cells in an undifferentiated state (36).

FTO also plays a role in chemotherapy resistance and relapse. Paired samples from AML patients collected at diagnosis and relapse show increased FTO expression following treatment. Mechanistically, FTO demethylates FOXO3 mRNA, a transcription factor that normally promotes differentiation. Less m6A on FOXO3 mRNA decreases its stability, reducing FOXO3 protein levels. This allows relapsed leukemia cells to resist differentiation therapy.

4.7 Connecting m6A to Metabolism: The ALKBH5-OGDH-TCA Cycle Axis

Recent work uncovered a strong connection between m6A modification and cellular metabolism. ALKBH5 deficiency leads to hypermethylation and destabilization of Ogdh mRNA, which encodes oxoglutarate dehydrogenase (OGDH), the rate-limiting enzyme in the tricarboxylic acid (TCA) cycle.

Lower OGDH levels slow the TCA cycle, causing the accumulation of α-ketoglutarate (α-KG). Excess α-KG is converted to L-2-hydroxyglutarate (L-2-HG), an oncometabolite that inhibits α-KG-dependent dioxygenases, including histone demethylases and TET enzymes (which regulate DNA methylation) (38). This creates a cascade from RNA demethylation (by ALKBH5) to altered TCA cycle flux, oncometabolite accumulation, chromatin changes, and altered gene expression. It beautifully illustrates how post-transcriptional regulation connects to metabolism and epigenetics (39).

In leukemia, this circuit can be exploited therapeutically, as shown in Figure 4. ALKBH5 inhibition disrupts metabolic homeostasis in LSCs, reducing their ATP production and impairing their competitive fitness. Several ALKBH5 inhibitors are in development, including DO-2728a and RD6 compounds, which have shown selective anti-leukemic effects in preclinical models (40).

4.8 m6A Readers: The Effectors of Methylation

m6A marks have little functional significance unless they are recognized by reader proteins that execute downstream functions. The Major m6A readers include YTH domain family proteins. YTHDF1 enhances translation, YTHDF2 promotes mRNA decay, and YTHDF3 cooperates with both. A nuclear

m6A reader that affects splicing and nuclear export has a critical role in HSC maintenance through microRNA processing (see section 4.7). As discussed earlier, the IGF2BP family acts as m6A readers that stabilize and enhance the translation of methylated mRNAs, creating a positive feedback loop in cancer cells. HNRNPA2B1 affects pri-miRNA processing and alternative splicing in an m6A-dependent manner (25,40).

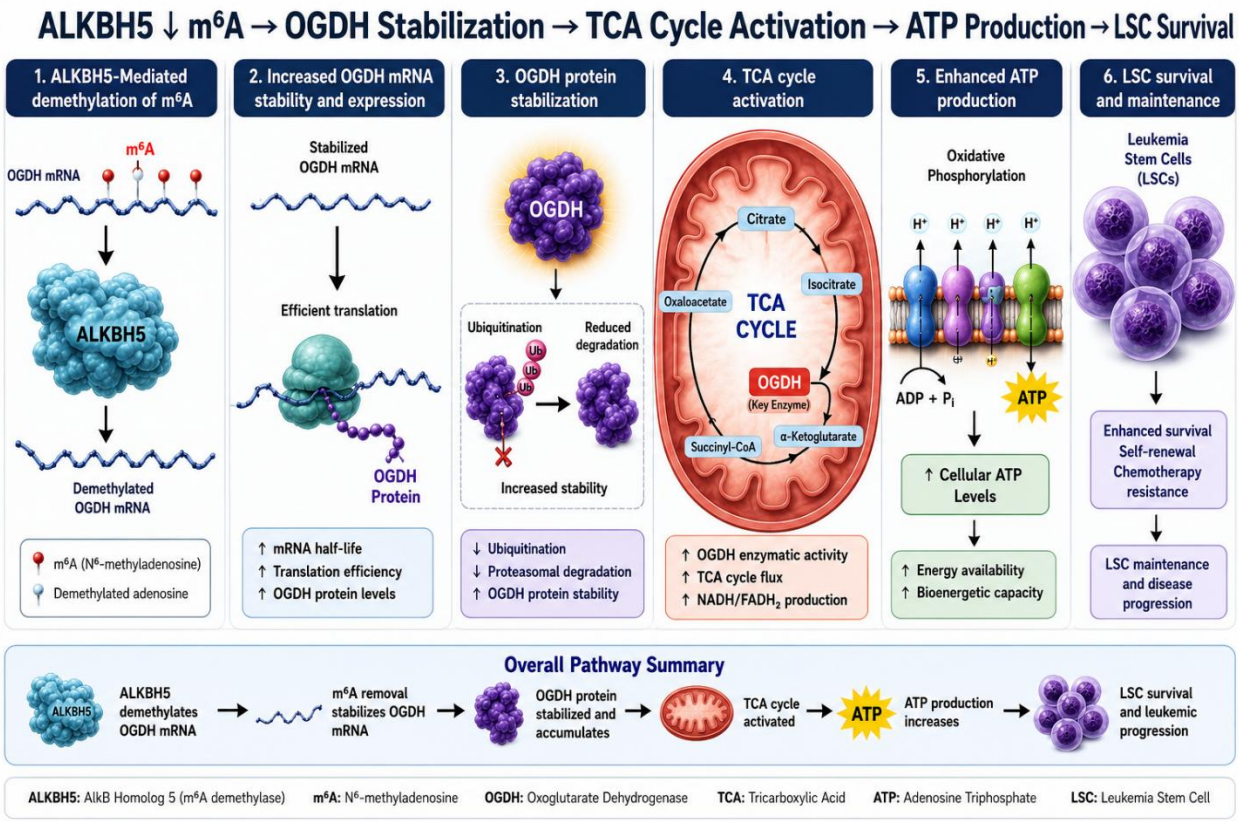

Figure 4. ALKBH5-OGDH axis links RNA demethylation to mitochondrial metabolism in leukemia stem cells.

The reader proteins create remarkable specificity. The same m6A mark on different mRNAs can have opposite effects, depending on which reader recognizes it in which cellular context (41).

4. Conclusion

The oncogenic role of METTL3/14 in AML sparked intense drug discovery efforts. The first breakthrough came with STM2457, a selective METTL3 inhibitor that showed anti-leukemic activity in mice without severe toxicity (42). Treated AML cells differentiated, stopped proliferating, and became sensitized to chemotherapy.

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Ethical Considerations and Compliance with Ethical Guidelines

Not applicable

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Conflict of interest

The authors declare that they have no conflicts of interest.

AI Using Declaration

The authors declare no artificial intelligent chatbot use.

Author's contributions

All authors equally contributed to the preparation of this article.

5.References

1. de Rooij L, et al. Post-transcriptional regulation in hematopoiesis: RNA binding proteins take control (1). Biochem Cell Biol. 2019 Feb;97(1):10-20. (DOI: 10.1139/bcb-2018-0097)
2. Herrejon Chavez F, et al. RNA binding protein SYNCRIP maintains proteostasis and self-renewal of hematopoietic stem and progenitor cells. Nat Commun. 2023;14(1):2290. (DOI: 10.1038/s41467-023-37988-7)
3. Raghav PK, Gangenahalli G, Hara T. Editorial: Advancements in hematopoietic stem cell proliferation and self-renewal maintenance. Front Cell Dev Biol. 2025;**13**: 1607145. (DOI: 10.3389/fcell.2025.1607145)
4. Xie W, et al. Crucial roles of different RNA-binding hnRNP proteins in Stem Cells. Int J Biol Sci. 2021;**17**(3):807-817. (DOI: 10.7150/ijbs.52977)
5. Minuesa G, et al. Small-molecule targeting of MUSASHI RNA-binding activity in acute myeloid leukemia. Int J Biol Sci. 2019;**10**(1): 2691. (DOI: 10.1038/s41467-019-10520-1)
6. Park SM, et al. Musashi2 sustains the mixed-lineage leukemia-driven stem cell regulatory program. J Clin Invest, 2015 Mar;125(3):1286-98. (DOI: 10.1172/JCI78440) (PMID)
7. karmakar, S., et al., Integrative genome-wide analysis reveals EIF3A as a key downstream regulator of translational repressor protein Musashi 2 (MSI2). NAR Cancer, 2022. 4(2). (Doi:10.1093/narcan/zcac015)
8. Tran, T.M. and D.S. Rao, RNA binding proteins in MLL-rearranged leukemia. Experimental Hematology & Oncology, 2022. 11(1): p. 80. (Doi:10.1186/s40164-022-00343-5)
9. Moradi F, et al. Signaling pathways involved in chronic myeloid leukemia pathogenesis: The importance of targeting Musashi2-Numb signaling to eradicate leukemia stem cells. Iran J Basic Med Sci. 2019 Jun;22(6):581-589. (DOI: 10.22038/ijbms.2019.33212.7923)
10. Niu Y, Zhou T, Li Y. Update on the Progress of Musashi-2 in Malignant Tumors. Front Biosci (Landmark Ed). 2025;30(1):24928. (PMID)
11. Kharas MG, et al. Musashi-2 regulates normal hematopoiesis and promotes aggressive myeloid leukemia. Nat Med. 2010 Aug;16(8):903-8. (DOI: 10.1038/nm.2187) (PMID)
12. Kwon C, et al. Notch post-translationally regulates ?-catenin protein in stem and progenitor cells. Nat Cell Biol. 2011 Oct;13(10):1244-51. (DOI: 10.1038/ncb2334) (PMID)
13.Lan L, et al. Human oncoprotein Musashi-2 N-terminal RNA recognition motif backbone assignment and identification of RNA-binding pocket. Oncotarget. 2017 Nov;8(1):63–66. (DOI:10.18632/oncotarget.22540) (PMID)
14.Ma S, Qin Y, Ren W. Insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) in hematological diseases. Mol Med. 2024;30(1):165. (DOI: 10.1186/s10020-024-00724-0)
15. Palanichamy JK, et al. RNA-binding protein IGF2BP3 targeting of oncogenic transcripts promotes hematopoietic progenitor proliferation. J Clin Invest. 2016 Apr;126(4):1495-511. (DOI: 10.1172/JCI80046) (PMID)
16.Elcheva IA, et al. RNA-binding protein IGF2BP1 maintains leukemia stem cell properties by regulating HOXB4, MYB, and ALDH1A1. Leukemia. 2020 May; 34(5):1354-63. (DOI: 10.1038/s41375-019-0668-4)
17.Cao J, Mu Q, Huang H. The Roles of Insulin-Like Growth Factor 2 mRNA-Binding Protein 2 in Cancer and Cancer Stem Cells. Stem Cells Int. 2018; 2018(1):4217259. (DOI: 10.1155/2018/4217259)
18. Weng H, et al. The m6A reader IGF2BP2 regulates glutamine metabolism and represents a therapeutic target in acute myeloid leukemia. Cancer Cell. 2022 Dec;40(12):1566–82. (DOI: 10.1016/j.ccell.2022.10.012) (PMID)
19. Liu, S., et al., IGF2BP2: an m6A reader that affects cellular function and disease progression. Cellular & Molecular Biology Letters, 2025. 30(1): p. 43. (Doi:10.1186/s11658-025-00723-9)
20. Li, D., et al., The Emerging Role of IGF2BP2 in Cancer Therapy Resistance: From Molecular Mechanism to Future Potential. Int J Mol Sci, 2024. 25(22). (Doi:10.3390/ijms252212150)
21. Zhang, H., et al., Combating cancer stem cells: RNA m6A methylation and small-molecule drug discovery. 2024. Volume 4 - 2024. (Doi:10.3389/fddsv.2024.1465222)
22. Wang S, et al. Enhancement of LIN28B-induced hematopoietic reprogramming by IGF2BP3. Genes Dev. 2019 Aug;33(15-16):1048–1068. (DOI: 10.1101/gad.324640.119) (PMID)
23. Sang L, et al. The m6A RNA methyltransferase METTL3/METTL14 promotes leukemogenesis through the MDM2/p53 pathway in acute myeloid leukemia. J Cancer. 2022;13(3):1019–30. (DOI: 10.7150/jca.67598)
24. Chen X, et al. RNA modification in normal hematopoiesis and hematologic malignancies. Blood Sci. 2024;5(11):e787. (PMID)
25. Zhao, W., et al., *METTL3 Facilitates Oral Squamous Cell Carcinoma Tumorigenesis by Enhancing c-Myc Stability via YTHDF1-Mediated m⁶A Modification.* Molecular Therapy Nucleic Acids, 2020. **20**: p. 1-12. (Doi:10.1016/j.omtn.2020.01.033)
26.Barbieri, I., et al., Promoter-bound METTL3 maintains myeloid leukaemia by m6A-dependent translation control. Nature, 2017. 552(7683): p. 126-131. (Doi:10.1038/nature24678)
27. Lee H, et al. Stage-specific requirement for Mettl3-dependent m6A mRNA methylation during haematopoietic stem cell differentiation. Nat Cell Biol. 2019 Jun;21(6):700–709. (DOI: 10.1038/s41556-019-0318-1) (PMID)
28. Cheng, Y., et al., m(6)A RNA Methylation Maintains Hematopoietic Stem Cell Identity and Symmetric

Commitment. Cell Rep, 2019. 28(7): p. 1703-1716.e6. (Doi:10.1016/j.celrep.2019.07.032)

29. Zhou, K.I. and T. Pan, Structures of the m(6)A Methyltransferase Complex: Two Subunits with Distinct but Coordinated Roles. Mol Cell, 2016. 63(2): p. 183-185. (Doi:10.1016/j.molcel.2016.07.005)

30. Wu, X., W. Ye, and Y. Gong, The Role of RNA Methyltransferase METTL3 in Normal and Malignant Hematopoiesis. 2022. Volume 12 - 2022. (Doi:10.3389/fonc.2022.873903)

31. Esteva-Socias, M. and F. Aguilo, METTL3 as a master regulator of translation in cancer: mechanisms and implications. NAR Cancer, 2024. 6(1). (Doi:10.1093/narcan/zcae009)

32. Kaur, P., et al., Altered Expression of m6A-Associated Genes Is Linked with Poor Prognosis in Pediatric Acute Myeloid Leukemia Patients. Biomolecules, 2025. 15(9). (Doi:10.3390/biom15091238)

33. Yao, L., et al., RNA methylation in hematological malignancies and its interactions with other epigenetic modifications. Leukemia, 2021. 35(5): p. 1243-1257. (Doi:10.1038/s41375-021-01225-1)

34. iang, L., et al., The m6A methyltransferase METTL14 promotes cell proliferation via SETBP1-mediated activation of PI3K-AKT signaling pathway in myelodysplastic. (Doi:10.1038/s41375-024-02350-3)

35.Zou, H., et al., RNA-binding protein complex LIN28/MSI2 enhances cancer stem cell-like properties by modulating Hippo-YAP1 signaling and independently of Let-7. Oncogene, 2022. 41(11): p. 1657-1672. (Doi:10.1038/s41388-022-02198-w)

36.Fang, M., et al., M6A Demethylase ALKBH5 in Human Diseases: From Structure to Mechanisms. 2025. 15(2): p. 157. (Doi:10.3390/biom15020157)

37.Shen, C., et al., RNA Demethylase ALKBH5 Selectively Promotes Tumorigenesis and Cancer Stem Cell Self-Renewal in Acute Myeloid Leukemia. Cell Stem Cell, 2020. 27(1): p. 64-80.e9. (Doi:10.1016/j.stem.2020.04.009)

38.Ye, J. and R. Blelloch, Regulation of pluripotency by RNA binding proteins. Cell Stem Cell, 2014. 15(3): p. 271-280. (Doi:10.1016/j.stem.2014.08.010)

39.Helgason, G.V., et al., Autophagy in chronic myeloid leukaemia: stem cell survival and implication in therapy. Curr Cancer Drug Targets, 2013. 13(7): p. 724-34. (Doi:10.2174/15680096113139990088)

40.Shi, H., et al., YTHDF3 facilitates translation and decay of N6-methyladenosine-modified RNA. Cell Research, 2017. 27(3): p. 315-328. (Doi:10.1038/cr.2017.15)

41.Wang, X., et al., N6-methyladenosine-dependent regulation of messenger RNA stability. Nature, 2014. 505(7481): p. 117-120. (Doi:10.1038/nature12730)

42.Gao Y, et al. ALKBH5 modulates hematopoietic stem and progenitor cell energy metabolism through m6A modification-mediated RNA stability control. Cell Rep. 2023;42(10):113163. (DOI: 10.1016/j.celrep.2023.113163)