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# Emerging roles of RNA m$^6$A modification in multiple myeloma pathogenesis and treatment resistance (Review)

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**Abstract.** Multiple myeloma (MM) is an incurable hematologic malignancy characterized by the clonal expansion of plasma cells in the bone marrow. Despite advances in therapeutic agents, including proteasome inhibitors, immunomodulatory drugs and immunotherapies, relapse driven by treatment resistance remains a major clinical challenge. This underscores the critical need to elucidate additional molecular mechanisms that drive MM pathogenesis and therapeutic failure. The emerging field of epitranscriptomics, which studies post-transcriptional RNA modifications, offers a promising perspective. Among these modifications, N6-methyladenosine (m$^6$A), the most abundant internal mRNA modification, has been implicated in regulating nearly every aspect of RNA metabolism. Growing evidence indicates that dysregulation of the m$^6$A modification machinery plays a pivotal role in MM heterogeneity, disease progression and drug resistance. The present review synthesized current knowledge on how specific m$^6$A regulators contribute to MM oncogenesis by modulating key signaling pathways, interactions with the bone marrow microenvironment and responses to therapy. It also discussed the potential of targeting m$^6$A pathways as a therapeutic strategy to overcome treatment resistance and improve patient outcomes. By highlighting recent advances and future directions, the present review underscored m$^6$A modification as an important frontier in the battle against MM.

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*Key words:* N6-methyladenosine, multiple myeloma, treatment resistance, biomarkers, targeted therapy

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## 1. Introduction

Multiple myeloma (MM) is an incurable hematologic malignancy characterized by clonal expansion and accumulation of plasma cells in the bone marrow (1,2). It is associated with the production of abnormal antibodies, referred to as monoclonal proteins or M proteins (3). Also known as plasma cell myeloma or simply myeloma, MM accounts for ~1% of all types of cancer and 15% of hematologic malignancies, with an incidence that increases with age and is higher in men than in women (4-7). Despite remarkable progress in its treatment, MM remains largely incurable, posing significant challenges because of its complex pathogenesis, frequent diagnostic delays caused by nonspecific symptoms and the almost inevitable development of treatment resistance (8,9).

The treatment paradigm for MM has undergone a profound transformation, moving from conventional chemotherapy to a multi-agent, mechanism-based approach. Foundational

regimens combining proteasome inhibitors (such as bortezomib and carfilzomib), immunomodulatory drugs (IMiDs; such as lenalidomide and pomalidomide) and corticosteroids formed the first major wave of therapeutic progress (10-17). More recently, immunotherapies, including monoclonal antibodies (such as daratumumab targeting CD38) and T-cell redirecting agents such as bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapy have further improved patient outcomes (18-21). Despite these advances, relapse and drug resistance remains a nearly universal challenge, highlighting the remarkable adaptability of MM cells and the urgent need for strategies that target the molecular basis of resistance (22-24).

These challenges are further compounded by the disease's complexity. Diagnosis is often delayed because of nonspecific initial symptoms (such as fatigue, bone pain and anemia) (4,25-27) and its pathogenesis involves a multifaceted interplay of genetic, epigenetic and bone marrow microenvironment factors that promote myeloma cell survival and drug resistance (1,4,28-30). The incomplete understanding of these resistance mechanisms limits the development of curative therapies for relapsed/refractory MM (18,20,31-33). Therefore, gaining deeper insights into MM biology from new perspectives is critical for improving patient outcomes.

Epitranscriptomics, the study of post-transcriptional RNA modifications, has emerged as a crucial layer of gene regulation (34-36). More than 170 chemical modifications have been identified and these alterations profoundly influence RNA metabolism, including stability, splicing and translation (37,38). Among them, N6-methyladenosine ($m^6A$), the most abundant internal mRNA modification, has garnered significant attention for its roles in normal biology and cancer pathogenesis (39,40). Growing evidence implicates dysregulated $m^6A$ modification in solid tumors and hematological malignancies, including MM, where it influences disease pathogenesis, therapeutic response and drug resistance (41-43).

The present review aimed to synthesize the current understanding of $m^6A$ dysregulation in MM, with a particular focus on its role in pathogenesis, bone marrow microenvironmental interactions and treatment resistance and to evaluate the potential of targeting this pathway therapeutically.

## 2. Methods

A literature search was performed in the PubMed/MEDLINE (pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://webofscience.clarivate.cn/) databases to identify relevant studies on $m^6A$ modification in MM and related epitranscriptomic mechanisms. Literature searches were performed to identify relevant studies published up to 20 December 2025 using combinations of controlled vocabulary and free-text terms, including: 'multiple myeloma' OR 'plasma cell myeloma' AND ('$m^6A$' OR 'N6-methyladenosine' OR 'epitranscriptomics' OR 'RNA methylation' OR 'RNA modification') and, where appropriate, individual regulator terms ('METTL3', 'METTL14', 'WTAP', 'VIRMA/KIAA1429', 'RBM15', 'FTO', 'ALKBH5', 'YTHDF1/2/3', 'YTHDC1/2', 'IGF2BP1/2/3', 'HNRNPA2B1', 'HNRNPC'). Additional searches combined MM with clinically oriented keywords ('drug resistance', 'bortezomib', 'lenalidomide', 'pomalidomide', 'daratumumab', 'CAR-T', 'microenvironment', 'exosome', 'immune infiltration', 'bone disease'). Reference lists of included articles and relevant reviews were also screened to identify additional primary studies.

Eligible records included original research articles, preclinical studies and clinical or translational reports that examined i) $m^6A$ regulators or $m^6A$-dependent mechanisms in MM models or patient samples, or ii) pharmacological or genetic modulation of $m^6A$ pathways with potential therapeutic relevance. Studies from other malignancies were included selectively when they provided key mechanistic insight or information on inhibitor development/chemical tractability and such evidence is explicitly identified as non-MM where discussed. Studies were excluded if they were i) published in non-English languages, ii) conference abstracts without accompanying full-text primary data, iii) retracted publications, or iv) not directly relevant to the core focus on RNA modification biology in MM.

## 3. Regulation and functional significance of RNA $m^6A$ modification

Traditionally, epigenetic regulation has focused on DNA methylation and histone modifications as key determinants of gene expression (44-46). The emergence of epitranscriptomics has now revealed reversible chemical modifications on RNA as a critical additional layer of gene regulation (47,48). Among known RNA modifications, $m^6A$ is the most prevalent internal modification on eukaryotic mRNA (49). The presence of $m^6A$ on a transcript serves as a direct binding platform for specific reader proteins, which markedly influence the RNA's fate by regulating its splicing, stability, export and translation (40,50,51). Another key mechanism of action involves the ability of $m^6A$ to function as an '$m^6A$ switch', in which the modification alters the RNA's secondary structure to reveal binding sites for proteins that would otherwise be inaccessible (52,53). This allows for rapid, post-transcriptional fine-tuning of gene expression in response to cellular signals, a process frequently dysregulated in cancer.

*The m6A regulatory machinery: Writers, readers and erasers*. RNA $m^6A$ modification is regulated by a cohort of enzymes that catalyze the installation, removal, recognition and function of these modifications (35,54). Writers, erasers and readers constitute the trio of components involved in $m^6A$ regulation (Fig. 1). The installation of $m^6A$ modification is carried out by a group of enzymes known as writers (55). For example, the $m^6A$ writer complex includes methyltransferase-like 3 (METTL3), METTL14 and Wilms tumor 1-associating protein (WTAP) among others. These enzymes collaboratively catalyze the methylation process, with METTL3 serving as the catalytic subunit (56,57). Accessory proteins such as vir-like $m^6A$ methyltransferase associated protein (VIRMA), RNA binding motif protein 15 (RBM15) and METTL16 further modulate the specificity and efficiency of $m^6A$ installation (58). Conversely, eraser enzymes such as fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5) are responsible for demethylating $m^6A$, removing the methyl group and thus

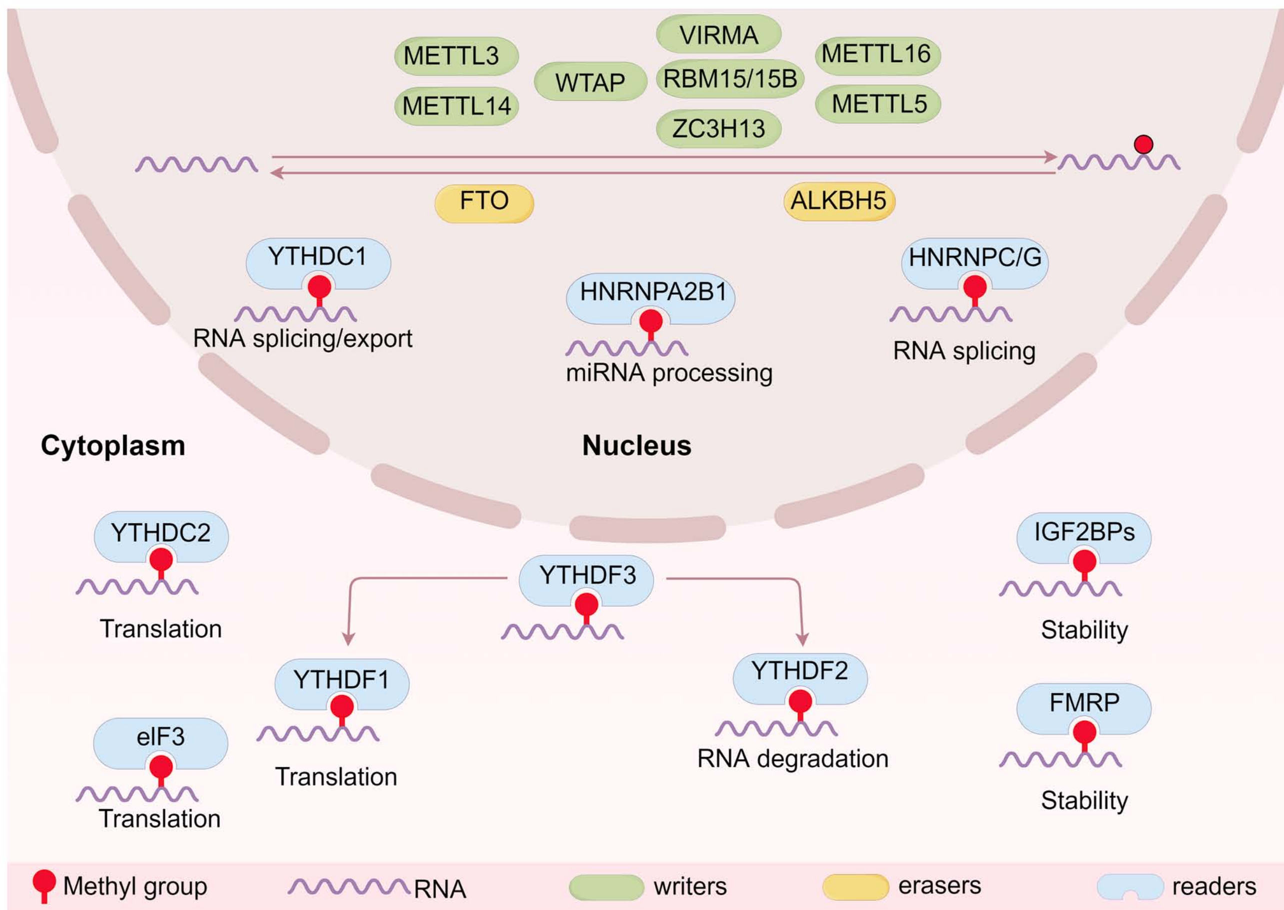


Figure 1. The m6A methylation regulatory machinery and its functional roles. The figure depicts the spatial organization of m6A regulatory proteins within a eukaryotic cell. In the nucleus, methyltransferase 'writers' (green) deposit m6A modifications on nascent RNA transcripts, while demethylase 'erasers' (yellow) catalyze their removal. Nuclear 'readers' (blue) recognize m6A marks to regulate RNA splicing, export and microRNA processing. In the cytoplasm, distinct reader proteins mediate translational enhancement, degradation, or stabilization of target transcripts, illustrating the functional diversity of m6A signaling in post-transcriptional control. Protein labels indicate key factors in each regulatory step. m6A, N6-methyladenosine; METTL3/5/14/16, methyltransferase-like 3/5/14/16; WTAP, Wilms tumor 1-associated protein; VIRMA, vir-like m6A methyltransferase associated; RBM15/15B, RNA-binding motif protein 15/15B; ZC3H13, zinc finger CCCH-type containing 13; FTO, fat mass and obesity-associated protein; ALKBH5, alkB homolog 5; YTHDC1/2, YTH domain-containing 1/2; YTHDF1/2/3, YTH domain family protein 1/2/3; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins; HNRNPC/G, heterogeneous nuclear ribonucleoprotein C/G; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1; FMRP, fragile X messenger ribonucleoprotein; eIF3, eukaryotic translation initiation factor 3. The figure was created in Figdraw (https://www.figdraw.com).

reversing the modification (56,59). This dynamic installation and removal establish a regulatory mechanism that finely tunes RNA function in response to cellular conditions.

The fate of m6A-modified RNA is tightly regulated by various reader proteins. For instance, YTH domain-containing proteins, recognize and bind to m6A-modified sites to influence mRNA stability and translation efficiency (56). Specifically, YTH domain family protein 1 (YTHDF1) primarily facilitates translation by interacting with translation initiation factors to enhance the translation efficiency of m6A-modified mRNAs; YTHDF2 is well-known for its role in promoting mRNA decay, targeting m6A-modified transcripts for degradation; by contrast, YTHDF3 acts as a multifaceted adapter that can coordinate with either YTHDF1 to promote translation or with YTHDF2 to expedite mRNA decay, thereby fine-tuning the balance between mRNA stability and translation (60). YTH domain containing protein 1 (YTHDC1) is involved in the regulation of splicing, while YTHDC2 affects multiple aspects of RNA metabolism, with reported roles in splicing and translation (61). The insulin-like growth factor 2 mRNA-binding proteins, which also recognize m6A sites, are known to enhance the stability and storage of their target mRNAs (62).

Additionally, heterogeneous nuclear ribonucleoproteins (hnRNPs), such as heterogeneous nuclear ribonucleoprotein C/G (hnRNPC/G) and heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNPA2B1), recognize m6A modifications and influence miRNA processing and splicing events by facilitating the recruitment of splicing factors and modulating alternative splicing patterns (63,64). Eukaryotic initiation factor 3 can bind to m6A sites, particularly near the 5' untranslated region (UTR) of mRNAs, to directly promote translation initiation in a cap-independent manner, enhancing the translation of specific transcripts under certain conditions (65). Fragile X mental retardation protein is another recognized m6A reader that plays a role in neuronal mRNA localization and stability, thereby influencing synaptic function and plasticity (66). This regulatory capacity of m6A modification, which spans mRNA splicing, localization, stability and translation efficiency, allows cells to finely tune gene expression in response to developmental cues and environmental stresses.

*Fundamental functions of m$^6$A in RNA metabolism and cellular physiology*. The m$^6$A modification serves as a fundamental regulator of RNA metabolism, exerting precise control over gene expression and a broad range of cellular processes. It governs nearly every stage of the mRNA life cycle: in the nucleus, it determines exon inclusion during splicing and facilitates mRNA export to the cytoplasm (67-70). Once in the cytoplasm, m$^6$A directly influences transcript stability and translation efficiency, thereby dictating mRNA half-life and protein synthesis levels (71,72). This multifaceted regulation is indispensable for directing critical cellular behaviors, including stem cell renewal, neurogenesis and other fate decisions, ensuring proper development and physiological function (73,74).

The dynamic nature of m$^6$A is crucial for cellular adaptation to various cues. Under stress conditions such as heat shock or oxidative stress, rapid m$^6$A remodeling enables selective stabilization or degradation of key transcripts, facilitating a swift response (75,76). Notably, this regulation can be recursive, as exemplified by an m$^6$A-modified transcript regulating the stability of its reader, IGF2BP1, under heat stress (77). m$^6$A also contributes to maintaining circadian rhythms by modulating the stability of clock gene transcripts, thereby ensuring cellular homeostasis (78,79). This capability to adapt both to intrinsic cycles and extrinsic stressors underscores m$^6$A's essential role in preserving the balance and functionality of cellular environments.

The regulatory scope of m$^6$A extends beyond mRNA to include non-coding RNAs (ncRNAs). It influences the biogenesis of microRNAs (miRNAs) and the function of long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), which themselves act as scaffolds, sponges, or epigenetic regulators (52,80-82). Furthermore, extensive crosstalk exists between the epitranscriptome and other epigenetic layers. m$^6$A can recruit chromatin modifiers to influence histone modifications and DNA methylation, thereby impacting transcription and chromatin accessibility (45,83). It also modulates diverse RNA-RNA, RNA-DNA and RNA-protein interactions crucial for various cellular processes and affects the formation of RNA-DNA hybrids (R-loops), which have implications for transcription and genome stability (84-86).

Taken together, the m$^6$A modification is a versatile and powerful regulator of gene expression. Its ability to integrate signals and coordinate complex cellular programs makes it indispensable for normal physiology. However, this same versatility means that its dysregulation can have profound consequences, directly contributing to the pathogenesis of human diseases, including cancer, by disrupting the precise control of oncogenic and tumor-suppressive pathways.

*Dysregulation of m$^6$A in human cancer*. The dysregulation of RNA m$^6$A modification has emerged as a critical mechanism in tumorigenesis, adding a new dimension to our understanding of gene expression control in cancer beyond traditional genetic and epigenetic alterations (87-89). By disrupting cellular homeostasis, aberrant m$^6$A modification contributes markedly to tumor initiation and progression (90-92). Accumulating evidence has demonstrated the implications of RNA m$^6$A modification in solid tumors and hematological malignancies. This section briefly summarizes the functional roles and clinical relevance of m$^6$A dysregulation in cancer.

The sophisticated regulatory functions of m$^6$A in normal cellular processes are frequently subverted in oncogenesis (49,93). By controlling mRNA stability, splicing, localization and translation, m$^6$A directly influences the expression of oncogenes and tumor suppressor genes, thereby driving cancer hallmarks such as uncontrolled proliferation, invasion and metastasis (94-96). This is mechanistically demonstrated in diverse types of cancer. For instance, METTL3 promotes the epithelial-mesenchymal transition by adding m$^6$A marks to Forkhead box protein O1 (*FOXO1*) mRNA, leading to its YTHDF2-mediated decay (97). Another study identified *Mettl3* as a crucial regulator for transitioning murine stem cells from the naive to the primed pluripotent state by promoting mRNA degradation of key pluripotency factors, linking cancer stem cell features to m$^6$A modification (98). In hepatocellular carcinoma, WTAP facilitates disease progression via an m$^6$A-dependent mechanism that epigenetically silences the tumor regulator erythroblast transformation specific 1 (*ETS1*) mRNA (99). Conversely, ALKBH5 maintains glioblastoma stem-like cells by demethylating and stabilizing *FOXM1* transcripts (100). Loss of YTHDF2 enhances macrophage recruitment and mitochondrial respiration of $CD8^+$ T cells, ultimately inhibiting the growth of melanoma tumor cells and improving survival in immunocompetent models (101). Wang *et a* (102) demonstrated that m$^6$A-mediated control of mRNA translation influences cancer-relevant gene expression, emphasizing its role in oncogenesis. The examples from various other solid tumors that are extensively reviewed elsewhere, underscore that m$^6$A modifiers can function as context-dependent oncogenes or tumor suppressors (103,104).

Similarly, m$^6$A dysregulation is a recognized hallmark of hematological malignancies, as detailed in other specialized reviews (34,105). It disrupts normal hematopoiesis and immune surveillance to promote leukemogenesis and progression (34,105,106). The roles of m$^6$A regulators are often complex and dualistic. For example, FTO has been demonstrated to promote the development of acute myeloid leukemia (AML) by reducing m$^6$A levels on transcripts, including *ASB2* and *RARA*, underscoring the oncogenic potential of FTO in AML (107). Conversely, other studies showed that METTL3, a core component of the m$^6$A writer complex, controls myeloid differentiation in both normal hematopoietic and leukemia cells (108,109). Depletion of METTL3 promotes cell differentiation and reduces cell proliferation, indicating a tumor-suppressive role of m$^6$A modulation in this context (108). IGF2BP3 is overexpressed in AML and drives disease progression by binding to and stabilizing *RCC2* transcripts in an m$^6$A-dependent manner (110). These studies illustrate the dual and context-dependent roles of m$^6$A modifications in hematopoiesis and leukemia.

Given this paradigm of m$^6$A's importance in oncology and hematology, its investigation in MM is a logical and critical frontier. The ability of m$^6$A modifications to alter the expression of critical oncogenes and tumor suppressors, as demonstrated in other cancers, strongly positions it as a key player in MM pathogenesis, progression and drug resistance. The following sections will focus exclusively on synthesizing the growing evidence for m$^6$A's role in this specific hematological cancer.

## 4. RNA m$^6$A modification in MM pathogenesis and progression

Dysregulation of the m$^6$A modification is increasingly recognized as a contributor of MM pathogenesis. By altering the expression of oncogenes and tumor suppressors, aberrant m$^6$A modification impacts crucial cellular processes, promoting tumorigenesis, disease progression and interaction with the tumor microenvironment (48,111). The clinical relevance of this dysregulation is underscored by bioinformatics studies, which have shown that m$^6$A regulator expression profiles can stratify MM patients into distinct prognostic groups and are associated with response to therapy (112,113). For instance, a study analyzing 21 m$^6$A regulators in MM patient samples identified three distinct clusters with significant differences in overall survival and established a two-gene prognostic signature (HNRNPA2B1 and KIAA1429) that served as an independent prognostic indicator (112). Another study developed and validated a gene-pairing model based on 13 m$^6$A regulators (CPSF6, FMR1, FTO, HNRNPA2B1, HNRNPC, IGF2BP2, METTL14, NUDT21, RBM15, SRSF10, YTHDF1, YTHDF2 and YTHDF3) in over 2,000 patients, where a high-risk score was an independent prognostic factor and, when combined with the International Staging System (ISS), created an 'm6A-enhanced ISS' with superior stratification accuracy (113). This model showed that its composite score increases stepwise across the disease continuum, from monoclonal gammopathy of undetermined significance to smoldering MM, active MM and ultimately plasma cell leukemia (113). These findings position m$^6$A status as a dynamic biomarker of both clinical stage and malignant transformation. The following sections detail the specific roles of m$^6$A writers, readers and erasers in this pathogenesis and progression.

*Oncogenic roles of m$^6$A writers*. The writer complex, responsible for installing m$^6$A marks, is frequently upregulated in MM. Pre-clinical studies predominantly report oncogenic functions for these writers, though clinical validation is ongoing. For instance, studies indicate METTL3 enhances the maturation of oncogenic miR-182-5p via m$^6$A modification, leading to downregulation of the proliferation inhibitor calcium/calmodulin-dependent protein kinase II inhibitor 1 (*CAMK2N1*) (Fig. 2A) (114). In a separate proposed axis, METTL3 stabilizes Yin Yang 1 (*YY1*) mRNA and promotes the maturation of primary-miR-27a-3p, suggesting a potential feedback loop that drives proliferation and stemness (Fig. 2B) (115). Furthermore, METTL3 upregulates the translation initiation regulator basic leucine zipper and W2 domains 2 (*BZW2*) through m$^6$A methylation, accelerating MM cell proliferation and inhibiting apoptosis (Fig. 2C) (116). In addition, METTL3 collaborates with the oncogenic lncRNA metastasis associated lung adenocarcinoma transcript 1 (*MALAT1*) to promote MM cell proliferation and *MALAT1* overexpression rescues the effects of METTL3 knockdown (117). The potential oncogenic role of METTL3 is further supported by evidence that the antidiabetic drug metformin exerts anti-myeloma effects partly by impairing METTL3-mediated m$^6$A modification of genes such as thyroid hormone receptor associated protein 3, RNA binding motif protein 25 and ubiquitin specific peptidase 4 (118-120). It is important to note that these METTL3-dependent axes are primarily supported by individual *in vitro* and xenograft studies. Their relative contributions and clinical relevance in heterogeneous MM patient populations require independent validation and further investigation.

Other writers also contribute to MM pathogenesis in pre-clinical contexts. For example, METTL5 has been shown to drive MM progression by enhancing the translation of selenoproteins such as selenophosphate synthetase 2 (*SEPHS2*), which is critical for mitigating oxidative stress (121). The accessory writer protein VIRMA (KIAA1429) is overexpressed in MM and experimental evidence suggests it promotes tumorigenesis by enhancing m$^6$A modification and expression of the oncogene forkhead box M1 (*FOXM1*) via the reader YTHDF1 (122). Beyond regulating oncogene expression, VIRMA has been linked to suppression of ferroptosis to promote MM cell survival (123). Mechanistically, VIRMA is stabilized by the lncRNA *FEZF1-AS1* and, in turn, enhances m$^6$A-dependent translation of OTU deubiquitinase, ubiquitin aldehyde binding 1 (*OTUB1*). OTUB1 then deubiquitinates and stabilizes the ferroptosis defense protein solute carrier family 7 member 11 (SLC7A11), protecting MM cells. The core writer complex component WTAP also appears to function as a critical oncogene. A recent study identified WTAP as overexpressed in MM patients and associated with poor survival (124). Mechanistically, this study reported that WTAP installs m$^6$A modifications on microtubule-associated protein 6 domain containing 1 mRNA, thereby regulating the Hippo signaling pathway to drive MM cell proliferation. Notably, the writer complex can be regulated post-translationally; research indicates protein arginine methyltransferase 1 methylates and stabilizes WTAP, which in turn enhances m$^6$A modification of NADH:ubiquinone oxidoreductase core subunit S6 mRNA, boosting its expression and activating oxidative phosphorylation to promote tumorigenesis (125).

Collectively, while these studies identify promising oncogenic roles for m$^6$A writers in MM, the current mechanistic understanding is predominantly derived from *in vitro* and mouse xenograft models. Independent replication and validation in primary patient samples are essential to establish their significance and prioritize translational efforts.

*m$^6$A readers as executors of pro-tumorigenic programs*. The functional output of m$^6$A methylation is largely determined by reader proteins, whose dysregulation in MM orchestrates diverse oncogenic programs. A pivotal player is YTHDF2, whose elevated expression correlates with poor patient prognosis (126). Loss- and gain-of-function experiments established a causal role for YTHDF2 in driving MM proliferation both *in vitro* and *in vivo*. Mechanistic insights revealed that YTHDF2 recognizes m$^6$A motifs on the signal transducer and activator of transcription 5A (*STAT5A*) transcript, promoting its degradation (126). Subsequent rescue experiments confirmed that STAT5A acts as a tumor suppressor by attenuating ERK phosphorylation via interaction with the mitogen-activated protein kinase kinase 2 (*MAP2K2*) promoter, thereby delineating the YTHDF2-STAT5A-MAP2K2-p-ERK axis as a key proliferative driver (Fig. 3A) (126). Parallel investigations established that YTHDF2 promotes $G_1$/S phase transition of

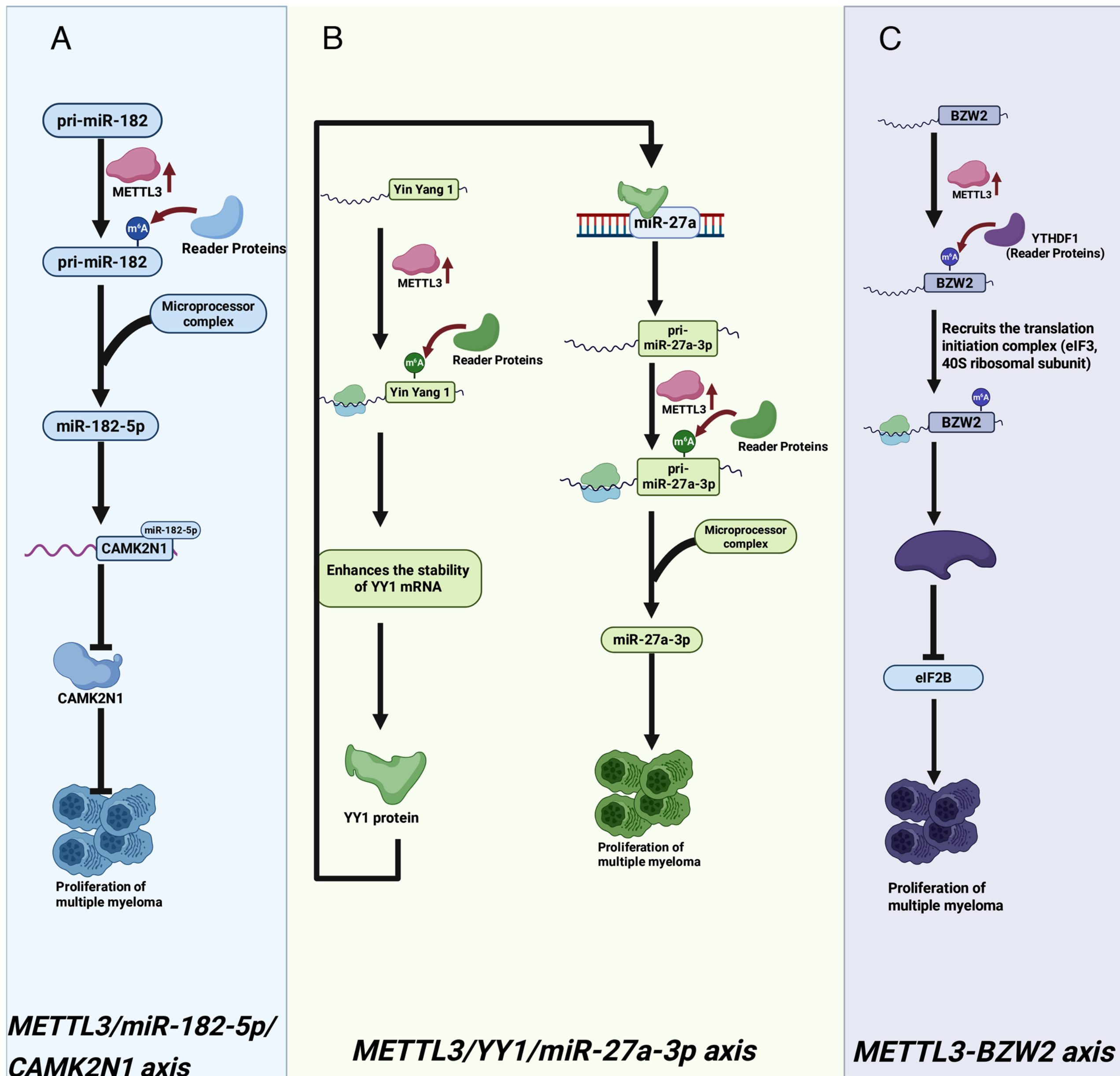


Figure 2. METTL3-driven oncogenic pathways in MM tumorigenesis. (A) METTL3 facilitates miR-182-5p maturation through m6A modification, suppresses *CAMK2N1* and drives MM proliferation and tumorigenesis (Main evidence: *in vitro* studies). (B) METTL3 upregulates *YY1* and miR-27a-3p via m6A modification, driving MM proliferation and stemness (Main evidence: *in vitro* assays and patient cohort analysis). (C) METTL3 upregulates *BZW2* via m6A modification, promoting MM proliferation and anti-apoptosis (Main evidence: *In vitro* functional validation). m6A, N6-methyladenosine; METTL3, methyltransferase-like 3; pri-miR-182, primary microRNA-182; pri-miR-27a, primary microRNA-27a; miR-182-5p, microRNA-182-5p; miR-27a-3p, microRNA-27a-3p; CAMK2N1, calcium/calmodulin-dependent protein kinase II inhibitor 1; YY1, Yin Yang 1; BZW2, basic leucine zipper and W2 domains 2; YTHDF1, YTH domain family protein 1; eIF3, eukaryotic translation initiation factor 3; eIF2B, eukaryotic translation initiation factor 2B; 40S, 40S ribosomal subunit. The figure was created in Biorender (https://BioRender.com).

MM cells by degrading the tumor suppressor early growth response 1 (EGR1). This model is solidified by the finding that EGR1 knockdown abrogates the cytostatic effect of YTHDF2 depletion, as EGR1 transactivates p21 and represses the CDK2/cyclin E1 complex (Fig. 3B) (127).

The oncogenic role of readers extends to genetically defined MM subgroups. IGF2BP1 is markedly overexpressed in patients with chromosome 1q gain, where it predicts an inferior clinical outcome (128). Mechanistically, IGF2BP1 directly binds to m6A sites within the cell division cycle 5-Like (*CDC5L*) mRNA, enhancing its stability and translation. The functional dependency of this axis was confirmed by the fact that genetic or pharmacological inhibition of IGF2BP1 suppressed the pro-tumor effects, revealing the IGF2BP1-CDC5L axis as a vulnerability in this high-risk population (128).

A paramount clinical challenge in MM is the bone disease and m6A readers are critically involved in this destructive process (129,130). The reader hnRNPA2B1 is a key orchestrator of myeloma bone disease, as its expression correlates with the number of osteolytic lesions. hnRNPA2B1 drives bone destruction via a dual exosomal miRNA mechanism. It promotes the maturation and exosomal packaging of specific miRNAs, such as miR-92a-2-5p and miR-373-3p, in an m6A-dependent manner. Upon delivery to the bone

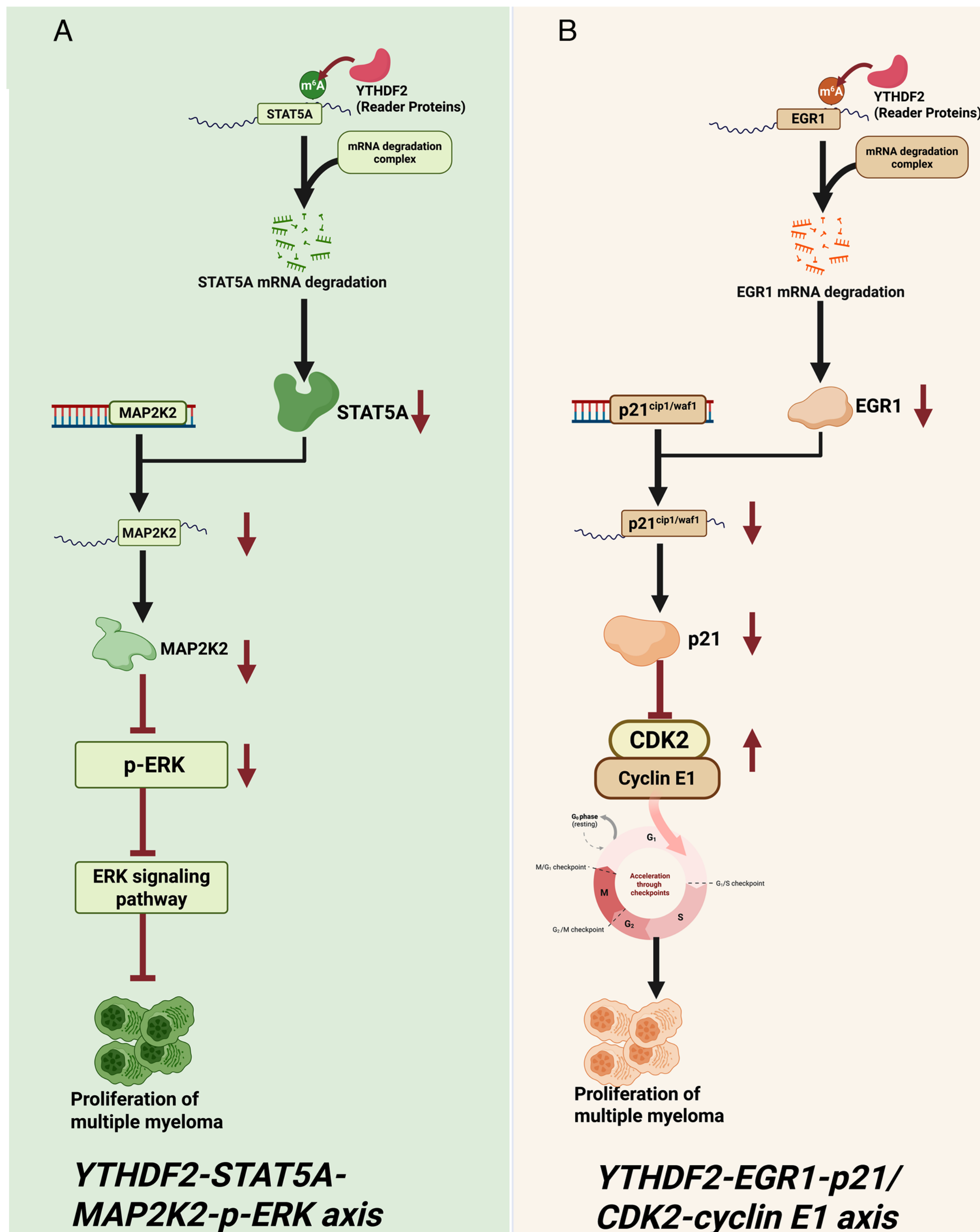


Figure 3. YTHDF2 promotes MM proliferation through dual m$^6$A-dependent pathways. (A) YTHDF2 promotes proliferation via m$^6$A-dependent *STAT5A* degradation and subsequent p-ERK activation (Main evidence: *In vitro* and *in vivo* mouse models). (B) YTHDF2 drives MM proliferation via m$^6$A-dependent EGR1 degradation, leading to dysregulation of the p21/CDK2-cyclin E1 axis (Main evidence: *In vitro* experiments and patient cohort correlation). m6A, N6-methyladenosine; YTHDF2, YTH domain family protein 2; STAT5A, signal transducer and activator of transcription 5A; MAP2K2, mitogen-activated protein kinase kinase 2; p-ERK, phosphorylated extracellular signal-regulated kinase; EGR1, early growth response protein 1; p21, cyclin-dependent kinase inhibitor 1 (also known as CDKN1A); CDK2, cyclin-dependent kinase 2; cyclin E1, cyclin E1. The figure was created in Biorender (https://BioRender.com).

marrow niche, these miRNAs disrupt bone homeostasis: miR-92a-2-5p suppresses the osteoclast inhibitor *IRF8* in monocytes/macrophages, enhancing osteoclastogenesis and bone resorption, while miR-373-3p inhibits the master osteogenic transcription factor *RUNX2* in mesenchymal stem cells, impairing bone formation (131). Cell-autonomously, HNRNPA2B1 also enhances MM cell survival by stabilizing interleukin enhancer binding factor 3 mRNA, leading to

AKT3 activation, a pathway corroborated by positive immunohistochemical correlations in patient samples (132). Another study revealed that hnRNPA2B1 sustains the activity of the central kinase CK2 and CK2 inhibition induces ER stress and autophagy to suppress proliferation and promote apoptosis in hnRNPA2B1-overexpressing MM cells, identifying CK2 as a critical downstream effector (133).

The clinical relevance of m$^6$A readers is further highlighted by the overexpression of leucine rich pentatricopeptide repeat containing, another m$^6$A-binding protein, in advanced-stage MM, where its knockdown induces apoptosis and cell cycle arrest, positioning it as a potential therapeutic node (134). The pro-tumorigenic functions of m6A readers such as YTHDF2, IGF2BP1 and HNRNPA2B1 have been confirmed in multiple preclinical studies through genetic manipulations and mechanistic experiments and are associated with patient prognosis. However, current understanding heavily relies on a limited set of cell line models and preclinical animal studies. To establish these readers as reliable clinical therapeutic targets, further validation in more diverse MM models is required.

*m$^6$A erasers in MM cell survival and stemness*. The erasers ALKBH5 and FTO, which mediate m$^6$A demethylation, are frequently overexpressed in MM. Pre-clinical evidence suggests they may function as oncogenes by stabilizing a network of transcripts crucial for survival, stemness and stress adaptation. ALKBH5 promotes tumorigenesis through multiple, distinct mechanisms. It stabilizes the lncRNA small nucleolar RNA host gene 15 (*SNHG15*) in an m$^6$A-dependent manner (135). Studies using cell line models indicate that this ALKBH5-SNHG15 axis subsequently facilitates the expression of the histone methyltransferase SET domain containing 2 (*SETD2*), altering the H3K36me3 landscape to enhance chromatin accessibility and transcriptional elongation (Fig. 4A). In a separate pathway, integrated MeRIP-seq and functional analyses from one study identified Salvador family WW domain containing protein 1 (*SAV1*), a core component of the HIPPO tumor suppressor pathway, as a key ALKBH5 target. ALKBH5-mediated demethylation destabilizes *SAV1* mRNA, leading to Yes-associated protein (YAP) activation and MM progression (136). Consistent with effects on cellular plasticity, ALKBH5 depletion suppressed the MM stem cell-like phenotype, as evidenced by reduced expression of pluripotency factors (*NANOG*, *SOX2* and *OCT4*), linking epitranscriptomic regulation to cellular plasticity (Fig. 4B). Mechanistically, suppression of *SAV1* perturbs Hippo signaling and enhances YAP activity and ALKBH5 depletion exerted an anti-myeloma effect by promoting expression of p21, p53 upregulated modulator of apoptosis and Bcl2 associated X (BAX) (136). Furthermore, another mechanistic report suggests ALKBH5 drives oncogenic signaling by reducing m$^6$A levels on the 3'UTR of TNF receptor associated factor 1 (*TRAF1*) mRNA, thereby enhancing its stability and activating both NF-κB and MAPK pathways to promote growth and survival (Fig. 4C) (137). These findings from pre-clinical studies suggest that ALKBH5 functions as an oncogene in MM and could serve as a potential biomarker and therapeutic target.

The other major eraser, FTO, exerts its oncogenic role by establishing a hypomethylated transcriptome (138). FTO is upregulated in MM and promotes tumor growth and metastasis. It specifically demethylates heat shock factor 1 (*HSF1*) mRNA, shielding it from YTHDF2-mediated decay and thus augmenting the heat shock response, a critical survival pathway under proteotoxic stress (139). Importantly, FTO activity is metabolically coupled. Isocitrate dehydrogenase 2 (IDH2), which generates the essential FTO cofactor α-ketoglutarate, is highly expressed in progressive MM. IDH2 depletion increased global m$^6$A levels and impaired growth, mechanistically through suppressing FTO-mediated hypomethylation and stabilization of Wnt family member 7B mRNA, which activates pro-tumorigenic Wnt signaling (140,141). The translational promise of targeting m$^6$A erasers is underscored by the finding that FTO inhibition synergizes with the frontline therapeutic drug bortezomib to suppress myeloma growth *in vivo*, presenting a compelling combinatorial strategy (139).

Taken together, the ALKBH5-SNHG15-SETD2, ALKBH5-SAV1-YAP and ALKBH5-TRAF1 axes, along with FTO-mediated regulation of HSF1 and Wnt signaling, represent important emerging mechanistic insights. However, the current evidence for these oncogenic roles of m$^6$A erasers is predominantly derived from *in vitro* and mouse xenograft models. Their overarching significance, interdependence and clinical relevance as therapeutic targets in primary MM require independent replication and further validation in patient cohorts.

*Emerging roles of other RNA modifications*. The epitranscriptomic landscape of MM extends beyond m$^6$A to include other chemically distinct modifications, such as N4-acetylcytidine (ac$^4$C), 5-methylcytidine (m$^5$C) and N1-methyladenosine (m$^1$A), which are increasingly recognized as potential contributors to disease pathology. The ac$^4$C writer N-acetyltransferase 10 (NAT10) is highly expressed in MM and associated with poor prognosis (142). NAT10 promotes MM cell proliferation by acetylating and stabilizing B-cell lymphoma-extra-large (*BCL-XL*) mRNA, a key anti-apoptotic regulator, thereby enhancing cell survival through the PI3K-AKT pathway. The dependency on this axis was confirmed by the potent anti-myeloma activity of Remodelin, a specific NAT10 inhibitor, which induced apoptosis both *in vitro* and *in vivo* (142). A separate study further showed that NAT10 also acetylates and stabilizes G protein-coupled receptor 37 (*GPR37*) mRNA (143). This NAT10-GPR37 axis drives MM progression by promoting cell cycle progression, glycolysis and immune evasion, while inhibiting apoptosis, effects that were recapitulated in a xenograft model.

Similarly, the role of m$^5$C modification is being unraveled through bioinformatics and immunological profiling. Studies mapping the m$^5$C regulome have identified distinct patient clusters with unique immune microenvironment signatures and metabolic features (144). A risk model based on m$^5$C-related genes effectively stratified patients and high m$^5$C scores were associated with specific immune cell infiltration patterns, suggesting that m$^5$C modifications contribute to the immunosuppressive niche in MM (144). Importantly, the primary m$^5$C methyltransferase NSUN2 is overexpressed in MM and correlates with poor prognosis (145). Functional studies demonstrate that NSUN2 drives MM progression by installing m$^5$C modifications on huntingtin interacting protein

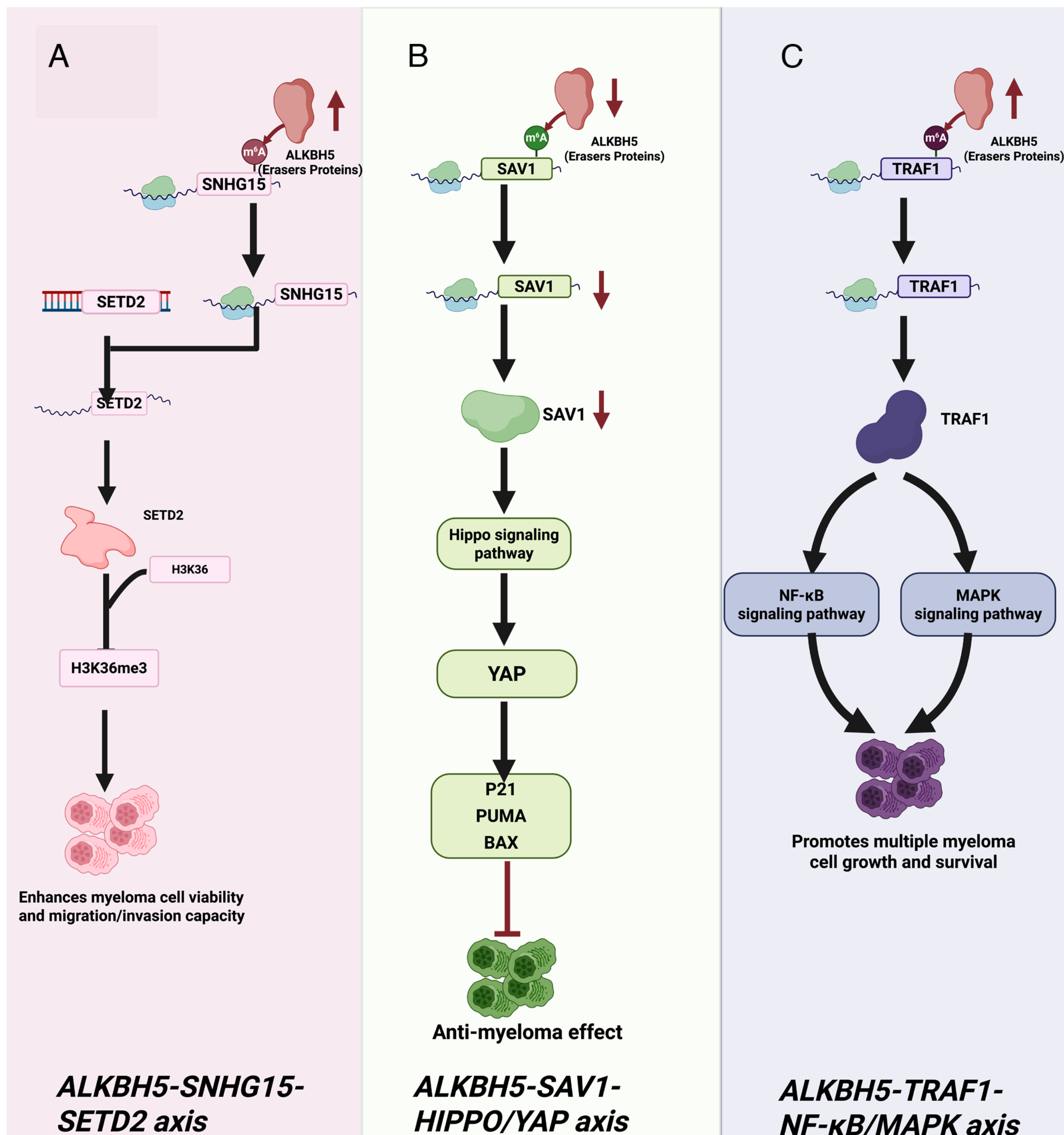


Figure 4. ALKBH5 promotes multiple oncogenic pathways in MM. (A) ALKBH5 stabilizes *SNHG15* to upregulate SETD2 and modify the epigenetic landscape (Main evidence: *in vitro* mechanistic studies). (B) ALKBH5 suppresses *SAV1* to inactivate the HIPPO pathway and activate YAP, while also reducing stemness (Main evidence: *In vitro* and *in vivo* models). (C) ALKBH5 hypomethylates *TRAF1* to activate NF-κB and MAPK signaling (Main evidence: *In vitro* assays and clinical sample analysis). ALKBH5, AlkB homolog 5; $m^6A$, N6-methyladenosine; ALKBH5, alkB homolog 5; SNHG15, small nucleolar RNA host gene 15; SETD2, SET domain-containing 2; H3K36me3, histone H3 lysine 36 trimethylation; SAV1, Salvador homolog 1; YAP, yes-associated protein; P21, cyclin-dependent kinase inhibitor 1 (also known as CDKN1A); PUMA, p53-upregulated modulator of apoptosis; BAX, BCL2-associated X protein; TRAF1, TNF receptor-associated factor 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase. The figure was created in Biorender (https://BioRender.com).

1 mRNA, thereby enhancing its stability and promoting tumor cell proliferation both *in vitro* and *in vivo*.

The $m^1A$ modification also holds significant prognostic and functional relevance in MM. Systematic analysis has identified specific $m^1A$ regulators (such as TRMT61A/B and YTHDF1-3) that are dysregulated in MM and are associated with patient outcomes (146). Notably, high expression of the $m^1A$ reader YTHDF2 was strongly associated with poor survival and was shown to promote MM cell proliferation while inhibiting apoptosis. Furthermore, YTHDF2 overexpression increased global $m^1A$ levels and its co-expressed partner SRSF10 was identified as a potential downstream effector (146). This positions the $m^1A$ machinery as a novel layer of epitranscriptomic regulation in MM pathogenesis.

Collectively, these findings from recent pre-clinical and bioinformatic studies illuminate an expanding epitranscriptomic network in MM. While $m^6A$ remains the most extensively characterized, the reported contributions of $ac^4C$ and $m^5C$ underscore the broader regulatory potential of RNA modifications. Targeting these pathways represents a promising but

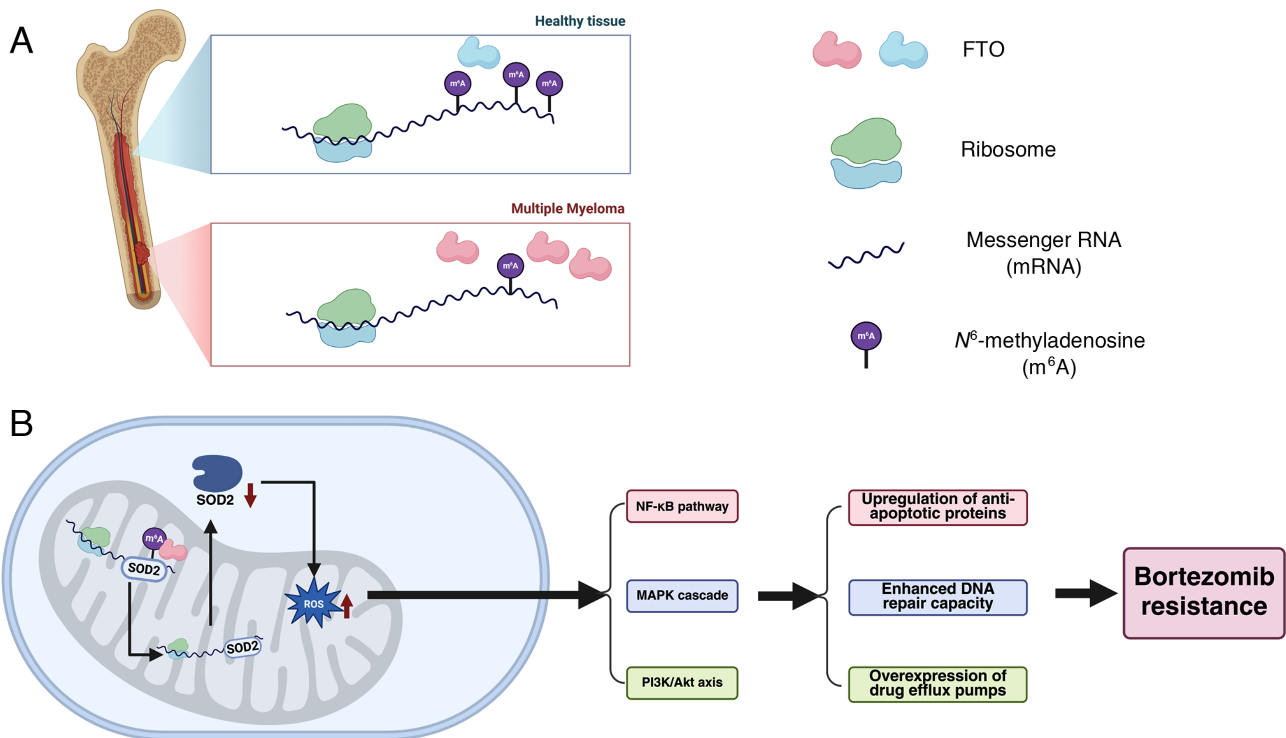


Figure 5. A proposed model for FTO-mediated drug resistance in MM. (A) Schematic representation of FTO expression and m6A levels in bone marrow tissues of MM patients and healthy donors. (B) Mechanistic model of the FTO-SOD2 axis in driving bortezomib resistance. Upregulated FTO demethylates m6A on *SOD2* mRNA, accelerating its decay and reducing antioxidant defense. The resulting chronic oxidative stress triggers compensatory activation of pro-survival pathways (such as NF-κB/MAPK), which desensitizes MM cells to bortezomib-induced apoptosis. m6A, N6-methyladenosine; FTO, fat mass and obesity-associated protein; SOD2, superoxide dismutase 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B. The figure was created in Biorender (https://BioRender.com).

early-stage frontier for developing novel therapeutic strategies aimed at overcoming drug resistance and improving patient outcomes.

## 5. m6A modification in MM microenvironment and drug resistance

The development of treatment resistance, a major driver of relapse and mortality in MM, is thought to be closely linked to dynamic adaptations in the epitranscriptome, particularly m6A modification, which may coordinate both cell-intrinsic survival pathways and extrinsic communication with the bone marrow niche (147-150). Beyond directly regulating oncogenic transcripts, m6A-mediated mechanisms are implicated in drug resistance by reshaping the chromatin landscape through crosstalk with other epigenetic modifiers and by modulating the expression of drug efflux pumps and metabolic enzymes, thereby reducing intracellular drug exposure and therapeutic efficacy (83,151-153). A comprehensive dissection of these epitranscriptomic pathways is therefore a current research priority to develop strategies to overcome resistance and prevent disease progression.

*m6A dysregulation shapes an immunosuppressive niche*. Bioinformatics analyses have suggested a link between the m6A machinery and the immunosuppressive tumor microenvironment in MM. For example, a study reported that a risk signature based on high expression of *HNRNPC*, *HNRNPA2B1* and *YTHDF2*, coupled with low *ZC3H13* expression, was associated with poor prognosis (154). Patients stratified into this high-risk group showed enrichment for hallmark MM pathways (such as MYC signaling and unfolded protein response) and, importantly, a markedly depleted immune landscape. This 'immune-cold' phenotype was characterized by a broad reduction in infiltrating immune cells, including both effector (such as CD8+ T cells and NK cells) and suppressive subsets (such as myeloid-derived suppressor cells and regulatory T cells) and by downregulation of HLA class II molecules (such as HLA-DMA, HLA-DMB, HLA-DPA1 and HLA-DQB1) on tumor cells, potentially impairing antigen presentation and the initiation of adaptive immune responses (154). While this suggests a role for m6A in immune evasion, the underlying mechanisms and the clinical utility of this signature require prospective validation.

*Mechanisms of m6A-mediated drug resistance*. Functional studies in selected models implicate multiple m6A modifiers as direct mediators of chemoresistance. A study by Wang *et al* (155) provides a mechanistic example of how m6A dysregulation directly confers chemoresistance in MM. The researchers established a bortezomib-resistant model *in vitro* by chronically exposing the human MM cell line RPMI 8226 to progressively increasing concentrations of the drug. Comparative analysis revealed that the resistant cells exhibited significant upregulation of the m6A eraser FTO alongside concomitant downregulation of the antioxidant enzyme SOD2 (Fig. 5). The investigators proposed a direct causal relationship: FTO demethylates m6A sites on *SOD2* mRNA, thereby

promoting its decay. In this model system, ectopic overexpression of FTO in sensitive cells induced a resistant phenotype, while genetic knockdown of FTO or exogenous restoration of SOD2 resensitized resistant cells. Pharmacological inhibition of FTO with FB23-2 reversed resistance *in vitro* and *in vivo* (155), suggesting the FTO-SOD2 axis as a potential therapeutic target. This finding presents a seemingly paradoxical phenomenon, as diminished antioxidant capacity would typically be expected to exacerbate bortezomib-induced oxidative stress and cell death (156,157). The study attributed this to adaptive cellular rewiring, where chronically low SOD2 drives compensatory upregulation of pro-survival signaling networks (such as NF-κB and MAPK) (155). This model aligns with prior observations that alterations in oxidative stress management correlate with therapeutic response (158-160).

Notably, the regulation of oxidative stress in MM reveals a complex picture. On one hand, METTL5 upregulates SEPHS2 expression, thereby enhances antioxidant defense (121). By contrast, FTO reduces SOD2 expression, diminishing antioxidant defense yet being reported to contribute to bortezomib resistance (155). This paradox may be explained by the dual role of reactive oxygen species (ROS), which at optimal levels can drive pro-tumorigenic signaling (161,162). Thus, cancer cells may manipulate different antioxidant pathways to maintain ROS within a survival-favorable range. Future studies are warranted to validate this effect and to determine how redox homeostasis can be therapeutically targeted (163,164).

ALKBH5 has also been implicated in resistance to targeted therapies. A recent study demonstrated that ALKBH5 overexpression attenuates the efficacy of the histone deacetylase inhibitor romidepsin by reducing m$^6$A methylation on *FOXM1* mRNA, thereby stabilizing it (165). Conversely, romidepsin treatment or ALKBH5 knockout increases *FOXM1* m$^6$A modification, accelerating its decay and synergistically enhancing apoptosis (165). This positions ALKBH5 as a key modulator of drug response in pre-clinical models.

Drug resistance is further proposed to be mediated through m$^6$A-dependent regulation of key signaling hubs and non-coding RNAs. The reader protein HNRNPA2B1 binds to m$^6$A sites on Toll-like receptor 4 (*TLR4*) mRNA, enhancing its stability and expression (166). Given that TLR4 signaling promotes a pro-survival and resistant state in MM, this HNRNPA2B1-TLR4 axis represents one mechanism that may contribute to microenvironment-associated resistance (167,168). Similarly, circular RNAs are co-opted in model systems; *circ_0000337* is upregulated in bortezomib-resistant cells, where it sponges miR-98-5p, leading to increased expression of the DNA repair protein DNA2. The stability of *circ_0000337* itself is regulated by m$^6$A modification, creating a positive feedback loop that enhances DNA repair capacity (169). In another layer, METTL3 installs m$^6$A marks on the lncRNA *H19*, which sequesters miR-184, relieving the suppression of the oncogenic coactivator-associated arginine methyltransferase 1 (*CARM1*) and driving a bortezomib-resistant phenotype in experimental models (170).

This concept extends to predicting response to combination therapies. In a cohort of patients relapsing after bortezomib-based regimens, a high m$^6$A risk score (with an Area Under the Curve of 0.9) was associated with non-response to salvage therapy with daratumumab, carfilzomib, lenalidomide and dexamethasone (DARA-KRD) (113). Although mechanisms such as FTO-SOD2 have been demonstrated to mediate resistance in preclinical models, these findings are primarily based on single studies or limited cohorts. The prevalence of these pathways in patient populations, particularly among those with different types of resistance and their interactions with classical resistance mechanisms remain insufficiently elucidated and warrant validation in large-scale, prospective clinical cohorts.

*The bone marrow niche and exosome-mediated drug resistance*. The bone marrow adipocyte niche has emerged as a proposed source of exosome-mediated transfer of chemoresistance, a process suggested to be governed by epitranscriptomic regulation. Adipocyte-derived exosomes are reported to enrich MM cells with the lncRNAs *LOC606724* and *SNHG1*, which inhibit apoptosis (171). Furthermore, the methyltransferase METTL7A, whose activity is potentiated by EZH2 in these models, promotes the m$^6$A modification of these lncRNAs, thereby enhancing their packaging into exosomes. Upon delivery to MM cells, these m$^6$A-modified lncRNAs drive *c-Myc* expression (171). This paradigm highlights a potential mechanism of niche-induced drug resistance that warrants further investigation.

Overall, preclinical studies suggest an interplay between m$^6$A modification, non-coding RNA networks and the tumor microenvironment may create a framework for drug resistance in MM. Targeting key nodes within this epitranscriptomic network may offer future opportunities for resensitizing refractory MM, pending further validation of their clinical relevance.

## 6. Therapeutic targeting of m$^6$A modifications in MM

The pervasive dysregulation of the m$^6$A epitranscriptome in MM pathogenesis and treatment resistance has positioned its constituent enzymes, writers, erasers and readers, as compelling therapeutic targets. Moving beyond conventional strategies, targeting RNA modifications represents a novel paradigm to disrupt the post-transcriptional circuitry that drives MM progression and relapse (172). The development of pharmacological and genetic tools to precisely modulate the m$^6$A landscape offers a promising avenue to alter the disease course and improve patient outcomes. The current translational challenge lies not merely in listing potential targets but in rationally prioritizing them for clinical development. This necessitates a framework capable of evaluating MM-specific preclinical validation, chemical tractability and the potential for integration with existing MM treatment regimens.

*A translational prioritization framework for m$^6$A targets in MM*. A systematic approach is required to navigate the landscape of m$^6$A regulators and identify the most promising candidates for drug discovery in MM. The present review proposed a multi-dimensional assessment framework based on the following criteria: First, the strength of MM-specific preclinical validation. This encompasses evidence from genetic dependency screens (such as CRISPR/Cas9 knockout) in MM cell lines, demonstration of robust anti-tumor efficacy in MM-specific *in vivo* models and clear correlation with poor prognosis, drug resistance, or key MM hallmarks in patient cohorts. Second, chemical tractability and drug development

Table I. Small molecules and natural compounds targeting RNA m$^6$A modification.

| Target | Inhibitors | Therapeutic application | Clinical stage | (Refs.) |
|---|---|---|---|---|
| FTO | Rhein | AML | Preclinical | (173) |
| | Meclofenamic Acid (MA) | AML, breast cancer, gastric cancer, lung cancer, glioma | Preclinical | (152,173-175) |
| | FB23-2 | AML, renal cancer, liver cancer, glioma | Preclinical | (173,176-178) |
| | Dac51 | Uterine Leiomyosarcoma | Preclinical | (179) |
| | CS1/CS2 | Obesity, metabolic disorders | Phase I/II | (180) |
| | FTO-43 | Glioblastoma, AML, gastric cancer | Preclinical | (181) |
| | Entacapone | AML, solid tumors | Preclinical | (182,183) |
| METTL3 | STM2457 | AML, NSCLC, HCC, pancreatic cancer | Phase I/II | (184-187) |
| | STC-15 | NSCLC, HNSC, melanoma, endometrial cancer | Phase Ib/II | (188) |
| | UZH1a/UZH1b | AML | Preclinical | (189-191) |
| ALKBH5 | MV1035 | Glioblastoma | Preclinical | (192) |
| | Alk-04 | Melanoma, colorectal cancer | Preclinical | (193) |
| | IOX1 | Glioma | Preclinical | (194) |
| YTHDF1 | SKLB-Y13 | Breast cancer | Preclinical | (128) |
| IGF2BP1 | BTYNB | Ovarian cancer | Preclinical | (195) |
| | AVJ16 | Melanoma, neuroblastoma *etc*. | Preclinical | (196) |
| IGF2BP2 | JX5 | Lung adenocarcinoma, T-ALL | Preclinical | (197,198) |

The listed inhibitors have been primarily studied in non-MM malignancies. Their therapeutic potential and applicability in MM remain to be experimentally validated. AML, acute myeloid leukemia; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; HNSC, head and neck squamous cell carcinoma; T-ALL, T-cell acute lymphoblastic leukemia; FTO, fat mass and obesity-associated protein; METTL3, methyltransferase-like 3; ALKBH5, alkB homolog 5; YTHDF1, YTH N6-methyladenosine RNA-binding protein 1; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2.

stage. This criterion assesses the availability of selective, potent and bioavailable small-molecule inhibitors, PROTAC degraders, or other pharmacological modalities targeting the m$^6$A regulator. Third, the potential for integration with existing MM therapies. This evaluates whether preclinical models demonstrate synergistic effects when combining modulation of the m$^6$A target with backbone MM therapies, such as proteasome inhibitors (bortezomib), immunomodulatory drugs (lenalidomide), or monoclonal antibodies (daratumumab). Targets that address core resistance mechanisms (such as FTO in bortezomib resistance) or modulate the tumor microenvironment to enhance therapy are considered particularly attractive.

*High-priority targets with a solid MM-specific rationale*. Targeting the catalytic core of m$^6$A regulatory enzymes with small-molecule inhibitors represents the most direct path for clinical translation (Table I) (128,152,173-198). Applying the proposed translational framework, several targets emerge with high priority.

The most compelling current evidence points to targeting the m$^6$A writer METTL3. Its MM-specific validation is robust, as knockdown consistently inhibits the proliferation and survival of MM cells. Furthermore, metformin's partial anti-myeloma effect, mediated through the impairment of METTL3 function, provides indirect translational support (117-119). Regarding chemical tractability, the METTL3 inhibitor STM2457 is currently in Phase I clinical trials for AML. This agent has demonstrated potent anti-leukemic effects by reducing global m6A levels and downregulating key oncogenic transcripts such as BRD4 and SP1 (184). In terms of potential for therapeutic integration, given METTL3's well-defined oncogenic role in MM, where it drives proliferation by stabilizing transcripts such as *YY1* and *BZW2* and promoting the maturation of miR-182-5p, its inhibitors are hypothesized to synergize with proteasome inhibitors, which induce proteotoxic and endoplasmic reticulum stress (115,116). Therefore, evaluating METTL3 inhibitors (such as STM2457, UZH1) in MM models, particularly their efficacy in combination with bortezomib, is a high-priority preclinical direction.

FTO is another high-priority target. MM-specific evidence shows that FTO is upregulated in patients and promotes bortezomib resistance through mechanisms including the disruption of the oxidative stress modulator SOD2 (Fig. 5) (155). The chemical tractability of FTO is supported by several inhibitors (such as FB23-2, CS1/CS2), which have demonstrated anti-tumor effects in leukemia models (173,176-178). The potential for integration is highly compelling. Synthetic small-molecule inhibitors like FB23-2 can selectively block FTO activity, leading to enhanced decay of oncogenic transcripts such as MYC. Accordingly, FTO inhibition warrants MM-specific validation as a resensitization strategy, including testing in acquired bortezomib-resistant models and in combination regimens with proteasome inhibitors.

The eraser ALKBH5 also presents a viable target. Its MM-specific validation is underscored by its role in driving tumorigenesis and mediating resistance to agents such as

Table II. Biological/biomedical interventions targeting m6A modification.

| First author/s, year | Target | Intervention | Type | Mechanism | Therapeutic application | (Refs.) |
|---|---|---|---|---|---|---|
| Du *et al*, 2024 | METTL3-METTL14 | UZH2-PROTAC | PROTAC degrader | Targets METTL3-14 for ubiquitination | AML | (199) |
| Rauff *et al*, 2023 | FTO | MTP1 peptide | Peptide | Inhibits the binding and demethylase activity of FTO | Breast cancer, lung cancer | (200) |
| Li *et al*, 2024 | METTL3 | RSM3 | Peptide | Blocks METTL3-14 interaction | Prostate cancer, lung cancer | (201) |
| Hua *et al*, 2025; Huang *et al*, 2022; Paris *et al*, 2019 | YTHDF2 | YTHDF2-siRNA | RNA interference | Silences YTHDF2 to stabilize tumor suppressor transcripts | Cholangiocarcinoma, AML, neuroblastoma | (202-204) |
| Bao *et al*, 2023; Wang *et al*, 2023 | YTHDF1 | Nanoparticle with siRNA | siRNA | Reduces YTHDF2 level | CRC, HCC | (205,206) |
| Xie *et al*, 2019 | m6A | Flavin Mononucleotide | Artificial enzyme | Oxidizes m6A independently of FTO/ALKBH5 | Research tool | (207) |
| Wilson *et al*, 2020 | Editing tool | dCas9-METTL3 | CRISPR-based | Site-specific m6A deposition | Research tool | (208) |
| Li *et al*, 2020 | Editing tool | dCas13b-ALKBH5 | CRISPR-based | Site-specific m6A elimination | Research tool | (209) |

These interventions represent emerging modalities that have shown promise in other cancer types. Their efficacy and delivery in MM-specific models require further investigation. AML, acute myeloid leukemia; ALKBH5, alkB homolog 5; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; Cas9, CRISPR-associated protein 9; CRC, colorectal cancer; HCC, hepatocellular carcinoma; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; m6A, N6-methyladenosine; MM, multiple myeloma; PROTAC, Proteolysis Targeting Chimera; siRNA, small interfering RNA; UZH2, ubiquitin ligase zinc finger H2-type 2; FTO, fat mass and obesity-associated protein; YTHDF1, YTH domain family protein 1; YTHDF2, YTH domain family protein 2.

the histone deacetylase inhibitor romidepsin by stabilizing FOXM1 mRNA (165). However, available ALKBH5 inhibitors (such as IOX1) are generally considered tool compounds and improved potency/selectivity and MM-specific pharmacological validation will be required. Modulating ALKBH5 may still be attractive for combination strategies if on-target activity and tolerability can be established (194).

Although the development of inhibitors targeting m$^6$A readers is still in its early stages, it offers unique opportunities for precision therapy. For instance, targeting IGF2BP1, which stabilizes *CDC5L* mRNA in high-risk 1q-amplified MM (128); inhibiting HNRNPA2B1, a driver of bone disease and survival signaling (131-133); or blocking YTHDF2, which promotes proliferation by degrading tumor suppressors such as *STAT5A* and *EGR1* (126,127) could each provide a highly targeted strategy with a potentially wider therapeutic window. Nevertheless, reader-targeting chemical matter remains relatively immature and robust pharmacodynamic assays and MM-specific validation will be essential to assess clinical feasibility.

Collectively, the inhibitors for METTL3 and FTO possess the strongest immediate translational rationale. However, it is critical to note that the current assessment of their efficacy largely draws on research from other hematologic malignancies such as AML. Specific pharmacodynamic data in MM, optimal combination regimens and potential resistance mechanisms await elucidation through future systematic preclinical studies dedicated to MM.

*Biomedical and genetic approaches targeting m$^6$A modification*. Beyond small molecules, genetic and targeted protein degradation technologies offer alternative paths for precise and potent modulation of the m$^6$A machinery (Table II) (199-209). CRISPR-Cas9-mediated knockout of METTL3 or ALKBH5 has proven effective in impairing cancer progression in various models, though *in vivo* delivery to MM cells in the bone marrow remains a challenge (194,210). More sophisticated epigenetic editing tools, such as dCas13b-ALKBH5 fusion systems, enable site-specific m$^6$A demethylation without altering the DNA sequence, offering the potential to reversibly silence specific driver genes such as *IRF4* while sparing normal hematopoiesis (208,211).

Proteolysis-targeting chimeras (PROTACs) represent a groundbreaking modality to achieve complete and selective degradation of target proteins. PROTACs such as WD6305, which recruit E3 ubiquitin ligases to degrade METTL3, have demonstrated potent anti-leukemic effects *in vivo* (199,212,213). This strategy could be particularly effective against MM cells that rely on METTL3 for survival,

potentially overcoming resistance mechanisms that arise with catalytic inhibitors. Similarly, antisense oligonucleotides (ASOs) designed to silence *METTL3* mRNA expression provide high specificity and could mitigate off-target effects associated with small molecules (214).

These next-generation approaches are poised to address the issues of tumor heterogeneity and acquired resistance that often plague conventional therapies. The future clinical application of these modalities will hinge on overcoming the critical challenge of delivery, efficiently and specifically targeting MM cells within the bone marrow niche. Advances in lipid nanoparticles, viral vectors, or cell-specific targeting moieties will be essential to unlock the full potential of genetic and degradation-based epitranscriptomic therapy for MM.

Notably, for targets such as ALKBH5 and YTHDF2, the rationale for targeted therapies primarily relies on genetic approaches (such as knockdown/knockout experiments) and the efficacy of tool compounds in non-MM models. Conclusive evidence of 'chemical tractability', such as highly selective and potent lead compounds, remains lacking in the context of MM. Furthermore, direct single-cell epitranscriptomic mapping of m$^6$A marks (rather than regulator expression) in MM subtypes remains limited, representing a key technical and conceptual gap.

Collectively, the targeting of the m$^6$A epitranscriptome opens a new frontier in MM therapeutics. The diversity of druggable targets, from writers and erasers to readers, provides multiple avenues to disrupt the post-transcriptional networks that sustain this disease. The immediate challenge lies in advancing the most promising agents, particularly METTL3 inhibitors, into robust preclinical validation in MM-specific models. Success in this endeavor promises to move beyond sequential therapy toward rational, biomarker-driven combinations that anticipate and delay resistance mechanisms. By precisely manipulating the RNA regulatory code, we may ultimately shift the treatment paradigm from managing relapse to achieving durable remissions in MM.

*Safety considerations and the path to clinical translation*. The translational potential of targeting the m$^6$A epitranscriptome must be balanced against the risk of on-target toxicities, as its core regulators (such as METTL3, FTO and ALKBH5) play indispensable roles in normal hematopoiesis and immune function (34,105,106). Mitigating potential adverse effects, such as bone marrow suppression, is therefore paramount. A viable path forward hinges on two complementary strategies: The development of highly selective inhibitors to minimize off-target effects and the pursuit of rational combination therapies. Combining an m$^6$A-targeted agent with a backbone MM therapy could allow for lower, more tolerable doses of each drug while achieving synergistic efficacy. Ultimately, the clinical success of this approach will depend on integrating predictive m$^6$A-based biomarkers to identify patients whose tumors are most dependent on these pathways, thereby maximizing the therapeutic window.

## 7. Concluding remarks and future perspectives

The burgeoning field of epitranscriptomics has fundamentally expanded our understanding of gene regulation in cancer. The present review consolidated compelling evidence that the m$^6$A modification machinery is an active regulatory layer linked to key aspects of MM pathogenesis, progression and therapy resistance. Through the dysregulated activity of writers, erasers and readers, m$^6$A modifications fine-tune the expression of oncogenic networks, remodel the bone marrow microenvironment and confer resilience to current therapies, positioning the epitranscriptome as a rich source of novel prognostic biomarkers and therapeutic vulnerabilities.

Notably, both m$^6$A writers and erasers are frequently upregulated in MM, suggesting a state of hyperdynamic RNA methylation rather than a simple shift in net m$^6$A abundance. This heightened flux may help maintain the plastic and adaptive gene expression programs that fuel MM progression and resistance. Although it may seem paradoxical, inhibiting either writers (reducing installation) or erasers (preventing removal) could disrupt this balance; however, whether 'lethal epitranscriptomic instability' can be therapeutically induced remains a working hypothesis that requires direct experimental testing in MM models. Future comparative studies should therefore evaluate writer vs. eraser inhibition across distinct MM genotypes, treatment states and microenvironmental contexts and determine whether synthetic vulnerabilities emerge in defined settings.

Major gaps remain regarding heterogeneity and clinical translation. MM is a heterogeneous disease characterized by varying molecular subtypes [such as hyperdiploid, t(11;14) and t(4;14)] (215,216), yet subtype-resolved m$^6$A mapping is still limited. Addressing this will require advanced approaches such as single-cell profiling and high-resolution mapping (217,218). In parallel, translation must account for the essential roles of m$^6$A regulators in normal hematopoiesis and immunity, which raises the risk of on-target toxicity and underscores the need for selective inhibitors/degraders, biomarker-guided patient selection and dosing or delivery strategies that maximize the therapeutic window.

In conclusion, targeting m$^6$A pathways represents a promising but still early strategy for MM, with near-term potential in overcoming drug resistance through rational combinations with standard regimens (such as proteasome inhibitors) (219,220). Key priorities include: i) Clinical/biomarker validation in large, multicenter cohorts integrating m$^6$A regulator profiles with genomic subtype, treatment exposure and outcome; ii) mechanistic replication in advanced models, including patient-derived cells, PDX models and microenvironment-informed or immunocompetent systems; and iii) rational combination strategies with proteasome inhibitors, IMiDs, anti-CD38 antibodies and emerging T-cell redirecting therapies, supported by biomarkers for response and toxicity (221).

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## Availability of data and materials

Not applicable.

## Authors' contributions

YM and MM performed study conception and design. YM and SH wrote the initial draft of the manuscript. MM, DB, YG, NB and WH reviewed and edited the manuscript. MM and WH conducted proofreading and further revisions. YM contributed to the acquisition of funds. Data authentication is not applicable. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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