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Review

Research progress on N6-methyladenosine and non-coding RNA in multiple myeloma

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Abstract
N6-methyladenosine (m6A) and non-coding RNA (ncRNA) play important roles in the occurrence, development, and prognosis of multiple myeloma (MM). They not only affect stemness, growth, and apoptosis of MM cells but also intervene in MM proliferation, migration, invasion, and even drug resistance. It is also a prognostic factor for poor MM survival. Therefore, in-depth research on the mechanisms of m6A and ncRNA in MM significant for diagnosis, treatment, and prognosis of MM.

Keywords N6-methyladenosine · Non-coding RNA · Multiple myeloma

1 Introduction

Multiple myeloma (MM) is a hematological malignancy characterized by abnormal proliferation of bone marrow plasma cells, which is prevalent in elderly population and has complex pathogenic factors. Despite significant progress in the treatment of MM, there are still patients experience high recurrences. Therefore, it is essential to search for new targets for diagnosis, treatment, and prognosis of MM. The N6-methyladenosine methylation (m6A) modification is one of the most abundant dynamic RNA modifications among the many other RNA modifications discovered today. In recent years, the increasing studies on the relationship between m6A modification and non-coding RNAs (ncRNAs) had suggested that they interact with each other and the potential in occurrence and progression of MM, which makes m6A and ncRNAs a promising treatment target in MM.

2 m6A modification and MM

2.1 Research progress on m6A modification

As a malignant tumor of the hematological system, there are still many gaps in the molecular mechanisms of its occurrence, development, and prognosis. Understanding the relevant mechanisms of the course of MM will provide new options for the treatment of its patients [1]. M6A modification is a common RNA modification in eukaryotes [2], and it has been found in microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) [3]. M6A modification may alter gene expression and function, thereby affecting disease progression. In recent years, many studies have

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elucidated the key role of m6A modification in various cancers, such as colorectal cancer [4], and gastric cancer [5]. Its roles in hematological diseases, such as leukemia [6], lymphoma [7], and MM [8] had also been explored. Specifically in MM, various stages of m6A modification is correlated with different stages of MM occurrence [9], progression [10, 11], prognosis [9], and treatment [12, 13]. However, the specific mechanism of regulation still needs further exploration.

The regulators of m6A can be divided into encoders, decoders, and readers, namely methyltransferases, m6A demethylases, and m6A methylated reading proteins [14]. Among them, m6A methyltransferase can cause m6A modification of mRNA bases, specifically methyltransferase like 3 (METTL3), methyltransferase like 14 (METTL14), and Wilms' tumor 1-associating protein (WTAP), which are core proteins of m6A methyltransferase. The m6A demethylases include Fat mass and obesity-associated protein (FTO) and Human Alk B homolog 5 (ALKBH5), where FTO has been shown to be closely related to acute myeloid leukemia [15]. In addition, m6A-methylated reading proteins can specifically bind to m6A-methylated regions, participate in downstream mRNA translation degradation and miRNA processing, and intervene in various disease processes. Known reading proteins such as YTH N6-Methyladenosine RNA Binding Protein C1-2 (YTHDC1-2) [16], YTH N6-Methyladenosine RNA Binding Protein C1-3 (YTHDF1-3) [17], eukaryotic initiation factor 3 (eIF3), and Heterogeneous Nuclear Ribonucleoprotein A2/B1 (HNRNPA2B1) [18] are involved in m6A modification and are closely related to cancer and immune system diseases.

3 Research progress on the relationship between m6A modification and MM

Research has shown that m6A modification and its regulatory factors are dysregulated in many cancers, and almost all known m6A regulatory proteins regulate tumor cells and disease progression by targeting specific genes. For example, METTL14 can promote the invasiveness of acute myeloid leukemia by regulating the m6A modification of Zinc Finger E-Box Binding Homeobox 1 (ZEB1) [19], while in hepatocellular carcinoma, inhibiting the m6A modification of circFUT8 can suppress disease progression [20]. These two studies have demonstrated the important role of m6A modification in disease progression, making us realize the bidirectional regulation of m6A modification can control disease progression. Therefore, targeted regulation of m6A modification via inhibitors or agonists is a promising strategy for disease treatment, especially for cancer treatment, which requires more in-depth research.

The role of m6A methylation-related enzymes in MM has been extensively studied, intervening in various aspects such as MM tumor growth [1], cell proliferation [21, 22] and osteoclastogenesis [23]. METTL3 is significantly upregulated in MM and promotes tumor growth via the miR-182/CAMK2N1 signaling axis [1]. It also stabilizes YY1 mRNA and facilitates the maturation of miR-27a-3p, thereby influencing MM cell proliferation, apoptosis, and stemness [21]. Conversely, inhibiting METTL3-mediated m6A methylation has been shown to reduce MM cell proliferation [22]. These findings collectively suggest that METTL3 is a critical driver of MM progression. However, conflicting evidence exists regarding the role of METTL3 in MM. While most studies highlight its oncogenic role, some suggest that METTL3's effects may be context-dependent, with potential variations across different MM subtypes [22, 24]. This complexity underscores the need for a nuanced understanding of METTL3's function in MM.Targeting METTL3 offers potential therapeutic benefits but also presents significant challenges. However, translating these findings into clinical practice is complicated by several factors. First, developing specific METTL3 inhibitors that do not affect other m6A methyltransferases is technically challenging. Second, ensuring efficient delivery of these inhibitors to MM cells while minimizing systemic toxicity remains a major hurdle. Third, METTL3's role in normal cellular processes raises concerns about potential off-target effects, which could lead to unintended adverse effects. Despite these challenges, targeting METTL3 presents notable opportunities. Future research should focus on developing specific inhibitors, optimizing delivery methods, and identifying predictive biomarkers to improve outcomes for MM patients.

Research has found that heat shock factor 1 (HSF1) is a m6A-modified functional target mediated by m6A demethylase FTO. FTO targets HSF1 in a YTHDF2-dependent manner, significantly promoting the proliferation, migration, and invasion of MM cells [25]. Simultaneously, high expression of FTO can also enhance MM's resistance to bortezomib [26], increasing the difficulty of clinical treatment. Therefore, reducing FTO expression could be a potential new therapeutic approach for MM.

ALKBH5 is a demethylase that affects RNA output and metabolism, playing an important role in the occurrence and development of tumors. It is highly expressed in primary MM cell lines isolated from patients and it can promote the proliferation, invasion, and migration ability of MM cells [27]. Concurrently, experiments have found that ALKBH5 can activate the NF-κB and MAPK signaling pathways to promote growth and survival of MM cells [28]. We speculate that ALKBH5 knock out can induce apoptosis, thus reduce proliferation and migration ability of MM cells. Therefore,

a ALKBH5 prognostic marker is effective for the diagnosis of MM and ALKBH5 inhibitors may have therapeutic effects on MM.

As m6A-reading proteins, HNRNPA2B1 and YTHDF2 have been implicated in promoting the proliferation of multiple myeloma (MM) cells and are associated with disease severity and poor prognosis [29–31]. Similarly, other m6A-reading proteins such as HNRNPC and FTP have been identified as prognostic markers for adverse clinical outcomes [32, 33]. These findings collectively suggest that m6A-reading proteins are strong predictors of unfavorable disease progression and could serve as potential therapeutic targets in MM.

However, it is crucial to critically evaluate the evidence and consider potential differences in the mechanisms by which these proteins contribute to MM progression. While HNRNPA2B1 and YTHDF2 are consistently associated with poor outcomes, their specific roles in MM biology may vary. For instance, HNRNPA2B1 may influence RNA metabolism through metabolism and inflammation compared to YTHDF2, which primarily affects mRNA translation and stability.

Studies have confirmed that protein arginine methyltransferase 1 (PRMT1) can methylate the key component Wilms' tumor 1-associating protein (WTAP) of the m6A methyltransferase complex. Knocking down PRMT1 reduces oxidative phosphorylation in MM cells and inhibits proliferation [8]. This underscores the importance of m6A modification in MM development and suggests that PRMT1 could be a potential therapeutic target. However, the development of small molecules or inhibitors that selectively target these proteins remains a technical challenge. So the clinical application of such inhibitors will require careful consideration of potential side effects and the development of specific delivery methods to minimize off-target impacts.

In summary, the m6A regulatory proteins, such as METTL3, FTO, ALKBH5, HNRNPA2B1, YTHDF2, and PRMT1 play important roles in the progression of multiple myeloma. METTL3, FTO, and YTHDF2 had been extensively study for their roles in apoptosis, proliferation, osteoclastogenesis, and drug resistance (Fig. 1). They are valuable diagnostic markers and promising treatment targets of MM. However targeting these m6A regulators presents both opportunities and challenges, with future research focusing on developing specific inhibitors, optimizing delivery methods, and identifying predictive biomarkers to improve outcomes for MM patients.

4 ncRNA

4.1 Progress in ncRNA research

ncRNA refers to RNA that does not encode proteins, and currently, the most commonly studied include miRNA, lncRNA, and circRNA. ncRNA can play a role at both the transcriptional and post-transcriptional levels [34] and in epigenetic

Fig. 1 Key targets and functions of m6A modification in multiple myeloma. Methylase type (green boxes): methyltransferase, demethylase, methylated reading protein. Core Regulatory Proteins (orange boxes): METTL3, PRMT1, ALKBH5, FTO, HNRNPA2B1, YTHDC2, eIF3. Intervention mechanism and approach (blue boxes): apoptosis, miR-182, cell proliferation, Osteoclast migration, oxidative phosphorylation, NF-κB MAPK, proliferation and migration, RNA Metabolism, apoptosis, cell proliferation

regulation of gene expression [35]. It involves various biological processes and has been shown to have impacts on various diseases, ranging from different stages of disease occurrence to development.

4.2 Relationship between circRNA and MM

circRNA has been extensively studied in cancer, such as lung cancer [36], gastric cancer [37], and prostate cancer [38]. It is also been explored in immunoproliferative cancers, such as osteosarcoma [39], acute lymphoma [40], acute lymphocytic leukemia [41], and multiple myeloma. The extensive research on circRNA in MM demonstrated that circRNA can intervene in the progression of MM through various pathways. One of the most common is by activating downstream target proteins of miRNA to intervene cell proliferation. Experiments have shown that the downregulation of Circ_0005615 can target miR-331-3p/IGF1R axis and thus block MM cells proliferation [42]. Therefore, inhibit Circ_0005615 expression can be a novel approach for MM treatment. circRNA can also affect apoptosis of MM cells, thereby influencing the progression of MM [43].

Studies have found that high expression of circXPO1 [44] and circ_0000190 [45] can promote the progression of MM. On the other hand, circ_0111738 can inhibit the oncogenic function of miR-1233-3p in MM patients [46], implying that circRNA regulation is bi-directional.

circRNA plays an significant role in the prognosis of multiple myeloma. High expression of circRFWD_2369aa [47] and circCCT3 [48] is correlated with poor prognosis. circ_0001821 can regulate the proliferation and apoptosis of MM cells and represents a poor prognosis of multiple myeloma [43].

In conclusion, the abnormal expression of circRNAs in MM may have significant implications for the treatment of MM. They can serve as prognostic markers for disease progression. circRNAs' functions in cell proliferation suggesting that appropriate regulation of their expression is a possible therapeutic avenue for MM patients. Nearby, Lipid Nanoparticles (LNPs) have been successfully used to deliver circRNA-based therapeutics. LNPs in MM has also begun to be explored preliminarily. I believe that this could be a promising direction for applying circRNAs in the treatment of MM.

4.3 Relationship between lncRNA and MM

The relationship between lncRNA and MM involves various aspects of diagnosis, development, and treatment. Its significance in diagnosis has been extensively studied. Through retrospective analysis and PCR validation, it was found that the expression of lncRNA CATG00000112921.1 was reduced in newly diagnosed MM patients compared to healthy controls. The study inferred that lncRNA CATG00000112921.1 may serve as a diagnostic marker for MM [49]. However, this experiment has certain limitations, such as small sample size and only one type of lncRNAs was validated. Further research is required to verify the differences in lncRNA expression between newly diagnosed MM patients and normal individuals, with a larger sample size to enhance the credibility of the experimental results and provide more evidence for lncRNA as a diagnostic marker for MM.

Many experimental studies have described various roles of lncRNA on MM progression. lncRNA FEZF1-AS1 can accelerate the progression through IGF2BP1/BZW2 signaling [50], while lncRNA NBR 2 can inhibit MM growth by activating the AMPK/mTOR pathway [51]. From these data, we inferred that lncRNA have both cell-proliferative and regulatory effect on MM, providing new ideas for repressing disease progression.

As a disease that has yet to be cured, it is urgent to search for therapeutic targets for MM. Currently, there are many studies exploring the therapeutic effect of lncRNA. For example, lncRNA NORAD and lncRNA NEAT1 can affect apoptosis in MM cells [52, 53]. High-expression LncRNA MALAT1 can promote MM tumorigenicity and angiogenesis [54], and high-expression LncRNA NEAT1 can promote MM cell immune escape [55]. LncRNA H19 can participate in osteoclast differentiation [56], and lncRNA MALAT1 silencing can inhibit MM cell proliferation and invasion [57]. These studies verified the important role of lncRNA in MM progression. However, delivering lncRNA-targeted drugs to MM cells remains a significant challenge. Currently, commonly used delivery systems include LNPs and viral vectors, which still have issues such as immunogenicity, delivery efficiency, and targeting accuracy. In the future, it will be necessary to develop more efficient and safer delivery systems to ensure that drugs can accurately reach the target cells and exert their therapeutic effects.

4.4 Relationship between miRNA and MM

There are significant differences in miRNA expression between healthy individuals and MM patients. Experiments have shown that upregulation of miR-26 expression inhibits MM cell proliferation and promotes apoptosis [58], similarly, miR-1179 also inhibits the progression by promoting apoptosis [59], suggesting that apoptosis may be an important pathway for miRNA intervention. On the other hand, some studies have found that upregulation of miR-182 promotes the metastasis of MM cells [60]. These indicate that miRNA plays both a regulatory and proliferative role in MM development. Therefore, development of miRNA-related targeted drugs to regulate miRNA expression levels may be a new avenue to accelerate apoptosis, reduce metastasis, and inhibit MM progression.

miRNA not only serve important roles in multiple myeloma (MM) growth but also resistance of existing MM treatment. Studies have shown that high expression of miR-182 enhances resistance to cabozantinib [60], high expression of miR-140-5p and miR-28-3p also resist bortezomib [61], and overexpression of miR-34a suppresses the activity and tumoricidal effect of CAR-T cells [62]. Therefore, regulating miRNA can not only control MM progression, but it also reduce patient resistance to existing therapies and enhance treatment efficacy, with the promise to prolong patient survival.

Finally, miRNA also plays a role in predicting MM prognosis. Studies have found that the expression of has-miR-223-3p [63], miR-16, and miR-21 [64] in the serum of MM patients changes significantly throughout the disease. Its high expression level is correlated with positive prognostic value. Based on this study, if the range of detection indicators is expanded, the sample size is increased, and the follow-up time is increased, miRNAs and their target genes would have significant differences in expression in the blood and bone marrow of MM patients from onset to complete remission before and after treatment.

In summary, different types of ncRNAs functions in proliferation, apoptosis, angiogenesis, immune escape, osteoclastogenesis, and drug resistance, affecting various aspects of MM occurrence, development, treatment, and prognosis (Fig. 2). Finding differentially expressed ncRNAs could bring unexpected therapeutic effects on MM treatment.

It should be noted that MM is a heterogeneous disease, with significant differences in ncRNA expression profiles among patients. In the future, it may be necessary to adopt personalized medicine approaches, tailoring treatment plans based on individual ncRNA expression profiles to enhance therapeutic efficacy. The primary research directions moving forward should focus on high-throughput sequencing and bioinformatics analysis to precisely identify the direct target

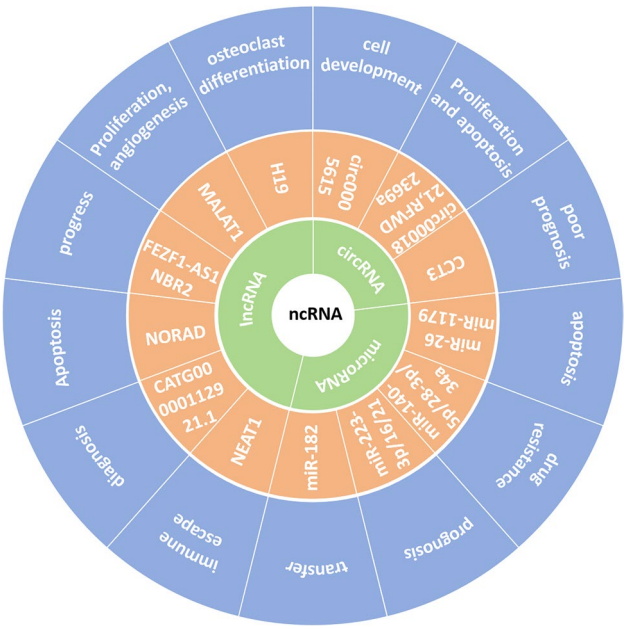

Fig. 2 Mechanisms of ncRNA in multiple myeloma progression and therapy. ncRNA Types (green boxes): lncRNA, circRNA, miRNA. Key RNA names (orange boxes): lncRNA include NEAT1, CATG00000112921.1, NORAD, FEZF1-AS1, NBR2, MALAT1 and H19. circRNA include Circ_0005615, circ_0001821, circRFWD_2369aa and circCCT3. miRNA include miR-26, miR-1179, miR-140-5p, miR-28-3p, miR-34a, miR-223-3p, miR-16, miR-21 and miR-182. Intervention mechanism and approach (blue boxes): Immune escape, diagnosis, apoptosis, progress, proliferation, migration, osteoclast differentiation, cell development, apoptosis, drug resistance, prognosis and transfer

genes of ncRNAs, thereby reducing off-target effects. Additionally, expanding the sample size to understand the ncRNA expression profiles and genetic heterogeneity in different MM patients is essential for developing personalized treatment strategies. Integrating the efforts of multiple disciplines, including oncology, molecular biology, pharmacology, and clinical medicine, will be crucial for advancing the clinical treatment of MM based on miRNA.

5 Relationship between m6A modification and ncRNA

5.1 Relationship between m6A modification and circRNA

Abnormalities in enzymes involved in m6A modification can cause a series of diseases. In recent years, the number of studies on m6A modification of ncRNAs has increased and gradually taken shape, but further in-depth mechanistic research is needed. Most circRNAs are located in the cytoplasm, and those containing introns are often found in the nucleus. Therefore, regulating the nuclear output of circRNAs is necessary. Previous studies have shown that YTHDC1, as a type of m6A reading protein, can affect the nuclear output of circRNA3634 [65]. Therefore, further study on m6A modification in circRNA may bring new inside into circRNA regulation.

M6A modification plays a crucial role in various aspects of circRNA metabolism. The hsa_circRNA_103820 regulated by m6A reader IGF2BP3 can inhibit the malignant progression of lung cancer cells [66]. Lowering the expression of circKEAP1 through m6A modification can promote the stemness, proliferation, and migration of osteosarcoma cells [39]. Lowering the expression of circ_1124554 can also promote the progression of rectal cancer [67]. In summary, m6A modification can regulate circRNA expression and function through various mechanisms, including affecting their subcellular localization, stability, and interactions with RNA-binding proteins or miRNAs. Further understanding of the m6A-circRNA axis and its impact on disease progression in MM could shed light on finding new therapeutic targets and biomarkers for this disease.

5.2 Relationship between m6A modification and lncRNA

The m6A modification of lncRNA can promote tumor progression. For example, m6A methyltransferase ZCCHC4 downregulates LncRNAGHRLOS to promote proliferation, migration, and invasion of colorectal cancer cells [68], and METTL14 can promote the progression of non-small cell carcinoma by upregulating MSTRG.292666.16 and increasing its m6A modification level [69]. The above research confirm that inhibit m6A modification of lncRNA may affect disease progression, providing new targets for disease diagnosis and treatment.

On the other hand, m6A modification of lncRNA can also inhibit disease progression and prevent disease occurrence. For example, m6A methyltransferase ZC3H13 can stabilize lncRNA A1BG-AS1, thereby preventing malignant tumors of prostate cancer cells [70], while METTL3 stabilizes LINC00894 in an m6A-dependent manner to inhibit the progression of thyroid cancer and lymph node metastasis, reducing the degree of tumor malignancy [71]. And the interaction between lncRNA FOXM1 and ALKBH5 disrupts the tumorigenesis of glioblastoma [72]. In MM, lncRNAs have been shown to interact with key signaling pathways and transcription factors, influencing disease progression. For instance, lncRNA FEZF1-AS1 can accelerate MM progression by interacting with the IGF2BP1/BZW2 signaling pathway [50]. Specifically, FEZF1-AS1 stabilizes IGF2BP1 mRNA through m6A modification, enhancing its translation and subsequent activation of the BZW2 pathway, which promotes MM cell proliferation and survival. Targeting this lncRNA or its interaction with IGF2BP1 could be a potential therapeutic strategy.

Based on these studies, it can be inferred that by regulating the expression levels of m6A-related proteins, lncRNA expression can be controlled, ultimately creating a positive impact on disease treatment. This can range from preventing tumor occurrence, inhibiting tumor cell metastasis, and disrupting tumor cell generation.

5.3 Relationship between m6A modification and miRNA

As mentioned earlier, we have found that in MM, specific miRNAs, influenced by m6A modification, play crucial roles in regulating cell proliferation, apoptosis, and drug resistance [58, 60, 61]. The m6A modification of miRNA affect various biological processes and significantly affect inflammation and tumors. For example, the enrichment of miR-193a induced by m6A modification plays an important regulatory role in the inflammatory response of myocardial cells in septic cardiomyopathy [73]. Secondly, reducing m6A modification and miR-140-3p binding can lead to the upregulation of BET1L to promote colorectal cancer tumorigenesis [74]. Finally, M6A methyltransferase METTL3-mediated m6A modification

can upregulate miR-19a-3p, thereby promoting the proliferation and invasion of nasopharyngeal carcinoma cells and driving their progression [75]. These research provide evidence for the rational to intervene m6A modification of miRNA to prevent the onset and development of various diseases.

In summary, m6A modification can interact with various ncRNAs and regulate expression of m6A-related proteins such as YTHDC1, IGF2BP3, METTL3, and ALKBH5. It can affect cell proliferation, invasion, metastasis, and inflammatory response of various cancers, thereby affecting the onset and treatment of diseases (Fig. 3). Among them, the role of METTL3 has been studied extensively and solidified its role in the progression and metastasis of different cancers. However, it is important to note the potential limitations of these studies. For instance, the findings are often based on in vitro experiments and may not fully reflect the complexity of the tumor microenvironment in vivo. Additionally, the targeting of miRNAs can have off-target effects, which may complicate the interpretation of results and the development of miRNA-based therapies. Therefore, further research is needed to validate these findings in clinical settings and to develop strategies to minimize off-target effects.

In summary, m6A modification can interact with various ncRNAs, and regulate the expression of m6A-related proteins such as YTHDC1, IGF2BP3, METTL3, and ALKBH5. These interactions can affect cell proliferation, invasion, metastasis, and inflammatory responses in various cancers, thereby influencing disease onset and treatment outcomes. While the role of METTL3 in cancer progression and metastasis has been extensively studied, further research is needed to elucidate the specific mechanisms by which m6A modification of miRNA influences MM progression and to develop targeted therapies that can overcome the limitations of current approaches.

6 m6A modification intervenes in the progression of multiple myeloma by intervening in ncRNA

In summary, m6A modification is closely related to ncRNA. m6A modification can regulate ncRNA through various pathways, ultimately affecting disease progression. For example, m6A methyltransferase METTL3 upregulates PTCH1 expression by enhancing PTCH1 m6A modification, thereby promoting the growth and stemness of esophageal cancer cells [76]. This not only confirms that m6A modification regulates ncRNA intervention in disease progression but once again confirm the promising therapeutics strategy of this m6A modification-ncRNA regulation.

Research has found that bone homeostasis imbalance is one of the causes of MM, and MM patients are often accompanied by inhibited osteoblast activity and excessive osteoclastogenesis [77]. Methyltransferase METTL3 can promote osteoblast differentiation by increasing the m6A modification level of the circuit [78], while miR-615-3p can also regulate the m6A reading protein YTHDF2 to promote the function of FBLN1, thereby affecting the osteogenic differentiation of umbilical cord blood mesenchymal stem cells [79]. HnRNPA2B1 in MM cells can upregulate the

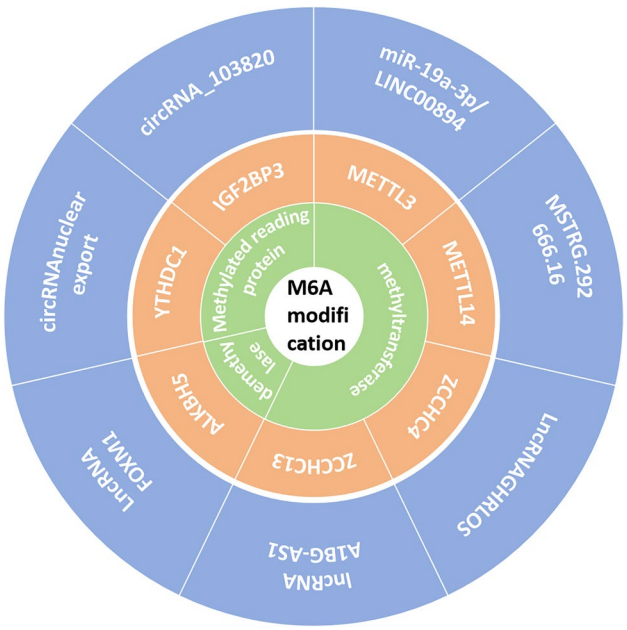

Fig. 3 Crosstalk between m6A modification and ncRNA in cancer pathogenesis. Methylase type (green boxes): methyltransferase, demethylase, methylated reading protein. Core Regulatory Proteins (orange boxes): METTL3, METTL14, ZCCHC4, ZCCHC13, ALKBH5, YTHDC1, IGF2BP3. Associated nc RNA (blue boxes): miR-19a-3p, LINC00894, MSTRG.292666.16, LncRNA GHRLOS, lncRNA A1BG-AS1, lncRNA FOXM1, circRNA nuclear export, circRNA_103820

expression of miR-92a-5p and miR-373-3p, thereby activating osteoclastogenesis and inhibiting osteoblast generation [80]. Therefore, m6A modification may be closely related to the progression of MM and may affect the progression of MM by regulating the activity of osteoblasts and osteoclasts. These findings confirm that m6A modification can regulate ncRNA, which can inhibit MM progression, improve patient quality of life. and serve as possible methods to prevent MM.

Many studies indirectly or directly confirmed m6A modification can regulate ncRNA in multiple myeloma. For example, METTL3 can regulate miRNA expression and affect the development of multiple myeloma [21]. Experimental verification has also found that ALKBH5 upregulates and stabilizes lncRNA SNHG15, which is elevated in MM [81]. Therefore, ALKBH5 regulation on SNHG15 expression plays an important role in disease progression. However, there are still significant research gaps in understanding the relationship between m6A modification and ncRNA in MM, which necessitates further investigation by the research community. This review provides some insights for plausible future research directions.

7 Conclusion

There have been many studies on the relationship between m6A modification and ncRNA intervention in the occurrence, development, and prognosis of multiple myeloma, which discovered throughout various stages of the disease. However, direct evidence that m6A modification intervenes in multiple myeloma by regulating ncRNA is still lacking. Based on the existing research, we speculate that there may be three possible therapeutics methods. First, knocking down ALKBH5 expression can affect ncRNA expression, promote MM cell apoptosis, and thus halt MM growth. Second is to inhibit ncRNA expression by reducing METTL3 expression, subsequently reducing osteoclast differentiation, and promoting osteoblast generation, thereby reducing the progression of disease. Lastly, by reducing the expression of FTO and thus controlling the expression of ncRNA, thereby reducing the resistance of MM patients to existing drugs, improving drug efficacy, and increasing patient survival. Further research on these three approaches may provide promising methods for the diagnosis, treatment, and prognosis of multiple myeloma. However, there are still some difficulties in the clinical application of these methods. They can be overcome by developing highly specific inhibitors to reduce off-target effects, optimizing delivery systems to overcome bone marrow microenvironment barriers, and stratifying patients with biomarkers to enhance treatment response rates. Future research can utilize single-cell sequencing and organoid models to explore how MM heterogeneity impacts the m6A-ncRNA network and to investigate the synergistic effects of combination therapies.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate The authors have no relevant financial or non-financial interests to disclose.

Conflict of interest The authors declare no competing interests.

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