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REVIEW

Novel Insights into the Regulatory Role of N6-Methyladenosine in the Pathogenesis and Clinical Treatment of Osteoarthritis: Research Status and Prospect

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Abstract: Osteoarthritis (OA) is caused by characteristic joint tissue lesions characterized by chronic joint pain, stiffness, and limited mobility. OA is one of the most common causes of chronic disability in adults, seriously affecting the quality of life of patients and causing huge medical and socio-economic burdens. N6-methyladenosine (m6A) is a methylation that occurs at the N6 position of adenosine and is the most common chemical modification on eukaryotic RNA. m6A modification is a dynamic regulation process involving "writers" (methyltransferases), "erasers" (demethylases), and "readers" (reading proteins). Disruption or interference of this dynamic modification may lead to dysregulation of cellular regulatory mechanisms, resulting in various diseases. This article summarized the regulatory mechanism of m6A modification in OA pathogenesis, including regulation of inflammatory response and immune infiltration, extracellular matrix (ECM) degradation, programmed cell death, bone homeostasis, and osteogenic differentiation. Finally, the application and future development prospects of m6A modification in the clinical treatment of OA were further discussed.

Keywords: osteoarthritis, m6A, DNA methylation, pathogenesis, clinical treatment

Introduction

Osteoarthritis (OA) is a type of arthritis that causes joint pain and functional impairment, affecting approximately 7.6% of the global population and causing significant medical and socio-economic burdens.[1–3] According to the latest research, the global burden of OA continues to escalate, and the number of patients with OA is expected to increase by 60% to 100% by 2050.[2] Previous studies have attributed OA to joint aging and wear. As research deepens, researchers gradually realize that genetic, metabolic, mechanical, and environmental factors induce chondrocyte aging, inflammatory responses, Extracellular Matrix (ECM degradation), and bone remodeling, leading to the occurrence and development of osteoarthritis. Based on this, researchers have developed numerous new drugs and small molecule compounds targeting the molecular level of OA, and have delved into the efficacy and potential mechanisms of traditional Chinese medicine and its chemical components in improving OA, expanding the treatment options for OA.[4–7]

However, there is still a lack of comprehensive understanding of the specific mechanisms underlying the occurrence and development of OA, and currently available treatment options for OA have not produced fully satisfactory results. Therefore, it is crucial to better understand the pathogenesis of OA for developing new diagnostic and therapeutic strategies. In recent years, with the continuous deepening of research in molecular biology, especially in the field of epigenetics, many important breakthroughs and innovations have been made in the study of the pathogenesis of OA.[8–10] N6-methyladenosine (m6A) modification is gaining attention for its important role as a common RNA modification form in eukaryotes.

During gene expression, RNA molecules acting as messengers translate genetic information into functional proteins and deliver them to cells. This process involves numerous post-transcriptional modifications that shape RNA function.[11,12] As the

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most abundant part of mRNA internal modifications, m6A involves the entire lifecycle of RNA molecules (including splicing, processing, translation, and degradation) and is widely involved in various physiological and pathological processes in organisms.[13] Moreover, m6A is closely related to the occurrence and development of various diseases.[14,15] In recent years, there have been significant progress in exploring the pathogenesis and new treatment strategies from the perspective of m6A modification.[16,17] Similarly, the crucial role of m6A modification in OA occurrence and development cannot be ignored.[18–20] For example, Rui et al have found that the absence of methyltransferase-like 3 (METTL3) can impair the homeostasis of chondrocytes, affect extracellular matrix (ECM) degradation and mechanical signal transduction in chondrocytes, and reduce the tolerance to abnormal mechanical stress in cartilage.[21] Therefore, the present study summarized the latest research on the role of m6A modification in OA and identified the key molecular mechanisms involved in OA pathogenesis. Additionally, the clinical significance and prospects of m6A modification as a therapeutic target for OA were also discussed, aiming to provide novel ideas for the clinical diagnosis and treatment of OA and the development of new drugs. The schematic diagram of the mechanism is shown in Figure 1.

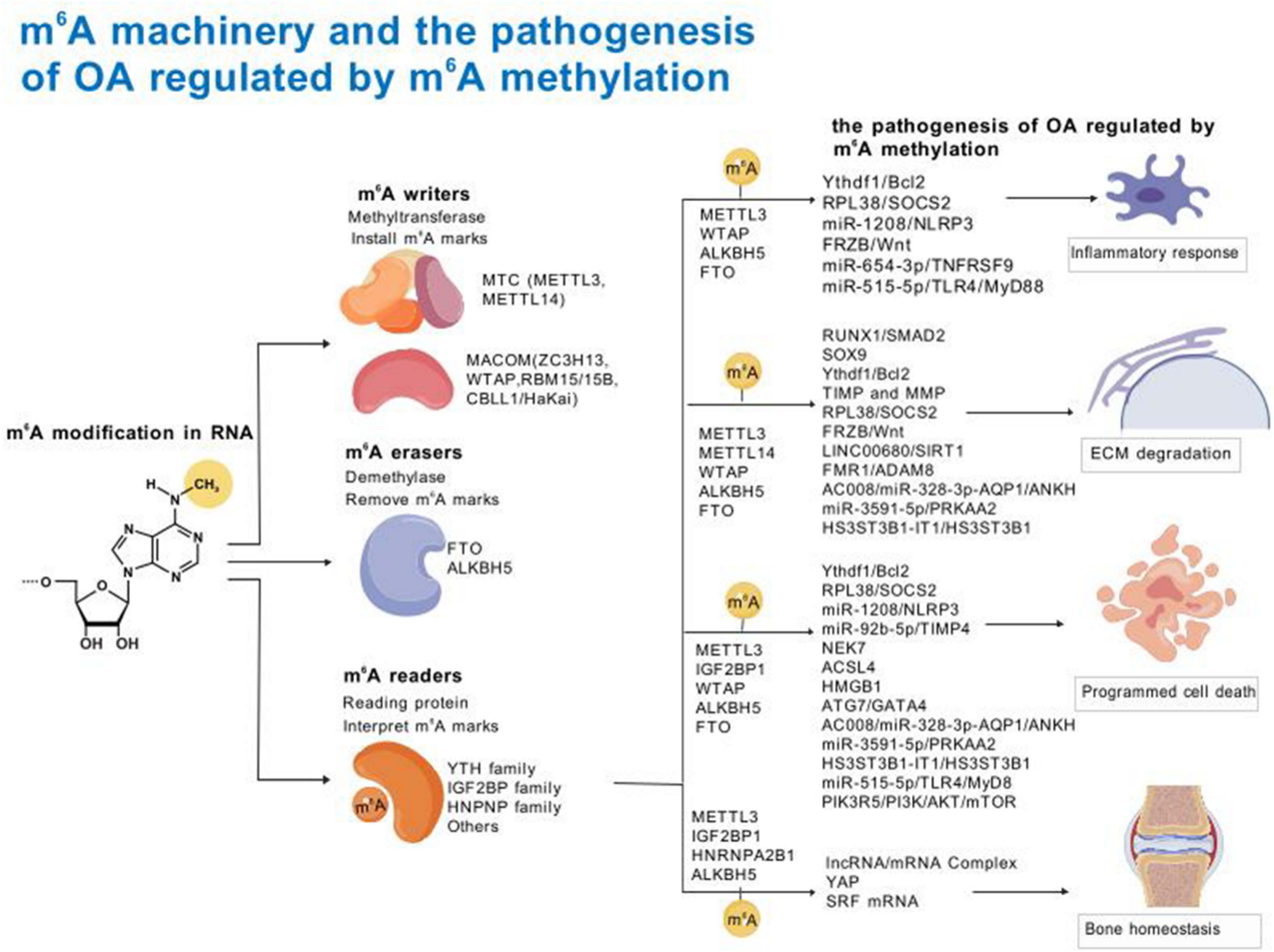

Figure 1 m6A machinery and the pathogenesis of OA regulated by m6A methylation. m^{6}A: N6-Methyladenosine. The chemical structure of m6A is shown (left). A variety of m6A writers, including the MTC(METTL3, METTL14), MACOM(ZC3H13, WTAP, RBM15/15B, CBLL1/Hakai) and m6A erasers including the FTO, ALKBH5 dynamically regulated the RNA m6A modification. A variety of m6A reader proteins, including the YT521-B homology (YTH) domain family, Insulin-like growth factor 2 mRNA-binding proteins (IGF2BP), and heterogeneous nuclear ribonucleoprotein(HNPNP) effectively binds to and recognizes m6A, ensuring that it is possible to regulate multiple biological processes involved in the occurrence and development of OA, including the inflammatory response, extracellular matrix (ECM) degradation, programmed cell death, and bone homeostasis.

Enzymes and Proteins Involved in m6A Modification

m6A refers to the methylation of adenosine base at the nitrogen-6 position, namely, a methyl group is added to the 6th position of the nitrogen (N) atom of adenosine on RNA.[22,23] As the most common form of post-transcriptional modification, m6A modification is involved in a wide range of regulatory mechanisms and controls gene expression in various physiological and pathological processes.[24]

In addition, research has found that m6A modification is not limited to the RNA level, but may also interact with other epigenetic modifications (such as DNA methylation, histone modifications, etc). to jointly regulate gene expression.[25] m6A modification is a dynamic and reversible process that is mainly controlled by the interactions between three enzymes and proteins, including the "writer" (methyltransferase), "eraser" (demethylase), and "reader" (reading protein). Detailed information is listed in Table 1. During the nuclear phase, methyltransferase methylates the 6th N atom of adenine on RNA, while demethylase demethylates m6A-modified RNA, thereby affecting mRNA splicing and other nuclear processes. After being exported to the cytoplasm, the reading protein recognizes the m6A modification of RNA and regulates a series of downstream biological processes (such as RNA degradation, nucleation, translation, and cleavage), affecting mRNA stability, translation, and/or localization.[26]

Table 1 Enzymes and Proteins Involved in Modification by m6A

Types	m6A Regulator	Full Names	Function	Ref
m6A writers	METTL3/4	Methyltransferase-like 3/4 complex	Transferring methyl groups from S-adenosyl-L-methionine to N6 amino groups of adenosine bases in RNA (m6A) and DNA (m6DA)	[27–29]
	WTAP	Wilm's tumor 1-associated protein	Targets METTL3/14 into nuclear speckles	[30–32]
	ZC3H13	Zinc Finger CCCH-Type Containing 13	Assist WTAP in nuclear localization	[33]
	RBM15/15B	RNA binding motif protein 15/15B	Mediators of methylation specificity	[34,35]
	CBLL1/HaKai	Cbl proto-oncogene-like 1	WTAP interaction proteome	[34,36]
m6A erasers	FTO	Fat mass and obesity-associated protein	Follows a traditional oxidative *N*-demethylation pathway to demethylate m6A	[37–41]
	ALKBH5	α-ketoglutarate-dependent dioxygenase alk B homolog 5	Direct demethylation of m6A through co localization with nuclear spots	[42–44]
m6A readers	YTHDF1/2/3 YTHDC1/2	YTH domain family	YTHDF1 enhances mRNA translation YTHDF2 promotes mRNA degradation YTHDF3 enhances both translation and degradation YTHDC1 promotes mRNA splicing and mRNA production YTHDC2 enhances the stability and translation efficiency of target RNA	[45–53]
	IGF2BP(IGF2BP1, IGF2BP2 and IGF2BP3)	Insulin-like growth factor 2 mRNA-binding proteins	Affects RNA stability, mRNA localization, and regulates mRNA translation	[54,55]
	HNRNP(HNRNPC, HNRNPG, HNRNPA2B1)	Heterogeneous nuclear ribonucleoprotein	HNRNPC and HNRNPG regulate RNA metabolism through the "m6A switch" HNRNPA2B1 directly bind to mRNA	[56–64]

Abbreviation: m6A, N6-Methyladenosine.

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m6A Writer (Methyltransferase)

The m6A writer consists of the catalytic subunit m6A methyltransferase complex (MTC) (including METTL3/METTL14) and the regulatory subunit m6A-METTL-associated complex (MACOM) [including Hakai, Wilms' tumor 1-associating protein (WTAP), VIRMA, ZC3H13, and RBM15/15B]. METTL3 and METTL14 are the core of m6A writers, which closely associate with each other and form stable heterodimers; the METTL3-METTL14 complex transfers a methyl group from S-adenosyl-L-methionine to N6 amino groups of adenosine bases in RNA (m6A) and DNA (m6DA).[27] In the METTL3-METTL14 complex, METTL3 is the only subunit with catalytic activity, playing an important role in substrate recognition and catalytic processes. METTL14 stabilizes METTL3 conformation to enhance its catalytic activity and plays a crucial role in substrate RNA recognition.[28,29] According to the latest mechanism research, the mixed DNA binding activity of METTL3-METTL14 complex disrupts its ability to methylate RNA, while WTAP and VIRMA, as two important regulatory proteins in MTC, counteract the binding of METTL3-METTL14 to double-stranded DNA (dsDNA) and thus maintain its RNA methylation activity.[30] WTAP is a splicing regulatory factor that assists METTL3/14 localization of nuclear speckles and does not possess methyltransferase activity on its own.[31] Specifically, the nuclear localization signals on WTAP and METTL3 mediate the nuclear input of WTAP and METTL3/14 heterodimers.[32] During this process, ZC3H13 acts as an interactor for WTAP, mainly responsible for connecting with RBM15 and assisting WTAP in nuclear localization.[33] The proteomic study of WTAP has initially identified rBM15 and rBM15B (two homologous RNA binding proteins) as potential WTAP interactors.[34] Another study has confirmed that rBM15 is primarily responsible for binding to METTL3/14 and promoting its recruitment to RNA for modification.[35] Similarly, CBLL1/Hakai is first identified in the WTAP interacting proteome.[34] Knockout of CBLL1/Hakai causes instability of several subunits of the MTC, leading to decreased m6A in mRNA.[36]

Overall, as a protein complex involved in catalyzing the m6A modification of adenosine residues on target RNA, MTC writes methylation modifications into specific RNA molecules, thereby mediating the RNA methylation modification process. In this process, MACOM plays an important collaborative role in ensuring the correct m6A methylation modification occurs on the target RNA molecule, thereby regulating RNA function and structure stability.

m6A Eraser (Demethylase)

The core function of m6A erasers is to restore the modified RNA to its original state, thereby achieving dynamic reversibility of m6A modification.[65] Fat mass and obesity-associated protein (FTO) is the first reported RNA demethylase to remove mRNA m6A, exhibiting efficient oxidative demethylation activity in vitro and targeting the abundant m6A residues in RNA.[37] In human cancer cells, FTO is localized in the cytoplasm, and m6A is removed from mRNA transcripts that contribute to cancer progression.[38,39,66] However, in mouse and human tissues, FTO often exhibits nuclear localization, and FTO-mediated m6A demethylation may regulate chromatin status during mammalian development.[38,40] After FTO, AlkB homolog 5 (ALKBH5), another mammalian demethylase, can oxidize and reverse m6A in mRNA both in vitro and in vivo.[42] Although both FTO and ALKBH5 belong to the non-heme Fe (II)/2-hydroxyglutarate dependent oxygenase-dependent dioxygenase family, they exhibit significant differences in RNA substrate preferences and cellular localization, particularly in catalyzing RNA oxidative demethylation pathways.[67,68] Specifically, FTO follows the traditional oxidation N demethylation pathway, and the FTO-mediated demethylation process requires three intermediates, including N6 hydroxymethyladenosine (hm6A), N6 formyladenosine (f6A), and N6 hydroperoxide methyladenosine (oxm6A).[41] In contrast, ALKBH5 directly demethylates m6A by co-localization with nuclear speckles.[43,44]

To sum up, during the m6A methylation modification process, demethylases (FTO and ALKBH5) can eliminate RNA methylation modification signals to achieve the dynamic reversibility of the m6A methylation modification process. The regulation of intermediary metabolism and/or post-translational modifications (PTMs) by FTO and ALKBH5 may be important contributors to the dynamic epitranscriptome.[69]

m6A Reader (Reading Protein)

The main function of the m6A "reader" is to recognize information after m6A methylation modification, thereby affecting the downstream biological effects of m6A-modified RNA.[70] The m6A "reader" mainly includes the YTH domain family (YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2), the HNRNP domain family (HNRNPA2B1, HNRNPC, and HNRNPG), and the IGF2BP domain family (IGF2BP1, IGF2BP2, and IGF2BP3). The YTH domain family is the earliest reported m6A reader. Research has shown that the YTH family proteins contain a YTH domain at the C-terminal region that can recognize m6A-containing RNA.[70,71] Additionally, the YTH domain also contains a crack rich in alkaline residues that interacts electrostatically with the RNA backbone.[72,73] The YTHDF family consists of three highly similar but functionally distinct paralogous compounds: YTHDF1, YTHDF2, and YTHDF3. The YTHDF family proteins are mainly localized in the cytoplasm.[74] Previous studies have suggested that YTHDF1 regulates translation, YTHDF2 regulates mRNA stability, and YTHDF3 functions as an mRNA transfer protein, promoting the transfer of m6A mRNA leaving the nucleus to YTHDF1 or YTHDF2.[45–48] The above functional differences can be attributed to their different RNA binding sites. However, in recent years, some researchers have put forward different views that YTHDF1 has no significant impact on translation and that YTHDF1, YTHDF2, and YTHDF3 promote m6A mRNA degradation together.[49–51] The current controversy over the function of YTHDF protein may be due to technical issues resulting in defective datasets, and differences in data analysis methods leading to different conclusions about the role and binding sites of YTHDF protein. Different from YTHDF family proteins, YTHDC1 mainly promotes mRNA splicing and mRNA production in the nucleus,[52] while YTHDC2 is expressed in both cytoplasm and nucleus, which can enhance the stability and translation efficiency of target RNA.[53]

Unlike the YTH domain family, the KH domain in the IGF2BP family plays a crucial role in the recognition and binding of m6A.[54] IGF2BP belongs to the RNA binding protein family, which regulates gene expression by binding to m6A binding sites in different RNA sequences, thereby affecting RNA stability and mRNA localization, and regulating mRNA translation.[55] The HNRNP domain family is a group of RNA-binding proteins that can recognize specific RNA sequences and often participate in processes such as mRNA pre-splicing, transcription, and translation regulation.[56] HNRNPA2B1, an important component of the HNRNP domain family, directly binds to mRNA to regulate RNA metabolism, thereby participating in viral replication and serving as a potential biomarker for cancer occurrence and development.[57–61] Additionally, HNRNPC and HNRNPG in the HNRNP domain family regulate RNA metabolism through the "m6A switch", which is their biggest difference from HNRNPA2B1 and the key to distinguishing them from other reading proteins.[62] Specifically, m6A methylation modification catalyzes mRNA precursor processing and maturation by altering the secondary structure of RNA through HNRNP binding, while HNRNPC and HNRNPG can regulate mRNA abundance and splicing after m6A recognition.[63,64]

In general, as the m6A methylation-modified regulatory protein, the m6A reader effectively binds to and recognizes m6A, ensuring that it is possible to regulate multiple biological processes mediated by m6A.

The Role of m6A Modification in OA Pathogenesis

In recent years, with the continuous development of bioinformatics technology and the gradual deepening of research on OA pathogenesis, researchers have been surprised that m6A modification plays an important role in OA occurrence and development. In 2012, a large genome-wide association study (GWAS) involving multiple countries showed that FTO involvement in weight regulation is a strong risk factor for OA.[75] Subsequently, increasing evidence has suggested that m6A modification-associated proteins (such as FTO, METTL3/14, WTAP, and ALKBH5) are abnormally expressed in OA chondrocytes and widely involved in regulating OA inflammatory response, ECM degradation, programmed cell death (apoptosis, autophagy, ferroptosis, and pyroptosis), bone homeostasis, and osteogenic differentiation.[76–81] The regulatory role of m6A modulators in the pathogenesis of OA is summarized in Table 2.

Regulating Inflammatory Response and Immune Infiltration in OA

Early research suggested that OA was a degenerative disease. However, recently, the role of immune infiltration and inflammatory response in OA pathogenesis has been increasingly recognized and further confirmed through

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Table 2 Role of m6A Modulators in the Pathogenesis of OA

Types	m6A Regulator	Cells	Animals	Expression	Targets	Biological Function	Ref
m6A writers	METTL3	ATDC5 cells	Collagen mouse mode	Up	NF-κB	Inflammatory response, apoptosis	[76]
	METTL3	Human articular Chondrocyte	Sprague Dawley rat	Up	SOX9	ECM degradation	[80]
	METTL3	Human articular Chondrocyte	-	Up	TIMP and MMP	ECM degradation, Inflammatory response	[82]
	METTL3	ATDC5 cells	MIA mouse model	Down	METTL3/Ythdf1/Bcl2	Inflammatory response, chondrocytes apoptosis, chondrocytes autophagy	[83]
	METTL3	Human articular Chondrocyte	DMM mouse model	-	RPL38/METTL3/SOCS2/JAK2/STAT3	Inflammatory response, ECM degradation, chondrocytes apoptosis	[84]
	METTL3	Human articular Chondrocyte, THP-1 cells	DMM mouse model	-	miR-1208/METTL3/NLRP3	Inflammatory response, apoptosis	[85]
	METTL3	Human articular Chondrocyte	-	Up	LINC00680/METTL3/SIRT1	ECM degradation	[86]
	METTL3	Human articular Chondrocyte	DMM mouse model	Up	NEK7	Chondrocytes pyroptosis	[87]
	METTL3	Mouse chondrocyte	DMM mouse model	Up	METTL3/ACSL4	Chondrocyte ferroptosis	[88]
	METTL3	Mouse chondrocyte	MIA mouse model	Up	HMGB1	Chondrocyte ferroptosis	[89]
	METTL3	Human fibroblast-like synoviocytes	DMM mouse model	Up	ATG7/GATA4	Autophagy	[90]
	METTL3	Mouse chondrocyte	DMM mouse model	-	ATG7	Autophagy	[91]
	METTL3	ATDC5 cells	Mettl3 conditional knockout mice	-	Lats1/YAP1	Bone homeostasis	[21]
	METTL3	Mouse chondrocyte	Rodent model of unilateral anterior crossbite	-	YAP/METTL3	Bone homeostasis	[92]
	METTL14	Human articular Chondrocyte	DMM mouse model	Up	FMR1/ADAM8/JAK/STAT3	ECM degradation	[93]
	WTAP	Human articular Chondrocyte	DMM mouse model	Up	WTAP/FRZB/Wnt/β-catenin	Inflammatory response, ECM degradation	[94]
	WTAP	Human articular Chondrocyte	-	Up	miR-92b-5p/TIMP4	ECM degradation, chondrocytes apoptosis	[95]

m6A erasers	FTO	Human articular Chondrocyte	DMM mouse model	Down	RUNX1/FTO/SMAD2/ YTHDF2	ECM degradation	[78]
	FTO	Human articular Chondrocyte	MIA mouse model	Down	FTO/AC008/miR-328-3p-AQP1/ANKH	ECM degradation, chondrocytes apoptosis	[96]
	FTO	Human articular Chondrocyte	DMM mouse model	Down	*FTO/miR-3591-5p/PRKAA2*	ECM degradation, chondrocytes apoptosis	[97]
	FTO	C28/I2	MIA mouse model	Down	miR-515-5p/TLR4/ MyD88/NF-κB	Chondrocytes apoptosis, Inflammatory response	[98]
	FTO	Mouse chondrocyte	A mixture of papain and cysteine mouse model	-	PIK3R5/PI3K/AKT/mTOR	Autophagy	[99]
	ALKBH5	Human articular Chondrocyte	DMM mouse model	Up	ALKBH5/miR-654-3p/ TNFRSF9/NF-κB	Inflammatory response	[100]
	ALKBH5	Human articular Chondrocyte	MIA mouse model	Down	ALKBH5/HS3ST3B1-IT1 /HS3ST3B1	ECM degradation, chondrocytes apoptosis	[101]
	ALKBH5	Mouse chondrocyte	Mandibular defect model in nude mice	-	lncRNA/mRNA Complex	Osteogenic differentiation	[102]
m6A readers	YTHDF2	Human knee synovial tissues	-	Down	hsa-miR-129-5p and hsa-miR-515-5p	Immune infiltration	[103]
	IGF2BP1	Human articular Chondrocyte	-	Up	MMP3	Chondrocyte ferroptosis	[104]
	HNRNPA2B1	MC3T3-E1 cells	C57BL/6J mice	Down	hnRNPA2B1	Osteogenic differentiation	[105]
	IGF2BP2	MC3T3-E1 subclone 14 cell	-	-	SRF mRNA	Osteogenic differentiation	[106]

Note: "-" representing missing relevant data.

Abbreviations: METTL3, Methyltransferase-like 3; ECM, Extracellular Matrix; WTAP, Wilm's tumor 1-associated protein; MIA, Monoiodoacetate; DMM, Destabilization of the Medial Meniscus; FTO, Fat mass and obesity-associated protein; ALKBH5, α-ketoglutarate- dependent dioxygenase alk B homolog 5; YTHDF2, YTH domain family; IGF2BP1/2, Insulin-like growth factor 2 mRNA-binding proteinsHNRNPA2B1; MMP3, Matrix Metalloproteinase-3; SRF, Serum Response Factor.

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bioinformatics analysis and clinical sample validation.[107,108] Ouyang et al have confirmed that the differences in m6A modification patterns lead to the complexity of the OA immune microenvironment; moreover, they have established a predictive model to assist in evaluating the m6A modification patterns and immune cell infiltration characteristics of OA patients, thereby predicting the disease development of OA patients.[18] Bian et al have revealed that YTHDF2, as a key m6A regulator in OA synovitis, has high diagnostic value and significantly affects the immune status of patients.[103] Meanwhile, Sang and Weilin et al have also provided evidence through bioinformatics analysis that METTL3 expression is reduced in OA; it's further confirmed that METTL3 mRNA expression and protein level are reduced in OA clinical sample cartilage tissues.[82] Additionally, He et al have found that METTL3 expression is reduced in TNF-α-induced chondrocytes and temporomandibular joint osteoarthritis (TMJOA) mice both in vitro and in vivo.[83] These findings have sparked scholars' interest in the modulation of OA inflammatory response by METTL3 modification. Shi, Liang et al have transfected RPL38 siRNA (si-RPL38) into interleukin-1β (IL-1β)-stimulated primary chondrocytes to investigate the effect of RPL38 knockdown on the secretion of inflammatory factors in OA chondrocytes; the results have demonstrated that RPL38 knockdown inhibits chondrocyte inflammation by regulating METTL3-mediated SOCS2 m6A modification.[84] Different from single-cell studies, Zhou et al have co-cultured human chondrocytes with THP-1 cells to simulate the inflammatory environment in OA, and they further prove that extracellular vesicles (EVs) decrease the m6A level of NLRP3 mRNA following miR-1208 targeted binding to METTL3, resulting in decreased release of inflammatory factors.[85] Unlike METTL3, methyltransferase WTAP is upregulated in both cartilage of clinical OA patients and human chondrocytes treated with pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α); meanwhile, the mRNA expression of inflammatory genes (IL-6, IL-8, and iNOS) increases. According to MeRIP seq and RNA seq analysis results, WTAP stabilizes frizzled-related protein (FRZB) mRNA in an m6A-dependent manner and activates the Wnt/β-catenin signaling pathway, inducing an inflammatory response in OA chondrocytes.[94]

The demethylase ALKBH5 has been reported to play a key role in the immune system.[109,110] Yu et al have first reported the role of ALKBH5 in OA and pointed out that ALKBH5 expression is upregulated in OA; excessive ALKBH5 inhibits the methylation of pri-miR-654 and decreases the expression of cartilage-protective miR-654-3p, thereby activating the NF-κB signaling pathway and inducing OA inflammation.[100]

In summary, inflammation and immune infiltration are involved in the occurrence and development of OA. The m6A reading protein YTHDF2 has a high diagnostic value for OA inflammation and immune infiltration. The low expression of METTL3 and the high expression of WTAP and ALKBH5 in OA promote inflammation and thus accelerate OA occurrence and development. In addition, m6A modification also participates in oxidative stress-related inflammatory responses, such as further exacerbating chondrocyte aging by regulating ROS levels and the expression of inflammatory factors.[107] However, the above studies are primarily based on bioinformatics to analyze the regulation of m6A modification on inflammatory response and immune infiltration, and more experiments are needed for verification. Additionally, the above studies are limited to phenomenon observation and its possible mechanisms should be further explored.

Regulating ECM Degradation in OA

ECM is a three-dimensional polymer structure that is the main component of articular cartilage.[111] Under normal circumstances, ECM accounts for over 90% of the volume of articular cartilage and contains multiple components crucial for maintaining the normal function of articular cartilage tissue, such as collagen type II/VI/IX (Col II/VI/IX), hyaluronic acid (HA), aggrecan (ACAN), and glycoprotein.[112,113] Matrix metalloproteinases (MMPs) are a family of zinc-dependent metalloendopeptidases, playing a critical role in cartilage ECM remodeling. Tissue inhibitors of metalloproteinases (TIMPs) are specific inhibitors of MMPs that can inhibit their activity. Both are important regulatory factors in maintaining the dynamic balance of ECM breakdown and synthesis metabolism.[114] Under healthy conditions, there is a balance between cartilage ECM breakdown and synthesis. However, during the development of OA, this balance is disrupted and ECM decomposition accelerates, which is also regulated by m6A modification.[115]

Sang et al have demonstrated through in vitro experiments that overexpression of METTL3 can regulate and adjust the balance between TIMP and MMP, thereby affecting ECM degradation in OA.[82] Additionally, METTL3 overexpression can bind to the m6A site of LINC00680 to promote its upregulation, thereby accelerating the degradation of ECM.[86] Another study has found that silenced METTL3 promotes ECM degradation and accelerates OA development via

reducing MMP-13 and Coll X expressions and increasing aggrecan and Coll II expressions in IL-1β-stimulated chondroprogenitor cell line ATDC5.[76] In addition, METTL14 is upregulated in OA mice and IL-1β-induced chondrocytes. Knocking out METTL14 inhibits the expression of FAS-AS1 and ADAM8 in an m6A-dependent manner, thereby suppressing ECM degradation in chondrocytes.[93] The expression of splicing regulatory factors WTAP and reading protein YTHDF2 is elevated in OA; WTAP knockdown regulates the miR-92b-5p/IMP4 axis in an m6A YTHDF2-dependent manner to inhibit ECM degradation in lipopolysaccharides (LPS)-induced OA chondrocytes, promote ECM synthesis, and alleviate OA progression.[95]

The regulatory effects of m6A demethylase FTO and ALKBH5 on ECM cannot be ignored. Yang et al have found that FTO in OA cartilage is significantly downregulated compared to that in normal cartilage, increasing AC008440.5 RNA stability and leading to high expression of AC008440.5 in OA cartilage, thereby reducing the vitality of OA chondrocytes and promoting ECM degradation.[96] Moreover, Liu et al have also confirmed that overexpression of FTO can decrease the expression of MMP-13 and ADAMTS-5, and enhance the expression of collagen II and aggrecan in LPS-treated chondrocytes.[97] Similarly, it has been revealed that ALKBH5 expression is decreased in OA cartilage, which increases m6A levels of HS3ST3B1-IT1 and accelerates the decay of HS3ST3B1-IT1 in a YTHDF2-dependent manner, promoting HS3ST3B1 protein degradation and ECM degradation.[101]

On the whole, the dysregulation of methyltransferase METTL3, WTAP, demethylase FTO, ALKBH5, and reading protein expression YTHDF2 is closely involved in regulating ECM degradation and OA occurrence and development, with dysregulated METTL3 expression being the most critical. However, the bioactive fragments of cartilage ECM are diverse, and existing research has not yet delved into the regulatory effects of m6A regulatory factors on ECM molecules and their bioactive fragments (such as matrikines and matricryptins). Further experiments are needed to reveal the molecular mechanisms of m6A regulatory factors in ECM degradation.

Regulating Programmed Cell Death in OA

Programmed cell death is an active cell death mode regulated by genes, mainly including apoptosis, autophagy, copper death, pyroptosis, and ferroptosis.[116,117] This pattern is not only common in the normal development process of organisms but also plays an important role in the occurrence and development of various diseases, such as tumors, endocrine diseases, and cardiovascular diseases.[118–122] Similarly, programmed cell death also occurs in OA. Generally speaking, apoptosis, autophagy, pyroptosis, and ferroptosis are the most common forms of cell death in OA, and these cell death modes are also regulated by m6A modification.[123,124]

Apoptosis of chondrocytes is one of the most important factors contributing to OA pathogenesis.[125] Under normal physiological conditions, apoptosis of chondrocytes is in a dynamic balance. However, the stimulation of mechanical injury, inflammatory response, and oxidative stress can induce excessive apoptosis of chondrocytes, accelerating cartilage damage and promoting OA development.[126–128] It has been reported that the silenced methyltransferase METTL3 can inhibit apoptosis of chondrocytes induced by pro-inflammatory factors (TNF-α and IL-1β) in vitro.[76,83] Shi et al have reported that RPL38 directly interacts with METTL3 and inhibits SOCS2 expression through METTL3-mediated m6A modification, activating the JAK2/STAT3 pro-inflammatory pathway and promoting IL-1β-induced chondrocyte apoptosis.[84] The demethylase FTO has been widely reported to be involved in the process of cell apoptosis in various diseases.[129–131] As has been evidenced previously, FTO expression is decreased in LPS-induced human normal chondrocytes (C28/I2), while the expression of anti-apoptotic protein Bcl-2 is inhibited, and the expression of pro-apoptotic proteins Bax and Cleaved caspase-3 is upregulated, along with increased apoptosis rate and elevated inflammatory markers (IL-6, IL-1β, and TNF). Overexpression of FTO inhibits the TLR4/MyD88/NF-κB axis in an m6A-dependent manner, reversing the above expression trends and reducing cell apoptosis and C28/I2 cell damage.[98]

Pyroptosis is a type of lytic cell death. Studies have shown that NLRP3 can induce chondrocyte pyroptosis, increase the levels of inflammatory factors (IL-1β and IL-18), and induce and exacerbate OA.[132,133] In an LPS-induced OA cell model, high expression of METTL3 leads to a significant decrease in cell survival rate, while the expression levels of apoptosis-related proteins (NLRP3, ASC, caspase 1, and GSDMD) and pro-inflammatory factors (IL-1β, IL-6, IL-18, and TNF) are increased. Additionally, the above expressions exhibit the opposite trends with the downregulation of METTL3, indicating that high expression of METTL3 in OA promotes cell apoptosis during the OA process.[87]

Ferroptosis is a cell death mode caused by excessive accumulation of iron, which increases reactive oxygen species (ROS) production and induces lipid peroxidation in the outer mitochondrial membrane.[134] Research has found that in OA cartilage synovial fluid, the concentration of iron ions increases and the content of ferroptosis inhibitor glutathione peroxidase 4 (GPX4) decreases.[135] Cheng et al have demonstrated that METTL3 overexpression in rat chondrocytes increases the levels of Fe^{2+}, ROS, and malate dehydrogenase (MDH), decreases glutathione (GSH) level, and induces ferroptosis in OA chondrocytes.[88] Correspondingly, depletion of METTL3 can alleviate cartilage damage and ferroptosis in KOA model rats.[89] Additionally, it has been reported that the reading protein IGF2BP1 is upregulated in IL-1β-induced chondrocytes, accompanied by increased Fe^{2+}, malondialdehyde (MDA), and ROS levels in chondrocytes and reduced GSH level, leading to ferroptosis in chondrocytes. Silenced IGF2BP1 binds to MMP3 through the m6A site, enhancing the stability of MMP3 mRNA in the ferroptosis microenvironment and inhibiting ferroptosis in chondrocytes.[104]

Autophagy is the self-digestion of cells to maintain the stability of the intracellular environment.[136] Chondrocytes can regulate their activity through autophagy to avoid apoptosis, thus effectively delaying OA progression.[137] Chen et al have found that METTL3 overexpression in an m6A-YTHDF2-dependent manner reduces the expression of E-1 enzyme, autophagy-related 7 (ATG7), which is crucial for autophagy formation, thereby impairing autophagy in OA-FLS; however, silencing METTL3 can promote autophagy remodeling and alleviate FLS aging.[90] This process is further confirmed by another experiment conducted in a mouse model of destabilization of medial meniscus (DMM) and an IL-1β-stimulated chondrocyte model.[91] Lv, Guohua et al have reported that EVs from dysfunctional chondrocytes regulate the stability of PIK3R5 mRNA through FTO-dependent regulation, activating the PI3K/AKT/mTOR pathway, inhibiting macrophage autophagy, and inducing collagen degradation and inflammatory cell infiltration in rats.[99]

In general, programmed cell death is an important pathway of cell metabolism, and its abnormal expression is involved in OA occurrence and development and is also regulated by m6A modification, especially the methyltransferase METTL3. However, programmed cell death is a complex process in which different modes of cell death interact with each other. There is currently no detailed study exploring the comprehensive effects of m6A modification on these cell death modes in OA.

Regulating Bone Homeostasis and Osteogenic Differentiation in OA

Bone homeostasis refers to the dynamic balance between osteoblasts and osteoclasts to maintain the stable morphology and strength of bones, which may be regulated by excessive mechanical stress (EMS).[138] It has been shown that METTL3 deficiency in chondrocytes leads to morphological changes in mandibular condyle cartilage, weakened adaptive response to abnormal mechanical stimuli, and early onset of temporomandibular joint OA.[21] Yang et al have validated this phenomenon in TMJOA rats; they have further pointed out that YAP deficiency promotes METTL3-dependent m6A modification, leading to abnormal mechanical stress and triggering chondrocyte aging and TMJOA progression in rats.[92] Osteogenic differentiation refers to the process of mesenchymal stem cells [such as bone marrow-derived mesenchymal stem cells (BM-MSCs)] transforming into osteoblasts, which is of great significance in bone development and repair.[139] Overproliferation and abnormal differentiation of osteoblasts are important factors in OA progression.[140] Studies have shown that ALKBH5 positively regulates the osteogenic differentiation of human adipose stem cells (hASCs) through lnc-AK311120.[102] The m6A reading protein HNRNPA2B1 is downregulated in an animal model of bone loss induced by abnormal mechanical stress, and overexpression of HNRNPA2B1 can weaken the inhibition of osteoblast differentiation by abnormal mechanical stress.[105] Additionally, the reading protein IGF2BP2 has been reported to possess the ability to promote osteoblast proliferation and osteogenic differentiation.[106]

In short, abnormal m6A modification can lead to excessive proliferation and abnormal differentiation of osteoblasts, as well as reduced adaptability of cartilage to abnormal mechanical stress, thereby inducing bone homeostasis imbalance and promoting OA occurrence and development. However, there is currently no relevant research to further explore the molecular mechanisms and numerous signaling pathways involved in the above process. Subsequent research should further analyze the signaling pathways involved in m6A modification in regulating bone homeostasis and osteogenic differentiation.

Overall, m6A modified proteins are widely involved in regulating OA inflammatory response, ECM degradation, programmed cell death (apoptosis, autophagy, ferroptosis, and pyroptosis), bone homeostasis, and osteogenic differentiation.

It should be emphasized that inconsistencies in methodology and research models have led to conflicting findings regarding METTL3, FTO, and WTAP. For example, METTL3 is downregulated in ATDC5 cells in the MIA mouse model and participates in regulating inflammatory response, chondrocytes apoptosis, and chondrocytes autophagy. In the MIA mouse model, chondrocyte expression is upregulated and participates in regulating chondrocyte ferroptosis.[83,89]

Application of m6A Modification in Clinical Treatment of OA

The different regulatory effects of m6A modification-related enzymes and proteins, as well as their differential expression levels in vivo, have revealed new targets for OA diagnosis and treatment. As a result, many scholars have begun to explore treatment strategies targeting m6A modification. BM-MSCs, a type of pluripotent stem cells that exist in the bone marrow, have shown significant therapeutic potential in diseases such as acute myocardial infarction, ischemic stroke, and osteoporosis.[141–143] Research has shown that BM-MSCs can exert therapeutic effects on OA by secreting anti-inflammatory substances to inhibit cartilage degradation and releasing EVs.[144–146] Therefore, BM-MSCs are considered potential new therapeutic drugs for OA treatment. Based on this, its therapeutic mechanism has been further explored. It has shown that BM-MSCs can exert a therapeutic effect on OA by regulating m6A modification. For example, Chen et al have reported that FTO-EVs derived from BM-MSCs can inhibit cell aging and apoptosis in LPS-treated chondrocytes and monosodium iodoacetate (MIA)-induced OA mouse tissues, as well as inhibit OA development by triggering protective autophagy through demethylation of m6A modification.[147] Extracellular vesicles (EXOS) are nanoscale membrane vesicles released by cells, rich in various bioactive substances that can protect the smooth delivery of bioactive molecules to target cells and participate in the regulation of cellular functions.[148] Research has shown that BM-MSCs-derived exosomes (BMSC-Exos) can alleviate METTL3-mediated m6A modification and regulate ACSL4 expression, thereby inhibiting ferritin deposition in chondrocytes and reducing ferroptosis in chondrocytes.[88]

Although extracellular vesicles have shown great potential in OA treatment and drug delivery, their clinical applications still face challenges such as immature isolation and purification technologies, high production costs for large-scale production, and unclear functional mechanisms and targets. Future research needs to make breakthroughs in technological optimization, mass production, and in-depth study of functional mechanisms to promote the widespread application of extracellular vesicles in clinical practice.

In clinical practice, traditional Chinese medicine (TCM) plays an important role in the treatment of OA due to its significant efficacy, minimal side effects, and low cost.[149–151] In recent years, with the continuous exploration of the mechanism of TCM in treating OA, researchers have found that TCM may exert its therapeutic effect on OA by regulating m6A modification. For example, curcumin, a bioactive compound in TCM turmeric, has been shown to alleviate chondrocyte damage, inhibit cell apoptosis, and promote ECM synthesis by upregulating the demethylase KDM6B of histone H3K27me3 and downregulating the succinic acid metabolism pathway.[152] Cui et al have confirmed that the TCM Gubi Dectomion (GBD) can effectively inhibit ATG7 m6A modification and METTL3 expression, thereby exerting a protective effect on chondrocyte autophagy and apoptosis.[91] Another TCM decoction, Bushenhuoxue decoction(BSHXD), has been reported to inhibit NLRP3 inflammasome activation and cell pyroptosis in chondrocytes in an m6A-dependent manner, thereby suppressing OA progression.[153] Treatments targeting m6A modification in OA are shown in Table 3.

Table 3 Treatment of m6A Modification in OA

Measures	m6A Regulator	Cells	Animals	Targets	Biological Function	Ref
FTO-EVs	METTL3/ YTHDF2	Mouse chondrocyte	MIA mouse model	ATG5/ ATG7/ BNIP3	Apoptosis, autophagy	[147]
BMSC-Exos	METTL3	Mouse chondrocyte	DMM mouse model	METTL3/ ACSL4	Chondrocyte ferroptosis	[88]

(*Continued*)

Table 3 (Continued).

Measures	m6A Regulator	Cells	Animals	Targets	Biological Function	Ref
Curcumin	KDM6B	Mouse chondrocyte	DMM mouse model	Histone H3K27me3	Bone homeostasis, ECM degradation, chondrocytes apoptosis	[151]
GBD	METTL3	Mouse chondrocyte	DMM mouse model	ATG7	Autophagy	[152]
BSHXD	m6A level	Mouse chondrocyte	Facet joint osteoarthritis mouse model	NLRP3	Inflammatory response, pyroptosis	[91]

Abbreviations: EVs, Extracellular vesicles; METTL3, Methyltransferase-like 3; MIA, Monoiodoacetate; DMM, Destabilization of the Medial Meniscus; FTO, Fat mass and obesity-associated protein; YTHDF2, YTH domain family; BMSC-Exos, BM-MSCs-derived exosomes; GBD, Gubi Dectomion; BSHXD, Bushenhuoxue decoction; m6A, N6-Methyladenosine.

As is well known, both OA and cancer involve complex inflammatory responses and pain management strategies. The regulatory effect of m6A modification also exists in the occurrence and development of cancer. Therefore, the development of m6A modified regulatory drugs in cancer research provides a new treatment approach for OA. For example, STC-15, which has entered the clinical trial stage, activates the interferon signaling pathway, enhances T cell activation, and anti-tumor immune response by inhibiting METTL3 and reducing m6A RNA methylation.[154,155] Immune microenvironment dysregulation and immune infiltration have been implicated in the occurrence and development of OA. Therefore, the METTL3 inhibitor STC-15, which targets T cell activation and anti-tumor immune response, is expected to play a role in improving the immune microenvironment of OA. In addition, the FTO inhibitor FB23 has shown strong potential in clinical trials of acute myeloid leukemia (AML) by directly binding to FTO and selectively inhibiting its m6A demethylation activity.[156] Studies have confirmed that FB23 regulates inflammatory response in acute lung injury and asthma by inhibiting FTO.[157,158] Therefore, exploring the regulatory role of FB23 in OA inflammatory response provides a new idea for the development of OA therapeutic drugs.

Summary and Outlook

m6A modification is closely related to the inflammatory response, ECM degradation, programmed cell death, bone homeostasis, and osteogenic differentiation in OA pathogenesis. However, early reviews focused more on the mechanisms and functions of m6A modification in bone development. Especially, there is insufficient research on the regulatory mechanism of m6A in OA inflammatory response and programmed cell death. Here, we comprehensively discuss the potential mechanisms by which m6A modified proteins are widely involved in regulating OA. And further discussed the latest research results on the application of m6A modification in the clinical treatment of OA.

Given the different regulatory effects of m6A modification enzymes and proteins, as well as their differential expression levels in vivo, it may bring breakthroughs for the early diagnosis and treatment of OA. However, there are still some issues that urgently need to be addressed. Firstly, most current research is based on bioinformatics and sequencing to conduct large-scale transcriptome level data analysis on the mechanism of m6A modification regulating OA, which makes it difficult to capture dynamic modification changes at the single-cell or single-molecule level. In the future, based on the integration of multiple sequencing technologies, further development of single-molecule m6A detection technology should be carried out to deeply study the dynamic changes of RNA modification and accelerate the establishment of bedside diagnostic tools that can be widely applied in clinical diagnosis and treatment. In addition, research in bioinformatics still needs to be validated through in vivo and in vitro experiments, and further validated through clinical patient testing of the function of biomarkers. Specifically, m6A modification may produce different biological effects in different tissues and organs. Therefore, when developing treatment plans, full consideration should be given to their specificity to avoid adverse effects on other organs. Finally, although there have been studies on m6A modified drugs (such as BM-MSCs), they are still in the stage of theoretical and mechanistic exploration, and clinical trials should be conducted as soon as possible to accelerate the drug development process.

In summary, accelerating the application of m6A regulatory factors in the clinical diagnosis of OA and advancing the clinical application of effective and specific drugs targeting m6A enzymes are the focus of future research.

Data Sharing Statement

There are no data and no material associated with this manuscript.

Ethics Approval and Consent to Participate

There is no human subject, and this is a review, so there is no need for ethical approval and consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interest in this work.

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