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REVIEW ARTICLE

The essential roles of m^{6}A modification in osteogenesis and common bone diseases

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Abstract N6-methyladenosine (m^{6}A) is the most prevalent modification in the eukaryotic transcriptome and has a wide range of functions in coding and noncoding RNAs. It affects the fate of the modified RNA, including its stability, splicing, and translation, and plays an important role in post-transcriptional regulation. Bones play a key role in supporting and protecting muscles and other organs, facilitating the movement of the organism, ensuring blood production, *etc*. Bone diseases such as osteoarthritis, osteoporosis, and bone tumors are serious public health problems. The processes of bone development and osteogenic differentiation require the precise regulation of gene expression through epigenetic mechanisms including histone, DNA, and RNA modifications. As a reversible dynamic epigenetic mark, m^{6}A modifications affect nearly every important biological process, cellular component, and molecular function, including skeletal development and homeostasis. In recent years, studies have shown that m^{6}A modification is involved in osteogenesis and bone-related diseases. In this review, we summarized the proteins involved in RNA m^{6}A modification and the latest progress in elucidating the regulatory role of m^{6}A modification in bone formation and stem cell directional differentiation. We also discussed the pathological roles and potential molecular mechanisms of m^{6}A modification in bone-related diseases like osteoporosis and osteosarcoma and suggested potential areas for new strategies that could be used to prevent or treat bone defects and bone diseases.

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Introduction

Bone is mineralized connective tissue composed of extracellular matrix and cell populations including osteoblasts, osteoclasts, osteocytes, and bone lining cells. The skeletal system accounts for about 40% of the body weight and has numerous important functions in physical support, movement, and tissue protection, as well as in blood production and immune function. Bone undergoes continuous renewal and remodeling. Bone homeostasis refers to the dynamic balance between the continuous renewal and remodeling associated with bone formation and bone resorption, being regulated by the osteoclasts and osteoblasts.[1,2] In general, bone has extraordinary healing potential. However, the bone regeneration capacity declines with age and certain pathological changes, resulting in decreased bone density or osteoporosis. With the aging of populations worldwide, bone-related diseases such as osteoporosis, osteoarthritis, and bone defects have become a major public health concern. The key to the healing of fractures and bone defects lies in the bone's ability to regenerate. The osteogenic differentiation of stem cells is a complicated process that requires the cooperation of cell proliferation and differentiation, and the formation and deposition of a mineralized extracellular matrix.[1] Osteogenesis is regulated by numerous transcription factors, cytokines, signaling pathways, and epigenetics.[2] Although stem cell therapy has been widely used in the field of bone regeneration, the precise regulation of osteogenic differentiation of stem cells remains a big challenge, and a better understanding of the process would yield better treatments.

Epigenetic modifications involve heritable changes in gene expression without DNA sequence alterations and are often associated with human disease. N6-methyladenosine (m^6A) is an abundant RNA modification that plays a crucial role in regulating RNA metabolism and covers almost the entire transcriptome. Notably, m^6A methylation is common in eukaryotes and affects macromolecular processes like RNA maturation, splicing, transport, degradation, and translation. Although m^6A was first reported in 1974,[3–6] the introduction of methylated RNA immunoprecipitation sequencing (MeRIP-Seq) in 2012 sparked renewed interest in m^6A research.[7,8] Through in-depth studies of m^6A modification in the transcriptome, it was discovered that m^6A modification sites have a typical DRACH consensus motif, which is mainly enriched in the coding sequence (CDS) and 3′ untranslated region (3′ UTR).[7,8]

The m^6A modification is under the dynamic regulation of the m^6A writing protein complex (methyltransferase complex, MTC), including methyltransferase like 3 (METTL3), METTL14, Wilms tumor-associated protein (WTAP), RNA binding motif protein 15 (RBM15), and zinc finger CCCH domain-containing protein 13 (ZC3H13).[9–13] Other methyltransferases that add m^6A modifications on different RNAs include the METTL5-TRMT112 complex and METTL16.[9,14] Demethylation is primarily accomplished by m^6A erasers including fat mass and obesity-associated protein (FTO) and AlkB homologue 5 (ALKBH5).[15,16] Dynamic levels of m^6A modification are regulated by both writers and erasers. RNA-binding proteins which can recognize m^6A and determine RNA fates are classified as m^6A readers and include the YT521-B homology domain family (YTHDF)[17] and the IGF2 mRNA-binding protein (IGF2BP).[18] The different fates of targeted RNAs are determined by m^6A readers. Currently, m^6A modification has been discovered to regulate RNA decay, stabilization, splicing, transport, and translation. It also regulates self-renewal, differentiation, immune response, and DNA damage response of stem cells. Accumulating evidence, including studies in our laboratory, indicates that m^6A modification regulates a large variety of biological processes, from tumorigenesis to osteogenic differentiation.[19,20] This article reviews m^6A and the current understanding of its roles in bone development and bone-related diseases.

The regulation of m^6A modification

Methyltransferases/writers write the m^6A modification

As noted above, the writing of m^6A is conducted by the MTC.[21] m^6A methyltransferase is composed of writers including METTL3, METTL5, METTL14, METTL16, WTAP, RBM15/15B, CBL proto-oncology Gene-like 1 (CBLL1), ZC3H13, and virus-like m^6A methyltransferase-associated (VIRMA). METTL3 is a principal element of MTCs and is highly conserved among different eukaryotes. METTL14 serves a structural role for the core MTC which stabilizes and facilitates the catalytic activity of METTL3.[22] WTAP functions as a subunit of m^6A MTC that recruits the complex into the nuclear speckles.[10] RBM15 and RBM15B can recruit the MTC to its target transcripts via binding to specific RNA sites for m^6A modification.[11,23] VIRMA preferentially localizes near the 3′ UTR and stop codon for RNA methylation modifications.[13] It has been reported that 80% of protein sequences containing ZC3H13 are low-complexity (LC) domains. The MTC is retained in the nuclear speckles due to interactions between its LC domain and ZC3H13 and WTAP, thereby enhancing its catalytic function.[11,24] METTL16 was first reported in 2017[25] as an independent methyltransferase, which could adjust mRNA stability and splicing. Its binding site is inconsistent with that of the METTL3/METTL14 MTC, and it catalyzes m^6A modifications of small nuclear RNAs, U6 snRNAs, and other noncoding RNAs.[25]

In addition to these proteins, there may be more undiscovered m^6A writers for mRNAs or non-coding RNAs involved in common or specific bioprocesses.

Demethylases/erasers removed the m^6A modification

The m^6A modification is dynamic and can be reversed by m^6A demethylases, also known as m^6A erasers, including FTO and ALKBH5.[26,27] FTO is a nuclear protein of the AlkB family and was the first reported m^6A demethylase.[26] ALKBH5 was discovered as the second m^6A eraser. FTO and ALKBH5 are both members of a family of iron (II)/α-ketoglutarate (α-KG)-dependent dioxygenases that recognize adenine and cytosine methylation in single-stranded DNA and RNA. A new m^6A demethylase ALKBH3 has

recently been reported to exhibit substrate specificity only for tRNAs.[28,29]

m^{6}A modification is recognized via m^{6}A readers

Although methylation and demethylation are accomplished by writers and erasers respectively, it is the readers that determine the functional outcome of m^{6}A modification. Readers are composed of YTHDF1/2/3,[30] YTH domain-containing protein 1/2 (YTHDC1/2),[31] the heterogeneous nuclear ribonucleoprotein (HNRNP) family,[30] eukaryotic translation initiation factor 3 (eIF3),[32] and insulin-like growth factor-2 mRNA-binding protein 1/2/3 (IGF2BP1/2/3).[18] YTHDF2 was the first identified. It recruits the CCR4—NOT complex via the binding of its N-terminal region binding to the SH domain of CNOT1 to accelerate the deadenylation and decay of m^{6}A-containing RNAs.[33] In the cytoplasm, YTHDF1 interacts with initiation factors to promote the initial phase of RNA translation.[34] YTHDF3 promotes translation by cooperating with YTHDF1 to promote protein synthesis and affects YTHDF2-mediated mRNA decay.[35] YTHDC1 could promote exon inclusion, similar to SRSF3 and the opposite of SRSF10.[36] YTHDC2, the fifth member of this family, is an RNA helicase whose helicase domain also contributes to RNA binding.[37] HNRNPA2/B1 binds to m^{6}A on primary-miRNA transcripts and interacts with DGCR8 to promote primary miRNA processing.[38] IGF2BP recognizes m^{6}A modification under both normal and stress conditions, enhancing the stability and translation of RNAs.[18] eIF3 is an m^{6}a reader that can initiate protein translation in a cap-independent manner when a 5′ UTR m^{6}a is present.[39]

Although it is clear that m^{6}A readers determine the function of m^{6}A on RNAs at multiple levels, further studies on the precise relationships among m^{6}A readers are needed.

m^{6}A modification regulates bone development

Bone development is regulated by various signaling pathways and epigenetics.[40,41] Bone marrow mesenchymal stem cells (BMSCs) are cells with multi-directional differentiation potential that play a crucial part in human bone health by balancing osteogenesis and adipogenesis.[42,43] Recently, m^{6}A was reported to be involved in the pluripotent differentiation and development of specific cell lineages,[44—47] including the osteogenesis of BMSCs.[48—50] For example, the expression of METTL3 was found to be negatively correlated with the adipogenesis of porcine BMSCs (pBMSCs).[51] METTL3 knockout in BMSCs has been reported to increase bone loss, resulting in impaired bone formation and the generation of pathological features of osteoporosis in mice.[49] Furthermore, down-regulation of METTL3 was found to lead to decreased ALP activity and fewer mineralized nodules during the osteoblast differentiation of BMSCs, suggesting that METTL3-mediated m^{6}A modification regulates the osteogenesis of BMSCs.[50] Additionally, METTL3 regulates osteoarthritis development by affecting the NF-kB pathway and extracellular matrix synthesis in chondrocytes.[52] Down-regulation of METTL3 can also promote osteogenesis through suppression of miR-7212—5p maturation.[53] It has also been reported that abnormal expression of METTL3 could be an important mechanism underlying osteoporosis.[54]

ALKBH5 is amplified in osteosarcoma and is highly expressed in osteosarcoma patients.[55] Recent studies have shown that ALKBH5 affects bone formation by targeting BMP2[56] and adipogenesis by targeting TRAF4.[57] FTO inhibits the osteogenic differentiation of MSCs through m^{6}A demethylation.[58] FTO expression was increased during the adipogenic differentiation of BMSCs and decreased during their osteogenic differentiation.[48] FTO was also reported to enhance the stability of mRNAs which protect osteoblasts from genotoxic damage. Notably, FTO down-regulation induced age-related bone loss.[59] An m^{6}A reader, YTHDF1, was reported to promote the osteogenesis of BMSCs via the translational regulation of ZNF893 (Fig. 1).[60]

Through writers, erasers, and readers, m^{6}A modifications are widely involved in bone formation and development. It is clear that m^{6}A regulates bone development via both mRNAs and non-coding RNAs, with an integral role in these biological processes. However, the roles of METTL3, one of the most important writers in m^{6}A, in bone metabolism are complicated. It is currently unclear whether it positively or negatively affects bone development or whether there is a balance between its effects that is further regulated by other factors. Further studies are needed to clarify the roles of METTL3 and other mediators in normal bone development and various pathological conditions affecting the bone.

m^{6}A affects the balance between the osteogenic and adipogenic differentiation of MSCs

It is often stated that "bone loss is fat gain", suggesting that the opposite of osteogenic differentiation is adipogenic differentiation.[61] Obesity may inhibit osteogenesis, and studies have found an association between obesity and osteoporosis.[62—64] BMSCs have the potential for both osteogenic and adipogenic differentiation,[65] and both share common regulatory pathways.[66] Normally, osteogenesis and adipogenesis are in balance. Recent studies have shown that m^{6}A methylation can regulate the balance between the osteogenesis and adipogenesis of MSCs. In 2018, it was reported that METTL3-mediated m^{6}A modification could regulate the osteogenic differentiation fate of BMSCs by adjusting the translation efficiency of the MSC lineage distributor PTH1R.[49] Other studies have reported that METTL3-mediated m^{6}A methylation is involved in the subtle regulation of the adipogenic and osteogenic differentiation of pBMSCs.[49,51,67] It was also found that METTL3 could facilitate the osteogenesis of BMSCs through the LINC00657/miR-144-3p/BMPR1B axis.[68] Another study reported that METLL3 could promote the osteogenesis of BMSCs by interacting with piRNA-36741.[69] However, METTL3 was also reported to inhibit osteogenesis through NF-κB signaling.[70]

As noted above, FTO is more inclined to induce MSCs to undergo adipogenic differentiation. It is up-regulated during adipogenesis and down-regulated during osteogenesis.[48] FTO regulates preadipocyte differentiation by adjusting the m^{6}A levels, and therefore the SRSF2 binding to the splice site to

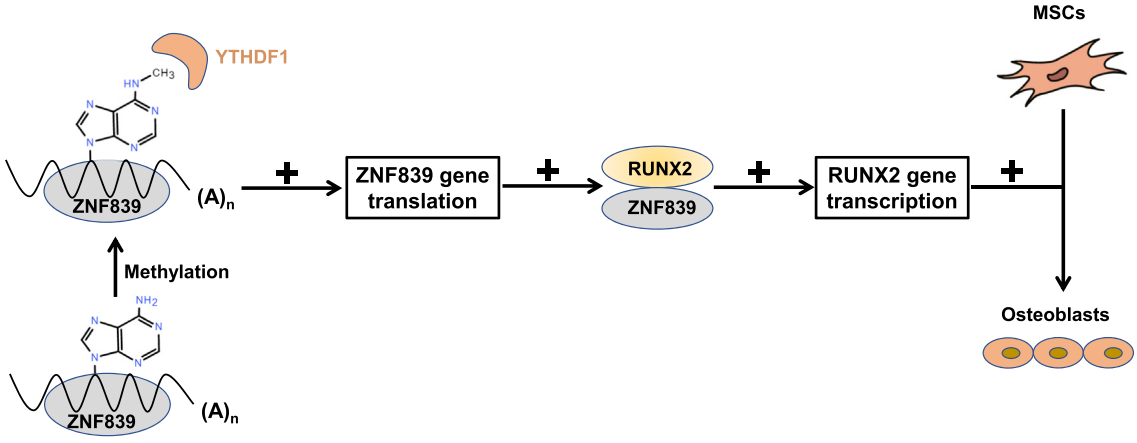

Figure 1 m^{6}A reader YTHDF1 regulates ZNF839 gene translation in an m^{6}A-dependent manner and therefore enhances RUNX2 gene transcription, finally potentiating osteogenesis of BMSCs.[60]

control the alternative splicing of RUNX1T1.[71] However, in another study, FTO was found to be up-regulated during the osteogenesis of MSCs and could promote the osteogenesis of MSCs through PPARG.[72] In addition, ALKBH1 might regulate the fate and bone-fat balance of BMSCs, because the knockdown of ALKBH1 shifted the differentiation of BMSCs toward adipogenesis.[73]

Studies have revealed that m^{6}A could not only adjust the differentiation capacity of MSCs but can also determine their fate. The m^{6}A modification usually promotes the differentiation of MSCs in one direction while inhibiting their differentiation in the other. It is likely that more lineage regulators involved in stem cell differentiation, potentially including regulators of m^{6}A will be discovered in the future.

m^{6}A modification impacts a variety of common bone diseases

Emerging studies have indicated that m^{6}A modifications play a crucial role in various bone-related diseases. The roles of m^{6}A regulators in bone development and bone-related diseases are shown in Figure 2 and Table 1, and potential regulatory relationships are presented in Figure 3.

m^{6}A modification is closely associated with the occurrence and clinical severity of osteoporosis

Osteoporosis stems from the imbalance of osteoblast-mediated bone formation and osteoclast-mediated bone resorption, manifested as decreased bone density, deterioration of the bone microstructure, and excessive accumulation of bone adipose tissue, resulting in the bones becoming weak and prone to fractures.[74] In patients with osteoporosis, the BMSCs are inclined to differentiate into adipocytes, generating increased bone marrow fat and bone loss.[75] METTL3-mediated m^{6}A modification can regulate the fate of BMSCs and osteoporosis.[49] Up-regulation of METTL3 could also prevent osteoporosis by affecting the translation of PTH1R in an m^{6}A-dependent manner and by regulating the osteogenic differentiation of MSCs via the PTH/PTH1R pathway.[49] Down-regulation of METTL3 expression is closely associated with the m^{6}A modification of RUNX2 and miR-320 precursors, inhibiting bone formation in osteoporosis or ovariectomized mouse models.[54] The METTL3 and m^{6}A levels were also found to be significantly reduced in osteoporosis and oophorectomy patients. Moreover, in patients with fragility fractures, the hMSCs showed signs of accelerated methylation aging due to insufficient osteoblast activity.[76] Meanwhile, FTO also affects the osteoporotic phenotype. FTO has been reported as a regulator for the fate determination of BMSCs in osteoporosis and is elevated in the regulating axis GDF11-FTO-PPAR. The expression of FTO is increased in aging and osteoporosis.[48] Systemic FTO knockout mice exhibit retarded growth, short body length, low body weight, and low bone density immediately after birth.[77] Further studies showed that FTO could promote osteoporosis by regulating NF-κB and the MYC/PI3K/AKT pathway.[58,78] Thus, FTO plays an important part in the pathogenesis of osteoporosis and could be a novel candidate for the prevention or treatment of osteoporosis.

However, more studies are needed to clarify which m^{6}A readers are involved in the m^{6}A-dependent regulation of osteoporosis and what the concrete outcomes of m^{6}A modification are in terms of bone differentiation, development, and preservation.

m^{6}A modification plays important roles in the development of osteosarcoma

Osteosarcoma, a common aggressive malignancy that inhibits bone growth, often occurs in children and adolescents.[79,80] Recent studies have reported that m^{6}A modification affects the pathogenesis and progression of several cancers, including osteosarcoma. Abnormal expression of m^{6}A-related molecules was related to the prognosis and development of metastasis in patients with osteosarcoma.[81] Both the m^{6}A and METTL3 levels were elevated in human osteosarcoma tissue and cell lines compared with normal osteoblasts.[81] Further studies showed that METTL3 facilitated the occurrence of osteosarcoma by adjusting the m^{6}A level of LEF1 and activating the Wnt/β-catenin axis.[82] METTL3 could also regulate the expression of TRAF6, DRG1, and ATAD2 through m^{6}A

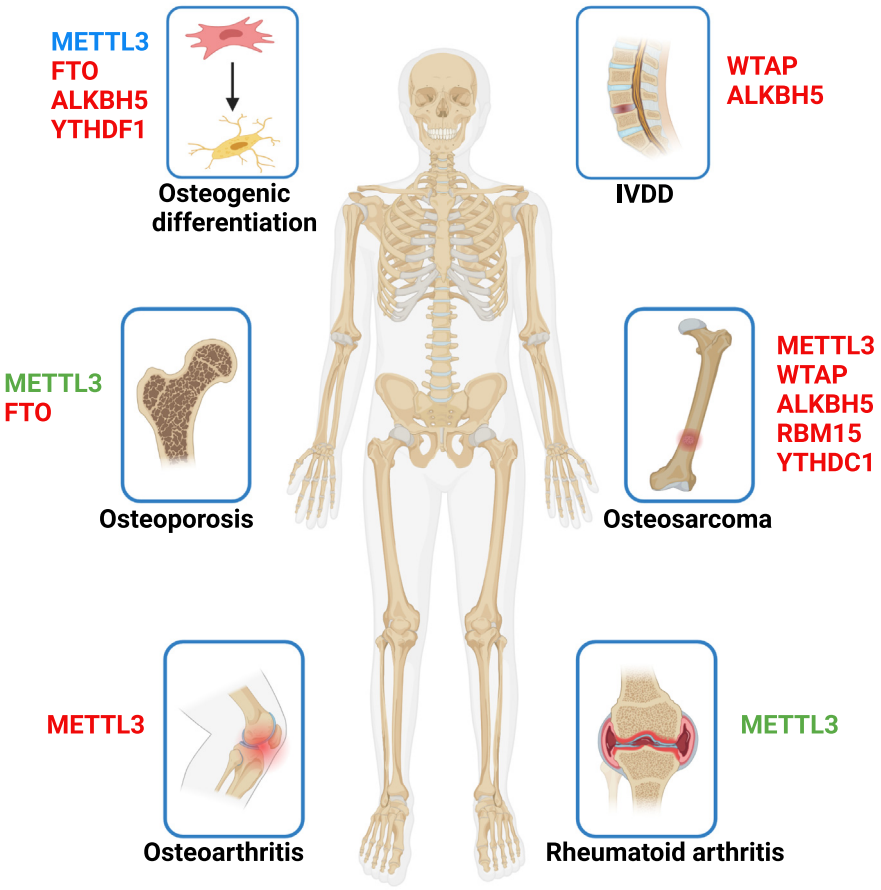

Figure 2 m^{6}A regulators in bone development and bone diseases. Red represents promotor, green represents inhibitor, and blue indicates a controversial role. The figure was created with BioRender.com.

modification, all of which might also promote the occurrence and development of osteosarcoma.[83–85] Other molecules involved in m^{6}A have also been shown to play a role in the development of osteosarcoma. For example, RBM15 was found to promote the metastasis of osteosarcoma and decrease the survival rate of osteosarcoma patients.[86] WTAP is highly expressed in osteosarcoma tissue and promotes osteosarcoma tumorigenesis by regulating HMBOX1 mRNA stability.[87] ALKBH5 was reported to be overexpressed in osteosarcoma and ALKBH5-mediated PVT1 up-regulation through m^{6}A modification promoted osteosarcoma tumorigenesis.[88] miR-451a-mediated YTHDC1 could activate the AKT/mTOR pathway via 3-phosphoinositide-dependent protein kinase 1 (PDPK1) in an m^{6}A-dependent manner to stimulate the progression of osteosarcoma.[89]

Nevertheless, few studies have focused on the impact of m^{6}A-dependent non-coding RNAs on osteosarcoma, which are important in the occurrence and development of osteosarcoma. Additionally, the role of m^{6}A in the tumor microenvironment is an interesting topic that remains to be researched.

m^{6}A modification is involved in intervertebral disc degeneration

Intervertebral disc (IVD) degeneration is a physiological and pathological process in which the intervertebral disc gradually loses its elasticity and shock absorption functions with age, resulting in irreversible degeneration. The degeneration of the IVD includes degeneration of the annulus fibrosus, nucleus pulposus, and cartilage endplate and manifests as limited lumbar activity, low back pain, neck pain, and decreased muscle strength.[90,91] Several studies have reported that m^{6}A regulation plays a crucial part in the occurrence and progression of IVD degeneration. It was reported that WTAP expression was increased in senescent

Table 1 The roles of m^{6}A regulators in bone development and bone-related diseases.

m^{6}A regulator	Bone-related process/diseases	Role	Target	Reference
Writer				
METTL3	Osteogenesis	Promotor	LINC00657	68
		Promotor	BMP2	69
		Inhibitor	MYD-88/NF-κB	70
	Osteoporosis	Inhibitor	PTH/Pth1r	49
		Inhibitor	RUNX2	54
	Osteosarcoma	Promotor	LEF1	82
		Promotor	TRAF6/DRG1/ATAD2	83–85
	Osteoarthritis	Promotor	NF-κB	52
	Rheumatoid arthritis	Inhibitor	NF-κB	97
	Bone resorption	Promotor	circ_0008542	105
METTL14	SONFH	Inhibitor	PTPN6	103
WTAP	Osteosarcoma	Promotor	HMBOX1	87
	IVDD	Promotor	lncRNA NORAD	92
Eraser				
FTO	Adipogenesis	Promotor	RUNX1T1	71
	Osteogenesis	Promotor	PPARG	72
	Osteoporosis	Promotor	PPARG	48
		Promotor	MYC/PI3K/AKT	58
		Promotor	NF-κB	78
ALKBH5	Osteogenesis	Promotor	BMP2	56
	Adipogenesis	Inhibitor	TRAF4	57
	Osteosarcoma	Promotor	PVT1	88
	IVDD	Promotor	DNMT3B	93
	Bone resorption	Inhibitor	circ_0008542	105
Reader				
YTHDF1	Osteogenesis	Promotor	ZNF893	60
YTHDC1	Osteosarcoma	Promotor	PDPK1	89

nucleus pulposus cells (NPCs) and promoted the m^{6}A methylation of lncRNA NORAD, increasing the cellular senescence via the NORAD/PUMILIO/E2F3 axis.[92] Another study reported that ALKBH5 expression is up-regulated in IVD degeneration and causes NPC senescence by demethylating DNMT3B transcripts.[93] However, more evidence is needed to determine the relationship between m^{6}A modification and IVD.

m^{6}A modification is involved in the pathogenesis of arthritis

Arthritis is a common chronic inflammatory disease occurring in the joints and surrounding tissues. It can be classified into dozens of separate diseases that are related to various factors such as degeneration and autoimmunity. Osteoarthritis (OA) and rheumatoid arthritis (RA) are the two main types of arthritis, both of which are characterized by clinical features like joint tenderness and swelling but have different underlying pathological mechanisms.[94–96] METTL3 is up-regulated in OA and could regulate OA progression via the NF-κB pathway and extracellular matrix synthesis of chondrocytes.[52] In patients with RA, the METTL3 expression was found to be elevated and positively correlated with the levels of CRP and ESR. Interestingly, overexpression of METTL3 could decrease the LPS-induced inflammation in macrophages via NF-κB.[97] Another study reported that YTHDF2 knockdown could increase the expression of proinflammatory cytokines and facilitate the inflammatory response in LPS-stimulated macrophages via the MAPK and NF-κB signaling pathways.[98]

As described above, m^{6}A appears to regulate OA and RA mainly through cytokines. Since the pathological mechanisms underlying both OA and RA are complex, more detailed studies on m^{6}A-mediated regulation of cytokines and immune responses are required.

m^{6}A modification plays an important part in periodontitis

Periodontitis is a chronic inflammatory disease of the periodontal tissue induced by multiple pathogenic species present in dental plaque. The clinical features include swollen gums, purulent discharge in the gingival pocket, absorption of alveolar bone, and loose teeth.[99] About 10.8% of people worldwide are suffering from periodontitis.[100] m^{6}A modification was proven to play an important part in the immune microenvironment of patients with periodontitis. Notably, m^{6}A regulators were found to be involved in periodontal processes, and their expression levels correlated with the immune characteristics of periodontitis.[101] Another study reported that various m^{6}A-SNPs could play an important part in the pathogenesis of periodontitis.[102] However, the specific regulatory effects of m^{6}A on periodontitis are still unknown and the roles of

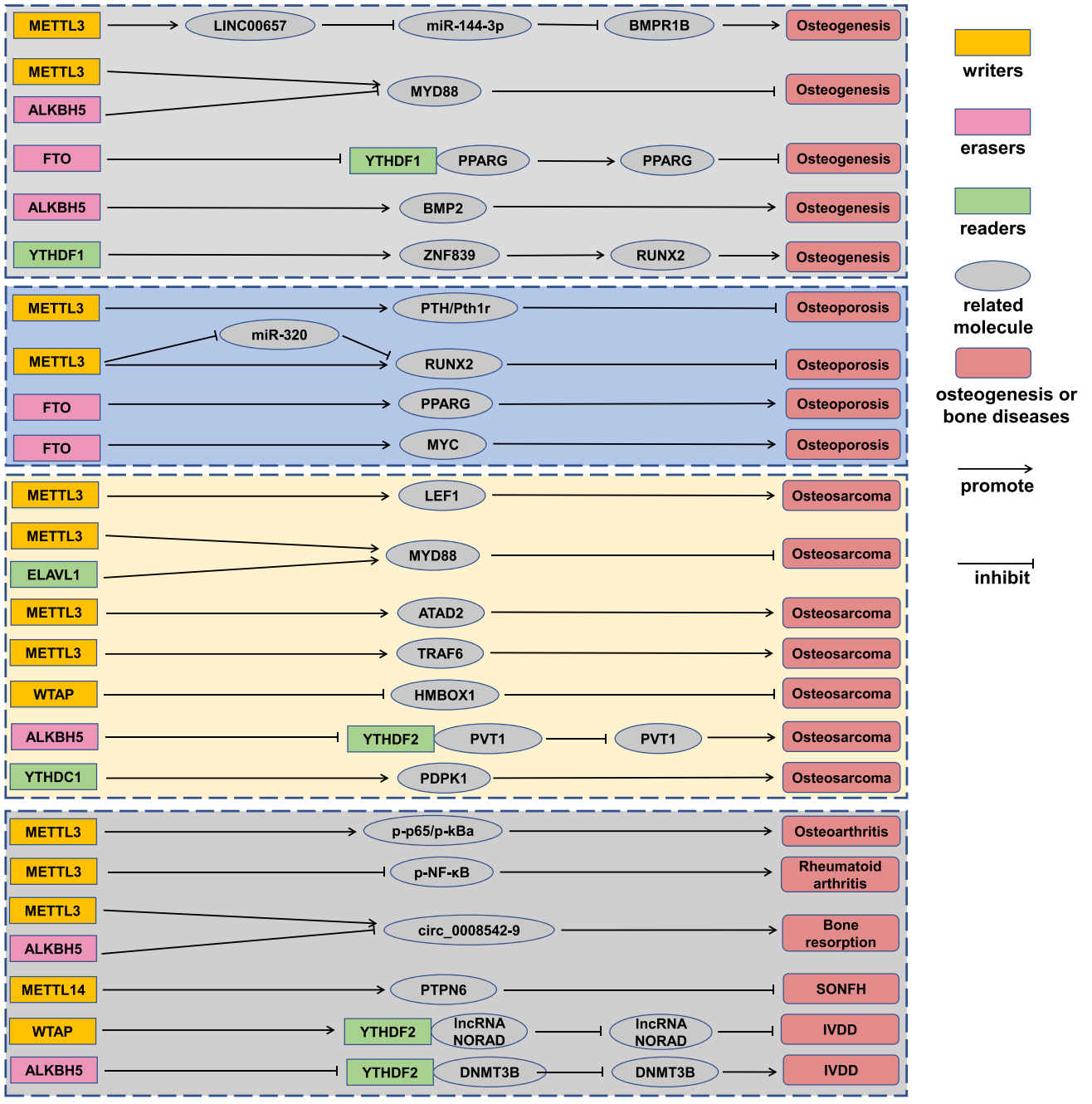

Figure 3 m^{6}A-mediated regulation in bone development and bone diseases.

m^{6}A writers, erasers, and readers in the pathogenesis of periodontitis are yet to be identified.

The functions of m^{6}A modification in other bone-related diseases

m^{6}A has also been reported to be associated with steroid-associated osteonecrosis of the femoral head (SONFH), ankylosing spondylitis, and osteoclast bone resorption after dental implant placement.[103–105] The expression levels of both m^{6}A and METTL14 were down-regulated in SONFH and METTL14 could mediate the development of SONFH by regulating PTPN6.[103] TNF-α-mediated overexpression of ELMO1 promoted MSC migration in ankylosing spondylitis patients, which was mediated by METTL14-dependent m^{6}A modification.[104] In the osseointegration microenvironment after dental implant placement, METTL3 could mediate the initiation of osteoclast bone resorption through m^{6}A modification of circ_0008542 and this process could be corrected by the overexpression of ALKBH5.[105] Though m^{6}A modification has been proven to be engaged in many bone diseases, the roles of m^{6}A in other bone diseases like hyperostosis and bone cyst are unclear and further study is needed.

Conclusions and prospects

The m^{6}A modification is common in eukaryotes, regulating homeostasis and normal cellular activities. In recent years, research on the involvement of m^{6}A methylation in the osteogenesis of stem cells has been increasing. More and more studies have demonstrated that m^{6}A methylation exists on many RNAs associated with bone development and affects the post-transcriptional regulation of RNAs. The homeostasis of m^{6}A methylation is critical for osteogenic differentiation and bone growth, and disturbance of this process can lead to various bone diseases. However, the gene-specific effects of m^{6}A modifications and the effects of different methylation abundance within the same gene remain to be explored. The roles of other components of m^{6}A, including writers (METTL5, METTL16, KIAA1429, RBM15/15B, VIRMA, ZC3H13, and ZCCHC4) and readers (IGF2BP1, HNRNPA2B1, YTHDC1, and eIF3) in osteogenesis and bone-related diseases also need to be explored in further study. The controversial role of METTL3 in bone development also needs to be examined. There are likely other writers, erasers, and readers in m^{6}A methylation that still need to be identified, some of which may shed new light on the mechanisms by which m^{6}A methylation affects osteogenesis. Based on the crucial functions of m^{6}A modification in regulating stem cell fates, cell differentiation, bone formation, and osteosarcoma, m^{6}A modification has the potential for broad application in regenerative medicine, bone tissue engineering, and the treatment of bone-related tumors. It is foreseeable that in the next few years, research focusing on this field will continue to increase, and m^{6}A modification is well on the way to b a valid target for regulating osteogenesis and treating bone diseases.

Author contributions

YG, YS, YP, and JL conceived the idea. YG wrote the manuscript and prepared the figures and tables. YS and JL edited the manuscript.

Conflict of interests

The authors declare that they have no competing interests.

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