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REVIEW ARTICLE

The role of m^{6}A RNA methylation in autoimmune diseases: Novel therapeutic opportunities

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Abstract N6-methyladenosine (m^{6}A) modifications, as one of the most common forms of internal RNA chemical modifications in eukaryotic cells, have gained increasing attention in recent years. The m^{6}A RNA modifications exert various crucial roles in various biological processes, such as embryonic development, neurogenesis, circadian rhythms, and tumorigenesis. Recent advances have highlighted that m^{6}A RNA modification plays an important role in immune response, especially in the initiation and progression of autoimmune diseases. In this review, we summarized the regulatory mechanisms of m^{6}A methylation and its biological functions in the immune system and mainly focused on recent progress in research on the potential role of m^{6}A RNA methylation in the pathogenesis of autoimmune diseases, thus providing possible biomarkers and potential targets for the prevention and treatment of autoimmune diseases.

Abbreviations: m^{6}A, N6-methyladenosine; ADs, autoimmune diseases; MTC, methyltransferase complex; METTL3, Methyltransferase-like 3; WTAP, Wilms tumor 1 associated protein; ZCCHC4, zinc finger CCHC-type containing 4; VIRMA, vir-like m^{6}A methyltransferase associated; RBM, RNA binding motif protein; FTO, fat mass and obesity-related protein; ALKBH, ALKB homolog; f^{6}A, N6-formyladenosine; FMN, Flavin mononucleotide; hnRNP, heterogeneous nuclear ribonucleoprotein; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins; eIF3, eukaryotic initiation factor 3; Prrc2a, Proline rich coiled-coil 2 A; FMRP, Fragile X mental retardation protein; SLE, Systemic Lupus Erythematosus; IBD, Inflammatory Bowel Disease; MS, Multiple Sclerosis; RA, Rheumatoid Arthritis; Ps, Psoriasis; T1DM, Type 1 Diabetes Mellitus; AITD, Autoimmune thyroid disease; MG, Myasthenia gravis.

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Introduction

Epitranscriptomics, also known as "RNA epigenetics" is a chemical modification used to regulate RNA, which has become increasingly important in the landscape of gene regulation in recent years.[1] According to the MODOMICS database, 180 kinds of RNA modifications have been identified in coding and non-coding RNAs since the discovery of post-transcriptional modifications of RNA approximately 60 years ago.[2] N6-methyladenosine (m^{6}A) is the methylation at the 6th position nitrogen atom of adenine (A).[3] As one of the most prevalent types of eukaryotic RNA methylation modifications,[4,5] m^{6}A was first identified in the poly(A) tract in eukaryotic mRNA in 1974.[6,7] With in-depth research, m^{6}A has been found to modify not only coding RNAs but also non-coding RNAs, including tRNAs, rRNAs, small nuclear RNA (snRNA), microRNA (miRNA) precursors, and long non-coding RNAs (lncRNAs).[8–10]

The m^{6}A sites are enriched near the termination codon, the 3′ untranslated region (3′UTR), and the long internal exon in mammals. An average of 1 000 nucleotides contains 1–2 m^{6}A residues, mainly occurring in RRACH sequences (where R = A or G, H = A, C, or U).[11] Accumulating data focusing on m^{6}A RNA methylation has shown an essential role for m^{6}A in a variety of diseases, such as cancer,[12] neurodevelopment and aging,[13] and cardiovascular diseases.[14] Recent advances have highlighted that m^{6}A modification acts a vital role in the pathogenesis of autoimmune diseases (ADs) by regulating the immune system. This review discusses the regulatory mechanisms of m^{6}A methylation modification and its role in immune responses. We will mainly focus on recent advances in the potential role of m^{6}A RNA methylation in the pathogenesis of ADs. This review will highlight the potential of m^{6}A machinery as a novel target and provide a reliable theoretical basis for the prevention and treatment of ADs.

Regulators of m^{6}A

m^{6}A modification relies on 3 types of enzymes, which are considered "writers" (methyltransferases), "erasers" (demethylases), and "readers" (m^{6}A-binding proteins). The writers and erasers are responsible for the dynamic and reversible regulation of m^{6}A methylation. The "reader" decodes m^{6}A methylation and mediates the recruitment of downstream functional complexes.[15] These enzymes play vital biological roles in m^{6}A modifications (Table 1 and Fig. 1).

m^{6}A methyltransferases/writers

m^{6}A methylation is catalyzed by the bulk methyltransferase complex (MTC). Methyltransferase-like 3 (METTL3) is the first component of RNA MTC discovered in 1997.[16] Knockdown of METTL3 has been reported to impair gene silencing mediated by long non-coding RNA X-inactive specific transcript (XIST).[17] METTL14, another active component of the m^{6}A MTC, facilitates the binding of the adjacent RNA polymerase II to m^{6}A MTC.[18] As a catalytic subunit, METTL3 cooperates with METTL14 to form the MTTTL3-METTL14 complex, which mediates the deposition of m^{6}A on nuclear RNA in mammalian cells.[19–23] Wilms tumor 1 associated protein (WTAP), another member of the m^{6}A MTC family, acts as a regulatory subunit to stabilize the METTL3-METTL14 complex and promotes m^{6}A by recruiting the complex to the nuclear speck.[24] WTAP-dependent methylation is negatively correlated to mRNA stability.[25] METTL16 directly methylates the "UAC(m^{6}A)GAGAA" motif and regulates S-adenosylmethionine (SAM) homeostasis in an m^{6}A-dependent manner.[26] In addition, METTL16 is responsible for m^{6}A methylation of human numerous lncRNA, A43 of the U6 spliceosomal snRNA, various ncRNAs, and pre-mRNAs.[26–28] As an m^{6}A methyltransferase of 18 S rRNA, METTL5 forms a heterodimeric METTL5–TRMT112 complex with methyltransferase activator TRMT112 to maintain intracellular metabolic stability.[9] In addition, other proteins such as zinc finger CCHC-type containing 4 (ZCCHC4), vir-like m^{6}A methyltransferase associated (VIRMA), ZC3H13, RNA binding motif protein (RBM)15 and their paralog RBM15B are the components of m^{6}A MTC. ZCCHC4 is responsible for 28 S rRNA m^{6}A modification and interacts with a subset of mRNAs.[9,29] VIRMA mediates selective methylation of the 3′UTR and near-stop codon regions by recruiting the catalytic core components METTL3/METTL14/WTAP.[25,30] ZC3H13 facilitates m^{6}A methylation and plays an essential role in the nuclear localization of the ZC3H13-WTAP-Virilizer-Hakai complex.[31] RBM15 and its paralogue RBM15B mediate XIST m^{6}A methylation and affect XIST-mediated gene silencing.[17,32] In addition, in the eukaryotic cells, the E3 ubiquitin ligase HAKAI is also involved in m^{6}A modification.[33]

m^{6}A demethylases/erasers

Demethylases act like erasers to remove m^{6}A modifications from RNA. In 2011, the discovery of the first m^{6}A demethylase, fat mass, and obesity-related protein (FTO) indicates that m^{6}A installation is a reversible dynamic process.[34] ALKB homolog 5 (ALKBH5) was soon identified as another RNA demethylase in 2013.[35] Both FTO and ALKBH5 belong to the α-ketoglutarate-dependent dioxygenase family and catalyze m^{6}A demethylation in a Fe(ii) and α-ketoglutarate-dependent manner. FTO oxidizes m^{6}A to form an intermediate modification named hm^{6}A, and then further oxidizes hm^{6}A to N6-formyladenosine (f^{6}A).[36,37] The f^{6}A is finally converted to adenosine (A) and the demethylation process is completed.[38] However, the substrate preference for FTO is controversial. One study showed that FTO can demethylate internal m^{6}A and capped m^{6}A in mRNA, and internal m^{6}mA in U6 RNA.[39] However, other

Table 1 Targets RNAs and functions of m^{6}A regulatory proteins.

Type	Enzymes	Target RNAs	Function	PMID
writer	**METTL3—METTL14**	nuclear RNA	Deposition of m^{6}A on nuclear RNA in mammalian cells	PMID: 27627798 PMID: 27281194 PMID: 24316715 PMID: 24394384
	METTL16	lncRNA snRNA mRNA	Regulation of the dynamic homeostasis of SAM	PMID: 28525753 PMID: 29051200
	METTL5-TRMT112	rRNA	Extrusion of the adenosine to be modified from the double-stranded nucleic acid; Responsible for 18 S rRNA m^{6}A modification	PMID: 31328227
	ZCCHC4	rRNA mRNA	Responsible for 28 S rRNA m^{6}A modification	PMID: 31328227
	WTAP	mRNA	Localization of the METTL3-METTL14 complex in nuclear patches enriched with pre-mRNA processing factors	PMID: 24316715 PMID: 24407421 PMID: 24394384
	HAKAI/CBLL1	mRNA	mRNA methylation in *Arabidopsis thaliana*	PMID: 28503769
	RBM15/15B	lncRNA mRNA	Recruiting MTC to specific sites in RNA; Silencing of a single X chromosome in female cells	PMID: 26190105 PMID: 27602518
	ZC3H13	mRNA	Nuclear localization of the ZC3H13-WTAP-Virilizer-Hakai complex; Regulation of self-renewal of mESC	PMID: 29547716
	VIRMA/KIAA1429	mRNA	Recruitment of catalytic core components METTL3/METTL14/WTAP	PMID: 29507755
Reader	**YTHDF1**	mRNA	promoting more efficient translations.	PMID: 26046440
	YTHDF2	mRNA	Reduced messenger stability; Regulated degradation; Affects the decay of methylated mRNA	PMID: 24284625 PMID: 24284625
	YTHDF3	mRNA	Promote translation	PMID: 28106076
	YTHDC1	mRNA	Mediation of the export of methylated mRNA from the nucleus to the cytoplasm; Regulation of m^{6}A-dependent mRNA splicing; Identification of m^{6}A residues on XIST	PMID: 28984244 PMID: 26876937 PMID: 27602518
	YTHDC2	mRNA	Spermatogenesis process	PMID: 28809393
	HNRNPG	mRNA	Altering the expression and variable splicing pattern of target mRNA	PMID: 28334903 PMID: 31445886
	HNRNPC	mRNA	Affects the abundance and selective splicing of target mRNAs	PMID: 25719671
	eIF3	mRNA	Recruitment of the 43 S complex to initiate translation	PMID: 26593424
	IGF2BP1/2/3	mRNA	Promotes the stabilization and storage of its target mRNAs and affects mRNA export	PMID: 29476152
	FMRP	mRNA	Nuclear export of m^{6}A-modified transcripts; Maintaining the stability of mRNA targets	PMID: 33883220 PMID: 30107516
	HNRNPA2B1	pri-miRNA	Nuclear pri-miRNA processing and selective splicing	PMID: 26321680
	Prrc2a	mRNA	Stabilization of olig 2 mRNA expression	PMID: 30514900
Eraser	**FTO/ALKBH9**	mRNA tRNA snRNA	Oxidation of m^{6}A to produce hm^{6}A for further oxidation to f^{6}A	PMID: 23653210
	ALKBH5	mRNA	Affects mRNA export from nuclear patches, RNA metabolism, and the assembly of mRNA processing factors.	PMID: 24616105
	TRMT10A	mRNA	Enhancement of m^{6}A demethylase activity of FTO	PMID: 32213595
	FMN	mRNA	Mediated photochemical demethylation of m^{6}A residues of RNA in living cells	PMID: 30756480
	ALKBH3	tRNA	Improvement of protein translation efficiency	PMID: 28205560

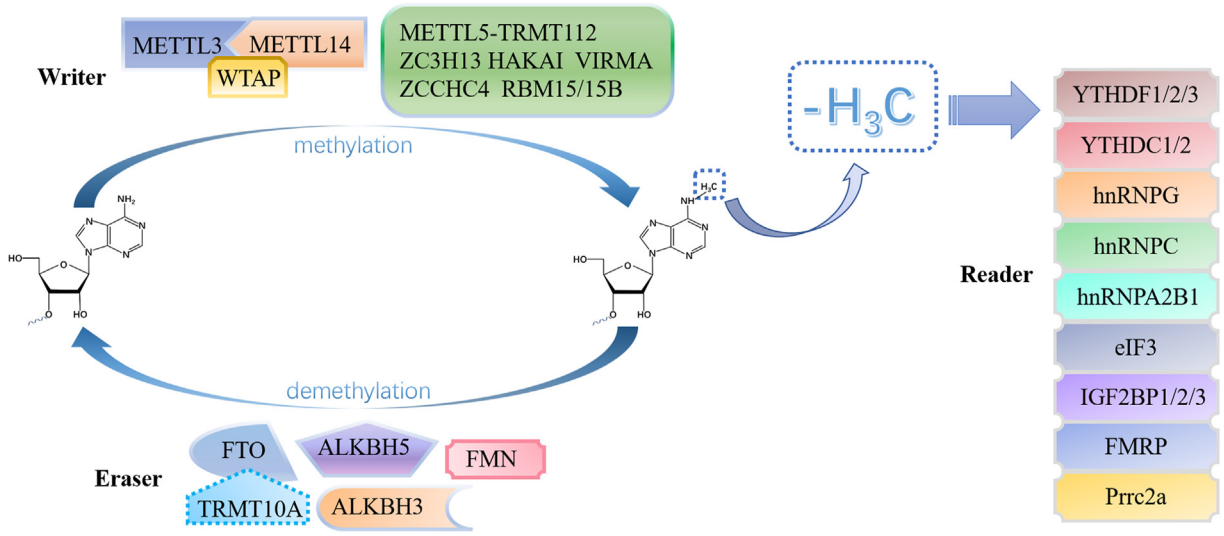

Figure 1 Dynamic regulation of m^{6}A RNA methylation by methyltransferases, demethylases, and binding proteins.

studies have reported abnormally low rates of FTO demethylation, arguing that only highly expressed FTO leads to small but measurable decreases in m^{6}A levels in specific mRNAs.[40,41] Therefore, some researchers have concluded that the process of m^{6}A is irreversible once formed.[42,43] TRMT10A facilitates substrate selectivity and works in conjunction with FTO.[44] ALKBH5 is a second RNA demethylase that alters Flip 3 conformation and efficiently demethylates m^{6}A-containing dsRNA.[35,45–47] Furthermore, another m^{6}A demethylase, ALKBH3, was recently discovered, which acts more on m^{6}A in tRNA than on mRNA or rRNA.[48] Flavin mononucleotide (FMN) was identified as a potent artificial m^{6}A demethylase.[49] With the widespread attention on m^{6}A demethylases, more m^{6}A "erasers" will be discovered in the future.

m^{6}A methylation/readers

The m^{6}A modification needs to be recognized by variable "readers" to perform different downstream functions.[50] Members of the YTH domain family, including YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2, possess a conserved m^{6}A-binding site, which directly reads and binds to m^{6}A-modified RNA at the RR (m^{6}A)CH consensus sequence.[38,51] Among them, YTHDF1/2/3 and YTHDC2 are cytoplasmic m^{6}A readers. YTHDF1 interacts with initiation factors to promote the initiation of RNA translation.[15] YTHDF2 recruits the CCR4—NOT complex through direct interaction between the SH domain of the CNOT1 subunit and the N-terminal region of YTHDF2, and this recruitment process is critical for the deadenylation of m^{6}A-containing RNAs.[52] YTHDF3 and YTHDF1 synergistically promote protein synthesis and affect the YTHDF2-mediated decay of methylated mRNAs.[53] YTHDC2 is particularly highly expressed in germ cells and plays an essential role in spermatogenesis.[54] YTHDC1 is a nuclear m^{6}A reader that affects RNA output and regulates gene expression by interacting with m^{6}A-containing transcripts and splicing factors.[55,56] In addition to members of the YTH domain family, the heterogeneous nuclear ribonucleoprotein (hnRNP) family has also been identified as m^{6}A readers. HnRNPA2B1 possesses multiple RRM domains that directly bind to the RGAC motifs and the C-terminal low-complexity region of m^{6}A-methylated RNAs, promoting primary miRNA processing and maturation.[57,58] The m^{6}A near the splice site in the nascent pre-mRNA regulates hnRNPG binding, thereby influencing RNAPII occupancy patterns and facilitating exon inclusion.[59] In addition, hnRNPC[59] and hnRNPG[58] also regulate mRNA abundance and splicing by processing m^{6}A-modified RNA transcripts. Notably, hnRNPA2B1, hnRNPC, and hnRNPG are all nuclear m^{6}A readers. Besides the family of YTH domain and hnRNP, insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) also serve as m^{6}A readers, recognizing the consensus GG (m^{6}A)C sequence, and then targeting thousands of mRNA transcripts.[60] IGF2BP1/2/3 facilitate the stability and translation efficiency of their target mRNA in an m^{6}A -dependent manner with the help of cofactors.[60,61] Additionally, several novel readers of m^{6}A have been identified. For example, eukaryotic initiation factor 3 (eIF3) binds directly to a single 5′UTR m^{6}A to initiate translation of the 43 S complex in the absence of eIF4E (a cap-binding factor).[62] Proline-rich coiled-coil 2 A (Prrc2a) stabilizes Olig 2 (a transcription factor associated with oligodendroglial specification) mRNA in an m^{6}A-dependent manner by binding to the consensus GGACU motif in the Olig2 coding sequence.[63] Fragile X mental retardation protein (FMRP), encoded by FMR1 (a sequence-context-dependent m^{6}A reader) gene, binds to the m^{6}A sites of its mRNA targets and interacts with the m^{6}A reader YTHDF2 in an RNA-independent manner.[64,65]

m^{6}A RNA modification in immune regulation

Host immune responses are classically divided into innate and adaptive immune, in which innate immune cells

respond rapidly and non-specifically when encountering pathogens (*e.g.*, viruses and bacteria), while adaptive immune responses develop slowly and specifically and lead to classical immune memory.[66] Recently, m^{6}A RNA modification has been found to play an important role in immune regulation.

m^{6}A RNA modification in the innate immune system

Innate immune cells, such as monocytes, macrophages, neutrophils, and natural killer cells, sense invading pathogens (*e.g.*, viruses and bacteria) and respond to pathogenic infections, establishing the body's first line of defense.[67] Increasing evidence shows that m^{6}A regulates the immune response process of innate immune cells such as dendritic cells, macrophages, and natural killer cells (Fig. 2).

Dendritic cells (DCs)

DCs are the most efficient antigen-presenting cells with key roles in initiating and regulating innate and adaptive immune responses.[68] One study found that YTHDF1 in DCs recognized m^{6}A-marked transcripts encoded by lysosomal proteases, and the binding of YTHDF1 to these transcripts increased the translation of lysosomal cathepsins in DCs.[69] Another study on the association between m^{6}A modification and DCs reported that m^{6}A modification levels are increased during DC maturation, and that RNA methyltransferase METTL3-mediated mRNA m^{6}A methylation promoted the activation and function of DC by up-regulating translation of the key transcripts in DC, including CD40, CD80, and the TLR signaling adaptor Tirap.[70] Another study explored the effect of METTL3 silencing on DCs and found that DCs with METTL3 knockout exhibited immature properties and prolonged allograft survival.[71] The lncRNA lnc-Dpf 3 inhibited CCR7-mediated DC migration in a feedback manner. The m^{6}A reader YTHDF2 recognized lnc-Dpf3 m^{6}A-modified sites and accelerated lnc-Dpf3 RNA degradation, leading to lnc-Dpf3 deficiency, which in turn increased CCR7-mediated DC migration, leading to disruption of immune homeostasis and excessive inflammatory damage.[72] In addition, analysis of the TIMER database exhibited that METTL14 and ZC3H13 gene expression was significantly positively correlated with DCs in breast cancer.[73]

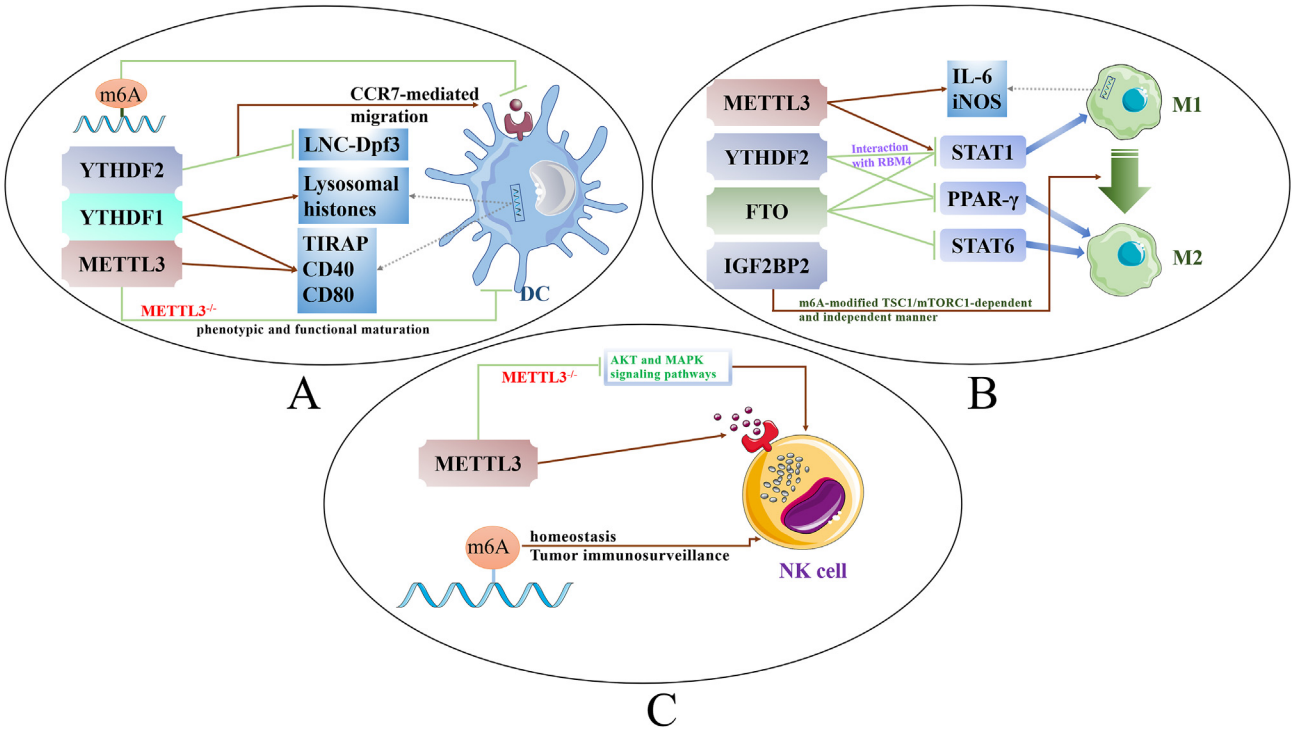

Figure 2 m^{6}A RNA modification in the innate immune system. **(A)** Positive correlation between effector molecules in NK cells and protein expression levels of METTL3; m^{6}A methylation protects NK cell homeostasis and tumor immunosurveillance; METTL3 deletion inhibits AKT and MAPK signaling pathways and alters the homeostasis of NK cells. **(B)** YTHDF2 reduces the genetic stability of STAT1 and PPAR-γ; METTL3 up-regulates STAT1 expression to promote M1 polarization; IGF2BP2 converts M1 to M2 activation in an m^{6}A-modified TSC1/mTORC1-dependent or independent manner; FTO deletion leads to down-regulation of STAT1 expression in M1-polarized macrophages; METTL3 deficiency leads to elevated IRAK-M levels; METTL3 overexpression promoted IL-6 expression and iNOS secretion in M1 macrophages. **(C)** m^{6}A reduces DC expression of activation markers and cytokines; YTHDF1 recognizes transcripts encoding lysosomal proteases modified by m^{6}A methylation, increasing the translation of lysosomal histones in DCs; YTHDF1 and METTL3 mediate the enhanced translation of TLR4 signaling adapters TIRAP, CD40, and CD80 by m^{6}A methylation in DCs; METTL3 deficiency affects phenotypic and functional maturation of DCs; YTHDF2 recognizes methylated LNC-Dpf 3 and accelerates its RNA degradation, thereby increasing CCR7-mediated DC migration; FTO-mediated m^{6}A demethylation reduced the response to anti-PD-1 blockade immunotherapy.

Macrophages

Macrophages are multifunctional antigen-presenting cells that are strategically distributed in tissues throughout the body. They play central roles in inflammation by ingesting and processing foreign substances, dead cells, and debris, and recruiting other macrophages in response to inflammatory signals.[74,75] Macrophage polarization is a driver of various inflammatory diseases especially those related to M1/M2 imbalance.[75] Studies have indicated that FTO and YTHDF2 significantly affected M1 and M2 polarization. FTO deficiency caused the down-regulation of STAT1, the main transcriptional factor controlling M1 macrophage polarization, and reduced STAT6 and PPAR-γ expression in M2-polarized macrophages. Moreover, YTHDF2 reduced the genetic stability of STAT1 and PPAR-γ, thus hindering macrophage activation.[75,76] RBM4 overexpression inhibited interferon-γ-induced M1 macrophage polarization. Another study indicated that YTHDF2 regulated M1 macrophage polarization by interacting with RBM4 and degrading methylation-modified STAT1 mRNA.[77] m^{6}A "writers" are also regulators of macrophage activation. A study by Liu et al reported that METTL3 directly methylated STAT1 mRNA to increase mRNA stability, and promoted M1 polarization by up-regulating STAT1 expression; Conversely, METTL3 deficiency significantly inhibited M1 but enhanced M2.[76] Tong et al found that METTL3 deficiency leads to a lack of m^{6}A modification on IRAKM mRNA, a negative regulator of TLR4 signaling, and slowed down its degradation, leading to elevated IRAKM levels and ultimately inhibiting TLR signaling-mediated macrophage activation.[78] Lei et al found that METTL3 could induce osteogenic differentiation and migration of bone marrow mesenchymal stem cells (BMSCs) by promoting M1 macrophage differentiation, and METTL3 overexpression promoted IL-6 expression and iNOS secretion in M1 macrophages.[79] Under co-culture conditions of macrophages and BMSCs, M1 macrophages with forced expression of METTL3 significantly enhanced the migratory and osteogenic capacity of BMSCs.[79] Tumor-associated macrophages (TAMs) are the major innate immune cells. Yin et al found that METTL3-deficient mice exhibited increased M1/M2-like TAMs and regulatory T (Treg) cells in tumors, and that METTL3 deletion impeded YTHDF1-mediated translation of SPRED2, enhancing activation of NF-kB and STAT3 through the ERK pathway, resulting in increased tumor growth and

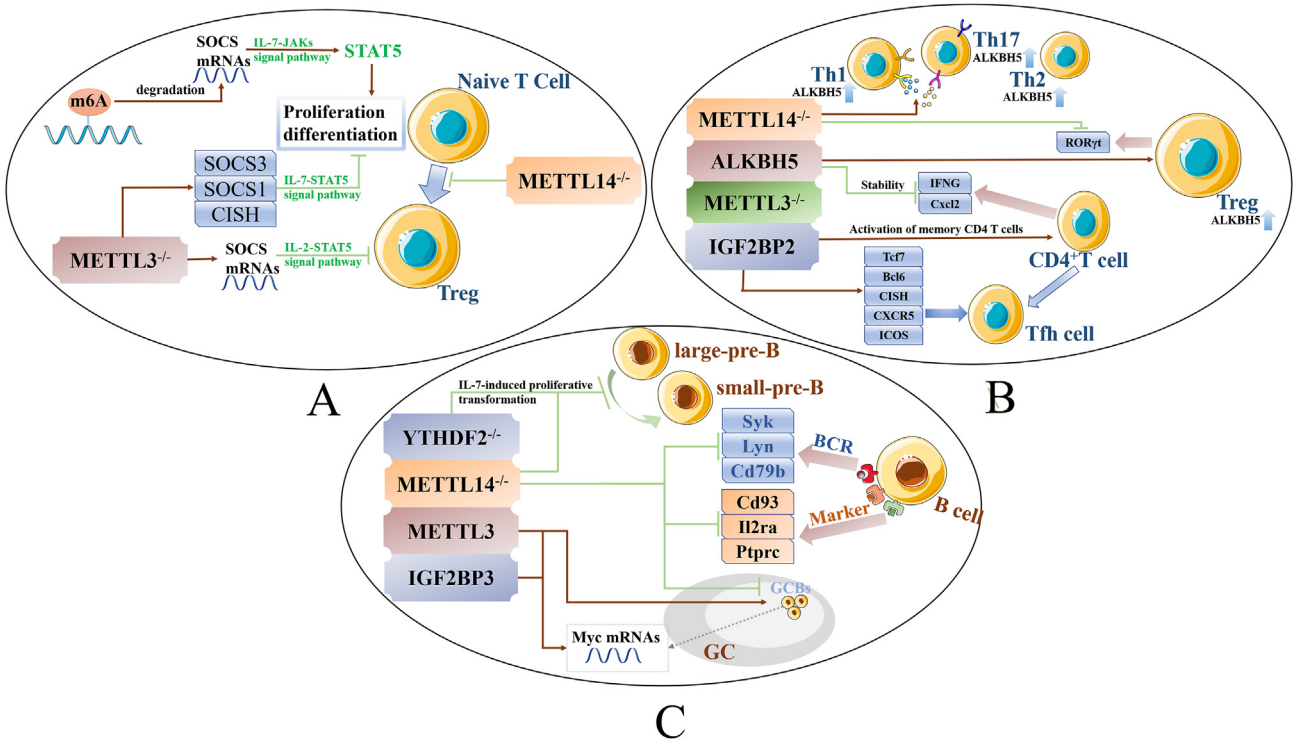

Figure 3 m^{6}A RNA modification in the adaptive immune system. **(A)** METTL3 deletion disrupts the dynamic homeostasis and differentiation of T cells; m^{6}A induces degradation of SOCS mRNAs; METTL14 deficiency inhibits the induction of naive T cells to Treg cells. **(B)** ALKBH5 regulates the composition of tumor-infiltrating Treg; the expression of the ALKBH5 gene is increased in TH1, TH2, TH17, and Treg cells; ALKBH5-deficient CD4$^+$ T cells have decreased stability of IFNG and Cxcl2 mRNA and protein; METTL14 deletion leads to increased Th1 and Th17 cytokines, and decreased RORγt expression in Treg cells; METTL3 intact methyltransferase activity is required for the expression of Tfh signaling genes (including Tcf 7, Bcl 6, Icos, and CXCR5); IGF2BP2 was positively correlated with activated memory CD4 T cells, while METTL14 was remarkably negatively associated with Treg cells; IGF2BP2 promoted the infiltration of activated memory CD4 T cells. **(C)** METTL14 and YTHDF2 deletion in developing B cells leads to impaired IL-7-induced proliferative transition of pre-B cells; METTL4 deletion down-regulates some key genes and damages the large-pre-B-small-pre-B cell transition; METTL3 and IGF2BP3 are required to stabilize of Myc genes and the expression of its target genes; METTL14 deletion in B cells resulted in the impaired proliferation and defective antibody responses in GCBCs.

metastasis.[80] A new study on the role of METTL3 in prostate cancer-associated macrophages found that the down-regulation of METTL3 in prostate cancer TAMs regulated macrophages toward an M2-like phenotype.[81] Dong et al found that C1q$^+$ TAMs were regulated by m^{6}A RNA methylation and that macrophage-specific knockdown of METTL14 promoted the dysfunction of CD8$^+$ T cells and tumor growth.[82] Du et al reported that m^{6}A of SOCS1 mRNA was necessary to maintain negative feedback control of macrophage activation; ablation of METTL14 in myeloid cells aggravated the response of macrophages to acute bacterial infection; and METTL14 depletion impaired SOCS1 m^{6}A methylation, leading to hyperactivation of TLR4/NF-κB signaling.[83] In addition, a recent study showed that METTL14 gene knockout markedly reduced the inflammatory response of macrophages in atherosclerosis and the atherosclerotic plaques development, which is mechanistically related to the regulation of NF-κB/IL-6 signaling pathway by METTL14.[84] IGF2BP2 was also found to play a key role in regulating macrophage activation. It converted M1 to M2 in an m^{6}A-dependent manner and regulated macrophage activation through an m^{6}A-modified TSC1/mTORC1-dependent and independent manner.[85] IGF2BP2-deficient macrophages were insensitive to IL-4-induced activation and exhibited an enhanced M1 phenotype.[85]

Natural killer (NK) cells

NK cells are also a critical component of the innate immune system. They can interact with macrophages, dendritic cells, T cells, and endothelial cells to limit or exacerbate immune responses, with important implications in anti-tumor immunotherapy, and autoimmune and inflammatory diseases.[86,87] Song et al showed that METTL3 expression was reduced in tumor-infiltrating NK cells, and the effector molecules in NK cells were positively correlated with the expression level of METTL3 protein[88]. Similarly, Luo et al reported that METTL3 expression in testicular germ cell tumor (TGCT) tissues was positively correlated with molecular markers and infiltration levels of CD8$^+$ and CD4$^+$ T cells and NK cells. Overexpression of METTL3 observably enhanced cell proliferation, invasion, and migration.[89] METTL3 deletion in NK cells altered the homeostasis of NK cells and inhibited the infiltration and function of NK cells in the tumor microenvironment, to accelerate tumor progression.[88] In addition, TISIDB (an integrated repository portal for tumor-immune system interactions) website analysis results also showed that NK cells were highly correlated with METTL3 expression.[90]

m^{6}A RNA modification in the adaptive immune system

Adaptive immunity works by activating antigen-specific T cells and B cells that specifically remove specific pathogens, ultimately establishing long-term immune memory.[67] Recent research evidence suggests that m^{6}A plays a critical role in adaptive immunity (Fig. 3).

T cells

T cells are a major component of the adaptive immune system. T-cell imbalance is essential in the pathogenesis of ADs.[91,92] Evidence has shown that m^{6}A modification played an important role in maintaining T cell homeostasis. METTL3 deletion in mouse T cells disrupted the dynamic homeostasis and differentiation of T cells. The activity of SOCS family members CISH, SOCS1, and SOCS3 in METTL3-deficient naive T cells was increased, which inhibited the activation of IL-7-STAT5 pathway signaling and T cell differentiation and proliferation.[93] Luo et al found that METTL3 expression was significantly down-regulated in testicular germ cell tumors and that METTL3 expression levels were positively correlated with molecular markers and infiltration levels of CD8$^+$ and CD4$^+$ T cells.[89] With a mouse model to investigate the correlation between METTL3 expression and myeloid-derived suppressor cell (MDSC) infiltration, Zhou et al showed that silencing of METTL3 in CRC cells reduced MDSC accumulation to maintain the activation and proliferation of CD4$^+$ and CD8$^+$ T cells.[94] METTL14 deficiency in T cells increased inflammatory cell infiltration and Th1 and Th17 cytokines, and decreased RORγt expression in Treg cells, resulting in a block in the induction of naive T cells to Treg cells.[95] Other studies have shown that deletion of METTL3 in Tregs also led to elevated SOCS mRNA levels, which in turn inhibited the IL-2-STAT5 signaling pathway, leading to loss of Treg suppressor function and severe ADs.[96,97] ALKBH5 was highly expressed in immune-rich organs and modulated the composition of myeloid-derived suppressor cells and tumor-infiltrating Tregs.[98] Zhou and colleagues found that ALKBH5 mRNA expression was specifically up-regulated upon T-cell activation. The expression of ALKBH5 mRNA was increased in Th1, Th2, Th17, and Treg cells compared with naive CD4$^+$ T cells.[99] Ablation of ALKBH5 enhanced m^{6}A modification on IFN-γ and CXCL2 mRNA in CD4$^+$ T cells, thereby resulting in decreased mRNA stability and protein expression, ultimately leading to impaired CD4$^+$ T cell function.[99] Moreover, Zhou et al found that deletion of ALKBH5 sensitized tumors to cancer immunotherapy and that ALKBH5 regulated the composition of tumor-infiltrating Treg and bone marrow-derived suppressor cells.[100] Follicular helper T (Tfh) cells are specialized CD4$^+$ T cells that play a key role in humoral immunity and are also regulated by m^{6}A modification. M^{6}A modification reduced the expression of ICOS, a key molecule for Tfh development. The expression of Tfh signaling genes required the intact methyltransferase activity of METTL3, and METTL3 deletion can lead to Tfh deficiency.[101,102] TIMER database analysis showed that the expression of METTL14 and ZC3H13 genes was positively correlated with CD4$^+$ T cells and CD8$^+$ T cells, and negatively correlated with Treg cells in breast cancer.[73] Dong et al found that METTL14 expression levels were inversely correlated with dysfunctional T cells in patients with colorectal cancer.[82] Xu et al analyzed the role of tumor-infiltrating immune cells (TIICs) in clear cell renal cell carcinoma (ccRCC) and found that IGF2BP2 was positively correlated with activated memory CD4 T

cells, while METTL14 was remarkably negatively associated with Treg cells. Their study suggested that IGF2BP2 promoted the infiltration of activated CD4 memory T cells, whereas METTL14 reduced the infiltration of Tregs in renal cancer tissues.[103]

B cells

RNA methylation also plays an essential effect in early B cell development. Recent studies showed that METTL14 deficiency not only severely impeded B cell development in mice but also impaired IL-7-induced pre-B cell proliferation and large pre-B to small pre—B transition. Moreover, METTL14 deficiency in developing B cells reduced YTHDF2 binding to its targets, and YTHDF2-mediated mRNA decay was critical for the transition from the pro-B stage to the large pre-B stage.[104] METTL4 deletion down-regulated several key genes, including key transcription factors mediating the large-pre-B-small-pre-B transition, B cell markers, B cell receptor signaling components, BCR recombinant components, and proliferation inhibitors.[104] A recent study revealed that knockout of METTL3 at the pro-B stage exerted minimal influence on B cell development and function, and had minimal effect on B cell profibrotic activity in liver fibrosis, revealing a role for METTL3-mediated m^{6}A in stage-specificity-dependent B cell development.[105] These two experiments revealed a stage-specific dependence on m^{6}A for B-cell development. Sustained immunity in humoral immunity depends on the production of protective antibodies through the germinal center (GC) response, during which high-affinity memory B cells with somatic mutations are generated.[106,107] A study by Grenov et al showed that METTL3 is required for the maintenance of an effective cell cycle in GC B cells (GCBCs) and those GCBCs with METTL3 deficiency exhibit a slowed cell cycle progression and reduced expression of proliferation and oxidative phosphorylation-related genes defective in generating an effective immune response.[108] In addition, Myc mRNA in GCBCs activates downstream cell cycle and metabolic gene programs; Myc mRNA is methylated at the typical m^{6}A site in B cells; METTL3 and IGF2BP3 are required to stabilize Myc genes and the expression of its target genes; Myc mRNA and protein levels are reduced in GCBCs defective in METTL3 and IGF2BP3.[108,109] GCBCs oxidize fatty acids mainly in the mitochondria and peroxisomes for respiration, and YTHDF2 indirectly regulates the expression of oxidative phosphorylation gene programs in GCBCs.[108,110,111] Moreover, a recent study showed that METTL14-mediated mRNA m^{6}A methylation was essential for GCBC responses in mice and that METTL14 deletion in B cells resulted in the impaired proliferation and defective antibody responses in GCBCs. METTL14-mediated m^{6}A regulation of GCBCs positively selected and expressed key genes for cell cycle regulation in a YTHDF2-dependent manner.[112] Diffuse large B-cell lymphoma (DLBCL) is a common subtype of lymphoma. One study has identified that both METTL3 and m^{6}A RNA methylation levels were up-regulated in DLBCL cell lines and tissues. METTL3 promoted DLBCL progression by regulating pigment epithelium-derived factor (PEDF) methylation levels, and silencing METTL3 inhibited DLBCL cell proliferation.[113] In addition, another study suggested that the piRNA-30473/WTAP/HK2 axis was involved in tumorigenesis by regulating m^{6}A RNA methylation in DLBCL. piRNA30473 increased the expression of its key target gene HK2 by up-regulating WTAP, thus increasing the m^{6}A level of HK2, thereby promoting DLBCL progression.[114]

m^{6}A RNA modification in autoimmune diseases

ADs are a group of diseases caused by self-destructive immune responses resulting from impaired immune tolerance mechanisms.[115] Currently, the exact etiology of ADs is not fully understood. Genetic, environmental, and psychological factors and microorganisms are thought to be responsible for triggering autoimmunity. In recent years, growing attention has been paid to the role of m^{6}A RNA modification in ADs. Cross-links among writers, erasers, and readers have been reported to be involved in the pathogenesis and progression of ADs (Fig. 4).

Systemic lupus erythematosus (SLE)

SLE is characterized by the aberrant activity of the immune system, leading to the formation of immune complexes, and inflammation of multi-organs.[116] The clinical manifestations of SLE are diverse, often involving single or multiple organs, such as the kidneys, joints, skin, and nervous system, with a chronic course, and easy recurrence.[116,117]

Studies have indicated an involvement of epigenetic modifications, including RNA methylation, in the pathogenesis of SLE.[118,119] A study in SLE patients showed elevated m^{6}A levels in CD4$^+$ T cells from the peripheral blood of SLE patients.[119] Luo et al explored the mRNA expression of m^{6}A "writers", "erasers", and "readers" in peripheral blood mononuclear cells (PBMCs) from SLE patients, and found that the mRNA expressions of METTL14, ALKBH5, and YTHDF2 in SLE patients were significantly lower than those in healthy controls.[120] Their further logistic regression analysis showed that decreased YTHDF2 mRNA expression was a risk factor for the onset of SLE.[120] However, direct mechanistic data are lacking to confirm the exact role of RNA methylation in SLE pathogenesis. The potential role of methylation modifications in SLE requires further investigation.

Inflammatory bowel disease (IBD)

IBD is a chronic, relapsing inflammatory disorder that consists of Crohn's disease (CD) and ulcerative colitis (UC).[121] It has become a worldwide healthcare problem with increasing incidence. Although the etiology of IBD remains largely unknown, studies suggest that the pathogenesis of IBD involves a complex interplay of genetic susceptibility, epigenetics, environmental factors, and gut microbiota. Numerous genome-wide association studies have identified more than one hundred susceptibility genes for IBD.[122—125] Growing evidence implicated that m^{6}A methylation, as a key mode of the post-transcriptional gene, is involved in the pathogenesis of IBD.[126]

It is well known that T cells play an integral role in the pathogenesis of IBD. Lu et al found that deletion of METTL14 in T cells induced the development of

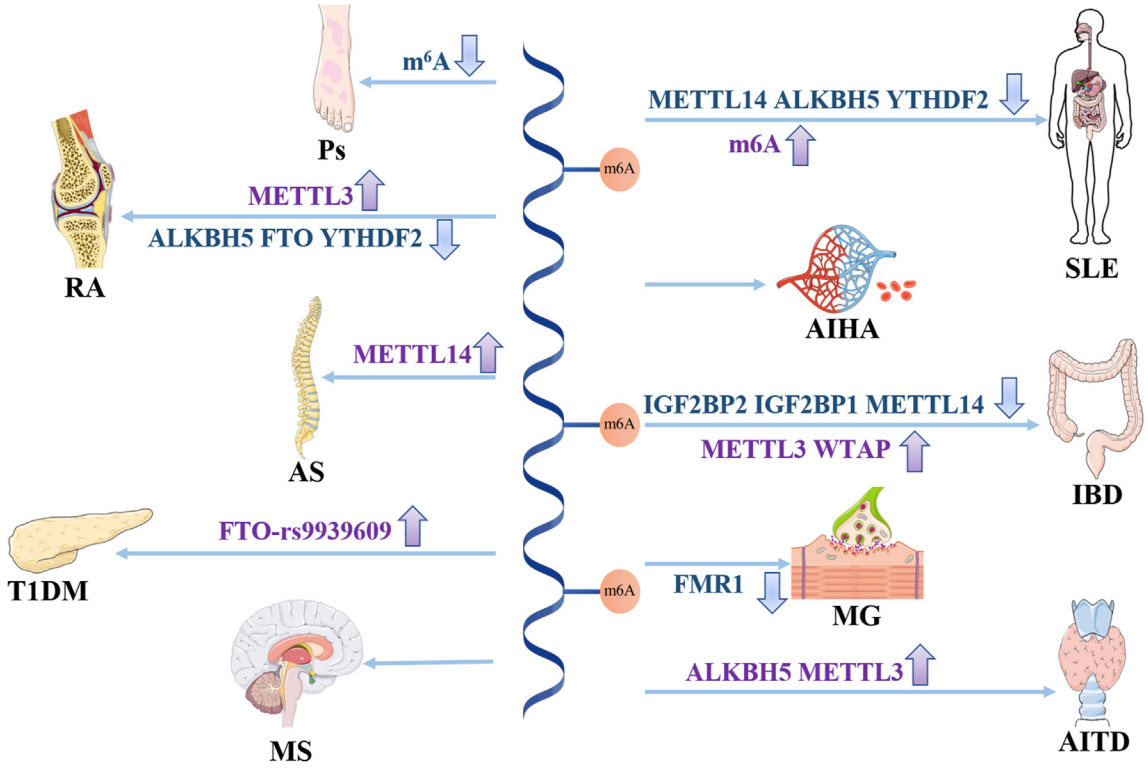

Figure 4 m^{6}A RNA methylation-related enzymes in autoimmune diseases.

spontaneous colitis in mice. Mechanistically, METTL14 deficiency in T cells resulted in blocked induction of naive T cells to Treg cells.[95] Emerging evidence demonstrated that METTL3 expression was significantly up-regulated in both IBD patients and dextran sulfate sodium (DSS)-induced IBD models in mice and that METTL3 knockdown significantly ameliorated DSS-induced IBD in mice by inhibiting the NF-κB signaling.[127] Furthermore, Tong et al found that Foxp3-mediated deletion of METTL3 in Tregs elicited severe systemic autoimmune responses in mice.[96] The novel m^{6}A-XPO1-NF-kB pathway activated in CD patients also clearly indicated a regulatory role of m^{6}A in IBD.[128] Chen et al analyzed the links between m^{6}A modification and immune infiltration in IBD by integrating genomic information from IBD tissues. Their results showed that the expressions of IGF2BP1 and IGF2BP2 were down-regulated in CD tissues and that IGF2BP2 was down-regulated in UC tissues compared to normal tissues. Furthermore, they found that expression of m^{6}A phenotype-related hub genes (*i.e.*, NUP37, SNRPG, H2AFZ) was up-regulated with high abundance in M1 macrophages, M0 macrophages, and naive B cells in IBD, suggesting that m^{6}A modifications may affect immune infiltration and treatment response in IBD.[129] Correspondingly, Wang et al found that IGF2BP2$^{-/-}$ mice exhibited enhanced development of DSS-induced colitis,[85] which together with the study by Chen et al suggested a critical role of IGF2BP2 in IBD. Another study using online available GWAS, m^{6}A, and transcriptome data available online to find IBD-related genes revealed that m^{6}A methylation enzymes (YTHDF1, WTAP, METTL3, and METTL14) were involved in the regulation of IBD-related genes.[130] Adoptive transfer colitis (ATC) is an autoimmune colitis model used to assess the expansion of naive T-cell homeostasis.[93] Zhou et al analyzed the composition of donor CD4$^+$ T cells after ATC induction and found that CD4$^+$ T cells from ALKBH5$^{flox/flox}$Cd4^{Cre} mice were infiltrated at lower rates in the colon of the recipient compared with cells from WT mice, suggesting that the deletion of ALKBH5 during ATC resulted in the inability of CD4$^+$ T cells to aggregate in colonic tissue.[99,93]

Multiple sclerosis (MS)

MS is an AD characterized by chronic inflammation, demyelination, and axonal degeneration of the central nervous system (CNS).[131] MS is divided into progressive multiple sclerosis (PMS, including secondary MS and primary PMS) and relapsing-remitting MS (RRMS).[132] Currently, more than 200 genetic loci have been identified as MS susceptibility genes.[133] Emerging evidence suggests that RNA methylation is involved in different pathophysiological processes of MS.[134]

SNPs located within or near m^{6}A motifs (m^{6}A-SNPs), a type of SNPs that affect m^{6}A by altering the RNA sequence of the target or key flanking nucleotides that are potential contributors to disease pathogenesis.[130] Researchers identified rs2288481 in DKKL1 and rs923829 in METTL21B as m^{6}A-SNPs associated with MS.[135,136] Rs2288481 and rs923829 may function by regulating gene expression in DKKL1 and METTL21B, respectively, elucidating the potential pathogenic role of m^{6}A-related proteins in MS for the first time.[135] A clinical study using 61 MS and 31 non-MS cerebrospinal fluid samples showed that 13 central m^{6}A RNA

methylation regulators were up-regulated in MS patients compared with non-MS patients.[137] This study also found that the m^{6}A RNA methylation levels and m^{6}A-related gene expression in RRMS samples were significantly higher than those in PMS, indicating that the dynamic modification of m^{6}A methylation is involved in the pathogenesis of MS and may serve as a novel CSF biomarker for distinguishing PMS from RRMS at the early onset of the disease.[137] Davis et al found that the risk-associated FTO rs9939609 A-allele was related to significantly elevated homocysteine levels in MS patients.[138] Similarly, Al-Serri et al found that rs9939609 was associated with increased disability in MS patients.[139] However, these two studies did not observe an association between MS risk and FTO variants. Another study by Gianfrancesco et al on Hispanics found a direct effect between MS risk and another FTO variant gene, rs1558902.[140] However, this was inconsistent with the findings of Al-Serri et al, possibly due to differences in the population studied and the variants selected. Experimental autoimmune encephalomyelitis (EAE) is currently an internationally recognized ideal animal model for MS, showing the same clinical, biochemical, immune, and pathological characteristics as human MS in many aspects. Recent studies have found that ALKBH5 deficiency in T cells mediates protection against experimental neuroinflammation by inhibiting CD4$^+$ T cell entry into the CNS during EAE and reducing IFN-γ secretion in the CNS.[99] Although researchers have actively explored the pathogenesis of m^{6}A RNA methylation in MS, little is known about the role of m^{6}A RNA methylation in MS. Studies in the future should focus on systematically elucidating the regulatory roles of m^{6}A RNA methylation in MS and its underlying mechanisms.

Rheumatoid arthritis (RA)

RA is an inflammatory AD involving symmetrical joints that causes cartilage and bone damage and even disability, usually characterized by persistent tenderness, pain, and joint destruction.[141] A recent genetic analysis identified more than 150 candidate loci with RA-associated polymorphisms.[142] Growing data from studies in the epigenetics of RA suggested that aberrant m^{6}A modifications are implicated in RA pathology. Wang et al observed that METTL3 expression was up-regulated in RA patients and positively correlated with C-reactive protein and erythrocyte sedimentation rate. Furthermore, METTL3 significantly inhibited the proliferation and activation of macrophages through the NF-κB pathway.[143] Similarly, another study showed that METTL3 played an important role in the progression of RA by regulating NF-κB signaling and extracellular matrix synthesis in chondrocytes.[144] Another genome-wide study of RA-associated m^{6}A SNPs identified a total of 37 m^{6}A SNPs and 23 SNP-gene-RA trios located at the RA locus.[145] Luo et al demonstrated that the mRNA expression of ALKBH5, FTO, and YTHDF2 in the peripheral blood of RA patients was lower than that of healthy controls, suggesting that ALKBH5, FTO, and YTHDF2 may be risk factors for RA.[146] In addition, although there are few studies on m^{6}A modification and RA, it provides a novel idea for the involvement of RNA methylation in the prevention and treatment of RA.

Psoriasis (Ps)

Ps is a chronic, immune-mediated genetic disorder with cutaneous and systemic manifestations, primarily in the joints or skin, or both.[147] Ps is widely regarded as a multifactorial disease caused by the interaction of environmental factors and genetic susceptibility alleles. More than 60 disease-susceptibility regions have been identified to date.[147,148] In recent years, epigenetic studies of Ps have become an expanding field.[149] While histone modifications, DNA methylation, and non-coding RNAs have been extensively studied in Ps, less research has been done on RNA m^{6}A methylome in Ps.[150,151] In a transcriptome-wide m^{6}A methylome profile of Ps assessed by MeRIP-Seq, Wang et al found that, compared with healthy control skin samples (NN) and uninvolved psoriatic skin (PN), transcripts from the affected psoriatic skin (PP) contained the lowest m^{6}A peak and m^{6}A peak density. They also found that hypermethylated m^{6}A was mainly enriched in CDS and 3′UTR, while hypomethylated m^{6}A was enriched not only in CDS and 3′UTR but also in 5′UTR.[152] In addition, a comprehensive analysis of m^{6}A methylation and mRNA levels revealed that hypermethylated transcripts in PP were associated with cytokine production, response-related terms, and olfactory transduction, whereas hypomethylated transcripts in PP were primarily related to the Wnt signaling pathway and development-related processes.[152] This study suggested that m^{6}A methylation played an important role in the physiology of Ps.

Type 1 diabetes mellitus (T1DM)

T1DM, also known as autoimmune diabetes mellitus, is a chronic disease with hyperglycemic symptoms caused by absolute insulin deficiency due to the loss of pancreatic β-cells.[153] It is currently believed that the pathogenesis of T1DM is related to T cell-mediated β-cell destruction, which is the result of the interaction of multiple genetic and environmental factors. In recent years, more than 100 non-human leukocyte antigen (HLA) gene loci that affect T1DM susceptibility have been identified.[153,154]

A previous study in 14,803 T1DM subjects and controls showed that FTO-rs9939609 increased the risk of childhood obesity and T2MD, but did not alter susceptibility to T1DM or the age at which T1DM occurred, suggesting that FTO does not make people vulnerable to T1DM by mediating weight gain.[155] In contrast, a study conducted by Nahid et al suggested that the FTO risk allele (FTO-rs9939609) played an important role in promoting latent autoimmune diabetes in adults.[156] Cognitive impairment is a serious diabetes-related complication. Li et al investigated the expression of m^{6}A-related regulatory proteins in the hippocampal region of mice with T1DM-induced cognitive impairment and found that the protein levels of YTHDC2 and ALKBH5 in the hippocampus of diabetic cognitive impairment mice were significantly up-regulated, while the expressions of YTHDF1, YTHDF3, and WTAP were significantly down-regulated. Furthermore, overexpression of YTHDF1 in the hippocampal region significantly improved diabetic cognitive dysfunction. This study indicated that m^{6}A-related regulatory protein YTHDF1 may serve as a therapeutic target for

the cognitive dysfunction of T1DM.[157] In addition, METTL3 can inhibit hepatic insulin sensitivity by mediating m^{6}A methylation of the fatty acid synthase (FASN) gene and promoting fatty acid metabolism.[158]

Autoimmune thyroid disease (AITD)

Autoimmune thyroid disease (AITD) is the most common ADs with high heritability. Many susceptibility loci associated with AITD autoimmunity have been identified.[159] A study using a case control of 979 AITD patients and 732 healthy individuals showed that ALKBH5 gene polymorphism was associated with AITD patients and that the ALKBH5 gene may be a susceptibility gene for AITD.[160] Another study used microarray analysis to identify differentially expressed genes in Graves' disease (GD) tissues and found that METTL3 and SOCS molecules were aberrantly expressed in GD thyroid tissues and CD4$^+$ T cells. Further experiments proved that METTL3 was involved in the occurrence of GD by inducing the mRNA m^{6}A methylation of SOCS family members.[161]

Other autoimmune diseases

In addition to the ADs mentioned above, there are also some shreds of evidence that m^{6}A RNA methylation is involved in the pathogenesis of other ADs. Myasthenia gravis (MG) is an AD affecting the neuromuscular junction.[162] Thomas et al demonstrated that FMR1 expression was reduced in the thymus of MG patients and that patients with FMRP-related syndrome are prone to autoimmune and inflammatory diseases. This study indicated that FMR1 may play an important role in MG.[163] Ankylosing spondylitis (AS) is a chronic progressive inflammatory rheumatic disease characterized by inflammatory back pain, limitation of spinal motion, spondylitis, and peripheral and extra-articular manifestations.[164] A recent study showed that engulfment and cell motility protein 1 (ELMO1) expression was increased in TNF-α-treated AS-mesenchymal stem cells (AS-MSCs) and that METTL14 regulated MSC directional migration by acting on the 3′UTR of a specific m^{6}A modification site in the ELMO1.[165]

Therapeutic potential

ADs are recognized as refractory diseases worldwide, and developing drugs that can be targeted and associated with self-exemption has attracted increasing attention. The study of epigenetic alterations in AD not only provides new candidate biomarkers that can be used as targets for future disease status, prognosis, and even disease treatment but also novel ideas for developing effective epigenetic modifiers for AD. Based on the largely reversible nature of RNA methylation, it is a challenging therapeutic target from the perspective of treatment. An increasing number of epigenetic modifiers have been developed in recent years, and new RNA-targeted therapies are expected to provide high efficiency and specificity, showing convincing promise in the treatment of multiple diseases.[166]

To date, inhibitors have almost exclusively targeted FTO and METTL3, the two most promising new therapeutic enzymes. Several small-molecule extracts of natural products have been involved in the mediation of RNA methylation as small-molecule inhibitors.[167–174] Rhein is the most effective compound studied so far, which can competitively bind to the active site of FTO *in vitro* and exhibits good inhibitory activity against intracellular m^{6}A demethylation.[173] Although the epigenetic modifying drugs studied so far are almost exclusively focused on the tumor, these studies reveal the powerful potential for RNA biology and drug discovery as well as the development of new therapeutics.[175] Extracts of natural products with few side effects, such as demethylases or selective modulators, promise more research in the new frontiers of m^{6}A methylation modifications related to disease pathogenesis.

Conclusion and future perspectives

The relevance of epigenetic alterations to the pathogenesis of ADs has been demonstrated. RNA methylation, as an RNA-associated epigenetic alteration, may unlock the mystery of AD pathogenesis.[176] In this review, we summarized the "life cycle" of m^{6}A methylation and its potential role in the immune system and ADs. The m^{6}A methylation modifications play a crucial role in maintaining homeostasis and immune cell activation *in vivo*, and m^{6}A modifications of different target gene transcripts regulate the fate and function of immune cells.

The current understanding of the link between m^{6}A methylation and ADs is the tip of the iceberg. Undoubtedly, further studies are needed to elucidate the regulatory mechanisms of m^{6}A methylation on ADs and the specific biological functions of ADs. It is necessary to further understand the biological functions of various proteins regulating m^{6}A methylation - "writer", "eraser", and "reader", to formulate better strategies for prevention, early diagnosis, and personalized treatment of ADs, and even predict and intervene the progress of AD-related diseases. The development of m^{6}A methylation-related targeted therapy for ADs will be a near-term focus. Targeted therapy for ADs based on m^{6}A methylation will provide more options for clinical control of the disease. In the future, more profound studies on RNA epigenetic mechanisms will drive innovation in molecular therapies for ADs.

Conflict of interests

The authors report no conflict of interests.

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