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REVIEW

The m^{6}A Modification in T Helper Cells Regulates the Pathogenesis of Autoimmune Diseases

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Abstract: The pathogenesis of autoimmune diseases remains unclear, which is associated with T helper (Th) cell subsets such as Th1, Th2, Treg and Tfh cells. Recent studies have indicated the involvement of N^6-methyladenosine (m^{6}A) modification in the pathogenesis of autoimmune diseases, and m^{6}A also affects the differentiation, and function of Th cells. However, few reports focused on the relationship between m^{6}A modification in Th cell subsets and autoimmune diseases. This review summarizes the latest research progress on m^{6}A modification in common autoimmune diseases, specifically highlighting how various m^{6}A-modifying enzymes influence the differentiation and function of Th cells and disease progression. Elucidating the relationship between m^{6}A modification and Th cells in autoimmune diseases may provide a new perspective for disease prevention and targeted therapy. Finally, this review also elaborates on the impact of m^{6}A on the clinical diagnosis and treatment of autoimmune diseases, as well as the challenges that need to be addressed.

Keywords: m^{6}A, T helper cells, treatment, autoimmune diseases

Introduction

N^6-methyladenosine (m^{6}A) modification was discovered in mouse hepatoma cells in 1974, but it was not thoroughly investigated until 1977 when methyltransferase-like3 (METTL3) was isolated from HeLa cells by researchers.[1,2] Since then, researchers have gradually developed a clearer understanding of m^{6}A methylation. Simply put, m^{6}A methylation is a chemical modification in which a methyl group is added to the nitrogen atom at the sixth position of adenosine in messenger RNA. This modification occurs after RNA synthesis, representing a form of post-transcriptional modification that is dynamic, reversible, and the most common form of mRNA modification (Figure 1). Methyltransferases, also known as m^{6}A "writers", primarily include METTL3, METTL5, METTL14, METTL16, Wilm's tumour 1-associated protein (WTAP), ZC3H13, RBM15/15B and VIRMA (also called KIAA1429), and their main role is to add m^{6}A modifications. Demethylases, referred to as m^{6}A methylation "erasers", mainly consist of fat mass and obesity-associated protein (FTO) and AlkB homologue 5 (ALKBH5), which function to remove m^{6}A modifications. The m^{6}A "readers" mainly comprise YT521-B homology (YTH) domain family (YTHDF1/2/3, YTHDC1/2), insulin-like growth factor 2 mRNA-binding proteins family (IGF2BP1/2/3), heterogeneous nuclear ribonucleoproteins (hnRNP) family (HNRNPC/G/A2B1), and ELAV-like protein 1 (ELAVL1), which recognize these modifications and convert the read information into functional signals.[3,4] METTL3 and METTL14 form a stable heterodimeric complex in a 1:1 ratio, where METTL3 serves as the catalytic subunit, while METTL14 is responsible for recognizing target RNA and structurally stabilizing METTL3. WTAP helps mediate the localization of the METTL3 and METTL14 heterodimer on nuclear speckles, acting as a key regulatory molecule of the m^{6}A methylation complex.[5] KIAA1429 is the largest

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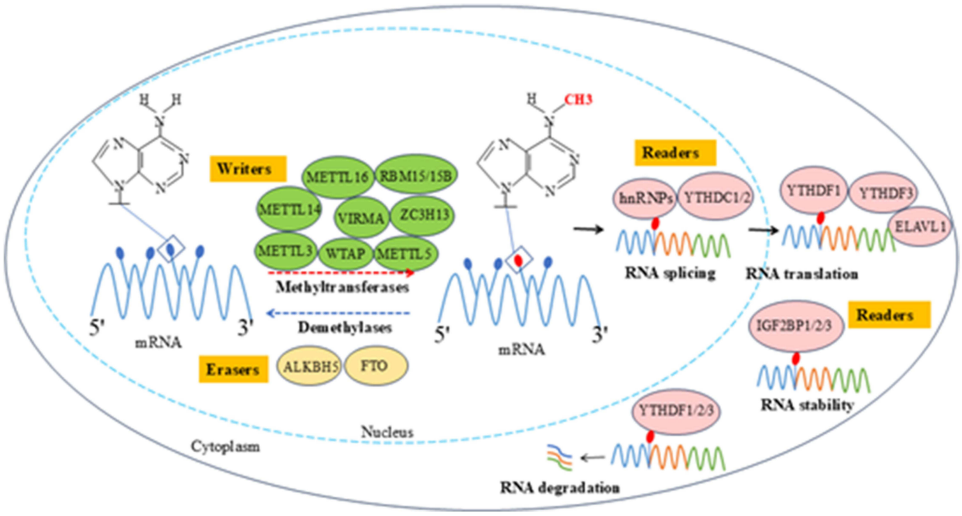

Figure 1 The dynamic methylation process of RNA m^{6}A modification. m^{6}A methylation is a dynamic and reversible biological process, regulated by the coordinated actions of methyltransferases ("writers"), demethylases ("erasers"), and methylation recognition proteins ("readers"). Writers (eg, METTL3, METTL14) catalyze the methylation of mRNA bases. Erasers (eg, FTO, ALKBH5) specifically remove methyl groups from mRNA. Readers (eg, YTHDF1/2/3) regulate mRNA stability, splicing, translation, and other processes.

scaffold component of this complex, primarily regulating m^{6}A methylation near the 3' untranslated regions (3' UTR) and stop codons.[6] FTO can reverse m^{6}A modifications in cells, stabilizing the 5' cap structure of mRNA.[7] ALKBH5 regulates RNA metabolism and mRNA export by reducing m^{6}A levels in nuclear speckles.[8] The m^{6}A methyltransferases and demethylases complement each other, maintaining m^{6}A methylation in a dynamic and reversible state. When m^{6}A methylation occurs, m^{6}A reader proteins recognize and bind to m6A-modified RNAs, regulating downstream functions and determining their fate. The YTHDF protein family mediates m^{6}A-dependent regulation of mRNA metabolism through selective degradation and translational enhancement. Specifically, YTHDF1 primarily accelerates mRNA translation, YTHDF2 predominantly facilitates mRNA decay, while YTHDF3 exhibits dual functionality in both translation and degradation processes.[9] The IGF2BP family is primarily responsible for enhancing mRNA stability and translation[10] (Table 1). m^{6}A modifications have been found in various types of RNA, including ribosomal RNA, transfer RNA, and non-coding RNA. These modifications regulate almost all aspects of mRNA metabolism, including export, splicing, translation, localization, and degradation, thereby affecting physiological processes such as metabolism, inflammatory responses, growth, and development. Abnormal m^{6}A modifications can mediate the occurrence of diseases, including those caused by imbalances in helper T cells.

Th cells are differentiated from naïve CD4$^+$ T cells upon stimulation by specific antigens. Based on the cytokines secreted after activation, they are classified into Th1, Th2, Th9, Th17, Th22, regulatory T cell (Treg), and T follicular helper (Tfh) cells.[11] Each subpopulation is activated by specific cytokines and transcription factors, and it exert its effects in autoimmune diseases through the cytokines they secrete. Th1 cells primarily produce interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin (IL)-2, with T-bet as the main transcription factor for Th1 cell differentiation. Th1 cells play a crucial role in the pathogenesis of inflammatory bowel disease (IBD).[12] Reports on the association between Th2 cells and m^{6}A in autoimmune diseases are scarce. Th2 cells play a pivotal role in mediating immune responses to allergic reactions and parasitic infections. The release of inflammatory cytokines such as IL-4, IL-5, and IL-13 leads to bronchial constriction, increased vascular permeability, and inflammatory cell infiltration, resulting in allergic symptoms. IL-4 and IL-13 are the primary inflammatory cytokines in atopic dermatitis (AD).[13] Macrophages with *IGF2BP2* knockout show a reduced response to IL-4 but an enhanced inflammatory response to lipopolysaccharide (LPS), indicating that *IGF2BP2* is involved in regulating macrophage activation in inflammatory diseases.[13] Th9 cells secrete IL-9 under the stimulation of transforming growth factor-β (TGF-β) and IL-4. Currently, there are no direct reports linking Th9 cells to m^{6}A in autoimmune diseases. Th17 cells, activated by the combined stimulation of IL-6 and TGF-β, activate their characteristic transcription factor retinoic acid-related orphan receptor γt (RORγt) and secrete

Table 1 The Regulators Involved in m^{6}A Methylation

Type	Proteins	Function
Writers	METTL3	Catalyzes the m^{6}A methylation reaction; currently the only known m^{6}A "writer" with catalytic activity.
	METTL14	Forms a core complex with METTL3, helps recognize RNA substrates and promotes the formation of m^{6}A.
	WTAP	Helps localize the complex to specific RNA targets within the nucleus, enhancing the stability of the complex.
	METTL5	Enhances the activity of protein synthesis.
	METTL16	Regulates RNA stability, transport and translation efficiency.
	KIAA1429 (VIRMA)	Assists the METTL3-METTL14-WTAP complex and regulates the position of methylation.
	RBM15/RBM15B	Interacts with WTAP to help m^{6}A methyltransferases locate to specific RNA regions.
	ZC3H13	Interacts with nuclear RNA-binding proteins to regulate m^{6}A deposition.
Erasers	FTO	Involved in cell cycle regulation, etc.
	ALKBH5	Regulates RNA metabolism and function.
Readers	YTHDF1	Recognizes and binds to m^{6}A sites through its YTH domain, enhancing the translation efficiency of m^{6}A-marked mRNAs.
	YTHDF2	Promotes the degradation of m^{6}A-marked mRNAs.
	YTHDF3	Collaborates with YTHDF1 and YTHDF2.
	YTHDC1	Regulates the processing and nuclear export of m^{6}A-marked mRNAs within the nucleus.
	YTHDC2	Increase the translation efficiency of m^{6}A-modified mRNAs.
	IGF2BP1,2,3	Enhance the stability and translation of target mRNAs.
	hnRNPs	RNA processing, transport, and maintaining stability, etc.
	ELAVL1	Promotes mRNA transcription and translation, increasing the expression level of target proteins.

inflammatory cytokines such as IL-17A, IL-17F, and IL-21 to exert immune functions. Th17 cells are involved in the disease progression of psoriasis and multiple sclerosis (MS).[14,15] IL-22 is the characteristic cytokine of Th22 cells. Under the stimulation of IL-1β, IL-6, IL-23, and TNF-α, the secretion of IL-22, IL-13, IL-26, and TNF-α increases. Th22 cells play a significant role in autoimmune thyroid disease (AITD).[16] Treg cells are a T cell subpopulation that exerts a prominent immunosuppressive effect and is one of the crucial factors maintaining immune tolerance in the body. Foxp3 is their characteristic transcription factor. Foxp3 is their characteristic transcription factor. Tregs exerts their effects by secreting inhibitory cytokines such as IL-10 and TGF-β. Tregs are closely associated with various autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Both quantitative deficiency and functional impairment of Tregs have been demonstrated to exacerbate disease progression in autoimmune conditions.[17,18] Under the induction of IL-6, IL-12, and IL-27, Tfh cells produce IL-21, which promotes the development of plasma cells and memory B cells. Bcl6 serves as the master transcriptional regulator of Tfh cells. Importantly, Tfh cells play a key role in the occurrence and development of primary Sjögren's syndrome (pSS).[19] This article mainly reviews the manifestations of m^{6}A methylation in common autoimmune diseases (Figure 2) and its relationship with Th1, Th17, Th22, Treg, and Tfh cells. Finally, it summarizes the impact of these findings on clinical practice and treatment, aiming to provide more comprehensive theoretical knowledge for disease treatment (Table 2).

Role of m^{6}A Modification in Autoimmune Diseases

Role of m^{6}A Modification in Th1-Related Autoimmune Diseases

IBD, an idiopathic intestinal inflammatory condition affecting the ileum, rectum, and colon, includes Crohn's disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD, which remains incompletely understood, may be related to individual genetic susceptibility, immune response, gut microbiota, and the external environment.[44] There is a high degree of heterogeneity in m^{6}A regulatory factors among healthy individuals and patients with UC and CD. The expression of IGF2BP2 was significantly reduced in UC tissues, while both IGF2BP1 and IGF2BP2 were downregulated in CD tissues. m^{6}A modification may affect immune infiltration in IBD and the response to treatment.[20] Selective knockout of *Mettl14* in T cells leads to an increase in Th1 cytokines (TNF-α, IFN-γ) and Th17 cytokines (IL-17a, IL-17c), a decrease in RORγt expression in Treg cells, and the induction of spontaneous colitis in mice.[45] A colon-specific

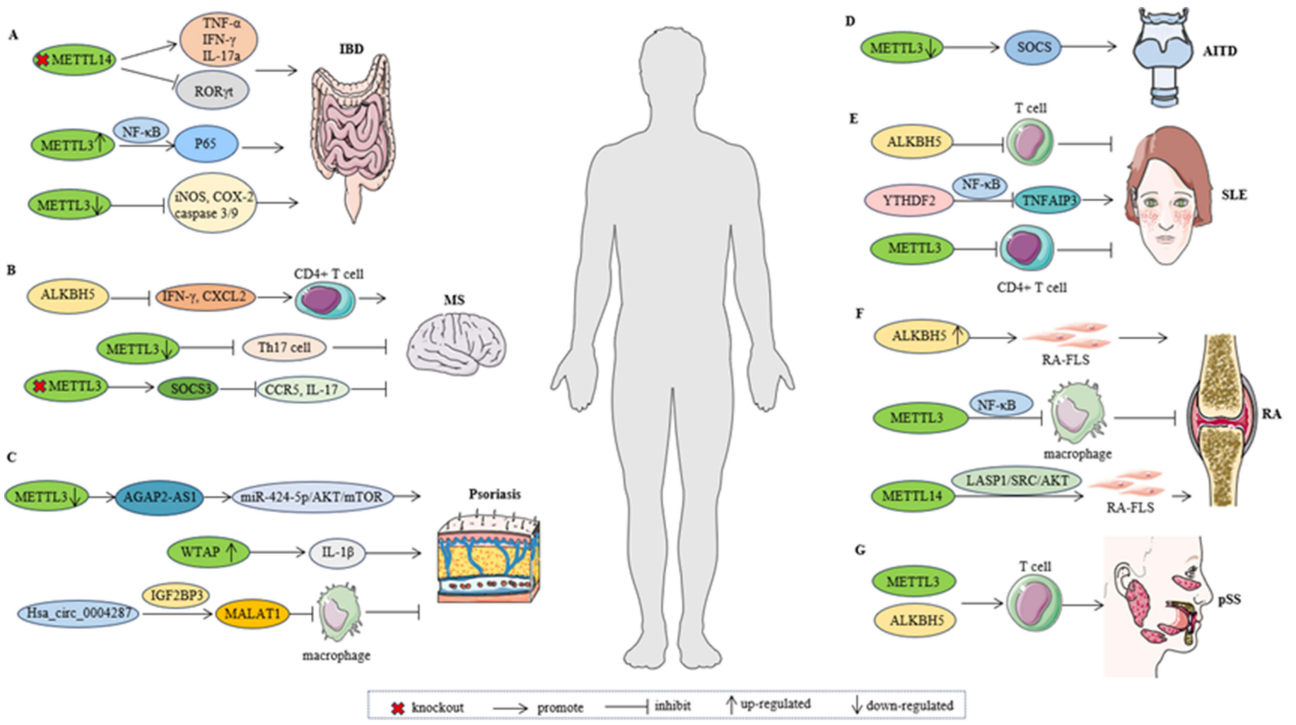

Figure 2 The possible mechanism of m6A methylase in various autoimmune diseases. (**A**). Knockout of Mettl14 in T cells leads to an increase in TNF-α, IFN-γ and IL-17a, a decrease in RORγt expression in Treg cells. Overexpression of METTL3 promotes the phosphorylation of p65. Knockdown of METTL3 reduces caspase 3/9 cleavage, and lowers levels of inflammatory enzymes. (**B**). ALKBH5 enhances the response of $CD4^+$ T cells and increases the infiltration of neutrophils into the central nervous system by reducing the m6A modification in IFN-γ and CXCL2. The loss of METTL3 in T cells diminishes Th17 cell differentiation. The absence of METTL3 in Th17 cells enhances the stability of SOCS3 mRNA, attenuates the expression of CCR5 and IL-17A. (**C**). Downregulation of METTL3 increases AGAP2-AS1 expression. Overexpression of WTAP leads to increased expression of IL-1β. Hsa_circ_0004287 binds to IGF2BP3 in an m^6A-dependent manner. (**D**). Knockdown of METTL3 reduces the expression of SOCS family members. (**E**). ALKBH5 may contribute to SLE pathogenesis by influencing T cell proliferation and apoptosis. Downregulates the level of YTHDF2 through the NF-κB pathway, thereby affecting the progression of SLE. Inhibiting METTL3 in SRBC-immunized mice significantly promotes $CD4^+$ T cell activation. (**F**). Overexpression of ALKBH5 promotes the function of RA FLSs. Overexpression of METTL3 attenuated the inflammatory response induced by LPS in macrophages. METTL14 promote RA-FLS activation through the LASP1/SRC/AKT signaling pathway. (**G**). METTL3 and ALKBH5 were closely related to T cells in pSS.

Abbreviations: IBD, Inflammatory bowel disease; MS, Multiple sclerosis; AITD, autoimmune thyroid disease; SLE, Systemic lupus erythematosus; RA, Rheumatoid arthritis; pSS, primary Sjögren's syndrome.

mouse model with *Mettl14* deficiency exhibits mucosal barrier dysfunction and colonic stem cell apoptosis, leading to severe colitis. Mettl14 may limit the death of colonic epithelial cells by regulating the stability of an inhibitor of NF-κB (*Nfkbia*).[21] Therefore, m^6A modification is essential for maintaining colonic epithelial homeostasis. In LPS-treated MODE-K cells (a mouse intestinal epithelial cell line), knockdown of *METTL3* inhibits apoptosis, reduces caspase 3/9 cleavage, and lowers levels of inflammatory enzymes (iNOS and COX-2) as well as proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. Similarly, overexpression of *METTL3* promotes the phosphorylation of p65 and exacerbates DSS-induced IBD in mice, suggesting the involvement of the NF-κB signaling pathway.[22] This demonstrates the important role of *METTL3* in inflammation regulation. Additionally, the loss of *METTL3* in T cells disrupts T cell homeostasis and differentiation. Naïve T cells lacking *Mettl3* show a reduction in Th1 and Th17 cells and an increase in Th2 cells[46] (Figure 3A). Taken together, these data highlight the pivotal role of m^6A methylation in regulating $CD4^+$ T cell proliferation and differentiation, positioning it as a potential new breakthrough for IBD treatment.

Role of m^6A Modification in Th17-Related Autoimmune Diseases

MS is a common and complex demyelinating disease of the central nervous system, with confirmed involvement of Th17 cells in its pathogenesis.[47] Most patients experience a distinct pattern of relapse and remission, referred to as relapsing-remitting multiple sclerosis (RRMS).[48] Studies have indicated that MS patients exhibit higher levels of 13 central m^6A RNA methylation regulatory factors compared to non-MS individuals. Additionally, patients with progressive multiple sclerosis (PMS) demonstrate elevated cerebrospinal fluid (CSF) m^6A methylation and enhanced expression

Table 2 m^6A Modifications in T-Helper Cell Subset Disorders

Subsets	Disease	Enzymes Involved and Its Expression	Sample Source	Function	Reference
Th1	IBD	IGF2B↓	Tissue	Influence immune infiltration and response to treatment	[20]
		Mettl14	Colonic epithelial cell	Mettl14 deletion causes mucosal barrier dysfunction, colon stem cell apoptosis and severe colitis	[21]
		METTL3	MODE-K cell	METTL3 knockdown reduces the pro-inflammatory level	[22]
Th17	Psoriasis	WTAP↑	Cell model; skin	Promotes keratinocytes proliferation, regulates cell cycle progression	[23]
		METTL3	Skin tissue	Downregulation of METTL3 up-regulate AGAP2-AS1, AGAP2-AS1 promotes keratinocyte proliferation through miR-424-5p/AKT/mTOR axis	[24]
	MS	13 m^6A regulators↑	CSF	A novel CSF biomarker for diagnosing MS	[25]
		ALKBH5	$CD4^+$T cell EAE model	Maintains naïve $CD4^+$ T cells to induce adoptive transfer colitis; ALKBH5 deficiency inhibits the IL-17 signaling pathway in $CD4^+$ T cells	[26]
Th22	AITD	ALKBH5; METTL3	Gene	Candidate gene for AITD susceptibility	[27,28]
		METTL3↓	PBMC	Involved in GD by inducing m^6A methylation of SOCS family members	[29]
Treg	SLE	METTL3, WTAP, FTO, ALKBH5, YTHDF2↓	Peripheral blood	ALKBH5 mRNA level is associated with antinucleosome, anti-dsDNA, rash and ulceration, and is a risk factor of SLE	[30]
		ALKBH5, MTEEL14, YTHDF2↓	PBMC	Decreased expression of YTHDF2 is a risk factor for SLE	[31]
		ALKBH5↓	PBMC	May affect apoptosis and T cells proliferation	[32]
		METTL3↓	Peripheral $CD4^+$ T cell	METTL3 promotes $CD4^+$ T cells activation and infuences Treg cells differentiation	[33]
	RA	METTL3*; ALKBH5, FTO, YTHDF2↓	Peripheral blood	Decreased expression of FTO, ALKBH5 and YTHDF2 is a risk factor for RA	[34]
		METTL3↑; METTL14, FTO, ALKBH5, YTHDF1, YTHDF2*	PBMC	METTL3 level is positively associated with disease activity. Overexpression of METTL3 attenuated the inflammatory response induced by LPS in macrophages	[35]
		YTHDF2↓	PBMC	Negatively-correlated with ESR, CRP level; associated with serum RF level and treatment	[36]
		METTL14↓	PBMC; CAIA mice	Correlated negatively with DAS28; knockdown of METTL14 promotes the IL-6 and IL-17 secretion	[37]
		METTL3↑	FLS; AIA animal model	May activate the NF-κB signaling pathway; METTL3 knockdown suppresses the IL-6, MMP-3/9 levels	[38]
		ALKBH5↑	FLS; synovium; CIA model	ALKBH5 knockdown can inhibit the migration, proliferation and invasion of FLSs	[39]
		METTL14↑	CIA model	METTL14 silencing suppresses the LASP1/Src/AKT axis and inhibits FLSs activation	[40]
		ALKBH5↑	FLS; synovium; CIA model	ALKBH5 increase promotes the migration and proliferation of FLSs and inflammation	[41]

(*Continued*)

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Table 2 (Continued).

Subsets	Disease	Enzymes Involved and Its Expression	Sample Source	Function	Reference
Tfh	pSS	METTL3, RBM15, ALKBH5, FTO, YTHDF1, YTHDF2, YTHDF3, YTHDC1, YTHDC2↑	PBMC	May indicate inflammation status and disease activity of pSS Elevated expression of ALKBH5 was a risk factor for pSS	[42]
		ALKBH5, RBMX, RBM15B, YTHDF1↓	Peripheral blood	Widely involved in the autophagy and immune infiltration of pSS	[43]

Note: "↓" means a decrease level compared to the healthy control; "↑" means an increase level compared to the healthy control; "*" indicates similar to the healthy control.

of m^6A-related genes relative to those with RRMS. Dynamic changes in m^6A RNA methylation levels correlate with MS disease progression, enabling early differentiation between PMS and RRMS. Therefore, m^6A RNA methylation level can serve as a novel CSF biomarker for MS diagnosis.[25] Furthermore, while ALKBH5 does not affect T-cell development and function under homeostatic conditions, it controls the ability of naïve $CD4^+$ T-cells to induce autoimmune colitis.

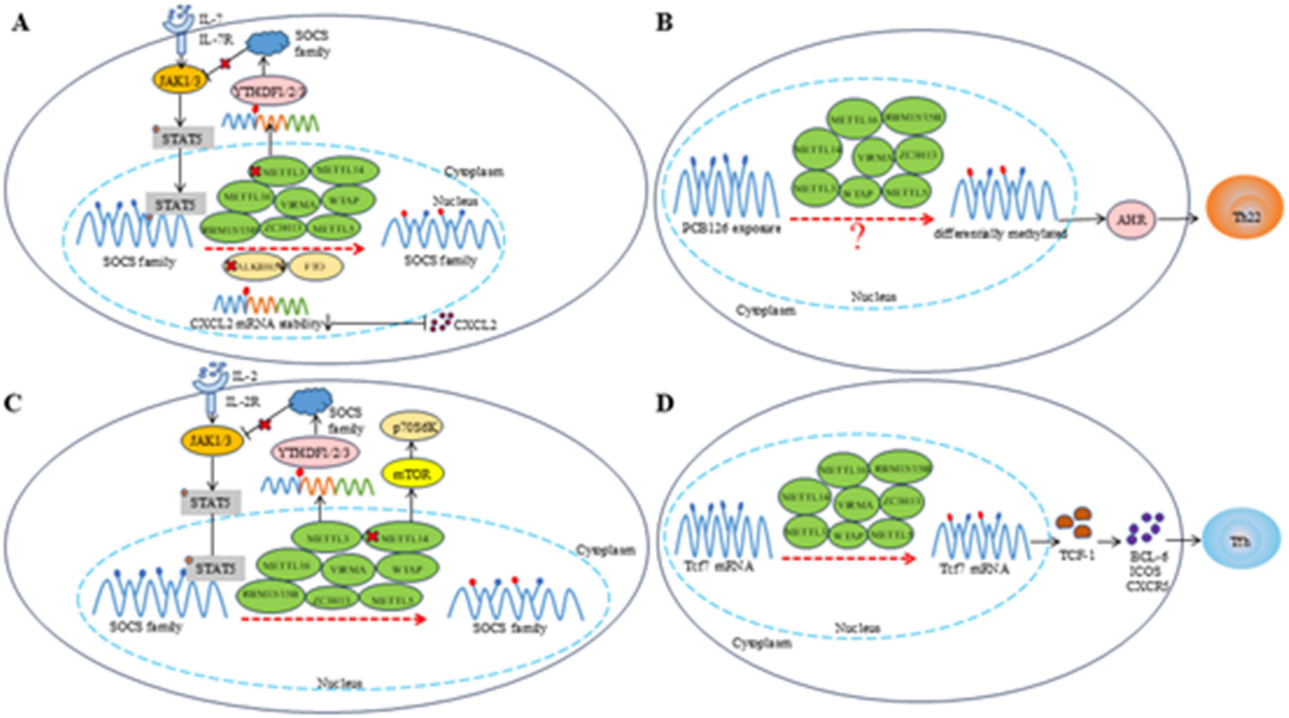

Figure 3 Schematic diagram of m6A modification. (**A**). m^6A modification promotes the proliferation and differentiation of Th1 cells by degrading SOCS mRNA and further activating the IL-7-STAT5 pathway. METTL3 deficiency can enhance the stability of SOCS3 mRNA and reduce the differentiation of Th17 cells, and ALKBH5 deficiency can reduce the stability of CXCL2 and alleviate local infiltration; (**B**). m^6A marked transcripts (AHR) exhibit differential methylation after exposure to a specific environment (PCB126), the exact mechanism of which is not yet clear; (**C**). METTL3 plays a key role in maintaining the inhibitory function of Tregs by degrading SOCS mRNA and activating the IL-2-STAT5 pathway. Mettl14 regulates iTreg inhibition through the mTOR pathway; (**D**). METTL3 stabilizes Tcf7 transcripts through m^6A modification and plays a key role in promoting Tfh cell differentiation.

The absence of *ALKBH5* leads to reduced IFN-γ secretion in the central nervous system (CNS) and inhibits the trafficking of $CD4^+$ T-cells to the CNS.[26] By decreasing m^6A modifications in IFN-γ and CXCL2, *ALKBH5* enhances transcript protein expression and stability, resulting in augmented $CD4^+$ T-cell responses and increased neutrophil infiltration into the CNS. In the commonly used animal model for MS, experimental autoimmune encephalomyelitis (EAE), the absence of *ALKBH5* suppresses the IL-17 signaling pathway in $CD4^+$ T-cells. Specific deletion of *ALKBH5* confers protective effects in EAE.[26,49] Additionally, the loss of *METTL3* in T-cells diminishes Th17 cell differentiation, thereby mitigating the progression of EAE. Concurrently, the absence of *METTL3* in Th17 cells enhances the stability of SOCS3 mRNA, attenuates the expression of CCR5 and IL-17A, reduces the migration of Th17 cells into the CNS, and consequently, alleviates the course of EAE[46](Figure 3A).

Psoriasis is a chronic, recurrent immune-mediated inflammatory skin disease. Both mRNA and protein expression levels of WTAP were elevated in psoriatic cell models and lesioned skin of psoriasis patients, and this overexpression was primarily observed in the epidermal layer rather than the dermal layer.[23] WTAP also affects the secretory function of keratinocytes. Overexpression of *WTAP* leads to increased expression of the inflammatory cytokine IL-1β, while knockdown of *WTAP* results in a decrease in IL-1β. WTAP also promotes keratinocyte proliferation, and excessive keratinocyte proliferation is a hallmark of psoriasis. WTAP may participate in the pathogenesis of psoriasis by accelerating cell cycle progression. Therefore, WTAP could potentially serve as a therapeutic target for psoriasis. Another study revealed methylation differences between uninvolved psoriatic skin, involved psoriatic skin, and healthy control (HC) skin. Specifically, involved psoriatic skin contained the fewest m^6A peaks. Hypomethylated m^6A was enriched in coding sequences (CDSs), 3'UTRs and 5'UTRs, while hypermethylated m^6A was enriched in CDSs and 3'UTRs. Hypermethylation in involved psoriatic was particularly associated with olfactory transduction and cytokine production, while hypomethylation was primarily linked to the Wnt signaling pathway and developmental processes. Interestingly, as gene expression increases, m^6A methylation also increases, further suggesting that m^6A plays a regulatory role in gene expression in involved psoriatic skin.[50] Additionally, the level of long noncoding RNA (lncRNA) AGAP2-AS1 in the skin tissue of psoriasis patients was higher than that in HC individuals. *AGAP2-AS1*, an endogenous competitive RNA, promotes keratinocyte proliferation and inhibits apoptosis. Downregulation of *METTL3* expression increases *AGAP2-AS1* expression in psoriasis patients. *AGAP2-AS1* may promote keratinocyte proliferation through the miR-424-5p/AKT/mTOR axis.[24] Studies have also shown that circular RNA (circRNA) Hsa_circ_0004287 is upregulated in PBMCs of patients with AD and psoriasis. In vitro inhibition of Hsa_circ_0004287 in macrophages upregulates IL-6, IL-1β, and TNF-α. Nuclear-localized circRNAs can function through interactions with their host genes. Knockdown of Hsa_circ_0004287 promotes the expression of its host gene *MALAT1*. Hsa_circ_0004287 binds to *IGF2BP3* in an m^6A-dependent manner, reducing *MALAT1* stability, thereby inhibiting macrophage activation and suppressing psoriasis progression.[51] In summary, m^6A methylation modification plays a crucial role in the pathogenesis and progression of both MS and psoriasis. These findings not only suggest novel therapeutic strategies targeting m^6A regulators (eg, WTAP or METTL3) but also indicate the potential of m^6A methylation levels as diagnostic biomarkers for MS.

Role of m^6A Modification in Th22-Related Autoimmune Diseases

AITD is considered an organ-specific autoimmune disease, in which thyroid autoantibodies can be detected in the blood of patients, including Graves' disease and Hashimoto's thyroiditis. Five genetic variations of *ALKBH5* have been detected in patients with GD and HT, suggesting that *ALKBH5* and *METTL3* may be susceptible candidate genes for GD and HT.[27,28] High-throughput microarray analysis has revealed abnormal expression of SOCS molecules and *METTL3* in $CD4^+$ T cells of GD patients. Upon *METTL3* knockdown, the expression of certain SOCS family members increases, indicating that *METTL3* may be involved in the pathogenesis of GD by inducing m^6A methylation of SOCS mRNA.[29] These studies collectively implicate m^6A methylation in the etiology of AITD, and Th22 cells are also known to contribute to the disease progression of AITD.[52,53] The transcription factor aryl hydrocarbon receptor (AhR) notably promotes the differentiation of naïve $CD4^+$ T cells into Th22 cells[54,55] (Figure 3B). Studies have shown that changes in m^6A levels can affect the expression patterns of developmental genes, and m^6A-marked transcripts undergo differential methylation upon exposure to certain environments. These transcripts include those activated by AHR agonists.

Currently, there is limited research directly linking m^{6}A to Th22 cells, necessitating further investigation to explore the specific mechanisms.

Role of m^{6}A Modification in Treg-Related Autoimmune Diseases

SLE is an immune disease with complex progression and diverse clinical manifestations. lncRNAs are involved in regulating the development and pathogenesis of SLE, and abnormal expression of m^{6}A-related lncRNAs was associated with the clinical manifestations of SLE patients.[56] circRNA represents a novel type of non-coding RNA, among which circGARS was specifically overexpressed in SLE. By binding to microRNA-19a (miR-19a), circGARS downregulates the expression of YTHDF2, modulates the immune response through the NF-κB pathway, downregulates TNFAIP3 expression, and thereby affects the progression of SLE.[57] Additionally, bioinformatics analysis suggests that the key regulatory factor of m^{6}A (IGFBP3) and two immune genes (*IDO1* and *CD14*) may be beneficial for the diagnosis and treatment of SLE.[58] Studies have shown significantly reduced mRNA levels of METTL3, ALKBH5, YTHDF2, and FTO in the peripheral whole blood of SLE patients.[30] Other research indicates lower levels of ALKBH5, METTL14, and YTHDF2 mRNA in the PBMCs of SLE patients compared to HCs. Decreased ALKBH5 mRNA correlates with CRP and fever. The reduced expression of YTHDF2 in PBMCs of SLE patients is a risk factor for SLE.[31] One of the key features of SLE is the production of anti-double-stranded DNA antibodies (anti-dsDNA). ALKBH5 mRNA levels were inversely correlated with anti-dsDNA antibody levels, making ALKBH5 a risk factor for SLE pathogenesis.[30] Both T cells and PBMCs from SLE patients show reduced ALKBH5 mRNA levels. Overexpression of ALKBH5 does not affect the T cell cycle but can inhibit T cell proliferation and promote apoptosis. The low levels of ALKBH5 in SLE patients may contribute to SLE pathogenesis by influencing T cell proliferation and apoptosis.[32] Furthermore, both the post-transcriptional RNA modifification enzyme 5-methylcytosine (m5C) and *NSUN2* expression were reduced in CD4$^+$ T cells of SLE patients.[59] METTL3 expression was also downregulated in CD4$^+$ T cells of SLE patients. Inhibiting METTL3 in SRBC-immunized mice significantly promotes CD4$^+$ T cell activation, weakens Treg and Tfh cell differentiation, and increases the proportion of Th1 and Th17 cells, with a particularly pronounced effect on Treg cells. Suppression of METTL3 elevates antibody production in a chronic graft-versus-host disease (cGVHD) mouse model, exacerbating the lupus-like phenotype. METTL3-mediated m^{6}A modification of Foxp3 mRNA maintains Foxp3 protein expression and transcript stability.[33]

RA is a chronic immune disease characterized by synovial inflammation and progressive destruction of articular cartilage. The imbalance between Treg and Th17 cells is one of the important factors affecting the progression of RA. In recent years, with the deepening of research on m^{6}A, there have been many reports on m^{6}A-related factors in RA. Jiang et al obtained the transcriptional profile of the fibroblast-like synoviocyte cell line MH7A through high-throughput sequencing, suggesting that m^{6}A modification was related to the occurrence of RA.[60] The total m^{6}A content in the peripheral blood of RA patients was remarkably increased, while the mRNA expression of FTO, ALKBH5, and YTHDF2 was significantly reduced. The degree of reduction was correlated with disease activity, and there was no distinct difference in METTL3 compared with the HC group.[34] The expression of METTL3 in PBMCs of RA patients was notably increased, while there was no obvious difference in METTL14 and YTHDF2 compared to the HC group.[35] Other studies have shown that the mRNA expression of YTHDF2 in PBMCs of RA patients was noticeably lower than that of HC group.[36] Tang et al found that the levels of m^{6}A and METTL14 in PBMCs of active RA patients were lower than those patients in remission and HCs. Knockdown of *METTL14* could down-regulate m^{6}A and promote the secretion of IL-6 and IL-17.[37] These inconsistencies in research results may be due to different cell types, but the conclusions were consistent regarding the impact of m^{6}A on synovial tissue and fibroblast-like synoviocytes (FLS) in RA. Current research results suggest that m^{6}A-related enzymes are involved in synovial hyperplasia and promote the proliferation, migration, and invasion of FLS. Knockdown of *ALKBH5* inhibits these functions of RA FLSs, while overexpression of *ALKBH5* shows the opposite effect. This phenomenon has also been confirmed in the CIA mouse model.[38,39,41,61] Under hypoxic conditions, the expression of ALKBH5 in FLS increases, and the HIF1α/2α-ALKBH5-CH25H pathway may be key to FLS attack and inflammation in this environment.[41] METTL14 may promote FLS activation through the LASP1/SRC/AKT signaling pathway and participate in related inflammatory responses.[40] In addition, in RA FLS, modular calcium-binding protein 2 (SMOC2) increases obviously. SMOC2 leads to increased levels of myosin 1c (MyO1C) through

ALKBH5-mediated m^{6}A modification, which causes RA FLS migration and invasion.[62] m^{6}A can also mediate the binding of lncRNA MAPKAPK5-AS1 to miR-146a-3p, affecting the inflammatory response and apoptosis of co-cultured RA-FLSs by targeting SIRT1.[63] The lack of METTL3 results in a decrease in the differentiation of naive T cells into Th1 and Th17 cells but has little effect on the number of Treg cells. The lack of METTL3 in Treg cells leads to an increase in SOCS expression, inhibiting the IL-2-STAT5 signaling pathway, which is crucial for Treg cells to exert their suppressive function.[46,64] Treg cells are divided into many different types, and Induced regulatory T cells (iTregs) can be formed in vitro. The treatment of certain autoimmune diseases using iTregs has attracted increasing attention from researchers. However, iTregs cannot maintain the inhibitory activity and expression of FoxP3. Zhao et al's research found that METTL14 can maintain the immunosuppressive function of iTregs and may regulate the inhibitory function through the mTOR pathway, which plays a significant role in maintaining the function and stability of iTregs to sustain FOXP3 expression[65] (Figure 3C). Taken together, m^{6}A methylation participates in disease pathogenesis by regulating immune-inflammatory responses and modulating T cell quantity and function. Despite discrepancies in research findings, m^{6}A methylation plays a pivotal regulatory role in both SLE and RA.

Role of m^{6}A Modification in Tfh-Related Autoimmune Diseases

pSS is a chronic autoimmune disease characterized by the hypofunction or loss of function of the human exocrine glands, especially the salivary and lacrimal glands.[66] One of the characteristics of pSS is the production of autoantibodies anti-SSA and anti-SSB. It has been reported that Tfh cells are involved in the pathogenesis of pSS.[67] Moreover, Tfh cells are a crucial component of humoral immunity. METTL3 is essential for maintaining the expression of characteristic genes in Tfh cells, including *CXCR5, BCL-6, ICOS*, and *Tcf7*, and plays a significant role in the proliferation and survival of Tfh cells[68] (Figure 3D). Some studies have analyzed the GEO database and found downregulated expression of ALKBH5, YTHDF1, RBMX, and RBM15B in the peripheral blood of pSS patients, as well as downregulated expression of ALKBH5, YTHDF1, METTL3, and RBM15B in labial gland tissue. Additionally, METTL3 and ALKBH5 were closely associated with the infiltrating immune cells such as T cells, indicating that m^{6}A methylation was involved in the autophagy processes and immune infiltration of pSS.[43] Other research has shown significantly elevated expression of METTL3, YTHDF1, YTHDF2, YTHDF3, ALKBH5, FTO, YTHDC1, and YTHDC2 in the peripheral blood of pSS patients compared to HCs. Elevated levels of ALKBH5 were a risk factor for pSS. m^{6}A methyltransferases play a role in the autoimmune initiation of pSS by stimulating ISG15 to activate the type I IFN signaling pathway.[42] He et al analyzed 23 m^{6}A-mediated RNA modification patterns in blood and parotid gland samples from pSS patients using bioinformatics. They found differential expression of m^{6}A regulators between the pSS group and the HC group. FMR1 was most remarkably expressed in blood samples, while FMR1 and HNRNPC were most notably expressed in parotid gland samples. m^{6}A regulators may play a role in immune cell infiltration in pSS parotid gland tissue.[69] In summary, m^{6}A methylation may become a new therapeutic target for pSS.

Clinical Value of m^{6}A Modifications for Autoimmune Diseases

The diverse manifestations of m^{6}A methylation modification in various autoimmune diseases and its significant role in the interaction with Th cells will promote research based on m^{6}A for diagnosis and treatment (Figure 3A–D). As discussed above, m^{6}A-related enzymes (METTL3, METTL14, FTO, ALKBH5, WTAP) exhibit paradoxical roles in autoimmune diseases, either promoting or inhibiting disease progression. The effects of m^{6}A modification appear to vary across different animal models. For instance, reducing METTL3 or METTL14 levels in T cells can produce opposing outcomes, likely due to differences in animal models and signaling pathways involved.[45,46] A similar phenomenon has been observed in RA research. Knockdown of METTL14 in the synovium of mice and rats also yielded contrasting effects.[37,40] Even when analyzing PBMCs from the same disease, inconsistent levels of m^{6}A-related enzymes suggest that m^{6}A modification may function differently depending on disease stage or activity.[36,37] Furthermore, the immune microenvironment may influence m^{6}A modification. For example, hypoxia upregulates ALKBH5 expression in FLSs. Thus, the function of m^{6}A enzymes likely depends on cellular context, disease status, and molecular mechanisms, highlighting the complexity and plasticity of epigenetic regulatory networks.

As mentioned earlier, the expression of m^{6}A methylation levels in IBD, MS, Psoriasis, AITD, SLE, RA, and pSS differs from that of the HC group. This differential expression makes it possible to use the detection of m^{6}A methylation levels in peripheral blood for early disease diagnosis. For instance, the level of m^{6}A RNA methylation can distinguish between PMS and RRMS early in the disease process, serving as a CSF marker for MS diagnosis.[25] The hypermethylated circRNA hsa_circ_0007259 activates the STAT3 signaling pathway via hsa_miR-21-5p. This circRNA plays a role in the pathophysiology of RA and can serve as a valuable biomarker for RA diagnosis.[70] Furthermore, researchers have identified five differentially expressed m^{6}A regulatory factors between healthy individuals and RA patients using the GEO database. Through software analysis, they constructed an m^{6}Asig system capable of distinguishing between RA C1 and C2 subtypes (associated with higher inflammatory responses). This system could potentially become a biomarker for inflammatory activity in RA.[71] Although researchers have made some progress in exploring the diagnostic value of m^{6}A methylation in early-stage diseases, further studies are still needed to verify the feasibility and accuracy of these findings.

Beyond diagnostics, m^{6}A modification impacts Th cell differentiation, function, and cytokine secretion, while interfering with RNA splicing, export, translation, and degradation through methyltransferases, demethylases, and binding proteins. This makes it possible to develop agonists or inhibitors of these enzymes and proteins to control disease progression. In 2012, some small-molecule inhibitors of FTO demethylase were discovered, with the natural product rhein emerging as the most potent by competitively binding to the FTO active site.[72] The natural compound radicicol also acts as an FTO inhibitor, exhibiting dose-dependent inhibition of FTO demethylation activity.[73] Furthermore, based on the protein-ligand interaction structure of FTO, researchers have identified two small-molecule inhibitors of FTO.[74,75] Interestingly, entacapone, a drug used in combination with other medications to treat Parkinson's disease, has also been found to inhibit FTO, which has been verified in experimental animals.[76] Additionally, a non-steroidal anti-inflammatory drug Meclofenamic acid (MA) has been discovered as a highly selective inhibitor of FTO, inhibiting its demethylation of m^{6}A. Mechanistic studies reveal that MA selectively inhibits FTO demethylation through competitive binding with m^{6}A-containing substrates, exhibiting greater potency than ALKBH5.[77] Currently, most reported inhibitors target FTO, possibly due to its early discovery as a demethylase in mammals. Researchers have screened two series of adenosine derivatives through high-throughput docking with METTL3, identifying ligands with good performance that selectively inhibit METTL3, although further studies are needed to confirm their specific effects.[78] Chinese Ecliptae herba extract and its main component wedelolactone may enhance osteoblastogenesis of bone marrow mesenchymal stem cells (BMSCs) by targeting METTL3-mediated m^{6}A methylation of VEGF-A and HIF-1α.[79] Paracetamol can alter total m^{6}A levels in IL-1β-treated chondrocytes (mimicking an inflammatory state), upregulating ALKBH5, downregulating METTL3, and inhibiting the secretion of inflammatory cytokines such as IL-6 and IL-8.[80] Besides the use of natural compounds or small molecules to modulate the expression of m^{6}A regulatory factors in disease treatment, the modification of these factors at the molecular level, as mentioned earlier in this review, also exhibits significant regulatory effects. While inhibitors of other methyltransferases have not been reported yet, these findings provide new insights and directions for drug development. Overall, m^{6}A modification has the potential to offer new insights for the diagnosis of autoimmune diseases and the development of clinical drugs.

Challenges of m^{6}A Methylation in Autoimmune Diseases

Accumulating evidence suggests that dynamic and reversible m^{6}A methylation affects multiple aspects of immune responses and Th cells, such as development, differentiation, migration, cytokine secretion, and inflammatory responses. Based on these functions, m^{6}A methylation has been linked to various immune-related diseases, including viral infections, inflammation, autoimmune diseases, and tumorigenesis.[81,82] So far, the role of m^{6}A methylation in tumorigenesis has garnered significant attention, leading researchers to conduct numerous studies and yield encouraging results. For instance, targeting METTL3 has demonstrated positive therapeutic effects in multiple tumors, including acute myeloid leukemia, breast cancer, lung cancer, liver cancer, and stomach cancer.[83,84] However, despite autoimmune diseases also being one of the significant health issues worldwide, research on the role of m^{6}A methylation in the development and progression of autoimmune diseases, therapeutic potential, and interaction with Th cells is still in its infancy. It is hoped that future research will further untangle the upstream mechanisms of these methylation enzymes,

and interventions targeting the upstream factors of these enzymatic modifications have the potential to become innovative methods for improving disease treatment. Although some progress has been made in understanding the underlying mechanisms of m^6A modification in the pathological and biological processes of autoimmune diseases, detailed studies on the role of m^6A modification in clinical diagnosis, treatment, and prognosis remain inadequate. Furthermore, many enzymes are involved in the entire methylation process, and while current research has primarily focused on METTL3, METTL14, WTAP, FTO, and ALKBH5, there is a paucity of studies on enzymes that read m^6A modifications. m^6A readers have a significant impact on the stability of the target mRNA regulated by methylation, highlighting the need for more comprehensive research in this area.

Conclusion and Prospective

With the advancement of molecular biology techniques, our understanding of disease mechanisms has gradually extended to genetic and epigenetic processes. Consequently, the role of m^6A methylation modification in autoimmune diseases has been uncovered with the development of life sciences and detection technology. In this review, we summarize the latest research progress on m^6A methylation in IBD, MS, Psoriasis, AITD, SLE, RA, and pSS, elucidating its impact on Th cell development, differentiation, and cytokine secretion in these diseases. Taken together, the m^6A modification has a critical impact on differentiation and function of Th cells that are involved into the pathogenesis of various autoimmune diseases, which deserves further investigation and discussion, and targeting m^6A regulatory factors may emerge as a new strategy for the treatment of autoimmune diseases.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis 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 that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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