Research Article

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The indispensability of methyltransferase-like 3 in the immune system: From maintaining homeostasis to driving function.

MingfuZhang[a#],ZhixianGou[c#],YiQu[a,b],XiaojuanSu[a,b*]

a. Department of Pediatrics/Key Laboratory of Birth Defects and Related Diseases of Women and Children (Ministry of Education), West China Second University Hospital, Sichuan University, Chengdu 610041, China
b. NHC Key Laboratory of Chronobiology (Sichuan University), Chengdu 610041, China
c. Department of Pediatrics, School of Clinical Medicine & the First Affiliated Hospital of Chengdu Medical College, Chengdu 610500, China

# These authors contributed equally

Corresponding author

Xiaojuan Su,
Department of Pediatrics/Key Laboratory of Birth Defects and Related Diseases of Women and Children (Ministry of Education), West China Second University Hospital, Sichuan University, Chengdu 610041, China.
Tel : +86-19980479677,
Fax : +86-28-85559065,
Email : xiaojuansu2017@163.com

ORCID: 0000-0001-5544-554X

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ABSTRACT

Methyltransferase-like 3(METTL3), recognized as the primary N^6-methyladenosine methyltransferase, influences cellular functions such as proliferation, migration, invasion, differentiation, and fate determination by regulating gene expression. Recent studies have highlighted the indispensability of METTL3 in various immune cells such as hematopoietic stem/progenitor cells, innate immune cells (monocytes, macrophages, dendritic cells), and adaptive immune cells (thymic epithelial cell, T cells, natural killer cells). However, a comprehensive summary and analysis of these findings to elucidate the relationship between METTL3 and the immune system is yet to be undertaken. Therefore, in this review, we systematically collate reports detailing the mechanism underlying the role of METTL3 in regulating various immune processes and examine the modification of METTL3 and its potential implications. This review suggests that METTL3 plays an essential role in the immune system, ranging from maintaining homeostasis to regulating functions. Collectively, this review provides a comprehensive analysis of the relationship between METTL3 and the immune system, serving convenient researchers to understand the frontiers of immunological research and facilitate future clinical applications.

Keywords : methyltransferase-like 3, hematopoietic stem/progenitor cells, innate immune cells, adaptive immune cells, immune homeostasis

1. INTRODUCTION

Functioning as the primary safeguard against infectious agents in the human body, the immune system encompasses various cells, molecules, tissues, and organs [1, 2]. Immune cells originate as precursors in the bone marrow and undergo transformative stages at various sites throughout the body to reach maturity [2-4]. Distributed uniquely throughout the body, each type of cell and molecule serves specific functions in response to infections, intercellular communication, and problem-solving, employing various mechanisms, including inhibiting tumor growth, initiating tissue repair processes, and regulating the immune system to promote overall health [5-7]. Therefore, a comprehensive understanding of the intricate mechanisms underlying the functional network of the immune system is invaluable for researchers to address immunological problems, spanning from infections to cancers. Currently, epigenetics represents the cutting-edge approach for mechanism study of gene expression [8, 9].

RNA N^6-methyladenosine (m^6A) modification is a distinctive mechanism of epigenetic regulation, which has been extensively reported to play pivotal roles in modulating cellular biological functions, including proliferation, differentiation, and fate determination, alongside other biological activities [10-15]. m^6A modification intricately regulates the splicing,

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translocation, stability, and translation of RNA through dynamic and reversible interactions with m^{6}A-specific regulatory proteins, such as methyltransferases, demethylases, and binding proteins [16-23]. Among these m^{6}A-specific regulatory proteins, methyltransferase-like (METTL3) is the most indispensable and contributing component, which is not only the first identified but also possesses catalytic activity in RNA m^{6}A modification [24]. A growing number of studies have demonstrated the involvement of METTL3 in the immune system, highlighting its crucial role in regulating various physiological events. Specifically, METTL3 functions in both the innate and adaptive immune cells. Although the roles and mechanisms of METTL3 in the immune system have been extensively investigated, reviews that systematically interpret their relationships are lacking. Therefore, this review focuses on summarizing findings from studies that report the roles and mechanisms of METTL3 in immune cells, thereby highlighting the prospective implications of METTL3 in the immune system alongside future research directions. Furthermore, this review provides an updated compilation of the role of METTL3 in the immune system, serving to facilitate future clinical applications and provide researchers with insights into the frontiers of immunological research (**Figure1**).

Figure 1

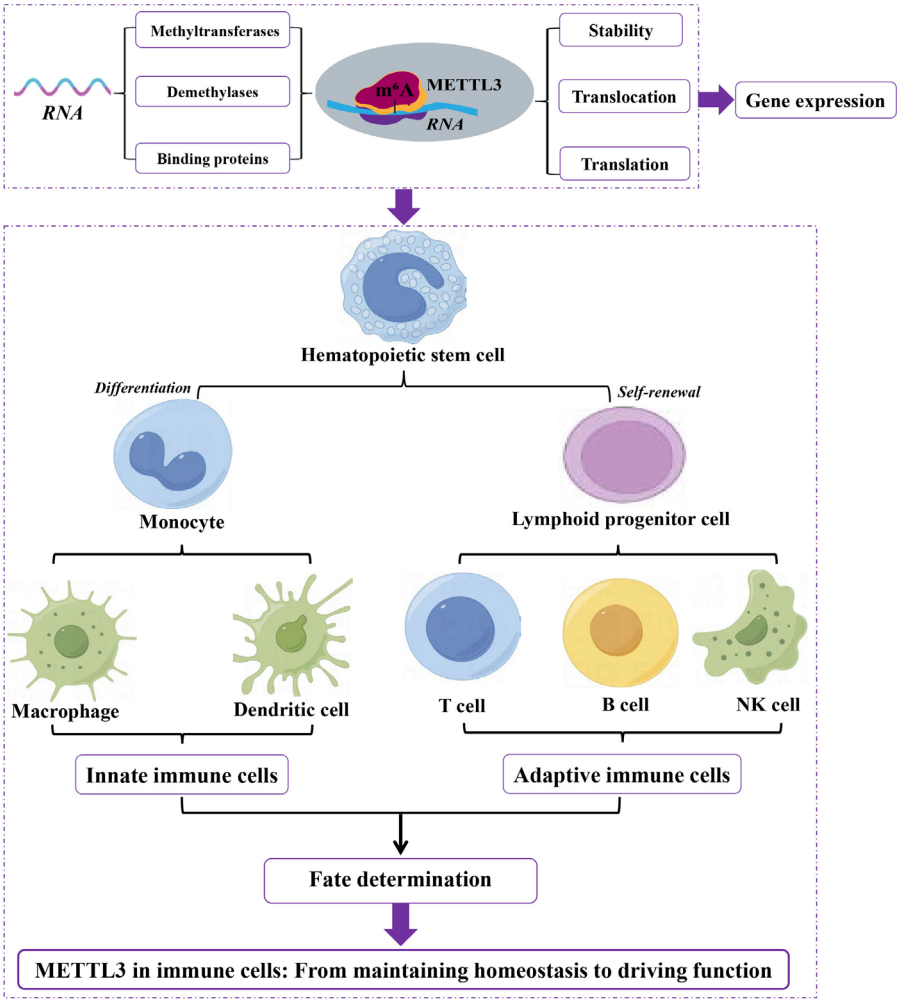


Figure 1 : Association between METTL3 and the immune system

Roles and mechanisms by which METTL3 regulates immune cellular functions were analyzed, providing insights into the research limitations and potential clinical applications of METTL3 in the immune system. This study also highlights the future perspectives of METTL3. Methyltransferase-like 3(METTL3). N6-methyladenosine (m6A).

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2. RELATIONSHIP BETWEEN METTL3 AND THE IMMUNE SYSTEM

The immune system, which combats microbes, is primarily divided into two distinct reactions: innate and adaptive immunity [25]. Innate immunity is a natural defense mechanism that confers protection from birth onwards [25]. For example, the skin acts as an effective barrier for the body, protecting against bacteria, viruses, and other disease-causing pathogens [26]. Conversely, adaptive immunity, which is acquired after birth, is honed over a lifetime through interactions with infectious agents or vaccinations [26]. Both types of immune responses require specific cells, which can be derived from stem cells, to execute their functions [26].

2.1 Roles and mechanisms of METTL3 in hematopoietic stem cells

Hematopoietic stem/progenitor cells (HSPCs), the predominant progenitor cells located in the bone marrow, can generate all types of blood cells, including those of myeloid and lymphoid lineages, while also possessing self-renewal capacity [27].

Recent studies have highlighted the crucial role of METTL3-mediated RNA m^{6}A modification in regulating HSPC function. For instance, during zebrafish embryogenesis, deletion of *METTL3* in embryos reduces m6A levels by promoting the decay of the arterial endothelial genes *notch1a* and *rhoca* in a YTH N6-methyladenosine RNA binding protein 2 (YTHDF2)-dependent manner, which subsequently activates the Notch signaling to block HSPC production [28]. Collectively, these findings demonstrate that METTL3-mediated m6A modification functions in the process of endothelial-to-hematopoietic transition to specify the earliest HSPCs [28]. Additionally, Gao et al. [29] demonstrated that specific deletion of METTL3 in the liver of murine fetuses results in hematopoietic deficiency and increases perinatal mortality. METTL3 activates the Mavs or RNase L signaling pathways, precipitating an aberrant innate immune response [29]. However, under pathological conditions of acute myeloid leukemia (AML), a converse function is reported, wherein the levels of METTL3 are elevated compared to those in healthy HSPCs [30]. Intriguingly, silencing METTL3 in HSPCs of human AML promotes HSPC differentiation by increasing p-AKT levels and facilitates apoptosis by promoting the mRNA translation of *c-MYC*, *BCL2*, and phosphatase and tensin homolog (*PTEN*) while inhibiting proliferation [30]. These findings suggest the detrimental role of METTL3 in the HSPCs of patients with AML, indicating its potential as a therapeutic target. In summary, the available studies highlight the pivotal role of METTL3 in regulating HSPC function. Although relatively elevated expression levels facilitate physiological differentiation, they may also contribute to pathological events.

2.2 Roles and mechanisms of METTL3 in innate immune cells

Common myeloid progenitor stem cells, which reside in the bone marrow, serve as precursors to generate various innate immune cells, including but not limited to neutrophils, eosinophils, basophils, mast cells, monocytes, dendritic cells (DCs), and macrophages [31]. These primary responders promptly act against infections, such as inflammation [25]. Therefore, maintaining their normal function is essential for an effective innate immune response. Given that METTL3 plays a crucial role in regulating the biological functions of various cells, numerous studies have reported its significance in these innate immune cells. Innate lymphoid cells (ILCs) can quickly switch from a quiescent state to an active state and rapidly produce effector molecules that provide critical early immune protection [32]. Zhang et al. [33] showed that deletion of METTL3 significantly diminishes ILC2 proliferation, migration, and effector cytokine production and results in impaired anti-helminth immunity. Importantly, the gene encoding the transcription factor *Gata3* is highly m^{6}A methylated in ILC2s [33]. Moreover, demethylation of m^{6}A weakens *Gata3* mRNA stability and impairs *Gata3* upregulation and ILC2 activation [33]. Notably, METTL3-mediated m^{6}A modification is essential for ILC state transition and immune response.

2.2.1 METTL3 triggers monocyte inflammation

Monocytes, which reside primarily in the bloodstream and tissues, can manipulate and respond to stimuli [34]. Zhang et al.[35] reported a mechanism of METTL3-mediated RNA m^{6}A that triggers monocyte inflammation in response to oxidized low-density lipoprotein (ox-LDL). This intricate process involves the coordinated actions of METTL3 and YTHDF2, which collaborate to promote peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PGC-1α)* mRNA degradation, leading to decreased PGC-1α expression and culminating in an escalated inflammatory response [35]. In addition to downregulating PGC-1α expression, this coordination also suppresses the expression levels of cytochrome c and NADH: ubiquinone oxidoreductase subunit C2 (NDUFC2), as well as ATP production and oxygen consumption rate [35]. Consequently, this cascade induces the accumulation of reactive oxygen species (ROS) in both the cellular and mitochondrial compartments, thereby enhancing pro-inflammatory cytokines in inflammatory monocytes [35]. These findings suggest that the METTL3/YTHDF2/PGC-1α axis plays a pivotal role in regulating monocyte-mediated inflammatory responses (**Figure 2**).

2.2.2 METTL3 functions in macrophage phenotype switch

Macrophages are crucial regulators of the innate immune and are also the major producers of inflammatory cytokines once activated by pathogen-associated molecular patterns

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[36]. Monocytes can differentiate into distinct macrophage phenotypes with remarkable phagocytic and bacterial degradation capabilities [37]. Upon activation by an external stimulus, monocytes collaborate with macrophages to induce an immune response by signaling other immune cells [38].

In addition to regulating the inflammatory response of monocytes, METTL3 is also crucial for maintaining macrophage function [39]. Liu et al. [40] found an upregulation of METTL3 during mouse M1 macrophage polarization. Moreover, METTL3 overexpression not only facilitates M1 macrophage polarization but also attenuates M2 polarization [40]. Conversely, METTL3 downregulation leads to contrasting effects. Mechanically, METTL3 functions by methylating the signal transducer and activator of transcription 1 (*STAT1*) mRNA at its coding sequence and 3'-untranslated region to enhance *STAT1* mRNA stability and subsequently upregulates STAT1 expression, which controls M1 macrophage polarization [40]. These results suggest that METTL3 plays a crucial role in promoting macrophage polarization toward the M1 pro-inflammatory phenotype by targeting STAT1 mRNA, rendering it a promising anti-inflammatory target in inflammation-induced diseases. For example, rheumatoid arthritis (RA) is strongly associated with monocyte-macrophage inflammation [41, 42]. Wang et al.[43] demonstrated that METTL3 expression is significantly upregulated in patients with RA and is positively correlated with C-reactive protein and erythrocyte sedimentation rate, which are markers of RA. METTL3 downregulation alleviates lipopolysaccharide (LPS)-induced inflammatory response in M1 macrophages [43]. Moreover, the impact of METTL3 on LPS-induced macrophage inflammation is closely associated with the NF-κB signaling pathway [43]. Notably, METTL3 promotes M1 pro-inflammatory phenotype activation in macrophages via the NF-κB pathway, highlighting the pivotal role of METTL3 in driving macrophage phenotype switch in RA and its potential utility as a biomarker for this condition.

Similarly, Tong et al. [44] showed that *Mettl3* knockdown in macrophages decreases tumor necrosis factor-α (TNF-α) expression upon LPS stimulation in vitro. Furthermore, mice with a specific knockdown of *Mettl3* in macrophages are more susceptible to bacterial infection and exhibit faster tumor growth [44]. METTL3 deregulation increases the stability and expression of *Irakm*, a negative regulator of toll-like receptor 4 (TLR4) signaling, which subsequently inhibits macrophage-mediated innate immune response to inflammation by deactivating TLR4 signaling [44]. These findings suggest that the METTL3/Irakm/TLR4 signaling pathway represents a novel mechanism for regulating macrophage-mediated innate immune responses, highlighting its clinical applications in immunotherapy. Yin et al. [45] demonstrated that the specific knockdown of *Mettl3* in the myeloid cells of mice leads to tumor progression by promoting the accumulation of M1/M2-like tumor-phenotype macrophage and facilitating the infiltration of regulatory T cell (Treg) into tumors. More importantly, the therapeutic efficacy of programmed cell death 1 (PDL-1) is compromised by the *Mettl3* downregulation, which obstructs the immune checkpoint [45]. This downregulation decreases sprouty-related EVH1 domain containing 2 (*SPRED2*) translation, mediated by YTHDF1, thereby activating the ERK pathway and enhancing NF-kB and STAT3 expression [45]. Therefore, *METTL3* collaborates with YTHDF1 to promote tumor progression and attenuate the efficacy of tumor therapy by targeting the SPRED2/ERK/NF-kB-STAT3 signaling pathway, highlighting the clinical possibilities of using *METTL3* as a target in tumor immunotherapy.

However, in contrast, Cai et al. [46] found that METTL3 attenuates LPS-induced proinflammatory pathways and the ROS generation process. Mechanically, METTL3-YTHDF2 enhances the *Pyk2* mRNA stability, which consequently activates the MAPKs and AKT signaling to promote the generation of proinflammatory cytokines and ROS [46]. The total levels of m^6A and METTL3 are decreased in LPS-stimulated macrophages. *Mettl3* knockdown significantly upregulates proinflammatory cytokines (TNF-α, IL-6, and NO), which enhances the mRNA stability and expression of NOD1 and RIPK2 by interacting with YTHDF1 and YTHDF2, respectively [47]. All findings suggest that METTL3 promotes the LPS-induced inflammatory response in macrophages through mediating m^6A modification on *NOD1* and *RIPK2*. Furthermore, METTL3 has a low expression level in monocyte-derived macrophages from patients with childhood allergic asthma [48]. Conditional knockout of *METTL3* in myeloid cells enhances Th2 cell response and aggravates allergic airway inflammation by facilitating M2 macrophage activation [48]. A low level of METTL3 suppresses PTX3 mRNA degradation and induces PTX3 expression in a YTHDF3-dependent manner [48]. Furthermore, the METTL3/ YTHDF3-PTX3 axis contributes to autophagy maturation in macrophages by modulating STX17 expression and thereby promoting M2 macrophage activation [48]. Notably, METTL3 promotes M2 macrophage activation via regulating the PTX3-STX17 axis, thereby identifying METTL3 as a potential target for controlling allergic asthma.

Macrophages also possess crucial non-immunological functions, such as clearing cellular debris and recycling of deceased cells (such as red blood cells) [38]. These "housekeeping" activities occur independently of immune response activation. METTL3-mediated RNA m^6A modification has been demonstrated to play a crucial role in regulating the intricate functions of macrophages. Zhao et al. [49] demonstrated that ox-LDL-induced DEAD-box helicase 5 (DDX5) upregulation facilitates lipid uptake in macrophages, which is not dependent on either the MAPK or NF-κB pathway. Mechanistically, DDX5 reduces METTL3 modification on macrophage scavenger receptor 1(*MSR1*) mRNA to maintain

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MSR1 stability [49]. Overall, these findings suggest that ox-LDL-induced lipid uptake in macrophages by targeting the DDX5/METTL3/MSR1 axis. Yin et al. [50] found that *Mettl3* deletion in monocyte-derived macrophages reduces the m^{6}A modification on DNA methyltransferase 3A (*Dnmt3a*) mRNA and impairs YTHDF1-mediated *Dnmt3a* translation, which in turn interacts with alpha-tubulin acetyltransferase 1 (*Atat1*) promoter to maintain its expression, improving cognitive function in an amyloid beta (Aβ)-induced Alzheimer's disease (AD) mouse model. Therefore, METTL3 promotes the migration of monocyte-derived macrophages and Aβ clearance by regulating the Dnmt3a-Atat1 axis, ultimately alleviating AD, highlighting that targeting METTL3 is a promising target for AD treatment in the future. Aberrant cross-talk between macrophages and bronchial epithelial cells is essential for the degradation of elastin which contributes to emphysema, in which METTL3 plays a critical role [51]. Xia et al. [51] established that METTL3-mediated m^{6}A modification promotes the production of excess mature microRNA-93 (miR-93) in bronchial epithelial cells, which are then transferred from bronchial epithelial cells into macrophages. In macrophages, miR-93 activates the JNK pathway by targeting dual-specificity phosphatase 2 (*DUSP2*), which elevates matrix metalloproteinase (MMP) 9 and MMP12 and induces elastin degradation, leading to emphysema [51]. Notably, METTL3 is critical for the aberrant cross-talk of epithelium-macrophages in emphysema and, thereby may be used in clinical diagnosis for emphysema (**Figure 2**).

Figure 2

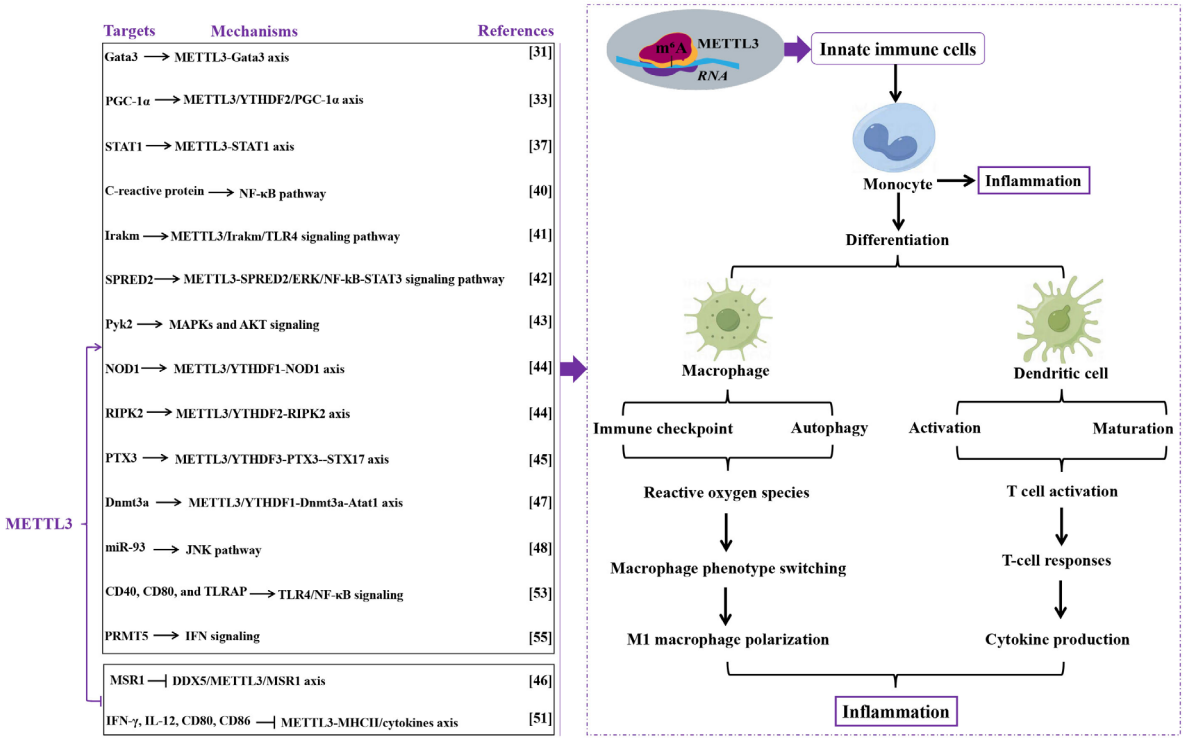


Figure 2 METTL3 regulates the biological functions of innate immune cells

Targets, mechanisms, functions, and outcomes of METTL3 in innate immune cells are analyzed. METTL3 is essential in regulating homeostasis and function through distinct targets and signaling pathways. Methyltransferase-like 3 (METTL3). N6-methyladenosine (m6A). Proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). YTH N6-methyladenosine RNA binding protein (YTHDF). Signal transducer and activator of transcription (STAT). Toll-like receptor 4 (TLR4). Sprouty related EVH1 domain containing 2(SPRED2). DNA methyltransferase 3A (Dnmt3a). Alpha-tubulin acetyltransferase 1 (Atat1). MicroRNA-93 (miR-93). TLR4 signaling adaptor (TIRAP). Protein arginine methyltransferase 5 (PRMT5). Interferon (IFN). DEAD box helicase 5(DDX5). Macrophage scavenger receptor 1(MSR1). Interferon-gamma (IFN-γ). Interleukin (IL). Major histocompatibility complex (MHC).

2.2.3 METTL3 contributes to DC activation and maturation

Monocytes can differentiate into DCs, which are crucial antigen-presenting cells (APCs) [52]. Similar to DCs, APCs play a vital role in breaking down large molecules into "readable" fragments or antigens recognizable by adaptive B or T cells [52]. However, T cell activation is contingent not only upon antigens but also upon the correct major histocompatibility complex (MHC) II expressed on the surface of APCs [53]. The MHC, which acts as a checkpoint, aids immune cells in distinguishing self from non-self [53]. This intricate process is regulated by METTL3-mediated m6A modification on RNAs.

Wu et al. [54] demonstrated that METTL3 knockdown in DCs reduces the level of MHCII costimulatory molecules (CD80, CD86) and DC-related cytokines (IFN-γ, IL-12) and inhibits its ability to activate T-cell proliferation, consistent with the characteristics of tolerogenic DCs. Moreover, METTL3 knockdown in DCs results in Th1/Th2 immune tolerance following mouse heart transplantation and prolongs allograft survival [54]. METTL3 plays an essential role in DC activation and optimal immune function. Another study showed that exosomes derived from METTL3-deficient DCs effectively prevent immune rejection in a mouse cardiac allograft model [55]. Furthermore, Wang et al. [56] reported that Mettl3 knockdown impedes the phenotypic and functional maturation of DCs. The METTL3-mediated m^{6}A methylation facilitates the translation of CD40, CD80, and TLRAP (a TLR4 signaling adaptor) in DCs to promote T cell activation and reinforces cytokine production induced by TLR4/NF-κB signaling [56]. These findings underscore the indispensability of METTL3-mediated m^{6}A modification in enhancing DC activation and maturation, as well as T-cell responses, which are achieved through stimulating the translation of specific immune transcripts.

Blastic plasmacytoid DC neoplasm (BPDCN) is a rare and aggressive hematologic malignancy with poor clinical outcomes [57]. BPDCN is highly associated with the low level of protein arginine methyltransferase 5 (PRMT5) [58]. Rethnam et al. [59] demonstrated that PRMT5 inhibition reduces METTL3 expression, which then activates the interferon (IFN) signaling. This increase in IFN signaling attenuates the sensitivity of METTL3 silencing to PRMT5 inhibition. Notably, the cellular function of METTL3-mediated RNA m^{6}A modification is also affected by PRMT5 inhibition [59]. Overall, these findings indicate that METTL3 and the IFN pathway regulate the response to PRMT5 inhibition in BPDCN, implicating the involvement of METTL3 in BPDCN (**Figure 2**).

In conclusion, these studies demonstrate that maintaining a relatively elevated level of METTL3 is indispensable for the normal function of innate immune cells. Furthermore, targeting METTL3 may be an effective therapeutic approach against diseases caused by immune cell dysfunction.

2.3 Roles and mechanisms of METTL3 in adaptive immune cells

The adaptive immune cells, including B, thymic epithelial, and natural killer (NK) cells, collectively known as lymphocytes, originated from common lymphoid progenitor stem cells [60]. When adaptive immune cells in the lymph nodes recognize microbial fragments from a distant region, they initiate an active immune response by activating, replicating, and exiting the lymph nodes to circulate and combat the pathogen [60]. METTL3-mediated RNA m^{6}A modification has been reported to be involved in regulating the function of adaptive immune cells, thus modulating the adaptive immune response.

2.3.1 METTL3 switches the phenotype of thymic epithelial cells

Zhou et al. [61] demonstrated that adipose-derived mesenchymal stem cells (ADSCs) expedite lymphatic endothelial cell proliferation, migration, and lymphangiogenesis via the METTL3/IGFBP2/VEGF-C pathway. Another study reported that METTL3 overexpression promotes the proliferation of diffuse large B-cell lymphoma cell lines by regulating the m^{6}A levels of the pigment epithelium-derived factor (*PEDF*) [62]. In this study, the expression level of METTL3 is elevated in thymic epithelial tumors (TET), contributing to the development of the TET phenotype by stimulating cell proliferation [62]. In addition, by relocating lncRNA MALAT1 in TET cells, METTL3 enhances the translation rate of c-MYC [63]. These studies demonstrate that the elevated levels of METTL3 contribute to the impairment of progenitor cells in the adaptive immune response, leading to the manifestation of the corresponding diseases (**Figure 3**).

2.3.2 METTL3 maintains the normal functions of T-cell

T cells, which are usually classified into CD4+ T or CD8+ cells, perform various functions, such as eliminating infected cells and activating or recruiting other immune cells [64]. T-cell activation is a highly regulated process, which is modulated by various immune regulatory proteins including cytokines, surface receptors, and co-stimulatory proteins [65, 66]. Li et al. [67] demonstrated that silencing *Mettl3* in mouse T cells disrupts cell homeostasis and differentiation. METTL3 plays a crucial role in regulating T cell homeostasis and differentiation by modulating the IL-7-mediated signal transducer and activator of transcription 5 (STAT5) axis [67]. Specifically, METTL3 downregulation in undifferentiated T cells increases the expression of Socs1, Socs3, and Cish, inhibits IL-7-induced STAT5 activation, and impairs T cell proliferation and differentiation [67]. Additionally, Yao et al. [68] discovered that the specific knockdown of *Mettl3* in CD4+ T cells impedes the normal differentiation of T follicular helper (TFH) cells in mice by inhibiting the expression of transcription factor 7(TCF7), a crucial TFH signature gene, suggesting the indispensable role of METTL3 in regulating the differentiation of TFH cells [68].

As a key component of the adaptive immune system, CD8+ T cells protect the body against various intracellular pathogens and clear autologous malignant cells [69]. Once activated, naive CD8+ T cells (Tn) proliferate rapidly and differentiate into cytotoxic effector cells (Te) with the capacity to produce proinflammatory cytokines such as IFN-γ and TNF-a and expressing cytolytic molecules such as perforin and granule enzymes [70]. Effector CD8+ T cells (Tm) are ascertained as a heterogeneous population that expresses high levels of interleukin 7 receptor [71]. Notably, CD8+ T cells at different

states (Tn, Te, and Tm) show stage-specific molecular, phenotypic, and functional characteristics [72]. Guo et al. [73] demonstrated that *METTL3* deletion specifically in CD8+ T cells weakens its effector cell expansion and terminal differentiation by stabilizing the *Tbx21* transcript in an m^{6}A-dependent manner, subsequently affecting memory formation and the secondary response of CD8+ T cells. This study suggests that METTL3 regulates the stage transition of CD8+ T cells by targeting *Tbx21* and underscores the importance of METTL3 in controlling CD8+ T cell functions.

m6A has been regarded as a novel regulator for CD40 ligand (CD40L) expression in human CD4+ lymphocytes [74]. METTL3 promotes *CD40L* mRNA degradation and affects the expression of CD40L via YTHDF2 recognizing the specific sequences on the *CD40L* mRNA [74]. Therefore, CD40L expression in human primary CD4+ T lymphocytes is regulated via the METTL3/YTHDF2-m^{6}A modification. This study elucidates a new regulatory mechanism in CD4+ T cell activation that can be used to modulate T cell responses in patients with immune-related diseases. Evidence also showed that the alloreactive CD4+ T cells play a central role in allograft rejection. Li et al. [75] found that graft-infiltrating CD4+ T cells show high levels of m^{6}A. Importantly, METTL3 inhibition reduces m^{6}A levels, inhibits T-cell proliferation, and suppresses effector differentiation of polyclonal CD4+ T cells [75]. Inhibition of METTL3 in alloreactive CD4+ T cells suppresses T-cell proliferation and T helper type 1 cell differentiation, arrests the cell cycle in the G0 phase, and elevates cell apoptosis [75]. Moreover, these impaired T-cell responses are accompanied by reduced expression levels of Ki-67, c-Myc, and T-bet [75]. These findings suggest that a low level of METTL3 impairs the T-cell effector program and suppresses alloreactive CD4+ T-cell effector function and differentiation by reducing the expression of Ki-67, c-Myc, and T-bet. Therefore, targeting METTL3 in CD4+ T cells represents an attractive therapeutic approach to prevent allograft rejection. Furthermore, Treg cells are a subset of CD4+ T cells that suppress the activity of other T cells, thereby preventing deleterious immune activation and maintaining tolerance to self-antigens [76]. Tong et al. [77] demonstrated that knockout of *Mettl3* in Treg cells of mice results in several adaptive immune responses such as autoimmune disease. These findings suggest that the inhibitory function of Treg cells is systematically compromised in the absence of m^{6}A RNA modification. The loss of METTL3/m^{6}A in Treg cells leads to the upregulation of *Socs* mRNA levels, which subsequently deactivate the IL-2/STAT5 signaling pathway, a crucial factor for maintaining Treg cell function and stability [77]. These studies suggest that the elevated level of METTL3 is necessary for preserving the normal function of T-cells, which is essential for adaptive immune responses.

T helper 17 (Th17) cells play a pivotal role in host defense and autoimmunity, which commonly consist of two distinct subsets: non-pathogenic and pathogenic Th17 cells [78, 79]. Nonpathogenic Th17 cells are generated in the presence of TGF-β, IL-6, IL-17, and IL-10 [80]. In contrast, IL-23 alone or together with IL-6 induces highly pathogenic Th17 cells that express signature genes including IL-17A, IL-17F, IL-23R, IL-1R, and granulocyte-macrophage colony-stimulating factor (GM-CSF)[81]. METTL3 silencing reduces IL-17A and CCR5 expression by enhancing *SOCS3* mRNA stability in pathogenic Th17 cells, disrupts Th17 cell differentiation and infiltration, and ultimately attenuates experimental autoimmune encephalomyelitis (EAE) development [82]. Therefore, the METTL3-SOCS3 axis regulates pathogenic Th17 cell functions, as well as implies METTL3 as a potential therapeutic target for pathogenic Th17 cell-mediated autoimmune disease. In contrast, Zhao et al. [83] found that METTL3 upregulation ameliorates the development of experimental autoimmune uveitis (EAU) and suppresses pathogenic Th17 cell responses *in vivo* and *in vitro* [83]. Mechanistically, METTL3/YTH domain-containing 2 (YTHDC2) promotes absent, small, or homeotic-like 1 (*ASH1L*) mRNA stability and upregulates ASH1L expression, which subsequently reduces the expression of IL-17 and IL-23R, ultimately impairs pathogenic Th17 responses [83]. Together, these data suggest that METTL3 controls pathogenic Th17 responses, and targeting METTL3 may contribute to human autoimmune disease therapy.

Γδ T cells make key contributions to tissue physiology and immune surveillance primarily through two functional subsets, γδT1 and γδT17[84]. METTL3-mediated m6A methylation controls the functional specification of γδT17 and γδT1 cells by preventing endogenous double-stranded RNA (*dsRNA*) formation and promoting *STAT1* mRNA degradation, which converges to prevent the over-activation of STAT1 signaling and ensuing inhibition of γδT17 [85]. Moreover, deleting *Mettl3* in γδT cells reduces IL-17 production and ameliorates γδT17-mediated psoriasis [85]. In summary, METTL3-mediated m6A methylation orchestrates *STAT1* mRNA stability and *dsRNA* contents to equilibrate γδT1 and γδT17 cells (**Figure 3**).

2.3.3 METTL3 is essential for maintaining NK cell functions

Unlike other adaptive immune cells, NK cells possess innate and adaptive immunity characteristics and are crucial for identifying and eliminating virus-infected cells or tumor cells [86].

A low level of METTL3 and effector molecules in NK cells that infiltrate tumors has been found [87]. The loss of *Mettl3* disrupts NK cell homeostasis and impedes their infiltration and function within the tumor microenvironment [87]. This ultimately promotes tumorigenesis and reduces the survival rates in mice [87]. Mechanistically, METTL3 suppresses SHP2 expression, thereby inhibiting the IL-15-activated AKT and MAPK signaling pathways in NK cells [87]. These findings

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demonstrate that METTL3 is essential for maintaining homeostasis and the tumor immunosurveillance function of NK cells by regulating the METTL3/SHP2/IL-15 axis.

The abnormal overexpression of METTL3 contributes to the pathogenesis and chemoresistance of NK cell-related tumors. For example, nasal-type NK/T-cell lymphoma (NKTCL) is a typical class of non-Hodgkin's lymphoma, which is quite malignant because of its high resistance to chemotherapy [88]. A high level of METTL3 is found in human NKTCL cell lines compared with normal NK cells, which stabilizes staphylococcal nuclease and Tudor domain-containing protein 1 (SND1) mRNA to enhance SND1 expression by depending on YTHDF1 [89]. Importantly, METTL3 impairs the sensitivity of NKTCL cells to *Cisplatin* by targeting *SND1* [89]. Silencing of *METTL3* or *SND1* suppresses tumor growth and enhances *Cisplatin* sensitivity. Taken together, these findings suggest that METTL3 contributes to NKTCL oncogenesis and *Cisplatin* resistance. Consistently, METTL3 regulates invariant NKT (iNKT) cell development and function in an m^{6}A-dependent manner. You et al. [90] showed that deletion of *Mettl3* specifically in CD4+ and CD8+ T cells disturbs the stability of the *Creb1* transcript, which in turn controls the protein and phosphorylation levels of *Creb1*, inhibiting iNKT cell proliferation, differentiation, and cytokine secretion, ultimately causing defects in B16F10 melanoma resistance [90]. Importantly, the deletion of *Creb1* in CD4+ and CD8+ T cells brings about phenotypes of iNKT cells that are similar to *Mettl3* deficiency [90]. Therefore, METTL3 regulates the development of iNKT cells by targeting Creb1 (**Figure 3**).

To sum up, METTL3 is required for maintaining the normal functions of adaptive immune cells, including its indispensable role in switching the phenotype of thymic epithelial cells, as well as essential for maintaining the functions of T-cells and NK cells.

Figure 3

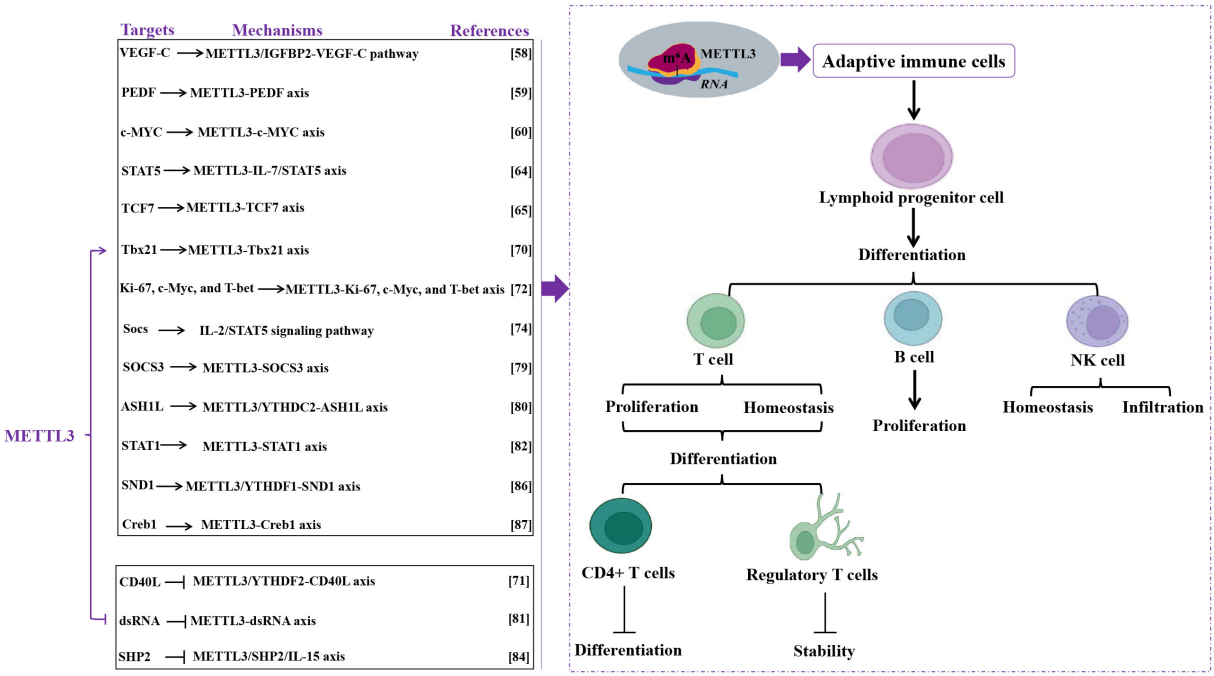


Figure 3 METTL3 maintains the function of adaptive immune cells

Targets, mechanisms, functions, and outcomes of METTL3 in adaptive immune cells are analyzed. METTL3 is essential for maintaining the homeostasis and function of adaptive immune cells through distinct targets and signaling pathways. Methyltransferase-like 3 (METTL3). N6-methyladenosine (m6A). Vascular endothelial growth factor (VEGF). Insulin-like growth factor 2 mRNA binding protein (IGFBP). Pigment epithelium-derived factor (PEDF) Signal transducer and activator of transcription (STAT). Interleukin (IL). Absent, small, or homeotic-like 1 (ASH1L). YTH domain-containing 2 (YTHDC2). Staphylococcal nuclease and Tudor domain-containing protein 1 (SND1). Double-stranded RNA (dsRNA). CD40 ligand (CD40L). Natural killer (NK).

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3. DISCUSSION

RNA m^{6}A modification is the most abundant form of post-transcriptional epigenetic modification in eukaryotes [10]. It functions in various cells and plays a crucial role in their biological processes [10]. METTL3, as the dominant component of m^{6}A, has specific catalytic capabilities that enable it to exert the effects of m^{6}A modification on RNA metabolism, encompassing processing, nucleosynthesis, translation, and even decay [91]. Owing to the significant advancements in m^{6}A RNA sequencing, the roles and mechanisms of m^{6}A modification in various normal immune system processes have been extensively explored. Owing to the wide range of investigations on METTL3 in the immune system but the notable absence of reviews, we present a comprehensive summary and analysis of these processes, which entails the functions and mechanisms of METTL3 in the immune system. Our analysis shows that METTL3 is indispensable for regulating the homeostasis and normal functioning of the immune system. Maintaining METTL3 at relatively elevated levels is critical for the normal functioning of innate immune cells, including monocytes, DCs, and macrophages. Moreover, a similar relationship is observed between METTL3 and the adaptive immune cells, including lymphatic endothelial, T, and NK cells, indicating that relatively elevated levels of METTL3 are beneficial for their normal functioning through various targets and signaling pathways. Therefore, based on these findings, we propose that the dysregulation of METTL3 may serve as an underlying trigger for immune system disorders. Consequently, targeting METTL3 would be a promising approach for the diagnosis, prognosis, and treatment of immune cell dysfunction-related disorders. However, in HSPCs, although relatively elevated expression levels of METTL3 contribute to physiological differentiation, a conclusive stance is challenging to establish. This is because of the limited number of original publications on METTL3 in HSPCs, which present slightly contrasting conclusions. Similar conditions are also found in monocytes and thymic epithelial cells. Therefore, the formation of firm conclusions remains elusive, underscoring the need for additional studies to bridge these gaps. Besides, studies on the relationship between METTL3 and B cells are lacking. Moreover, the dearth of studies conducted in clinical settings to confirm the relevance of METTL3 in HSPCs, monocytes, thymic epithelial cells, and B, and T cells is also apparent. Therefore, future research should prioritize these areas of investigation.

Cumulatively, this review suggests that METTL3 operates in a nearly identical manner across innate and adaptive immune cells. In each case, METTL3 is essential for regulating homeostasis and functioning through distinct targets and signaling pathways. However, studies on the relationship between METTL3 and some immune cells such as HSPCs, monocytes, thymic epithelial cells, B, and T cells remain limited. Moreover, although we have garnered insights into the relevance of METTL3 for immune cells and its potential in clinical settings, the paucity of clinical studies to substantiate these assertions remains. Therefore, we suggest that future research should prioritize these areas of investigation.

Overall, this review provides a comprehensive interpretation of the relationship between METTL3 and the immune system, providing novel insights into research gaps that require attention in both research and clinical settings. Furthermore, this review may serve as a valuable reference for researchers and clinicians.

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Declarations of interest

None

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Author contributions

MZ contributed to the conception and drafting of the manuscript. **ZG** prepared the figure for this manuscript. **YQ** revised and offered funding for the manuscript. **XS** contributed to the revision, supervision, and final approval of this research.

Data availability

No new data were generated or analyzed in support of this research.

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