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RNA m^{6}A Modification in Immunocytes and DNA Repair: The Biological Functions and Prospects in Clinical Application

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As the most prevalent internal modification in mRNA, N^6-methyladenosine (m^{6}A) plays broad biological functions *via* fine-tuning gene expression at the post-transcription level. Such modifications are deposited by methyltransferases (i.e., m^{6}A Writers), removed by demethylases (i.e., m^{6}A Erasers), and recognized by m^{6}A binding proteins (i.e., m^{6}A Readers). The m^{6}A decorations regulate the stability, splicing, translocation, and translation efficiency of mRNAs, and exert crucial effects on proliferation, differentiation, and immunologic functions of immunocytes, such as T lymphocyte, B lymphocyte, dendritic cell (DC), and macrophage. Recent studies have revealed the association of dysregulated m^{6}A modification machinery with various types of diseases, including AIDS, cancer, autoimmune disease, and atherosclerosis. Given the crucial roles of m^{6}A modification in activating immunocytes and promoting DNA repair in cells under physiological or pathological states, targeting dysregulated m^{6}A machinery holds therapeutic potential in clinical application. Here, we summarize the biological functions of m^{6}A machinery in immunocytes and the potential clinical applications *via* targeting m^{6}A machinery.

Keywords: m^{6}A (N^6-methyladenosine), immunocyte, epigenetics, immunotherapy, DNA repair

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INTRODUCTION

While RNA modification was first identified in 1970s, it becomes a research focus in recent years. It broadly exists in different species, including fungi (Bodi et al., 2015), plants (Yue et al., 2019), and animals (Yoon et al., 2017; Xia et al., 2018). During the past decades, researchers have found that RNA methylation is a widespread modification in coding sequence and non-coding sequence (Huang et al., 2020), most of which are located at the amine group outside ring, special nitrogen and carbon positions of purine and pyrimidine, and the oxygen atom of the 2′-OH moiety (Liu and Jia, 2014). If classified by the modified position, RNA methylation mainly consists of N^6-methyladenosine (m^{6}A), 5-methylcytosine (m^{5}C), N^7-methylguanosine (m^{7}G), etc., among which m^{7}G cap at the 5′end of RNA sequence has been rigorously studied for decades (Devarkar et al., 2016; Pandolfini et al., 2019). However, m^{6}A modification, representing the most abundant modification, needs further study.

As reported, m^{6}A modifications are localized in the conversed DRACH motifs (D = G/A/U, R = G/A, H = A/U/C). The distribution of m^{6}A is usually in the coding and 3′ untranslated regions,

especially enriched in the upstream of stop codon in mRNA (Roundtree et al., 2017). Recent researches find that m^{6}A modification is also an important biological mark of endogenous circular RNA (circRNA) (Chen et al., 2019). Moreover, m^{6}A modification in lncRNA can regulate the efficiency of glycolysis (Liu J et al., 2019) or promote oncogenesis (Chen et al., 2020). Since m^{6}A modification is dynamic and reversible, the biological function and molecular mechanism of m^{6}A modification have become a research hotspot in many medical fields.

WRITERS, ERASERS, AND READERS

The most momentous breakthrough in this field is the discovery of the m^{6}A machinery involved in m^{6}A modification, including "Writers," "Erasers" and "Readers," performing the function of methyltransferase, demethylase, and recognizing the m^{6}A structure, respectively. They dynamically regulate the homeostasis of m^{6}A and its functions in cells.

Writers

With the function of forming m^{6}A structure, "Writers" protein is a 1 MDa complex composed of multiple subunits, containing Methyltransferase like-3 (METTL3) (Liu et al., 2014), Methyltransferase like-14 (METTL14) (Weng et al., 2018), Wilm's Tumor 1-associating protein (WTAP) (Ping et al., 2014; Sorci et al., 2018), etc. METTL3 is responsible for catalyzing the transfer of methyl group with the support of S-adenosyl-methionine (SAM) in many types of RNA including mRNA and miRNA, while METTL14 is a catalytic cofactor capable of recognizing and binding the target mRNA. WTAP is in charge of recruiting the targeting RNA and locating the METTL3/METTL14/WTAP complex into the nuclear speckles, which is relevant to the prognosis and cisplatin resistance (Ma et al., 2021) of cancer and the infiltration of T lymphocyte within tumors (Li H et al., 2020). New subunits, termed RBM15/RBM15B (Knuckles et al., 2018), KIAA1429 (Lan et al., 2019), ZFP217 (Song et al., 2019), and ZC3H3 (Silla et al., 2020), have been identified, and their functions involve in the recruitment, m^{6}A modification of mRNA or lncRNA, and regulation of the m^{6}A catalytic efficiency. Different types of "Writers" may interact with each other, as a result of which may influence the progression of some diseases such as colorectal cancer (Chen H et al., 2021).

Erasers

The m^{6}A structure can be erased by the "Erasers" protein. Fat mass and obesity-associated protein (FTO) (Jia et al., 2011) was supposed to be the first demethylase discovered, whose existence confirmed the reversibility of m^{6}A modification. FTO and the second identified "Erasers" called AlkB Homolog 5 (ALKBH5) (Zheng et al., 2013) jointly counter the m^{6}A modification of "Writers," thus maintaining the homeostasis of m^{6}A level in cells, whereas the distribution of the two proteins are tissue-specific. The amino acid sequence HXDXnH and RXXXXXR (X = any amino acid) with demethylase activity are contained in their mutual AlkB domain. Both of them remove the m^{6}A methylation from mRNA with the Fe (II)/α-ketoglutarate-dependent dioxygenase (Fedeles et al., 2015). The demonstration of "Writers" and "Erasers" initiates a new branch, namely, m^{6}A research, in the field of epigenetics. Recent studies on ALKBH5 gradually elucidate its multiple functions in disease progressing and therapeutic efficacy, including CD4$^+$ T cell pathogenicity in autoimmunity (Zhou et al., 2021), anti PD-1 response in tumor treatment (Li N et al., 2020), glucocorticoid resistance in T-cell acute lymphoblastic leukemia cell treatment (Gong et al., 2021), etc.

Readers

The level of m^{6}A in cells is dynamically modulated by "Writers" and "Erasers," while "Readers" can recognize the m^{6}A structure and regulate the subsequent cell processes such as translation and stability of mRNA. The YTH domain-containing family is the first confirmed component of "Readers," characterized by the YTH domain at C terminus. YTHDF1~3 and YTHDC1~2 (Kasowitz et al., 2018; Zhou et al., 2020) are identified as m^{6}A binding proteins, among which researches concerning YTHDF are more detailed. Generally speaking, the aforementioned m^{6}A "Readers" proteins have the same function of binding the m^{6}A-modified mRNA with the consensus YTH domain at C terminus, while YTHDF1 promote translation by binding the m^{6}A at translation initiation site (Zhuang et al., 2019); YTHDF2, characterized by the P/Q/N-rich domain at N terminus, recruits the CCR4-NOT deadenylase complex and brings the target mRNA to cytoplasmic P bodies (Du et al., 2016), resulting in the destabilization of mRNA (Paris et al., 2019); YTHDF3 is also related to mRNA decay, but it is regarded to have a synergistic effect on YTHDF1 and YTHDF2 (Ni et al., 2019). In contrast to YTHDF, additional Readers such as insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) (Hanniford et al., 2020) can uniquely stabilize the target mRNA, while the eukaryotic initiation factor 3 (eIF3) (Meyer et al., 2015; Wolf et al., 2020) can promote cap-independent translation of mRNA with 5′-UTR m^{6}A modified. Moreover, other m^{6}A Readers like ELAVL1 (Zhang et al., 2017) are being studied recently.

ROLES OF M^{6}A MODIFICATION IN IMMUNOCYTES

Immunocytes play a crucial role in a variety of bioprocesses, such as recognizing and presenting the pathogen and immune response, whose depletion or dysfunction is the important pathological basis of tumorigenesis, viral infection, and autoimmune diseases, etc. Previous researches focused on the function of m^{6}A in cancer cells, including endometrial cancer (Liu et al., 2018), breast cancer (Cai et al., 2018), bladder cancer (Cheng et al., 2019), hepatocellular cancer (Zhao X et al., 2018), nasopharyngeal cancer (Zhang et al., 2018), glioblastoma stem cells (Cui et al., 2017), acute myeloid leukemia (Cui et al., 2017), etc. Nevertheless, recent m^{6}A researches on T lymphocyte, B lymphocyte, DC, and macrophage broaden our cognition

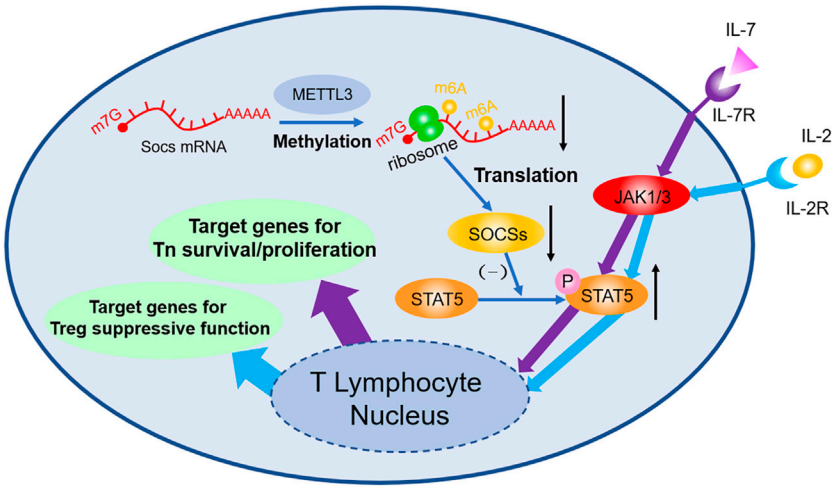

FIGURE 1 | m^{6}A decoration contributes to the regulation of Tn differentiation and Treg function both through JAK-STAT5 pathway. m^{6}A modifications in *Soc1*, *Soc3*, and *Cish* mRNA accelerate their degradation, thus decreasing the expression of SOCS. As a consequence, through the JAK/STAT5 pathway, IL-7 induced differentiation of Tn and IL-2 induced suppressive function of Treg are both influenced afterwards.

towards the human immune system, which are the latest achievements of m^{6}A modification.

T Lymphocyte

T lymphocyte is the executant of human adaptive immune system, which is related to antitumor immunity and autoimmune diseases. Furthermore, T lymphocyte is likely to have interaction with neural stem cells, thus inhibiting its proliferation and resulting in age-related brain disease (Dulken et al., 2019); the abnormal level of m5C, another form of RNA methylation, in CD^{4+} T lymphocytes may have a potential link with the pathogenesis of systemic lupus erythematosus (SLE) (Guo G et al., 2020). According to the differences in function and phenotype, T lymphocyte can be divided into subtypes including naïve T cell (Tn), cytotoxic T cell, regulatory T cell (Treg), helper T cell (Th), etc., which is mainly driven by the stimulation of inflammation factor such as interleukin (IL) and tumor necrosis factor (TNF). Recently, bile acid has been proved to be an accessional regulator of Th17 (Hang et al., 2019) and Treg differentiation. The newly discovered subtype termed exhausted T cell (Tex) along with its key transcription factor called thymocyte selection-associated high mobility group box (TOX) (Scott et al., 2019) is a breakthrough in antitumor study, although the connection between Tex and m^{6}A remains to be explored.

Studies focusing on m^{6}A in T lymphocyte mark the initiation of m^{6}A study in adaptive immune field. Li H-B et al. (2017) found that 5 weeks after transplant of wild type Tn, Rag$^{-/-}$ mice develop colitis due to the differentiation of Tn into effector T cell, whereas Rag$^{-/-}$ mice with Mettl3$^{-/-}$ transplanted exhibit no sign of similar symptoms and no T cell infiltration or inflammation inside spleen and colon can be observed. FACS shows the dysfunction of Mettl3$^{-/-}$ Tn differentiation. Molecular biology studies indicate that *Soc1*, *Soc3*, and *Cish* mRNA are stabilized owing to the lack of m^{6}A modification; afterwards, elevated SOCS protein inhibits the phosphorylation of STAT5, then the IL-7 mediated JAK-STAT5 pathway will be blocked, and thus the differentiation of Tn is suffocated. However, because Mettl3$^{-/-}$ strengthen ERK and APK pathway simultaneously, no obvious increase in T cell apoptosis can be observed. Follow-up study (Tong et al., 2018) found that Tn homeostasis of Mettl3$^{f/f}$; CD4-Cre mice can be destroyed and have colitis 3 months after being born, because Treg's suppression of effector T cell is faulted. During this process, genetic depletion of *Mettl3* reduces the m^{6}A modification of *Socs* mRNA, then stabilizes mRNA, and upregulates its expression. High level SOCS protein inhibits IL-2-STAT5 pathway, resulting in the dysfunction of Treg. Additionally, it is demonstrated that Treg can strengthen type-II DC's ability of presenting antigen (Binnewies et al., 2019), enhance antitumor response, and improve prognosis of checkpoint blockade such as PD-1 block immunotherapy (shown in **Figure 1**).

Another study (Lu et al., 2020) unveils the function of *Mettl14* in T lymphocytes. In this research, CD4-Cre$^{+/Tg}$ Mettl14$^{FL/FL}$ conditional knockout mice have found to develop spontaneous colitis due to the increased level in Th1 cytokines, such as IFN-γ and TNF-α. Follow-up studies show that RORγt expression in *Mettl14* deficient Tregs is downregulated compared to the wild-type Tregs and the induction efficacy of *Mettl14* deficient Tn to iTreg is obviously impaired. As a consequence, both the reduction of iTregs, whose function has reported to be controlling the experimental colitis, and the dysfunctional Mettl14 deficient Tregs lead to the development of spontaneous colitis. With the function of METTL3 in T follicular helper cell differentiation being clarified recently (Yao et al., 2021), plenty of evidences have persuade us that m^{6}A may play an irreplaceable role in all subtypes of T cells.

Furthermore, in acute myeloid leukemia (AML), FTO inhibition can lead to downregulation of leukocyte immunoglobulin-like receptor subfamily B member 4 (LILRB4), render AML cells vulnerable to activated T cells,

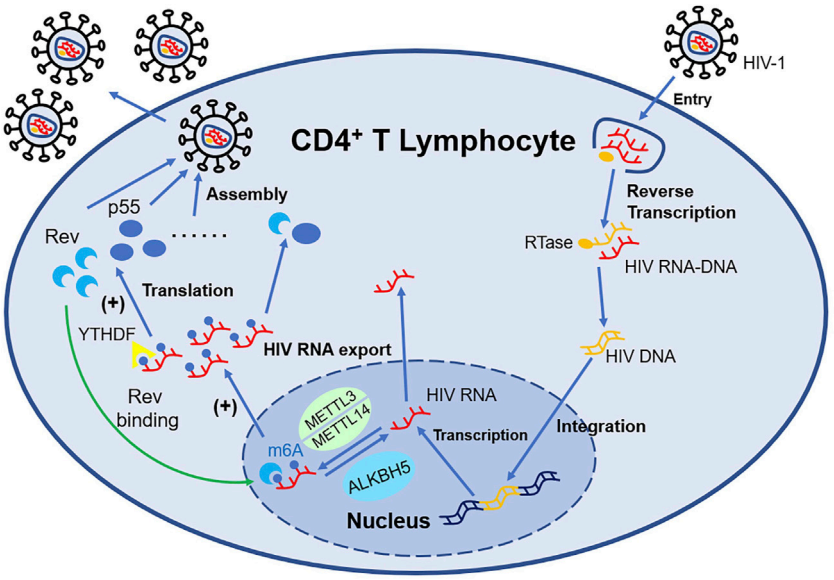

FIGURE 2 | m^{6}A-associated proteins in HIV-infected T lymphocytes regulate the expression of HIV mRNA. METTL3/METTL14 can install m^{6}A decoration on HIV mRNA, while ALKBH5 can remove such modification. YTHDF1-3 recognize the m^{6}A structure and influence the expression of HIV mRNA such as Rev and p55. With the support of Rev, HIV mRNA modified by m^{6}A can export nucleus more easily, which promote the replication of HIV.

and simultaneously overcome hypomethylating agent (HMA)-induced immune evasion. FTO's function in anti-tumor immunity, especially its function in T cells, can be a promising therapeutic strategy in the field of m^{6}A research (Su et al., 2020).

In addition, when CD4$^+$ T cell is infected by the Human Immunodeficiency Virus (HIV), both HIV RNA and intrinsic RNA will be obviously increased (Lichinchi et al., 2016) independent of virus replication. Only gp120 will upregulate the level of m^{6}A without influencing the expression of Writers and Erasers (Tirumuru and Wu, 2019). The m^{6}A modification position of HIV RNA mainly distributes at 3′-UTR (Kennedy et al., 2016), which is directly involved in the regulation of viral mRNA nuclear export and protein synthesis. The m^{6}A modification machinery, such as YTHDF (Tirumuru et al., 2016), METTL3/METTL14, and ALKBH5 (Lichinchi et al., 2016), act as a crucial regulator of this process. The m^{6}A modification of HIV RNA will affect the expression of viral proteins including p55 (the product of gene *gag*) and Rev, consequently impacting the viral infectivity and replication, while suppressing the expression of IFN-I in monocytic cells and macrophages at the same time (Chen S et al., 2021). Therefore, antibodies neutralizing gp120 or CD4$^+$ probably have the potential to counter HIV. Besides, Fu et al. (2019) for the first time applied HIV transgenic rats for m^{6}A research and elucidated the role of m^{6}A modification in mRNA in chronic HIV diseases, especially neurologic disorder (shown in **Figure 2**).

In conclusion, the effect of YTHDF2 on virus remains to be ascertained or can be bidirectional (Toro-Ascuy et al., 2016; Lu W et al., 2018); YTHDF3 weakens the viral infectivity and inhibits the viral replication. Uniquely, YTHDF3 can be incorporated into the virion and still keep its antiviral activation, but the HIV protease can cleave the virion containing YTHDF3. This mechanism prevents HIV from being killed thoroughly and provides a new thought for HIV treatment (Jurczyszak et al., 2020).

All the researches above reveal that m^{6}A along with associated protein can alter the stability of mRNA and regulate nuclear export and translation of mRNA, thus influencing the bioprocess of T cell with different phenotype and promoting the progression of certain diseases.

B Lymphocyte

B lymphocyte is involved in the humoral immunity by producing antibodies. Applying bioengineering technology to design special improbable immunogen can induce the synthesis of antibodies with high affinity, which have the potential to treat virus infection, such as HIV (Saunders et al., 2019). A recent clinical study suggests that m^{6}A modification is closely related to the oncogenesis and progress of mantle cell lymphoma (Zhang W et al., 2019). Mantle cell lymphocyte is a kind of non-hodgkin B cell lymphoma characterized by aggressive phenotype and rapid rate of progression. After analysis of 123 samples of clinical patients, the hazard ratios of YTHDF3, METTL3, FTO, METTL14, ALKBH5, YTHDF2, and WTAP are below 1, while those of YTHDF1, KIAA1429, and ELAVL1 are above 1, among which the maximum is ELAVL while the minimum is YTHDF3, implying that ELAVL and YTHDF3 might be the most important regulators of mantle cell lymphoma. Moreover, "m^{6}A index" is proposed to evaluate the prognosis of patients. Without much available biology research data, this statistical study directs a path for the following m^{6}A research concerning B lymphocyte.

Recent studies have shown that the deletion of *Mettl14* can decrease the m^{6}A level in developing B cells and inhibit some

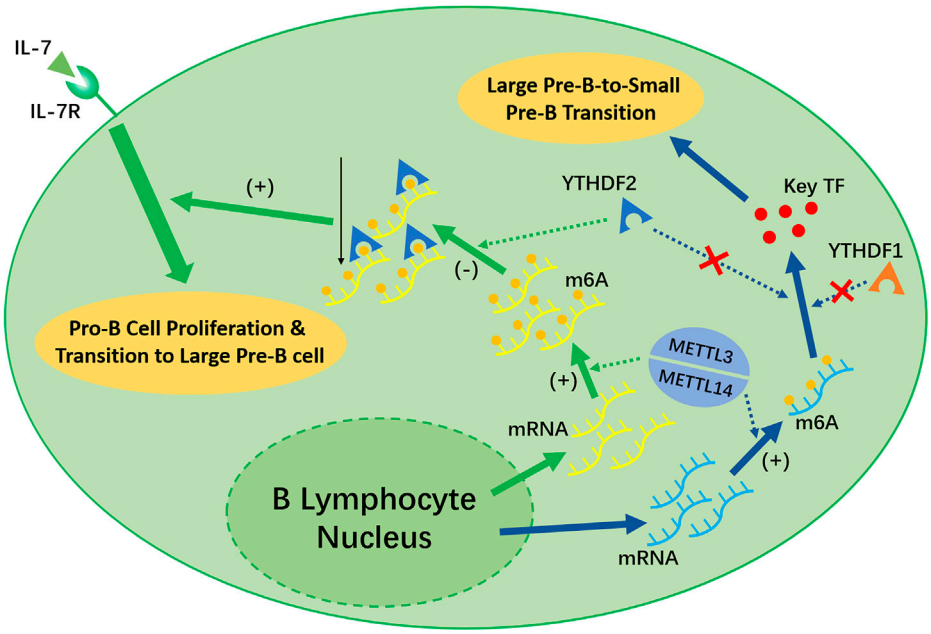

FIGURE 3 | METTL3/METTL14 complex and YTHDF1 is necessary for the early development of B lymphocytes. METTL14 plays an unreplaceable role in the IL-7 induced Pro-B lymphocyte proliferation, Pro-B-to-Large-Pre-B transition, and Large-Pre-B-to-Small-Pre-B transition. YTHDF2 will recognize the m^{6}A modification afterwards and decrease the transcripts as a result, which promote early B lymphocyte development. Notably, YTHDF2 only facilitate in the first two process. The Large-Pre-B-to Small-Pre-B Transition is independent of YTHDF1 or YTHDF2.

important processes, such as the IL-7-induced Pro-B cell proliferation and the transition to the Large Pre-B Stage, which depends on the function of YTHDF2 (Zheng et al., 2020) (shown in **Figure 3**). However, the Large-Pre-B-to-Small-Pre-B Transition depends on METTL14, but is independent of YTHDF1 or YTHDF2 (shown in **Figure 3**).

The pathogenesis of diffuse large B-cell lymphoma (DLBCL), which is the most common subtype of lymphoma derived from B lymphocytes, has been illustrated to have a link with upregulated METTL3 and the m^{6}A level of the mRNA of pigment epithelium-derived factor (Cheng et al., 2020), while PIWI-interacting RNAs have been identified to function in this process recently (Han et al., 2021). The association between B lymphocytes and other m^{6}A methylation-related proteins remains to be explored.

Besides, Kaposi's sarcoma (KS) is evidently associated with infection of HIV and Kaposi's sarcoma-associated herpesvirus (KSHV). KSHV shows strong lymphotropic and invades B cells in the circulation (Myoung and Ganem, 2011). During this process, m^{6}A Reader protein YTHDF2 plays a positive role in KSHV replication (Hesser et al., 2018). However, inconsistent with its feature *in vivo*, KSHV exhibits weaken infectivity and proliferation in B cells lines *in vitro*, so the role of m^{6}A and associated protein in the oncogenesis of KS remains to be explored.

DC

As the bridge between the innate and adaptive immune, DCs function as antigen-presenting cells and can also produce VEGF-α for the recruitment of neutrophil to control cutaneous bacterial infections (Janela et al., 2019). Therefore, DCs play a core role in the eradication of pathogen and inducement of immune tolerance. It has been evidenced that the dysfunction of DC activation is involved in the progression of multiple inflammation, cancer, and autoimmune diseases. Tyrosine kinase AXL can induce the expression of PD-1. IFN-γ and IL-4 can respectively promote and inhibit the production of IL-12; thus, blockade of IL-4 receptor can strengthen antitumor response by expanding the infiltration of T lymphocyte at tumor position (Maier et al., 2020). Though the association between the suppression of DCs and extracellular m^{6}A-modified RNA has been confirmed for decades (Karikó et al., 2005), studies concerning m^{6}A in DCs are still at its infant stage.

Wang H et al. (2019) found that total level of m^{6}A in DCs is increasing parallel with its maturation. The distribution of m^{6}A is mainly located in NLR, TNF, and NF-κB pathways, which are responsible for the induction of co-stimulatory factors and pro-inflammation factors which promote maturation of DCs. METTL3 was involved in this physiological process. Distinct from most of the previous laboratory findings, the fundamental mechanism is the upregulation of translation efficiency, but not the stability of mRNA (Wang H et al., 2019) (shown in **Figure 4**).

Han et al. (2019) discovered the connection between upregulated translation and YTHDF1. The depletion of YTHDF1 in DCs will limit the expression of lysosomal protease, which decelerates the degradation of antigen, thus improving DCs' ability of presenting antigen and activating

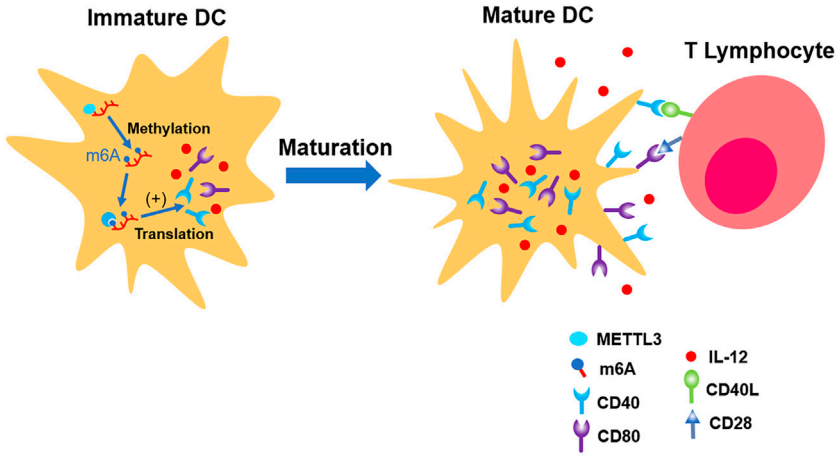

FIGURE 4 | METTL3 up-regulates the expression of CD40, CD80, and IL-12, which promote the maturation of immature DC. In the end, its ability of presenting antigen and interaction with T lymphocytes are strengthened.

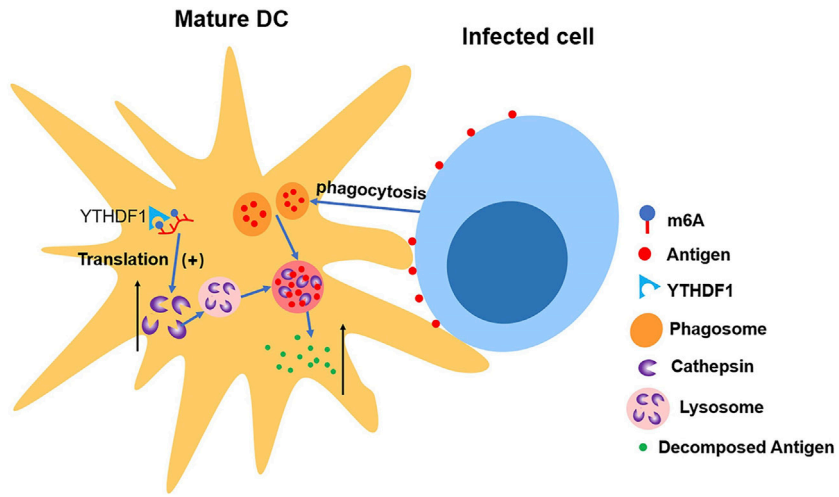

FIGURE 5 | YTHDF1 increases the level of cathepsin in mature DCs, which accelerates the cleavage of antigens in phagosome, making DCs' ability of presenting antigen impaired.

$CD8^+$ T cell. This suggests a new mechanism of immune escape as well as an important reason for weak antitumor immune response in certain clinical cases (Han et al., 2019) (shown in **Figure 5**).

Macrophage

Macrophage is a kind of innate immune cell dwelling in various tissues with multiple subtypes, which can be classified into classically activated macrophages (M1) and alternatively activated macrophages (M2). Early researches have implied the possibility of m^{6}A weakening immune response (Durbin et al., 2016). However, recent researches indicate that m^{6}A modification plays an important role in antivirus, negative feedback control of macrophage activation (Du et al., 2020), and the polarization of macrophages. Roles of m^{6}A Writers, Erasers, and Readers in macrophages are summarized in **Table 1**.

In detail, "Writers" METTL3 catalyzes the m^{6}A methylation at coding sequence (CDS) and 3′-UTR of *STAT1* mRNA, facilitating the polarization of M1, but having opposite impact on M2 (Liu Y et al., 2019). Another study has also illustrated METTL3's function in promoting M1 differentiation, which afterwards benefits bone marrow mesenchymal stem cells (Lei et al., 2021). Moreover, METTL3 can methylate hnRNPA2B1 and *Cgas*, *Ifi16*, and *Sting* mRNA simultaneously, and then the affinity of hnRNPA2B1 to three mRNA above is improved, which ultimately increases the production of IFN-β and amplifies the immune response to DNA virus (Wang L et al., 2019). In addition, METTL3 deficiency have proved to impede the activation of macrophages through TLR4 signaling pathway

TABLE 1 | Roles of m^{6}A Writers, Erasers, and Readers in macrophages.

m^{6}A regulator	Cell subtype	Target genes	Biological function
Writers			
METTL3	M1	*STAT1*	Promote polarization
	M2	*STAT1*	Inhibit polarization
	M1/M2	*Cgas, Ifi16, Sting, hnRNPA2B1*	Increase the production of IFN-β Amplify the immune response to DNA virus
		Irakm	Promote activation
METTL14	M1/M2	*Ebi3*	suppress CD8$^+$ T cell dysfunction and tumor growth
Erasers			
FTO	M1	*STAT1*	Promote polarization
	M2	*STAT6, PPAR-γ*	
ALKBH5	M1/M2	*Mavs, Traf3, Traf6*	Inhibit translation and production of IFN
Readers			
YTHDF2	M1/M2	*STAT1, PPAR-γ*	Impede macrophage activation
		MAP2K4, MAP4K4	Inhibit the expression of pro-inflammatory cytokine and inflammatory response
YTHDF3		*FOX O 3*	Impede the expression of IFN-stimulated genes and immunity response to VSV
IGF2BP2		*TSC1, PPAR-γ*	regulate macrophage phenotypic activation and inflammatory diseases

by stabilizing *Irakm* transcripts (Tong et al., 2021). As for METTL14, there is also indirect evidence indicating its function in suppressing CD8$^+$ T cell dysfunction and tumor growth (Dong et al., 2021).

After knockout of "Erasers" *FTO*, the polarization of both M1 and M2 can be inhibited, during which the expression of STAT1 in M1 was decreased, while the degradation of *STAT6* and *PPAR-γ* mRNA is increased (Gu et al., 2020). Furthermore, ALKBH5 demethylate DDX46-binded *Mavs*, *Traf3*, and *Traf6* mRNAs, leading to the retention of these mRNAs inside nuclear, indirectly inhibiting translation and reducing the production of IFN. In the end, antiviral activation of macrophages is weakened (Zheng et al., 2017).

Knockdown of "Readers" *YTHDF2* can stimulate the expression of *STAT1* (Huangfu et al., 2020) and *PPAR-γ* mRNA (Gu et al., 2020), while forced expression of YTHDF2 could destabilize *MAP2K4* and *MAP4K4* mRNA and activate the NF-κB and MAPK pathway (Yu et al., 2019), which will facilitate LPS-induced osteoclastogenesis and inflammatory response (Fang et al., 2021). YTHDF3 was regarded as a negative regulator of antivirus. With the assistance of PABP1 and elF4G2, YTHDF3 can bind the translation initiation site of *FOXO3* mRNA and promote translation. As a result, the expression of IFN-stimulated genes is inhibited, which weakens the immunity response to Vesicular stomatitis virus (VSV) (Zhang Y et al., 2019). Moreover, another reader IGF2BP2 has also proved to be associated with the phenotypic activation of macrophage (Wang X et al., 2021).

Researches focusing on m^{6}A modification in macrophages reveal its association with some diseases. The occurrence of atherosclerosis (AS) has proved to be linked with m^{6}A modification. During this progress, ox-LDL induces the expression of DDX5 in macrophages and limits the function of METTL3 which transfers the methyl group to macrophages scavenger receptor A (*MSR1*) mRNA. Ultimately, *MSR1* mRNA is stabilized, and more MSR1 is synthesized. Uptake of more lipids further facilitates the formation of foam cells, resulting in the progression of AS (Zhao W et al., 2018). In another study, Zhang X et al. (2021) has also identified the function of METTL3 in promoting ox-LDL-induced inflammation and mitochondrial dysfunction by methylating peroxisome proliferator-activated receptor-γ coactivator 1-alpha (PGC-1α) mRNA with the assistance of YTHDF2. Intriguingly, m5C, another form of RNA methylation, can deteriorate AS induced by hyper-homocysteinemia (Wang et al., 2017), while acute coronary syndrome, whose main pathological basis is AS, is also related to the m^{6}A modification of circ-0029589 in macrophage (Guo M et al., 2020).

The dysfunction of m^{6}A in macrophages is also a pathogenesis factor of autoimmune diseases. Wang J et al. (2019) found that in patients with rheumatoid arthritis, METTL3 in macrophages is obviously improved and positively associated with CRP and ESR. Moreover, lipopolysaccharide (LPS) can stimulate the expression of METTL3 in macrophages and then slack the immune response to inflammation through NF-κB pathway (Wang J et al., 2019). Other autoimmune diseases such as osteoarthritis (Liu Q et al., 2019) and SLE (Li et al., 2018) show possibility of having connection with m^{6}A dysfunction in macrophages.

THE APPLICATION OF M^{6}A MODIFICATION AND ITS DEVELOPMENT PROSPECT

Given the identification of aberrant m^{6}A modification in various diseases, targeting m^{6}A machinery in specific cells can be regarded as a new treatment for viral infection, cancer, and autoimmune diseases. However, changes in m^{6}A levels in different diseases are lack of consistency, so treatment targeting m^{6}A should be supposed to modulating m^{6}A level to normal level, instead of simply accelerating or decelerating m^{6}A modification (Wang et al., 2018).

m^{6}A-Associated Proteins Modulating DNA Repair

Plenty of researches have confirmed the correlation between m^{6}A and DNA repair in different situations. Zhang et al. have reported the

TABLE 2 | m^{6}A-associated proteins in DNA repair.

m^{6}A regulator	Biological function
Writers	
METTL3	Modulate DNA-RNA hybrid accumulation Regulate accumulation of the three-stranded R-loops Regulate the m^{6}A modification in ultraviolet-induced DNA damage Direct the recruitment of Pol κ to the DNA damage sites
METTL14	Enhance translation of DNA repair genes Suppress ultraviolet-induced skin tumorigenesis
KIAA1429	Interfere with DNA damage response in cisplatin-treated germ cell tumor
Erasers	
FTO	Regulate the m^{6}A modification in ultraviolet-induced DNA damage
ALKBH5	Regulate ROS-induced DNA damage response
Readers	
YTHDC1	Modulate DNA-RNA hybrid accumulation
YTHDF2	Regulate accumulation of the three-stranded R-loops
IGF2BP2	Extend mRNA half time in ROS-induced DNA damage response

METTL3-m^{6}A-YTHDC1 axis which promotes the double-strand breaks by modulating DNA-RNA hybrid accumulation (Zhang et al., 2020). Other researches indicate that accumulation of the three-stranded R-loops, formed by RNA: DNA hybrid and single stranded DNA, is regulated by YTHDF2 (Abakir et al., 2020), METTL3, and tonicity-responsive enhancer binding protein (TonEBP) (Kang et al., 2021). More surprisingly, the arginine substrates of METTL14 itself at intrinsically disordered C terminus can also be methylated. It proved to be an initial signal of interaction between METTL14 and RNA polymerase II, which will afterwards implement the m^{6}A modification of target mRNA. Subsequent studies have confirmed that METTL14 arginine methylation is associated with the enhanced translation of DNA repair genes (Wang Z et al., 2021). Recent studies even clarified the correlation between DNA damage repair and m^{6}A-modified retrotransposable element (RTE) RNAs, in which intronic Long Interspersed Element-1 (LINE-1) interacts with the hosting gene transcription, resulting in the downregulation of its expression (Xiong et al., 2021). KIAA1429 was also recently discovered to have close links with the modulation of response to cisplatin in germ cell tumor by interfering with DNA damage response (Miranda-Gonçalves et al., 2021).

As for Erasers, the homologs of AlkB (ALKBHs), which originally function as repair proteins in *E. coli*, are also important regulators of DNA repair and m^{6}A modification at the same time in mammalian cells (Müller et al., 2017; Müller et al., 2018). Recently, the ERK/JNK/ALKBH5-PTMs/m^{6}A axis has been reported to participate in the regulation of ROS-induced DNA damage response, in which progress IGF2BP also plays a part in extending mRNA half time (Yu et al., 2021). METTL3 and FTO can jointly regulate the m^{6}A modification in RNA at DNA damage sites induced by ultraviolet. The function of DNA polymerase κ (Pol κ), which is the key DNA repair enzyme, require the catalytic activity of METTL3, implying the m^{6}A modification directs the recruitment of Pol κ to the DNA damage sites (Xiang et al., 2017). Furthermore, METTL14 has proved to play a tumor-suppressive role in ultraviolet-induced skin tumorigenesis (Yang et al., 2021). All the m^{6}A-associated proteins which regulate DNA repair are summarized in **Table 2**.

In conclusion, since m^{6}A, along with its associated proteins, plays an important role in the pathogenesis and facilitating DNA repair, attaching m^{6}A-targeted therapy to traditional chemo- or radiotherapy may improve the prognosis of some diseases such as carcinoma through two mechanisms.

Medication Targeting m^{6}A

Abnormally elevated m^{6}A level is the feature of most malignant tumor, so developing new drugs inhibiting m^{6}A modification is the most fundamental idea to treat these diseases. Actually, this kind of drugs has been developed for decades. 3-Deaza-Adenosine (DAA) with its analogue can block S-adenosylhomocysteine (SAH) hydrolase, which results in the accumulation of SAH and feedback suppression of SAM (Chiang, 1998). So DAA can indirectly inhibit the m^{6}A modification of mRNA. However, since DAA can suppress the m^{6}A modification in many physiological or pathological processes, there will be many unexpected side effects, such as the prevention of T lymphocyte activation, hypotensive effect, and activation of gene expression. At present, DAA is mainly used for the treatment of AIDS (Kennedy et al., 2016).

Moreover, some diseases like acute myeloid leukemia (AML) are characterized by the aberrant decrease of m^{6}A (Li Z et al., 2017). Rhein (Chen et al., 2012), curcumin (Lu N et al., 2018), meclofenamic acid (Huang et al., 2015), and Saikosaponin-D (Sun et al., 2021) can inhibit the function of FTO by binding the active site of FTO or m^{6}A position of mRNA. Two emerging small molecules targeting FTO demethylase called FB32 and FB32-2, which can dramatically inhibit the progression of AML cells *in vitro* and *in vivo*, have been developed recently (Huang et al., 2019). Coupled with the latest advancement called STM2457, which is a highly potent and selective first-in-class catalytic inhibitor of METTL3 (Yankova et al., 2021),

we can foresee that the era of treating AML or other diseases featured by m^{6}A level unbalance using m^{6}A-targeted method is coming.

Immunotherapy Targeting m^{6}A

Although solid researches data is unavailable, the regulatory function of m^{6}A modification to immunocytes makes it possible for m^{6}A to be a new target for immunotherapy. It has been demonstrated that m^{6}A is a regulator of Tn differentiation, T lymphocyte homeostasis (Li H-B et al., 2017), and suppressive function of Tregs (Tong et al., 2018). Recent studies have found that loss of METTL3 in myeloid cells reprograms the macrophages and increases Treg infiltration into tumors by influencing the YTHDF1-mediated translation of SPRED2 (Yin et al., 2021). Therefore, inhibiting mRNA m^{6}A modification of Tregs at tumor site or myeloid cells can motivate the antitumor activation of CD8$^+$ T cell, which can be a promising immunotherapy. Meanwhile, inhibiting mRNA m^{6}A modification in Tn can reduce the formation of effector T cell, which is helpful for the treatment for autoimmune diseases. Furthermore, regulating the expression of METTL3 (Wang H et al., 2019) and YTHDF1 to a suitable level can improve DCs' ability of presenting tumor neoantigen. More importantly, depletion of YTHDF1 and blockade of checkpoint have a synergistic effect on strengthening antitumor immunity (Han et al., 2019), and ALKBH5 (Li N et al., 2020) and METTL3/14 (Wang et al., 2020) have also proved to regulate anti PD-1 response. So as for patients resistant to the PD-1 immunotherapy, targeting m^{6}A can be a new alternative treatment. Since m^{6}A decoration of viral double-stranded RNA can also downregulate the innate sensing pathway of antiviral response (Qiu et al., 2021), immunotherapy targeting m^{6}A is bound to be a promising therapy for various diseases including viral infections, autoimmune disorders, cancers, etc.

DISCUSSION

As the most abundant post-transcriptional mRNA modification in mammals, m^{6}A is involved in the occurrence of several diseases. Recently, an enormous amount of m^{6}A related studies in immunocytes highlight the fact that targeting m^{6}A can be a promising new treatment strategy for viral infection, cancer, and autoimmune diseases. However, in different cell lines, diseases, even different types of the same diseases, the changes of m^{6}A level, as well as functions of three m^{6}A-associated enzymes lack consistency. Moreover, m^{6}A modification is widely involved in a variety of cellular processes and medication targeting m^{6}A is not selective. All these reasons indicate that clinical treatment *via* targeting m^{6}A modification may be not safe enough. Thus, there is unmet need to develop more sophisticated techniques for m^{6}A detection (Dai et al., 2018; Castellanos-Rubio et al., 2019). Moreover, detailed studies on disease mechanisms are required to realize the clinical application of m^{6}A-targeting treatment. Pharmaceutical researches on drugs with high selectivity or combination of existing drugs and targeted drug delivery system can also promote the accurate treatment of diseases through the m^{6}A-targeting method. Some recent experimental results have indicated the promising prospects of this field (Zhu et al., 2021). Last but not least, m^{6}A modification is supposed to be highly relevant to gut microbiota (Jabs et al., 2020), heat shock proteins (Feng et al., 2020), sepsis (Sun et al., 2020; Xing et al., 2021), and pulmonary hypertension (Pan et al., 2020) and even peripheral nerve injury (Zhang L et al., 2021). These studies can provide valuable experimental basis for development of new treatments.

AUTHOR CONTRIBUTIONS

WL and NS contributed to the design of the topic. MZ and JZ searched and organized the relevant papers. MZ and JZ wrote the first draft of the manuscript. MZ drew the figures and tables in the manuscript. WL and NS contributed to the polish of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REFERENCES

Abakir, A., Giles, T. C., Cristini, A., Foster, J. M., Dai, N., Starczak, M., et al. (2020). N6-methyladenosine Regulates the Stability of RNA:DNA Hybrids in Human Cells. *Nat. Genet.* 52 (1), 48–55. doi:10.1038/s41588-019-0549-x

Binnewies, M., Mujal, A. M., Pollack, J. L., Combes, A. J., Hardison, E. A., Barry, K. C., et al. (2019). Unleashing Type-2 Dendritic Cells to Drive Protective Antitumor CD4+ T Cell Immunity. *Cell* 177 (3), 556–571. doi:10.1016/j.cell.2019.02.005

Bodi, Z., Bottley, A., Archer, N., May, S. T., and Fray, R. G. (2015). Yeast m6A Methylated mRNAs Are Enriched on Translating Ribosomes during Meiosis, and under Rapamycin Treatment. *PLoS One* 10, e0132090. doi:10.1371/journal.pone.0132090

Cai, X., Wang, X., Cao, C., Gao, Y., Zhang, S., Yang, Z., et al. (2018). HBXIP-elevated Methyltransferase METTL3 Promotes the Progression of Breast Cancer via Inhibiting Tumor Suppressor Let-7g. *Cancer Lett.* 415, 11–19. doi:10.1016/j.canlet.2017.11.018

Castellanos-Rubio, A., Santin, I., Olazagoitia-Garmendia, A., Romero-Garmendia, I., Jauregi-Miguel, A., Legarda, M., et al. (2019). A Novel RT-QPCR-Based Assay for the Relative Quantification of Residue Specific m6A RNA Methylation. *Sci. Rep.* 9 (1), 4220. doi:10.1038/s41598-019-40018-6

Chen, B., Ye, F., Yu, L., Jia, G., Huang, X., Zhang, X., et al. (2012). Development of Cell-Active N6-Methyladenosine RNA Demethylase FTO Inhibitor. *J. Am. Chem. Soc.* 134 (43), 17963–17971. doi:10.1021/ja3064149

Chen, H., Yao, J., Bao, R., Dong, Y., Zhang, T., Du, Y., et al. (2021). Cross-talk of Four Types of RNA Modification Writers Defines Tumor Microenvironment and Pharmacogenomic Landscape in Colorectal Cancer. *Mol. Cancer* 20 (1), 29. doi:10.1186/s12943-021-01322-w

Chen, S., Kumar, S., Espada, C. E., Tirumuru, N., Cahill, M. P., Hu, L., et al. (2021). N6-methyladenosine Modification of HIV-1 RNA Suppresses Type-I

Interferon Induction in Differentiated Monocytic Cells and Primary Macrophages. *Plos Pathog.* 17, e1009421. doi:10.1371/journal.ppat.1009421

Chen, S., Zhou, L., and Wang, Y. (2020). ALKBH5-mediated m6A Demethylation of lncRNA PVT1 Plays an Oncogenic Role in Osteosarcoma. *Cancer Cel Int* 20, 34. doi:10.1186/s12935-020-1105-6

Chen, Y. G., Chen, R., Ahmad, S., Verma, R., Kasturi, S. P., Amaya, L., et al. (2019). N6-Methyladenosine Modification Controls Circular RNA Immunity. *Mol. Cel* 76 (1), 96–109. doi:10.1016/j.molcel.2019.07.016

Cheng, M., Sheng, L., Gao, Q., Xiong, Q., Zhang, H., Wu, M., et al. (2019). The m6A Methyltransferase METTL3 Promotes Bladder Cancer Progression via AFF4/NF-Kb/MYC Signaling Network. *Oncogene* 38 (19), 3667–3680. doi:10.1038/s41388-019-0683-z

Cheng, Y., Fu, Y., Wang, Y., and Wang, J. (2020). The m6A Methyltransferase METTL3 Is Functionally Implicated in DLBCL Development by Regulating m6A Modification in PEDF. *Front. Genet.* 11, 955. doi:10.3389/fgene.2020.00955

Chiang, P. K. (1998). Biological Effects of Inhibitors of S-Adenosylhomocysteine Hydrolase. *Pharmacol. Ther.* 77 (2), 115–134. doi:10.1016/s0163-7258(97)00089-2

Cui, Q., Shi, H., Ye, P., Li, L., Qu, Q., Sun, G., et al. (2017). m 6 A RNA Methylation Regulates the Self-Renewal and Tumorigenesis of Glioblastoma Stem Cells. *Cel Rep.* 18 (11), 2622–2634. doi:10.1016/j.celrep.2017.02.059

Dai, T., Pu, Q., Guo, Y., Zuo, C., Bai, S., Yang, Y., et al. (2018). Analogous Modified DNA Probe and Immune Competition Method-Based Electrochemical Biosensor for RNA Modification. *Biosens. Bioelectron.* 114, 72–77. doi:10.1016/j.bios.2018.05.018

Devarkar, S. C., Wang, C., Miller, M. T., Ramanathan, A., Jiang, F., Khan, A. G., et al. (2016). Structural Basis for m7G Recognition and 2′-O-Methyl Discrimination in Capped RNAs by the Innate Immune Receptor RIG-I. *Proc. Natl. Acad. Sci. USA* 113 (3), 596–601. doi:10.1073/pnas.1515152113

Dong, L., Chen, C., Zhang, Y., Guo, P., Wang, Z., Li, J., et al. (2021). The Loss of RNA N6-Adenosine Methyltransferase Mettl14 in Tumor-Associated Macrophages Promotes CD8+ T Cell Dysfunction and Tumor Growth. *Cancer Cell* 39 (7), 945–957. doi:10.1016/j.ccell.2021.04.016

Du, H., Zhao, Y., He, J., Zhang, Y., Xi, H., Liu, M., et al. (2016). YTHDF2 Destabilizes m6A-Containing RNA through Direct Recruitment of the CCR4-Not Deadenylase Complex. *Nat. Commun.* 7, 12626. doi:10.1038/ncomms12626

Du, J., Liao, W., Liu, W., Deb, D. K., He, L., Hsu, P. J., et al. (2020). N6-Adenosine Methylation of Socs1 mRNA Is Required to Sustain the Negative Feedback Control of Macrophage Activation. *Developmental Cel* 55 (6), 737–753. doi:10.1016/j.devcel.2020.10.023

Dulken, B. W., Buckley, M. T., Navarro Negredo, P., Saligrama, N., Cayrol, R., Leeman, D. S., et al. (2019). Single-cell Analysis Reveals T Cell Infiltration in Old Neurogenic Niches. *Nature* 571 (7764), 205–210. doi:10.1038/s41586-019-1362-5

Durbin, A. F., Wang, C., Marcotrigiano, J., and Gehrke, L. (2016). RNAs Containing Modified Nucleotides Fail to Trigger RIG-I Conformational Changes for Innate Immune Signaling. *mBio* 7, e00833–16. doi:10.1128/mBio.00833-16

Fang, C., He, M., Li, D., and Xu, Q. (2021). YTHDF2 Mediates LPS-Induced Osteoclastogenesis and Inflammatory Response via the NF-Kb and MAPK Signaling Pathways. *Cell Signal.* 85, 110060. doi:10.1016/j.cellsig.2021.110060

Fedeles, B. I., Singh, V., Delaney, J. C., Li, D., and Essigmann, J. M. (2015). The AlkB Family of Fe(II)/α-Ketoglutarate-dependent Dioxygenases: Repairing Nucleic Acid Alkylation Damage and beyond. *J. Biol. Chem.* 290 (34), 20734–20742. doi:10.1074/jbc.r115.656462

Feng, Y., Hu, Y., Hou, Z., Sun, Q., Jia, Y., and Zhao, R. (2020). Chronic Corticosterone Exposure Induces Liver Inflammation and Fibrosis in Association with m6A-Linked post-transcriptional Suppression of Heat Shock Proteins in Chicken. *Cell Stress and Chaperones* 25 (1), 47–56. doi:10.1007/s12192-019-01034-7

Fu, Y., Zorman, B., Sumazin, P., Sanna, P. P., and Repunte-Canonigo, V. (2019). Epitranscriptomics: Correlation of N6-Methyladenosine RNA Methylation and Pathway Dysregulation in the hippocampus of HIV Transgenic Rats. *PLoS One* 14, e0203566. doi:10.1371/journal.pone.0203566

Gong, H., Liu, L., Cui, L., Ma, H., and Shen, L. (2021). ALKBH5-mediated m6A-demethylation of USP1 Regulated T-cell Acute Lymphoblastic Leukemia Cell Glucocorticoid Resistance by Aurora B. *Mol. Carcinogenesis* 60 (9), 644–657. doi:10.1002/mc.23330

Gu, X., Zhang, Y., Li, D., Cai, H., Cai, L., and Xu, Q. (2020). N6-methyladenosine Demethylase FTO Promotes M1 and M2 Macrophage Activation. *Cell Signal.* 69, 109553. doi:10.1016/j.cellsig.2020.109553

Guo, G., Wang, H., Shi, X., Ye, L., Yan, K., Chen, Z., et al. (2020). Disease Activity-Associated Alteration of mRNA M5 C Methylation in CD4+ T Cells of Systemic Lupus Erythematosus. *Front. Cel Dev. Biol.* 8, 430. doi:10.3389/fcell.2020.00430

Guo, M., Yan, R., Ji, Q., Yao, H., Sun, M., Duan, L., et al. (2020). IFN Regulatory Factor-1 Induced Macrophage Pyroptosis by Modulating m6A Modification of Circ_0029589 in Patients with Acute Coronary Syndrome. *Int. Immunopharmacology* 86, 106800. doi:10.1016/j.intimp.2020.106800

Han, D., Liu, J., Chen, C., Dong, L., Liu, Y., Chang, R., et al. (2019). Anti-tumour Immunity Controlled through mRNA m6A Methylation and YTHDF1 in Dendritic Cells. *Nature* 566 (7743), 270–274. doi:10.1038/s41586-019-0916-x

Han, H., Fan, G., Song, S., Jiang, Y., Qian, C. a., Zhang, W., et al. (2021). piRNA-30473 Contributes to Tumorigenesis and Poor Prognosis by Regulating m6A RNA Methylation in DLBCL. *Blood* 137 (12), 1603–1614. doi:10.1182/blood.2019003764

Hang, S., Paik, D., Yao, L., Kim, E., Trinath, J., Lu, J., et al. (2019). Bile Acid Metabolites Control TH17 and Treg Cell Differentiation. *Nature* 576 (7785), 143–148. doi:10.1038/s41586-019-1785-z

Hanniford, D., Ulloa-Morales, A., Karz, A., Berzoti-Coelho, M. G., Moubarak, R. S., Sánchez-Sendra, B., et al. (2020). Epigenetic Silencing of CDR1as Drives IGF2BP3-Mediated Melanoma Invasion and Metastasis. *Cancer Cell* 37 (1), 55–70. doi:10.1016/j.ccell.2019.12.007

Hesser, C. R., Karijolich, J., Dominissini, D., He, C., and Glaunsinger, B. A. (2018). N6-methyladenosine Modification and the YTHDF2 Reader Protein Play Cell Type Specific Roles in Lytic Viral Gene Expression during Kaposi's Sarcoma-Associated Herpesvirus Infection. *Plos Pathog.* 14, e1006995. doi:10.1371/journal.ppat.1006995

Huang, H., Weng, H., and Chen, J. (2020). m6A Modification in Coding and Non-coding RNAs: Roles and Therapeutic Implications in Cancer. *Cancer Cell* 37 (3), 270–288. doi:10.1016/j.ccell.2020.02.004

Huang, Y., Su, R., Sheng, Y., Dong, L., Dong, Z., Xu, H., et al. (2019). Small-Molecule Targeting of Oncogenic FTO Demethylase in Acute Myeloid Leukemia. *Cancer Cell* 35 (4), 677–691. doi:10.1016/j.ccell.2019.03.006

Huang, Y., Yan, J., Li, Q., Li, J., Gong, S., Zhou, H., et al. (2015). Meclofenamic Acid Selectively Inhibits FTO Demethylation of m6A over ALKBH5. *Nucleic Acids Res.* 43 (1), 373–384. doi:10.1093/nar/gku1276

Huangfu, N., Zheng, W., Xu, Z., Wang, S., Wang, Y., Cheng, J., et al. (2020). RBM4 Regulates M1 Macrophages Polarization through Targeting STAT1-Mediated Glycolysis. *Int. Immunopharmacology* 83, 106432. doi:10.1016/j.intimp.2020.106432

Jabs, S., Biton, A., Bécavin, C., Nahori, M.-A., Ghozlane, A., Pagliuso, A., et al. (2020). Impact of the Gut Microbiota on the m6A Epitranscriptome of Mouse Cecum and Liver. *Nat. Commun.* 11 (1), 1344. doi:10.1038/s41467-020-15126-x

Janela, B., Patel, A. A., Lau, M. C., Goh, C. C., Msallam, R., Kong, W. T., et al. (2019). A Subset of Type I Conventional Dendritic Cells Controls Cutaneous Bacterial Infections through VEGFα-Mediated Recruitment of Neutrophils. *Immunity* 50 (4), 1069–1083. doi:10.1016/j.immuni.2019.03.001

Jia, G., Fu, Y., Zhao, X., Dai, Q., Zheng, G., Yang, Y., et al. (2011). N6-methyladenosine in Nuclear RNA Is a Major Substrate of the Obesity-Associated FTO. *Nat. Chem. Biol.* 7 (12), 885–887. doi:10.1038/nchembio.687

Jurczyszak, D., Zhang, W., Terry, S. N., Kehrer, T., Bermúdez González, M. C., McGregor, E., et al. (2020). HIV Protease Cleaves the Antiviral m6A Reader Protein YTHDF3 in the Viral Particle. *Plos Pathog.* 16, e1008305. doi:10.1371/journal.ppat.1008305

Kang, H. J., Cheon, N. Y., Park, H., Jeong, G. W., Ye, B. J., Yoo, E. J., et al. (2021). TonEBP Recognizes R-Loops and Initiates m6A RNA Methylation for R-Loop Resolution. *Nucleic Acids Res.* 49 (1), 269–284. doi:10.1093/nar/gkaa1162

Karikó, K., Buckstein, M., Ni, H., and Weissman, D. (2005). Suppression of RNA Recognition by Toll-like Receptors: the Impact of Nucleoside Modification and the Evolutionary Origin of RNA. *Immunity* 23 (2), 165–175. doi:10.1016/j.immuni.2005.06.008

Kasowitz, S. D., Ma, J., Anderson, S. J., Leu, N. A., Xu, Y., Gregory, B. D., et al. (2018). Nuclear m6A Reader YTHDC1 Regulates Alternative Polyadenylation

and Splicing during Mouse Oocyte Development. *Plos Genet.* 14, e1007412. doi:10.1371/journal.pgen.1007412

Kennedy, E. M., Bogerd, H. P., Kornepati, A. V. R., Kang, D., Ghoshal, D., Marshall, J. B., et al. (2016). Posttranscriptional M 6 A Editing of HIV-1 mRNAs Enhances Viral Gene Expression. *Cell Host & Microbe* 19 (5), 675–685. doi:10.1016/j.chom.2016.04.002

Knuckles, P., Lence, T., Haussmann, I. U., Jacob, D., Kreim, N., Carl, S. H., et al. (2018). Zc3h13/Flacc Is Required for Adenosine Methylation by Bridging the mRNA-Binding Factor Rbm15/Spenito to the m6A Machinery Component Wtap/Fl(2)d. *Genes Dev.* 32 (5-6), 415–429. doi:10.1101/gad.309146.117

Lan, T., Li, H., Zhang, D., Xu, L., Liu, H., Hao, X., et al. (2019). KIAA1429 Contributes to Liver Cancer Progression through N6-methyladenosine-dependent post-transcriptional Modification of GATA3. *Mol. Cancer* 18 (1), 186. doi:10.1186/s12943-019-1106-z

Lei, H., He, M., He, X., Li, G., Wang, Y., Gao, Y., et al. (2021). METTL3 Induces Bone Marrow Mesenchymal Stem Cells Osteogenic Differentiation and Migration through Facilitating M1 Macrophage Differentiation. *Am. J. Transl Res.* 13 (5), 4376–4388.

Li, H.-B., Tong, J., Zhu, S., Batista, P. J., Duffy, E. E., Zhao, J., et al. (2017). m6A mRNA Methylation Controls T Cell Homeostasis by Targeting the IL-7/STAT5/SOCS Pathways. *Nature* 548 (7667), 338–342. doi:10.1038/nature23450

Li, H., Su, Q., Li, B., Lan, L., Wang, C., Li, W., et al. (2020). High Expression of WTAP Leads to Poor Prognosis of Gastric Cancer by Influencing Tumour-associated T Lymphocyte Infiltration. *J. Cel Mol Med* 24 (8), 4452–4465. doi:10.1111/jcmm.15104

Li, L.-J., Fan, Y.-G., Leng, R.-X., Pan, H.-F., and Ye, D.-Q. (2018). Potential Link between M 6 A Modification and Systemic Lupus Erythematosus. *Mol. Immunol.* 93, 55–63. doi:10.1016/j.molimm.2017.11.009

Li, N., Kang, Y., Wang, L., Huff, S., Tang, R., Hui, H., et al. (2020). ALKBH5 Regulates Anti-PD-1 Therapy Response by Modulating Lactate and Suppressive Immune Cell Accumulation in Tumor Microenvironment. *Proc. Natl. Acad. Sci. USA* 117 (33), 20159–20170. doi:10.1073/pnas.1918986117

Li, Z., Weng, H., Su, R., Weng, X., Zuo, Z., Li, C., et al. (2017). FTO Plays an Oncogenic Role in Acute Myeloid Leukemia as a N 6 -Methyladenosine RNA Demethylase. *Cancer Cell* 31 (1), 127–141. doi:10.1016/j.ccell.2016.11.017

Lichinchi, G., Gao, S., Saletore, Y., Gonzalez, G. M., Bansal, V., Wang, Y., et al. (2016). Dynamics of the Human and Viral m6A RNA Methylomes during HIV-1 Infection of T Cells. *Nat. Microbiol.* 1, 16011. doi:10.1038/nmicrobiol.2016.11

Liu, J., Eckert, M. A., Harada, B. T., Liu, S.-M., Lu, Z., Yu, K., et al. (2018). m6A mRNA Methylation Regulates AKT Activity to Promote the Proliferation and Tumorigenicity of Endometrial Cancer. *Nat. Cel Biol* 20 (9), 1074–1083. doi:10.1038/s41556-018-0174-4

Liu, J., and Jia, G. (2014). Methylation Modifications in Eukaryotic Messenger RNA. *J. Genet. Genomics* 41 (1), 21–33. doi:10.1016/j.jgg.2013.10.002

Liu, J., Yue, Y., Han, D., Wang, X., Fu, Y., Zhang, L., et al. (2014). A METTL3-METTL14 Complex Mediates Mammalian Nuclear RNA N6-Adenosine Methylation. *Nat. Chem. Biol.* 10 (2), 93–95. doi:10.1038/nchembio.1432

Liu, J., Zhang, X., Chen, K., Cheng, Y., Liu, S., Xia, M., et al. (2019). CCR7 Chemokine Receptor-Inducible Lnc-Dpf3 Restrains Dendritic Cell Migration by Inhibiting HIF-1α-Mediated Glycolysis. *Immunity* 50 (3), 600–615. doi:10.1016/j.immuni.2019.01.021

Liu, Q., Li, M., Jiang, L., Jiang, R., and Fu, B. (2019). METTL3 Promotes Experimental Osteoarthritis Development by Regulating Inflammatory Response and Apoptosis in Chondrocyte. *Biochem. Biophysical Res. Commun.* 516 (1), 22–27. doi:10.1016/j.bbrc.2019.05.168

Liu, Y., Liu, Z., Tang, H., Shen, Y., Gong, Z., Xie, N., et al. (2019). The N6-Methyladenosine (m6A)-Forming Enzyme METTL3 Facilitates M1 Macrophage Polarization through the Methylation of STAT1 mRNA. *Am. J. Physiol. Cel Physiol* 317, C762. doi:10.1152/ajpcell.00212.2019

Lu, N., Li, X., Yu, J., Li, Y., Wang, C., Zhang, L., et al. (2018). Curcumin Attenuates Lipopolysaccharide-Induced Hepatic Lipid Metabolism Disorder by Modification of M6 A RNA Methylation in Piglets. *Lipids* 53 (1), 53–63. doi:10.1002/lipd.12023

Lu, T. X., Zheng, Z., Zhang, L., Sun, H.-L., Bissonnette, M., Huang, H., et al. (2020). A New Model of Spontaneous Colitis in Mice Induced by Deletion of an RNA m6A Methyltransferase Component METTL14 in T Cells. *Cell Mol. Gastroenterol. Hepatol.* 10 (4), 747–761. doi:10.1016/j.jcmgh.2020.07.001

Lu, W., Tirumuru, N., St. Gelais, C., Koneru, P. C., Liu, C., Kvaratskhelia, M., et al. (2018). N6-Methyladenosine-binding Proteins Suppress HIV-1 Infectivity and Viral Production. *J. Biol. Chem.* 293 (34), 12992–13005. doi:10.1074/jbc.ra118.004215

Ma, H., Shen, L., Yang, H., Gong, H., Du, X., and Li, J. (2021). m6A Methyltransferase Wilms' Tumor 1-associated Protein Facilitates Cell Proliferation and Cisplatin Resistance in NK/T Cell Lymphoma by Regulating Dual-specificity Phosphatases 6 Expression via m6A RNA Methylation. *IUBMB Life* 73 (1), 108–117. doi:10.1002/iub.2410

Maier, B., Leader, A. M., Chen, S. T., Tung, N., Chang, C., LeBerichel, J., et al. (2020). A Conserved Dendritic-Cell Regulatory Program Limits Antitumour Immunity. *Nature* 580 (7802), 257–262. doi:10.1038/s41586-020-2134-y

Meyer, K. D., Patil, D. P., Zhou, J., Zinoviev, A., Skabkin, M. A., Elemento, O., et al. (2015). 5′ UTR m6A Promotes Cap-independent Translation. *Cell* 163 (4), 999–1010. doi:10.1016/j.cell.2015.10.012

Miranda-Gonçalves, V., Lobo, J., Guimarães-Teixeira, C., Barros-Silva, D., Guimarães, R., Cantante, M., et al. (2021). The Component of the m6A Writer Complex VIRMA Is Implicated in Aggressive Tumor Phenotype, DNA Damage Response and Cisplatin Resistance in Germ Cell Tumors. *J. Exp. Clin. Cancer Res.* 40 (1), 268. doi:10.1186/s13046-021-02072-9

Müller, T. A., Struble, S. L., Meek, K., and Hausinger, R. P. (2018). Characterization of Human AlkB Homolog 1 Produced in Mammalian Cells and Demonstration of Mitochondrial Dysfunction in ALKBH1-Deficient Cells. *Biochem. Biophysical Res. Commun.* 495 (1), 98–103. doi:10.1016/j.bbrc.2017.10.158

Müller, T. A., Tobar, M. A., Perian, M. N., and Hausinger, R. P. (2017). Biochemical Characterization of AP Lyase and m6A Demethylase Activities of Human AlkB Homologue 1 (ALKBH1). *Biochemistry* 56 (13), 1899–1910. doi:10.1021/acs.biochem.7b00060

Myoung, J., and Ganem, D. (2011). Infection of Lymphoblastoid Cell Lines by Kaposi's Sarcoma. *J. Virol.* 85 (19), 9767–9777. doi:10.1128/jvi.05136-11

Ni, W., Yao, S., Zhou, Y., Liu, Y., Huang, P., Zhou, A., et al. (2019). Long Noncoding RNA GAS5 Inhibits Progression of Colorectal Cancer by Interacting with and Triggering YAP Phosphorylation and Degradation and Is Negatively Regulated by the m6A Reader YTHDF3. *Mol. Cancer* 18 (1), 143. doi:10.1186/s12943-019-1079-y

Pan, Y. Y., Yang, J. X., Xu, Y. F., and Mao, W. (2020). Yin Yang-1 Suppresses CD40 ligand-CD40 Signaling-mediated Anti-inflammatory Cytokine Interleukin-10 Expression in Pulmonary Adventitial Fibroblasts by Promoting Histone H3 Tri-methylation at Lysine 27 Modification on Interleukin-10 Promoter. *Cell Biol Int* 44 (7), 1544–1555. doi:10.1002/cbin.11351

Pandolfini, L., Barbieri, I., Bannister, A. J., Hendrick, A., Andrews, B., Webster, N., et al. (2019). METTL1 Promotes Let-7 MicroRNA Processing via m7G Methylation. *Mol. Cel* 74 (6), 1278–1290. doi:10.1016/j.molcel.2019.03.040

Paris, J., Morgan, M., Campos, J., Spencer, G. J., Shmakova, A., Ivanova, I., et al. (2019). Targeting the RNA m6A Reader YTHDF2 Selectively Compromises Cancer Stem Cells in Acute Myeloid Leukemia. *Cell Stem Cell* 25 (1), 137–148. doi:10.1016/j.stem.2019.03.021

Ping, X.-L., Sun, B.-F., Wang, L., Xiao, W., Yang, X., Wang, W.-J., et al. (2014). Mammalian WTAP Is a Regulatory Subunit of the RNA N6-Methyladenosine Methyltransferase. *Cell Res* 24 (2), 177–189. doi:10.1038/cr.2014.3

Qiu, W., Zhang, Q., Zhang, R., Lu, Y., Wang, X., Tian, H., et al. (2021). N6-methyladenosine RNA Modification Suppresses Antiviral Innate Sensing Pathways via Reshaping Double-Stranded RNA. *Nat. Commun.* 12 (1), 1582. doi:10.1038/s41467-021-21904-y

Roundtree, I. A., Evans, M. E., Pan, T., and He, C. (2017). Dynamic RNA Modifications in Gene Expression Regulation. *Cell* 169 (7), 1187–1200. doi:10.1016/j.cell.2017.05.045

Saunders, K. O., Wiehe, K., Tian, M., Acharya, P., Bradley, T., Alam, S. M., et al. (2019). Targeted Selection of HIV-specific Antibody Mutations by Engineering B Cell Maturation. *Science* 366, e7199. doi:10.1126/science.aay7199

Scott, A. C., Dündar, F., Zumbo, P., Chandran, S. S., Klebanoff, C. A., Shakiba, M., et al. (2019). TOX Is a Critical Regulator of Tumour-specific T Cell Differentiation. *Nature* 571 (7764), 270–274. doi:10.1038/s41586-019-1324-y

Silla, T., Schmid, M., Dou, Y., Garland, W., Milek, M., Imami, K., et al. (2020). The Human ZC3H3 and RBM26/27 Proteins Are Critical for PAXT-Mediated Nuclear RNA Decay. *Nucleic Acids Res.* 48 (5), 2518–2530. doi:10.1093/nar/gkz1238

Song, T., Yang, Y., Wei, H., Xie, X., Lu, J., Zeng, Q., et al. (2019). Zfp217 Mediates m6A mRNA Methylation to Orchestrate Transcriptional and post-transcriptional Regulation to Promote Adipogenic Differentiation. *Nucleic Acids Res.* 47 (12), 6130–6144. doi:10.1093/nar/gkz312

Sorci, M., Ianniello, Z., Cruciani, S., Larivera, S., Ginistrelli, L. C., Capuano, E., et al. (2018). METTL3 Regulates WTAP Protein Homeostasis. *Cell Death Dis* 9 (8), 796. doi:10.1038/s41419-018-0843-z

Su, R., Dong, L., Li, Y., Gao, M., Han, L., Wunderlich, M., et al. (2020). Targeting FTO Suppresses Cancer Stem Cell Maintenance and Immune Evasion. *Cancer Cell* 38 (1), 79–96. doi:10.1016/j.ccell.2020.04.017

Sun, K., Du, Y., Hou, Y., Zhao, M., Li, J., Du, Y., et al. (2021). Saikosaponin D Exhibits Anti-leukemic Activity by Targeting FTO/m6A Signaling. *Theranostics* 11 (12), 5831–5846. doi:10.7150/thno.55574

Sun, X., Dai, Y., Tan, G., Liu, Y., and Li, N. (2020). Integration Analysis of m6A-SNPs and eQTLs Associated with Sepsis Reveals Platelet Degranulation and *Staphylococcus aureus* Infection Are Mediated by m6A mRNA Methylation. *Front. Genet.* 11, 7. doi:10.3389/fgene.2020.00007

Tirumuru, N., Zhao, B. S., Lu, W., Lu, Z., He, C., and Wu, L. (2016). N(6)-methyladenosine of HIV-1 RNA Regulates Viral Infection and HIV-1 Gag Protein Expression. *eLife* 5, e15528. doi:10.7554/eLife.15528

Tirumuru, N., and Wu, L. (2019). HIV-1 Envelope Proteins Up-Regulate N6-Methyladenosine Levels of Cellular RNA Independently of Viral Replication. *J. Biol. Chem.* 294 (9), 3249–3260. doi:10.1074/jbc.ra118.005608

Tong, J., Wang, X., Liu, Y., Ren, X., Wang, A., Chen, Z., et al. (2021). Pooled CRISPR Screening Identifies m6A as a Positive Regulator of Macrophage Activation. *Sci. Adv.* 7, eabd4742. doi:10.1126/sciadv.abd4742

Tong, J., Cao, G., Zhang, T., Sefik, E., Amezcua Vesely, M. C., Broughton, J. P., et al. (2018). m6A mRNA Methylation Sustains Treg Suppressive Functions. *Cel Res* 28 (2), 253–256. doi:10.1038/cr.2018.7

Toro-Ascuy, D., Rojas-Araya, B., Valiente-Echeverría, F., and Soto-Rifo, R. (2016). Interactions between the HIV-1 Unspliced mRNA and Host mRNA Decay Machineries. *Viruses* 8 (11), 320. doi:10.3390/v8110320

Wang, H., Hu, X., Huang, M., Liu, J., Gu, Y., Ma, L., et al. (2019). Mettl3-mediated mRNA m6A Methylation Promotes Dendritic Cell Activation. *Nat. Commun.* 10 (1), 1898. doi:10.1038/s41467-019-09903-6

Wang, J., Yan, S., Lu, H., Wang, S., and Xu, D. (2019). METTL3 Attenuates LPS-Induced Inflammatory Response in Macrophages via NF-Kb Signaling Pathway. *Mediators Inflamm.* 2019, 3120391. doi:10.1155/2019/3120391

Wang, L., Hui, H., Agrawal, K., Kang, Y., Li, N., Tang, R., et al. (2020). m6 A RNA Methyltransferases METTL3/14 Regulate Immune Responses to Anti-PD-1 Therapy. *EMBO J.* 39, e104514. doi:10.15252/embj.2020104514

Wang, L., Wen, M., and Cao, X. (2019). Nuclear hnRNPA2B1 Initiates and Amplifies the Innate Immune Response to DNA Viruses. *Science* 365, eaav0758. doi:10.1126/science.aav0758

Wang, N., Tang, H., Wang, X., Wang, W., and Feng, J. (2017). Homocysteine Upregulates interleukin-17A Expression via NSun2-Mediated RNA Methylation in T Lymphocytes. *Biochem. Biophysical Res. Commun.* 493 (1), 94–99. doi:10.1016/j.bbrc.2017.09.069

Wang, S., Chai, P., Jia, R., and Jia, R. (2018). Novel Insights on m6A RNA Methylation in Tumorigenesis: a Double-Edged Sword. *Mol. Cancer* 17 (1), 101. doi:10.1186/s12943-018-0847-4

Wang, X., Ji, Y., Feng, P., Liu, R., Li, G., Zheng, J., et al. (2021). The m6A Reader IGF2BP2 Regulates Macrophage Phenotypic Activation and Inflammatory Diseases by Stabilizing TSC1 and PPAR γ. *Adv. Sci.* 8 (13), 2100209. doi:10.1002/advs.202100209

Wang, Z., Pan, Z., Adhikari, S., Harada, B. T., Shen, L., Yuan, W., et al. (2021). m(6) A Deposition Is Regulated by PRMT1-Mediated Arginine Methylation of METTL14 in its Disordered C-Terminal Region. *EMBO J.* 40 (5), e106309. doi:10.15252/embj.2020106309

Weng, H., Huang, H., Wu, H., Qin, X., Zhao, B. S., Dong, L., et al. (2018). METTL14 Inhibits Hematopoietic Stem/Progenitor Differentiation and Promotes Leukemogenesis via mRNA m6A Modification. *Cell Stem Cell* 22 (2), 191–205. doi:10.1016/j.stem.2017.11.016

Wolf, D. A., Lin, Y., Duan, H., and Cheng, Y. (2020). eIF-Three to Tango: Emerging Functions of Translation Initiation Factor eIF3 in Protein Synthesis and Disease. *J. Mol. Cel Biol* 12 (6), 403–409. doi:10.1093/jmcb/mjaa018

Xia, H., Zhong, C., Wu, X., Chen, J., Tao, B., Xia, X., et al. (2018). Mettl3 Mutation Disrupts Gamete Maturation and Reduces Fertility in Zebrafish. *Genetics* 208 (2), 729–743. doi:10.1534/genetics.117.300574

Xiang, Y., Laurent, B., Hsu, C.-H., Nachtergaele, S., Lu, Z., Sheng, W., et al. (2017). RNA m6A Methylation Regulates the Ultraviolet-Induced DNA Damage Response. *Nature* 543 (7646), 573–576. doi:10.1038/nature21671

Xing, Y., Cheng, D., Shi, C., and Shen, Z. (2021). The Protective Role of YTHDF1-Knock Down Macrophages on the Immune Paralysis of Severe Sepsis Rats with ECMO. *Microvasc. Res.* 137, 104178. doi:10.1016/j.mvr.2021.104178

Xiong, F., Wang, R., Lee, J.-H., Li, S., Chen, S.-F., Liao, Z., et al. (2021). RNA m6A Modification Orchestrates a LINE-1-Host Interaction that Facilitates Retrotransposition and Contributes to Long Gene Vulnerability. *Cel Res* 31 (8), 861–885. doi:10.1038/s41422-021-00515-8

Yang, Z., Yang, S., Cui, Y-H., Wei, J., Shah, P., Park, G., et al. (2021). METTL14 Facilitates Global Genome Repair and Suppresses Skin Tumorigenesis. *Proc. Natl. Acad. Sci. U S A.* 118 (35), e2025948118. doi:10.1073/pnas.2025948118

Yankova, E., Blackaby, W., Albertella, M., Rak, J., De Braekeleer, E., Tsagkogeorga, G., et al. (2021). Small-molecule Inhibition of METTL3 as a Strategy against Myeloid Leukaemia. *Nature* 593 (7860), 597–601. doi:10.1038/s41586-021-03536-w

Yao, Y., Yang, Y., Guo, W., Xu, L., You, M., Zhang, Y.-C., et al. (2021). METTL3-dependent m6A Modification Programs T Follicular Helper Cell Differentiation. *Nat. Commun.* 12 (1), 1333. doi:10.1038/s41467-021-21594-6

Yin, H., Zhang, X., Yang, P., Zhang, X., Peng, Y., Li, D., et al. (2021). RNA m6A Methylation Orchestrates Cancer Growth and Metastasis via Macrophage Reprogramming. *Nat. Commun.* 12 (1), 1394. doi:10.1038/s41467-021-21514-8

Yoon, K.-J., Ringeling, F. R., Vissers, C., Jacob, F., Pokrass, M., Jimenez-Cyrus, D., et al. (2017). Temporal Control of Mammalian Cortical Neurogenesis by m6A Methylation. *Cell* 171 (4), 877–889. doi:10.1016/j.cell.2017.09.003

Yu, F., Wei, J., Cui, X., Yu, C., Ni, W., Bungert, J., et al. (2021). Post-translational Modification of RNA m6A Demethylase ALKBH5 Regulates ROS-Induced DNA Damage Response. *Nucleic Acids Res.* 49 (10), 5779–5797. doi:10.1093/nar/gkab415

Yu, R., Li, Q., Feng, Z., Cai, L., and Xu, Q. (2019). m6A Reader YTHDF2 Regulates LPS-Induced Inflammatory Response. *Ijms* 20 (6), 1323. doi:10.3390/ijms20061323

Yue, H., Nie, X., Yan, Z., and Weining, S. (2019). N6-methyladenosine Regulatory Machinery in Plants: Composition, Function and Evolution. *Plant Biotechnol. J.* 17 (7), 1194–1208. doi:10.1111/pbi.13149

Zhang, C., Chen, L., Peng, D., Jiang, A., He, Y., Zeng, Y., et al. (2020). METTL3 and N6-Methyladenosine Promote Homologous Recombination-Mediated Repair of DSBs by Modulating DNA-RNA Hybrid Accumulation. *Mol. Cel* 79 (3), 425–442. doi:10.1016/j.molcel.2020.06.017

Zhang, J., Kong, L., Guo, S., Bu, M., Guo, Q., Xiong, Y., et al. (2017). hnRNPs and ELAVL1 Cooperate with uORFs to Inhibit Protein Translation. *Nucleic Acids Res.* 45 (5), 2849–2864. doi:10.1093/nar/gkw991

Zhang, L., Hao, D., Ma, P., Ma, B., Qin, J., Tian, G., et al. (2021). Epitranscriptomic Analysis of m6A Methylome after Peripheral Nerve Injury. *Front. Genet.* 12, 686000. doi:10.3389/fgene.2021.686000

Zhang, P., He, Q., Lei, Y., Li, Y., Wen, X., Hong, M., et al. (2018). m6A-mediated ZNF750 Repression Facilitates Nasopharyngeal Carcinoma Progression. *Cel Death Dis* 9 (12), 1169. doi:10.1038/s41419-018-1224-3

Zhang, W., He, X., Hu, J., Yang, P., Liu, C., Wang, J., et al. (2019). Dysregulation of N6-Methyladenosine Regulators Predicts Poor Patient Survival in Mantle Cell Lymphoma. *Oncol. Lett.* 18 (4), 3682–3690. doi:10.3892/ol.2019.10708

Zhang, X., Li, X., Jia, H., An, G., and Ni, J. (2021). The m6A Methyltransferase METTL3 Modifies PGC-1α mRNA Promoting Mitochondrial Dysfunction and oxLDL-Induced Inflammation in Monocytes. *J. Biol. Chem.* 297, 101058. doi:10.1016/j.jbc.2021.101058

Zhang, Y., Wang, X., Zhang, X., Wang, J., Ma, Y., Zhang, L., et al. (2019). RNA-binding Protein YTHDF3 Suppresses Interferon-dependent Antiviral Responses by Promoting FOXO3 Translation. *Proc. Natl. Acad. Sci. USA* 116 (3), 976–981. doi:10.1073/pnas.1812536116

Zhao, W., Wang, Z., Sun, Z., He, Y., Jian, D., Hu, X., et al. (2018). RNA Helicase DDX5 Participates in oxLDL-Induced Macrophage Scavenger Receptor 1

Expression by Suppressing mRNA Degradation. *Exp. Cel Res.* 366 (2), 114–120. doi:10.1016/j.yexcr.2018.03.003

Zhao, X., Chen, Y., Mao, Q., Jiang, X., Jiang, W., Chen, J., et al. (2018). Overexpression of YTHDF1 Is Associated with Poor Prognosis in Patients with Hepatocellular Carcinoma. *Cbm* 21 (4), 859–868. doi:10.3233/cbm-170791

Zheng, G., Dahl, J. A., Niu, Y., Fedorcsak, P., Huang, C.-M., Li, C. J., et al. (2013). ALKBH5 Is a Mammalian RNA Demethylase that Impacts RNA Metabolism and Mouse Fertility. *Mol. Cel* 49 (1), 18–29. doi:10.1016/j.molcel.2012.10.015

Zheng, Q., Hou, J., Zhou, Y., Li, Z., and Cao, X. (2017). The RNA Helicase DDX46 Inhibits Innate Immunity by Entrapping m6A-Demethylated Antiviral Transcripts in the Nucleus. *Nat. Immunol.* 18 (10), 1094–1103. doi:10.1038/ni.3830

Zheng, Z., Zhang, L., Cui, X.-L., Yu, X., Hsu, P. J., Lyu, R., et al. (2020). Control of Early B Cell Development by the RNA N6-Methyladenosine Methylation. *Cel Rep.* 31 (13), 107819. doi:10.1016/j.celrep.2020.107819

Zhou, B., Liu, C., Xu, L., Yuan, Y., Zhao, J., Zhao, W., et al. (2020). N 6 -Methyladenosine Reader Protein YT521-B Homology Domain-Containing 2 Suppresses Liver Steatosis by Regulation of mRNA Stability of Lipogenic Genes. *Hepatology* 73 (1), 91–103. doi:10.1002/hep.31220

Zhou, J., Zhang, X., Hu, J., Qu, R., Yu, Z., Xu, H., et al. (2021). m6A Demethylase ALKBH5 Controls CD4+ T Cell Pathogenicity and Promotes Autoimmunity. *Sci. Adv.* 7, eabg0470. doi:10.1126/sciadv.abg0470

Zhu, X. J., Feng, J. Q., Zheng, M. Z., Yang, Z. R., Zhao, L., Zhang, W., et al. (2021). Metal-Protein Nanoparticles Facilitate Anti-VSV and H1N1 Viruses through the Coordinative Actions on Innate Immune Responses and METTL14. *Macromol Biosci.* 21, e2000382. doi:10.1002/mabi.202000382

Zhuang, M., Li, X., Zhu, J., Zhang, J., Niu, F., Liang, F., et al. (2019). The m6A Reader YTHDF1 Regulates Axon Guidance through Translational Control of Robo3.1 Expression. *Nucleic Acids Res.* 47 (9), 4765–4777. doi:10.1093/nar/gkz157

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