

Review

Role of m⁶A RNA Methylation in T Cell Biology and Immunotherapy

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Abstract

RNA modifications act as crucial post-transcriptional regulators that fine-tune gene expression to modulate cell function. Among these, N6-methyladenosine (m⁶A) is the most prevalent RNA modification in eukaryotic cells, regulating several RNA metabolism pathways including RNA splicing, nuclear export, stability, and translation. These processes are particularly important in rapidly responding immune cells such as T cells, which require dynamic changes in gene expression to support differentiation and effector function. This review focuses on the interplay between immunity and epitranscriptomics and explores the direct and indirect effects of m⁶A modification on T cells. Specifically, we discuss the role of different writers, erasers, and readers in modulating CD4+ and CD8+ T cell homeostasis, differentiation, and function. In addition, we summarize current evidence linking m⁶A regulators to anti-tumor T cell responses. Finally, we discuss the recent advances in the field of m⁶A and immunotherapy by highlighting the potential of pharmacological modulation of m⁶A regulators in augmenting the efficacy of existing immune therapies. Collectively, by integrating emerging mechanistic and translational insights, this review highlights the pivotal role of m⁶A regulation in T cell biology and underscores its potential to optimize next-generation immunotherapies.

Keywords: m⁶A RNA modification; CD8+ T cell; CD4+ T cell; immunotherapy; METTL3

1. Introduction

Epigenetic modifications are reversible chemical changes that modulate gene expression without altering the DNA sequence. Consequently, they control multiple cellular processes, including DNA replication, cell cycle, cellular differentiation, and cell death [1,2]. Historically, epigenetics has encompassed DNA methylation, chromatin remodeling, and histone modification. However, recent advances have expanded the classical view of epigenetic regulation to include epitranscriptomics, in which RNA modifications constitute an additional layer of gene regulation. There are more than 170 RNA modifications that can be found on mRNA, tRNA, rRNA, and short and long non-coding RNAs [3,4]. These RNA modifications play important roles in regulating cellular processes such as autophagy, cell death, proliferation, differentiation, migration, and metabolism [5,6], by modulating RNA stability, degradation, transport, splicing, polyadenylation, and translation [6,7]. Consequently, the significance of RNA modifications extends into clinical pathology, as imbalance in the epitranscriptomic profile can drive the development of complex diseases like cancer and autoimmune disorders [1,2].



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While the epitranscriptomic landscape is diverse, N6-methyladenosine (m^6A) represents the most prevalent and highly conserved RNA modification in eukaryotic cells [8]. m^6A is characterized by the addition of a methyl group at the sixth nitrogenous base of the adenine ring. The frequency of m^6A methylation is 0.1–0.6% of total adenosines in cellular RNA [9,10]. m^6A modification is dynamically regulated by two classes of enzymes, known as writers and erasers, which deposit and remove the methylation on the RNA, respectively [11] (Figure 1). Reader proteins recognize the m^6A residues and translate this mark into distinct functional outcomes [11] (Figure 1). m^6A modification is mostly enriched near the stop codons and 3'UTR of the mRNAs, but low levels can also be found in 5'UTR and the coding sequence, within specific sequence motifs called DRACH (where D = A/G/U; R = G/A; H = A/C/U) [4,12,13]. Recently, a fraction of m^6A modifications were reported in non-DRACH motifs, with the identified sites varying depending on the cell type and sequencing method used [14–16].

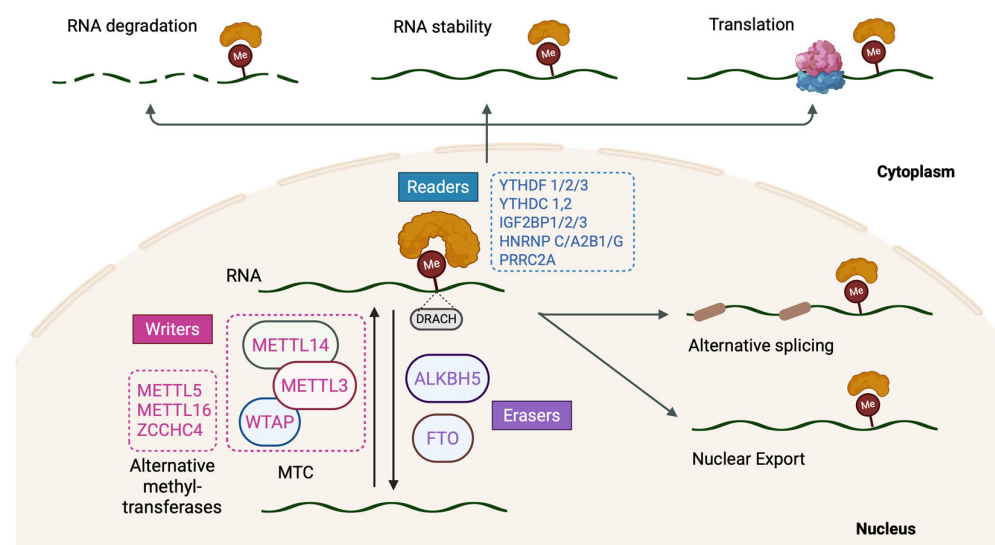


Figure 1. Illustration of the m^6A -related proteins and their function. The m^6A methyltransferase complex (MTC, core subunit of writers) primarily methylates RNAs by transferring a methyl group to adenines within specific sequence motifs called DRACH. METTL3 is the most studied methyltransferase that catalyzes this reaction with the help of associated proteins METTL14, WTAP, VIRMA, CBLL1, RBM15, and ZC3H13. In addition to METTL3, METTL5, METTL16, and ZCCHC4 can act as alternative methyltransferases. m^6A is a reversible process, and thus the methylation can be removed by demethylases (also called erasers). The two known erasers are FTO and ALKBH5. The methylated RNA can then be recognized by RNA-binding proteins (also called readers) that regulate downstream regulatory pathways, including RNA splicing, nuclear export, degradation, stability, and translation. The figure was created in BioRender. Butt, Y.A. (2026) <https://BioRender.com/dhvvmkx>.

Over the past decade, different technologies have been developed to detect m^6A modifications on cellular RNAs. These technologies are broadly categorized into sequencing-independent (e.g., LC/MS, SELECT, and ELISA kits); antibody-based m^6A immunoprecipitation followed by second-generation sequencing (e.g., MeRIP and miCLIP); chemical or enzymatic m^6A recognition followed by RNA sequencing (e.g., GLORI and MAZTER-seq); and methods based on third-generation sequencing (e.g., Oxford Nanopore Technology) [17]. A comprehensive description and comparison of these methods was recently reviewed [17]. These techniques have provided important insights into the cellular function and regulation of m^6A RNA modification. The most widely used approaches to date are MeRIP, which enables mapping of m^6A sites within a ~100 nucleotide window [13], and miCLIP, where UV crosslinking allows for individual nucleotide resolution of the m^6A sites on RNA transcripts [18]. Although the available technologies have revolutionized the

epitranscriptomic field, several limitations and challenges still remain, which should be considered before describing specific transcripts as bona fide m⁶A targets. For example, antibody-based assays are limited by antibody cross-reactivity, which could generate false-positive results, whereas some antibody-independent methods, such as MAZTER-seq, are restricted to DRACH motifs, and the third-generation sequencing methods still provide limited accuracy [17]. ELISA kits and LC/MS quantify global m⁶A levels on the RNA and do not distinguish between different transcripts. SELECT, on the other hand, examines m⁶A status on specific, already known sites of interest [19]. Therefore, identification of novel m⁶A sites should be supported by multiple complementary methods to account for technical limitations.

The deposition of m⁶A on RNA is catalyzed by a methyltransferase complex (MTC) primarily consisting of a METTL3-METTL14 heterodimer [20–22]. Methyltransferase-like 3 (METTL3) functions as the core catalytic subunit of the MTC, responsible for transferring a methyl group from S-adenosylmethionine (SAM) to adenosine residues of RNA. Methyltransferase-like 14 (METTL14) acts as the RNA-binding subunit, providing structural stability. Wilms Tumor 1-Associating Protein (WTAP) is another critical component of the MTC, responsible for proper localization and stability of the METTL3-METTL14 heterodimer [20–22]. Other known writers facilitating m⁶A deposition by acting as regulatory, scaffolding, or adapter proteins include vir-like m⁶A methyltransferase-associated protein (VIRMA), also known as KIAA1429, the RNA Binding Motif Protein 15/15B (RBM15/RBM15B), the Zinc Finger CCCH-Type Containing 13 (ZC3H13), and casitas B-lineage proto-oncogene like 1 (CBLL1) [20–22]. In addition to METTL3, Methyltransferase-like 16 (METTL16), Zinc Finger CCCH-Type Containing 4 (ZCCHC4), and Methyltransferase-like 5 (METTL5) can also deposit m⁶A methylation to distinct substrates [23–25]. ZCCHC4 and METTL5 are rRNA methyltransferases that mediate m⁶A modification of human 28S and 18S rRNA [25,26]. METTL16, on the other hand, catalyzes methylation on U6 spliceosomal RNA and specific other mRNAs, such as *MAT2A* [23,24].

m⁶A methylation is reversible and can be removed with the help of the erasers, including the AlkB homolog 5 (ALKBH5) and the fat mass and obesity-associated (FTO) proteins. Both FTO and ALKBH5 belong to the ALKB family of Fe(II)/ α -ketoglutarate-dependent dioxygenases [8,27]. FTO is the first RNA demethylase identified that is localized both in the nucleus and cytoplasm [8,27]. On the contrary, ALKBH5 is predominantly localized in the nucleus and has higher specificity for m⁶A residues within mRNAs [8]. Although FTO and ALKBH5 are expressed across diverse tissues and cell types, FTO is highly expressed in the hypothalamus while ALKBH5 is largely found in testes and lungs [8,28]. FTO and ALKBH5 differ in their ability to demethylate RNA, with ALKBH5 directly converting m⁶A to A, while FTO first converts m⁶A to hm⁶A and then to A [28].

The readers for m⁶A methylation are localized in both the nucleus and the cytoplasm, where they regulate multiple aspects of RNA metabolism. Primary readers include YTH family members, YTH domain-containing family proteins 1–3 (YTHDF1/2/3) and YTH domain-containing proteins 1–2 (YTHDC1/2), insulin-like growth factor 2 mRNA binding proteins 1/2/3 (IGF2BP1/2/3), and heterogeneous nuclear ribonucleoprotein C, A2B1, and G (HNRNP C/A2B1/G) [20–22,29–31]. YTHDF1, YTHDF3, and YTHDC2 are generally known to regulate translation, while YTHDF2 enables the degradation of mRNA transcripts. YTHDC1 is involved in mRNA splicing and nuclear export [8,21]. IGF2BP family members affect RNA stability, while HNRNP members are involved in pre-mRNA processing, alternative splicing, and X chromosome inactivation [8,21,22,31]. In addition to these major reader families, PRRC2A has been identified as an m⁶A reader that also regulates mRNA stability [32,33]. Recently, machine learning models have also been used to identify novel m⁶A readers, including FUBP3, FXR2, L1TD1, and DDX6 [34].

m⁶A methylation plays a role in several cellular processes including stem cell differentiation, cell proliferation, fate determination, cell death, immune responses, and inflammation [35–38]. Consequently, changes in m⁶A abundance have also been implicated in the pathogenesis of several diseases, including cancer, aging, neurological diseases, autoimmune diseases, and cardiovascular and metabolic diseases [39–42]. While our basic understanding of m⁶A methylation derives primarily from stem cell biology and cancer research, studies over the last decade have expanded to immune regulation [9,43,44]. This shift was predominantly catalyzed by the discovery that m⁶A serves as a critical post-transcriptional regulator of transcription, splicing, nuclear export, translation, RNA stability, and decay, thereby facilitating precise and rapid tuning of genetic expression required for immune cell activation, differentiation, and homeostasis [38,44,45].

Innate and adaptive immunity represent the two pillars of the immune system, each playing distinct yet complementary roles in host defense. While innate immunity provides immediate and short-term protection, the adaptive immune response emerges later and is characterized by its specificity and capacity to provide long-term protection. The adaptive immune response is orchestrated by B cells, which produce antigen-specific antibodies, and T cells, which eliminate infected or malignant cells. The role of m⁶A in innate immunity has been extensively reviewed before [46–48]. Thus, this review will solely focus on the effect of m⁶A on T cells and T cell-based immunotherapies.

T cells are broadly classified into two major subsets: CD8⁺ cytotoxic T cells and CD4⁺ helper T cells. CD8⁺ T cells recognize peptides presented on major histocompatibility complex (MHC) class I molecules, which are ubiquitously expressed on all nucleated cells, whereas CD4⁺ T cells are restricted to antigens presented by MHC class II molecules, expressed primarily on antigen-presenting cells (APCs) [49,50]. Upon antigen recognition, naive CD8⁺ T cells (TN) undergo clonal expansion and differentiate into effector T cells (TE), which eliminate target cells by the production of cytokines and other cytotoxic effector molecules. Following pathogen clearance, most effector T cells undergo apoptosis, while a small subset survives and differentiates into long-lived memory T cells (TM). These memory CD8⁺ T cells persist within the host, enabling a rapid and robust response upon antigen re-encounter [50]. Unlike CD8⁺ T cells, CD4⁺ T cells primarily function as orchestrators of the immune response, activating and coordinating other immune cells, including B cells, macrophages, and CD8⁺ T cells, through the secretion of cytokines [49]. Although CD4⁺ T cells are not generally considered direct killers, certain subsets have been shown to exhibit cytotoxic activity under specific conditions [51]. This coordinated interplay is essential to facilitate functional immune homeostasis for effective pathogen clearance and long-term immune memory.

To better understand the regulatory influence of m⁶A on T cell biology and its therapeutic relevance, this review highlights how m⁶A regulators, including writers, erasers, and readers, affect CD8⁺ and CD4⁺ T cell differentiation and function, alongside their therapeutic potential. Since the available literature is currently heavily centered on the role of METTL3 in T cell biology and on the combination of m⁶A manipulation with immune checkpoint blockade, this review reflects that emphasis.

2. Role of m⁶A Methylation in CD4⁺ T Cells

Upon activation by antigen-presenting cells, naive CD4⁺ T cells differentiate into effector helper subsets (T-helper 1 (Th1), T-helper 2 (Th2), T-helper 9 (Th9), T-helper 17 (Th17), T-helper 22 (Th22)), follicular helper T cells (Tfh), or regulatory T cells (Treg). This differentiation is directed by specific cytokine milieus and lineage-defining transcription factors [49]. The resulting CD4⁺ helper subsets mediate specialized immune responses tailored to different classes of pathogens through the production of distinct sets of cytokines

that coordinate the activity of other immune cells. Th1 cells are characterized by their ability to produce IFN- γ (interferon gamma), and their induction relies on the transcription factor T-bet (T-box expressed in T cells). Th2 CD4⁺ T cells are GATA3 (GATA binding protein 3) and STAT5 (signal transducer and activator of transcription 5) dependent and produce IL-4/IL-5 (interleukin 4/5). ROR γ t (retinoic acid receptor-related orphan receptor gamma t) and Bcl6 (B-cell lymphoma 6) govern the differentiation of Th17 and Th22. Th17 produces IL-17 and IL-22 while Th22 produces IL-22. The transcription factors PU.1 (purine-rich box 1), BATF (basic leucine zipper ATF-like transcription factor), and IRF4 (interferon regulatory factor 4) orchestrate together the differentiation of CD4⁺ T cells into IL-9-producing Th9 cells [52–54]. Finally, the transcription factor Foxp3 (forkhead box P3) regulates Treg differentiation, which produces IL-10 and TGF- β (transforming growth factor beta) [49]. Emerging evidence demonstrates that m⁶A is a key determinant of CD4⁺ T cell fate by regulating multiple key transcription factors and cytokines involved in CD4⁺ T cell differentiation and function. The subsequent sections will elucidate the role of writers, erasers, and readers in governing CD4⁺ T cell-intrinsic responses.

2.1. Writers

Among the different components of the m⁶A machinery, the methyltransferases are the most extensively studied in T cells. m⁶A RNA methylation plays an important role in thymic T cell development, even prior to commitment towards single CD4⁺ or CD8⁺ T cells [55,56]. *Mettl3* depletion in mice caused loss of $\alpha\beta$ T cells due to increased apoptosis and reduced the double-positive CD4⁺CD8⁺ population while increasing the double-negative CD4[−]CD8[−] population compared with wild-type mice [56]. Similarly, *Wtap* depletion decreased TCR- β (T cell receptor beta) surface expression on both CD4 and CD8 single-positive cells [55]. These findings highlight the essential role of m⁶A writers in thymocyte T cell development and survival.

Beyond their role in thymocyte development, m⁶A writers also play crucial roles in mature peripheral CD4⁺ T cells (Table S1). In naive CD4⁺ T cells, the expression of METTL3 increases upon stimulation and reaches a peak after 6 h of activation, whereas METTL14 follows a similar pattern but peaks later at 48 h of activation [57]. Following activation in naive T cells, METTL3 interacts with the alternative polyadenylation factor NUDT21 to promote 3'UTR lengthening of target transcripts [57]. Genetic studies further demonstrated that lineage-specific deletion of *Mettl3* and *Mettl14* in CD4-cre mice resulted in impaired CD4⁺ T cell homeostasis [58]. Adoptively transferred *Mettl3*-knockout naive T cells into lymphopenic mice retained their naive phenotype, proliferated more slowly than their WT counterparts, but remained viable for up to 12 weeks [58]. The impaired homeostatic expansion of METTL3-deficient CD4⁺ T cells was attributed to reduced IL7R signaling, reflected by decreased phosphorylation of Janus kinase 1 (JAK1) and STAT5. This decreased phosphorylation hampered their ability to translocate to the nucleus and initiate transcription [58]. This phenotype was driven by increased expression of the suppressor of cytokine signaling proteins (SOCS1, SOCS3, and CISH) as METTL3-deficient cells increased mRNA stability of these transcripts [58]. Similar results were obtained by Yao et al., who showed increased *Socs1* mRNA levels in *Mettl3*-knockout Tfh cells [59].

In addition to its role in CD4⁺ T cell homeostasis, METTL3 has been shown to regulate T cell differentiation. In an acute LCMV infection mouse model, it was shown that T cell-specific depletion of METTL3 resulted in a modest skewing towards a Th1 fate and a substantial reduction in Tfh cells, indicating that METTL3 is essential for Tfh development [59]. In contrast, Th2 and Treg differentiation were largely unaffected, whereas Th17 differentiation was reduced following immunization with Keyhole Limpet Hemocyanin (KLH) [59]. Bone marrow chimeras and adoptive transfer experiments further demon-

strated that the effect of METTL3 on Tfh differentiation is T cell intrinsic [59]. In fact, *Mettl3*-deficient Tfh cells showed decreased protein and mRNA expression of key Tfh genes *Cxcr5*, *Pdcd1* (PD-1), *Icos*, and *Bcl6*, and the transcription factor TCF-1 (T cell factor 1). Notably, forced expression of TCF-1 in METTL3-deficient T cells rescued the defect in Tfh differentiation, highlighting that TCF-1 is a key downstream target through which METTL3 regulates Tfh lineage commitment [59].

Contrasting findings regarding CD4⁺ T cell differentiation were reported in the context of autoimmunity [60]. In fact, inhibition of METTL3 in a DBA/2 graft-versus-host disease (GvHD) mouse model resulted in reduced frequencies of naive CD4⁺ T cells and Tregs and increased frequencies of effector memory and IL-17-producing CD4⁺ T cells [60]. Inhibition of METTL3 exacerbated the pathogenesis of systemic lupus erythematosus (SLE), an autoimmune disease characterized by dysregulated CD4⁺ T cell responses, in mice. Interestingly, reduced METTL3 expression was also found in CD4⁺ T cells from SLE patients, and a negative association was shown between the severity of SLE and METTL3 expression, suggesting a role for METTL3 in SLE pathogenesis [60].

In addition to its role in conventional CD4⁺ T cell differentiation, METTL3 has also been implicated in mediating Treg differentiation. In mice, METTL3-deficient CD4⁺ T cells retained the capacity to differentiate into Tregs both in vitro under Treg-polarizing conditions and in vivo following KLH immunization [58,59]. In contrast, knockdown or inhibition of METTL3 in human CD4⁺ T cells impaired Treg differentiation, which was attributed to METTL3 directly methylating and stabilizing *Foxp3* mRNA [60].

Beyond its role in Treg differentiation, METTL3 is also essential for maintaining Treg function. Treg-specific ablation of *Mettl3* causes severe autoimmune disease and increases mortality in mice, consistent with markedly reduced suppressive capacity of METTL3-deficient Tregs [61]. Mechanistically, this defect was driven by reduced IL-2 signaling and linked to increased expression of *Socs* family members, known for acting as negative regulators of the IL-2-STAT signaling pathway [61]. In agreement with these findings, deletion of *Wtap* in Tregs led to systemic inflammation, characterized by enlarged spleen and lymph nodes as well as colitis in mice [55]. While the frequency of regulatory T cells in the spleen of WTAP-deficient mice remained unchanged, their proportion was significantly reduced in the lamina propria, accompanied by increased production of IL-17 and IFN- γ and increased mRNA expression levels of other inflammatory cytokines, including *Tnf* (tumor necrosis factor), *Il1 β* , *Il2*, *Il6*, *Ifng*, and *Tgfb* [55]. This phenotype was attributed to a reduction in the ROR γ ⁺ Treg population, a Treg subset important for intestinal immune suppression [55].

Similar results were obtained in mice lacking METTL14, a subunit of the writer complex, in CD4⁺ T cells [62]. In fact, METTL14-deficient CD4⁺ T cells displayed a decreased ability to differentiate into ROR γ ⁺ Tregs, and METTL14-deficient Tregs were unable to suppress colitis in a naive CD4 T cell adoptive transfer model [62]. Consistent with these findings, Treg heterozygous deletion of *Mettl14* also impaired immune tolerance in a transplantation model, resulting in allograft rejection accompanied by increased CD4⁺ and CD8⁺ T cell infiltration and reduced Treg expansion and suppressive function [63]. This phenotype was associated with decreased expression of pro-tolerogenic factors (TGF- β , IL-2, and IL-10) and increased IFN- γ and expansion of Th1, Th2, and Th17 subsets. Similar to the observations made in METTL3-deficient Tregs, these effects were attributed to altered RNA expression of *Socs* genes and genes involved in the JAK-STAT signaling pathway [63].

The m⁶A writer complex also regulates receptor-mediated clonal expansion of CD4⁺ T cells. Adoptive transfer of *Wtap*-depleted CD4⁺ T cells into lymphopenic hosts revealed that, although these cells retained partial proliferative capacity, they exhibited remarkably impaired antigen-driven expansion, resulting in reduced T cell numbers in the lymph

nodes [55]. Depletion of both *Mettl3* and *Wtap* also increased apoptosis upon TCR restimulation [55]. Moreover, *Wtap*-depleted CD4⁺ T cells in the spleen exhibited spontaneous activation, which correlated with the impaired survival of these mice [55]. These findings indicate that m⁶A writers are important for robust T cell proliferation and homeostatic expansion [48].

2.2. Erasers

m⁶A methylation modulates cytokine expression in human CD4⁺ T cells [64]. m⁶A methylome profiling identified hundreds of activation-induced m⁶A sites, including enrichment within the *TNF* 3'UTR. Functional studies showed that inhibition of the demethylase FTO reduced, whereas METTL3 inhibition increased *TNF* transcript and protein levels, indicating a direct role for m⁶A in regulating cytokine expression. These effects were attributed to altered *TNF* mRNA stability, as pre-mRNA levels remained unchanged [64]. FTO has also been shown to promote CD4⁺ T cell differentiation into the Th1 lineage, as FTO ablation restricted Th1 expansion [65]. Consequently, *Fto*-knockout CD4⁺ T cells failed to elicit an effective Th1⁺ response, rendering the host susceptible to bacterial infections. This impaired response was accompanied by lower T-bet and IFN- γ levels, while transcriptome-wide analysis further revealed a global reduction in Th1-associated gene expression [65].

ALKBH5, another m⁶A demethylase, was identified as a driver of CD4⁺ T cell pathogenicity, as adoptive transfer of ALKBH5-depleted CD4⁺ T cells decreased colitis severity in mice [66]. In addition, ALKBH5 ablation protects against experimental autoimmune encephalomyelitis (EAE), which is a CD4⁺ T cell-mediated autoimmune disease that leads to neuroinflammation and paralysis in rodents [66]. ALKBH5 ablation suppressed the capacity of CD4⁺ T cells to recruit neutrophils and lowered Th17 levels in the central nervous system. Mechanistically, ALKBH5 deficiency increased the methylation and decreased the stability of *Cxcl2* (C-X-C motif chemokine ligand) and *Ifng* mRNAs (IL-17 signaling pathway members), thereby decreasing their protein expression and ultimately limiting the effector CD4⁺ T cell responses [66].

2.3. Readers

m⁶A-specific binding proteins can also modulate cytokine expression and maintain CD4⁺ T cell homeostasis and functions. For example, the m⁶A binding protein YTHDF2 binds *TNF* mRNA in human CD4⁺ T cells, facilitating mRNA degradation and thus, reduced cytokine expression [64]. Parallel to this finding, YTHDF2 also regulates Treg function within the tumor microenvironment [67]. Treg-specific YTHDF2 depletion led to reduced Treg infiltration into the tumor, significantly slowing down melanoma and colon tumor growth in mice [67]. Although YTHDF2 ablation had a negligible effect on Treg migration, it compromised the survival of tumor-infiltrating Tregs. Mechanistically, YTHDF2 deficiency altered TNF-NF κ B signaling, reducing Treg suppressive function and enhancing antitumor immunity. Interestingly, YTHDF2 deficiency did not disrupt peripheral immune homeostasis, suggesting that the effects on Treg function were tumor restricted, highlighting YTHDF2 as a potential target for cancer immunotherapy [67]. YTHDF2 has also been shown to inhibit mouse and human Th9 differentiation by destabilizing *Gata3* and *Smad3* mRNAs under Th9-polarizing cytokines IL-4 and TGF- β [68]. Furthermore, YTHDF2-deficient Th9 cells produce increased levels of IL-9 and IL-21, thereby promoting the recruitment of Natural Killer (NK) cells and CD8⁺ T cells into the tumor microenvironment [68].

Collectively, these studies demonstrate that m⁶A methylation regulates CD4⁺ T cell proliferation, differentiation, and function (Figure 2). Through the coordinated actions of writers, erasers, and readers, m⁶A machinery dynamically controls cytokine signaling,

transcriptional programs, and immune homeostasis across multiple CD4⁺ T cell subsets (Table S1). Dysregulation of these pathways can contribute to pathology, highlighting the need for further investigation into the role of the m⁶A machinery in T cell biology in health and disease.

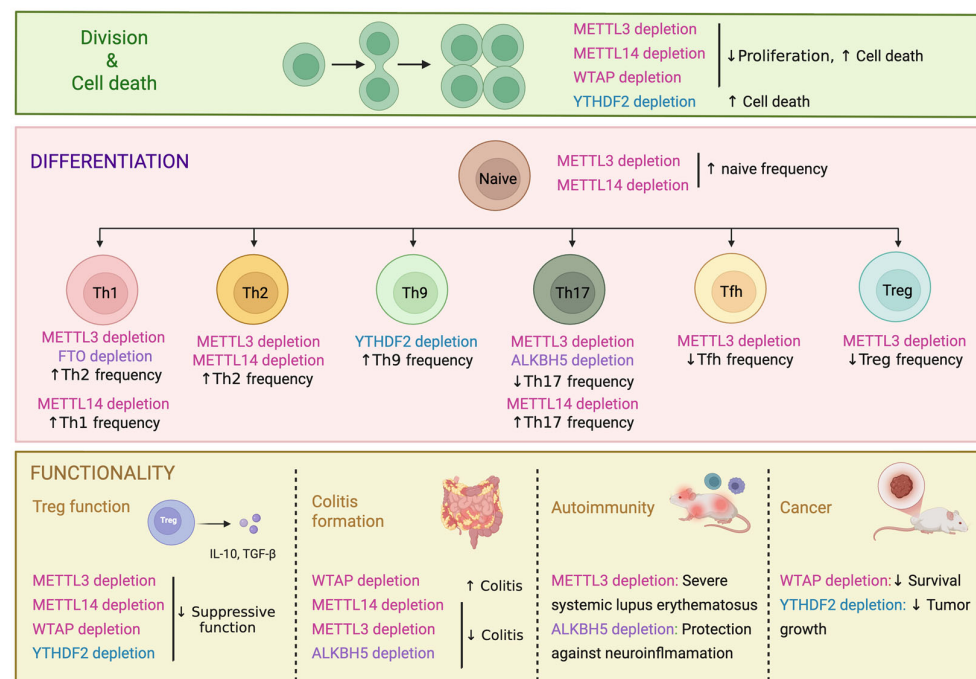


Figure 2. Regulatory role of the m⁶A machinery in CD4⁺ T cell-intrinsic responses. m⁶A methylation modulates CD4⁺ T cells by regulating key mechanisms such as cell proliferation, differentiation, and function. The m⁶A writers are depicted in pink, the erasers are depicted in purple, and the readers are in blue. Upward and downward arrows indicate an increase or decrease, respectively, relative to the control condition. The figure was created in BioRender. Butt, Y.A. (2026) <https://BioRender.com/t9acpi2>.

3. Role of m⁶A Methylation in CD8⁺ T Cells

CD8⁺ T cells are crucial players of adaptive immunity, due to their paramount role in killing malignant and virally infected cells. When CD8⁺ T cells encounter malignant or infected cells, they produce high levels of effector molecules, such as cytokines and granzymes, to eliminate the target cells. After target cell clearance, most effector CD8⁺ T cells undergo apoptosis, but importantly, a subset differentiates into memory cells, which persist for extended periods and provide long-term immunity. The subsequent sections describe how m⁶A mRNA methylation controls CD8⁺ T cell survival, proliferation, differentiation, and function through both T cell-intrinsic and T cell-extrinsic mechanisms (Table S2). Specifically, we discuss how m⁶A regulators directly affect CD8⁺ T cell biology (intrinsic effects), as well as how modulation of these regulators in other cell types (e.g., cancer cells, tumor-associated macrophages, dendritic cells) can indirectly shape CD8⁺ T cell responses (extrinsic effects).

3.1. Writers

While many studies have investigated the intrinsic effects of m⁶A regulators in CD4⁺ T cells, comparatively little attention has been paid to their intrinsic roles in CD8⁺ T cells. A recent study by Gameiro et al. has provided a new framework for understanding the effects of m⁶A methylation in activated human CD8⁺ T cells by identifying a class of meta-unstable mRNAs [69]. The authors revealed a mechanism in which m⁶A modifications are functionally connected to AU-rich elements (AREs), suggesting an additional regulatory layer that modifies the CD8⁺ T cell transcriptome. It is well established that AREs, abundant

sequences in the 3' untranslated region (3'UTR), represent an important mechanism of regulation of cytokine mRNAs in CD8+ T cells [70]. To achieve deep insights into site-specific regulation, Gameiro et al. utilized genome-wide mapping techniques, such as miCLIP and GLORI-sequencing, and identified critical m⁶A sites in primary human CD8+ T cells upon activation [69]. The study revealed that a subset of mRNAs contained m⁶A sites flanked by ARE sites, which rapidly decayed upon CD8+ T cell activation and were characterized as 'meta-unstable mRNAs'. These meta-unstable transcripts encoded genes involved in immune activation, T cell memory, cytokines, and cytokine-related genes. Tight regulation of these transcripts is critical to ensure timely expression and to prevent prolonged or aberrant signaling. Functional analysis confirmed that m⁶A promotes the decay of the meta-unstable transcripts, and METTL3 inhibition increased the mRNA stability and protein expression for some of these targets (e.g., IL7R α) [69]. The authors further demonstrated that the ARE-flanking m⁶A sites recruit both established m⁶A-specific RNA-binding proteins (RBPs), including YTHDF and YTHDC family members, as well as newly identified RBPs, such as members of the Like-Sm (LSM) protein family [69].

In addition to these findings in human CD8+ T cells, Guo et al. showed the importance of METTL3 in effector CD8+ T cell differentiation and memory formation in mice. Microarray data analysis revealed that the expression levels of METTL3, METTL14, and METTL16 increase during CD8+ T cell activation and the memory phase, whereas they decrease during the effector phase [71]. These temporal fluctuations point towards a sophisticated m⁶A regulatory program in a T cell differentiation state-specific manner. The authors also showed that upon acute infection, the frequency of CD8+ T cells was reduced in *Mettl3* conditional knockout mice. However, these defects were more pronounced in effector CD8+ T cells than in naive T cells, indicating impaired expansion of the effector population. The *Mettl3*-deficient effector CD8+ T cells also had decreased levels of IFN- γ , TNF- α , and IL-2, resulting in lower cytotoxic activity. Consistent with these findings, the expression of the transcription factor T-bet was reduced following *Mettl3* depletion. The *Tbx21* transcript, which encodes T-bet, was identified as a direct METTL3 target, and its destabilization impaired effector CD8+ T cell differentiation. In addition to effector CD8+ T cell differentiation, the authors showed that METTL3 modulated memory formation of CD8+ T cells [71]. METTL3-deficient CD8+ T cells failed to mount an effective secondary response upon secondary infection, indicating the importance of METTL3-mediated m⁶A methylation in establishing long-term CD8+ T cell immunity [71].

In line with the negative effects of METTL3 inhibition in controlling infection, decreased METTL3 levels in intratumoral CD8+ T cells reduce T cell migration via lowering the levels of β 1-integrin (ITGB1)—an important T cell infiltration molecule [72]. Interestingly, the decreased expression of METTL3 in the CD8+ T cells was caused by extracellular tumoral acidity—a hallmark of the immunosuppressive tumor microenvironment (TME) [72]. METTL3 inhibition also decreased T cell infiltration in 2D and 3D models with reduced migration capacity and ITGB1 levels. Overexpression of METTL3 or ITGB1 in CD8+ T cells reversed this phenotype, leading to better infiltration and antitumor activity in mice [72]. These results indicate the presence of a sophisticated interplay between the T cell-intrinsic m⁶A regulators and the tumor microenvironment in shaping CD8+ T cell function.

While most research focuses on METTL3, recent evidence also suggests a role for WTAP in CD8+ T cell biology and tumor progression. Tumor-infiltrating CD8+ T cells showed increased WTAP expression in patients with hepatocellular carcinoma (HCC) [73]. Functional in vitro analysis revealed that WTAP overexpression in CD8+ T cells inhibited CD8+ T cell proliferation and effector function and reduced cytokine expression, including perforin, IFN- γ , Granzyme-B (Gzmb), and TNF- α . This demonstrates that WTAP directly regulates CD8+ T cell immune responses [73]. In addition, WTAP-dependent m⁶A

methylation of *PDCD1* mRNA, which encodes PD-1 (programmed cell death protein 1), enhanced its translation through interaction with the reader protein YTHDF1, but not YTHDF2, highlighting the target specificity of distinct m⁶A readers. In line with this, the effects of *WTAP* overexpression on CD8⁺ T cell phenotype and cytokine production were reversed following *YTHDF1*-knockdown. These findings indicate a functional link between *WTAP* and *YTHDF1* and imply that *YTHDF1* is the functional executor of *WTAP*-mediated signaling [73].

In contrast to the conventional view of cell-intrinsic effects of m⁶A methylation on CD8⁺ T cells, many studies have focused on how modulating m⁶A levels in neighboring cells can affect CD8⁺ T cell migration, differentiation, and function. For instance, m⁶A methylation can exert its effects indirectly via tumor-associated macrophages (TAMs) [74]. *METTL14* deficiency in TAMs indirectly alters CD8⁺ T cell anti-tumor efficacy and drives them towards a dysfunctional state. The decrease in anti-tumor efficacy is driven by the loss of m⁶A levels in *Ebi3*, a cytokine subunit of IL-27 and IL-35, linked to CD8⁺ T cell dysfunction and exhaustion. Subsequently, high *EBI3* levels in the TME increase immunosuppression, which leads to decreased cytotoxic activity of CD8⁺ T cells. The tumor-infiltrating CD8⁺ T cells also showed a dysfunctional phenotype, with increased levels of exhaustion markers (TIM-3, LAG-3, TIGIT, and CD39) and reduced cytokine levels (IFN- γ , GZMB) in *Mettl14*-knockout mice [74]. Overall, *METTL14* in macrophages is important for proper CD8⁺ T cell function and tumor control. These results indicate that m⁶A methylation via *METTL14* is a crucial regulator of macrophage–T cell crosstalk, which alters CD8⁺ T cell anti-tumor efficacy.

METTL3 levels in tumor cells can also orchestrate CD8⁺ T cell fate and promote immune evasion. *METTL3*-knockdown in breast cancer cells leads to increased anti-tumor activity by cytokine-induced killer cells expressing high levels of IL-2 and IFN- γ in co-culture in vitro experiments [75]. Similar results were observed in xenograft mouse models, which showed increased T cell infiltration, primarily due to decreased PD-L1 (programmed death-ligand 1) expression in breast cancer cells. PD-L1, a key mediator of tumor immune evasion, was identified as a downstream target of *METTL3*-dependent m⁶A methylation, and its expression positively correlated with *METTL3* levels in breast cancer cells [75]. Similar results were reported in non-small-cell lung carcinoma (NSCLC) [76]. Specifically, NSCLC patients had higher expression of the circular RNA circIGF2BP3 as a result of *METTL3*-dependent m⁶A modification, and higher circIGF2BP3 expression was negatively correlated with CD8⁺ tumor-infiltrating lymphocytes (TIL) infiltration. Functional assays revealed that the circIGF2BP3 upregulated plakophilin 3 (PKP3) expression, which in turn stabilized PD-L1 expression in tumor cells, thereby suppressing the anti-tumor responses of CD8⁺ T cells [76]. Most importantly, PKP3 blockade increased the efficacy of PD-1 blockade therapy.

In addition, in co-culture models of mouse melanoma, mouse breast cancer, and human ovarian cancer, *METTL3* inhibition enhanced anti-tumor responses only when applied to tumor cells, as pre-treating CD8⁺ T cells with a *METTL3* inhibitor did not yield significant effects [77]. *METTL3* inhibition of human ovarian cancer cells increased the expression levels of IFN- γ , IL-1 β , and TNF- α in T cells [77]. Mechanistically, it was shown that *METTL3* inhibition in tumor cells leads to a cell-intrinsic IFN- γ response via double-stranded RNA formation, which increases the antigen-dependent tumor killing via CD8⁺ T cells [77]. Supporting findings were reported in a hepatocyte-specific *Mettl3*-knock-in (KI) model of non-alcoholic fatty liver disease causing hepatocellular carcinoma (NAFLD-HCC), in which *METTL3* overexpression promoted tumor growth, liver damage, and lipid accumulation in mice, whereas *Mettl3*-knockout showed opposite results [78]. *Mettl3*-knockin resulted in reduced serum IFN- γ levels, fewer IFN- γ ⁺ and GZMB⁺ CD8⁺ T cells, and increased PD-1⁺ T cells [78]. CD8⁺ T cell depletion reversed these effects,

indicating that tumor-derived METTL3 promotes NAFLD-HCC progression by impairing CD8⁺ T cell activation and anti-tumor function. Mechanistically, this immunosuppressive effect was linked to METTL3-driven cholesterol biosynthesis, which attenuated CD8⁺ T cell function [78].

Parallel to the METTL3 results, another study yielded comparable outcomes with METTL14 [79]. In a syngeneic lung tumor model, *Mettl14*-knockdown decreased tumor progression and increased CD8⁺ T cell infiltration, accompanied by elevated intratumoral IFN- γ and TNF- α levels. In vitro, *Mettl14* depletion reduced tumor cell proliferation, invasion, and migration while increasing tumor cell death. Mechanistically, METTL14 promoted m⁶A methylation of *HSD17B6* mRNA, decreasing its stability. Given that HSD17B6 over-expression improved CD8⁺ T cell activation, these findings suggest that METTL14 is an important suppressor of anti-tumor T cell functions [79].

3.2. Erasers

FTO is an important regulator that directly affects CD8⁺ T cell biology by maintaining T cell expansion and survival during immune responses. *Fto*-deficient CD8⁺ T cells exhibited progressively impaired expansion in an adoptive transfer model following infection [80]. Interestingly, FTO deletion affected the apoptosis of activated CD8⁺ T cells but not their proliferation. The effect on apoptosis was shown to be regulated via m⁶A hypermethylation of the *Fas* mRNA and protein levels in *Fto*-knockout CD8⁺ T cells in vivo. In addition, after antigen-specific bacterial infection, mice receiving *Fto*-knockout CD8⁺ T cells showed reduced TNF- α expression and impaired bacterial clearance, implying that FTO plays a role in maintaining optimal CD8⁺ T cell effector functions [80].

In contrast to the CD8⁺ T cell-intrinsic effects of FTO, *FTO*-knockdown in hepatocellular carcinoma (HCC) suppressed tumor growth and enhanced anti-tumor immunity [81]. *FTO* depletion in the cancer cells increased the infiltration of CD45⁺ cells and cytotoxic CD8⁺ T cells while reducing the proportion of exhausted PD-1⁺ CD8⁺ T cells in tumors in mice. In vitro, co-culture of CD8⁺ T cells with *FTO*-deficient HCC cells increased CD8⁺ T cell proliferation and promoted the effector memory population. Collectively, these findings indicate that tumor-specific *FTO*-knockdown enhances CD8⁺ T cell infiltration, activation, and survival within the tumor microenvironment through a GPNMB (glycoprotein non-metastatic melanoma protein B)-dependent pathway [81]. Similar effects were observed in other cancers. RNA-Seq data from The Cancer Genome Atlas were used to define a cytotoxic T lymphocyte (CTL) score of functional CD8⁺ TILs, which was negatively correlated with FTO expression in tumor cells in multiple cancer types [82]. *FTO*-knockdown in mouse melanoma and lung cancer cells increased T cell infiltration in vivo and enhanced CD8⁺ T cell-mediated cytotoxicity both in vitro and in vivo. Mechanistically, FTO expression in tumor cells promoted the expression of glycolytic genes by preserving the basic leucine zipper (bZIP) family of transcription factors (c-Jun, JunB, and C/EBP β) in an m⁶A-dependent manner [82]. Accordingly, decreased expression or chemical inhibition of FTO reduced the mRNA and protein levels of bZIP transcription factors, resulting in decreased transcription of glycolysis-associated genes and likely removing this metabolic barrier to CD8⁺ T cell activation. In addition, chemical inhibition of FTO enhanced the therapeutic efficacy of PD-L1 blockade [82].

Similar findings were reported following *Alkbh5*-knockout in mouse glioblastoma (GBM) cells, which resulted in decreased tumor growth and improved survival in mice [83]. These effects were accompanied by increased infiltration of both CD4⁺ and CD8⁺ T cells and a higher cytotoxic-to-helper T cell ratio within the *Alkbh5*-deficient tumors. Further analysis showed increased levels of the pro-inflammatory cytokines IFN- γ and IL-2 and

reduced levels of the anti-inflammatory cytokines IL-10 and IL-13, which is collectively consistent with enhanced anti-tumor T cell activity [83].

3.3. Readers

YTHDF2 has recently been reported to have an important CD8⁺ T cell-intrinsic role in polyfunctionality and anti-tumor function [84]. Specifically, YTHDF2 is highly expressed during early CD8⁺ T cell activation and ensures the longevity and tumoricidal activity of CD8⁺ T effector and effector-like cells. *Ythdf2* conditional knockout in T cells failed to control tumor growth in mouse hepatocellular carcinoma, melanoma, and colorectal carcinoma models due to lower numbers and anti-tumor activity of CD8⁺ TILs [84]. Mechanistically, YTHDF2 had both transcriptional and posttranscriptional roles in enhancing the antitumor function of CD8⁺ T cells. Specifically, nuclear YTHDF2 interacted with the transcriptional repressor IKZF1/3 (Ikaros Family Zinc Finger 1/3) to maintain gene transcription and T cell function, while cytoplasmic YTHDF2 mediated mRNA decay to improve mitochondrial fitness and persistence of tumor-reactive T cells. Interestingly, m⁶A recognition was essential for the nuclear translocation of YTHDF2, which highlights the important crosstalk between RNA modification and chromatin regulation in CD8⁺ T cells [84].

Beyond the CD8⁺ T cell-intrinsic effects discussed above, m⁶A readers can also indirectly shape CD8⁺ T responses by modulating dendritic and tumor cell functions. Specifically, YTHDF1 modulates the efficiency of antigen presentation in dendritic cells, regulating as such CD8⁺ T cell responses [85]. Global *Ythdf1* knockout in mice decreased tumor growth and improved survival in multiple tumor models [85]. Immunological profiling exhibited that *Ythdf1* deficiency increased CD8⁺ T cell tumor infiltration. Moreover, upon antigen stimulation, these CD8⁺ T cells produced more IFN- γ ex vivo, depicting enhanced antigen-specific anti-tumor capacity. The observed anti-tumor effect was abrogated following CD8⁺ T cell depletion, confirming that *Ythdf1* deficiency decreased tumor growth via a CD8⁺ T cell-mediated mechanism. Mechanistically, loss of YTHDF1 in dendritic cells enhanced tumor antigen cross-presentation, promoting, as such, the priming and clonal expansion of CD8⁺ T cells in the tumor models. YTHDF1 was found to regulate this process via translational control of lysosomal proteases. This ultimately affected the functionality of the CD8⁺ T cells, leading to stronger tumor rejection [85].

Tumor cells exploit m⁶A readers for immune evasion. For example, YTHDF1 and IGF2BP1 are associated with poor prognosis in colorectal cancer patients [86,87]. YTHDF1-deficient colorectal tumors showed reduced tumor growth in mice, accompanied by increased IFN- γ ⁺ GZMB⁺ CD8⁺ T cells, indicative of enhanced cytotoxic function. The anti-tumor effects of YTHDF1 deficiency were partially dependent on CD8⁺ T cells, as depletion of CD8⁺ T cells restored tumor growth [87]. Regarding IGF2BP1, co-culture experiments with human colon cancer cells overexpressing IGF2BP1 suppressed T cell cytotoxic activity and reduced TNF- α and IFN- γ secretion, whereas the opposite results were observed in IGF2BP1-silenced cancer cells [86]. Mechanistically, IGF2BP1 promoted the m⁶A-dependent *CD274* mRNA stabilization, which encodes for the PD-L1 protein. Consistent with this mechanism, although PD-L1 overexpression in cancer cells reduced T cell cytotoxic activity as expected, the combination of PD-L1 overexpression and IGF2BP1 knockdown in the cancer cells reversed the T cell-mediated cytotoxicity in vitro [86]. Similar findings have been reported for YTHDF2 [88]. Specifically, tumor-intrinsic *Ythdf2* knockout in multiple tumor-bearing mice showed reduced tumor growth and increased survival. Depletion of CD8⁺ T cells in these tumor models abolished the beneficial effect of the knockout compared to WT tumors. These effects revealed that *Ythdf2*-deficient tumor cells increase CD8⁺ T cell tumor infiltration and cytotoxic capacity, as the intratumoral CD8⁺ T cells produced higher IFN- γ levels. Mechanistically, IFN- γ promoted the autophagic

degradation of tumoral YTHDF2, which led to increased susceptibility to CD8⁺ T cell-mediated cytotoxicity. In addition, CD8⁺ T cells co-cultured with *Ythdf2*-deficient cancer cells showed improved metabolic fitness with increased mitochondrial respiration [88]. HNRNPA2B1, another m⁶A reader, was recently reported to facilitate NSCLC immune escape [89]. HNRNPA2B1 levels were increased in NSCLC clinical samples compared to the neighboring non-tumoral samples, and its expression was positively correlated to PD-L1. In vitro co-cultures of HNRNPA2B1-overexpressing NSCLC cancer cells with CD8⁺ T cells reduced CD8⁺ T cell cytotoxicity and cytokine release. Mechanistically, HNRNPA2B1 bound to m⁶A sites on *LDHA* (lactate dehydrogenase A) mRNA, enhanced its stability in cancer cells, and potentially released immunosuppressive lactate in the TME. HNRNPA2B1 silencing in cancer cells reduced tumor growth, decreased LDHA expression, and increased the number of CD8⁺ TILs producing IFN- γ [89].

Collectively, the above studies demonstrate the critical role of m⁶A RNA methylation on CD8⁺ T cell activation, differentiation, and anti-tumor function (Table S2 and Figure 3). Whereas m⁶A regulators acting within CD8⁺ T cells directly control their activation and effector function (Figure 3A), m⁶A regulators in other cells of the TME, particularly cancer cells, indirectly modulate CD8⁺ T cell infiltration and cytotoxicity by altering the microenvironment, expressing T cell inhibitory receptors, or dampening CD8⁺ T cell activation (Figure 3B). Dysregulation of these pathways can promote immune evasion and impaired anti-tumor immunity, highlighting the therapeutic potential of targeting m⁶A regulators in cancer immunotherapy.

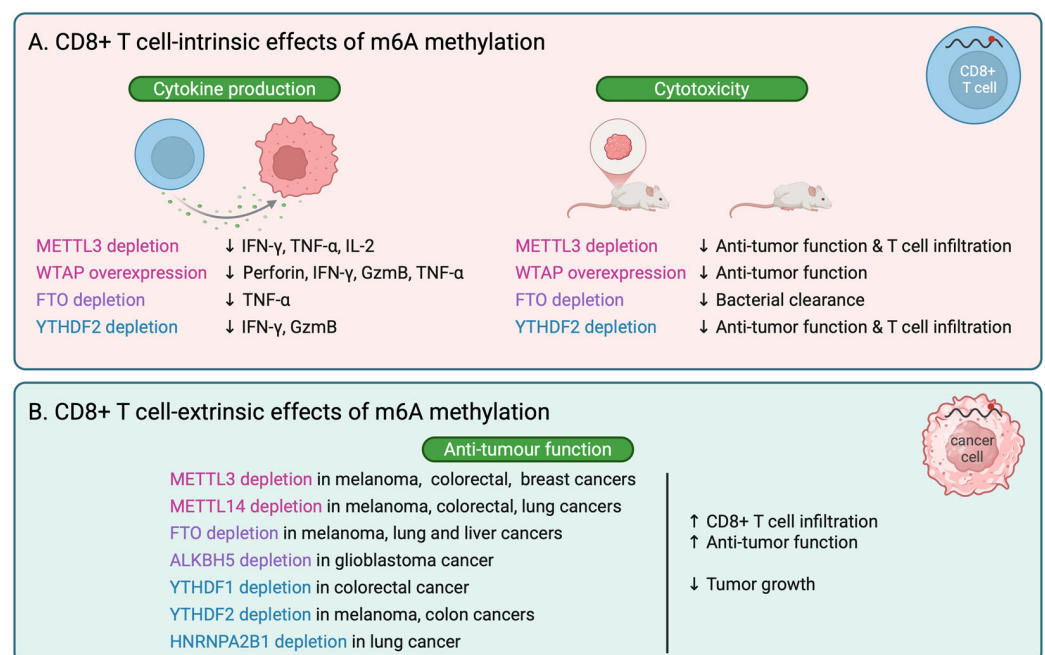


Figure 3. Effect of m⁶A methylation on CD8⁺ T cell function through both T cell-intrinsic and T cell-extrinsic mechanisms. m⁶A methylation regulates CD8⁺ T cell function through cell-intrinsic mechanisms (A) or indirectly via modulation of m⁶A regulators in cancer cells (B). The m⁶A writers are depicted in pink, the erasers are depicted in purple, and the readers are in blue. Upward and downward arrows indicate an increase or decrease, respectively, relative to the control condition. The figure was created in BioRender. Butt, Y.A. (2026) <https://BioRender.com/zwez65i>.

4. Role of m⁶A Methylation in $\gamma\delta$ T Cells

Gamma delta T cells ($\gamma\delta$ T cells) are a unique T cell subset characterized by the expression of a T cell receptor (TCR) composed of one gamma and one delta chain. Unlike conventional $\alpha\beta$ T cells, $\gamma\delta$ T cells recognize antigens independently of MHC presentation.

$\gamma\delta$ T cells bridge innate and adaptive immunity through their rapid responses, cytokine production, cytotoxic activity, and tissue surveillance. Depending on the context, $\gamma\delta$ T cells can exert protective or pathogenic roles in cancer, infections, and autoimmune diseases, making them attractive targets for future immunotherapies [90]. However, compared with conventional T cell subsets, only limited studies have investigated the role of m⁶A regulation in $\gamma\delta$ T cells, which are discussed below.

4.1. Writers

It has been shown that METTL3 regulates the differentiation, maturation, and function of $\gamma\delta$ T cells. Specifically, METTL3 deficiency promoted $\gamma\delta$ T1 differentiation while reducing the $\gamma\delta$ T17 population [56]. Consistent with this transition, expression of the $\gamma\delta$ T17-associated transcription factor ROR γ t was decreased, whereas the $\gamma\delta$ T1 marker EOMES was upregulated. Functionally, METTL3 ablation reduced IL-17 levels and increased IFN- γ expression. Mechanistically, it was shown that impaired $\gamma\delta$ T17 differentiation was linked to dysregulated STAT1 signaling, a direct METTL3 target, and increased production of double-stranded RNA (dsRNA) [56]. Another study showed V γ 9V δ 2 T cells, the most abundant $\gamma\delta$ T cell subset in human peripheral blood, expressed higher IFN- γ and TNF- α levels when cultured with exosomes derived from the plasma of gastric cancer patients [91]. Proteomic analysis revealed that these exosomes contained Thrombospondin 1 (THBS1), which upregulated the expression of genes associated with the retinoic acid-inducible gene I (RIG-I)-like receptor signaling pathway, an important activator of innate immune functions. Intriguingly, this effect was m⁶A-dependent, as exosomal THBS1 directly interacted with METTL3 and reduced its protein levels in V γ 9V δ 2 T cells. In agreement, treatment of V γ 9V δ 2 T cells with a METTL3 inhibitor significantly increased the expression and stability of mRNAs involved in the RIG-I signaling [91].

4.2. Erasers

ALKBH5 plays a critical role in murine $\gamma\delta$ T cell development in the thymus and periphery. ALKBH5 deletion during T cell development selectively promoted $\gamma\delta$ T cell expansion and protected mice against gastrointestinal infection [92]. However, this improved immune response was not driven by altered cytokine production, but due to increased expansion of $\gamma\delta$ T cell progenitors. Mechanistically, it was shown that ALKBH5 ablation increased m⁶A methylation of *Jagged1* and *Notch2* transcripts, reducing their stability and expression, promoting as such $\gamma\delta$ T cell proliferation and differentiation [92]. These findings highlight the importance of m⁶A-mediated regulation of the Jagged1/Notch2 signaling pathway in controlling $\gamma\delta$ T cell differentiation.

5. Role of m⁶A Methylation in Immunotherapy

Current literature has demonstrated the role of m⁶A modification in T cell biology and its potential to enhance immunotherapeutic efficacy (Table S3). However, existing literature is heavily skewed towards immune checkpoint blockade therapy (ICB), especially anti-PD-1 therapy. Limited research has been performed on the effect of m⁶A on other forms of immunotherapy, such as adoptive cell therapy (CAR- T cell, TIL therapy), vaccine-based therapies, oncolytic virus therapies, and cytokine therapies, leading to a considerable knowledge gap. In the following section, we summarize the existing literature, predominantly centered on ICB, that has elucidated how m⁶A regulators influence the sensitivity and efficacy of anti-PD-1/PD-L1 therapy (Figure 4).

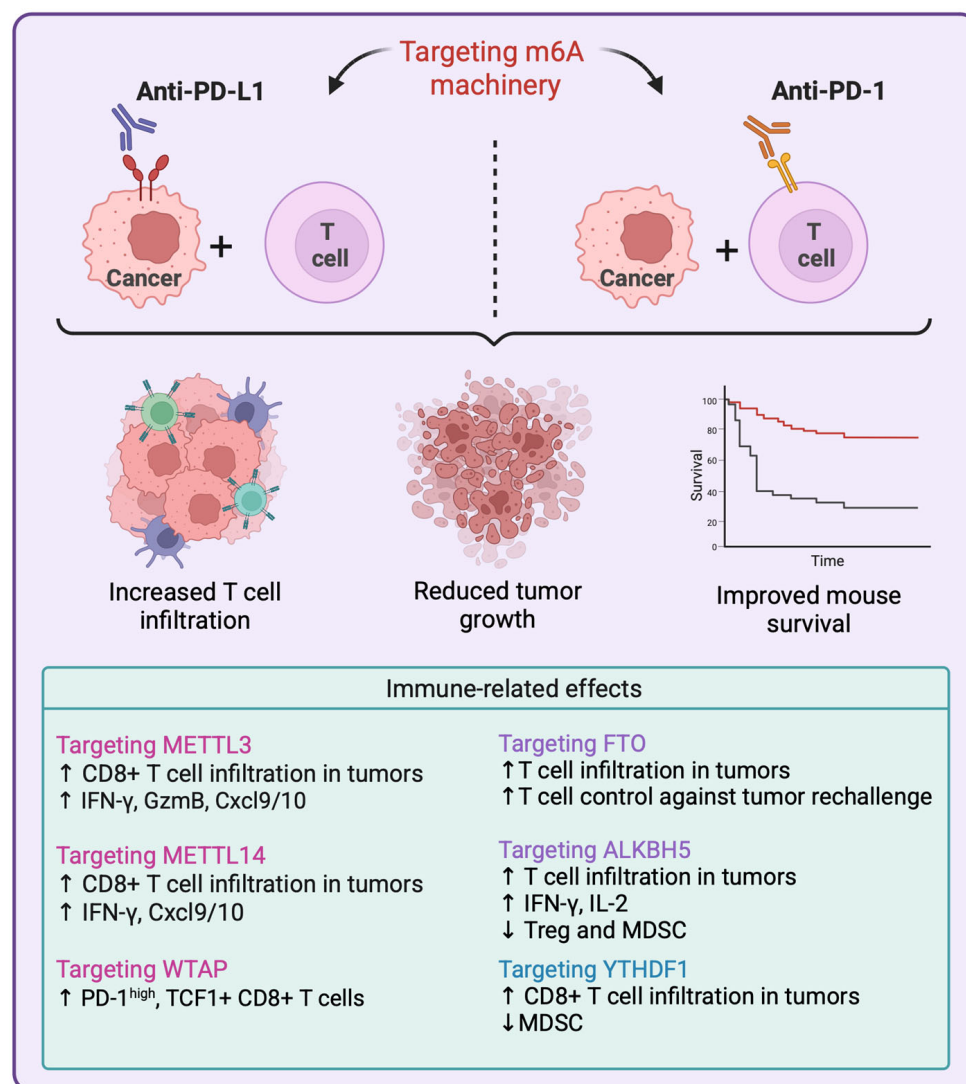


Figure 4. Therapeutic modulation of m⁶A regulators in combination with anti-PD-1/PD-L1 immune checkpoint blockade (ICB). Genetic or pharmacological targeting of m⁶A regulators can enhance responses to ICB. However, because m⁶A regulators exert context-dependent functions in tumor and immune cells, therapeutic efficacy is likely to depend on the cellular context and mode of targeting. The m⁶A writers are depicted in pink, the erasers are depicted in purple, and the readers are in blue. Upward and downward arrows indicate an increase or decrease, respectively, relative to the control condition. The figure was created in BioRender. Butt, Y.A. (2026) <https://BioRender.com/i7zdc8u>.

5.1. Writers

Accumulating evidence indicates that m⁶A regulators affect treatment responses in cancer patients. For example, a computational study showed that m⁶A molecular expression patterns could predict responses to immunotherapeutic drugs in patients with hepatocellular carcinoma (HCC) [93]. Patients with a high m⁶A score were associated with favorable outcomes and more intratumoral immune and stromal cells, whereas a low m⁶A score was associated with adverse outcomes, tumor purity, and eventually poor prognosis [93]. Additionally, the authors evaluated if the m⁶A score could predict the effectiveness of immunotherapy in HCC patients and found that a low m⁶A score may predict sensitivity to anti-PD-L1 therapy. These findings showcase the potential of m⁶A-based signatures as biomarkers for predicting immunotherapy responses and suggest that combination strategies targeting m⁶A regulators may represent a promising strategy to modulate tumor immune infiltration in HCC patients.

Building on mechanistic insights into the role of m⁶A regulation in tumor biology, investigators have explored whether modulation of m⁶A writers could enhance the efficacy of monotherapies. *Mettl3*-knockdown in tumor cells reduced tumor growth and increased intratumoral CD4⁺ and CD8⁺ T cells, in similar levels to anti-PD-L1 treatment, with increased IFN- γ and IL-2 production [75]. Several other studies have shown the therapeutic potential of METTL3 inhibition/ablation in enhancing the efficacy of PD-1 blockade therapy in hematological and solid tumors [77,78,94]. Specifically, combining METTL3 targeting with anti-PD-1 therapy delayed tumor growth and increased survival in carcinoma, melanoma, and NAFLD-HCC models, accompanied by increased CD8⁺ TILs expressing high levels of GZMB and IFN- γ [78,94]. Interestingly, short-term METTL3 inhibition (5 days) was sufficient to enhance the efficacy of anti-PD-1 therapy [77], suggesting that transient METTL3 targeting could improve therapeutic responses. This finding may have important translational implications, as it suggests that intermittent METTL3 targeting could provide sufficient antitumor effects, while potentially limiting toxicity associated with continuous inhibition. Further analysis revealed that malignant clones resistant to either METTL3 inhibition or anti-PD-1 treatment could only be effectively targeted by combination therapy, indicating the potential for METTL3 inhibition as a means to potentiate ICB responses in recalcitrant tumors [77].

Similarly, METTL14 knockdown in carcinoma, melanoma, and lung tumor models reduced tumor growth and improved survival outcomes when combined with anti-PD-1 therapy [79,94]. This effect was associated with increased cytotoxic CD8⁺ TILs with high levels of GZMB, IFN- γ , and CXCL9/10, suggesting that modulation of m⁶A writers in cancer cells could influence the TME by regulating immune cell recruitment and activation. Corroborating these findings, WTAP overexpression in CD8⁺ T cells was shown to increase PD-1 expression in CD8⁺ T cells in tumors and promote HCC tumor growth [73]. WTAP depletion in combination with anti-PD-1 therapy led to reduced tumor growth and decreased PD-1+TCF1⁺ CD8⁺ T cells compared to single treatment alone [73]. Collectively, these data support the notion that m⁶A writers may serve as potential therapeutic targets for augmenting the clinical efficacy of anti-PD-1 therapy. However, the multiple and sometimes contrasting functions of m⁶A writers in tumor and immune cells (as discussed in the above sections) suggest that therapeutic benefit will likely depend on the cellular context and method of targeting.

Although substantial progress has been made in understanding the role of m⁶A writers in combination with ICB, research exploring their involvement in CAR-T cell therapy remains limited. The first direct link between m⁶A regulation and CAR-T cell engineering was reported in a recent study by Lao et al. The authors generated CD19 CAR-T cells using in vitro transcribed (IVT) mRNA and demonstrated that m⁶A modification in DRACH motifs in the coding region enhanced CD19 CAR-T cell expression [95]. Inhibition of METTL3 reduced CD19 CAR-T cell expression, although this effect was not mediated via RNA degradation but rather reduced translational efficacy [95]. Given that CAR surface expression has been implicated to affect T cell fitness and activity [96], it is conceivable that modulating m⁶A sites within CAR constructs could optimize CAR expression and improve therapeutic efficacy. An additional indirect link between m⁶A regulation and CAR-T cell therapy was described by Wang et al. [72]. The study showed that tumor-associated extracellular acidity suppressed METTL3-mediated expression of ITGB1 in T cells. Since ITGB1 is a crucial factor for T cell infiltration into tumors, this suppression reduced anti-tumor responses. The authors then overexpressed ITGB1 in CAR-T cells and showed enhanced CAR-T cell infiltration and improved antitumor activity [72].

5.2. Erasers

Growing evidence identifies m⁶A erasers as important regulators of tumor biology, making them a subject of investigation as potential therapeutic targets. Consistent with this, FTO has been linked to melanoma progression, with *Fto* depletion in cancer cells reducing tumor growth in mice [97]. *Fto* ablation also decreased PD-1 levels in melanoma cells and enhanced tumor sensitivity to anti-PD-1 therapy by sensitizing melanoma cells to IFN- γ -induced cell death. Although the combination therapy was dependent on the immune system, the number of infiltrated IFN- γ -producing cytotoxic TILs was not affected [97]. Similarly, pharmacological inhibition of FTO in B16-OVA melanoma and MC38 colon adenocarcinoma models synergized with anti-PD-L1 blockade and significantly reduced tumor growth, prolonged overall survival, and elicited strong T cell memory responses that protected mice from tumor relapse [82]. Collectively, these findings reveal that melanoma cell-intrinsic FTO contributes to resistance against PD-1 blockade. Consistent with these observations, Chen et al. showed that *Fto* knockdown in HCC decreased tumor growth, while combining FTO depletion or inhibition with anti-PD1 or tyrosine kinase inhibitors further enhanced antitumor efficacy compared with either treatment alone [81]. This effect was associated with increased tumor infiltration by CD8+ T cells [81].

Similarly to FTO, both depletion and inhibition of ALKBH5 in multiple tumor models enhanced the response to anti-PD-1 therapy, resulting in reduced tumor growth and improved survival in mice [98]. These effects were independent of CD8+ or CD4+ T cell tumor infiltration and were instead mediated by reduced accumulation of immunosuppressive cells, including Tregs and myeloid-derived suppressor cells. Mechanistically, ALKBH5 deletion increased the m⁶A modification of *Mct4* mRNA, which encodes a lactate transporter, thereby reducing intratumoral lactate levels and enhancing the response to anti-PD-1 therapy [98]. Similar effects were observed in glioblastoma (GBM), the most aggressive and lethal form of brain tumors, for which limited treatment options are available. Specifically, *Alkbh5* depletion in GBM cells improved tumor response in mice [83]. Patient data further revealed a positive correlation between ALKBH5 and PD-L1 expression, with anti-PD-1-resistant GBM patients exhibiting higher levels of both markers compared to anti-PD-1-sensitive patients. Interestingly, combining *Alkbh5* knockout with anti-PD-1 therapy further reduced GBM tumor growth and prolonged survival compared with *Alkbh5* depletion alone in mouse models. This enhanced response was accompanied by increased infiltration of T cells, elevated levels of anti-tumor cytokines (IFN- γ , IL-2), and reduced levels of pro-tumorigenic cytokines (IL-10, IL-13). Similar results were observed with the ALKBH5 inhibitor IOX1, indicating that targeting ALKBH5 may enhance the therapeutic efficacy of PD-1 therapy in GBM [83]. Together, these studies identify m⁶A erasers as potential regulators of tumor immune evasion and support their inhibition as a promising strategy to enhance the efficacy of immune checkpoint blockade.

5.3. Readers

Beyond the core components of the m⁶A machinery, the m⁶A readers also provide an additional layer of regulation and may also represent potential therapeutic targets. For example, *Ythdf1*-deficient mice display an increased anti-tumor CD8+ T cell response [85]. Additionally, *Ythdf1* deficiency markedly enhanced the efficacy of PD-L1 blockade, resulting in complete tumor-free survival in a melanoma model [85]. Similar findings have been reported for colorectal cancer [87]. *Ythdf1* depletion enhanced anti-PD-1 efficacy in vivo, resulting in reduced tumor growth and increased survival. This effect was associated with enhanced CD8+ T cell infiltration, including an increase in IFN- γ + and GZMB+ CD8+ T cells, and reduced myeloid-derived suppressor cells (MDSCs). Importantly, *Ythdf1*

depletion increased the efficacy of anti-PD-1 therapy in mice that were previously not responding to ICB therapy [87].

YTHDF2 has also emerged as a potential regulator of immunotherapy responses. Specifically, YTHDF2-deficient CD4⁺ CAR-T cells targeting EGFR (epidermal growth factor receptor) or PSCA (prostate stem cell antigen) exhibited enhanced tumor control in pancreatic and NSCLC cancer xenograft mouse models. This improved antitumor activity was attributed to enhanced CAR-T cell persistence and increased IFN- γ production [68]. In addition, in B cell acute lymphocytic leukemia, YTHDF2 is overexpressed and promotes the m⁶A-dependent destabilization of CD19 and MHC-II transcripts, thereby reducing the surface expression of both molecules and impairing the efficacy of CD19-targeted CAR-T cell therapy or the bispecific T cell engager blinatumomab [99]. Inhibition of YTHDF2 with a small molecule suppressed aggressive B cell malignancies and sensitized them to CAR-T cell therapy [99]. Collectively, these findings indicate that targeting the m⁶A readers YTHDF1 and YTHDF2 could serve as a critical strategy for enhancing immunotherapy responses across multiple treatment modalities.

In conclusion, although the studies discussed above highlight the therapeutic potential of targeting m⁶A regulators to enhance immunotherapy, their functions are highly context-dependent, and caution is needed when considering systemic inhibition. While some preclinical studies demonstrate improved responses to ICB following inhibition of m⁶A regulators (Figure 4), accumulating evidence indicates that several of these regulators are also essential for maintaining T cell homeostasis, differentiation, and effector function. These observations highlight that future therapeutic strategies should require cell type-specific delivery, transient modulation, or context-dependent targeting of m⁶A regulators to maximize antitumor efficacy while preserving immune responses.

6. Conclusions

m⁶A methylation has emerged as a central regulator of both CD4⁺ and CD8⁺ T cell biology, with writers, erasers, and readers dynamically controlling RNA fate and gene expression to shape T cell activation, differentiation, function, and survival. m⁶A-mediated regulation modulates immune responses in both physiological and pathological contexts, including the tumor microenvironment. Despite the recent advances in understanding the immunoregulatory role of m⁶A, the context-dependent and sometimes contradictory functions of individual m⁶A regulators across different immune cell populations underscore the complexity of m⁶A-mediated immune regulation. Nevertheless, preclinical studies highlight the potential of targeting m⁶A regulators to enhance antitumor immunity. However, because individual m⁶A regulators often exert distinct and sometimes opposing functions in tumor cells, antigen-presenting cells, and T cells, the success of future therapeutic strategies will likely depend on achieving cell type-specific or temporally controlled modulation rather than systemic continuous inhibition.

7. Future Outlook

Although significant progress has been made over the past decade, several important knowledge gaps remain. The majority of current evidence for the m⁶A-mediated immune regulation comes from murine models, emphasizing the need for validation and mechanistic investigation of human T cells to ensure translational relevance. Additionally, since the m⁶A modification on mRNAs is a highly dynamic process, more time-resolved studies are required to better understand its role during T cell activation. Furthermore, emerging readers, including PRRC2A and hnRNPG, as well as recently predicted m⁶A reader candidates, may represent a novel layer of regulation in T cell biology and function. However,

their roles remain largely unexplored, and further research is necessary to investigate the potential m⁶A-dependent functions of these readers in T cells.

A deeper understanding of the interplay among m⁶A writers, erasers, and readers is also needed, as these factors may function cooperatively or competitively to regulate RNA metabolism and immune responses. Additionally, since m⁶A enzymes are highly dependent on cellular metabolites for their function, future studies should investigate how metabolic regulation influences m⁶A activity and thus T cell function.

From a therapeutic perspective, most current research has focused on cancer immunotherapy and immune checkpoint blockade (ICB), while little is known about the therapeutic efficacy of combining m⁶A-targeted approaches with adoptive cell transfer therapies, such as CAR-T cells. This could represent an important area for future investigation and potential therapeutic innovation. Perhaps most importantly, the existing literature is heavily focused on cancer, whereas the role of m⁶A regulation in chronic infections, inflammation, and autoimmune diseases remains largely unexplored. Addressing these knowledge gaps may facilitate the development of novel and more effective immunotherapeutic strategies across a broad range of diseases.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/immuno6030050/s1>, Table S1: Summary of m⁶A methylation regulators on CD4⁺ T cell function; Table S2: Summary of m⁶A methylation regulators on CD8⁺ T cell function, Table S3: Summary of combination therapy of m⁶A regulation and immunotherapy.

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Abbreviations

3'UTR	3' Untranslated Region
ALKBH5	AlkB Homolog 5
AML	Acute Myeloid Leukemia
APC	Antigen Presenting Cell
ARE	AU-Rich Element
BATF	Basic Leucine Zipper ATF-Like Transcription Factor
BCL6	B-Cell Lymphoma 6
bZIP	Basic leucine Zipper (bZIP) transcription factors
CAR-T cell	Chimeric Antigen Receptor T Cell
CBLL1	Casitas B-Lineage Lymphoma Transforming Sequence Like Protein 1 (also known as HAKAI)
CD	Cluster of Differentiation
CISH	Cytokine-Inducible SH2-Containing Protein
CTL	Cytotoxic T Lymphocyte
CXCL	C-X-C Motif Chemokine Ligand
CXCR	C-X-C Motif Chemokine Receptor

DDX6	DEAD-Box Helicase 6
DNA	Deoxyribonucleic Acid
dsRNA	Double-Stranded RNA
EAE	Experimental Autoimmune Encephalomyelitis
EBI3	Epstein–Barr Virus-Induced Gene 3
EGFR	Epidermal Growth Factor Receptor
EOMES	Eomesodermin
FOXP3	Forkhead Box P3
FTO	Fat Mass and Obesity-Associated Protein
FUBP3	Far Upstream Element-Binding Protein 3
FXR2	Fragile X Mental Retardation Syndrome-Related Protein 2
GATA3	GATA Binding Protein 3
GBM	Glioblastoma
GLORI	Glyoxal and Nitrite-Mediated Deamination for m ⁶ A Identification
GPNCMB	Glycoprotein Non-Metastatic Melanoma Protein B
GvHD	graft versus host disease
GZMB	Granzyme B
HCC	Hepatocellular Carcinoma
HNRNP	Heterogeneous Nuclear Ribonucleoprotein
ICB	Immune Checkpoint Blockade
ICOS	Inducible T Cell Costimulator
IFN- γ	Interferon Gamma
IGF2BP	Insulin-Like Growth Factor 2 mRNA Binding Protein (family)
IL	Interleukin
IRF4	(Interferon Regulatory Factor 4)
ITGB1	Beta 1 Integrin
IVT	In Vitro Transcribed
JAK	Janus Kinase
KI	Knock In
KLH	Keyhole Limpet Hemocyanin
L1TD1	LINE-1 Type Transposase Domain Containing Protein 1
LAG-3	Lymphocyte Activation Gene 3
LCMV	Lymphocytic Choriomeningitis Virus
LDHA	Lactate dehydrogenase A
LSM	Like-Sm Protein
m ⁶ A	N ⁶ -methyladenosine
MDSC	Myeloid-Derived Suppressor Cell
METTL14	Methyltransferase-Like 14
METTL16	Methyltransferase-Like 16
METTL3	Methyltransferase-Like 3
METTL5	Methyltransferase-Like 5
MHC	Major Histocompatibility Complex
miCLIP	m ⁶ A Individual Nucleotide Resolution Cross Linking and Immunoprecipitation
mRNA	Messenger RNA
MTC	Methyltransferase Complex
NAFLD	Non-Alcoholic Fatty Liver Disease
NF κ B	Nuclear Factor Kappa B
NK	Natural Killer cell
NSCLC	Non-Small Cell Lung Cancer
PD-1	Programmed Cell Death protein-1
PD-L1	Programmed Death-Ligand 1
PDCD1	Programmed Cell Death Protein 1
PKP3	Plakophilin 3

PRRC2A	Proline Rich Coiled-Coil 2A
PSCA	Prostate Stem Cell Antigen
PU.1	Purine-Rich Box 1
RBM15/RBM15B	RNA Binding Motif Protein 15/15B
RBP	RNA-Binding Protein
RNA	Ribonucleic Acid
ROR γ t	Retinoic Acid Receptor-Related Orphan Receptor Gamma t
rRNA	Ribosomal RNA
SAM	S-Adenosylmethionine
SLE	Systemic Lupus Erythematosus
SOCS	Suppressor of Cytokine Signaling
STAT5	Signal Transducer and Activator of Transcription 5
T-Bet	T-Box Expressed in T Cells
TAM	Tumor Associated Macrophage
TCF-1	T Cell Factor 1
TCR	T Cell Receptor
TE	Effector T cell
Tfh	Follicular Helper T Cell
TGF- β	Transforming Growth Factor Beta
Th1	T-Helper 1
Th17	T-Helper 17
Th2	T-Helper 2
Th22	T-Helper 22
Th9	T-Helper 9
TIGIT	T Cell Immunoreceptor with Ig and ITIM Domains
TIL	Tumor-Infiltrating Lymphocyte
TIM-3	T Cell Immunoglobulin and Mucin Domain-Containing Protein 3
TM	Memory T cell
TME	Tumor Microenvironment
TN	Naive T cell
TNF α	Tumor Necrosis Factor alpha
Treg	Regulatory T Cell
tRNA	Transfer RNA
VIRMA	Vir-Like m ⁶ A Methyltransferase-Associated Protein (also known as KIAA1429)
WTAP	Wilms Tumor 1-Associating Protein
YTHDC	YTH Domain-Containing Protein (family)
YTHDF	YTH Domain Family Protein (family)
ZC3H13	Zinc Finger CCCH-Type Containing 13
ZCCHC4	Zinc Finger CCHC-Type Containing 4
$\gamma\delta$ T cell	Gamma Delta T Cell

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