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m6A RNA methylation: a pivotal regulator of tumor immunity and a promising target for cancer immunotherapy

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Abstract

M6A modification is one of the most common regulatory mechanisms of gene expression in eukaryotic cells, influencing processes such as RNA splicing, degradation, stability, and protein translation. Studies have shown that m6A methylation is closely associated with tumorigenesis and progression, and it plays a key regulatory role in tumor immune responses. m6A modification participates in regulating the differentiation and maturation of immune cells, as well as related anti-tumor immune responses. In the tumor microenvironment, m6A modification can also affect immune cell recruitment, activation, and polarization, thereby promoting or inhibiting tumor cell proliferation and metastasis, and reshaping the tumor immune microenvironment. In recent years, immunotherapies for tumors, such as immune checkpoint inhibitors and adoptive cell immunotherapy, have been increasingly applied in clinical settings, achieving favorable outcomes. Targeting m6A modifications to modulate the immune system, such as using small-molecule inhibitors to target dysregulated m6A regulatory factors or inducing immune cell reprogramming, can enhance anti-tumor immune responses and strengthen immune cell recognition and cytotoxicity against tumor cells. m6A modification represents a new direction in tumor immunotherapy with promising clinical potential. This review discusses the regulatory role of m6A methylation on immune cells and tumor immune responses and explores new strategies for immunotherapy.

Keywords m6A methylation, Innate immunity, Adaptive immunity, Tumor immunity, Immunotherapy

Introduction

RNA epigenetic modifications are chemical modifications occurring at the RNA molecular level, involved in both transcriptional and post-transcriptional regulation [1]. These modifications can alter the chemical properties of RNA, including its secondary structure, base pairing, and interactions with proteins, ultimately regulating gene expression and exerting various biological functions. To date, more than 170 types of epigenetic modifications have been identified in both coding and non-coding RNAs, with common modifications including N6-methyladenosine (m6A), N1-methyladenosine (m1A), 5-methylcytosine (m5C), N7-methylguanosine (m7G), adenosine-to-inosine (A-I) editing, and pseudouridine

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(Ψ) [2–7]. RNA epigenetic modifications play a crucial role in maintaining normal physiological functions by regulating the biological processes of immune cells. Studies have indicated that aberrant RNA modifications are involved in the development of various diseases, including liver cancer, Alzheimer's disease, and systemic lupus erythematosus [8–11]. Therefore, a deeper understanding of RNA epigenetic modifications and their mechanisms in immune cells holds significant clinical value for studying the pathogenesis and progression of immune-related diseases.

Immune cells refer to cells involved in or associated with immune responses, including those responsible for innate immunity, such as dendritic cells, macrophages, and natural killer (NK) cells, as well as T lymphocytes and B lymphocytes, which mediate adaptive immunity. Immune cells play a crucial role in inflammation, autoimmune diseases, and anti-tumor responses [12, 13]. They detect extracellular or intracellular stimuli through immune receptors, such as pattern recognition receptors, cytokine receptors, and immunoglobulin Fc receptors. These receptors activate various signaling pathways, regulate the expression of target genes, and trigger post-translational modifications, leading to immune cell activation, proliferation, and differentiation [14, 15]. This results in non-specific or specific immune responses and immunological effects that help recognize and eliminate pathogens, remove dead or damaged cells and regulate immune response intensity to maintain homeostasis, ensuring normal physiological functions and vital activities of the organism.

m6A methylation modification is regulated by methyltransferases, demethylases, and m6A recognition proteins [16]. These factors are responsible for adding, removing, or recognizing m6A modifications, influencing various metabolic processes of m6A-containing RNA, and maintaining the dynamic balance of m6A modification [17]. m6A modification can alter the expression levels of target genes, thereby affecting related cellular processes and physiological functions. At the molecular level, m6A participates in various steps of RNA metabolism, including mRNA translation, degradation, splicing, and folding [18]. Recent studies have shown that m6A modification also regulates immune cell activation and promotes immune cell infiltration into the tumor microenvironment (TME), potentially affecting the efficacy of immunotherapy [19–21]. However, due to the complexity of m6A epigenetic modifications and the diversity of immune cells, the interactions between m6A epigenetic modifications and immune cells remain largely unclear and require further elucidation. Therefore, based on the current state of research, this review summarizes the role of m6A epigenetic modification in immune cell biology.

The significance of this review lies in exploring the mechanisms by which m6A epigenetic modifications regulate immune cell function and anti-tumor immunotherapy. As one of the most common modifications in RNA, m6A has been proven to play a significant role in various biological processes, particularly in cancer development and progression. However, research on the function of m6A modifications in the immune system, especially in anti-tumor immunity, is still in its early stages. A systematic review of the role of m6A modifications in immune cells, revealing their potential mechanisms in immune evasion, tumor microenvironment regulation, and immunotherapy response, will provide a theoretical foundation for the development of more precise tumor immunotherapies in the future.

The originality of this review lies in its first attempt to link m6A epigenetic modifications with anti-tumor immunity, aiming to reveal, from an RNA epigenetic perspective, how m6A modifications influence immune cell development, differentiation, and functional regulation. In particular, it explores how m6A modifications affect anti-tumor effector cells such as T cells and natural killer (NK) cells. Firstly, this review integrates the latest research on m6A modifications, exploring their potential applications in immunotherapies, such as immune checkpoint inhibitors and CAR-T cell therapy. Secondly, it proposes mechanisms of m6A modification in the tumor microenvironment that have not yet been widely studied and offers forward-looking perspectives and suggestions for future research directions. These innovations contribute to advancing research on m6A modifications in the field of tumor immunity and provide new insights for optimizing anti-tumor therapeutic strategies.

Biological processes of m6A modification

m6A is an RNA methylation modification named for its presence at the sixth nitrogen atom of adenine in RNA. Discovered in the 1970s, m6A is widely distributed in mammalian mRNA. High-throughput sequencing has revealed that m6A is primarily enriched in exons, stop codons, and 3′ UTRs of RNA, with its most common sequence motif being RRACH, where R stands for guanine or adenine, and H represents uracil, adenine, or cytosine [22, 23]. For instance, the RRACH motif is crucial in the context of m6A modification, where it is recognized by m6A reader proteins like YTHDF2. This recognition plays a significant role in regulating mRNA stability and translation, impacting processes such as RNA splicing, maturation, and degradation [24]. One example is the regulation of key genes in cancer progression, where the binding of YTHDF2 to m6A-modified mRNA in the RRACH motif has been shown to promote the degradation of certain oncogenes, thereby influencing tumorigenesis [25].

m6A methylation is a dynamic and reversible biological process regulated by methyltransferase "writers" and demethylases "erasers." m6A-modified RNA can be recognized and bound by specific "reader" proteins, ultimately influencing various biological processes such as RNA processing, translation, and stability.

The "writers" that regulate m6A modification are primarily composed of the methyltransferase-like protein 3 (METTL3), methyltransferase-like protein 14 (METTL14), and Wilms tumor 1-associated protein (WTAP), forming a complex. Although both METTL3 and METTL14 contain methyltransferase domains, METTL14 lacks a SAM-binding motif in its catalytic site, making its primary function to facilitate the binding of METTL3 to RNA substrates [26]. WTAP lacks methyltransferase activity itself and mainly functions to stabilize the METTL3-METTL14 complex, promoting m6A modification on RNA [27–30]. In addition to these core components, several new m6A "writers" have been discovered, including virus-like m6A methyltransferase-associated protein (VIRMA), RNA-binding motif protein 15 (RBM15), methyltransferase-like protein 16 (METTL16), zinc finger CCHC domain-containing 4 (ZCCHC4), zinc finger CCCH domain-containing protein 13 (ZC3H13), and CBL proto-oncogene-like protein 1 (CBLL1), among others [31–37]. m6A was the first reversible RNA modification discovered in eukaryotes, and it can be removed by "eraser" proteins, including FTO and ALKBH5 [3, 38–41]. FTO exerts its demethylation function by oxidizing m6A into N6-hydroxymethyl adenosine and N6-formyladenosine, further hydrolyzing these intermediates into adenine [42, 43]. In contrast, ALKBH5 directly removes m6A modifications from adenosine without producing intermediates [4, 44]. Recently, our lab revealed that RNA-binding protein RBM33 can recognize m6A-modified RNA substrates, recruit, and activate the demethylase activity of ALKBH5, facilitating m6A demethylation [44]. Another study discovered that PSPC1 serves as a regulatory subunit of ALKBH5 [45]. By recruiting ALKBH5 to RNA m6A sites through K235 acetylation, PSPC1 enhances ALKBH5's ability to demethylate RNA m6A, establishing a new model for ALKBH5-mediated m6A removal.

The biological functions mediated by m6A modifications largely depend on recognition by "reader" proteins. The major m6A "readers" include YTH domain-containing proteins, heterogeneous nuclear ribonucleoproteins (hnRNPs), and the insulin-like growth factor 2 mRNA-binding protein (IGF2BP) family [46–48],. YTH domain family proteins include YTHDF1-3 and YTHDC1-2 [29, 49–52]. YTHDF1 promotes mRNA translation by recruiting eukaryotic initiation factor 3 (eIF3) to m6A-modified mRNA [53]. Conversely, YTHDF2 facilitates the degradation of m6A-modified RNA through two different mechanisms. First, YTHDF2 recruits the CCR4-NOT deadenylation complex, leading to the degradation of m6A-modified RNA by removing its poly(A) tail [54]. Second, YTHDF2 promotes RNA cleavage through the HRSP12-mediated endonucleolytic pathway [51, 55]. The mechanism YTHDF2 uses depends on the presence of HRSP12 binding sites on m6A-modified RNA. However, whether these pathways can act synergistically to regulate mRNA degradation remains unclear. Unlike YTHDF1 and YTHDF2, YTHDF3 primarily serves an auxiliary role, collaborating with YTHDF1 or YTHDF2 to promote mRNA translation or degradation. Other m6A "readers" include YTHDC1, the only known nuclear "reader," which promotes mRNA splicing by binding to serine/arginine-rich splicing factor 3 (SRSF3) [56, 57]. In this paper, we provide a detailed summary of the biological processes of m6A modification, including the m6A methyltransferases, demethylases, and the various m6A reader proteins, and their biological functions in regulating gene expression through m6A modification (Fig. 1). We hope this will offer readers a better understanding of the biological process of m6A modification. In conclusion, m6A modification plays a pivotal role in regulating a wide range of biological processes, influencing gene expression, RNA stability, and cellular functions. As our understanding of this dynamic epitranscriptomic modification deepens, it becomes clear that m6A is not only critical for normal cellular homeostasis but also for the progression of various diseases, including cancer. Its potential as a therapeutic target offers exciting prospects for future research, underscoring the importance of continued exploration into its broader biological and clinical significance.

The role of m6A modification in tumor innate immunity

Innate immunity is a non-specific defense mechanism that develops during the organism's growth, playing essential roles such as antigen presentation and phagocytosis, thus serving as the first line of defense against tumors [58]. Innate immune cells include dendritic cells (DC), natural killer (NK) cells, tumor-associated macrophages (TAM), monocytes, neutrophils, myeloid-derived suppressor cells (MDSC), γδ T cells, mast cells, and others [59]. The function and mechanisms of m6A modification in tumor innate immunity primarily manifest through its multi-faceted impact on the development, differentiation, and functional regulation of innate immune cells. As one of the most prevalent epigenetic modifications on RNA, m6A directly influences the immune functions of innate immune cells such as NK cells, macrophages, and dendritic cells by regulating mRNA stability, splicing, and translation efficiency [60]. Overall, the mechanisms of m6A modification in tumor innate immunity are complex and diverse; by affecting different

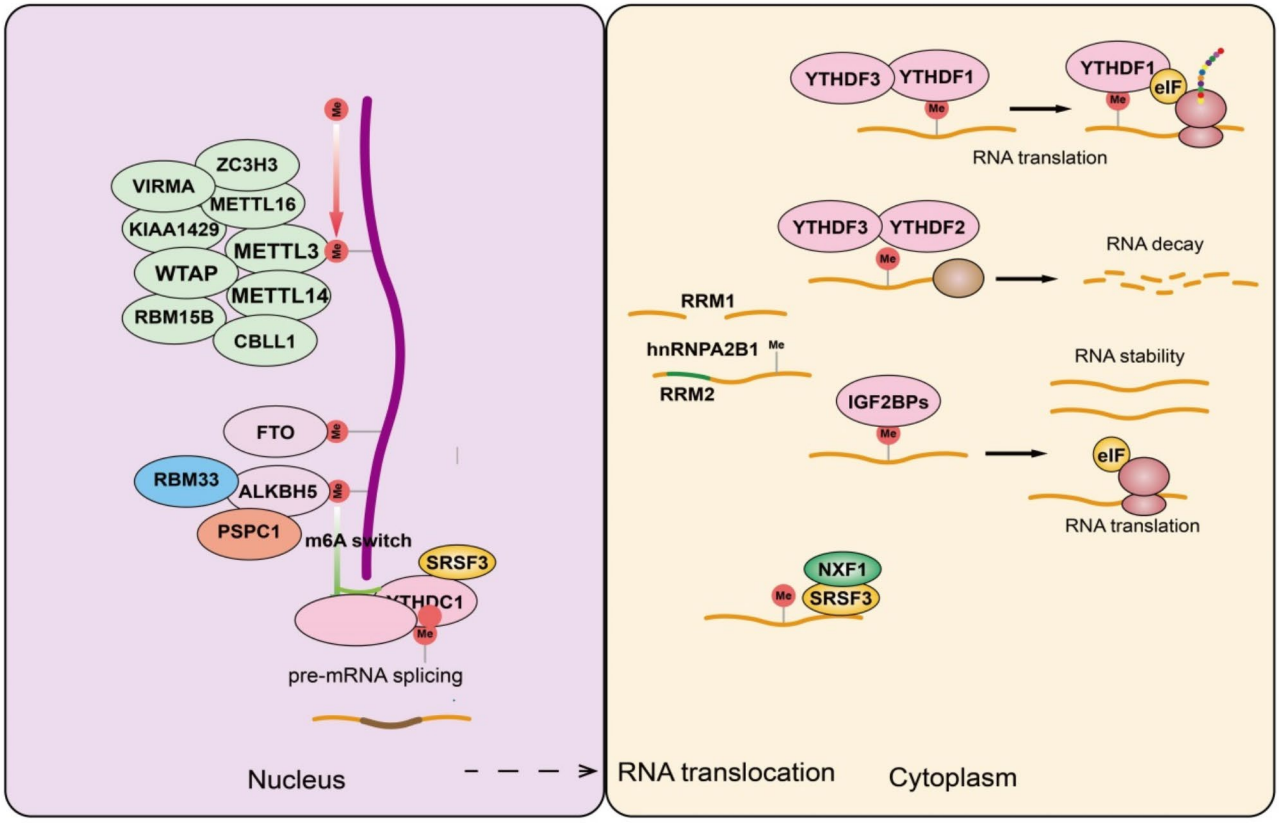

Fig. 1 The biological process of m6A modification. The m6A modification process consists of three steps: "writing," "erasing," and "reading." First, the methyltransferase complex (comprising the catalytic subunit METTL3, the auxiliary catalytic subunit METTL14, and regulatory proteins such as WTAP) catalyzes the addition of a methyl group to the N6 position of adenosine, a step known as "writing." Next, demethylases (such as FTO and ALKBH5) can remove the m6A modification from RNA, a process termed "erasing," allowing for dynamic regulation of the modification. Furthermore, m6A modifications are recognized by "reader" proteins (such as the YTH/IGF2BP family), which regulate the fate of mRNA, including its translation efficiency, stability, localization, and splicing

stages of innate immune cells, m6A indirectly regulates tumorigenesis, development, and responses to immunotherapy. Therefore, in-depth research on the functions of m6A modification in innate immunity will aid in elucidating mechanisms of tumor immune evasion and provide a theoretical basis for developing new immunotherapy strategies. For example, m6A modification affects the function of tumor-associated macrophages (TAMs), which can either suppress or promote tumor growth depending on their polarization. Research has shown that m6A modification on specific genes in TAMs can skew them toward a pro-tumor M2 phenotype, enhancing their immunosuppressive abilities. On the other hand, m6A modulation has been linked to enhanced anti-tumor activity in dendritic cells (DCs), which are essential for initiating adaptive immune responses [61]. For instance, m6A modification of the gene encoding for the transcription factor IRF8 has been found to regulate DC differentiation and function, impacting their ability to present tumor antigens and activate T cells [62].

Furthermore, m6A regulates cytokine production in natural killer (NK) cells, which are vital for recognizing and killing tumor cells. Studies show that m6A modification of certain cytokine genes in NK cells can alter their anti-tumor activity, affecting the overall immune surveillance of tumors [63]. These examples underscore the importance of m6A in shaping tumor immunity, highlighting its potential as a therapeutic target for enhancing anti-tumor immunity and overcoming immune evasion. Here, we review the functions and mechanisms of m6A modifications in natural killer (NK) cells, tumor-associated macrophages (TAM), neutrophils, and myeloid-derived suppressor cells (MDSC) (Fig. 2).

NK cells

NK cells are cytotoxic lymphocytes with direct killing effects within the innate immune system and are associated with anti-tumor activity, anti-viral infections, and immune regulation. NK cells possess strong anti-tumor capabilities and are considered the most promising tumor-killing effector cells after T cells [64]. Studies have

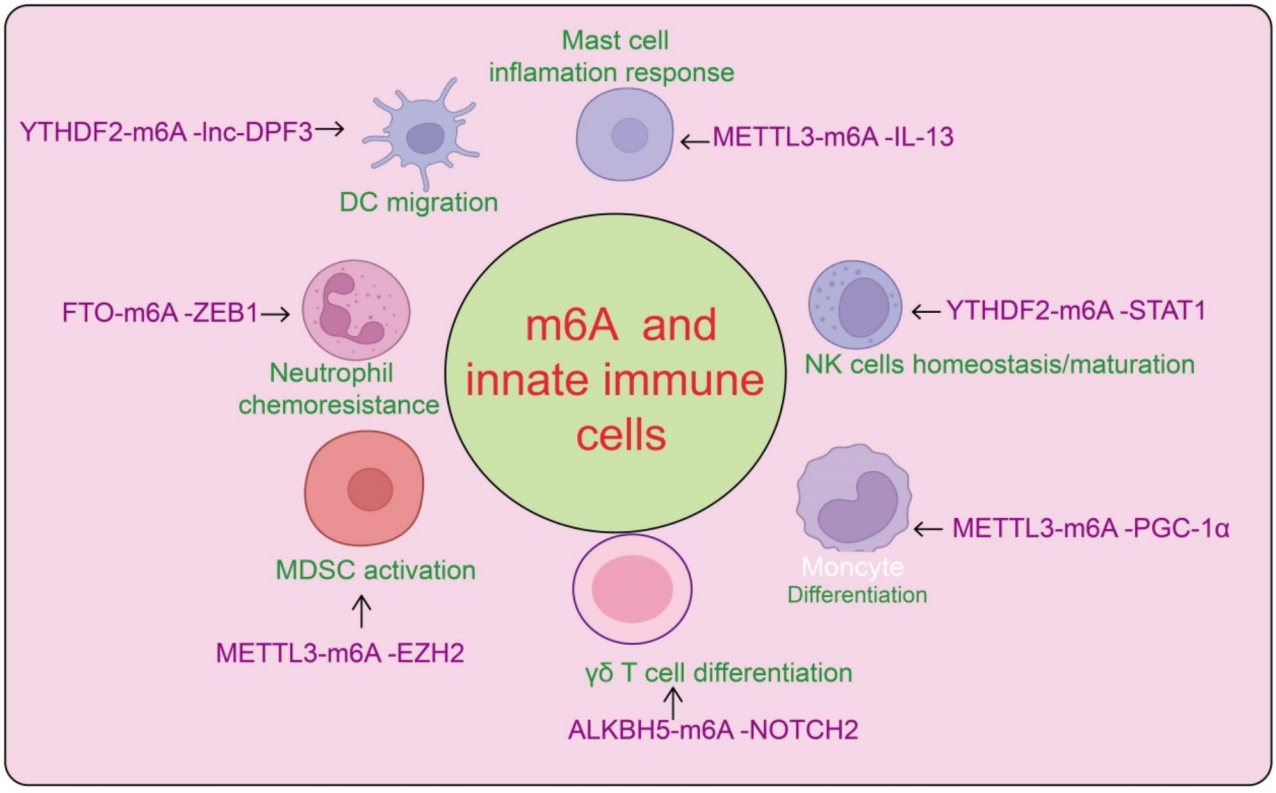

Fig. 2 The role of m6A modification in regulating different target genes in innate immune cells. In innate immune cells, m6A modification primarily influences immune function and responses by regulating the expression of genes involved in immune signaling pathways, the production of inflammatory cytokines, and cell survival and activation. Through these mechanisms, m6A modification modulates the function and immune response of innate immune cells

found that m6A modification plays an important role in maintaining NK cell homeostasis and functional efficacy. In melanoma, the protein expression level of METTL3 in NK cells positively correlates with effector molecules, and the absence of METTL3 disrupts the dynamic balance of NK cells, inhibiting their cytotoxic functions in the tumor microenvironment [65]. YTHDF2 also contributes to maintaining NK cell homeostasis and terminal maturation. The expression of YTHDF2 increases in activated NK cells, promoting NK cell effector functions through the formation of a STAT5-YTHDF2 positive feedback loop; it can also regulate NK cell proliferation and survival by decreasing the stability of Tardb gene transcription RNA [63] (Fig. 2).

Dendritic cells

Dendritic cells (DC) are the most potent antigen-presenting cells (APC) and play a crucial role in activating naive T cells during the initiation phase of immune responses [66]. Dysfunction in DC can lead to immune evasion, facilitating tumor development [67]. Research has shown that METTL3-mediated m6A modification enhances the translation of CD40, CD80, and the Toll-like receptor 4 (TLR4) signaling adapter protein Toll/interleukin-1β receptor domain-containing adapter protein (TIRAP) in DC, stimulating T cell activation and enhancing TLR4/NF-κB signal-induced cytokine production [68] (Fig. 2). m6A methylation can also impact DC migration. By removing the m6A modification from the non-coding RNA lnc-Dpf3 in DC, the reduction of YTHDF2-mediated lnc-Dpf3 degradation can hinder DC migration, affecting the initiation of immune responses [69] (Fig. 2). Furthermore, Han et al. [70] discovered that YTHDF1 can recognize m6A-marked transcripts of lysosomal proteases, increasing their translation in DC and degrading antigens taken up by DC. The absence of YTHDF1 downregulates the expression of lysosomal proteases, enhancing DC's ability to present tumor antigens and thereby effectively activating T cell anti-tumor responses.

Tumor-associated macrophages

Tumor-associated macrophages (TAM) are macrophages infiltrating tumor tissues and play significant roles in the formation of the tumor microenvironment [71]. Under the influence of the tumor microenvironment and various stimuli, macrophages can polarize in different directions; M1-type macrophages can promote immune responses and anti-tumor effects, while

M2-type macrophages exhibit immunosuppressive properties and facilitate tumor progression [72–74]. METTL3 can enhance the stability of STAT1 mRNA by mediating its methylation modification, leading to increased expression of STAT1 and promoting M1 polarization [75]. YIN et al. also demonstrated the regulatory role of METTL3 on TAM. In mouse models of melanoma or lung cancer, METTL3-deficient mice showed increased infiltration of TAM in tumors, and the absence of METTL3 reduced YTHDF1-mediated translation of SPRED2, enhancing NF-κB/STAT3 activation through the ERK pathway, resulting in tumor growth and metastasis [76]. Research has shown that YTHDF2 can also regulate the anti-tumor functions of TAM. The absence of YTHDF2 in TAM can reprogram them to an anti-tumor phenotype by targeting the interferon-γ (IFN-γ)-STAT1 signaling pathway, thereby enhancing their cross-presentation capability of antigens and boosting cytotoxic T cell-mediated anti-tumor immunity [61]. In conclusion, tumor-associated macrophages (TAMs) play a pivotal role in tumor progression by modulating the tumor microenvironment, influencing immune suppression, and supporting tumor growth and metastasis. As key contributors to both pro-tumorigenic and immunosuppressive processes, TAMs exhibit functional plasticity that can be influenced by various molecular regulators, including m6A methylation. Specifically, METTL3, a major methyltransferase responsible for the addition of m6A marks, has been shown to regulate the polarization of TAMs towards a pro-tumor M2 phenotype, thereby promoting immune evasion and tumor progression [54]. Conversely, YTHDF2, an m6A reader protein, affects the stability of mRNA transcripts within TAMs, further enhancing their immunosuppressive functions [61]. These findings highlight the critical role of m6A modification in shaping TAM activity and emphasize its potential as a therapeutic target to reprogram TAMs and improve anti-tumor immunity. By targeting METTL3, YTHDF2, or other key regulators of m6A, it may be possible to develop novel strategies to modulate TAMs for more effective cancer therapies.

Myeloid-derived suppressor cells

MDSCs are a heterogeneous population of bone marrow cells composed of immature precursor monocytes and neutrophils, characterized by potent immunosuppressive activity [77–79]. They are closely associated with the regulation of immune responses under various pathological conditions and are linked to poor prognosis in tumors [80].

The accumulation of MDSCs in the tumor microenvironment (TME) is a complex and gradual process governed by various factors. Karin described the recruitment of MDSCs from the bone marrow to the tumor site from a migratory perspective, which consists of four main steps: myelopoiesis, mobilization into the bloodstream, homing to the tumor site, and retention at the tumor site. Abnormally accumulated MDSCs in the bone marrow are mobilized into the bloodstream and spleen and are eventually recruited to the tumor site by chemokines, establishing a microenvironment that promotes tumor cell immune evasion [81]. In the TME, MDSCs undergo massive expansion under the influence of tumor-derived factors or inflammatory signals, thereby suppressing the host's anti-tumor response [82]. The immunosuppressive function of MDSCs can be regulated by different mechanisms. Studies have shown that MDSCs promote immunosuppression through soluble mediators, cell-cell interactions, and metabolic pathways. MDSCs inhibit T cell proliferation, differentiation, and function by depleting amino acids essential for T cell responses, releasing reactive oxygen species (ROS) and reactive nitrogen species (RNS), promoting the secretion of immunosuppressive cytokines, and altering receptor-ligand signaling [83]. MDSCs also cooperate with other immune cells to promote tumor immune evasion. For example, they enhance the expansion of Tregs, induce macrophage differentiation into the M2 phenotype, inhibit the maturation of dendritic cells (DCs) by reducing antigen uptake, and suppress B cell activation [84]. With the advent of single-cell sequencing, spatial transcriptomics, and reporter gene mapping technologies, numerous studies have explored the characterization, immunosuppressive functions, and isolation markers of abnormally expanded myeloid cell subtypes in different disease models and species. For instance, markers such as lectin-like oxidized LDL receptor 1 (LOX-1) and S100A9 have been used to improve the identification of human G-MDSCs and PMN-MDSCs [85], providing a more accurate definition of MDSCs. However, to avoid confusion and facilitate functional exploration, more research is needed to clearly define each MDSC subset in mice and humans.

RNA m6A modification affects MDSC expansion and function

Recent studies have investigated the significant role of m6A modification in MDSC expansion and immunosuppressive function. YTHDF2, a reader protein that recognizes m6A modifications, influences biological processes such as cell cycle progression and hematopoietic stem cell (HSC) expansion. Recent research has explored the intrinsic role of YTHDF2 in immune cells. Wang et al. used high-throughput single-cell RNA sequencing (scRNA-seq) to analyze immune cells in the tumor tissue of mice subjected to ionizing radiation (IR), discovering that IR significantly altered the subtypes and numbers of tumor-infiltrating immune cells in the TME, with a notable increase in MDSC numbers. They also studied the effects of IR on epitranscriptomic modifications driven

by RNA m6A methylation and observed an increased expression of YTHDF2 in MDSCs after IR.

YTHDF2 knockout reduced MDSC numbers in both tumors and the bloodstream [54]. Ni et al. confirmed that METTL3-mediated m6A RNA modification in tumor tissues of cervical cancer patients was positively correlated with MDSC expansion, inducing the differentiation of CD33 + cells into MDSCs in the TME and influencing cervical cancer progression and prognosis. Moreover, both METTL3 and CD33 + MDSCs are independent prognostic factors for cervical cancer [86]. Fibrocytic MDSCs (f-MDSCs) are a novel MDSC subset characterized by fibrocytic and MDSC surface markers with immunomodulatory properties [87]. G-CSF is a key cytokine mediating the immunoregulatory effects of cisplatin, stimulating granulopoiesis and cell differentiation in the innate immune system, and playing a crucial role in f-MDSC development [88]. Mu et al. demonstrated that in bladder cancer, cisplatin regulates f-MDSC expansion and immunosuppressive capacity by targeting METTL3 to inhibit G-CSF methylation, thereby suppressing tumor proliferation and metastasis [89]. Olfr29-ps1 is a lncRNA pseudogene upregulated by the pro-inflammatory cytokine IL-6 in MDSCs. Shang et al. found that the function of Olfr29-ps1 depends on IL-6-mediated m6A modification and promotes MDSC differentiation and immunosuppressive function both in vitro and in vivo. Mechanistically, Olfr29-ps1 regulates MDSC differentiation and function in the TME via the METTL3-modified Ofr29-ps1/miR-214-3P/MyD88 axis, revealing regulatory mechanisms in myeloid cells and providing potential targets for anti-tumor immunotherapy [90].

RNA m6A modification affects MDSC recruitment

Cytokines play an indispensable role in communication between cancer cells and immune cells. MDSCs are recruited from the bone marrow to primary and metastatic tumor sites by cytokines secreted by tumor and stromal cells. Chemokines regulating this process include chemokine (C-C motif) ligand 2/5 (CCL2/5) and chemokine (C-X-C motif) ligand 1/5/6/10 (CXCL1/5/6/10) [91]. Chen et al. used METTL3 knockout mouse models and found that silencing METTL3 significantly reduced MDSC numbers. In vitro studies showed that METTL3 promotes the expression of basic helix-loop-helix family member e41 (BHLHE41) in an m6A-dependent manner, inducing CXCL1 transcription and promoting MDSC recruitment in colorectal cancer [92]. The team also found that the deletion of YTHDF1 in colorectal cancer cells reduced MDSC numbers and increased functional T-cell infiltration. Studies using myeloid-specific METTL3 knockout mice revealed that the loss of METTL3 in the bone marrow cell lineage promoted MDSC recruitment, offering new insights into METTL3-mediated m6A methylation [93]. YTHDF1 promotes MDSC recruitment in the tumor microenvironment through the m6A-P65-CXCL1/CXCR2 axis, suppressing T cell function and disrupting anti-tumor immunity, thus promoting colorectal cancer development [94]. Additionally, Wang et al. found that in non-alcoholic steatohepatitis-associated hepatocellular carcinoma, YTHDF1 recruits and activates MDSCs through enhancer of zest homolog 2 (EZH2)-interleukin 6 (IL-6) signaling, leading to CD8 + T cell dysfunction [95]. This finding provides a theoretical basis for developing YTHDF1 inhibitors for liver cancer treatment. Recent research has revealed the role of ALKBH5 in the formation of the colorectal cancer tumor microenvironment. Mechanistically, ALKBH5 promotes the recruitment of immunosuppressive MDSCs to the colorectal cancer TME via the m6A- axis inhibition protein 2 (Axin2) -Wnt- dickkopf-1 (DKK1) axis, limiting the antitumor activity of NK cells and CD8 + T cells [96]. Mct4 is an enzyme that catalyzes lactate transport, with lactate being a metabolite directly affecting the recruitment of MDSCs and Tregs to tumor sites [97] Mct4 is a target gene of ALKBH5, regulating lactate concentrations and influencing Tregs and MDSC aggregation in the TME during treatment [48]. ALKBH5-mediated m6A modification regulates mRNA splicing and expression, playing a key role in modulating tumor responses to immunotherapy, suggesting that ALKBH5 may serve as a target for cancer treatment, either alone or in combination with immune checkpoint blockade (ICB). In summary, the upregulation or downregulation of m6A regulators in tumor cells can influence the recruitment of MDSCs in the TME by activating gene expression in tumor-related signaling pathways.

These findings have direct therapeutic implications. By targeting the m6A pathway, specifically METTL3 or YTHDF2, it may be possible to block the recruitment of MDSCs to tumors, thus reducing their immunosuppressive effect [61]. In preclinical models, inhibition of METTL3 resulted in a decrease in MDSC infiltration and a subsequent enhancement of anti-tumor immunity [54]. These results suggest that small molecules or RNA-based therapies that modulate m6A pathways could offer a new avenue for cancer treatment, potentially restoring the immune system's ability to recognize and eliminate tumor cells. Furthermore, targeting m6A modification in combination with existing immunotherapies, such as immune checkpoint inhibitors (e.g., PD-1/PD-L1 antibodies), could improve therapeutic outcomes. By reducing MDSC-mediated immune suppression, the combination of m6A inhibition and immune checkpoint blockade might enhance the efficacy of these treatments [54]. This approach could help overcome the limitations of current immunotherapy strategies, which are often hindered by

MDSC-induced immune suppression. Therefore, targeting m6A modifications provides a promising strategy for augmenting the anti-tumor immune response and improving the effectiveness of cancer immunotherapies.

Neutrophils

Neutrophils exhibit dual roles within the tumor microenvironment, as they can directly kill tumor cells or mediate anti-tumor responses through interactions with other immune components [98], while also promoting tumor progression via mechanisms such as angiogenesis, extracellular matrix remodeling, and immunosuppression [99]. It has been confirmed that the C5aR1 + neutrophil subset upregulates ENO1, inducing glycolysis in breast cancer cells through WTAP-mediated m6A methylation, which correlates with tumor progression and adverse patient prognosis [100]. Epithelial-Mesenchymal Transition (EMT) is a biological process where epithelial cells, which are normally structured, tightly connected, and line surfaces, transform into mesenchymal cells [101]. Mesenchymal cells are more flexible, and migratory, and can invade surrounding tissues. This process is vital in embryonic development, wound healing, and cancer progression, where it enables tumor cells to spread to other parts of the body (metastasis) [101]. Senescent neutrophils secrete exosomal piRNA-17,560, which enhances FTO expression in breast cancer cells. FTO decreases m6A methylation, thereby enhancing the stability of the zinc finger E-box binding homeobox 1 (ZEB1) gene, leading to chemotherapy resistance and epithelial-mesenchymal transition in tumor cells. Senescent neutrophils may serve as potential therapeutic targets in breast cancer [102].

Monocytes

Monocytes in the bloodstream can phagocytize and clear damaged or senescent cells and their debris, and they can migrate into tissues to differentiate into macrophages [103]. In the peripheral blood immune cells of colorectal cancer patients, the level of m6A in monocytes negatively correlates with monocyte immune responses [104]. Additionally, ZHANG et al. found that METTL3-mediated m6A modification and YTHDF2-mediated recognition can promote the degradation of PGC-1α mRNA, inducing the differentiation of monocytes into M1 and M2 macrophages, thereby playing a regulatory role in tumor immunity [105].

γδ T cells

γδ T cells are T cells that perform innate immune functions, characterized by their T cell receptors (TCR) composed of γ and δ chains, and are distributed in mucosal and subcutaneous tissues such as the intestine, respiratory tract, and urogenital tract [106]. γδ T cells can kill tumor cells and recognize certain tumor antigens, thus participating in anti-tumor immune responses [107]. Studies indicate that the m6A demethylase ALKBH5 regulates γδ T cell development; the absence of ALKBH5 in thymocytes impairs Jagged1/Notch2 signaling, facilitating the proliferation and differentiation of γδ T cell precursors [108]. METTL3-mediated m6A methylation can regulate mRNA stability and double-stranded RNA (dsRNA) content, balancing the two major functionally distinct subpopulations of γδ T1 and γδ T17 cells [109].

Mast cells

Mast cells are involved in immune regulation through the secretion of various cytokines. Infiltrating tumor tissues, mast cells secrete histamine, vascular endothelial growth factor, and other factors, which can stimulate tumor angiogenesis, promoting tumor growth and metastasis [110, 111]. They can also modulate the recruitment and activity of T cells and other immune cells, thereby influencing anti-tumor immunity [112]. Studies have found that METTL3, WTAP, and other components are highly expressed in esophageal squamous cell carcinoma and gastric cancer, with increased infiltration of mast cells and other immune cells in tumors, suggesting that mast cell infiltration is influenced by m6A methylation [113, 114]. The m6A methylation modification is also closely related to mast cell function. The m6A methyltransferase complex participates in regulating the growth and proliferation of mast cells and can affect the stability of cytokine mRNA, inhibiting mast cell-mediated inflammatory responses [115].

The role of m6A modification in tumor adaptive immunity

Adaptive immunity, also known as specific immunity, is the immune response generated by the organism in response to antigen stimulation [116]. Tumor-associated antigens are recognized and captured by antigen-presenting cells (APCs) and subsequently presented to effector cells, including T cells and B cells, thereby initiating an anti-tumor immune response [117]. The function and mechanisms of m6A modification in tumor adaptive immunity mainly operate through the regulation of T cell and B cell development, differentiation, and function. In the tumor microenvironment, m6A modification regulates the activation, immune response intensity, and tumor antigen recognition of adaptive immune cells by influencing the mRNA stability and translation efficiency of key immune molecules [118]. In T cells, m6A modification regulates their differentiation into various subtypes (such as effector T cells and regulatory T cells), thereby affecting their anti-tumor immune activity. Research indicates that m6A modifies the expression of immune checkpoint molecules such as PD-1 and CTLA-4, influencing the exhaustion status of T cells and

thereby modulating tumor immune evasion mechanisms [69]. Moreover, m6A modification plays a crucial role in CAR-T cell therapy by enhancing T cell anti-tumor activity and improving therapeutic efficacy. In B cells, m6A modification regulates antibody production and B cell activation, potentially influencing the recognition of tumor antigens and the immune response, thereby affecting tumor immune evasion and progression. Overall, the mechanisms of m6A modification in tumor adaptive immunity are complex and extensive. In-depth research on its regulatory pathways will help elucidate key aspects of tumor immune evasion and provide new targets and strategies for improving the efficacy of tumor immunotherapy [119]. Here, we discuss the roles and mechanisms of m6A modifications in the regulation of tumor adaptive immunity (Fig. 3).

m6A and T cells

T lymphocytes originate from hematopoietic stem cells in the bone marrow and migrate to the periphery after differentiation and maturation in the thymus, where they fulfill various immune functions. T cells possess multiple biological functions, including directly killing target cells, regulating or assisting the functions of other immune cells, and producing cytokines. They play a dominant role in anti-tumor immunity [120, 121]. T cells can be categorized into several subpopulations based on their functions and surface markers. m6A modification regulates various aspects of T cell biology, including differentiation, activation, and response to tumors. Recently, one study demonstrated that m6A modification, mediated by the methyltransferase METTL3, influences T-cell differentiation. They found that METTL3 regulates the transition of naive CD4 + T cells into T helper 17 (Th17) cells, a subset important for anti-tumor immunity [122]. In METTL3-deficient mice, Th17 cell differentiation was impaired, leading to reduced anti-tumor immune responses. The study highlighted that m6A modification regulates the expression of key transcription factors involved in T cell differentiation, such as RORγt and STAT3, suggesting that m6A-mediated regulation of these pathways is crucial for T cell functionality in tumor immunity [123] (Fig. 3). Moreover, Wang et al. (2020) showed that YTHDF1, an m6A reader protein, controls T-cell activation. YTHDF1 recognizes m6A marks on mRNA transcripts related to T cell receptor (TCR) signaling, stabilizing these transcripts and promoting robust T cell activation. The loss of YTHDF1 in T cells resulted in impaired activation and a reduced ability to mount immune responses, which was especially evident in tumor models where T cell dysfunction contributes to immune evasion [94] (Fig. 3). These findings underscore the critical role of m6A modification in regulating T cell activation and its potential as a target for enhancing T cell-mediated anti-tumor immunity.

m6A and CD4 + helper T cells

Naive CD4 + T cells differentiate into various types of helper T cells under the stimulation and regulation of different antigens and cytokines. Among these, the Th1 subtype assists cytotoxic CD8 + T cells and B cells in exerting anti-tumor functions and can produce cytokines such as IFN-γ and TNF-α, which directly act on tumor cells. In contrast, the Th2 subtype primarily secretes

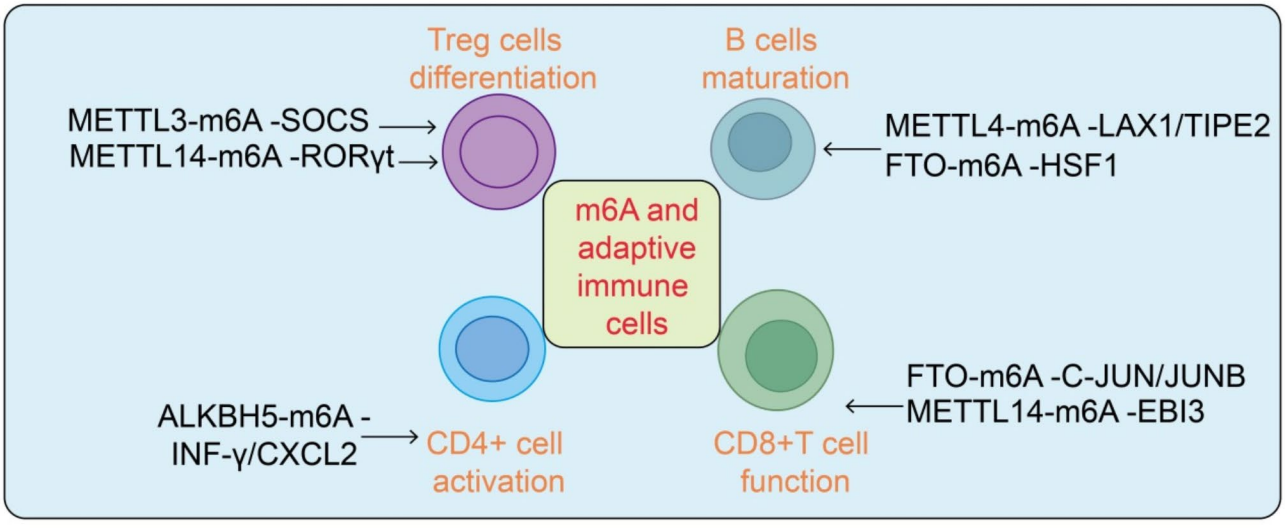

Fig. 3 The role of m6A modification in regulating different target genes in adaptive immune cells. m6A modification also plays a crucial regulatory role in adaptive immune cells by modulating the expression of specific target genes, thereby influencing the development, differentiation, and function of T cells, B cells, and other adaptive immune cells. This modification is involved in immune responses, cell fate determination, and immune tolerance within the adaptive immune system

cytokines like IL-4 and IL-13, which can suppress the cytotoxic effects of T cells [124] Research has shown that m6A modification influences the differentiation of naive CD4 + T cells. Initial T cells deficient in METTL3 exhibit a reduction in Th1 cells and an increase in Th2 cells. Knockout of the METTL3 gene in naive T cells leads to suppressed protein levels of suppressor of cytokine signaling 1 (SOCS1), SOCS3, and CISH, which in turn inhibits the IL-7/STAT5 signaling pathway, affecting T cell homeostasis and differentiation [125] (Fig. 3>). Furthermore, m6A methylation also impacts the functions of CD4 + T cells. The demethylase ALKBH5 enhances the stability and translation of mRNA by reducing m6A levels in CXCL2 and IFN-γ, thereby promoting Th1 cell functionality [126].

m6A and regulatory T Cells

Regulatory T cells (Tregs) are a subset of CD4 + T cells that mediate the negative regulation of immune cell functions. Studies indicate that m6A methylation also plays a crucial role in the differentiation and effector functions of Tregs. The absence of METTL14 leads to an inability of naive T cells to maintain differentiation into induced Tregs [44]. METTL3-mediated m6A methylation is essential for sustaining the suppressive functions of Tregs. In Tregs, the deficiency of METTL3 increases SOCS mRNA levels, resulting in the inactivation of the IL-2/STAT5 signaling pathway, ultimately compromising Treg function and stability [127].

m6A and CD8 + T cells

CD8 + T cells are cytotoxic T cells that, upon activation, can release perforin and granzymes to kill tumor cells. Numerous studies have indicated a close correlation between m6A methylation modifications and the tumor infiltration of CD8 + T cells. In the stroma of colorectal cancer, the expression of METTL14 positively correlates with m6A levels and the extent of CD8 + T cell infiltration [128]. In non-small cell lung cancer (NSCLC), high expression of YTHDF1 and YTHDF2 significantly increases the infiltration of lymphocyte subpopulations, including CD8 + T cells, within the tumor stroma [129]. Similarly, in NSCLC, LIU et al. discovered that METTL3 mediates the m6A modification of circular RNA circIGF2BP3, promoting its circularization. CircIGF2BP3 competitively upregulates PKP3 through miR-328-3p and miR-3173-5p, thereby reducing CD8 + T cell infiltration and suppressing the tumor immune response [130] (Fig. 3). Moreover, murine melanoma cells can inhibit CD8 + T cell activation and evade immune surveillance through a glycolytic pathway mediated by FTO; however, knockout of the FTO gene results in decreased glycolytic activity in tumor cells and restoration of CD8 + T cell functionality [119].

m6A and B cells

B cells can differentiate into plasma cells upon antigenic stimulation, producing antibodies that mediate humoral immune responses [131]. In tumor immunity, B cells primarily rely on the secretion of antibodies against tumor-associated antigens, and activated B cells can also facilitate T cell activation through antigen presentation, thereby exerting anti-tumor effects [132]. Research has indicated that m6A modifications are involved in regulating early B cell development; for example, the deficiency of METTL14 can block the transition of immature B cells from pro-B cells to large pre-B cells, thereby affecting B cell maturation [133]. Another study demonstrated that METTL14-mediated m6A modifications promote the decay of mRNA for negative immune regulators (such as Lax1 and Tipe2), which impacts the positive selection and proliferation of germinal center B cells [134]. Conversely, aberrant m6A modifications in B cells can regulate tumorigenesis and progression. In plasma cells from patients with multiple myeloma, FTO expression is upregulated, and m6A methylation levels are significantly decreased, promoting the proliferation, migration, and invasion of multiple myeloma cells [135]. Furthermore, a recent study demonstrated that m6A modification affects B cell receptor (BCR) signaling and antibody production. By regulating key B cell signaling molecules, m6A modification ensures optimal activation and expansion of B cells following antigen exposure. They showed that m6A modification controls the expression of BCL6, a transcription factor crucial for B cell proliferation and differentiation into plasma cells [136]. Inhibition of METTL3 in B cells resulted in decreased B cell proliferation and reduced antibody production, highlighting the importance of m6A in the regulation of humoral immunity.

m6A modification and CAR-T cell therapy

m6A modification plays a crucial role in enhancing the function and persistence of CAR-T cells, which are genetically engineered T cells designed to target and eliminate tumor cells. The regulation of m6A modification can influence various aspects of CAR-T cell biology, including activation, expansion, and memory formation, which are essential for the long-term success of CAR-T cell therapies. Researchers found that METTL3, the enzyme responsible for adding m6A marks, regulates CAR-T cell expansion and persistence in vivo. In their study, they demonstrated that METTL3 deletion in CAR-T cells resulted in diminished expansion and shorter persistence after infusion into tumor-bearing mice. This effect was attributed to a decrease in the stability of key cytokine mRNAs that are essential for CAR-T cell activation and survival, such as IL-2 and IFN-γ [137, 138]. These findings suggested that m6A-mediated regulation of mRNA stability is crucial for maintaining the

robust activity and long-term efficacy of CAR-T cells in cancer treatment. Additionally, the study showed that YTHDF2, a m6A reader protein, regulates the activation of CAR-T cells by modulating the translation of specific cytokine receptors. YTHDF2-mediated stabilization of cytokine receptor mRNAs led to enhanced signaling through these pathways, supporting the persistence and anti-tumor activity of CAR-T cells [139]. This study underscores the importance of m6A modification in CAR-T cell therapy, highlighting how modulation of the m6A pathway can potentially improve the therapeutic outcomes by enhancing the persistence and activation of CAR-T cells. By targeting METTL3 or other components of the m6A pathway, it may be possible to develop strategies to improve CAR-T cell therapy, particularly in overcoming challenges such as the short-lived nature of CAR-T cells and their limited persistence in the tumor microenvironment.

m6A modifications and anti-tumor immunity

Tumor immunotherapy aims to externally intervene in the immune system to restore and enhance the body's anti-tumor immune response, thereby improving the recognition and elimination of tumor cells [140]. Currently, the primary clinical approaches to tumor immunotherapy include immune checkpoint inhibitor therapy and adoptive cell immunotherapy. Targeting m6A modifications to regulate the body's immune response against tumors may represent a new direction in immunotherapy. Therefore, we summarize the current research progress on targeting m6A regulatory factors in cancer therapy (Fig. 4).

Targeting m6A modifications to assist immune checkpoint therapy

Tumor immunotherapy has become one of the mainstream methods for cancer treatment, achieving significant success. Immune checkpoint inhibitors (ICIs) are critical immunotherapeutic agents that primarily target cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed cell death-1 (PD-1), and programmed cell death-ligand 1 (PD-L1) [141]. Over the past few decades, these therapies have markedly improved the prognosis of patients with advanced cancers. However, despite some effectiveness when ICIs are combined with other therapies, many patients may exhibit no response or only a limited response to treatment, leading to issues of resistance and relapse. Recent studies have shown that m6A modifications play an important role in regulating tumor immune evasion [142]. These modifications can significantly affect the efficacy of ICIs by directly or indirectly

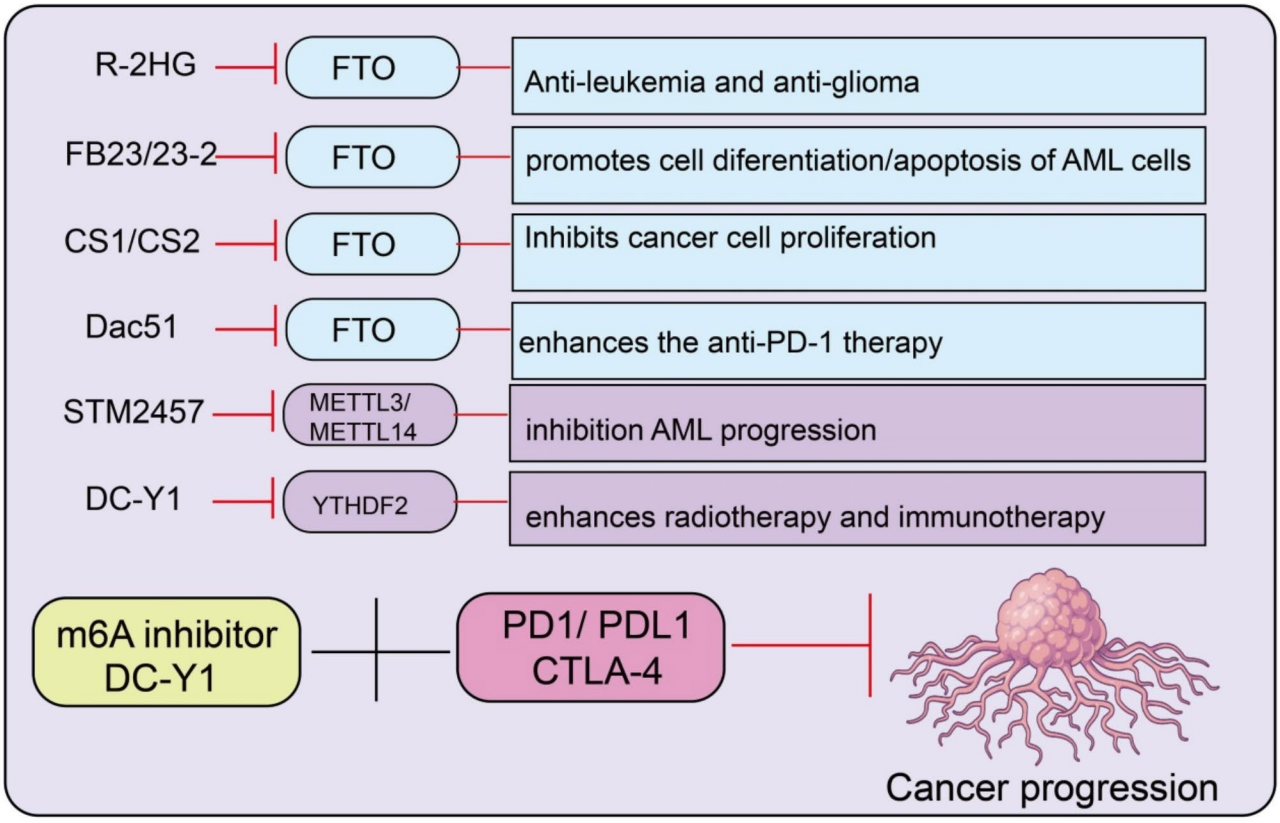

Fig. 4 Targeting m6A modification in combination with immune checkpoint inhibitors to suppress tumor progression

influencing the expression levels of ICI targets (including PD-1, PD-L1, CTLA4, and other checkpoints) or key signaling pathways.

m6A modification plays a significant role in the immune response to cancer and can affect the efficacy of immune checkpoint inhibitors (ICIs), such as PD-1/PD-L1 inhibitors, which are widely used in cancer immunotherapy. It has been found that m6A modification regulates the expression of immune checkpoint molecules such as PD-L1, which is often overexpressed on tumor cells to suppress immune responses. They found that YTHDF2, an m6A reader protein, controls the stability of PD-L1 mRNA, promoting its expression in tumor cells. By targeting YTHDF2 or other m6A regulators, they demonstrated enhanced anti-tumor immunity in combination with PD-1 blockade [61] (Fig. 4). These results suggest that m6A modification not only affects immune cell activation but also influences the expression of immune checkpoint molecules on tumor cells, further impacting the effectiveness of ICIs. These studies highlight the potential of targeting the m6A pathway to improve ICI efficacy. By modulating m6A regulators like METTL3 or YTHDF2, it may be possible to enhance T cell responses and reduce tumor-mediated immune suppression, thereby improving the clinical outcomes of PD-1/PD-L1 inhibitors and other immune checkpoint therapies.

m6A modifications and PD-1

Recent research increasingly demonstrates a significant association between changes in m6A regulatory factors and the expression levels of PD-1 [114]. YANG et al. found that high expression of FTO promotes the growth of melanoma by removing RNA m6A modifications, which decreases the response to anti-PD-1 blockade immunotherapy. Conversely, downregulation of FTO increases the m6A methylation levels of key oncogenic melanoma genes, including PD-1, CXCR4, and SOX10, resulting in increased RNA decay mediated by the m6A reader YTHDF2, thereby enhancing mouse responses to anti-PD-1 therapy. This indicates that FTO, as an m6A demethylase, plays a crucial role in promoting melanoma progression and resistance to anti-PD-1 treatment [143] (Fig. 4). Another study identified a positive correlation between IGF2BP expression and PD-1 expression, suggesting that m6A modifications regulated by the IGF2BP family may confer potential benefits to lung adenocarcinoma patients undergoing ICI therapy [144]. Research establishing an m6A score prognostic model revealed that a high-risk score is an independent prognostic indicator for pancreatic cancer, with higher risk scores associated with reduced overall survival; low m6A scores were correlated with low abundances of PD-1 and CTLA-4, indicating that m6A plays a critical role in predicting the efficacy of ICIs in pancreatic cancer patients [145]. ZHANG et al. developed a scoring system (m6A score) to quantify m6A modification patterns in gastric cancer, linking these patterns to immune cell infiltration characteristics in the tumor microenvironment. They found that the m6A methylation modification patterns were significantly associated with tumor immune phenotypes and responses to anti-PD-1/programmed cell death ligand 1 (PD-L1) immunotherapy. These results suggest that m6Ascore may help predict responses to anti-PD-1/L1 immunotherapy, serving as a reliable biomarker for assessing prognosis and clinical outcomes in immunotherapy.

m6A modifications and PD-L1

As a ligand for PD-1, PD-L1 is another critical immune checkpoint protein that facilitates immune evasion by cancer cells through its interaction with PD-1. Studies indicate that dysregulation of m6A-related regulatory factors significantly impacts PD-L1 expression. In breast cancer, the expression level of METTL3 is negatively correlated with patient survival and the infiltration of CD8 + and CD4 + T cells. Knockdown of METTL3 significantly reduces m6A modifications on PD-L1 mRNA, leading to decreased recognition of m6A by IGF2BP3 and promoting PD-L1 mRNA degradation [146]. In bladder cancer, the JNK signaling pathway promotes METTL3 expression, thereby inhibiting CD8 + T cell function within the tumor microenvironment (TME). Inhibition of the JNK/METTL3 signaling axis restores the cytotoxic function of CD8 + T cells, subsequently suppressing tumor progression. The high expression of METTL3 enhances the m6A modification of the 3′-UTR region of PD-L1 mRNA, with IGF2BP1 mediating PD-L1 expression through its binding to the mRNA, thus inhibiting CD8 + T cell functionality [147]. Furthermore, in non-small cell lung carcinoma (NSCLC), METTL3 can also regulate PD-L1 expression by influencing the metabolism of circular IGF2BP3. Circular IGF2BP3 stabilizes OTUB1 mRNA in a PKP3-dependent manner, which reduces the ubiquitination levels of PD-L1 in NSCLC cells, leading to increased PD-L1 expression and ultimately mediating immune evasion [130]. Similarly, in cholangiocarcinoma (CCA), METTL14 triggers m6A modifications by binding to Siah2 (Seven in absentia homolog 2) mRNA in the 3′-UTR region, promoting its degradation in a YTHDF2-dependent manner. Removal of Siah2 increases the protein stability of PD-L1, subsequently inhibiting T cell proliferation and T cell-mediated anti-tumor activity, indicating the clinical potential of the METTL14-Siah2-PD-L1 regulatory axis in CCA immunotherapy [148]. In intrahepatic cholangiocarcinoma (ICC), the loss of ALKBH5 increases the abundance of m6A modifications in the 3′-UTR region of PD-L1 transcripts in a

Table 1 Summarizing the targeting of various m6A components in tumor progression and anti-tumor immunity

m6A regulator	Impact on Tumor Progression	Impact on Anti-Tumor Immunity	Key Findings	Ref
METTL3	Inhibition of METTL3 reduced tumor growth in vivo.	Reduced T cell activation and immune response to tumors.	METTL3 regulates T-cell differentiation, impacting immune responses and the effectiveness of PD-1 inhibitors.	[123]
YTHDF1	Increased tumor growth when YTHDF1 was deleted in T cells.	Impaired T cell activation and reduced anti-tumor immunity.	YTHDF1 stabilizes cytokine receptor mRNAs, promoting T cell activation and anti-tumor immunity.	[94]
YTHDF2	Enhanced tumor growth when YTHDF2 was overexpressed in tumor cells.	Increased immune suppression by promoting PD-L1 expression.	YTHDF2 stabilizes PD-L1 mRNA, reducing T-cell responses and enhancing tumor immune evasion.	[61]
METTL14	METTL14 inhibition reduced tumor metastasis and promoted anti-tumor immunity.	Enhanced T cell and NK cell responses in the tumor microenvironment.	METTL14 affects immune cell infiltration and promotes tumor suppression by enhancing immune responses.	[128]
METTL3	METTL3-deficient mice showed decreased tumor growth.	Enhanced T cell-mediated immunity in the tumor microenvironment.	METTL3 controls the differentiation of immune cells, and its inhibition enhances anti-tumor immunity.	[159]
METTL3 and YTHDF2	Dual targeting of METTL3 and YTHDF2 slowed tumor growth significantly.	Improved efficacy of immune checkpoint inhibitors (e.g., PD-1) in combination with m6A inhibition.	Targeting METTL3 and YTHDF2 enhances anti-tumor immunity and promotes the effectiveness of immunotherapy.	[160]

YTHDF2-dependent manner [149], leading to downregulation of PD-L1 expression. In breast cancer, the expression of PD-L1 is positively correlated with the expressions of METTL3 and IGF2BP3, with METTL3 promoting PD-L1 mRNA stability in an m6A-IGF2BP3-dependent manner, thereby upregulating PD-L1 expression [146]. Additionally, m6A regulatory factors also modulate PD-L1 expression in other cancer types; for instance, the knockdown of IGF2BP1 downregulates PD-L1 expression and activates immune cell infiltration, thereby inhibiting the progression of hepatocellular carcinoma [150]. These findings provide new avenues for immunotherapy in cancers such as breast cancer and hepatocellular carcinoma.

m6A modifications and other immune checkpoints

m6A not only influences PD-1 and PD-L1 but also regulates other checkpoints such as CD80, ICOS, and VISTA (V-type immunoglobulin domain-containing suppressor of T cell activation). Similar to PD-1 and PD-L1, studies have found that METTL3 can enhance the translation of CD80, promoting dendritic cell activation and maturation in an m6A-dependent manner [68]. Additionally, METTL3 promotes the differentiation of follicular helper T cells (TFH) through m6A modifications. In METTL3-deficient TFH cells, both m6A levels and the expression of inducible co-stimulatory molecules (ICOS) are significantly reduced, indicating that m6A modifications can regulate ICOS expression [151]. Likewise, YTHDF1 enhances the protein levels of PD-L1 and VISTA in colorectal cancer (CRC) in an m6A-dependent manner [152]. In addition to the well-established regulation of PD-1 and PD-L1 by m6A, the role of m6A in regulating other immune checkpoint molecules, such as LAG3, TIGIT, and CTLA4, is gaining attention. These immune checkpoints play crucial roles in modulating T cell activation and immune responses within the tumor microenvironment, and their regulation by m6A can influence the efficacy of immune checkpoint inhibitors (ICIs). Targeting m6A regulators that control the expression of these immune checkpoint molecules could offer a comprehensive strategy to enhance the efficacy of immune checkpoint inhibitors and restore immune responses in cancer patients (Table 1).

Targeting m6A regulatory factors to enhance immune response

Despite significant advances in immunotherapy, low response rates remain a challenge. As discussed, m6A modifications play a crucial role in tumor immunotherapy by mediating the expression of immune checkpoints. Therefore, developing inhibitors or agonists of m6A regulatory factors may represent a promising therapeutic strategy to enhance anti-tumor immune responses, potentially resensitizing tumor cells to anticancer drugs when used in conjunction with immune checkpoint inhibitors (ICIs). Although these inhibitors and agonists have not yet been widely applied in clinical practice, their potential to inhibit tumor growth has been demonstrated in cancer animal models. Among these, FTO is currently the most promising target for developing inhibitors of m6A regulatory factors. To date, over ten FTO inhibitors have been identified, with therapeutic efficacy validated across various models [153]. Among them, rhubarb acid is the first FTO inhibitor discovered, which inhibits FTO-mediated m6A demethylation through reversible binding to the catalytic domain of FTO while exhibiting relatively low cytotoxicity. YAN et al. found that the combination of rhubarb acid with tyrosine kinase inhibitors (TKIs) showed good inhibitory effects on leukemia cells, with drug-resistant cells becoming more sensitive to TKIs and displaying reduced colony formation [154]. However,

no studies have yet reported the effects of rhubarb acid in combination with immunotherapy on tumors. Furthermore, GNPIPP12MA is a GSH bioimprinted nanocomposite that carries FTO inhibitors along with the non-steroidal anti-inflammatory drug meclofenamic acid (MA).

Depletion of reduced glutathione (GSH) can lower intracellular GSH levels and induce ferroptosis. Acute myeloid leukemia (AML) cells and leukemia stem cells (LSCs) uptake GNPIPP12MA, which enhances the efficacy of anti-PD-L1 treatment by promoting T-cell infiltration and IFN-γ secretion [155]. Recent studies have reported that FTO deficiency can facilitate the infiltration of CD8 + T cells into tumors, thereby inhibiting tumor growth and blocking FTO-mediated immune evasion. The novel FTO inhibitor Dac51 enhances the efficacy of PD-L1 blockade therapy by promoting T-cell infiltration, thereby serving as an effective strategy to synergistically improve immune responses in melanoma and NSCLC [119]. STM2457, as an inhibitor of METTL3, targets key stem cell populations in AML and reverses the malignant phenotype of AML, demonstrating the potential for AML treatment [156]. In cervical squamous cell carcinoma (CESC), immune activation markers such as ICOS, KIR2DL4, TNFSF9, and CD86 are negatively correlated with METTL3 expression. Additionally, METTL3 plays a role in the infiltration of immune cells, including M1 macrophages, dendritic cells, and M2 macrophages. The combination of STM2457 with PD-1 blockade inhibits the progression of CESC in vivo [157]. Researchers found that mice carrying YTHDF1-knockdown CT26 and MC38 tumor cells in colorectal cancer (CRC) exhibited significantly reduced tumor growth rate and weight. Compared to the single treatment group, mice receiving combined therapy showed significantly extended overall survival [158]. These findings suggest that YTHDF1 deficiency may enhance the efficacy of anti-PD-L1 immunotherapy. Unfortunately, no corresponding YTHDF1 inhibitors have been developed for clinical application to date. In summary, these studies indicate that drugs such as GNPIPP12MA, Dac51, and STM2457 possess synergistic anti-tumor effects in immunotherapy and are expected to advance to clinical trials.

In conclusion, targeting m6A regulatory factors presents a promising strategy to enhance immune responses, particularly in the context of cancer immunotherapy. By modulating key enzymes like METTL3, METTL14, and YTHDF2, it is possible to regulate the differentiation, activation, and persistence of immune cells, such as T cells and macrophages, which are critical for effective anti-tumor immunity. Inhibiting these m6A regulators could improve the efficacy of immune checkpoint inhibitors, CAR-T cell therapies, and other immunotherapies by enhancing immune cell function and overcoming tumor-induced immune suppression. As a result, m6A modifications hold significant therapeutic potential, offering a novel avenue for optimizing immune-based treatments and improving clinical outcomes for cancer patients.

Advantages and limitations of targeting m6A regulatory factors in tumor immunotherapy

The advantages of targeting m6A regulatory factors in tumor immunotherapy lie in their ability to precisely modulate the epigenetic modifications at the RNA level, thereby influencing immune cell function and the tumor microenvironment. By regulating m6A modifications, it is possible to enhance the activity of anti-tumor effector cells such as T cells and NK cells, thereby reducing the opportunities for tumor immune evasion. For instance, inhibiting m6A methyltransferases or demethylases can regulate the expression of immune checkpoint molecules (such as PD-1), thereby improving the efficacy of immunotherapy. Moreover, targeting m6A modifications may offer unique advantages in enhancing the durability and specificity of immune responses, particularly when used in combination with existing immune checkpoint inhibitors or CAR-T cell therapies, potentially increasing therapeutic efficacy. However, the limitations of targeting m6A regulatory factors cannot be overlooked. Firstly, m6A modifications are broadly involved in various biological processes, and systemic inhibition could lead to immune system imbalances or adverse effects in non-target cells. Secondly, the mechanisms of m6A modifications in different immune cell types and tumor varieties are not yet fully understood, and the effectiveness of targeting m6A may be limited in certain tumor types. Additionally, the development of drugs targeting m6A regulatory factors and their clinical translation still faces challenges related to technology and safety, necessitating further preclinical and clinical research to validate their safety and efficacy. In summary, while targeting m6A regulatory factors exhibits tremendous potential in tumor immunotherapy, it is essential to overcome the associated limitations to facilitate better clinical application.

Conclusion and prospect

This review discusses the biological characteristics of m6A writers, erasers, and readers, as well as their regulation of tumor immunity. m6A writers catalyze the addition of m6A modifications to RNA, while erasers remove these modifications. Readers recognize m6A methylation and influence the biological processes of RNA. Research has demonstrated that these m6A regulatory factors play crucial roles in the biological processes of tumorigenesis, progression, metastasis, and drug resistance. The potential application of m6A in cancer therapy positions it as a promising target. Various inhibitors targeting m6A

regulatory factors have been developed, and numerous preclinical studies have shown their significant antitumor activity, particularly in synergy with immune checkpoint inhibitors. The combination of m6A inhibitors with immune checkpoint blockade therapy holds the potential for enhancing the role of m6A modifications in tumor immunotherapy, thereby addressing the limitations of current immunotherapeutic approaches. Although m6A inhibitors have yet to enter clinical trials, they provide a promising direction for the discovery of novel cancer therapies. However, research on m6A in various tumor types remains in its infancy, and a deeper understanding of the molecular mechanisms underlying m6A modifications will provide critical information for personalized treatment strategies.

The development of effective, cost-efficient, and high-resolution m6A sequencing technologies holds great promise for applications in tumor immunotherapy. Although existing m6A sequencing techniques, such as MeRIP-seq and m6A-CLIP, can detect m6A modification sites across the entire genome, they still face limitations in terms of resolution, sensitivity, and cost-effectiveness, making it challenging to meet the demand for in-depth analysis of the dynamic regulation of m6A modifications within the tumor immune microenvironment. Therefore, the development of higher-resolution and more cost-effective m6A detection technologies will not only facilitate a deeper exploration of the precise regulation of immune cell functions by m6A modifications but also uncover key RNA modification targets in tumor immune evasion mechanisms.

In the future, with technological advancements, novel m6A sequencing methods may enable the generation of m6A modification maps at the single-cell level. Coupled with the need for tumor immunotherapy, this could reveal the m6A modification characteristics of different cell types and their roles in immunotherapy responses. Furthermore, reducing the costs of m6A sequencing will make large-scale clinical applications feasible, promoting the development and application of m6A modifications as biomarkers in immunotherapy, and thereby assisting in tumor classification, efficacy prediction, and the formulation of personalized treatment strategies. These advancements will accelerate the clinical translation of m6A modifications in tumor immunotherapy, aiding in the identification of additional key immune regulatory molecules and potential therapeutic targets, ultimately enhancing the efficacy and safety of immunotherapy and providing patients with more precise and economical treatment options.

The future application prospects of Cas9 gene knockout technology targeting m6A modifications in combination with immunotherapy hold immense potential. The CRISPR-Cas9 technology enables precise knockout of specific genes, and when combined with m6A modification targets, it can facilitate the molecular-level regulation of m6A modifications on key genes, thereby modulating immune cell functions. This technology can be utilized to knock out m6A regulatory factors, such as METTL3 and FTO, allowing for an in-depth investigation of their specific roles in immune cells and the tumor microenvironment, as well as elucidating their regulatory mechanisms in tumor immune evasion and responses to immunotherapy. By targeting m6A modifications through Cas9 technology, it becomes possible to enhance the functionality of anti-tumor effector cells, such as T cells and NK cells, thereby improving the immune system's ability to recognize and eliminate tumor cells. Particularly when this technology is combined with existing immune checkpoint inhibitors or CAR-T cell therapies, it can further enhance the efficacy of immunotherapy and overcome resistance to treatment in certain patients. Furthermore, the high specificity and programmability of Cas9 gene knockout technology enable the targeting of various m6A regulatory factors, providing new possibilities for personalized tumor immunotherapy strategies. In the future, as CRISPR-Cas9 technology continues to be optimized and translated into clinical practice, gene knockout technology targeting m6A modifications is expected to emerge as a precise and effective therapeutic strategy. By synergizing with immunoth rapy, this approach could further enhance the efficacy of tumor treatments and improve patient survival rates. Moreover, this technology may play a crucial role in overcoming tumor immune evasion and increasing the response rates to immunotherapy, thereby opening new pathways for cancer treatment.

Abbreviations

AAA	Abdominal Aortic Aneurysm
ACC	Adrenocortical carcinoma
ACER2	Alkaline ceramidase 2
ALKBH1	α-Ketoglutarate-dependent dioxygenase ABH1
ALKBH5	AlkB homolog 5
ALYREF	Aly/REF export factor
AML	Acute myeloid leukemia
APC	Antigen presenting cells
APOE	Apolipoprotein E
BCAA	Branched-chain amino acid
BCAT1	Branched-chain amino acid transaminase 1
BMDMs	Bone marrow-derived macrophages
CAFs	Cancer-associated fibroblasts
CDKN1A	Cyclin-dependent kinase inhibitor 1 A
CESC	Cervical squamous cell carcinoma
CSF-1	Cytokine macrophage colony-stimulating factor
CTLs	Cytotoxic T lymphocytes
DKK1	Dickkopf-related protein 1
DLBCL	Diffuse large B-cell lymphoma
DNMT2	DNA methyltransferase 2
EBV	Epstein–Barr virus
EC	Esophageal cancer
eIF3	Eukaryotic translation initiation factor 3
FTO	Obesity-associated protein
GBM	Glioblastoma
GC	Gastric cancer

GLS	Glutaminase
Gys2	The liver-specific glycogen synthase
HBXIP	HBx-interacting protein
HCC	Hepatocellular carcinoma
HDGF	Heparin Binding Growth Factor
HIF	Hypoxia-inducible factors
hm5C	5-Hydroxymethylcytidine
ICC	Intrahepatic cholangiocarcinoma
ICIs	Immune checkpoint inhibitors
ICOS	Inducible co-stimulatory
IFN	Interferon
IGF2BP1	Insulin-like growth factor 2 mRNA-binding protein 1
IL-12	Interleukin-12
LSCs	Leukemia stem cells
m6A	N6-methyladenosine
MDSCs	Myeloid-derived suppressor cells
METTL3	Methyltransferase-like 3
MM	Multiple myeloma
M-MDSCs	Monocyte-related myeloid-derived suppressor cells
MPNSTs	Malignant peripheral nerve sheath tumors
MTC	Methyltransferase complex
NAFLD	Nonalcoholic fatty liver disease
NML	Nucleomethylin
NSCLC	Non-small cell lung cancer
OXPHOS	Oxidative phosphorylation
PABP	Poly(A) binding protein
PDAC	Pancreatic ductal adenocarcinoma
PRMT1	Protein arginine N-methyltransferases 1
R255	Arginine 255
RAM	RNMT-activating miniprotein
RCC	Renal cell carcinoma
RCC2	Regulator of chromosome condensation 2
RNMT	RNA guanine-7 methyltransferase
SCD1	Stearoyl-CoA desaturase1
SCLC	Small-cell lung cancer
SHMT2	Serine hydroxymethyltransferase 2
SLE	Systemic lupus erythematosus
TAMs	Tumor-associated macrophages
TET1/2/3	Ten-eleven translocation proteins1/2/3
TIME	Tumor immune microenvironment
TME	Tumor microenvironment
YBX1	Y-box-binding protein 1
YTHDF1	YTH N6-methyladenosine RNA binding protein 1

Supplementary information

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Supplementary Material 1

Supplementary Material 2

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