

Targeting m⁶A in cancer – new prospective

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Introduction

The field of mRNA modifications has rapidly developed over the last years, outlining a new realm of gene expression regulation that appears to play a major role in health and disease states including cancer. Considering the information regarding chemical modifications of DNA and proteins, decades of research proved beyond any doubt that chemical modifications affect chromatin structure as well as enzymatic activity. *So, why did the field of RNA modifications and more specifically, mRNA modifications, lagged behind?* The answer rests in the combination of technical difficulties to globally map these modifications and the low abundance of each mRNA transcript in total or even purified messenger RNA samples. The major breakthrough emerged in 2012 with the first approach to map N⁶-methyladenosine (m⁶A) in a transcriptome-wide manner [1,2], and the discovery of dedicated RNA binding proteins that exclusively recognize m⁶A-methylated sequences [1]. These proteins, later termed readers (see below), exert the roles of m⁶A in regulation of gene expression. In addition, m⁶A demethylases, termed erasers, grant this modification a dynamic nature, making it suitable for sensing changing conditions and adjusting the expression of genes accordingly [3,4]. Thus, m⁶A distribution and abundance together with its dynamics provide cells with a means to regulate sets of transcripts, enabling switching between transcription programs that are needed for transitions between cell states. For example, during early mouse embryonic stem cells differentiation, m⁶A promotes rapid degradation of mRNAs associated with pluripotency genes to safeguard lineage priming and differentiation [5].

The discovery that mRNA m⁶A is essential for resolution of pluripotency raised the possibility that it may also play a role in cancer, or more specifically, changes in m⁶A mRNA methylation may lead to tumor formation and progression. In fact, global mapping of m⁶A in normal and cancer samples revealed differential methylation patterns of cancer-associated transcripts, reflecting dysregulation of its associated proteins and proving that m⁶A plays a critical role in almost every type of cancer [6–9].

In this mini-review, we outline the principles of m⁶A regulation, explain how imbalanced expression of m⁶A-associated proteins (also called m⁶A regulators) contributes to tumor development and discuss the harnessing of novel inhibitors of m⁶A-associated proteins to fight cancer. It is important to note that although m⁶A is present in mRNA of all eukaryotes, focusing on its part in cancer, we will discuss here only m⁶A data of human and mouse.

m⁶A Metabolism

The notion that m⁶A is highly prevalent in mRNA underlined the need for its global mapping as a first step to unravel its roles. Indeed, transcriptome-wide mapping of mRNA m⁶A provided much more than just a collection of sites. The non-random site distribution of m⁶A was the first step in understanding its biological functions [1,2]. Further insights into the biology of m⁶A came from the identification of m⁶A-associated proteins: writers, erasers and readers (**Figures 1A and 1B**). The main writer complex of mRNA m⁶A includes METTL3, METTL14, WTAP, RBM15/15B, ZCH3H13, VIRMA and HAKAI, which together make the methyltransferase complex (MTC) [10]. The core subunit of MTC consists of a heterodimer of METTL3 and METTL14 (the catalytic and allosteric activator components, respectively). Other components are responsible for anchoring and stabilizing the interaction with target transcripts [10] (**Figure 1A**).

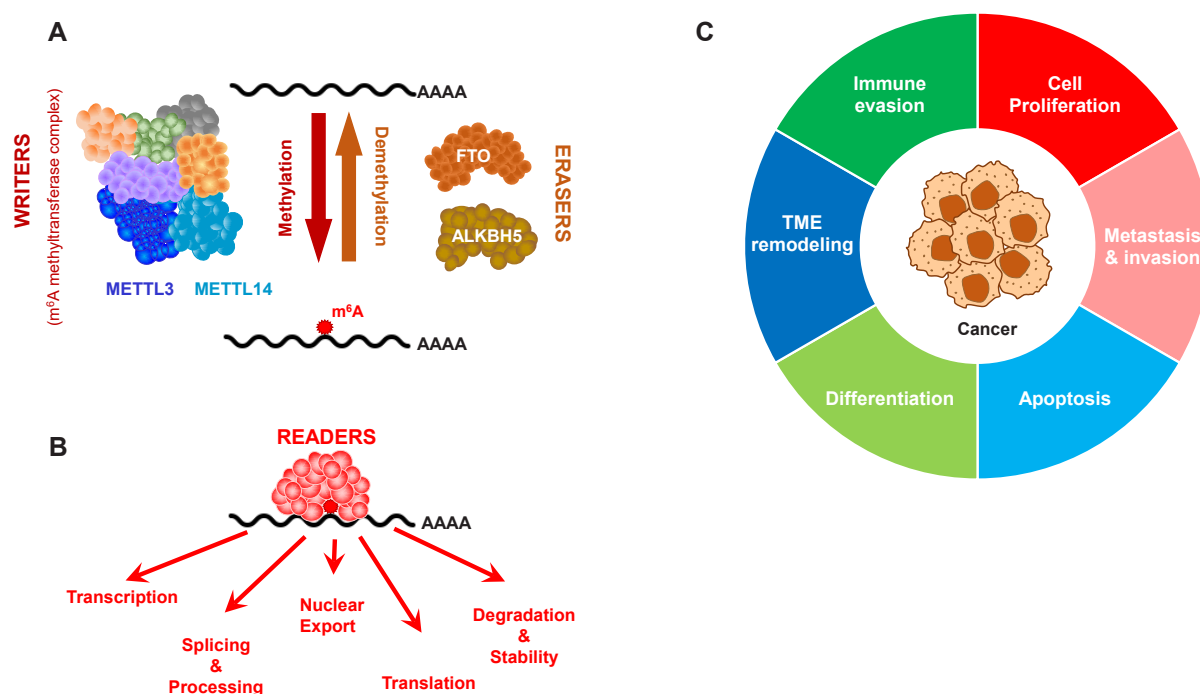


Figure 1. A. mRNA m⁶A is installed by writers that methylate mRNA transcripts. Demethylation is carried out by erasers, together granting m⁶A a dynamic nature. **B.** Reader proteins bind methylated transcripts to exert the regulatory roles of m⁶A, affecting transcription, splicing and processing, nuclear export, translation and stability/decay. In cancer, the most studied reader proteins belong to the YTH domain containing protein family (YTHDF1-3 and YTHDC1) and inulin-like growth factor 2 mRNA-binding proteins (IGF2BP1-3). **C.** m⁶A is implicated in carcinogenesis through its effects on the indicated processes.

Demethylation of mRNA m⁶A is carried out by two Fe²⁺- and 2-oxoglutarate (2OG)-dependent oxygenases, FTO [3] and ALKBH5 [4] (**Figure 1A**). These erasers function in the nucleus and the cytoplasm, conferring m⁶A its dynamic nature and enabling a rapid response to changing cellular and environmental cues.

Of particular significance are m⁶A reader proteins, which are RNA binding proteins that recognize methylated RNA sequences in a specific context and exert their regulatory roles [11,12]. An in-depth discussion of m⁶A readers and their multiple roles is beyond the scope of this mini-review and can be appreciated in dedicated reviews [13–16]. Yet, it is important to emphasize that m⁶A reader proteins affect multiple aspects of the mRNA life cycle including splicing, nuclear export, transcript decay and translation. Two major families of m⁶A reader proteins, the YTH domain containing family (YTHDF1-3 and YTHDC1-2, [17]) and the insulin-like growth factor 2 mRNA-binding proteins (IGF2BP1-3 [18]), have been extensively implicated in cancer.

m⁶A Regulation of Signaling Pathways and Feedback Loops

Insights into regulatory mechanisms that involve m⁶A reveal its envelopment in activation of signaling pathways and in feedback loops. As m⁶A is involved in almost every aspect of gene expression, it is expected to affect multiple signaling cascades. The first indication for the implication of m⁶A in signaling emerged in 2012, showing that decreased METT3 levels modulated the p53 signaling pathway, through differential methylation, splicing and expression of 23 of its

pathway members, including reduced levels of MDMX (also named MDM4), a negative regulator of p53 signaling cascade [1].

Since then, the role of m⁶A in regulation of additional signaling pathways was extensively studied, mostly of pathways that drive cancer (see more information in the next section). Research exposed how m⁶A rewires gene expression programs that are central to cancer, revealing that additional major oncogenic signal transduction pathways, such as PI3K/AKT, TGFβ, ERK, RAS/MAPK and the canonical Wnt pathway, are regulated by m⁶A. In such cases, m⁶A differentially methylates central proteins in these cascades during activation (as discussed in multiple reviews such as [19] and [20]). It is now well established that dysregulation of m⁶A leads to imbalanced activation of signaling pathways, which impacts cell proliferation, metastasis, and response/resistance to treatments (reviewed in publication such as [21,22]). For example, upregulation of METTL3 in prostate cancer [23] and hepatoblastoma [24], enhances the expression of β-catenin and LEF1 transcripts (both m⁶A-methylated), stabilizing β-catenin to activate the Wnt signaling pathway, stimulating cell proliferation and inhibiting differentiation [23,24].

Beyond direct modulation of signaling cascades, m⁶A also participates in intricate feedback mechanisms that link gene expression to chromatin state. Feedback loops involving m⁶A tightly regulate gene expression by bridging transcription dynamics with methylation and translation efficiency. Methylated transcripts recruit m⁶A readers that alter the chromatin state and transcriptional availability of specific regions in the genomic DNA. YTHDC1

binds methylated transcripts contributing to the formation of heterochromatin that restrain the activity of transposable elements in mouse embryonic stem cells [25]. In addition, m⁶A methylation of chromosome-associated regulatory RNAs (carRNAs), which physically interact with chromatin, decrease their stability and lead to a more open chromatin and active transcription [26].

Evidence for the existence of cross-talk between RNA and histone modifications uncovered the involvement of m⁶A in epigenetic regulation through m⁶A deposition on transcripts encoding histone modifying proteins. For instance, m⁶A destabilizes the histone acetyltransferase P300/CBP mRNAs in neural stem cells. P300/CBP increases the prevalence of H3K27ac and H3K9ac, dictating a more relaxed accessible chromatin conformation, which facilitates transcription activation [27]. Moreover, m⁶A regulates H3K9me2 (associated with transcription repression) through YTHDC1. The latter recruits the H3K9me2 demethylase, KDM3B, coupling m⁶A with heterochromatin state [28]. Such intertwined feedback circuits are critical for cell homeostasis, development and some disease states [29].

Expanding this regulatory landscape, a large body of evidence demonstrates that mRNA modifications beyond m⁶A also regulate gene expression, with indications for crosstalk between different mRNA modifications (reviewed in [30]). In fact, the mRNA modification N¹-methyladenosine (m¹A) accelerates degradation of transcripts co-modified with m⁶A [31]. Another study predicted the co-occurrence of m⁶A and 5-methylcytosine (m5C), based on a novel tool for analyzing direct RNA sequencing data (CHEUI, CH3 Estimation Using Ionic current). CHEUI analysis revealed non-random profiles of the two modifications, co-occurring on the same transcripts. This finding supports an interplay between these two mRNA marks [32].

Epigenetic mechanisms, including DNA methylation and histone modifications, demonstrate an interplay with mRNA modifications as well. m⁶A and m5C were both associated with influencing chromatin state [33,34]. Chemical modifications of proteins other than histones are also at play. Interesting discovery shows that m⁶A levels are regulated by symmetric dimethylarginine modification of METTL14, demonstrating a novel interplay between post-translational protein modifications of m⁶A writers and m⁶A levels [35]. Together, these findings sketch a convoluted network of regulation that is central in health and diseases, of which only the tip of the iceberg seems to be exposed.

The Roles of m⁶A in Cancer

Cancer cells often exhibit altered expression of subsets of genes that act in concert to maintain the hallmarks of cancer, including sustained proliferation, resistance to cell death, replicative immortality, angiogenesis, invasiveness, metabolic reprogramming and immune evasion (**Figure 1C**) [36]. It is therefore not surprising that m⁶A machinery is disrupted in many cancers [37]. In fact, alterations in m⁶A levels have been shown to affect almost every cancer hallmarks. Interestingly, dysregulation of m⁶A-associated proteins may result in opposite effects in different types of cancer and even within the same cancer type, in a context specific manner (see examples in [38]). Here, we focus on two key major hallmarks of cancer – chronic proliferation and immune evasion. The role of m⁶A in the regulation of other cancer hallmarks is discussed elsewhere [39–42].

Sustained proliferation can be acquired by excessive production of growth factors, overexpression of growth factor receptors and constitutive activation of signaling pathways downstream of growth receptors. Accumulated data revealed that dysregulation of m⁶A is implicated in all these mechanisms. For instance, increased m⁶A modification promotes the translation of epidermal growth factor receptor (EGFR), a tyrosine kinase receptor, in a wide range of tumors such as lung adenocarcinoma [14], hepatocellular carcinoma [43] and melanoma [44], activating downstream signaling pathways and acting as an oncogene. In addition, increased levels of m⁶A methylation drives overexpression of other oncogenic tyrosine kinase receptors, such as c-Met, in different cancer types including breast [45], gastric [46] and melanoma [45]. Alternatively, dysregulated deposition and demethylation of m⁶A can result in overexpression of transcription factors (TFs) that drive proliferation. One prominent example is that of the master transcription factor, MYC [47]. On the whole, unbalanced expression of TFs skews the expression of their targets, resulting in changes of gene expression across multiple genes, simultaneously. In fact, increased expression of METTL3 [48], METTL14 [49] and WTAP [50] as well as the eraser, FTO [51], modulates m⁶A levels to enhance MYC mRNA stability and translation in acute myeloid leukemia (AML). Furthermore, overexpression of IGF2BPs, is evident in numerous types of cancers: MYC and its homologue MYCN are regulated by IGF2BP1 and IGF2BP3, which stabilize methylated target transcripts in cholangiocarcinoma [52], gastric cancer (where it inhibits proliferation) [53], neuroblastoma [54,55] and nasopharyngeal carcinoma [56]. Of note, YTHDF2, which destabilizes mRNA transcripts, has been shown to exert an opposite effect on MYC in glioblastoma [46]. Importantly, while overexpression of MYC enhances the tumorigenic phenotype, reducing its levels contributes to the ability of cells to escape chemotherapy [57–59]. Such convoluted and opposite effects of m⁶A highlight its dual role resulting in either pro or anti-tumorigenic effects depending on the specific cellular and molecular context.

In order to survive, cancer cells employ various mechanisms to evade the multiple arms of the immune systems including the downregulation of antigen presentation, suppression of the major histocompatibility complex (MHC) I, upregulation immune checkpoints, such as PD-L1, PD-L2, and B7-H3, recruitment of immunosuppressive cells to the tumor microenvironment (TME), such as T regulatory cells and M2 macrophages.

m⁶A has been shown to regulate the expression of the surface expression of MHC-I. For example, in melanoma cells, YTHDF1 was shown to increase the expression of lysosomal genes, enhancing MHC-I degradation, driving immune evasion, and resistance to immunotherapy, promoting tumor survival [60]. Furthermore, YTHDF1 silencing promoted cell cycle arrest of pancreatic and breast cancer cells, leading to inhibition of lysosomal protein translation and upregulation of MHC-I expression [61].

Dysregulation of m⁶A writers and erasers has also been shown to remodel the TME compartment of multiple tumor types. For instance, imbalanced m⁶A patterns, due to changes in METTL3/METTL14 expression levels, impacts T cells homeostasis, activation, differentiation and the release of inflammatory cytokines through m⁶A-mediated degradation of mRNAs [62,63]. The balance between different subpopulations of T cells in the TME is critical for anti-tumor immunity. A recent pan-cancer analysis revealed that m⁶A

methylation by METTL3 mediates T cell exhaustion [64], enabling cancer cells to evade the cytotoxic effect of T cells. Moreover, deletion of METTL3 in natural killer (NK) cells inhibited NK cells infiltration in melanoma models and rendered them hyposensitive to IL-15 [65]. Finally, inhibition of METTL3 in melanoma models has been shown to polarize tumor associated macrophages towards a more immunosuppressive M2 phenotype [66].

In addition, several recent studies suggest that the m⁶A machinery regulates the expression of PD-L1 and the secretion of pro- and anti-inflammatory signals by cancer cells. However, m⁶A writers exhibit a complex role in cancer immunity. Knockout of METTL3 and METTL14 enhanced the anti-PD-L1 therapy efficacy and stimulated the secretion of pro-inflammatory cytokines (including IFN- γ , CXCL9 and CXCL10) [67]. In another study, METTL3 was found to promote PD-L1 expression of via IGF2BP3-dependent mechanisms in breast cancer [68]. In addition, inhibition of FTO downregulates PD-L1 and LILRB4 in AML cells and sensitizes them to T cell cytotoxicity [69]. Furthermore, inhibition of ALKBH5 potentiates the response to immune checkpoint blockade in melanoma and colon cancer by modulating the composition of the TME [70] and by increasing PD-L1 expression in intrahepatic cholangiocarcinoma [71].

In conclusion, the normal phenotype is a result of a highly concerted equilibrium of m⁶A writers, erasers and readers. Any deviation from this balance is prone to lead to dysregulated cell states resulting in rapid proliferation, halted differentiation and escape from apoptosis.

Targeting m⁶A Machinery to Fight Cancer

Targeting the m⁶A machinery has emerged as a promising therapeutic strategy [72]. Recent advances in our understanding of m⁶A biology has prompted the development of specific small molecule inhibitors of m⁶A regulators. Screening for such inhibitors was successful due to the improved and more accurate structural data of m⁶A regulators, defining targetable domains to impair their actions. Importantly, most such inhibitors are still in their discovery phase, but a few have entered clinical trials. The field of m⁶A inhibitors is rapidly developing [73,74]. In this mini-review, we focus on several examples of inhibitors, their mechanism of action and pharmacokinetics:

Inhibiting m⁶A writers, such as METTL3 and METTL14 leads to reduced mRNA m⁶A levels, which affect the expression of many genes, including oncogenes. The METTL3 inhibitor, STM2457, potently blocks its enzymatic activity at low nanomolar range (IC₅₀ of 16.9 nM in AML cells [75]) by competitively binding the S-adenosylmethionine (SAM, the methyl donor) pocket, with high affinity (K_d=1.4 mM) [75]. Further improvement of this inhibitor generated STM3006, which exhibits a greater cellular potency, having higher efficiency and affinity in AML cells (K_d=55 pM, IC₅₀=5 nM) [76]. Both inhibitors showed *in vitro* and *in vivo* efficacy in AML, resulting in apoptosis, increased secretion of IFN- α [76] and triggering activation of IFN- α response [76,77]. The first METTL3 inhibitor that entered clinical trials, STC-15, an improved derivative of STM2457 [78], is now in Phase I for patients with refractory AML (NCT05584111) [79]. Similar to STM2457 and STM3006, STC-15 also activates the IFN- α signaling

response, remodeling the TME towards pro-inflammatory state and downregulates the anti-apoptotic protein BCL-2 [73]. Phase I results showed that STC-15 is well-tolerated across a range of doses in AML patients which supports the development of subsequent phase trials for STC-15 (<http://www.stormtherapeutics.com/news/press-releases/storm-therapeutics-announces-first-patient-dosed-in-clinical-collaboration-to-evaluate-stc-15-in-combination-with-loqtorzi/>). Inhibition of METTL3 results in reduced cell proliferation, increased apoptosis and remodeling of the TME in additional cancer types including colorectal cancer, ovarian cancer, thyroid cancer prostate cancer, non-small cell lung cancer and myelodysplastic neoplasms [76,80–85].

Inhibition of m⁶A erasers, FTO or ALKBH5, results in increased mRNA m⁶A levels, which has broad consequences [86]. FTO inhibition by several tool compounds including FB23, FB23-2 and R-2HG showed increased killing of AML cells. Clinical FTO inhibitors, CS1 (bisantrene) and CS2 (brequinar), exhibit high inhibitory potential, with IC₅₀ values in the nanomolar range [69], resulting in suppression of AML stem cells and decreased expression of the immune checkpoint gene, LILRB4 [51,69]. Early phase clinical trials using bisantrene for the treatment of AML have shown both safety and efficacy (NCT04989335) [87]. A Phase II study of bisantrene in relapsed/refractory AML (NCT03820908) reported a 40% overall response rate with low toxicity [87]. Of note, inhibitors of ALKBH5 and m⁶A readers are still in their infancy. FTO inhibition by CS1 and CS2 induced increased methylation on MYC, promoting its transcript degradation and reducing its expression, suppressing the MYC targets V1 and V2 pathways, and exerting anti-cancer effects [69,88,89]. Moreover, CS1 and CS2 suppress PI3K/AKT pathway activation caused by FTO overexpression in several cancer cell lines [90–92]. Development of clinical specific inhibitors allows for their incorporation into combination regimens for cancer treatment. **Table 1** lists examples of successive m⁶A-mediated approaches for combining m⁶A inhibitors with other cancer therapy modalities.

The most widely used therapy modality is chemotherapy and several studies have shown that inhibition of METTL3 or FTO can sensitize cancer cells to chemotherapy. For instance, inhibition of METTL3 enhanced the cytotoxic effects of cisplatin in ovarian cancer [93] and doxorubicin in AML [94]. Furthermore, immunotherapy, which has revolutionized the field of cancer, can also be combined with m⁶A inhibitors. For example, inhibition of METTL3 in AML and melanoma has been shown to upregulate PD-L1, enhancing the efficacy of immune checkpoint inhibition [77]. Furthermore, inhibition of FTO results in downregulation of the immune checkpoint gene LILRB4 and enhances cytotoxicity of T cells [69]. Modulation of m⁶A regulators has also been shown to affect the immune landscape of several tumors. For instance, inhibition of METTL3 suppressed the function of regulatory T cells in melanoma and colorectal adenocarcinoma [95]. Importantly, while inhibition of METTL3 may decrease the viability of cancer cells and enhance T cell cytotoxicity, it has also been shown to promote polarization from M1 macrophages towards M2 phenotype [66], thus representing a double edge sword. In this respect, studies in AML, using METTL3 [79] and FTO inhibitors [87] demonstrate two complementary but mechanistically opposed therapeutic strategies, achieving success through inverse manipulation of the same epitranscriptomic mark.

Table 1. Examples of successive m⁶A-mediated approaches that combine m⁶A inhibitors with cancer therapy.

Target	m ⁶ A inhibitor	Treatment	Outcome	Cancer type	Ref
METTL3	STM2457 STM3006 STC-15	Chemotherapy (PTX, CBP, venetoclax, anlotinib, dox)	• Synergistic effect with chemotherapy • Reduced tumor size, decreased cell proliferation and enhanced apoptosis • STM2457 enhanced chemo-sensitivity and reverse chemo-resistance	NSCLC ESCC OSCC AML NBL SCLC BC OC	[98–104]
		Immunotherapy (anti-PD1; anti-VISTA; anti-BET (HJP-178 and OTX-015))	• Additive effect with immunotherapy • Improve the effect of immunotherapy • Boost T cell cytotoxicity • Revers T cell exhaustion • Induction of IFN response • Reshaping TME • Tumor regression	Melanoma OC GA NSCLC CRC BLC AML	[76,95,105–109]
FTO	CS1 CS2 FB23/FB23-2 Rhein	Chemotherapy (PTX; 5-FU)	• Reduce chemo-resistance • Suppress immune evasion • Increase chemo-sensitivity • Reduce cell proliferation • Increase apoptosis	AML NBL CRC GIC Melanoma	[69,110–113]
		Immunotherapy (anti-PD1)	• Suppress tumor growth and metastasis • Enhanced immune activation • Reduce resistance to treatment	AML HCC Melanoma	[114–116]

PTX: Paclitaxel; CBP: Carboplatin; Dox: Doxorubicin; Bromodomain and Extra-Terminal domain proteins; VISTA: V-domain Immunoglobulin Suppressor of T cell Activation; 5-FU: 5-fluorouracil; NSCLC: Non-Small Cell Lung Cancer; ESCC: Esophageal Squamous Cell Carcinoma; OSCC: Oral Squamous Cell Carcinoma; BC: Breast Cancer; NBL: Neuroblastoma; OC: Ovarian Cancer; GA: Gastric Cancer; BLC: Bladder Cancer; HCC: Hepatocellular Carcinoma

Future Prospective

The development of m⁶A inhibitors marks a significant step toward translating our accumulating knowledge regarding this prevalent mRNA modification into new regimes to fight cancer. With the emergence of clinical trials testing the efficacy of m⁶A inhibitors in various cancer types, we anticipate a growing number of additional clinical trials combining this strategy with chemotherapy, radiation, immune checkpoint inhibitors, and chimeric antigen receptor (CAR) T cells.

Despite the promising advances of m⁶A inhibitors, several obstacles remain to be addressed prior to development and clinical application of m⁶A-targeted therapies. One of the major challenges is the potential development of therapy resistance to these inhibitors. Since the use of this new class of drugs is in its infancy, little is known about mechanisms of therapy resistance warranting future research. Moreover, depletion of m⁶A writers and erasers can have pervasive consequences [5,96], making it imperative to determine the safe and effective window of each drug. In addition, as m⁶A modifications are ubiquitous in normal tissues, side effects are expected to occur in a dose dependent manner. The toxicity profile of the m⁶A inhibitors is still being investigated, however, the FTO inhibitor CS1 (bisantrene) was well tolerated in a phase II clinical trial at our institution [87]. Results from ongoing clinical trials will shed more light on the toxicity of m⁶A inhibitors.

Finally, it is important to remember that the effect of a specific m⁶A inhibitor results from the disruption of m⁶A methylation on multiple transcripts in parallel. Due to their lack of specificity, such drugs are anticipated to have a wide “off-target” effect. Recent advancements in nucleic acid editing supports the development of targeted RNA editing technology using the inactive Cas13 (dCas13) enzyme coupled to FTO [97], enabling the m⁶A manipulation of a single transcript. While this technology is still restricted for basic research purposes, targeting specific m⁶A sites in oncogenes or tumor suppressors using CRISPR-dCas13 may emerge as a novel and effective therapeutic strategy.

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