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REVIEW ARTICLE

The crucial roles of m^{6}A RNA modifications in cutaneous cancers: Implications in pathogenesis, metastasis, drug resistance, and targeted therapies

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Abstract N6-methyladenosine (m^{6}A) is the most abundant internal modification on RNA. It is a dynamical and reversible process, which is regulated by m^{6}A methyltransferase and m^{6}A demethylase. The m^{6}A modified RNA can be specifically recognized by the m^{6}A reader, leading to RNA splicing, maturation, degradation or translation. The abnormality of m^{6}A RNA modification is closely related to a variety of biological processes, especially the occurrence and development of tumors. Recent studies have shown that m^{6}A RNA modification is involved in the pathogenesis of skin cancers. However, the precise molecular mechanisms of m^{6}A-mediated cutaneous tumorigenesis have not been fully elucidated. Therefore, this review will summarize the biological characteristics of m^{6}A modification, its regulatory role and mechanism in skin cancers, and the recent research progress of m^{6}A-related molecular drugs, aiming to provide new ideas for clinical diagnosis and targeted therapy of cutaneous cancers.

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Introduction

Epigenetic abnormalities, including DNA methylation, histone modification, and chromatin remodeling are important carcinogenic mechanisms.[1–4] In recent years, more and more studies have shown that a new epigenetic regulation, called m^{6}A RNA methylation, plays important roles in the initiation and development of cancers.[5–9] m^{6}A RNA methylation is a dynamic and reversible modification process, which is mainly modulated by m^{6}A methyltransferase complex (also known as m^{6}A writers), m^{6}A demethylase (m^{6}A erasers), and m^{6}A readers (Fig. 1).

The essential players of m^{6}A RNA modifications

The m^{6}A methyltransferase complex (m^{6}A writers) transfer the methyl donor from S-adenosylmethionine to the adenine of the receptor RNA, leading to its m^{6}A methylation. The main components of m^{6}A methyltransferase complex include methyltransferase-like protein 3 (METTL3), methyltransferase-like protein 14 (METTL14), and Wilms tumor 1 associated protein (WTAP). METTL3 is the first discovered m^{6}A methyltransferase and the core subunit of the m^{6}A methyltransferase complex, which plays a major catalytic role in promoting m^{6}A RNA methylation.[10] Knockout of METTL3 leads to almost completely loss of m^{6}A modification *in vitro* and *in vivo*.[10] METTL14 itself hardly holds any m^{6}A methyltransferase activities, but it can form a stable heterodimer with METTL3 and enhance the catalytic activities of METTL3.[11] The role of WTAP is to stabilize the METTL3-METTL14 complex and promote the accurate localization of the complex in the nucleocapsid.[12] Besides, some other factors, such as vir-like m^{6}A methyltransferase associated (VIRMA), RNA binding motif protein 15 (RBM15), Cbl proto-oncogene like 1 (CBLL1), CCCH-type zinc finger protein 13 (ZC3H13), and methyltransferase-like protein 16 (METTL16), have been shown to be important components of the m^{6}A methyltransferase complex, which may also affect the m^{6}A methyltransferase process.[13–17]

m^{6}A erasers can "erase" the RNA methylation signals, that is, mediate the process of RNA demethylation. Fatty obesity-related protein (FTO) and ALKB homolog 5 (ALKBH5) are two main m^{6}A demethylases that have been identified. In 2011, Jia et al discovered for the first time that FTO has efficient oxidative demethylation activity and induces m^{6}A demethylation *in vivo*, proving the reversibility of m^{6}A modification.[18] Interestingly, unlike the oxidation-mediated demethylation of FTO, ALKBH5 preferentially regulates m^{6}A modification in a sequence-specific way.[19] ALKBH5 is expressed in most tissues and predominantly located in the nucleus. Meanwhile, ALKBH5 deletion lead to a comprehensive reduction of mRNA in the cytoplasm, suggesting its possible role in mRNA transport.[19]

m^{6}A readers are responsible for "reading" the information of m^{6}A RNA modification and affecting the fate of target RNA through regulating RNA maturation, translation, degradation, and so on. There are two modes of "reading", and one is direct reading, which refers to the direct binding of m^{6}A readers to the RNA that contains m^{6}A methylation sites. The YTH domain families, including YTHDF1-3, YTHDC1, and YTHDC2, are the major identified "direct m^{6}A readers".[20–26] Functionally, YTHDF1/YTHDF2/YTHDF3 enhances the translation, the decay or the metabolism of m^{6}A methylated RNA, YTHDC1 binds to the m^{6}A modification site and mediates the alternative splicing of RNA precursors, while YTHDC2 improves the translational efficiency and reduces mRNA abundance.[20–26] The other mode is indirect reading, that is, m^{6}A modification changes the secondary structure of target RNA. These structural changes

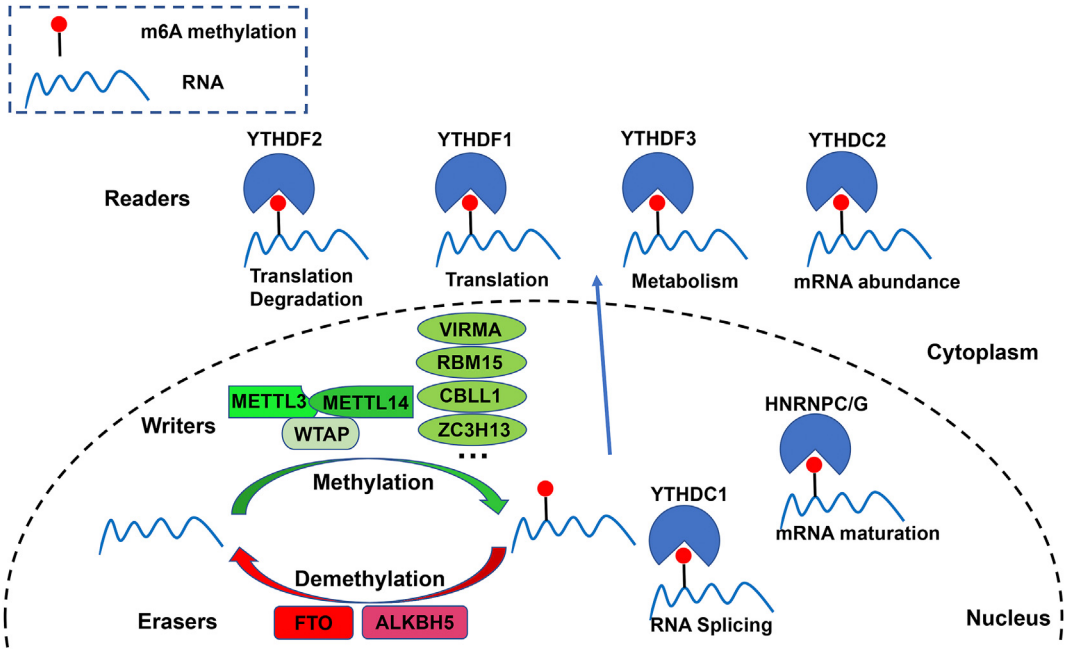

Figure 1 The modification process and molecular function of m^{6}A RNA methylation.

promote the binding of transcripts to heterogeneous nuclear ribonucleoprotein C (HNRNPC) and heterogeneous nuclear ribonucleoprotein G (HNRNPG), which are responsible for pre-mRNA processing and mRNA maturation.[27]

m^{6}A RNA modifications play crucial roles in multiple physiological and pathological processes

As mentioned above, m^{6}A writers add methyl groups to RNAs, while different "m^{6}A readers" recognize those m^{6}A-modified RNAs and affect their fates. The m^{6}A erasers make the m^{6}A modification a reversible process via mediating the RNA demethylation. More and more evidences have shown that m^{6}A RNA modifications play important roles in multiple physiological and pathological processes.[28–30] For example, the abnormal demethylase of m^{6}A is associated with metabolic disorder, which may lead to obesity.[18,31] Besides, the dysregulation of m^{6}A modification may impair fertility both in male and female.[19,25,32] Meanwhile, m^{6}A RNA modification is involved in the development of multiple organs or systems, like the nervous system and the hematological system.[33–37] Moreover, m^{6}A RNA modification participates in the regulation of innate and/or adaptive immunity.[38–40] As one of the most abundant RNA internal modifications in mammalian, m^{6}A RNA modifications have also attracted the attention of scientists who work on cancers. To date, m^{6}A RNA modifications or m^{6}A-related regulators have been proven to play critical roles in multiple cancer types, including acute myeloid leukemia (AML),[41] breast cancer,[42] bladder cancer,[43] cervical cancer,[44] glioma,[45] and so on. Particularly, increasing numbers of studies are examining the relationship between m^{6}A modifications and cutaneous cancers.[46–48] In this review, we will take cutaneous squamous cell carcinoma (cSCC) and cutaneous melanoma as examples to highlight the insights into the recent progress of m^{6}A study in skin cancers.

The regulatory role of m^{6}A modification in cutaneous squamous cell carcinoma

Skin cancer is the uncontrolled growth of abnormal cells that occurs in the skin, which seriously threatens the human health and life. Among all the skin malignancies, cSCC and melanoma are two common forms. cSCC is a non-melanoma skin cancer (NMSC), which accounts for about 20% of all cutaneous malignancies.[49,50] Although most of the primary cSCC can be successfully treated with surgery, advanced cSCC is still difficult to cure effectively, with a large portion of cSCC patients undergoing recurrence.[51,52] Meanwhile, the 10-year survival rate for local lymph node metastasized cSCC is less than 20%, while even less than 10% for distant metastasized cSCC. Therefore, treatment for recurrent or metastatic cSCC has become an urgent clinical problem to be solved. Recent studies have shown that multiple m^{6}A regulators are dysregulated in recurrent or metastatic cSCC, suggesting a possible role of m^{6}A modification in cSCC carcinogenesis.

m^{6}A writers (METTL3/METTL14)

METTL3, the well-known m^{6}A writer, is significantly elevated in human cSCC samples, compared with normal skin tissues.[46] Additionally, METTL3 knock-down impaired the stem cell-like properties (one of the characteristics for cSCC recurrence) of cSCC *in vitro* and *in vivo*.[46] Therefore, the m^{6}A methyltransferase METTL3 works as a critical oncogene in cSCC carcinogenesis and it may serve as a therapeutic target for recurrent cSCC treatment. Coincidentally, in oral squamous cell carcinoma (oSCC), METTL3 is consistently upregulated and higher METTL3 expression is correlated with unfavorable prognosis of oSCC patients.[53,54] Meanwhile, METTL3 overexpression promoted the proliferation, invasion, and migration of oSCC *in vitro*, while METTL3 knockdown inhibited tumor growth and metastasis *in vivo*, confirming that METTL3-m^{6}A axis may act as a prognostic biomarker and/or therapeutic target in patients with squamous cell carcinoma.[53,54]

Mettl14, a critical component of the m^{6}A RNA methyltransferase complex, has been shown to be decreased in UVB-irradiated skin as compared with sham-treated skin in mice.[55] In parallel, METTL14 is highly expressed in normal human skin, while down-regulated in human cSCC samples. Moreover, conditional deletion of Mettl14 increases UVB-induced cSCC carcinogenesis in mouse skin. Thus, METTL14 plays a tumor-suppressive role in UVB-induced skin cancer, although it has been reported to be either an oncogene or a tumor suppressor in other different cancers.[5,6]

Ban et al found that the m^{6}A modification mediated by METTL3 and METTL14 enhanced the stability of LNCAROD, while LNCAROD is highly expressed in head and neck squamous cell carcinoma (HNSCC) and plays an oncogenic role in HNSCC.[56] Thus, the interaction between long non-coding RNA and m^{6}A regulators indicates a novel mechanism in squamous cell carcinoma progression. Besides, a recent study showed that METTL3 stabilizes the expression of a specific circRNA (circCUX1) through mediating its m^{6}A methylation.[57] Meanwhile, circCUX1 decreases the sensitivity of hypopharyngeal cancer cells to radiotherapy via blocking the release of inflammatory factors.[57] Therefore, the crosstalk between circRNA and m^{6}A regulator METTL3 may also represent a potential mechanism for the radiotherapy-tolerance in squamous cell carcinoma. It is not surprised that the interplay between m^{6}A modification and non-coding RNAs contributes to SCC carcinogenesis, as one of the most important regulatory roles for m^{6}A modification is to modulate the maturation and stability of non-coding RNAs.

m^{6}A eraser (FTO)

Fatty obesity-related protein (FTO) was the first identified regulatory protein to play roles in catalyzing m^{6}A demethylation.[18] Most of the previous research focused on its function in affecting obesity or body mass index (BMI).[18,58] It was also reported that FTO affects the proliferation and self-renewal of neural stem cells (NSCs).[59] Recently, increasing evidence showed that FTO is abnormally expressed in multiple cancers and may be correlated with cancer progression.[60,61] Interestingly, Cui and his colleagues reported that

m^{6}A methylation level is downregulated, while FTO is upregulated in arsenic-related human skin lesions.[62] It is widely known that low-level of arsenic exposure may promote the tumorigenesis in skin.[63,64] Therefore, it is reasonable to speculate that arsenic-induced upregulation of FTO correlates with skin malignancy. In fact, skin-specific deletion of FTO inhibits arsenic-induced cSCC formation in the presence or absence of UVB irradiation in mice.[62] Mechanistically, arsenic stabilizes and upregulates FTO protein. Upregulated FTO in turn inhibits keratinocyte autophagy, which helps to promote arsenic-induced carcinogenesis in skin.[62] Thus, FTO is a key determinant of arsenic-associated skin cancer, while genetically or pharmacologically targeting FTO reveals a promising therapeutic intervention for the arsenic-induced malignance.

m^{6}A reader (YTHDF1)

YTHDF1 is one of the first identified "direct m^{6}A readers", which belongs to the YTH domain family.[20] It could promote efficient mRNA translation by interacting with translation initiating factors of target gene.[20] Meanwhile, YTHDF1 could promote protein synthesis by synergizing with YTHDF3.[22] It was reported that YTHDF1 deficiency in dendritic cells (DCs) leads to enhanced antitumor immunity.[65] Basically, the dysregulation of YTHDF1 results in multiple pathogenic conditions, including impaired learning and memory,[66] abnormal immune response,[67] and cancers.[68–70] Recently, its expression was shown to be closely correlated with intratumoral iron concentrations in hypopharyngeal SCC (HPSCC) patients.[71] At the same time, YTHDF1 methyltransferase domain interacts with both the 3′ UTR and 5′ UTR of *TRFC* mRNA and positively regulates its translation, leading to increased iron metabolism and HPSCC carcinogenesis.[71] Thus, the m^{6}A reader YTHDF1 plays a crucial role in iron metabolism and HPSCC formation, and targeting YTHDF1 represents a potential strategy for squamous cell carcinoma treatment.

The regulatory role of m^{6}A modification in cutaneous melanoma pathogenesis

Cutaneous melanoma (CM) is the most malignant and lethal form of skin cancers, which accounts for 75% of all skin cancer deaths.[72–74] Moreover, melanoma is one of the most metastatic cutaneous cancers with decreased survival and high mortality. Generally, CM is thought to develop mainly as a result of multiple genetic alterations, a number of which may be linked to the functional dysregulation of m^{6}A-related regulators.[75–77] As shown in Figure 2, genomic alterations of m^{6}A related modulators including m^{6}A writers, erasers, and readers were frequently observed in 363 melanoma samples collected from The Cancer Genome Atlas (TCGA) database, suggesting that m^{6}A-related regulators may play important roles in melanoma tumorigenesis. Recently, Lin et al revealed that patients with high-frequency genomic m^{6}A alterations tend to develop an unfavorable prognosis.[48] Moreover, based on the m^{6}A-related gene profile, patients with poor prognosis and enhanced immune infiltration could be efficiently identified, suggesting a novel mechanism and a potential m^{6}A-based prediction methodology in CM.[48]

m^{6}A writers (METTL3 and WTAP)

By quantitative reverse transcription-PCR analysis, Dahal et al found that *METTL3* was highly upregulated in melanoma cells as compared with the normal human melanocytes.[78] Further functional studies showed that METTL3 increased colony formation and invasiveness in melanoma cells, uncovering a regulatory role of m^{6}A writer METTL3 in melanoma tumorigenesis.[78] Although these results need to be further confirmed by *in vivo* studies, they suggest a potential therapeutic benefit of METTL3 inhibitors in melanoma treatment. More recently, Feng et al identified WTAP as a protective gene in cutaneous melanoma prognosis, as forced expression of WTAP increased apoptosis, inhibited proliferation, and impeded migration in melanoma cells, confirming the tumor-suppressive role of WTAP in melanoma.[79]

m^{6}A erasers (FTO and ALKBH5)

Recently, a variant in *FTO* gene, namely rs12596638, was shown to be positively correlated with histological ulceration in CM, which broads our understanding of *FTO* gene as an obesity-related gene.[80] Actually, it was not the first time that single-nucleotide polymorphisms (SNPs) in *FTO* were reported to be associated with melanoma risk. In 2013, Iles and colleagues reported that 6 *FTO* SNPs (rs12933928, rs12932428, rs1125338, rs12599672, rs12600192, and rs16953002), which were neither located in the BMI-related region nor associated with BMI, showed association with melanoma risk, suggesting that *FTO* variants not only correlated with obesity but also closely linked with multiple other biological traits including melanoma pathogenesis.[81] However, the precise mechanism how *FTO* SNP variations modulate melanoma pathogenesis still needs more *in vitro* and *in vivo* experiments to be clarified.

The other m^{6}A eraser, ALKBH5, is positively correlated with the immunotherapy response of melanoma patients.[75] Using a well-established immune checkpoint blockage (ICB) mouse model of melanoma, Li et al found that *Alkbh5* deletion in the B16 mouse melanoma had no effect on tumor growth in untreated mice, whereas *Alkbh5* knockout significantly reduced tumor growth and prolonged mouse survival during immunotherapy, demonstrating that m^{6}A demethylation contributes to the efficacy of immunotherapy in melanoma.[75] Thus, targeting ALKBH5 may enhance the immunotherapy outcome in melanoma patients who are resistant to ICB therapy.

m^{6}A readers (YTHDF1 and HNRNPA2B1)

By analyzing the expression profile of m^{6}A erasers, writers, and readers based on public databases, the up-regulation of YTHDF1 and HNRNPA2B1 in melanoma patients are revealed.[76] Moreover, genes related to p53-signaling are positively correlated with either YTHDF1 or HNRNPA2B1, suggesting a possible crosstalk between p53 pathway and m^{6}A modification.[76] However, the molecular mechanism

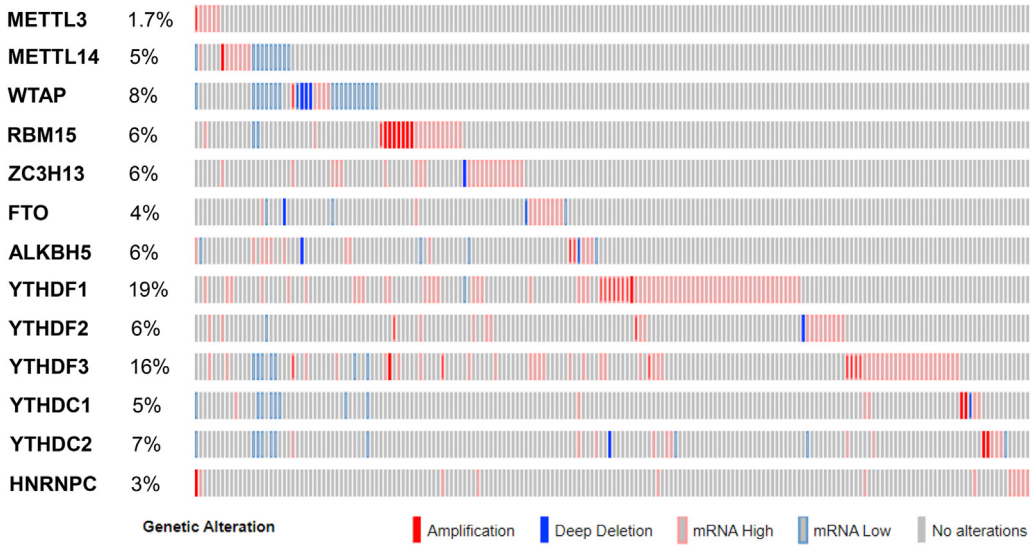

Figure 2 Genomic alterations of m^{6}A regulatory genes in melanoma cohort were identified using the cBioPortal. Data were obtained from the cBio database for cancer genomics (http://cbioportal.org/public-portal/). Cancer type: Skin Cutaneous Melanoma (TCGA, PanCancer Atlas); Total patient numbers: Complete samples (363 patients/samples); m^{6}A regulatory genes included m^{6}A writers (METTL3, METTL14, WTAP, RBM15, and ZC3H13), m^{6}A erasers (FTO and ALKBH5), and m^{6}A readers (YTHDF1, YTHDF2, YTHDF3, YTHDC1, YTHDC2, and HNRNPC).

how YTHDF1 and/or HNRNPA2B1 influence the disease development of melanoma remains unclear.

The regulatory role of m^{6}A modification in melanoma metastasis

Compared with most of the other skin cancers, a feature of melanoma is its highly metastatic capacity, although the precise mechanism that confer this is not well understood.[82–85] Up-regulation of UCK2 has been proven to be associated with poor survival and an essential factor for metastatic melanoma.[86] Interestingly, increased m^{6}A modification mediated by METTL3 leads to enhanced *UCK2* mRNA stability, indicating a potential role of m^{6}A/METTL3/UCK2 axis in melanoma metastasis.[86] Recently, 24 m^{6}A-associated lncRNAs significantly linked to the overall survival of metastatic melanoma patients were reported, revealing a potential network in m^{6}A-mediated modification for metastatic melanoma and providing potential biomarkers to predict survival of metastatic melanoma patients.[87] However, the precise mechanism that m^{6}A modulators regulating melanoma metastasis still needs more evidence to prove.

The regulatory role of m^{6}A modification in drug-resistant melanoma

BRAF mutations occur in roughly half of all melanomas, and treatment with BRAF or MEK inhibitors efficiently induces tumor shrinkage.[88–90] However, the anti-tumor efficacy of BRAF/MEK inhibitors is individual-dependent, and some of the melanoma patients might be tolerant to chemo-based therapy. For example, chemo-resistance to BRAF inhibitor (BRAFi) treatment arises after 6–8 months in advanced melanoma.[91–93] Strikingly, knockdown of METTL3 and/or WTAP lead to the abrogation of a subpopulation of BRAF^{V600} mutant melanoma cells that acquires drug-resistance to BRAF and MEK inhibitors, indicating that the combination of METTL3 inhibitor with BRAF/MEK inhibitors may help to overcome the chemo-resistance in melanoma.[94]

Anti-PD-1 therapy leads to remarkable clinical responses in advanced melanoma.[95,96] However, only a small percentage of melanoma patients can benefit from the anti-PD-1 immunotherapy.[97–100] To date, there has been insufficient evidence to reveal the relationship between m^{6}A modification and the immunotherapy efficacy in melanoma. Recently, Wang et al reported that the disruption of m^{6}A methyltransferases (*Mettl3* and *Mettl14*) enhanced response to anti-PD-1 treatment in melanoma.[101] Mechanistically, *Mettl3* or *Mettl14* deletion stabilized the *Stat1* and *Irf1* mRNA mediated by *Ythdf2*, leading to the sensitization of melanoma to PD-1 blockade.[101] More recently, Meng et al constructed a m^{6}A score system by analyzing 23 m^{6}A regulators using CM samples from the public databases.[102] Besides, they found that patient's m^{6}A score is positively correlated with ICB gene expression and the regulatory T and helper T-cell content, which may contribute to the immunotherapy response, suggesting that the m^{6}A score system can be used to predict immunotherapy outcome in melanoma.[102] However, the limitation of this study is obvious, as the researchers conducted the study based on public databases, whereas no *in vitro* or *in vivo* experiments were performed to confirm the precise mechanism between m^{6}A regulators and CM.

Research progress in targeted therapy for m^{6}A modification

In recent years, targeted therapy with m^{6}A modification as the core content has become a research hot spot for new

drug development. The main therapeutic targets for m^{6}A modification include FTO inhibitors, METTL3-14 activators/inhibitors, and the combination of chemo/immunotherapy with m^{6}A modification (Table 1).

FTO inhibitors

The m^{6}A demethylase FTO is highly elevated in multiple tumor tissues and negatively correlated with the disease prognosis.[103—105] Therefore, it is generally recognized as an oncogene in leukemia, breast cancer, renal cell carcinoma and other tumors.[103—105] In the past few years, researchers have been committed to screening or synthesizing FTO inhibitors, with the purpose of developing new anti-tumor drugs. Studies have shown that treatment of small/non-small cell lung cancer with Rhein (a FTO inhibitor) leads to decreased tumorigenesis.[106,107] However, due to the poor water solubility of Rhein, its anti-tumor efficiency and application prospects are obviously limited.

Recently, Huang et al found that meclofenamic acid (MA), an anti-inflammatory drug, specifically compete with FTO to bind to the m^{6}A modification sites, leading to increased m^{6}A modification level in glioma cells.[108] Meanwhile, the administration of MA can significantly inhibit tumor progression and prolong the survival time of glioma-transplanted mice, indicating that MA represents a novel therapeutic strategy for glioblastoma.[108] Similarly but differently, Demertzi et al reported that the lung adenocarcinoma cell A549 is less sensitive to MA, with a 50% inhibitory concentration (IC_{50}) of 139 μmol/L.[109] After further modification of MA, the MA organotin complex greatly improves the anti-proliferative activity in A549 cells, as the IC_{50} value is reduced to 0.43 μmol/L, suggesting the increased sensitivity of lung adenocarcinoma to MA.[110]

As mentioned above, MA holds potential for glioblastoma and lung cancer prevention. However, MA is poorly target selective, making it less suitable for clinical application. More recently, Huff et al described a novel FTO inhibitor, called FTO-04, prevented glioblastoma stem cell neurosphere formation in multiple patient-derived stem cell lines without impairing the healthy neural stem cell neurosphere growth, supporting FTO-04 as a more specific and effective drug for the treatment of glioblastoma.[111]

Besides, Huang et al developed two promising FTO inhibitors, namely FB23 and FB23-2, both of which directly bind to FTO and inhibit FTO's m^{6}A demethylase activity.[112] Moreover, the anti-proliferative activity of FB23-2 is stronger than FB23. Functionally, FB23-2 dramatically suppresses the progression of human acute myeloid leukemia *in vitro* and *in vivo*, suggesting that targeting FTO by FB23-2 holds great potential to treat cancer.[112]

METTL3-14 activators/inhibitors

METTL3/METTL14 methyltransferase complex may play either oncogenic or tumor-suppressive roles in human cancers.[5,6,113—115] In AML, METTL3 works as a oncogene by promoting the initiation and maintenance of AML.[36,116] Recently, STM2457, a highly potent and selective inhibitor of METTL3, was reported to be a pharmacological inhibitor of AML by reducing its growth *in vitro* and impairing engraftment *in vivo*, further confirming that METTL3 inhibition represents a potential anticancer therapy against AML.[117] Selberg et al found that 4 small molecule

Table 1 m^{6}A-related small molecular drugs used in cancer treatment.

Names	Therapeutic targets	Cancer/cell types	Functions	Refs
Rhein	FTO inhibitor	Small/Non-small cell lung cancer (NSCLC)	Rhein is capable of inducing apoptosis in small cell lung cancer. Meanwhile, it arrests cell cycle in the G2/M phase and stimulates cellular apoptosis in NSCLC cells. Additionally, Rhein inhibits NSCLC growth in xenografted mouse models	106,107
Meclofenamic acid	FTO inhibitor	Glioma	The administration of MA significantly inhibits tumor progression and prolongs the survival time of glioma-transplanted mice	108
Meclofenamic acid	FTO inhibitor	Lung adenocarcinoma cells	The MA organotin complex greatly improves the anti-proliferative activity in A549	109,110
FTO-04	FTO inhibitor	Glioblastoma stem cells	FTO-04 specifically inhibited glioblastoma stem cell neurosphere formation in patient-derived stem cell lines without impairing the healthy neural stem cell neurosphere growth	111
FB23-2	FTO inhibitor	Acute myeloid leukemia (AML)	FB23-2 dramatically suppresses the progression of human AML *in vitro* and *in vivo*	112
STM2457	METTL3 inhibitor	AML	It works as a pharmacological inhibitor of AML by reducing AML growth *in vitro* and impairing engraftment *in vivo*	117
Rhein + Pemetrexed	Combined Therapy	Lung adenocarcinoma cells	FTO inhibitor increases the sensitivity of lung adenocarcinoma to pemetrexed chemotherapy	123
ALK-04 + anti-PD-1	Combined Therapy	Melanoma	ALK-04 could enhance the efficacy of anti-PD-1 therapy in mouse B16 melanoma	75

compounds can bind to and activate the METTL3/METTL14 complex, resulting in an increase in the overall m^{6}A level of mRNA and rRNA.[118] However, large numbers of *in vitro* and *in vivo* experiments are still needed to confirm whether these small molecules that activate METTL3/METTL14 can be used for cancer treatment.

Combined therapy

Studies have shown that the abnormal m^{6}A modifications can lead to tumor resistance to chemotherapy.[119–122] Thus, therapy based on m^{6}A modulation provides the possibility of reversing the chemotherapy resistance. In lung adenocarcinoma cells, the combination of Rhein with pemetrexed reduced the cell survival rate from 65% to 16%, indicating that the FTO inhibitor significantly increased the sensitivity of lung adenocarcinoma to pemetrexed chemotherapy.[123]

At present, immune checkpoint blocking therapy has achieved relatively good results in cancer treatment. Many drugs, such as Nivolumab, Pembrolizumab, and Atezolizumab have been approved by the FDA for clinical treatment in cancers. However, only small portion of patients benefit from the immunotherapy, while most of the patients show resistance to immunotherapy. In 2019, Yang et al showed that m^{6}A mRNA demethylation by FTO decreased the sensitization of melanoma cells to anti-PD-1 treatment, while knockdown of FTO in melanoma increased the sensitivity of cancer cells to gamma interferon and PD-1 immunotherapy, suggesting that the combination of FTO inhibitors with anti-PD-1 blockade may represent a new strategy to prevent melanoma.[124]

In the B16 mouse melanoma cells, loss of *Alkbh5* potentiates the efficacy of anti-PD-1 therapy.[75] Notably, pharmacological inhibition of Alkbh5 using ALK-04 also enhanced the efficacy of cancer immunotherapy, which is consistent with the previous findings in *Alkbh5*-knockout tumor.[75] Thus, ALK-04, the ALKBH5 inhibitor holds great promising for treating melanoma patients who are resistant to immunotherapy.

Although the inhibitors or activators for m^{6}A-related regulatory proteins show great potential for cancer intervention, the development of m^{6}A-related drugs is still in its infancy. Generally, most of the existing m^{6}A-related drugs have relatively low activity and poor specificity. Moreover, they affect too many intracellular processes and the mechanism is not so clear. Furthermore, most of the m^{6}A-related inhibitors or activators are mainly used in cellular or mouse models, while quite few pre-clinical or clinical studies are conducted. However, with the development of drug synthesis and screening technology, it is believed that drugs targeting m^{6}A modifications will be more widely used in clinical anti-skin cancer treatments in the future.

Prospect and perspectives

m^{6}A modifications are increasingly being recognized as important regulatory mechanisms in cancer pathogenesis. Thus far, large numbers of m^{6}A regulators have been identified as crucial factors in cutaneous cancer initiation and development.[75–77] Undoubtedly, an in-depth understanding of m^{6}A modification in cutaneous cancer is essential for the development of new therapeutics. Although molecules targeting cancer-related m^{6}A regulatory proteins hold great therapeutic potential for skin cancers, the detailed and precise mechanisms remain to be elucidated, and many problems remain to be solved for a better clinical application of these m^{6}A inhibitors or activators:

1. The dysregulations of m^{6}A or m^{6}A-related modulators are common in skin cancers, suggesting their crucial roles in the pathogenesis of cutaneous cancers. However, most of the recent research about the implication of m^{6}A in skin cancers focuses on SCC and CM, while few attentions were paid to the regulatory role of m^{6}A modification in other skin cancers, like basal cell carcinoma, Merkel cell carcinoma, and so on.
2. Molecules that target m^{6}A-related regulators represent a novel therapeutic strategy for cancers. Some compounds, which specifically target FTO or METTL3/METTL14, have been proven to be effective in cancer chemotherapy. As mentioned above, small molecules, like Rhein, meclofenamic acid (MA), and ALK-04 have shown therapeutic intervention potential for cancers. However, to date, the most efficient first-in-class METTL3 inhibitor (STM2457) was used to treat AML, while almost no attempt has been made in the treatment of skin cancers.
3. Most of the researchers focus on the association between skin-related cancers (especially melanoma) and m^{6}A modification, while few attentions were paid to non-cancer skin diseases, which account for most of the skin diseases. Thus, exploring the possible function of m^{6}A modification in non-cancer skin diseases, including psoriasis, lupus, and atopic dermatitis holds great research value and application prospects.
4. Most of the current studies regarding m^{6}A modification and cutaneous cancers were conducted on cellular or mouse models, but to translate these findings into clinical applications, investigations involving clinical samples or pre-clinical studies are also required.

Conflict of interests

The authors declare no conflict of interests.

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