Regulatory roles of N6-methyladenosine methylation factors in melanoma invasion and metastasis (Review)

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Abstract. Melanoma, a malignant skin tumor, has an increasing incidence rate annually and affects the skin, eyes and mucous membranes. Despite advancements in early diagnosis and treatment improving survival rates, invasion and metastasis of melanoma remain major challenges. In-depth research into the pathogenesis of melanoma and novel therapies is essential to enhance patient outcomes. N6-methyladenosine (m6A) methylation, a key RNA modification, regulates gene expression and cellular functions, influencing cell proliferation, differentiation, apoptosis and signal transduction. It is implicated in various diseases, including tumors. In melanoma, m6A methylation regulates genes involved in tumor invasion and metastasis, impacting cell migration and drug resistance. Understanding the role of m6A methylation in melanoma can uncover disease mechanisms and inform therapeutic strategies.

Contents

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1. Introduction

N6-methyladenosine (m6A) represents one of the most prevalent chemical modifications in eukaryotic messenger RNA (mRNA) and non-coding RNA, and it serves a key role in several aspects of RNA metabolism (1), including splicing, nuclear export, translation and degradation. This dynamic and reversible modification is installed by methyltransferase complexes, primarily composed of methyltransferase-like 3 (METTL3) (2-4) and METTL14 (5-7), and removed by demethylases such as Fat mass and obesity-associated protein (FTO) (8-10) and AlkB homolog 5 (ALKBH5) (11-14). Emerging evidence has highlighted the critical role of m6A modifications in the pathogenesis and progression of various types of cancer, including melanoma. Melanoma is a highly aggressive malignancy with a persistently increasing global incidence (15), while its development has been strongly associated with dysregulation of m6A homeostasis (16,17). These imbalances can affect the expression and stability of oncogenes or tumor suppressors, thus influencing tumor cell proliferation, migration and invasion. Consequently, elucidating the mechanistic roles of m6A modifications in melanoma is essential for uncovering the underlying molecular mechanisms of this disease and identifying novel diagnostic and therapeutic targets.

However, the regulatory network of m6A modification in melanoma, a specific tumor type, remains unclear; in particular how it integrates different signaling pathways to synergistically regulate tumor invasion and metastasis, which are core malignant phenotypes. The present review aimed to systematically summarize the latest progress of m6A regulatory factors in melanoma invasion and metastasis, focusing on the specific signaling axes mediated by key molecules such as METTL3, ALKBH5 and FTO, and outlining a clearer m6A regulatory network to provide a theoretical basis for a deeper understanding of melanoma pathogenesis and the development of new therapeutic strategies.

2. Epidemiological features and clinical impact of melanoma

Melanoma is a highly malignant cutaneous neoplasm with an increasing incidence worldwide. Epidemiological data indicate that its risk rises with advancing age (18). Globally, ~232,100 new cases of cutaneous melanoma are diagnosed annually, accounting for ~55,500 mortalities, or ~0.7% of all cancer-related mortality (15).

The clinical severity of melanoma stems primarily from its aggressive biological behavior and metastatic potential. While early-stage melanoma is commonly curable, metastatic disease is associated with poor prognosis (19). The most common sites of metastasis include lymph nodes, lungs, liver, and brain, and treatment outcomes for disseminated disease are generally unfavorable (20,21). The frequent lack of obvious symptoms during the early stages of the disease can result in delayed diagnosis or misdiagnosis, eventually leading to missed opportunities for early intervention. Therefore, improving public awareness, enhancing early prevention and implementing effective screening programs are essential for mitigating disease burden and improving survival outcomes.

Melanomagenesis and metastasis are driven by complex molecular mechanisms, including mutations in BRAF (22), alterations in p53 (23) and CDKN2A (24), and dynamic changes in the tumor microenvironment (25). Although advances in immunotherapy and targeted therapy have markedly improved patient outcomes, the management of advanced melanoma remains a major clinical challenge.

3. Overview of m6A modification

m6A is the most abundant internal post-transcriptional RNA modification. It is widely distributed across mammals, plants and some prokaryotes, and serves a key role in regulating RNA metabolism, including RNA transport, stability, splicing, translation and RNA-protein interactions (26,27). The presence of m6A in RNA was first reported in viral transcripts (28). m6A methylation predominantly occurs near stop codons and within 3' untranslated regions (3'-UTRs). The dynamic regulation of m6A is mediated by three classes of regulatory factors: 'Writers' (methyltransferases), 'erasers' (demethylases) and 'readers' (m6A-binding proteins) (29). Writers catalyze the deposition of m6A; reader proteins interpret these modifications to determine RNA fate; and erasers remove these modifications to maintain dynamic regulation. The METTL3-METTL14 complex serves as the core catalytic machinery for m6A installation, while FTO and ALKBH5 function as the primary erasers (30). Dysregulation of m6A modification has been implicated in the pathogenesis of several types of cancer, including leukemia, breast cancer and melanoma (31,32). Due to its involvement in a wide range of pathological conditions, including type 2 diabetes (33), non-alcoholic fatty liver disease (34), gastric cancer (2) and bladder cancer (3), m6A methylation is increasingly recognized as a promising biomarker for early diagnosis and prognosis assessment in several diseases.

4. Regulators of m6A modification

m6A methyltransferases (writers). METTL3 is the core catalytic component of the m6A methyltransferase complex and is primarily responsible for catalyzing m6A deposition on mRNA (35). Using S-adenosylmethionine as a methyl donor, METTL3 methylates adenosine residues within the consensus DRACH motif. METTL3 contains several functional domains, including an N-terminal helix domain, a nuclear localization signal domain and a zinc finger CCCH domain that promotes RNA binding and methylation. METTL3 is essential for various physiological processes, such as embryonic development, cellular reprogramming, and maintenance of cellular homeostasis (36). This METTL3-METTL14 heterodimer forms the core m6A methyltransferase complex (MAC) (37), which is further regulated by additional regulatory subunits constituting the m6A-METTL associated complex (38).

METTL14 is an essential, albeit non-catalytic, structural component of the m6A methyltransferase complex that acts in cooperation with METTL3 (39). Structurally, the N-terminus of METTL14 interacts with METTL3 through loop and helical domains, while their respective C- and N-terminal regions form parallel helices, which stabilize the heterodimer and facilitate efficient m6A catalysis (40). A key feature of METTL14 is its C-terminal RGG repeat sequence, which is critical for RNA substrate recognition and accurate methylation site selection (41,42). By serving as an RNA-binding scaffold, METTL14 acts as a critical adaptor that notably enhances the catalytic efficiency of METTL3 (43).

Wilms' tumor 1-associating protein (WTAP) interacts with the METTL3-METTL14 heterodimer and promotes its localization to specific nuclear regions, particularly nuclear speckles (44). WTAP serves as a key regulatory component of the m6A methylation complex (45). Beyond its role in m6A regulation, WTAP is involved in diverse biological processes, including embryogenesis, cell cycle progression, differentiation, pre-mRNA splicing and antiviral responses (45). Notably, WTAP serves a vital role in the efficient recruitment of RNA substrates to the methyltransferase complex. Although it lacks catalytic activity, WTAP depletion can lead to a global reduction in m6A levels and impaired RNA binding, thus underscoring its essential role in maintaining m6A modification integrity (46).

m6A demethylases (erasers). The FTO protein is an iron and 2-oxoglutarate-dependent dioxygenase that acts as an m6A demethylase in eukaryotic cells, thereby contributing to the dynamic regulation of RNA methylation (47). Its catalytic domain, located in the N-terminal region, adopts a double-stranded β-helix (DSBH) fold that is critical for demethylase activity (48). The C-terminal domain, composed of α-helices, stabilizes the N-terminal conformation and activates demethylation (8). Particular domains, including loops such as the βI-βII loop, within the FTO structure serve critical roles in RNA substrate recognition and demethylation (9). In addition to its role in RNA metabolism, FTO has been involved in obesity, type 2 diabetes and tumorigenesis (49), highlighting its potential as a therapeutic target in metabolic and neoplastic diseases.

ALKBH5 represents another major m6A demethylase that primarily removes m6A marks from mRNA, thereby inversely regulating RNA metabolism compared with writers. ALKBH5 commonly exerts context-dependent effects on tumor initiation, progression and metastasis

via erasing m6A modifications (50). As a member of the α-ketoglutarate-dependent dioxygenase family, the catalytic activity of ALKBH5 relies on a conserved DSBH domain composed of eight β-strands. Its nucleotide recognition lid (NRL), formed by two β-hairpin loops (NRL1 and NRL2), is essential for substrate recognition and the demethylation activity. The N-terminal region, which encompasses multiple alanine residues and a unique helical structure (51), contributes to subcellular localization, whereas the C terminal domain, which is enriched in arginine and serine, facilitates RNA binding. Functionally, ALKBH5 regulates diverse cellular processes, including proliferation, invasion and tumor growth. Its dysregulation across different types of cancer highlights its potential as a therapeutic target (11).

m6A binding proteins (readers). m6A reader proteins recognize and bind to modified RNA transcripts, thereby regulating multiple stages of RNA metabolism, including stability, splicing, structural conformation, nuclear export and translation. Major reader families include YTH domain-containing proteins (YTHDFs, YTHDCs), insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) and certain heterogeneous nuclear ribonucleoproteins (hnRNPs) (52-54).

The IGF2BP family, comprising of IGF2BP1, IGF2BP2 and IGF2BP3, enhances the stability and translation efficiency of m6A-modified mRNAs by recognizing and binding to m6A sites, thereby regulating protein expression (55,56). Dysregulation of IGF2BP members has been closely associated with the onset, progression and metastasis of several types of cancer. For instance, IGF2BPs can contribute to malignant phenotypes via regulating m6A-modified transcripts (56).

Overall, m6A reader proteins serve a key role in determining RNA fate through diverse mechanisms and subcellular distribution patterns, thereby markedly affecting gene expression networks. The role of m6A modification on melanoma invasion and metastasis is predominantly mediated by these regulatory factors (Fig. 1).

5. Impact of m6A regulators on tumor invasion and metastasis

METTL3 in tumor invasion and metastasis. Elevated METTL3 expression is commonly associated with enhanced tumor invasion and metastasis through multiple mechanisms. A previous study demonstrated that METTL3 could enhance lung cancer cell proliferation via upregulation of proliferation-associated genes such as c-Myc through m6A modification, thereby facilitating early tumor expansion (57). In addition, METTL3 promoted epithelial-mesenchymal transition (EMT), a critical process in metastasis, via regulating the expression of EMT-inducing transcription factors, including SNAIL (58) and zinc finger E-box-binding homeobox 1 (59). METTL3 also contributes to immune escape via modulating immune-related genes. For example, a study revealed that it enhanced m6A modification of programmed death-ligand 1 (PD-L1) mRNA in breast cancer, thus enabling tumor cells to evade immune surveillance and promoting metastasis (60). Finally, METTL3 can also promote a pro-tumorigenic microenvironment (TME) via regulating intercellular communication and signaling pathways within the tumor stroma, thus facilitating tumor progression (61).

Overall, METTL3 is recognized as a critical regulator in multiple malignancies (62). Its upregulation in cancers such as gastric cancer (63), bladder cancer (3) and intrahepatic cholangiocarcinoma (64) is frequently associated with poor prognosis, highlighting its potential as a therapeutic target. Targeting METTL3-mediated m6A modifications can therefore represent a promising strategy for inhibiting tumor progression.

METTL14 in tumor invasion and metastasis. METTL14 serves a key role in tumor invasion and metastasis primarily through its regulation by m6A modifications. Particularly, it has been reported that METTL14 can regulate EMT. For instance, METTL14 has been reported to regulate the expression of EMT-related genes, such as RUNX2, via m6A modifications, thereby affecting melanoma invasion and metastasis (6,7).

Furthermore, METTL14 exerts context-dependent functions, acting as either an oncogene or a tumor suppressor. However, its role in different types of cancer warrants further mechanistic exploration. Liu *et al* (41) demonstrated that METTL14 expression was regulated by several mechanisms, and its functional outcomes varied across cancer types. Several factors may account for this apparent contradiction. First, tissue-specific transcriptomic landscapes determine METTL14 target selection; it preferentially modifies oncogenic transcripts in pancreatic (65) and breast cancer (66), while regulating tumor suppressor pathways in colorectal (67) and liver cancers (5). Second, the availability of cofactors could influence its activity; notably, METTL3 and METTL14 exhibit consistent roles in some malignancies, including acute myeloid leukemia and breast cancer, but opposing roles in others, such as hepatocellular and gastric cancer (41). For example, METTL14 has been shown to suppress gastric cancer (68) and colorectal cancer (69). Third, cellular context and microenvironmental conditions, such as hypoxia and inflammatory signals, can further modulate the downstream effects of METTL14-mediated m6A modifications. In melanoma, emerging evidence has suggested that METTL14 function can be subtype-dependent, with distinct roles observed in cutaneous vs. uveal melanoma (UM) (6,7). Therefore, further studies are needed to fully elucidate the context-dependent functions of METTL14.

In summary, the role of METTL14 in tumorigenesis is complex and highly tissue-specific, thus affecting tumor invasion and metastasis in a tissue-dependent manner via modulating the m6A epitranscriptome of key regulatory genes.

WTAP in tumor invasion and metastasis. In addition to METTL3 and METTL14, WTAP can also affect cancer cell invasion and migration by modulating the expression of EMT-related genes through m6A-dependent mechanisms. For example, in liver cancer, increased WTAP expression is associated with enhanced cell invasion and metastasis (70). As a component of the METTL3-METTL14 complex, WTAP can affect m6A modifications, stability and translation efficiency of numerous critical tumor-related genes. Its upregulation has been associated with the stabilization of oncogenic mRNAs, thereby promoting tumor cell migration and invasion (71).

ALKBH5 in tumor invasion and metastasis. ALKBH5 has been reported to suppress tumor invasion and metastasis via erasing m6A modifications from transcripts encoding

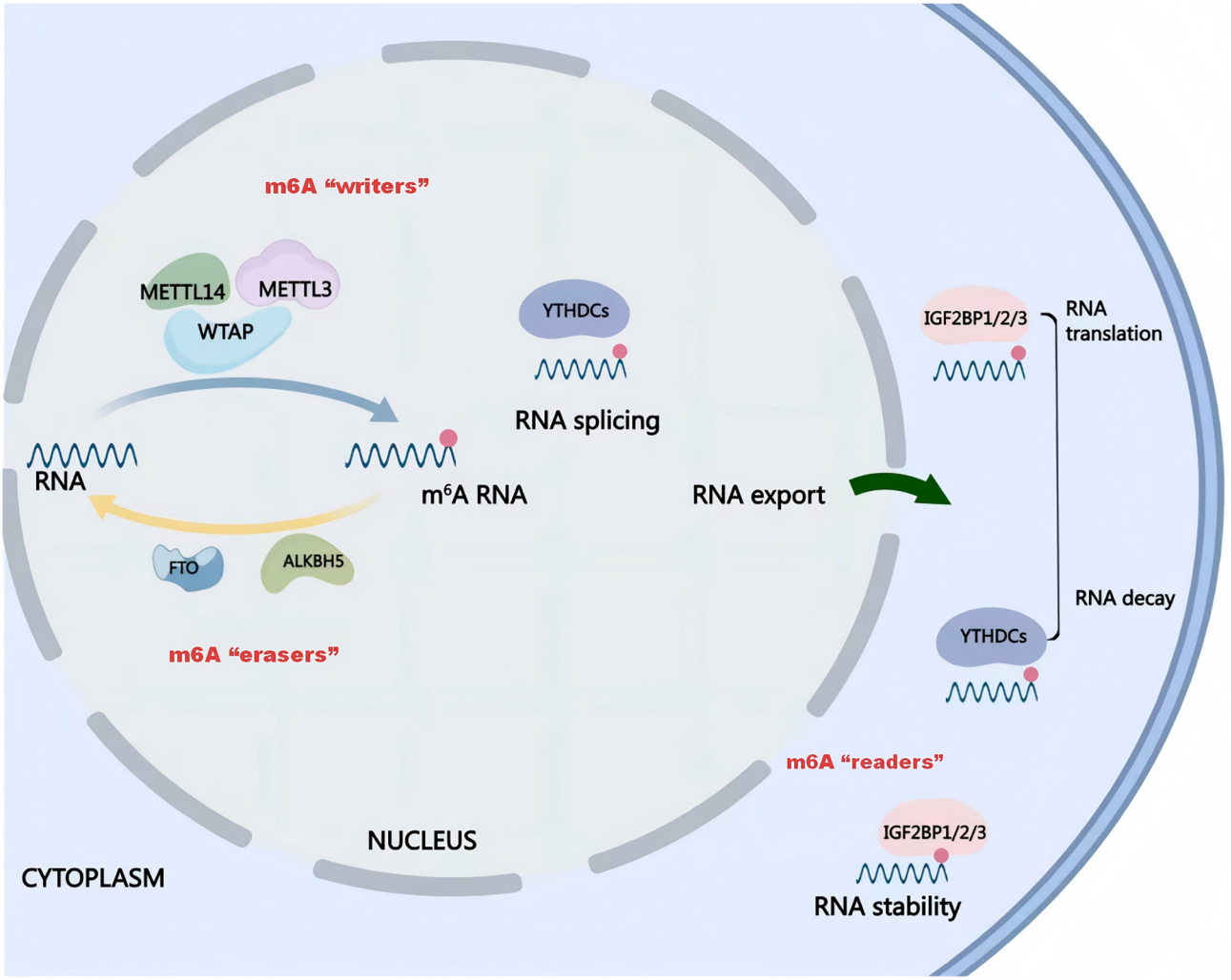

Figure 1. m6A methylation mechanism. m6A methylation is catalyzed by a multi-component m6A methyltransferase complex ('m6A writers'), primarily composed of two main proteins, namely METTL3 and METTL14, along with their regulatory cofactors, such as WTAP. m6A methylation can be reversed by demethylases, including FTO and ALKBH5 ('m6A erasers'). m6A modifications can affect RNA via recruiting m6A-binding proteins ('m6A readers'), such as YTHDCs and IGFBPs. m6A methylation is involved in several processes associated with RNA metabolism, including RNA splicing, localization, translation efficiency, stability and degradation. m6A, N6-methyladenosine; METTL3, methyltransferase-like 3; WTAP, Wilms' tumor 1-associating protein; FTO, fat mass and obesity-associated protein; ALKBH5, AlkB homolog 5; YTHDCs, YTH domain-containing proteins; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins.

EMT-related genes. This reduction can reduce the stability and translation of these genes, thereby attenuating the invasive and metastatic potential of tumor cells. Such effects have been previously observed in studies involving trophoblast cells and melanoma (72) and gastric cancer (73).

ALKBH5 is also involved in immune evasion via modulating immune checkpoint expression. A previous study demonstrated that ALKBH5 promoted PD-L1-mediated immune evasion via demethylating ZDHHC palmitoyltransferase 3 mRNA, thus facilitating glioma cell metastasis (74).

FTO in tumor invasion and metastasis. FTO has been shown to promote melanoma tumorigenesis and progression, in part through the regulation of genes involved in cell proliferation, survival and metastatic potential (10). In addition, FTO serves a key role in shaping the TME by regulating the expression of cytokines, growth factors and other mediators. In lung adenocarcinoma, FTO modulated immune cell function, angiogenesis and matrix composition, thereby promoting tumor invasiveness (75). Beyond its role in RNA demethylation, FTO is involved in metabolic reprogramming; in breast cancer, it modulates energy and lipid metabolism, which could indirectly support tumor growth and metastasis (76).

IGF2BPs in tumor invasion and metastasis. IGF2BPs facilitate tumor progression by stabilizing specific target mRNAs in an m6A-dependent manner. For example, in pancreatic ductal adenocarcinoma, IGF2BP stabilizes GLUT1 mRNA, thereby promoting cancer cell proliferation and eventually metastasis (77).

YTHDCs in tumor invasion and metastasis. It has been also reported that YTHDC1 and YTHDC2 can affect cell proliferation, migration and invasion via regulating specific m6A-modified transcripts involved in key biological processes such as cell cycle progression, cell adhesion and motility (78,79) (Fig. 2).

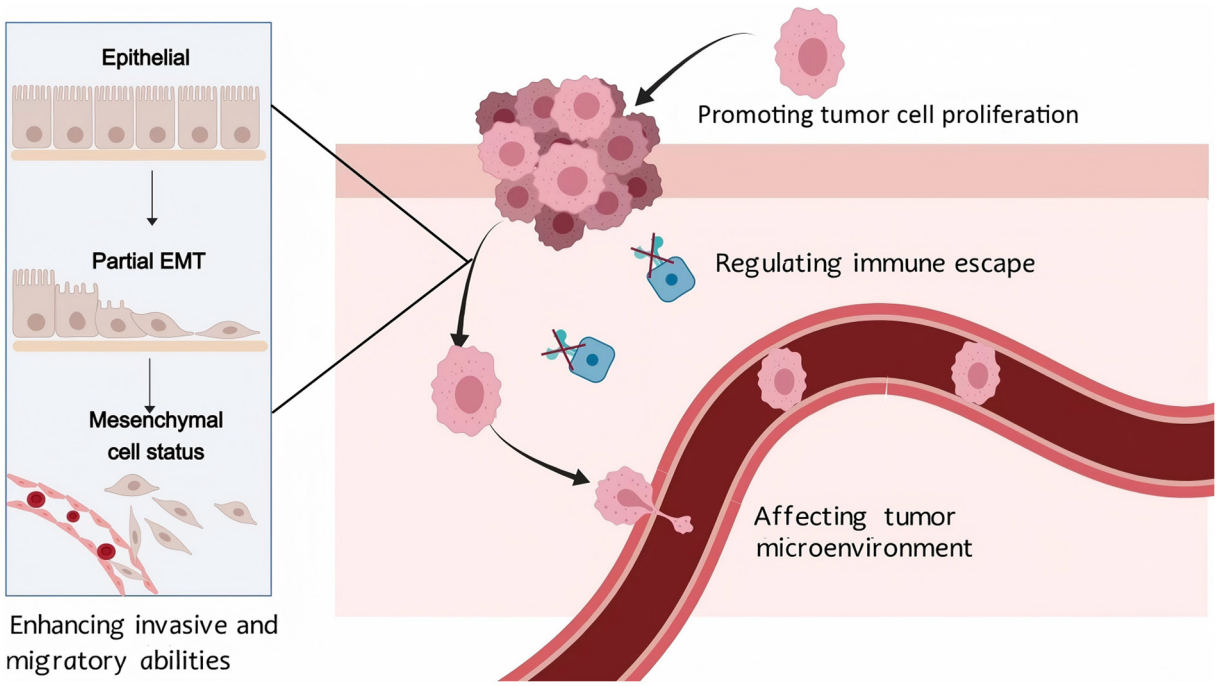

Figure 2. Mechanisms underlying tumor cell invasion and metastasis. Tumor proliferation includes the rapid growth of tumor cells, eventually contributing to increased tumor volume and local tissue invasion. EMT allows epithelial cells to acquire enhanced migratory and invasive capacities, facilitating detachment from the primary tumor and metastasis to distant tissues. Immune evasion allows tumor cells to escape immune surveillance, thus promoting their survival and metastatic spread. The tumor microenvironment, composed of non-cancer cells and signaling molecules, serves a key role in regulating tumor growth, angiogenesis and metastasis, thereby driving tumor invasion and dissemination. EMT, epithelial-to-mesenchymal transition.

6. Effect of m6A on melanoma migration and invasion

Melanoma migration and invasion are critical biological processes in which tumor cells dissociate from the primary tumor, infiltrate surrounding tissues and ultimately establish metastases at distant sites. These capabilities are fundamental to melanoma progression and serve as major determinants of patient prognosis. Highly invasive melanomas are more prone to disseminate and metastasize to organs such as lymph nodes, lungs, liver and brain (80,81). These metastatic lesions are notoriously difficult to treat and are associated with poor outcomes.

Therefore, a deep understanding of the molecular mechanisms underlying the migration and invasion of melanoma cells is critical for predicting disease course, guiding therapeutic decision-making, and improving patient survival and quality of life. Investigating such mechanisms could support the development of novel therapeutic targets aimed at preventing metastasis.

7. Research on m6A modifications in melanoma

Role of m6A modifications in melanoma metastasis and invasion. METTL3 is commonly upregulated in melanoma and serves a key role in melanoma cell proliferation, clonogenicity and invasive potential (82). METTL3 silencing could impair cell viability, colony formation and invasion, whereas its overexpression exerted the opposite effect. Mechanistically, METTL3 overexpression promoted the accumulation of pro-invasive proteins, including matrix metalloproteinase-2 and N-cadherin, highlighting the importance of its m6A catalytic activity. Other studies demonstrated that METTL3 knockdown suppressed melanoma cell proliferation, migration and invasion, and reduced tumor growth in xenograft models (83). A study by Chu *et al* (4) revealed that METTL3 knockdown decreased m6A levels and the expression of the long non-coding RNA SNHG3. SNHG3 acts as a molecular sponge for microRNA (miR)-330-5p, thereby upregulating cellular nucleic acid binding protein (CNBP). Restoration of SNHG3 counteracted the tumor-suppressive effects of METTL3 depletion, and restored alterations in miR-330-5p and CNBP levels. Clinically, SNHG3 expression was positively associated with METTL3 and negatively with miR-330-5p, thus supporting the notion that METTL3-mediated m6A modification of SNHG3 could promote melanoma invasion and metastasis via the miR-330-5p/CNBP axis.

Role of WTAP in melanoma invasion and metastasis. The role of WTAP in cancer development is gaining increasing attention. Aberrant WTAP expression and function has been closely associated with the pathogenesis of several types of cancer, highlighting its potential as a therapeutic target. Therefore, understanding the particular functions of WTAP in m6A modifications and associated processes could provide novel insights into the development of novel therapeutic strategies for improving outcomes of patients with cancer (84).

Role of METTL14 in melanoma invasion and metastasis. It has been reported that METTL14 contributes to shaping the dynamic m6A landscape in choroidal melanoma (CM) (6). It is closely associated with activation of the Wnt/β-catenin

signaling pathway (Wβ-CSP), a key regulator of tumor cell migration, invasion and metastasis in CM and other tumors. Notably inhibition of this pathway can suppress the aforementioned biological processes (85). METTL14 expression is positively associated with m6A levels. Therefore, METTL14 overexpression in CM cell lines could activate Wβ-CSP and increase phosphorylated GSK3β. Mechanistically, METTL14-mediated epigenetic changes promoted m6A modifications within the 3'UTR of RUNX2, thereby facilitating CM cell migration and invasion. By contrast, in UM, METTL14 expression was suppressed by reduced histone acetylation. Notably, METTL14 silencing attenuated the antitumor effects of histone deacetylase inhibitors both *in vitro* and *in vivo*, indicating that METTL14 loss could inhibit ocular melanoma cell invasion and migration (7,86).

Role of ALKBH5 in melanoma invasion and metastasis. ALKBH5 serves a critical role in melanoma progression. Liquid chromatography-mass spectrometry analyses demonstrated that ALKBH5 overexpression reduced global m6A levels in melanoma cells, suggesting it has a role in the progression of skin cutaneous melanoma (SKCM) via m6A demethylation. Functionally, ALKBH5 exhibits oncogenic properties in SKCM via promoting migration, invasion, proliferation and clonogenicity, while inhibiting autophagy, thereby driving tumor growth and metastasis (14). Similarly, in UM, ALKBH5 expression is markedly upregulated, while its silencing has been linked with reduced tumor growth *in vivo*. High ALKBH5 expression was also associated with poor prognosis in patients with UM. Additionally, EP300-induced acetylation of histone H3 lysine 27 could increase ALKBH5 expression, while ALKBH5 knockdown suppressed UM cell proliferation, migration and invasion, and induced apoptosis *in vitro*. Mechanistically, ALKBH5 could promote EMT through demethylating FOXM1, thereby enhancing its expression and stability. Collectively, these findings identified ALKBH5 as a potential prognostic biomarker and therapeutic target in UM (16).

Role of FTO in melanoma invasion and metastasis. FTO serves a pivotal role in the metabolic adaptation of melanoma cells. Yang *et al* (10) systematically elucidated the mechanism by which FTO could promote melanoma tumorigenesis and mediate resistance to anti-programmed cell death protein 1 (PD-1/PDCD1) immunotherapy. Under metabolic stress conditions, such as nutrient deprivation, FTO expression is increased through the activation of the autophagy/NF-κB signaling pathway. As an m6A demethylase, FTO can remove m6A modifications from PDCD1, C-X-C motif chemokine receptor 4 (CXCR4) and SOX10 mRNAs. Under physiological conditions, the m6A reader YTHDF2 binds to m6A-methylated transcripts and promotes their degradation. However, FTO-mediated demethylation can prevent YTHDF2 binding, thus resulting in increased mRNA stability and subsequent elevated protein expression of PD-1, CXCR4 and SOX10. This FTO/PD-1 axis represents a critical component of metabolic stress adaptation in melanoma cells. Immune checkpoint blockade has demonstrated clinical efficacy in multiple malignancies (87,88), and PD-1 may also exert melanoma cell-intrinsic functions (89). Notably, FTO knockdown could sensitize melanoma to anti-PD-1 therapy in immunocompetent mouse models, whereas this effect was abrogated in immunodeficient NOD-scid IL2Rγ null mice suggesting dependence on adaptive immunity. Additionally, FTO could confer resistance to IFNγ-induced apoptosis; FTO depletion enhanced IFNγ-mediated apoptosis, whereas FTO overexpression suppressed it (10).

Mechanistically, this pathway can be summarized as follows: Metabolic stress → activation of the autophagy/NF-κB pathway → upregulation of FTO → demethylation of PDCD1, CXCR4 and SOX10 mRNAs → reduced YTHDF2-mediated decay → increased mRNA stability → enhanced expression of PD-1, CXCR4 and SOX10 → promotion of tumor growth and immune evasion → FTO knockout or inhibition sensitizes melanoma to anti-PD-1 therapy (10).

Although direct experimental evidence for the regulation of LAG-3 or TIM-3 by m6A modification in melanoma is currently lacking, studies in other cancers have demonstrated that m6A-related gene signatures are associated with the expression of these alternative immune checkpoint molecules. For example, Ma *et al* (90) reported that in hepatocellular carcinoma, patients with a high m6A score exhibited markedly upregulated lymphocyte activation gene 3 (LAG3) and T cell immunoglobulin and mucin domain-containing protein 3 (TIM3) expression, along with an immunosuppressive tumor microenvironment characterized by abundant M2-polarized macrophages and regulatory T cell infiltration. These findings suggest a potential link between m6A modification and alternative immune checkpoints, which warrants further investigation in melanoma.

Collectively, the aforementioned findings demonstrate that m6A modifications shape the tumor immune microenvironment and influence immunotherapy responses through multiple mechanisms, including the regulation of chemokine receptors (such as CXCR4), modulation of cytokine sensitivity (such as IFNγ), alteration of immune cell infiltration patterns and potential crosstalk with alternative immune checkpoints such as LAG3 and TIM3. Thus, the impact of m6A on the immune landscape extends well beyond the PD-1/PD-L1 axis.

Role of YTHDC1 and IGF2BP3 in melanoma invasion and metastasis. The IGF2BP family (IGF2BP1/2/3) recognizes m6A modifications and, in contrast to decay-promoting readers, enhance target mRNA stability and translation in an m6A-dependent manner (35). IGF2BPs have been implicated in melanoma progression and metastasis, suggesting that they represent potential therapeutic targets and may provide important biological insights. For instance, IGF2BP3 interacts with the circular RNA CDR1as, and the loss of CDR1as expression in melanoma can permit IGF2BP3-mediated pro-metastatic activity, thereby contributing to tumor invasion and metastasis.

Integrative analyses examining the associations between IGF2BP3, other m6A regulators, tumor immunity and metastasis have identified the metastasis-associated gene small proline rich protein 1B (SPRR1B) as a key factor. SPRR1B, a member of the small proline-rich protein family, is commonly altered in melanoma and exhibits a notable inverse association with IGF2BP3 expression. Notably, a previous study (91) provided new perspectives on the integrated role of m6A factors in SKCM and, for the first time, identified SPRR1B as a promoter of melanoma cell proliferation, invasion and migration.

In tumor immunity, the m6A regulators, including YTHDC1, YTHDC2, WTAP and FTO, are strongly associated with immune cell subtypes. Weighted gene co-expression network analysis indicated that YTHDC1, YTHDC2 and WTAP were notably positively associated with selected antitumor immune genes. WTAP, YTHDC1 and YTHDC2 showed a broad positive association with immune-related genes, whereas IGF2BP3 was broadly negatively associated, implicating a potential role in immune evasion mechanisms in SKCM (91,92).

Subtype-specific roles of m6A regulators in melanoma. Melanoma encompasses heterogeneous molecular subtypes characterized by diverse genetic drivers and clinical behaviors, including BRAF-mutant, NRAS proto-oncogene, GTPase (NRAS)-mutant, neurofibromatosis type 1-loss and triple-negative subtypes, as well as site-specific variants, such as those in cutaneous, uveal and mucosal melanoma. Emerging evidence has suggested that m6A regulatory networks exhibit subtype-specific functions across different contexts.

In BRAF-mutant melanoma, whether FTO directly contributes to BRAF inhibitor resistance has not been clearly established. However, FTO is known to be upregulated in melanoma and promotes tumorigenesis through m^6A-dependent stabilization of key melanoma cell-intrinsic genes (10). Given that FTO-mediated demethylation can enhance the expression of pro-survival factors, it is plausible that FTO could activate alternative survival pathways, thereby enabling tumor cells to bypass MAPK pathway inhibition. Further studies are required to test this hypothesis. Similarly, METTL3 has been reported to shape the tumor immune microenvironment and affect therapeutic responses (93). ALKBH5 has been implicated in modulating the tumor microenvironment, thus affecting responses to both targeted therapy and immunotherapy (94).

In UM, distinct m6A signatures have been identified. METTL14 promotes tumor cell migration and invasion through m6A-mediated RUNX2 methylation (6), while ALKBH5 drives tumor progression through demethylation of FOXM1 (16). Notably, epigenetic regulation differs between uveal and cutaneous melanoma; for instance, histone acetylation status could differentially modulate METTL14 expression across these subtypes (7,86).

With respect to immunotherapy, FTO expression levels can serve as a predictive biomarker for response to anti-PD-1 therapy (10). Tumors with elevated FTO expression exhibit increased PD-1 (PDCD1) expression and can be less responsive to immune checkpoint blockade. However, this association appears to vary among melanoma subtypes, potentially due to differences in baseline immune infiltration and tumor immunogenicity. Future studies should systematically characterize m6A regulator expression and function across molecular subtypes to identify context-dependent vulnerabilities and guide the development of more precise therapeutic strategies.

8. Potential applications of m6A targeting in melanoma therapy

Targeting the m6A modification machinery holds promise for melanoma treatment. Due to the critical role of m6A modifications in tumorigenesis (93,94), and the documented dysregulation of key m6A-related proteins such as METTL3 (93) and ALKBH5 (94) in melanoma, which both associate with clinical features and patient prognosis, uncovering the m6A regulatory network in this type of cancer could unveil novel therapeutic targets. Potential therapeutic approaches include inhibition of m6A methylation or modulation of the activity of writers or erasers. However, further studies and clinical trials are warranted to validate the safety and efficacy of the above therapeutic approaches.

9. Conclusions and future perspectives

The present review systematically summarized the emerging evidence implicating m6A RNA methylation in melanoma invasion and metastasis. Accumulating data from the literature indicated that m6A regulators, including writers (METTL3, METTL14, WTAP), erasers (FTO, ALKBH5) and readers (IGF2BPs, YTHDCs), are commonly dysregulated in melanoma and functionally contribute to malignant progression through diverse mechanisms, including enhanced proliferation, induction of EMT, modulation of immune evasion and remodeling of the tumor microenvironment.

Several notable themes emerge from this body of evidence. First, m6A regulators exhibit context-dependent functions that vary across cancer types and even among melanoma subtypes. METTL14 exemplifies this functional duality, acting as either an oncogene or tumor suppressor depending on cellular context. Second, m6A modifications serve a critical role in shaping responses to immunotherapy through multiple mechanisms, with the FTO/PD-1 axis representing a well-characterized pathway that is potentially targetable (10). Third, m6A regulators operate within an integrated network with potential compensatory and feedback interactions that could influence therapeutic outcomes.

Despite notable progress, several challenges and knowledge gaps remain: First, subtype-specific heterogeneity remains poorly explored. The majority of studies have treated melanoma as a homogeneous entity. Future research should systematically characterize m6A landscapes across BRAF- and NRAS-mutant, and other molecular subtypes, as well as across cutaneous, uveal and mucosal melanomas, to identify subtype-specific vulnerabilities.

Second, compensatory mechanisms and network dynamics are also poorly understood. The potential for feedback regulation between writers and erasers, for instance whether METTL3 inhibition could trigger ALKBH5 or FTO upregulation, remains largely unexplored in melanoma. Notably, Panneerdoss *et al* (95) demonstrated in other cancer models that METTL14 and ALKBH5 could reciprocally regulate each other, eventually forming a positive feedback loop that could maintain m6A homeostasis. Clarifying whether similar compensatory mechanisms exist in melanoma warrants further investigation for guiding the design of combination therapies.

Third, crosstalk with other RNA modifications should not be excluded. While the present review focused on m6A, other RNA modifications such as m5C and m1A also contribute to epitranscriptomic regulation in cancer. Mao *et al* (96) comprehensively analyzed a total of 100 RNA modification regulators in lung adenocarcinoma and revealed extensive expression associations and coordinated networks across different

modification systems, suggesting that these regulators could collectively shape tumor microenvironment characteristics and cancer hallmarks. Similarly, Qi *et al* (97) demonstrated notable cross-talk among m6A, m5C, m1A and m7G regulators in soft tissue sarcoma, where a network of 32 regulators exhibited extensive inter-modification associations and distinct regulator clusters were characterized by markedly different prognoses and TME landscapes. Therefore, it is plausible that different RNA modifications (such as m6A, m5C and m1A) do not act in isolation but jointly form a complex epitranscriptomic regulatory network that drives malignant progression. While direct evidence in melanoma is still lacking, the extensive crosstalk observed in other cancers strongly supports this hypothesis. Future integrated multi-omics approaches are needed to decipher such synergistic networks in melanoma.

Fourth, clinical translation remains a notable challenge. Although preclinical studies support targeting m6A regulators in melanoma, the development of selective inhibitors with favorable pharmacokinetic profiles is still at an early stage. The safety and efficacy of these agents, particularly in combination with immunotherapy or targeted therapy, require rigorous evaluation in clinical trials.

Finally, developing novel biomarkers is of notable importance. The potential of m6A regulator expression patterns or global m6A modification levels as diagnostic, prognostic or predictive biomarkers in melanoma warrants prospective validation in large, well-annotated clinical cohorts.

In conclusion, m6A methylation has emerged as a critical layer of epitranscriptomic regulation in melanoma invasion and metastasis. Deciphering the complex m6A regulatory network, with particular attention to context-specific functions, network dynamics and therapeutic vulnerabilities, holds promise for advancing the understanding of melanoma biology and for the development of innovative treatment strategies. As the field progresses toward precision oncology, integrating epitranscriptomic profiling into melanoma management could enable more personalized therapeutic approaches to improve patient outcomes.

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Authors' contributions

ZhX, WY, JL, XC, SML, ZeX, QY and WX contributed to the conception and design. ZhX and WY drafted the manuscript. JL, XC and SML performed the literature search. ZeX and QY revised the manuscript critically for important intellectual content. WX gave final approval of the version to be published. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ru W, Zhang X, Yue B, Qi A, Shen X, Huang Y, Lan X, Lei C and Chen H: Insight into m^{6}A methylation from occurrence to functions. Open Biol 10: 200091, 2020.
2. Wang Q, Chen C, Ding Q, Zhao Y, Wang Z, Chen J, Jiang Z, Zhang Y, Xu G, Zhang J, *et al*: METTL3-mediated m^{6}A modification of HDGF mRNA promotes gastric cancer progression and has prognostic significance. Gut 69: 1193-1205, 2020.
3. Han J, Wang JZ, Yang X, Yu H, Zhou R, Lu HC, Yuan WB, Lu JC, Zhou ZJ, Lu Q, *et al*: METTL3 promote tumor proliferation of bladder cancer by accelerating pri-miR221/222 maturation in m6A-dependent manner. Mol Cancer 18: 110, 2019.
4. Chu S, Li Y, Wu B, Rong G, Hou Q, Zhou Q, Du D and Li Y: METTL3 promotes the growth and invasion of melanoma cells by regulating the lncRNA SNHG3/miR-330-5p axis. Cell Transplant 32: 9636897231188300, 2023.
5. Ma JZ, Yang F, Zhou CC, Liu F, Yuan JH, Wang F, Wang TT, Xu QG, Zhou WP and Sun SH: METTL14 suppresses the metastatic potential of hepatocellular carcinoma by modulating N^6-methyladenosine-dependent primary MicroRNA processing. Hepatology 65: 529-543, 2017.
6. Zhang X, Zhang X, Liu T, Zhang Z, Piao C and Ning H: METTL14 promotes migration and invasion of choroidal melanoma by targeting RUNX2 mRNA via m6A modification. J Cell Mol Med 26: 5602-5613, 2022.
7. Zhuang A, Gu X, Ge T, Wang S, Ge S, Chai P, Jia R and Fan X: Targeting histone deacetylase suppresses tumor growth through eliciting METTL14-modified m^6 A RNA methylation in ocular melanoma. Cancer Commun (Lond) 43: 1185-1206, 2023.
8. Popović AM, Huđek Turković A, Žuna K, Bačun-Družina V, Rubelj I and Matovinović M: FTO gene polymorphisms at the crossroads of metabolic pathways of obesity and epigenetic influences. Food Technol Biotechnol 61: 14-26, 2023.
9. Huang M, Guo J, Liu L, Jin H, Chen X and Zou J: m6A demethylase FTO and osteoporosis: Potential therapeutic interventions. Front Cell Dev Biol 11: 1275475, 2023.
10. Yang S, Wei J, Cui YH, Park G, Shah P, Deng Y, Aplin AE, Lu Z, Hwang S, He C and He YY: m6A mRNA demethylase FTO regulates melanoma tumorigenicity and response to anti-PD-1 blockade. Nat Commun 10: 2782, 2019.
11. Ye J, Chen X, Jiang X, Dong Z, Hu S and Xiao M: RNA demethylase ALKBH5 regulates hypopharyngeal squamous cell carcinoma ferroptosis by posttranscriptionally activating NFE2L2/NRF2 in an m^6 A-IGF2BP2-dependent manner. J Clin Lab Anal 36: e24514, 2022.
12. Qu J, Yan H, Hou Y, Cao W, Liu Y, Zhang E, He J and Cai Z: RNA demethylase ALKBH5 in cancer: From mechanisms to therapeutic potential. J Hematol Oncol 15: 8, 2022.
13. You Y, Wen D, Zeng L, Lu J, Xiao X, Chen Y, Song H and Liu Z: ALKBH5/MAP3K8 axis regulates PD-L1+ macrophage infiltration and promotes hepatocellular carcinoma progression. Int J Biol Sci 18: 5001-5018, 2022.
14. Wang H, Zhao S, Liu H, Liu Y, Zhang Z, Zhou Z, Wang P, Qi S and Xie J: ALKBH5 facilitates the progression of skin cutaneous melanoma via mediating ABCA1 demethylation and modulating autophagy in an m^{6}A-dependent manner. Int J Biol Sci 20: 1729-1743, 2024.

15. Schadendorf D, van Akkooi ACJ, Berking C, Griewank KG, Gutzmer R, Hauschild A, Stang A, Roesch A and Ugurel S: Melanoma. Lancet 392: 971-984, 2018.
16. Hao L, Yin J, Yang H, Li C, Zhu L, Liu L and Zhong J: ALKBH5-mediated m^{6}A demethylation of FOXM1 mRNA promotes progression of uveal melanoma. Aging (Albany NY) 13: 4045-4062, 2021.
17. Jia R, Chai P, Wang S, Sun B, Xu Y, Yang Y, Ge S, Jia R, Yang YG and Fan X: m^{6}A modification suppresses ocular melanoma through modulating HINT2 mRNA translation. Mol Cancer 18: 161, 2019.
18. O'Neill CH and Scoggins CR: Melanoma. J Surg Oncol 120: 873-881, 2019.
19. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, Bastholt L, Bataille V, Del Marmol V, Dréno B, *et al*: European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update 2022. Eur J Cancer 170: 236-255, 2022.
20. Rietschel P, Panageas KS, Hanlon C, Patel A, Abramson DH and Chapman PB: Variates of survival in metastatic uveal melanoma. J Clin Oncol 23: 8076-8080, 2005.
21. Goldemberg DC, de Melo AC, de Melo Pino LC and Thuler LCS: Epidemiological profile of mucosal melanoma in Brazil. Sci Rep 10: 505, 2020.
22. Tsao H, Chin L, Garraway LA and Fisher DE: Melanoma: From mutations to medicine. Genes Dev 26: 1131-1155, 2012.
23. Houben R, Hesbacher S, Schmid CP, Kauczok CS, Flohr U, Haferkamp S, Müller CS, Schrama D, Wischhusen J and Becker JC: High-level expression of wild-type p53 in melanoma cells is frequently associated with inactivity in p53 reporter gene assays. PLoS One 6: e22096, 2011.
24. Nikolaou V, Kang X, Stratigos A, Gogas H, Latorre MC, Gabree M, Plaka M, Njauw CN, Kypreou K, Mirmigi I, *et al*: Comprehensive mutational analysis of CDKN2A and CDK4 in Greek patients with cutaneous melanoma. Br J Dermatol 165: 1219-1222, 2011.
25. Boussadia Z, Gambardella AR, Mattei F and Parolini I: Acidic and hypoxic microenvironment in melanoma: Impact of tumour exosomes on disease progression. Cells 10: 3311, 2021.
26. Chen J, Ye M, Bai J, Hu C, Lu F, Gu D, Yu P and Tang Q: Novel insights into the interplay between m6A modification and programmed cell death in cancer. Int J Biol Sci 19: 1748-1763, 2023.
27. Cheung JCT, Deng G, Wong N, Dong Y and Ng SSM: More than a duologue: In-depth insights into epitranscriptomics and ferroptosis. Front Cell Dev Biol 10: 982606, 2022.
28. Canaani D, Kahana C, Lavi S and Groner Y: Identification and mapping of N6-methyladenosine containing sequences in simian virus 40 RNA. Nucleic Acids Res 6: 2879-2899, 1979.
29. He L, Li H, Wu A, Peng Y, Shu G and Yin G: Functions of N6-methyladenosine and its role in cancer. Mol Cancer 18: 176, 2019.
30. Zaccara S, Ries RJ and Jaffrey SR: Reading, writing and erasing mRNA methylation. Nat Rev Mol Cell Biol 20: 608-624, 2019.
31. He PC and He C: m^6 A RNA methylation: From mechanisms to therapeutic potential. EMBO J 40: e105977, 2021.
32. Jiang X, Liu B, Nie Z, Duan L, Xiong Q, Jin Z, Yang C and Chen Y: The role of m6A modification in the biological functions and diseases. Signal Transduct Target Ther 6: 74, 2021.
33. De Jesus DF, Zhang Z, Kahraman S, Brown NK, Chen M, Hu J, Gupta MK, He C and Kulkarni RN: m^{6}A mRNA methylation regulates human β-cell biology in physiological states and in type 2 diabetes. Nat Metab 1: 765-774, 2019.
34. Guo J, Ren W, Li A, Ding Y, Guo W, Su D, Hu C, Xu K, Chen H, Xu X, *et al*: Fat mass and obesity-associated gene enhances oxidative stress and lipogenesis in nonalcoholic fatty liver disease. Dig Dis Sci 58: 1004-1009, 2013.
35. Lin Y, Shen X, Ke Y, Lan C, Chen X, Liang B, Zhang Y and Yan S: Activation of osteoblast ferroptosis via the METTL3/ASK1-p38 signaling pathway in high glucose and high fat (HGHF)-induced diabetic bone loss. FASEB J 36: e22147, 2022.
36. Geula S, Moshitch-Moshkovitz S, Dominissini D, Mansour AA, Kol N, Salmon-Divon M, Hershkovitz V, Peer E, Mor N, Manor YS, *et al*: Stem cells. m6A mRNA methylation facilitates resolution of naïve pluripotency toward differentiation. Science 347: 1002-1006, 2015.
37. Liu J, Yue Y, Han D, Wang X, Fu Y, Zhang L, Jia G, Yu M, Lu Z, Deng X, *et al*: A METTL3-METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation. Nat Chem Biol 10: 93-95, 2014.
38. Ping XL, Sun BF, Wang L, Xiao W, Yang X, Wang WJ, Adhikari S, Shi Y, Lv Y, Chen YS, *et al*: Mammalian WTAP is a regulatory subunit of the RNA N6-methyladenosine methyltransferase. Cell Res 24: 177-189, 2014.
39. Oerum S, Meynier V, Catala M and Tisné C: A comprehensive review of m6A/m6Am RNA methyltransferase structures. Nucleic Acids Res 49: 7239-7255, 2021.
40. Wang P, Doxtader KA and Nam Y: Structural basis for cooperative function of Mettl3 and Mettl14 methyltransferases. Mol Cell 63: 306-317, 2016.
41. Liu X, Du Y, Huang Z, Qin H, Chen J and Zhao Y: Insights into roles of METTL14 in tumors. Cell Prolif 55: e13168, 2022.
42. Wu R, Jiang D, Wang Y and Wang X: N (6)-Methyladenosine (m(6)A) methylation in mRNA with A dynamic and reversible epigenetic modification. Mol Biotechnol 58: 450-459, 2016.
43. Mathoux J, Henshall DC and Brennan GP: Regulatory mechanisms of the RNA modification m^{6}A and significance in brain function in health and disease. Front Cell Neurosci 15: 671932, 2021.
44. Meyer KD and Jaffrey SR: Rethinking m^{6}A readers, writers, and erasers. Annu Rev Cell Dev Biol 33: 319-342, 2017.
45. Ju G, Lei J, Cai S, Liu S, Yin X and Peng C: The emerging, multifaceted role of WTAP in cancer and cancer therapeutics. Cancers (Basel) 15: 3053, 2023.
46. Huang Q, Mo J, Liao Z, Chen X and Zhang B: The RNA m^{6}A writer WTAP in diseases: Structure, roles, and mechanisms. Cell Death Dis 13: 852, 2022.
47. Li Y, Su R, Deng X, Chen Y and Chen J: FTO in cancer: Functions, molecular mechanisms, and therapeutic implications. Trends Cancer 8: 598-614, 2022.
48. Han Z, Niu T, Chang J, Lei X, Zhao M, Wang Q, Cheng W, Wang J, Feng Y and Chai J: Crystal structure of the FTO protein reveals basis for its substrate specificity. Nature 464: 1205-1209, 2010.
49. You Y, Fu Y, Huang M, Shen D, Zhao B, Liu H, Zheng Y and Huang L: Recent advances of m6A demethylases inhibitors and their biological functions in human diseases. Int J Mol Sci 23: 5815, 2022.
50. Xiao D, Fang TX, Lei Y, Xiao SJ, Xia JW, Lin TY, Li YL, Zhai JX, Li XY, Huang SH, *et al*: m^{6}A demethylase ALKBH5 suppression contributes to esophageal squamous cell carcinoma progression. Aging (Albany NY) 13: 21497-21512, 2021.
51. Xu C, Liu K, Tempel W, Demetriades M, Aik W, Schofield CJ and Min J: Structures of human ALKBH5 reveal a unique binding mode for single-stranded RNA substrates. J Biol Chem 289: 17299-17311, 2014.
52. Wang Y, Lu G, Xue X, Xie M, Wang Z, Ma Z, Feng Y, Shao C, Duan H, Pan M, *et al*: Characterization and validation of a ferroptosis-related LncRNA signature as a novel prognostic model for lung adenocarcinoma in tumor microenvironment. Front Immunol 13: 903758, 2022.
53. Tang Z, Huang X, Mei H and Zheng Z: Silencing of METTL3 suppressed ferroptosis of myocardial cells by m6A modification of SLC7A11 in a YTHDF2 manner. J Bioenerg Biomembr 56: 149-157, 2024.
54. Wang S, Wang Y, Li Q, Zeng K, Li X and Feng X: RUNX1-IT1 favors breast cancer carcinogenesis through regulation of IGF2BP1/GPX4 axis. Discov Oncol 14: 42, 2023.
55. Bell JL, Wächter K, Mühleck B, Pazaitis N, Köhn M, Lederer M and Hüttelmaier S: Insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs): Post-transcriptional drivers of cancer progression? Cell Mol Life Sci 70: 2657-2675, 2013.
56. Lu Z, Yang H, Shao Y, Sun W, Jiang Y and Li J: IGF2BP3-NRF2 axis regulates ferroptosis in hepatocellular carcinoma. Biochem Biophys Res Commun 627: 103-110, 2022.
57. Wu H, Li F and Zhu R: miR-338-5p inhibits cell growth and migration via inhibition of the METTL3/m6A/c-Myc pathway in lung cancer. Acta Biochim Biophys Sin (Shanghai) 53: 304-316, 2021.
58. Wen J, Zhang G, Meng Y, Zhang L, Jiang M and Yu Z: RNA m^{6}A methyltransferase METTL3 promotes colorectal cancer cell proliferation and invasion by regulating Snail expression. Oncol Lett 22: 711, 2021.
59. Shen S, Jin H, Zhang X, Zhang Y, Li X, Yan W, Xie S, Yu B, Hu J, Liu H, *et al*: LINC00426, a novel m^{6}A-regulated long non-coding RNA, induces EMT in cervical cancer by binding to ZEB1. Cell Signal 109: 110788, 2023.
60. Wan W, Ao X, Chen Q, Yu Y, Ao L, Xing W, Guo W, Wu X, Pu C, Hu X, *et al*: METTL3/IGF2BP3 axis inhibits tumor immune surveillance by upregulating N^6-methyladenosine modification of PD-L1 mRNA in breast cancer. Mol Cancer 21: 60, 2022.

61. Hu C, Liu J, Li Y, Jiang W, Ji D, Liu W and Ma T: Multifaceted Roles of the N^6-methyladenosine RNA methyltransferase METTL3 in cancer and immune microenvironment. Biomolecules 12: 1042, 2022.
62. Liao Y, Han P, Zhang Y and Ni B: Physio-pathological effects of m6A modification and its potential contribution to melanoma. Clin Transl Oncol 23: 2269-2279, 2021.
63. Yue B, Song C, Yang L, Cui R, Cheng X, Zhang Z and Zhao G: METTL3-mediated N6-methyladenosine modification is critical for epithelial-mesenchymal transition and metastasis of gastric cancer. Mol Cancer 18: 142, 2019.
64. Xu QC, Tien YC, Shi YH, Chen S, Zhu YQ, Huang XT, Huang CS, Zhao W and Yin XY: METTL3 promotes intrahepatic cholangiocarcinoma progression by regulating IFIT2 expression in an m^6A-YTHDF2-dependent manner. Oncogene 41: 1622-1633, 2022.
65. Wang M, Liu J, Zhao Y, He R, Xu X, Guo X, Li X, Xu S, Miao J, Guo J, *et al*: Upregulation of METTL14 mediates the elevation of PERP mRNA N^6 adenosine methylation promoting the growth and metastasis of pancreatic cancer. Mol Cancer 19: 130, 2020.
66. Yi D, Wang R, Shi X, Xu L, Yilihamu Y and Sang J: METTL14 promotes the migration and invasion of breast cancer cells by modulating N6-methyladenosine and hsa-miR-146a-5p expression. Oncol Rep 43: 1375-1386, 2020.
67. Xu D, Han S, Yue X, Xu X, Huang T: METTL14 suppresses tumor stemness and metastasis of colon cancer cells by modulating m6A-modified SCD1. Mol Biotechnol 66: 2095-2105, 2024.
68. Fan HN, Chen ZY, Chen XY, Chen M, Yi YC, Zhu JS and Zhang J: METTL14-mediated m^6A modification of circORC5 suppresses gastric cancer progression by regulating miR-30c-2-3p/AKT1S1 axis. Mol Cancer 21: 51, 2022.
69. Yang X, Zhang S, He C, Xue P, Zhang L, He Z, Zang L, Feng B, Sun J and Zheng M: METTL14 suppresses proliferation and metastasis of colorectal cancer by down-regulating oncogenic long non-coding RNA XIST. Mol Cancer 19: 46, 2020.
70. Liu W, Gao X, Chen X, Zhao N, Sun Y, Zou Y, Guan Y, Yang L, Pei X, Wang G, *et al*: miR-139-5p loss-mediated WTAP activation contributes to hepatocellular carcinoma progression by promoting the epithelial to mesenchymal transition. Front Oncol 11: 611544, 2021.
71. Schöller E, Weichmann F, Treiber T, Ringle S, Treiber N, Flatley A, Feederle R, Bruckmann A and Meister G: Interactions, localization, and phosphorylation of the m^6A generating METTL3-METTL14-WTAP complex. RNA 24: 499-512, 2018.
72. He J, Li X, Lü M, Wang J, Tang J, Luo S and Qian Y: ALKBH5 suppresses migration and invasion of human trophoblast cells by inhibiting epithelial-mesenchymal transition. Nan Fang Yi Ke Da Xue Xue Bao 40: 1720-1725, 2020 (In Chinese).
73. Zheng Z, Lin F, Zhao B, Chen G, Wei C, Chen X, Nie R, Zhang R, Zhao Z, Zhou Z, *et al*: ALKBH5 suppresses gastric cancer tumorigenesis and metastasis by inhibiting the translation of uncapped WRAP53 RNA isoforms in an m6A-dependent manner. Mol Cancer 24: 19, 2025.
74. Tang W, Xu N, Zhou J, He Z, Lenahan C, Wang C, Ji H, Liu B, Zou Y, Zeng H and Guo H: ALKBH5 promotes PD-L1-mediated immune escape through m6A modification of ZDHHC3 in glioma. Cell Death Discov 8: 497, 2022.
75. Li Y, Gu J, Xu F, Zhu Q, Chen Y, Ge D and Lu C: Molecular characterization, biological function, tumor microenvironment association and clinical significance of m6A regulators in lung adenocarcinoma. Brief Bioinform 22: bbaa225, 2021.
76. Liu Y, Wang R, Zhang L, Li J, Lou K and Shi B: The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol Lett 13: 4685-4690, 2017.
77. Huang S, Wu Z, Cheng Y, Wei W and Hao L: Insulin-like growth factor 2 mRNA binding protein 2 promotes aerobic glycolysis and cell proliferation in pancreatic ductal adenocarcinoma via stabilizing GLUT1 mRNA. Acta Biochim Biophys Sin (Shanghai) 51: 743-752, 2019.
78. Tan B, Zhou K, Liu W, Prince E, Qing Y, Li Y, Han L, Qin X, Su R, Pokharel SP, *et al*: RNA N^6-methyladenosine reader YTHDC1 is essential for TGF-beta-mediated metastasis of triple negative breast cancer. Theranostics 12: 5727-5743, 2022.
79. Cao D, Ge S and Li M: MiR-451a promotes cell growth, migration and EMT in osteosarcoma by regulating YTHDC1-mediated m6A methylation to activate the AKT/mTOR signaling pathway. J Bone Oncol 33: 100412, 2022.
80. Yde SS, Sjoegren P, Heje M and Stolle LB: Mucosal melanoma: A literature review. Curr Oncol Rep 20: 28, 2018.
81. Lee KA and Nathan P: Cutaneous melanoma-A review of systemic therapies. Acta Derm Venereol 100: adv00141, 2020.
82. Dahal U, Le K and Gupta M: RNA m6A methyltransferase METTL3 regulates invasiveness of melanoma cells by matrix metallopeptidase 2. Melanoma Res 29: 382-389, 2019.
83. Yue Z, Cao M, Hong A, Zhang Q, Zhang G, Jin Z, Zhao L, Wang Q, Fang F, Wang Y and Sun J: m6A methyltransferase METTL3 promotes the progression of primary acral melanoma via mediating TXNDC5 methylation. Front Oncol 11: 770325, 2022.
84. Feng ZY, Wang T, Su X and Guo S: Identification of the m6A RNA methylation regulators WTAP as a novel prognostic biomarker and genomic alterations in cutaneous melanoma. Front Mol Biosci 8: 665222, 2021.
85. Krishnamurthy N and Kurzrock R: Targeting the Wnt/beta-catenin pathway in cancer: Update on effectors and inhibitors. Cancer Treat Rev 62: 50-60, 2018.
86. Durante MA, Rodriguez DA, Kurtenbach S, Kuznetsov JN, Sanchez MI, Decatur CL, Snyder H, Feun LG, Livingstone AS and Harbour JW: Single-cell analysis reveals new evolutionary complexity in uveal melanoma. Nat Commun 11: 496, 2020.
87. Mehnert JM, Varga A, Brose MS, Aggarwal RR, Lin CC, Prawira A, de Braud F, Tamura K, Doi T, Piha-Paul SA, *et al*: Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced, PD-L1-positive papillary or follicular thyroid cancer. BMC Cancer 19: 196, 2019.
88. Bu X, Yao Y and Li X: Immune checkpoint blockade in breast cancer therapy. Adv Exp Med Biol 1026: 383-402, 2017.
89. Kleffel S, Posch C, Barthel SR, Mueller H, Schlapbach C, Guenova E, Elco CP, Lee N, Juneja VR, Zhan Q, *et al*: Melanoma cell-intrinsic PD-1 receptor functions promote tumor growth. Cell 162: 1242-1256, 2015.
90. Ma E, Li J, Shen C, Gu Y, Zhang X, Li L, Zhao J and Wang Z: The m^6A-related gene signature stratifies poor prognosis patients and characterizes immunosuppressive microenvironment in hepatocellular carcinoma. Front Immunol 14: 1227593, 2023.
91. Shi S, Fan Z, Liu Y, Huang C and Zhou J: Integration analysis of m6a related genes in skin cutaneous melanoma and the biological function research of the SPRR1B. Front Oncol 11: 729045, 2021.
92. Wu L, Hu X, Dai H, Chen K and Liu B: Identification of an m6A regulators-mediated prognosis signature for survival prediction and its relevance to immune infiltration in melanoma. Front Cell Dev Biol 9: 718912, 2021.
93. Wu H, Xu H, Jia D, Li T and Xia L: METTL3-induced UCK2 m^6A hypermethylation promotes melanoma cancer cell metastasis via the WNT/β-catenin pathway. Ann Transl Med 9: 1155, 2021.
94. Li N, Kang Y, Wang L, Huff S, Tang R, Hui H, Agrawal K, Gonzalez GM, Wang Y, Patel SP and Rana TM: ALKBH5 regulates anti-PD-1 therapy response by modulating lactate and suppressive immune cell accumulation in tumor microenvironment. Proc Natl Acad Sci USA 117: 20159-20170, 2020.
95. Panneerdoss S, Eedunuri VK, Yadav P, Timilsina S, Rajamanickam S, Viswanadhapalli S, Abdelfattah N, Onyeagucha BC, Cui X, Lai Z, *et al*: Cross-talk among writers, readers, and erasers of m^6A regulates cancer growth and progression. Sci Adv 4: eaar8263, 2018.
96. Mao S, Chen Z, Wu Y, Xiong H and Yuan X: Crosstalk of eight types of RNA modification regulators defines tumor microenvironments, cancer hallmarks, and prognosis of lung adenocarcinoma. J Oncol 2022: 1285632, 2022.
97. Qi L, Zhang W, Ren X, Xu R, Yang Z, Chen R, Tu C and Li Z: Cross-talk of multiple types of RNA modification regulators uncovers the tumor microenvironment and immune infiltrates in soft tissue sarcoma. Front Immunol 13: 921223, 2022.