Roles of m⁶A modification in oral cancer (Review)

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Abstract. Oral cancer is one of the highly malignant tumors with poor prognosis. The pathogenic mechanisms of oral cancer have remained to be fully elucidated and this brings significant challenges to the treatment. RNA modification is a common intracellular chemical modification that has been related to various pathological processes, such as blood diseases, immune system diseases and cancer. As the most common and abundant RNA modification in eukaryotic mRNA, N^6-methyladenosine (m^6A) modification has a crucial role in several cancers, including oral cancer. m^6A modification directly affects gene expression levels and regulates various physiological and pathological processes. It has been demonstrated that m^6A modification may affect the proliferation, migration and invasion of oral cancer cells by regulating the level of m^6A modification. In the present review, the effects of m^6A modification on the proliferation and death of oral cancer cells, as well as the occurrence and development of oral cancer, were analyzed in order to provide a new target for treatment. Furthermore, the roles of m^6A modification in chemotherapy resistance and potential immunotherapy were analyzed and new treatment ideas were provided.

Contents

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Abbreviations: ALKBH5, AlkB homolog 5; BMI1, B-cell-specific Moloney murine leukemia virus integration site 1; BCL2, B cell lymphoma-2; BNIP3, Bcl-2/adenovirus E1B 19kDa interacting protein 3; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CSC, cancer stem cell; DDX3, DEAD-box helicase 3; ERCC1, excision repair cross-complementing group 1; eIF4G1, eukaryotic translation initiation factor 4 gamma 1; EMT, epithelial mesenchymal transition; FTO, fat mass and obesity associated; FGF14, fibroblast growth factor 14; Foxa2, Forkhead box protein A2; GSDMD, Gasdermin D; GBM, glioblastoma; HNRNPA2/B1, heterogeneous nuclear ribonucleoprotein A2/B1; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; IRF3, interferon regulatory factor 3; KLF4, Krüppel-like factor 4; LINE-1, long-interspersed nucleotide element-1; METTL3, methyltransferase-like 3; MMP9, matrix metalloproteinase-9; OSCC, oral squamous cell carcinoma; PKG, protein kinase G; PTEN, phosphatase and tensin homolog; PRMT5, protein arginine methyltransferase 5; PD-L1, programmed cell death 1 ligand; RIG-I, retinoic acid-inducible gene I; SOX2, sex determining region Y-box 2; Smad2, similar to mothers against decapentaplegic homolog 2; SLC7A11, solute carrier family 7 member 11; TBK1, TANK binding kinase 1; TGF-β1, transforming growth factor-β1; WTAP, Wilms' tumor 1-associating protein; YTHDF1, YTH domain family 1; YTHDC1, YTH-domain-containing protein 1; ZC3H13, zinc finger CCCH-type containing 13; ZNF750, zinc finger protein 750; 6PGD, 6-phosphogluconate dehydrogenase

Key words: RNA modified, m^6A autophagy, proliferation, metastasis, oral cancer

1. Introduction

Head and neck cancer is the most common cancer type globally and may include the nasopharynx, larynx, pharynx and oral cavity (1,2). Oral cancer may be categorized into buccal carcinoma, gingival carcinoma, maxillary sinus carcinoma, tongue cancer and carcinoma of the floor of the mouth, 90% of which are squamous cell carcinoma (1,3). According to 2020 statistics, ~177,757 patients died of cancer in these parts within the oral cavity (4). In general, the occurrence and development of oral cancer are related to various factors, including excessive smoking, drinking, betel nut chewing and other external factors, gene mutation, human papillomavirus infection, epigenetic modification and other internal factors (1,5-9). With the in-depth study of epigenetics, RNA modification has been indicated to be involved in various physiological processes, including cell proliferation (10). Furthermore, it is closely associated with the pathological processes of cancer (11).

Human epigenetics include DNA methylation, histone modification and RNA modification, and are closely related to various physiological activities, such as cell transcription and differentiation, and have a critical role in gene expression and regulation (12,13). Certain epigenetic changes are related to oral squamous cell carcinoma (OSCC) (6). RNA modification is a chemical modification in cells that may efficiently and specifically regulate the gene expression and function of biological macromolecules (14). It is suggested that >170 kinds of RNA modifications have been identified (15). The most common RNA modifications include N^6-methyladenosine (m^{6}A), m^{7}G, m^{1}A and m^{5}C, which have different roles in cells (14).

m^{6}A modification is the most common and abundant RNA modification, closely related to various biological functions, and has a vital role in cells (16). m^{6}A is a dynamic and reversible modification process, which mainly includes 'writers', 'erasers' and 'readers'. These components interact with each other to regulate intracellular biological processes (17). m^{6}A has a vital role in various diseases and is closely associated with the occurrence and development of cancer (18). Studies have revealed that m^{6}A modification may affect the pathological processes of cancer through different mechanisms. It may cause abnormal gene expression, leading to the occurrence and development of cancer through oncogenes or tumor suppressor genes (16). Recent studies suggested that m^{6}A modification also has an essential role in oral cancer (19,20). The present review elaborates on the specific role and mechanism of m^{6}A modification during oral cancer.

2. RNA modification and m^{6}A

Human epigenetic mechanisms involve DNA methylation, histone modification and RNA modification. These modifications directly participate in gene expression and regulate biological growth (13). RNA modification is an integral part of the epigenetic mechanism and is closely associated with the normal function of RNAs (21). RNA modifications mainly occur on transfer RNA (tRNA) and non-coding RNA (15). Common RNA modifications include m^{6}A, m^{7}G, m^{1}A and m^{5}C. m^{7}G modification in mRNA may be related to protein translation (22). m^{1}A modification increases the structural stability of tRNA and induces precise tRNA folding (23,24). m^{5}C may affect the translation accuracy of mRNA and regulate tRNA stability (25). m^{6}A modification involves the methylation of the sixth nitrogen atom on the base A of RNA molecules (26). It is the most abundant chemical modification within eukaryotic mRNA modification (27). Meanwhile, m^{6}A modification also exists on long intergenic non-coding RNAs, primary microRNAs and ribosomal RNA (28-30). m^{6}A modification is dynamic and reversible, including the joint action of several catalytic enzymes (27,31). Methyltransferase, demethylase and methylated reading protein are the main components that affect the stability, splicing and translation of mRNA (27,31) (Fig. 1).

m^{6}A methyltransferases (Writers) mainly include methyltransferase-like 3 (METTL3), METTL14 and Wilms' tumor 1-associating protein (WTAP) (32). METTL3 and METTL14 combine with the WTAP regulatory subunit at a 1:1 ratio to form a stable complex. METTL3 has a catalytic role, while METTL14 stabilizes the METTL3-METTL14 complex and determines a specific RNA sequence as the catalytic substrate (32-37). m^{6}A methyltransferase is involved in the development of cancers. Several studies have indicated that METTL3 and METTL14 are closely associated with cancer cell proliferation, the epithelial to mesenchymal transition (EMT) process and autophagy, and are essential genes to regulate intracellular activities (38-43).

m^{6}A methylated reading protein (Readers) may bind to mRNA with m^{6}A methylation and exert different biological functions (16). m^{6}A readers include the family members of YTH domain proteins [YTH domain family 1 (YTHDF1), YTHDF2, YTHDF3, YTH-domain-containing protein 1 (YTHDC1) and YTHDC2], insulin-like growth factor 2 mRNA binding protein (IGF2BP)1, -2 and -3 and heterogeneous ribonucleoprotein (HNRNPC and HNRNPA2B1) (18). Different methylated reading proteins perform different biological functions. YTHDF1 promotes the translation of target mRNA, and YTHDF2 reduces the stability and accelerates mRNA degradation with m^{6}A methylation (44). The majority of m^{6}A sites are enriched in the vicinity of the stop codon and in the 3'UTR (45). However, emerging evidence suggested that heat shock stress led to YTHDF2 specifically bound to mRNA bearing m^{6}A methylation markers at the 5'UTR, which subsequently facilitated protein translation (45). This implies that YTHDF2 is involved in the translation of protein. Furthermore, YTHDF3 cooperates with YTHDF1 and YTHDF2 to mediate the translation or degradation of the target mRNA (44,46). YTHDC1 promotes the m^{6}A methylated mRNA output from the nucleus and YTHDC2 enhances the translational efficiency of the target RNA (16,47). HNRNPA2B1 promotes primary microRNA (miR) processing and mRNA splicing and HNRNPC regulates mRNA splicing (44,48,49). IGF2BP1/2/3 may improve the stability of mRNA (50). When m^{6}A occurs, m^{6}A readers bind specifically to m^{6}A-methylated RNAs to mediate gene expression (44). Studies have identified that different readers have separate roles in cancer. Evidence suggests that YTHDF1 is closely associated with autophagy, proliferation and metastasis (51-53). YTHDF2 is related to autophagy and metastasis, IGF2BP1 is involved in the metastasis process

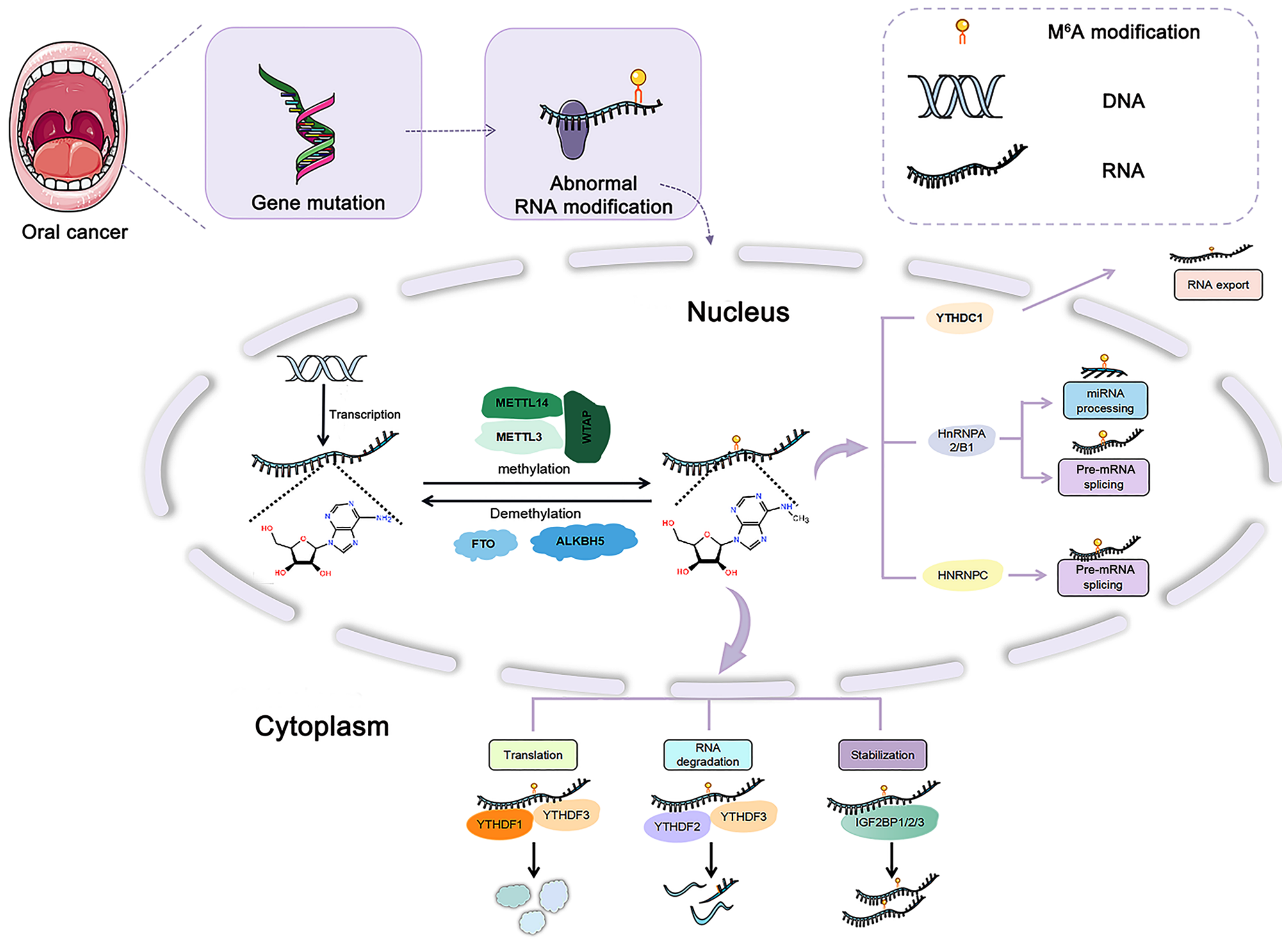

Figure 1. m6A RNA modifying processes in oral cancer. m6A methylation is catalyzed by writers, including METTL3, METTL14 and WTAP. The m6A modification is demethylated by erasers, including FTO and ALKBH5. Reader proteins recognize m6A and act accordingly. m6A, N6-methyladenosine; miRNA, microRNA; pr-mRNA, pre-mRNA; METTL3, methyltransferase-like 3; WTAP, Wilms' tumor 1-associating protein; FTO, fat mass and obesity associated; ALKBH5, AlkB homolog 5; YTHDF1, YTH domain family 1; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; HNRNPA2/B1, heterogeneous nuclear ribonucleoprotein A2/B1.

of cancer cells and IGF2BP2 has a vital role in autophagy and proliferation. HNRNPC and HNRNPA2B1 promotes the EMT process (20,39,41,54-57).

m6A demethylase (Eraser) includes fat mass and obesity associated (FTO) and AlkB homolog 5 (ALKBH5). FTO is the first discovered m6A demethylase and its modification is a dynamically reversible process (58). FTO and ALKBH5 belong to the α-ketoglutarate-dependent dioxygenase family, catalyzing the demethylation of m6A using Fe(II) and α-ketoglutarate (16). First, it oxidizes m6A to N6-hydroxymethyl adenosine (Hm6A), then converts Hm6A to N6-formyl adenosine (F6A) and ultimately converts F6A to adenosine to finalize the m6A demethylation process (16). Studies have indicated that FTO is involved in autophagy, cell proliferation and chemotherapy resistance (59-61). Furthermore, ALKBH5 has been closely associated with chemotherapy resistance (62). The above evidence suggests that almost every component of m6A modification is closely associated with the occurrence and development of cancer with different roles. Furthermore, various m6A components have different roles in oral cancer (20,56,60). Therefore, the present study focuses on m6A modification and its role in oral cancer.

3. m6A and cancer

m6A is one of the most common RNA modifications in eukaryotes and is involved in various biological activities, including the regulation of gene expression levels (63). This indicates that abnormal m6A levels in cells may lead to various diseases. m6A modification governs the whole process of cellular activities of living organisms, particularly in cancer.

Solid tumors. Several studies have indicated that m6A modification is closely related to solid tumor pathology, usually achieved by changing the m6A level to affect gene expression (Table I) (16). A study suggested that m6A modification may interact with long non-coding (lnc)RNAs to regulate the cyclic adenosine monophosphate and cyclic guanosine monophosphate-protein kinase G signaling pathways in gastric cancer (64). A previous report indicated that m6A regulators are involved in regulating the immune microenvironment and are closely associated with the prognosis and immune status of patients with pancreatic cancer (65). A recent study suggested that HNRNPA2B1 and zinc finger CCCH-type containing 13 have an essential role in prostate cancer (66). Highly tumorigenic GBM stem cells present an obstacle to the treatment of glioblastoma (GBM) (67).

Table I. Role of m6A in solid tumors.

Cancer type	m6A component	m6A type	Role	Related genes	Related cellular activity	(Refs.)
Gastric cancer	-	-	-	cAMP and cGMP-PKG signaling pathways	-	(64)
Pancreatic cancer	-	-	-	-	Participation in the regulation of immune microenvironment	(65)
Prostate cancer	HNRNPA2B1	Reader	Oncogene	ZC3H13	Related to the prognosis of patients	(66)
Glioblastoma	METTL3	Writer	Oncogene	SOX2	Promotion of radiation resistance of glioma stem cells	(67)
Cervical squamous cell carcinoma	FTO	Eraser	Oncogene	β-catenin and ERCC1	Enhancement of chemotherapeutic resistance	(69)
Lung cancer	YTHDF2	Reader	Oncogene	6PGD	Promotion of growth	(70)

m6A, N6-methyladenosine; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; METTL3, methyltransferase-like 3; FTO, fat mass and obesity associated; YTHDF1, YTH domain family 1; HNRNPA2/B1, heterogeneous nuclear ribonucleoprotein A2/B1; PKG, protein kinase G; ZC3H13, zinc finger CCCH-type containing 13; ZNF750, zinc finger protein 750; 6PGD, 6-phosphogluconate dehydrogenase; SOX2, Sex determining region Y-box 2; ERCC1, excision repair cross-complementing group 1.

METTL3 promotes the methylation of mRNA and increases sex determining region Y-box 2 (SOX2) protein expression, enabling the maintenance and radiation resistance of the glioma stem cells (67). Cervical squamous cell carcinoma is one of the most common female malignancies with a significantly poor prognosis (68). Increased expression of m6A demethylase FTO was observed in cervical squamous cell carcinoma tissues, m6A levels of β-catenin were downregulated and the expression of β-catenin and excision repair cross-complementing group 1 (ERCC1) were upregulated (69). These abnormally expressed genes enhance chemotherapeutic resistance in patients with cervical squamous cell carcinoma (69). The expression of YTHDF2 is upregulated, which may recognize and bind to the m6A site in the 3'UTR of 6-phosphogluconate dehydrogenase (6PGD) mRNA, promote its protein translation and the growth of lung cancer cells without affecting the expression level of 6PGD mRNA (70). The above evidence indicates that m6A modifications regulate the development of multiple solid tumors.

Head and neck cancer. Nasopharyngeal carcinoma is a kind of malignant tumor of the head and neck (71). Studies have revealed that METTL3 may inhibit the expression of zinc finger protein 750 (ZNF750) and fibroblast growth factor (FGF)14 from promoting the development of nasopharyngeal carcinoma (72). A recent study suggested that ALKBH5 expression was abnormally elevated in cancerous tissues of patients with head and neck squamous cell carcinoma (HNSCC). It inhibited interferon α secretion by downregulating RIG-I expression through the IκB kinase ε/TANK binding kinase 1/interferon regulatory factor 3 signaling pathway, inhibiting immune infiltration and promoting HNSCC progression (73). Another study on HNSCC suggested that IGF2BP2 was overexpressed to promote slug mRNA stability in HNSCC tissues and was significantly associated with lymphatic metastasis and poor prognosis (74). As with solid tumors, m6A modifications affected the progression of HNSCC (Table II).

Oral cancer. Oral cancer is a crucial component of head and neck solid tumors. METTL3 and B-cell-specific Moloney murine leukemia virus integration site 1 (BMI1) expression are upregulated, and when the METTL3 gene is knocked down, BMI1 expression is reduced, and the proliferation, migration and invasion abilities among oral cancer cells become inhibited (54). Further studies have indicated that METTL3 was able to facilitate OSCC development by promoting the m6A methylation of BMI1 (54). Furthermore, the m6A demethylase FTO may regulate the oral cancer cell cycle and promote progression by regulating the expression of Cyclin D1 (75). m6A modifications have multiple roles and may control oral cancer progression (Table II).

Non-solid tumors. Numerous studies have indicated that m6A modification exerts important roles in solid tumors. It also has a crucial role in non-solid tumors (Table III). Compared to normal hematopoietic cells, METTL3 abundance was elevated within leukemic cells (76). Downregulation of METTL3 induced apoptosis in leukemic cells. Further investigation revealed that m6A promotes the translation of c-MYC, B-cell lymphoma-2 and phosphatase and tensin homolog (PTEN) mRNA in human myeloid leukemia MOLM13 cells (76). In addition, HNRNPA2B1 levels were overexpressed in multiple myeloma (MM) patients and negatively correlated with prognosis (77). A subsequent study indicated that HNRNPA2B1

Table II. Role of m^{6}A in head and neck cancer.

Cancer type	m^{6}A component	m^{6}A type	Role	Related gene	Related cellular activity	(Refs.)
Nasopharyngeal carcinoma	METTL3	Writer	Oncogene	ZNF750 and FGF14	Promotion of growth	(72)
HNSCC	ALKBH5	Eraser	Oncogene	RIG-I and IKKε/TBK1/IRF3 signaling pathway	Inhibition of immune infiltration	(73)
HNSCC	IGF2BP2	Reader	Oncogene	Slug	Promotion of migration and invasion	(74)
Oral cancer	METTL3	Writer	Oncogene	BMI1	Promotion of proliferation, migration and invasion	(54)
Oral cancer	FTO	Eraser	Oncogene	Cyclin D1	Promotion of progression	(75)

m^{6}A, N^6-methyladenosine; HNSCC, head and neck squamous cell carcinoma; METTL3, methyltransferase-like 3; FTO, fat mass and obesity associated; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; ALKBH5, AlkB homolog 5; BMI1, B-cell-specific Moloney murine leukemia virus integration site 1; ZNF750, zinc finger protein 750; FGF14, fibroblast growth factor 14; RIG-I, retinoic acid-inducible gene I; IRF3, interferon regulatory factor 3; TBK1, TANK binding kinase 1.

Table III. Roles of m^{6}A in non-solid tumors.

Cancer type	m^{6}A component	m^{6}A type	Role	Related gene	Related cellular activity	(Refs.)
Leukemia	METTL3	Writer	Oncogene	c-MYC, BCL2 and PTEN	Inhibition of apoptosis	(76)
Multiple myeloma	HnRNPA2B1	Reader	Oncogene	AKT3 and ILF3	Promotion of proliferation	(77)
Diffuse large B-cell lymphoma	WTAP	Writer	Oncogene	HK2	Promotion of progression	(78)

m^{6}A, N^6-methyladenosine; METTL3, methyltransferase-like 3; HNRNPA2/B1, heterogeneous nuclear ribonucleoprotein A2/B1; WTAP, Wilms' tumor 1-associating protein; BCL2, B cell lymphoma-2; PTEN, phosphatase and tensin homolog; ILF3, interleukin enhancer-binding factor 3; HK2, the hexokinase 2.

promotes AKT3 expression and MM progression by promoting interleukin enhancer-binding factor 3 mRNA stability through m^{6}A (77). In addition, it was reported that PIWI-interacting RNA 30473 was able to upregulate WTAP, which enhanced the expression of the hexokinase 2 by increasing its m^{6}A level, thus promoting diffuse large B-cell lymphoma progression (78).

4. m^{6}A-mediated cell death in oral cancer

A characteristic of cancer cells is their resistance against cell death. Cell death includes apoptosis, autophagic cell death, ferroptosis, necroptosis and pyroptosis (79,80). Cell death is involved in the progression of multiple malignancies and it is closely associated with m^{6}A modifications (81). Therefore, the interaction between cell death and m^{6}A modification has been elaborated in oral cancer.

Apoptosis. Apoptosis is the programmed death of cells controlled by certain genes to maintain the internal environment stability of cells (82). Cancer features malignant proliferation and less apoptosis (82). Therefore, cancer treatment includes cell proliferation, metastasis and apoptosis as the therapeutic targets. Furthermore, the expression of m^{6}A demethylase FTO is upregulated and significantly inhibits cell apoptosis (83). Further study indicated that Bcl-2/adenovirus E1B 19kDa interacting protein 3 (BNIP3) is the downstream target of FTO-mediated m^{6}A modification. FTO regulates m^{6}A demethylation of BNIP3 and induces its degradation via the YTHDF2-independent mechanism. The inhibition of FTO expression leads to the promotion of BNIP3 expression, increasing apoptosis of breast cancer cells and inhibiting their proliferation (83). In nasopharyngeal carcinoma, inhibition of METTL3 expression promoted ZNF750 expression and then upregulated FGF14 expression, promoting cancer cell apoptosis (72). m^{6}A reader IGF2BP1 in hepatocellular carcinoma is the target gene of miR-196b (84). Furthermore, miR-196b overexpression may inhibit the expression of IGF2BP1 and reduce the expression level of c-Myc. Thus, it promotes apoptosis of hepatocellular carcinoma cells (84). The above evidence indicates that m6A modification may affect the apoptosis of various tumor cells, thus inhibiting tumor progression; it is essential to further clarify the relationship between m6A and apoptosis.

Autophagic cell death. Autophagy is a regular type of physiological activity in eukaryotic cells involving the degradation of organelles, proteins and other substances transferred to lysosomes. It is associated with various diseases, including neurodegenerative, inflammatory and autoimmune conditions, as well as cancer (85,86). Autophagy has a complex role in the development of tumors. It may produce protective autophagy to promote tumor growth and cytotoxic autophagy to inhibit tumor growth (87,88). Furthermore, autophagy influences cell behavior (89,90). Thus, autophagy is closely related to cell death and proliferation (91).

m6A modification affects tumor development of various cancers by interacting with autophagy. Recent studies have identified that m6A demethylase FTO regulates autophagy and tumorigenesis in OSCC (59). FTO expression in OSCC tissue increased and the m6A level of eukaryotic translation initiation factor 4 gamma 1 (eIF4G1) decreased in OSCC. Furthermore, m6A reader YTHDF2 was able to target m6A in eIF4G1 transcripts and mediate mRNA degradation. Therefore, reducing the m6A level of eIF4G1 may upregulate the expression of eIF4G1, inhibit autophagy and promote the migration, invasion and proliferation of oral cancer cells (59). In addition, the METTL14 level in cancer tissues of patients with advanced oral tumors was low and the autophagy level decreased after METTL14 was silenced within oral cancer cells (39). Further exploration revealed that METTL14 downregulated the stability of eIF4G1mRNA using YTHDF2-mediated m6A to promote autophagy and inhibit oral cancer development (39). These studies suggest that inhibition of autophagy may encourage oral cancer development through m6A modification.

Ferroptosis. Ferroptosis is an iron-dependent form of cell death with a potential application in cancer therapy (92). A recent study suggested that m6A modification may be involved in the process of ferroptosis in oral cancer (93). In this report, immunological analyses indicated differential expression of m6A in high-risk and low-risk groups of oral squamous carcinoma patients. Furthermore, a prognostic model based on eight ferroptosis lncRNAs was able to provide a prognostic assessment and immunological analysis for patients with OSCC (93). This indicates that ferroptosis has a critical role in oral cancer progression in which m6A was involved.

Necroptosis. Necroptosis is a newly discovered form of programmed cell death (94). It is characterized by necrotic features, including membrane permeability, cell swelling and release of damage-associated molecular patterns (95). Necroptosis has been observed in the foci of necrosis inside the tissues of patients with HNSCC. Furthermore, the degree of necroptosis may be an independent prognostic marker for overall survival and progression-free survival in patients with HNSCC (96). Therefore, necroptosis is associated with oral cancer. One study suggested that high expression of tumor necrosis factor receptor-associated factor (TRAF)6 was associated with the malignant behavior of oral cancers, such as increased cell proliferation and migration (97). Of note, the overexpression of METTL3 in colorectal cancer may regulate necroptosis by downregulating the expression of TRAF5 (as a family member of TRAFs) to elevate drug resistance (98). This indicates that in oral cancer, m6A modification may potentially have a close regulatory relationship with necroptosis. The association between m6A modification and necroptosis in oral cancer remains elusive and requires continued exploration.

Pyroptosis. Pyroptosis is another form of cell death that is distinct from apoptosis (99). Gasdermin D (GSDMD), a major pyroptosis-related protein, is highly expressed in oral squamous carcinoma tissues and is positively associated with prognosis (100). GSDMD-mediated chemotherapy-induced pyroptosis has a role in the antitumor response (100). By contrast, several lncRNAs associated with pyroptosis were observed in cutaneous melanoma correlating with m6A-related genes (101). This indicates a possible association between pyroptosis and m6A in oral cancer.

5. m6A affects oral cancer by promoting proliferation

Rapid and uncontrolled proliferation is the most basic and essential characteristic of cancer (102). Most abnormal proliferation of cancer cells is associated with the expression changes of a series of genes or activating signal pathways through epigenetic modification (103). In particular, m6A modification is closely related to the proliferation of cancer cells (42). It was indicated that the expression of programmed cell death 1 ligand (PD-L1) is upregulated in patients with OSCC. Furthermore, m6A eraser FTO promotes the expression of PD-L1 by mediating m6A modification and MYC activity and upregulating PD-L1 to promote cell proliferation (19). It is well known that betel nut chewing is a risk factor for oral cancer. Furthermore, arecoline exposure may significantly upregulate FTO, MYC and PD-L1 in OSCC (19). Another study reported that knockdown of transcription factor forkhead box (Fox)a2 was able to negatively regulate FTO expression and promote cell proliferation in OSCC (60). METTL3 is significantly expressed in OSCC and may stimulate solute carrier family 7 member 11 (SLC7A11) expression through m6A-mediated IGF2BP2 binding, thus facilitating OSCC proliferation (20). The study also observed that triptolide may inhibit OSCC progression by inhibiting the METTL3-SLC7A11 axis (20). Furthermore, another study indicated that knocking down the expression of METTL3 impaired the stem cell-like activity in OSCC cells (104). It may reduce the m6A level, downregulate p38 expression and inhibit the cells' proliferation ability (104). METTL3 also enhances the stability of c-Myc through YTHDF1-mediated m6A modification and promotes the occurrence and development of OSCC (105). Previous report observed that METTL3 may enable the expression of protein arginine methyltransferase 5 (PRMT5) and PD-L1, thus facilitating OSCC proliferation (106). METTL3 may also promote OSCC proliferation by promoting m6A methylation of BMI1 (54). To date, the studies on the effect of m6A on cell proliferation involving OSCC were primarily focused on METTL3 and FTO. m6A is able to promote proliferation through various regulatory mechanisms, indicating a complex effect of m6A modification on OSCC.

6. m^{6}A affects metastasis of oral cancer

Most tumors have the characteristics of invasion and metastasis. EMT has a critical role in cancer metastasis. EMT is a cellular process involving cells losing their epithelial characteristics and acquiring mesenchymal characteristics (107). It has several biological functions during the process of tumor metastasis. Its occurrence markers usually refer to the loss of the epithelial marker E-cadherin and upregulation of the interstitial marker Vimentin (107).

In oral cancer, m^{6}A modification affected tumor metastasis by regulating EMT. A report revealed that the m^{6}A level in OSCC was increased, with abnormal expression of m^{6}A-regulated genes (56). Furthermore, the expression of m^{6}A reader protein HNRNPA2B1 is elevated in OSCC may promote EMT occurrence, migration and invasion in OSCC. A mechanistic study suggested that overexpression of HNRNPA2B1 significantly elevated the protein level of long-interspersed nucleotide element-1 (LINE-1), inducing EMT. Targeted EMT through the LINE-1/TGF-β1/Smad2/SLUG signaling pathway may promote the development and metastasis of OSCC. Thus, HNRNPA2B1 may be a potential target for the treatment of OSCC (56). In another study on OSCC, m^{6}A reader protein HNRNPC was indicated to be an independent biomarker (57). The expression levels of m^{6}A and HNRNPC were significantly elevated in OSCC. Overexpression of HNRNPC in SCC-9 and Cal-27 cells markedly stimulated the migration and invasion of OSCC cells. A further study indicated that overexpression of HNRNPC increased the expression of N-cadherin, MMP9 and Vimentin, and inhibited E-cadherin expression. Thus, it triggered EMT to promote metastasis of OSCC (57). In addition, METTL3 was observed to mediate m^{6}A modification of 30 non-coding regions of the BMI1 gene in cooperation with IGF2BP1. It enables the translation of BMI1 and thus facilitates metastasis of OSCC (54). The above evidence indicates that m^{6}A modification affects EMT development in oral cancer and then affects tumor metastasis.

7. m^{6}A promotes chemotherapy resistance of oral cancer

Chemotherapy resistance is a complex problem in OSCC treatment. It is a defensive mechanism of tumor cells to maintain their homeostasis. The inducement of chemotherapy resistance includes gene mutation, gene amplification and epigenetic changes (108). Furthermore, cancer stem cells (CSCs) are also important for drug resistance in tumors (109). Previous studies have revealed that arecoline-treated OSCC cells may upregulate FTO expression and enhance their resistance to cisplatin, a cancer chemotherapy drug. By contrast, the mRNA and protein levels of tumor stem cell pluripotent transcription factors Nanog, SOX2 and Kruppel-like factor 4 (KLF4) are all upregulated (60). However, downregulating the expression level of FTO may increase the sensitivity of OSCC cells toward cisplatin (60). In addition, the expression levels of the pluripotent transcription factors videlicet Nanog, SOX2 and KLF4 in tumor stem cells decreased to varying degrees, rendering FTO a potential therapeutic target for cisplatin resistance in OSCC (60). Another m^{6}A demethylase, ALKBH5, has also been indicated to be closely associated with chemotherapy resistance in OSCC (110). A study has demonstrated that the human RNA helicase DEAD-box helicase 3 (DDX3) expression is upregulated in cisplatin-resistant OSCC cells. When DDX3 expression is downregulated, the CSC marker is also downregulated in chemotherapy-resistant OSCC cells. Furthermore, DDX3 regulates the expression of the CSC transcription factors FoxM1 and Nanog, through ALKBH5, thereby promoting cisplatin resistance in OSCC (110). The emergence of chemotherapy resistance challenges oral cancer treatment, which is closely associated with various mechanisms, including m^{6}A. Elucidating the mechanisms of chemotherapy resistance is of great significance in understanding oral cancer development.

8. Immunomodulatory potential of m^{6}A modification in oral cancer

Immunotherapy has gradually become the focus of the in-depth understanding of tumor immunology. Tumor cells downregulate the expression of antigens on the cell surface and escape immune surveillance through various mechanisms (111). Furthermore, m^{6}A modifications have essential roles during the generation of immune responses (112). A previous study indicated that, depending on m^{6}A regulation-related genes, a prognostic marker may effectively determine the prognosis of HNSCC (113). This prognostic marker was associated with immune cell infiltration in HNSCC (113). A recent study suggested that METTL3 expression was increased in OSCC and inhibited CD8$^+$ T-cell activation (106). Furthermore, METTL3 was indicated to regulate the expression of PRMT5 and PD-L1 through methylation modification, thereby modulating OSCC immunity (106). Another study determined that in OSCC, FTO was involved in the resistance to T-cell lethality by regulating the MYC/PD-L1 signaling pathway (60). Thus, studying immune response and m^{6}A may provide novel therapeutic targets for immunotherapy in oral cancer.

9. Discussion

In-depth epigenetics studies may help reveal the biological mechanisms of cancer and provide new targets for cancer treatment. RNA modification has a critical regulatory role in several cancers as an essential branch of epigenetics. It causes changes in the expression of certain proteins in cells by regulating the expression of various genes, leading to carcinogenesis (16). For instance, METTL3 promotes the maturation of miR221/222 to reduce the expression of PTEN protein to encourage the proliferation of bladder cancer cells (42). In oral cancer, FTO promotes PD-L1 expression to facilitate cell proliferation (19). Furthermore, METTL3 promotes SLC7A11 expression through m^{6}A-mediated IGF2BP2 binding, thereby enabling OSCC proliferation (20). m^{6}A modification is the most common mRNA modification, with substantial research significance (14). m^{6}A includes a variety of modifying enzyme components. m^{6}A writer catalyzes the methylation of m^{6}A on RNA. The recognition of m^{6}A methylation by the reader affects the splicing, output, degradation, translation and other biological processes of mRNA. m^{6}A eraser may remove these modifications, resulting in a dynamic and reversible process (16). In addition, m^{6}A modification affects miRNAs, the processing of miRNAs, and the biological function of

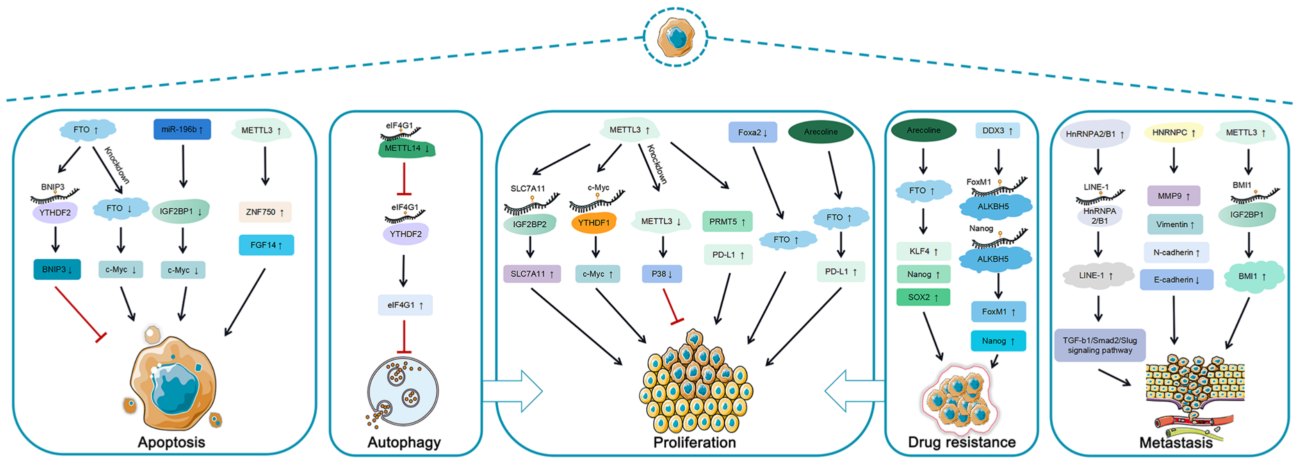

Figure 2. Mechanisms of m6A modification during cancer. Roles of m6A modifications in apoptosis, autophagy, cell proliferation, drug resistance and metastasis. Black arrows represent promotion and red lines represent inhibition. m6A, N6-methyladenosine; miRNA, microRNA; METTL3, methyltransferase-like 3; FTO, fat mass and obesity associated; ALKBH5, AlkB homolog 5; BNIP3, Bcl-2/adenovirus E1B 19kDa interacting protein 3; YTHDF1, YTH domain family 1; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; HNRNPA2/B1, heterogeneous nuclear ribonucleoprotein A2/B1; BMI1, B-cell-specific Moloney murine leukemia virus integration site 1; FGF14, fibroblast growth factor 14; ZNF750, zinc finger protein 750; eIF4G1, eukaryotic translation initiation factor 4 gamma 1; Foxa2, forkhead box protein A2; PD-L1, programmed cell death 1 ligand; SLC7A11, solute carrier family 7 member 11; PRMT5, protein arginine methyltransferase 5; DDX3, DEAD-box helicase 3; KLF4, Krüppel-like factor 4; SOX2, Sex determining region Y-box 2; LINE-1, long-interspersed nucleotide element-1; Smad2, similar to mothers against decapentaplegic homolog 2; TGF-β1, transforming growth factor-β1.

lncRNAs and promotes the translation of circRNAs (16). m6A modification may have a direct or indirect regulatory role in numerous intracellular activities.

The intracellular changes due to m6A modification have complex mechanisms (Fig. 2). For instance, METTL3 may improve the stability of c-Myc through YTHDF1-mediated m6A modification and promote the occurrence and development of OSCC (20). Furthermore, METTL3 may facilitate OSCC proliferation by promoting PRMT5 and PD-L1 expression (106). In addition, m6A-modifying enzymes may affect cancer progression through different cellular activities. METTL3 may promote the proliferation, metastasis and progression of oral cancer (20,54). The components of RNA modification are complex and various RNA modification enzymes have varying regulatory effects on cancer. m6A demethylase FTO may promote the development of oral cancer cells by inhibiting autophagy (59). By contrast, m6A reader protein HNRNPA2B1 may enable the occurrence of EMT and then facilitate the migration and invasion of OSCC cells (56,59). Therefore, m6A modification is involved in various cellular activities in oral cancer and may form a complex network of mechanisms requiring further exploration.

Oral cancer progression is associated with various cancer cell behaviors, such as cell proliferation, migration, invasion and autophagy (114,115). m6A modification may promote oral cancer progression by regulating m6A-related gene expression to influence cell proliferation, metastasis and aggression, and inhibiting autophagy (19,39,56,59,110). In addition, the abnormal expression of m6A may lead to chemotherapy resistance in oral cancer (60). Apoptosis is a crucial cellular behavior among cancer cells (116). Studies have indicated that m6A modification affected the fate of cancer cells by regulating apoptosis (72,83,84). For instance, IGF2BP1, FTO and METTL3 may induce apoptosis (72,83,84). Therefore, m6A modification and m6A-related genes may affect cell behavior in oral cancer. Furthermore, it was observed that certain drugs may target m6A to inhibit oral cancer progression. Oxymatrine reduces the expression of CXC motif chemokine receptor 4 by downregulating METTL3 and m6A modification levels, thus inhibiting the progression of OSCC (117). Triptolide inhibits METTL3-mediated expression of SLC7A11, thereby suppressing the malignancy of OSCC (20). Allocryptopine reduces METTL3 expression and inhibits m6A modification of patched receptor 1 and the proliferation and EMT of OSCC through the m6A-mediated Hedgehog signaling pathway (118). Therefore, m6A may be a potential therapeutic target for oral cancer.

10. Conclusion

In conclusion, m6A modification has an essential role in the physiological and pathological processes of cells. Increasing evidence indicated that m6A modification regulates oral cancer and may affect it through different mechanisms. The functions of m6A modification in oral cancer are diverse. Furthermore, the elucidation of these complex mechanisms may provide novel targets for the treatment of oral cancer.

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Authors' contributions

HL and YW wrote the manuscript. HL, DW, WL, TX, SK, MH, ZY, YG collected the references and prepared figures. All authors reviewed the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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