RNA m6A methylation regulators in endometrial cancer (Review)

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Received May 10, 2022; Accepted October 4, 2022

DOI: 10.3892/ijo.2022.5445

Abstract. As one of the three major malignant tumor types of the female reproductive system, endometrial cancer (EC) is the most prevalent gynecologic cancer in developed countries. In recent years, the incidence of EC has increased worldwide, threatening the health and well-being of women. Recent research has indicated that the expression of multiple N6-methyladenosine (m6A) regulators is up- or downregulated in EC and that abnormalities in m6A methylation and the expression of associated regulators are critical to the pathogenesis and progression of EC. m6A is the most abundant internal modification of mRNA. Several studies have demonstrated a close association between the development and progression of malignant tumors and the epigenetic phenomenon of m6A methylation. In the present study, the current status of research on m6A methylation in EC was reviewed. The mechanisms of methyltransferase, demethylase and m6A binding protein in regulating the development and progression of EC by modifying mRNA were introduced. The related research results will provide novel methods and approaches for the prevention and treatment of EC.

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Key words: endometrial cancer, N6-methyladenosine, regulator, methylation

1. Introduction

Endometrial cancer (EC) is the most prevalent gynecologic cancer in developed countries and its incidence rate has rapidly increased in recent years (1). The most common histological subtype is endometrioid adenocarcinoma originating from the endometrial glands. The mainstay of treatment includes total hysterectomy and bilateral salpingo-oophorectomy, followed by adjuvant treatment according to the final histology and stage (2). Although the prognosis of patients with an early diagnosis of EC is favorable, there are fewer choices and shorter median overall survival (OS) for patients with recurrent or metastatic diseases (3).

N6-methyladenosine (m6A) is the most abundant RNA modification in mammalian mRNA and has a crucial role in the occurrence and development of various diseases, particularly malignant tumors (4,5). As a hot topic in epigenetics, m6A modification is essential for regulating various biological processes, such as splicing, translation and stability of mRNA through related regulators, thus affecting the proliferation, invasion, metastasis and self-renewal of tumor cells (6,7). In recent years, the function of m6A in the pathogenesis and progression of diseases has attracted considerable attention, particularly in the prevention and treatment of malignant tumors. It is anticipated that m6A and the associated regulators will emerge as new therapeutic targets and prognostic indicators (8).

Although the exploration of RNA-based therapy is in its infancy, it has already gained widespread acceptance, as methylated RNA molecules have important roles in regulating almost all aspects of cellular biology and may be specifically identified (9), indicating that therapies based on RNA modifications may be a valuable method in the field of cancer treatment. Recent studies reported that the expression of multiple m6A regulators is up- or downregulated in EC and that m6A methylation and related regulators are critical to the pathogenesis and progression of EC. This review discusses the relationship between m6A methylation modification, related regulators and EC in the hope that the related findings will provide novel avenues and approaches for the prevention, early diagnosis and treatment of EC.

2. EC

ECs are a group of epithelial malignancies that occur in the endometrium, with adenocarcinoma originating from the

endometrial glands being the most common. It is a major malignancy of the female reproductive tract and the most prevalent gynecological cancer in developed countries. In recent years, its incidence has increased worldwide (2,10,11), threatening the health and well-being of women (12).

EC is usually divided into two histological types, with a significant prognostic difference between them. Type I is estrogen-dependent and may occur under continuous estrogen stimulation in the absence of progesterone antagonism, resulting in abnormal proliferation of endometrial epithelial cells (13). Type I EC is frequently associated with obesity, hypertension, diabetes, anovulatory uterine bleeding and long-term use of single estrogen or tamoxifen. Type I EC is histologically classified as well-differentiated to moderately differentiated tumors, with at least 90% of cases expressing moderate to high levels of the estrogen receptor. Type I tumors are characterized by phosphatase and tensin homolog deletion and mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α, KRAS and β-catenin, as well as microsatellite instability (MSI) (14,15). By contrast, type II EC is not related to hyperestrogenemia or endometrial hyperplasia, frequently occurs in nonobese women and is unrelated to metabolic or endocrine disorders. Histologically, type II tumors are poorly differentiated and are most commonly of plasmacytotic, clear cell or carcinosarcoma subtypes. They are clinically aggressive and are related to a more advanced stage at initial presentation and a higher risk of recurrence (16). Type II tumors are not estrogen-related and are usually distinguished by a genetic alteration in p53, HER2/neu, p16 and E-cadherin (14,15).

Recent studies have indicated that despite the dualistic typing of EC, there are a considerable number of cases that exhibit an intersection of molecular characteristics, and not all cases are completely consistent with the pathological characteristics. Therefore, through genome sequencing analysis, EC may instead be divided into four subtypes according to the molecular characteristics: DNA polymerase epsilon (POLE) ultramutated, MSI, copy-number high (CN high) and CN low (17,18). Molecular typing has a high predictive value for the prognosis of EC (19). It has been indicated that 60% of POLE ultramutated EC cases are high-grade endometrioid lesions with favorable prognostic outcomes, while the prognosis of CN-high is the most unfavorable (20-22).

With the continuous growth of the population, the incidence of EC has increased rapidly in the past decade due to the high prevalence of obesity and metabolic syndrome (23,24). Obesity is more closely associated with the progression of EC than any other type of female-specific cancer. The rate of obesity in the population is increasing and more than half of all EC cases are currently attributable to obesity, which is regarded as an independent risk factor for EC (13). This relationship may be largely explained by the prevalence of a high level of estrogen in obese women. Obesity is also related to a high level of insulin. Higher levels of insulin and estrogen are associated with the risk of EC (25,26). However, the pathogenesis of EC remains to be fully elucidated. Therefore, further research on the mechanisms underlying the development of EC remains crucial for the development of scientifically effective preventative and therapeutic measures.

3. m6A

Relatively recently, m6A has become a topic of intense interest in the field of epigenetics. It is of great significance in the development and progression of a diverse range of diseases, particularly malignant tumors (4,5). m6A refers to a specific methylation modification formed by the catalysis of the sixth nitrogen atom (N) on adenine (A) by methyltransferase. The m6A modification sites are primarily distributed close to the termination codon and the 3'-untranslated region (3'UTR) (27). They are widely found in mRNAs and non-coding RNAs (ncRNAs) (28), having important roles in influencing the biological behavior of RNAs. m6A exists in a variety of RNAs but is most abundant in eukaryotic mRNAs (29,30), adding additional complexity to the RNA world. This modification is dynamic and reversible, and it is catalyzed by three main types of regulator: It may be installed by methyltransferases [methyltransferase-like 3 (METTL3), METTL14, Wilms tumor 1-associated protein (WTAP), vir-like m6A methyltransferase-associated protein (VIRMA, also called KIAA1429), RNA binding motif protein 15/15B (RBM15/15B) and zinc finger CCCH domain-containing protein 13 (ZC3H13)], erased by demethylases [fat mass and obesity-associated protein (FTO), AlkB homolog 5 (ALKBH5)] and interacts with RNA-binding proteins such as the YT521-B homology (YTH) domain family, heterogeneous nuclear ribonucleoprotein (HNRNP) protein family and insulin-like growth factor 2 mRNA binding proteins (IGF2BP) family to exert their biological effects. By influencing several phases of an mRNA's life, m6A alterations and associated regulators have critical roles in terms of gene expression (31-33). The regular functions of these regulators are significant and abnormal expression is clearly associated with human cancer (7).

m6A writers. METTL3, METTL14 and WTAP form the m6A methyltransferase core complex, and are also referred to as 'writers'. METTL3 is the catalytic core enzyme of this complex (34). METTL14 is the structural support partner of METTL3 and has a structural role in stabilizing METTL3 and recognizing target RNAs. Together, they form a stable heterodimeric core complex that allows m6A to be deposited on mammalian nuclear RNAs (35,36). WTAP has a crucial role in the localization of METTL3/14 at the nuclear speckles and may interact with this complex to influence this methylation (34,35,37). In addition to the core components, there are several additional regulatory factors involved in the m6A methylation process. For instance, it was discovered that the elements linked to WTAP in mammalian cells include VIRMA (KIAA1429) and HAKAI. VIRMA mediates preferential mRNA methylation in the 3'UTR and close to the termination codon. VIRMA enlists the methyltransferase core complex as its catalytic core member to control region-selective methylation (38). RBM15/15B binds to U-rich sequences preferentially to attract the m6A complex and may encourage the methylation of particular RNAs (39). ZC3H13 is a CCCH zinc finger protein that suppresses the growth of tumors by influencing the Ras-ERK signaling pathway (40). WTAP, VIRMA and HAKAI are anchored in the nucleus by ZC3H13, which regulates m6A methylation and mESC self-renewal (41). The functions of m6A writers are summarized in Table I.

Table I. Functions of m6A 'writers'.

Regulator	Effect on m6A modification	(Refs.)
METTL3	The catalytic core of methyltransferase	(34)
METTL14	Forms a heterodimer with METTL3 and catalyze m6A modification	(35,36)
WTAP	Recruits METTL3 and METTL14 into the nuclear speckles	(37)
KIAA1429 (VIRMA)	Interacts with WTAP and attaches m6A to the 3' UTR	(38)
RBM15/15B	Recruits the methyltransferase complex	(39)
ZC3H13	Promotes the WTAP localization and m6A deposition	(41)

m6A, N6-methyladenosine; METTL3, methyltransferase-like 3; WTAP, Wilms tumor 1-associated protein; VIRMA, also called KIAA1429, vir-like m6A methyltransferase-associated protein; RBM15/15B, RNA binding motif protein 15/15B; ZC3H13, zinc finger CCCH domain-containing protein 13.

Table II. Functions of m6A 'erasers'.

Regulators	Effect on m6A modification	(Refs.)
FTO	Removes m6A modification, regulates pre-mRNA alternative splicing and 3' UTR processing	(43,45)
ALKBH5	Removes m6A modification, regulates RNA metabolism, pre-mRNA processing, mRNA decay and translation	(48)

m6A, N6-methyladenosine; FTO, fat mass and obesity-associated protein; ALKBH5, AlkB homolog 5.

m6A erasers. To date, FTO and ALKBH5 are the only two m6A demethylases that have been reported (42). These 'erasers' are members of the AlkB dioxygenases family and require oxygen, ferrous ion and α-ketoglutarate to function. FTO, the first m6A demethylase, was identified in 2011 as being effective in removing m6A modifications from RNA, indicating that m6A RNA methylation is reversible (43). FTO is localized in the cytoplasm and nucleus with different substrate preferences at these two sites (44). FTO knockdown may increase the level of m6A in mRNA, whereas FTO overexpression may decrease the level of m6A in mRNA. Recent research has revealed that FTO preferentially mediates pre-mRNA alternative splicing and 3'UTR processing (45). Furthermore, FTO is closely related to weight growth and fat in humans (46).

ALKBH5, the second eraser, was subsequently discovered in 2013. ALKBH5 is localized to nuclear speckles and contributes to the assembly of mRNA processing factors that regulate gene expression by affecting RNA metabolism, pre-mRNA processing, mRNA decay and translation (47,48). ALKBH5 deficiency increases m6A levels, whereas ALKBH5 overexpression decreases m6A levels in mRNA. Aberrant expression of either FTO or ALKBH5 affects m6A levels, which then influence certain biological processes in tumor cells through a complex series of mechanisms. The functions of m6A erasers are listed in Table II.

m6A readers. The m6A recognition protein regulates the relevant biological behaviors of mRNA and performs corresponding functions by reading m6A methylation. The YTH family may directly identify m6A methylation and its binding leads to changes in the translation and stability of m6A-modified RNAs. Members of the YTH family include YTHDC1-2 and YTHDF1-3 (49).

YTHDF2 may accelerate the degradation of m6A methylated transcripts by directly recruiting the CCR4-NOT deadenylase complex (50,51). In addition, YTHDF2 may prevent FTO from demethylating the 5'UTR, stabilizing the methylation levels in cells (52). YTHDF1 may facilitate the translation efficiency of m6A-modified transcripts, attaches to the m6A sites near the termination codon and improves the translation of target RNAs by cooperating with the translation initiation mechanism (53,54). YTHDF3 cooperates with YTHDF1 to promote RNA translation, while accelerating mRNA degradation by cooperating with YTHDF2, suggesting a cooperative relationship between YTHDF proteins (55,56). YTHDC1 is widely distributed in the nucleus with multiple regulatory functions. YTHDC1 recruits a variety of splicing factors to promote exon inclusion. YTHDC1 may accelerate the nuclear export of m6A-modified mRNAs (57,58). In addition, YTHDC1 may silence the X chromosome (39), and encourage the degradation of certain transcripts (59). YTHDC2 increases the translation efficiency and decreases the abundance of mRNAs by identifying methylated mRNAs (60).

In addition to the YTH structural domain family, the HNRNP family and IGF2BPs serve as m6A readers and may recognize m6A modifications (49). HNRNPA2B1 promotes the processing of primary microRNAs (miRNAs) in an m6A-dependent manner (61). Furthermore, HNRNPC and HNRNPG influence

Table III. Functions of m6A 'readers'.

Regulators	Effect on m6A modification	(Refs.)
YTH domain family		
YTHDF1	Facilitates the translation of m6A-modified RNA	(53)
YTHDF2	Accelerates the degradation of m6A-modified RNA	(50)
YTHDF3	Facilitates the translation and degradation of m6A-modified RNA	(55,56)
YTHDC1	Regulates the splicing and nuclear export of m6A-modified RNA	(57,58)
YTHDC2	Increases the translation efficiency of m6A-modified RNA	(60)
HNRNP family		
HNRNPA2B1	Promotes the processing of primary miRNA	(61)
HNRNPC and HNRNPG	Regulate the abundance and splicing of m6A-modified RNA	(62,63)
IGF2BP1-3	Promotes the stability of m6A-modified RNA	(64)

m6A, N6-methyladenosine; miRNA, microRNA; YTH, YT521-B homology; YTHDF1, YTH domain family 1; YTHDC1, YTH domain containing 1; HNRNP, heterogeneous nuclear ribonucleoprotein protein; IGF2BP, insulin-like growth factor 2 mRNA binding protein.

mRNA abundance and splicing by dealing with transcripts with the m6A modification. The RNA secondary structure is impacted by m6A, which makes it easier for transcripts to bind to HNRNPC and HNRNPG and modulate mRNA abundance and splicing (62,63). IGF2BPs are conserved m6A-binding proteins that enhance the stability of their target mRNAs and improve translation efficiency in an m6A-dependent manner, impacting gene regulation and cancer biology (64). The functions of m6A readers are summarized in Table III.

4. M6A and EC

According to reports, m6A methylation may mediate post-transcriptional gene expression in EC by regulating functional gene components, particularly gene promoters and the 3'UTR. Further research revealed that highly methylated genes were associated with insulin resistance (IR), while genes with low levels of methylation were notably enriched in extracellular matrix (ECM) tissues and adhesive plaques (65). Therefore, m6A methylation regulates EC progression by focusing on IR and ECM-related genes.

A growing number of studies suggested that m6A regulatory factors are associated with tumors, which may function as oncogenes or tumor suppressor genes to participate in the proliferation, invasion and metastasis of tumor cells (31,66). It was determined that the expression of multiple m6A regulators was up- or downregulated in EC, and that m6A methylation and the expression of the related regulators are critical to the pathogenesis and progression of EC.

In addition, multiple signaling pathways are actively functioning in EC cells, including the MAPK signaling pathway (67,68) and the PI3K/AKT/mTOR signaling pathway (69,70). Research has demonstrated that altering the degree of m6A modification may influence the activity of these signaling pathways and the downstream targets, thereby stimulating the proliferation and invasion of EC cells.

These signaling pathways are involved in numerous physiological and pathological activities. Future studies should thus focus on controlling the activity of these signaling pathways by m6A methylation, as aberrant activation of these pathways may be a significant oncogenic driver of human malignancies. m6A methylation is involved in various biological processes in EC by affecting RNA metabolism and participating in the regulation of RNA expression, translation and decay (71).

The following is a summary of the primary contributions of certain significant m6A regulators in the occurrence and progression of EC (Fig. 1).

METTL3 in EC. The multiple functions, mechanisms and abnormal regulation of METTL3 are associated with a wide range of human tumors. METTL3 is related to a variety of processes in neoplasm progression, including proliferation, aggressiveness, metastasis and drug resistance (72). These outcomes are mediated by stem cell self-renewal, miRNA processing via DGCR8, EMT, apoptosis, the PI3K/AKT pathway and recruitment of eIF3h. Most potential mechanisms involve multiple m6A-dependent signaling pathways, including the PI3K/AKT pathway. METTL3 knockout resulted in a decrease in m6A and thus facilitated the proliferation and invasive ability of tumor cells by activating the PI3K-AKT signaling pathway. METTL3 has different roles in different types of cancers (73). In most cancer tissues, METTL3 is found to be upregulated and carcinogenic, such as lung cancer (74), leukemia (75,76), gastric cancer (77,78) and ovarian cancer (79). By contrast, METTL3 is downregulated in renal cell carcinoma where it acts as a tumor suppressor (80).

Even in the same type of cancer, certain studies have indicated mutually contradictory outcomes. For instance, METTL3 is highly upregulated and associated with unfavorable prognosis in bladder cancer (81,82). On the contrary, other studies revealed that the absence of METTL3 notably stimulated the growth of bladder cancer cells and acted as a tumor suppressor gene in the disease (83). Likewise, Cai *et al* (84) found that METTL3, as an oncogene, was upregulated in breast cancer. Instead, Wu *et al* (85) reported that METTL3, as a tumor suppressor, was downregulated in breast cancer.

According to Liu *et al* (86), loss of function mutations in METTL14 or decreased METTL3 expression may underlie

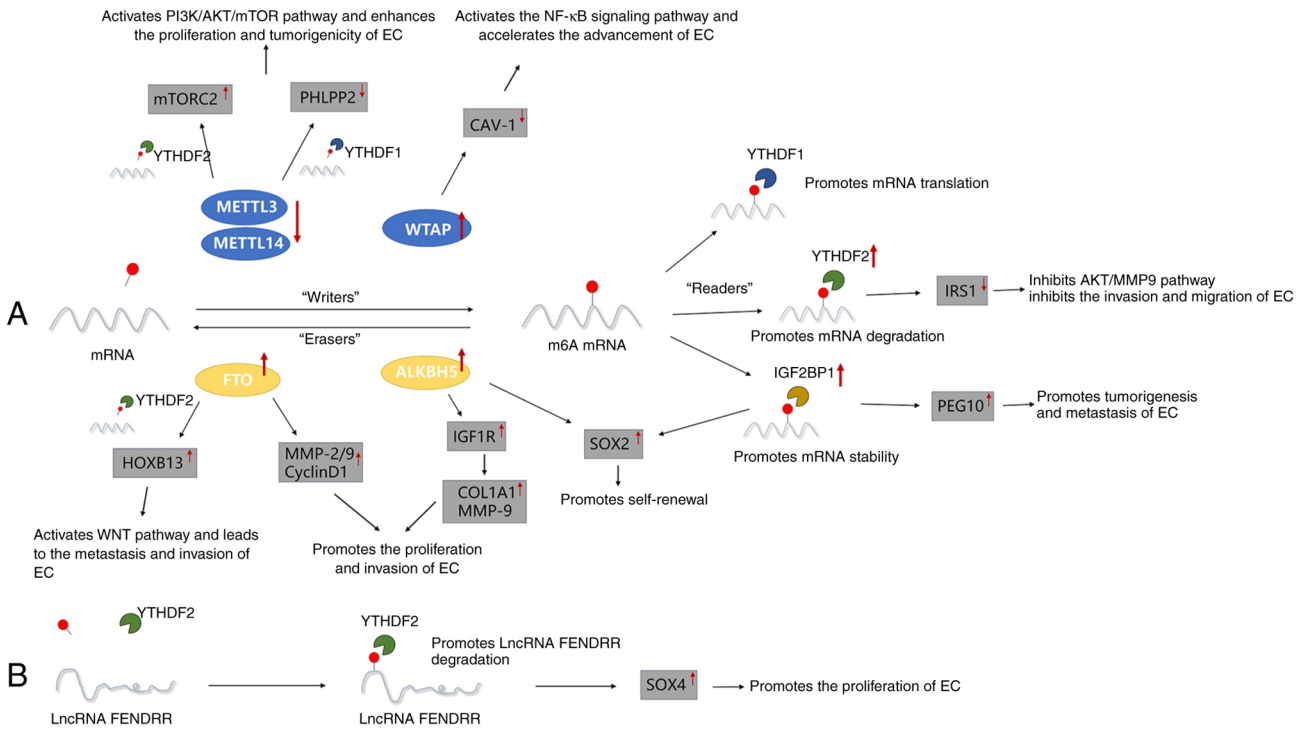

Figure 1. Major roles of different m6A regulators in the occurrence and development of EC. (A) m6A methylation regulators METTL3/14, WTAP, FTO, ALKBH5, YTHDF1/2 and IGF2BP1 promote or inhibit the proliferation, invasion, metastasis and self-renewal of EC by regulating the m6A-related pathway. (B) m6A methylation regulator YTHDF2 promotes the proliferation of EC by downregulating the expression of lncRNA-FENDRR. EC, endometrial cancer; METTL3/14, methyltransferase-like 3/14; mTORC2, mammalian target of rapamycin complex 2; PHLPP2, pleckstrin homology domain and leucine-rich repeat protein phosphatase 2; WTAP, Wilms' tumor 1-associated protein; CAV1, caveolin-1; FTO, fat mass and obesity-associated protein; ALKBH5, AlkB homolog 5; HOXB13, homeobox B13; MMP-2/9, matrix metalloproteinases-2/9; IGF1R, insulin-like growth factor 1 receptor; COL1A1, collagen type I alpha 1; SOX2, sex-determining region Y-box 2; YTHDF1/2, YT521-B homology domain family 1/2; IRS1, insulin receptor substrate 1; IGF2BP1, IGF2 mRNA-binding protein 1; PEG10, paternally expressed gene 10; lncRNA, long non-coding RNA; SOX4, SRY-related HMG box transcription factor 4; m6A, N6-methyladenosine.

the fact that m6A methylation levels in ~70% of EC were much lower than those in normal endometrial tissues.

The levels of m6A modifications were reduced due to the decreased expression of METTL3 and METTL14, which increased the proliferation and tumorigenicity of EC. According to further research, a reduction in the levels of m6A methylation may boost cell growth by regulating vital enzymes in the AKT signaling pathway. Dysfunctional AKT signaling may lead to cancer, IR, type-2 diabetes, autoimmune diseases and cardiovascular disease, as well as inflammatory and neurological disorders (87,88). The genomic investigation demonstrated that the PI3K/AKT/mTOR signaling pathway, essential for cell metabolism, growth and survival (89), is typically upregulated in EC (69).

In terms of the mechanism, the major AKT Ser473 kinase is the mTORC2. AKT lacking Ser473 phosphorylation is active but the activity is markedly reduced, and phosphorylation of Ser473 stabilizes both Thr308 phosphorylation and the activation state of AKT. The decrease in m6A methylation levels may prevent the decay of the mRNA encoding the mTORC2 complex, which is promoted by YTHDF2, increasing the expression of mTORC2. mTORC2 is a positive regulator of AKT activation and promotes AKT activation by phosphorylating the serine residue at position 473 (69,87,89). On the contrary, m6A methylation reduction reduces PHLPP2 translation promoted by YTHDF1. PHLPP2 is a negative regulatory factor in AKT activation and inhibits the AKT signaling pathway through dephosphorylation of a serine residue at position 473. Since the loss of PHLPP activity leads to the hyperphosphorylation of AKT, it stands to reason that the expression of PHLPP1/2 is reduced or lost in several types of cancer (87).

Therefore, the decrease of m6A mRNA methylation will affect a variety of AKT pathway components and promote the proliferation and tumorigenicity of tumor cells by activating the AKT signaling pathway. The possible mechanism is presented in Fig. 2. On the contrary, the enhanced proliferation brought about by a reduction in m6A methylation was reversed by inhibiting AKT activation.

In conclusion, the reduction in m6A methylation may be an oncogenic mechanism in EC and the PI3K/AKT/mTOR pathway may serve as a therapeutic target, suggesting that altering the activity of AKT through an m6A-dependent approach may provide novel approaches for the treatment of malignancies (86).

However, according to Ralser *et al* (90), the expression levels of METTL3 were increased, which had prognostic significance and was connected to the short OS of patients with EC. They speculated that increased METTL3 expression may result in lower sensitivity to platinum-based chemotherapy, which is the first-line chemotherapeutic regimen for advanced EC.

As the main catalytic enzyme in m6A methylation, METTL3 functions via a complex mechanism and involves

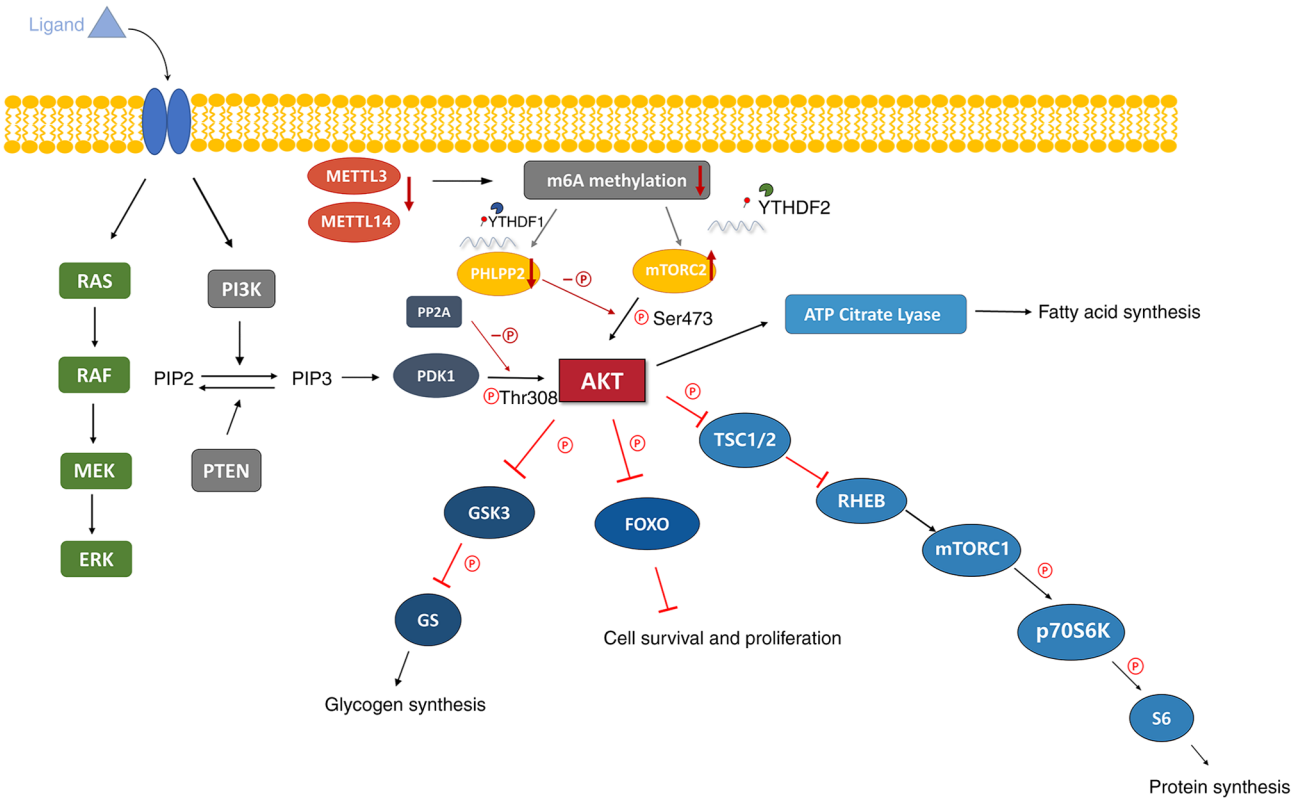

Figure 2. The levels of m6A modifications were reduced due to the decreased expression of METTL3 and METTL14, which influenced the expression of PHLPP2 and mTORC2 through YTHDF1/2, activating AKT signaling pathway to promote the proliferation and tumorigenicity of tumor cells. PI3K/AKT signaling pathway. AKT is a serine and threonine kinase, which leads to the phosphorylation of serine and threonine residues on target proteins. The growth factor binds to its ligands and activates RTK or GPCR on the cell membrane, so as to activate PI3K. The activated PI3K phosphorylates PIP2 and converts it into PIP3, which increases the level of PIP3, activates PDK1 and activates AKT. i) AKT phosphorylates GSK3, which is an inhibitor of glycogen synthesis, and inhibits its activity, resulting in the activation of GS and increasing glycogen synthesis. ii) AKT inhibits FOXO, which inhibits cell survival and proliferation, thereby increasing cell survival and proliferation. iii) AKT phosphorylates TSC1/2 and inhibits its negative regulation of RHEB, which is an activator of mTORC1, thereby activating mTORC1, resulting in the activation of P70S6K and S6 and promoting protein synthesis. iv) AKT activates ATP citrate lyase and promotes fatty acid synthesis. RTK, receptor tyrosine kinase; GPCR, G protein coupled receptors; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol (3-5)-triphosphate; PDK1, 3-phosphoinositide-dependent kinase 1; GSK3, glycogen synthase kinase 3; FOXO, forkhead box O; TSC1/2, Tuberous Sclerosis Complex 1/2; RHEB, Ras homologue enriched in brain; mTORC1/2, mammalian target of rapamycin complex 1/2; P70S6K, protein 70 S6 kinase; METTL3/14, methyltransferase-like 3/14; YTHDF1/2, YT521-B homology domain family 1/2; PHLPP2, pleckstrin homology domain and leucine-rich repeat protein phosphatase 2; PP2A, protein phosphatase 2 A.

a variety of signaling pathways. The exact mechanisms in cancer remain to be completely elucidated and require further research.

WTAP in EC. WTAP is a nuclear protein that functions as a mammalian splicing factor. An increasing body of knowledge has indicated that WTAP, as an oncogene, is closely related to different malignancies. For instance, WTAP is substantially expressed in high-grade serous ovarian cancer (HGSOC), where it is significantly correlated with lymph node metastasis and a poor prognostic outcome. It is a prognostic marker of HGSOC and regulates the progression of ovarian cancer cells (91). In diffuse large B-cell lymphoma tissues, WTAP is continuously upregulated, promoting cell growth and counteracting apoptosis, and WTAP was able to form a complex with BCL6 via Hsp90 (92). WTAP physically binds to the 3'UTR of CDK2 transcripts and increases the stability of those transcripts and is significantly overexpressed and serves as an oncogene in renal cell cancer (93). WTAP is overexpressed in hepatocellular carcinoma and is closely associated with poor prognosis (94). In gastric cancer, WTAP enhances the stability of HK2 mRNA and promotes the Warburg effect and tumor cell proliferation (95).

However, it remains to be fully elucidated how WTAP may affect EC. Li *et al* (96) studied the expression levels of WTAP in cancer tissues and para-cancerous tissues from a patient with EC. They observed that WTAP was markedly overexpressed in cancer tissues and associated with poor prognosis. *In vivo* and *in vitro*, cell proliferation, invasion and migration were enhanced, and EC apoptosis was reduced, indicating a higher degree of malignancy and unfavorable survival outcomes. Cell invasion and migration may be significantly decreased by WTAP knockdown. When WTAP was knocked out, the expression of CAV-1, a possible WTAP target, was increased and the enrichment of m6A and METTL3 in its 3'UTR was lowered. In addition, CAV1 prevented activation of the NF-κB signaling pathway. In conclusion, WTAP may methylate the 3'UTR of CAV-1 and inhibit its expression in order to activate the NF-κB signaling pathway, thus accelerating the advancement of EC.

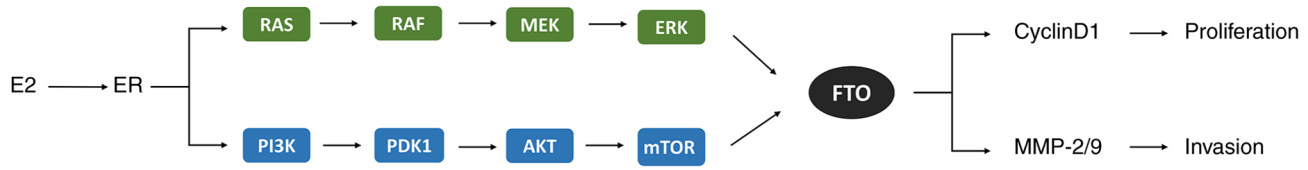

Figure 3. E2 induces FTO overexpression by binding to the ER and activating the PI3K/AKT and MAPK signaling pathways to reduce m6A methylation and upregulate MMP-2, MMP-9 and cyclin D1 molecules, promoting the proliferation and invasion in endometrial cancer cells. E2, estradiol; ER, estrogen receptor; MAPK, mitogen-activated protein kinase; RAS, a small GTP-binding protein; RAF, MAP kinase kinase kinase (MAPKKK); MEK, MAP kinase kinase (MAPKK); ERK, extracellular signal-regulated kinase (MAPK); PI3K, phosphoinositide 3-kinase; PDK1, 3-phosphoinositide-dependent kinase 1; mTOR, mammalian target of rapamycin complex; FTO, fat mass and obesity-associated protein; MMP-2/9, matrix metalloproteinases-2/9.

FTO in EC. Previous reports have indicated that FTO is abundantly expressed in various human malignancies (97) and increases cancer cell metabolism, thus leading to tumorigenesis and chemotherapeutic resistance (98). The elevated expression of FTO in bladder tumor tissue and its association with a poorer prognosis highlights the potential of FTO in the diagnosis and/or prognosis of this disease (99). FTO is involved in maintaining self-renewal and immune evasion of cancer stem cells. FTO is overexpressed in leukemia and FTO inhibition renders leukemia cells susceptible to T-cell cytotoxicity and thus overcome immune escape (100), indicating that FTO is a prospective therapeutic target.

There has been a constant rise in both the incidence and mortality of EC. This trend is largely the result of the worldwide obesity epidemic. Obesity is more strongly associated with the progression of EC than any other group of female cancers (13). Despite the fact that the connection between obesity and EC has been confirmed by numerous studies, the molecular mechanisms underlying this association have not been fully elucidated.

FTO is overexpressed in EC and serves as an indicator of poor prognosis (101). Recently, it was reported that FTO removes m6A modification from HOXB13 mRNA, prevents YTHDF2-mediated HOXB13 from being degraded, enhances its expression, and accelerates the metastasis and invasion of EC (102), which are significant biological processes that contribute to poor prognosis (103). Mechanistically, HOXB13 is a homeobox transcription factor whose expression is increased in EC, leading to an increase in invasive capacity. It is possible that HOXB13 contributes to the promotion of tumor metastasis during the course of tumor development. FTO may catalyze the demethylation of the HOXB13 mRNA 3' UTR region, which inhibits the recognition of m6A modifications by YTHDF2, preventing the degradation of HOXB13 mRNA, increasing its expression and thereby activating the WNT signaling pathway, and thus promoting EC invasion and metastasis.

In addition, growing evidence suggests a connection between long-term estrogen exposure and the development of type I EC. Estrogen is still regarded as a significant factor in abnormal hyperplasia and tumorigenesis, as in the absence of progesterone antagonism, constant estrogen stimulation results in abnormal hyperplasia of endometrial epithelial cells (104).

Zhang *et al* (101) discovered that estradiol may induce FTO expression and upregulate MMP-2, MMP-9 and cyclin D1 expression by binding to estrogen receptors (ER) and activating the PI3K/AKT and MAPK signaling pathways, promoting the proliferation and invasion of EC cells.

Zhu *et al* (105) further determined that estrogen may promote FTO protein nuclear localization and promote proliferation through the mTOR signaling pathway in EC cells. The possible mechanism is presented in Fig. 3.

ALKBH5 in EC. ALKBH5, another RNA demethylase, is involved in the pathological processes of several types of cancer. In glioblastoma stem-like cells (GSCs), ALKBH5 expression is upregulated, which in turn increases FOXM1 expression, maintaining the tumorigenicity of GSCs and being indicative of poor prognosis (106). Similarly, under intermittent hypoxia, ALKBH5 downregulated m6A modification, increased FOXM1 expression and promoted the proliferation and invasion of lung adenocarcinoma cells (107). ALKBH5 promotes tumorigenesis and self-renewal of tumor stem cells in acute myeloid leukemia (AML) and its increased expression is also associated with poor prognostic outcomes in AML (108). In addition, ALKBH5 has been reported as a target of HIF-1α (109). Hypoxia induces ALKBH5 expression in breast cancer cells. HIF-dependent ALKBH5 stabilizes NANOG mRNA by removing m6A methylation and induces a breast cancer stem cell phenotype (110). By contrast, ALKBH5 levels were low in most pancreatic cancer (PC) samples. Deletion of ALKBH5 is a feature of the occurrence and adverse clinicopathological findings of patients with PC. ALKBH5 activates PER1 through m6A demethylation in a YTHDF2-dependent manner, thereby inhibiting tumor proliferation and invasion and preventing PC progression (111). In conclusion, ALKBH5 exerts differential effects in different tumor types through complex mechanisms. ALKBH5 is significantly upregulated in EC. Pu *et al* (112) found that downregulation ALKBH5 inhibited the growth and invasive ability of EC cells and IGF1R expression regulation is a crucial intermediate mechanism of these ALKBH5-mediated alterations in endometrial cell invasion. Mechanistically, ALKBH5 primarily regulates the demethylation of IGF1R, thereby stabilizing IGF1R mRNA and promoting its translation, and activating the IGF1R signaling pathway, which in turn stimulated the production of COL1A1 and MMP9 and promoted the proliferation and invasion of EC, indicating that it is a potential target for the treatment of EC.

Furthermore, alterations to IGF1 expression and signaling are crucial for regulating normal uterine physiology (112). Elevated levels of IGF1 and hyperinsulinemia are involved in the pathogenesis of EC. Endometrial hyperplasia is

associated with increased insulin and IGF1 receptor expression, which increases the susceptibility of these cells to insulin and IGF1 and promotes the hyperactivity of MAPK and PI3K/AKT/mTOR signaling frequently observed in EC (13).

Chen *et al* (113) indicated that ALKBH5 promoted SOX2 transcription through HIF-dependent m6A demethylation, maintaining the EC stem cell (ECSC) status and tumor characteristics. ECSCs are stem cell-like cells with the ability to differentiate and self-renew, which are essential for the progression of EC. Under hypoxic conditions, the levels of ALKBH5 are significantly increased in ECSCs, which decreases m6A levels and promotes SOX2 expression. SOX2 is a core stem cell transcription factor and mediates the early steps of tumorigenesis. In summary, these studies suggest that the HIF-ALKBH5-SOX2 axis mediated by m6A methylation has a crucial function in the process of ECSC expansion under hypoxic conditions. ALKBH5, as a promising therapeutic target, highlights novel avenues for the clinical treatment of malignant tumors.

YTHDF2 in EC. YTHDF2 is an m6A reader protein that accelerates the degradation of m6A-modified transcripts (50). Several tumors have been indicated to abnormally express YTHDF2, including ovarian cancer (114,115), cervical cancer (116), gastric carcinoma (117) and hepatocellular carcinoma (118).

YTHDF2 was significantly upregulated in EC. According to Hong *et al* (119), YTHDF2 knockdown markedly accelerated endometrial cell proliferation, migration and invasion. Conversely, overexpression of YTHDF2 exerted a significant inhibitory role, indicating that YTHDF2 may inhibit the activity of EC cells. Furthermore, they confirmed that knockdown of YTHDF2 increased MMP9 expression. In subsequent studies, based on m6A-seq data, it was indicated that insulin receptor substrate 1 (IRS1) had m6A methylation modifications in EC. By immunoprecipitation, the presence of m6A sites on the IRS1 transcript was confirmed and it was indicated that YTHDF2 inhibited the activity of EC cells likely through inhibition of MMP9 expression in an IRS1-dependent manner.

IRSs, including IRS1 and IRS2, have a central role in the insulin signaling cascade by linking insulin and IGF1R to PI3K/AKT activation (120). According to reports, IRS1 is critical for cancer cell hyperplasia and mediates drug resistance, while IRS2 primarily affects the motility and metastasis of cancer cells (121). IRS1 and IRS2 phosphorylation attracts downstream factors to activate the MAPK and PI3K cascades (122).

Mechanistically, YTHDF2 promotes the degradation of IRS1 mRNA, thereby inhibiting its expression, leading to the inhibition of the AKT/MMP9 signaling pathway, ultimately inhibiting the activity of EC cells (119). When YTHDF2 was knocked down, IRS1 expression was increased and the AKT signaling pathway was activated. These results indicate that YTHDF2 may be a tumor suppressor.

Conversely, Shen *et al* (123) found that the degradation of long ncRNA (lncRNA) FENDRR mediated by YTHDF2 stimulated cell proliferation in EC. NcRNAs are associated with m6A modification, thereby affecting gene expression and the development of cancer (124). LncRNA FENDRR is a well-known tumor suppressor gene in several malignancies, including breast cancer (125), colon cancer (126) and prostate cancer (127). Dysregulation of lncRNA FENDDR is closely associated with the development of several types of cancer, including EC. Recently, lncRNA FENDRR was identified as an aberrantly expressed molecule in ERα-related EC (68), although the mechanisms of action remain elusive.

According to Shen *et al* (123), EC tissues had higher levels of m6A methylation of the lncRNA FENDRR, whilst exhibiting lower levels of lncRNA FENDRR expression. *In vitro* and *in vivo* experiments indicated that YTHDF2 recognized the m6A-modified lncRNA FENDRR and promoted its degradation. Overexpression of lncRNA FENDRR inhibited the proliferation and promoted the apoptosis of the EC cells by decreasing SOX4 protein levels.

In conclusion, the higher levels of m6A modification of lncRNA FENDRR in EC tissues promote the degradation of lncRNA FENDRR, reducing its expression by recruiting YTHDF2. Subsequently, SOX4 protein accumulates, which promotes the proliferation of EC cells. These findings suggest that YTHDF2 may be an oncogene.

In addition, atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia (EAH/EIN) has a higher risk of developing into endometrioid adenocarcinoma (EMAC) than endometrial hyperplasia without atypia (EHWA) and is considered a precancerous lesion of EMAC.

According to Bian *et al* (128), YTHDF2 was weakly expressed in the normal endometrium and EHWA, whilst being upregulated in EAH/EIN and EMAC, indicating that YTHDF2 may be a valuable marker for differentiating between EAH/EIN and EHWA, which makes earlier clinical detection and intervention of these precancerous lesions possible.

IGF2BP1 in EC. IGF2BPs, including IGF2BP1/2/3, are a distinct group of m6A readers that are able to identify m6A modifications (64). IGF2BPs influence gene regulation and cancer biology by enhancing the stability and storage of their target mRNAs. IGF2BP1 is a conserved oncogenic driver with significantly upregulated expression in various types of cancer (129,130).

It was discovered that IGF2BP1 has a critical part in the regulation of EC through the recognition of m6A-modified PEG10 mRNA. IGF2BP1 mRNA expression was significantly higher in EC tissues than in normal tissues and it was associated with unfavorable prognosis, tumor grade and stage (131). IGF2BP1 regulates the tumor cell cycle and tumor growth and is able to stimulate or inhibit cell proliferation when it is upregulated or knocked down, respectively.

Zhang *et al* (132) indicated that IGF2BP1 is able to recognize and interact with PEG10 mRNA and promote PEG10 mRNA stability and expression. The stability of PEG10 mRNA and protein expression were both markedly decreased when IGF2BP1 was silenced. They further indicated that PABPC1 functions in this mechanism in a synergistic manner. PABPC1 is a typical poly-A binding protein that is able to bind to and stabilize mRNA, preventing the mRNA tail from being cut off by nucleases (133). PEG10 is suspected to be an oncogene that has a role in tumor cell proliferation, apoptosis and metastasis (134). Previous research suggested that PEG10 is overexpressed in several diseases, including liver cancer, pancreatic cancer and bladder cancer (135-137).

According to research by Zhang *et al* (132), PEG10 was upregulated in EC and was directly associated with the survival rate. Mechanistically, IGF2BP1 recognizes the m6A modification of the 3'UTR of PEG10 mRNA and recruits PABPC1 to synergistically stabilize PEG10 mRNA to promote its protein expression and proliferation of EC cells. Furthermore, a significant portion of the PEG10 protein binds to the p16 and p18 promoter regions, limiting RNA and protein expression and increasing cell cycle progression.

According to Xue *et al* (67), MEK1 citrullination caused by PADI2 activates ERK1/2 and helps IGF2BP1 to stabilize SOX2 mRNA in EC. In fact, several different malignancies have been reported to exhibit upregulation of PADIs compared with the respective healthy tissues (138). PADI2 converts arginine to citrulline; its expression is positively associated with the development of EC and it is required for proliferation, migration and invasion.

Mechanistically, PADI2 interacts with and catalyzes MEK1 citrullination, which activates ERK1/2, thereby increasing the expression of IGF2BP1. IGF2BP1 enhances the stability of SOX2 mRNA. There is an enrichment of three nonredundant m6A sites (GGACH) around the 3'UTR of the SOX2 gene and m6A modification on these three sites stabilizes SOX2 mRNA and increases its protein expression. IGF2BP1 binds to these three m6A sites to maintain the stability of the transcripts and prevent SOX2 mRNA degradation. Aberrant expression of IGF2BP1 mediated by PADI2/MEK1/ERK signaling leads to the accumulation of SOX2, supporting the malignant state of EC. Thus, patients with EC may benefit from a therapeutic strategy that targets the PADI2/MEK1/ERK/IGF2BP1 axis (67).

Other m6A regulators in EC. The prognosis of EC is tightly associated with changes in the m6A regulator, whose alterations may serve as a valid and trustworthy marker for EC prognosis (139,140). According to research by Ma *et al* (131), the expression of ZC3H13, YTHDC1 and METTL14 in EC tissues was significantly decreased, which were thus considered potential diagnostic and prognostic biomarkers for EC. The expression of ZC3H13, YTHDC1 and METTL14 in EC tissues is positively correlated with PD-L1 expression; PD-L1 interacts with PD-1 to suppress anti-tumor immunity, while blocking PD-L1/PD-1 interaction significantly enhances the anti-tumor immune response (141), indicating that blocking these proteins may enhance the effects of immunotherapy.

According to Zhai *et al* (142), RBM15/15B, YTHDF1 and IGF2BP1/2 are upregulated in endometrial adenocarcinoma. By contrast, FTO, KIAA1429, METTL14, ZC3H13 and YTHDC1 expression was downregulated. In their study, decreased FTO expression in tumors conflicted with previous findings; they speculated that this discrepancy may be related to the pathological type of EC used in their study. RBM15, FTO and YTHDF1 were identified as prognostic biomarkers in EC that may be involved in cell cycle regulation, affect RNA processing and translation, and contribute to tumor-associated processes and prognosis of endometrial adenocarcinoma. However, the exact mechanisms of these regulators have remained to be fully elucidated and further study is required.

5. Conclusions and future perspectives

At present, the primary treatment of EC comprises surgery, radiation and chemotherapy. These conventional treatment methods may result in trauma for patients and the adverse reactions of radiotherapy and chemotherapy are well documented, which seriously affect the quality of a patient's life.

As a hot topic in epigenetics, m6A modifications have attracted considerable attention, providing us with novel ideas and methods for the treatment of EC. A total of three types of regulators carry out the dynamic reversible m6A modification process: Methyltransferases (referred to as writers), demethylases (referred to as erasers) and m6A binding proteins (referred to as readers). Through these regulators, splicing, translation, stability and the decay of mRNAs are regulated. Oncogenes and tumor suppressor genes are regulated by m6A modifications, which have an impact on the occurrence and development of malignancies. At the same time, m6A modification may affect its role in cancer by regulating the levels of m6A modifications and the expression of regulators. Therefore, m6A regulators are anticipated to become potential targets for cancer therapy. Recent research has indicated that the expression of multiple m6A regulators is either up- or downregulated in EC, and m6A methylation, as well as related regulators, are critical in the development and progression of EC.

Despite the fact that m6A modifications were initially identified in the 1970s (143), its function was not investigated in detail until ~2012. The development of high-throughput sequencing technologies has made it easier than ever to study RNA modifications (144) and has provided a necessary basis for elucidating the unique molecular characteristics of transcriptomes on m6A (145). Future studies using m6A-seq and MeRIP will help to deeper analyze m6A regulators in EC. By determining the genetic risk prognosis model to forecast the rate of survival of patients with EC, certain m6A regulatory factors may be employed as promising markers to predict clinical outcomes of cancer patients and offer a theoretical foundation or target for the treatment of EC.

The present review summarized the primary functions of the significant m6A regulators in EC, with the aim of providing novel methods and approaches for the diagnosis or prognosis of EC. To date, certain small chemical molecule inhibitors that target m6A regulators have demonstrated considerable promise for preventing the growth of cancer (7). For instance, R-2-hydroxyglutarate (R-2HG) reduces FTO activity and raises m6A levels in R-2HG-sensitive leukemia cells, further reducing the stability of MYC/CEBPA transcripts and finally inhibiting the activity of leukemia cells, promoting cell cycle arrest and apoptosis, and exerting anti-leukemic effects (146). Carbonic anhydrase IV interacts with WTAP and promotes WTAP protein degradation, facilitates the transcriptional activity of WT1, an inhibitor of the WNT pathway, and inhibits the occurrence and development of colon cancer (147). In general, m6A regulator-specific inhibitors offer a potentially valuable alternative approach for cancer treatment.

The research on m6A in EC is still in its early stages and there are numerous up- and downstream m6A regulators whose precise mechanisms remain elusive and require to be investigated. In addition, the changes in the levels of certain

m6A regulators were demonstrated to be closely related to the prognosis of EC and different types of EC with different molecular characteristics also have different prognoses. We speculate whether there are any differences in m6A RNA methylation levels, the expression of regulatory factors, and related mechanisms in different molecular types of EC. At present, the research on RNA m6A methylation in different molecular types of EC is still insufficient. It is hypothesized that m6A regulators will serve as valuable targets for cancer therapy and offer novel approaches for treating malignancies. However, the clinical application of m6A-based cancer treatment requires a considerable amount of research before these treatments may be used in the clinic.

Acknowledgements

Not applicable.

Funding

This work was supported by a special research fund for gynecological oncology 'Le Foundation' (grant no. KH-2021-LZJJ-001).

Availability of data and materials

Not applicable.

Authors' contributions

JT and JG designed the study. SS selected/searched the literature and drafted the manuscript. NL and QC revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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