Role of N^6-methyladenosine in the pathogenesis, diagnosis and treatment of prostate cancer (Review)

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Abstract. Prostate cancer (PCa) affects males of all racial and ethnic groups, and leads to higher rates of mortality in those belonging to a lower socioeconomic status due to the late detection of the disease. PCa affects middle-aged males between the ages of 45 and 60 years, and is the highest cause of cancer-associated mortality in Western countries. As the most abundant and common mRNA modification in higher eukaryotes, N^6-methyladenosine (m^6A) is widely distributed in mammalian cells and influences various aspects of mRNA metabolism. Recent studies have found that abnormal expression levels of various m^6A regulators significantly affect the development and progression of various types of cancer, including PCa. The present review discusses the influence of m^6A regulatory factors on the pathogenesis and progression of PCa through mRNA modification based on the current state of research on m^6A methylation modification in PCa. It is considered that the treatment of PCa with micro-molecular drugs that target the epigenetics of the m^6A regulator to correct abnormal m^6A modifications is a direction for future research into current diagnostic and therapeutic approaches for PCa.

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1. Introduction

PCa is the leading non-cutaneous malignant tumors in males in China (1). PCa is the most common type of cancer affecting males (20%) and accounts for 6.8% of male cancer-related deaths worldwide. According to statistics, in 2020, the number of new cases of PCa reached 1.41 million and caused 375,000 deaths. The number of new cases and deaths from PCa is expected to nearly double by the year 2040 (2). In 2019, the number of cases of PCa in China reached 150,000 and there were 54,000 related deaths (3). In recent years, technological progress and the development of new methods have largely led to an increased understanding of the underlying molecular mechanisms that promote tumor growth and progression (4). The advent of current drug and therapy combinations has enriched the treatment options for PCa, providing more treatment options for patients with PCa (5). However, there are certain challenges for clinical practitioners. The early stages of PCa often present with subtle or asymptomatic manifestations, which may be easily overlooked. The emergence of PARP inhibitors has brought the diagnosis and treatment of PCa into an era of precision, and has individualized treatment possible based on the results of genetic testing, which is the future trend of treatment development (6). The combination of an AKT (PI3K signaling gene) inhibitor and abiraterone has been shown to improve radiological progression-free survival in patients with metastatic castration-resistant PCa (mCRPC) and tumor suppressor gene PTEN deletion (7). Cyclin-dependent kinases 4 and 6 (CDK4/6) are activated during the G1-S checkpoint of the cell, which promotes cancer cell proliferation. A

phase III study [CYCLONE-03 (NCT05288166)], which is a phase III, randomized, double-blind, placebo-controlled study, using either abemaciclib (a selective CDK4/6 inhibitor) or a placebo, plus abiraterone and prednisone is investigating the treatment of high-risk metastatic hormone-sensitive PCa (8).

Currently, the main treatment strategies for patients with PCa are surgery, endocrine therapy, radiotherapy, chemotherapy, cryotherapy and immunotherapy. Some patients are often diagnosed with advanced-stage or metastatic PCa due to a lack of clear early clinical signs and awareness of PCa screening. Even if PCa is treated promptly at an early stage, it continues to progress and subsequently evolves into CRPC (9).

N^6-methyladenosine (m^{6}A) methylation, a modification of RNA molecules, was first discovered in 1974 (10). It is mainly distributed around stop codons, 3'UTRs, and long internal exons, and occurs mainly in RRACH sequences (where R=A or G, H=A, C, or U) (11). M^{6}A is the most abundant modification of higher eukaryotic messenger RNAs(mRNAs), including methyltransferases, demethylases, and m^{6}A-binding proteins, which play essential roles in the various biological functions of RNA (12). In addition to mRNAs, m^{6}A methylation modifications are present on different non-coding RNAs. Modification by methylation of m^{6}A is a dynamic reversible modification similar to DNA and histones. It is involved in the whole life cycle of RNA translation, processing, and degradation (13). The association between m^{6}A methylation modification and tumorigenesis and development has gradually received attention in recent years; however, m^{6}A methylation modification and PCa have not been extensively studied.

Recent research has demonstrated that m^{6}A methylation modification, which plays a crucial role in the tumor development process, and related genes influenced by it, may be key targets for cancer diagnosis and treatment (14). It has been suggested that m^{6}A and its associated regulators can become novel prognostic indicators and novel therapeutic targets in clinical practice (15). The present review focuses on the role of m^{6}A regulators in the progression of PCa and discusses new directions for future research on m^{6}A therapy.

2. PCa

PCa stems from the epithelial tissue of the prostate and is a disease that mainly affects middle-aged and older males (16). The main feature of PCa is the abnormal division of prostate cells, leading toabnormal prostate cell hyperplasia (17). PCa is the most common non-cutaneous cancer with an estimated 1,600,000 cases and 366,000 related deaths annually (18). According to a study published in 2022, PCa has become the third most common and fifth most lethal type of cancer among the diagnosed cases of cancer in the USA (19). In China, the incidence of PCa in the population has been increasing each year due to improvements in living conditions in recent years (19).

According to the fifth edition of the World Health Organization classification of urological and male reproductive system tumors, PCa can be divided into the following: Prostate ductal adenocarcinoma, neuroendocrine PCa and adenoid cystic carcinoma (20). Ductal adenocarcinoma does not occur alone and is frequently intermingled with acinar adenocarcinoma. Both are typically driven by aberrations in speckle type BTB/POZ protein, forkhead box (FOX)A1 and other molecules, and have similar androgen receptor (AR) expression levels (20). The studies by Lotan *et al* (21), Gillard *et al* (22) and Schweizer *et al* (23) have demonstrated that ERG fusion rearrangements and molecular abnormalities are more common in ductal adenocarcinoma than in ductal carcinoma, as well as mutations in the WNT signaling pathway genes, catenin beta-1 and adenomatous polyposis coli. PIN-like carcinomas, characterized by large discrete glands lined with flattened or tufted epithelium, and a high frequency of activation mutations in the RAF/RAS pathway, were reclassified as acinar subtypes. It has been found that transdifferentiation in PIN-like carcinomas is associated with the deletion of TP53, RB1 and PTEN, and epigenetic alterations in a specific genomic environment. Neuroendocrine adenocarcinoma has the histological and immunohistochemical features of simple small-cell or, less commonly, large-cell neuroendocrine carcinoma, which has a mixture of tumors with high-grade components. p53 immunohistochemical staining is often positive in neuroendocrine carcinoma, while prostate-specific antigen (PSA) and prostate acid phosphatase are usually lost. Adenoid cystic (basal cell) carcinoma histologically presents as an adenoid cystic pattern with hyaline globules (inspissated secretion); a basal pattern comprising small solid nests of basal cells; or a mixture of both. Fluorescence *in situ* hybridization reveals the fusion of the MYB-NFIB gene in more adenoid cystic carcinoma (20). The study by Epstein *et al* (24) demonstrated that intraductal carcinoma of the prostate was caused by carcinogenesis of the prostate gland and ductal epithelium and/or intraductal spread of aggressive PCa. Microcystic adenocarcinoma is a benign variant of acinar PCa, which is easily confused with benign atrophied glandular cystic changes. Pleomorphic giant cell adenocarcinoma is a rare type of PCa, which is a giant cell with pleomorphic and relatively homogeneous nuclei. In addition, a rare new variant of neuroendocrine tumor, termed NE PCa, is not dissimilar to that of large cell neuroendocrine carcinoma of other organs in a way of morphology (25). A new classification method for PCa is emerging that relies mainly on molecular markers of different PCa subtypes for fine classification, which helps to personalize the description of PCa rather than relying solely on morphological information (26,27).

Currently, there is no uniform standard for prognostic markers for PCa. Novel biomarkers improve risk stratification for PCa diagnosis and treatment (28). A previous study found that RNA-binding protein was one of the meaningful biomarkers of PCa. The high expression of small nuclear ribonucleoprotein polypeptide A' in RNA-binding proteins in PCa tissue was positively associated with the Gleason score and pathological TNM stage, which is critical for determining the prognosis of patients with PCa (29). The expression patterns of endosomal genes are also interesting in a new indicator for predicting PCa prognosis. The expression of adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1), Ras-related protein Rab-5A (RAB5A), early endosome antigen 1 (EEA1), programmed cell death 6-interacting protein (PDCD6IP), nicotinamide adenine dinucleotide oxidase 4 (NOX4) and sortilin 1 (SORT1) in malignant prostate tissue differs from that in benign or normal prostate tissue (30). Serum total testosterone and 25-hydroxyvitamin D have been reported to predict the prognosis of patients with

PCa (31,32). However, the study by Holt *et al* (31) did not find sufficient evidence that prostate cancer prognosis is affected by serum vitamin D levels measured following diagnosis. Izumi *et al* (32) demonstrated that both low and high serum TT levels indicated a poor prognosis of patients with PCa.

At present, the clinical indicators for the diagnosis of PCa are a PSA value ≥4 ng/ml and a positive digital rectal test (33). A previous study found that in patients undergoing a radical prostatectomy, a higher body mass index (BMI) was associated with a higher prostate weight and PSA, as well as higher pT staging and pathological Gleason score (34). A higher percentage of fatty tissue around the prostate has been shown to be significantly associated with a higher Gleason score (35). BMI constitutes another risk factor in addition to PSA. Moreover, in individuals with abdominal obesity, the larger the waist circumference, the greater the linear association between the risk of developing PCa and BMI (36). However, some scholars argue that the role of BMI is unclear and that there is a lack of valid evidence to support BMI as a risk factor for males with PCa (37). However, PCa involves a variety of risk factors and complex mechanisms that require further research.

3. M^{6}A

Recently, the epigenetics of m^{6}A modification has attracted increasing attention from scholars. M^{6}A modification directly affects the expression levels of genes that regulate a variety of physiological and pathological processes in the body, and ultimately affect the occurrence and development of tumors (38). It has been found that m^{6}A RNA methylation modification causes cancer cells to metabolize and reorganize by altering molecules and pathways associated with tumor metabolism, meeting the growth needs of cancer cells, and maintaining the balance of the surrounding tissue environment. The m^{6}A modification not only participates in all phases of the RNA cycle but also modulates non-coding RNA (39). Similar to DNA or protein methylation, m^{6}A methylation modification is dynamically and reversible regulated by different types of regulators, among which the molecules that play a biological role, mainly include methyltransferases (writers), demethylases (erasers) and m^{6}A-binding proteins (readers) (40,41). Among these, writers are mainly methyltransferase complexes composed of methyltransferase-like (METTL)3, METTL14 and their cofactor, Wilm's tumor 1-associated protein (WTAP), accompanied by other necessary proteins, which play the role of methylation modification. The demethylation function of erasers works mainly through fat mass and obesity-associated protein (FTO) and alpha-ketoglutarate-dependent dioxygenase homolog (ALKBH)5. In addition, some unknown members of the ALKB subfamily may contain m^{6}A demethylase function (42). M^{6}A functions mainly by recruiting m^{6}A-binding proteins, of which the readers are effector proteins, the most well-known of which are the YTH N^6-methyladenosine RNA binding protein (YTHDF) family and the insulin-like growth factor 2 mRNA binding protein (IGF2BP) family without the Yth domain (43,44). It has been shown that the various regulatory factors involved in the modification of m^{6}A are closely related to the occurrence and development of cancer, and play an essential role in this process (38) (Fig. 1).

M^{6}A writers. M^{6}A refers to the methylation modification of the sixth nitrogen atom of adenine (45). As an epigenetic marker that acts primarily on RNA, m^{6}A methylation modification relies on the m^{6}A methyl-conversion enzyme. It has been demonstrated that m^{6}A methyltransferases consist of a catalytic subunit m^{6}A-METTL complex and a regulatory subunit m^{6}A-METTL associated complex, also known as a 'writer' (46). The m^{6}A methyltransferase complex consists of two protein substances, METTL3 and METTL14, and contains WTAP, KIAA1429 (Virilizer), Hakai, RNA binding motif protein 15 (RBM15), METTL16 and additional co-regulatory subunits (45,47). The METTL3-METTL14 complex exhibits more potent *in vitro* methyltransferase activity than any single protein. Thus, METTL3 and METTL14 are the core components of the m^{6}A writer complex. Although METTL14 lacks the catalytic activity of methyltransferase and is a pseudo methyltransferase in the complex, it plays an integral role in maintaining the activity of the writer complex. METTL14 plays an essential role in maintaining the structural integrity of the binary complex of METTL3-METTL14 complex to improve the catalytic activity of the m^{6}A writer complex. Recombinant METTL3 monomers exhibit weak methyltransferase catalytic activity. METTL3 exhibits a significant increase in methyltransferase catalytic activity when METTL3 and METTL14 with methyltransferase domains form heterodimeric complexes (48). WTAP has a unique localization role in recruiting METTL3 and METTL14 into the nuclear spot. In addition, WTAP participates in the m^{6}A methylation modification process as part of the m^{6}A methyltransferase complex, along with METTL3, METTL14, and other methyltransferases (49). RBM15, as a member of a family of adapter proteins that contain RNA binding motifs, primarily recruits m^{6}A methylated RNA into U-rich regions (50). Vir like m^{6}A methyltransferase associated (Virma), also known as KIAA1429, recruits the WTAP-METTL3-METTL14 complex by binding to WTAP. Alternatively, Virma may interact with plant cleavage factors linked to m^{6}A methylation and polyadenylation mechanisms, participating in mRNA processing (51). METTL5 is an 18srRNA m^{6}A methyltransferase that acquires metabolic stability by forming parallel β zippers between the backbone atoms and heterodimers with the tRNA methyltransferase homolog 112. METTL16 can directly methylate mRNA containing the UAC m^{6}A GAGAA motif (52). Zinc refers to the CCCH domain-containing protein 13 (ZC3H13) and E3 ubiquitin-protein ligase Hakai, which interacts with the methyltransferase complex to affect the RNA methylation process (48) (Table I).

M^{6}A erasers. Thus far, only two types of m^{6}A demethylase have been identified: FTO and ALKBH5. FTO, also known as ALKBH9, belongs to the non-heme KGFe(II)/α-KG-dependent family of dioxygenase ALKB (ABH1-9) and is the m^{6}A demethylase of the first eukaryotic mRNA enzyme. The role of FTO in adipogenesis and tumorigenesis is related to its m^{6}A demethylase activity. It can also interact with melanocortin receptor 4 (MC4R) through m^{6}A modification to control the proliferation, migration, and the invasion of PCa cells (53).

FTO has been reported to play a key role as a demethylase in a various types of cancer. FTO is responsible for the dynamic modification of m^{6}A and mediates m^{6}A and the

Table I. Functions of m^{6}A 'writers'.

Regulator	Effect on m^{6}A modification	Role	(Refs.)
METTL3	Methyltransferase activity	Activator	(45,47,48)
METTL14	Maintain the structural integrity of binary complexes	Activator	(48)
WTAP	METTL3 and METTL14 are recruited into nuclear spots and involved in m^{6}A methylation	Activator	(49)
Virma/KIAA1429	Recruitment of WTAP-METTL3-METTL14 complex and participate in mRNA processing	Activator	(51)
RBM15	m^{6}A methyl bodies are recruited into U-rich regions	Activator	(50)
ZC3H13	Interacts with methyltransferase complex components and affects methylation pathways	Activator	(48)
METTL5	18S rRNA m^{6}A methyltransferase	Activator	(52)
METTL16	Methylation of specific sequences of mRNA	Activator	(52)

m^{6}A, N^6-methyladenosine; METTL, methyltransferase-like; WTAP, Wilm's tumor 1-associated protein; Virma, Vir like m^{6}A methyltransferase associated; ZC3H13, Zinc finger CCCH domain-containing protein 13; RBM15, RNA binding motif protein 15.

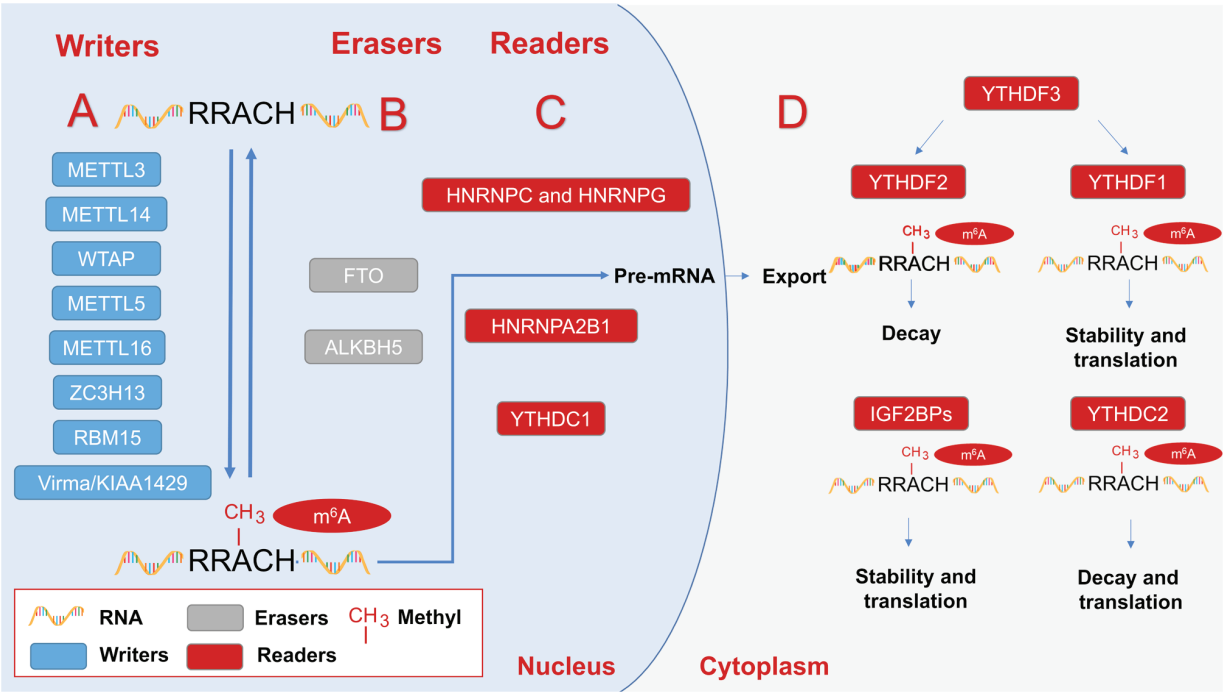

Figure 1. Regulators involved in m^{6}A modification and play an influential role in regulating the occurrence and development of prostate cancer. (A) Methyltransferases mainly include METTL3, METTL14, WTAP, METTL5, METTL15, ZC3H13, RBM15, Virma/KIAA1429, etc., which play the role of RNA m^{6}A methylation modification. (B) Demethylase mainly includes FTO and ALKBH5, which plays the role of removing m^{6}A methylation modification. (C) The m^{6}A binding proteins in the nucleus mainly include YTHDC1, HNRNPA2B1, HNRNPC and HNRNPG, which can recognize the methylation modification of m^{6}A. (D) The cytoplasmic m^{6}A binding proteins mainly include YTHDF1-3, IGF2BPs and YTHDC2, which can recognize the methylation modification of m^{6}A. Writers, erasers, and readers work together to form the reversible modification of m^{6}A. Readers can be divided into readers (YTHDC1, HNRNPA2B1, HNRNPC, and HNRNPG) in the nucleus and readers (YTHDF1-3, IGF2BPs, YTHDC2) in the cytoplasm according to the different intracellular localization. Readers within the nucleus are mainly involved in the splicing of precursor mRNA and the delivery of RNA from the nucleus into the cytoplasm. The role of readers in the cytoplasm is not the same. IGF2BPs play a role in improving the stability of m^{6}A methylation modification mRNA and promoting m^{6}A methylation modification mRNA translation. YTHDC2 plays a role in promoting the decay and translation of m^{6}A methylation-modified mRNA. YTHDF3 can play a role in promoting the decay and translation processes of m^{6}A methylation-modified mRNA, respectively, by affecting YTHDF1 and YTHDF2. METTL, methyltransferase-like; WTAP, Wilm's tumor 1-associated protein; ZC3H13, Zinc finger CCCH domain-containing protein 13; RBM15, RNA binding motif protein 15; Virma, Vir like m^{6}A methyltransferase associated; m^{6}A, N^6-methyladenosine; FTO, fat mass and obesity-associated protein; ALKBH, alpha-ketoglutarate-dependent dioxygenase homolog; YTHD, YTH N^6-methyladenosine RNA binding protein; IGF2BP, insulin-like growth factor 2 mRNA binding protein; HNRNP, heterogeneous nuclear ribonucleoprotein protein.

N6,2-O-dimethyladenosine (m^{6}Am) demethylation of poly(A) RNA. The demethylation of m^{6}A is first mediated when FTO is in the nucleus, and demethylation of m^{6}A and m^{6}Am is first mediated when FTO is in the cytoplasm. FTO demethylase

Table II. Functions of m^{6}A 'erasers'.

Regulator	Effect on m^{6}A modification	Role	(Refs.)
FTO	Remove m^{6}A modifications and promote RNA decay	Inhibitor	(53-55)
ALKBH5	Remove m^{6}A modifications	Inhibitor	(56-58)

m^{6}A, N^6-methyladenosine; FTO, fat mass and obesity-associated protein; ALKBH, alpha-ketoglutarate-dependent dioxygenase homolog.

promotes abnormal m^{6}A modification in PCa. This suggests that FTO has a tumor-suppressing effect in PCa (54). In addition, FTO depletion first significantly increases the m^{6}A levels of chloride intracellular channel protein 4 (CLIC4) mRNA, and subsequently inhibits PCa proliferation and transfer by reducing mRNA stability and promoting CLIC4 mRNA degradation (55).

ALKBH5, by removing m^{6}A methylation, leads to the erasure of m^{6}A methylation modifications, returning m^{6}A to its previously unregulated state. Of note, seven m^{6}A-associated crosstalk genes, including ALKBH5, are differently expressed in PCa and periodontitis. These genes have significantly increased expression levels in several signaling pathways, including nuclear plasticity transport, ubiquitin-mediated protein breakdown, p53 signal transduction, cellular senescence, and transcriptional regulation disorders (56). The expression of the ALKBH5 gene with abnormal copy number changes is strongly associated with the prognosis of PCa (57). This suggests that the pattern of ALKBH5 copy number variation is significantly associated with relapse-free survival in PCa (56). Furthermore, it has been found that FTO and ALKBH5 are negatively associated with the Gleason grade and are less well expressed in PCa (58). The abnormal expression of FTO or ALKBH5 primarily affects m^{6}A levels, which then, through complex biological mechanisms, affect certain biological processes of tumorigenesis and development (Table II).

M^{6}A readers. M^{6}A methylation modifications perform their corresponding biological functions with the involvement of the writer and eraser and with the recognition of m^{6}A modifications by m^{6}A recognition proteins. IYT521-B homologous (YTH) family proteins were the first m^{6}A reader proteins to be discovered. It was found that m^{6}A readers are primarily involved in the occurrence and development of cancer by regulating the metabolism of targeted RNA, including RNA splicing, output, translation and degradation, which result in changes in the biological function of RNA. At present, a total of five proteins containing the YTH domain in the human genome have been found and divided into three types of m^{6}A reader proteins: YTH m^{6}A-binding protein 1-3 (YTHDF1-3), YTH domain 1 (YTHDC1) and YTH domain 2 (YTHDC2) (59).

The degradation of mRNA and tje translation of YTH family members, with different reader proteins, play their respective roles through different pathways. YTHDF1 may recruit argonaute 2 protein and miRNA via the YTH domain and interact to form P-body (mRNA degradation centers in yeast cells and animal cells, also known as cytoplasmic bodies, Dcp bodies, or GW bodies) to degrade mRNA. Moreover, YTHDF1 facilitates the translation of m^{6}A-modified mRNA (10,60). In addition, YTHDF1 recognizes m^{6}A-modified target genes through multiple mechanisms. Thus, YTHDF1 improves the stability of RNA and thus promotes expression (61). YTHDF2 relies primarily on m^{6}A modifications to regulate signaling pathways in cancer cells. YTHDF2 promotes the degradation of targeted mRNA transcripts by recruiting the CCR4-NOT deadenylase complex. YTHDF2 can also promote tumor cell proliferation by binding to tumor suppressors, triggering a downstream cascade that can do the opposite by interacting with oncogenes (62). YTHDF2 also affects various aspects of RNA metabolism, including mRNA degradation and ribosome pre-RNA processing (10). The YTHDF family protein DF1-3 is the dominant cytosolic m^{6}A-binding protein and is considered to mediate the action of m^{6}A in cells. All three DF proteins contribute to the destabilization of mRNA and together, mediate the degradation of mRNAs containing m^{6}A (63). YTHDF3 functions synergistically with YTHDF1 to promote protein synthesis and mediates the decay of methylated mRNA by affecting YTHDF2. YTHDF1-3 cooperates and plays a crucial role in facilitating the metabolism of m^{6}A-modified mRNA in the cytoplasm (64). YTHDC1 is also the only m^{6}A reader in the YTH protein family that is localized in the nucleus. YTHDC1 is a protein that interacts with splicing factors that regulate RNA splicing. Its m^{6}A-dependent functions include selective polyadenylation and the nuclear production of m^{6}A-modified mRNAs, which control the maturation of intranuclear mRNA. Recent research has demonstrated that there is a close association between chromatin-associated RNAs, non-coding RNAs, and regulatory RNAs, which can control the expression of genes within cells (65). It has been shown that YTHDC1 plays a crucial role in cellular functions, such as cancer cell proliferation. YTHDC1 may also have the potential to promote the efficacy of tumor immunotherapy (66). YTHDC2 plays its biological role in using its distinct RNA binding domain to bind to targeted m^{6}A RNA and bridge between ribosomes, which reduces the abundance of related mRNAs and increases the translation efficiency of related mRNAs (67,68).

The reader protein includes not only the YTH structural protein family, but also the heterogeneous nuclear ribonucleoprotein protein (HNRNP) family and IGF2BP1, IGF2BP2, and IGF2BP3. The HNRNP family and IGF2BP1-3 together recognize m^{6}A-modified fragments in RNA (69). HNRNPC is regulated as an m^{6}A switch, which affects the abundance and selective splicing of target RNAs by altering their binding activity. HNRNPC can also facilitate the conversion of fresh heteronuclear RNAs into mature mRNAs, and can stabilize the structure of mRNAs and control their translation process (70). The RGG motif of HNRNPG directly binds to the phosphorylated carboxyl terminal domain of RNA

Table III. Functions of m^{6}A 'readers'.

Regulator	Effect on m^{6}A modification	(Refs.)
YTH domain family		
YTHDF1	Promotes mRNA degradation and translation	(10,60,61,63)
YTHDF2	Degrades mRNA and affects RNA metabolism	(10,62,63)
YTHDF3	Mediated methylated mRNA decay	(63,64)
YTHDC1	Regulates splicing factors for RNA splicing and controls intranuclear mRNA maturation	(65,66)
YTHDC2	Facilitate mRNA translation	(67,68)
HNRNP family		
HNRNPC and HNRNPG	Promote the maturation of nuclear RNAs and stabilize the structure of mRNAs and control their translation process	(69,70,71)
HNRNPA2B1	Recruitment of microprocessor complexes to facilitate primary microRNA processing	(72)
IGF2BP1-3	Promotes stability, storage, and translation of mRNA targets and causes cancer	(73,74)

m^{6}A, N^6-methyladenosine; YTHD, YTH N^6-methyladenosine RNA binding protein; IGF2BP, insulin-like growth factor 2 mRNA binding protein; HNRNP, heterogeneous nuclear ribonucleoprotein protein.

polymerase II (RNAPII). The interaction between the phosphorylated carboxyl terminal domain and the new RNA leads to the co-transcription of HNRNPG and RNAPII. Finally, selective splicing of new RNA (71). HNRNPA2B1 specifically recognizes and directly binds with elevated affinity to RNAs that share the m^{6}A-modified RNAs containing the m^{6}A co-sequence RGm^{6}ACH. M^{6}A can boost the binding capability of HNRNPA2B1 to certain sites, which enhances its nuclear event capability. In addition, HNRNPA2B1 recruits the microprocessor complexes, Drosha and DGCR8, to facilitate primary miRNA processing by binding m^{6}A to primary miRNA transcripts (72). IGF2BPs first identify m^{6}A-modified mRNA and improve the stability of the mRNA target which facilitates storage, translation, and gene expression output. IGF2BPs may exert oncogenic effects on cancer cells by enhancing the stability of methylated mRNAs of oncogenic targets (73,74) (Table III).

M^{6}A induces specific drug resistance. Recent research has demonstrated that chemotherapeutic resistance in cancer is associated with m^{6}A RNA methylation, which leads to the abnormal expression of various targets and pathways. For example, the resistance of lung adenocarcinoma to the clinically used drugs nicotine and oseltamivir is due to an increase in MET-TL7B content in the cancer tissue, which enables m^{6}A expression and reactive oxygen species (ROS) clearance dependence (75). The development of resistance to gefitinib in lung adenocarcinoma has also been found to be associated with the ribonucleic acid cleavage of m^{6}A-modified circASK1 produced by YTHDF2 (76). Resistance to the chemotherapeutic drug, cisplatin, in esophageal squamous epithelial carcinoma has also been found to be associated with m^{6}A. The stability of the CASC8 transcription process is enhanced by the m^{6}A demethylation induced by ALKBH5, which induces drug resistance in esophageal squamous epithelial carcinoma (77). In addition, resistance to cisplatin in intrahepatic cholangiocarcinoma promotes the degradation of CDKN1B mRNA via YTHDF2 in an m^{6}A-dependent manner (78). Tamoxifen is a conventional chemotherapy drug for breast cancer (79). Breast cancer develops tamoxifen resistance due to an increased ROS production and p38 activation. One of the reasons for this mechanism is that AK4mRNA translation is enhanced by METTL3-mediated m^{6}A overexpression (80). HNRNPA2B1 activates the ser/thr kinase growth factor signaling pathway in an m^{6}A-dependent manner to abnormally regulate downstream targets, leading to tamoxifen resistance in cancer tissue. Resistance to temozolomide in glioblastoma multiforme arises from the transcription of histone-associated genes modified by METTL3-mediated m^{6}A (81). Strong resistance to tyrosine kinase inhibitors in clear cell renal cell carcinoma is regulated by the YTHDC1-mediated m^{6}A-dependent YTHDC1/ANXA1 axis (82). In addition, the decreased sensitivity of PCa to enzalutamide is due to the methylation of nuclear receptor subfamily 5 group A member 2 (NR5A2), which is caused by the low expression of METTL3 (83). The mechanism of m^{6}A development and enhancement of cancer resistance is receiving increasing attention, which provides insight for future drug development and potential therapeutic targets which can be used to reduce resistance.

4. Role of m^{6}A regulators in PCa

PCa is associated with five key m^{6}A methylation regulators according to clinical data analysis. These regulators are tRNA methyltransferase activated subunit 11-2, nuclear RNA output factor 1, YTHDF1, HNRNPG and HNRNPA2B1, which integrate novel prognostic features that independently predict PCa prognosis. In the tumor microenvironment, three different modes of m^{6}A regulation have been found in PCa through the identification of m^{6}A regulatory molecules. Each m^{6}a regulatory mode has

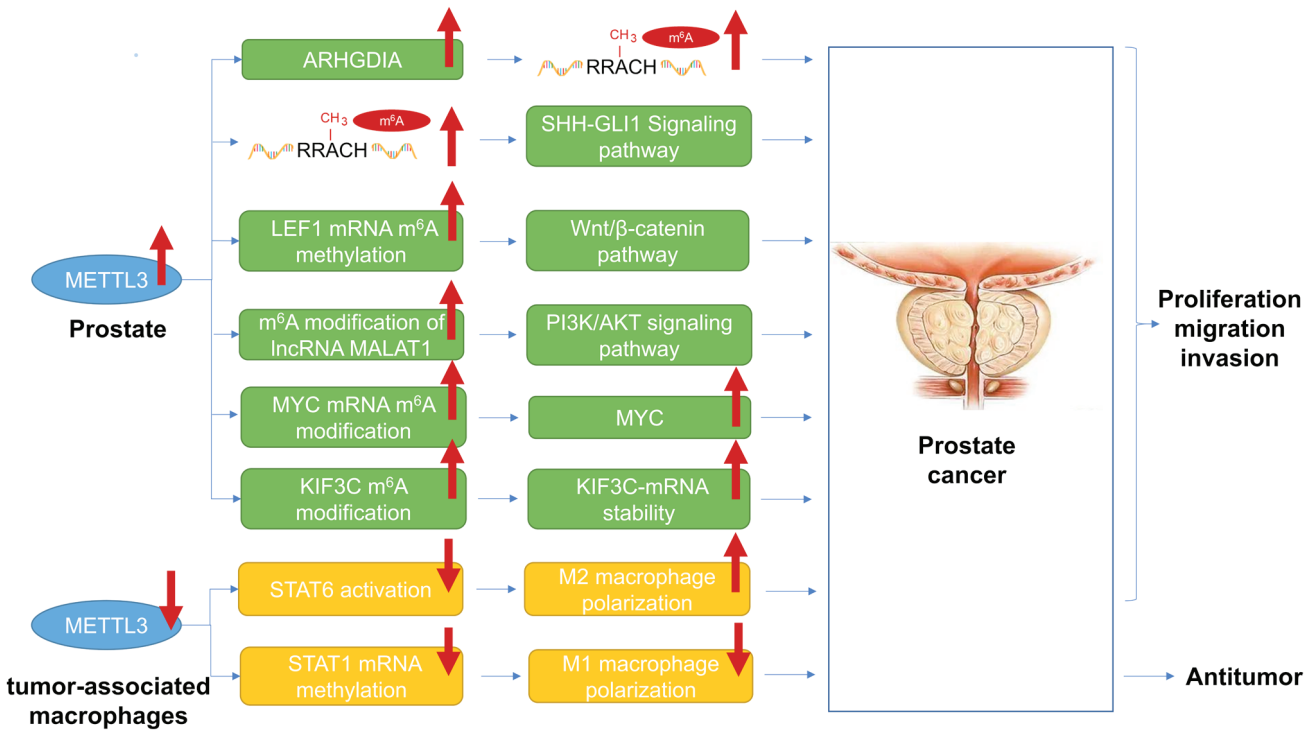

Figure 2. MEETL3 plays a crucial role in the progression of prostate cancer. METTL3 expression levels increase in prostate cancer cells, but decrease in tumor-associated macrophages. METTL3 plays a role in the malignant progression of prostate cancer mainly through the following six pathways: i) An increase in the content of ARHGDIA promotes an increase in the total m^{6}A level; ii) an increase in the total m^{6}A level activates the SHH-GLI1 signaling pathway; and iii) an increase in the m^{6}A modification of LEF1 mRNA activates Wnt/β-catenin signaling pathway; iv) lncRNA MALAT1 m^{6}A modification increases the activation of the PI3K/AKT signaling pathway; v) the increased modification of MYC mRNA m^{6}A leads to an increase in the MYC content; vi) the KIF3C m^{6}A modification increases the stability of KIF3C mRNA. In addition, METTL3 is expressed at low levels in tumor-related macrophages, promoting the proliferation, migration, and metastasis of prostate cancer by inhibiting the activation of STAT6 and leading to the activation of M2 macrophages. The low-level expression of METTL3 in tumor-associated macrophages exerts its anti-prostate cancer effect by inhibiting the methylation of STAT1 mRNA and promoting the activation of M1 macrophages. METTL, methyltransferase-like; ALKBH, alpha-ketoglutarate-dependent dioxygenase homolog; SHH, Sonic hedgehog; GLI1, -GLI family zinc finger 1; KIF3C, kinesin superfamily protein 3C.

a different proportion of C3 immune subtypes. It has been suggested that m^{6}A regulation in PCa is closely related to the tumor immune microenvironment. In addition, patients with PCa present with an increased expression of m^{6}A 'writers' or a decreased expression of 'erasers' (84). Thus, the m^{6}A methylation regulator manipulates the occurrence and progression of PCa.

METTL3 in PCa. It has been shown that an increased expression of METTL3 may have a tumor-promoting effect (85). Increased expression levels of METTL3 can promote the proliferation, migration and invasion of PCa by promoting ARHGDIA expression, and leading to an upregulation of the total m^{6}A methylation modification level in PCa tissue (86). In addition, the overexpression of METTL3 increases the m^{6}A content, and promotes the growth and invasion of PCa cells through Sonic hedgehog (SHH)-GLI family zinc finger 1 (GLI1) signaling (87). The m^{6}A methylation of lymphoid enhancer-binding factor 1 mRNA is mediated by METTL3. Lymphoid enhancer-binding factor 1 enhances the activity of the Wnt/β-catenin pathway, promotes the proliferation of prostate cancer cells and inhibits cell differentiation (88). METTL3 promotes the maturation of pre-miRNAs by upregulating the m^{6}A content and interacting with the microprocessor protein, DGCR8, to mediate m^{6}A modification, which recognizes pre-miR-182 (89). The m^{6}A modification of the METTL3-mediated long non-coding RNA (lncRNA) MALAT1 can also promote PCa cell growth and transfer by activating PI3K/AKT signaling (90). METTL3 increases the m^{6}A level of MYC mRNA transcription and enhances MYC expression, which leads to the occurrence and development of PCa (91). METTL3 can also induce m^{6}A modification on kinesin superfamily protein 3C (KIF3C) by increasing the stability of IGF2-binding protein 1 to KIF3C-mRNA. KIF3C is overexpressed in PCa, which promotes its growth, migration and invasion during the m^{6}A-dependent miR-320d/METTL3 (92). The tiny lipid molecule, lipoxin A4, in PCa cells promotes the polarization of M2-like macrophages by inhibiting the METTL3-mediated activation of STAT6, which produces effects that enhance tumor metastasis and growth activity. M^{6}A levels were reduced in tumor-associated macrophages in PCa patients. METTL3 drives M1 macrophage polarization through the methylation of STAT1 mRNA, which exerts antitumor effects (93). METTL3 levels in patients with PCa are up-regulated, promoting cell proliferation, migration and invasion in PCa via a variety of mechanisms (Fig. 2).

WTAP in PCa. WTAP is a writer for m^{6}A methylation modification in PCa tissue (58). In PCa, WTAP has been shown to promote cell proliferation and metastasis by binding to the corresponding androgen receptor. STAT1, FOXO1,

Interferon regulatory factor 1, glucocorticoid receptor and PPARγ transcription factor binding sites were identified in the promoter region of the WTAP gene. WTAP expression may be affected by these tumor-associated transcripts to promote tumorigenesis (94). WTAP may play a role in the processing of androgen-responsive circular RNA (circRNA) biogenesis. circRNAs can be used as non-invasive markers for PCa diagnosis and prognosis (95).

FTO in PCa. A lack of FTO attenuates growth rates and elevated levels of FTO expression can lead to weight gain due to an increased energy intake; FTO was first identified as a gene associated with weight and obesity. It has been shown that FTO can function as an eraser of m^{6}A methylation modifications, which manipulate m^{6}A methylation reversals and participate in dynamically reversible m^{6}A modifications (54). It was found that FTO is downregulated in PCa. FTO and ALKBH5 are inversely correlated with the Gleason classification of PCa (58). It has been suggested that FTO is an oncogene in PCa (96). FTO m^{6}A demethylase inhibits the invasion and migration of PCa cells by regulating total m^{6}A levels. When FTO is present in the nucleus, it first promotes the demethylation of m^{6}A. It first promotes the demethylation of m^{6}A and m^{6}Am when FTO is present in the cytosol. It has been shown that FTO in PCa cells is primarily found in the nucleus. mRNA decay experiments have also shown that the knockout of FTO does not affect the stability of the target mRNA in PCa cell lines. Increased levels of FTO expression may be associated with obesity-associated FTO single nucleotide polymorphisms, and promote tumorigenesis and progression (54). In addition, the m^{6}A modification is positively associated with the degree of tumor malignancy, which suggests a tumor suppressor effect of FTO in PCa (54).

It has been shown that FTO can also affect the occurrence and development of PCa by modulating the MC4R content. It promotes mRNA stability and modulates nuclear processes, miRNA processing and retinol-binding protein interactions. FTO is capable of oxidizing single-stranded DNA and single-stranded RNA *in vitro* to demethylate m-3T and m-3U. Moreover, the FTO and MC4R expression levels exhibit a significant negative correlation. The high expression of FTO partially modifies the boosting effect of high MC4R expression on the PCa malignant phenotype (53).

In addition, CLIC4 is one of the functional targets of FTO-mediated m^{6}A modification by multiple assays. FTO depletion suppresses PCa proliferation and transfer by increasing m^{6}A levels of CLIC4 mRNA which decreases mRNA stability. Functionally, FTO inhibits PCa cell proliferation and metastasis *in vitro* and *in vivo*, which are associated with a poor prognosis of patients with PCa, while the ectopic expression of FTO has the opposite effect (55).

The polymorphisms rs9930506 and rs9939609 in the FTO gene have been found to be associated with obesity and PCa (97). Both rs9930506 and rs9939609 are associated with high BMI in the European population, while obesity is associated with a high risk of developing PCa, which suggests an association between FTO genotypes and the risk of developing PCa. The mutation of rs9939609 is negatively associated with the risk of developing PCa and is positively associated with being overweight. Cases of severe PCa are more likely to occur in individuals who are overweight and have a mutation in the rs9939609 gene. The prevalence of heterozygous forms of rs9939609 suggests that its 'A' allele may be related to the phenotype of PCa (97). The rs9939609 A allele has been found to be associated with cancer risk in PCa cases, which is not with the occurrence of an increased risk of PCa itself. The data suggest that the rs9939609 A allele reduces PCa risk and the likelihood of detecting low-grade PCa, which may increase the likelihood of elevated-grade PCa (98). In addition, it has been suggested that FTO rs8050136 polymorphisms are not associated with PCa (97,99).

ALKBH5 in PCa. ALKBH5 is a member of the m^{6}A 'eraser', which functions as a demethylase. In model-based studies, ALKBH5 has been shown to affect PCa diagnosis and prognosis. Lower levels of ALKBH5 reduce protein expression in the tumor. It has been suggested that a reduction in the ALKBH5 level, which is caused by the deletion of the ALKBH5 amplification gene, is a factor in the development and progression of PCa (57). The expression of ALKBH5 has been shown to be significantly increased in patients with PCa compared to the normal population. Patients with CRPC with bone metastases have been found to have higher levels of ALKBH5 than patients with CRPC with lymph node metastases. Furthermore, ALKBH5 is negatively associated with the Gleason score, which suggests that ALKBH5 may be an indicator of PCa prognosis (56,58). The differential methylation of the ALKBH5 CpG site may enhance the progression of PCa transfer, although the specific molecular mechanisms remain unknown (100).

YTHDF2 in PCa. YTHDF2 and METTL3 have been found to be expressed at increased levels in PCa, which suggests a lower overall survival. The *in vitro* and *in vivo* inhibition of YTHDF2 and METTL3 has been shown to inhibit PCa development. This suggests an association between YTHDF2/METTL3 and PCa (101). YTHDF2 is overexpressed in PCa and CRPC with lymph node metastasis and is positively associated with the Gleason grade in PCa (58). The C and N terminal domains of YTHDF2 play the roles of specifically binding to the m^{6}A modification site, recruiting the CCR4-NOT complex and mediating the localization of the YTHDF2mRNA complex to the cellular RNA decay site, respectively. METTL3 functions as a core writer-catalyzed m^{6}A modification, which can promote YTHDF2 to play a regulatory role. YTHDF2 can directly bind to the m^{6}A modification sites of NK3 homeobox 1 (NKX3-1) and phospholysine phosphohistidine inorganic pyrophosphate phosphatase (LHPP), and degrade their mRNA, which indirectly induces AKT phosphorylation modification and promotes PCa occurrence and development in an m^{6}A-dependent manner. The increased expression of NKX3-1 suppresses the development of PCa, while LHPP suppresses AKT phosphorylation modification to regulate tumor progression (56,101). In addition, YTHDF2 is a target gene for miR-495 and is negatively associated with it. miR-495 can bind to the mRNA of YTHDF2. The knockout of miR-495 has been shown to significantly reduce cell proliferation and transfer in the DU-145 and PC3 PCa cell lines. YTHDF2 overexpression attenuates the inhibitory effect of miR-495 on PCa development and induces apoptotic effects (102). In

addition, as previously demonstrated, YTHDF2 can recruit the RNA-binding protein HNRNPD and bind to ubiquitin specific protease 4 (USP4) mRNA, which induces mRNA degradation. The reduction in the USP4 level fails to remove the ubiquitin group in the ELAVL1 protein, which results in a reduction in the ELAVL1 protein content. It allows ARHGDIA to be over-expressed and promotes PCa development (86). In addition, the expression levels of YTHDF2 are increased in PCa tissue and in the DU-145 and PC3 cell lines, while miR-493-3p expression is decreased, suggesting an inverse correlation (103). The target protein of miR-493-3p is YTHDF2, which is also an upstream factor in the inhibition of PCa cell line development by YTHDF2. The overexpression of miR-493-3p leads to an increase in m^{6}A levels, while the inhibition of miR-493-3p leads to a decrease in m^{6}A levels. The miR-493-3p-mediated downregulation of YTHDF2 significantly suppresses PCa progression by increasing the m^{6}A levels. YTHDF2 and miR-493-3p indirectly alter the occurrence and development of PCa in an m^{6}A-dependent manner (103).

IGF2BP1 in PCa. It has been shown that the IGF2BP1 protein family primarily acts as a recognition enzyme for m^{6}A methylation modification and as a cancer promoter. METTL3 induces an increase in the level of m^{6}A methylation modification of KIF3C, improving the stability of IGF2BP1 against KIF3C mRNA and reducing KIF3C mRNA degradation. KIF3C is expressed at peak levels in PCa tissues and cell lines, which is positively associated with PCa growth, migration and invasion. Following the knockdown if METLL3, the expression of m^{6}A and KIF3C is reduced. The expression and stability of KIF3C are reduced following the knockout of IGF2BP1. Thus, IGFBP1 positively modulates the stability and expression of KIF3C by relying on m^{6}A (92).

Other m^{6}A regulators in PCa. It has been shown that METTL14 facilitates the occurrence and development of PCa *in vitro* and *in vivo*. METTL14 recruits the YTHDF2 protein in an m^{6}A-dependent manner to inhibit thrombospondin 1 (THBS1) mRNA expression (104). METTL14 methylates the THBS1 mRNA in an m^{6}A-dependent manner. Methylated THBS1 mRNA can be recognized by the YTHDF2 protein which binds to the m^{6}A site in the cytoplasm leading to the degradation of the THBS1 mRNA. In addition, METTL14 can inhibit the angiogenesis inhibitory effect of THBS1 in an m^{6}A-dependent manner, which provides sufficient energy and oxygen for the growth of PCa tissues and cell lines (104).

In addition, increased METTL14 and ZC3H13 expression levels are positively associated with the number of Th1 cells and Th17 cells, as well as with the mesenchymal fraction and transforming growth factor-β responses. An increased mesenchymal fraction of Th1 cell and Th17 cell numbers suggests a good prognosis in PCa (105).

The expression of KIA1429 and HNRPA2B1 leads to m^{6}A methylation modification, which indicates a poor prognosis in PCa. This will lead to increased intracellular heterogeneity and Th2 cell penetration within PCa tissues and cell lines, with lower Th17 cell penetration and macrophage M1/M2 polarization (105).

The overexpression of Virma leads to increased levels of m^{6}A RNA methylation in androgen-independent PCa cells and CRPCs. It has been shown that the viability and proliferation of PC-3 cells can be suppressed by Virma inhibition. The downregulation of Virma attenuates PCa migration and aggressiveness by inhibiting m^{6}A expression, which decreases the stability and abundance of lncRNA, and reduces the malignant phenotype of PCa (106).

The expression levels of YTHDC2 and YTHDF1 are elevated in PCa and CRPC with lymphoma metastases, suggesting a poor prognosis (58). In addition, YTHDF1 overexpression induces the occurrence and development of PCa. It has been shown that the downstream factor of YTHDF1 is polo-related kinase1 (PLK1). YTHDF1 recognizes PLK1 mRNA and interacts with the m^{6}A modification of PLK1 mRNA 3' non-coding region in an m^{6}A modification-dependent manner, which improves the translation efficiency of PLK1 mRNA and increases the level of PLK1. It can promote the activation of the PI3K/AKT signaling pathway. Finally, YTHDF1 promotes the occurrence and development of PCa by increasing the PLK1 protein content and activating the PI3K/AKT signaling pathway (107).

HNRNPA2B1 promotes the genesis and development of PCa tissue in an m^{6}A-dependent manner, including several nuclear processes (108). In addition, HNRNPA2B1 has been shown to be associated with recurrence-free survival in PCa, which suggests its association with a poor prognosis (96). HNRNPA2B1 can also enhance its expression levels through lncRNA-PCAT6 (PCAT6), which promotes the occurrence and development of PCa. The knockout of the hnRNPA2B1 gene significantly reduces the ability of PCa cells to grow and migrate due to PCAT6 (109).

The HNRNPC protein can enhance the stability of the nucleosome assembly protein (NAP1) L2 mRNA by binding to lncNAP1L6, which is recruited into the m^{6}A-methylated modified NAP1L2 mRNA. HNRNPC indirectly promotes the increase of NAP1L2 in NAP1L2 translational expression products, and induces PCa transfer and invasion by the activation of the MMP signaling pathway (110).

The protein IGF2BP2 recognizes m^{6}A-methylated PCAT6 and enhances RNA stability, which shortens the half-life of PCAT6. PCAT6 is overexpressed in PCa tissues with bone metastases and is associated with the poor prognosis of patients with PCa (111).

IGF2BP3 binds to hsa_circ_0003258 and enhances the stability of the HDAC4 mRNA, which activates the ERK signaling pathway and accelerates the transfer and invasion of PCa tissue (112).

In the process of PCa, multiple m^{6}A regulators are required to participate in regulation. Each regulator is interconnected or mutually restricted and jointly regulates the body's m^{6}A levels. The complex and diverse regulatory mechanisms make it difficult to study the association between m^{6}A and PCa.

5. The m^{6}A and non-coding RNA modifications

The role of coding RNAs in the development and metastasis of PCa has been continuously revealed. However, the majority of the RNAs in the human genome are non-coding RNAs. The association between non-coding RNAs and PCa has not received ample attention (113). Non-coding RNAs are not only abundant, but also versatile (114). For example, non-coding

RNAs from liquid biopsies of patients with PCa have shown some benefits in terms of diagnosis, prognosis and detection (115). Although determining the role of non-coding RNA in PCa requires a certain scale and in-depth study, the results of such studies may be beneficial for the adjuvant treatment of patients with PCa and the development of novel therapeutic agents (116). The potential clinical operability of non-coding RNAs is being explored (114).

m^{6}A and miRNAs in cancer metabolism. Existing studies have shown that tumor metabolic activity is related to miRNAs; however, the metabolic effects of m^{6}A on the regulation of tumor cells by miRNAs have not yet been fully elucidated (117). In mammalian cells, DGCR8 recognizes and acts on pre-miRNAs undergoing METTL3-induced methylation. Of these, miR-182 can mature under m^{6}A-dependent METTL3 methylation modification and promote proliferation, migration, and invasion of prostate cells (83). In addition, METTL3 in PCa cells can induce the methylation modification of KIF3C in an m^{6}A-dependent manner and enhance the stability of KIF3C mRNA through IGF2BP1 which results in abnormally elevated KIF3Cd levels and promotes PCa progression. miR-320d can inhibit the occurrence and progression of PCa by specifically modulating METTL3 expression levels, thereby reducing KIF3C content (92). miR-141-3p inhibits the m^{6}A methylation modification of PRMT6 by mediating the low-level expression of ALKBH5. PRMT6 is not inhibited by ALKBH, which is highly expressed and promotes the occurrence and development of PCa (118). Lysine-specific demethylase 5A can inhibit its transcription and expression by binding to the promoter sequence of miR-495. YTHDF2 can recognize MOB3B mRNA. Due to the low expression level of miR-495, this leads to the degradation of MOB3B mRNA, thereby reducing MOB3B expression. The low expression of MOB3B ultimately promotes malignancy progression in PCa (102). HNRNPA2B1 interacts with primary miRNA-93 through the oncogenic axis of protein 6 of the HNRNPA2B1/miR-93-5p/FERM domain to stimulate PCa progression in an m^{6}A-dependent manner (119).

m^{6}A and lncRNAs in cancer metabolism. lncRNAs consist of >200 nucleotides, which are non-coding RNAs that can participate in important processes in epigenetics, the cell cycle, cell differentiation, and even cancer cell metabolism (111). MALAT1 is a long non-coding RNA that contributes to the development and progression of cancer in cancer cells by promoting the glycolysis process and inhibiting gluconetics. Studies have linked the lncRNA MALAT1 and the m^{6}A methyltransferase METTL3 to malignancy progression in PCa. The m^{6}A modification of lncRNA MALAT1 can be mediated by METTL3, thereby activating the PI3K/AKT signaling pathway, which promotes malignancy progression in PCa (90). Elevated levels of the lncRNA nuclear enriched abundant transcript (NEAT)1-1 recognize and activate the activity of CYCLOINL1 and form a different complex with extreme levels of CDK19 in PCa, which ultimately acts on the promoter Runt-related transcription factor 2 (RUNX2). NEAT1-1 promotes bone metastasis in PCa through RUNX2 and other related signaling pathways which can survive, proliferate, and invade the bone environment (120). The stability and expression levels of the LncRNA CCAT1/2 transcript are reduced by the Virma content, as well as the intracellular m^{6}A levels. Low expression of oncogenic LncRNA CCAT1/2 reduces prostate aggressiveness (106). Furthermore, the m^{6}A methylation of lncRNA NAP1L2 is mediated by the METTL14/METTL3 complex and stabilized by the HNRNPC protein recruited by lncNAP1L6. The improvement of metastatic capacity in PCa relies on increased levels of lncRNA NAP1L2 and YY1 mediated MMP2 and MMP9 transcription (110). M^{6}A methyltransferase ZC3H13 is modified by lncRNA A1BG derived from exosomes. The modified LncRNA A1BG is stably expressed, which inhibits the progression of PCa (121).

m^{6}A and circRNAs in cancer metabolism. circRNAs are stable closed-loop RNA structures that are less susceptible to degradation by RNA exonuclease than regular linear RNAs. In addition, circRNAs compete with endogenous RNAs for miRNA sites. Although circRNAs and m^{6}A methylation have been relatively poorly studied in cancer tissue metabolism, circRNAs have been shown to affect the metabolic activity of cancer cells and thus, tumor development (122,123). CircPDE5A interferes with the formation of m^{6}A methylation by recognizing and binding to specific sites of WTAP, which results in decreased m^{6}A methylation levels of eukaryotic translation initiation factor 3 subunit C (EIF3C) mRNA. YTHDF1 reduces the translation efficiency of the EIF3C mRNA m^{6}A with low methylation levels, which leads to the inactivation of the MAPK pathway and the inhibition of PCa development (122). CircFAM126A exhibits a high expression in PCa and an enhanced transcriptional stability through m^{6}A modification, promoting PCa progression *in vitro*. CircFAM126A mediates calnexin by targeting miR-505-3p. The low expression of calnexin can inhibit cholesterol synthesis in PCa cells and the malignant progression of PCa (124). CircDDIT4 is expressed at a low level as a tumor suppressor in PCa. The modification of circDDIT4 by m^{6}A promotes the biogenesis of circDDIT4. The methyltransferase complex is composed of WTAP/METTL3/METTL14, which increases circDDIT4 levels, while FTO exerts the opposite effect (125). The circRBM33-FMR1 complex stabilizes PDHA1 mRNA in an m^{6}A-dependent manner and activates the mitochondrial metabolism of PCa, thereby promoting PCa progression (126).

6. PCa and m^{6}A

M^{6}A modification plays a multifaceted role in the pathogenesis, diagnosis and treatment of PCa. Further research into the exact mechanisms of m^{6}A dysregulation in PCa and the development of targeted therapeutic interventions is required in order to improve patient outcomes in the future.

Pathogenesis. METTL3 plays a direct role in AR expression. The knockdown of METTL3 leads to the increased expression of the AR target gene, NKX3.1, and to the decreased expression of PSA. The knockdown of METTL3 leads to an increase in the key regulatory factor lysine-specific demethylase-1. Lysine-specific demethylase-1 is involved in the development of PCa and affects the expression and function of AR (127). The high expression of HNRNPA2B1 can promote the proliferation and metastasis of PCa. In a new oncogenic axis HNRNPA2B1/miR-93-5p/FERM domain-containing

protein 6, HNRNPA2B1 promotes the maturation of miR-93-5p in an m^{6}A-dependent manner. Thus, the expression of tumor suppressor FERM domain-containing protein 6 is reduced (119).

As an epithelial-mesenchymal transition (EMT) regulator in PCa, FTO can inhibit the m^{6}A modification level of EMT tumor cells. When the FTO gene is knocked out, EMT occurs in tumor cells, and promotes cell migration and proliferation (128). In addition, it has been shown that NAP1L2 and lncNAP1L6 are involved in the migration, invasion and EMT processes of PCa cells (110).

RNA binding motif 3 over methylated m^{6}A on catenin β1 (CTNNB1) mRNA in a manner dependent on METTL3. Alterations in β-catenin signaling can affect stem-like properties and the self-renewal ability of tumor cells. The stability of CTNNB1 mRNA was reduced by methylation of m^{6}A. This results in the inactivation of the Wnt signaling pathway, and eventually, the stemness remodeling of PCa cells by osteoblasts was inhibited (129).

Diagnosis. The transfer of PCa is associated with m^{6}A-modified mRNA. Methylated RNA immunoprecipitation sequencing (MeRIP-Seq) is a technique that combines RNA-protein immunoprecipitation and high-throughput sequencing. MeRIP-Seq can map m^{6}A methylated mRNA (130). The score of m^{6}A modified mRNA was calculated by the results of MeRIP-Seq. A higher m^{6}A-modified mRNA score is associated with a shorter biochemical relapse time in patients with PCa, and m^{6}A hypomethylation may contribute to PCa initiation. By contrast, the transfer group exhibits more m^{6}A modification peaks than the primary group. MeRIP-Seq helps study the prognosis and diagnosis of PCa (131). MeRIP-seq can also predict the results of PCa by detecting the content of m^{6}A methylated lncRNA in PCa tissues and calculating the lncRNA score modified by m^{6}A (132).

Compared with normal tissues, malignant tissues of patients with PCa have a lower FTO content and higher m^{6}A levels. Higher levels of FTO expression have been detected in patients with PCa with a poor prognosis. This indicates that the expression level of FTO is associated with the prognosis of PCa, suggesting that FTO is one of the diagnostic markers of PCa (133). THBS1 is a tumor suppressor that can inhibit the proliferation of PCa. In the nucleus, METTL14 inhibits THBS1 expression in an m^{6}A-dependent manner, leading to PCa proliferation. Therefore, METTL14 may be a prognostic marker and an effective therapeutic target for PCa (104). METTL3 is highly expressed in tumor cells and is predictive of a poor prognosis; thus, it is a promising diagnostic and prognostic marker (134).

Treatment. The methylation of m^{6}A is associated with immune response, tumor growth and metastasis (135). M^{6}A regulators cluster 3 modulates METTL14 and ZC3H13 expression levels and increases Th1 cells, Th17 cells, mesenchymal fraction and transforming growth factor-β. Of these, Th1 cells can initiate an antitumor immune response. The interstitial fraction is inversely related to the degree of malignancy of the tumor. TGF-β can inhibit the Th1 response and reduce the effect of ICIs. In addition, Th17 cells are a good prognostic indicator of PCa, which is related to the efficacy of PD-1 blockade in PCa treatment (105). Additionally, it has been shown that the m^{6}A methylation regulators HNRNPA2B1 and METTL3 affect the immune microenvironment of PCa (136).

The latest research suggests that the radiosensitivity of tumors can be modulated by methylation modifications of m^{6}A, which greatly increase the role of radiotherapy in cancer. The pathogenesis and progression of bone metastatic PCa can be inhibited by deletion of the MLXIPe/KHSRP/PSMD9 regulatory complex *in vitro* and *in vivo*, thereby improving the efficacy of radiotherapy. This mechanism is achieved by the RNA-binding protein KHSRP, which simultaneously recognizes m^{6}A on the enhancer RNA and m^{6}Am on the 5'-UTR, while resisting degradation by the exonuclease XRN2 (137).

METTL3, FTO, YTHDC1-2, YTHDF1-3 and IGF2BP1-3 proteins generally promote tumorigenesis. METTL3, METTL14, FTO and ALKBH5 can promote or inhibit the progression of cancer cells. Similarly, METTL3, FTO and ALKBH5 can alter the susceptibility or resistance of cancer cells to anticancer treatments (138). By identifying appropriate treatments that affect the functions leading to the development of PCa, it may be possible to treat PCa. Treatment with enzalutamide combined with METTL3 knockdown has been shown to result in AR-independent upregulation of gastrointestinal-specific gene features driven by nuclear receptor NR5A2, which result in enzalutamide resistance. This suggests that NR5A2 and other downstream pathway genes may be one of the targets for the treatment of CRPC (83). The functional inhibition of METTL3 may reduce tumor chemotherapeutic resistance induced by METTL3 and restore tumor sensitivity to chemotherapy drugs (134). PCa photothermal immunotherapy is also a treatment direction for PCa. Meclofenamic acid, a highly selective FTO inhibitor, can be combined with a gold nanorod-based nanoplatform to promote photothermal immunotherapy for PCa (139). Curcumin can inhibit the expression of m^{6}A-dependent TNF receptor-associated factor 4 induced by ALKBH5 and YTHDF1 (140). In addition, the potentially beneficial effect of curcumin in reducing PSA in patients with intermittent androgen deprivation PCa has also been demonstrated in a clinical trial (141).

Solute carrier family 12 member 5 is a neuron-specific potassium chloride cotransporter 2. Solute carrier family 12 member 5 promotes the tumorigenesis and development of PCa through YTHDC1 and the transcription factor, homeobox B13 (HOXB13). Solute carrier family 12 member 5 inhibitors may be used in the treatment of PCa (142). METTL3 knockdown combined with enzalutamide treatment has been shown to result in the development of resistance to enzalutamide in PCa cells. This suggests the mechanism by which PCa cells develop resistance to enzalutamide and may be an effective therapeutic target (83).

The change in drug delivery has largely enabled precision therapy. The treatment based on nanotechnology can improve the systemic toxicity and low efficacy of paclitaxel, adriamycin, docetaxel and other classical chemotherapy drugs, providing a new exploration direction for the precise targeted therapy of PCa (143). Gold nanoparticles coated with bovine serum albumin can be potentially cytotoxic to PCa (144). Multifunctional self-assembly magnetic nanocarriers can effectively improve the delivery efficiency of prostate tumors in the process of photothermal therapy, which enhances the

efficacy of photothermal therapy on PCa and plays an anti-tumor role (145). The microwave-induced expression of heat shock protein (HSP)70 in prostate tissue and the transfer of HSP70 to the cell membrane have been studied. The HSP70 antibody is then coated with nanoparticles and doxorubicin is precisely ablated and released under near-infrared irradiation, enabling precise drug therapy (146).

7. Conclusion and future perspectives

Currently, PCa remains one of the most common types of cancer worldwide among males, where it accounts for more than a quarter of cancer diagnoses. Current diagnostic and prognostic markers for PCa are also diverse. As regards the treatment of PCa, the this is mainly selected in relation to objective factors, such as the Gleason score and clinical stage; the corresponding clinical treatment methods, such as radical surgical treatment, external radiation therapy, brachytherapy therapy, the experimental local treatment of PCa, endocrine therapy and chemotherapy are selected to treat patients (147). While there are numerous treatments for PCa, they still have their strengths and weaknesses, and some treatments can even cause damage to the body. For patients with advanced-stage PCa, treatment can only prolong survival and relieve symptoms, and cannot completely cure the disease.

As one of the hot topics of discussion in epigenetics, the mechanism of m^{6}A and its biological impact on cancer development is gradually being elucidated. For example, FTO can promote the proliferation of oral cancer cells by renewing PD-1 expression (38). The methylation modification of m^{6}A plays a crucial role in the occurrence and development of cancer and has led to new insight and approaches for the diagnosis, treatment and prognosis of PCa. During m^{6}A modification, methyltransferases, demethylases and m^{6}A-binding proteins act as three different types of m^{6}A regulators to modify various types of specific RNA molecules in the same dynamic and reversible methylation of various types of RNA molecules as DNA and histones. Androgen function related gene TRIM68 plays a key role in prostate cancer progression. It was found that YTHDF1-mediated m6A modification promoted PCa progression by regulating TRIM68 in PCa (148). This suggests that m^{6}A modification may also be involved in the regulation of tumor-related genes. In addition, the association between changes in the expression levels of three types of partial regulators in PCa, and the development and progression of PCa have been demonstrated (113,127). The three regulators interact to specifically regulate RNA splicing, translation, stability and other aspects in an m^{6}A-dependent manner, and promote specific biological behaviors such as proliferation, migration, and invasion of cancerous tissues. The level of m^{6}A methylation modification and the expression content of its regulatory factors may have different biological effects on different tumors. As a result, m^{6}A and its regulators may become targets for PCa diagnosis and treatment, both specific and non-specific, as well as current prognostic markers.

The changes in PCa caused by m^{6}A modification have a complex biological mechanism. For example, an increase in the expression level of the m^{6}A methyltransferase METTL3 promotes m^{6}A modification and the expression of the hedgehog pathway GLI1, thereby promoting the proliferation, migration and invasion of PCa cells (87). In addition, the m^{6}A demethylase FTO inhibits the development and progression of PCa by increasing m^{6}A methylation modification levels and reducing CLIC4 mRNA degradation (55). In addition, the neuron-specific potassium chloride transporter solute carrier family 12 member 5 in the nucleus forms a complex with the m^{6}A-binding protein YTHDC1, which in turn regulates HOXB13 to promote PCa progression, particularly castration-resistant PCa (142). This suggests that the development of PCa tissue is regulated by different pathways of the m^{6}A modification regulator. Thus, all three classes of m^{6}A-modified regulatory factors are involved in multiple cellular activities in PCa. The interplay of these three may together constitute a complex mechanistic network of PCa, whose specific biological mechanisms need to be further explored.

The present review provides an overview of the association between m^{6}A methylation modification and PCa, in an aim to provide new insight and methods for the prevention, diagnosis, prognosis and treatment of PCa. Existing research has shown that m^{6}A regulatory agents have become effective in the clinical prevention and treatment of cancer. The shift in m^{6}A levels effectively promotes or suppresses the occurrence and development of tumor tissue. Restoring the balance of m^{6}A modifications by targeting specific imbalance modulators could be a novel anticancer strategy (149). MA2, for example, is the ethyl ester form of meclofenamic acid and acts as a highly selective FTO inhibitor, inhibiting the development and progression of glioblastoma (44). In addition, STM2457 inhibits METTL3 expression and reduces the level of m^{6}A modification, which has become a new direction in the treatment of acute myeloid leukemia (150). However, current research on micro-molecular drugs targeting the epigenetics of m^{6}A regulators is still insufficient and needs to be explored in the long-term. Moreover, m^{6}A modification has both advantages and disadvantages for tumor development. In the face of the fact that the mechanism of action of m^{6}A cannot be adequately elucidated, the lack of a reliable theoretical basis for the corresponding drug development has become one of the major limiting factors in the development of micro-molecular drugs for the regulation of m^{6}A (149). The elucidation of the essential targets of the m^{6}A regulator in PCa and the treatment of PCa by correcting abnormal m^{6}A modifications by targeting the epigenetic action of the m^{6}A regulator may prove to be a direction for future research and may improve the diagnosis and treatment of patients with PCa.

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Authors' contributions

QX and JP conceived the review and critically revised the manuscript. QX, JP and FT drafted the manuscript. NR, YY, LR and JP drew the figures and collected the related references. FG conceived and designed the study and provided academic leadership and guidance. QX and JP supervised and 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.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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