

Functions and mechanisms of N6-methyladenosine in prostate cancer (Review)

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Abstract. Prostate cancer (PCa) has long been a major public health problem affecting men worldwide. Even with treatment, it can develop into castration-resistant PCa. With the continuous advancement in epigenetics, researchers have explored N6-methyladenosine (m⁶A) in search of a more effective and lasting treatment for PCa. m⁶A is widely distributed in mammalian cells and influences various aspects of mRNA metabolism. Recently, it has been associated with the development or suppression of various types of cancer, including PCa. This review summarizes the recent findings on m⁶A regulation and its functions and mechanisms in cells, focusing on the various functional proteins operating within m⁶A in PCa cells. Moreover, the potential clinical value of exploiting m⁶A modification as an early diagnostic marker in PCa diagnosis and therapeutics was discussed. m⁶A may also be used as an indicator to evaluate treatment outcome and prognosis.

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Introduction

With an increasing global population and the problems of the aging population, prostate cancer (PCa) has remained a major public health challenge affecting men worldwide (1). It is a highly prevalent malignancy, the second most common cancer, and the leading cause of cancer-related deaths in men, accounting for an estimated 1.6 million cases and 366,000 deaths annually (2).

The high risk of PCa is mainly due to its aggressive metastatic nature. Due to the silent nature of this tumor, early diagnosis and treatment is difficult. In many cases, by the time of diagnosis, the tumor tissue has already developed extraprostatic or even bone metastasis (3,4). The global incidence of PCa has continued to increase in recent years, largely due to increased diagnosis owing to the widespread use of prostate-specific antigen testing; which has allowed the detection of more early-stage cancers. In addition, PCa prevalence increases with age; at present, more than half of Caucasian and Asian men aged >80 years-old have an indolent PCa (5).

PCa is considered a highly heterogeneous cancer characterized by multiple genomic alterations. Accordingly, tumors are graded by clinical hazards ranging from indolent to highly aggressive. Clinicians dealing with PCa patients need to distinguish between PCa and benign prostatic hyperplasia and determine the aggressiveness and metastatic nature of the tumor (1). Hormone therapy, or more accurately, androgen-deficiency treatment (or testosterone therapy), was shown to be effective in the early stages of PCa. However, advanced PCa usually progresses despite androgen ablation, develops castration resistance, and progresses to lethal PCa, which is considered incurable (4,6-8). Therefore, more effective and lasting treatment for PCa is urgently needed. Currently, proteomics, gene therapy and exosome research, among other approaches are the focus of cancer research. With the recent and growing progress of epigenetics, several researchers have focused on PCa.

2. N6-methyladenosine (m⁶A): New hope for PCa

With the advancement in technology for detecting epigenetic modifications, the study of DNA methylation and histone modifications, which are directly linked to tumors, has progressed significantly. Meanwhile, non-coding RNAs

have also been increasingly studied (1,9-11). Consequently, the relationship between RNA modification and PCa was also revealed recently. In particular, the m⁶A as methylation modification garnered much attention.

m⁶A is a modification at the sixth position of adenine (A) bases in RNA and occurs in several species (12-14). Initially reported in 1974, it did not receive much attention until the detection method was proposed (3). m⁶A modifications are abundant within the long internal exons, 3' untranslated (UTR) regions of linear RNAs, and around stop codons. They occur mostly in the RRACH sequence (R=G or A; H=A, C, or U) (15). Similar to other RNA modifications, the m⁶A modification is regulated by three protein types: methyltransferases, demethylases and binding proteins—more commonly—writers, erasers and readers (16). m⁶A is involved in various aspects of mRNA metabolism, including mRNA structure, maturation, stabilization, splicing, output, translation and decay. It also affects the cell cycle and differentiation and influences the maintenance of circadian rhythms (17). Besides, m⁶A can influence tumor occurrence and development via various mechanisms. Furthermore, m⁶A regulation can affect the progression of cancer and other diseases (18-20).

3. Multiple possibilities: Some mechanisms currently known in PCa databases

The Cancer Genome Atlas and various genomic databases are particularly beneficial for researchers to analyze mRNAs and find targets for characteristic m⁶A modifications. In previous studies, it was found that approximately all the m⁶A regulatory factors were associated with androgen receptor (AR), a primary oncogene driver of PCa. Of these regulatory factors, the expression of methyltransferase-like (METTL) 14, fat mass and obesity-associated protein (FTO) and human AlkB homolog H5 (ALKBH5) was reduced, while that of METTL3, YTH domain-containing protein 2 (YTHDC2), YTHDF1, and YTHDF2 was elevated in patients with PCa at different Gleason grades. At advanced pathological stages, the expression levels of Vir-like m⁶A methyltransferase-associated (VIRMA) and YTHDF3 mRNA were significantly increased (3,21). Recurrence-free survival of PCa was also influenced by IGF2BP3, hnRNP A2/B1, METTL14 and ALKBH5 (22). In AR-dependent and castration-resistant target genes, Somasekharan *et al* (23) identified that AR mRNA translation is coordinately regulated by the RNA binding proteins YTHDF3 and G3BP1. AR-regulated PCa cell lines subjected to AR pathway inhibition (ARPI) stress showed the recruitment of m⁶A-modified AR mRNA from actively translating polysomes to RNA-protein stress granules, leading to reduced AR mRNA translation. YTHDF3 or G3BP1 silencing could block ARPI-induced stress granule formation and decrease PCa cell death resulting from ARPI stress (23). However, further research is required to validate these results. A precise understanding of these mechanisms may provide insights into the prevention and treatment of recurrent tumors (24-26). In addition, drug development targeting corresponding targets may improve the clinical outcomes of CRPC. Studies focusing on both m⁶A modification and the tumor immune microenvironment in PCa can lead to more effective immunotherapy approaches (27).

Although database mining resolves several problems, it cannot explain the specific mechanism of m⁶A methylation in PCa development and progression, especially related molecular mechanisms. Therefore, further experimental exploration is required to determine therapeutic targets for PCa.

4. Three parts of m⁶A: Functional proteins and cancer

Collectively, three distinct proteins—readers, writers and erasers—affect cancer development and tumor cell growth. During m⁶A methylation modification, they cooperate to regulate the position of m⁶A. They are important targets or components of important pathways in the development of cancer, and should be carefully considered in the field of tumor therapy.

Writers. First, we researched the term 'writers,' among which, METTL3 is actively being investigated. METTL3 was the first m⁶A writer identified, followed by other components of the methylation complex, namely, METTL14, METTL4, METTL16, Wilms tumor 1-associating protein (WTAP), KIAA1429/VIRMA, and RNA binding motif protein 15 (RBM15, RBM15B) (3). METTL3/14 is found in the nucleus localized to nuclear speckles. METTL3 and METTL14 are hypothesized to form an m⁶A-generating heterodimeric enzyme complex on mRNAs, while WTAP functions as the splicing regulator (Fig. 1A) (28). The other writers similarly influence the regulation of m⁶A modification.

Writers are associated with some altered pathways. In urologic malignancies, the low expression of METTL3 and METTL14 can negatively regulate cell growth-related pathways (mTOR, EMT, and P2XR6) and positively regulate cell death-related pathways or tumor suppressors such as P53, PTEN, and Notch1 (Fig. 1A). Furthermore, METTL3 positively regulated proliferation-related pathways (NK-kB and SHH-GLI) and negatively regulated PTEN (29). The elevated expression of METTL3 in PCa tumor cells promoted the expression of GLI1 in the hedgehog pathway, the growth of PCa, and the motility of cancer cells (30). Similarly, decreased METTL3 expression inhibited LEF1 in the Wnt pathway, thereby preventing tumor cell migration (31). In tumorigenesis, METTL3 was shown to enhance MYC (c-myc) expression by increasing m⁶A levels of MYC mRNA transcript, triggering PCa (32). Another study revealed that in promoting the proliferation of PCa cells, like YTHDF3, METTL3 could inhibit corresponding mRNA degradation by targeting LHPP and NKX3-1, regulating AKT phosphorylation to induce cancer progression (33).

METTL3 induces m⁶A modification on Kinesin Family Member 3C (KIF3C) mRNA, promoting the stabilization of KIF3C mRNA by IGF2BP1. Tumor-suppressor factor miR-320d inhibits KIF3C expression by targeting METTL3 and restrains PCa growth, migration and invasion (34). METTL3 mediates m⁶A modification of ubiquitin-specific peptidase 4 (USP4) mRNA at A2696, and m⁶A reader protein YTHDF2 binds to and induces the degradation of USP4 mRNA by recruiting RNA-binding protein heterogeneous nuclear ribonucleoprotein D (HNRNPD) to the mRNA. Decreased USP4 levels do not remove the ubiquitin group from ELAV like RNA binding protein 1 (ELAVL1), resulting in a reduction in ELAVL1 protein, which increases Rho GDP dissociation inhibitor

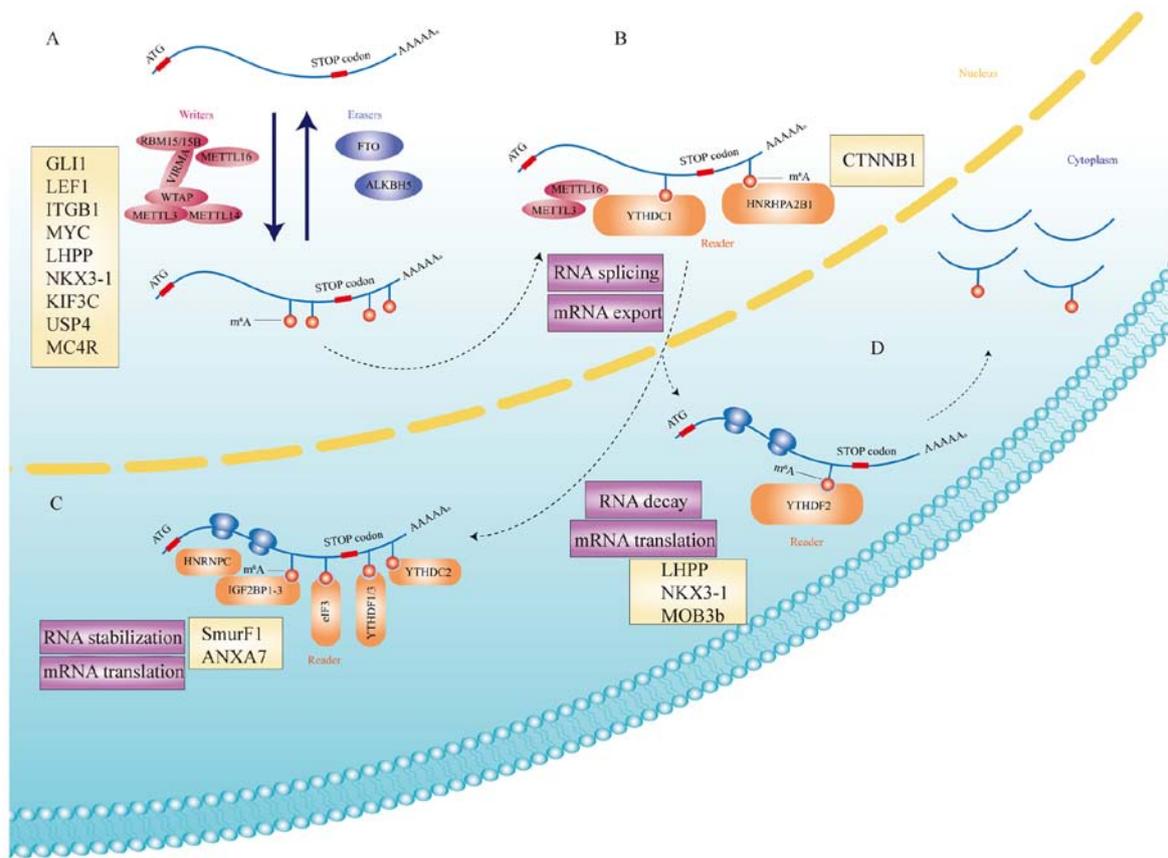


Figure 1. The mechanism of m⁶A and its roles in cells. (A) m⁶A is deposited by an m⁶A multiprotein 'writer' complex (METTL3, METTL14, METTL16, WTAP, VIRMA and RBM 15/15B) and removed by 'eraser' demethylases (FTO and ALKBH5). Targets of m⁶A multiprotein 'writer' complex and 'eraser' demethylases (*GLI1*, *LEF1*, *ITGB1*, *MYC*, *LHPP*, *NKX3-1*, *KIF3C*, *USP4*, and *MC4R*) can affect the progress of PCa. (B) METTL3, METTL16 and part of 'reader' protein (YTHDC1 and hnRHP A2/B1) affect RNA splicing and mRNA export. *CTNNB1* is the target of hnRHP A2/B1 in PCa. (C) In the cytoplasm, m⁶A modifications are recognized by 'reader' proteins (hnRNPC, IGF2BP1-3, eIF3, YTHDF1/3, and YTHDC2), resulting in mRNA stabilization and enhanced translation. *SmurF1* and *ANXA7* are targets of some of 'reader' proteins in PCa. (D) YTHDF2 can regulate mRNA translation and mediate RNA decay. *LHPP*, *NKX3-1*, and *MOB3b* are main targets of YTHDF2. m⁶A, N⁶-methyladenosine; METTL, methyltransferase-like; WTAP, Wilms tumor 1-associated protein; VIRMA, Vir-like m⁶A methyltransferase-associated; RBM, RNA binding motif protein; FTO, fat mass and obesity-associated protein; ALKBH5, human AlkB homolog H5; PCa, prostate cancer; YTHDC1, YTH domain-containing protein 1; CTNNB1, catenin β1.

alpha (*ARHGDI1A*) expression, promoting the migration and invasion of PCa cells (35). Furthermore, reader proteins and methyltransferase complexes, METTL14 inclusive, can cause poor prognosis by affecting subcellular protein localization (22). Li *et al* (36) found that METTL3 could enhance the expression of *ITGB1* and the adhesion of cancer cells and type I collagen bone matrix, promoting bone metastasis in PCa.

WTAP was shown to affect the development of urinary tumors heterogeneously. It interacted with the Wilms tumor suppressor (*WT1*) and was also a regulator of the m⁶A methylation complex, which was responsible for regulating mRNA stability. In addition, binding sites for signal transducer and activator of transcription 1, forkhead box protein O1, interferon regulatory factor 1, glucocorticoid receptor, and peroxisome proliferator-activated receptor γ transcription factor exist in the upstream region of WTAP, which may affect the function of WTAP in tumor formation (37). However, to the best of our knowledge, no detailed reports exist on the mechanism of WTAP action in PCa.

Erasers. The term 'erasers' refers to demethylases and mainly comprises two kinds of proteins-FTO and human ALKBH5. These two proteins regulate m⁶A modification and render the

RNA modification dynamic and reversible (Fig. 1A) (3,16). Increasing evidence suggested that FTO is highly expressed in some types of cancer and is associated with a poor prognosis. However, FTO also acts as a tumor suppressor in thyroid cancer. Low protein expression of FTO was consistent with high tumor grade and increased lymph node metastasis (20). ALKBH5, another m⁶A demethylase, was shown to either inhibit or promote tumorigenesis. Both FTO and ALKBH5 belong to the AlkB family; the differential recognition and interactions between them and RNA largely result from different conformational outcomes in RNAs, which are induced by m⁶A. In conclusion, m⁶A may serve as a conformational marker in regulating the changes in FTO and ALKBH5 expression (38,39).

FTOs are a class of eraser proteins that are downregulated in PCa tissues and cell lines (40). They can downregulate the m⁶A level and thus inhibit tumor invasion and migration in PCa by regulating total m⁶A levels (41). For years, FTO mutations rs9939609 and rs9930506 have been reported in the tumor tissues of patients with PCa, and rs9939609 has been negatively associated with overall PCa cases (42-44). Li and Cao revealed that FTO could restrain the proliferation, migration and invasion of PCa by downregulating the expression

of melanocortin 4 receptor (MC4R) (45). ALKBH5 is also an important reader in cancers, but it remains unexplored in PCa. Studies on m⁶A erasers are undoubtedly limited to meta-studies, and research on the specific mechanism of FTO and ALKBH5 remains a hot topic.

Readers. ‘Readers’ include YTH domain-containing protein 1 (YTHDC1), YTHDC2, YTHDF family proteins (YTHDF1, YTHDF2, and YTHDF3), eukaryotic initiation factor 3 (eIF3), heterogeneous nuclear ribonucleoprotein C (hnRNP C), hnRNP A2/B1 and IGF2BP family proteins (IGF2BP1, IGF2BP2 and IGF2BP3) that bind m⁶A in RNA to regulate the fate of the corresponding RNA and adjust downstream functions (Fig. 1B-D).

The YTH family is divided into the following three major classes: DC1, DC2 and DF (16). They contain an RNA-binding domain, which is a conserved aromatic ring that can recognize the m⁶A modification (46). YTHDF1 and YTHDF3 can both promote the translation of m⁶A RNA, while YTHDF2 interferes with the stability of m⁶A RNA and causes RNA decay. Additionally, YTHDF3 can contribute to mRNA degradation (Fig. 1C and D). By contrast, YTHDC1 is enriched in the nucleus and functions in regulating RNA splicing. Along with the complex functions of YTHDC2, it regulates RNA stability and promotes RNA degradation and translation (47). Furthermore, YTHDC1 modulates mRNA splice site selection in a concentration-dependent manner (Fig. 1B). Another reader, the subunit of eukaryotic initiation factor 3 (eIF3), is closely related to cancer occurrence and development. IGF2BP family proteins recognize and bind the GG(m⁶A) C sequence via their K homology domains (16). IGF2BP1 (IMP-1)-a non-catalytic post-transcriptional enhancer of tumor growth-is upregulated and associated with adverse prognosis in solid cancers. It shortened the G1 phase of the tumor cells by relying on 3'UTR-, miRNA- and m⁶A-dependent regulations (48). Like the rest of the family, the overexpression of IGF2BP3 (IMP3) was associated with cancer progression and survival. Using a new RNA sequencing technique, it was found that hnRNP functioned as an RNA nucleosome in RNA packaging and masking decoy splice (49). While hnRNP A2/B1 was an important cleavage factor, it was an independent prognostic factor, mainly affecting the cell cycle by delaying or promoting cancer progression (50,51). Besides, multiple hnRNP complexes triggered abnormal transcription and splicing of annexin-A7 (ANXA7), a tumor suppressor, thus affecting hnRNP A2/B1 function (52).

Many studies revealed that some readers, including YTHDC1, eIF3f, eIF3S3, and IGF2BP3 (IMP-3), play a corresponding role in influencing PCa progression. Luxton *et al* found that the oncogene metadherin collocated with YTHDC1 subnuclear spots and regulated the ability of YTHDC1 to affect PCa progression (53). Similarly, the downregulation of eIF3f expression reduces Akt levels, inhibiting PCa growth and progression (54). In some of the earliest studies of advanced PCa, researchers found that upregulated eIF3S3 gene expression was a common phenomenon, suggesting that eIF3S3 overexpression promoted tumor growth (55-57). Furthermore, *IMP3* was overly altered in tumor tissue, which increased the ubiquitination of PTEN mediated by SMAD-specific E3 ubiquitin-protein ligase 1 (Smurf1) and ultimately activated

the PI3K/Akt/mTOR pathway and promoted PCa progression (58).

YTHDF2, eIF3d, EIF3h and IGF2BP1(IMP-1) are all associated with the invasion and proliferation of PCa. YTHDF2 was a direct target of miR-495 and miR-493-3p. In the lysine demethylase 5a (KDM5a)/miRNA-495/YTHDF2/ m⁶A-MOB3b axis, YTHDF2 recognized the m⁶A of MOB3b mRNA and induced the degradation of MOB3b mRNA to inhibit its expression. miR-493-3p inhibited the expression of YTHDF2 and thus, increased m⁶A levels. Thus, high levels of YTHDF2 promoted the proliferation, migration and invasion of PCa cells (59,60). Moreover, eIF3d knockout inhibited the proliferation, invasion and colony formation of tumor cells and arrested the cell cycle in the G2/M phase (61), while EIF3h functions by affecting mRNA translation. High levels of eIF3h directly stimulated protein synthesis and played a key role in establishing and maintaining a malignant state in cells (62). In PCa, 8S-lipoxygenase (8S-LOX) and 15S-LOX-2 inhibited the c-myc mRNA coding region on the determinant-binding protein/insulin-like growth factor-2 mRNA-binding protein 1 (CRD-BP/IMP-1), thereby inhibiting the proliferation of the PCa cell line PC-3 (63).

PCa prognosis was also associated with readers, namely, eIF3b, eIF3c, eIF3L, IGF2BP3 and hnRNP A2/B1. Among them, eIF3b is a strong oncogenic factor and can affect PCa prognosis (64,65), while eIF3c regulates the PI3K/Akt/NF-κB signaling pathway (66). eIF3b silencing leads to a significant increase in tumor suppressor genes *PTEN*, *DIT3* and *CDKN1B* and a significant decrease in oncogenic genes *IRS1* and *CDH1* (65). In cancer cells, eIF3b depletion inhibits G1-S cell cycle transformation by altering the expression of cyclin A, cyclin E, retinoblastoma and p27Kip1 proteins, but not RNA. eIF3b depletion also inhibits the migration of cancer cells and destroys their actin cytoskeleton and local adhesions (64). Furthermore, studies showed that androgen-induced eIF3L could facilitate the early diagnosis of PCa disease. A high level of androgen-induced palmitoylation of eIF3L is an obvious marker of PCa. Moreover, as eIF3L acts as an initiation factor, palmitoylated eIF3L may cooperate with the initiation complex and enhance mRNA translation (67), palmitoylated eIF3L can be used to treat castration-resistant PCa (CRPC) (68). Case studies showed that IGF2BP3 was associated with invasive recurrence of tumors, which mainly included extracapsular extension, seminal vesicle invasion, lymphovascular invasion, and a high pathological Gleason score (69). Cheng *et al* (70) reasoned that hnRNP A2/B1 mainly promoted proliferation, and its high expression in CRPC cells worsens PCa prognosis. Moreover, hnRNP A2/B1 enables *CTNNB1* 3'-UTR mRNA regulation to alter the expression of β-catenin and other cancer-relevant genes to influence cancer cell phenotypes (71).

Readers can also affect bone metastasis in PCa. Lin *et al* (72) found that penta-o-galloyl-β-D-glucose, could inhibit the PI3K/Akt/mTOR pathway and reduce epidermal growth factor (EGF) levels to induce the expression of eIF3i and reduce the rate of bone metastasis (72). Moreover, IGF2BP3 was hypothesized to be associated with recurrence and bone metastasis in PCa (73). During PCa metastasis, IGF2BP3 physically binds to circular RNAhsa_circ_0003258 in the cytoplasm to enhance HDAC4 mRNA stability, activate ERK signaling pathway, and trigger EMT programming, ultimately accelerating metastasis (74).

Table I. Review of the literature regarding m⁶A modification related proteins, main target and pathway in PCa.

Gene symbol	Type of enzyme	Role	Regulatory factors	Main target	Pathway	Expression in cancer	Impact in PCa	(Refs.)
<i>METTL3</i>	Writer	Oncogene	-	<i>GLI1</i>	Hedgehog	Upregulated	Growth and movement	(23)
		Oncogene	-	<i>LEF1</i>	Wnt	Upregulated	Migration	(24)
		Oncogene	-	<i>ITGB1</i>	-	Upregulated	Bone metastasis	(29)
		Oncogene	-	<i>MYC</i>	-	Upregulated	Formation	(25)
		Oncogene	-	<i>LHPP, NKX3-1</i>	-	Upregulated	Promote AKT phosphorylation and progression of cancer	(26)
<i>FTO</i>		Oncogene	miR-320d	<i>KIF3C</i>	-	Upregulated	Growth, migration and invasion	(27)
		Oncogene	-	<i>USP4</i>	-	Upregulated	Migration and invasion	(28)
	Erasers	Anti-oncogene	-	<i>MC4R</i>	-	Downregulated	Proliferation, migration and invasion	(38)
<i>YTHDC1</i>	Reader	Oncogene	Metadherin	-	-	Upregulated	Progression of PCa	(46)
<i>YTHDF2</i>	Reader	Oncogene	-	<i>LHPP, NKX3-1</i>	-	Upregulated	Promote AKT phosphorylation and progression of cancer	(26)
<i>eIF3b</i>		Oncogene	miR-495	<i>MOB3b</i>	-	Upregulated	Proliferation, migration and invasion	(53)
		Oncogene	miR-493-3p	-	-	Upregulated	Proliferation, migration and invasion	(52)
	Reader	Oncogene	-	-	-	Upregulated	Poor prognosis	(57, 58)
	Reader	Oncogene	-	-	PI3K/Akt/ NF- κ b	Upregulated	Poor prognosis	(59)
<i>eIF3d</i>	Reader	Oncogene	-	-	-	Upregulated	Proliferation, invasion, colony formation and down-cell cycle in the G2/M phase	(54)
<i>eIF3f</i>	Reader	Oncogene	-	-	-	Upregulated	High Akt level and progression of PCa	(47)
	Reader	Oncogene	-	-	-	Upregulated	Malignant state in cells	(55)
	Reader	Oncogene	<i>PGG</i>	-	PI3K/Akt/mTOR	Upregulated	Bone metastasis	(64)
	Reader	Oncogene	-	-	-	Upregulated	Palmytilation to treat CRPC	(60)
	Reader	Oncogene	-	-	-	Upregulated	Growth	(48-50)
	Reader	Oncogene	8S- <i>LOX, 15S-LOX-2</i>	-	-	Upregulated	Proliferation	(56)
	Reader	Oncogene	-	-	-	Upregulated	Advance PCa	(66)
	Reader	Oncogene	-	-	-	Upregulated	Progression, recurrence, metastasis and PCa-specific survival	(61,65,73)
		Oncogene	-	<i>SmurF1</i>	PI3K/Akt/mTOR	Upregulated	PTEN ubiquitination, apoptosis inhibition and proliferation	(51)
		Oncogene	-	-	-	Upregulated	Poor prognosis in CRPC	(62)
<i>HNRNPA2B1</i>	Reader	Oncogene	-	<i>CTNNB1</i>	-	Upregulated	High stage of tumor	(63)
	Reader	Oncogene	-	<i>ANXA7</i>	-	Upregulated	Affects the function of tumor suppressor factors	(45)
<i>HNRNP complexes</i>	Reader	Oncogene	-	-	-	Upregulated	-	-

GLI1, GLI family zinc finger 1; LEF1, lymphoid enhancer binding factor 1; ITGB1, integrin subunit β 1; LHPP, phospholysine phosphohistidine inorganic pyrophosphate phosphatase; NKX3-1, NK3 Homeobox 1; miR-495, microRNA 495; MOB3b, MOB kinase activator 3B; miR-493-3p, microRNA 493-3p; PI3K, phosphoinositide 3-kinase; NF- κ b, nuclear factor κ B; mTOR, mechanistic target of rapamycin kinase; PTEN, phosphatase and tensin homolog; CTNNB1, catenin β 1; CDK19, cyclin-dependent kinase 19.

Although the mechanism of some reader proteins remains unexplored, some evidence suggests that reader proteins and their subunits could regulate tumor cell proliferation and development in an m⁶A-dependent manner, and may be targeted for tumor diagnosis and treatment. For instance, in the IgG reactivity screening of two independent patient cohorts, the response to antigen IgF2BP2 in patients with advanced PCa was higher than that in patients with early PCa, which suggested the possibility of new drug development (75). All of the aforementioned molecular relationships are presented in Table I.

5. Discussion

The risk of PCa—a major long-standing public health problem that affects men worldwide—is mainly due to its aggressive metastatic nature. Castration resistance PCa and advancement to lethal PCa are considered incurable. Understanding the relationship between RNA modification and PCa may lead to the development of new strategies for PCa treatment and thus, m⁶A modification in the light of PCa is increasingly being studied.

m⁶A modifications occur in every step of mRNA transcription, splicing, translation and expression; they can systematically change the expression of specific genes and the formation of related proteins. In PCa, many functional groups and regulatory targets show potential as effective treatment. Three types of proteins associated with m⁶A can equivalently affect the occurrence, development and invasion of cancer. m⁶A-related mRNAs can be affected by these proteins to modify their expression, which is necessary for the transformation into corresponding oncogenic or tumor-suppressor factors. For PCa treatment, the association between genes and their expressed proteins and corresponding oncogenic or tumor-suppressor factors, including multiple protein pathways and their corresponding targets, have been suggested. Several studies have shown that various m⁶A-related gene expression changes (whether up- or down-regulated) affect PCa prognosis and progression. Therefore, targeted therapies offer great promise (22,76).

However, compared with that of other tumors, the study of m⁶A in PCa is not comprehensive, and many related protein mechanisms are yet to be explored. Therefore, understanding the precise mechanisms of m⁶A in PCa, especially PCa-related proteins and genes, may promote the development of more effective cancer treatment. For instance, lysine-specific demethylase 5 (KDM5) family members act as oncogenic drivers in PCa via activation of the KDM5A/miRNA-495/YTHDF2/m⁶A-MOB3B axis (59).

The m⁶A signatures may also serve as an early diagnostic marker to supplement prostate-specific antigen diagnosis, which would improve PCa diagnosis. m⁶A may also be used as an indicator to evaluate treatment outcome and prognosis follow-up. Although the mechanisms of some gene targets remain unexplored, some writers and readers in m⁶A have been revealed to promote or inhibit cancer. The development of drugs targeting these targets has great potential for improving PCa treatment.

In summary, the literature on m⁶A and its mechanism of action in tumors, especially PCa, suggests the rapidly advancing epigenetics approach for cancer treatment, which will benefit patients with PCa.

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Availability of data and materials

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' contributions

HYW and YYF were major contributors in writing the manuscript. JJW determined the specific research direction of the manuscript and sorted out the data collected. HYW and JJW created the figure. YYF and JJW performed the literature search. LJZ and YYM made substantial contributions to the design of the manuscript and revised it critically for important intellectual content. All authors have read and approved the final version of the 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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