Role of methyltransferase-like enzyme 3 and methyltransferase-like enzyme 14 of N6-methyladenosine in the urological cancers

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N6-methyladenosine (m6A) modification can modify eukaryotic messenger RNA (mRNA), long non-coding RNAs (lncRNAs), microRNA (miRNA). A number of studies find that m6A show close relationship with cancer cells. Methyltransferase-like enzyme 3 (METTL3) and methyltransferase-like enzyme (METTL14), as two major enzymes in m6A modification, play a vital role in various cancers. However, the role and regulation mechanism of METTL3 and METTL14 in urological cancers are largely unknown. In this review, we summarize the present research results of METTL3/METTL14 and find potential pathways in kidney cancer, bladder cancer and prostate cancer. We found that METTL3 and METTL14 show different expression in three types of urological cancers. METTL3 is high expression in bladder/prostate cancer and has a positive regulatory effect on cancer cells. But its expression and role are opposite in kidney cancer. METTL14 is always low-expressed in kidney and bladder cancer, playing a negative regulatory role. When METTL3 or METTL14 is low expression in cancel cells, they always negatively regulate cell growth-pathways, such as mTOR, EMT, P2XR6, but positively regulate cell death-related pathways, such as P53, PTEN and Notch1. When METTL3 is high expression, it positively regulates NF-kB/SHH-GL1pathways and negatively regulates PTEN. These results suggest that although METTL3 and METTL14 show different expression and regulation mechanism in urological cancers. But they control cancer cell fate by cell growth- and cell death-related pathways. It provides a potential possibility for using m6A as a new therapeutic target in urological cancer.

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Abstract

N6-methyladenosine (m6A) modification can modify eukaryotic messenger RNA (mRNA), long non-coding RNAs (lncRNAs), microRNA (miRNA). A number of studies find that m6A show close relationship with cancer cells. Methyltransferase-like enzyme 3 (METTL3) and methyltransferase-like enzyme (METTL14), as two major enzymes in m6A modification, play a vital role in various cancers. However, the role and regulation mechanism of METTL3 and METTL14 in urological cancers are largely unknown. In this review, we summarize the present research results of METTL3/METTL14 and find potential pathways in kidney cancer, bladder cancer and prostate cancer. We found that METTL3 and METTL14 show different expression in three types of urological cancers. METTL3 is high expression in bladder/prostate cancer and has a positive regulatory effect on cancer cells. But its expression and role are opposite in kidney cancer. METTL14 is always low-expressed in kidney and bladder cancer, playing a negative regulatory role. When METTL3 or METTL14 is low expression in cancel cells, they always negatively regulate cell growth-pathways, such as mTOR, EMT, P2XR6, but positively regulate cell death-related pathways, such as P53, PTEN and Notch1. When METTL3 is high expression, it positively regulates NF-kB/SHH-GL1pathways and negatively regulates PTEN. These results suggest that although METTL3 and METTL14 show different expression and regulation mechanism in urological cancers. But they control cancer cell fate by cell growth- and cell death-related pathways. It provides a potential possibility for using m6A as a new therapeutic target in urological cancer.

Introduction

Chemical modifications of eukaryotic RNAs are known from decades. However, their role in tumor development was largely unknown until recent years. According to MODOMICS data, 163 different RNA chemical modifications have been identified in all living entities (Boccaletto et al. 2018). N6-methyladenosine (m6A) modification is considered to be one of the most common, invertible and ample modifications inside the RNA molecules, which can modify eukaryotic messenger RNA (mRNA), microRNA (miRNA) , long non-coding RNAs (lncRNAs) and other RNA molecules，and affects the transcription, processing, translation and metabolism of these molecules(Zheng et al. 2019). m6A modification is a dynamic process involving three major classes of enzymes: ‘Writers’, ‘Erasers’ and ‘Readers’ (Vu et al. 2019). Writers include methyltransferase-like enzyme 3 (METTL3) , methyltransferase-like enzyme (METTL14) , Wilms tumor 1 associated protein (WTAP) , RNA Binding Motif Protein 15/15B (RBM15/15B)

, and Vir Like M6A Methyltransferase Associated (VIRMA) , which are responsible for catalyzing the process of m6A generation; Erasers include fat and obesity-related protein (FTO) and alkB homolog 5 (ALKBH5) , which are responsible for catalyzing the demethylation process; Readers include proteins containing the YT521-B homology (YTH) domain , eukaryotic initiation factor (eIF3) , the IGF2 mRNA binding protein (IGF2BP) family , and heterogeneous nuclear ribonucleoproteins (HNRNP) protein family , they recognize m6A methylation and generate functional signals(Chen et al. 2019b).

METTL3 was first identified as a 70 kDa protein from Hela cell lysate (Bokar et al. 1997), subsequent research found that it contains two domains that bind S-adenosylmethionine (SAM) and catalyzes the formation of m6A, and has the activity of independently catalyzing the formation of m6A modification of RNA(Leach & Tuck 2001). WTAP promotes METTL3 localization in nuclear spots and greatly improves its catalytic activity (Ping et al. 2014). Studies have also shown that METTL3 acts as a positive regulator of mRNA translation independent of methyltransferase activity: promoting translation by interacting with translation initiation mechanisms in the cytoplasm (Ke et al. 2017). It has been reported that METTL3 can play the role without METTL14 and can promote translation of specific mRNAs independently of its catalytic activity in vitro (Ke et al. 2017). METTL3 is the core of catalytic activity in the N6-methyltransferase complex formed by the METTL3-METTL14 heterodimer. Adenosine residues at the N (6) position of some RNAs are methylated this complex (5, 9-21). METTL14 is a scaffold of binding RNA that identifies the substrate of N6-methyltransferase complex formed by METTL3-METTL14 heterodimer (Liu et al. 2014; Liu et al. 2015; Ping et al. 2014; Scholler et al. 2018; Sledz & Jinek 2016; Wang et al. 2016a; Wang et al. 2016b). METTL14 shares about 22% sequence identity and a nearly identical topology with the domains of METTL3. In the METTL3-METTL14 heterodimer, METTL14 is thought to assume a pseudomethyltransferase function that helps to bind with RNA and stabilize METTL3. However, it is possible that methyltransferase activity of METTL14 manifests after binding additional factors (Wang et al. 2017). In mRNA, the methylation site is located in the 5 '-[AG] GAC-3' consensus site of some mRNAs, and plays an important role in mRNA stability, processing, translation efficiency and editing (Alarcon et al. 2015a; Alarcon et al. 2015b; Bokar et al. 1997; Dominissini et al. 2012; Liu et al. 2015; Meyer et al. 2015; Wang et al. 2014; Xiang et al. 2017). It has been shown that methylation is completed after the mRNA is released into the nucleoplasm and promotes mRNA instability and degradation (Ke et al. 2017).

With the continuous research in recent years, the role of m6A in various tumors has been revealed, such as leukemia, brain tumor, cervical tumor, endometrial tumor, breast tumor, liver tumor and lung tumor etc.(Chen et al. 2018; Choe et al. 2018; Liu et al. 2018; Vu et al. 2017;

Weng et al. 2018; Zhang et al. 2016; Zhang et al. 2017). m6A shows a significant role of regulatory function in tumorigenesis and development by modifying many target genes (Deng et al. 2018; Liu et al. 2018). Interestingly, m6A may have carcinogenic or suppressive functions of tumor in different environments in cells (Cui et al. 2017; Li et al. 2017b; Lin et al. 2016; Ma et al. 2017; Visvanathan et al. 2018; Vu et al. 2017; Zhang et al. 2016; Zhang et al. 2017). A study proved that METTL3 mediated post-transcriptional silencing of SOCS2 through YTHDF2 dependent way and promoted liver cancer progression (Chen et al. 2018). METTL14 was confirmed that it lowly expresses in liver cancer cells and hematopoietic stem cells, and it impairs the tumorigenesis of Acute Myelocytic Leukemia (AML) (Weng et al. 2018). It was also revealed that METTL14 exhibits an inhibitory role in liver tumorigenesis and metastasis (Li et al. 2017b). Some studies have shown that abnormal m6A modification is necessary for the growth and progression in cancer (Cui et al. 2017; Li et al. 2017b; Lin et al. 2016; Ma et al. 2017; Visvanathan et al. 2018; Vu et al. 2017; Zhang et al. 2016; Zhang et al. 2017), suggesting that the pathway of m6A modification may be a promising therapeutic target for malignant tumors. In this review, we summarized the present research progress about METTL3 and METTL14 in urological tumors.

Survey methodology

In order to search literatures exhaustively, we used keywords ‘METTL3’, ‘Methyltransferase-like enzyme 3’, ‘METTL14’, ‘Methyltransferase-like enzyme 14’, ‘kidney cancer’, ‘renal cell carcinoma’, ‘bladder cancer’, ‘prostate cancer’ to search articles in the PubMed, Web of Science and CNKI. We excluded the articles which were not associated with METTL3, METTL14 and urological cancers.

Methyltransferase in urological cancer

1.Kidney cancer

According to the data of GLOBOCAN statistics, 403,262 people were diagnosed with renal cancer throughout the world and 175,098 people died, which made renal cancer become the 14th most common cancer in the world. Besides, males have a higher incidence than females in renal cancer (Bray et al. 2018). Many patients remain asymptomatic until the renal masses (RMs) progress to advanced stages because of the special position of kidney in the body. In the World Health Organization (WHO) 2016 classification, renal cancers are divided into three main sub

categories: clear cell renal cell carcinoma (ccRCC), which is the most common and aggressive type; chromophobe renal cell carcinoma (chRCC); and papillary renal cell carcinoma (pRCC) which has two styles, types 1 and 2(Hao et al. 2019; Moch et al. 2016). So far, there are four articles studying methyltransferase in kidney cancer, one on METTL3, two on METTL14 and one for both. All of them suggested that METTL3 and METTL14 are tumor suppressor in renal cancer. In addition, two articles studied about ccRCC subtypes, others were unknown (Gong et al. 2019; Li et al. 2017a; Wang et al. 2019; Zhou et al. 2019).

1.1 METTL3 in kidney cancer

METTL3 is more prone to copy number variations (CNV) or mutation than other genes in ccRCC，and patients affected by METTL3 shallow deletions (a form of CNV) has poorer disease-free survival (DFS) and overall survival (OS)(Zhou et al. 2019). METTL3 mRNA and protein expression in RCC are lower. Its expression level is negatively related with higher histological grade, larger tumor size, shorter OS and shorter DFS (Li et al. 2017a; Zhou et al. 2019). Study from cell line of RCC (CAKI-1/2 and ACHN) examined knocking down METTL3 can significantly promote cancer cell proliferation, migration and invasion (Li et al. 2017a). The VHL-HIF-ZNF217-METTL3 pathway may be involved in m6A regulation in ccRCC cells by mediating two downstream targets of m6A: the PI3K/AKT/mTOR and p53 signaling pathways (Li et al. 2017a; Zhou et al. 2019). In various cellular processes, the PI3K/AKT/mTOR pathway shows a significant role on cell proliferation, growth and survival (O'Reilly et al. 2006; Shaw & Cantley 2006). In addition, METTL3 might be involved in down-regulated invasion and migration of RCC by epithelial-mesenchymal transition (EMT) pathway. In the procedure of EMT, epithelial cells gain mesenchymal fibroblast-like properties (Lim et al. 2014), which may provide motility, migration and invasion functions for tumor cells (Fuchs et al. 2008; McConkey et al. 2009) and contribute to the potential of tumor metastasis. Besides, it was demonstrated that EMT is related to the prognosis of RCC patients (Chen et al. 2014). When METTL3 is down-regulated, the expression of vimentin, β-catenin and N-cadherin are significantly at a higher level, while E-cadherin is at a lower level. Based on the above results, pathway of EMT may be involved in potential mechanisms. (Li et al. 2017a).

The GSEA analysis with ccRCC patients suggested that low expression level of METTL3 is also related to some critical biological processes, such as mTOR pathway, adipogenesis and reactive oxygen species (ROS), which partially validate the RCC cell line results. Therefore, evidences from human tissues and cell line implied that the mTOR pathway, compared to other pathway,

may be the key target of m6A modification in kidney cancer. On the other hand, METTL3 can also regulate cell cycle. It was indicated that down-regulation of METTL3 significantly decrease arrest in G1 phase of cell cycle, whereas up-regulation of METTL3 increase arrest in G1 phase (Zhou et al. 2019).

1.2. METTL14 in kidney cancer

Similar to METTL3, METTL14 are more predisposed to mutation or CNV ， and patients affected by shallow deletions of METTL14 have poorer OS and DFS(Zhou et al. 2019). METTL14 is mainly located in the nucleus of ccRCC cells. Compared with normal kidney tissues, the expression of METTL14 mRNA is significantly lower in ccRCC tissues. It was shown that the expression level of METTL14 has a significantly negative correlation with RCC pathological stages and clinical stages, while OS is opposite (Wang et al. 2019). For METTL14, VHL-HIF-ZNF217-METTL14 pathway regulates m6A in ccRCC cells by two pathways: the PI3K/AKT/mTOR and p53 signaling, which is same with METTL3(Li et al. 2017a; Zhou et al. 2019). Other two regulating pathways in METTL14 also have been found. The first one is P2RX6, a non-selective cation channel protein which is a preferred receptor for ATP (Chadet et al. 2014; North 2002). METTL14 expression is negatively correlated with P2RX6, and low METTL14 expression shows shorter OS, while P2RX6 is opposite. METTL14 may increase the pre-mRNA splicing of P2RX6 by increasing the methylation of P2RX6 mRNA and achieving inhibition effect of P2RX6. Low METTL14 expression in cancer cells leads to high P2RX6 expression by acting on the ATP-P2RX6-Ca2+-p-ERK1/2-MMP9 signaling pathway and promotes renal tumor cell metastasis and invasion (Gong et al. 2019). The second one is PTEN, a tumor suppressor, whose duty is encoding phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and preferentially dephosphorylating phosphoinositide substrates. The METTL14 mRNA expression level is positively related to PTEN. Low METTL14 and PTEN expression show shorter OS. METTL14 stabilizes PTEN mRNA by regulating the m6A level of PTEN mRNA. PTEN acts as a tumor suppressor through regulating the AKT/PKB signaling pathway negatively. Besides, synergistic effects may be generated by the interaction between EIF3A and METTL14, which regulate the progress of kidney cancer. In addition, further study showed that 24 circRNAs (such as circ-0023414, circ-0031772 etc.) interact with 4 miRNAs(miR-130a-3p, miR-106b-5p , miR-130b-3p, and miR-301a-3p), which have a significantly negative relation with METTL14 mRNA, and these circRNAs may act as 4 miRNAs sponge and regulate METTL14 mRNA (Wang et al. 2019).

In general, METTL3 and METTL4 show low expression in kidney cancer and play negative effect on regulation of cancer cell. Low expression of METTL3 promotes cancer cell growth, proliferation, motility, invasion and migration functions through negative regulation of mTOR pathway, EMT pathway and positive regulation of P53. For the METTL4， in addition to regulating mTOR pathway and P53 pathway as same as METTL3, METTL14 plays negative role in kidney cancer also by negative regulation of P2RX6 pathway and positive regulation of PTEN (Fig.1).

2. Bladder Cancer

Bladder cancer was the 12th most common cancer in the world, with 549,393 new diagnosed cases and 199,922 deaths in 2018, according to the data of GLOBOCAN statistics. Besides, incidence varies by gender, with males taking greater risks than females (Bray et al. 2018). Urothelial carcinoma is the common histological style of bladder cancer. The non-papillary muscle-invasive tumors and the papillary non-muscle-invasive ones are two main molecular, clinical and pathological types of the disease (Sanli et al. 2017; Wu et al. 2019). So far, there are seven articles studying methyltransferase in bladder cancer，six on METTL3 and one on METTL14. Most of them suggested that METTL3 is tumor promoter in bladder cancer, and METTL14 is tumor suppressor.

2.1 METTL3 in bladder cancer

METTL3 highly expresses in bladder cancer tissues (Chen et al. 2019a). METTL3 mRNA and protein expression in bladder cancer significantly increase, Over-expressing METTL3 significantly promote the growth and invasion of bladder tumor cells. Knocking down of METTL3 impairs bladder tumor cells' ability of proliferation, invasion and viability, reduces the proportion of cell cycle S phase and raises the proportion of cell cycle G1 phase. Therefore, METTL3 may maintain the characteristics of bladder cancer stem cells by inducing m6A modification of SOX2, a marker of bladder cancer stem cells both in vivo and in vitro (Zhu et al. 2017). Patients with high METTL3 expression in bladder cancer have higher histological scores, worse prognosis, and shorter survival time. METTL3 exhibits a carcinogenic role in bladder cancer.

AFF4/NF-κB/MYC signal network plays the important role in mediated up-regulation of METTL3 on bladder cancer. This network contains three patterns: (1) METTL3 directly increases the m6A site abundance of MYC mRNA to improve the stability of MYC transcripts,

and increase the expression of MYC protein; (2) METTL3 increases the m6A site abundance of AFF4 mRNA to improve the stability of AFF4 transcripts and increase the expression of AFF4 protein. AFF4 protein directly combines with the promoter of MYC to promote the extension of MYC transcription and up-regulate MYC expression; (3) METTL3 may promote the expression of IKBKB and RELA (two key regulators of the NF-κB pathway) by regulating translation efficiency, and then induce MYC transcription. It is not difficult to find that METTL3-mediated m6A modification of different signal pathways eventually converges to MYC expression. Therefore, this m6A-regulated malignant regulatory network effectively increases the level of MYC protein in bladder cancer and may lead to difficulties in reducing MYC results by blocking single signaling (Cheng et al. 2019).

There is another pathway in mediating up-regulation of METTL3 in bladder cancer: METTL3-DGCR8-pri-mi221/222-PTEN pathway. METTL3 can actively regulate pri-miR221/222 in a m6A-dependent manner by interacting with the DGCR8, a micro-processor protein, and promote pri-miR221/222 to become a mature miR221/222 in bladder cancer. Subsequently, miR221/222 binds to 3′-untranslated region (UTR) of PTEN mRNA, which leads to a decrease in mRNA expression of PTEN and finally to a reduction in protein expression of PTEN (Han et al. 2019).

Two other pathways have also been identified for up-regulation of METTL3 on bladder cancer: METTL3 -CDCP1 axis and METTL3-ITGA6 axis. METTL3 and CDCP1 are up-regulated in the samples of bladder cancer patients. METTL3 and CDCP1 are related with the status of progression in the bladder cancer. Inhibiting the METTL3-CDCP1 axis leads to reduced growth and progression of bladder cancer cells and chemical-transformed cells. In vitro and vivo, it is important that METTL3-CDCP1 axis and chemical carcinogens have synergistic effect in promoting malignant transformation of uroepithelial cells and bladder cancer tumorigenesis (Yang et al. 2019). For METTL3-ITGA6 axis, METTL3 highly enriches the m6A methylation level of ITGA6 mRNA 3’-UTR region and promotes translation of ITGA6 mRNA, at the same time, the binding of YTHDF1/ YTHDF3 to the m6A motif in ITGA6 3'UTR region also promotes ITGA6 translation, resulting in increased expression of ITGA6 protein. The overexpression of ITGA6 increases adhesion, proliferation, and migration of bladder tumor cells, and enhances the growth and metastasis of bladder tumor cells. Therefore, ITGA6 as a carcinogen is a key target of METTL3 function in bladder cancer (Jin et al. 2019).

However, there is a different viewpoint about the role of METTL3 in bladder cancer that METTL3 is a bladder cancer suppressor gene. They worked out an integrated statistical model-based method called driver MAPS that identifies METTL3 as driver gene in cohort bladder cancer. Interestingly, in subsequent experimental verification, they found that knockdown of

METTL3 significantly increases cell proliferation, and METTL3 somatic mutations can promote cancer cell growth by interrupting the methylation process of RNA. Therefore, they believed that METTL3 acts as a gene of tumor suppressor for bladder cancer (Zhao et al. 2019).

2.2 METTL14 in bladder cancer

METTL14 has low expression level in bladder cancer and bladder tumor initiating cells (TICs). TICs are a handful of cells in bladder cancer and have self-renewal, differentiation and tumor-initiating abilities. METTL14 inhibits the proliferation, self-renewal, maintenance, metastasis and bladder TICs tumor initiating ability. The expression of METTL14 is negatively associated with the severity of bladder cancer and clinical outcome. METTL14 is significantly related to T stage of TNM stage system (Chen et al. 2019a) and promotes the stability of some mRNA such as MYC (Cheng et al. 2019).

Notch1 exhibits an important role in bladder tumorigenesis and TICs self-renewing. Notch1 is downstream target of METTL14. m6A modification by METTL14 on Notch1 inhibits its RNA stability, and then inhibits bladder cancer and bladder tumor initiating cells. Their work proved that METTL14 is a gene of tumor suppressor in bladder cancer and plays a key role in the occurrence of bladder tumors and bladder TICs through the METTL14-Notch1 pathway (Gu et al. 2019).

In general, METTL3 shows high expression in bladder cancer and promotes cancer cell growth through positive regulation of NF-kB and negative regulation of PTEN. In contrast, low expression level of METTL14 in bladder cancer plays negative effect in tumor cell by positive regulation on Notch1, which also has a suppressive role in bladder TICs (Fig.2).

3. Prostate Cancer

Prostate cancer (PC) was the third most common cancer in the world, according to the data of GLOBOCAN statistics, with 1,276,106 new diagnosed cases and 358,989 deaths in 2018(Bray et al. 2018). Because of the growth and aging of the population, prostate cancer has become a main public health problem in men (Center et al. 2012). This tumor is often silent in clinical practice and usually is found when it invades other tissue (Guo et al. 2019; Roobol & Carlsson 2013; Shen & Abate-Shen 2010). Until now, there are only two articles studying methyltransferase in prostate cancer, both are about METTL3. They suggested that METTL3 is tumor promotor in prostate cancer.

The expression level of METTL3 protein and mRNA in prostate cancer are significantly higher than those in adjacent benign tissues. METTL3 is mainly localized in the nucleus of the prostate cells, but distribute in a small amount in the cytoplasm. It has been reported that METTL3 mRNA and protein level are positively correlated with prostate specific antigen (PSA) value and Gleason score. Therefore, METTL3 plays a carcinogenic role in prostate cancer and may be used in combination with PSA as a diagnostic marker for prostate cancer (Xianyong et al. 2019). Evidence from cell line (C4-2, C4-2B, LNCaP, PC3 and DU-145) revealed that knocking down METTL3 reduces m6A content and inhibit survival, cell proliferation, colony formation and invasion. Mechanistic analysis indicated that the decreased expression level of GLI1 after METTL3 depletion. GLI1 is an important component of SHH-GLI signaling which is positively correlated with the PC severity. GLI1 has been shown to act as a negative modulator for androgen receptor and contribute to the androgen-independent growth of PC. The mRNA levels of c-Myc and Cyclin D1, which are SHH signaling downstream targets, are also inhibited, and finally result in cell apoptosis (Cai et al. 2019) (Fig.3).

Conclusions

In general, from the limited studies, we found that METTL3 and METTL14 show different expression in three types of urological cancers. METTL3 is high expression in the bladder and prostate cancers, playing the positive regulation for cancer cells. But for kidney cancer, expression of METTL3 is low. METTL14 is always low expression in the kidney cancer and bladder cancer, playing negative regulation in cancer cells. But high expression of METTL14 is not found in the urological cancers. No matter which type of those three cancers, when METTL3 or METTL14 is low expression, they always negatively regulate these pathways that promote cell growth, such as mTOR, EMT, P2XR6, but positively regulate cell death-related pathways or tumor suppressors, such as P53, PTEN and Notch1. When METTL3 is high expression, it positively regulates NF-kB/SHH-GL1 pathways (two cell proliferation-related pathways) and negatively regulates PTEN (see table). Compared to METTL14, METTL3 seemly shows various expression pattern and different regulation pathways in urological cancers, suggesting that METTL3 has organ-specific characteristics in expression and mechanism regulation. It provides a research theoretical basis for using m6A regulator as a new therapeutic target. However, because of limited number of available studies, we are not able to fully elucidate the molecular mechanism of m6A in urological tumors. It calls for more studies to reveal the mechanism and clinical application potential of m6A regulator in urological tumors. However,

according to existing research results, METTL3 and METTL14 control cancer cell fate by cell growth- and cell death-related pathways.

In this review, the potential molecular pathway networks are described through organizing the existing researches. Although m6A has just emerged in the field of urological tumors, it has already shown researchers a promising way. As some researchers have reported, m6A regulator may become new targets for treatment and act as a biomarker for diagnosis or prognosis of urological cancers in the future.

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Figure 1

METTL3 and METTL14 regulatory network in kidney cancer

The red arrow in the figure represents the promoting effect, and the yellow arrow represents the inhibiting effect. PI3K / AKT / mTOR, EMT and P2RX6 play a pro-cancer role in bladder cancer, while p53 and PTEN play a tumor-suppressive role. METTL3 and METTL14 play a role in suppressing kidney cancer by inhibiting or promoting some pathways, respectively. At the same time, they also accept regulation from upstream molecules or pathways.

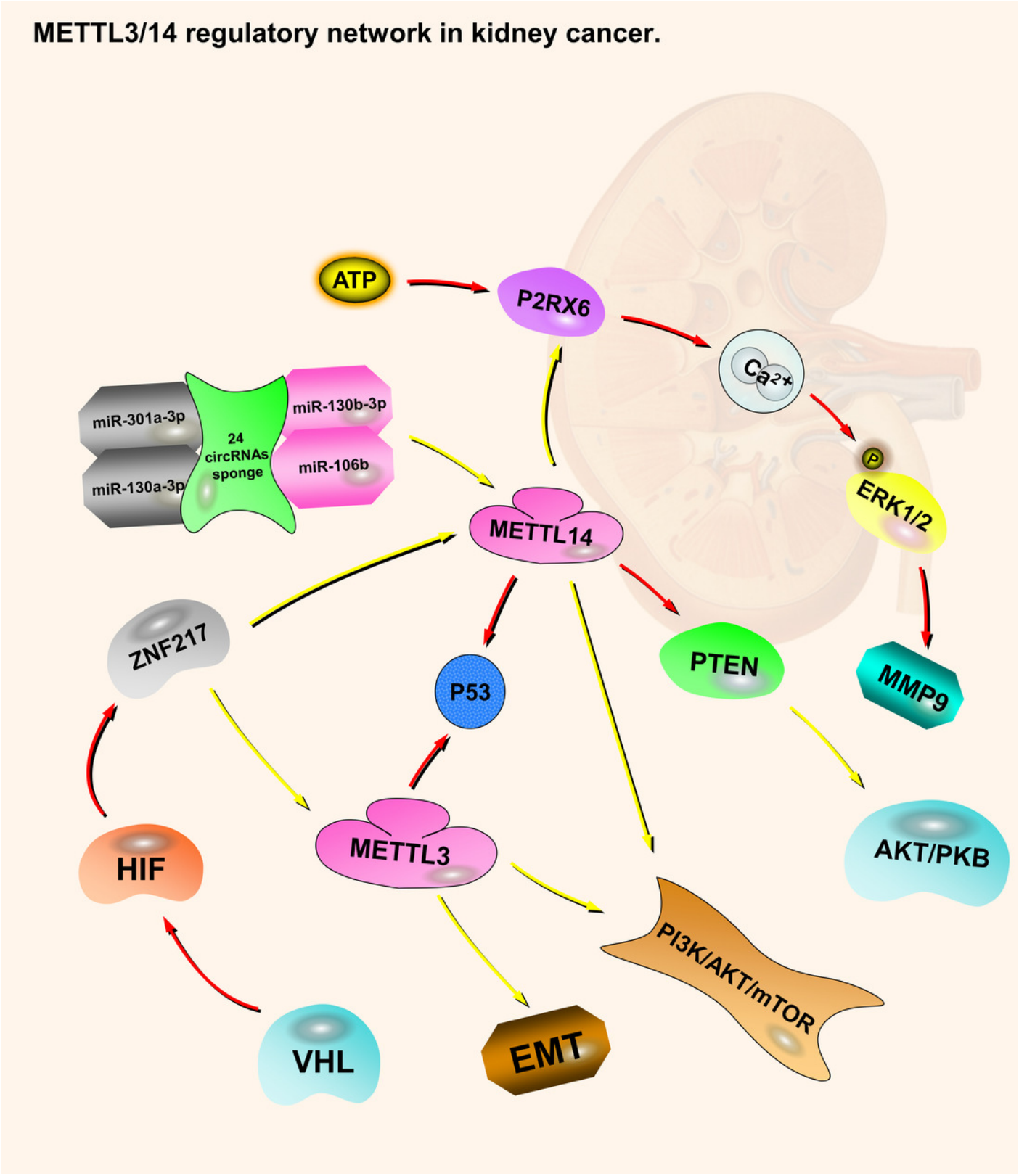
METTL3/14 regulatory network in kidney cancer.
ATP
P2RX6
Ca2+
P
ERK1/2
miR-301a-3p
miR-130a-3p
24 circRNAs sponge
miR-130b-3p
miR-106b
METTL14
ZNF217
P53
PTEN
MMP9
HIF
METTL3
AKT/PKB
PI3K/AKT/mTOR
VHL
EMT

Figure 2

METTL3 and METTL14 regulatory network in bladder cancer.

The red arrow in the figure represents the promoting effect, and the yellow arrow represents the inhibiting effect. AFF4 /NF-κB/ MYC, DGCR8-pri-miR221/222-PTEN, CDCP1, ITGA6 and Notch1 play carcinogenic role in bladder cancer. METTL3 can play a carcinogenic role in bladder cancer through a variety of pathways. METTL14 is the opposite, although there are not many related studies, it is certain that it plays a tumor suppressive role in bladder cancer.

METTL3/14 regulatory network in bladder cancer.

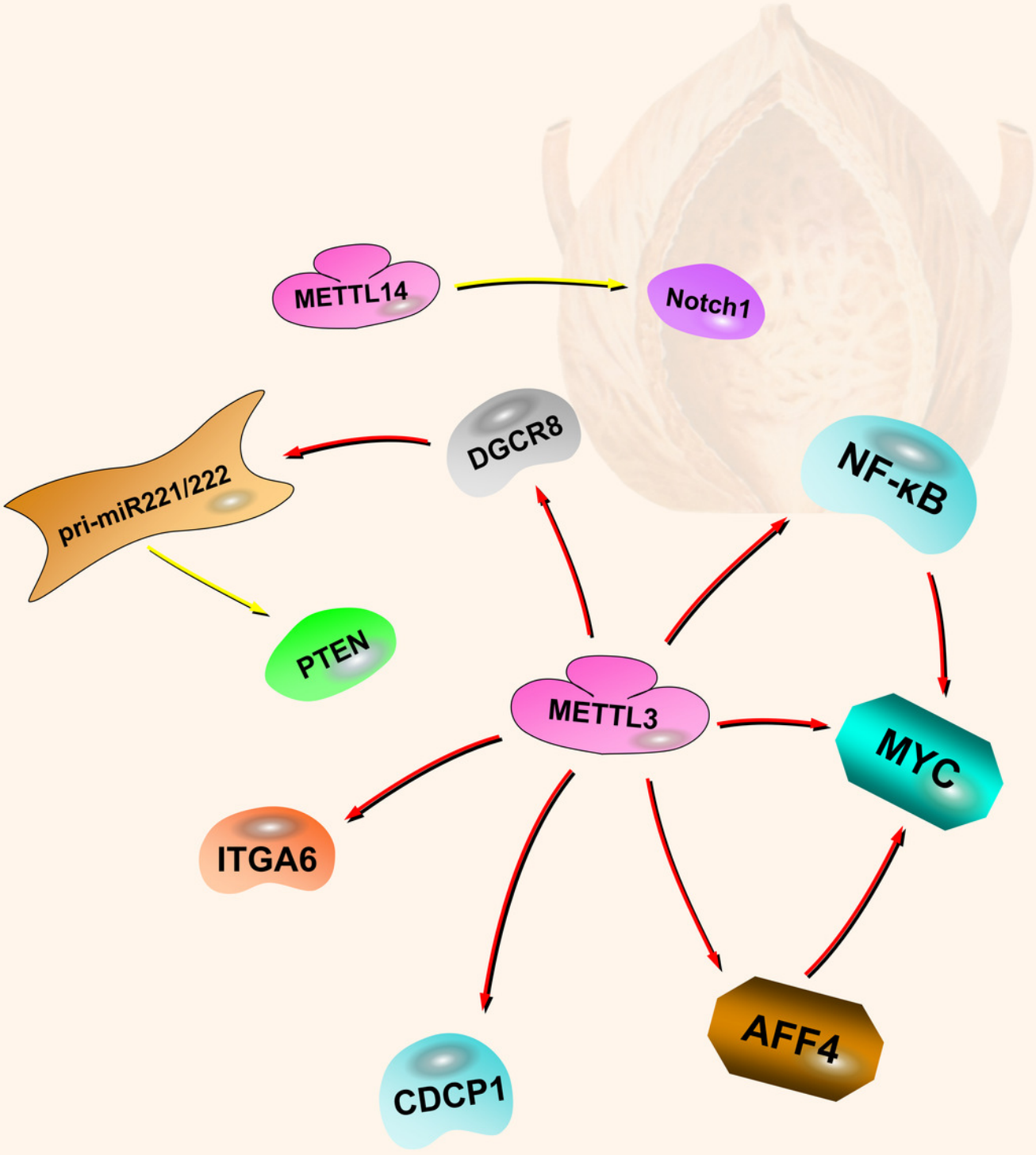

Figure 3

METTL3 regulatory network in prostate cancer.

The red arrow in the figure represents the promoting effect, and the yellow arrow represents the inhibiting effect. There are not many researches on METTL3 in prostate cancer. It is certain that it plays a role in promoting cancer by affecting downstream pathway SHH-GLI1.

METTL3 regulatory network in prostate cancer.

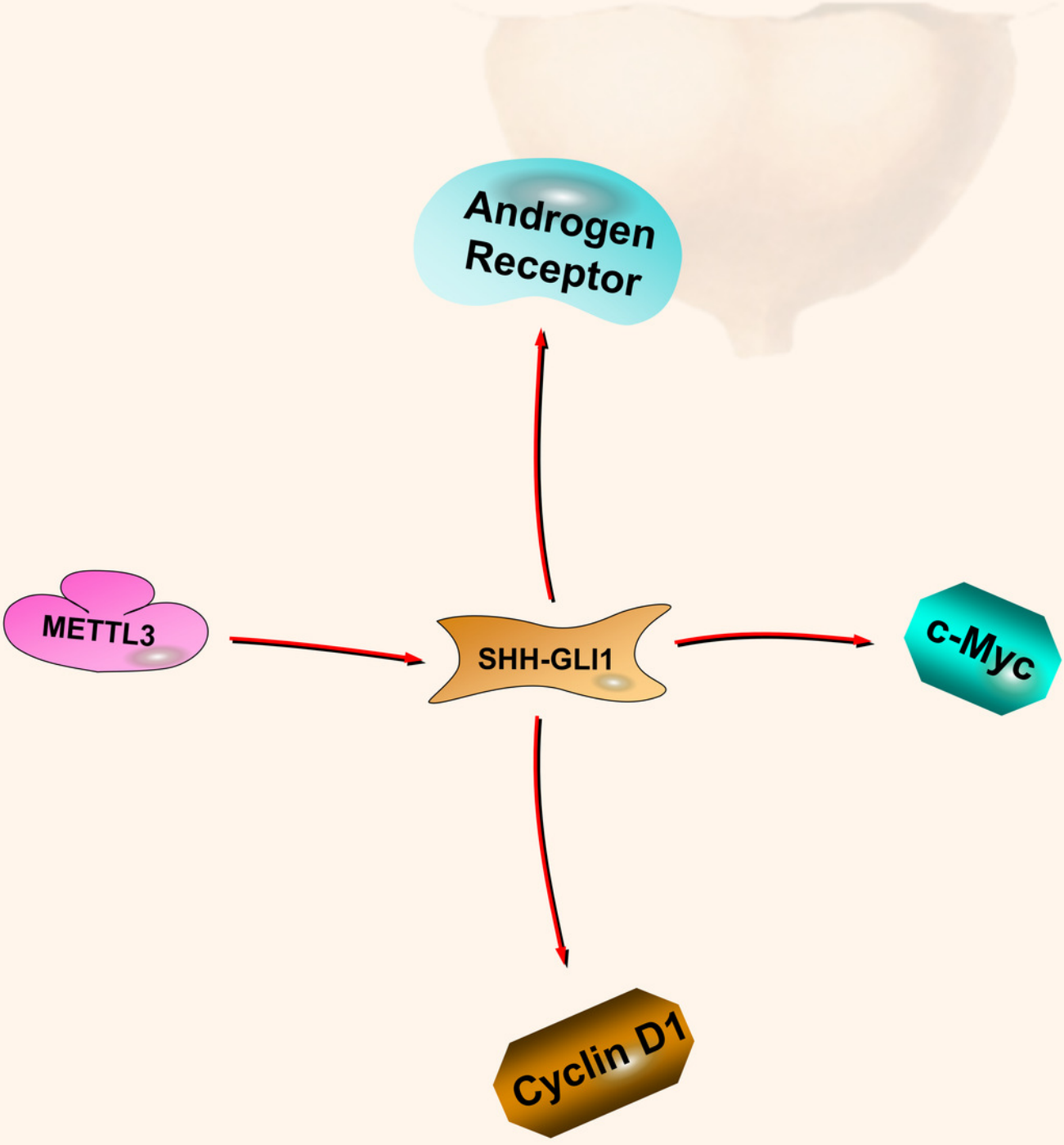

Table 1(on next page)

Multiple functions exerted by Methyltransferase in kidney, bladder and prostate cancers

1 **Table 1:** Multiple functions exerted by Methyltransferase in kidney, bladder and prostate cancers

Diseases	component	Role	Source of experimental evidence	Regulation	Potential Signal pathway	Author & Refs
Kidney cancer	METTL3	Anti-oncogene	RCC and matched histologically-normal renal tissue are from 145 RCC patients; RCC cell lines (CAKI-1, CAKI-2 and ACHN); a normal renal tubular epithelial cell line (HK-2); BALB/c nude mice	Down-regulation	METTL3-PI3K/AKT/mTOR METTL3-EMT	Li et al. 2017
	METTL3	Anti-oncogene	528 ccRCC patients with CNV data and pathology reports from the TCGA database; GSEA database	Up-regulation	VHL-HIF-ZNF217-METTL3-PI3K/AKT/mTOR VHL-HIF-ZNF217-METTL3-p53	Zhou et al. 2019
	METTL14	Anti-oncogene	528 ccRCC patients with CNV data and pathology reports from the TCGA database; GSEA database	Up-regulation	VHL-HIF-ZNF217-METTL14-PI3K/AKT/mTOR VHL-HIF- ZNF217-METTL14-p53	Zhou et al. 2019
	METTL14	Anti-oncogene	Online databases (TCGAportal,GTExPortal,UALCAN,GEPIA2,MEXPRESS,RMBasev2.0,OncoLnc,starBase,circBank,STRING…)	Down-regulation	circRNAs-miRNAs-METTL14-PTEN-AKT/PKB	Wang et al. 2019
	METTL14	Anti-oncogene	17 groups of renal cell carcinoma tissues and adjacent tissues received in patients with partial or complete kidney resection; Renal cancer cell line(OS-RC-2,786-O,HEK-293，SN12-PM6，SW839，A498); Human cortical proximal tubule epithelial cell line (HK-2); Nude mice; Online databases (TCGA, UALCAN…)	Down-regulation	METTL14-P2RX6-Ca2+-p-ERK1/2-MMP9	Gong et al. 2019
Bladder cancer	METTL3	Oncogene	Human/mouse bladder cancer samples; bladder cancer cell lines (5637, UM-UC-3); Immortalized epithelial cells (SV-HUC-1); GSEA database	Up-regulation	METTL3-AFF4 /NF-κB/ MYC	Cheng et al. 2019
	METTL3	Oncogene	Human/mouse bladder cancer samples; bladder cancer cell lines (EJ, T24)	Up-regulation	METTL3-DGCR8-pri-miR221/222-PTEN	Han et al. 2019
	METTL3	Oncogene	Formalin-fixed paraffin-embedded (FFPE) tissue from 114 cases of bladder cancer and 30 cases of cystitis with radical cystectomy and bladder biopsy; Human prostate	Up-regulation	METTL3 -CDCP1	Yang et al. 2019

			epithelial cell line(RWPE-1); Human bladder cancer cell line(T24，UM-UC-3); urethral epithelial cells (SV-HUC-1); 3-methylcholesterol transformed urethral epithelial cells(MC-SV-HUC T2);NOD / SCID mice			
	METTL3	Oncogene	TCGA GDAC Firehose; bladder cancer cell lines(T24)	Up-regulation	METTL3- ITGA6	Jin et al. 2019
	METTL14	Anti-oncogene	Primary bladder cancer specimens from 6 bladder cancer patients	Down-regulation	METTL14-Notch1	Gu et al. 2019
Prostate cancer	METTL3	Oncogene	Human prostate cancer cell lines(LNCaP, PC3, C4-2, C4-2B, DU-145); Human normal prostate epithelial cell line(RWPE-1); Six-week-old male NOD/SCID mice	Up-regulation	METTL3-SHH/GLI1-C-Myc/cyclin D1	Cai et al. 2019