Role of DNA methylation transferase in urinary system diseases: From basic to clinical perspectives (Review)

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Received June 9, 2024; Accepted October 4, 2024

DOI: 10.3892/ijmm.2024.5460

Abstract. DNA methylation is one of the earliest discovered and most extensively studied epigenetic regulatory mechanisms. Broadly, DNA methylation refers to the transfer of a methyl group on S-adenosine-L-methionine (SAM) to the C5 site of cytosine, a reaction catalysed by DNA methyltransferase (DNMT). This process can either up- or down-regulate gene expression due to gene promoter methylation, leading to the occurrence of certain diseases. Urinary system diseases, known for their high prevalence and complex pathogenesis, significantly affect the lives and health of patients. Urological tumours, in particular, represent a non-negligible disease burden worldwide. With the development of epigenetics, an increasing number of studies have demonstrated that DNMT plays an important role in urinary system disease. The present review aims to explore the relationship between DNMT and urinary system diseases and the potential of DNMT in the clinical management of these diseases.

Contents

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Key words: DNA methylation transferase, urinary system diseases, urinary tumour, mechanism, clinical management

1. Introduction

The urinary system is narrowly defined to include kidneys, ureters, the bladder and the urethra. In a broader context, it encompasses the cervix, vulva, adnexa, ovaries and fallopian tubes in women, and the prostate, vas deferens, testes and epididymis in men. Diseases can affect each of these organs and impact the entire system. Common urinary system diseases mainly include infections, tumours, stones and inflammation, congenital malformation and trauma. Among these, tumours are the most fatal and have been a major focus of academic research. In 2022, there were 434,419 new cases of kidney cancer and 155,702 kidney cancer-associated mortalities worldwide (1); studies have reflected the rising incidence of urological tumours in recent years (2-4). Non-muscle invasive bladder cancer (NMIBC) has a recurrence rate of ≥70% requiring repeated, costly and invasive testing, making bladder cancer (BCa) the most expensive cancer to treat per capita (5). Urological tumours, therefore, pose a threat to the quality of human life and incur substantial economic costs.

The pathogenesis of urinary system diseases is complex and remains to be actively explored. Epigenetics is an emerging theme in disease pathogenesis, with a major focus on DNA methylation and histone acetylation (6). Previous studies have highlighted that DNA methylation plays an essential role in urinary system diseases recently (5,7,8). DNA methylation is a stable epigenetic marker in humans and has been recognized, along with other regulatory factors, as a major factor influencing gene activity. The DNA methyltransferase (DNMT) family comprises a conserved set of DNA-modifying enzymes central to epigenetic gene regulation (9). A total of three DNMTs, DNMT1, DNMT3A and DNMT3B, catalyze the transfer of a methyl group from

S-adenosyl-L-methionine (SAM) to the C5 position of cytosine (10), a process known as methylation. Methylation predominantly occurs at cytosine-phospho-guanine (CpG) islands; which are CpG-rich regions (≥50% of cytosines and guanines) in the genome with a size >200 bp (11,12).

Methylation occurs not only in specific regions of the X chromosome, such as retrotransposon elements and centromere regions, and the result of methylation in these regions usually leads to genes inactivation (13). Studies have shown a significant association between the DNA methylation process in genes and urinary system diseases, with this chemical modification contributing to the development of urinary system disease and holding potential for diagnostic and prognostic applications (14-17). Therefore, the present study systematically explored the pathogenic mechanism and clinical application of DNMTs in urinary system diseases, opening a window of opportunity for improved clinical management.

2. Overview of urinary system diseases

Urinary system diseases can occur in all organs of the urinary system (kidneys, ureters, bladder and urethra) and spread throughout the system. It manifests itself in a variety of symptoms, including difficulty urinating, abnormal urine (such as changes in colour, clarity or smell), stone formation and a sense of pain. At the same time, it may indirectly cause other health problems, such as high blood pressure, oedema and anemia (18).

Non-oncological diseases of the urinary system. Common non-neoplastic urinary system diseases include autonomic-induced urinary dysfunction, urinary tract infections (UTIs) and urinary stones. Autonomic nerves are essential in urinary tract development, growth factors production and homeostasis control (19-21). The function of the lower urinary tract (storage and periodic elimination of urine) highly depends on the complex neural control system in the brain, spinal cord and peripheral ganglia. Additionally, injury or disease of the corresponding nerve may trigger neurogenic bladder or lower urinary tract dysfunction (22-24).

UTIs are an inflammatory response of the urinary tract epithelium caused by bacterial invasion. It is one of the most common community and hospital-acquired infections (25). Infectious microorganisms, including Gram-negative and Gram-positive bacteria and certain fungi, can cause UTIs via the hematogenous route and ascending routes (26). As one of the most common pathogens, *Escherichia coli* (*E. coli*) has multiple virulence factors, including pili, capsule, siderophore receptor, flagella, toxins and lipopolysaccharides, and they work together to cause a UTI (25,27). The conventional UTI treatment is mainly based on the use of antibiotics such as β-lactams, trimethoprim, nitrofurantoin and quinolones; however, antibiotic misuse has led to increased *E. coli* resistance, driven by genetic variation and horizontal gene transfer (28,29). Consequently, researchers are exploring alternative therapeutic strategies for UTI. The widely conserved respiratory quinoline oxidase cytochrome bd is essential for urothelial intracellular infection; hence, developing drugs targeting this enzyme may be a good research direction (30).

Urolithiasis is a common disease with a growing prevalence and high recurrence rate worldwide (31,32). Urinary stones are classified into two main categories: Metabolic and infected stones. Infectious urinary calculi account for 15% of urinary calculi, often caused by urease positive pathogens (33). The main treatment options include extracorporeal shock wave lithotripsy (ESWL), surgery and drug therapy. ESWL is typically used for renal and upper ureteral stones with diameter ≤2 cm in diameter. In rare diseases such as congenital anatomical anomalies where surgeons have difficulty in accomplishing the treatment of kidney stone disease through ESWL, percutaneous nephrolithotomy, ureteroscopy and minimally invasive surgery. Often they can only accomplish stone removal through open surgery (34).

Urinary system diseases caused by tumours. Epidemiological studies have shown that the incidence of urinary system tumours is increasing globally, significantly impacting the health and quality of life of patients (35,36). According to the global cancer statistics in 2020, there were >2.4 million new cases of urinary tract tumours reported worldwide, accounting for 12.5% of cancer diagnoses and 7.7% of new cancer-associated mortalities (37). Tumours of the urinary system are divided into three categories: i) Urothelial carcinoma of the renal pelvis, ureter and bladder; ii) renal malignant tumours, such as renal cell carcinoma (RCC) and Wilms tumour; and iii) non-urethral epithelial tumours of various organs. The relative rarity of upper tract urothelial carcinoma (UTUC) complicates the establishment of diagnostic and management strategies (38,39). Although advances in optical diagnostic technology should reduce invasive testing for UTUC, urinary cytology remains a primary methods for screening and monitoring urothelial carcinoma (40,41). The mechanisms underlying urinary system tumours remain a significant focus of academic research. Epigenetic alterations, such as histone methylation, acetylation and DNA methylation, are ubiquitous in urological tumours, and have garnered considerable scholarly attention (42).

3. Overview of DNMTs

The enzymes that build, recognize and eliminate DNA methylation are divided into three categories: i) Writing; ii) erasing; and iii) reading enzymes. DNMTs are known as writing enzymes. The DNMTs are a conserved family of cytosine methylases with a critical role in epigenetic regulation, catalysing DNA methylation by transferring a methyl group from SAM to the fifth carbon of a cytosine residue, forming 5mC (43). DNA methylation occurs mainly at the CpG dinucleotide site, and it occurs less frequently at cytosine-phosphothymine, cytosine-phosphoadenine and cytosine-phosphocytosine sites, which are collectively referred to as non-CpG sites (44).

The human genome encodes five DNMTs: DNMT1, DNMT2, DNMT3A, DNMT3B and DNMT3L. DNMT1, DNMT3A and DNMT3B are canonical cytosine-5 DNMTs that catalyse the addition of methyl groups to genomic DNA. By contrast, DNMT2 and DNMT3L are considered non-canonical family members because they lack catalytic DNMT activity (9). *De novo* methylation and maintenance methylation are important physiological processes in epigenetics. *De novo*

methylation refers to the methylation of cytosine C5 at a new site on the DNA chain. Maintenance methylation is the process of DNA replication that leaves the methylation of the original site unchanged; that is, the process of methylation modification at the corresponding position of the nascent strand results from the semi-conserved replication of methylated DNA (45). DNMT3A/3B is designated as a *de novo* DNMT and DNMT1 is designated as a maintenance DNMT. However, DNMT3A/3B participates in DNA maintenance methylation and DNMT1 in *de novo* methylation (46).

Structure of DNMTs. DNMTs typically comprise an N-terminal regulatory structural domain and a C-terminal catalytic structural domain. DNMT3A has two isoforms while DNMT3B has >30 isoforms. Despite this variation, both share similar domain structures: i) A Pro-T rp-T rp-Pro (pWWP) domain; ii) an ATRX-DNMT3L-DNMT3A (ADD) domain; and iii) a C-terminal catalytic domain. The pWWP domain recognizes H3K36me3 and the ADD domain binds the free N-terminal tail of histone H3 (27121154) (47). Among the three typical cytosine-5 DNMTs, DNMT1 is the most abundant DNMT and is considered to be the critical methyltransferase in mammals (48).

DNMT1 prioritizes the methylation of hemi-methylated DNA, thereby maintaining the epigenetic stability of genetic information. The unique N-terminal regulatory region of DNMT1 contains several structural domains, including the DNA replication foci structural domain (RFD) and the CXXC structural domain, playing the role of the corresponding structural domains. For example, the RFD directs DNMT1 to replicate DNA, while the CXXC domain recognizes and binds DNA containing unmethylated CpG sites.

Activity of DNMTs. The induction of epigenetic alterations, particularly aberrant DNA methylation, is strongly associated with chronic inflammation and various human diseases, including cancer, neurodegenerative diseases and metabolic disorders. Takeshima *et al* (49) demonstrated that the DNMT activation, triggered by nitrogen oxide (NO) production, is responsible for abnormal methylation in human tissues, indicating that DNMT activity plays a key role in the development and progression of multiple human diseases.

Activity of DNMT1. DNMT1 activity is modulated by a number of molecular interactions. Lymphoid-specific helicase (LSH), a DNA decoupling enzyme belonging to the SNF2 family, has long been recognized to enhance DNMT activity (50,51). Ubiquitin-like, containing PHD and RING finger domains 1 (UHRF1), an E3-ubiquitin protein ligase that interacts with DNMT1, is essential for maintaining DNA methylation when it binds to DNA (9). A previous study has shown that LSH interacts with UHRF1 in an ATPase activity-dependent manner, facilitating DNMT1 recruitment to replication forks and DNA methylation processes. In particular, UHRF1 enhances the binding of LSH to replication forks. This interaction enhances UHRF1 binding to chromatin and promotes UHRF1-catalyzed histone H3 ubiquitination, activating DNMT1 and facilitating its recruitment during the S phase of the cell cycle (52).

DNMT1 activity is affected by its microenvironment. Atrazine, a non-competitive inhibitor of the DNMT reaction, significantly reduces DNMT1 activity. Atrazine exposure at the embryonic stage may, therefore, have toxic effects on various organs by modulating genes (53-56). Duraisamy *et al* (57) reported that DNMT1 activity in retinal endothelial cells incubated in high glucose initially decreases after 6 h but increases after 24 h.

Studies have shown that DNMT1 fidelity is related to gene complexity and regional differences (58-60). High-complexity repeats and active gene promoter regions exhibit relatively high fidelity, while low-complexity repeats and methylated sequences in intermediate regions show relatively lower fidelity (58-60). However, DNMT1 can correct its inaccuracies through neighbour-guided correction, where changes in local DNA methylation alter the *de novo* and maintenance activity of DNMT1; at this point, DNMT1 becomes a key 'tuner', effectively improving fidelity (61). Thus, the inaccuracies and neighbour-guided correction of DNMT1 constitute essential mechanisms for maintaining DNA methylation (61).

Activity of DNMT3A and DNMT3B. The activity of DNMT3A and DNMT3B is significant in pathological processes. Studies have shown that eicosatetraenoic acid inhibits histone deacetylase 1 (HDAC1) and DNMT transcription and activity by acting as a natural proliferator-activated receptor γ (PPARγ) ligand and activator (62). Activated peroxisome PPARγ primarily decreases HDAC1 activity, followed by decreases in expression and activity of DNMT 3A and 3B. This process eventually leads to the up-regulation of tumour-suppressor genes (TSGs) (63).

Recently, Zhao *et al* (64) reported that Oroxylin A can inhibit methionine cycle metabolism in hematopoietic stem cells and reduces the expression of methionine adenosyltransferase 2A, a key enzyme in methionine cycle metabolism, leading to lower levels of SAM, which in turn affects the DNMT activity. The down-regulation of DNMT3A activity inhibits the methylation of cyclic GMP-AMP synthase (cGAS) gene and promotes the activation of the cGAS-STING pathway, thus accelerating the aging of hepatic stellate cells (64). In cases where SAM levels are significantly reduced, DNMT-3A and DNMT-3B may catalyse the demethylation of 5mC through their deamination activity, converting it back to unmodified cytosine. This process may involve the base excision repair pathway, where unmodified cytosine replaces the original methylated cytosine (65).

A recent study reported how genetically encoded photicaged amino acid controls DNMT activity. The technique enables the production of DNMTs, which is otherwise inactive. and can be rapidly activated by light irradiation. The results of this study contribute to a deeper understanding of how cancer-associated DNMT mutations affect their activity in organisms, providing an important foundation for future research and ad.vancements in cancer treatment (66).

Function of DNMTs in T cells. Epigenetic modifications, particularly covalent modifications of DNA itself by DNA methylation, are recognized as critical in determining T cell fate (67,68). Throughout the development of T lymphocytes in the thymus and their subsequent migration to the periphery for differentiation, they are influenced by a series of precisely regulated molecular mechanisms. DNMT3A plays a pivotal role as an epigenetic mechanism component in maintaining the stability of T cell responses (69-71). In mice with

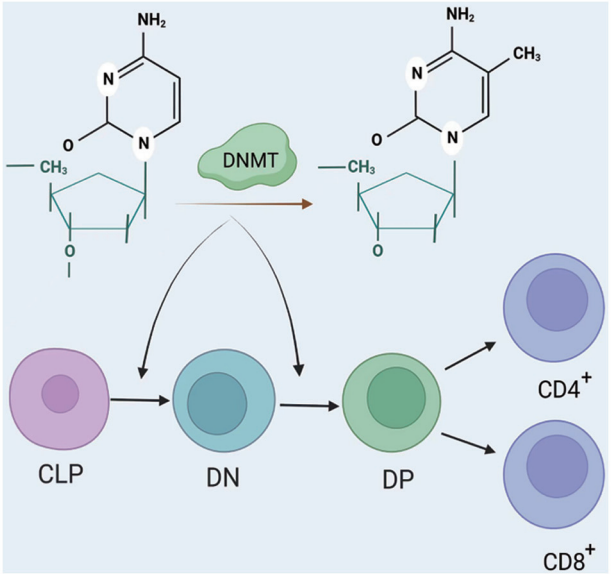

Figure 1. Role of DNMT in T cell differentiation. DNMT, DNA methyltransferase; CLP common lymphoid precursor; DN, double-negative T cell; DP, double-positive T cell.

DNMT3A knocked out, acute graft-vs.-host disease was observed, accompanied by a significant increase in inflammatory cytokine levels and higher pathological scores in organ tissues. T cells from DNMT3A knockout mice migrated and proliferated earlier in secondary lymphoid organs and showed a tendency to migrate to the small intestine. These findings underscore the vital role for DNMT3A in regulating T cell allogeneic responsiveness (69). Additionally, DNMT1 plays an important regulatory role in Foxp3 expression. In regulatory T (Treg) cells, the Foxp3 promoter region remains hypomethylated (70). Lv *et al* (71) further explored the important role of DNMT1-promoted Treg differentiation. The results showed that pcDNA3.1(+)-mDNMT-1 blocked polymer protein-promoted IL-10 and Foxp3 expression and Treg differentiation (Fig. 1).

Role of DNMTs in diseases. DNA methylation levels undergo tissue- and organ-specific changes, contributing to various diseases including neurological disorders, cancers, atherosclerosis and osteoporosis. A distinctive feature of cancer is widespread DNA repeat hypomethylation, a phenomenon that affects a large DNA region and is accompanied by frequent local DNA hypermethylation events (72). The degree of hypermethylation has been shown to correlate with cancer aggressiveness (73-75). DNMTs are abnormally expressed in various malignancies, including BCa (76,77), prostate cancer (PCa) (78), colorectal cancer (79) and osteosarcoma (OSA) (80). Genes affected by hypermethylation in cancer cells mainly include TSGs and DNA mismatch repair (MMR) genes. The low expression of TSGs and the silencing of DNA MMR genes are important mechanisms for cancer development (81,82). For instance, DNMT1 mediates hypermethylation of CpG islands in the microRNA (miR)-34a promoter region, leading to miR-34a deficiency and overexpression of Notch proteins, ultimately promoting metastasis and progression of OSA (83). The DNMT-1 inhibitor enhances miR-34a expression in OSA cells, leading to an antitumour effect and may be a promising therapeutic strategy for OSA (83). Studies have shown that hypermethylation of oncogenes and MMR genes due to aberrant DMNT function may activate the MAPK (84), PI3K/ACT (85) and Wnt/b-catenin (75) signalling pathways, which contribute to tumourigenesis (86).

In summary, DNMTs plays a crucial role in the pathogenesis of various diseases and can serve as a potential therapeutic targets for the corresponding diseases. With the rapid development of epigenetics, the role and clinical application of DNMT in urinary system diseases have received widespread attention.

4. Function of DNMTs in various types of urinary system diseases

Growing evidence shows that DNMTs play a significant role in the development of urinary system diseases. Overexpression of DNMTs exacerbates renal fibrosis (87), tubular degeneration (88), polycystic kidney disease (89,90), chronic bladder obstruction (91), as well as the progression of urinary system tumours (5,77,92,93). The aforementioned studies suggest that DNMT is involved in the mechanisms of multiple urinary system diseases development. The present review examines the role and specific mechanisms of DNMTs in seven urological disorders. In conclusion, abnormal expression of DNMTs plays an important role in these diseases (Fig. 2).

Non-oncological diseases of the urinary system

Cystitis. Cystitis is a physiological process that characterizes a number of bladder diseases such as UTIs and haemorrhagic cystitis. Cystitis involves aberrant epigenetic alterations through DNA methylation and histone deacetylation. These histone modifications recruit DNMTs, mediate DNA methylation and regulate the expression of genes implicated in pathology (94).

A study used urine specimens from women with interstitial cystitis/painful bladder syndrome (IC/BPS) to assess DNA methylation, and the findings suggest that genes within or downstream of the MAPK pathway exhibit altered methylation in IC/BPS (95). Infection of mammalian tissues with bacteria, viruses and other pathogens results in DNA methylation. *In vitro* studies have shown that infection of bladder uroepithelial cells with uropathogenic *E. coli* results in hypermethylation of the TSG CDKN2A (96-98). This hypermethylation may be triggered by lipopolysaccharides (96,99), which activate NF-κB signal transduction via Toll-like receptors, enables mimicking of the inflammation process, and produces certain oxidants such as superoxide and NO (100).

Damaged cytosine products resulting from inflammation, particularly halogenated cytosine residues, are likely to facilitate binding with methyl-binding proteins and enzymatic methylation (101). Uropathogenic *E. coli* infection modulates the host cell epigenome (96). Systemic chemotherapeutic agents, particularly cyclophosphamide (CPX) and other nitrogen mustard alkylating agents, cause severe clinical manifestations such as cystitis (102). Haldar *et al* (103) showed that exposure of mouse bladders to CPX results in the DNA methylation of the Ogg1 promoter, which down-regulates gene expression. Furthermore, Choi *et al* (104) demonstrated that DNA methylation changes are observed in the Calca, tissue inhibitor of metalloproteinase 3 (Timp3), matrix

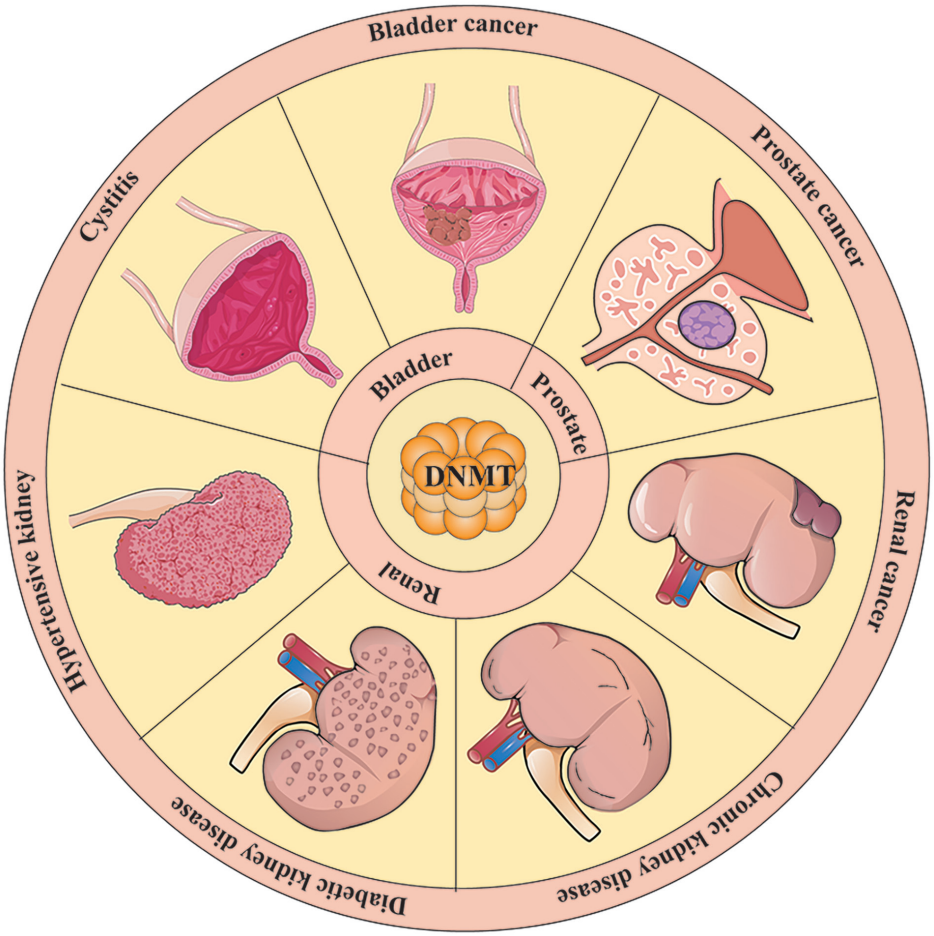

Figure 2. DNMT plays a role in different diseases of the urinary system. DNMT, DNA methyltransferase.

metallopeptidase 2 (Mmp2) and insulin-like growth factor 2 receptor (Igf2r) genes in a mouse model of chronic bladder inflammation induced by CYP (104).

Hypertensive nephropathy. Hypertensive nephropathy is the second leading cause of end-stage renal disease, following diabetes. At present, hypertension has attracted the attention of the medical community due to its high prevalence (105). Data shows that individuals with hypertension account for ~33% of the global population (106,107). Long-term persistent hypertension often leads to chronic renal failure, and in malignant hypertension, renal failure can occur in the short term (108). Studies have shown that the activities of superoxide dismutase (SOD), catalase and glutathione peroxidase are lower in patients with hypertension compared with healthy individuals (109-112). Concurrently, the expression of key enzymes producing reactive oxygen species (ROS), such as NADPH oxidase, increase. Since NADPH oxidase isoforms are highly expressed in the kidneys, oxidative stress is one of the important mechanisms of hypertensive nephropathy (113).

The mechanism of methylation also plays an important role in this process. In an animal study involving Ang-II-induced hypertension, the researchers reported that in addition to the increase in blood pressure, the Ang-II-treated group also had increased expression of DNMT1 and DNMT3A, which act as an antioxidant defence systems to eliminate ROS (113). However, SOD and Sirtuin 1 genes are hypermethylated and inhibited in transcription, which impairs antioxidant function (113,114). Moreover, animal studies have shown that a maternal low-protein diet induces hypermethylation and increased expression of prostaglandin E receptor 1 in the kidneys of young rats, which is associated with subsequent salt-sensitive hypertension in adult rats (115,116). Understanding the methylation mechanism in hypertensive nephropathy will help clarify the specific pathogenesis and potentially lead to novel therapeutic strategies in the future.

Diabetic nephropathy (DN). DN is a major global public health issue. The number of individuals with diabetes may reach 578 million by 2030 and 700 million by 2045 (117). Approximately 35% of individuals with diabetes develop DN (118), making it the long-term complication of diabetes with the most significant social and family burden (119). Therefore, the study of DN has always been a focal point in the academic community. In recent years, a number of studies have shown that epigenetic changes play a role in the pathogenesis of kidney disease (87,120-122). For example, DNMT1 expression has been observed to be increased in damaged glomerular podocytes of diabetic mice. The actin α4 (ACTN4) gene is hypermethylated in podocytes, but this can be down-regulated using DNA methylation inhibitors such as 5-Aza or epigallocatechin-3-gallate (EGCG). These interventions ensure the integrity of podocytes, effectively reduce the level of urinary protein in diabetic mice, reduce glomerular

damage and basement membrane thickening, and protect the kidneys (123,124).

In previous years, studies have reported that the hypermethylation and low expression of the let-7a-3 gene can influence the occurrence and development of DN by targeting UHRF1/DNMT1. Therefore, the let-7a-3 gene is used as the target to inhibit its hypermethylation. Moreover, it may be one of the treatment directions for DN in the future (125,126). Additionally, depletion of the calmodulin regulatory factor 1 (RCAN1) aggravates podocyte injury, impairs the glomerular filtration barrier and increases proteinuria, suggesting that RCAN1 is a protective factor for podocytes (127). However, under high glucose conditions, RCAN1 hypermethylation and decreased expression aggravates kidney injuries, which is one of the mechanisms of DN (128). Hypermethylation of insulin-like growth factor-binding protein-1 (129), methylenetetrahydrofolate reductase (130) and KLOTHO (131) promoters have been associated with DN. EGCG alleviates high glucose-induced kidney injury by reversing KLOTHO promoter methylation (131). Therefore, exploring the relationship between gene methylation and DN helps advance DN pathogenesis research and design new therapeutic strategies.

Chronic kidney disease (CKD). CKD refers to the structural or functional impairment of the kidneys by various causes (history of renal impairment >3 months) (132). The disease burden of CKD remains substantial and continues to grow globally. Globally, incident cases and DALYs of CKD was 18.99 million and 41.54 million in 2019, respectively (133), imposing a significant societal and individual burden. The clinical manifestations of CKD in different stages are different, but it's typical feature is renal fibrosis. One of the important factors promoting renal fibrosis is epigenetic changes (134-138). Research has confirmed that the methylation of specific genes can promote CKD progression. For example, HOXA5 promoter hypermethylation can enhance the expression of Jagged 1 (JAG1) gene expression, activate the JAG1-Notch signalling pathway and promote renal fibrosis (138). Similarly, the expression of the anti-fibrotic KLOTHO gene in the kidney is decreased due to hypermethylation in the early stage of renal injury. DNMT1/3A inhibition can reduce the loss of the KLOTHO gene, attenuating renal fibrosis and structural damage (137,139). Long-term cadmium exposure induces a compensatory increase in DNMT (140) and promotes hypermethylation of RASAL1, which is associated with a decreased estimated glomerular filtration rate (141). RASAL1 hypermethylation has been confirmed as an important mechanism in CKD *in vitro* (87,142). The study of epigenetics in CKD offers new diagnostic and therapeutic targets, and provides a new direction for the study of pathogenesis, diagnosis and treatment strategies.

Urinary dysfunction due to neurodegeneration. Parkinson's disease (PD) is a neurodegenerative disorder characterized by the abnormal deposition of α-synuclein (α-Syn), with the main clinical manifestation being movement disorders. With further research, non-motor symptoms of PD are gradually being recognized, with urinary dysfunction being one of the most common autonomic dysfunctions in patients with PD, affecting 27-85% of individuals with the disease (143). Although no studies have directly linked DNMT with urinary symptoms in PD, research has shown that mutations in DNMT1 can lead to defects in DNA methylation activity, resulting in neurodegenerative diseases (144). In addition, the abnormal accumulation of α-Syn in neurons of patients with PD can cause a vicious cycle of α-Syn accumulation by withholding DNMT1, leading to a decrease in the methylation level of the SNCA intron in the α-Syn gene. These findings suggest that DNMT may contribute to urinary dysfunction in PD by interacting with neurodegenerative processes (145).

Urological tumours

RCC. It is estimated that by 2024 kidney cancer will be the sixth most common cancer among men, with an incidence number of 52,380, and the ninth most common cancer among women, with an incidence number of 29,230 (2). The National Cancer Database, which conducted an epidemiological analysis of 262,597 patients diagnosed with renal cell carcinoma (2004-2015) across more than facilities, found that the metastatic rate of renal cell carcinoma was ~11 percent (146), leading to poor prognosis. For example, the 5-year survival rate for the most common clear cell RCC after metastasis is <10% (147). Therefore, early diagnosis and treatment are crucial for improving prognosis. As a malignant tumour, the role of epigenetics in RCC is significant. Overexpression of DNMTs often increases gene promoter hypermethylation, indicating gene inactivation or decreased expression ability (148). TSGs such as von Hippel-Lindau (VHL) (149), p16/CDKN2a, p14ARF, adenomatous polyposis coli (APC), RAS association domain family protein 1A (RASSF1A), B-cell translocation gene 3 (BTG3) and Timp-3 are hypermethylated in patients with RCC (150). The hypermethylation rate of the apoptotic protease-activating factor 1 promoter that induces apoptosis in RCC is ~100%, and the pro-apoptotic gene hypermethylation rate of ASC/TMS1 is ~41.1% (151,152). Promoter methylation of the HIG1 domain family member 1A and death-associated protein kinase 1 (DAPK-1) genes, which inhibit tumour metastasis, are strongly associated with RCC (153).

Additionally, promoter methylation of secreted frizzled-related protein 1 (sFRPs) (154,155), SCUBE3 (156) and GATA-5 (157,158) is associated with poor prognosis in RCC. However, surface hypomethylating agents have shown the potential to effectively reduce kidney damage and improve prognosis (159,160). Screening for specific gene methylation in the blood or urine of patients and applying demethylation drugs to the corresponding targets may become a future research directions for early non-invasive RCC diagnosis.

PCa. PCa is the fifth most common cancer in men, following lung cancer. In 2020, ~1,414,000 new cases were diagnosed, and 375,304 PCa-associated mortalities occurred worldwide (161), placing a significant burden on society. Although the prognosis of PCa is generally favourable, ~15% of the patients with high-risk forms of PCa may die within a few years (162). In the past few years, the rate of early diagnosis of PCa has increased due to the discovery of prostate-specific antigen (PSA) testing, reducing the mortality rate (163). However, due to concerns about the overdiagnosis and treatment of PCa and the complications of screening, the controversy about PSA continues, reducing the willingness to screen in certain

countries and slowing the decline of PCa mortality (164,165). Therefore, identifying new targets to replace or supplement PSA screening is one of the hot spots in PCa research (166).

Epigenetic changes are one of the important characteristics of PCa, offering potential new therapeutic directions by using them as a target (167). The androgen receptor (AR) gene is hypermethylated in advanced PCa, and may be related to metastasis (168,169), providing a new prognostic biomarker for PCa. Genes such as ubiquitin carboxyl-terminal hydrolase 1 (170), APC (171), E-Cadherin (172), ASC (173), cyclin d2, glutathione S-transferase pi-1 (GSTP1), retinoic acid receptor β (RARB), CD44 and RASSF1A, which are hypermethylated and suppressed in PCa, have high specificity and sensitivity, and are associated with poor pathological classification of PCa (174,175). Prostate cells are observed in urine, which may serve as important markers for early non-invasive diagnosis and prognosis of PCa in the future (176). The recurrence of PCa after treatment and the time to recurrence are the concerns of patients. Studies have reported that the methylation of CD44 and prostaglandin-endoperoxide synthase 2 (PTGS2) genes are associated with a shorter recurrence time, offering a valuable detection target for predicting the prognosis of PCa after surgery (177). The existing research results of epigenetics are significant for PCa diagnosis and treatment. For example, antitumour drugs such as methylation inhibitors 5-azacytidine and 5-aza-2'-deoxycytidine can specifically inhibit the methylation of certain genes that suppress tumour growth and metastasis and regulate cell cycle, playing a corresponding role in curbing tumour proliferation with fewer side effects; these drugs are likely to be significant in cancer treatment in the future (170,178-181). Therefore, epigenetic modification represents promising directions in PCa research.

BCa. BCa is the most lethal malignant tumour in the urinary system, with 549,393 diagnoses and 199,922 mortalities globally in 2018 (182). The incidence and mortality of BCa continue to rise (183), significantly affecting quality of life. NMIBC has a poor prognosis, with a 5-year recurrence rate of up to 78% (184). Unlike PCa, there is currently no universally accepted screening method for BCa, and patients with NMIBC often endure repeated cystoscopy, imaging and subsequent surgery, which are physically and psychologically stressful (185). Therefore, identifying feasible targets for early non-invasive diagnosis is crucial. The pathogenesis of BCa is complex, and epigenetic changes are one of its important characteristics. The methylation of certain specific genes has been proven to be a good biomarker (186). Promoter methylation of APC is significantly increased in BCa tissue and is associated with disease occurrence and progression, making it a key biomarker for the non-invasive detection of BCa.

Other genes, such as p14ARF (187,188), O6-methylguanine-DNA-methyltransferase (189), BCL2, CDKN2A, Nidogen (NID) (186), E-cadherin (CDH1) (190), CDH13 (191), RASSF1A (190), DAPK (192,193), fragile histidine triad (FHIT) (194), TIMP3 (195), growth/differentiation factor 15 (GDF15) and Transmembrane protein with an EGF-like and two Follistatin-like domains 2 (TMEFF2) (196) and vimentin (VIM) (196) are hypermethylated in BCa tissues, aiding early diagnosis. A methylation panel comprising of gene such as GDF15, TMEFF2 and VIM (196) has shown improved sensitivity and specificity for detection. DAPK, combined with B-ultrasound examination, has demonstrated consistency with cystoscopy results and has great significance in detecting recurrent BCa (193).

Each cancer has a specific methylation pattern (194), which makes the biomarkers specific and of great application value. However, the degree of gene methylation can vary across different populations due to ethnic differences (197), necessitating the development of other criteria based on ethnic differences. The degree of gene methylation is associated with aging, highlighting aging as a risk factors for BCa (190). These epigenetic biomarkers are important targets for early non-invasive diagnosis and treatment of BCa, and are indicators of treatment efficacy and prognosis. They help to explore the pathogenesis of BCa and identify risk factors related to BCa.

5. Molecular mechanisms of DNMTs in urinary system diseases

Decline in kidney function. The kidneys are closely related to the urinary system. In clinical practice, if renal function is impaired, it often leads to abnormal urinary drainage function of the urinary system. Studies have shown that epigenetic repair, especially DNA methylation, can severely affect kidney function. Oxidative stress is a major pathological factor contributing to aging-related diseases. Nuclear factor erythroid-derived 2-like 2 (NRF2) and KLOTHO, two major antiaging factors with antioxidant capacities, are suppressed with aging, which is associated with increased incidence of aging-related kidney disorders. A recent study has shown that upregulation of DNMT1/3a/3b expression results in promoter hypermethylation of NRF2 and KLOTHO and decreased expression of NRF2 and KLOTHO, resulting in structural and functional alterations in renal senescence (198). NRF2 inhibition significantly promotes ROS production while suppressing the antioxidant capacity of renal TEC under Ang II conditions (199). Zhao *et al* (200) showed that ROS production in turn promotes the up-regulation of DNMT1/3a/3b expression, leading to hypermethylation of the NDRG promoter and promoting renal fibrosis. Moreover, ROS activate the NF-κB signalling pathway to induce mitochondrial dysfunction, enhance autophagy and promote apoptosis in renal tubular epithelial cells (201). The Y-box binding protein-1 (YB-1) regulates fibrosis-related genes (for example, Col1a1, Mmp2 and Tgfβ1) and contributes significantly to disease progression. YB-1 binds to specific structural motifs in DNA, thereby recruiting DNMT to the promoter of KLOTHO, resulting in a decrease in KLOTHO expression, which subsequently leads to activation of the Wnt/β-catenin and TGFβ/Smad signalling pathways (202,203). Activation of the Wnt/β-catenin signalling pathway inhibits the mitochondrial biogenesis regulator Pparg coactivator 1α in renal tubular cells and reduces the mitochondrial membrane potential, oxygen consumption and ATP production, which is closely related to renal fibrosis (204). Whereas TGF-β increases DNMT1 and DNMT3a expression by inhibiting miR-152 and miR-30a in fibrotic kidneys thereby inhibiting KLOTHO expression (137). In addition, a recent study by Xiao *et al* found that the expression of DNMT1, DNMT3a and DNMT3b are significantly increased in CKD,

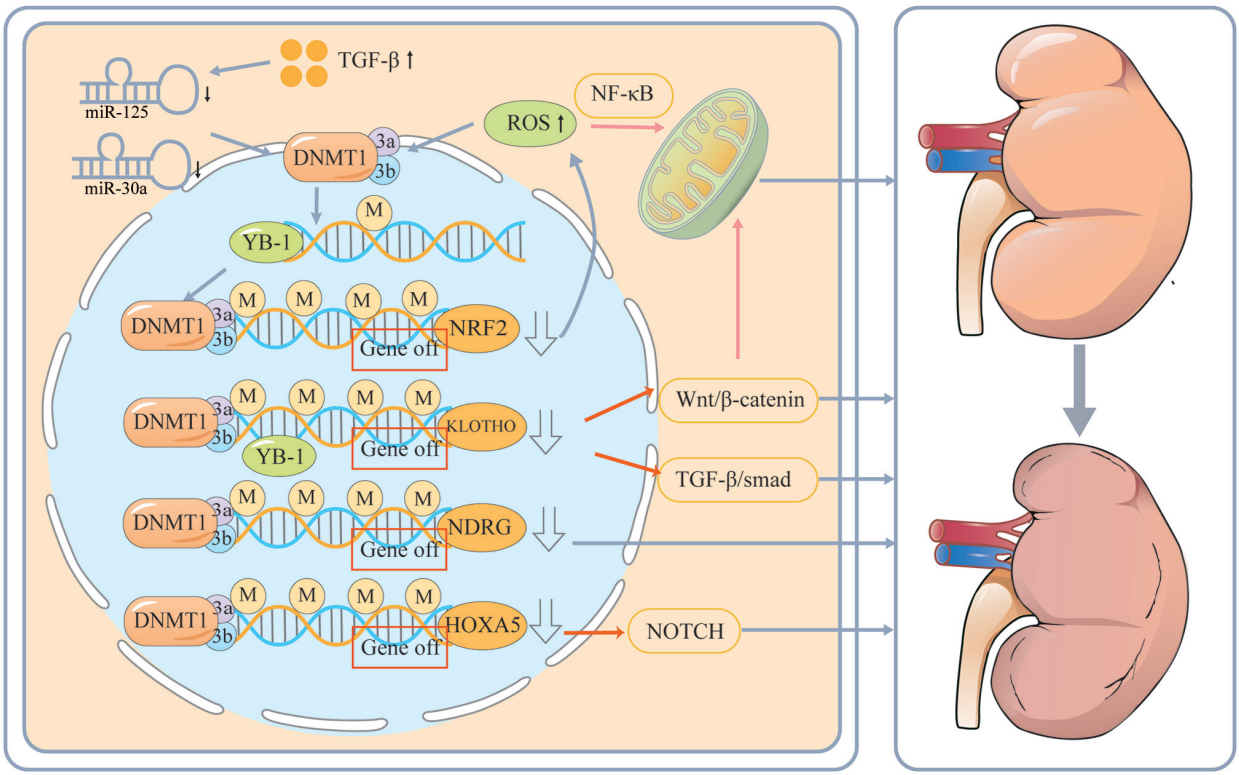

Figure 3. Role played by DNMT in the decline of renal function. DNMT, DNA methyltransferase; ROS, reactive oxygen species; NRF2, nuclear factor erythroid 2-related factor 2.

which leads to the hypermethylation of the promoter of HOXA4 and decreases its expression (138). A decrease in the expression of HOXA5 increases the expression of JAG1, which activates the NOTCH signalling pathway, resulting in fibrosis in the kidney (Fig. 3) (138,205).

Development of tumours of the urinary system. Aberrant DNA methylation (genome-wide hypomethylation and site-specific hypermethylation) are observed in numerous types of cancer (206-208). Abnormal DNA methylation has been shown to be strongly associated with numerous types of cancers, particularly with tumour suppressor genes, which play an important role in tumourigenesis and development (209). The active methyl group is transferred to the covalent bond at the 5' carbon position of cytosine of tumour suppressor genes mediated by the DNMT family, using S-adenosylmethylsulfonine as the methyl carrier. Silencing of gene expression due to hypermethylation of TSGs promoter regions is an important driver of tumourigenesis and progression (210). It remains less well understood how DNMTs are targeted to specific loci in the context of aberrant hypermethylation in cancer cells (211,212). Two possible molecular mechanisms have been proposed (213), one being that during genotoxic stress-induced DNA deletion, the aggregation of DNMT, histone deacetylase complexes and multi-comb complexes at CpG-rich promoters throughout the genome inhibits transcription (214). Alternatively, loss of ten-eleven translocation (TET) activity in cancer cells results in shortening of CpG islands and decreased gene expression through histone H3 lysine 4 mono-methylation (H3K4me1)-induced *de novo* DNMT invasion of DNA methylation (213). Early findings suggested that DNMT-mediated focal hypermethylation of TSGs directly triggers transcriptional silencing of TSGs and activation of signalling pathways such as Wnt/β-catenin (215), PI3K/AKT (216) and MAPK (217), which promotes cancerous aggravation. These three pathways play important roles in the occurrence and development of cancer.

Multiple studies have shown that Wnt plays a role in maintaining stem cells, assisting their self-renewal and cell generation capacity (218,219), and its abnormal changes are associated with the occurrence and development of a variety of cancers (220,221). For example, APC inactivation leads to the abnormal activation of β-catenin, thereby affecting the Wnt/β-catenin signalling pathway (222), leading to the progression of familial adenomatosis (FAP) to colorectal cancer (223). The phosphatidylinositol 3-kinase (PI3K/Akt) signalling pathway functions in regulating cell cycle, differentiation and metabolism (224), so the abnormality of this signalling pathway is common in cancer. The channel PI3K3A gene mutations or phosphate and tensin homolog (PTEN) gene promoter methylation leading to the decrease of the expression level is often associated with the development of breast cancer (225-227). The serine/threonine protein kinase MAPK, also known as ERK, is a key component of the Raf/MEK/ERK signalling pathway (228). Alterations in this pathway are the most common in human cancers and promote malignant proliferation of cancer cells (229). These three pathways are closely related to DNMT, suggesting that the methylation machinery is involved in the mutation and activation of the pathway (Fig. 4).

Promoter hypermethylation of TSGs is often the main mechanism of their loss of function in prostate cancer. Overall,

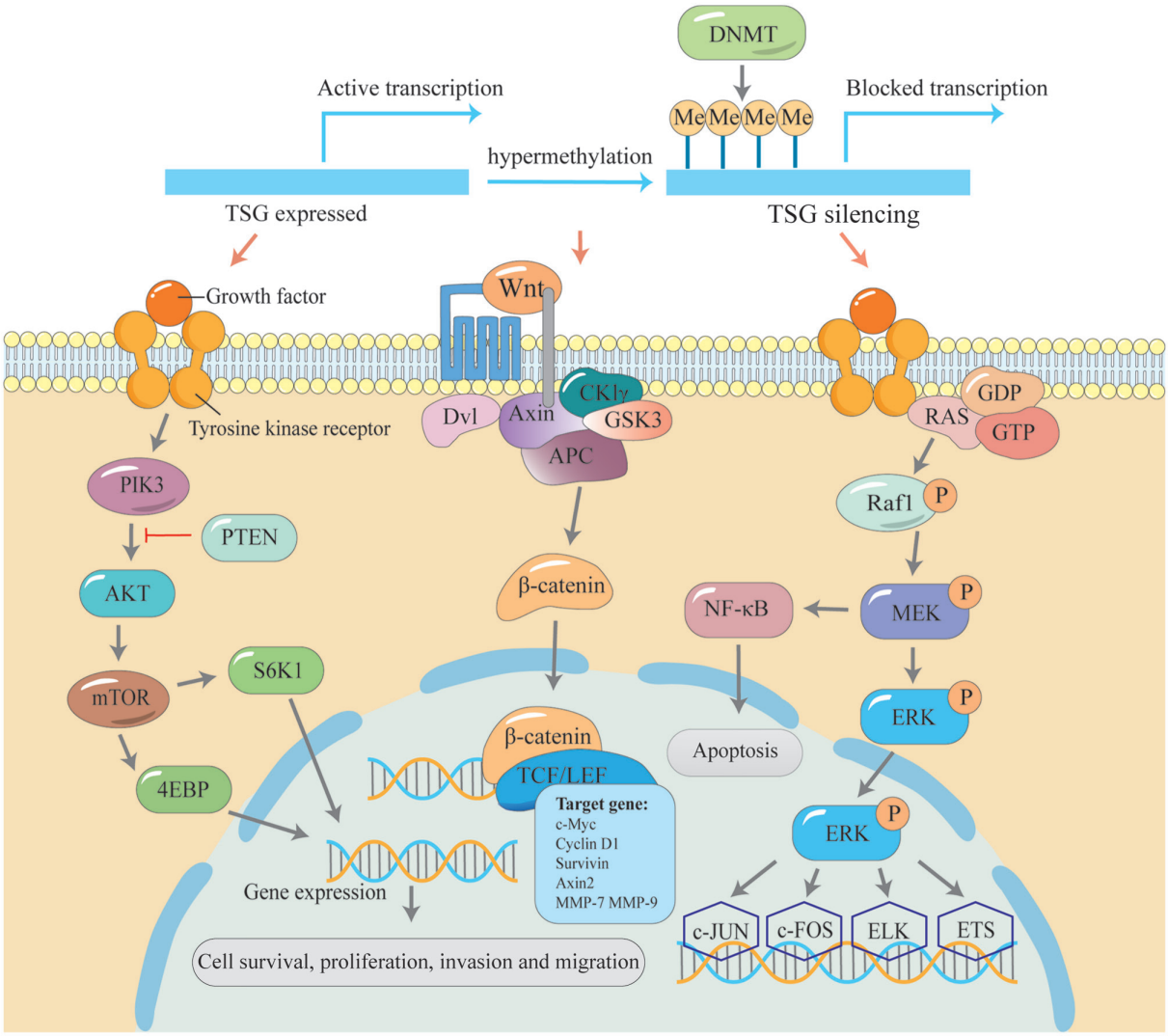

Figure 4. DNMT exerts pathogenic effects in urinary system tumours through three pathways. DNMT, DNA methyltransferase; TSG, tumour-suppressor genes; APC, adenomatous polyposis coli; Dvl, Dishevelled; GSK3, Glycogen Synthase Kinase-3; CK1 γ, casein kinase I γ; 4EBP; 6K1, S6 Kinase 1; Raf1, Raf-1 proto-oncogene, serine/threonine kinase; TCF/LEF,T-cell factor/lymphoid enhancer-binding factor.

>30 genes have been reported to be abnormally hypermethylated in prostate cancer, including genes involved in hormonal response, cell cycle regulation, cell invasion and DNA damage repair. Inappropriate silencing of these genes can lead to the occurrence, progression, invasion and metastasis of prostate cancer. The present review found that miR-148a, miR-152 and miR-200b increase DNMT1 expression, which results in the reduction of PTEN expression, which leads to the activation of the PIK3/AKT signalling pathway. In addition, loss of PTEN may lead to decreased expression of NK3 homeobox 1, thereby up-regulating AR-related signalling (230). Dickkopf Wnt signalling pathway inhibitor 3 (DKK3) inhibits the transmission of Wnt/β-catenin signalling pathway, and studies have shown that its expression is decreased in prostate cancer (231-233). Bhattacharyya *et al* (234) showed that increased DNMT activity and expression lead to methylation of the DKK3 promoter, which leads to the activation of Wnt/β-catenin signalling.

In renal cancers, the p16 and Thrombospondin 1 (THBS-1) genes seem to be hot spots of regional DNA hypermethylation during multistage renal tumourigenesis (235). Inhibition of THBS-1 expression can activate the PI3K/AKT pathway (236). In addition, KLOTHO, a tumour suppressor gene, normally binds to Wnt ligands to block the Wnt pathway (237-240). When DNMT activity is increased, KLOTHO methylation expression is decreased, and Wnt can be over-activated synergistically with TGF-β to induce epithelial-mesenchymal transition (241) and promote the differentiation of cancer stem cells (242), which can promote the occurrence and development of renal cell carcinoma. In conclusion, DNMT may down-regulate THBS-1 through the methylation of THSB-1 promoter and KLOTHO promoter to activate the PI3K/AKT and Wnt signalling pathways to promote cell proliferation in renal cell carcinoma.

In the detection of methylation of bladder cancer protective genes that are also Wnt antagonist genes such as secreted frizzled-related protein 1 (SFRP1), WNT inhibitory factor-1 (WIF1), APC and CDH1, it was found that in all the samples, at least one gene was found to be methylated and then down-regulated, leading to excessive activation of Wnt pathway and uncontrolled proliferation of bladder cells, which promote the occurrence and development of bladder cancer (243,244). In addition to antagonising the Wnt pathway, the SFRP1 gene

also inhibits the MAPK pathway (233,245). Therefore, when the activity of DNMT is increased, SFRP1 in the methylated state tends to promote the proliferation of bladder tumour cells. Decreased expression of a tumour suppressor gene may promote cancer cell proliferation through multiple mechanisms, so the importance of methylation is self-evident.

6. Potential clinical value of DNMT in human urinary system disease

Epigenetic changes are the common mechanism of a variety of diseases in the urinary system. Methylation may lead to specific gene expression decrease or even inactivation, affecting the function of the gene, and eventually leading to lesions (246). Fortunately, there are a variety of studies exploring how to use this feature for clinical use. DNA methylation plays an important role in early diagnosis, accurate treatment and prognosis evaluation. Firstly, some malignant tumours have been found to be associated with the methylation of tumour suppressor genes (247), and the present review found that there are some methylated genes in urinary system diseases such as kidney cancer, bladder cancer, prostate cancer and other malignant tumours that are specific due to the different methylation patterns of different cancers (194). As methylation variation can exist in the whole genome (248), Epigenetic Cancer of the Prostate Test in Urine (epiCaPture), as a detection method for high-risk PCA urine DNA methylation, measures the DNA hypermethylation in the 5' regulatory region of six genes (GSTP1, SFRP2, IGFBP3, IGFBP7, APC and PTGS2), all of which had previously been reported in PCa combined with PSA, the sensitivity and specificity of PCA assay are >70% (249). DNA methylation is stable and can be detected in almost any body fluid or tissue of the human body (250). Therefore, it is also non-invasive and effective in alleviating the pain of patients. In addition, methylated genes can also be combined with other examination methods such as DAPK combined with B ultrasound examination, which has been confirmed to be as accurate as cystoscopy (193).

At present, a variety of methylated genes have been found to have application value in the diagnosis of diseases. As an epigenetic marker in prostate cancer, GSTP1 has been shown to be hypermethylated in cancer tissues and various body fluid (251). Detection of GSTP1 in urine is even more relevant to the disease status than analysis of Gleason score in biopsy (252). ConfirmMDx, developed by MDxHealth Laboratories, has a negative predictive value of >90% for hypermethylated GSTP1, RASSF1 and APC (253). Therefore, the present study hypothesises that methylated genes can be used as one of the detection markers for early diagnosis in the future. Restoring the function of genes inactivated by methylation is the key to study the treatment strategy. Studies have revealed that reactivating tumour suppressor genes inactivated by methylation through targeted therapy may help treat specific types of cancer (254,255).

In addition to this, the use of specific drugs or techniques to intervene in the DNA methylation process has received widespread attention. For example, the expression of genes silenced by methylation is restored by inhibiting the activity of DNA methyltransferases or facilitating the action of DNA demethylases. At present, a variety of studies have found that DNMT inhibitors or demethylases play an important role in the cure of diseases, including diabetic nephropathy, chronic kidney disease, renal cell carcinoma, prostate cancer and bladder cancer (Table I) (160,198,256-260). For example, RG108, a non-nucleoside inhibitor of DNMT, exerts an antitumour effect by reversing the silencing of antitumour genes such as GSTP1 and APC in prostate cancer (258). In addition to its effect on malignant tumours, DNMT inhibitor SGI-1072 can also reduce renal aging changes by reversing the methylation of anti-aging factor KLOTHO and enhancing its expression (198), and this mechanism is related to the inhibition of oxidative stress, fibrosis and apoptosis (261). OLP, a DNMT inhibitor similar to SGI-1072, has been found to have a demethylation ability in D-galactose-induced senescent renal cells, effectively reducing DNMT1/3a/3b expression, decreasing the loss of antioxidant senescence factors KLOTHO and NRF2, and then ameliorating renal cellular senescence (198). Thus, they may also have a role in chronic kidney disease.

In addition, DNMT inhibitors can also be combined with other drugs, such as synergism with the HDAC inhibitor TSC, to effectively inhibit the proliferation of bladder cancer (259). As a pan-DNMT inhibitor, decitabine exerts important antitumour effects in highly DNMT-expressing neuroendocrine prostate cancer, inhibiting tumour progression mainly by suppressing the expression of neuroendocrine profile markers (77). Further study has shown that decitabine can also increase the expression of the drug target B7-h3, and an experiment has demonstrated that decitabine combined with the B7-h3-targeting agent DS-7300a (i-DXd) can effectively enhance the anti-tumour effect (262). As early as 2009, the combination of 5-Azacytidine with cisplatin has been reported to improve antitumour effects and reduce nephrotoxicity (263). 5-Azacytidine inhibits the expression of genes related to oxidative stress and reduces metallothionein gene expression, which reduces nephrotoxicity (263,264). 5-Azacytidine is also known to inhibit the expression of genes related to oxidative stress and reduce metallothionein gene expression, which reduces nephrotoxicity (263,264). The The combination of 5-Azacytidine with cisplatin has been reported to increase sensitivity and resistance (265,266). The reversal of methylation is relatively mild, and the side effects of DNMT inhibitors are relatively small (267), which can also effectively improve the quality of life of patients.

In addition, epigenetic changes, especially gene methylation, can respond to a variety of mechanisms, so it is also beneficial to explore the aetiology and pathogenesis of diseases. For example, if a certain gene methylation degree is found to be higher in hypertensive nephropathy and diabetic nephropathy than in healthy individuals, it can be verified by designed experiments when the causal relationship is not clear, which is helpful to find new treatment ideas. Finally, the prognosis of the disease can also be determined according to the degree of gene methylation. Several studies have confirmed that the hypermethylation of the BNC1 (268), GATA5 (157) and SCUBE3 (156) promoters often predicts poor prognosis of patients with renal cell carcinoma. The methylation levels of LAD1 (154,269) and NEFH (270) can also reflect the outcome of drug treatment of renal cell carcinoma to a certain extent, helping physicians to adjust the treatment plan in time. The promoters of p16INK4a and p14ARF are hypermethylated

Table I. Abnormally methylated genes and DNMT involved in corresponding processes in urinary system diseases.

Urinary system disease	DNMT	Hypermethylated genes	DNMT inhibitor	(Refs.)
Cystitis	-	CDKN2A, RASSF1A TIMP3, Calca, Timp3 Mmp2, Igf2r, Ogg	-	(98,103,104)
Hypertensive nephropathy	DNMT1 DNMT3a	SOD, Strt1	-	(113-114)
Diabetic nephropathy	DNMT1 DNMT3a	ACTN4, let-7a-3, RCAN1, MTHFR, KLOTHO,	5-Aza	(123,125-127, 130-131)
Chronic kidney disease	DNMT1 DNMT3a	HOXA5, KLOTHO, RASAL1	SGI-1072, OLP	(138,139,141)
Renal cell carcinoma	DNMT3b DNMT3a DNMT1	VHL, p16/CDKN2a, p14ARF, APC, RASSF1A, BTG3, Timp-3, APAF-1, ASC/TMS1, HIGD1A, DAPK-1, SCUBE3, GATA-5	Genistein 5-azacytidine	(148-160)
Prostate cancer	DNMT3b	UCHL1, APC, E-cadherin, ASC, cyclin d2, GSTP1, RARB, CD44, RASSF1A, PTGS2, GSTP, SFRP2, IGFBP3, IGFBP7,	Decitabine; RG108	(170-177,244, 249,271,272)
Bladder cancer	DNMT3b DNMT3a	APC, MGMT, BCL2, CDKN2A, NID, CDH1, CDH13, p14ARF, RASSF1A, DAPK, FHIT, TIMP3, TMEFF2, GDF15, VIM,	Decitabine; 5-azacytidine	(186-196)
Neurodegeneration	-	SNCA	-	(145)

DNMT, DNA methyltransferase.

in bladder cancer, and the degree of methylation is related to the malignant degree of bladder cancer. For example, the methylation of invasive bladder cancer is higher than that of superficial bladder cancer (188). The recurrence of prostate cancer after treatment and the time to recurrence are the concerns of patients. Studies have found that the methylation of CD44 is correlated with progression and metastasis in prostate cancer (271,272) and Yegnasubramanian *et al* (273) indicated that the hypermethylation of PTGS2 CpG islands predicted an increased risk of prostate cancer recurrence in 2004. Moreover, the methylation of CD44 and PTGS2 genes are associated with a shorter recurrence time, which provides a good detection target for predicting the prognosis of prostate cancer after surgery (177).

7. Future expectations

Rapid advances in the field of epigenetics not only reveal complex genetic phenomena at the molecular level, but also offer new hope for the treatment of diseases, especially cancer (274). Epigenetic changes have reversible properties, meaning that biological traits can be affected by reversing these changes under certain conditions. DNA methylation, histone modification and regulation of non-coding RNA have become the focus of epigenetic therapy. Currently, several epigenetic-based treatments have been developed, such as DNMTi. However, the main disadvantage of these methods is their lack of specificity, which can lead to off-target effects and other side effects (275-277). The CRISPR/Cas9 technology is a powerful tool that is currently widely used for genome editing. Its modular design is not only suitable for direct modification of DNA, but can also be used to introduce specific epigenetic modifications, such as methylation or demethylation (278). dCas9 fuses with the catalytic domain of DNMT or TET proteins, and the CRISPR/DCas9-DNMT or DCas9-TET system enables precise editing of DNA methylation. Liang *et al* (279) demonstrated that this fusion protein enables site-specific DNA methylation editing in zebrafish.

Because zebrafish embryos are transparent, grow rapidly and are highly homologous to human genes, they are an ideal model for studying vertebrates. Therefore, DNMTs fusion technology combined with CRISPR/Cas9 system has the potential to be used to specifically edit human DNA methylation in the future.

In the field of urinary tumours, some key epigenetic changes have also been found in prostate cancer. For example, GSTP1 and HOX family member genes are inhibited by hypermethylation in the promoter region. Kardooni *et al* (232) reported that downregulation of the DKK3 gene is associated with the growth of prostate tumours. The Dkk-3 protein encoded by the DKK3 gene maintains the stable state of normal prostate epithelial cells by regulating the TGF-β/Smad signalling pathway (261). Going forward, using CRISPR/dCas9-DNMT technology, it will be possible to regulate the expression of these genes through methylation or demethylation, thereby controlling tumour growth.

8. Conclusion

In conclusion, with the deepening understanding of epigenetics, more and more studies have demonstrated that DNMT-mediated aberrant methylation of genes plays an important role in the development of urinary system diseases. The present review systematically reviewed the mechanism and clinical value of DNMT in a variety of urinary system diseases. We found that targeting DNMT to find corresponding therapeutic approaches is of great significance in the treatment of urinary system diseases. It is hypothesised that DNMT will provide novel therapeutic ideas for urinary system diseases.

Acknowledgements

Not applicable.

Funding

This work was supported by the Weifang Municipal Health Commission Project (grant no. WFWSJK-2021-140) and Shandong Province Medicine and Health Science and Technology Development Programme Project (grant no. 2021BJ000026).

Availability of data and materials

Not applicable.

Authors' contributions

AW, YY and HW conceived the study. YY, YW, XF and XX wrote and edited the manuscript. XW, TS, YG, SL, AW and JT revised the manuscript. AW put forward constructive opinions on the topic selection of the article. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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