DNA Damage Repair and DNA Methylation in the Kidney

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Abstract

The DNA repair system is essential for the maintenance of genome integrity and is mainly investigated in the areas of aging and cancer. The DNA repair system is strikingly cell-type specific, depending on the expression of DNA repair factors; therefore, different DNA repair systems may exist in each type of kidney cell. Importance of DNA repair in the kidney is suggested by renal phenotypes caused by both genetic mutations in the DNA repair pathway and increased stimuli of DNA damage. Recently, we reported the importance of DNA double-strand break repair in glomerular podocytes and its involvement in the alteration of DNA methylation status, which regulates podocyte phenotypes. In this review, we summarize the roles of the DNA repair system in the kidneys and possible associations with altered kidney DNA methylation, which have been infrequently reported together. Investigations of DNA damage repair and epigenetic changes in the kidneys may achieve a profound understanding of kidney aging and diseases.

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Summary of the DNA Damage Repair System

DNA damage is caused by various stresses, including exogenous stress, such as UV radiation and chemicals, and endogenous stress, such as reactive oxygen species,

DNA replication errors, spontaneous reactions, and mechanical stress [1, 2]. Chronic stimulation by these stresses induces DNA damage, which is linked to aging and various diseases [3]. Eukaryotes have a DNA repair system in response to DNA damage to maintain genome integrity for survival. Various types of DNA damage exist, including double-strand breaks (DSBs), base adducts, interstrand crosslinks, and mismatch. Base adducts include oxidative and alkylating lesions, some of which may be mutagenic such as 7,8-dihydro-8-oxoguanine or toxic [4]. Interstrand crosslinks are toxic DNA lesions preventing transcription and replication by inhibition of DNA strand separation. Base mismatch arises during DNA replication and recombination. Injured DNA are repaired through DNA repair pathways, including nonhomologous end joining (NHEJ), homologous recombination (HR), base excision repair (BER), nucleotide excision repair (NER), translesion synthesis and mismatch repair (MMR), as shown in Figure 1 [1, 4].

In particular, DNA DSBs are biologically important since their repair is intrinsically more difficult than other types of DNA damage [5]. DNA DSBs are repaired by HR during cell division or by NHEJ in nondividing conditions. The Mre11-Rad50-Nijmegen breakage syndrome protein 1 complex is involved in both the NHEJ and HR pathways for DNA DSB sensing. NHEJ is a dominant pathway for repairing DNA DSBs in eukaryotes. The process of NHEJ is divided into 3 steps as follows: end bridging, end processing, and end joining to resect damaged DNA, fill in new DNA, and restore integrity to the DNA strands (Fig. 2). When a DSB occurs in vertebrates, a

Fig. 1. DNA damage repair pathways and the related factors. DNA DSB is a cytotoxic injury induced by radiation or chemicals. Base adducts is a mutagenic injury typically in cancer-causing chemicals. ICLs are covalent links of DNA duplexes, preventing transcription and replication. Base mismatch arises during DNA replication and recombination. DSB, double-strand break; ICL, interstrand crosslink; D-NHEJ, DNA-PKcs-dependent nonhomologous end joining; B-NHEJ, a backup to DNA-PKcs-dependent nonhomologous end joining; HR, homologous recombination; BER, base excision repair; NER, nucleotide excision repair; GG-NER, global genome NER; TC-NER, transcription-coupled NER; TLS, translesion synthesis; MMR, mismatch repair; SP, short-patch; LP, long-patch; MRN complex, meiotic recombination 11 homolog 1 (Mre11)-Rad50-Nijmegen breakage syndrome protein 1 (Nbs1) complex; ATM, ataxia telangiectasia mutated; KAT5, lysine acetyltransferase 5; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; 53BP1, p53-binding protein 1; PNK, polynucleotide

kinase; TDT, terminal deoxynucleotidyl transferase; XRCC, X-ray repair cross-complementing protein; XLF, XRCC4-like factor; POLII, RNA polymerase II; POLμ, λ, β, δ, ε, DNA polymerase μ, λ, β, δ, ε; LIG IV, III, I, DNA ligase IV, III, I; PARP1, poly(ADP-ribose) polymerase 1; CtIP, C-terminal-binding protein (CTBP)-interacting protein; BRCA1, breast cancer 1; EXO1, exonuclease 1; BLM, Bloom's syndrome protein; TDG, Thymine-DNA glycosylase; NTHL1, nth like DNA glycosylase 1; PCNA, proliferating cell nuclear antigen; FEN1, flap structure-specific endonuclease 1; XPC, XPE, XPB, XPD, XPA, XPG, XPF, Xeroderma pigmentosum, complementation group C, E, B, D, A, G, F protein; DDB1, 2, damage-specific DNA-binding protein 1, 2; RFC, replication factor C; ERCC8, 6, 3, 2, 1, excision repair 8, 6, 3, 2, 1; CSA, B, Cockayne syndrome A, B ortholog; TTDA, L(+)-tartrate dehydratase subunit alpha, MLH1, mutL homolog 1; PMS2, PMS1 homolog 2, MSH2, 6, 3, mutS homolog 2, 6, 3.

dimeric protein complex Ku70/80 X-ray repair cross-complementing protein (XRCC6/XRCC5) first binds the damaged DNA end, and the nuclease complex of Artemis and DNA-dependent protein kinase catalytic subunit (DNA-PKcs), some polymerases, including DNA polymerase λ and μ, and the ligase (LIG) complex of XRCC4, XRCC4-like factor, and DNA LIG IV are recruited [2].

This repair pathway is called the DNA-PKcs-dependent NHEJ (D-NHEJ) [2, 6]. Recent studies have demonstrated that there is an alternative form of NHEJ functioning as a backup to D-NHEJ, which is called B-NHEJ. In B-NHEJ, histone H1 and poly(ADP-ribose) polymerase 1 helps align the DNA ends prior to ligation without Ku and DNA-PKcs, followed by end processing and ligation

Fig. 2. Scheme of D-NHEJ and B-NHEJ pathways in DNA DSB repair. D-NHEJ, DNA-PKcs-dependent nonhomologous end joining; B-NHEJ, a backup to DNA-PKcs-dependent nonhomologous end joining; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; 53BP1, p53-binding protein 1; MRN complex, meiotic recombination 11 homolog 1 (Mre11)-Rad50-Nijmegen breakage syndrome protein 1 (Nbs1) complex; XRCC4, 1, X-ray repair cross-complementing protein 4, 1; XLF, XRCC4-like factor; PARP1, poly(ADP-ribose) polymerase 1; CtIP, C-terminal-binding protein (CTBP)-interacting protein; DSB, double strand break.

with C-terminal-binding protein-interacting protein, XRCC1, and DNA LIGIII [2, 6]. NHEJ is critical not only for the repair of DSBs induced by stresses but also for the repair of physiologic DSBs created during variable (diversity) joining V(D)J recombination and class switch recombination. Therefore, patients lacking normal NHEJ are not only sensitive to ionizing radiation but also severely immune deficient [2].

BER is the primary DNA repair pathway that corrects base lesions and facilitates the repair via 2 pathways as follows: short-patch (a single nucleotide repair) and long-patch (at least 2 nucleotides repair) [7, 8]. The BER pathway is initiated by glycosylases, such as thymine-DNA glycosylase by excision of damaged bases, and is followed by strand incision, gap-filling, and ligation; these processes are mediated by DNA polymerase β , XRCC1, and LIGIII in short-patch or by DNA polymerase $\delta\epsilon$, flap endonuclease-1, proliferating cell nuclear antigen, replication factor C, and DNA LIGI in long-patch [7, 8].

NER can be subdivided into several subpathways, including global genome repair and transcription-coupled repair (TCR, TC-NER) [4, 9]. TCR is conducted in the transcribed strand of active genes, which are nec-

essary to be repaired with higher priority. Global genome repair covers the component of NER that is not TCR.

MMR is conducted by MutSa homolog (MSH2-MSH6 heterodimer) or MutS β (MSH2-MSH3 heterodimer), MutL homolog 1-PMS1 homolog 2 heterodimer, proliferating cell nuclear antigen, replication factor C, and human exonuclease 1 [7].

Renal Phenotypes in Genetic Deletion of DNA Repair Pathways

Genetic deletion of these DNA repair pathways causes progeria, cancer, or immunodeficiency as summarized in Table 1. Precise mechanism of each repair pathway is not completely elucidated, and several DNA repair-deficient human syndromes are expected to remain undiscovered.

Renal phenotypes with genetic mutations of DNA repair factors may suggest the possible roles of the DNA damage repair system in kidney homeostasis. Kidney is classified as a slowly proliferative organ, which can divide in response to damages, and quite different from prolifer-

Table 1. Genetic deletion of DNA repair factors and renal phenotypes

Mutated genes	Affected pathways	Syndrome	Phenotypes	Renal manifestations
CSA (ERCC8)	TC-NER; GG-NER	CS type A	Progeria	Nephrotic synd, RPGN; glomerulosclerosis, hypertension [88], GBM thickening [89]
CSB (ERCC6)	TC-NER; GG-NER	CS type B	Progeria	Csa ^{-/-} or Csb ^{m/m} mice: protect from IR injury [26]
XPB, XPD, TTDA	GG-NER, TC-NER	TTD	Progeria	XP/TTD overlap: adult onset kidney failure [90]
CSB, XPD, XPG	TC-NER; GG-NER	COFS	Progeria	Not mentioned (high expression of XPG in human kidney [91])
XPF/ERCC1	TC-NER; GG-NER, ICL, HR	XPF-ERCC1 progeria (XFE)	Progeria	Liver-specific Ercc1 TG Ercc1 ^{-/-} mice: proteinuria, ESRD [14]
XPC	GG-NER	XP	Cancer	Not mentioned
XPB, XPF, XPD, XPG	TC-NER; GG-NER	XP combined with CS (XPCS)	Progeria/cancer	Nephrotic syndrome [92]
NTHL1	BER	NTHL1 deficiency	Cancer	Not mentioned
PMS2, MLH1, MSH2, MSH6, MLH3, MSH3	MMR	Lynch syndrome, HNPCC	Cancer	Not mentioned
FANC, BRCA2, FAN1	ICL repair	Fanconi anemia	Progeria/cancer	2/30 patients had CKD, 14/30 patients had anatomical abnormalities of the kidneys [93] Karyomegalic interstitial nephritis linking to chronic kidney failure [94]
BRCA1	DSB repair (HR)	Breast cancer 1, early onset	Cancer	Renal cell carcinoma [95]
BRCA2	DSB repair (HR)	Breast cancer 2, late onset	Cancer	Zebrafish BRCA2: essential for pronephros development [96]
ATM	DSB repair	AT	Progeria/cancer	Not mentioned
MRE11, PCNA	DSB repair, BER	ATLD	Progeria/cancer	Not mentioned
MRE11, ZNF423, CEP164SDCCAG8	DSB repair	NPHP-RC	Degenerative disorder	Renal fibrosis, ESRD [22–24]
NBS1	DSB repair	NBS	Progeria/cancer	Congenital renal anomalies (hypoplasia/aplasia, horseshoe or double kidney, ectopic/dystopic kidneys) are relatively frequent
LIGIV	DSB repair (NHEJ)	LIG4 syndrome, MPD	Cancer, (S)CID	Not mentioned
XLFI (Cernunnos)	DSB repair (NHEJ)	XLFI/Cernunnos immunodeficiency	Cancer, (S)CID	Not mentioned
Artemis (DCLRE1C)	DSB repair (NHEJ)	ARTEMIS deficiency, ART-SCID	Cancer, (S)CID	Not mentioned
DNA-PKcs	DSB repair (NHEJ)	DNA-PKcs deficiency	Cancer, (S)CID	Not mentioned
XRCC4 (XPF)	DSB repair (NHEJ)	MPD	Progeria	Not mentioned

(S)CID, (severe) combined immunodeficiency; RPGN, rapid progressive glomerulonephritis; IR, ischemic reperfusion; ERCC, excision repair; CSA, Cockayne syndrome A; XPC, XPB, XPF, XPD, XPG, Xeroderma pigmentosum, complementation group C, B, F, D, G, protein; NTHL1, nth like DNA glycosylase 1; PMS2, PMS1 homolog 2; MLH1, mutL homolog 1; BRCA2, breast cancer 2; ATM, ataxia telangiectasia mutated; MRE11, meiotic recombination 11 homolog; NBS1, Nijmegen breakage syndrome protein 1; XLFI, XRCC4-like factor; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; XRCC4, X-ray repair cross-complementing protein 4; TC-NER, transcription-coupled nucleotide excision repair; GG-NER, global genome NER; BER, base excision repair; MMR, mismatch repair; ICL, interstrand crosslinks; DSB, double strand break; CS, Cockayne syndrome; TTD, trichothiodystrophy; COFS, Cerebro-oculo-facio-skeletal syndrome; HNPCC, Hereditary non-polyposis colorectal cancer; AT, Ataxia Telangiectasia; ATLD, Ataxia Telangiectasia-like disorder; NPHP-RC, Nephronophthisis-related ciliopathies; LIG4, DNA ligase 4; MPD, microcephalic primordial dwarfism; CKD, chronic kidney disease; HR, homologous recombination.

erative organs, including skin, guts, myeloid, and testis. Genetic mutation in DNA repair factors causes malignancies in proliferative organs or degenerative manifestations in slowly- or nonproliferative organs, such as liver, kidney, and brain, if the individual escape from early death due to malignancy or severe immunodeficiency. If a repair factor is essential for kidney development, defect of the factor causes lethality, or anatomical renal abnormalities. DNA repair-deficient syndromes without kidney manifestations may indicate several possibilities. If deletion of a DNA repair pathway is lethal or causes malignancy early in life, kidney failure may be masked. Another possibility is the different degree of contribution to kidney DNA repair among the repair pathways. In addition, kidney is consisted of various cell types with different proliferative capacity; for instance, tubular cells and collecting duct cells are slowly proliferative while podocytes are basically nonproliferative. Therefore, it is distinctive that cell dysfunction caused by an impaired DNA damage repair pathway can induce various manifestations in diseases.

Deletion of the NER pathway causes accelerated aging with shortened lifespan with renal abnormalities and neurological impairment [10, 11]; examples include the Cockayne syndrome, which is caused by mutations in excision repair (ERCC)6 (Cockayne syndrome B, CSB) or ERCC8 (Cockayne syndrome A, CSA), trichothiodystrophy caused by mutations in ERCC2 (XPD), ERCC3 (XPB), or L(+)-tartrate dehydratase subunit alpha, and XPF-ERCC1 progeria, which is caused by dysfunction of the XPF-ERCC1 heterodimer [12, 13]. ERCC1-knockout mice suffer from severe neurological abnormalities and die before 3–5 weeks of age. A modified ERCC1 knockout mouse model expressing a liver-specific ERCC1 rescue transgene to prevent hepatic insufficiency develops proteinuria, segmental glomerulosclerosis, and considerable nuclear pleomorphism in proximal tubules at 3 weeks of age and progresses to end-stage renal failure [14]. Therefore, DNA damage repair through the NER pathway is considered to play a possible role in renal function.

On the other hand, a germline homozygous mutation in the BER gene *nth* like DNA glycosylase 1, a DNA glycosylase, causes colorectal malignancy, but renal complications are not mentioned [15]. Constitutional MMR deficiency, due to biallelic mutations of MMR genes, results in lymphoblastic T cell lymphoma, colorectal adenocarcinoma, and urinary tract tumors occurring mostly in childhood [16].

DNA DSBs are repaired through HR during cell division or NHEJ, and NHEJ is the dominant pathway in eu-

karyotes. Mutations in NHEJ-related genes, including DNA LIG IV, XRCC4-like factor-Cernunnos, Artemis, or DNA-PKcs, have been identified in patients with a malignancy and/or combined immunodeficiency since the NHEJ pathway is essential for V(D)J recombination [17]. Recently, patients with mutations in XRCC4 were reported to have symptoms similar to those of Cockayne syndrome, as previously described above [18, 19]. The Ku70/Ku80 mutation in patients has not been identified, although Ku80-knockout mice develop renal tubular anisokaryosis and cortical and medullary atrophy [20]. Anatomical renal abnormalities are reported in Nijmegen breakage syndrome, which is caused by a mutation of Nijmegen breakage syndrome protein 1 [21]. Nephropathosis and related ciliopathies are recently demonstrated to show altered DNA DSB repair pathway in humans [22, 23], and Apoptosis Antagonizing Transcription Factor is a key regulator in the mice nephropathosis and related ciliopathies model [24]. In addition, polymorphic allele of XRCC1 gene is recently reported to be significantly related with type 2 diabetes and diabetic nephropathy [25].

Several benefits associated with DNA repair deficiency have also been reported. Deficiency of a NER factor CSA or CSB in mice showed a protective effect against ischemic-reperfusion injury [26]. In addition, overexpression of *nth* like DNA glycosylase 1 glycosylase, a BER factor, causes genomic instability and cancer [27]. These results suggest that unrepaired DNA damage leads to either detrimental effects or beneficial adaptive changes depending on the tissue or cell types, which may contribute to the specificity of disease phenotypes. We summarize genetic mutations of DNA repair pathways and renal phenotypes in Table 1.

DNA Damage and Repair in Kidney Diseases

In addition to renal phenotypes of genetic deletion of DNA repair pathways, changes in the environment of kidney DNA damage repair, including increased DNA damage induced by activated renin angiotensin system, sepsis, and drugs, and impaired DNA repair caused by decreased expression of DNA repair factors, are reported in kidney diseases. Angiotensin II and aldosterone, which are key players in chronic kidney disease (CKD) progression, can cause DNA damage such as DSBs and DNA base modification to 8-hydroxy-2'-deoxy-guanosine [28, 29]. Increased DNA damage is also reported in acute kidney injury, including ischemia-reperfusion in-

jury [30] and sepsis induced by *Staphylococcus aureus* [31]. It is not difficult to anticipate that drug-induced kidney injury was associated with the DNA damage response [32, 33]. Puromycin aminonucleoside is a traditionally used agent to provoke minimal change nephrotic syndrome, and its effects are shown to be ascribed in part to DNA damage through reactive oxygen species in podocytes [34]. Of note, platinum drugs induce caspase-mediated apoptosis in tubular cells, while glomerular epithelial cells favor G2/M arrest when treated with equitoxic platinum doses [35, 36]. These results may suggest that activation of the DNA damage repair system is strikingly agent- and cell type-specific being reflected by the different expression of DNA repair factors [35]. Kidney is consisted of various types of cells, including endothelial cells, mesangial cells and podocytes in a glomerulus, tubular cells, collecting duct cells, and fibroblasts. Although the repair capacity of these cells has not been clearly identified, different responses to therapy may indicate the variability of DNA repair capacity in each cell type as described above. Further examination in each kidney cell type is necessary to elucidate the importance of DNA damage repair in kidney diseases.

Renal cell carcinoma (RCC) is also relevant to estimate an importance of DNA repair factors in the kidney. Dalgliesh et al. [37] reported systematic sequencing of RCC, and some cases existed with mutations in DNA repair genes. These results suggest an importance of the DNA repair factors, especially in tubular cells that RCC is mainly originated from.

Interestingly, recent studies suggest that the state of nutrition is associated with an environment of DNA damage induction and repair [38], although the molecular mechanism has not been fully demonstrated. In diabetic nephropathy, which is a representative of nutritional and metabolic kidney disorders, DNA damage is increased such as serum 8-hydroxy-2'-deoxy-guanosine, a biomarker for oxidative DNA base modification, and DNA DSBs [39, 40]. Recently, we have reported that the expression of the DNA DSB repair factor lysine acetyltransferase 5, Tip60 (KAT5) in podocytes is reduced in diabetic nephropathy in mouse models and humans. It has been revealed that high glucose causes not only increased induction of DNA DSBs but also decreased KAT5 expression, both of which lead to the accumulation of DNA DSBs [40].

In addition, DNA damage response-regulated kinases act on multiple substrates involved in glucose metabolism [41, 42]; therefore, it is possible that the DNA damage re-

sponse directly modulates certain aspects of energy metabolism and vascular physiology that are relevant to metabolic syndromes [43].

Association of DNA DSB Repair with Altered DNA Methylation

When damaged DNA is repaired, epigenetic marks are also reconstituted. Therefore, many epigenetic modulators are involved in the DNA repair process [44]. The accumulation of repair failures may cause changes in the epigenome, including histone modifications and DNA methylation, and in gene expression, as shown in Figure 3 [45, 46]. In particular, DNA methylation is considered to be more stable than other types of epigenetic marks and may contribute to sustained changes in gene expression. Therefore, this review is focused on DNA methylation and DNA damage repair.

In tumorigenesis, DSBs induce DNA hypermethylation of the gene promoter region, which leads to decreased gene expression in in vitro models [47, 48]. Several studies have suggested a relationship between DNA methylation and DNA damage repair. DNA methyltransferase 1 (DNMT1) is recruited to DSB sites where it colocalizes with the phosphorylated histone H2AX (γ H2AX) to silence the repaired gene [44]. Increased DNA methylation due to DNMT1 action may indicate epigenetic memory denoting a former damage [46, 47]. Although DNMT1 is basically a maintenance methyltransferase that mainly methylates hemimethylated CpG sites during cell division, recent studies have revealed that it may also have a role in de novo methylation [49–51]. Previous reports have indicated that the cooperation of DNMT3 enzymes with DNMT1 achieved de novo DNA methylation more efficiently [52, 53]. However, how DNA damage and repair can lead to the acquisition of aberrant DNA methylation is not still uncovered, especially in in vivo disease models.

DNA DSB Repair and DNA Methylation in Kidney Podocytes

Recently, growing evidence has suggested that epigenetic mechanisms are associated with kidney functions and diseases [54]. Combining the results of the GWAS meta-analysis and chromatin annotation maps, the importance of altered transcriptional regulation as a contributing mechanism to CKD has been demonstrated [55]. Moreover, recent epigenome-wide studies have identified the

Fig. 3. DNA damage, DNA methylation, and diseases. DNA DSBs followed by its sensing and signal transduction, cause either DNA repair or apoptosis depending on the severity of the damage. Impaired DNA repair may induce epigenetic changes such as altered DNA methylation, which leads to dysregulation of the genes and genomic instability. Me, DNA CpG methylation; PARP1, poly(ADP-ribose) polymerase 1; ATM, ataxia telangiectasia mutated; DSB, double strand break.

DNA methylation status associated with kidney function using saliva, whole blood or kidney specimen to analyze DNA methylation sites [56–60]. These results indicate that the investigation of epigenetic changes associated with CKD is important to understand the pathogenesis of CKD.

Possible roles of podocyte DNA methylation on CKD have been suggested in several *in vivo* models [61–63]. Altered DNA methylation causes phenotypical changes in podocytes [64, 65] and may lead to disruption of the slit membrane, proteinuria, and glomerulosclerosis. Podocytes, visceral epithelial cells, are terminally differentiated cells with a very low capacity of regeneration in adult mice under normal conditions [66, 67]; thus, it may contribute to the irreversibility of glomerulosclerosis and kidney aging [68]. Why and how changes in DNA methylation occur in podocytes without cell division? One of the mechanisms may be involved in the DNA damage repair system. It is reported that there are an estimated 10–50 DSBs per day in dividing cells [2, 69]. In nondividing cells, estimates of DSB frequency are difficult because they do not undergo metaphase. Therefore, it is not clear how many DSBs are induced in podocytes per day, although a large amount of DSB stress may exist around

podocytes. Very few DNA DSB sites, which are shown as γ H2AX-positive areas, were observed in the kidneys of healthy young mice [40], suggesting that the DNA repair mechanism may be important in podocytes with physiological states.

Recently, it was reported that knockdown of podocyte KAT5 expression causes focal segmental glomerulosclerosis with increased DNA DSBs and phenotypical changes in podocytes [40], suggesting the importance of the KAT5-mediated DNA repair system for the maintenance of healthy podocytes. TIP60/KAT5 is a member of the MYST family of histone acetyltransferases. KAT5 activates ATM and DNA-PKcs, which is an important factor for NHEJ repair. Acetylation of γ H2AX by KAT5 induces the initiation of ubiquitination of γ H2AX, which promotes the release of γ H2AX from chromatin following DSBs [70].

Impaired KAT5-mediated DNA repair is associated with increased DNA methylation through DNMT1 and DNMT3B in podocytes. Although each deletion of DNMT1, DNMT3A, or DNMT3B in podocytes lacked phenotype development [71], double knockdown of DNMT1 and DNMT3B in cultured podocytes caused significant changes in DNA methylation of the nephrin

promoter region and nephrin expression [40]. Similar results have shown in brain neurons that DNMT1 and DNMT3A play an essential coordinately role on memory formation [72]; however, the precise mechanism has not been clarified. Similar to neurons, maintenance of DNA methylation mediated by the coordinate action of DNMTs may be necessary in podocytes and that epigenetic alterations may occur even in static states. Future investigations are necessary to establish an evident role of maintenance DNA methylation in podocyte function. The association of DNA damage repair with DNA methylation changes in other kidney cells would be revealed in future studies.

The involvement of DNA damage repair in altered DNA methylation may be one of the reasons for site-specific changes in DNA methylation. The frequency of DNA damage depends on the chromatin status of condensation [73–75], and DNA wrapped in nucleosomes is not a good substrate for DNMTs [76–78]. A more relaxed or “open” chromatin conformation is prone to both exogenous and endogenous damages and leads to an enhanced DNA damage response. Therefore, the specificity of changes in DNA methylation may be partially dependent on chromatin accessibility.

Conclusion and Future Perspectives

Recent advances in the research of the DNA damage repair system, including the discovery of related factors and elucidation of the association with nutrition and metabolism, will help us understand kidney diseases from a new aspect. The importance of the DNA damage repair processes has been mainly investigated in aging. Aging and age-related diseases are caused in part by the accumulation of DNA damage, which is probably due to declining DNA repair capacity as well as ongoing DNA damage induction [43, 79]. Further studies of DNA damage repair in the kidney may lead to investigating strategies for the protection of renal function against kidney aging as well as kidney diseases.

Moreover, the association of DNA damage repair with altered DNA methylation may provide an explanation of cell-specific or gene-specific changes in DNA methylation in various diseases. We speculate that the specificity may be determined in part by the environment of DNA damage repair, including the chromatin status (open or closed), length of the genes [38], dividing or nondividing conditions, and expression of DNA repair factors. In our experiment, deletion of DNA DSB repair factor KAT5 in

podocytes develops massive proteinuria and renal failure, whereas deletion of KAT5 in proximal tubular cells or endothelial cells caused no significant renal manifestations (unpublished data). These results suggest the cell-specific pathway of DNA repair in the kidney. Recent techniques of single-cell analysis may contribute to elucidate kidney cell-specific DNA repair pathway [80]. Park et al. [81] reported gene expression data analyzed by single-cell transcriptomics study in the kidney. There are differences between the gene expressions of DNA repair factors in each cell type. Future study may reveal the relationship between different expression of DNA repair factors and kidney phenotypes of diseases.

To apply epigenetic therapy for kidney disease, focusing on the mechanism of cell-specific epigenetic changes is important for preventing side effects. Remodeling of cell-specific epigenetic status that is altered in pathophysiological conditions may become novel therapeutic approach for CKD. DNMT inhibitors and histone deacetylase inhibitors are available for clinical use in hematological malignancies; however, there are concerns about the side effects of applying these drugs for kidney diseases. The association of the DNA repair system with epigenetic alterations may suggest a novel approach, targeting the kidney epigenome. In general, numerous ethical issues are expected to be raised by epigenetic modulation for therapy. Because epigenome is heritable, epigenetic changes caused in gamete formation may affect the next generations. Careful discussion is necessary especially in considering the application for persons with future reproduction.

Transcription factors may also be good candidates because the specificity of epigenetic modulation is determined in part by a combination of transcription factors and epigenetic modifiers, which often form a complex [82, 83]. It has been reported that the transcription factor Kruppel-like factor 4 mediates gene-specific epigenetic regulation in podocytes, which is associated with the renin angiotensin system and CKD progression [61, 62]. Investigation of the epigenetic-modifying complex, including Kruppel-like factor 4, in podocytes may be helpful for the development of epigenetic therapy for CKD. For applying transcription factors as therapeutic targets, to investigate the molecules acting as activators, inducers or stabilizer of the transcription factors may be one of the approaches, such as Nrf2 [84, 85] and hypoxia-inducible factor [86, 87]. The pleiotropic effects of transcription factors may sometimes be harmful in clinical use, as transcription factors often regulate multiple target genes. To reduce the side effects, it is necessary to explore specific

induction pathways in a particular tissue or cell type and to develop a novel drug delivery system to the specific target cells.

DNA damage repair and altered epigenetic regulation have been infrequently reported together; however, the possible relationship of these systems may contribute to a novel approach against kidney aging and diseases. Future investigations about the environment of DNA damage repair and epigenetic alterations in the kidney are needed.

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Disclosure Statement

The authors declare no conflicts of interest related to this study.

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