INTRODUCTION

Although ROS and RNS play an essential role in the maintenance of human health, an excess of ROS or RNS has been implicated in the pathogenesis of various diseases.1 The kidneys are remarkable organs, performing many of the functions that are essential to regulating body fluids and blood pressure, waste product excretion, and red blood cell production. Kidney diseases pose a worldwide health problem, and cause significant morbidity and mortality among adults, particularly among older people. Although blood supply to the kidney accounts for 20% of cardiac output, the presence of oxygen shunt diffusion between the arterial and venous vessels, which run parallel to and in close contact with each other, means that renal tissue oxygen tension is relatively low2,3 (Figure 1). The O2 consumption rates of kidney mitochondria are higher than those of other organs,4 and hydrogen peroxide (H2O2) release accounts for 0.1%–0.2% of total consumed oxygen.5 Lower oxygen tension reduces oxidative phosphorylation and participates in generation of O2•− and NO, which in turn initiates the formation of a range of other ROS and RNS (Figure 2). Here, we review the physiological and pathophysiological role of ROS and RNS in normal kidney function and in various kidney diseases.

PHYSIOLOGICAL ROLE OF ROS AND RNS IN THE KIDNEY

The number of mitochondria in kidney cells varies from cell to cell. The renal phenotypes of most mitochondrial diseases associated with increased ROS are tubulopathies and focal segmental sclerosis,6 suggesting that the main source of ROS differs among kidney cells (Figure 3). Most research to date has focused on the adverse effects of ROS in kidney diseases. However, Dugan et al7 showed that O2•− generation was significantly lower in diabetic kidneys than...
in the non-diabetic controls; high plasma glucose levels reduced mitochondrial $O_2^{\cdot-}$ production in cortical homogenates of diabetic mice; and that high levels of mitochondrial $O_2^{\cdot-}$ were protective and restored renal function in an AMPK-dependent manner. In addition, Haque et al. \(^8\) showed that the endogenous production of $O_2^{\cdot-}$ induced by vascular nicotinamide adenine dinucleotide phosphate oxidase (Nox) plays an important regulatory role in maintaining normal renal vascular tone using gp91$^{\text{PHOX}}$, a subunit of Nox, knockout mice. In addition, myeloperoxidase (MPO), a peroxidase enzyme, knockout mice were reported to show exacerbated atherosclerosis, \(^9\) while chronic antioxidant supplementation was reported to impair coronary endothelial function and myocardial perfusion in normal pigs. These findings suggest that ROS are more than simply "unwanted" second messengers, but rather play some physiological role in the kidney.

In the case of RNS, three isoforms of NO synthase (NOS) are expressed at various locations in the kidney, \(^{10}\) with higher NO levels observed in the medulla. \(^{11}\) In general, NO acts as a vasodilator and contributes to lowering vascular tone in the kidney. \(^{12}\) On the other hand, NO produced by the macula densa is involved in renin secretion and tubuloglomerular feedback via vasoconstriction of the afferent artery. \(^{13,14}\) These findings suggest that the vascular response to RNS might depend on the amount of RNS and the vascular bed, as is also observed with ROS. The proximal tubules (PTs) play the major role in solute and fluid reabsorption in the kidney and regulate the pH of the filtrate by exchanging hydrogen ions (H$^+$) in the cytoplasm and bicarbonate ions in the filtrate. They also secrete organic acids, including creatinine, into the filtrate. Fluid is also reabsorbed into the peritubular capillaries from the lumen of the PTs via Na$^+$/K$^+$-ATPase and the Na$^+$/H$^+$ exchanger. \(^3\) In rats, intratubular administration of N$\omega$-nitro-L-arginine methyl ester, an NOS inhibitor, increased fluid reabsorption, \(^{15}\) and nNOS knockout mice showed higher fluid reabsorption rates than wild-type mice. \(^{16}\) In contrast, another report showed that high concentrations of NO also stimulate reabsorption in the PT. \(^{17}\) In addition, nNOS and iNOS knockout mice have lower PT reabsorption rates than wild-type mice. \(^{18,19}\) These results suggest that NO intricately regulates reabsorption in the PTs.

### 3 | ROS AND RNS IN ACUTE KIDNEY INJURY

Acute kidney injury (AKI), defined as abrupt renal dysfunction, is a common complication in critically ill patients. About 30% of patients...
admitted to intensive care units (ICUs) develop AKI, which is associated with high levels of morbidity and mortality.\textsuperscript{20} AKI is not a transient pathology, and is a major risk factor for chronic kidney disease (CKD).\textsuperscript{21,22} Numerous studies suggest that oxidative stress and its systemic effects play pivotal roles in the development of AKI. In this section we review the pathological role of ROS in AKI (Figure 4).

### 3.1 Ischaemia–reperfusion injury

Ischaemia–reperfusion injury (IRI) is another important pathological condition that leads to AKI. IRI-induced AKI occurs in association with several clinical conditions, and is the main cause of delayed graft function or graft loss after kidney transplantation.\textsuperscript{23} Ischaemic cells die if blood flow is not restored, but most IRI damage is in fact initiated during reperfusion. The first damaging event that occurs after reperfusion is a burst of $O_2^\cdot-$ production from the mitochondria. This triggers the pathology that develops over the minutes, days, and weeks that follow reperfusion.\textsuperscript{24,25} This mechanism contributes to the initiation and maintenance of AKI.\textsuperscript{26} Even under normal physiologic conditions, oxygen delivery to the outer renal medulla is poor, because of the distance between the outer renal medulla and the descending vasa recta. The S3 segments of the PTs in the outer renal medulla are particularly susceptible to both the ischaemic and reperfusion phases of IRI, which can lead to acute tubular necrosis.\textsuperscript{27} IRI induces an early infiltration of inflammatory cells that consist mainly of neutrophils.\textsuperscript{28} ROS from neutrophils are prominent in inflammatory mechanisms, but the ROS themselves are important for neutrophil recruitment. Recently, Tanaka et al\textsuperscript{29} showed that vascular adhesion protein-1 in pericytes, namely stromal cells which support the vasculature, plays a critical role in the pathophysiology of renal IRI. It does this by enhancing neutrophil infiltration via generation of a local $H_2O_2$ gradient. Furthermore, the importance of ROS has been confirmed by the findings of a study that showed the importance of nuclear factor erythroid 2-related factor 2 (Nrf2), which is the master regulator of the oxidative stress response.\textsuperscript{30} Following IRI, Nrf2-regulated cell defense genes have been found to be elevated in the kidney of wild-type but not Nrf2-knockout mice\textsuperscript{31,32} and the severity of renal IRI is exacerbated by the loss of Nrf2.\textsuperscript{32} In addition, hyperactivation of Nrf2 in tubules prevents the progression of tubular damage by suppressing IRI-mediated oxidative stress during the early progressive phase of renal IRI injury.\textsuperscript{33}

### 3.2 Septic acute kidney injury

Sepsis is the most common pathological condition that causes AKI in ICUs.\textsuperscript{34} While a variety of bacterial products cause the inflammatory response that occurs in sepsis, one of the most important endotoxins is lipopolysaccharide (LPS), a major component of the outer membrane of Gram-negative bacteria. A family of transmembrane proteins, the Toll-like receptors (TLRs), recognize and bind to a variety of bacterial products, including LPS. This binding triggers innate immune responses and the development of antigen-specific acquired immunity.\textsuperscript{35} The LPS ligand is specific to TLR4 and, once activated by ligand binding, TLR4 transduces its downstream signalling mainly through the inhibitor of I\(\kappa\)B kinase (IKK)/inhibitor of kappaB (I\(\kappa\)B)/NF-xB signalling pathway. IKK phosphorylates I\(\kappa\)B and induces its degradation, consequently leading to NF-xB nuclear translocation and the transcriptional induction of pro-inflammatory...
cytokines/mediators, including tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). TNF-α and IL-1β promote H₂O₂ generation and exacerbate the inflammatory response. Cunningham et al. showed that mice that lacked TLR4 were resistant to LPS-induced mortality and LPS-induced AKI. In addition, TLR4 knockout mice were resistant to cecal ligation and puncture, which is a well-established animal model of septic AKI. These data indicate that the increase in the level of ROS induced by LPS-TLR4 signalling is the main pathological manifestation that underlies septic AKI.

3.3 | Contrast-induced nephropathy

Contrast-induced nephropathy (CIN) is defined as an impairment of renal function. This condition occurs when the serum creatinine (sCr) level increases by 25% from baseline or when the absolute sCr value increases to 0.5 mg/dL (44 μmol/L) within 72 hours of an intravascular injection of iodinated radiographic contrast media, which is used to improve the visibility of organs and structures in X-ray-based imaging techniques, including computed tomography. The iodine-containing non-ionic radiocontrast iodixanol directly constricts the outer medullary descending vasa recta by reducing the bioavailability of NO and significantly increases the vasoconstriction induced by angiotensin II, thereby causing severe local hypoxia. Animal experiments have demonstrated that the reductions in cortical and medullary microvascular blood flows induced by contrast medium are partly accounted for by the downregulation of endogenous renal cortical and medullary NO synthesis. The protective effect of superoxide dismutase (SOD) against CIN has been demonstrated in animal models. The SOD mimetic Tempol lessens the iodixanol-induced vasoconstriction by reducing the levels of NO generated in the medullary descending vasa recta during the administration of contrast media. Recombinant SOD2 reduced renal oxidative stress when administered to rats that had received diatrizoate, thereby preventing reductions in glomerular filtration rate (GFR) and the renal histologic damage that follows the administration of contrast media. Although clinical trials have investigated the protective effects of antioxidants against CIN, findings have not clearly demonstrated a protective effect of N-acetyl-L-cysteine or ascorbic acid against CIN.

4 | ROS AND RNS IN CHRONIC KIDNEY DISEASE

Chronic kidney disease is the progressive loss of kidney function over months or years. Chronic hypoxia in the tubulointerstitium is thought to be the final common pathway to end-stage renal failure, and, as described above, a major manifestation that induces oxidative stress. Many antioxidant systems protect the kidney against ROS-induced oxidative stress, and the major cellular defense against O₂⁻ is SOD. All three SOD isoforms are present in the kidney. The SOD1 isoform accounts for up to 80% of the total SOD activity in the mammalian kidney. SOD1 activity declined in a chronic hypoxic kidney model induced by unilateral renal artery stenosis. Furthermore, expression of SOD1 is lower in the kidneys of patients who have glomerular nephritis compared with that in healthy control individuals. Usually, SOD levels in the mitochondrial matrix are low. Moreover, expression of the SOD2 gene in neutrophils from CKD patients is downregulated after LPS stimulation. Besides, interstitial fibrosis is the common process in CKD, and ROS and oxidative stress appear to be important in renal fibrosis in a manner that is independent of the primary cause, leading to kidney damage.
this section, we review the importance of ROS in the pathophysiology of the major causes of CKD.

4.1 | Diabetic kidney disease

Hyperglycaemia can cause a rise in the concentration of both $O_2^-$ and NO. Indeed, an increase in the production of ROS/RNS, and the subsequent changes in the redox state and in cellular homeostasis, have been described in association with diabetes. While there are many sources of ROS/RNS, we will focus on the mitochondria. Nox and peroxynitrite (ONOO$^-$) in diabetic kidney disease (DKD). A master regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor $\gamma$ coactivator 1$\alpha$ (PGC-1$\alpha$), is downregulated in patients with diabetes, and a decrease in the mitochondrial DNA (mtDNA) content has been found in the peripheral blood of patients with non-insulin-dependent diabetes mellitus before diabetes developed. MtDNA is essential for normal mitochondrial function, and a decrease in mtDNA is associated with an increase in the production of $O_2^-$ from the mitochondria. In addition to regulating mitochondrial biogenesis, PGC-1$\alpha$ is a broad and powerful regulator of ROS metabolism that induces ROS-detoxifying enzymes, which are associated with increases in ROS levels in DKD. A renoprotective role of PGC-1$\alpha$ has been reported but is still elusive in diabetes. Mitochondria are extremely dynamic organelles that shift between elongation (fusion) and fragmentation (fission). Mitochondrial fragmentation is the key mechanism in high glucose-induced increases in mitochondrial ROS production. Patients with type 2 diabetes have reduced expression of the mitochondrial fusion protein mitofusin-$2$, and increased levels of activity of the fission protein dynamin-related protein 1 (Drp1). Deletion of Drp1 from podocytes isolated from diabetic mice reduced $O_2^-$ production, and the pharmacologic Drp1 inhibitor, Mdivi-1, reduced the high glucose-induced mitochondrial $O_2^-$ levels in podocytes. However, the question of whether mitochondria increase $O_2^-$ production in DKD is controversial. Some reports have shown decreased mitochondrial $O_2^-$ production in DKD. This discrepancy among studies might be explained by the different animal models used and different stages of DKD. In any case, the relationships among mitochondria and oxidative stress in DKD require further investigation.
Nox is a key source of $O_2^\cdot$ production in different organs, including the kidney, under hyperglycaemic conditions. Nox4 is a major source of $O_2^\cdot$ in the kidney, and plays a pivotal role in the initiation and development of DN. $^6$ Nox4 expression is elevated in the diabetic rat kidney, $^7$ and Nox4 inhibition or the genetic deletion of Nox4 protects against DN. $^8$ High glucose-induced increases in Nox4 expression also involved reductions in the activity of adenosine monophosphate-activated protein kinase (AMPK), while the activation of AMPK by 5-aminonimidazole-4-carboxamide-1-β-D-ribofuranoside inhibited Nox4 and Nox4-dependent kidney hypertrophy, albuminuria, and matrix protein expression. $^9$

ONOO$^-$ and its secondary metabolites can damage a variety of cellular components. Due to the extremely short lifetime (~10 ms) of ONOO$^-$ in physiological environments, it has proved difficult to measure, but recent progress in fluorescent image methods has shown an increase in ONOO$^-$ levels in the kidney of diabetic rats. $^8$ This finding is consistent with previous findings of increased ONOO$^-$ in renal homogenates. $^9$ In this manner, the importance of RNS in the pathophysiology of diabetic kidney might in future be revealed.

### 4.2 | Nephrosclerosis

Nephrosclerosis is a gradual and prolonged deterioration of the renal arteries. However, renal vascular lesions are seen in some patients in the absence of or preceding the onset of hypertension, $^8$ and aging kidneys display lesions that are similar to those associated with nephrosclerosis without the accompanying high blood pressure. The direct and indirect actions of ROS may cause vasoconstriction of the intrarenal vessels. $^7$ ROS can inactivate endothelial NO, which results in impaired vasodilatation, and excessive oxidative stress is involved in impaired endothelium-dependent vasodilatation in patients with renovascular hypertension. $^8$ While ROS can induce vasoconstriction or vasodilation, depending on the amount produced and the vascular bed, $^8$ the more common response to $O_2^\cdot$ is vasoconstriction. $^2$ $O_2^\cdot$ induces an increase in intracellular calcium levels in smooth muscle and endothelial cells, $^8$ which mediate the actions of other vasoconstrictors, including angiotensin II. Oxidative stress also plays a central role in the pathophysiology of sodium and water retention, given that angiotensin II increases aldosterone secretion and antidiuretic hormone production, which accelerate hypertension.

### 4.3 | Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic disorders. $^8$ ADPKD causes a gradual decline in renal function and the formation and enlargement of multiple renal cysts. This cyst growth is due to the proliferation of cyst epithelial cells. Clinical studies have shown that an increase in oxidative stress is present during the early stages of ADPKD, even when a patient’s renal function is preserved. $^8$ We found that a decrease in intracellular calcium concentration caused by polycystin-1 dysfunction, which causes ADPKD, downregulates PGC-1α, thereby reducing mtDNA and increasing mitochondrial $O_2^\cdot$ levels in the cyst epithelial cells. This in turn enhances proliferation via extracellular signal-related kinase 1 and 2 activation. $^8$ In addition, a recent study suggested a direct role of polycystin-1 in regulating mitochondrial function in renal epithelial cells. $^8$ These various findings indicate that mitochondria and $O_2^\cdot$ play important roles in the pathogenesis of ADPKD.

### 5 | Recent Clinical Trials Targeting Oxidative Stress

Chronic kidney disease-associated oxidative stress is caused by the increased production of ROS and a diminished antioxidant capacity. The latter is largely caused by impaired Nrf2. Indeed, rats in which CKD was induced by 5/6 nephrectomy showed marked and time-dependent reductions in nuclear Nrf2 content in the remnant kidneys. $^8$ The renal protective effect of Nrf2 is supported by evidence that Nrf2 gene ablation intensifies diabetes-induced inflammation, oxidative stress, and renal injury in an animal model of CKD. $^8$ The most potent known activators of the Nrf2 pathway are the synthetic triterpenoid bardoxolone methyl and its analogues. Clinical trials have investigated the renoprotective effect of bardoxolone methyl in patients with type 2 diabetes and CKD. The first trial targeted patients with type 2 diabetes and stages 3b and 4 CKD, and showed that bardoxolone methyl increased kidney function after treatment for 56 days. $^8$ The second study investigated the longer term effects of bardoxolone methyl in patients with CKD and type 2 diabetes, and showed improvements in estimated GFR at 24 weeks which persisted at 52 weeks. $^8$ While a third clinical trial also demonstrated that patients treated with bardoxolone methyl showed significant improvements in their estimated GFRs compared with placebo, the patients administered bardoxolone methyl also showed a significantly higher incidence of cardiovascular events, and the trial was terminated early because of safety concerns. $^9$ However, all of these findings showed improvements in kidney function. Based on these results, a new clinical study (the TSUBAKI Study, https://clinicaltrials.gov/ct2/show/NCT02316821) is ongoing in Japan, because the incidence of cardiovascular diseases is lower among Japanese people than in European and American people. The individuals participating in the TSUBAKI study are patients with stages 3-4 CKD and type 2 diabetes who do not have cardiovascular risks, and the results show improvements in the GFR that are calculated based on insulin clearance (unpublished).

### 6 | Conclusions

In summary, ROS and RNS are important intracellular messengers in both the kidneys as well as other organs. ROS itself is not harmful; rather, problems arise in relation to the strength and duration of exposure to ROS. Rather than inhibit ROS totally, it is important to control ROS moderately at the right time. As explained in this review,
the kidney has strong associations with ROS, and progress in this area of research will improve the prognosis of patients who are diagnosed with kidney disease.

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The authors declare that they have no competing financial interests.

ORCID

Yu Ishimoto  http://orcid.org/0000-0001-5773-8637
Reiko Inagi  http://orcid.org/0000-0001-7032-7736

REFERENCES

1. Finkel T. Signal transduction by reactive oxygen species. J Cell Biol. 2011;194:7-15.
2. Brezis M, Rosen S, Silva P, Epstein FH. Renal ischemia: a new perspective. Kidney Int. 1984;26:375-383.
3. Schurek HJ, Jost U, Baumgärtl H, Bertram H, Heckmann U. Evidence for a preglomerular oxygen diffusion shunt in rat renal cortex. Am J Physiol. 1990;259:F910-F915.
4. Cancherini DV, Trabuco LG, Reboluças NA, Kowaltowski AJ. ATP-sensitive K+ channels in renal mitochondria. Am J Physiol Renal Physiol. 2003;285:F1291-F1296.
5. Tahara EB, Navarrete FD, Kowaltowski AJ. Tissue-, substrate-, and site-specific characteristics of mitochondrial reactive oxygen species generation. Free Radic Biol Med. 2009;46:1283-1297.
6. O’Toole JF. Renal manifestations of genetic mitochondrial disease. Int J Nephrol Renovasc Dis. 2014;7:57-67.
7. Dugan LL, You YH, Ali SS, et al. AMPK dysregulation promotes diabetes-related reduction of superoxide and mitochondrial function. J Clin Invest. 2013;123:4888-4899.
8. Haque MZ, Majid DS. Assessment of renal functional phenotype in mice lacking gp91PHOX subunit of NAD(P)H oxidase. Hypertension. 2004;43:335-340.
9. Brennan ML, Anderson DD, Shih DM, et al. Increased atherosclerosis in myeloperoxidase-deficient mice. J Clin Invest. 2001;107:419-430.
10. Bachmann S, Bosse HM, Mundel P. Topography of nitric oxide synthesis by localizing constitutive NO synthases in mammalian kidney. Am J Physiol. 1995;268:F885-F898.
11. Kim YS, Ha Y, Sim J, Suh M, Lee Y. Location-dependent sensing of nitric oxide and calcium ions in living rat kidney using an amperometric/potentiometric dual microsensor. Analyst. 2016;141:297-304.
12. Navar LG, Insho EW, Majid SA, Imig JD, Harrison-Bernard LM, Mitchell KD. Paracrine regulation of the renal microcirculation. Physiol Rev. 1996;76:425-453.
13. Castrop H, Schweda F, Mizel D, et al. Permissive role of nitric oxide in macula densa control of renin secretion. Am J Physiol Renal Physiol. 2004;286:F488-F487.
14. Ren YL, Garvin JL, Carretero OA. Role of macula densa nitric oxide and cGMP in the regulation of tubuloglomerular feedback. Kidney Int. 2000;58:2053-2060.
15. Wu XC, Harris PJ, Johns EJ. Nitric oxide and renal nerve-mediated proximal tubular reabsorption in normotensive and hypertensive rats. Am J Physiol. 1999;277:F560-F566.
16. Vallon V, Traynor T, Barajas L, Huang YG, Briggs JP, Schnermann J. Feedback control of glomerular vascular tone in neuronal nitric oxide synthase knockout mice. J Am Soc Nephrol. 2001;12:1599-1606.
17. Wang T. Nitric oxide regulates HCO3- and Na+ transport by a cGMP-mediated mechanism in the kidney proximal tubule. Am J Physiol. 1997;272:F242-F248.
18. Wang T. Role of iNOS and eNOS in modulating proximal tubule transport and acid-base balance. Am J Physiol Renal Physiol. 2002;283:F658-F662.
19. Wang T, Inglis FM, Kal RG. Defective fluid and HCO3(4-) absorption in proximal tubule of neuronal nitric oxide synthase-knockout mice. Am J Physiol Renal Physiol. 2000;279:F518-F524.
20. Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
21. Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int. 2009;76:1089-1097.
22. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20:223-228.
23. Schrier RW, Wang W, Poole B, Mitra A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. J Clin Invest. 2004;114:5-14.
24. Zweier JL, Flaherty JT, Weisfledt ML. Direct measurement of free radical generation following reperfusion of ischemic myocardium. Proc Natl Acad Sci U S A. 1987;84:1404-1407.
25. Chouchani ET, Pell VR, James AM, et al. A unifying mechanism for mitochondrial superoxide production during ischemia-reperfusion injury. Cell Metab. 2016;23:254-263.
26. Nath KA, Norby SM. Reactive oxygen species and acute renal failure. Am J Med. 2000;109:665-678.
27. Shanley PF, Rosen MD, Brezis M, Silva P, Epstein FH, Rosen S. Topography of focal proximal tubular necrosis after ischemia with reflow in the rat kidney. Am J Pathol. 1986;122:462-468.
28. Friedewald JJ, Rabb H. Inflammatory cells in ischemic acute renal failure. Kidney Int. 2004;66:486-491.
29. Tanaka S, Tanaka T, Kawakami T, et al. Vascular adhesion protein-1 enhances neutrophil infiltration by generation of hydrogen peroxide in renal ischemia/reperfusion injury. Kidney Int. 2017;92:154-164.
30. Ruiz S, Pergola PE, Zager RA, Vaziri ND. Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int. 2013;83:1029-1041.
31. Leonard MO, Kieran NE, Howell K, et al. Reoxygenation-specific activation of the antioxidant transcription factor Nrf2 mediates cytoprotective gene expression in ischemia-reperfusion injury. FASEB J. 2006;20:2624-2626.
32. Liu M, Grigoryev DN, Crow MT, et al. Transcription factor Nrf2 hyperactivation in early-phase renal ischemia-reperfusion injury prevents tubular damage progression. Kidney Int. 2017;91:387-401.
33. Nezu M, Souma T, Yu L, et al. Transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int. 2006;281:1495-1505.
37. Cunningham PN, Wang Y, Guo R, He G, Quigg RJ. Role of Toll-like receptor 4 in endotoxin-induced acute renal failure. *J Immunol*. 2004;172:2629-2635.

38. Doi K, Leeahavanichkul A, Yuen PS, Star RA. Animal models of sepsis and sepsis-induced kidney injury. *J Clin Invest*. 2009;119:2868-2878.

39. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl*. 2006;69:S11-S15.

40. Sendeski M, Patzak A, Pallone TL, Cao C, Persson AE, Persson PB. Liodxanol, constriction of medullary descending vasa recta, and risk for contrast medium-induced nephropathy. *Radiology*. 2009;251:697-704.

41. Myers SI, Wang L, Liu F, Bartula LL. Iodinated contrast induced renal vasoconstriction is due in part to the downregulation of renal cortical and medullary nitric oxide synthesis. *J Vasc Surg*. 2006;44:383-391.

42. Pisani A, Sabbatini M, Riccio E, et al. Effect of a recombinant manganese superoxide dismutase on prevention of contrast-induced acute kidney injury. *Clin Exp Nephrol*. 2014;18:424-431.

43. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). *Circulation*. 2011;124:1250-1259.

44. Briguori C, Airoldi F, D’Andrea D, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation*. 2007;115:1211-1217.

45. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. *J Am Soc Nephrol*. 2006;17:17-25.

46. Thaete LG, Crouch RK, Schulte BA, Spicer SS. The immunolocalization of copper-zinc superoxide dismutase in canine tissues. *J Histochem Cytochem*. 1983;31:1399-1406.

47. Oberley TD, Coursin DB, Cihla HP, Oberley LW, et al. Nox4 NAD(P)H oxidase mediates hypertrophy and fibroblast activation during heart failure. *Circulation*. 2016;133:2733-2747.

48. Ayanga BA, Badal SS, Wang Y, et al. Dynamin-related protein 1 deficiency improves mitochondrial function and protects against progression of diabetic nephropathy. *J Am Soc Nephrol*. 2016;27:2733-2747.
76. Meyrier A, Simon P. Nephroangiosclerosis and hypertension: things are not as simple as you might think. *Nephrol Dial Transplant*. 1996;11:2116-2120.

77. Schnackenberg CG. Physiological and pathophysiological roles of oxygen radicals in the renal microvasculature. *Am J Physiol Regul Integr Comp Physiol*. 2002;282:R335-R342.

78. Higashi Y, Sasaki S, Nakagawa K, Matsuura H, Oshima T, Chayama K. Endothelial function and oxidative stress in renovascular hypertension. *N Engl J Med*. 2002;346:1954-1962.

79. Dröge W. Free radicals in the physiological control of cell function. *Physiol Rev*. 2002;82:47-95.

80. Lounsbury KM, Hu Q, Ziegelstein RC. Calcium signaling and oxidant stress in the vasculature. *Free Radic Biol Med*. 2000;28:1362-1369.

81. Harris PC. Molecular basis of polycystic kidney disease: PKD1, PKD2 and PKHD1. *Curr Opin Nephrol Hypertens*. 2002;11:309-314.

82. Menon V, Rudym D, Chandra P, Miskulin D, Perrone R, Sarnak M. Inflammation, oxidative stress, and insulin resistance in polycystic kidney disease. *Clin J Am Soc Nephrol*. 2011;6:7-13.

83. Ishimoto Y, Inagi R, Yoshihara D, et al. Mitochondrial abnormality facilitates cyst formation in autosomal dominant polycystic kidney disease. *Mol Cell Biol*. 2017, MCB.00337-17. https://doi.org/10.1128/MCB.00337-17. [Epub ahead of print].

84. Lin CC, Kurashige M, Liu Y, et al. A cleavage product of Polycystin-1 is a mitochondrial matrix protein that affects mitochondria morphology and function when heterologously expressed. *Sci Rep*. 2018;8:2743.

85. Kim HJ, Vaziri ND. Contribution of impaired Nrf2-Keap1 pathway to oxidative stress and inflammation in chronic renal failure. *Am J Physiol Renal Physiol*. 2010;298:F662-F671.

86. Yoh K, Hirayama A, Ishizaki K, et al. Hyperglycemia induces oxidative and nitrosative stress and increases renal functional impairment in Nrf2-deficient mice. *Genes Cells*. 2008;13:1159-1170.

87. Yoh K, Itoh K, Enomoto A, et al. Nrf2-deficient female mice develop lupus-like autoimmune nephritis. *Kidney Int*. 2001;60:1343-1353.

88. Pergola PE, Krauth M, Huff JW, et al. Effect of bardoxolone methyl on kidney function in patients with T2D and Stage 3b-4 CKD. *Am J Nephrol*. 2011;33:469-476.

89. Pergola PE, Raskin P, Toto RD, et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N Engl J Med*. 2011;365:327-336.

90. de Zeeuw D, Akizawa T, Audhya P, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med*. 2013;369:2492-2503.

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