Renal Aging: Causes and Consequences

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ABSTRACT

Individuals age >65 years old are the fastest expanding population demographic throughout the developed world. Consequently, more aged patients than before are receiving diagnoses of impaired renal function and nephrosclerosis—age–associated histologic changes in the kidneys. Recent studies have shown that the aged kidney undergoes a range of structural changes and has altered transcriptomic, hemodynamic, and physiologic behavior at rest and in response to renal insults. These changes impair the ability of the kidney to withstand and recover from injury, contributing to the high susceptibility of the aged population to AKI and their increased propensity to develop subsequent progressive CKD. In this review, we examine these features of the aged kidney and explore the various validated and putative pathways contributing to the changes observed with aging in both experimental animal models and humans. We also discuss the potential for additional study to increase understanding of the aged kidney and lead to novel therapeutic strategies.


The Centers for Disease Control and Prevention predicts that 72 million Americans will be ages 65 years old or older by 2030, accounting for approximately 20% of the United States population.\(^1\) Eurostat predicts that 28% of Europeans will be ages over 65 years old by 2060.\(^2\) These increasing numbers of elderly individuals will inevitably lead to increasing diagnoses of age–related kidney impairment.

In renal aging, a complex interplay of genetics, environmental change, and cellular dysfunction leads to characteristic structural and functional changes.\(^3\) This review summarizes our current understanding of the factors driving age–associated changes in the kidney.

CLINICAL FEATURES OF RENAL AGING IN HUMANS

Structural Changes of Aging

With age, there is a decline in total nephron size and number, tubulointerstitial changes, glomerular basement membrane thickening, and increased glomerulosclerosis (Figure 1).\(^4,5\) This age–related histologic appearance is frequently described as nephrosclerosis, and it describes a combination of two or more histologic features: any global glomerulosclerosis, tubular atrophy, interstitial fibrosis >5%, and any arteriosclerosis. A study of healthy kidney donors showed nephrosclerosis in only 2.7% of biopsies from donors <30 years old, 58% from donors 60–69 years old, and 73% from donors >70 years old.\(^6\) Cadaver studies estimate that the upper limit of normal glomerulosclerosis in aging exceeds 10%.\(^7\)

Nephrosclerosis remains a poorly understood observation, and its importance within an aging kidney is far from clear. We know that nephrosclerosis correlates with aging and mild hypertension in healthy living donor kidneys.\(^8\) Importantly, however, age-related decline in measured GFR does not correlate with the presence or absence of nephrosclerosis.\(^9\) In fact, nephrosclerosis does not correlate with urine albumin excretion, family history of ESRD, body mass index, serum cholesterol, glucose, or uric acid.\(^6\) It remains unclear then whether nephrosclerotic changes have any contribution to the functional changes seen in aging or are perhaps distinct and unrelated.\(^10,11\)

The Aging-CKD Spectrum

Our understanding of the pathways underlying renal aging is incomplete and derived from studies of healthy aging kidneys and extrapolation from experimental and clinical studies of CKD.

It is important to note the distinction between these conditions, with the mechanisms of progressive genetic–, immune–, or toxin–mediated injury seen in CKD distinct from the gradual, prevalent changes seen in the aging kidney. Throughout this review, we will focus on the changes seen in the healthy aged kidney, although due to the paucity of experimental and clinical data available in aging kidneys, at times, reference will be made to mechanisms in progressive CKD, which may also be of relevance to the uninjured but aged kidney. Processes discussed below, such as cellular senescence, fibrosis, vascular rarefaction, and glomerular loss, are...
common to both aging and CKD, despite differences in causation and natural history. Similarities are also seen in the behavior of the chronically damaged kidney and the aged kidney, including their heightened susceptibility to additional insults.

Declining GFR
Population GFR declines with age, with longitudinal studies differing in their reported rates of decline. Although the Modification of Diet in Renal Disease Study suggested renal function declined at a rate of 3.8 ml/min per year per 1.73 m², rates as low as 0.4 ml/min per year per 1.73 m² in The Netherlands have been described. A Japanese cohort study suggests that the rate of GFR decline increases with advancing age.

Studies of robustly phenotyped Kuna Indians with minimal prevalence of hypertension and cardiovascular disease show comparable declines in renal function over time, suggesting that there is a true age-related decline rather than the cumulative effects of cardiovascular disease. How a significant minority of individuals apparently remains free of nephrosclerosis and GFR loss remains poorly understood and merits additional study.

Decreased Tubular Function
Aging is characterized by progressive tubular dysfunction, decreased sodium reabsorption, potassium excretion, and urine concentrating capacity potentially contributing to an increased susceptibility to AKI. Elderly patients show decreased transtubular potassium gradients and fail to increase distal tubule potassium excretion when hyperkalemic or in response to fludrocortisone. Decreased potassium excretion correlates with decreasing GFR and may reflect a degree of reduced sodium and chloride delivery to the distal convoluted tubule.

Vascular Changes
There are important changes to blood vessel structure and function in the aging kidney. There is increased extracellular matrix (ECM) deposition, increased intimal cell proliferation in periglomerular arterioles, and increased intrarenal shunting and capillary bypassing predominantly affecting the cortex.

Increased renal sympathetic tone increases vasoconstriction, whereas aortic baroreceptor attenuation of sympathetic tone decreases with age. Renal vasodilators, such as atrial natriuretic peptide, nitric oxide (NO), and amino acids, become less effective. Human studies show decreased NO production and platelet responsiveness, with accumulation of the NO synthase inhibitor asymmetric dimethylarginine in elderly individuals. In particular, aging men become increasingly NO dependent to maintain renal plasma flow.

BIOLOGIC PROCESSES AND MEDIATORS IMPLICATED IN EXPERIMENTAL AGING

Most rodent experimental models of renal disease are undertaken in young animals, potentially affecting their relevance to the aging kidney. There are limited or no data available regarding the response of the aged rodent kidney to experimental GN, AKI, ureteric obstruction, diabetic nephropathy, 5/6th nephrectomy, adriamycin nephropathy, or renal transplantation. Some aspects of renal aging may be studied in vitro, but others require study in vivo in aged mice or other experimental animals (Table 1).

Studies have shown increased susceptibility of the aged kidney to ischemia-reperfusion injury (IRI) or toxic AKI. Aged mice exhibit increased mortality, AKI severity, and chemokine/cytokine responses in a model of uterine sepsis. Furthermore, aged mice exhibited increased mortality, prolonged injury, reduced regeneration, increased scarring, and microvascular rarefaction after renal IRI compared with young mice.

The biology of aging is complex, involving diverse changes to cells, tissues, organs, and the surrounding microenvironment (Figure 2). Many of these processes and mediators are discussed below, but the reader should appreciate that this list is not exhaustive.

Signaling Pathways and Oxidative Stress in the Aging Kidney

Falling Klotho Levels
Klotho is a transmembrane protein strongly expressed in the kidney and a coreceptor for fibroblast growth factor-23 (FGF-23). Although its exact physiologic role in aging remains incompletely understood, Klotho has a role in modulating diverse aging–associated pathways. These include calcium and phosphate metabolism, with implications for vascular calcification, hypoxia, cellular regeneration, and senescence. Indeed, homozygous transgenic Klotho knockout mice show arteriosclerosis and vascular changes as part of their aging phenotype. Similarly, FGF-23 knockout mice display high serum
phosphate and increased renal phosphate reabsorption in addition to their aging-like phenotypes.\textsuperscript{40,41} It may be that these vascular changes contribute directly to the aging phenotype that we observe.

Klotho's effects on tissue function, autophagy, and fibrosis could contribute to abnormal healing and possibly, nephrosclerosis.\textsuperscript{42,43} Importantly, Klotho-deficient mice exhibit reduced lifespan, skin and muscle atrophy, osteoporosis, and ectopic calcification.\textsuperscript{44} Conversely, mice overexpressing Klotho have a longer mean lifespan.\textsuperscript{42}

Klotho decreases epithelial senescence in response to oxidative stress, reduces binding of NFκB, and increases cell survival in experimental uremia.\textsuperscript{45} Klotho also represses insulin and IGF1 signaling, likely contributing to reduced oxidative stress in mice and in vitro models using Klotho overexpression.\textsuperscript{42,44,46} Importantly, Klotho supplementation in a rat UUO model attenuated renal fibrosis.\textsuperscript{47}

**Increasing Wnt Activation**

Mechanisms for the antifibrotic effects of Klotho include suppression of FGF and modulation of Wnt signaling.\textsuperscript{58–50} Wnt is a conserved signaling pathway activated postinjury that promotes profibrotic gene expression.\textsuperscript{51} As Klotho levels fall during aging, Wnt signaling increases, promoting fibrosis and vascular calcification.\textsuperscript{52} Although additional experiments are required to clarify causality, Wnt activation promotes renal fibrosis in murine models and is a target for inhibition.\textsuperscript{53,54} With antagonism of Wnt and its downstream targets ameliorating experimental renal fibrosis,\textsuperscript{55,56} The interplay between potentially causative pathways is illustrated by studies showing that renin-angiotensin-aldosterone signaling is Wnt mediated, with experimental blockade protecting mice from postinjury fibrosis and proteinuria.\textsuperscript{57}

**Declining Peroxisome Proliferator–Activated Receptor-γ Levels**

Peroxisome proliferator–activated receptor-γ (PPARγ) is a nuclear receptor with activity...
that decreases with age in experimental rodent models, whereas PPARγ agonists increase Klotho expression.58,59 The PPARγ pathway protects against oxidative stress and improves vascular function in vitro and in aging rats,60–62 with PPARγ agonists protecting human fibroblasts against features of aging and oxidative stress in vitro.63 PPARγ agonism by pioglitazone or baicalin improves cell growth and ECM accumulation,66 Angiotensin II (AT2) is increased in aged rats compared with young controls,65 driving increased fibrosis, glomerular cell growth and ECM accumulation,66 altered mitochondrial redox function, and cytoplasmic oxidative stress in the aging kidney.65,67,68 Angiotensin I receptor activation stimulates the profibrotic β-catenin/Wnt pathway mentioned above.69 Treating aging rats with captopril reduces TGF-β activity and attenuates renal fibrosis.70,71 AT2 antagonism via ACEi/ARB improves mitochondrial number and function in rats, and additional studies are warranted.72

Oxidative Stress
A balance exists in tissues between reactive oxygen species (ROS) generation and oxidant scavenging and defense mechanisms. When this balance is disturbed by increased generation of ROS, decreased detoxification, or both, then oxidative stress may occur. It has been hypothesized that oxidative stress leads to tissue damage and contributes to the aging phenotype. Certainly, there is evidence in murine and human studies of both increased ROS generation and altered oxidant removal in aging.73–75

There is a continuous generation of oxidative species through various mechanisms, including mitochondrial oxidative phosphorylation, which increases within the aging kidney.75,76 Studies in aged rat kidneys support the theory that there is also reduced oxidant defense showing decreased antioxidative capacity and reduced levels of Cu/Zn-SOD, catalase, and GSH reductase.77,78 This overall increased oxidative load may contribute to chronic cellular stress and mitochondrial injury76 as well as apoptosis and possibly, may induce tubular cell damage.79,80

Contributing to this increased oxidative stress, it has been noted that sirtuins (important antioxidant molecules) are diminished with age. Sirtuins protect against renal inflammation, fibrosis, and apoptosis while improving autophagy.81,82 Thus, defective ability to respond to cell stress in aged kidneys may contribute to the aged phenotype.83 Mouse models of reduced SIRT-1 expression showed increased apoptosis and fibrosis after UUO.84 Additional Sirtuin functions include histone deacetylation and regulation of transcription factors controlling cellular stress and survival.85,86 Altered Sirtuin levels in aging may contribute to aging phenotypes by altering the kidney's capacity to respond to oxidative stress and thus, suffering increased oxidative DNA damage.87,88 Interestingly, AT2 downregulates SIRT-3 in vitro, suggesting that the damaging effects of raised AT2 levels and low Sirtuin levels may be related in the aging kidney.89

Cell Cycle Progression in the Aged Kidney
Aged animals have reduced proliferative responses after experimental IRI. Tubular epithelial cells in aged mice express higher levels of zinc-α-(2)–glycoprotein (AZGP1), limiting proliferation after IRI.90 Although reduced proliferation might be expected to delay recovery, AZGP1 knockout mice displayed worsened fibrosis after IRI, with AZGP1 administration being protective, implicating control of proliferation as a mechanism-limiting fibrosis with aging.91 Studies in several CKD models show that G2/M arrest in tubular epithelial cells promotes renal fibrosis, but no studies have examined G2/M arrest in aging kidneys.92

Cellular senescence, defined as a state of permanent cell cycle arrest, is a key anti-proliferative response to aging and injury. This crucial process shuts down damaged cells, protects against malignant transformation, and limits excess fibrosis at both baseline and after injury.93

Senescence may occur as a result of repeated cell division and telomere shortening (replicative senescence) or after factors, such as oxidative stress or genotoxic injury (stress-induced premature senescence) (Figure 3).94 Increased numbers of senescent cells accumulate in multiple organs, including the kidney with advancing age (identified by p16INK4a or senescence–associated β-galactosidase expression).

Cell senescence limits fibroblast proliferation in tissue wounds; however, there is increasing interest in the role of the Senescence–Associated Secretory Phenotype (SASP) in promoting fibrosis.95 SASP promotes fibrosis and organ dysfunction in aging via release of factors, including IL-6, IL-8, Wnt16B, and GROα.95–97 Studies in murine renal
transplantation showed that renal p16\textsuperscript{INK4a} deletion reduced pathologic changes and interstitial fibrosis post-IRI, supporting clinical findings that cellular senescence contributes to adverse long-term allograft outcomes.\textsuperscript{98} Cell stress is known to induce stress–induced premature senescence, and consistent with this, porcine models have shown that renal p16\textsuperscript{INK4a} expression increases after IRI.\textsuperscript{99} Interestingly, p16\textsuperscript{INK4a} knockout mice exposed to experimental renal injury show improved recovery after IRI but worsened fibrosis after UUO.\textsuperscript{100,101} These superficially inconsistent findings may reflect the different pathologic processes at play, with p16\textsuperscript{INK4a} deficiency leading to less cell death and enhanced regenerative proliferation in AKI but the lack of p16\textsuperscript{INK4a} induced senescence inducing an exaggerated, maladaptive fibroblast response to ongoing injury in UUO.

Recent seminal studies used transgenic animals to induce specific depletion of p16\textsuperscript{INK4a} expressing senescent cells and showed reduced markers of aging in multiple organs, including the kidney, and increased overall lifespan.\textsuperscript{102} Other work has used Bcl2/xL inhibitors to deplete senescent cells in nontransgenic animals.\textsuperscript{103} Although these findings open up exciting new therapeutic avenues for the selective targeting of senescent cells to prolong healthy lifespan, additional studies focusing on the aging kidney are required.

**Telomere Shortening**

Telomeres are nucleotide sequences that act as a defensive cap, limiting activation of DNA repair pathways, protecting genetic material, and minimizing background cellular stress response.\textsuperscript{104,105} Although telomere length declines with age, it remains controversial whether this is a primary process or a byproduct of aging.\textsuperscript{104,106} As telomeres shorten with aging and oxidative stress, chromosome instability ensues, leading to cellular instability, senescence, and subsequent apoptosis.\textsuperscript{107}

Increased telomere shortening in telomerase-deficient mice is associated with increased tubular injury and reduced tubular proliferation after renal IRI, with reduced tubular cell autophagy implicated in the limited regenerative response.\textsuperscript{108,109} This implies a potential causal role for telomere shortening in some of the vulnerability of aging kidneys to injury, and it is noteworthy that experimental elongation of shortened telomeres resulted in partial reversal of aged organ degeneration.\textsuperscript{110}

**Hypoxic Damage and Disordered Repair**

Under physiologic conditions, the kidney is supported by a network of resident mononuclear phagocytes and pericytes contributing to tissue homeostasis and vascular stability. Renal oxygen delivery and the functional status of resident and recruited cells in the kidney have been shown to alter in aged and injured experimental animals.

**Hypoxia**

Although the healthy kidney has areas of low oxygen tension, reduced capillary density and increased hypoxia are recognized as potential drivers of CKD, and the role in normal aging is being explored. In experimental CKD, the expected angiogenic response to hypoxia fails, instead resulting in fibrosis.\textsuperscript{111} Increased renal hypoxia has also been shown throughout aged rat kidneys, most prominently in the cortical zones, as detected by use of the hypoxia–sensitive marker pimonidazole.\textsuperscript{112} Aged rat kidneys show decreased VEGF globally and increased antiangiogenic thrombospondin-1, resulting in capillary loss with increased glomerular sclerosis.\textsuperscript{113} Recently reported techniques to quantify subtle changes in the renal vasculature have potential to yield new information on the evolution of renal circulatory changes and hypoxia with advancing age.\textsuperscript{114}

**Leukocytes**

Changes in leukocyte function promoting inflammatory activation occur with aging, although whether this is a cause or effect of aging remains unclear.\textsuperscript{115} Increased inflammatory signaling and macrophage infiltration\textsuperscript{116} with alterations in inflammasome components, such as NOD–like receptor P3, NLRC4,
procaspase-1, NFκB, and cytokines, including IL-1β and IL-18, occur in aging.118 Healthy aged mice have increased glomerular macrophage numbers with increased macrophage infiltration evident postinjury, with renal IRI models showing an increased influx of macrophage and T lymphocytes.38,119 Additionally, aged mice show defective upregulation of the cytoprotective enzyme hemoxygense-1 after IRI, with pharmacologic macrophage hemoxygenase-1 induction protecting against subsequent IRI.15 Finally, aged macrophages express reduced anti-inflammatory IL-10 during tissue repair in noneural injury models.120

Given the importance of IL-10 and the negative prognostic role of macrophage infiltrates in human renal disease, these aging-associated changes potentially contribute to the increased rates of injury and maladaptive repair seen in aged kidneys.

Additional evidence for the importance of the aging immune system in renal aging comes from young-old bone marrow transplant studies showing that aged animals receiving bone marrow transplants from young mice exhibited reduced renal fibrosis and cellular senescence.121

Pericytes

Although important for microvascular health, pericytes are also recognized as key cells in renal fibrosis.122,123 In aged mice, renal pericytes decline in number and adopt a profibrotic phenotype,124 implicating them in aging-related fibrotic changes. Pericyte-endothelial detachment under pathologic conditions and their differentiation into myofibroblasts promote microvascular rarefaction, hypoxia, and fibrosis.125,126 Proposed mediators of this pericyte-endothelial crosstalk include VEGF and PDGF,127 and blocking this pericyte-endothelial interaction attenuates microvascular damage and interstitial fibrosis.128,129

Disordered Repair

The normal enzymatic equilibrium is disturbed in aging, and the balance of metalloproteinases (MMPs) shifts toward fibrosis, potentially via upregulation of tissue inhibitor of MMP1 and increased leukocyte recruitment,60 a pattern likely to result in increased collagen deposition. Longitudinal studies of aging mice show increased Collagen I, Collagen III, and TGF-β1,60 whereas aging rat kidneys exhibit increased ECM deposition and TGF-β3 expression and decreased MMP1 activity, suggesting altered collagen production and processing.130 Additional noninflammatory pathways may contribute to the histologic changes seen, including pathways driven by Wnt and AT2 as mentioned.34

THE AGING HUMAN KIDNEY

The clinical implications of renal aging in humans extend beyond changes in glomerular and tubular function. Although data generated by animal studies implicate multiple pathways of potential importance for human renal aging (Figure 4), data supporting their involvement in humans are currently sparse, with additional studies required.

Signaling Pathways and Oxidative Stress in the Aging Kidney

**Falling Klotho Levels**

Klotho and FGF-23 are present in human kidneys.131 Klotho levels decline with age and are implicated in accelerated age-related CKD and atherosclerosis.132,133 Conversely, patients with increased functional Klotho expression are reported to have increased lifespan.134 As Klotho falls, FGF-23 levels increase and alter phosphate and calcium homeostasis. Clinical studies in patients on dialysis and patients with CKD show that higher FGF-23 levels associate with increased mortality.135

**Increasing Wnt Activation**

Although direct evidence of Wnt activation in human aging is lacking, several Wnt antagonists are now undergoing phase 1 clinical trials for cancer therapy in humans.136 If effective, these agents offer new therapeutic options for aging-associated or fibrotic renal disease.

Declining PPARγ Levels

Agonists of PPARγ are used clinically as antidiabetic agents. Retrospective reviews of renal outcomes in clinical practice suggest that augmented PPARγ activity opposes proteinuria in these patients.137 A meta-analysis of PPARγ use has also shown that they associate with reduced rates of cerebrovascular disease, supporting a role in delaying age-associated pathology.138 There is a need for prospective trials assessing their effects on renal function.

AT2

Despite decreased plasma renin activity in the elderly, serum AT2 levels do not fall, and hypersensitivity to AT2 develops in the renal vasculature.139,140 Although ACEi and ARB drugs are in widespread use, there is a lack of human data on the effect of AT2 blocking treatments on normal renal aging and outcomes at present.

Oxidative Stress

As discussed, oxidative stress represents a disruption of the balance of oxidant handling in tissues. In humans, longitudinal studies show increased oxidative stress in normal aging and CKD.73,141 Research has focused on advanced glycation end products as drivers of oxidative stress in aging. These molecules accumulate with age and are associated with increased arterial stiffness, inflammation, oxidative stress, and declining renal function.142 One pharmacologic attempt to modify antioxidant status in patients with diabetic nephropathy showed no effect on proteinuria, despite increased circulating antioxidant levels.143 Whether an alternative, longer-term treatment approach in the healthy aged population might have efficacy remains untested.

Cell Cycle Progression in the Aged Kidney

The presence of increased numbers of senescent cells has been noted in chronic allograft nephropathy and proposed as drivers of the progressive fibrosis seen.144 Recent advances in our understanding of the roles of aging and stress in inducing the detrimental SASP phenotype
add to the importance of senescence cells found in both aged and disease–affected human renal biopsies. In humans, senescence is maximal in the medulla, potentially reflecting increased oxidative and cellular stress and relative hypoxia resulting from the vascular changes discussed previously.

Telomeres
Telomeres shorten in human kidneys at a rate of 0.25% length per year. Although telomere shortening provides an elegant explanation of cellular aging, currently, no data exist to link shorter telomeres to any histologic or functional measure of renal aging. Shorter telomeres associate with CKD and worse cardiovascular outcomes and are shorter in diabetic nephropathy, where they associate with rates of disease progression. Furthermore, studies of patients on hemodialysis show increased rates of telomere attrition, suggesting that they shorten in response to the physiologic stress. Although intriguing, the importance of telomere shortening in human aging remains to be elucidated.

Hypoxia, Inflammation, and Nephrosclerosis in the Aged Kidney
Because of the inherent risks of renal biopsy, samples of healthy aged kidney are seldom available for assessment of levels of nephrosclerosis, and there are no time course studies available to chart the temporal relationships of the histologic findings in the aged kidney. Ongoing progress in imaging technology should enable serial noninvasive assessment of renal perfusion, vascular resistance, hypoxia, inflammation, and atrophy in healthy young and aged volunteers.

Hypoxia
The clinical use of BOLD MRI imaging has shown a lower PO2 in older kidneys compared with younger subjects. Because intrarenal vascular disease contributes to increased glomerular sclerosis in aged biopsies, it is possible that subclinical disease leads to hypoxia before marked macroscopic changes occur.

Inflammation
Inflammation is increased within the aging kidney in humans, with proinflammatory cytokines detectable in the serum correlating with age–related renal disease.

FUTURE RESEARCH
Reviewing the current evidence base in clinical and experimental renal aging, it is clear that more work is required to understand which pathways are dispensable and which represent master regulators of the aging phenotype. Studies in aged animals should allow characterization of both the importance and interdependence of factors predisposing aged kidneys to injury, fibrosis, and maladaptive repair, with subsequent validation in humans. Because of the time and cost constraints inherent in using aged animals, establishing whether models of genetically accelerated aging, such as the BubR1 progeroid mouse, represent useful models of renal aging will be of value. BubR1 mice have a shortened lifespan and exhibit a variety of age–related phenotypes, including sarcopenia, cataracts, fat loss, cardiac arrhythmias, arterial wall stiffening, and impaired wound healing. Specific to kidney research, BubR1–deficient mice also show higher senescence–associated β-galactosidase activity in kidney sections than aged matched controls. Whether they truly manifest a renal aging phenotype has yet to be determined.

Circulating Factors
Heterochronic parabiosis with aged and young mice sharing a common circulation has provided evidence in nonrenal models that circulating factors may modulate features of aging, including impaired regeneration and increased fibrosis. Proposed factors include β2-microglobulin and growth differentiation factor 11, and reversal of changes in the brain, cardiac, and skeletal muscle has been shown. Debate continues as to the significance of individual factors. Whether such factors affect the function of the aged kidney remains completely unknown.

Novel Experimental Species
Undertaking studies of experimental renal disease in aged mice is challenging, and
Novel Therapeutic Strategies

Many pathways implicated in the aging process are the target of interventions to improve the aging phenotype in experimental mice (Figure 5). Klotho agonists are under investigation via repurposing of established agents, including PPARγ agonists and ACEi and ARB drugs. The importance of maintaining a normal renal microvasculature and pericyte pool is increasingly understood, and developing strategies to quantify microvascular function and promote endothelial and pericyte health are a pressing clinical need.114

Drugs targeting cellular senescence (senolytics) include siRNA therapies, the experimental agent navitoclax, and the licensed drugs dasatinib and quercetin.174 In experiments, these agents show selective toxicity to senescent cells, and their potential utility in animal models and humans merits additional study.

Genetics

Genome-wide association studies (GWASs) have identified upregulation of several genes with aging. Although cumulative damage may well influence much of the elderly genetic milieu, candidate genes have declared themselves as being consistently highly expressed in aged kidneys.175–177 Despite the utility of GWAS in identifying disease-specific pathways, it has proved difficult to discover any canonical aging pathways with GWAS.178

The most promising genes encode for modulators of the glomerular filtration barrier, fibrosis, and inflammatory mediators, although difficulty arises when identified candidate genes do not match the experimental observations or models.179,180 Transcriptomic analysis identified 427 genes strongly associated with renal aging, including mortalin-2, a heat shock protein that may counteract cell senescence, and IGF receptor, a target of Klotho.181–183

GWAS remains, however, a promising tool, because whole-genome analyses of GWAS data suggest that over 80% of the heritability of aging is explained by common genetic variants.184 Future GWASs will continue to generate meaningful results as more advanced statistical techniques develop and researchers increase statistical power by increasing samples number, combining studies using meta-analytic techniques, using multicenter collaborations, and including more extreme phenotypes in the data.185,186

Epigenetics

Epigenetics is the study of genome changes that do not alter DNA sequence. Epigenetic changes in aging include methylation and deacetylation of histone lysine residues, chromatin changes, and increased transcriptional noise.178,188 Interestingly, similar changes in DNA methylation and histones are associated with CKD disease progression.189–191 The role of microRNA expression in modifying gene expression and nephrosclerosis is of interest, with data in other organs suggesting an influence on aging.192

CONCLUSION

Renal aging is complex and remains incompletely understood. Decreased protective factors, hypoxia, and microenvironmental stress drive increasingly disordered inflammation and renal fibrosis. The resulting fibrosis, senescence, and microvascular rarefaction exacerbate damage and promote progression. The future of treating renal aging is likely in understanding the key initiating events and the common downstream pathways present in kidney aging that may be shared with CKD. This knowledge should allow the development of therapies capable of arresting the key mechanisms early to preserve kidney function throughout life.

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DISCLOSURES

None.
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