MINI-REVIEW

Chronic Kidney Disease

A Vicarious Relation to Premature Cell Senescence

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Chronic kidney disease (CKD), commonly fostering nonrenal complications, themselves more life threatening than renal pathology, remains enigmatic. Despite more than a century of intense research, therapeutic options to halt or reverse renal disease are rather limited. Recently, similarity between manifestations of progressive CKD and aging kidney has attracted investigative attention that revealed senescent cells and secreting proinflammatory and profibrotic mediators in all renal compartments, even at young age, in patients with kidney maladies. The overlapping features of these categories have been noticed previously and are briefly summarized herein. I propose two hypothetical scenarios for interactive association of kidney diseases and cell senescence, both culminating in progressive deterioration of renal function. Persistence of senescent cells is considered as a critical contributor to this association; and the mechanisms explaining persistence, such as activation of cell cycle regulators, anti-apoptotic stimuli, metabolic aberrations, and their interactions, are discussed. The mutual encroachment of underlying kidney disease and cell senescence bring about the conclusion that both entities merge along the natural history of the disease. This putative interpretation of vicarious relation between cell senescence and CKD may expand the arsenal of pharmacotherapy to include the judicious use of senotherapeutics in the management of renal disease. (*Am J Pathol* 2020, 190: 1164–1171; <https://doi.org/10.1016/j.ajpath.2020.01.016>)

Chronic kidney disease (CKD) afflicts >13% population globally.¹ The list of conditions culminating in CKD is a long one and includes primary and secondary glomerulopathies, tubulointerstitial, nephrotoxic, and systemic diseases, and acute-to-chronic kidney disease continuum. Remarkably, individual features of these discreet diseases leading to CKD become blurred and, in the natural course of the disease, are almost invariably followed by the general presentations of the final common pathway—progressive glomerulosclerosis, tubular atrophy, and interstitial fibrosis with the loss of excretory and incretory kidney functions. Intriguingly, CKD is accompanied by multiorgan involvement—heart, vasculature (accelerated atherosclerosis), endocrine, musculoskeletal, neural, and adipose. What could be the root cause(s) of such a consistency of kidney injury and multiplicity of affected organs?

Individual molecular mediators of fibrosis are many, as has been exhaustively reviewed.^{2,3} Yet, it is difficult to attribute the final common pathway with its array of targeted organs to any individual molecular mediator of fibrosis, each acting locally. The Ockham's razor logic of multiorgan involvement in CKD progression calls for the existence of systemic mediators. Among possible contenders, the cell senescence and accompanying secretion of senescence-associated secretory products (SASPs) that affect all cells, including stem cells, and leading to accelerated organ aging has been gaining appreciation. Cell senescence is traditionally subdivided into two types: Hayflick-type replicative

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senescence, characterized by the attrition of telomeres; and stress-induced premature senescence (SIPS), induced by cytotoxic (in our case, nephrotoxic) and genotoxic insults. Many similarities exist between replicative senescence and SIPS, as documented by the DNA screen detecting parallels in genes involved in the regulation of cell proliferation, defense, DNA damage, morphogenesis, extracellular matrix, and prostaglandin synthesis.⁴ The major distinction between the two, although specific markers are absent at the time of this writing, is that the reduction of telomerase activity and attrition of telomeres characterize replicative senescence, whereas the SIPS does not require these events, thus conferring potential reversibility onto this process. In either case, however, cell senescence is characterized by the G₁/S or G₂/M cell cycle arrest, suppression of the apoptotic cell death pathway, persistence of high metabolic rate, and secretion of SASP.⁵ Among the most uniform components of SASP are profibrotic and proinflammatory agents, such as IL-1, IL-6, and IL-8, connective tissue growth factor, transforming growth factors, plasminogen activator inhibitor 1, monocyte chemoattractant protein-1 (MCP-1), granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, hepatocyte growth factor (HGF), insulin-like growth factor, platelet-derived growth factor, vascular endothelial growth factor, and matrix metalloproteinases (MMPs),⁶ acting in paracrine, autocrine, and juxtacrine manner, which explains persistence of senescent cells and propagation of their deleterious effects on neighboring cells. Detection of individual, albeit alone not highly specific, markers of senescence (ie, senescence-associated β -galactosidase, γ -H2AX and senescence-associated heterochromatin foci, overexpression of p16^{INK4a} and p21^{CIP1}, lack of proliferation markers, and loss of the nuclear high-mobility group box 1 protein) in a heterologous field of renal resident cells invariably highlights different cell types; however, it would be difficult to assign priority to any one of them the primary role of the original donor of SASP.^{6,7}

A Brief History of Studies of Senescence in CKD

The milestones for key studies of cell senescence in CKD are as follows. First, the high prevalence of senescent cells has been noted in kidney biopsies of young individuals with diverse CKD.⁸ These observations were pursued by multiple investigators and extended to a broad range of etiologic causes of renal diseases, as studiously reviewed recently,^{7,9,10} and include hypertensive kidney disease, diabetic nephropathy, IgA nephropathy and membranous nephropathy, focal segmental glomerulosclerosis, and delayed graft function after kidney transplantation. Notably, it remains to be elucidated whether non-progressive forms of any of those nephropathies are associated with a lesser senescence burden. Second, it has been realized that senescent cells, despite being G₁/S or G₂/M cell cycle arrested, remain metabolically active and secrete several products (SASPs) potentially responsible

for the proinflammatory and profibrotic signaling and acquisition of senescent phenotype by the neighboring cells.⁵ Third, it has been demonstrated that elimination of senescent cells improves longevity, organ function, and regeneration.^{11–14} Furthermore, it has been shown that rejuvenation of senescent cells is feasible and pharmacologic rejuvenation strategies are capable of reversing organ dysfunction.¹⁵ Remarkably, similar pathogenic mechanisms are involved in aging and CKD, such as the secretion of profibrotic and proinflammatory factors (SASP and CKD-associated secretory phenotype, according to Wang et al¹⁶), the loss of renoprotective factors Klotho and bone morphogenetic proteins, vascular rarefaction, and oxidative stress.¹⁷ Incidentally, it is this feature of senescence—local and systemic release of SASP with the propagating cell dysfunction—that undermines attempts to use stem cell therapies and compromises the future functioning of even the best *ex vivo* engineered organs. This historic overview of similarities between CKD and aging kidney tends to point out the fact that the progressive nature of their clinical presentations, involvement of multiple other organs in developing dysfunction, and molecular signatures of both appear to overlap.

Similarity Analysis of Attributes of CKD and Cell Senescence

The features of CKD with poorly defined boundaries (requiring several consecutive Kidney Disease: Improving Global Outcomes meetings) and, at the same time, significantly overlapping with such a nebulous entity as senescence or SIPS underlie the proposed view of CKD as a forme fruste of premature senescence or premature kidney aging. This latter term, initially used in numismatics to describe a worn-down coin, is intended to not only emphasize the inherent similarity of CKD and premature senescence, but equally to attribute multiple features of CKD to premature senescence or accelerated kidney aging. Such a point of view, if correct, would envisage potential reversibility of premature cell senescence CKD progression is in many ways resembling cell senescence or accelerated kidney aging, thus suggesting that CKD progression should be also reversible. The cornerstone of this logistical prediction lies in the idea of similarity, one of the categories of cognitive sciences.¹⁸ From the standpoint of cognitive sciences, similarity between two entities is a weighted function of matching and mismatching features (namely, shared features with subtracted individual features of each).¹⁹ Let us compare, therefore, the attributes of our operating entities, CKD and senescence.

CKD is broadly defined by an authoritative source as “kidney damage for at least 3 months,... increased number of systemic complications (cardiovascular disease [CVD], hypertension, mineral and bone disorders, and anemia), morbidity and mortality associated with declining eGFR, and ... a greater risk of death from CVD than from

progression to kidney failure and ESRD.^{20,pp.21} A similar definition has been proposed by Kidney Disease: Improving Global Outcomes: “abnormalities of kidney structure or function present for more than 3 months, with implications for health.”^{20,pp.22} It is, however, a collective term that places emphasis on the outcome rather than its origin. The attributes of CKD are declining glomerular filtration rate and proteinuria. Notably, the prevalence of senescent cells in the renal parenchyma, predominantly in the cortex, is increased in all compartments: glomerular, tubular, and vascular.^{8–10}

Cell senescence (ie, aging kidney), on the other hand, is characterized as “mild loss of function in the presence of no underlying illness.”^{21,pp.126} Yet, the functional attributes of aging kidney are represented by the increased proportion of senescent cells in the kidney, declining glomerular filtration rate, and higher prevalence of microalbuminuria or albuminuria.²² Morphologic changes in aging kidneys and CKD kidneys are also remarkably similar: glomerulosclerosis, tubular atrophy, interstitial fibrosis, and microvascular rarefaction.²¹ Chronological aging remarkably resembles SIPS and accelerated kidney aging in that all are detected using the same sets of markers, all impinge on the function, and all have generalized and, in many instances, deleterious effects via senescence-associated secretory products.

Hence, the multiple matching attributes of CKD and senescence/aging kidney are ostensibly overlapping (Figure 1A). There is, however, a mismatch: the former suggests the existence of a primary insult, whereas the latter

suggests no underlying illness. Alas, for every practicing physician, this difference would appear to be tenuous. (Obviously, this discussion excludes rapidly progressive glomerulonephritides and nephropathies of systemic diseases, although these also are associated with increased proportion of senescent cells.) Some primary renal insults may be indolent with minimal, if any, clinical manifestations, thus making detection of such a primary event nearly unachievable. Therefore, this differential attribute is a feeble one, leaving the weighted function of matching to favor the notion of the existing similarity between two entities. In conclusion, kidney disease, metaphorically speaking, is a palimpsest with senescent cells inscribed all over it.

Hypothetical Scenarios for Interaction between Cell Senescence with Accelerated Kidney Aging and Progression of Kidney Disease

In the intricate network of mechanistic pathways of developing each of those entities, CKD and senescence, two hypothetical scenarios, appear to be best supported by existing evidence. In the first scenario (Figure 1B), an acute renal insult is followed by a burst in stress-induced premature senescence of resident cells (acute senescence, according to Sturmlechner et al⁷). Jin et al²³ report that senescent tubular epithelial cells are found within a few days of acute kidney injury induced by folic acid. Remarkably, this is mediated via toll-like and IL-1 receptors, and inhibition of the downstream

Figure 1 Vicarious relations between cell senescence and chronic kidney disease (CKD) progression. **A:** Venn diagram of overlapping mechanisms for progression of renal disease. **B:** Hypothetical dynamics of the primary insult, senescent cell burden, and fibrosis in progression of renal disease. Shaded areas represent possible variability. **Dashed lines** indicate the possible salutary consequences of reducing senescent cell burden in two scenarios of progression of CKD (*Hypothetical Scenarios for Interaction between Cell Senescence with Accelerated Kidney Aging and Progression of Kidney Disease*).

In the second tentative scenario (Figure 1B), prototypical of aging-associated disorders, insidious accumulation of senescent cells (chronic senescent cells, according to Sturmlechner et al.⁷) in the aging kidney with the yet compensated function²¹ precedes an ischemic or nephrotoxic insult. This could result in further rapid accumulation of SIPS cells with acute-on-chronic release of SASP, leading to renal inflammation, fibrogenesis, and functional deterioration. The finding that senolytic therapy may rescue such a kidney supports this conjecture.^{7,13} In

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metabolic aberrations underpins persistency of cell senescence (Figure 2). Induction of cyclin-dependent kinase inhibitors p53, p21^{CIP1}, and p16^{INK4a} represents the key step toward senescence. Up-regulation of these inhibitors occurs as a component of DNA damage response, as in the radiation-induced premature senescence involved in glomerular diseases²⁷; telomere attrition as a result of excessive cell division; and cell stressors, like oxidative stress, a common companion of SIPS. Induction of cyclin-dependent kinase inhibitors represents a default response to the stressors that prevent division of damaged cells and earmarks them for apoptotic cell death. Decreased c-Myc expression induces oxidative stress-induced SIPS via a telomere-independent mechanism driven by a member of polycomb group histone methyltransferase, Bmi-1, and a member of gate-keeping tumor suppressor, p16^{INK4a}, in human fibroblasts and endothelial cells.²⁸ A ring finger protein Mel-18 down-regulates Bmi-1, resulting in accelerated senescence.²⁹ This effect of Mel-18 is linked to the down-regulation of c-Myc. In stress situations, increase in p38 mitogen-activated protein kinase, ataxia-telangiectasia mutated kinase activity, and a companion burst in reactive oxygen species lead to enhanced phosphorylation of p53, p21^{CIP1}, and p16^{INK4a}, thus delaying their degradation, inhibiting cyclin-dependent kinase, and causing hypophosphorylation of retinoblastoma tumor suppressor Rb and inhibition of cell cycle progression.³⁰ The same causative factors induce pro-apoptotic (phorbol-12-myristate-13-acetate-induced protein, Bcl-2 homology domain 3 only protein, and p53 up-regulated modulator of apoptosis) and anti-apoptotic (B-cell lymphoma 2 family members) signals. The balance between these two determines whether cells succumb to apoptosis or acquire resistance to apoptosis. In the latter case, combined with the halted cell cycle progression, premature cell senescence ensues. An intriguing biphasic effect of p53 activation has been noticed: although sustained elevation of p53 levels predominantly leads to apoptosis or senescence, lower and transient increases predispose to temporary cell cycle arrest.^{6,31,32} In a parallel pathway, p53 acetylation has been described as a driver for premature renal cell senescence in cisplatin-induced nephropathy; in turn, sirtuin 1 activation is followed by p53 deacetylation, which results in reduced cell senescence and fibrosis.³³ These findings invoke the role of sirtuin-dependent post-translational modification as a contributor to irreversibility of senescence phenotype in such conditions. Sharpless and DePinho³⁴ argue that senescence-promoting pathways, like p16^{INK4a}, ADP-ribosylation factors (ARF)-p53, or Forkhead box protein family (FOXO)—reactive oxygen species, are repressed by the activity of Polycomb group proteins. These regulators are linked with the forkhead box transcription factor FoxM1c, and its deficiency results in SIPS.³⁵ Elevated levels of the cyclin-dependent kinase inhibitor p16^{INK4a} represent the hallmark of both replicatively and prematurely senescent cells. In fact, genetically triggered elimination p16^{INK4a}-expressing

cells delay the onset of aging-associated disorders.¹¹ As opposed to the p16^{INK4a}-dependent cell-autonomous mechanism of senescence, the Delta-like 1-induced senescence¹¹ represents an example of the non-cell-autonomous mechanism. In this latter category of pro-senescence pathways, senescent cells reinforce and propagate signals, such as inflammatory cytokines, transforming growth factor- β , Dkkopff-1 antagonist of Wnt signaling, insulin, and insulin-like growth factor-1, to compel increasing numbers of neighboring cells to cell cycle arrest and functional demise of the organ.³⁶

Sirtuin deacetylation pathway is linked to the mechanistic target of rapamycin (mTOR) and its effects on autophagy.³⁷ Inhibition of autophagy has emerged as a powerful pro-aging mechanism.^{38,39} Long before the modern conceptualization of therapeutic effects of calorie-restricted diet, Kleinknecht documented its benefits in rats with experimental renal disease or aging.⁴ These observations predated more recent demonstration of calorie-restricted diet preventing aging-associated glomerulosclerosis in rats.⁴⁰ In acute and chronic kidney disease, autophagy either may play adaptive role, supplying cells with nutrients, or may be conducive of apoptotic cell death.^{41,42} Autophagy is modulated by the mTOR, which in its active state is associated with lysosomes and mediates anabolic effects, whereas its dissociation signals catabolic states. Notably, activation of mTOR is downstream of insulin and insulin-like growth factor signaling pathways, which contribute to premature senescence. Targets of mTOR include, in addition to inhibition of autophagy, regulation of ribosomal biogenesis, protein translation, mitochondrial metabolism, and lipid synthesis. Defective autophagy is responsible for the accumulation of unfolded proteins in the endoplasmic reticulum and induction of unfolded protein response. Anti-apoptotic Bcl-2 proteins, often increased in senescent cells, interact with the autophagy protein Beclin1 and inhibit autophagosome formation, thus further disabling autophagic functions. Activation of mTOR pathway serves as a mediator of Wnt/ β -catenin pathway.⁴³ Wnt pathway is chronically activated in a mutant mouse strain deficient in Klotho, a model of premature senescence. Alternative splicing of Klotho gene results in the synthesis of a membrane form of the protein (a coreceptor for fibroblast growth factor 23) and a secreted form, which regulates activities of insulin and insulin-like growth factor-1. Recent work identified the retinoic acid-inducible gene-1 as a target suppressed by the intracellular form of Klotho. Moreover, retinoic acid-inducible gene-1 is a potent inducer of IL-6 and IL-8; therefore, defective Klotho signaling reactivates retinoic acid-inducible gene-1 and enhances secretion of IL-6 and IL-8, both proinflammatory components of the SASP.⁴⁴

Remarkably, mTOR also regulates SASP by promoting IL-1A translation.⁴⁵ On the other hand, the role of sirtuin 1 in cell fate and metabolic regulation is based on its effects augmenting FOXO-regulated stress resistance and interaction with p53, E2F1, peroxisome proliferator-activated

receptor γ coactivator-1 α , peroxisome proliferator-activated receptor- γ , endothelial nitric oxide synthase, and NF- κ B, to name a few,^{46,47} thus regulating cell viability, mitogenesis, and proinflammatory and metabolic pathways. The mTOR and sirtuin pathways are connected via the energy-sensing AMP-activated protein kinase (AMPK), as sirtuin 1 deacetylates liver kinase B1, an activator of AMPK, thus activating it.⁴⁸ In turn, AMPK modulates mTOR activity via its upstream regulator tuberous sclerosis protein 2 (TSC2) and Raptor component of mTOR complex 1.^{49,50} In fact, this nexus may represent the point of AMPK interaction with the Wnt pathway, potentially involved in the persistence of senescent state after an insult. Notably, mTOR is activated in senescent cells, which also show enhanced Wnt signaling; and Wnt9a has been linked to induction of senescence and fibrogenesis in kidneys subjected to ischemia-reperfusion injury.⁵¹ It is revealing that rapamycin and its analogs, rapalogues, are attracting increasing attention as pharmaceuticals for use in kidney disease, not only in transplantation, but also in polycystic kidney disease, renal cell carcinomas, and diabetic nephropathy.⁵² Notably, factors responsible for persistence of senescent state or SASP are also known inducers of fibrogenesis. Again, it is this vicarious relation manifesting in common drivers for both of them.

How the Concept of CKD Being the *Forme Fruste* of Senescence May Shape Pharmacotherapy

Having accepted this view on CKD progression as a function of senescent cell burden, it is conceivable that recently developed senotherapies should be, if judiciously implemented, beneficial in halting the progression of and reversing CKD. Several excellent reviews dealing with the subject of senotherapy have recently been published.^{6,9,30} Briefly, senotherapeutics are subdivided into senomorphics (modulation of SASP), senolytics, and rejuvenating agents. The first group includes an AMPK stimulator, metformin, and an mTOR inhibitor, rapamycin, both inducing autophagy and suppressing SASP. Senolytic agents capable of killing senescent cells include small molecules shifting anti-apoptotic balance toward apoptosis, such as Bcl-2 homology domain mimetics, like venetoclax, navitoclax, obatoclax, flavonoids quercetin and dasatinib, FOXO-4/p53 competitive inhibitor peptide FOXO4-D-Retro-Inverso,⁵³ and several other experimental compounds.³⁰ More recently, anti-inflamm-aging effects of long-term caloric restriction have been linked to activation of sirtuins and overexpression of single Ig IL-1 related receptor and blockade of toll-like receptor-4/NF- κ B pathway.⁵⁴ A mitochondrion-targeted antioxidant, elamipretide, has been tested in aging mice and shown to reduce senescence of parietal epithelial cells and attenuate glomerulosclerosis.⁵⁵ Activation of sirtuins using resveratrol, as an example of rejuvenating strategy that also reduces oxidative stress and

ameliorates proinflammatory components of SASP, has shown experimental benefits.¹⁶ More recently, several small-molecule sirtuin 1 activators (STACs) have been synthesized⁵⁶ and include, in addition to resveratrol, quercetin, butein (first generation), SRT 1720, 1460, and 2183 (second generation), and STAC-5, STAC-9, and STAC-10 (third generation), all extending life and health span. These compounds, presently undergoing clinical trials, represent novel venues of rejuvenation therapy. Another compound emerging in this category is NAD⁺, a cofactor necessary for activation of several sirtuins. NAD⁺ bioavailability is reduced in disease states and aging,^{57,58} and its precursor, nicotinamide, is therapeutic in correcting NAD⁺ deficiency.

In conclusion, presented evidence implies that many instances of CKD and aging or prematurely aging kidney have a lot in common and that it is difficult, at times, to segregate them; thus, I propose to consider some forms of CKD a *forme fruste* of senescence. In this context, the overlapping entities are akin to a palimpsest with senescent cells inscribed afresh all over CKD. Elimination of senescent cells reveals the original script, whereas their rejuvenation may restore the missing text of the original.

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