Senescence-associated secretory phenotype and accelerated renal aging in chronic kidney disease: a new frontier in targeted therapies

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Chronic kidney disease (CKD) affects over 850 million people globally and represents a paradigm of accelerated biological aging. Cellular senescence, characterized by irreversible growth arrest and the development of a senescence-associated secretory phenotype (SASP), has emerged as a central mechanism driving CKD progression, vascular complications, and systemic frailty. The SASP comprises a complex array of pro-inflammatory cytokines, chemokines, growth factors, and matrix-remodeling enzymes that perpetuate inflammation, fibrosis, and tissue dysfunction. This review synthesizes current understanding of SASP biology in the context of renal aging and inflammaging, examining its contribution to tubular atrophy, glomerulosclerosis, vascular calcification, and the uremic milieu. We critically evaluate emerging senotherapeutic strategies, including senolytic agents (dasatinib, quercetin, navitoclax, fisetin) and senomorphic compounds that modulate SASP secretion, discussing their nephroprotective potential based on preclinical and early clinical evidence. Furthermore, we explore the relevance of cellular senescence in dialysis-dependent patients and kidney transplant recipients, populations characterized by premature aging phenotypes. Finally, we address the translational challenges and opportunities for biomarker development, highlighting how SASP components may serve as both therapeutic targets and prognostic indicators in CKD management.

Keywords:
cellular senescence, chronic kidney disease, inflammaging, renal fibrosis, senescence-associated secretory phenotype, senolytics, senomorphics

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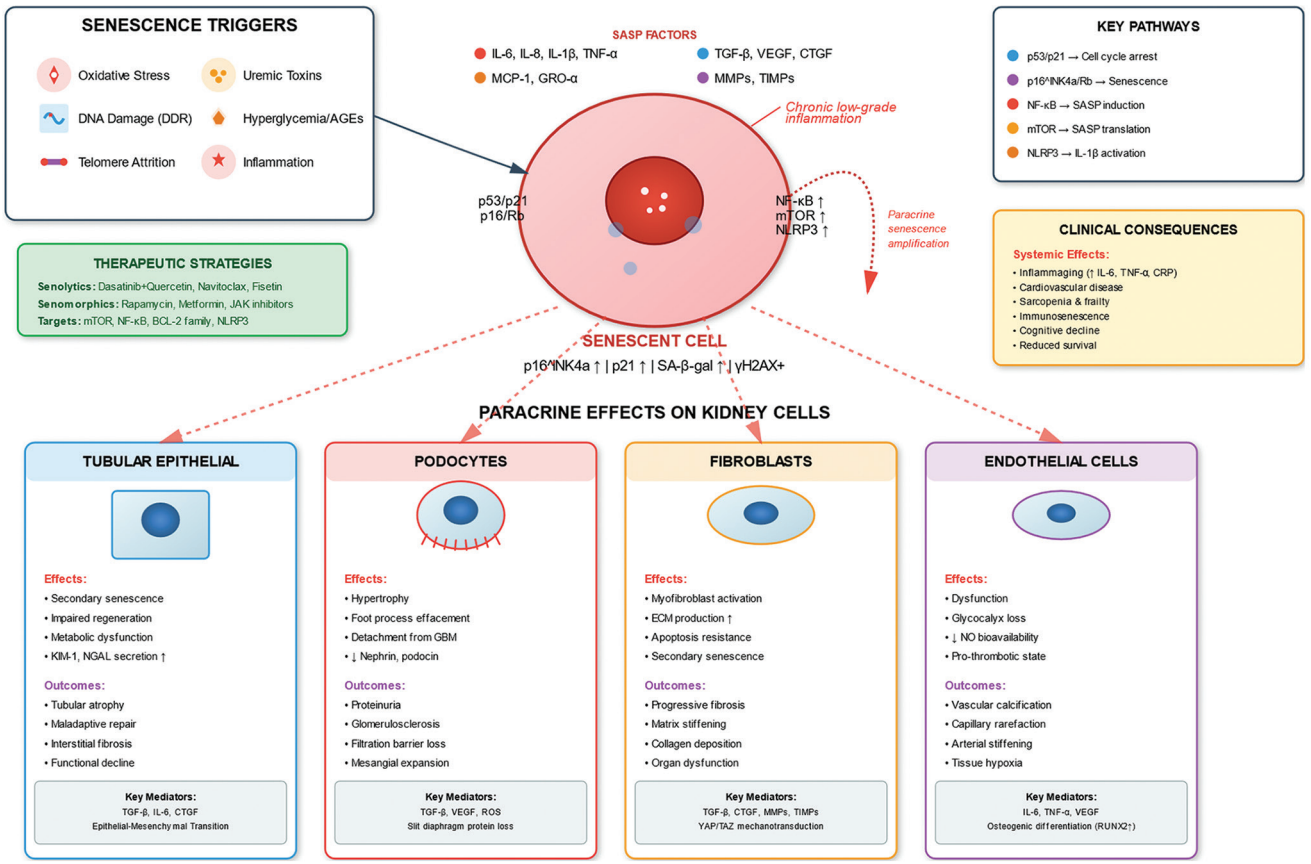
Introduction

Chronic kidney disease (CKD) represents a global health crisis, with prevalence estimates exceeding 13% of the adult population worldwide [1]. Beyond its traditional classification based on glomerular filtration rate and albuminuria, CKD is increasingly recognized as a state of premature biological aging, wherein patients exhibit phenotypic characteristics typically associated with advanced chronological age [2,3]. This accelerated aging manifests across multiple domains: cardiovascular disease develops decades earlier than in the general population, immune dysfunction resembles immunosenescence, cognitive decline occurs at younger ages, and physical frailty emerges as a dominant clinical syndrome [2].

Cellular senescence, first described by Hayflick and Moorhead in 1961, has evolved from a tissue culture curiosity to a fundamental biological process implicated in aging and age-related diseases [4]. Senescent cells accumulate with age and in response to various stressors, including oxidative damage, telomere dysfunction, DNA damage, and oncogene activation [5]. While cellular senescence serves beneficial functions in wound healing, tumor suppression, and embryonic development, chronic accumulation of senescent cells contributes to tissue dysfunction through both cell-autonomous mechanisms and nonautonomous effects mediated by the senescence-associated secretory phenotype (SASP) [5].

The SASP represents the hallmark feature of senescent cells, comprising over 100 secreted factors including interleukin-6 (IL-6), IL-8, monocyte chemoattractant protein-1 (MCP-1), growth-related oncogene-α, matrix metalloproteinases (MMPs), and various growth factors [6]. These factors create a pro-inflammatory, pro-fibrotic microenvironment that affects neighboring cells, recruits immune cells, and disrupts tissue architecture [7]. In the kidney, SASP-mediated paracrine signaling amplifies injury responses, promotes maladaptive repair, and accelerates functional decline [2] (Figs. 1–6 for a schematic representation of senescence triggers, SASP, and its effects on the kidney).

Figure 1



Cellular senescence and SASP in chronic kidney disease. SASP, senescence-associated secretory phenotype.

Recent advances have identified cellular senescence as a druggable target, spawning the development of senotherapeutics: pharmacological agents designed to eliminate senescent cells (senolytics) or suppress SASP secretion (senomorphics) [8]. Preclinical studies demonstrate that selective clearance of senescent cells can extend healthspan, delay age-related pathologies, and ameliorate experimental kidney disease [9,10]. These findings have catalyzed translational research efforts, with several senolytic compounds entering clinical trials for age-related conditions, including some with potential nephroprotective effects [10].

This review examines the emerging intersection of cellular senescence, SASP biology, and kidney disease, focusing on mechanistic insights, pathophysiological consequences, and therapeutic implications. We synthesize evidence from molecular studies, animal models, and human investigations to provide a comprehensive framework for understanding how senescence-related processes contribute to CKD progression and how targeted interventions might modify disease trajectories (Tables 1–3 and Fig. 6).

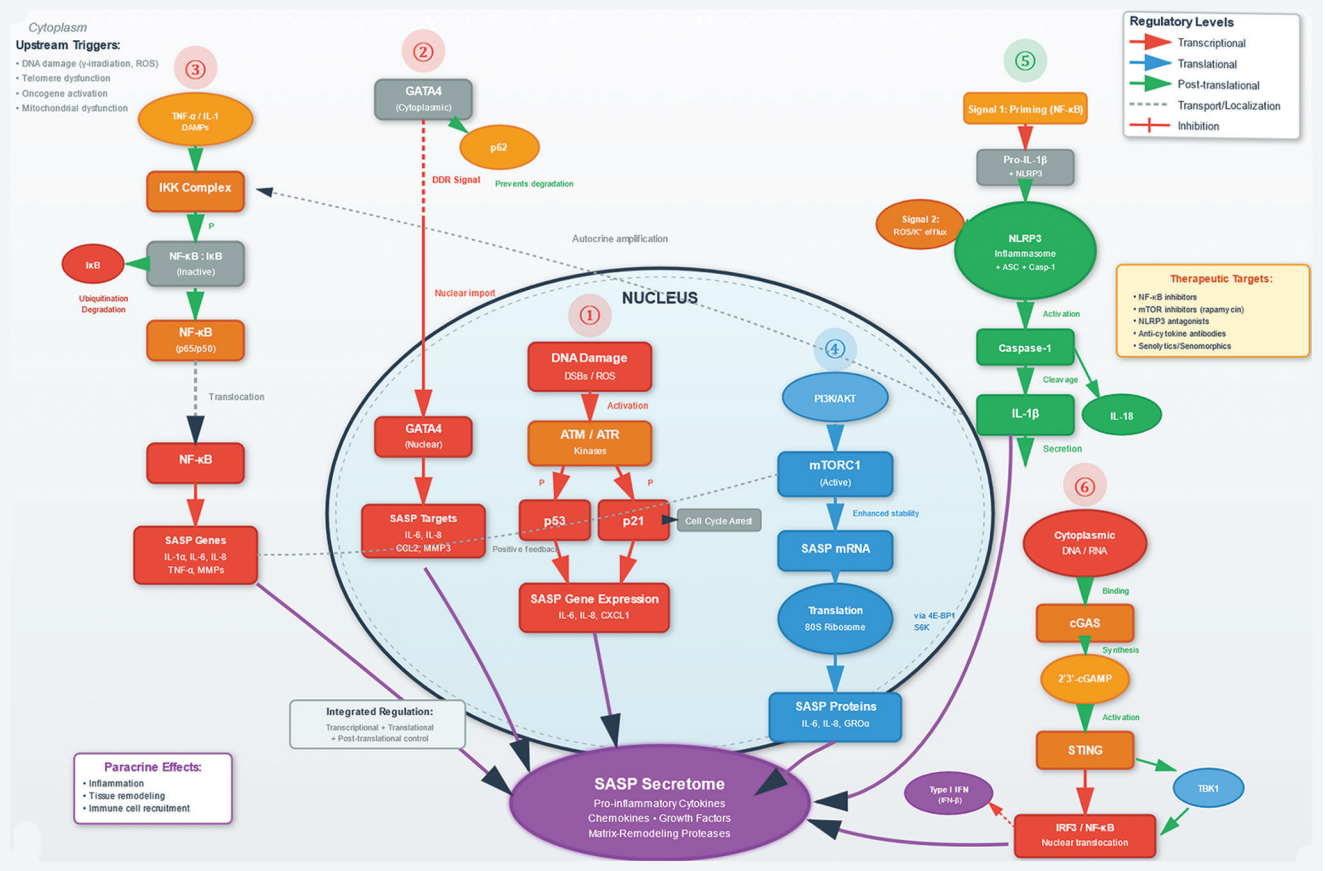
Cellular senescence: molecular mechanisms and senescence-associated secretory phenotype biology

Triggers and pathways of cellular senescence

Cellular senescence can be induced through multiple pathways, broadly categorized as replicative senescence (driven by telomere attrition) and stress-induced premature senescence [11]. In the kidney, stress-induced premature senescence predominates, triggered by oxidative stress, mitochondrial dysfunction, DNA damage, inflammatory stimuli, and metabolic perturbations characteristic of the uremic environment [11].

The molecular circuitry governing senescence centers on the p53/p21 and p16INK4a/Rb tumor suppressor pathways [12]. DNA damage response (DDR) activation leads to p53 stabilization and transcriptional upregulation of p21WAF1/CIP1 (CDKN1A), a cyclin-dependent kinase inhibitor that enforces cell cycle arrest [12]. Independently, the p16INK4a (CDKN2A) pathway becomes activated through chromatin remodeling and epigenetic changes, particularly in response to oxidative stress and inflammation [12]. Both pathways converge on

Figure 2



Molecular mechanisms of SASP regulation. SASP, senescence-associated secretory phenotype.

Table 1 Major components of the senescence-associated secretory phenotype and their roles in chronic kidney disease progression

SASP component	Category	Primary renal effects	Mechanisms	References
IL-6	Pro-inflammatory cytokine	Promotes inflammation, activates fibroblasts, induces tubular injury	JAK-STAT signaling, NF-κB activation	[6]
IL-8 (CXCL8)	Chemokine	Recruits neutrophils, promotes angiogenesis, tubular damage	CXCR1/2 signaling	[6,14]
MCP-1 (CCL2)	Chemokine	Macrophage recruitment, promotes fibrosis	CCR2 signaling	[6,14]
TGF-β1	Growth factor	Fibroblast activation, EMT, matrix deposition	SMAD2/3 signaling	[15]
CTGF (CCN2)	Growth factor	Synergizes with TGF-β, enhances fibrosis	Integrin binding	[15]
VEGF	Growth factor	Glomerular hyperfiltration, endothelial dysfunction	VEGFR signaling	[15,16]
MMP-1, -3, -9	Proteases	Matrix remodeling, basement membrane degradation	Collagen/gelatin degradation	[17]
PAI-1	Protease inhibitor	Impairs fibrinolysis, promotes fibrosis	Inhibits plasminogen activation	[18]
TNF-α	Pro-inflammatory cytokine	Tubular apoptosis, inflammation, insulin resistance	TNFR signaling	[19]
GDF-15	Growth factor	Marker of mitochondrial stress, correlates with mortality	TGF-β superfamily signaling	[20]

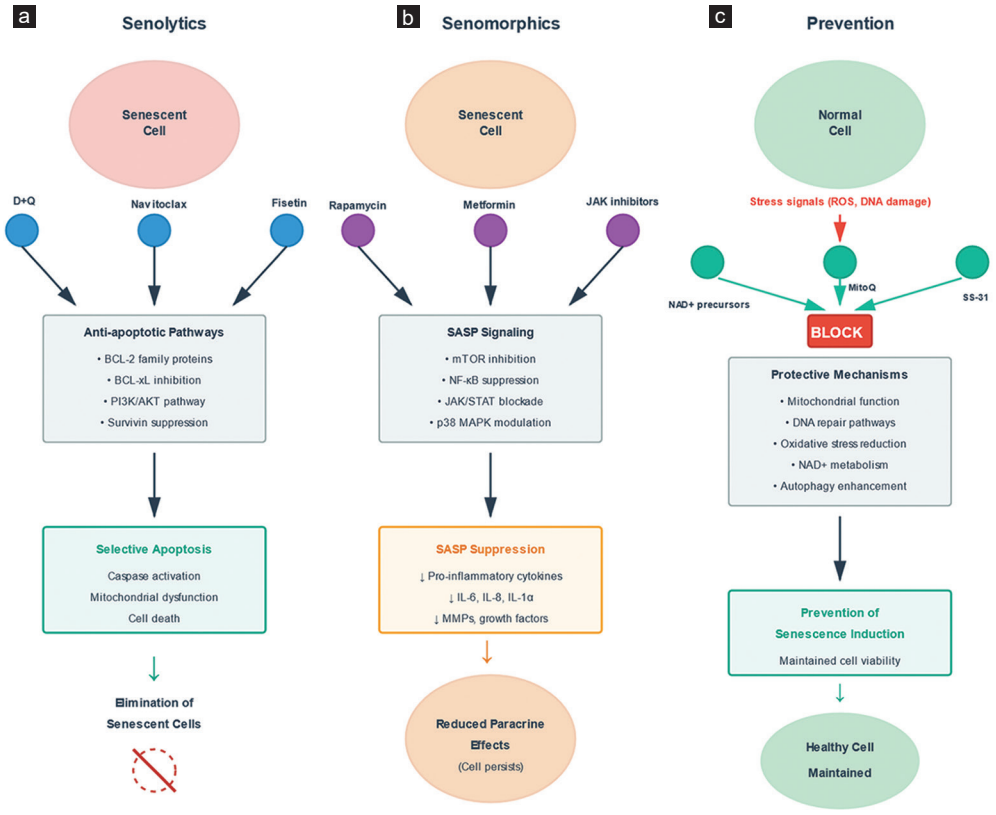
retinoblastoma protein (Rb) hypophosphorylation, maintaining cells in irreversible growth arrest [12].

Persistent DDR signaling manifests as persistent nuclear foci containing phosphorylated histone H2AX (γH2AX), 53BP1, and other DNA repair proteins, collectively termed DNA damage foci or DNA-SCARS (segments with chromatin alterations reinforcing senescence) [13]. These structures contribute to the senescent phenotype and correlate with SASP activation [13].

The senescence-associated secretory phenotype: composition and regulation

The SASP encompasses a diverse secretome including pro-inflammatory cytokines (IL-6, IL-1α, IL-1β, TNF-α), chemokines (IL-8/CXCL8, MCP-1/CCL2, MIP-1α/CCL3), growth factors (TGF-β, VEGF, IGF-binding proteins), proteases (MMP-1, MMP-3, MMP-9, MMP-12), and lipid mediators [6,14]. The composition varies depending on cell type, senescence inducer, and temporal dynamics, reflecting both common core factors and context-specific elements [Table 1] [11].

Figure 3



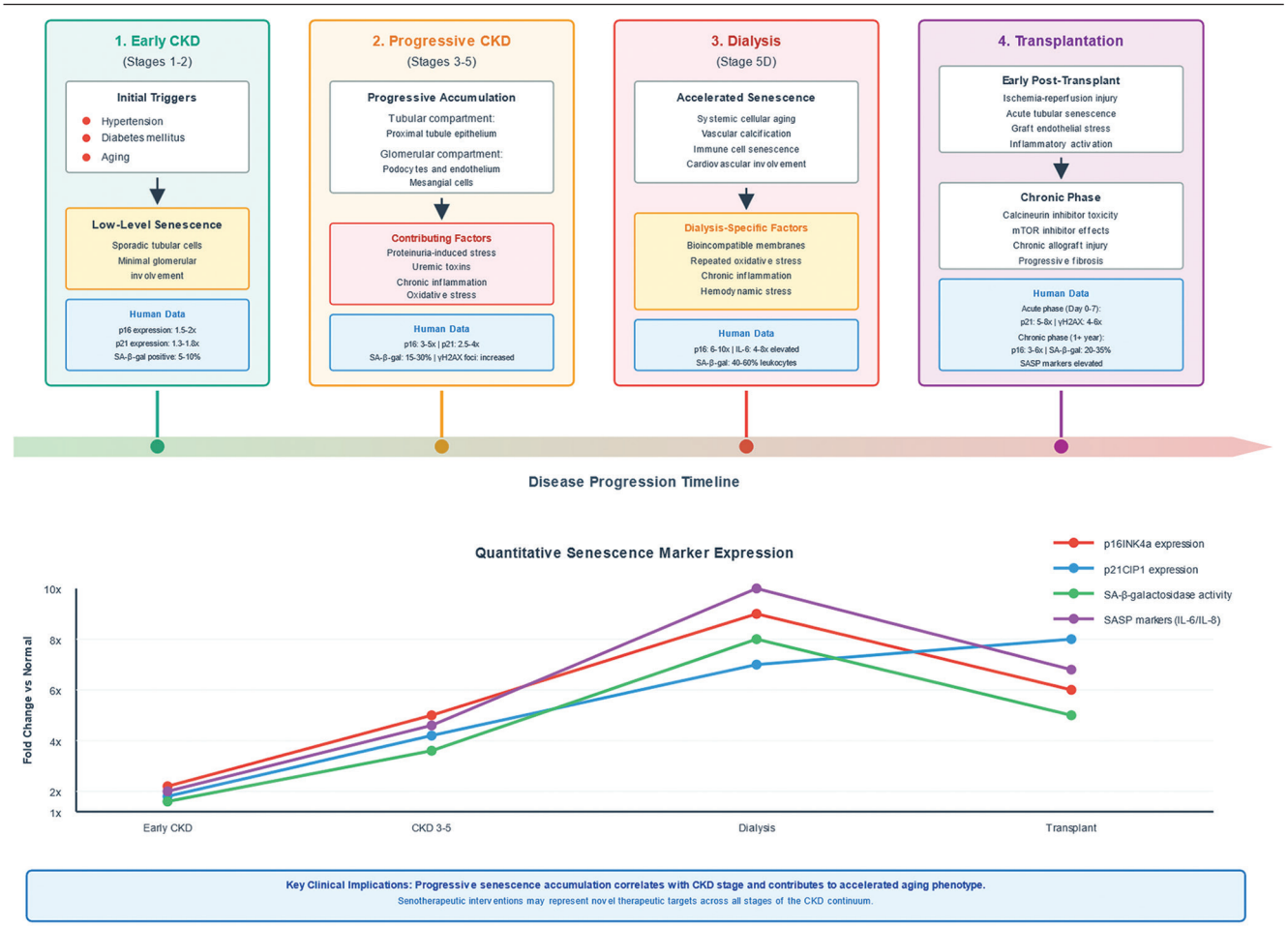
Senotherapeutic mechanisms of action. (a) Senolytics: agents such as Dasatinib+Quercetin (D+Q), Navitoclax, and Fisetin target anti-apoptotic pathways (BCL-2 family proteins, PI3K/AKT, survivin) in senescent cells, leading to selective apoptosis and elimination of senescent cells. (b) Senomorphics: agents including Rapamycin, Metformin, and JAK inhibitors suppress SASP signalling through mTOR inhibition, NF-κB suppression, and JAK/STAT blockade, reducing pro-inflammatory cytokine secretion while senescent cells persist. (c) Prevention: strategies employing NAD+ precursors, MitoQ, and SS-31 block stress signals (ROS, DNA damage) in normal cells, protecting mitochondrial function, enhancing DNA repair, and maintaining cell viability to prevent senescence induction. D+Q = Dasatinib + Quercetin; SASP = Senescence-Associated Secretory Phenotype; MMP = Matrix Metalloproteinase; ROS = Reactive Oxygen Species; NAD+ = Nicotinamide Adenine Dinucleotide.

Table 2 Senolytic and senomorphic agents: mechanisms and evidence in chronic kidney disease

Agents	Class	Mechanism of action	Preclinical CKD evidence	Clinical status	Key references
Dasatinib + Quercetin	Senolytic	Inhibits pro-survival pathways (tyrosine kinases, PI3K)	Reduces fibrosis in UUO, improves function in aged mice	Phase 2 trials in DKD completed	[10,34]
Navitoclax	Senolytic	BCL-2/BCL-XL/BCL-w inhibitor	Reduces senescent cells and fibrosis in kidney injury models	Approved for cancer; CKD trials pending	[60]
Fisetin	Senolytic	Flavonoid, multiple kinase inhibition	Ameliorates adenine-induced CKD	Phase 2 trial in frailty ongoing	[61]
Rapamycin/ sirolimus	Senomorphic	mTOR inhibition, suppresses SASP translation	Reduces graft senescence in transplant	Approved immunosuppressant	[50,52]
Metformin	Senomorphic	AMPK activation, mTOR suppression	Slows progression in diabetic nephropathy models	Widely used; senomorphic properties emerging	[62]
Ruxolitinib	Senomorphic	JAK1/2 inhibitor, suppresses SASP signaling	Reduces inflammation in experimental CKD	Approved for myeloproliferative disorders	[63]
NAD+ precursors	Prevention	Restores NAD+ levels, enhances DNA repair	Improves mitochondrial function, reduces tubular injury	Clinical trials in various conditions	[64,65]
MitoQ	Prevention	Mitochondria-targeted antioxidant	Reduces oxidative stress and senescence	Phase 2 trials in CKD	[66]

SASP induction occurs through coordinated activation of transcription factors and signaling cascades [21]. The DDR triggers ATM and ATR kinases, which phosphorylate downstream effectors including NF-κB [21]. Simultaneously, the transcription factor GATA4 stabilizes through suppression of its negative regulator and activates a senescence-associated transcriptional program [21]. The C/EBPβ transcription factor becomes activated in a NF-κB-dependent manner and drives expression of key SASP genes including IL-6 and IL-8 [21].

Figure 4



Cellular senescence across the CKD continuum. CKD, chronic kidney disease.

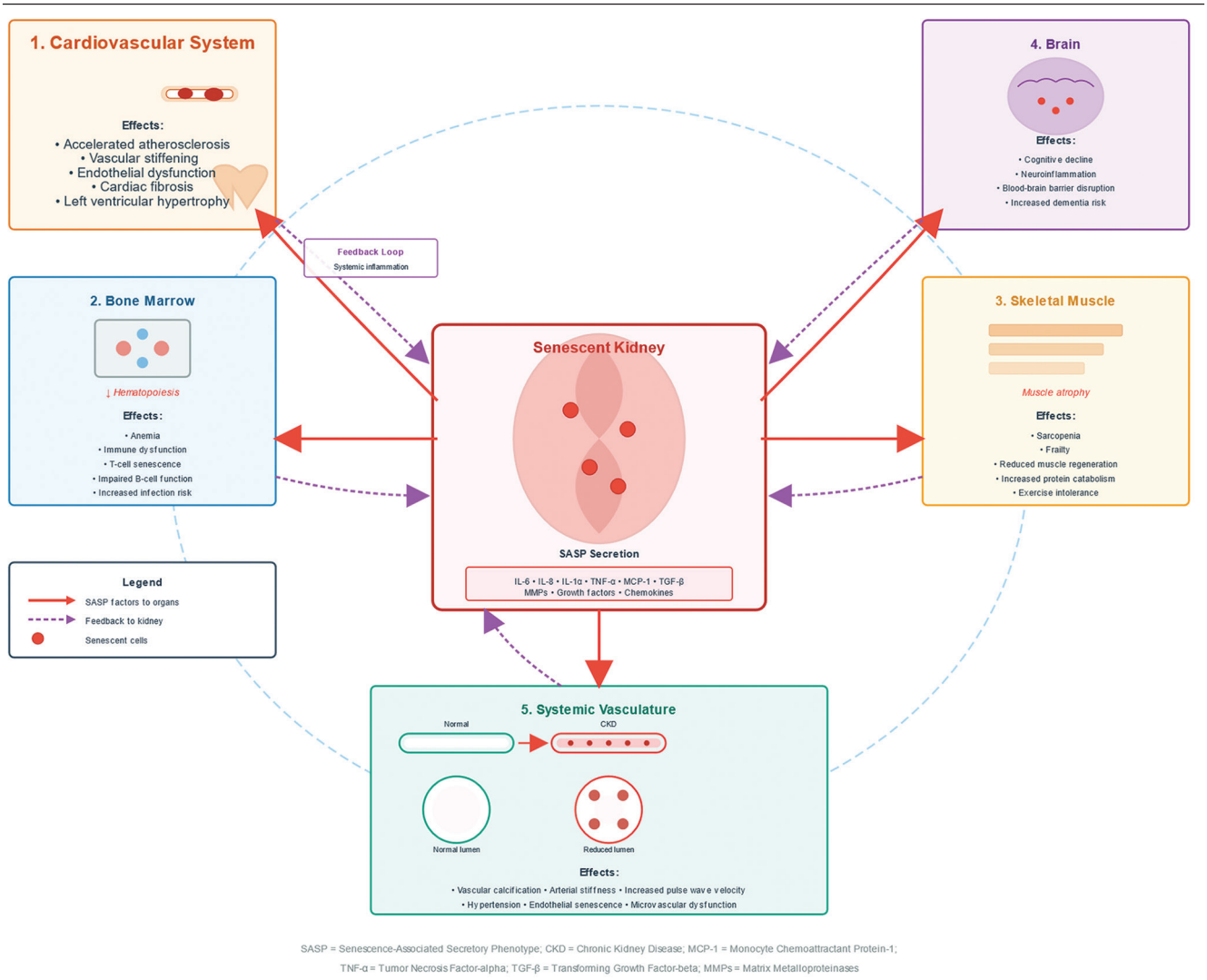
Table 3 Senescence biomarkers in chronic kidney disease: current status and future directions

Biomarker types	Specific markers	Sample source	Advantages	Limitations	Validation status
SASP factors	IL-6, IL-8, MCP-1, GDF-15, MMP-9	Plasma/serum	Noninvasive, readily measurable	Limited specificity for senescence	Extensively studied, correlates with outcomes
Senescence-associated glycoprotein	SAG	Plasma	Potentially senescence-specific	Requires further validation in humans	Experimental
Cell-free DNA methylation	Epigenetic age, senescence signatures	Plasma	Reflects biological aging	Complex analysis, standardization needed	Emerging evidence
Urinary markers	IL-6, MCP-1, TGF-β, exosomal miRNAs	Urine	Non-invasive, kidney-specific	Variable correlation with tissue burden	Moderate validation
Imaging markers	P16-targeted tracers	PET/CT	Direct visualization of senescent cells	Requires tracer development	Preclinical only
Tissue markers	p16INK4a, p21, SA-β-gal, γH2AX	Kidney biopsy	Direct assessment of renal senescence	Invasive, sampling bias	Gold standard but impractical

The inflammasome, particularly the NLRP3 complex, plays a critical role in SASP regulation through processing pro-IL-1β and pro-IL-18 into their active forms [14]. Senescent cells exhibit elevated inflammasome activity, creating a feed-forward loop wherein IL-1α released from senescent cells activates NF-κB in an autocrine manner, amplifying SASP production [14]. The NLRP3 inflammasome is a multi-protein complex that consists of the sensor protein NLRP3, the adaptor protein ASC, and the effector protein pro-caspase-1. Upon activation by a variety of stimuli, including pathogen-associated molecular patterns and damage-associated molecular patterns, NLRP3 oligomerizes and recruits ASC and pro-caspase-1, leading to caspase-1 activation. Activated caspase-1 then cleaves pro-IL-1β and pro-IL-18 into their mature, secreted forms.

Recent research has identified mTOR (mammalian target of rapamycin) as a central regulator of SASP translation and secretion [22]. mTOR inhibition selectively suppresses SASP without affecting senescence establishment,

Figure 5



SASP-mediated organ crosstalk in CKD. CKD, chronic kidney disease; SASP, senescence-associated secretory phenotype.

providing a mechanistic basis for senomorphic strategies [22]. Additionally, the cGAS-STING pathway responds to cytoplasmic chromatin fragments and mitochondrial DNA released during senescence, further amplifying interferon-stimulated genes and SASP factors [22] (Fig. 2).

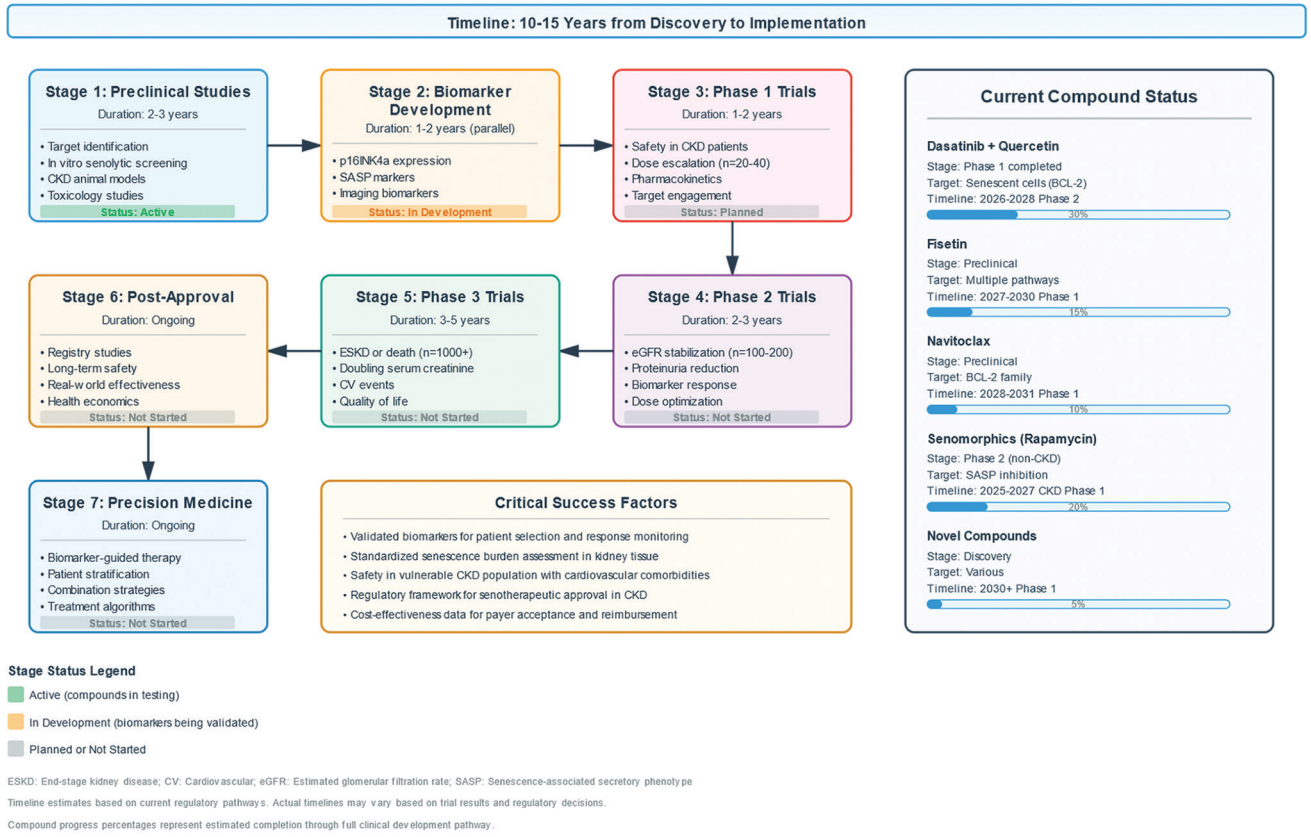
Functional consequences of senescence-associated secretory phenotype

The SASP exerts pleiotropic effects on tissue microenvironments [23]. Pro-inflammatory cytokines recruit immune cells, creating chronic low-grade inflammation termed "inflammaging" [24]. Chemokines like IL-8 and MCP-1 attract neutrophils, monocytes, and T cells, establishing inflammatory infiltrates that paradoxically fail to clear senescent cells efficiently [25]. This immune surveillance evasion occurs through multiple mechanisms, including expression of immune checkpoint ligands and secretion of immunosuppressive factors [25].

MMPs degrade extracellular matrix components, compromising tissue architecture [17]. Simultaneously, SASP factors stimulate fibroblast activation and collagen deposition through TGF-β signaling, creating a paradoxical combination of matrix degradation and pathological fibrosis [23]. Growth factors like VEGF promote angiogenesis in some contexts but contribute to vascular dysfunction in others, particularly when combined with pro-inflammatory mediators [15].

The SASP exhibits temporal heterogeneity, with early, intermediate, and late phases characterized by distinct secretory profiles [23]. Early SASP includes immediate damage-associated molecular patterns, while late SASP develops more pronounced pro-inflammatory characteristics requiring NF-κB and C/EBPβ activation [23]. This temporal evolution has implications for therapeutic targeting, as different intervention windows may require distinct strategies [11].

Figure 6



Clinical translation roadmap for senotherapeutics in CKD. CKD, chronic kidney disease

Cellular senescence in kidney disease: cell types and distribution

Renal tubular epithelial cell senescence

Tubular epithelial cells represent the primary site of senescence in CKD, particularly in the proximal tubule, which faces high metabolic demands and oxidative stress [26]. Acute kidney injury triggers widespread tubular senescence through ischemia-reperfusion injury, toxin exposure, or sepsis-induced inflammation [26]. While transient senescence may facilitate tissue repair through SASP-mediated recruitment of regenerative cells, persistent senescence impairs tubular regeneration and promotes maladaptive repair [27].

Studies using senescence markers including p16INK4a expression, senescence-associated β-galactosidase (SA-β-gal) activity, and γH2AX foci demonstrate progressive accumulation of senescent tubular cells in experimental CKD models [28]. Human kidney biopsies from patients with diabetic nephropathy, hypertensive nephrosclerosis, and chronic glomerulonephritis show elevated senescence markers correlating with severity of tubulointerstitial fibrosis and functional decline [28].

The tubular SASP includes particularly high levels of kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, IL-6, TGF-β1, and connective tissue growth factor (CTGF) [28]. These factors drive epithelial-mesenchymal transition, activate resident fibroblasts, and recruit inflammatory cells, creating a profibrotic microenvironment [27]. Additionally, senescent tubular cells exhibit impaired metabolic function, particularly mitochondrial dysfunction and reduced fatty acid oxidation, contributing to energy deficit and functional decline [27].

Glomerular senescence: podocytes and endothelial cells

Podocytes, highly differentiated post-mitotic cells critical for glomerular filtration barrier integrity, exhibit unique senescence characteristics [29]. These cells rarely undergo replicative senescence but frequently develop stress-induced senescence in response to hyperglycemia, oxidative stress, mechanical strain, and inflammatory mediators [30]. Podocyte senescence manifests as hypertrophy, foot process effacement, and detachment from the glomerular basement membrane, contributing to proteinuria [30].

The podocyte SASP includes elevated TGF-β, VEGF, and matrix proteins that disrupt glomerular architecture [29]. Senescent podocytes exhibit reduced expression of nephrin, podocin, and other slit diaphragm proteins, compromising filtration barrier function [30]. Furthermore, podocyte-derived SASP

factors affect adjacent mesangial cells and endothelial cells, amplifying glomerular injury through paracrine mechanisms [30].

Glomerular endothelial cells develop senescence in response to uremic toxins, oxidative stress, and hemodynamic stress [31]. Endothelial senescence contributes to loss of the glycocalyx, increased permeability, reduced nitric oxide bioavailability, and pro-thrombotic phenotype transformation [31]. The endothelial SASP promotes leukocyte adhesion and transmigration, creating an inflammatory glomerular milieu [31].

Interstitial cells: fibroblasts and pericytes

Renal fibroblasts and pericytes represent key effector cells in CKD progression, and their senescence has emerged as a critical pathogenic mechanism [32]. Following kidney injury, a subset of activated fibroblasts enters senescence rather than undergoing apoptosis, persisting in the interstitium and maintaining chronic SASP secretion [33]. This fibroblast senescence paradoxically coexists with myofibroblast activation, as different fibroblast subpopulations exhibit distinct fates [32].

Senescent fibroblasts secrete abundant collagen I, fibronectin, MMPs, and pro-fibrotic growth factors, directly contributing to extracellular matrix accumulation [5]. Their SASP includes factors that recruit additional inflammatory cells and activate neighboring fibroblasts, amplifying the fibrotic response [34]. Importantly, senescent fibroblasts exhibit resistance to apoptosis through upregulation of anti-apoptotic BCL-2 family proteins, explaining their persistent presence despite pro-apoptotic signals [34].

Pericyte senescence affects microvascular integrity and contributes to capillary rarefaction, a hallmark of progressive CKD [35]. Senescent pericytes detach from capillaries, reducing vascular stability and impairing oxygen delivery to tubular cells [35]. The resulting hypoxia triggers additional tubular senescence, creating a vicious cycle of microvascular loss and tissue injury [35,36].

Senescence-associated secretory phenotype-mediated mechanisms in chronic kidney disease progression

Inflammaging and chronic kidney disease

The concept of inflammaging – chronic, sterile, low-grade inflammation that develops with aging – accurately characterizes the CKD milieu [37]. SASP factors contribute significantly to systemic inflammation in CKD patients, with circulating levels of IL-6, TNF-α, and C-reactive protein correlating with kidney function decline and cardiovascular mortality [19].

Multiple mechanisms perpetuate SASP-driven inflammation in CKD [37]. Uremic toxins, including indoxyl sulfate and p-cresyl sulfate, induce cellular senescence and amplify SASP production in renal and vascular cells [38]. Impaired renal clearance leads to accumulation of advanced glycation end products and oxidized lipoproteins, which further stimulate senescence through RAGE (receptor for AGE) signaling [16]. Gut dysbiosis, common in CKD, increases translocation of bacterial products like lipopolysaccharide, activating inflammasome pathways and enhancing SASP [39].

The systemic consequences of SASP-mediated inflammaging extend beyond the kidney [39]. Bone marrow dysfunction occurs through senescent cell accumulation, contributing to anemia and immune dysfunction [19]. Skeletal muscle undergoes accelerated sarcopenia through inflammatory myokine signaling and impaired regeneration [40]. Cardiovascular tissues accumulate senescent cells, promoting atherosclerosis, arterial stiffening, and cardiac fibrosis [19].

Fibrogenesis and extracellular matrix remodeling

Renal fibrosis represents the final common pathway of progressive CKD, and SASP-mediated mechanisms play central roles in its pathogenesis [33]. TGF-β, a prominent SASP component, activates canonical SMAD2/3 signaling in fibroblasts, promoting their differentiation into collagen-secreting myofibroblasts [15]. Simultaneously, SASP-derived CTGF synergizes with TGF-β to enhance fibroblast activation and matrix production [15].

The SASP creates a complex balance between matrix synthesis and degradation [33]. While MMPs theoretically degrade excessive collagen, their activity becomes dysregulated in the senescent microenvironment [17]. Tissue inhibitors of metalloproteinases, also part of the SASP, accumulate and shift the balance toward matrix accumulation [17]. Additionally, specific MMPs paradoxically promote fibrosis through activation of latent TGF-β and degradation of basement membranes, facilitating myofibroblast migration [17].

Cross-linking enzymes secreted by senescent cells, including lysyl oxidase and transglutaminases, increase collagen cross-linking, rendering fibrotic tissue more resistant to degradation [41]. This creates

mechanically stiff environments that further activate mechanosensitive pathways in fibroblasts through integrin signaling and YAP/TAZ transcription factors, perpetuating the fibrotic process [41].

Vascular calcification and premature vascular aging

Vascular calcification, a near-universal complication in advanced CKD, reflects accelerated vascular aging strongly influenced by cellular senescence [42]. Vascular smooth muscle cells (VSMCs) and endothelial cells accumulate senescence markers in calcified vessels, with SASP factors promoting osteogenic differentiation [18].

The uremic milieu creates a perfect storm for calcification-inducing senescence [43]. Hyperphosphatemia directly induces VSMC senescence through oxidative stress and DNA damage [43]. Calcification inhibitor deficiency, particularly of fetuin-A and matrix Gla protein, combines with elevated calcium-phosphate product to precipitate hydroxyapatite crystals [43]. Senescent VSMCs exhibit reduced expression of calcification inhibitors and increased expression of osteogenic transcription factors like RUNX2 [18].

SASP-derived inflammatory cytokines amplify calcification through multiple mechanisms [43]. IL-6 and TNF-α suppress VSMC contractile markers and promote osteochondrogenic phenotype switching [43]. Matrix vesicles released by senescent VSMCs serve as nucleation sites for calcium phosphate precipitation [43]. Additionally, SASP-mediated alkaline phosphatase secretion generates inorganic phosphate locally, further promoting mineralization [43].

The consequences of vascular calcification extend beyond structural changes [44]. Arterial stiffening increases pulse wave velocity, elevating systolic blood pressure and pulse pressure, which further damages kidneys through hemodynamic stress [44]. Calcified vessels exhibit endothelial dysfunction, impaired vasodilation, and reduced oxygen delivery to tissues [44]. Cardiac valvular calcification increases with CKD progression, contributing to left ventricular hypertrophy and heart failure [44].

Cellular senescence in special CKD populations

Dialysis-dependent patients

Patients receiving maintenance dialysis exhibit hallmarks of accelerated aging across multiple biological systems [2]. Compared to age-matched controls, dialysis patients demonstrate shortened leukocyte telomere length, increased expression of senescence markers in circulating cells, and elevated plasma SASP factors [45,46].

Multiple dialysis-related factors contribute to senescence acceleration [46]. Bioincompatible dialysis membranes activate complement and inflammatory cascades, triggering cellular stress [46]. Endotoxin fragments from contaminated dialysate induce chronic immune activation [46]. Repeated vascular access procedures cause localized injury and senescence in vascular tissues [19]. Hemoconcentration and ultrafiltration create oxidative stress through changes in osmolarity and electrolyte fluctuations [45].

The accumulation of senescent cells in dialysis patients correlates with clinical outcomes [46]. Higher proportions of senescent T cells associate with increased infection risk and reduced vaccine responses [46]. Circulating SASP factors predict cardiovascular events and mortality independent of traditional risk factors [45]. Bone marrow senescence contributes to erythropoietin resistance and refractory anemia [47].

Peritoneal dialysis presents unique considerations regarding cellular senescence [48]. The peritoneal membrane undergoes progressive fibrosis, angiogenesis, and functional decline driven by chronic exposure to glucose-containing dialysate [49]. Mesothelial cell senescence accumulates with dialysis vintage, with cells exhibiting epithelial-to-mesenchymal transition and enhanced SASP secretion [49]. Peritoneal effluent contains elevated IL-6, VEGF, and TGF-β derived from senescent mesothelial cells [49].

Kidney transplant recipients

Kidney transplantation extends survival and improves quality of life compared to dialysis, yet recipients still exhibit accelerated aging phenotypes [50]. Both donor kidney age and recipient biological age influence transplant outcomes, with cellular senescence serving as a potential mediator [50].

Donor kidneys from older individuals contain more senescent cells at baseline, contributing to delayed graft function and reduced long-term survival [51]. Ischemia-reperfusion injury during organ procurement and transplantation induces additional senescence in tubular and endothelial cells [50]. Cold and warm ischemia times correlate with senescence marker expression and SASP levels in posttransplant biopsies [50].

Immunosuppressive medications influence cellular senescence in complex ways [52]. Calcineurin

inhibitors (tacrolimus, cyclosporine) induce cellular senescence through oxidative stress, mitochondrial dysfunction, and DNA damage [50]. These drugs also promote premature vascular aging and accelerate atherosclerosis [50]. Conversely, mTOR inhibitors (sirolimus, everolimus) possess senomorphic properties, suppressing SASP through their primary mechanism of action [53].

Chronic antibody-mediated rejection involves senescence of graft microvascular endothelial cells [54]. Donor-specific antibodies trigger complement activation and endothelial injury, promoting senescence and SASP secretion [54]. The resulting inflammatory microenvironment attracts immune cells and promotes fibrosis, contributing to chronic allograft nephropathy [55].

Diabetic kidney disease

Diabetic kidney disease (DKD) exemplifies senescence-driven pathology, with hyperglycemia serving as a potent senescence inducer [16,56]. Advanced glycation end products formed through non-enzymatic glycation bind RAGE receptors, triggering oxidative stress and senescence in multiple renal cell types [16]. Protein kinase C activation by hyperglycemia induces NADPH oxidase and reactive oxygen species generation, damaging DNA and promoting senescence [57].

Podocyte senescence plays particularly important roles in DKD progression [57]. High glucose concentrations induce podocyte senescence through p53 and p21 pathway activation, leading to hypertrophy, detachment, and glomerulosclerosis [57]. Senescent podocytes secrete VEGF at elevated levels, contributing to hyperfiltration and endothelial dysfunction [16].

The SASP in DKD exhibits distinctive characteristics, with high TGF-β and CTGF driving aggressive tubulointerstitial fibrosis [15]. Tubular senescence contributes to albuminuria through impaired protein reabsorption and degradation [57]. Senescent tubular cells also exhibit defective autophagy, creating a vicious cycle wherein impaired cellular quality control accelerates senescence [30].

Metabolic memory – the persistence of hyperglycemia-induced damage despite subsequent glucose normalization – may be partially mediated by cellular senescence [58,59]. Senescent cells established during periods of poor glycemic control persist and continue secreting SASP factors even after glucose levels improve, explaining why early intervention provides superior outcomes [58].

Senotherapeutic strategies: from bench to bedside

Senolytic agents

Senolytics selectively eliminate senescent cells by targeting their anti-apoptotic pathways [Table 2] [8]. These agents exploit the senescent cell anti-apoptotic phenotype, wherein senescent cells upregulate BCL-2 family proteins, heat shock proteins, and other survival factors to resist apoptosis despite accumulating damage [9,60].

Dasatinib plus Quercetin (D + Q): this combination represents the most extensively studied senolytic regimen [34]. Dasatinib, a tyrosine kinase inhibitor used in chronic myeloid leukemia, targets ephrin receptor pathways important for senescent cell survival [34]. Quercetin, a natural flavonoid, inhibits multiple pro-survival kinases including PI3K [34]. The combination exhibits synergistic senolytic effects across diverse cell types [67].

In preclinical kidney disease models, D + Q treatment reduces senescent cell burden, attenuates inflammation, improves renal function, and extends lifespan [34]. In a unilateral ureteral obstruction model, D + Q eliminated p16-positive tubular cells and reduced fibrosis [34]. In aged mice with pre-existing kidney dysfunction, intermittent D + Q dosing improved renal blood flow and reduced albuminuria [34].

Human studies of D + Q are emerging. A pilot trial in idiopathic pulmonary fibrosis patients demonstrated safety and potential efficacy [10]. A study in DKD patients (NCT02848131) investigated D + Q effects on renal function and senescence biomarkers, with results suggesting improved physical function and reduced adipose tissue senescence, though specific renal outcomes require further investigation [10,67].

Navitoclax: this BCL-2 family inhibitor developed for cancer therapy exhibits potent senolytic activity [60]. Navitoclax binds BCL-2, BCL-XL, and BCL-w, triggering apoptosis in cells dependent on these survival proteins [60]. In preclinical kidney disease models, navitoclax reduces senescent cell accumulation and ameliorates fibrosis [60].

Dose-limiting thrombocytopenia, resulting from BCL-XL inhibition in platelets, complicates clinical use of navitoclax [60]. Newer BCL-2 selective inhibitors like venetoclax may offer improved safety profiles, though their senolytic efficacy appears cell-type dependent [60].

Fisetin: this naturally occurring flavonoid demonstrates senolytic properties at higher concentrations than

quercetin [61]. Fisetin reduces senescent cell burden in aged mice and improves healthspan parameters [61]. In an adenine-induced CKD model, fisetin ameliorated renal dysfunction, reduced tubular senescence, and attenuated fibrosis [61]. A clinical trial (NCT03675724) is evaluating fisetin in frail older adults, including assessment of kidney function [61].

Other senolytic candidates: HSP90 inhibitors, cardiac glycosides, piperlongumine, and UBX0101 (MDM2 inhibitor) show senolytic activity in specific contexts [60]. However, their nephroprotective potential remains less well characterized than D + Q or fisetin [67].

Senomorphic approaches

Senomorphics suppress SASP without eliminating senescent cells, potentially avoiding risks associated with broad cellular depletion [63]. These agents target SASP regulatory pathways including NF-κB, mTOR, p38 MAPK, and JAK-STAT signaling [67].

Rapamycin and rapalogs: mTOR inhibitors suppress SASP translation through their canonical mechanism [52]. In kidney transplantation, conversion from calcineurin inhibitors to sirolimus associates with reduced graft senescence and improved long-term function in some studies [52]. However, proteinuria and impaired wound healing complicate clinical use [50].

Intermittent rapamycin dosing shows promise in preclinical aging studies, extending lifespan and healthspan with fewer side effects than continuous administration [52]. This approach may prove applicable to CKD, though clinical trials are needed [52].

Metformin: beyond its glucose-lowering effects, metformin exhibits senomorphic properties through AMPK activation and mTOR suppression [62]. Retrospective studies suggest metformin use in diabetic CKD patients associates with slower progression and reduced cardiovascular events compared to other antihyperglycemic agents [62]. Prospective trials examining metformin's senomorphic effects in CKD are warranted [62].

JAK inhibitors: the JAK-STAT pathway mediates SASP cytokine signaling, making it an attractive therapeutic target [63]. Ruxolitinib and baricitinib suppress SASP in preclinical models [63]. While primarily used for myeloproliferative disorders and rheumatoid arthritis, their potential in CKD-related inflammaging deserves exploration [63].

Glucocorticoids: despite their broad immunosuppressive effects, glucocorticoids suppress specific SASP components through NF-κB inhibition [68]. However, their adverse metabolic and bone effects limit chronic use, and they may paradoxically promote senescence in some contexts [68].

Natural compounds: resveratrol, curcumin, and epigallocatechin gallate demonstrate senomorphic properties in experimental systems [68]. However, bioavailability challenges and limited clinical data restrict their current therapeutic utility [68].

Targeting senescence pathways

Alternative strategies target senescence induction pathways or enhance senescent cell clearance [68].

NAD+ precursors: nicotinamide adenine dinucleotide (NAD+) declines with aging and CKD, impairing cellular energy metabolism and DNA repair [64]. NAD+ precursors including nicotinamide riboside and nicotinamide mononucleotide restore NAD+ levels and may prevent senescence [64]. In experimental CKD models, NAD+ supplementation improves mitochondrial function and reduces tubular injury [65].

Mitochondrial-targeted antioxidants: mitochondrial dysfunction drives senescence through reactive oxygen species generation [69]. MitoQ and SkQ1, mitochondria-targeted antioxidants, reduce cellular senescence and ameliorate kidney injury in animal models [66]. Human trials evaluating MitoQ in CKD are underway [66].

Immune enhancement: improving immune-mediated clearance of senescent cells represents an attractive strategy [70]. Natural killer (NK) cells and macrophages eliminate senescent cells under physiological conditions, but this surveillance declines with aging [70]. Approaches to enhance NK cell function or macrophage clearance capacity may augment endogenous senescent cell elimination [70].

Autophagy enhancers: defective autophagy contributes to senescent cell accumulation [71]. Spermidine, urolithin A, and other autophagy inducers reduce senescence markers and improve cellular function [71]. In experimental CKD, these compounds attenuate disease progression, though mechanisms may extend beyond autophagy [71].

Biomarker development and clinical translation

Senescence biomarkers in CKD

Identifying reliable senescence biomarkers in CKD patients remains challenging but essential for clinical

translation [72]. Ideal biomarkers should reflect senescent cell burden, predict disease progression, and respond to therapeutic interventions [Table 3] [72].

Circulating SASP factors: plasma or serum levels of IL-6, IL-8, MCP-1, GDF-15, and MMP-9 correlate with kidney function decline and mortality in CKD patients [20,37]. However, these factors lack specificity for cellular senescence versus other inflammatory processes [33]. Multimarker panels combining several SASP components may improve diagnostic accuracy [73].

Senescence-associated glycoprotein: recently identified as a senescence-specific biomarker, senescence-associated glycoprotein shows promise in animal models but requires validation in human CKD [73].

Cell-free DNA and methylation patterns: circulating cell-free DNA exhibits senescence-associated methylation changes detectable in plasma [74]. Epigenetic clocks based on DNA methylation reflect biological aging and may capture senescence burden [74]. These approaches show potential but require standardization for clinical use [74].

Imaging biomarkers: emerging imaging techniques may visualize senescent cell accumulation noninvasively [75]. Positivity for p16INK4a can be detected using molecular imaging probes in preclinical models [75]. Translation to clinical practice awaits development of appropriate radiotracers and validation studies [73].

Urinary markers: urinary SASP factors and exosomal markers derived from senescent tubular cells represent promising noninvasive biomarkers [76]. Urinary IL-6, MCP-1, and TGF-β correlate with fibrosis severity in kidney biopsies [76]. Exosomal miRNAs associated with senescence may provide additional diagnostic information [76].

Clinical trial design considerations

Senotherapeutic trials in CKD face unique challenges requiring thoughtful study design [77].

Patient selection: enriching trials with patients exhibiting high senescent cell burden may improve detection of treatment effects [52]. Biomarker-guided enrollment could identify individuals most likely to benefit [78].

Dosing regimens: unlike conventional daily medications, senolytics may be administered intermittently, potentially reducing side effects [67]. Determining optimal dosing frequency and duration requires careful investigation [73].

Outcome measures: traditional renal endpoints like GFR decline or doubling of serum creatinine require large sample sizes and long follow-up [79]. Incorporating surrogate markers including albuminuria change, fibrosis biomarkers, or histological endpoints on serial biopsies may expedite signal detection [3].

Safety monitoring: senolytic-induced elimination of senescent cells could theoretically impair wound healing or regeneration in some contexts [80]. Careful monitoring for adverse effects including impaired recovery from intercurrent illness or surgical procedures is essential [80].

Combination therapies: Combining senotherapeutics with established CKD treatments including renin-angiotensin system inhibitors or SGLT2 inhibitors may yield synergistic benefits [81,82]. Early-phase trials should evaluate safety and potential interactions before pursuing combination efficacy studies [82].

Therapeutic challenges and future directions

Cell-type specificity and heterogeneity

A major challenge in senotherapeutic development lies in the heterogeneity of senescent cells across different tissues and contexts [83]. Renal tubular epithelial senescence may require different targeting strategies than endothelial or fibroblast senescence [67]. Current senolytics exhibit variable efficacy across cell types, with D + Q showing broader activity than BCL-2 family inhibitors, which preferentially target specific populations [60].

Single-cell RNA sequencing studies reveal transcriptional heterogeneity among senescent cells within the same tissue, with distinct subpopulations exhibiting different SASP profiles and survival dependencies [11]. Some senescent cells express high BCL-2, making them vulnerable to navitoclax, while others rely on different anti-apoptotic pathways [11]. Developing cell-type-specific senolytics or personalized approaches based on individual senescence profiles may optimize therapeutic efficacy [11].

The temporal dynamics of senescence add additional complexity [83]. Acute senescence following kidney injury may serve beneficial functions by limiting fibroblast proliferation and promoting tissue remodeling, whereas chronic senescence drives maladaptive responses [80]. Timing of senotherapeutic

intervention relative to disease stage may critically influence outcomes [7].

Beneficial roles of senescence

While this review emphasizes pathogenic aspects of cellular senescence, important beneficial functions must be acknowledged [84]. Senescence serves as a tumor suppressor mechanism, preventing proliferation of cells with oncogenic mutations [84]. In wound healing, transient senescence of fibroblasts limits scar formation and facilitates tissue remodeling [70]. During embryonic development, programmed senescence sculpts tissues and eliminates transient structures [85].

Concerns exist that chronic senolytic therapy might increase cancer risk by eliminating senescent premalignant cells [9]. However, long-term studies in mice show that genetic or pharmacological senescent cell clearance reduces cancer incidence, possibly by eliminating SASP-mediated tumor promotion [84]. Nevertheless, careful oncological surveillance in senotherapeutic trials remains prudent [6].

Impaired wound healing represents another theoretical concern, as senescent cells participate in tissue repair [80]. Intermittent senolytic dosing may mitigate this risk by allowing senescent cell accumulation during acute injury responses while preventing chronic accumulation [8]. Clinical experience with D + Q suggests acceptable safety profiles, though wound healing complications have not been systematically evaluated [10].

Organ crosstalk and systemic effects

CKD exemplifies systemic disease, with bidirectional interactions between kidneys and distant organs [19]. Senescent cells accumulating in cardiovascular tissues, bone marrow, skeletal muscle, and brain contribute to CKD complications through remote SASP effects [86]. Conversely, renal-derived SASP factors circulate systemically, promoting senescence in distant tissues [86].

This organ crosstalk presents both challenges and opportunities for senotherapeutic intervention [87]. Kidney-specific delivery of senolytics might minimize systemic side effects but fail to address extra-renal senescence contributing to CKD complications [88]. Conversely, systemic senolytic administration could simultaneously target multiple senescent cell populations, providing comprehensive benefits [67].

Understanding these complex interactions requires integrated approaches combining renal and systemic assessments [8]. Biomarker studies should measure both circulating and tissue-specific senescence markers [67]. Preclinical models should evaluate multiorgan effects of senotherapeutics beyond traditional renal endpoints [84].

Mechanisms of senescent cell resistance

Senescent cells exhibit remarkable resistance to elimination, both by immune cells and apoptotic signals [84]. Multiple mechanisms contribute to this resistance, presenting targets for therapeutic development [89].

The senescent cell anti-apoptotic phenotype involves upregulation of BCL-2 family proteins, survivin, PAI-1, and heat shock proteins [18]. Additionally, senescent cells express immune checkpoint molecules including PD-L1 and CD47 ("don't eat me" signals) that inhibit immune-mediated clearance [70,90]. Hypoxia-inducible factor 1α stabilization in senescent cells further enhances survival under stress conditions [23].

Combination approaches targeting multiple resistance mechanisms may improve senescent cell elimination [84]. For example, combining senolytics with immune checkpoint inhibitors or CD47-blocking antibodies could enhance clearance [84,88]. However, such strategies require careful safety evaluation given potential immune-related adverse effects [84].

Senescence in regenerative medicine

Cell-based therapies for kidney disease must consider cellular senescence as a barrier to regeneration [87]. Mesenchymal stem cells (MSCs) used in experimental kidney disease treatment can themselves undergo senescence, particularly after *ex vivo* expansion [87]. Senescent MSCs exhibit impaired regenerative capacity and paradoxically secrete pro-inflammatory SASP factors [87].

Strategies to prevent or reverse MSC senescence may enhance therapeutic efficacy [91]. Brief exposure to senolytics can eliminate senescent cells from MSC preparations [87]. Preconditioning MSCs with rapamycin or other senomorphics may enhance their regenerative potential [52]. Gene editing approaches could engineer MSCs resistant to senescence-inducing stimuli encountered in diseased kidneys [91].

Induced pluripotent stem cells offer another regenerative avenue [91]. However, reprogramming efficiency declines in cells from aged or CKD patients, potentially due to senescence-associated epigenetic changes [91]. Transient senolytic treatment before

cellular reprogramming improves induced pluripotent stem cells generation from aged donors [91].

Precision medicine approaches

Individual variability in senescent cell accumulation, SASP composition, and therapeutic responses necessitates precision medicine strategies [8]. Genetic polymorphisms in senescence-regulatory genes influence CKD progression rates [92]. For example, variations in CDKN2A/B locus associate with increased kidney disease risk [92].

Pharmacogenomic considerations may guide senotherapeutic selection [92]. Patients with specific genetic profiles might exhibit enhanced responses to particular senolytics or increased susceptibility to side effects [92]. Machine learning algorithms integrating clinical, genetic, and biomarker data could predict individual responses and optimize treatment selection [93].

Kidney biopsy analysis, though invasive, provides direct assessment of senescent cell burden and distribution [3]. Multiplexed immunofluorescence or spatial transcriptomics can map senescent cell populations and SASP profiles at single-cell resolution [94]. Such detailed characterization could guide personalized senotherapeutic approaches [94].

Economic and healthcare system considerations

The potential economic impact of effective senotherapeutics deserves consideration [95]. CKD imposes enormous healthcare costs through dialysis, transplantation, cardiovascular complications, and reduced workforce participation [95]. Therapies that slow progression or prevent complications could generate substantial cost savings despite potentially high drug acquisition costs [95].

Value-based pricing models incorporating quality-adjusted life years and healthcare utilization reductions may justify senotherapeutic development [95]. Comparative effectiveness research should evaluate senotherapeutics against existing standard-of-care treatments [93]. Real-world evidence from postapproval studies will inform optimal clinical use and cost-effectiveness [95].

Access and equity issues require attention, as novel therapies often face adoption barriers in resource-limited settings where CKD burden is highest [95]. Generic formulations of repurposed drugs like dasatinib and natural compounds like quercetin may facilitate broader access compared to novel molecular entities [95].

Emerging concepts and paradigm shifts

Senescence as a therapeutic target across the CKD spectrum

Traditional CKD management emphasizes risk factor modification and symptom control [47]. The senescence paradigm offers opportunities for disease modification across all stages [17]. In early CKD, preventing senescent cell accumulation could slow progression [79]. In advanced CKD, eliminating established senescent cells might partially restore function or improve complications [33]. Even in dialysis patients, senotherapeutics could reduce cardiovascular events and improve quality of life [45].

This paradigm shift requires reconceptualizing CKD not merely as irreversible nephron loss but as a dynamic state wherein harmful cellular populations can be targeted [35,96]. Proof-of-concept studies demonstrating functional improvement following senolytic treatment in advanced experimental CKD support this view [34].

Integration with other aging biology concepts

Cellular senescence represents one of nine hallmarks of aging identified in landmark reviews [69]. Other hallmarks including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, stem cell exhaustion, and altered intercellular communication intersect with senescence [97].

Integrated therapeutic approaches targeting multiple aging hallmarks may prove superior to single-target strategies [98]. For example, combining senolytics with NAD+ precursors (targeting metabolic dysfunction), metformin (nutrient sensing), or mitochondrial antioxidants (organellar dysfunction) could provide synergistic benefits [62]. Clinical trials evaluating such combination approaches are emerging [62].

The geroscience hypothesis posits that targeting fundamental aging mechanisms delays multiple age-related diseases simultaneously [98]. By this logic, senotherapeutics developed for CKD should benefit other age-related conditions, and vice versa [97]. This concept could accelerate drug development through indication expansion and repurposing [98].

Microenvironment modulation beyond senescence

While senescent cells represent key therapeutic targets, the broader tissue microenvironment influences CKD progression [32]. Extracellular matrix stiffness, hypoxia, metabolic alterations, and immune cell infiltration interact with senescence in complex networks [33].

Matrix stiffness mechanically activates fibroblasts and promotes senescence through integrin-mediated mechanotransduction [15]. Therapies targeting matrix cross-linking or mechanosensing pathways could complement senotherapeutics [99]. Lysyl oxidase inhibitors and relaxin analogs show promise in experimental fibrosis models [99].

Tissue hypoxia, resulting from capillary rarefaction and anemia, promotes senescence while activating HIF pathways that paradoxically enable senescent cell survival [35,100]. HIF stabilizers approved for CKD anemia might have complex effects on senescence, requiring careful investigation [101]. Alternatively, improving tissue oxygenation through revascularization strategies could reduce senescence burden [35].

Prevention versus treatment paradigms

Most senotherapeutic research focuses on eliminating established senescent cells or suppressing existing SASP [8]. However, preventing senescence induction represents an alternative strategy [11]. Lifestyle interventions including exercise, caloric restriction, and dietary modifications reduce cellular senescence in animal models and potentially humans [102].

In CKD patients, optimizing modifiable risk factors could prevent senescence accumulation [103]. Strict glycemic control in diabetes, blood pressure management, avoidance of nephrotoxins, and treatment of uremic toxins through dietary measures or adsorbents may reduce senescence-inducing stimuli [38,104]. Combining prevention strategies with periodic senolytic therapy could provide comprehensive benefits [104].

Long-term safety and ethical considerations

As senotherapeutics advance toward clinical implementation, long-term safety data remain limited [83]. Most studies span months to a few years, insufficient to detect rare adverse events or delayed complications [104]. Extended observation periods and registry-based surveillance will be essential [102].

Ethical considerations arise regarding senotherapeutic use in different populations [77]. Should these therapies be reserved for patients with established disease or offered to at-risk individuals for prevention? [77] How should we balance potential benefits against uncertain long-term risks? [77] Informed consent processes must clearly communicate the investigational nature of senotherapeutics and knowledge gaps [77].

The possibility of anti-aging effects beyond kidney disease raises additional ethical questions [77]. If senotherapeutics extend healthspan and lifespan, access and allocation issues become paramount [62]. Regulatory pathways must balance innovation encouragement with patient protection [77].

Conclusions and future directions

Cellular senescence and the SASP have emerged as central drivers of accelerated aging and disease progression in CKD. The evidence synthesized in this review strongly supports the characterization of CKD as a state of premature senescence, where the accumulation of senescent cells in the kidney and other organ systems perpetuates a vicious cycle of inflammation, fibrosis, and functional decline. The SASP, with its complex secretome of pro-inflammatory and pro-fibrotic factors, lies at the heart of this process, mediating organ cross-talk and amplifying tissue injury.

The most critical take-home messages for clinicians and researchers are threefold. First, cellular senescence is not merely a consequence of kidney damage but an active contributor to it. Second, the SASP provides a rich source of novel biomarkers for risk stratification and therapeutic monitoring in CKD. Third, the development of senotherapeutics, including senolytics and senomorphics, represents a paradigm shift in nephrology, moving beyond supportive care to targeting the fundamental mechanisms of renal aging.

Looking forward, the field must prioritize several actionable goals. A concerted effort is needed to validate SASP biomarkers in large, prospective CKD cohorts to establish their clinical utility. Head-to-head comparisons of different senotherapeutic strategies in preclinical models of CKD are essential to identify the most promising candidates for clinical translation. Furthermore, the design of rigorous clinical trials for senolytics and senomorphics in CKD patients is the next frontier. These trials must incorporate robust biomarker strategies to demonstrate target engagement and patient selection. Ultimately, harnessing the power of senotherapeutics holds the promise of not only slowing the progression of CKD but also mitigating its systemic complications, thereby extending the healthspan of millions of patients worldwide.

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Conflicts of interest

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