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REVIEW

Update of cellular senescence in kidney fibrosis: from mechanism to potential interventions

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Abstract **Kidney fibrosis is the final common pathway of virtually all chronic kidney disease (CKD). However, despite great progress in recent years, no targeted antifibrotic therapies have been approved. Epidemiologic, clinical, and molecular evidence suggest that aging is a major contributor to the increasing incidence of CKD. Senescent renal tubular cells, fibroblasts, endothelial cells, and podocytes have been detected in the kidneys of patients with CKD and animal models. Nonetheless, although accumulated evidence supports the essential role of cellular senescence in CKD, the mechanisms that promote cell senescence and how senescent cells contribute to CKD remain largely unknown. In this review, we summarize the features of the cellular senescence of the kidney and discuss the possible functions of senescent cells in the pathogenesis of kidney fibrosis. We also address whether pharmacological approaches targeting senescent cells can be used to retard the the progression of kidney fibrosis.**

Keywords cellular senescence; kidney fibrosis; cell cycle arrest; SASP; senolytics; senomorphics

Introduction

Chronic kidney disease (CKD) is global public health concern that affects > 10% of the global population and increases the risk of cardiovascular diseases, accounting for 1.5% of deaths worldwide [1, 2]. As the geriatric population grows and life expectancy extends, the incidence and severity of acute kidney injury (AKI) and CKD continue to increase and impose substantial social and economic burden.

The kidney is a complex organ composed of various cell types, and its function relies on the coordination and balance among cells. In acute kidney disease or CKD, the accumulation of senescent cells enhances immune response, promotes cell-to-cell interaction, and aggravates renal fibrosis, leading to a continuous decline in kidney function [3–5]. In this review, we describe the current understanding of age-related changes in renal cells and their effects on disease processes, focusing on kidney fibrosis. By providing a comprehensive analysis of existing literature, we hope to offer readers a holistic perspective on the role of cellular senescence in the pathogenesis of kidney fibrosis. We also discuss the potential of depleting senescent cells or targeting the characteristics of senescent cells as a novel therapeutic approach for the treatment of kidney fibrosis.

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Cellular senescence

Definition of cellular senescence

In 1961, Hayflick and Moorehead first observed that the lifespan of primary human cells undergo approximately 60 divisions before becoming permanently growth arrested [6]. This phenomenon is known as cellular senescence or cellular replicative senescence. Senescent cells exhibit several distinct biological characteristics, including cell cycle arrest, telomere shortening, DNA damage, cell type–specific senescence–associated secretory phenotype (SASP), resistance to apoptosis, and morphological changes [7,8]. The induction of senescence occurs as an intrinsic physiologic process during development or in response to various insults, such as genotoxic injury, oncogene activation, cellular stress, mitochondrial dysfunction, nutrient deprivation, and hypoxia [9]. These characteristics endow senescent cells

with the capacity to fulfill physiologic and pathological functions within tissues in states of health and disease.

Identification of senescent cells

Under different pathological conditions, the program of cellular senescence is complex and highly heterogeneous. The accurate identification of senescent cells *in vivo* and *in vitro* remains a formidable challenge, primarily because the singular marker that exhibits specificity toward senescent cells is lacking. Based on the characteristic features of senescent cells, several markers are commonly employed in evaluating cellular senescence (Table 1). According to the consensus issued by the International Cell Senescence Association [10], the identification of senescent cells usually has three steps. The first step involves staining for senescence-associated β-galactosidase (SA-β-gal) or lipofuscin and co-staining to confirm the absence of proliferation markers, such as Ki-67. The second step enhances identification by assessing the increased expression of pivotal cyclin-dependent kinase inhibitors (CDKIs), such as $p16^{INK4A}$ (p16) and/or $p21^{CIP1}$ (p21), diminished laminB1 levels, and shifts in core senescence transcript levels. The third step expands the evaluation and includes assays for multiple proteins secreted as components of the SASP. Figure 1 outlines typical phenotypes, markers, and steps for identifying senescent cells.

Although the identification methods and steps suggested in the consensus are well understood, several issues should be addressed. SA-β-gal, which serves as the most widely used marker of senescent cells, increases considerably in senescent cells under pH 6.0 and reflects the enhanced lysosomal content of senescent cells. However, SA-β-gal may exhibit increased expression in nonsenescent cells, such as macrophages [11]. Notably, SA-β-gal activity itself may not be necessary for cellular senescence to occur. Besides, SA-β-gal cannot be used for paraffin-embedded tissue sections or in live cells. Thus, SA-β-gal staining is a static method and does not provide dynamic information about the process of cellular senescence.

The high expression levels of the CDKIs p16 and p21 are indicative of a cell cycle arrest. Additionally, the measurement of colony-formation potential or the DNA synthesis rate by BrdU/EdU-incorporation assays can be used to manifest cell cycle arrest [12]. Some senescent cells exhibit nuclear alterations characterized by the presence of senescence-associated heterochromatic foci (SAHFs), as evidenced by 4′,6-diamidino-2-phenylindole staining. Markers associated with heterochromatin, such as H3K9me3 and HP1g, are prominently enriched within these SAHFs [13]. Senescence induced by DNA damage response can be measured using the levels of γ-H2A.X and phosphorylated p53, which are sensitive indicators of DNA damage.

SASP is one of the most crucial phenotypes exhibited by senescent cells, whose constituents vary over time and

Table 1 Common characteristics and markers of senescent cells

Phenotype	Markers	Expression	Description
Cell morphology change	–	–	Irregular cell shape and enlargement, exceedingly twice the size of normal cells, with mitochondrial swelling
	SA-β-gal	↑	Reflects increased activity of lysosomal enzyme at pH 6.0 in senescent cells
Cell cycle arrest	$p16^{INK4A}$	↑	Cyclin-dependent kinase inhibitor bind to CDK4 and 6 complexes, resulting in dephosphorylation of pRb and maintaining cell cycle arrest in the G1/S phase
	$p21^{CIP1}$	↑	Inhibits CDK2, inducing cell cycle arrest in the G1/S phase
	p53 and phosphorylated p53	↑	Tumor suppressor protein, activation triggers cell cycle arrest
	$p14^{ARF}$/$p19^{ARF}$	↑	A central activator of senescence, whose product activates p53 through Mdm2 sequestration
DDR	γ-H2A.X	↑	Histone protein variant that plays a pivotal role in the DNA damage response, particularly in the detection and repair of DNA double-strand breaks
SASP	IL-6, IL-8, TNF-α, MMP-3	↑	Pro-inflammatory cytokines and proteases as main components of SASP factors
Resistance of apoptosis	Bcl-2, Bcl-w, Bcl-xL	↑	Various anti-apoptotic molecules that prevent their recognition and clearance by immune cells
Nuclear changes	SAHFs	↑	Specialized domains of facultative heterochromatin, related to chromatin reorganization
	LaminB1	↓	Leads to nuclear membrane integrity disruption and chromatin condensation
Cell proliferation ceases	Ki-67	↓	A nuclear protein that typically serves as a marker of cell proliferation, indirectly reflecting the cell cycle arrest of senescent cells

SA-β-gal, senescence-associated β-galactosidase; DDR, DNA-damage response; MMP-3, matrix metalloproteinase-3; SAHFs, senescence-associated heterochromatin foci; SASP, senescence-associated secretory phenotype; Bcl, B cell lymphoma

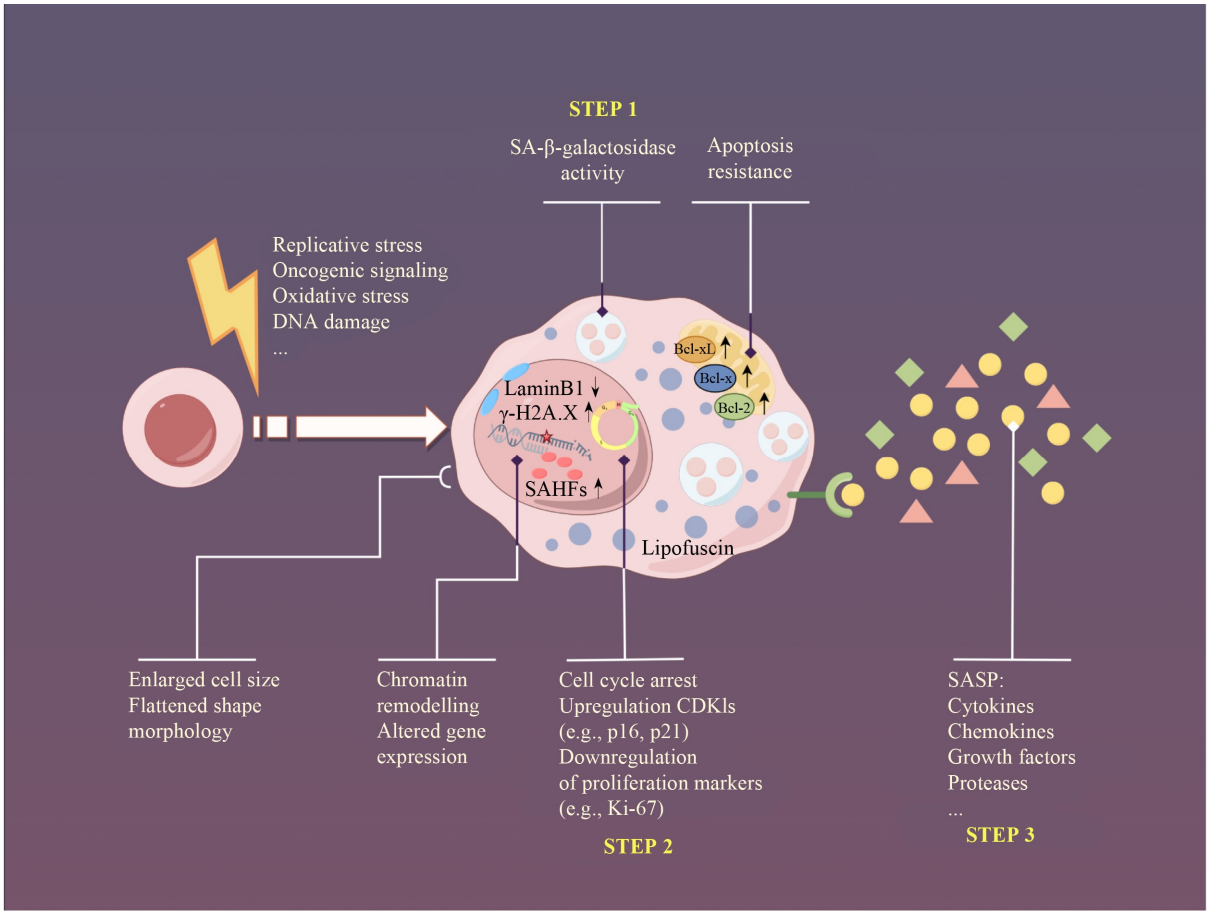

Fig. 1 Phenotypes, markers, and steps of identification of senescent cells. Senescent cells are characterized by permanent cell cycle arrest, SASP, and apoptosis resistance. Enlarged cell size, irregular shape, and chromatin remodeling were observed. SA-β-gal, lipofuscin, γ-H2A.X, SAHFs, and CDKIs involved in cell cycle control, such as p16, and p21, increased. The proliferation marker Ki-67 and nuclear membrane integrity mediator laminB1 were downregulated in the senescent cells' nuclei. Negative regulators, such as Bcl-2, Bcl-x, and Bcl-xL, were upregulated to impede apoptosis. SASP, senescence-associated secretory phenotype; SAHF, senescence-associated heterochromatin foci; CDKIs, cyclin-dependent kinase inhibitors; Bcl-xL, B cell lymphoma-extra-large. This image was drawn using Figdraw (RUWOP4b11b).

are specific to cell type. Therefore, no unified evaluation metric for identifying SASP factors has been adopted. SASP factors primarily consist of cytokines, chemokines, and growth factors, including interleukin (IL)-1α, IL-1β, IL-6, IL-8, tumor necrosis factor α (TNF-α), and matrix metalloproteinase-3. These factors appear to be more prevalent than other SASP components [14]. Additionally, the upregulation of BCL-proteins Bcl-2, Bcl-w, and Bcl-xL has been utilized as a marker for senescence, along with the characteristics of resistance to apoptosis [15].

Overall, any single parameter is insufficient for the definitive identification of a senescent cell. The comprehensive and reliable evaluation of senescent cells needs an evaluation of the various characteristics of the cells.

Type of cellular senescence

Cellular senescence can be classified into several types according to the causes and timing of its onset. From the aspects of causes of senescence, four different types of cellular senescence have been identified (Table 2): replicative senescence, stress-induced premature senescence (SIPS), oncogene-induced senescence (OIS), and developmental senescence. Replicative senescence is the growth arrest observed during passages, which is dependent on telomere shortening, while SIPS can achieve with non-chronological stress conditions, such as oxidative stress, nutrient depletion, chronic inflammation, and mitochondrial dysfunction [16]. OIS is a robust tumor-suppressive mechanism due to oncogene activation [17]. Developmental senescence is a normal, transient, and programmed process found throughout embryonic development. Distinctions among these four types of cellular senescence primarily manifest in their respective biological functionalities.

The absence of DNA damage triggers, lack of upregulation of SASP factors (IL-6 and IL-8), and

Table 2 Type of cellular senescence

Type of senescence	Description	Triggering factors	Characteristics
Classification of different causes			
Replicative senescence	Cells cease to divide after a finite number of divisions, reaching the Hayflick limit	Telomere shortening	Cell cycle arrest decreased telomerase activity
Stress-induced premature senescence (SIPS)	Cells enter a state of senescence before reaching their replicative limit due to stress	Multiple stress induces DNA damage	Prevents damaged cells from further proliferation
Oncogene-induced senescence (OIS)	Cells enter senescence due to the activation of oncogenes, acting as a barrier to tumorigenesis	Oncogene activation	Serves as a cell-autonomous tumor-suppressive mechanism
Developmental senescence	Programmed senescence during the developmental process	Developmental regulation	Tissue morphogenesis and organ formation
Classification of different timing			
Acute cellular senescence	Rapid onset of the senescent state, often in response to a sudden cellular stress or insult	Multiple stress	Serves as a rapid response mechanism to prevent the propagation of damaged or potentially harmful cells
Chronic cellular senescence	A long-lasting or persistent state of senescence that can occur over an extended period	Multiple stress	With continuous secretion of SASP components and persistent cell cycle arrest markers. Contribute to age-related diseases and tissue degeneration

efficient clearance by immune-mediated or apoptotic mechanisms constitute considerable distinctions between developmental senescence and SIPS [18]. Developmental senescence plays an instructive role during vertebrate embryogenesis, contributing to tissue growth, cellular population balance, and tissue regression. Senescent cells have been identified in various regions of the organs of mice, including the apical ectodermal ridge of the limb, mesonephros, neural tube, and endolymphatic sac of the inner ear [19–21]. These cells are nonproliferative and share features with OIS, including the expression of cell cycle regulators, such as p21, p15, and SASP [22]. The genetic depletion of p21 decreases senescence but leads to developmental abnormalities in the kidney, limbs, and vagina in mice [23].

According to the timing of senescence, senescent cells have two main categories: acute senescence, and chronic senescence [24]. Acute cellular senescence is a beneficial and specific physiologic process, which has the characteristics of a clear senescence trigger, short-term senescence signal, and rapid senescence cell clearance, and the whole process is strictly controlled. Acute senescence causes the cell cycle to be temporarily blocked, preventing uncontrolled mitosis and increasing time for DNA repair. Research into the pathogenesis of AKI has demonstrated that cell cycle arrest plays an important role in self-protection and adaptive repair of tubular epithelial cells [25]. Besides, the SASP released by acutely senescent cells can clear senescent cells and prevent their transition to chronic senescence, thereby limiting fibrosis [26].

In contrast to acute senescence, chronic senescence lacks a specific program and instead follows a stochastic process. Multiple types of persistent stress act on tissues and organs, leading to chronic senescence. The accumulation of chronically senescent cells with features of apoptosis resistance can induce severe senescence through the sustained secretion of SASP and ultimately lead to organ dysfunction. A study investigated the senescence of dynamic proximal tubular epithelial cells (PTECs) in rhabdomyolysis-induced acute kidney injury, utilizing a special p16-CreERT2-tdTomato mouse model that allows for the labeling of cells expressing high levels of p16 [27]. The results showed that after the onset of AKI, cellular senescence predominantly occurred in PTECs and was observed mainly within 1–3 days post-AKI. These acutely senescent PTECs were found to be spontaneously eliminated by day 15. However, the generation of senescence in PTECs persisted during the chronic recovery phase and was associated with incomplete recovery after AKI, potentially contributing to the progression of CKD [27]. Similarly, repeated low-dose cisplatin treatment induces chronic cellular senescence in PTECs, accompanied with tubular degeneration and profibrotic phenotype transformation toward profibrotic characteristics, ultimately leads to maladaptive repair and the development of renal fibrosis [28]. Besides, senescent macrophages were found to contribute to vascular calcification in CKD [29].

Overall, acute senescent cells showed the beneficial effects of wound healing and tissue repair, while chronic senescent cells led to detrimental consequences, such as glomerulus injury, tubular degeneration, and kidney fibrosis [30]. The persistent stress stimulation and immune system disorder may cause acute senescence to turn into chronic senescence. Further elucidating the mechanisms underlying the transition from acute senescence to chronic senescence will help in developing new therapeutic strategies.

Types of renal cells that undergo cellular senescence in the progression of renal fibrosis

Accumulating studies indicate that cellular senescence contributes to a profibrotic milieu, from the tissue maladaptive repair after acute injury to chronic inflammation and continuous damage. During kidney fibrosis, senescent cells can be detected in the various anatomical sites of the kidneys, predominantly within the tubular epithelial cells and podocyte. Naturally aging human and mouse kidneys are accompanied by changes in renal fibrosis, and multiple senescent cells, including tubular epithelial cells, podocytes, and interstitial cells [31–33]. In a mouse model of AKI to CKD, tubular cell senescence represents an early pivotal mechanism that triggers the subsequent accumulation of senescent cells after kidney injury, thereby driving the progression of renal damage [34]. In diabetic kidney disease (DKD), senescent cells are found in the glomerulus and renal tubules, which positively correlates with the severity of DKD [35–38]. Endothelial senescence promotes podocyte apoptosis by producing plasminogen activator inhibitor-1 (PAI-1) in aged mice [39]. In other glomerular diseases, senescent glomerular and tubular cells accumulate, also resulting in renal filtration and reabsorption dysfunction. The expression of p16 was found to be elevated in the parietal epithelial cells and glomeruli of patients with membranous nephropathy [40]. Similarly, the expression levels of p16, p21, and SA-β-gal in renal tubular cells gradually increase with disease progression and exhibit significant correlations with renal morphological changes, blood pressure levels, and renal function in patients diagnosed with IgA nephropathy [41]. Renal biopsies from patients with active lupus nephritis (LN) display an increase in p16-positive cells, which is associated with higher fibrosis and $CD8^+$ T cell infiltration [42]. In mouse model of LN, p16 is highly expressed in various cells, including glomeruli, parietal epithelial cells, and tubular cells [43]. Besides, the accumulation of various senescent cells have been observed in other fibrotic mouse models, such as unilateral ureteric obstruction, folic acid–induced nephropathies, and hypertensive kidney injury [44–46]. In addition to senescent tubular cells and podocytes, senescent fibroblasts promote renal fibrosis by upregulating profibrotic genes expression [47]. Vascular cells may contribute to kidney fibrosis in hypertensive kidney injury in mice and renal transplantation receipt [48, 49]. The cell types of senescent cells under various pathological kidney conditions with fibrotic change are presented in Table 3.

Major phenotypes of cellular senescence in kidney fibrosis

Cell cycle arrest

Cell cycle arrest is primarily mediated by the activation of either the p53/p21 or p16/pRB pathway, initiating a series of physiologic and metabolic processes for DNA replication and subsequent cell division. *In vivo* and

Table 3 Origin of senescent cells and their roles in renal fibrosis

Pathological condition	Species	Phenotype	Cell type	Effect	References
Aging	Human	$p16^{INK4a}$, p53, $p27^{KIP1}$, $p14^{ARF}$	Cortical tubules, parietal epithelial cells, podocytes, interstitial cells	Detrimental	[31]
	Mouse	SA-β-gal, $p16^{INK4a}$, $p19^{ARF}$, $p21^{CIP1}$	Tubules, glomeruli, interstitial cells	Detrimental	[32, 33]
AKI-CKD	Mouse	SA-β-gal, $p21^{CIP1}$, γ-H2A.X, $p16^{INK4a}$	Proximal tubular cells	Detrimental	[34]
DKD	Human	SA-β-gal, $p21^{CIP1}$, γ-H2A.X, $p16^{INK4a}$	Tubular cells, glomeruli	Detrimental	[35]
	Mouse	SA-β-gal, γ-H2A.X, $p16^{INK4a}$, p53, $p66^{ShcA}$	Tubular cells, glomeruli	Detrimental	[36–38]
MN	Human	$p16^{INK4a}$	Parietal epithelial cells, glomeruli	Detrimental	[40]
IgAN	Human	SA-β-gal, $p21^{CIP1}$, $p16^{INK4a}$	Renal tubular epithelial cells	Detrimental	[41]
LN	Human	SA-β-gal, $p16^{INK4a}$	Glomeruli, parietal epithelial cells in Bowman's capsules, proximal or distal tubular cells, and interstitial cells	Detrimental	[42]
	Mouse	SA-β-gal, $p16^{INK4a}$	Glomeruli, parietal epithelial cells, tubular cells	Detrimental	[43]
Fibrotic kidney	Mouse	SA-β-gal, $p16^{INK4a}$, p53, γ-H2A.X	Renal tubular epithelial cells, fibroblast	Detrimental	[44–47]
Hypertensive kidney injury	Mouse	$p16^{INK4a}$	Tubular, glomeruli, interstitial cells, vascular cells	Detrimental	[48]
Renal transplantation	Human	SA-β-gal, $p16^{INK4a}$, $p27^{Kip1}$	Infiltrating cells in the interstitial area, tubular cells, vascular cells	Detrimental	[49]

AKI, acute kidney injury; CKD, chronic kidney disease; DKD, diabetes kidney disease; MN, membranous nephropathy; MCD, minimal change disease; IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; LN, lupus nephritis; SA-β-gal, senescence-associated β-galactosidase.

in vitro, p53, p21, and p16 are upregulated in fibrotic kidneys from humans and mice. For instance, the p53/p21 pathway is activated, and p16 expression considerably increases in primary proximal tubular cells upon exposure to cyclosporine A [50]. The expression of p53 is upregulated in human proximal tubular cell line HK-2 treated with indoxyl sulfate and in tubular cells from rats with 4/5-nephrectomy, thereby promoting the progression of kidney fibrosis [51]. In a unilateral ureteral obstruction (UUO) model, immunostaining results showed that p16 expression increased in the tubular epithelium [52]. In aristolochic acid–induced nephropathy, p53 and p21 expression levels increase in the cortex [53]. The upregulation of integrin β3 is implicated in tubular cell senescence through p53 activation, thereby contributing to the development of kidney fibrosis in three different mouse models of CKD, including DN, UUO, and passive Heymannn nephritis [54]. Furthermore, the expression of endothelial nitric oxide synthase (eNOS) and apolipoprotein E (ApoE) may play a regulatory role in the activation of CDKIs, including p16, p21, and p53. The dual depletion of *eNOS* and *ApoE* genes in a UUO mouse model significantly upregulated the expression of p16, p21, and p53, thereby exacerbating kidney fibrosis and senescence [55]. Currently, although the causal relationships between cell cycle arrest and kidney fibrosis are well established, the intricate regulatory mechanisms governing this process remain largely unclear.

Telomere shortening

Telomere shortening, a hallmark of aging, is accelerated by kidney injury–induced stresses, leading to increased cellular senescence and reduced regenerative capacity in the kidney. Short telomeres are associated with CKD progression, and cell telomeres are shorter in patients with ESRD, kidney transplantation patients, and patients with DN than in healthy individuals [56, 57]. In two independent mouse models of kidney fibrosis, short telomeres sensitize the kidneys to develop fibrosis in response to folic acid and exacerbate epithelial-to-mesenchymal transition (EMT) [58]. Additionally, the occurrence of mutations in poly(A)-specific ribonuclease and a reduction in telomeric G-tail length are frequently observed in hemodialysis patients [59]. Thus, elongating telomeres by reactivating telomerase activity may delay aging and organ degeneration [60].

SASP

Despite being in a state of growth arrest, senescent cells still could exert influence on the surrounding microenvironment and neighboring cells by secreting a complex mixture of factors, thereby modulating the behavior of adjacent nonsenescent cells. Most senescent cells developed altered secretory activities referred to as SASP. The composition of SASP varies based on the duration of triggers, duration, and cell type of senescence [61]. In fibrotic kidney diseases, the SASP predominantly consists of cytokines (TGF-β1, TNF-α, IL-1β, and IL-6, IL-4), chemokines (IL-8 and MCP-1), growth factors (CTGF), and proteases (MMP-2 and PAI-1), which contribute to renal inflammation and accelerate the progress of renal fibrosis [14]. SASP factors may participate in fibrosis by regulating cell cycle arrest, EMT, and endothelial-to-mesenchymal transition (EndoMT). G2/M cell cycle arrest leads to fibrosis, accompanied by the increased expression of pro-fibrotic factors, such as CTGF and TGF-β, in the mouse models of IRI-induced AKI, aristolochic acid nephrotoxicity, and UUO [62]. Besides, TGF-β drives EMT and EndoMT, enabling transitioning cells to migrate from the basement membrane to the interstitial space and differentiate into fibroblasts [63, 64]. The regulation of SASP secretion in fibrotic kidney disease has not received widespread interest, and the majority of SASP components overlap with extensively studied profibrotic factors. Moreover, the identification of the origin of SASP factors and the determination of key factors that play a significant pathological role still pose challenges. Thus, additional research is needed.

Apoptosis resistance

Upon entering the state of senescence, cells exhibit enhanced resistance to apoptotic stimuli. The resistance of senescent cells to apoptosis can be achieved by overexpressing various anti-apoptotic molecules, such as Bcl-2/Bcl-xL, Bcl-w, and heat shock proteins, such as HSP9, thereby evading recognition and clearance by immune cells [65]. The anti-apoptotic factor BCL-xL is considerably overexpressed in old and injured kidneys, suggesting age-related apoptosis suppression [66]. Immunostaining revealed that the expression levels of Bcl-2 and p53 in tubular cells considerably increased in UUO mouse kidneys, suggesting a concurrent anti-apoptotic effect of senescent cells [52]. Apoptotic resistance inhibits the elimination of senescent cells and leads to their accumulation, which promotes kidney fibrosis by sustaining SASP factors.

The exploration of mechanism apoptosis resistance in kidney diseases remains in infancy. DcR2 mediates apoptotic resistance in senescent RTECs by enhancing GRP78-caspase 7 interaction and promoting Akt phosphorylation [67]. Specifically knocking out *Intu,* which is a key effector protein of planar cell polarity, from kidney tubules, reduces senescent cells and increases apoptosis during kidney repair after renal IRI [68]. This finding indicates that the knockout of tubular *Intu* mitigates renal fibrosis by preventing apoptosis

resistance in senescent RTECs.

Notably, the pathological effect of apoptosis of injured cells or senescent cells may act in opposite directions in kidney fibrosis. The inhibition of apoptosis reduces kidney fibrosis [69, 70], whereas the selective promotion of the apoptosis of senescent cells exerts a renal protective effect [71].

Signaling pathways leading to cellular senescence in kidney fibrosis

TGF-β/Smads

TGF-β exhibits a potent capacity to impede cellular proliferation across various cell types and govern cellular growth regulation and senescence. On the one hand, TGF-β regulates the cell cycle arrest by inducing the CDKIs p15Ink4b, p21, and p27, and suppressing several proliferation factors, including c-Myc [72, 73]. On the other hand, TGF-β orchestrates with other senescence phenotypes, such as SASP factor secretion and ROS production which leads to DNA damage.

In the case of DN and LN, TGF-β1 is overexpressed in renal tubulointerstitial in patients and mice models and induces senescence of RTECs and proliferation of renal fibroblasts [74, 75]. In UUO and folic acid induced kidney fibrosis mouse models, ubiquitin specific protease 11 can promote the development of cellular senescence by deubiquitinating Tgfbr2 [76]. In addition, klotho, a well-studied antiaging protein, exerts protective effects against renal aging by inhibiting TGF-β1 signaling pathways [77]. Polycomb protein Bmi1 knockout mice exhibit oxidative stress, DDR activation, RTEC senescence, SASP, and age-related fibrosis in kidneys by upregulating TGFβ1 [78]. PAI-1, a common SASP factor induced by oxidative stress, is upregulated by TGF-β in human fibroblasts [79].

Integrin beta 3, which is regulated by polycomb protein CBX7, can accelerate the onset of senescence in human primary fibroblasts by activating the TGF-β pathway in a cell-autonomous and non-cell-autonomous manner [80]. Furthermore, it can induce p53 pathway activation and the secretion of TGF-β, which in turn results in senescent and profibrotic phenotype change in cultured tubular cells [54]. Besides, long noncoding RNA ATB overexpression exerts effects that promote inflammation, cell apoptosis, and senescence in HK-2 cells by activating the TGF-β/SMAD2/3 signaling pathway [81].

Wnt/β-catenin/RAS

The Wnt/β-catenin/RAS signaling pathway is a highly conserved mechanism that plays crucial roles in organogenesis and tissue regeneration [82,83]. Wnt/β-catenin signaling is silent but is reactivated after kidney injury in a wide range of CKD models and is highly associated with kidney fibrosis [84]. The accumulation of β-catenin in the nucleus triggers the activation of target genes associated with renal fibrosis and RAS genes, resulting in cellular proliferation, RAAS activation, occurrence of EMT, and accumulation of extracellular matrix during the initiation of renal fibrosis [85]. The activation of the Wnt/β-catenin pathway plays a decisive role in tubular senescence during renal fibrosis. Increase in Wnt9 level has been observed in multiple types of clinical nephropathy and experimental CKD models and is associated with tubular senescence [86]. Zhou *et al.* reported that chemokine receptor 2 (CXCR2) expression in tubules, along with p16 and β-catenin co-localization, plays a role in renal fibrosis. Mechanically, IL-8 exacerbates β-catenin activation, mitochondrial dysfunction, tubular cell senescence, and renal fibrosis through CXCR2 signaling. Conversely, inhibiting p16 attenuates these effects [87]. Brahma-related gene 1 induces tubular senescence by inhibiting autophagy via the Wnt/β-catenin pathway, ultimately contributing to the development of renal fibrosis [88]. Zhu *et al*. found that KYA1797K, which is a small molecule destabilizing β-catenin by activating the axin–GSK3β complex, exerts an effect that inhibits cellular senescence, preserving mitochondrial homeostasis and retarding age-related fibrotic changes [89]. *Corallodiscus flabellate* extracts can attenuate renal fibrosis in senescence-accelerated mouse-prone 8 mice via the Wnt/β-catenin/RAS signaling pathway [90]. The inhibition of angiotensin type 1 receptor can impede cellular senescence in the human proximal tubular by deactivating the Wnt/β-catenin/RAS pathway [91]. Notably, the mediation of the Wnt/β-catenin/RAS signaling pathway on age-related renal fibrosis is associated with mitochondrial dysfunction and klotho. The expression of klotho can retard renal fibrosis by targeting cellular senescence in human RTECs via inhibited Wnt1- and Wnt9a-induced mitochondrial injury, cellular senescence, and fibrotic lesions [92]. The overexpression of klotho has promising therapeutic effect that delays aging or attenuates cellular senescence-associated tissue injury. The transplantation of klotho–GFP–bone marrow mesenchymal stem cells into mice with AKI ameliorates kidney fibrosis, enhances proliferative capacity, and augments immunoregulatory potential by suppressing the Wnt/β-catenin pathway in RTECs [93].

NF-κB

The triggers of cellular senescence can simultaneously activate NF-κB signaling pathways, such as DNA damage, oxidative stress, and immune responses. The activation of the NF-κB pathway can promote the secretion of SASP factors and accelerate cell senescence.

The pivotal role of NF-κB signaling in promoting the manifestation of SASP during kidney cellular senescence has been extensively explored with distinct research models. In senescent human PTECs, a positive feedback loop involving lysophosphatidic acid receptor1 (LPAR1) and NF-κB contribute to the interplay between senescence and fibrosis. The suppression of LPAR1 leads to a reduction in NF-κB activity and subsequent attenuation of inflammatory cytokine production, whereas the inhibition of NF-κB results in the decreased expression of LPAR1 [94]. Loss of function of mouse Glis2 induces senescence and NF-κB activation in kidney tubular cells. Activation of NF-κB signaling in Glis2 knockout renal epithelial cells was observed and genetic ablation of toll-like receptor (TLR)/IL-1 receptor or pharmacological elimination of senescent cells effectively exerted the effects of alleviation tubular damage, fibrosis, and apoptosis in the Glis2 mouse model of nephronophthisis were further reported [95]. In indoxyl sulfate induced proximal tubular cell senescence, the inhibition of NF-κB with small molecular inhibitors or small interfering RNA demonstrates promising therapeutic potential in ameliorating senescence and fibrosis [96].

Nrf2/ARE

The Nrf2/ARE pathway is a crucial antioxidant regulatory pathway that plays a pivotal role in mediating cell stress response to oxidation. The overexpression of intelectin 1 can ameliorate radiation-induced kidney injury in rats by activating the Akt/GSK3β/Nrf2 signaling pathway, thereby suppressing oxidative stress, cell apoptosis, inflammation, cellular senescence, and fibrosis [97]. In diabetic mice, the upregulation of GSK3β impairs Nrf2 antioxidant response and exacerbates oxidative stress, ultimately leading to increased podocyte injury and senescence [98]. Additionally, in an IRI model, the ablation of cellular communication network factor 2 (CCN2) effectively ameliorates AKI by attenuating oxidative stress induced DNA damage and subsequent DDR by downregulating Nrf2 pathway expression levels [99].

mTOR

mTOR signaling influences longevity and aging. The inhibition of the mTOR complex 1 (mTORC1) with rapamycin is currently the only known pharmacological treatment that increases lifespan in all model organisms studied [100]. In kidney transplantation, the inhibition of mTOR protected all kidney compartments from the accumulation of p16-positive cells in the tubules, interstitial, and glomeruli, inhibited inflammatory response, and improved functional recovery without a negative impact on glucose homeostasis and growth [101]. Besides, short-term caloric restriction exerts a promising therapeutic effect that can alleviate autophagic activity, oxidative damage, senescence, and fibrosis of aging kidneys through 5′-AMP-activated protein kinase (AMPK)/mTOR signaling [102, 103].

Insulin-like growth factor binding proteins

The role of insulin-like growth factor binding proteins (IGFBPs) in kidney diseases is increasingly recognized [104]. Specifically, IGFBP-5 has been linked to responses following epithelial injury and inhibits EMT and cellular senescence [105]. In cisplatin induced acute kidney injury transitioning to CKD, IGF2BP3's abnormal expression plays a critical role in renal tubular senescence. Mechanistically, IGF2BP3 promotes the stability of cyclin-dependent kinase 6 mRNA, thus inhibiting the cellular senescence of renal tubular cells [106]. Additionally, silencing IGF2BP2 disrupts the stability of lncRNA taurine upregulated 1, leading to mitochondrial quality control imbalance, increased senescence, and renal fibrosis [107].

Therapeutic potential of senotherapy in kidney fibrosis

Senotherapeutics has two types: senolytics, which means the elimination of senescent cells, and senomorphics, which mitigate their pathological pro-inflammatory secretory phenotype to promote cellular homeostasis. As shown in Fig. 2, we summarized potential therapeutic strategies for targeting senescent cells in kidney fibrosis.

Senolytics

Senescent cells can be eliminated by modulating their permanent cell cycle arrest and ensuring their engagement in the apoptotic program. Consequently, two strategies have been proposed for senescent cell clearance: inhibiting the expression of cell cycle arrest associated proteins through gene editing and attenuating the resistance of senescent cells toward apoptosis and promoting their transition into an apoptotic state. The genetic depletion of CDKIs, including p16 and p21, may impede the progression of cell senescence and decrease the number of senescent cells selectively. p16 deletion ameliorates renal tubulointerstitial injury in a stress-induced premature senescence model of bmi-1 deficiency [108]. Genetic knockout of p21 demonstrates its potential in ameliorating fibrosis in the UUO mouse model [109].

The resistance of senescent cells to apoptosis is primarily regulated by anti-apoptotic proteins, such as Bcl-2, Bcl-xL, and Bcl-w. Thus, inhibiting these proteins provides a potential way to kill senescent cells. Despite

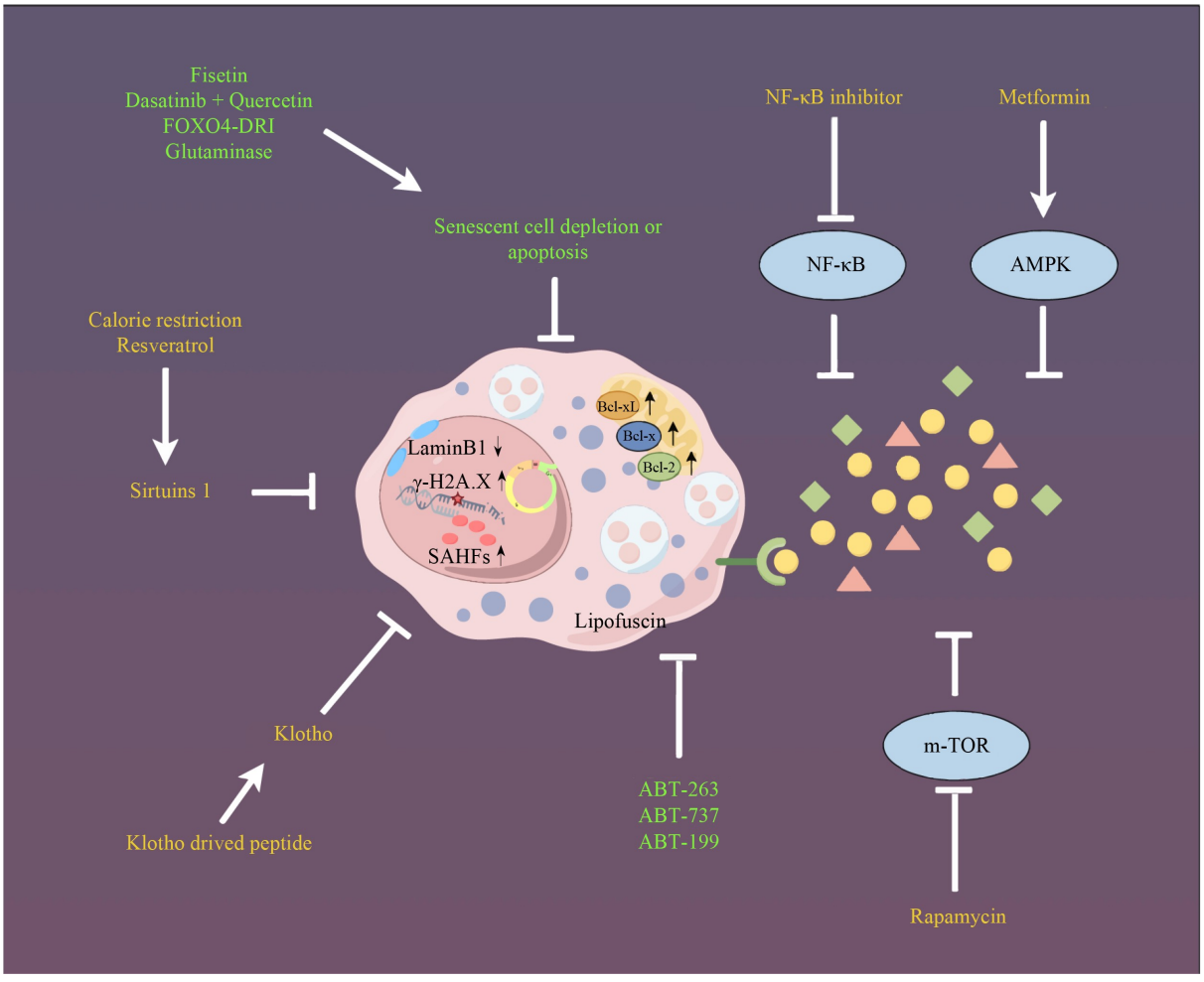

Fig. 2 Potential therapeutic strategies for targeting senescence in kidney fibrosis. The green words of interventions are the senolytics, and the yellow words of interventions are the senomorphics. The blue cycle with black word is the therapeutic target. SASP, senescence-associated secretory phenotype; FOXO4, forkhead box 4; NF-κB, nuclear factor kappa B; AMPK, AMP-activated protein kinase; m-TOR, mammalian target of rapamycin; SAHF, senescence-associated heterochromatin foci; CDKIs, cyclin-dependent kinase inhibitors; Bcl-xL, B cell lymphoma-extra-large. This image was drawn using Figdraw (ID:OTRUYceeee).

the application of numerous inhibitors targeting anti-apoptotic proteins to eliminate senescent cells in various diseases, limited research has investigated their efficacy in the context of kidney fibrosis. ABT-263, ABT-737, and ABT-199 are Bcl-2/xL/w inhibitors that can selectively clear senescent cells by more than 65% and not negatively affect normal cells. The treatment of aged and irradiated mice with an ABT-263 inhibitor targeting Bcl-2/w/xL reduced the number of senescent cells and restored a regenerative phenotype in the kidneys and is characterized by enhanced tubular proliferation, improved function, and reduced fibrosis following subsequent IRI [110]. In the LN mouse model, treatment with fisetin resulted in a reduction in the population of senescent RTECs and myofibroblasts, thereby mitigating kidney fibrosis, suppressing the expression of SASP, and promoting RTEC proliferation [75]. A combination of dasatinib and quercetin reduced senescence and renal fibrosis in ischemia reperfusion models of AKI and cisplatin nephrotoxicity models [111]. Besides, by competitively binding to p53, the interfering peptide FOXO4-DRI activates p53-mediated apoptosis in senescent cells. Treatment with FOXO4-DRI effectively reduces the population of senescent cells in the kidney, thereby preserving renal function and inhibiting IL-6 expression in mouse models. Studies reported that senescent cells rely on glutaminolysis for survival [112]. Interestingly, the inhibition of kidney-glutaminase-dependent glutaminolysis in aged mice eliminated senescent cells and ameliorated age-associated organ dysfunction [113].

Senomorphics

Modulating the expression of SASP factors, which play a key role in kidney fibrosis, is another strategy for serotherapy or senomorphics. In general, senomorphics exert anti-senescence effects by suppressing the

expression of SASP through the modulation of NF-κB, mTOR, AMPK, and other signaling pathways.

NF-κB inhibitor

NF-κB is a major SASP regulator. Therefore, the inhibition of NF-κB can decrease SASP factor secretion. NF-κB inhibitors, such as pyrrolidine dithiocarbonate, and parthenolide, reduced renal interstitial fibrosis and inflammation in CKD mouse models [114, 115]. Although these studies described the inhibitory effect of NF-κB inhibitors on SASP factors, they did not further evaluate other phenotypes of cellular senescence in the kidney. Additional experiments are required to further clarify the association between NF-κB inhibitors and cellular senescence in the kidney.

Rapamycin

Rapamycin, an mTOR inhibitor, exerts potent protective effects against oxidative injury by suppressing protein synthesis and promoting intracellular repair and autophagy processes associated with the development of cellular senescence. The antifibrotic effect of rapamycin has been demonstrated in multiple mouse models of CKD [116, 117]. However, whether this antifibrotic effect specifically targets renal cellular senescence is unlcear. In rat kidney transplantation model, low-dose rapamycin protected from premature cellular senescence [101].

Metformin

Metformin is a widely utilized anti-hyperglycemic drug that functions as an activator of AMPK. It enhances insulin sensitivity, facilitates cellular repair, exhibits anti-inflammatory properties, and acts as an antioxidant. All of these attributes contribute to its anti-aging effects [118]. Metformin treatment attenuates cellular senescence of mesenchymal stem cells (MSC) of CKD patients. Compared with untreated MSCs, metformin-treated MSCs effectively attenuated inflammation and renal fibrosis induced by UUO, indicating that metformin preconditioning may exhibit a therapeutic benefit by targeting accelerated senescence of MSCs is CKD [119]. Additionally, metformin effectively mitigates high glucose-induced senescence of RTECs through the downregulation of E2F1 expression [120]. Similarly, metformin reduces the senescence of RTECs in diabetic nephropathy via the MBNL1/miR-130a-3p/STAT3 pathway [121].

Klotho supplementation

Klotho, an anti-aging protein, primarily synthesized in the kidney, declines significantly in CKD patients and mouse models. Klotho deficiency is associated with poor clinical outcomes in patients with CKD, whereas an excess of Klotho inhibits renal inflammation and attenuates kidney fibrosis. Given the reported association between cellular senescence and kidney fibrosis, recent investigations have been conducted to elucidate the role of Klotho in impeding cellular senescence. The association between the loss of klotho and augmented cellular senescence has been observed by numerous studies. In hypertensive rats, indoxyl sulfate reduced klotho expression, promoted senescence, and augmented fibrosis [122]. Klotho considerably decreased, accompanied by the increased tubular senescence in the kidneys of aristolochic acid-treated mice [123]. Thus, supplementing with klotho may present an approach to attenuate the cellular senescence. Following intravenous injections, klotho-derived peptide primarily accumulates in the injured kidney, thereby inhibiting the TGF-β1-induced signaling pathway to limit kidney fibrosis [124]. Supplementation with klotho attenuates the kidney epithelial senescence induced by high phosphate [125].

Sirtuins 1 activator

Similar to klotho, sirtuins 1 (SIRT1) expression decreases during the progression of CKD. The upregulation of SIRT1 attenuates cellular senescence. Calorie restriction and resveratrol can activate the SIRT1 signaling in aged kidneys and protect the kidney from inflammation, oxidative stress, and fibrosis [126, 127].

Conclusions and perspectives

Aging kidneys and CKD share many common features, including clinical manifestations, pathological presentations, and underlying mechanisms. Notably, despite extensive research confirming the pivotal role of senescent cells and SASP secretion in renal fibrosis, studies clearly delineating signaling pathways that mediate cellular senescence during the progression of renal fibrosis still lacking. The heterogeneity of senescent cells and the secretion variability of SASP remains significant challenges. The heterogeneity of senescent cells includes differences in cell types, functions, and the secretion of SASP. Therefore, the key to addressing this challenge lies in identifying the subgroups of senescent cells involved in renal fibrosis and describing the spatiotemporal dynamics of SASP molecules. Single-cell transcriptomics and spatial transcriptomics technologies offer an opportunity to address this challenge [128]. These technologies increase understanding of the cellular landscape, paving the way for targeted therapies that can harness the beneficial aspects of senescence while mitigating its detrimental effects. Another challenge in this field is that most established cell lines, such as those derived from immortalized cancer cells, exhibit

behavioral changes that do not fully reflect the complexity of primary cells, hindering the drug screening and translational research. However, recent advances have generated conditionally immortalized cell models, such as cell models utilizing doxycycline-induced Simian Virus 40 large T antigen (SV40LT) vectors, which provides a controlled environment to study cellular senescence and facilitate the screening of senolytic drugs [129]. Finally, the safety and efficacy of new senotherapeutics in CKD patients should be rigorously evaluated, including through large-scale randomized controlled trials, before their therapeutic application.

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Compliance with ethics guidelines

Conflicts of interest Lina Yang, Liang Ma, Ping Fu, and Jing Nie declare no competing interests.

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