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REVIEW

The Role of Renal Cell Senescence in Diabetic Kidney Disease: Mechanisms and Therapeutic Advances

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Abstract: Diabetic Kidney Disease (DKD), one of the most severe microvascular complications of diabetes, significantly elevates risks of end-stage renal disease and mortality. Despite current therapies, its multifactorial pathogenesis limits effective renoprotection. Cellular senescence, a stable cell cycle arrest state representing an adaptive response to cumulative damage, emerges as a pivotal driver of DKD progression. Hyperglycemic environment directly interferes with cell cycle regulatory mechanisms or indirectly induces cell cycle arrest to accelerate renal cell senescence through various pathways, including mitochondrial dysfunction, impaired autophagy, endoplasmic reticulum stress, oxidative stress, disordered iron metabolism and inflammatory responses. This process ultimately compromises tissue repair mechanisms and exacerbates renal injury. The review systematically synthesizes current knowledge on the core biological hallmarks of cellular senescence and their mechanistic roles across key renal cell types (renal tubular epithelial cells, glomerular endothelial cells, mesangial cells and podocytes) in DKD pathogenesis. Furthermore, we evaluate emerging therapeutic strategies that target cellular senescence-associated pathways, with particular emphasis on the multi-target potential of natural products. By delineating the interplay between metabolic dysregulation and cellular senescence-driven renal decline, this work provides a foundational framework for developing novel interventions to halt DKD progression.

Keywords: natural products, cellular senescence, pharmaceutical, diabetic complications, multi-target therapy

Introduction

Diabetic kidney disease (DKD) is one of the most severe microvascular complications of diabetes mellitus (DM). Its pathological features include a series of renal structural abnormalities, including deposition of glomerular mesangial matrix, basement membrane thickening, glomerulosclerosis, podocyte injury, and tubulointerstitial fibrosis.[1] Recent epidemiological data reveal that the global adult DM population reached approximately 589 million in 2024; notably, China accounts for roughly 148 million adult DM patients, making it the country with the highest disease burden worldwide.[2] Importantly, approximately 30–40% of DM patients will ultimately progress to DKD, establishing it as a leading cause of end-stage renal disease.[3] Substantial evidence further links prediabetes (defined as fasting plasma glucose levels exceeding 100 mg/dL) to an elevated risk of both early kidney disease and chronic kidney disease.[4,5] Reflecting this trajectory, the Global Burden of Disease Study underscores the substantial and increasing health burden imposed by DKD globally. Although the rate of increase may slow over the next 15 years, the absolute number of cases is projected to rise significantly.[6] While early application of renin-angiotensin-aldosterone system inhibitors or combination therapies with glycemic control agents can partially slow DKD progression, the efficacy of current treatments in reducing DKD-related vascular events and patient mortality remains suboptimal.[7] Consequently, the exploration of novel therapeutic strategies is imperative.

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In recent years, the role of cellular senescence in the pathogenesis of DKD and its potential as a therapeutic target have garnered increasing attention.[8] Research indicates that the pathological accumulation of senescent cells within renal tissues not only impairs the tissue's self-repair capacity but, more critically, these cells secrete a Senescence-Associated Secretory Phenotype (SASP), which releases a plethora of pro-fibrotic, pro-inflammatory, and pro-apoptotic factors. These factors act in autocrine and paracrine manners on the local microenvironment, triggering chronic inflammatory responses that further exacerbate the cellular senescence process. This ultimately leads to tubular damage, interstitial fibrosis, and glomerulosclerosis,[9] thereby establishing a vicious cycle of "metabolic disturbance - cellular senescence - renal injury".[10] It is particularly noteworthy that studies have demonstrated that hyperglycemia accelerates senescence in various renal cell types, including renal tubular epithelial cells,[11] mesangial cells,[12] podocytes,[13] and glomerular endothelial cells,[14] resulting in renal histopathological damage and functional impairment. This strongly suggests that targeted intervention against cellular senescence represents a highly promising novel strategy for DKD prevention and treatment. However, the precise molecular mechanisms by which hyperglycemia drives renal cell senescence require further elucidation. Traditional Chinese Medicine (TCM), with a history spanning over two millennia, has developed a unique theoretical system and accumulating a rich repository of natural botanical drugs. TCM demonstrates significant advantages in holistic regulation for disease treatment.[15] Chinese herbal medicines and their natural active components exhibit unique potential in modulating complex cellular senescence-related signaling networks due to their characteristics of multi-target and multi-pathway regulation.[16]

Based on this background, this review will first outline the key biomarkers of cellular senescence and systematically summarize the molecular mechanisms underlying senescence in major renal cell types affected in DKD, including renal tubular epithelial cells, podocytes, mesangial cells, and endothelial cells. Finally, we will explore the latest research progress and therapeutic efficacy of various agents, including Chinese herbal medicines and their natural active constituents, in targeting cellular senescence to intervene in DKD. The aim is to provide a solid theoretical basis and innovative insights for the clinical management of DKD.

Characteristics of Cellular Senescence

Cellular senescence represents a key pathological process in aging-associated diseases. It manifests as a stable cell cycle arrest induced by diverse factors and constitutes an important stress response mechanism employed by cells to counteract cumulative damage.[17] The biological basis of this phenomenon traces back to the pioneering work by Hayflick et al in 1961: experiments culturing 25 strains of human diploid fibroblasts in vitro demonstrated an inherent limit to cellular proliferative capacity.[18] Further research indicates that, beyond replicative senescence, pathological stimuli such as metabolic disturbances, oxidative stress, inflammation, mitochondrial dysfunction, and proteotoxic stress can accelerate the senescence process.[19,20] Senescent cells possess unique biological identifiers and can be recognized through multi-dimensional characteristics. Figure 1 systematically illustrates the typical biological feature differences between senescent cells and normal cells.

At the morphological level, senescent cells typically exhibit increased size and a flattened appearance, accompanied by a reduced nuclear-to-cytoplasmic ratio.[21] Upon entering senescence, cells establish a permanent cell cycle arrest. The core molecular drivers of this arrest primarily include the activation of CDKN2A (p16INK4a, hereafter P16) and CDKN1A (p21CIP, hereafter P21). Consequently, these genes are widely utilized as unique and relatively specific markers for identifying senescent cells both in vitro and in vivo.[22,23] Recent studies indicate that the DNA damage response during cellular senescence triggers two major cellular senescence-associated pathways involving P21 and P16 - the P53/P21 and P16/Rb pathways - to mediate cell cycle arrest.[24] Within this process, the phosphorylation of the histone variant H2AX at Ser-139 (forming γH2AX) constitutes an early response event to DNA double-strand breaks.[25] Therefore, the accumulation of γH2AX foci is also recognized as a useful marker of cellular senescence.

Senescent cells exhibit distinct nuclear alterations, prominently featuring enlarged nuclear morphology. This phenomenon is closely linked to the marked downregulation of Lamin B1[26]—a core structural component of the nuclear lamina that maintains nuclear integrity through chromatin interactions. Beyond its structural role, Lamin B1 critically regulates chromosomal organization, DNA replication, transcription, and cell division, positioning it as a key modulator of cellular proliferation and senescence.[27,28] During cellular senescence, the downregulation of Lamin B1 promotes the spatial relocation of heterochromatin, leading to the formation of senescence-associated heterochromatin foci (SAHF).[29] SAHF are characterized by focal aggregates of heterochromatin structures on chromosomes. Proteins such as H3K9me2/3, MacroH2A, and HP1 serve as characteristic

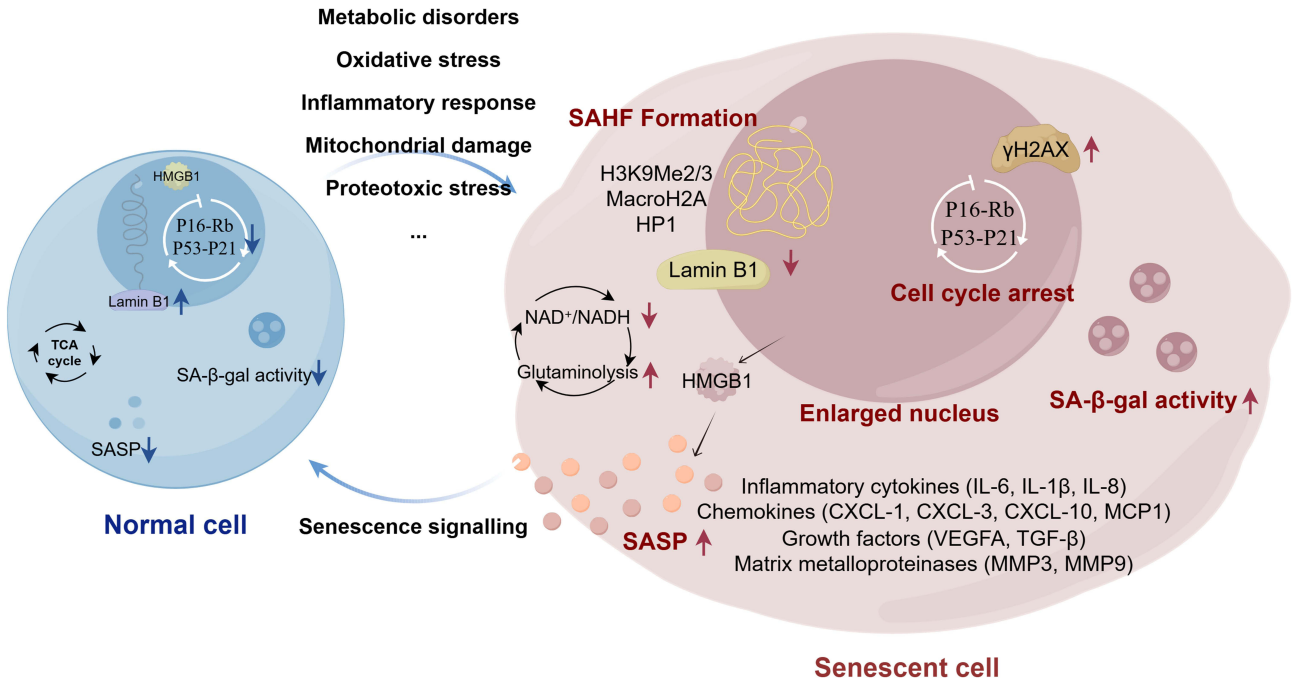

Figure 1 Biological Characteristics of Cellular Senescence (by Figdraw). This figure provides a comprehensive visual summary of the key hallmarks distinguishing senescent cells from their normal counterparts. It highlights critical features such as morphological changes (eg, enlarged, flattened morphology), cell cycle arrest markers (eg, P16, P21), DNA damage response (eg, γH2AX foci), nuclear alterations (eg, reduced Lamin B1, SAHF formation, HMGB1 nucleocytoplasmic translocation), increased senescence-associated secretory phenotype (SASP), TCA cycle impairment (eg, NAD+/NADH imbalance, Glutaminolysis) and elevated senescence-associated β-galactosidase (SA-β-gal) activity. Upward arrows indicate upregulation and downward arrows indicate downregulation.

protein markers for SAHF formation.[30] Concurrently, the nuclear protein HMGB1 undergoes significant relocalization during senescence. While normally functioning as a DNA chaperone in nuclear processes including DNA repair, chromatin remodeling, and telomere maintenance,[31] HMGB1 translocates from the nucleus to the cytoplasm in senescent cells. It is subsequently secreted, where it activates NF-κB via Toll-like receptor signaling and amplifies the senescence-associated secretory phenotype (SASP), thereby serving as a potent paracrine effector.[32,33]

Senescent cells secrete a constellation of characteristic factors, collectively termed the SASP that includes various inflammatory cytokines (eg, IL-6, IL-1β, IL-8), chemokines (eg, CXCL-1, CXCL-3, CXCL-10, MCP-1), growth factors (eg, VEGFA, TGF-β), and matrix metalloproteinases (eg, MMP-3, MMP-9). These factors influence the local microenvironment, promoting a state of chronic inflammation within the organism. SASP factors can act in an autocrine manner to reinforce the senescent phenotype of the secreting cell itself, or in a paracrine manner to transmit senescence signals to neighboring cells, inducing senescence in them.[34,35] Under pathological conditions, including various kidney diseases, senescent cells undergoing cell cycle arrest accumulate aberrantly within the kidney. Targeting the clearance of senescent cells or inhibiting the SASP has been shown to improve renal function in DKD.[36]

The orderly progression of the cell cycle requires the coordinated and efficient operation of numerous metabolic pathways to provide sufficient biomass and energy supply. A hallmark of cellular senescence is the gradual shift in its metabolic profile from glycolysis and glutaminolysis, which support coordinated proliferation, towards the utilization of glucose for cellular maintenance and growth.[21] Consistent with observations that diminished glutamine-dependent metabolism accompanies the progression of replicative senescence, studies have shown that inhibiting glutaminolysis is an effective driver of cellular senescence.[37] Conversely, selective inhibition of glutaminolysis has been demonstrated to induce apoptosis in senescent cells and ameliorate various age-related diseases.[38] Another key metabolic feature of cellular senescence is a reduction in the NAD+/NADH ratio or total NAD levels, which promotes cell cycle arrest by influencing the SASP. Supplementation with NAD+ precursors extends the replicative lifespan of primary cells and improves the healthspan of prematurely aging BUBR1± mice.[39–41]

The detection of lysosomal enzyme Senescence-Associated β-Galactosidase (SA-β-gal) activity remains one of the most commonly used and convenient methods for assessing cellular senescence both in vitro and in vivo. Its increased

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activity stems from the elevated number and size of lysosomes within senescent cells. Since SA-β-gal is upregulated during senescence, its activity is measured at pH 6.0.[42,43] This marker is specifically present in senescent cells and is generally undetectable in presenescent, quiescent, immortalized, or tumor cells. Therefore, SA-β-gal activity is widely employed as a reliable marker for detecting senescent cells in diverse biological systems.[44,45] However, this marker cannot be effectively detected in formalin-fixed, paraffin-embedded tissue or cell samples, significantly limiting its application in certain research contexts.

Molecular Mechanisms of Renal Cell Senescence in DKD

Age, obesity, and metabolic disturbances are major risk factors for the development of DM. These factors are closely associated with the abnormal accumulation of senescent cells in the body.[46,47] Notably, diabetes itself can accelerate cellular senescence, which in turn further promotes disease progression. In recent years, renal cell senescence induced by the hyperglycemic microenvironment has been recognized as a key mechanism underlying renal functional impairment in DKD. Consequently, therapeutic strategies targeting renal cell senescence have garnered widespread attention from researchers globally.[48,49] Accumulation of senescent cells in the kidney and aberrant expression of cellular senescence-associated markers such as SA-β-gal activity and cell cycle inhibitors P16 and P21 have been observed in DKD patients, animal models, and cell culture models. Research suggests that oxidative stress, mitochondrial dysfunction, chronic inflammation, aberrant epigenetic regulation, dysregulated autophagy, iron metabolism disorders, and cell cycle arrest may constitute core factors driving renal cell senescence.[50–53]

The kidney comprises numerous distinct cell types, including renal tubular epithelial cells, macula densa cells, glomerular endothelial cells, podocytes, mesangial cells, and parietal epithelial cells, which work synergistically to perform vital physiological functions.[54] Among these, renal tubular epithelial cells (particularly proximal tubular epithelial cells) are key structural components of the nephron and are crucial for maintaining renal function. However, the proximal tubule, due to its high energy demands and reliance on aerobic metabolism, is especially vulnerable to injury under diabetic conditions.[55] Diabetes-associated pathological states and physiological disturbances can induce senescence in these tubular epithelial cells, leading to a decline in renal function, manifested as increased urinary albumin excretion and reduced creatinine clearance.[56,57] Furthermore, although substantial research has focused on cellular senescence in tubular epithelial cells (especially proximal), increasing evidence indicates that glomerular podocytes, endothelial cells, and mesangial cells also undergo cellular senescence, resulting in abnormal key physiological functions.[56]

Based on this pathological background, elucidating how key molecular mechanisms drive the cellular senescence process in tubular epithelial cells, podocytes, mesangial cells, and endothelial cells will help uncover the core pathways linking metabolic disturbance to renal injury in DKD. This understanding will provide a solid scientific foundation for developing innovative intervention strategies targeting senescent cells. Table 1 and Figure 2 illustrates the complex network of molecular mechanisms driving renal cell senescence in DKD.

Oxidative Stress Promotes Cellular Senescence

Oxidative stress acts as a "key molecular initiator" in cellular senescence during DKD. Within the kidney, excessive reactive oxygen species (ROS) generation primarily stems from mitochondrial electron transport chain (ETC) protein dysfunction, impaired mitophagy, and dysregulation of the tricarboxylic acid (TCA) cycle and fatty acid β-oxidation. While physiological ROS levels regulate cellular signaling, supraphysiological ROS induces oxidative stress.[74,75] Hyperglycemia-induced mitochondrial dysfunction leads to excessive generation of ROS in renal cells, exceeding the scavenging capacity of endogenous antioxidant systems. ROS can directly activate cell cycle arrest-related signaling pathways by damaging DNA or oxidatively modifying senescence-associated proteins.[8,76] Additionally, ROS activate stress signaling pathways such as autophagy and MAPK, synergizing with inflammatory and metabolic disturbance signals to collectively promote the senescent phenotype.[77,78] More critically, ROS accumulation also causes oxidation of mitochondrial proteins and enzymes, further impairing mitochondrial function. When mitochondrial dysfunction occurs, reduced oxidative phosphorylation efficiency and increased ROS production create a cascade culminating in a "oxidative damage-organelle dysfunction-senescent phenotype" pathway.[79] Studies have found that the suppression of antioxidant enzymes such as superoxide dismutase and catalase is

Table 1 Molecular Mechanisms and Models of Renal Cell Senescence in DKD

Cell Type	Models	Mechanisms	Results	References
Renal Tubular Epithelial Cells	STZ-induced C57/BL6J mice	Promote SLGT2 and SASP by upregulating HHIP	Cell cycle arrest; Inflammation	[11]
	db/db mice; HFD-induced C57Bl/6 mice; high glucoseinduced human primary renal proximal tubular cells	Promote CYP24A1	Cell cycle arrest	[58]
	db/db mice; H_2O_2-induced HK-2 cells	Activate SGLT2 to inhibit NRF2 expression	Oxidative stress; cell cycle arrest	[59]
	STZ-induced C57BL/6J mice; high glucose-induced HK-2 cells	Promote P-STAT3	Cell cycle arrest	[57]
	db/db mice	Promote E2F1, resulting in DNA damage	Cell cycle arrest	[60]
	DKD patients; high glucose- induced mouse primary renal tubular epithelial cells	Inhibit OPTN-mediated mitophagy	Mitochondrial damage; Cell cycle arrest	[61]
	HFD + STZ-induced C57BL/6 mice	Inhibit YME1L to reduce P-BCL2L13 and its interaction with LC3, resulting in suppressing mitophagy	Mitochondrial damage; Cell cycle arrest	[62]
	STZ-induced C57BL/6J mice; high glucose-induced primary mouse renal tubular epithelial cells	Promote DcR2 and P-PRDX1	Cell cycle arrest	[63]
	STZ-induced C57BL/6J mice; high glucose-induced primary mouse renal tubular epithelial cells	Inhibit Parkin to reduce GATA4 ubiquitination and promotes GATA4/GAS1 signaling	Cell cycle arrest; Inflammation	[64]
	High glucose-induced HK-2 cells; HFD + STZ-induced SD rats	Inhibits autophagic flux	Autophagy; Cell cycle arrest,	[65]
	High glucose-induced primary mouse renal tubular epithelial cells	Inhibit ATF4-P16	Endoplasmic reticulum stress; Cell cycle arrest	[66]
	DKD patients; STZ-induced C57BL/6J mice; high glucose-treated primary mouse renal tubular epithelial cells	Inhibit Glis1 expression to enhance interaction of KAT5 with histone H3, thereby increasing histone lactylation	Cell cycle arrest	[67]
Podocytes	High glucose + TGF-β1-induced mouse podocytes; STZ-induced C57BL/6 mice	Promote GSK3β-mediated Nrf2 phosphorylation, resulting in Nrf2 nuclear export and degradation	Oxidative stress; Cell cycle arrest	[13]
	High glucose + TNF-α + IL-6 + insulin-induced mouse podocytes; db/db mice	Promote GSK3β to inhibit Nrf2	Oxidative stress; Cell cycle arrest	[68]
	DKD patients; STZ + HFD-induced C57BL/6 mice; db/db mice; high glucose-induced human podocytes	Inhibit GRP124 to activate FAK, causing mitochondrial dynamics disorder	Mitochondrial damage; Cell cycle arrest	[51]

(*Continued*)

Table 1 (Continued).

Cell Type	Models	Mechanisms	Results	References
Glomerular Mesangial Cells	STZ-induced Wistar rats; high glucose-induced human mesangial cells	Promote Ras-ERK1/2 signaling pathway	Oxidative stress; Cell cycle arrest	[69]
	STZ + HFD-induced C57BL/6J mice; high glucose-induced HBZY-1 and HK-2 cells	Promote iron homeostasis disorder	Cell cycle arrest	[12]
	High glucose-induced Human glomerular mesangial cells	Promote telomere-P53-P21-Rb and JAK/STAT pathways	Cell cycle arrest	[70]
	DKD patients; high glucose-induced rat primary glomerular mesangial cells	Inhibit AMPK signaling to reduce connexin43	Cell cycle arrest	[71]
	STZ-induced C57B6 mice; diabetic mouse glomerular mesangial cells	Promotes JNK signaling pathway, leading to inflammation	Oxidative stress; Cell cycle arrest	[72]
Glomerular Endothelial Cells	STZ-induced C57BL/6 mice; high glucose-induced human glomerular endothelial cells	Promote M1 macrophage accumulation; Promote ROS and MAPK signaling pathway	Oxidative stress; Cell cycle arrest	[14]
	STZ-induced B6; 129 mice; high glucose-induced mouse glomerular endothelial cells	Regulate Id1	Oxidative stress; Cell cycle arrest	[73]

associated with renal injury and renal cell senescence in spontaneous DKD mice.[50,80] Targeting this mechanism by activating antioxidant pathways can restore cellular homeostasis and delay cellular senescence.[81,82]

Heterogeneity exists in cellular senescence mechanisms across different renal cell types. Cellular senescence in tubular epithelial cells is closely linked to hyperglycemia-induced activation of SGLT2, while SGLT2 inhibitors can

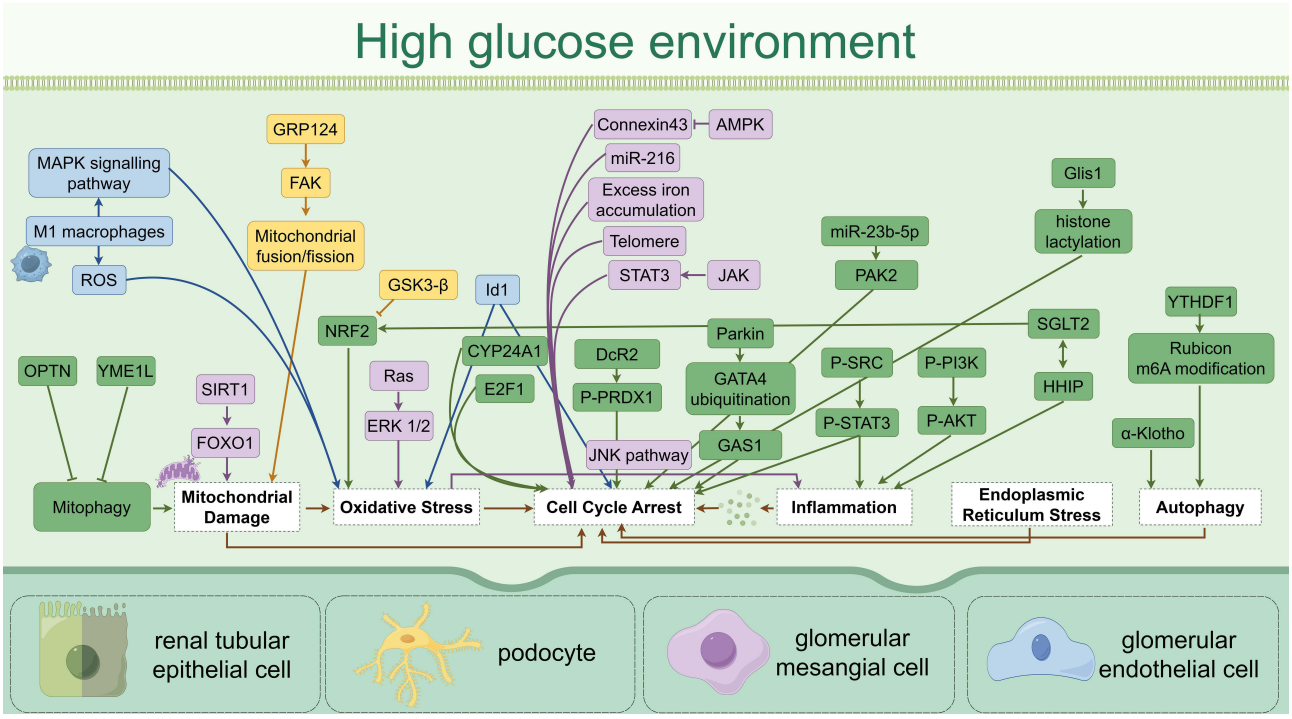

Figure 2 Molecular Mechanisms Driving Renal Cell Senescence in DKD (by Figdraw). This schematic diagram depicts the intricate network of interconnected molecular pathways contributing to cellular senescence in key renal cell types (tubular epithelial cells, podocytes, mesangial cells, endothelial cells) under diabetic conditions. It highlights the central roles of oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, impaired autophagy, chronic inflammation, epigenetic dysregulation, iron dysmetabolism, and consequent cell cycle arrest in promoting the senescent phenotype and DKD progression.

ameliorate cellular senescence via the NRF2-mediated antioxidant pathway.[59] In podocytes, high glucose enhances GSK3β-mediated phosphorylation of NRF2, promoting its nuclear export and degradation, thereby exacerbating oxidative stress and accelerating senescence.[13,68] In glomerular mesangial cells, hyperglycemia elevates serum osmolality, activates the Ras-ERK1/2 pathway, increases oxidative stress, and induces cellular senescence.[69] Increased oxidative stress in mesangial cells of DKD mice activates the JNK signaling pathway, leading to a pro-inflammatory senescent phenotype.[72] Infiltration of M1 macrophages in the kidneys of diabetic mice correlates closely with the upregulation of cellular senescence markers (SA-β-gal activity, P16, P21, and P53 protein levels, and SASP mRNA expression). In vitro co-culture models confirmed that M1 macrophages induce senescence in glomerular endothelial cells via ROS and MAPK signaling, and inhibiting this pathway delays cellular senescence.[14] Furthermore, studies reveal the critical protective role of Id1 in endothelial cells: hyperglycemia-induced oxidative stress and DNA damage are partially counteracted by Id1 upregulation, while its knockout accelerates endothelial senescence and microvascular damage.[73] These findings collectively elucidate the complex regulatory network of oxidative stress in cellular senescence during DKD, offering multi-layered therapeutic targets.

Mitochondrial Damage and Cellular Senescence

Mitochondrial dysfunction, a core feature of cellular senescence, involves pathological mechanisms closely linked to imbalances in mitophagy, mitochondrial biogenesis and dynamics regulation.[79,83] Under physiological conditions, mitophagy precisely removes damaged mitochondria, while fission-fusion dynamics maintain organelle homeostasis. This quality control mechanism is crucial for ensuring energy metabolism and redox balance.[84] Moreover, studies show that mitophagy function is diminished and dynamics are imbalanced in senescent cells, leading to the accumulation of abnormal mitochondria. Excessive ROS produced by damaged mitochondria exacerbate mitochondrial DNA (mtDNA) mutations, which in turn further inhibit mitochondrial function, creating a vicious cycle that drives the senescent phenotype.[85] In the context of diabetic complications, the destructive effects of high glucose on mitochondria are particularly significant. Preclinical studies confirm that high glucose downregulates the expression of key mitophagy proteins in retinal pigment epithelial cells and aortic endothelial cells. This blockade of autophagy flux not only accelerates cellular senescence but is also a key driver of diabetic retinopathy and atherosclerosis.[86,87]

Notably, this mechanism also exists in DKD renal tubular epithelial cells: animal models and in vitro studies demonstrate that sustained high glucose specifically inhibits mitophagy activity in tubular epithelial cells, resulting in the accumulation of damaged mitochondria and induction of cellular senescence.[61] In this process, OPTN-mediated inhibition of mitophagy is directly correlated with DKD progression, and its expression level negatively correlates with serum creatinine, estimated glomerular filtration rate, and tubulointerstitial damage.[61] Additionally, high glucose-induced downregulation of YME1L further disrupts mitophagy and promotes cellular senescence by reducing BCL2L13 phosphorylation and its binding to LC3.[62] Imbalanced mitochondrial dynamics is another important pathway for generating the senescent phenotype in hyperglycemic environments.[88] In renal biopsy tissues from DKD patients, podocyte GPR124 expression is reduced and positively correlates with glomerular filtration rate. In animal models, podocyte-specific knockout of GPR124 causes mitochondrial dynamics imbalance by modulating FAK signaling, accelerating podocyte senescence and functional loss, while its overexpression protects against high glucose-induced senescence.[51] Based on these mechanisms, targeting mitochondrial quality control pathways can not only clear damaged mitochondria and improve energy metabolism but also offer novel strategies for DKD prevention and treatment by delaying renal cell senescence.

Inflammatory Response and Cellular Senescence

The inflammatory response is a systemic biological process triggered by endogenous damage signals or exogenous stimuli, involving immune cell activation, altered vascular permeability, and release of inflammatory mediators.[89] Chronic inflammation, by continuously secreting cytokines that sustain oxidative stress pressure, forms a vicious cycle with cellular senescence and is a core driver of renal cell senescence in DKD.[90] The hyperglycemic microenvironment activates pro-inflammatory cytokines (eg, IL-6, TNF-α, IL-1β), triggering abnormal activation of inflammatory signaling pathways and inducing the release of SASP-related inflammatory factors in the kidney.[11,50] Furthermore, infiltration of immune cells like M1 macrophages, resulting from hyperglycemia, exacerbates senescence in diabetes-related target

organs and cells through inflammatory signaling pathways.[91–93] This inflammatory response locks in the cellular senescence program via a dual mechanism: on one hand, inflammatory mediators secreted by immune-inflammatory cells increase oxidative stress levels and upregulate cell cycle-related protein expression, thereby forcing renal cells into senescence; on the other hand, SASP factors secreted by senescent cells themselves remodel the renal microenvironment through paracrine actions, establishing a "inflammation-cellular senescence-renal injury" vicious cycle.[94]

In-depth molecular mechanism studies found that abnormally high expression of Hedgehog-interacting protein (HHIP) induced by the hyperglycemic environment has dual pro-senescence effects: it increases intracellular glucose accumulation by stimulating SGLT2 expression and directly promotes SASP secretion in tubular epithelial cells, collectively driving tubular damage and senescence. Experiments confirmed that tubule-specific knockout of HHIP significantly reduced SA-β-gal activity, decreased SASP secretion, and downregulated P16/P21/P53 expression, thereby ameliorating cellular senescence and renal function.[11] Additionally, high glucose inhibits Parkin, reducing GATA4 ubiquitination and promoting GATA4/GAS1 signaling. This not only exacerbates the inflammatory response in tubular epithelial cells but also directly promotes cellular senescence by inducing cell cycle arrest.[64] Notably, these molecular mechanisms intersect with mitochondrial dysfunction. For instance, Parkin, a key regulator of mitophagy, whose functional inhibition may simultaneously affect mitochondrial quality control and inflammatory signaling, suggesting deep molecular network interactions between diabetes-related inflammation and organelle dysfunction in the senescence process. These findings provide a theoretical basis for developing synergistic therapeutic strategies that simultaneously target inflammatory pathways and organelle homeostasis.

Epigenetic Modifications and Cellular Senescence

Growing evidence indicates that epigenetic regulatory mechanisms governing gene expression play an indispensable role in the manifestation and maintenance of aging-associated diseases.[95] Non-coding RNAs, ubiquitination modifications, lactylation modifications, and m6A modifications, as key components of epigenetic regulation, act synergistically in renal cell senescence during DKD. Research has found that a high-glucose environment can promote histone lactylation levels, mitigating accelerated tubular senescence and renal fibrosis during DKD progression.[67] It can also inhibit the protein quality control function of the ubiquitination system, leading to abnormal accumulation of senescence-associated transcription factors (eg, GATA4), which directly activate cell cycle arrest and inflammatory signaling pathways.[64] Furthermore, expression reprogramming of non-coding RNAs (eg, miR-126, miR-23b-3p) amplifies senescence-associated phenotypes by targeting key signaling nodes (eg, AKT-P53, PAK2).[96,97] The m6A modification reader protein YTHDF1 induces renal cell senescence in DKD by mediating the m6A modification of Rubicon, a negative regulator of autophagy.[98]

Although these mechanisms are currently validated independently, they likely collectively constitute a pathological hub within an epigenetic network: aberrant m6A modification affects RNA stability and subsequent protein translation levels, abnormal ubiquitination affects protein stability, non-coding RNAs regulate downstream gene expression, and histone lactylation alters chromatin state. Ultimately, they synergistically regulate the cell cycle and promote tubular senescence and fibrosis. Therefore, targeting epigenetic regulation may ameliorate cellular senescence and restore cellular homeostasis, thereby delaying DKD progression.

Endoplasmic Reticulum Stress, Impaired Autophagy, Iron Metabolism Dysregulation, and Cellular Senescence

Imbalance in proteostasis plays a significant role in cellular senescence, with its core mechanism closely linked to the aberrant activation of endoplasmic reticulum stress (ERS) and the unfolded protein response (UPR). The endoplasmic reticulum (ER) is an intracellular organelle where most secretory and transmembrane proteins are translated, fold into their native structures, and are then transported to appropriate locations to perform their vital functions. Restoring proteostasis can reduce the decline in organ function during cellular senescence.[99,100] In the pathological progression of various diseases, including DKD, ERS drives tissue and cellular functional damage through a unique molecular cascade involving the synergistic regulation of three transmembrane sensors: the IRE1α-XBP1 pathway, the PERK-eIF2α-ATF4 signaling axis, and the ATF6-endoplasmic reticulum-associated degradation system.[101] High-glucose causes abnormal

accumulation of unfolded proteins in the ER lumen, persistently activating ERS. Among the pathways, abnormal activation of the ATF4/P16 axis directly induces senescence in tubular epithelial cells and promotes fibrosis, indicating that ERS is a key hub connecting metabolic disturbance with organ dysfunction.[66] This pathological cascade demonstrates that ERS-driven collapse of proteostasis is not only a trigger for cellular senescence but also a critical nexus linking metabolic dysregulation to organ impairment.

Autophagy and iron metabolism dysregulation also participate in the cellular senescence process. The high-glucose environment impairs clearance of damaged proteins and organelles by inhibiting autophagic flux while simultaneously disrupting iron homeostasis, causing iron overload. Both factors synergistically exacerbate DNA damage in tubular epithelial cells or mesangial cells, accelerating cellular senescence.[12,65] Studies found that in STZ-induced diabetic mice, iron imbalance coupled with macrophage infiltration activates cell cycle inhibitory proteins and amplifies the senescent phenotype.[102] Abnormal binding of the autophagy regulatory complex Beclin1-Bcl2 not only suppresses autophagy activity but also aggravates renal functional decline by enhancing SASP release.[103] This suggests that modulating the ERS-UPR system, autophagy, and iron homeostasis may also be effective approaches to ameliorate renal cell senescence in DKD.

Cell Cycle Arrest and Cellular Senescence

Cell cycle arrest is the core execution step of cellular senescence in DKD, integrating multi-dimensional pathological signals to drive the senescence process in renal cells.[104] The hyperglycemic environment can indirectly activate pathways such as oxidative stress, mitochondrial damage, endoplasmic reticulum stress, aberrant epigenetic modifications, and inflammatory responses and also directly regulate key cell cycle proteins, locking cells into a state of cycle arrest and leading to senescence. Moreover, senescent cells can create a vicious cycle by releasing SASP factors, which induce cell cycle arrest in neighboring cells via paracrine signaling, accelerating tubular damage, interstitial fibrosis, and glomerulosclerosis.[105]

At the molecular level, cell cycle regulation in renal cells during DKD exhibits a characteristic of multi-pathway synergistic imbalance. In tubular epithelial cells, abnormally high expression of the vitamin D-metabolizing enzyme CYP24A1 disrupts vitamin D homeostasis, inducing G1 phase arrest and promoting apoptosis and cellular senescence.[58] Furthermore, the high-glucose environment promotes the expression of E2F1 and P-STAT3, regulating cell cycle-related proteins and promoting cellular senescence in tubular epithelial cells.[57,60] Glis1 expression is significantly downregulated in DKD mice and in tubular epithelial cells under high-glucose condition. This downregulation increases the binding capacity of KAT5 to histones, promoting histone lactylation. Overexpression of Glis1 can inhibit histone lactylation by promoting its binding to KAT5, reducing renal cell senescence and alleviating renal fibrosis during DKD development.[67] DcR2 is specifically expressed in senescent tubular epithelial cells. This molecule affects the cell cycle and senescence process by promoting the phosphorylation level of PRDX1 and correlates with renal function and pathological damage in DKD patients and STZ-induced mice. Knockout of DcR2 or PRDX1 improves renal function and inhibits the expression of senescence-associated markers.[63] For glomerular mesangial cells, high glucose induces G1 phase arrest by activating the telomere dysfunction-P53-P21-Rb signaling cascade and the JAK/STAT pathway. It also suppresses AMPK signaling, leading to downregulation of connexin43 expression, ultimately promoting cell cycle arrest and senescence.[70,71] These findings reveal the significant role of the cell cycle regulatory network in DKD renal injury, with its core centered on the abnormal expression of key nodal proteins, ultimately resulting in loss of proliferative potential and activation of the senescent phenotype. Targeting this mechanism requires intervention strategies that concurrently regulate the cell cycle and clear senescent cells, thereby breaking the cascade amplification of pathological signals and offering new approaches to reverse DKD progression.

In summary, DKD progression is closely associated with renal cell senescence. Hyperglycemia drives senescence in renal tubular epithelial cells, podocytes, mesangial cells, and endothelial cells by regulating mechanisms such as cell cycle control, oxidative stress, chronic inflammation, mitochondrial damage, endoplasmic reticulum stress, and epigenetic modifications. This manifests as abnormal expression of cellular senescence-associated markers, including DNA damage, cell cycle inhibitors (eg, P16, P21, P53), SASP levels, and SA-β-gal activity. Concurrently, senescent cells exacerbate the disease by worsening microvascular damage and organ dysfunction. Intervention strategies targeting cellular senescence—such as combinations of senolytic drugs, balancing mitochondrial quality control, activating autophagy, administering antioxidants, and targeting key genes—can improve the senescent renal microenvironment, providing potential therapeutic directions for

delaying DKD progression. Precise modulation of cellular senescence may become a key breakthrough for improving renal function in the future.

Therapeutic Strategies Targeting Cellular Senescence

Targeting Renal Cell Senescence: Current and Emerging Therapies for DKD

Cellular senescence is a key driver of DKD progression, highlighting that targeting renal cells is a critical focus for therapeutic intervention. This section systematically explores strategies to ameliorate renal cell senescence, including therapies based on TCM and its natural constituents, targeted modulation of key genes or mechanisms, and analyzes their mechanisms of action. It also reviews emerging therapies and potential interventions, aiming to provide new perspectives for enhancing DKD treatment efficacy, as shown in Figure 3.

Interventions Targeting Key Genes or Core Mechanisms

Histone deacetylase (HDAC) inhibitors, such as valproic acid, have demonstrated renal protective effects in preclinical studies. They induce histone acetylation and modulate DNA and histone methylation states, thereby regulating gene expression. It has been shown that valproic acid reduces cellular senescence markers and the SASP by inhibiting the upregulation of the C5a receptor in the DKD kidney.[106] Furthermore, improvements in urinary protein, renal function, inflammation, and the cellular senescence phenotype were also observed in diabetic mice treated with the C5a receptor antagonist PMX53.[107] β-hydroxybutyrate, a major component of ketone bodies, exhibits protective activity in aging and metabolic diseases. It has been demonstrated that β-hydroxybutyrate significantly alleviates podocyte senescence in DKD

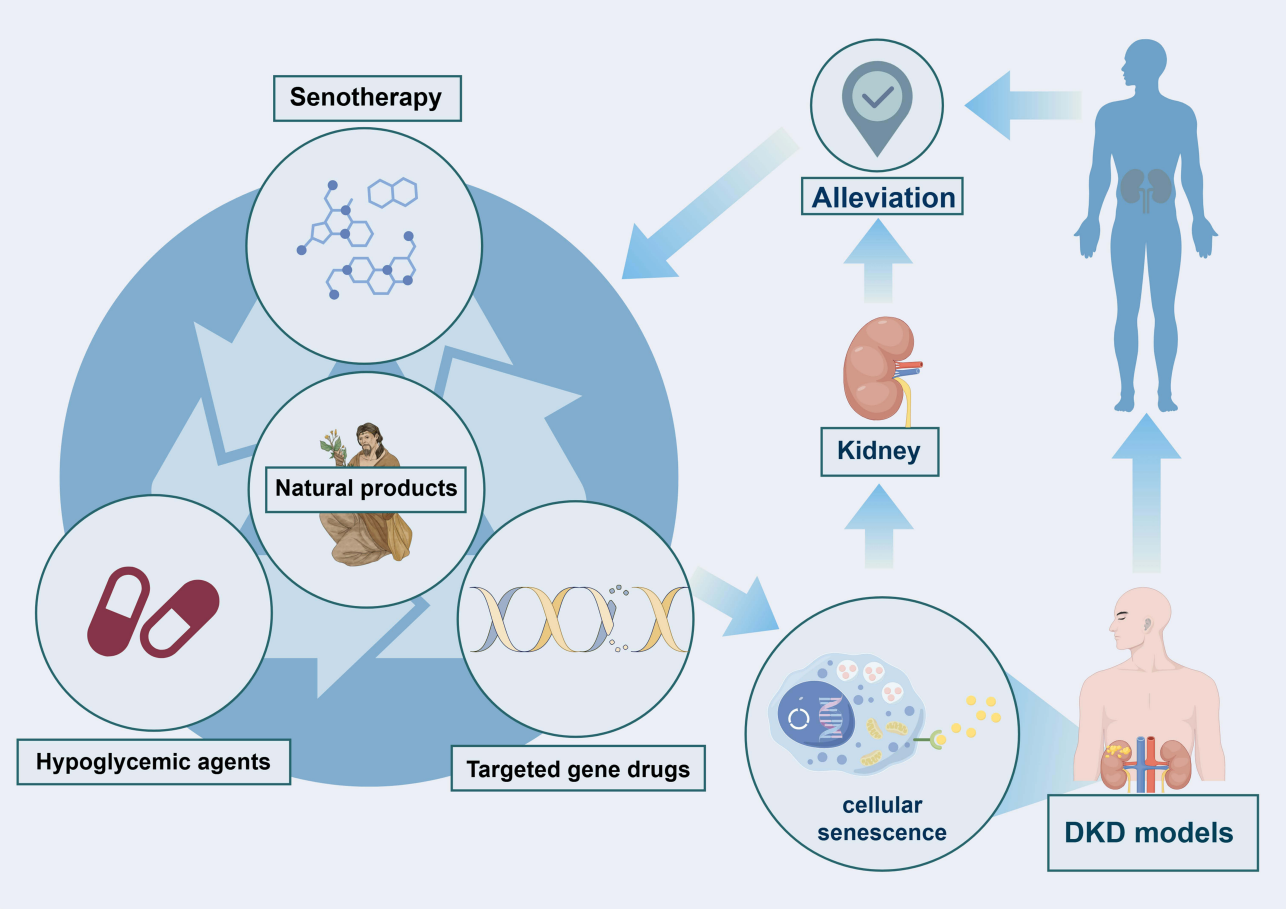

Figure 3 Therapeutic strategies targeting renal cell senescence in DKD (by Figdraw). This schematic illustrates the multifaceted approaches to combat cellular senescence in DKD. It categorizes strategies including senotherapy, pharmacological targeting of core molecular mechanisms, repurposing of common glucose-lowering drugs with anti-senescence effects, and the application of Chinese herbal medicines and their active natural compounds acting through multiple pathways.

by targeting GSK3β to promote NRF2 nuclear translocation and activate the antioxidant response.[13] Melatonin, an endogenous hormone involved in circadian rhythm regulation, also attenuates renal cell senescence and apoptosis in DKD by inhibiting STAT3 phosphorylation.[57] Iron homeostasis modulators, such as the iron chelator deferasirox, prevent renal iron accumulation and macrophage infiltration in STZ-induced mice, reduce the expression of cell cycle inhibitory proteins, and ameliorate cellular senescence.[102] Recent research indicates that liposomal clodronate, as a macrophage-depleting agent, can attenuate immunosenescence in DKD renal cells by modulating GDF-15 and Klotho, improving renal function and alleviating the chronic inflammation and oxidative stress driving DKD progression.[108] This finding suggests that targeting immunosenescence pathways is also a potential therapeutic approach for DKD. Notably, M1 macrophages can induce senescence in human glomerular endothelial cells, accompanied by a significant increase in ROS levels. Treatment with the well-known antioxidant N-acetylcysteine markedly reduces glomerular endothelial cell senescence induced by high-glucose conditions.[14]

Common Hypoglycemic Agents

Drugs commonly used in clinical DKD management, such as metformin and dapagliflozin, can also significantly reduce the expression levels of senescence-associated markers in renal cells. Metformin, the most widely used oral hypoglycemic agent in clinical practice, is now a first-line treatment for type 2 diabetes. The high-profile ongoing "Targeting Aging with Metformin" clinical trial is dedicated to investigating the clinical value of this drug in delaying the aging process. The research team systematically evaluates its intervention effects and molecular mechanisms on the occurrence and development of age-related diseases by analyzing cellular senescence molecular pathways.[109] Basic research confirms that metformin reduces the senescent cell burden: in glucose-induced renal proximal tubular epithelial cell models, it significantly delays the senescence process by downregulating P21 expression and inhibiting SA-β-gal activity.[110] In type 2 diabetic animal models, it also shows therapeutic potential in ameliorating the senescent phenotype of tubular epithelial cells under hyperglycemic conditions.[60,111] In-depth mechanistic studies reveal that metformin may exert its anti-senescence biological effects by regulating the Keap1/Nrf2 signaling pathway, enhancing mitophagy activity, and boosting antioxidant stress capacity.[60] Sodium-glucose cotransporter 2 inhibitors (SGLT2i, eg, empagliflozin, dapagliflozin, canagliflozin) possess renoprotective effects beyond their glucose-lowering action. They selectively target the SGLT2 membrane protein in the proximal tubule, preventing glucose reabsorption while preserving GFR through increased tubuloglomerular feedback and reduced hyperfiltration. Research shows that SGLT2 inhibitors exhibit adjunctive protective effects beyond glycemic control, with improvements in cardiovascular and renal outcomes also observed in the absence of diabetes.[112,113] SGLT2 inhibitors have also been found to enhance the clearance of senescent cells, thereby improving age-related phenotypic changes.[114] It has been reported that dapagliflozin increases plasma β-hydroxybutyrate levels, exerting therapeutic effects by improving DNA and senescence-related damage through NRF2 nuclear translocation-mediated antioxidant pathways.[59] Canagliflozin can also inhibit HHIP overexpression induced under DKD conditions, which triggers tubular epithelial cell senescence and lesions.[115]

Senotherapy

Senotherapy refers to therapeutic agents and methods specifically targeting senescent cells, aiming to restore tissue integrity by eliminating senescent cells or removing the source of chronic inflammation to mitigate the adverse effects associated with cellular senescence.[116] Currently, "senolytic drugs" have been developed to pharmacologically eliminate senescent cells by inhibiting SASP and other senescence markers.[117] The combination of dasatinib and quercetin is the first senolytic intervention to enter human clinical studies. It reduces SA-β-gal positivity and P16/P21 expression in adipose tissue and skin of DKD patients, and also inhibits inflammatory cytokines such as IL-1α and IL-6 in blood samples. Therefore, this therapy improves the systemic inflammatory state and ameliorates cellular senescence by targeting SASP-related inflammatory factors.[118] Additionally, this therapy alleviates age-related adipose tissue inflammation and improves systemic metabolic function, highlighting its potential in treating metabolic dysfunction in the elderly.[119]

Chinese Herbal Medicines and Natural Active Components

TCM and some active compounds derived from natural products demonstrate significant therapeutic potential in ameliorating renal cell senescence and renal injury in DKD. Through multiple mechanisms such as modulating oxidative

stress, promoting autophagy, improving mitochondrial function, and inhibiting inflammatory responses, TCM holds promise as an important means for treating DKD, as summarized in Table 2.

Shenkang injection, a TCM compound preparation composed of Radix Astragali (Huangqi), Radix et Rhizoma Rhei (Dahuang), Flos Carthami (Honghua), and Radix et Rhizoma Salviae Miltiorrhizae (Danshen), has been shown to improve clinical symptoms and renal function impairment in patients with DKD. In high glucose-induced primary renal tubular epithelial cell models, Shenkang injection inhibits the formation of SAHF, reduces the expression of senescence-associated markers such as P16 and P21, and decreases SA-β-gal activity. It also suppresses the upregulation of DcR2, prevents the activation of pro-senescence molecules mTOR and p66Shc, and counteracts the downregulation of anti-senescence molecules including Klotho, SIRT1, and PPARγ.[120]

Huangqi Compound granules, primarily composed of Radix Astragali (Huangqi), Rehmannia glutinosa (Shengdi), Dioscoreae Rhizoma (Shanyao), and Radix et Rhizoma Salviae Miltiorrhizae (Danshen), exhibit anti-senescence effects in DKD. Drug-containing serum derived from this formula delays cellular senescence and injury in high glucose-induced rat glomerular mesangial cells. The mechanism is associated with upregulation of the SIRT1/FOXO1 signaling pathway, alleviation of mitochondrial damage, and reduction in ROS generation.[121,125]

Shenyan Fangshuai decoction, composed of seven herbs including Radix Astragali (Huangqi), Angelica sinensis (Danggui), Rhei Radix et Rhizoma (Dahuang), and Trionycis Carapax (Biejia), ameliorates tubular epithelial cell senescence in DKD by regulating α-Klotho-mediated autophagy, thereby protecting renal function and preventing pathological tissue damage.[122]

Table 2 Molecular Mechanisms by Which TCM and Its Active Components Derived from Natural Products Ameliorate Renal Cell Senescence in DKD

Name	Models	Mechanisms	Results	References
Shenkang injection	High glucose- induced primary renal proximal tubular epithelial cells	Inhibit mTOR, P66shc, Dcr2; Promote PPAR-γ, Sirt1, Klotho	Improve cell cycle arrest	[120]
Huangqi Compound granules	High glucose- induced rat glomerular mesangial cells	Promote SIRT1/FOXO1 pathway	Improve mitochondrial damage, oxidative stress, cell cycle arrest	[1,21,121]
Shenyan Fangshuai decoction	STZ + Unilateral Nephrectomy in SD rats; AGEs-induced HK-2 cells	Promote α-Klotho	Promote autophagy	[122]
Suoquan Yishen formula	db/db mice; High glucose-induced HK-2 cells	Inhibit the YTHDF1-Rubicon axis	Promote autophagy; Improve cell cycle arrest	[98]
Alpiniae Oxyphyllae Fructus	db/db mice; High glucose-induced HK-2 cells	Inhibit PI3K/AKT and SRC/STAT3 signaling pathways	Improve inflammatory, cell cycle arrest	[50]
Tea Polyphenols	High glucose-induced human glomerular mesangial cells	Promote miR-126; Regulate AKT-P53-P21 signaling pathway	Improve cell cycle arrest	[97]
Quercetin/ Resveratrol	High glucose-induced HEK-293 cells	Promote SMP30	Improve oxidative stress	[123]
Oleuropein	db/db mice	Promote cGMP-PKG signaling pathway; Inhibit P53 signaling pathway	Improve cell cycle arrest	[124]
Icariin	Urinary exosomes from DKD patients-induced HK-2 cells	Inhibit miR-23b-3p to promote PAK2	Improve cell cycle arrest	[96]

Suoquan Yishen formula (SQYSF), derived from the classical formula Suoquan pill, consists of Alpiniae oxyphyllae fructus (Yizhiren), Linderae Radix (Wuyao), Poria (Fuling), Atractylodis Rhizoma (Cangzhu), Salviae Miltiorrhizae Radix et Rhizoma (Danshen), Paeoniae Radix Rubra (Chishao), and Radix Trichosanthis (Tianhuafen). It has shown promising efficacy in improving clinical symptoms, reducing urinary protein, enhancing renal function, decreasing serum inflammatory factors, and alleviating renal microinflammation in DKD patients.[126,127] Studies have shown that both SQYSF extract and SQYSF-containing serum ameliorate renal injury in db/db mice and rescue impaired viability and senescent phenotype in high glucose-treated HK-2 cells. This effect is associated with the regulation of YTHDF1-mediated Rubicon m6A modification, thereby promoting autophagy.[98]

Alpiniae oxyphyllae fructus (AOF), the dried ripe fruit of Alpinia oxyphylla Miq. (Zingiberaceae), has been widely used in China for thousands of years to treat chronic glomerulonephritis, nephrotic syndrome, and other kidney-related diseases.[128] In db/db mice and high glucose-stressed HK-2 cell models, AOF modulates the PI3K/AKT and SRC/STAT3 signaling pathways, reduces inflammatory cytokine levels and immune-inflammatory cell infiltration, improves renal cell senescence, and delays DKD progression.[50]

Tea polyphenols have been shown to delay high glucose-induced cellular senescence in human glomerular mesangial cells by modulating the miR-126 and AKT-P53-P21 signaling pathways.[97]

Resveratrol and quercetin, as potent herbal antioxidants, can effectively improve the progression of various metabolic diseases.[129,130] Studies have shown that quercetin and resveratrol, administered either alone or in combination, significantly increase the expression of SMP30 protein and improve the expression levels of renal cell senescence markers under high-glucose conditions.[123]

Chlorogenic acid has been identified through bioinformatics, machine learning, and molecular docking approaches as a potential therapeutic agent for ameliorating glomerular cell senescence in DKD.[131]

Oleuropein, a phenolic compound primarily found in olive leaves and unripe olive fruits, upregulates the cGMP–PKG signaling pathway while downregulating P53 and other senescence-associated pathways, thereby alleviating renal inflammation, fibrosis, apoptosis, and pathological tissue damage in DKD.[124]

Icariin has been found to attenuate tubular epithelial cell senescence by targeting PAK2 via miR-23b-3p in an in vitro model established by co-incubating HK-2 cells with urinary exosomes derived from DKD patients.[96]

Discussion

The progression of DKD is intricately linked to the cascade of renal cell senescence. Its molecular mechanisms involve the dynamic interplay of multidimensional pathological signaling, including oxidative stress, mitochondrial damage, inflammation, and epigenetic regulation. This review systematically deciphers the driving network of renal cell senescence under hyperglycemic microenvironments and explores intervention strategies targeting senescent cells, providing a theoretical foundation for developing novel therapeutic modalities.

Molecular Mechanisms of Renal Cell Senescence in DKD: From Single Targets to Network Regulation

During DKD progression, the hyperglycemic environment can directly induce cell cycle arrest or indirectly promote arrest by mediating pathways such as mitochondrial damage, ERS, oxidative stress, and inflammatory responses. This impairs renal tissue repair capacity and exacerbates renal injury. Furthermore, the pathological accumulation of senescent cells releases pro-inflammatory and pro-fibrotic factors via the SASP, aggravating inflammation in the renal microenvironment and further driving neighboring cells into cycle arrest, forming a vicious cycle of "damage-senescence-recurrent damage". Notably, epigenetic regulation (eg, m6A modification, histone lactylation) dynamically controls the expression of senescence-associated genes by converting signals of metabolic dysregulation into persistent epigenetic memory. This mechanism may underpin the irreversibility of cellular senescence in DKD kidneys.[132–134]

Current research reveals both shared and distinct senescence mechanisms in renal tubular epithelial cells, podocytes, mesangial cells, and endothelial cells during DKD progression. This not only underscores the complexity of DKD's pathological mechanisms but also highlights the importance of multi-targeted therapy. Oxidative stress and cell cycle

arrest are observed in glomerular podocytes, endothelial cells, mesangial cells, and tubular epithelial cells.[13,59,71–73] However, under diabetic conditions, senescence in tubular epithelial cells is closely associated with impaired mitophagy and ERS;[61,66] podocyte senescence is strongly linked to mitochondrial dynamics dysregulation;[51] and endothelial cell senescence correlates with the infiltration of inflammatory cells such as M1 macrophages.[14] These cell-type-specific senescence mechanisms provide a rationale for precise interventions. Simultaneously, this complexity necessitates therapeutic approaches targeting multiple mechanisms concurrently.

Natural Products: Unique Advantages and Challenges in Multi-Target Network Regulation

Importantly, the multi-target regulatory properties of TCM, such as simultaneously regulating autophagy, inhibiting inflammation, and improving mitochondrial function, align well with the need to intervene in complex cellular senescence networks. Faced with the multifactorial, multi-pathway pathogenesis of renal cell senescence in DKD, natural products exhibit unique advantages over single-target drugs due to the synergistic effects of their multiple constituents. Studies demonstrate that various TCM formulas and active ingredients can systematically intervene in senescence-related signaling networks. Their mechanisms of action include, but are not limited to: concurrently inhibiting key pro-senescence molecules (eg, mTOR, p66Shc) and activating anti-senescence molecules (eg, Klotho, SIRT1, PPARγ); modulating inflammation-related signaling axes (eg, PI3K/AKT, SRC/STAT3) to mitigate inflammation-driven senescence; and influencing exosome-mediated senescence signaling by regulating non-coding RNAs (eg, miRNAs).[50,96,120] Collectively, these studies highlight the significant value of TCM and its natural products in ameliorating the renal microenvironment through their comprehensive anti-senescence effects, thereby delaying renal functional impairment in DKD.

Furthermore, the newly developed senotherapy strategies targeting senescent cell clearance and SASP inhibition have opened new avenues for DKD treatment.[135] Senolytic therapies, exemplified by the dasatinib-quercetin (D+Q) combination, have demonstrated dual efficacy in reducing senescent cells and downregulating inflammatory factors in clinical trials.[118] In preclinical models, this anti-senescence approach, targeting a core mechanism of aging (ie, a fundamental "root cause" shared by multiple diseases), shows broad application potential. It can alleviate over 40 conditions including frailty, cancer, cardiovascular disease, and metabolic disorders, paving new ways for treating age-related dysfunction and diseases.[136]

Challenges and Translational Directions

The complex molecular mechanisms of DKD suggest that future research must move beyond studying single molecular mechanisms. Focus should shift towards the dynamic integration of multidimensional signaling networks to decipher the full chain of events from senescence initiation to execution. Future studies could leverage single-cell sequencing or spatial transcriptomics to further dissect intercellular communication mechanisms within the senescent microenvironment, laying the groundwork for developing cell-type-specific intervention strategies.

Simultaneously, the molecular mechanisms by which natural products ameliorate renal cell senescence in DKD remain incompletely defined, posing significant challenges for clinical translation. The multi-component nature of natural products complicates the identification of their precise targets and pathways. Integrating multi-omics analysis techniques —such as Network Pharmacology, single-cell transcriptomics, proteomics, and metabolomics—is crucial to deeply explore the causal relationships between key components and senescence regulation.[137]

Additionally, most current research relies on animal models or single cell types, which inadequately recapitulate the complex microenvironment of human DKD. Future efforts should develop more clinically relevant models, such as organoids or 3D co-culture systems, to validate drug effects on senescence in multi-cellular interactions. Moreover, while some therapeutic agents are already in clinical use, there is a lack of large-scale, multi-center randomized controlled clinical trials. Future research must further validate their clinical efficacy and safety across different stages of DKD.

Furthermore, exploring modern formulation technologies to enhance the stability and bioavailability of natural products, or investigating their synergistic effects when combined with Western medicines, represents a promising direction. Finally, strengthening the seamless integration between basic research and clinical translation, combined with modern medical technologies, is essential to advance the development of personalized precision treatment strategies.

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Disclosure

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