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REVIEW

Diabetic Kidney Disease: Disease Progression Driven by Positive Feedback Loops and Therapeutic Strategies Targeting Pathogenic Pathways

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Abstract: Diabetic kidney disease (DKD) is a major complication of diabetes mellitus, with its pathogenesis intricately regulated by dynamic feedback mechanisms. This comprehensive review systematically analyzes the hierarchical feedback networks driving DKD progression, spanning from systemic interactions to molecular cross-talks. We reveal that self-amplifying positive feedback loops dominate the disease process, manifested through three key dimensions: (1) The systemic triad of hyperglycemia-hypertension-proteinuria establishes a vicious cycle accelerating renal dysfunction; (2) Cellular homeostasis collapse through cross-amplified cell death modalities (apoptosis, pyroptosis, ferroptosis) and cell cycle dysregulation; (3) Molecular cascades centered on AGE/RAGE signaling that fuel chronic inflammation and fibrotic transformation. Collectively, these form a major positive feedback loop where PKC activation, oxidative stress propagation, and TGF-β-mediated fibrosis induced by hyperglycemia lead to progressive renal deterioration and fibrosis. Therapeutically, we propose a dual intervention strategy targeting both the acute phase through AGE/RAGE axis inhibition, coupled with chronic phase via precision modulation of fibrotic pathways. These findings redefine DKD progression as a self-reinforcing network disorder, providing a roadmap for developing multi-target therapies that disrupt pathological feedback loops while preserving renal repair mechanisms.

Plain Language Summary:

- Positive feedback exists in diabetic kidney disease to drive disease progression.
- High glucose induced cell death and cell cycle disruption alter the cellular homeostasis.
- Fibrosis and inflammatory response, cell adhesion, angiogenesis, and thrombogenesis promote each other.
- The gradual development of the disease may lead to renal fibrosis and even end-stage renal disease.
- Diabetic kidney disease can be treated through intervention in the positive feedback process.

Keywords: diabetic kidney disease, feedback, hyperglycemia, advanced glycation end products, fibrosis, treatment

Introduction

Diabetes affects a large population of people worldwide. The global diabetes prevalence in 20–79 year olds in 2021 was estimated to be 10.5% (536.6 million people).[1–6] Diabetic kidney disease (DKD) is defined as persistent albuminuria and/or the decrease of estimated glomerular filtration rate attributed to diabetes.[7] It develops in approximately 40% of patients

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who are diabetic and is the leading cause of chronic kidney disease worldwide. And it is one of the most common microvascular complications of diabetes, and also the main cause of end-stage renal disease (ESRD) and global renal failure, which seriously affects the quality of life of patients.[8–10] With the continuous increase of the global prevalence of diabetes, the incidence rate of DKD is also increasing year by year, which has brought a heavy burden to patients and the society.[11,12]

Dynamic feedback mechanisms are biological control systems where outputs (eg, molecular signals) recursively modulate their own production. In healthy organisms, feedback regulation is a mechanism used by organisms to maintain homeostasis, which is the stable internal environment required for optimal function. Feedback regulation is divided into negative feedback and positive feedback. Negative feedback can counteract or reduce the impact of stimuli. Positive feedback amplifies changes rather than reversing them. In DKD, the latter is more common.

In DKD, after the homeostasis is disrupted, pathogenic factors continuously promote the disease process through forming pathological loops that amplify damage. While previous reviews have focused on isolated pathways (eg, hyperglycemia or fibrosis), this work uniquely integrates multi-scale feedback networks to reveal how cross-tier interactions create self-sustaining disease progression. Our synthesis provides the first hierarchical framework categorizing DKD feedback loops into three tiers: systemic (eg, hyperglycemia-hypertension cross-talk), cellular (eg, apoptosis-ferroptosis synergy), and molecular (eg, AGE/RAGE-TGF-β axis). This approach uncovers previously overlooked amplification nodes that synchronize damage across biological scales.

A deep understanding of the feedbacks in the occurrence and development of DKD is of great significance for revealing the disease process and finding new therapeutic targets. Crucially, the hierarchical nature of these feedback systems implies that effective interventions must simultaneously target multiple regulatory tiers. For instance, breaking the systemic triad (hyperglycemia-hypertension-proteinuria) may require combined glycemic control and RAAS blockade, while molecular-level therapies could disrupt the feedforward amplification between oxidative stress and epigenetic dysregulation. This paradigm shift toward multi-tiered targeting forms the foundation for the therapeutic strategies discussed in subsequent sections.

DKD and Feedback of the System

It is well-established that feedback regulation at systemic level plays a key role in the development and progress of DKD.[13,14] Macroscopically, sustained hyperglycemia and changes in renal hemodynamics lead to an increase in renal microvascular pressure. If this elevation is not strictly controlled, it usually leads to a gradual decline in kidney function. As the pressure inside the glomerulus increases, the structural integrity of the glomerulus is compromised, resulting in damage to the glomerular capillary walls. This type of damage causes protein leak from the blood into the urine, resulting in proteinuria.[15] As proteinuria progresses to a more serious form, such as proteinuria within the scope of nephrosis, it will lead to severe water and sodium retention, and damage the body's fluid balance. Meanwhile, impaired kidney function may result in the inability to effectively eliminate excess sodium and water, leading to fluid accumulation in the body. This accumulation will increase the blood volume and pressure inside the blood vessels, thereby exacerbating hypertension.[16,17] A vicious cycle has been formed, where elevated blood pressure further damages the kidneys, increases kidney pressure, and worsens the condition. Therefore, early intervention is crucial for breaking this cycle and preventing disease progression.

Feedback in Cell Death (Figure 1)

In kidney injury, a complex interplay of various cell death mechanisms often coexist, disrupting distinct cellular functions and signaling pathways, thereby triggering cell death through diverse processes. Although multiple pathways may be involved, several predominant routes of cell death are typically observed. These primary pathways not only rely on the signals that initiate the cell death cascade but also on the specific cell types that respond to these signals, as well as individual genetic and environmental factors. Moreover, these different forms of cell death are interconnected, influencing each other in a complex network.[18,19]

During the early stage of DKD, without timely preventive interventions, a hyperglycemic environment can trigger an inflammatory response and lead to the release of inflammasomes and damage-associated molecular patterns (DAMPs).

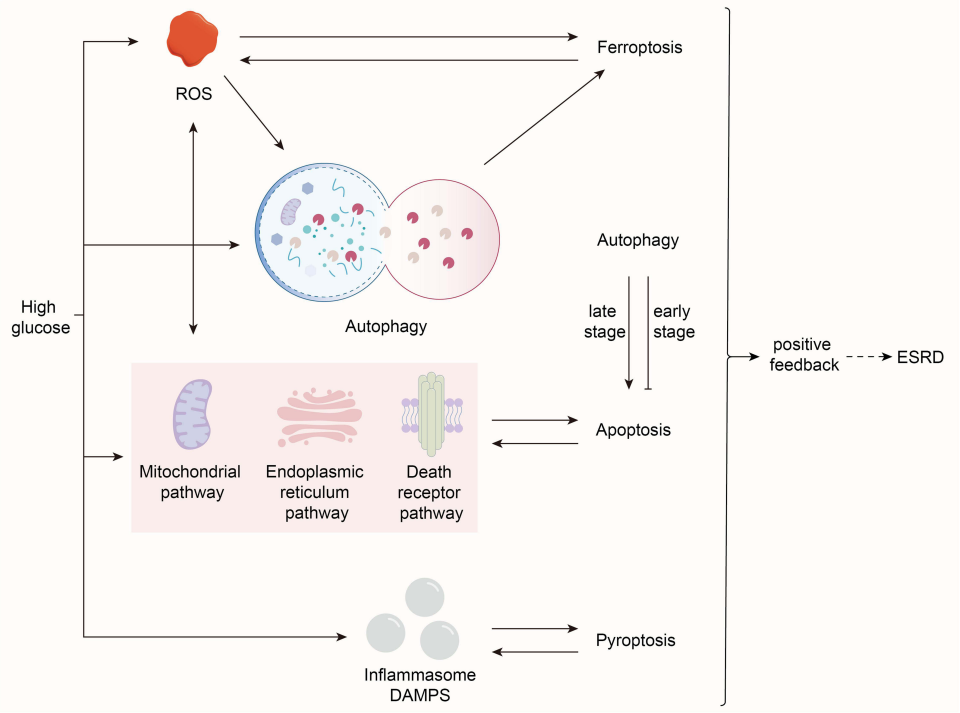

Figure 1 Feedback in Cell Death. High blood glucose, as a triggering factor, triggers a series of reactions through different pathways. Apoptosis is induced through the mitochondrial pathway, endoplasmic reticulum stress pathway, and death receptor pathway, respectively. These pathways activate ROS generation. High blood sugar can also trigger other forms of cell death. Autophagy exhibits dual-phase regulation in DKD progression: serving a protective role during early stages while paradoxically promoting apoptotic processes in advanced disease stages. In addition, there are other types of cell death mechanisms, such as ferroptosis and inflammatory mediator mediated pyroptosis. All these processes are involved in the progression of the disease and form a positive feedback loop, leading to gradual deterioration of kidney function and ultimately potentially causing ESRD.

Abbreviations: ESRD, end-stage renal disease; DAMPs, damage-associated molecular patterns; ROS, reactive oxygen species.

Under the control of inflammatory cytokines, such as interleukins and tumor necrosis factor-alpha (TNF-α), a form of programmed cell death known as pyroptosis occurs.[20] As the disease progresses and cellular damage accumulates, inflammatory factors are continuously secreted, exacerbating the inflammatory milieu as a positive feedback.[21]

Simultaneously, persistent production of reactive oxygen species (ROS) leads to mitochondrial dysfunction, causing the release of cytochrome c and apoptosis-inducing factors into the cytoplasm of kidney cells, promoting mitochondrial-mediated apoptosis. This is accompanied by excessive endoplasmic reticulum (ER) stress and activation of the death receptor pathway mediated by TNF-α, further accelerating the apoptotic program of cells.[22,23]

Mitochondrial damage results in depletion of intracellular glutathione, leading to an accumulation of ROS. Increased expression of the transferrin receptor allows more ferric iron (Fe3+) to enter the cell. Ferric iron is then reduced to ferrous iron (Fe2+) by iron reductases, and through the Fenton reaction, a positive feedback loop is established that amplifies ROS production, disturbing iron homeostasis and triggering ferroptosis, a form of regulated cell death characterized by lipid peroxidation.[24]

In the early stage of DKD, the process of autophagy can help clear excess or damaged organelles and protein aggregates. However, with the positive feedback loop involving proximal tubular injury, mitochondrial dysfunction, and an inflammatory response, autophagy undergo a transition from a protective mechanism to one that promotes cell death, particularly apoptosis.[25,26]

As mentioned above, mechanisms of different programmed cell death (eg, apoptosis, pyroptosis, ferroptosis and autophagy) together form a large positive feedback regulation, continuously exacerbating cell death and worsening the patients' condition. Many DKD patients do not receive effective intervention in the early stage, and with the amplification of positive feedback effects, they may even develop ESRD. Targeting the induction of specific cell death mode or inhibiting unnecessary cell death by modulating key feedback loops could represent promising therapeutic strategies for

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kidney diseases. By understanding and intervening in these complex pathways, it may be possible to develop novel treatments aimed at preserving renal function and preventing the progression of kidney disease.

Feedback in Cell Cycle Disorder (Figure 2)

In the normal adult kidney, most kidney cells are primarily in a quiescent state, maintaining a stable and balanced environment essential for proper renal function.[27] When DKD occurs, hemodynamic changes, high blood glucose levels, inflammatory factors, and other stimuli impact virtually all types of kidney cells. Under mild stimulation, cell cycle regulation may provide negative feedback to aid in the repair of kidney damage. However, a prolonged hyperglycemic condition often leads to cell cycle dysregulation, exacerbating kidney damage through a positive feedback loop involving cellular injury and metabolic disturbances.[28]

In the glomerulus, podocytes, which are critical for maintaining the filtration barrier, are often stimulated by hyperglycemia to re-enter the cell cycle, a process that can promote mitotic catastrophe.[29] Persistent or severe podocyte damage leads to cell detachment, barrier dysfunction, and ultimately proteinuria.[30] Podocyte loss disrupts the glomerular filtration barrier, allowing proteins to pass into the urine, which is a hallmark of early DKD.

Mesangial cells (MCs), another important component of the glomerulus, are also activated and undergo excessive proliferation. They produce extracellular matrix (ECM) components and continuously deposit them, contributing to glomerulosclerosis.[31] This accumulation of ECM components alters the glomerular structure, leading to thickening of the basement membrane and reduced filtration capacity.

The migration, proliferation, and differentiation of glomerular endothelial cells (GECs) are tightly regulated by the vascular endothelial growth factor A (VEGF-A)/vascular endothelial growth factor receptor 2 (VEGFR-2) system. Vascular endothelial growth factor (VEGF) is secreted by podocytes and is initially upregulated in the early stage of DKD, promoting neovascularization.[15] However, as the disease progresses and podocytes are lost, VEGF secretion decreases, leading to thinning of the glomerular capillaries and renal fibrosis.[16] This reduction in VEGF secretion can contribute to the ischemia and hypoxia in the late stage of DKD.

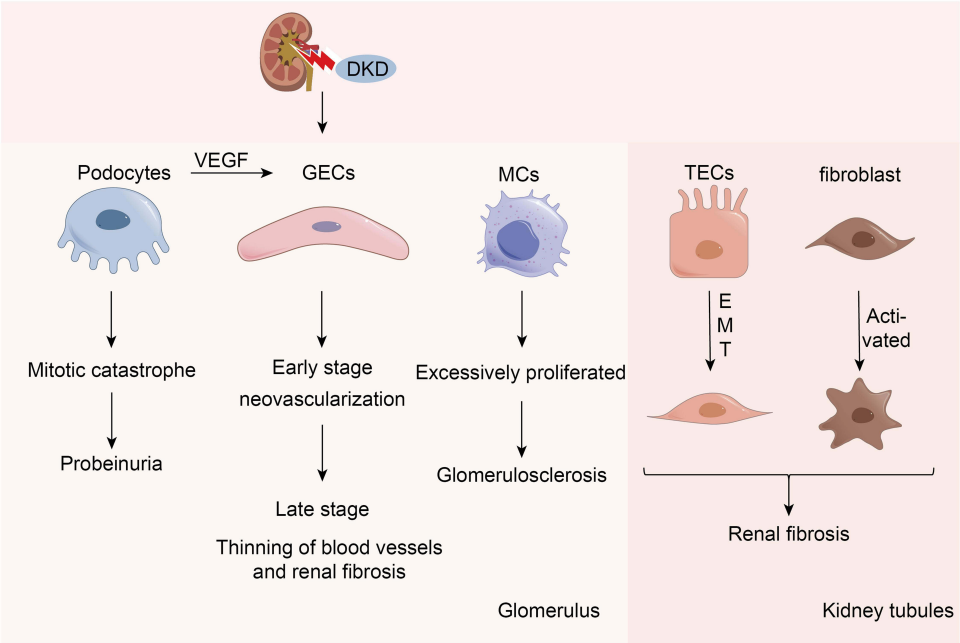

Figure 2 Feedback in cell cycle disorder. In the process of DKD, various major cell types exhibit different pathological characteristics and perform different functions. Podocytes undergo mitotic catastrophe, leading to proteinuria, while paracrine VEGF mediates the differentiation process of GECs. In the early stage, it promotes neovascularization, and in the late stage, with VEGF secretion degradations, leading to thinning of the glomerular capillaries and renal fibrosis. Over proliferation of MCs leads to glomerulosclerosis. TECs undergo EMT and fibroblast activation, manifested as the appearance of myofibroblasts, which progress to renal fibrosis.
Abbreviations: DKD, diabetic kidney disease; MCs, mesangial cells; GECs, glomerular endothelial cells; VEGF, Vascular endothelial growth factor; TECs, tubular epithelial cells; EMT, epithelial-mesenchymal transition.

In the renal tubules, tubular epithelial cells (TECs) may undergo epithelial-mesenchymal transition (EMT), a process where they lose their epithelial characteristics and acquire mesenchymal features. Meanwhile, fibroblasts are activated.[32] This transition contributes to fibroblast activation and the deposition of ECM components. Alongside the release of profibrotic factors, such as transforming growth factor-beta (TGF-β), the development of renal fibrosis is accelerated. The accumulation of ECM components and the transformation of TECs and fibroblasts into myofibroblasts contribute to the progressive decline in renal function and the development of interstitial fibrosis.

Overall, changes in cell cycle regulation, cell behavior, and ECM deposition play a critical role in the pathogenesis of DKD, forming a positive feedback loop that continuously exacerbates cellular morphological and functional abnormalities, which highlights the need for targeted therapies aimed at restoring normal cell cycle dynamics and inhibiting fibrotic processes.

Feedbacks in Molecular Level

Molecular Mechanism of Acute Phase (Figure 3)

The acute phase of DKD mainly focuses on mechanisms related to acute cellular injury, emphasizing inflammation, stress, apoptosis, and other aspects. Feedback regulation in this case plays a crucial role in the onset and progression of the disease. Research has shown that under hyperglycemic conditions, protein kinase C (PKC) is activated,[33,34] which not only directly participates in oxidative stress-induced cell damage, leading to the accumulation of intracellular ROS and advanced glycation end products (AGEs), but also regulates vascular function, increases vascular permeability, and affects the expression of important vasoactive substances.[13]

The polyol pathway, a minor pathway in normal glucose metabolism, becomes overactive during sustained hyperglycemia. Glucose is reduced to sorbitol by aldose reductase (AR), and this sorbitol is further converted to fructose by sorbitol dehydrogenase. During chronic hyperglycemia, the accumulation of sorbitol and fructose leads to osmotic stress within cells and can undergo non-enzymatic glycation reactions with proteins, forming AGEs through a positive feedback mechanism. This process consumes large amounts of antioxidants and increases oxidative stress, further exacerbating the damaging effects of hyperglycemia.[35,36]

The latest evidence suggests that the receptor for advanced glycation end products (RAGE) plays a central role in the occurrence of DKD. In patients with DKD, high blood glucose levels stimulate the formation of AGEs, which are primarily metabolized by the kidneys and tend to deposit in renal tissue. Concurrently, the expression of RAGE is upregulated,[13,14] and the downstream signaling pathways mediated by the AGE/RAGE interaction are activated. These include the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB),[37] phosphoinositide 3-kinase/protein kinase B (PI3K/Akt),[38] mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK),[39] and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways.[36,40,41]

These signaling cascades activate a variety of pro-inflammatory factors (inducible nitric oxide synthase,[41] TNF-α,[42] interleukin-6 [IL-6],[43] NOD-like receptor family pyrin domain containing 3 inflammasome [NLRP3][44,45]), adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1]),[46,47] and profibrotic mediators (angiotensin II [Ang II],[48] connective tissue growth factor [CTGF],[49] VEGF,[50] TGF-β,[51] lysyl oxidase [LOX])[52] Additionally, the expression of cell cycle regulatory proteins (p53,[53] p21[54,55]) is altered, contributing to cellular senescence and dysfunction.

At the same time, these pathways interact with each other, inducing oxidative stress, inflammatory reactions, cellular senescence, and further increasing the formation of AGEs.[56,57] Throughout this process, there is also a protective factor, nuclear factor erythroid 2-related factor 2 (Nrf2), which has negative feedback mechanism and regulates the disease progression of DKD by activating antioxidant response elements (ARE), inhibiting inflammatory responses, and regulating fibrosis processes.[58,59]

As the disease progresses, symptoms such as thickening of the glomerular basement membrane, accumulation of ECM, glomerulosclerosis, vascular damage, and interstitial fibrosis worsen. The feedback loop composed of the AGE/RAGE axis and its downstream signaling pathways continues to exacerbate the condition of DKD, forming a vicious cycle that may ultimately lead to ESRD.[60,61]

This complex interplay of signaling pathways and feedback mechanisms underscores the importance of targeting these processes in the development of novel therapeutic strategies for DKD.

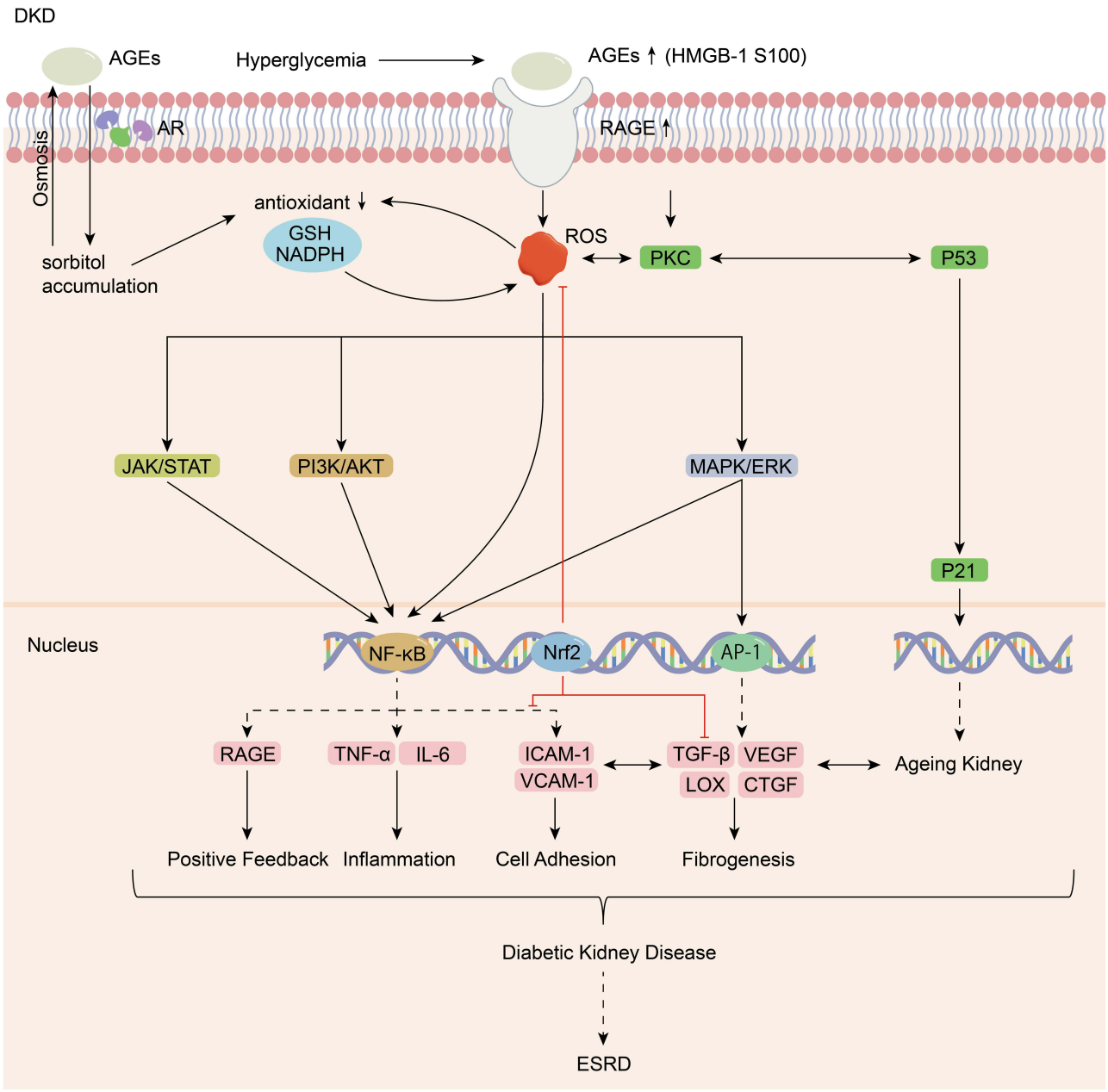

Figure 3 Molecular mechanism of acute phase. The binding of RAGE to various ligands (including AGEs, HMGB-1, S100, among which AGEs can also directly lead to the accumulation of sorbitol and fructose through the polyol pathway, consuming intracellular antioxidants) activates numerous downstream molecules. The most crucial one among them is ROS. Next, various signaling pathways are utilized, such as NF-κB, PI3K/Akt, MAPK/ERK, JAK/STAT, Nrf2, and p53/p52. By regulating with mainly positive feedbacks, the disease process is affected and downstream pro inflammatory factors, adhesion molecules, and profibrotic mediators are released, which participate in promoting fibrosis and inflammatory response, cell adhesion, angiogenesis, and thrombogenesis. These feedbacks may lead to worsening of the condition or even progression to ESRD.

Abbreviations: AGEs, advanced glycation end products; AR, aldose reductase; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; GSH, Glutathione; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; MAPK, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinases; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; Ang II, angiotensin II; TGF-β, transforming growth factor-beta; VEGF, Vascular endothelial growth factor; CTGF, connective tissue growth factor; LOX, lysyl oxidase.

Molecular Mechanism of Chronic Phase (Figure 4)

As previously discussed, factors such as hyperglycemia and hypertension damage the intrinsic cells of the kidney, including TECs, podocytes, and MCs. The acute phase features are mainly manifested in inflammation, stress, apoptosis and other aspects. The molecular mechanisms that lead to sustained disease progression also include chronic phase,

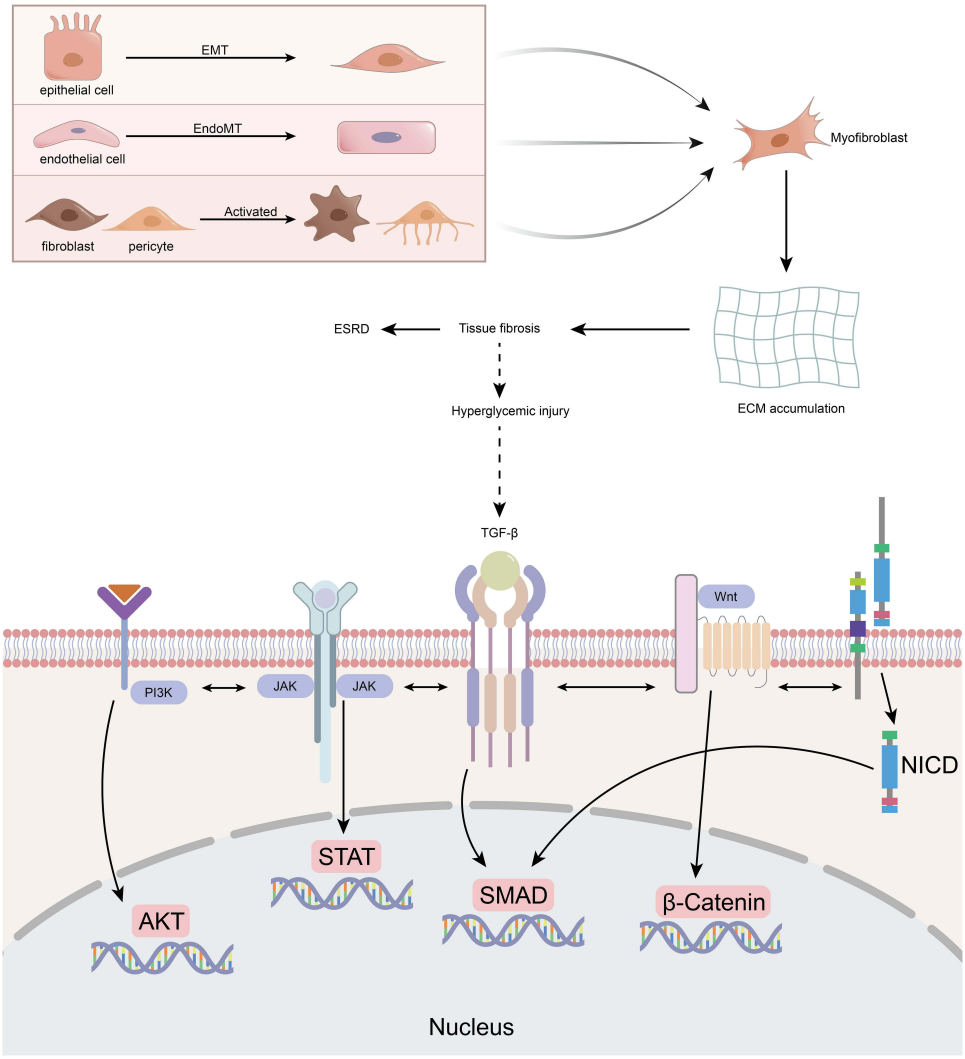

Figure 4 Molecular mechanism of chronic phase. During the chronic phase, it mainly involves fibrosis of the kidneys. Activation of multiple pathways such as TGF-β, MAPK, Wnt/β-catenin, PI3K/Akt, JAK/STAT, and Notch pathways through TECs, podocytes, and MCs initiates the process of chronic fibrosis. During this process, the cell phenotype gradually undergoes a transformation. Renal tubular epithelial cells undergo EMT, endothelial cells undergo EndoMT, and fibroblasts and pericytes are activated. These cells are transformed into myofibroblasts, and ECM is deposited in large quantities to promote the fibrosis process, which aggravates the damage of diabetes nephropathy.

Abbreviations: TGF-β, transforming growth factor-beta; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; JAK, Janus kinase; STAT, signal transducer and activator of transcription; IL-6, interleukin-6; EMT, epithelial-mesenchymal transition; EndoMT, endothelial-mesenchymal transition; NICD, Notch intracellular domain; ECM, extracellular matrix; ESRD, end-stage renal disease.

mainly manifested as abnormal tissue repair, such as fibrosis, etc. This damage leads to the release of profibrotic factors, cytokines, and growth factors thereby initiating the process of chronic fibrosis. The process involves the activation and interaction of multiple signaling pathways, primarily including TGF-β,[51,62] MAPK,[39] Wnt/β-catenin,[63,64] PI3K/Akt,[38] JAK/STAT,[22] and Notch pathways.[65] While the pro-fibrotic role of TGF-β considered as a key mediator in renal fibrosis and induces renal scarring. Studies from gene knockout mice demonstrate that TGF-β1 acts by stimulating its downstream Smads to diversely regulate kidney injury. In the context of renal fibrosis and inflammation, Smad3 is pathogenic,[66] while Smad2 and Smad7 are protective.[67,68]

Gradually, as kidney cell damage intensifies, cell phenotype transformations occur. Renal tubular epithelial cells undergo EMT,[32,69] a process where they lose their epithelial characteristics and acquire mesenchymal features, such as increased migratory ability and the ability to secrete ECM components. Similarly, endothelial cells undergo endothelial-mesenchymal transition (EndoMT),[53] which is a special EMT subset that occurs in endothelial cells and is like EMT,

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further contributing to the accumulation of ECM components. Fibroblasts and pericytes are also activated, participating in the fibrotic process.[32,69]

These pathological processes accelerate the irreversible formation of myofibroblasts, specialized cells that secrete large amounts of ECM components, including collagen and fibronectin. As ECM synthesis increases and degradation decreases, excessive ECM accumulates in the renal interstitium, leading to tissue hardening and structural remodeling. Accumulation of ECM components alters the normal architecture of the kidney, impairing its function and contributing to the development of fibrosis.

Intriguingly, certain self-limiting mechanisms may transiently mitigate damage. For instance, stress-induced tubular cell senescence may paradoxically suppress TGF-β1-mediated fibrosis in early-stage DKD through cell cycle arrest, though this protective adaptation is ultimately overwhelmed by persistent metabolic insults. Such similar negative feedback mechanisms may serve as potential protective factors for renal function.

On the other hand, the loss of functional nephrons leads to a positive feedback loop of symptoms such as cellular autophagy, inflammatory response, and proteinuria, further exacerbating kidney damage.[70] Proteinuria indicates significant damage to the glomerular filtration barrier and is a hallmark of DKD progression. Eventually, as kidney function gradually declines, the disease enters the irreversible stage of renal fibrosis, leading to ESRD.

Treatment

As mentioned above, there are many positive feedback mechanisms whereas negative feedback modes are limited in DKD, and there are intervention measures correspondingly based on the pathogenic effects of these regulatory mechanisms. It can be divided into treatments targeting AGEs/RAGE axis and treatments targeting fibrosis.

Targeting AGEs/RAGE Axis

In the context of DKD and aging kidneys, the aim is to block or alleviate oxidative stress, inflammatory response,[71] and tissue damage caused by the interaction between AGEs and RAGE.

The Most Important Goal Is to Inhibit the Formation and Accumulation of AGEs

Adopting a low-AGEs diet by reducing intake of high-sugar and high-temperature processed foods can effectively decrease exogenous AGEs intake. This is because ingested AGEs can accumulate in the gastrointestinal tract, thereby altering the gut microbiota, regulating immune signaling, and reducing antioxidant enzyme activity to induce inflammation.[72,73] Natural anti-glycation agents derived from botanical sources, including Eucommia ulmoides Oliv[74] and diphlorethohydroxycarmalol (DPHC),[75] have shown efficacy in inhibiting AGEs formation. They inhibit the formation of AGEs and RAGE expression, reducing the damage to cells. Feeding mice with rapid peptide Maillard reaction products can optimize the abundance and diversity of the gut microbiota, inhibit pathogenic bacteria while increasing beneficial bacteria, reduce oxidative stress, and delay organ aging.[76]

In the Process of RAGE Signal Transduction, Timely Artificial Regulation Should Be Carried Out

Developing specific RAGE antagonists or neutralizing antibodies that directly block AGEs-RAGE binding represents a promising strategy to mitigate downstream inflammatory and oxidative stress responses. Alternatively, small molecule inhibitors or other drugs can be used to reduce the transmission of downstream harmful signals. Drugs such as FPS-ZM1 are designed to selectively inhibit RAGE, which can protect the glomerular filtration barrier and improve the renal function of diabetic rats, and when combined with angiotensin receptor blockers (such as valsartan), they can more effectively reduce the activation of RAGE and its downstream NF-κB.[77,78] Hepatic β-Hydroxy-β–methyl-glutaryl-Co-A (HMG-CoA) reductase inhibitors and ezetimibe may exert their effects via targeting intracellular ROS, NRP-1 function, and RAGE related genes (ie NF-κB, TGF-β, and MMP-2) to treat oxidative stress and tissue damage induced by AGEs in DKD.[79] Fluorofenidone and osthole inhibit the PKC/NOX pathway[80] and JAK2-STAT1/STAT3 signaling transduction,[81] respectively.

Activate Protective Signaling Pathways

By using compounds that can activate Nrf2/ARE, such as certain plant extracts and drugs, the antioxidant capacity of cells can be enhanced, oxidative stress caused by AGEs can be counteracted and their accumulation can be reduced, thus delaying the progression of DKD.[82,83]

Targeting Fibrosis

Renal fibrosis is a chronic pathological process involving multiple factors and pathways, which ultimately leads to tissue restructuring and functional decline through the interaction and feedback regulation of multiple signaling pathways.[84,85] Accurately regulating these pathways and their interactions is beneficial for reversing the fibrosis process:

Use Renal Protective Drugs

Angiotensin converting enzyme inhibitors or angiotensin receptor blockers partially interfere with Ang II mediated TGF-β expression, delay hyperglycemia-induced renal cell fibrosis, reduce proteinuria, and delay renal function decline.[86] Metformin not only has the effect of lowering blood glucose levels, but also inhibits mammalian target of rapamycin, PI3K/AKT, and TGF-β pathways by activating AMP-activated kinase, regulating renal cell autophagy, restoring cell repair mechanisms, and reducing ER stress.[87] Metformin also has great potential as a renal protective drug by reducing the expression of HIF-1α and improving renal cell hypoxia by lowering ATP levels and renal oxygen consumption.[88]

Use Signal Pathway Inhibitors

Develop specific inhibitors targeting signaling pathways such as TGF-β, MAPK, Wnt/β-catenin, PI3K/Akt, JAK/STAT, and Notch that promote fibrosis. Pirfenidone antagonizes the TGF-β and MAPK pathways to alleviate EMT and renal fibrosis.[89] Triptolide, an inhibitor of the PI3K/Akt signaling pathway, can reduce the production of CTGF, fibronectin, and collagen through the interaction between miR-188-5p and phosphatase and tensin homolog, and slow down renal EMT.[90] Oral administration of selective inhibitor Baricitinib can mitigate albuminuria, inhibit JAK1/JAK2, and treat DKD.[91] TGF-β antibodies and Wnt/β-catenin signaling pathway inhibitors are used to reduce the production of fibrosis related proteins, decrease ECM deposition, and alleviate renal interstitial fibrosis.[64,92–94]

Prospect

Understanding these feedback mechanisms is crucial for developing targeted therapies and improving the management of DKD. For example, interventions aimed at suppressing hypertension and proteinuria circulation can significantly slow down the progression of kidney injury. At the cellular level, targeting specific pathways involved in cell death, such as pyroptosis and ferroptosis, or alleviating autophagic dysfunction, and at the molecular level, inhibiting or activating specific feedback pathways may provide new therapeutic opportunities.

Looking ahead, it is necessary to continue research to elucidate the precise mechanisms behind these feedback loops, understand whether drugs targeting different feedback pathways interact, and identify new biomarkers that can predict disease progression. As exploration deepens, it is believed that new targets and therapeutic drugs will continue to emerge. With the advancement of genomics and proteomics, the development of personalized medical methods is expected to tailor treatment methods according to the needs of individual patients.

Conclusion

In conclusion, DKD progression is fundamentally driven by self-reinforcing feedback networks, which is a paradigm shift from traditional single-pathway models. This review provides three key advances over previous studies: (1) We establish the first hierarchical framework integrating systemic, cellular and molecular feedback loops in DKD pathogenesis; (2) We reveal how cross-tier amplification between acute inflammatory drivers (eg, AGE/RAGE axis) and chronic fibrotic processes creates irreversible disease momentum; (3) We propose time-sensitive therapeutic strategies targeting these networked feedback systems. For instance, early intervention combining RAGE antagonists with Nrf2 activators could break the acute-phase oxidative stress-inflammation cycle, while precision modulation of fibrotic pathways using TGF-β/JAK-STAT dual inhibitors may attenuate established fibrosis.

Our analysis identifies previously unrecognized therapeutic nodes, which enable two transformative clinical approaches: First, specific interventions for different stages - targeting AGEs/RAGE axis to suppressing the acute phase feedbacks before fibrosis establishment, then switching to inhibitors targeting signaling pathways such as TGF-β and JAK/STAT that promote fibrosis. Second, precision medicine map dominant feedback loops in individual patients, enabling tailored combinations like RAGE antagonists for predominant glycation stress or JAK inhibitors for inflammatory phenotypes.

Future research should focus on three frontiers: (1) Developing feedback-aware therapeutic indices that quantify network disruption while preserving physiological repair mechanisms; (2) Creating computational models simulating feedback loop interactions to predict treatment outcomes; (3) Validating novel combination therapies through clinical trials stratified by feedback pathway activation patterns. By redefining DKD as a network disorder of maladaptive feedbacks, this framework opens new avenues for intercepting disease progression through temporally and spatially coordinated interventions.

Abbreviations

DKD, diabetic kidney disease; ESRD, end-stage renal disease; DAMPs, damage-associated molecular patterns; TNF-α, tumor necrosis factor-alpha; ROS, reactive oxygen species; ER, endoplasmic reticulum; MCs, mesangial cells; ECM, extracellular matrix; GECs, glomerular endothelial cells; VEGF, Vascular endothelial growth factor; TECs, tubular epithelial cells; EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor-beta; PKC, protein kinase C; AGEs, advanced glycation end products; AR, aldose reductase; RAGE, receptor for advanced glycation end products; GSH, Glutathione; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; MAPK, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinases; JAK, Janus kinase; STAT, signal transducer and activator of transcription; IL-6, interleukin-6; NLRP3, NOD-like receptor family pyrin domain containing 3 inflammasome; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; Ang II, angiotensin II; CTGF, connective tissue growth factor; LOX, lysyl oxidase; Nrf2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant response elements; EndoMT, endothelial-mesenchymal transition; NICD, Notch intracellular domain; DPHC, diphlorethohydroxycarmalol; HMG-CoA, Hepatic β-Hydroxy-β–methyl-glutaryl-Co-A.

Consent for Publication

All authors agreed to publish the review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, visualization, project administration, or in all these areas. All authors took part in drafting, revising or critically reviewing the article. All authors gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted. All authors agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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