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REVIEW

# SIRT2 in Diabetic Kidney Disease: Multifaceted Regulatory Roles and Therapeutic Challenges

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**Abstract:** Diabetic kidney disease (DKD) is a significant microvascular complication of diabetes, characterized by a complex interplay between metabolic dysregulation and chronic inflammation. This review methodically elucidates the pivotal role of the deacetylase sirtuin 2 (SIRT2) within this pathological network. SIRT2, a nicotinamide adenine dinucleotide dependent metabolic sensor, deacetylates multiple substrates to regulate renal intrinsic cell functions (eg, podocytes and tubular epithelial cells). It suppresses nuclear factor kappaB and nod-like receptor protein 3 inflammasome pathways, modulates macrophage polarization, and influences "metabolic memory". However, these critical functions exhibit cell- and context-dependent specificity. For instance, in podocytes, SIRT2 maintains cytoskeletal stability by deacetylating α-tubulin. Conversely, in certain models of renal tubular injury, SIRT2 may exacerbate damage, underscoring its highly context-dependent function. Consequently, the targeting of SIRT2 (including the development of selective modulators and the exploration of combination therapies with existing treatments such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists) is considered a promising therapeutic strategy. Notwithstanding, SIRT2-targeted therapies face a multitude of challenges, including functional duality, tissue-specific delivery, and clinical translation. This necessitates meticulous evaluation for clinical application. Future efforts should leverage cutting-edge technologies to deepen mechanistic understanding and advance biomarker-guided precision medicine, thereby providing a theoretical foundation for novel DKD therapies.

**Keywords:** sirtuin 2, diabetic kidney disease, inflammation, metabolic memory, precision medicine

## Introduction

Diabetic kidney disease (DKD) is a severe and prevalent microvascular complication of diabetes that has emerged as the leading cause of end-stage renal disease (ESRD) on a global scale.[1,2] This condition imposes a significant public health and economic burden.[1,2] Despite recent advancements in glycemic and blood pressure management, alongside the application of renin-angiotensin-aldosterone system (RAAS) inhibitors, a significant proportion of patients continue to experience progressive renal disease.[3–5] This underscores the incomplete understanding of DKD's complex pathogenesis and highlights the urgent need to identify novel therapeutic targets beyond conventional therapies.

The prevailing pathophysiological network of DKD is predicated on metabolic dysregulation initiated by persistent hyperglycemia. This includes the accumulation of advanced glycation end products (AGEs), abnormal activation of the polyol and hexosamine biosynthetic pathways, excessive activation of protein kinase C (PKC), and excessive production of mitochondrial-derived reactive oxygen species (ROS).[1,6,7] The combination of these factors engenders a deleterious metabolic milieu that directly compromises intrinsic renal cells, particularly podocytes, mesangial cells, and tubular epithelial cells.[7,8] However, mounting evidence establishes inflammation as another core pathway running throughout DKD development—not merely a "downstream consequence" of metabolic injury, but an active "driver" of declining glomerular filtration rate and renal fibrosis.[7,9–12] The infiltration of immune cells (eg, macrophages, T cells) and activated intrinsic cells within the kidney results in the release of substantial quantities of cytokines, chemokines, and pro-fibrotic factors. This process establishes a self-reinforcing inflammatory microenvironment that ultimately leads to irreversible damage to the nephron.[13–15]

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Recent research has shifted focus from the previous practice of separately describing "metabolic abnormalities" and "inflammatory responses" to exploring the profound interactive mechanisms between them—the "metabolic-inflammatory axis".[7,16,17] This concept underscores the notion that hyperglycemia and its associated metabolic distress can directly "ignite" and persistently "fuel" the inflammatory process through multiple pathways. These include reprogramming immune cell function, modifying inflammation-related signaling proteins, inducing organelle stress (eg, mitochondria, endoplasmic reticulum), and releasing damage-associated molecular patterns.[7,12,18] It is imperative to note that this aberrant signaling pattern, initiated by early metabolic disruption, can establish what is referred to as "metabolic memory" through mechanisms such as epigenetic modifications. This memory persists even after subsequent glycemic control, continuously driving inflammation and tissue damage. This offers a novel perspective on the sustained progression of DKD.[6,19,20]

In light of these observations, identifying key hub molecules that can sense cellular metabolic states and regulate inflammatory pathways is a promising approach to overcoming current therapeutic limitations. Sirtuin 2 (SIRT2) has emerged as a promising candidate target at this nexus. SIRT2, a cytoplasm-localized nicotinamide adenine dinucleotide ($NAD^+$) -dependent deacetylase within the Sirtuin family, functions as a core sensor of cellular energy status.[21–23] Its activity is directly regulated by the $NAD^+$/NADH ratio, thereby linking cellular nutritional and energy states to a wide range of physiological functions.[23,24] A comprehensive review of the extant literature suggests that SIRT2 plays an indispensable role in regulating a variety of physiological processes, including the cell cycle, autophagy, oxidative stress, glucose and lipid metabolism, and innate immune and inflammatory signaling pathways. This function is thought to be achieved by deacetylating a series of key substrates.[25,26] For instance, it directly deacetylates and inhibits the transcriptional activity of the nuclear factor kappaB (NF-κB) p65 subunit, or suppresses interleukin-1beta (IL-1β) maturation by affecting nod-like receptor protein 3 (NLRP3) inflammasome assembly, thereby acting as a multi-level "brake" on inflammation.[27–30] SIRT2 has been shown to directly deacetylate histone H3K9 and H4K16, as well as transcription factors. This process contributes to the remodeling of chromatin states and gene expression programs, suggesting a critical role for SIRT2 in cellular processes such as transcription and gene expression.[31–33] This provides a direct mechanistic link for its regulatory role in metabolic memory.

In addition, AMP-activated protein kinase (AMPK), a pivotal sensor of cellular energy status, has been shown to play a substantial role in DKD.[34,35] AMPK has been shown to regulate glucose and lipid metabolism, autophagy, and mitochondrial function. Moreover, studies have demonstrated that AMPK activation can modulate deacetylase activity by influencing $NAD^+$ levels or directly phosphorylating SIRT2.[36,37] Conversely, SIRT2 has been shown to promote AMPK activation.[38] Consequently, a bidirectional regulatory relationship has been identified between SIRT2 and AMPK, which collectively form a core signaling network that coordinates metabolic stress and inflammatory responses.[39] This finding provides novel cross-target opportunities for the treatment of DKD. In recent years, novel hypoglycemic agents, such as sodium-glucose cotransporter 2 (SGLT2) Inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have demonstrated renal protective effects beyond glucose control in DKD.[5,40] Recent research suggests that these drugs may partially exert their effects by modulating SIRT2-related pathways. For instance, SGLT2 inhibitors activate AMPK by elevating the AMP/ATP ratio, thereby increasing $NAD^+$ levels and enhancing SIRT2 activity.[41] It has been reported that GLP-1 receptor agonists can inhibit NLRP3 inflammasomes.[42] This process is intricately linked to the deacetylation regulatory mechanism of SIRT2. These findings provide new experimental evidence supporting SIRT2 as a target for combination therapy.

Consequently, a fundamental scientific inquiry emerges: The objective of this review is to elucidate the precise role of SIRT2 within the complex pathological network of DKD and to clarify whether this pathway functions as an adaptive protective factor against metabolic and inflammatory stress or whether its dysfunction per se contributes to disease development. A comprehensive understanding of SIRT2's actions in distinct renal cell types, the dynamics of its activity, and its integration of upstream metabolic disturbance signals while modulating downstream inflammatory and fibrotic effects is imperative for elucidating novel mechanisms of DKD.

In light of these findings, the present review aims to organize and evaluate the extant research on SIRT2's role in diabetic kidney disease. The subsequent discussion will elucidate the fundamental biological characteristics of SIRT2, followed by an in-depth analysis of its specific molecular mechanisms that regulate renal intrinsic cell function, immune-inflammatory responses, metabolic memory, and fibrotic processes within the context of DKD. Finally, we will explore the potential of

targeting SIRT2 as a novel therapeutic strategy, the current challenges encountered, and future research directions. We aim to provide theoretical foundations and innovative insights to develop precise renal-protective therapies.

# Structure, Expression, and Biological Functions of SIRT2

## Molecular Structural Basis of SIRT2

The *SIRT2* gene is located on human chromosome 19 (19q13.2) and encodes a 389-amino acid protein.[43] The core of the SIRT2 protein is its highly conserved catalytic domain, which adopts a classic "Rossmann fold" conformation. This domain is the primary region for binding the cofactor $NAD^+$ and executing deacetylase activity.[44] This structural element is instrumental in delineating the fundamental properties of SIRT2 as an energy sensor and a metabolic effector. The activity of this enzyme is directly dependent on intracellular $NAD^+$ levels; that is, its function is closely linked to cellular energy metabolism.[45]

Beyond the core catalytic domain, the SIRT2 molecule incorporates N- and C-terminal regulatory domains at both ends.[23] Despite their high degree of structural variability, these regions are crucial for SIRT2's subcellular localization, substrate-specific recognition, and interactions with other proteins.[23] For instance, these domains have been shown to facilitate selective binding to diverse substrate categories, including tubulin and histones.[23,26] Furthermore, SIRT2 exhibits multiple isoforms generated by alternative splicing, with SIRT2.1 (full-length isoform) and SIRT2.2 (N-terminal truncated isoform) being the most extensively studied.[46] The potential for variation among these isoforms in terms of tissue distribution, subcellular localization (predominantly cytoplasmic but capable of shuttling between the nucleus and cytoplasm), and catalytic activity contributes to the complexity of their functional regulation.[26]

## Expression and Regulation of SIRT2

The expression and activity of SIRT2 are subject to a multi-level, dynamic, and precise regulatory process, thereby enabling flexible responses to changes in both intracellular and extracellular environments.[25,26] Specifically, at the transcriptional and translational levels, multiple transcription factors can modulate *SIRT2* gene expression in response to growth factors, stress signals, or metabolic alterations. For instance, under certain metabolic stress conditions, SIRT2 expression may be upregulated as an adaptive response.[22,25,47] At the post-translational modification level, SIRT2's own function is regulated by modifications such as phosphorylation and SUMOylation. These modifications influence its enzymatic activity, stability, and subcellular localization, forming complex feedback loops.[23,48,49] At the metabolite level, the most critical regulation stems from the availability of its cofactor $NAD^+$. The dynamic equilibrium between the $NAD^+$ biosynthesis and consumption pathways directly determines SIRT2's activity level.[50] In diabetes, factors such as nutritional excess and oxidative stress have been shown to disrupt $NAD^+$ metabolism, thereby significantly impacting SIRT2 function.[51,52] Furthermore, through protein interactions, SIRT2 can bind to various partner proteins, thereby being recruited to specific substrates or organelles, thereby achieving spatiotemporal specificity in its function.[22,53]

## Core Biological Functions of SIRT2

SIRT2 has been shown to deacetylate numerous substrate proteins, thereby regulating a range of core cellular processes essential for maintaining tissue homeostasis and responding to stress.

Metabolic Regulation and Energy Sensing: SIRT2, an $NAD^+$–dependent enzyme, functions as a central sensor and regulator of cellular metabolic states. It modulates hepatic glucose metabolism by deacetylating and activating key gluconeogenic enzymes, including phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase).[54,55] Concurrently, it exerts regulatory influence on fatty acid oxidation by deacetylating specific targets, such as acetyl-CoA synthetase.[56] Within the context of insulin signaling pathways, SIRT2 has been observed to exert its effects by modulating kinase activity, including that of Akt.[57] Consequently, SIRT2 occupies a pivotal position in integrating glucose, lipid, and energy metabolic networks.

Cytoskeletal Dynamics and Cell Cycle: SIRT2 has been identified as the primary deacetylase for tubulin.[58,59] SIRT2 maintains α-tubulin in a hypoacetylated state, thereby regulating microtubule stability, mitotic progression, and cell morphology.[60,61] This renders it crucial for cell-cycle checkpoint regulation and for maintaining epithelial cell polarity.

Oxidative Stress Response: SIRT2 has been shown to promote the expression of antioxidant enzymes, such as superoxide dismutase and catalase, by deacetylating and activating key transcription factors of the antioxidant defense system, including Forkhead Box O1 (FOXO1). This process helps clear excess ROS and mitigate oxidative damage.[62–64]

Inflammation and Immune Signaling: SIRT2 has been shown to be a key regulator of innate immunity and inflammatory responses. It directly modulates core inflammatory signaling pathways, including NF-κB and NLRP3, through deacetylation. Additionally, it influences the functional phenotypes of immune cells, such as macrophages. Consequently, it plays a central role in regulating tissue inflammatory processes.[65–68]

In summary, leveraging its unique molecular structure, SIRT2 functions as a highly regulated metabolic sensor and signal modulator, performing extensive and vital physiological roles within the cytoplasm. Through deacetylation, it meticulously calibrates a multitude of fundamental biological processes, ranging from metabolism and cytoskeletal organization to inflammatory responses, thereby establishing a complex signaling network. In the context of DKD, metabolic dysregulation, such as hyperglycemia, has been demonstrated to disrupt SIRT2's normal function and regulatory network by affecting factors like $NAD^+$ levels. This disruption impairs its homeostatic function, thereby contributing to disease progression (Figure 1).

## Molecular Mechanisms of SIRT2 in DKD

In healthy kidneys, SIRT2 exhibits extensive yet non-uniform expression patterns. Immunohistochemical and molecular biological studies indicate its presence in podocytes, mesangial cells, tubular epithelial cells (particularly proximal tubules), and some interstitial cells. This distribution suggests that SIRT2 may play a regulatory role in the homeostasis of multiple renal cell types.[69] The function of SIRT2 in DKD is not as straightforward as either a passive protector or an active aggressor. Instead, it functions as a dynamic integrator of metabolic and inflammatory signaling networks, exerting multifaceted and sometimes seemingly contradictory effects across different cell types and pathological stages (Figure 2).[70]

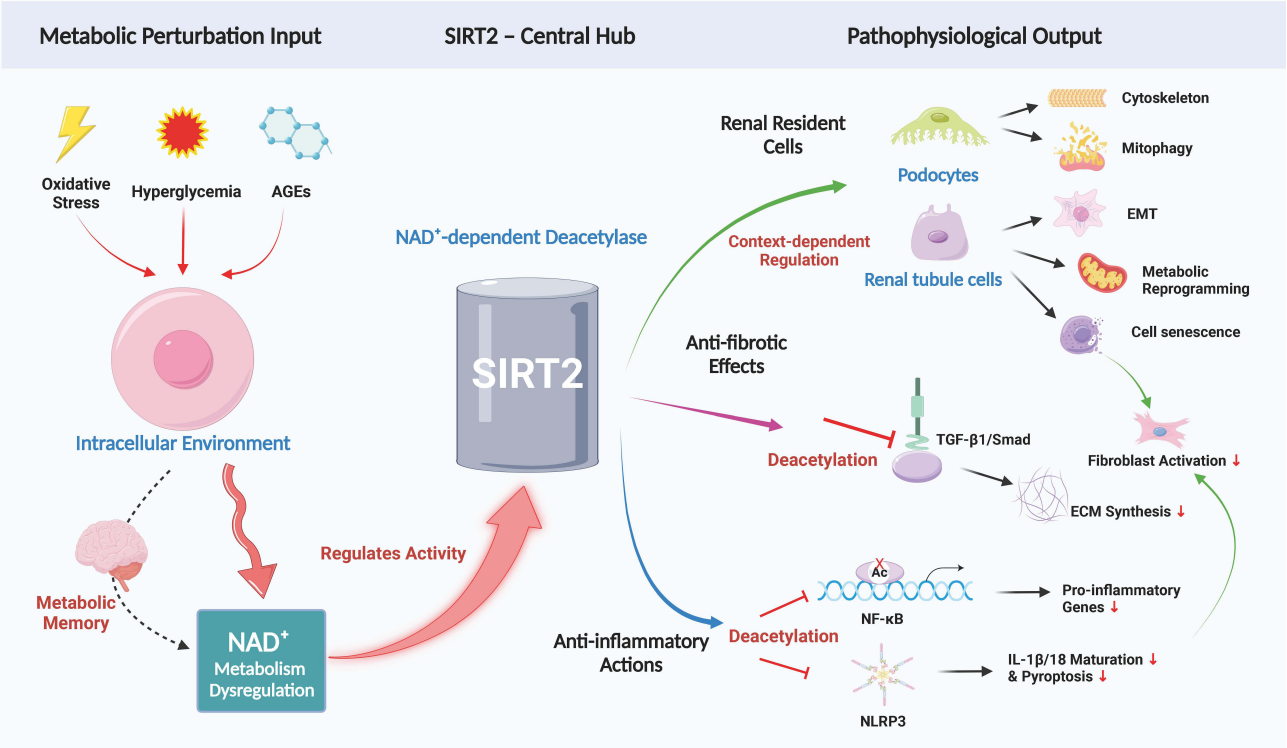


**Figure 1** The core integrating role of SIRT2 in the "metabolism-inflammation" axis of DKD. The figure illustrates how SIRT2 functions as a central integrator, orchestrating signals from upstream metabolic disorders to modulate downstream inflammatory and fibrotic processes.

**Abbreviations**: SIRT2, Sirtuin 2; DKD, Diabetic Kidney Disease; AGEs, Advanced Glycation End-products; ECM, Extracellular Matrix; IL-1β, Interleukin-1 beta; IL-18, Interleukin-18; $NAD^+$, Nicotinamide Adenine Dinucleotide; NLRP3, Nod-like receptor protein 3.


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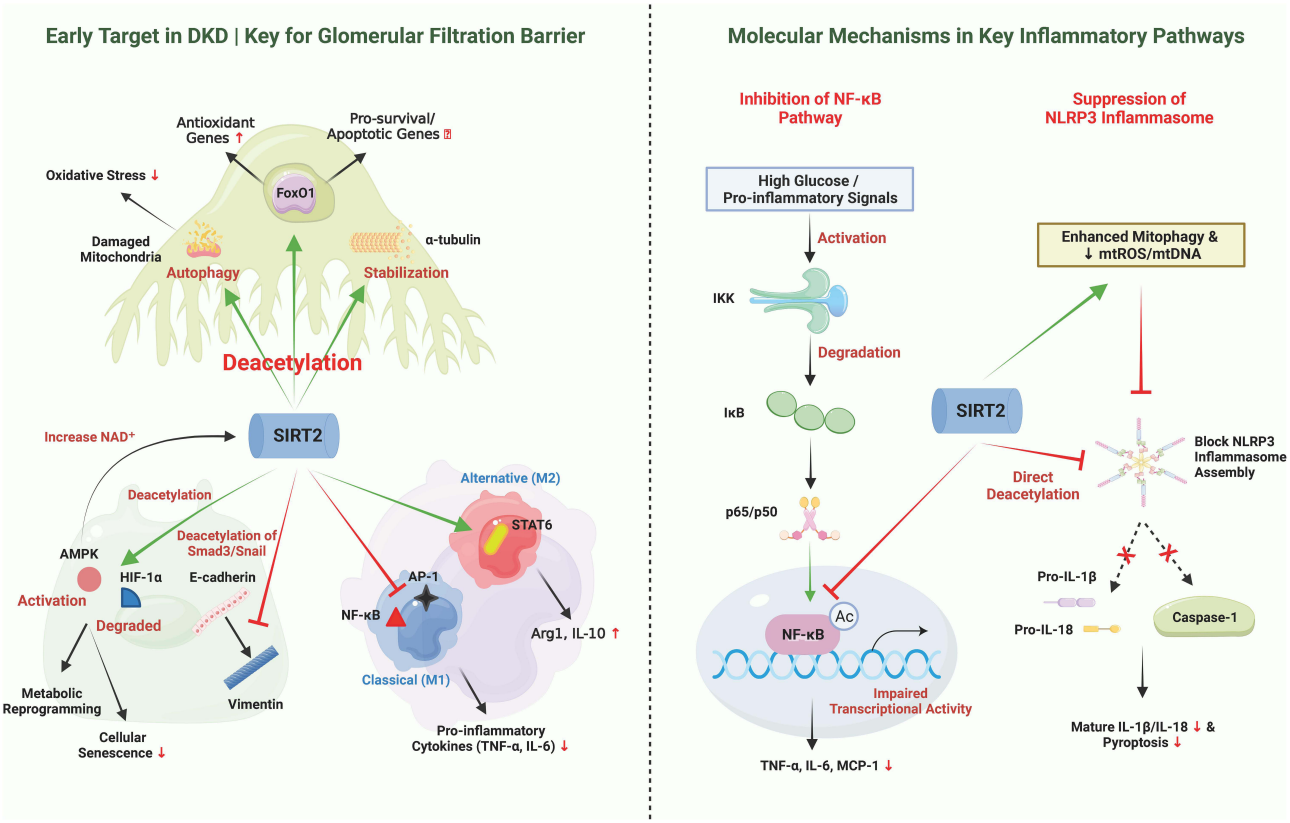


**Figure 2** Detailed cellular and molecular mechanisms of SIRT2 in DKD. The figure delineates the precise mechanisms of action and downstream effects of SIRT2 in primary target cells and major inflammatory pathways.

**Abbreviations**: SIRT2, Sirtuin 2; DKD, Diabetic Kidney Disease; AMPK, AMP-activated protein kinase; $NAD^+$, Nicotinamide Adenine Dinucleotide; AP-1, Activator protein 1; ATG5/7, Autophagy related 5/7; EMT, Epithelial-Mesenchymal Transition; FoxO1, Forkhead box protein O1; HIF-1α, Hypoxia-inducible factor 1-alpha; IκB, Inhibitor of nuclear factor kappa B; IKK, IκB kinase; IL-6, Interleukin-6; IL-10, Interleukin-10; MCP-1, Monocyte Chemoattractant Protein-1; NF-κB, Nuclear factor kappa B; STAT6, Signal transducer and activator of transcription 6; NLRP3, Nod-like receptor protein 3; TGF-β, Transforming growth factor beta; TNF-α, Tumor necrosis factor alpha.

## SIRT2 in Injury and Defense of Renal Intrinsic Cells

The dysfunction of renal intrinsic cells constitutes the initiation and core component of DKD, with SIRT2 serving as a precise regulator in this process.

Podocytes: The key cells that maintain the integrity of the glomerular filtration barrier are a primary target for early injury in DKD. A multitude of studies have demonstrated that SIRT2 plays a pivotal role in preserving podocyte homeostasis by regulating multiple signaling pathways. First, preserving cytoskeletal and barrier function is imperative. SIRT2 deacetylates α-tubulin, thereby maintaining the stability and dynamics of the intracellular cytoskeleton within foot processes. In hyperglycemic conditions, SIRT2 dysfunction has been shown to result in excessive microtubule acetylation, leading to disruption of cellular structure, augmentation of abnormal motility, and compromise of filtration barrier integrity.[59,60] Secondly, the regulation of mitochondrial autophagy and energy metabolism is imperative. Podocytes exhibit a high degree of dependence on mitochondrial energy supply. In this context, SIRT2 deacetylates and activates key autophagy proteins, thereby promoting clearance of damaged mitochondria and mitigating high-glucose-induced oxidative stress.[71,72] Concurrently, it modulates mitochondrial biogenesis and fatty acid oxidation by regulating PGC-1α activity, thereby maintaining cellular energy homeostasis.[73] Thirdly, the suppression of inflammatory and apoptotic signaling must be considered. At the signaling level, SIRT2 has been observed to inhibit inflammatory pathways, such as NF-κB, thereby reducing local production of proinflammatory factors.[65,66,68] Furthermore, SIRT2 deacetylation of FoxO1 enhances its transcriptional activity, thereby regulating the expression of antioxidant and cell-survival-related genes. However, the ultimate effects of this process depend on signal integration within the cell's specific microenvironment.[74] Research has demonstrated that the SIRT2-septin4 deacetylation axis plays a crucial role in


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overcoming oxidative stress and suppressing podocyte apoptosis, thereby reducing glomerulosclerosis and protecting against hypertensive kidney injury.[75]

Renal Tubular Epithelial Cells: Tubular injury and subsequent interstitial fibrosis represent hallmarks of advanced DKD progression, with SIRT2 exhibiting a multifaceted role in this process. On the one hand, it has been observed to participate in regulating epithelial-mesenchymal transition (EMT). Chronic hyperglycemia and inflammatory stimuli induce EMT, whereas SIRT2 antagonizes this process by deacetylating and inhibiting key proteins such as Smad3 or Snail.[76] However, studies also indicate that under specific stress conditions, SIRT2 may promote EMT through different substrates, highlighting its highly context-dependent function.[77,78] Conversely, SIRT2 exerts a regulatory influence on cellular senescence and metabolic reprogramming. As a potential regulator of senescence, its reduced activity may accelerate the senescence process in tubular epithelial cells. These senescent cells then secrete large amounts of inflammatory and pro-fibrotic factors via the senescence-associated secretory phenotype.[50,79] Concurrently, SIRT2 exerts a regulatory influence on cellular metabolic reprogramming from oxidative phosphorylation to glycolysis by modulating hypoxia-inducible factor-1 alpha (HIF-1α) stability (typically promoting its degradation) and AMPK signaling. This metabolic shift has been found to be closely associated with cellular injury and fibrosis progression.[70,80,81] Furthermore, studies indicate that SIRT2 deficiency or knockout in specific models (eg, LPS- or cisplatin-induced injury) may paradoxically mitigate acute tubular injury and inflammatory responses by regulating mitogen-activated protein kinase phosphatase-1 (MKP-1) expression or influencing c-Jun/c-Fos acetylation.[82–84] This finding further substantiates the notion that the effects of SIRT2 are not unidirectional and require rigorous analysis within the specific context of particular pathological conditions.

## Global Regulation of Renal Inflammatory Networks by SIRT2

SIRT2 functions as a pivotal hub linking metabolic dysregulation and immune inflammation, with its regulatory role in the renal immune microenvironment being critically important.

Inhibition of the Classic NF-κB Pathway: This finding represents the most well-established anti-inflammatory mechanism of SIRT2. In immune cells (eg, macrophages) and renal resident cells, stimuli such as hyperglycemia activate the IkappaB kinase (IKK) complex, leading to IκB degradation and nuclear translocation of the NF-κB p65 subunit.[85] SIRT2 has been shown to recruit to the p65 transcription complex, specifically deacetylating its Lys310 site.[65] This modification has been shown to impair p65's DNA-binding capacity and interactions with coactivators, thereby potently suppressing the transcription of key proinflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). This effect disrupts the positive feedback loop of inflammation.[68,86,87]

Regulation of the NLRP3 Inflammasome: Excessive NLRP3 inflammasome activation is a key amplifier of inflammatory damage in DKD, and SIRT2 exerts inhibitory effects through two potential mechanisms. The initial mechanism under consideration is a direct deacetylation mechanism, in which SIRT2 binds to NLRP3 or the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC), thereby inhibiting inflammasome polymerization through deacetylation.[29,88] The second is an indirect regulatory mechanism: SIRT2 has been shown to eliminate key NLRP3-activating "danger signals" by enhancing mitochondrial autophagy, reducing mitochondrial ROS production, and preventing mitochondrial DNA release. This action effectively blocks caspase-1 activation, thereby reducing IL-1β and interleukin-18 (IL-18) maturation and inhibiting pyroptosis.[66,68,89,90]

Regulation of Macrophage Phenotype Polarization: The phenotypic balance of kidney-infiltrating macrophages (M1 proinflammatory vs M2 reparative) determines the course of inflammatory responses, with SIRT2 serving as a key regulator of this equilibrium.[67,91] During M1 polarization, SIRT2 has been shown to limit proinflammatory cytokine production by inhibiting NF-κB and activator protein-1 (AP-1) signaling.[92,93] Conversely, during M2 polarization, SIRT2 likely promotes the expression of M2-marker genes, such as arginase 1 (*ARG1*) and interleukin-10 (*IL10*), by deacetylating and activating transcription factors, including signal transducer and activator of transcription 6 (STAT6).[91,92] Consequently, preserving optimal SIRT2 function has been shown to facilitate the transition of macrophages towards an anti-inflammatory, reparative M2 phenotype, thereby enhancing tissue repair and reducing fibrosis.

Synergistic Regulation of the AMPK/SIRT2 Axis in DKD: AMPK and SIRT2 have been shown to exhibit synergistic effects in energy sensing and metabolic regulation.[39] In the DKD environment, suppression of AMPK activity due to hyperglycemia or lipotoxicity can reduce $NAD^+$ levels, thereby impairing SIRT2 function.[37] Conversely, AMPK activators (eg, metformin) or energy stress (eg, increased AMP/ATP ratio induced by SGLT2 inhibitors) elevate $NAD^+$ and enhance SIRT2 activity, thereby promoting autophagy, suppressing NF-κB and NLRP3 inflammasomes, and improving mitochondrial function.[41,94] This bidirectional regulatory axis provides the molecular basis for the metabolic-inflammatory crosstalk.

## SIRT2 and the Link Between "Metabolic Memory" and Fibrosis

Potential Role in "metabolic memory": SIRT2, an $NAD^+$ -dependent class III deacetylase, functions as a sensor of cellular metabolic states. Changes in its activity may contribute to the formation of memory through the following mechanisms: On the one hand, SIRT2 modifies chromosomal structure and transcription factor activity by deacetylating histones (eg, H3K9, H4K16) or non-histones (eg, NF-κB p65), leaving persistent "epigenetic imprints".[31–33] Secondly, SIRT2 modulates mitochondrial function and oxidative stress levels, thereby influencing physiological states that can persistently alter cellular behavior.[95,96]

Regulating Renal Fibrosis Progression: Fibrosis signifies the terminal pathway of DKD, and SIRT2 antagonizes this process through multifaceted actions. First, it directly targets the transforming growth factor-beta1 (TGF-β1)/Smad signaling pathway by deacetylating Smad3, thereby inhibiting its transcriptional activity and reducing the synthesis of extracellular matrix proteins such as collagen I and fibronectin.[76] Secondly, SIRT2 has been shown to suppress inflammation-driven fibrosis through its potent anti-inflammatory effects. It has been demonstrated that this mechanism functions by impeding the autonomous or collaborative stimulation of fibroblasts by TGF-β1, a process that is achieved by diminishing the generation of pro-fibrotic factors, including TNF-α and IL-1β.[86,93] Furthermore, SIRT2 may influence fibrosis progression by regulating senescence in renal tubular epithelial cells. Impaired clearance of senescent cells promotes the formation of a fibrotic microenvironment, a process that may be influenced by SIRT2 activity.[50,79] However, studies also suggest that SIRT2 inhibition may attenuate the fibrotic response by promoting autophagy-mediated ciliogenesis or modulating the murine double minute 2 (MDM2) pathway, further highlighting the complexity of its actions.[78,97]

## Dynamic Evolution of SIRT2 Function in DKD Progression

In the early stages of DKD, cells adaptively increase SIRT2 expression or activity in response to metabolic stressors like hyperglycemia. This enables SIRT2 to function as a crucial metabolic sensor with protective effects.[72] At this stage, SIRT2 helps cells resist early damage by maintaining podocyte cytoskeletal stability, promoting autophagic clearance of damaged mitochondria, and suppressing classic inflammatory pathways such as NF-κB. Its primary function is to maintain homeostasis.[61,68,72]

As the disease progresses, prolonged metabolic dysfunction exacerbates pathological conditions such as oxidative stress, leading to a progressive decline in intracellular $NAD^+$ levels due to continuous depletion. Consequently, the activity of SIRT2, an $NAD^+$ dependent enzyme, is impaired. This phenomenon, termed the "failure of energy sensing", impedes its capacity to regulate cellular homeostasis.[50] The consequences of this process include excessive tubulin acetylation, which causes podocyte structural damage; impaired mitochondrial autophagy, which triggers bursts of ROS; and failure to suppress NF-κB and NLRP3 inflammasomes. This process has been shown to exacerbate inflammatory cascades, further increasing tissue injury.[68]

In advanced disease stages, within specific microenvironments (eg, severe oxidative stress, massive accumulation of AGEs), SIRT2's functional output may undergo a fundamental shift. Its substrate selectivity may undergo alteration, or it may interact abnormally with other stress signaling pathways, such as JNK, thereby participating in or even driving the injury process.[77,78,83] For instance, in aged or severely damaged renal tubular cells, SIRT2 may promote the expression of pro-inflammatory factors by deacetylating specific substrates, such as c-Jun.[84] Conversely, in certain acute injury models, the inhibition of SIRT2 activity has been shown to mitigate damage.[82,83] This apparent contradiction stems from SIRT2's role as a central node for signaling integration. The final output of its downstream pathways depends on the cell's specific energy

state, redox state, and pathological stage. Therefore, a comprehensive understanding of SIRT2's role transition during disease progression is imperative for the development of precise intervention strategies.

## Therapeutic Potential and Strategies Targeting SIRT2

Given SIRT2's pivotal role as a central integrator within the complex pathophysiological network of DKD, targeting it as a therapeutic agent has emerged as an auspicious research direction (Table 1).

### Re-Examining the Complexity of SIRT2 Function: Dual Roles in Protection and Injury

The primary prerequisite for developing targeting strategies is understanding SIRT2's seemingly contradictory dual roles in DKD. This "double-edged sword" characteristic is primarily attributable to its cellular specificity, disease-stage dependence, and substrate selectivity.[26,30]

Mainstream Evidence for Protective Effects: A substantial body of research supports SIRT2 as a protective factor in renal tissue across a wide range of conditions. Its mechanisms, as previously described, primarily include the following: exerting anti-inflammatory effects by inhibiting NF-κB and NLRP3 inflammasomes to alleviate systemic and local renal inflammation; maintaining metabolic homeostasis by regulating cellular energy metabolism, mitochondrial function, and autophagy to aid cellular adaptation to stress; exercising anti-fibrotic effects by inhibiting TGF-β/Smad signaling and EMT processes; and enhancing antioxidant defenses through pathways like FoxO activation. According to available data, renal-specific or systemic expression of SIRT2 in animal models, as well as the use of SIRT2 agonists, has been shown to reduce proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis substantially.[75,76]

**Table 1** Classification, Mechanisms, and Challenges of SIRT2 Modulators

| Modulator Type | Representative Compounds | Primary Mechanism of Action | Potential Application/ Findings in DKD Models | Key Development Challenges |
|---|---|---|---|---|
| **SIRT2 Inhibitors** | AGK2, SirReal2, Gliquidone | Competitively or allosterically inhibit the deacetylase activity of SIRT2. | May suppress inflammation or fibrosis in specific models; Gliquidone demonstrates multi-pathway renoprotective effects. | 1. **Functional Risk:** Inhibition may be detrimental as SIRT2 is primarily viewed as protective in DKD.<br>2. **Selectivity:** High selectivity over SIRT1 and SIRT3 is required.<br>3. **Delivery:** Kidney-targeted delivery systems are needed. |
| **SIRT2 Activators** | High-selectivity compounds to be developed | Enhance SIRT2's enzymatic activity towards its native substrates. | Theoretically boost protective functions in early disease; considered the primary development strategy. | 1. **Compound Scarcity:** Few reports on potent, high-selectivity agonists.<br>2. **Off-target Risk:** Potential side effects like cell cycle arrest from over-activation.<br>3. **Delivery:** Kidney-targeted delivery systems are needed. |
| **Indirect/ Natural Modulators** | Resveratrol, $NAD^+$ precursors (eg, NMN, NR) | Indirectly influences SIRT2 activity by elevating $NAD^+$ levels or through multi-target actions. | Serve as adjuvant strategies to improve metabolic and oxidative stress broadly. | Weak potency, low bioavailability, and complex mechanisms of action. |
| **Combination therapy drugs** | RAAS inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, etc. | Synergistic effects with SIRT2 function through AMPK activation, $NAD^+$ elevation, or inhibition of inflammatory pathways. | Demonstrated renal protective effects in preclinical and clinical studies, with significant potential for combination use with SIRT2 modulators. | The optimal timing for combination therapy, dosage, and patient stratification strategies must be clearly defined. |

**Abbreviations**: SIRT2, Sirtuin 2; DKD, Diabetic Kidney Disease; $NAD^+$, Nicotinamide Adenine Dinucleotide; NMN, Nicotinamide Mononucleotide; NR, Nicotinamide Riboside.

Potential Adverse Scenarios: Several studies indicate that SIRT2 may exert deleterious effects under certain conditions. For instance, in specific cell types or during periods of severe, protracted stress, SIRT2 may contribute to cell death induction by deacetylating specific substrates (eg, certain pro-apoptotic proteins).[72,98] Its inhibitory effects on cell cycle and proliferation may prove deleterious during phases of injury repair that necessitate regeneration.[99] In addition, clinical studies have indicated that sustained high SIRT2 expression may be associated with adverse outcomes in DKD.[100,101] A recent study found serum SIRT2 levels to rise in conjunction with the presence and severity of DKD.[101] A subsequent study revealed a strong correlation between urinary SIRT2 levels and eGFR, tubular injury, and urinary albumin excretion in patients with type 2 diabetes.[100]

The dual role of protection and damage, though seemingly contradictory, reveals the profound complexity of SIRT2 function rather than a simple misinterpretation. This inquiry can be approached through the lens of several interconnected hypotheses.

One perspective that merits consideration is the compensatory upregulation hypothesis. In the advanced stages of the disease, when the body is experiencing significant metabolic and inflammatory stress, a compensatory response may be initiated, involving the upregulation of SIRT2 expression. However, given the potential depletion of the core intracellular cofactor $NAD^+$ or alterations in key signaling networks at this stage, this increased expression may fail to effectively translate into protective deacetylase activity. Consequently, elevated circulating SIRT2 levels may merely reflect the failure of these compensatory efforts, serving as a biomarker correlated with the severity of tissue damage rather than a direct indicator of functional activity.

The cell origin and localization hypothesis provides an alternative explanation. The distribution of SIRT2 appears to be predominantly derived from damaged, apoptotic, or activated cell types, including infiltrating immune cells and severely injured renal tubular epithelial cells. Consequently, its elevated levels more directly reflect tissue injury and the release of cellular contents. This finding does not contradict the protective regulatory role of intracellular SIRT2, especially in functional podocytes or tubular cells. Consequently, the distribution of SIRT2 may function primarily as an "injury marker", while the active, intracellular form of SIRT2 acts as a "protective regulator". A critical examination of these two forms reveals the necessity to distinguish between them based on their origins and significance.

Additionally, the gain-of-function hypothesis cannot be disregarded. Within the distinctive pathological microenvironment of advanced DKD, marked by remarkably elevated levels of AGEs, acidosis, and persistent oxidative stress, the SIRT2 protein itself may undergo atypical post-translational modifications (eg, nitrosylation) or shifts in its substrate selectivity and affinity. This could result in a shift in its functional output from a primarily protective role to a state that potentially promotes inflammation, fibrosis, or cellular senescence.[23] Furthermore, the potential for distinct roles of different SIRT2 isoforms across various stages of disease development introduces a degree of complexity to functional analysis.[26]

In summary, the simplistic categorization of SIRT2 as either a "protective" or "harmful" molecule is reductive and inconsistent with its biological properties. The ultimate effects of this phenomenon result from the integrated output of multiple-dimensional factors, including cell type, disease stage, local microenvironment (particularly $NAD^+$ availability), underlying isoforms, and post-translational modification status. This profound understanding is crucial for developing precision therapeutic strategies. Future therapeutic interventions should avoid the indiscriminate activation or inhibition of SIRT2. Instead, these interventions should concentrate on correcting their imbalanced functional state through precise means within specific pathological spatiotemporal contexts. This would restore SIRT2's normal homeostatic regulatory capacity.

## Development Progress of SIRT2 Modulators

From a pharmacological perspective, the modulation of SIRT2 activity can be categorized into two distinct classifications: inhibitors and activators. It is imperative to acknowledge that the "beneficial" or "harmful" implications of this pharmacological classification must be assessed within the framework of specific diseases.

SIRT2 Inhibitors: These compounds have been observed to inhibit SIRT2's deacetylase activity, with inhibition categorized as either competitive or non-competitive, depending on the specific compound and its interaction with the enzyme. Inhibition occurs by occupation of either the catalytic domain or the allosteric sites within the enzyme's structure. Representative compounds include AGK2, an early-discovered, highly selective SIRT2 inhibitor that has been extensively studied in neurodegenerative

disease models, such as Parkinson's disease, where it exerts neuroprotective effects by inhibiting SIRT2.[102,103] AGK2's anti-inflammatory effects in the kidney manifest as reduced expression of IL-6, TNF-α, and IL-1β in renal tissue, thereby alleviating inflammatory responses.[74] Furthermore, AGK2 has been shown to inhibit the activation of renal fibroblasts.[77] The Tenovin Series has been identified as p53 activators; the compounds Tenovin-1 and Tenovin-6 have been found to inhibit SIRT1 and SIRT2.[104] Research findings indicate that Tenovin-1 exerts a positive effect on renal fibrosis in high-fat diet-induced DKD, achieved through antioxidant and anti-inflammatory pathways.[105] SirReal2 is a structurally designed, highly selective, potent SIRT2 inhibitor that is frequently utilized as a chemical probe for mechanism studies.[106] Inhibitors may hold value in specific DKD scenarios. For instance, if SIRT2 is confirmed to promote fibrosis in specific cell types (eg, activated fibroblasts) during advanced DKD, localized inhibition could be beneficial. Furthermore, transient, moderate SIRT2 suppression has the potential to disrupt the abnormal "metabolic memory" epigenetic state it helps maintain. Nevertheless, this approach entails considerable risks and necessitates the development of exact targeted delivery systems.

SIRT2 Activators: The objective of these compounds is to enhance SIRT2's deacetylase activity toward its natural substrates. In contrast to inhibitors, highly selective, potent SIRT2 activators are comparatively limited, predominantly in the early stages of research, necessitating further validation of their efficacy and selectivity. Extensive evidence supports SIRT2's protective role across most DKD models and stages, including its anti-inflammatory effects and maintenance of metabolic homeostasis. Consequently, the development of selective agonists is considered the most promising therapeutic strategy. In principle, enhancing SIRT2 function during the early stages of disease or during metabolic/inflammatory stress phases could restore cellular homeostasis and counteract hyperglycemia-induced damage. Key challenges in development include preventing off-target effects, such as cell cycle arrest caused by excessive SIRT2 activation, and ensuring effective drug delivery to renal target cells. Furthermore, preliminary studies have identified certain natural products and indirect modulators that exhibit partial effects associated with SIRT2 regulation. For instance, resveratrol has been shown to activate SIRT1 directly and to upregulate SIRT2 expression, thereby exerting a combined anti-inflammatory and antioxidant effect.[107] While these substances are attractive due to their multi-targeted and low-toxicity characteristics, their relatively weak effects, low bioavailability, and complex mechanisms render them more suitable as adjunctive or preventive strategies.

## Synergistic Treatment Strategies: Combination with Existing Standard Therapies

In the context of multi-targeted, synergistic approaches to DKD treatment, combining SIRT2 modulators with standard therapies is a cutting-edge strategy to optimize renal protection.

Combination with RAAS Inhibitors: RAAS inhibitors (eg, ACEIs/ARBs) serve as the primary treatment for DKD, achieving this by reducing intraglomerular hypertension and directly blocking pro-inflammatory and pro-fibrotic signals triggered by angiotensin II (Ang II) through its receptors.[108,109] Conversely, SIRT2 modulators enhance intrinsic cellular stress tolerance by maintaining cytoskeletal integrity, promoting autophagy, and suppressing inflammatory transcription. This combined therapeutic strategy thus establishes a complementary framework: RAAS inhibitors have been shown to alleviate initial renal stress and injury signals from a macro-level hemodynamic and circulating hormone perspective, while SIRT2 modulators have been demonstrated to reinforce cellular defense and repair capabilities by stabilizing the micro-level intracellular environment. This dual-action approach aims to comprehensively address the entire pathological chain—from injury initiation and inflammatory amplification to the final stage of fibrosis—potentially yielding superior renal protective effects compared to monotherapy.

Combination with SGLT2 Inhibitors: SGLT2 inhibitors have emerged as a significant advancement in the treatment of DKD.[5,40,110,111] SGLT2 inhibitors induce osmotic diuresis and glucose excretion by inhibiting renal tubular glucose reabsorption. This process engenders a mild energy stress state in the proximal tubules, manifesting as an elevated AMP/ATP ratio.[112–114] This modified energy state serves as a pivotal signal that activates AMPK.[115] AMPK activation has been shown to directly phosphorylate downstream targets, thereby inhibiting inflammatory and fibrotic pathways. Additionally, AMPK has been observed to promote intracellular $NAD^+$ biosynthesis by upregulating rate-limiting enzymes, such as nicotinamide phosphoribosyltransferase (NAMPT).[116] Elevated levels of $NAD^+$ directly provide ample active substrates for SIRT2, an $NAD^+$-dependent deacetylase. Furthermore, its antioxidant and anti-inflammatory effects, independent of glucose-lowering, show significant synergistic potential with SIRT2-regulated

metabolic-inflammatory pathways.[117] Consequently, the concomitant utilization of SGLT2 inhibitors and SIRT2 activators may yield additive or synergistic renal protective effects by establishing a sequential signaling axis: The sequence of events begins with energy stress (SGLT2i), which activates AMPK. This activation elevates $NAD^+$ levels and enhances SIRT2 function. This approach has the potential to alleviate metabolic stress in tubular cells while concurrently suppressing inflammatory responses with high efficacy.

Combination with GLP-1 Receptor Agonists: GLP-1 receptor agonists have been shown to improve renal function beyond glucose control.[5,118–120] The renal protective effects of GLP-1 receptor agonists are partially attributable to their inhibition of NLRP3 inflammasome activation. This mechanism may involve the cAMP-PKA signaling pathway.[42,114,120,121] SIRT2 has also been demonstrated to suppress inflammasome assembly and activation by directly deacetylating NLRP3 or the adaptor protein ASC.[29,88] The combination of these two agents may be intended to achieve a "dual lockdown" on the NLRP3 inflammasome at both the "cell membrane receptor signaling level" (via GLP-1RAs through cAMP) and the "intracellular protein post-translational modification level" (via SIRT2 through deacetylation). This approach has the potential to yield more comprehensive and prolonged anti-inflammatory effects. In addition, GLP-1RAs have been shown to enhance systemic glucose and lipid metabolism, as well as insulin sensitivity, thereby establishing a more conducive systemic metabolic environment. This indirect support for normal SIRT2 function fosters synergy across both inflammation suppression and metabolic enhancement.

Nutritional Intervention Based on $NAD^+$ Precursors: Supplementing $NAD^+$ precursors, such as nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR), aims to elevate intracellular $NAD^+$ levels at their source. This, in turn, "empowers" all $NAD^+$-dependent sirtuins, including SIRT2.[50,122–124] This upstream intervention strategy has been shown to have extensive metabolic regulatory potential and to be effective in models of aging and metabolic disease. It may serve as a foundational adjunct to enhance the effectiveness of other targeted therapies.[50,122–124]

Other Combination Targets with Anti-inflammatory Potential: Nonsteroidal mineralocorticoid receptor antagonists (eg, finerenone) have been observed to synergize with SIRT2's anti-inflammatory and anti-fibrotic functions by inhibiting mineralocorticoid receptor-mediated inflammatory and fibrotic signaling.[5] Endothelin-A receptor antagonists may also complement SIRT2-regulated vascular inflammatory pathways by improving endothelial function and suppressing inflammatory cell infiltration.[125] These findings necessitate further investigation in subsequent studies.

## Current Challenges and Future Prospects

While targeting SIRT2 presents a promising new approach to treating DKD, translating this from fundamental research to clinical application is fraught with significant scientific challenges. Concurrently, emerging technologies and innovative research paradigms aim to overcome these bottlenecks and enable precise interventions.

### Major Current Challenges

The Complexity and Duality of SIRT2's Biological Functions: SIRT2 does not function in a unidimensional manner as either a "protector" or "damager" in DKD; its functions exhibit significant context-dependence and cell-specificity. For instance, recent single-cell sequencing studies have revealed markedly altered SIRT2 expression patterns in renal endothelial cells during mid-differentiation in DKD models. This suggests that its functions may dynamically shift with cellular state and disease progression.[126] This complexity suggests that modifying SIRT2 activity, whether by upregulation or inhibition, may have unintended consequences given the system's multifaceted nature. For instance, while SIRT2 is believed to exert anti-inflammatory effects by suppressing pathways such as NF-κB, it may also participate in pro-fibrotic or pro-apoptotic signaling in specific cells or advanced disease settings. Consequently, ascertaining the most effective moment to intervene with SIRT2, in addition to the optimal location and methodology, poses a significant scientific challenge.

The Challenge of Tissue- and Cell-specific Targeting: SIRT2 is expressed in various renal cell types, including podocytes, tubular epithelial cells, mesangial cells, endothelial cells, and infiltrating immune cells. These cell types potentially exhibit distinct functions. Systemic administration cannot distinguish between these cell types, which may result in the protection of one cell type while disrupting the normal physiological function of another. The development

of nanocarriers or prodrug systems capable of precise delivery to specific renal cell types represents a critical technological bottleneck for achieving effective and safe treatment.

A substantial discrepancy exists between fundamental research and its clinical translation, manifesting in two primary domains. Initially, the model's constraints constitute a considerable impediment. The prevailing approach in mechanism studies and efficacy validation involves the utilization of animal models, such as mice. However, it is imperative to exercise extreme caution when extrapolating findings from these models to humans, given the well-documented disparities in disease progression and immune systems between animals and humans. Secondly, human heterogeneity poses another significant challenge. The patient population suffering from DKD exhibits substantial genetic and clinical heterogeneity. For instance, research has demonstrated a correlation between polymorphisms in the *SIRT2* gene and the risk of renal injury in patients with type 2 diabetes.[127] This observation suggests that the efficacy of a given SIRT2-targeting strategy may vary among patients, indicating that a one-size-fits-all approach may not be applicable in this context. The dearth of biomarkers capable of predicting treatment efficacy has emerged as a substantial challenge in clinical trial design. Furthermore, the process of drug development is inherently challenging. While experimental SIRT2 modulators, such as AGK2, have been identified, further research is necessary to optimize their pharmacokinetics, long-term safety, and renal targeting. The process of transitioning from a lead compound to a clinical candidate is both time-consuming and financially burdensome.

Insufficient Understanding of the SIRT2 Regulatory Network: SIRT2 exerts its effects by deacetylating numerous downstream substrates, forming a complex regulatory network. The prevailing focus of contemporary research is on discrete pathways, such as NF-κB or NLRP3, thereby neglecting to map the global substrate profile and interactome of DKD comprehensively. This limitation hinders our ability to design smart drugs that can precisely regulate specific downstream effects while avoiding off-target effects.

## Future Research Directions and Outlook

Deepening Mechanistic Understanding with Cutting-Edge Technologies: Future research endeavors should integrate multi-omics and high-resolution techniques to address existing knowledge gaps. On the one hand, spatiotemporal dynamic analysis is required, which would entail using single-cell multi-omics sequencing and spatial transcriptomics to map the comprehensive landscape of SIRT2 expression, activity, and downstream signaling across different stages of diabetic kidney disease and diverse renal cell types. This will elucidate precise cellular targets and temporal windows in which SIRT2 exerts critical effects. Conversely, cross-validation of mechanisms is imperative. This approach integrates proteomics and metabolomics to systematically identify key proteins deacetylated by SIRT2 under DKD conditions and the resulting metabolic changes. This comprehensive approach aims to elucidate the molecular network that links metabolism and inflammation. For instance, recent studies employing metabolome-proteome correlation analysis have positioned SIRT2 as a pivotal hub linking energy metabolism and innate immune responses, suggesting that it acts through pathways such as HIF-1α/vascular endothelial growth factor A (VEGFA).[70]

Development of Innovative Therapeutic Strategies: Subsequent endeavors must prioritize the development of innovative therapeutic methodologies. The repurposing of existing drugs is a promising strategy for expediting the development of new treatments. This approach circumvents the high risks and lengthy development cycles associated with novel drug research. It involves using computational biology methods to screen approved drugs for compounds that modulate SIRT2. For instance, recent studies have found that the antidiabetic drug gliquidone acts as an effective SIRT2 inhibitor, exerting renal protection in cellular models through multiple synergistic pathways, including induction of autophagy, suppression of the NLRP3 inflammasome, and inhibition of fibrosis.[128] The implementation of such strategies has been shown to reduce the duration of clinical translation timelines substantially. Secondly, the development of precision and combination therapies is imperative. The elements above include the following: Biomarker-based stratification, which involves the identification and validation of circulating or urinary biomarkers (eg, specific acetylated protein profiles) reflecting renal SIRT2 pathway activity to identify patient subgroups most suitable for SIRT2-targeted therapy; Synergistic combination therapies, which explore the co-administration of SIRT2 modulators with existing standard treatments (eg, SGLT2 inhibitors, GLP-1 receptor agonists), which may exhibit synergistic effects in improving cellular metabolic stress and suppressing inflammation, potentially yielding enhanced renal protection; Conditional

intervention strategies. The development of "smart" drug delivery systems that are responsive to disease microenvironments (eg, high reactive oxygen species, specific pH levels) is crucial for achieving precise activation or release at the lesion site.

Advancing Clinical Translation and Precision Medicine: To expedite translational outcomes, future efforts should concentrate on two primary domains. First, conducting prospective clinical studies: The design of early-phase clinical trials should be informed by well-defined mechanisms and should rigorously evaluate the safety, pharmacokinetics, and preliminary efficacy signals of SIRT2 modulators (particularly repurposed drug candidates) in patients with DKD. Secondly, predictive models should be developed by integrating patient genomics (eg, SIRT2 gene polymorphisms), clinical phenotypes, and multi-omics data. The use of artificial intelligence in developing treatment-response prediction models holds great potential to enable precise classification and personalized therapy for DKD.

## Conclusion

Intricate interactions among metabolism, inflammation, and fibrosis characterize the pathogenesis of DKD. This review systematically examines the central regulatory role of SIRT2 within this network. The extant evidence suggests that, in its capacity as an $NAD^+$-dependent deacetylase, SIRT2 plays a pivotal role in linking cellular metabolic states to inflammatory signaling pathways. Its actions exhibit significant context-dependent properties, primarily manifested in the following ways: suppression of classical inflammatory pathways by deacetylating proteins such as NF-κB p65; regulation of NLRP3 inflammasome activity to influence pyroptosis; and participation in maintaining cytoskeletal stability, regulating autophagy and mitochondrial function in renal intrinsic cells like podocytes and renal tubular epithelial cells, thereby affecting cellular homeostasis. However, the functions of SIRT2 may vary with disease stage, cell type, and microenvironment, thereby reflecting the complexity of its biological effects.

SIRT2 functions as a pivotal integrator within the intricate network of metabolism, inflammation, and fibrosis in DKD, with its role being contingent on cell type and disease stage. This feature unveils both unique prospects for targeted intervention and substantial challenges for clinical translation. The most pressing research gaps in this field currently focus on several areas: elucidating the dynamic activity profile of SIRT2 across various human kidney cell types as disease progresses; developing delivery systems capable of precisely targeting specific cells (such as podocytes or damaged tubules); and establishing biomarkers that predict therapeutic response to enable effective patient stratification. In the future, research should aim to develop an integrated translational framework that encompasses "mechanism elucidation-targeted delivery-clinical validation". This framework should be explored in conjunction with intelligent combination strategies that integrate SIRT2 modulators with existing therapies, such as SGLT2 inhibitors and nonsteroidal mineralocorticoid receptor antagonists. The transformation of SIRT2 from a promising molecular target into a precision therapeutic approach that genuinely improves the prognosis of diabetic nephropathy is only possible through interdisciplinary collaboration and continuous technological innovation.

## Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

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## Author Contributions

Conceptualization and methodology, F.Z. and W.L.; visualization and supervision, W.L.; Writing - original draft, F.Z.; Writing - review and editing, W.L.; All authors have read and agreed to the published version of the paper.

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

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The authors declare no conflicts of interest in this study.

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