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REVIEW

Roles of SIRT6 in kidney disease: a novel therapeutic target

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Abstract

SIRT6 is an NAD^+ dependent deacetylase that belongs to the mammalian sirtuin family. SIRT6 is mainly located in the nucleus and regulates chromatin remodeling, genome stability, and gene transcription. SIRT6 extensively participates in various physiological activities such as DNA repair, energy metabolism, oxidative stress, inflammation, and fibrosis. In recent years, the role of epigenetics such as acetylation modification in renal disease has gradually received widespread attention. SIRT6 reduces oxidative stress, inflammation, and renal fibrosis, which is of great importance in maintaining cellular homeostasis and delaying the chronic progression of kidney disease. Here, we review the structure and biological function of SIRT6 and summarize the regulatory mechanisms of SIRT6 in kidney disease. Moreover, the role of SIRT6 as a potential therapeutic target for the progression of kidney disease will be discussed.

Graphical abstract

SIRT6 plays an important role in kidney disease. SIRT6 regulates mitochondrial dynamics and mitochondrial biogenesis, induces G2/M cycle arrest, and plays an antioxidant role in nephrotoxicity, IR, obstructive nephropathy, and sepsis-induced AKI. SIRT6 prevents and delays progressive CKD induced by hyperglycemia, kidney senescence, hypertension, and lipid accumulation by regulating mitochondrial biogenesis, and has antioxidant, anti-inflammatory, and antifibrosis effects. Additionally, hypoxia, inflammation, and fibrosis are the main mechanisms of the AKI-to-CKD transition. SIRT6 plays a critical

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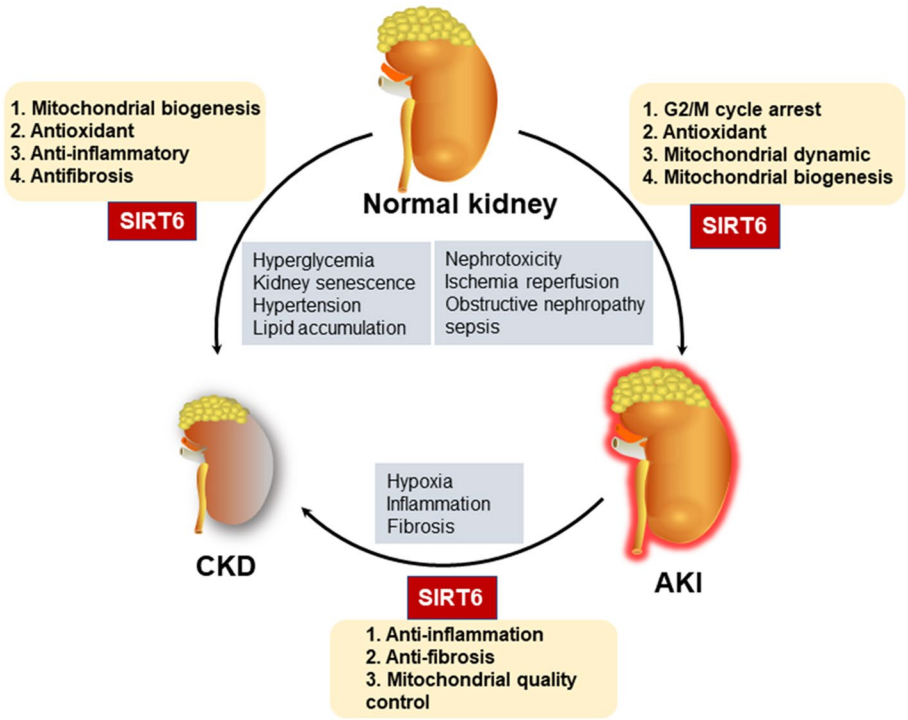
role in the AKI-to-CKD transition and kidney repair through anti-inflammatory, antifibrotic, and mitochondrial quality control mechanisms. *AKI* Acute kidney injury, *CKD* Chronic kidney disease.



Keywords SIRT6 · Chronic kidney disease · Acute kidney disease · Epigenetics · Energy metabolism · Oxidative stress · Cellular homeostasis

Introduction

The kidney is one of the main energy-consuming organs in the human body [1]. Persistent chronic inflammation and incomplete recovery of kidney function after acute kidney injury (AKI) accelerate the progression to chronic kidney disease (CKD), which ultimately leads to an increased incidence of end-stage renal disease (ESRD) [2]. Under conditions of oxidative stress and aging, the physiological stress response capacity is reduced. The decreased antioxidant capacity exacerbates renal tubular epithelial cell (TEC) damage, vascular endothelial cell activation, and the inflammatory response, promoting abnormal kidney repair and ultimately resulting in irreversible kidney damage [3]. Identifying the key regulatory molecules and effective therapeutic targets is of vital importance in the prevention and treatment of kidney disease.

Mammalian sirtuins (SIRT1-7) are Class III histone deacetylases, which are a highly conserved protein family and are closely related to the development of diseases, including metabolic syndrome, diabetes, cancers, and aging [4, 5]. Among sirtuins, SIRT1, SIRT2, and SIRT3 belong to Class I based on sequence-based phylogenetic analysis, while SIRT4 belongs to Class II, SIRT5 is in Class III, and SIRT6 and SIRT7 are in Class IV [6]. Sirtuins localize in different subcellular compartments and perform different functions. SIRT1, the most well-studied sirtuin, is mainly located in the nucleus. SIRT1 shows strong histone deacetylation activity and shuttles between the nucleus and the cytoplasm, playing a vital role in DNA repair and the stress response [7]. SIRT2 is located in the nucleoplasm and exhibits robust deacetylase activity. SIRT2 mainly regulates the cell cycle and tumorigenesis [8]. SIRT3 is located in mitochondrial matrix, and is a mitochondrial protein deacetylase that regulates mitochondrial dynamics and metabolism [9]. SIRT4 is located in mitochondria, mainly functions as an ADP-ribosyltransferase and has weak substrate-specific deacetylase activity. SIRT4 plays a vital role in metabolism regulation [10]. SIRT5 primarily resides in mitochondria and exerts demalonylase, lysine desuccinylase, and deglutarylase activity, participating in the urea cycle and regulating metabolism [11]. SIRT6 is mainly located in the nucleus, is involved in DNA repair and energy metabolism, and plays a regulatory

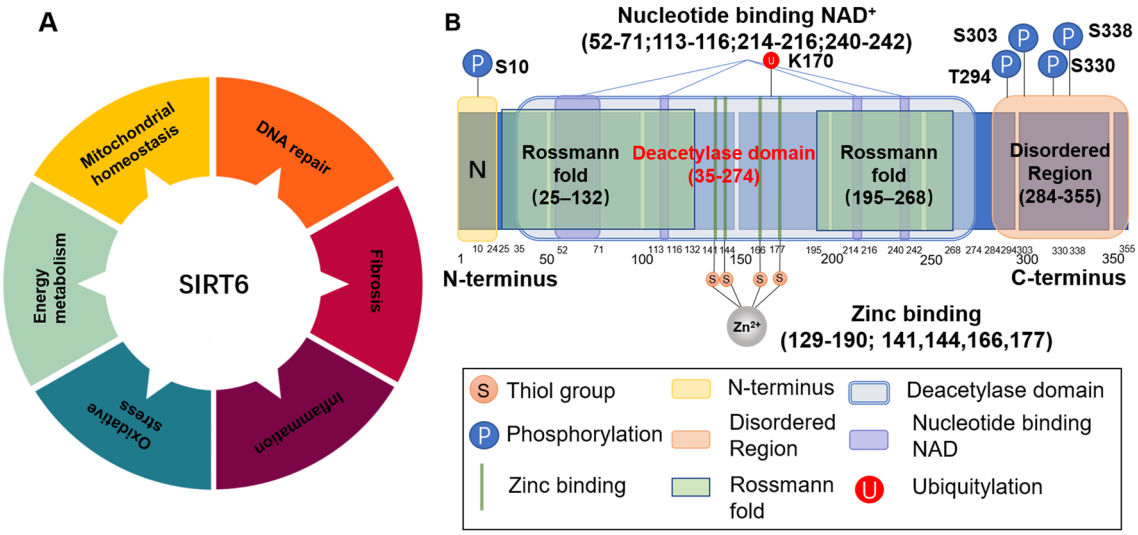


Fig. 1 Structural features and biological functions of SIRT6. **A** Biological functions of SIRT6. SIRT6 can regulate telomere maintenance, DNA repair, energy metabolism, oxidative stress, the inflammatory response, and fibrosis to maintain cellular homeostasis. **B** Structural features of SIRT6. SIRT6 is composed of an N terminus (1–24), a C terminus (269–355), and a conserved central domain (25–274) and has a total length of 355 amino acids (aa). The conserved central domain is the main catalytic core, which includes the NAD^+-binding Rossmann fold domain (RFD) (25–132 and 195–268) and a zinc-binding domain. Cysteine residues that bind to Zn^{2+} ions are located at positions 141, 144, 166, and 177. The C terminus is a disordered region that is proline-rich. The main phosphorylation and ubiquitylation sites are highlighted

role in lifespan [12]. SIRT7 localizes in the nucleus and interacts with RNA polymerase I to regulate DNA repair and the aging process [13, 14]. Recently, SIRT6, which is a potential therapeutic target, has gradually drawn attention in maintaining kidney function and has been proven to participate in renal disease by regulating oxidative stress, inflammation, fibrosis, and mitochondrial biosynthesis [15–17]. In this review, we first summarize the structure and main biological functions of SIRT6 and then describe the regulatory mechanisms and potential role of SIRT6 as a target in kidney disease.

Structural features and biological functions of SIRT6

SIRT6 is composed of an N-terminal, a C-terminal, and a conserved central domain. The C terminus is a structural region related to nuclear localization that regulates the positioning of SIRT6. Central domain maintains catalytic activity. The N terminus of SIRT6 binds to the chromosome and contributes to intrinsic catalytic activity, such as regulating H3K9 and H3K56 deacetylation [18]. In contrast to other sirtuin family members, SIRT6 lacks a cofactor-binding loop and has a single helix instead. The crystal structure of SIRT6 contains two globular domains: a splayed zinc-binding domain and a stable single helix for NAD^+ binding. Although SIRT6 lacks a conserved and highly flexible NAD^+-binding loop, it can bind tightly to NAD^+ in the absence of acetylated substrates [19]. SIRT6 possesses both NAD^+-dependent protein deacetylase activity and ADP ribosyl transferase activity, participating in gene transcription, metabolism, telomere integrity, and DNA repair [20]. SIRT6 also exerts defatty acylase activity and plays an important role in protein secretion [21]. The unique structure and enzymatic activity of SIRT6 exerts a variety of unique biological effects. SIRT6 is actively recruited to target gene promoters and deacetylates H3K9, H3K18, and H3K56 to maintain cellular homeostasis [22–24]. The ADP ribosylation activity of SIRT6 is involved in DNA double-strand break (DSB) repair [25] (Fig. 1).

SIRT6 in cellular homeostasis

As an upstream nucleoprotein, SIRT6 can regulate cell function and survival. SIRT6 plays a critical role in maintaining cellular homeostasis in multiple ways, including telomere maintenance, DNA repair, energy metabolism, oxidative stress, the inflammatory response, and fibrosis [26] (Fig. 1).

Telomere maintenance and DNA repair

Telomeres are specialized DNA protein structures at the end of chromosomal DNA that protect chromosome ends from degradation and the DNA damage response (DDR).

Telomeres exhibit structural abnormalities and random loss of telomere sequences when SIRT6 is deficient [27]. SIRT6-deficient cells show base excision repair defects and genomic instability. Upregulation of SIRT6 may improve the ability of base excision repair to combat DNA damage and rescue genome instability [28]. The main types of DNA damage include base deletion, mismatch, DNA cross-linking, and DNA strand breaks that consist of DNA single-strand breaks (SSBs) and DSBs. SSBs occur more frequently in cells, but DSBs are the most toxic form of DNA damage that lead to impaired gene integrity and the subsequent partial loss of the genome [29, 30]. The repair of both SSBs and DSBs is closely related to SIRT6 [31, 32]. SIRT6 directly binds to DSBs and recruits key factors associated with DDR [33]. Upon DSB damage, H2AX is rapidly phosphorylated by ataxia-telangiectasia mutated (ATM) kinase. The phosphorylated histone H2A variant γH2AX anchors to SIRT6 and binds with DNA DSB sites to initiate the cellular DDR [30, 34]. Oxidative stress results in severe DNA damage, especially DSBs [35]. Under oxidative stress conditions, SIRT6 mono-ADP-ribosylates poly (ADP-ribose) polymerase 1 (PARP1) on lysine 521 to stimulate PARP1 activity, which enhances DSB repair [36]. c-Jun N-terminal kinases (JNKs) phosphorylate SIRT6 on serine 10, stimulating SIRT6 mono-ADP-ribosylation of PARP1 and promoting PARP1 recruitment to DNA breaks [37]. SIRT6 can also facilitate the recruitment of DNA repair factors, including Rad51 and NBS1 [38]. Telomere repeat binding factor 2 (TRF2) is involved in telomere maintenance and DDR. SIRT6 interacts with TRF2 and deacetylates the TRFH domain of TRF2, which is then ubiquitylated, activating ubiquitin-dependent proteolysis to regulate its stability [39]. SIRT6 responds to damaged telomeres in the early stage and then recruits MutY homolog (MYH) and Rad9-Rad1-Hus1 (9-1-1) to form the MYH/SIRT6/9-1-1 complex, which is important in DNA repair and maintaining telomere integrity [40]. In response to UV irradiation, SIRT6 binds with and deacetylates damage-specific DNA-binding protein 2 (DDB2) at the lysine residues K35 and K77 and then promotes DDB2 ubiquitination and segregation from chromatin, thereby facilitating nucleotide excision repair signal transduction [41]. SIRT6 mono-ADP ribosylates the lysine demethylase JHDM1A/histone demethylase 2A (KDM2A), which results in rapid displacement of KDM2A from chromatin and increased levels of H3K36me2, which recruits heterochromatin protein 1-alpha (HP1α) and promotes deposition of the H3K9me3 mark, leading to local chromatin compaction [42]. Chromodomain helicase DNA-binding protein 4 (CHD4) is a core subunit of mammalian nucleosome remodeling and the histone deacetylase (NuRD) complex, and is recruited to DNA damage sites. SIRT6 interacts with CHD4 and is required for the recruitment of CHD4 to mediate the DDR [28]. We also verified that SIRT6 alleviates DNA DSBs through the nuclear factor erythroid-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) pathway [43]. This evidence suggests that SIRT6 plays an important role in telomere maintenance and DNA repair.

Mitochondrial homeostasis

SIRT3 is highly expressed in mitochondria and is the most thoroughly studied mitochondrial sirtuin [44]. SIRT3 regulates mitochondrial energy metabolism by adjusting mitochondrial dynamics through fusion and fission, clearing damaged mitochondria through autophagy and generating new mitochondria through biosynthesis. SIRT3 overexpression activates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)-related mitochondrial protection mechanisms and blocks caspase 9-related apoptosis pathways, thus alleviating high glucose-induced endothelial cell injury [45]. In addition, renal ischemia–reperfusion (IR) leads to SIRT3 deficiency. SIRT3 enhances mitochondrial fusion triggered by optical atrophy 1 (OPA1) and thus maintains mitochondrial homeostasis and protects renal TECs from IR injury [46]. This evidence shows that SIRT3 maintains cellular mitochondrial homeostasis. Interestingly, SIRT6 overexpression may regulate mitochondrial homeostasis by cooperating with SIRT3. Under stress conditions, the lack of SIRT3 causes mitochondrial dysfunction and promotes mitochondrial reactive oxygen species (ROS) overproduction accompanied by the downregulation of SIRT6. SIRT3 overexpression significantly upregulates SIRT6 and reverses oxidative stress damage [47]. SIRT3 is an Nrf2-dependent gene, and it has also been proven that SIRT6 can activate Nrf2 to regulate downstream gene expression [48, 49]. SIRT6 promotes the recruitment and activation of RNA polymerase II to Nrf2-regulated antioxidant genes and then exerts antioxidant effects. In addition, SIRT6 inhibits the binding of Kelch-like ECH-associated protein 1 (Keap1) and Nrf2, stabilizes Nrf2 and activates the transcription of the Nrf2-dependent gene SIRT3, further maintaining mitochondrial homeostasis [50]. In addition, SIRT6 plasmid transfection significantly alleviated high glucose-induced mitochondrial defects by activating the AMP-activated protein kinase (AMPK) pathway [51]. In summary, SIRT6 participates in the regulation of mitochondrial function and is critical to mitochondrial homeostasis (Fig. 2).

Energy metabolism

As one of the most basic characteristics of life, energy metabolism has been examined in various research fields, including kidney disease research. Multiple studies have confirmed that SIRT6 acts as a regulator of glucose and lipid metabolism [52, 53]. SIRT6-knockout mice showed gradually increased blood glucose levels and fat mass, indicating

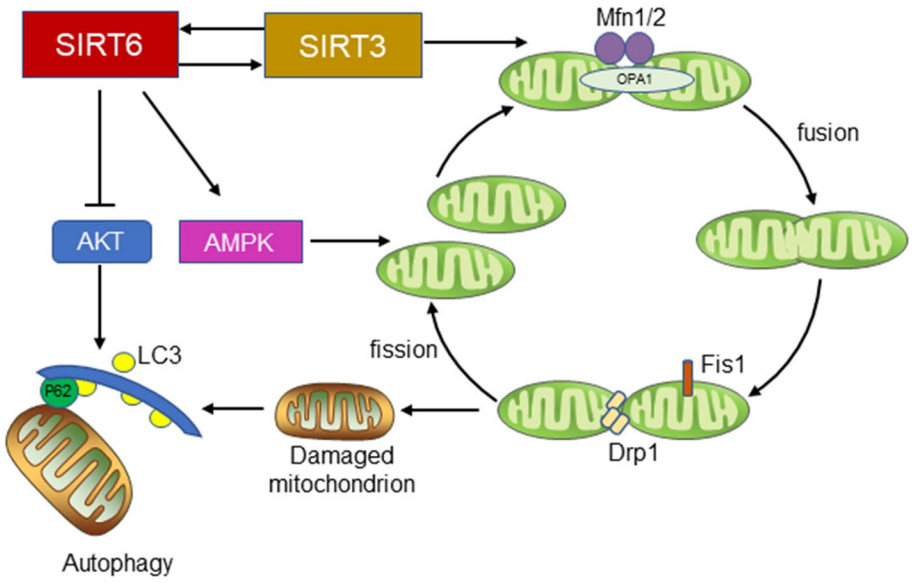


Fig. 2 The role of SIRT6 in the regulation of mitochondrial homeostasis. Under stress conditions, SIRT6 coordinates with SIRT3 to regulate mitochondrial dynamics through fission and fusion. In addition, SIRT6 activates AMPK signaling to promote autophagy and maintain mitochondrial homeostasis. *AMPK* AMP-activated protein kinase, *LC3* Microtubule-associated protein 1 light chain 3, *P62/SQSTM1* sequestosome-1, *Mfn1/2* Mitofusin 1/2, *Fis1* Mitochondrial fission protein 1, *Drp1* Dynamin-related protein 1

the potential role of SIRT6 in regulating metabolism [54]. Next, we will summarize the role of SIRT6 in adjusting energy metabolism, including glucose metabolism and lipid metabolism.

Glucose metabolism

Glucose metabolism is crucial for tissue and organ energy supply. SIRT6 can directly regulate glycometabolism by inhibiting glucose metabolism genes. SIRT6 interacts with hypoxia inducible factor-1α (HIF-1α), deacetylates H3K9 at the HIF-1α promoter, regulates glucose metabolic genes such as phosphofructokinase-1 (PFK1), lactate dehydrogenase (LDH), and pyruvate dehydrogenase kinase (PDK), promotes glycolysis, and regulates mitochondrial respiration [55]. SIRT6 increases the liver gluconeogenic gene and NAD^+ from de novo synthesis, and enhances glycerol release from adipose tissue to delay aging [56]. A lack of SIRT6 enhances the membrane association of glucose transporter 1 (GLUT1) and GLUT4, promoting glucose uptake. Simultaneously, SIRT6 regulates AKT signaling, which is negatively correlated with the effects of insulin [57]. Forkhead box protein O1 (FoxO1) and PGC-1α are transcriptional components of the insulin signaling pathway, and play crucial roles in gluconeogenesis. FoxO1, the first identified transcription factor for gluconeogenesis, is activated by PGC-1α. The interaction between FoxO1 and PGC-1α regulates gluconeogenesis [58]. Evidence suggests that statins increase the expression of the SIRT6 inhibitor microRNA (miR)-495 and then acetylate FoxO1, leading to increased gluconeogenesis and hyperglycemia [59]. In addition, SIRT6 controls gluconeogenesis by uniquely upregulating the acetylation of PGC-1α by activating and modifying general control nonrepressed 5 (GCN5) [60].

Lipid metabolism

SIRT6 is also a regulator of lipid metabolism [61]. SIRT6 deficiency results in the upregulation of triglycerides (TGs), cholesterol, and long-chain fatty acid uptake genes, but inhibits β-oxidation [62]. SIRT6 modulates lipid homeostasis by regulating peroxisome proliferator-activated receptor (PPAR) γ-related genes [63]. SIRT6 deficiency enhances the binding rate of the transcription factor PPARγ, thereby promoting fatty acid transporter expression, leading to lipid accumulation and fatty acid uptake [64]. Rosiglitazone (RGZ) is an agonist of PPARγ that can ameliorate hepatic lipid accumulation and increase SIRT6 expression [65, 66]. SIRT6 regulates cholesterol levels by repressing sterol regulatory element-binding proteins 1/2 (SREBP-1/2) and activating AMPK by increasing the AMP/ATP ratio [67]. The proprotein convertase subtilisin/kexin type 9 (PCSK9) gene plays a vital role in regulating LDL cholesterol metabolism. PCSK9 can be regulated by SIRT6 and FoxO3. FoxO3 recruits SIRT6 to the promoter of PCSK9 and deacetylates H3K9 and H3K56 to suppress PCSK9 expression, thus maintaining LDL cholesterol homeostasis [68]. Ubiquitin-specific peptidase 10 (USP10) deficiency induces metabolic dysfunction in high-fat diet (HFD)-treated mice, which can be ameliorated by SIRT6 [69]. SIRT6 can also modulate cholesterol efflux by regulating ATP-binding cassette transporter G1 (ABCG1) expression [70].

Oxidative stress

Under oxidative stress conditions stimulated by pathological factors, excessive ROS are generated. A disruption in the dynamic balance of oxidation and antioxidant capacity causes lipid, protein, and nucleic acid turbulences. Excessive

ROS production directly damages tissues and organs, and acts as a second messenger to induce an immune inflammatory response [71]. Excessive ROS also lead to cellular phenotype transformation and induces apoptosis and necrosis [72–74]. Nrf2 is a crucial redox-sensitive transcription factor that belongs to the Cap-n-Collar (CNC) protein family, and is widely present in the liver, kidney, lung, and other organs. Nrf2 regulates redox homeostasis by interacting with antioxidant response elements (AREs) [75]. SIRT6 is known to attenuate apoptosis and oxidative stress by activating the Nrf2/ARE signaling pathway [76]. SIRT6 can act as a positive regulator of Nrf2. Studies have shown that SIRT6 activates the Nrf2 signaling pathway, mediates the expression of catalase, HO-1, and other downstream antioxidant proteins, and protects proximal renal TECs from oxidative stress [77]. Low SIRT6 expression is related to oxidative stress in diabetes, and patients with type 2 diabetes who are treated with sodium-dependent glucose transporter 2 (SGLT2) inhibitors have increased SIRT6 expression and reduced oxidative stress [78]. USP10 protects against a variety of environmental stresses, including oxidative stress [79]. USP10 promotes activation of the Nrf2/HO-1 pathway through SIRT6 to reduce oxidative stress and attenuate cell injury [80]. SIRT6 directly interacts with and deacetylates PGC-1α through the AMPK pathway to maintain mitochondrial homeostasis and oxidative stress [81]. SIRT6 can also reduce oxidative stress by regulating the AKT signaling pathway. SIRT6 directly controls AKT signaling at the chromatin level through H3K9 and H3K56 deacetylation, negatively regulates the level of phosphorylated AKT, and induces autophagy, thus exerting an antioxidant effect [82–84]. Moreover, SIRT6 overexpression activates the phosphorylation of AMPKα, increases the levels of FoxO3α, decreases the phosphorylation activity of the protein kinase AKT, and further increases the expression of the downstream antioxidant proteins MnSOD and Catalase [85]. This evidence indicates that SIRT6 can inhibit oxidative stress through multiple pathways and exert a protective effect (Fig. 3).

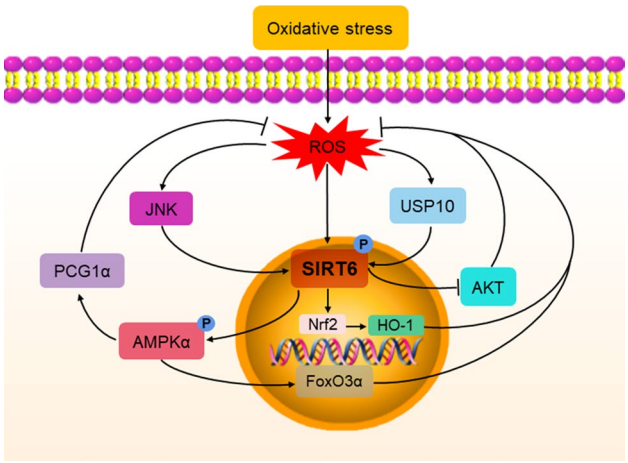


Fig. 3 The role of SIRT6 in the regulation of oxidative stress. ROS overproduction activates JNK, phosphorylates Ser10 on SIRT6, recruits SIRT6 to DNA damage sites, and regulates DNA repair. USP10 promotes activation of the Nrf2/HO-1 pathway through SIRT6, and further alleviates oxidative stress. SIRT6 inhibits AKT signaling and activates AMPK to regulate mitochondrial biogenesis and has an antioxidative effect. *JNK* Jun-N-terminal kinase, *USP10* Ubiquitin-specific peptidase 10, *AMPK* AMP-activated protein kinase, *Nrf2* Nuclear factor erythroid-related factor 2, *HO-1* heme oxygenase 1, *ROS* Reactive oxygen species, *FoxO3α* Forkhead box O3α, *PGC1α* Peroxisome proliferator-activated receptor gamma coactivator 1-alpha

Inflammation

SIRT6 also plays a unique regulatory role in the immune inflammatory response. SIRT6 deficiency increases pro-inflammatory cytokine production and adhesion molecule expression, leading to chronic inflammation and fibrosis [86]. SIRT6 deficiency promotes the expression of nuclear factor kappa-B (NF-κB) which is a well-known inflammatory factor that is widely expressed in cells [87]. The NF-κB transcription factor family can regulate inflammation-related gene expression and affect cellular activities that are closely related to various biological processes [88]. NF-κB activation induces an inflammatory response by promoting the release of inflammatory mediators from monocytes. NF-κB enables downstream pyrin domain containing protein 3 (NLRP3) signaling and tumor necrosis factor alpha (TNF-α) expression, further promoting the release of pro-interleukin-18 (pro-IL-18) and pro-IL-1β and the downstream inflammatory factors IL-1β and IL-18. SIRT6 can act as a negative regulator of NF-κB to regulate inflammation through histone H3K9 deacetylation [89, 90]. Mechanistically, SIRT6 binds to p65/RelA in the NF-κB promoter region, deacetylates histone H3K9, stabilizes RelA on chromatin, and inhibits transcriptional activity to terminate NF-κB signaling [91]. Additionally, SIRT6 plays an anti-inflammatory role by inhibiting the expression of c-JUN-dependent proinflammatory genes monocyte chemotactic protein 1 (MCP1) and IL-6 [92]. Notch signaling exacerbates cell damage by mediating the inflammatory response, apoptosis, and autophagy inhibition, which can be regulated by epigenetic modifications and is a potential target of SIRT6 [93]. A reduction in SIRT6 leads to increased H3K9 acetylation in the Notch1 and Notch4 promoters, and the activation of Notch signaling further exacerbates cell damage [94]. Multiple studies have shown the protective role of SIRT6 in alleviating inflammation, as mentioned previously, and SIRT6 increases TNF-α secretion by removing the fatty acyl modification on K19 and K20 of TNFα [95]. The precise modulatory effect of SIRT6 on inflammation needs further elucidation (Fig. 4).

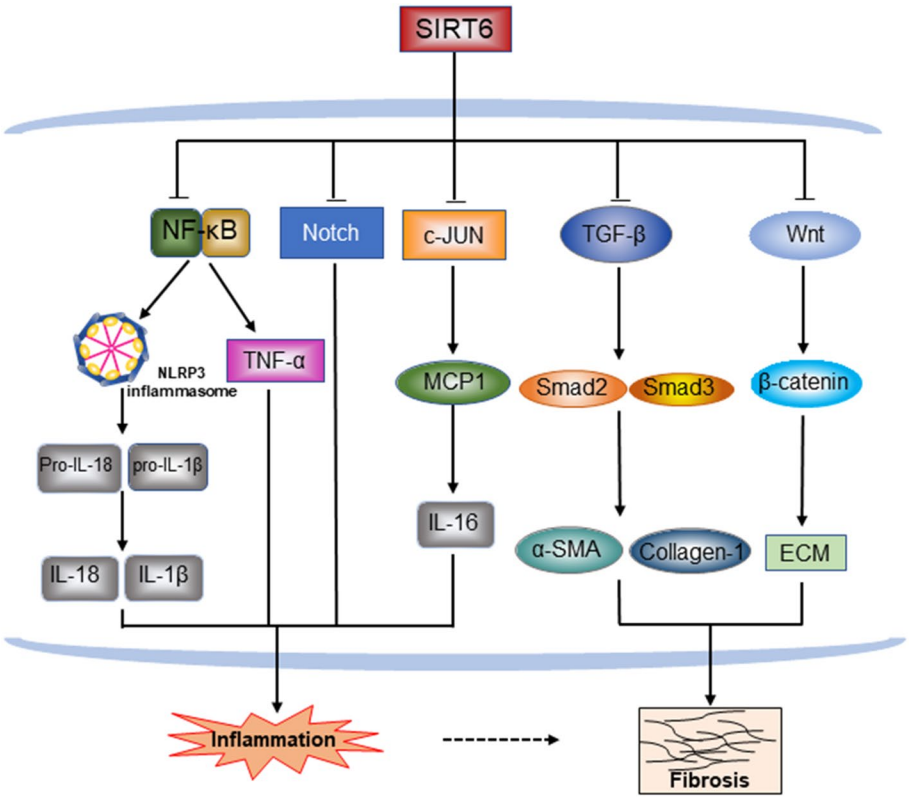


Fig. 4 The role of SIRT6 in the regulation of inflammation and fibrosis. SIRT6 plays a unique role in regulating inflammation and fibrosis. SIRT6 can act as a negative regulator of NF-κB to inhibit NLRP3 and TNF-α expression, and further reduce the release of pro-interleukin-18 (pro-IL-18) and pro-IL-1β and the downstream inflammatory factors IL-1β and IL-18. Additionally, SIRT6 plays an anti-inflammatory role by inhibiting the expression of the c-JUN-dependent pro-inflammatory genes MCP1 and IL-6. Notch signaling also promotes inflammation and can be negatively regulated by SIRT6. Fibrosis is the main pathological process of various chronic diseases at the end stage and can be driven by inflammation. SIRT6 negatively regulates TGF-β and reduces the activation of downstream Smad signaling. SIRT6 can also negatively regulate Wnt/β-catenin, thus alleviating fibrosis. *c-JUN* c-Jun-N-terminal kinase, *TNF-α* Tumor necrosis factor alpha, *NF-κB* Nuclear factor kappa-B, *ECM* Extracellular matrix, *MCP1* Monocyte chemotactic protein 1

Fibrosis

Fibrosis is driven by inflammation and is the main pathological process of various chronic diseases that progress to an end stage [96]. TGF-β is the main factor involved in the phenotypic transformation of fibroblasts. While participating in cell growth and differentiation, TGF-β also plays an important role in regulating intercellular substance production, apoptosis, and the inflammatory response [97, 98]. TGF-β type II receptor (TGF-βR II) is activated through the autophosphorylation of Ser213 and Ser409, and then activated TGF-βR II interacts with TGF-βR I and enhances the enzymatic activity of TGF-βR I. Activated TGF-βR I further recruits and activates downstream Smad proteins to accumulate in the nucleus and acts as a transcription factor to regulate transcription [99]. In addition, TGF-β can also activate MAPK, PI3K–AKT, and PAK2 signaling molecules through nonclassical pathways to regulate fibrosis [100–102]. Wnt is a crucial pathway for regulating epithelial–mesenchymal transition (EMT). Wnt/β-catenin signaling regulates cell differentiation and regeneration and cross-linking with TGF-β and Notch signals [103]. TGF-β can activate the classic Wnt signaling pathway by downregulating the expression of the Wnt signaling pathway antagonist Dickkopf 1 (DKK1). On one hand, SIRT6 negatively regulates TGF-β, reduces the activation of downstream Smad signaling, and alleviates fibrosis [104]. On the other hand, SIRT6 interacts with β-catenin to regulate TGF-β, binds to the β-catenin promoter, and causes the deacetylation of histone H3K56, thereby preventing the transcription of genes related to fibrosis [16]. Some studies have proven that SIRT6 can directly or indirectly influence Notch signaling factor expression [105, 106]. The activation of Notch signaling induces TEC dedifferentiation and renal fibroblast proliferation, thus promoting renal fibrosis [107]. The interaction between Wnt and Notch signaling is critical for maintaining cellular function. Inhibiting the Wnt signaling pathway can restore the phenotype induced by the blockade of Notch signaling [108]. Collectively, SIRT6 can serve as a therapeutic target for fibrosis (Fig. 4).

SIRT6 in kidney disease

The high incidence of kidney disease remains a challenge worldwide in public health management. Exploring the pathogenesis and preventive mechanisms will help us to find better ways to treat kidney disease. SIRT6 has been proven to be involved in the progression of kidney disease. The potential role of SIRT6 in kidney disease needs to be further studied.

CKD

Diabetic kidney disease (DKD)

DKD is a common microvascular disease and one of the most serious chronic complications of diabetes [109]. With the increasing incidence of diabetes, DKD has become the main cause of ESRD [110]. The pathogenesis of DKD is complex. It is currently believed that genetic factors, hemodynamic changes, oxidative stress, inflammation, and mitochondrial damage jointly participate in the occurrence and development of DKD [111–113]. High glucose induces mitochondrial superoxide production in podocytes, further promoting mitochondrial dysfunction associated with mitochondrial morphological alterations and decreased mitochondrial membrane potential [114]. SIRT6 upregulation by plasmid transfection can protect mitochondrial function and alleviate oxidative stress by increasing AMPK phosphorylation, indicating that SIRT6 protects mitochondria and exerts antiapoptotic effects by activating the AMPK pathway [51]. Inflammation is also one of the main pathological features of DKD [115]. The mRNA levels of the inflammation-related factors IL-1β, IL-6, and TNF-α in podocytes were reduced by SIRT6. High glucose can activate the Notch signaling pathway in podocytes, and podocyte-specific overexpression of the intracellular domain of Notch1 (ICN1) induces proteinuria and glomerulosclerosis [116]. Activation of the Notch signaling pathway leads to endocytosis of nephrin and podocin, thereby destroying the structure of the podocyte split membrane and inducing proteinuria [117, 118]. SIRT6 protects against podocyte inflammation through epigenetic regulation of the Notch signaling pathway, suggesting that SIRT6 is a potential therapeutic target to protect podocytes from high glucose-induced injury. In brief, SIRT6 regulates the action of H3K9 deacetylation and binds to the promoter regions of Notch1 and Notch4 to inhibit transcription and activation of the downstream PTEN signaling pathway, further increasing autophagic flux and alleviating apoptosis and inflammation in podocytes [93]. In addition, SIRT6 protects podocytes against DKD by activating M2 macrophage transformation and acts as an immune regulator in inflammatory injury [119]. In addition, the NMN-producing enzyme nicotinamide phosphoribosyl-transferase (Nampt) has been proven to have a protective role in DKD. Proximal tubule Nampt-specific knockout mice showed SIRT6 downregulation, resulting in collagen deposition and a fibrotic phenotype, suggesting the protective role of Nampt-SIRT6 signaling in DKD [120]. This evidence shows that SIRT6 plays a protective role in high glucose-induced renal injury by reducing oxidative stress, mitochondrial damage, and inflammation, suggesting that SIRT6 could be a potential therapeutic target for preventing and delaying the progression of DKD.

Hypertensive kidney lesion

Hypertension is a chronic disease characterized by elevated systemic blood pressure and is considered to be a vital risk factor for coronary heart disease and CKD [121]. Endothelial dysfunction is associated with the occurrence of hypertension and is the main cause of hypertension-induced injury [122]. Although multiple pathogenic factors in hypertension have been revealed, the precise pathogenesis remains unclear. Previous studies have showed that hypertension reduces the level of the endothelium-dependent vasodilator nitric oxide, changes the permeability of endothelial cells, promotes the production of endothelin 1 (ET-1) and angiotensin II (Ang II), and then exacerbates target organ damage, including renal and cardiovascular injury [123]. The sirtuin family is involved in pathological processes associated with regulating blood pressure, fibrotic remodeling, and cell apoptosis [70, 124, 125]. As recently revealed, SIRT6 delays vascular aging and prevents hypertension by maintaining endothelial homeostatic functions [126]. MiR-122, acting as a risk biomarker of vascular fibrosis, has been confirmed to participate in the development of hypertension by inducing endothelial dysfunction [127]. SIRT6 is directly targeted by miR-122. Activation of the SIRT6-ELA pathway inhibits miR-122 and alleviates vascular oxidative injury and subsequent inflammation, negatively regulating Ang II-induced hypertension [128]. Additionally, SIRT6 overexpression weakens Ang II-induced apoptosis and oxidative stress in vascular cells by promoting Nrf2 signaling pathway activation [76]. SIRT6 also induces the expression of the blood pressure-related gene GATA5 by inhibiting the transcription of Nkx3.2, which is essential for endothelial homeostasis and protects vascular endothelial cells against hypertension and related organ injury [124]. Ang II induces cholesterol accumulation in podocytes and promotes CKD progression. Specific deletion of SIRT6 in podocytes exacerbates Ang II-induced kidney injury and affects cholesterol efflux by regulating the expression of ABCG1, suggesting that SIRT6

plays a protective role in the regulation of cholesterol metabolism in podocytes [70]. These studies indicate the unique role of SIRT6 signaling in the regulation of blood pressure and kidney injury.

Kidney senescence

Aging is an irreversible process and an important risk factor for multiple diseases [129]. Cellular senescence occurs in all renal cells, including TECs, mesangial cells, and podocytes. Age-related disruptions in kidney disease are associated with cellular senescence [130]. In kidney disease, age-related disruptions induce renal fibrosis and diminish glomerular filtration, decreasing kidney function. The reduction in renoprotective factors exacerbates cellular senescence. Mitochondrial ROS (mtROS) production drives stress-induced senescence and further leads to chronic inflammation and renal dysfunction, particularly in renal tubular cells [131]. Among the sirtuin members, SIRT6 has been implicated in regulating cellular senescence by attenuating inflammation, maintaining telomere integrity, and participating in DNA repair [132, 133]. SIRT6 knockdown results in activation of the NF-κB signaling pathway and accelerates cellular senescence. Caloric restriction (CR) significantly enhances SIRT6 expression and reverses age-dependent renal insufficiency [134]. In addition, SIRT6 maintains podocyte homeostasis and plays an important role in aging-associated glomerular function. SIRT6-deficient aging mice exhibit chronic inflammation and fibrosis and the loss of glomerular function [135]. This evidence supports the protective role of SIRT6 in renal cellular senescence.

Renal cancer

As a specific type of longevity gene, SIRT6 is considered as a tumor suppressor in renal cell carcinoma (RCC) [136]. SIRT6 is upregulated in RCC. Silencing SIRT6 expression promotes G1/S phase arrest and suppresses tumor growth [137]. The expression level of SIRT6 depends on tumor stage and histological grade and further corelates with prognosis in clear cell renal cell carcinoma (ccRCC) [138]. SIRT6 inhibition increases the sensitivity of ccRCC to cisplatin, which is strongly associated with Bcl-2 and BAX expression, and further initiates apoptosis-related processes [139].

AKI

Unilateral ureteral obstruction (UUO)

Obstructive nephropathy is a severe health problem and a critical factor in the development of CKD worldwide [140]. Persistent obstruction leads to renal pelvic effusion and irreversible kidney damage. UUO is characterized by progressive fibrosis [141, 142]. After UUO, tubular and interstitial cells release damage-associated molecular patterns (DAMPs), which are recognized by pattern recognition receptors (PRRs) and mediate the immune response, leading to inflammatory cell infiltration, increased levels of profibrotic factors, and matrix deposition [143]. SIRT6 deficiency specifically increases H3K56 acetylation at the promoter region of β-catenin, amplifies fibrosis-related protein expression, and exacerbates UUO-induced renal injury and fibrosis. The interaction between SIRT6 and TGF-β weakens the expression of β-catenin target genes and plays an antifibrotic role [16]. In addition, SIRT6 reduces inflammation by negatively regulating the NF-κB signaling pathway and synergistically regulates chronic renal fibrosis in ureteral obstruction [144]. In addition, accumulating evidence has confirmed that inflammation and fibrosis induced by UUO are closely related to mitochondrial dysfunction [145]. However, there is still no clear evidence indicating that SIRT6 alleviates UUO-induced AKI by regulating mitochondrial function. Based on this evidence, we conclude that SIRT6 ameliorates inflammation and fibrosis, and may be a therapeutic target for UUO.

Cisplatin-induced kidney damage

Cisplatin is an effective chemotherapeutic drug and is widely used to treat solid tumors, but severe side effects limit its applications [146]. Consecutive cisplatin administration results in irreversible nephrotoxicity [147]. Tubulointerstitial injury is the main pathological characteristic of cisplatin-induced renal injury. The accumulation of cisplatin in proximal tubular cells results in apoptosis and necrosis [148]. Nrf2 has been proven to play a significant role in cisplatin-induced renal injury by eliminating oxidative stress and subsequent inflammation mediated by NF-κB signaling [149]. SIRT6 is a positive regulator of the Nrf2 signaling pathway and acts as an antioxidative agent in cisplatin-induced renal injury [77]. Daphnetin, a natural coumarin, acts as an antioxidant in cisplatin-induced kidney damage through SIRT1/SIRT6-Nrf2 activation [77]. SIRT6 deficiency worsens cisplatin-mediated proximal tubular cell apoptosis, while SIRT6 overexpression inhibits extracellular signal-regulated kinase 1 (ERK1) and ERK2 expression, further inhibiting NF-κB signaling, suggesting that SIRT6 acts as an inhibitor of cisplatin-induced nephrotoxicity [151]. Taken together, this evidence hints at the protective role of SIRT6 in cisplatin-induced kidney damage, and SIRT6 may be a therapeutic target for nephrotoxic drug-induced kidney injury.

Other AKI models

In addition to kidney injury models, as mentioned previously, SIRT6 also plays a vital role in sepsis-induced AKI and cadmium-induced kidney toxicity. Sepsis caused by infection is a life-threatening condition and a crucial cause of AKI [152]. In the lipopolysaccharide (LPS)-induced sepsis AKI model, SIRT6 overexpression alleviated the LPS-induced inflammatory response and apoptosis in epithelial cells by promoting autophagy [153]. Cadmium exposure is a high-risk factor for kidney disease. Continuous exposure to cadmium increases the incidence of apoptosis and necrosis in proximal tubular cells [154]. SIRT6 has been shown to regulate cell apoptosis induced by cadmium through the polyubiquitinated (polyUb)-p62/SIRT6 signaling pathway [155]. These findings confirm that SIRT6 promotes autophagy and alleviates apoptosis and inflammation under stress conditions [156, 157].

SIRT6 in the AKI-to-CKD transition and kidney repair

AKI is a common complication among hospitalized patients and has become a growing public health problem associated with a high risk of developing CKD. Although the kidney has a strong compensatory ability, studies have shown that AKI causes irreversible microvasculature damage and impairs kidney structure and function [158, 159]. The incomplete recovery of renal function after AKI causes persistent chronic inflammation and fibrosis, which eventually progresses to ESRD [160]. The molecular mechanisms of the conversion of AKI to CKD are complicated. It is currently recognized that proximal tubular cell injury is the main pathological feature of chronic progression of AKI due to high energy demands [161, 162]. Proximal tubular cells are rich in mitochondria, which are sensitive to hypoxia and easily perceive changes in energy metabolism [163]. Persistent renal tubular injury caused by ischemia and hypoxia, mitochondrial dysfunction, and inflammation contribute to metabolic constraints and induce cytoskeletal rearrangement, extracellular matrix (ECM), and EMT in TECs. ECM accumulation and EMT account for tubulointerstitial fibrosis (TIF), leading to the development of CKD, and are considered to be the common pathway to ESRD [95, 164, 165]. SIRT6 has been shown to have a regulatory role in the progression of kidney disease. However, the current understanding of the pathological process, mechanisms of action, and clinical applications of SIRT6 in kidney disease, especially chronic progression, is still limited. SIRT6 may serve as a therapeutic target, and finding suitable treatments to prevent the chronic progression of kidney disease is critical. Here, we summarize the potential role of SIRT6 in the AKI-to-CKD transition and kidney repair.

Hypoperfusion after AKI causes persistent tissue ischemia and hypoxia, further leading to vascular endothelial cell damage, microvascular reductions, and proximal tubular cell injury [166]. Hypoxia leads to insufficient energy supply and inflammatory factor production in renal tubule epithelial cells. After renal tubule injury, the remaining epithelial cells enter the cell cycle and participate in regeneration through dedifferentiation and proliferation under the action of growth factors and chemokines [167]. However, in severe ischemia, hypoxia, persistent exposure to nephrotoxic drugs and inflammation, cell cycle arrest, and TGF-β activate profibrotic factor release, resulting in the accumulation of ECM [168, 169]. In addition, inflammatory factors initiate EMT, which promotes renal interstitial fibrosis [170, 171]. Hypoxia reduces the expression of SIRT6 in renal TECs. SIRT6 deficiency exacerbates hypoxia-induced inflammation and G2/M cycle arrest in renal TECs, which can be reversed by upregulating SIRT6, suggesting that SIRT6 protects renal TECs from hypoxia-induced tubular interstitial injury [172].

Mitochondria are central hubs that maintain cellular and redox homeostasis. The loss of mitochondrial quality control is the main mediator of incomplete repair after AKI [173]. ROS overproduction induces renal tubular cell injury and nephron dropout, further impairing mitochondrial structural integrity. Nrf2, acting as an antioxidant, has been proven to regulate mitochondrial quality control by binding to the promoter region of PINK1 [174]. SIRT6 activates Nrf2 and prevents Keap1 proteasomal degradation, increasing mitochondrial biogenesis, mitophagy, and the mitochondrial antioxidant response [49]. Additionally, the activation of AMPK stimulates downstream AKT signaling, phosphorylates FoxO3α, and further attenuates mitochondrial dysfunction [175]. SIRT6 promotes autophagy-related protein expression and maintains mitochondrial function by AMPK signaling pathway activation under oxidative stress conditions [176]. Collectively, mitochondrial quality control shows a protective role in kidney repair after AKI. SIRT6 increases the ROS-scavenging capacity and maintains mitochondrial quality, which is critical in AKI and kidney repair.

Lipid accumulation is involved in the progression of kidney disease [177]. The enzymes associated with fatty acid oxidation (FAO) are reduced in kidney fibrosis models, and restoring FAO through genetics may prevent the progression of CKD [178]. CK2 activity is regulated by SIRT6 and plays an important role in adipogenesis [179]. SIRT6 expression is decreased in obese pre-DM subjects, while the expression of NF-κB, PPAR-γ and SREBP-1 is increased. Of note, these effects can be reversed by metformin treatment [180].

Fibrosis is the common pathway associated with irreversible and progressive processes causing chronic development of kidney disease. TIF is mainly triggered by persistent chronic inflammation and fibrillary collagen accumulation.

Table 1 The regulatory roles of SIRT6 in kidney disease

Kidney disease		SIRT6 intervention and molecular signaling	Biological effects	References
CKD	DKD	M2 macrophage transformation	Attenuated podocyte injury	[119]
		Notch signaling pathway	Attenuated podocyte injury	[94, 116–118]
		Nampt/SIRT6 signaling pathway	Attenuated fibrotic extracellular matrix remodeling	[120]
		AMPK signaling pathway	Attenuated podocyte injury	[51]
	Hypertensive kidney lesion	ABCG1	Attenuated podocyte injury	[70]
	Kidney senescence	NF-κB signaling pathway	Attenuated chronic inflammation and fibrosis	[134]
	Renal cancer	G1/S phase arrest	suppresses tumor growth	[137]
		Bcl-2	inhibiting mitochondrial apoptotic	[139]
AKI	UUO	TGF-β/Smad3 and NF-κB signaling pathway	Attenuated renal inflammation and fibrosis	[144]
		β-Catenin signaling pathway	Anti-fibrosis	[16]
	Cisplatin-induced kidney damage	Nrf2 signaling pathway	Antioxidation	[77, 150]
		ERK1 and ERK2 pathway	Regulated inflammation and apoptosis	[151]
	Sepsis-induced AKI	Autophagy	Alleviated renal epithelial cell apoptosis	[153]
	Cadmium-induced kidney toxicity	polyUb-p62/SIRT6 signaling	Alleviated cell apoptosis and inflammation	[155]

DKD Diabetic kidney disease, *UUO* Unilateral ureteral obstruction, *AMPK* AMP-activated protein kinase, *ERK1*/2 extracellular signal-regulated kinase 1/2, *AKI* Acute kidney injury, *polyUb* polyubiquitinated

Increased proinflammatory cytokines interfere with intrarenal microcirculation and perfusion, contributing to EMT [181]. Activation of the inflammatory response-associated transcription factors NF-κB and STAT promotes tubulointerstitial inflammation and kidney fibrosis, and inhibiting these factors can ameliorate kidney fibrosis [182]. The TGF-β signaling pathway is the central mediator of renal fibrosis in progressive CKD. TGF-β promotes EMT and inhibits ECM degradation in renal tubular cells during the progression of CKD [183]. Wnt/β-catenin signaling regulates fibrosis and participates in the progression of CKD. β-Catenin overexpression in tubular cells induces epithelial dedifferentiation and EMT in mice [184]. The Notch signaling pathway also plays an important role in orchestrating the development of kidney disease. Notch expression in podocytes promotes glomerulosclerosis and albuminuria. Additionally, Notch expression in TECs promotes EMT-related snail1 and snail2 expression, thus contributing to TIF [185]. It is worth noting that the inflammatory response is also regulated by epigenetics. SIRT6 depletion induces chronic inflammation and fibrosis in the kidney and eventually leads to podocyte depletion, proteinuria, and the loss of kidney function. Studies have confirmed that SIRT6 negatively regulates the TGF-β and Wnt/β-catenin signaling pathways and plays an antifibrotic role [16]. In addition, high mobility group box 1 (HMGB1) exacerbates CKD progression by promoting vascular calcification. Bone marrow mesenchymal stem cell (BMSC)-derived exosomes downregulate HMGB1 expression through the SIRT6–HMGB1 pathway and ameliorate CKD-related fibrosis [17].

Overall, in-depth investigation of energy metabolism, inflammatory response, and fibrosis inhibition in kidney disease is essential in identifying specific and efficacious approaches for disease transition.

Conclusion and prospects

As a member of the sirtuin family, SIRT6 maintains intracellular homeostasis and is considered to be a powerful regulator of disease occurrence and development. In this review, we summarize the structure and biological function of SIRT6. We further summarize the regulatory mechanisms and potential roles of SIRT6 in multiple kidney diseases (Table 1). SIRT6 has shown a powerful regulatory effect on DNA repair, energy metabolism, oxidative stress, mitochondrial homeostasis, inflammation, fibrosis, and aging. Mechanistically, SIRT6 regulates transcription factors by deacetylating of histone H3K9, H3K56, and H3K18 on target gene promoters and controls downstream gene expression, thus maintaining cellular homeostasis. In kidney disease, SIRT6 regulates oxidative stress under hypoxia and stress conditions by regulating the Nrf2, AMPK, and AKT signaling pathways. SIRT6 participates in the pathogenesis of chronic inflammation and renal fibrosis by regulating the TGF-β1/Smad3, Wnt/β-catenin, NF-κB, β-catenin, and

Notch signaling pathways. Moreover, SIRT6 synergistically maintains the content and integrity of mitochondria. These regulatory mechanisms are closely related to renal repair and survival. In-depth study of the regulatory mechanism of SIRT6 will help to identify new targets for kidney disease. Further exploration of the characteristics of SIRT6 has potential value and provides new ideas for the treatment of the chronic progression of kidney disease. In summary, focusing on SIRT6 as a target has important clinical significance for the prevention and treatment of kidney disease.

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