

Sirtuin 1: A Target for Kidney Diseases

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Sirtuin 1 (SIRT1) is an evolutionarily conserved NAD⁺-dependent histone deacetylase that is necessary for caloric restriction-related lifespan extension. SIRT1, as an intracellular energy sensor, detects the concentration of intracellular NAD⁺ and uses this information to adapt cellular energy output to cellular energy requirements. Previous studies on SIRT1 have confirmed its beneficial effects on cellular immunity to oxidative stress, reduction of fibrosis, suppression of inflammation, inhibition of apoptosis, regulation of metabolism, induction of autophagy and regulation of blood pressure. All of the above biological processes are involved in the pathogenesis of kidney diseases. Therefore, the activation of SIRT1 may become a therapeutic target to improve the clinical outcome of kidney diseases. In this review, we give an overview of SIRT1 and its molecular targets as well as SIRT1-modulated biological processes, with a particular focus on the role of SIRT1 in kidney diseases.

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INTRODUCTION

Acetylation is an evolutionarily conserved posttranslational modification occurring on lysine residues. Increasing evidence has demonstrated the critical role of histone acetylation/deacetylation in gene transcription (1,2). Histone acetylation mediated by histone acetyltransferases promotes an open chromatin formation, which provides binding sites for basal transcription factors and RNA polymerase II to facilitate gene transcription. In contrast, histone deacetylases (HDACs) remove acetyl group from lysine residues of histone, resulting in chromatin compaction and transcription repression (3). In addition, emerging evidence indicates that transcription factors

and transcriptional coregulatory proteins are also regulated by acetylation/deacetylation (3–6). Three classes of mammalian HDACs have been identified, of which silent information regulator 2 (Sir2) or class III HDACs are NAD⁺-dependent HDACs using coenzyme NAD⁺ for the removal of acetyl groups from lysine residues of histone proteins and nonhistone proteins (7).

Sirtuins, a group of NAD⁺-dependent HDACs, are members of the Sir2 family. Mammals have several different sirtuins. Because of their different acylprotein substrate specificity, binding partners and intracellular localization, sirtuins are divided into sirtuin 1–7 (SIRT1–7) (8). SIRT1 and SIRT2 can be found in both

the cytoplasm and the nucleus. SIRT6 and SIRT7 are almost exclusively in the nucleus, but at different subnuclear localizations. SIRT3 to SIRT5 are located in the mitochondria (9). The most studied mammalian sirtuin is SIRT1, which is identified as an important molecule necessary for caloric restriction-related longevity. Upon calorie restriction, increased intracellular NAD⁺ concentrations promote SIRT1 activity. By using the coenzyme NAD⁺, SIRT1 promotes chromatin silencing and transcriptional repression through deacetylation of histones (10). Furthermore, histone methylation and acetylation are often coordinately regulated. Histone deacetylation by SIRT1 may also enhance histone methylation (11,12). Histone methylation could activate or repress gene expression, depending on the methylation sites (13). For example, methylation at H3K9, H4K20 and H3K27 represses gene expression, whereas methylation at H3K4, H3K36, and H3K79 results in chromatin activation in transcriptional controls (14). In addition, several transcription factors and transcriptional coregulatory proteins, such as p53 and nuclear factor- κ B (NF- κ B), also serve as substrates for SIRT1 (15,16). Acetylation of transcription factors and transcriptional coregula-

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tory proteins has been demonstrated to modulate their functions by altering their stability, activity, subcellular localization, DNA-binding ability and protein–protein interactions (17,18). It is noteworthy that, depending on the protein and acetylation site, deacetylation may exert divergent, or even opposite, effects. For example, deacetylation of p53 reduced its DNA-binding ability (15). However, deacetylation caused enhanced DNA-binding ability of forkhead box O1 (FOXO1) (19). Through deacetylation of histones and transcriptional regulators, SIRT1 regulates transcriptional activity and is therefore linked to cellular energy metabolism, fibrosis, mitochondrial biogenesis, stress responses, apoptosis, inflammation and autophagy. Consistent with its dual cellular localization, SIRT1 targets can be found in both the nucleus and the cytoplasm. SIRT1 activation exerts protective effects on multiple organs upon oxidative stress, including kidney (12,20–23), whereas SIRT1 knockout (KO) mice show aggravation of renal changes occurring in diabetes and acute kidney injury (12,24).

SIRT1 ACTIONS

SIRT1 Preserves Podocyte Function by Targeting Claudin-1

Diabetic nephropathy (DN) is one of the microvascular complications of diabetes. One of the earliest features in DN is the loss of podocytes, also known as glomerular epithelial cells (25). The glomerular filtration barrier consists of three parts: endothelial cells, the glomerular basement membrane and podocytes. Podocytes have a prominent role in albumin handling and maintaining the integrity of the glomerular filter, and podocyte injury leads to progressive proteinuric kidney diseases. Through mitochondrial and NADPH oxidase pathways, high blood glucose stimulates the generation of reactive oxygen species and leads to activation of proapoptotic p38 mitogen-activated protein kinase and caspase 3, eventually resulting in apoptosis of podocytes and proteinuria.

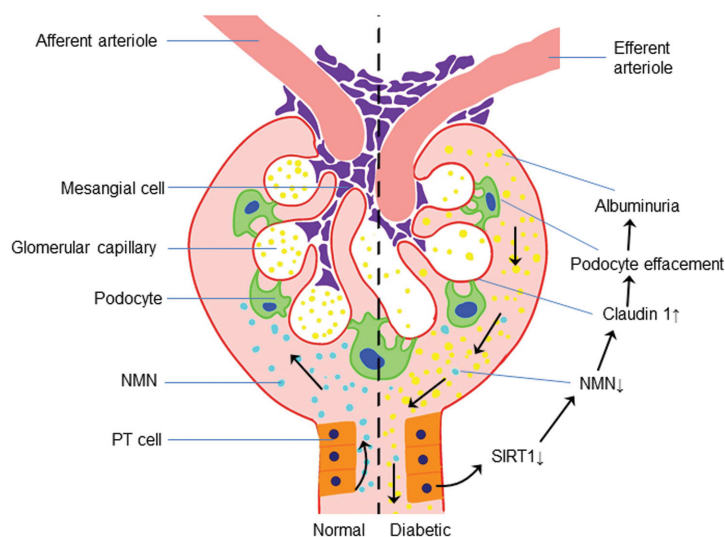


Figure 1. Renal tubule SIRT1 preserves podocyte function. Normally, SIRT1 in PT maintains glomerular NMN concentrations that lead to epigenetic silencing of *claudin-1* promoter in podocytes. PT SIRT1 decreases in response to diabetes, followed by decreased glomerular NMN concentrations that in turn reduce SIRT1 expression in podocytes. *Claudin-1* promoter is no longer silenced because of the downregulation of SIRT1. Consequently, high levels of claudin-1 in podocytes induce podocyte effacement and albuminuria.

It is generally believed that the glomerulus is the primary site of injury in DN. However, its progression correlates best with tubular epithelial degeneration and interstitial fibrosis (26,27).

Studies by Hasegawa *et al.* (12) showed that renal proximal tubule (PT)-specific SIRT1 could epigenetically downregulate the expression of the tight junction protein claudin-1 in podocytes and protect the glomerular changes induced by diabetes. Claudins, which are important components of tight junctions, are reported to be involved in the pathogenesis of albuminuria (28,29). Hasegawa *et al.* found a target for methylation, CpG islands, within the *claudin-1* genes. Claudin-1 expression was regulated epigenetically through deacetylation of histone H3 and H4 by SIRT1, with subsequent CpG methylation of the *claudin-1* gene by recruited DNA methyltransferase 1. For the first time, their study provided pivotal evidence for interaction between PT cells and podocytes through nicotinamide mononucleotide (NMN). Under normal conditions, high concentrations of NMN led to deacetylation of

both H3 and H4 histones and enhanced CpG methylation of the *claudin-1* gene by SIRT1, and eventually *claudin-1* promoter was silenced in podocytes. Under diabetic conditions, PT SIRT1 expression was decreased, which decreased NMN concentrations around glomeruli. Low concentrations of NMN induced low levels of SIRT1 in podocytes, with subsequent acetylation of both H3 and H4 and hypomethylation of *claudin-1* CpG regions, which led to claudin-1 overexpression in podocytes. High levels of claudin-1 in podocytes induced podocyte effacement and albuminuria (Figure 1). To confirm the above results, the investigators measured renal expression of SIRT1 and claudin-1 in human specimens with diabetes. They found that SIRT1 and claudin-1 were negatively correlated with each other. The former and the latter were negatively and positively correlated with proteinuria, respectively. Their study suggested a model in which SIRT1 in PT affected glomerular podocytes and proteinuria by maintaining NMN concentrations around glomeruli. Their study is important. On one hand, it identified

SIRT1 as an important regulator of claudin-1, a key regulator of albuminuria and glomerular function. On the other hand, it suggested the SIRT1–claudin-1 crosstalk between renal tubules and glomerulus regulated renal function. The study also helps us to understand the communication among different cells in different segments of the nephron. However, more studies are needed to determine the mechanism regulating NMN concentrations in PT based on glucose condition or SIRT1 expression level. Also, their data suggest that NMN derived from PT cells is absorbed by podocytes, but how NMN goes upstream against glomerular filtration force remains unclear. Nevertheless, their exciting results encourage further investigation of SIRT1 and claudin-1 as therapeutic targets of DN. Furthermore, there was also a study suggesting that claudin-1 contributed to crescent formation in crescentic glomerulonephritis (30). Thus, future studies are needed to investigate whether SIRT1, as a negative regulator of claudin-1, can serve as a potential target to prevent or treat crescentic glomerulonephritis.

SIRT1 Reduces Fibrosis by Smad3 (Targeting Mothers against Decapentaplegic Homolog 3) and Smad4

Transforming growth factor (TGF)- β is an important cytokine regulating apoptosis, cell cycle, differentiation and extracellular matrix accumulation (31–33). A large body of evidence has linked TGF- β /Smad signaling to the development and progression of renal fibrosis (34–36). Reversal of Smad3 acetylation via SIRT1 inhibited the TGF- β 1–induced profibrotic response *in vitro* and unilateral-ureteric-obstruction–induced interstitial fibrosis *in vivo* (37–39). Furthermore, coimmunoprecipitation assay provided direct evidence of an interaction between Smad3 and SIRT1 (38,39).

In addition, the loss of SIRT1 in kidney tubular epithelial cells exacerbated injury-induced kidney fibrosis, but SIRT1 reduced epithelial-to-mesenchymal transition (EMT) in kidney fibrosis by

deacetylating Smad4 and repressing the effect of TGF- β signaling on matrix metalloproteinase-7, a Smad4 target protein (40).

SIRT1 Inhibits Apoptosis by Targeting p53, Smad7, FOXO3 and FOXO4

Apoptosis removes unwanted or damaged cells and has been implicated in the pathogenesis of various kidney diseases, including DN (41–44). Under diabetic conditions, oxidative stress caused by various stressors such as high glucose, angiotensin II and advanced glycation end products enhances apoptosis of glomerular mesangial cells, podocytes and renal tubular cells (44–46). Reportedly, SIRT1 deacetylates several apoptosis-related proteins, such as p53, Smad7, FOXO3 and FOXO4, protecting renal cells against damage-induced apoptosis (47–51).

As discussed above, loss of podocytes takes an important role in the pathogenesis of DN. *In vitro* study showed that high glucose–induced apoptosis in podocytes was mediated by p53 pathways (52). *In vivo* study showed that advanced oxidation protein products induced by diabetes led to podocyte apoptosis by a p53 apoptotic pathway, which was preceded by the increase in albuminuria (53). P53 was upregulated and activated in the renal cortex of *db/db* mice and streptozotocin (STZ)-induced diabetic mice and rats, leading to the increased podocyte apoptosis and albuminuria (53,54). In addition, p53 could also increase the apoptosis of mesangial cells and tubular cells, resulting in the aggravation of kidney damage (43,54,55). Furthermore, deletion of the *p53* gene or inhibition of p53 protein function by its inhibitor conferred a protective phenotype because of the reduced apoptosis of renal cells (53,54). SIRT1 bound and deacetylated the C-terminal Lys382 of p53, which destabilized the p53 protein and reduced its transcriptional activity, resulting in the decrease of apoptosis (15,56,57). Resveratrol, a SIRT1 activator, was reported to ameliorate the acetylation of p53 and renal damage induced by

diabetes and cisplatin (47,48). These findings suggest that the downregulation of p53 function by SIRT1 could be a possible strategy to attenuate oxidative stress–induced apoptosis of glomerular mesangial cells, podocytes and renal tubular cells. Actually, a regulatory feedback loop exists between SIRT1 and p53: SIRT1 interacts with and deacetylates p53, inhibiting its transcriptional activity; p53 can repress SIRT1 transcription through binding to two response elements within the *SIRT1* promoter (58).

Studies by Kume *et al.* (49) have identified Smad7 as a new substrate for SIRT1. SIRT1 directly interacted with and deacetylated the lysine residues (Lys-64 and -70) of Smad7, leading to the enhanced degradation and reduced expression of Smad7 in SIRT1-overexpressing mesangial cells. Overexpression of Smad7 and stimulation by TGF- β increased mesangial cell apoptosis, but this effect was blocked by SIRT1 overexpression.

Members of FOXO are key regulators of apoptosis, lipid metabolism, cellular proliferation, inflammation, and autophagy and stress resistance (59,60). The transcriptional activity of FOXO is tightly regulated by posttranslational modification, including acetylation, phosphorylation and ubiquitination. SIRT1 could interact with and deacetylate FOXO3 (61). It is noteworthy that deacetylation of FOXO3 by SIRT1 inhibited its transcriptional activity on proapoptotic genes but drove its actions toward the induction of antioxidant and cytoprotective genes, whereas highly acetylated forms of FOXO3 favored expression of apoptosis-related genes, such as *Bim*, *TRAIL* and *FasL* (61). SIRT1 protected renal tubular cells against apoptosis by the bidirectional regulation of catalase expression via deacetylation of FOXO3 (50). In addition, SIRT1 reduced FOXO4 acetylation, preventing podocyte from apoptosis in diabetes (51). Actually, the study by Nemoto *et al.* (62) indicated SIRT1 expression to be regulated in a feed-forward loop by FOXO3a. The above observations should stimulate the investigation of SIRT1 as a therapeutic

target to prevent renal cells from diabetes-induced apoptosis.

SIRT1 Suppresses Inflammation by Targeting NF- κ B and High-Mobility Group Box 1 (HMGB1)

NF- κ B is a ubiquitously distributed transcription factor that affects inflammation, apoptosis, adhesion, angiogenesis and cell cycle through the regulation of its target genes. It consists of homo- and heterodimers of a group of proteins, namely RelA (also called p65), c-Rel, NF- κ B1 (p50 and its precursor p105), NF- κ B2 (p52 and its precursor p100) and RelB (63,64). Under physiological conditions, the dimers of NF- κ B are bound to I κ B proteins, which mask the nuclear translocation signal of NF- κ B and retain NF- κ B in the cytoplasm. Because of that, NF- κ B remains inactive. In response to diverse stimuli, its inhibitory proteins, namely I κ B, are phosphorylated. Consequently, NF- κ B is free from I κ B and NF- κ B translocates into nuclear to interact with promoters of target genes, thus activating the transcription of many inflammatory genes coding for cytokines and adhesion molecules.

Inflammation is one of the key mechanisms responsible for the development and progression of acute and chronic kidney diseases, including acute kidney injury and DN. Many inflammation-related proteins regulated by NF- κ B, such as vascular cell adhesion protein 1, intercellular adhesion molecule 1 and monocyte chemoattractant protein 1, play important roles in kidney diseases (65–69). Many stimuli relevant to kidney injury can activate NF- κ B, such as high glucose, advanced glycosylation end products, cytokines, growth factors, toll-like receptors and proteinuria. Large amounts of experimental results have demonstrated that inhibition of NF- κ B ameliorates inflammation, conferring a renoprotective phenotype (70–74).

Transcriptionally active NF- κ B is usually composed of a heterodimeric protein complex that contains a DNA-binding component and an acidic transactivation domain (16). The most studied one is the

heterodimer consisting of the p65 and p50 protein. SIRT1 binds and deacetylates Lys310 of p65 subunit, inhibiting transcriptional activity (16,75). Furthermore, SIRT1 deletion activated NF- κ B because of the increased NF- κ B acetylation, resulting in enhanced inflammation and aggravated acute kidney injury after lipopolysaccharide challenge (24). SIRT1 overexpression decreased cisplatin-induced acetylation of NF- κ B p65 subunit and cytotoxicity in renal PT cells (76). Evidence also indicated that renal inflammation was induced by increased levels of acetylated NF- κ B p65 owing to reduced SIRT1 protein expression, whereas dietary restriction exerted anti-inflammatory effects by restoring SIRT1 expression in the kidney of the diabetic Wistar fatty (*fa/fa*) rat (77). Actually, the study by Katto *et al.* (64) indicated SIRT1 expression is regulated in a positive feedback loop by NF- κ B. These authors also identified the NF- κ B binding sites within the *SIRT1* promoter by using electrophoretic mobility shift assay. However, these results have been controversial. There were also results suggesting that NF- κ B inhibited SIRT1 expression and signaling (78,79) (see Regulation by Transcription Factors below).

HMGB1, known as a nuclear factor and secreted protein (80), was also served as the target of SIRT1. HMGB1 is a 215-amino acid protein and its structure is extremely conservative (81). Under physiological conditions, HMGB1 is mainly in the nucleus, where it acts as an architectural chromatin-binding factor to stabilize nucleosomes. During stress, HMGB1 can be released from nonlethally damaged and necrotic cells into the extracellular milieu, where it activates macrophage and induces systemic inflammation via Toll-like receptor 4 and the receptor for advanced glycosylation end products (82,83). More recent study has shown that HMGB1 acetylation plays an important role in HMGB1 localization and SIRT1 deacetylated the lysine residues (Lys-55, -88, -90 and -177) of HMGB1 (84). Deletion of SIRT1 increased HMGB1 acetylation and reduced nuclear

HMGB1, resulting in enhanced HMGB1 release into circulation and increased renal damage. Resveratrol, known as the SIRT1 activator, deacetylated HMGB1, leading to increased nuclear HMGB1 and reduced tubular damage during acute kidney injury (84).

SIRT1 Induces Autophagy by Targeting Autophagy-Related Genes and FOXO3

Autophagy, a lysosomal degradation process, plays a key role in removing protein aggregates as well as damaged or excess organelles under various stress conditions. However, the function of autophagy is not only the simple elimination of cytoplasmic materials, but also serves as a dynamic recycling system that produces new building blocks and energy for cellular renovation and homeostasis (85). In nutrient excess conditions, autophagic activity is decreased, but once nutrients are depleted, autophagy is activated to provide energy resources for cells. The study of autophagy has revealed that autophagy deficiencies under nutrient excess conditions were involved in the pathogenesis of aging-related or metabolic diseases, including kidney disease (85,86). Currently, nephrologists are also entering this exciting field, and it has been revealed that autophagy has a renoprotective effect in a number of animal models including those used for acute kidney injury and aging (86–91). More specifically, autophagy enhances cell adaptation to hypoxia and maintains podocyte homeostasis in aging mice (86,87). In addition, autophagy protects kidney from acute ischemic and ischemia-reperfusion injury as well as cisplatin-induced nephrotoxicity (89,92). SIRT1-mediated autophagy was reportedly essential in the calorie restriction-mediated protection of aged kidneys (86). SIRT1 directly deacetylated Atg5, Atg7 and Atg8 in an NAD-dependent fashion, forming a molecular complex with several components of autophagy machinery including deacetylated Atg5, Atg7 and Atg8. Consequently, autophagy was induced by

SIRT1 (93). Nevertheless, autophagy was inhibited in SIRT1 KO mice during starvation, leading to the accumulation of damaged organelles, especially mitochondria, and disruption of energy homeostasis. The same phenomenon was observed in Atg5 KO mice (93). However, the substrate residues and consequences of the deacetylation remain unclear.

Under nutrient excess conditions, such as obesity and diabetes, high plasma levels of free fatty acids and high glucose levels enhance the production of reactive oxygen species. Intracellular accumulation of reactive oxygen species causes injury to the mitochondria. Thus, restoring autophagic activity and removing the damaged mitochondria under nutrient excess conditions are likely to be essential for maintaining healthy populations of functional mitochondria. However, direct evidence showing the relationship between autophagy and DN is still not clear. Podocytes, the key element of the glomerular filtration barrier, are highly differentiated and unable to proliferate. Podocyte injury or loss contributes to progressive proteinuria in DN. Podocytes exhibited high basal level of autophagy, indicating that autophagy plays an essential role in maintaining podocyte homeostasis under nonstress conditions (94). In addition, podocyte-specific deletion of Atg5 led to a glomerulopathy and accumulation of oxidized and ubiquitinated proteins, endoplasmic reticulum (ER) stress and proteinuria in aging mice (87). A recent report showed that under high glucose conditions *in vitro* and under diabetic conditions *in vivo*, high basal levels of podocyte autophagy decreased because of the failure of ER cytoprotective function in response to high glucose-induced unmitigated stress. Consequently, the defective autophagy facilitated podocyte injury (95). These results suggested that diabetes reduced autophagic activity in podocytes, which contributed to the pathogenesis of DN. Nevertheless, SIRT1 protects the kidneys against

diabetes-induced kidney disease by inducing autophagy.

In addition, SIRT1-mediated FOXO3 deacetylation also promoted autophagy in mouse aged kidney, which enhanced cell adaptation to hypoxia (86). According to their study, hypoxia causes damage to the mitochondria, and it also stimulates autophagy to remove the damaged mitochondria. Hypoxia-induced autophagy was dependent on Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3 (Bnip3). Normally, Beclin 1 interacts with Bcl-2 proteins, but this interaction could be disrupted by Bnip3, liberating Beclin 1 from Bcl-2 to induce autophagy (96). Beclin 1 was positively regulated by FOXO3a in aged kidneys (86). Calorie restriction-induced SIRT1 activation deacetylated and activated FOXO3a, which promoted Bnip3-mediated autophagy in aged kidneys, attenuating hypoxia-induced mitochondrial and renal damage. Deacetylation of FOXO1 by SIRT1 increased starvation-induced autophagy in cardiac myocytes (97). Consistent with this study, treatment with the SIRT1 activator, resveratrol, significantly increased FOXO1 activity in diabetic kidney, attenuating diabetes-induced oxidative stress and fibrosis (98).

SIRT1 Regulates Blood Pressure by Targeting Endothelial Nitric Oxide Synthase and Angiotensin II Type 1 Receptors

Hypertension plays an important role in the progression of chronic kidney disease. Nitric oxide (NO), a potent vasodilator, can protect blood vessels from thrombosis and atherosclerosis (99). In the vasculature, it is mainly generated by endothelial nitric oxide synthase (eNOS). Recent studies indicated that eNOS was involved in mitochondrial biogenesis, longevity and anti-aging effects (100,101). Nevertheless, the defective eNOS due to endothelial cell dysfunction contributed to kidney disease and cardiovascular disease, including atherosclerosis, hypertension, hypertensive nephropathy and DN (102,103). Deficiency of eNOS conferred susceptibility

to DN in *db/db* mice (104) and in STZ-induced animal models of DN on the nephropathy-resistant C57BL/6J background (105). Reportedly, eNOS also served as a substrate for SIRT1. SIRT1 interacted with and deacetylated Lys-496 and Lys-506 in the calmodulin-binding domain of eNOS, enhancing eNOS activity and promoting endothelial NO-dependent vasodilation. Inhibition of SIRT1 decreased NO bioavailability, inhibiting NO-dependent vasodilation (106). In addition, SIRT1 suppressed the expression of angiotensin II type 1 receptor (AT1R), inhibiting AT1R-induced hypertension (107). Thus, SIRT1-induced vasodilation may contribute, at least in part, to the renoprotection of SIRT1.

SIRT1 Enhances Mitochondrial Biogenesis by Targeting Peroxisome Proliferator-Activated Receptor- γ Coactivator 1 α

Peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC-1 α), a transcriptional coactivator of peroxisome proliferator-activated receptor (PPAR)- γ , is a master regulator of mitochondrial biogenesis. It coactivates nuclear respiratory factor-1, which binds to the promoter of mitochondrial transcription factor A, leading to the upregulation of mitochondrial DNA replication (108). The overexpression of PGC-1 α resulted in the increase in mitochondrial number, respiratory capacity and mitochondrial protein markers (109,110). What is more, the repression of PGC-1 α induced mitochondrial dysfunction and EMT in renal epithelial cells (111). As a major regulator of mitochondrial biogenesis, deacetylated PGC-1 α was more effective in recruiting transcription factors to induce the expression of its target genes. Reportedly, SIRT1 catalyzed PGC-1 α deacetylation, enhancing its activity (112,113). Aldosterone reduced PGC-1 α expression through increasing its acetylation, leading to mitochondrial dysfunction, EMT and podocyte damage. Both overexpression of SIRT1 and resveratrol, the SIRT1 activator, restored aldosterone-in-

duced mitochondrial dysfunction, EMT and podocyte injury through upregulation of PGC-1 α expression (111,114). SRT1720, another SIRT1 activator, rescued mitochondrial function after oxidant-induced renal PT cell injury. This effect depended on SIRT1 deacetylase activity, correlated with deacetylated PGC-1 α (115).

SIRT1 Modulates Hypoxic Responses by Targeting Hypoxia-Inducible Factor-1 α (HIF-1 α) and HIF-2 α

HIF-1 and HIF-2 are oxygen-sensitive transcription factors that facilitate oxygen delivery and cellular adaptation to hypoxia. Even so, they have distinct functions and only partially overlap. HIF-1 is the main regulator of glycolytic genes (116), but hypoxic vascular endothelial growth factor and erythropoietin (EPO) induction is predominantly regulated by HIF-2 (117,118). HIFs consist of an oxygen-sensitive α -subunit and a constitutively expressed β -subunit (119). Normally, HIF-1 α is expressed in most cell types of fully developed kidney, whereas HIF-2 α is mainly located in renal endothelial cells and interstitial fibroblast-like cells. The activity and stability of HIF-1 predominantly depend on HIF-1 α . Under conditions of normal PO₂, SIRT1 reportedly inactivated HIF-1 by deacetylation of HIF-1 α at Lys-674 and consequently repressed HIF-1 target genes (120). In response to hypoxia, SIRT1 activity decreased due to the reduced NAD⁺ levels, which allowed the acetylation and activation of HIF-1 α (120). Thus, their results proposed a model whereby the NAD⁺-dependent regulation of SIRT1 ensured the normoxic inactivation and the hypoxic activation of HIF-1 α . However, studies by Dioum *et al.* (121) showed that SIRT1 positively regulated HIF-2 signaling by deacetylating HIF-2 α at Lys-741, leading to the increased EPO levels. It seems that the roles of SIRT1 in HIF-1 α and HIF-2 α functions are controversial. Further study *in vitro* showed that SIRT1 inhibited HIF-1 α activity constantly in 10 cell

lines, but regulated HIF-2 α activity cell type-dependently. Knockdown of the *SIRT1* gene inhibited HIF-2 α activity in three cell lines, but activated that in seven cell lines. In HEK293T (human embryonic kidney) cell lines, SIRT1 inactivated HIF-1 α but activated HIF-2 α (122). However, whether SIRT1 could protect the kidney from hypoxia-induced damage or serve as a therapeutic target for renal anemia treatment by deacetylating HIFs remains unknown.

SIRT1 Regulates Metabolism by Targeting Sterol Regulatory Element-Binding Protein, Liver X Receptor, Nuclear Bile Acid Receptor and Insulin Receptor Substrate-2

SIRT1 regulates lipid homeostasis through the regulation of sterol regulatory element-binding protein (SREBP), liver X receptor (LXR) and nuclear bile acid receptor (FXR). SIRT1 directly deacetylates SREBP, inhibiting SREBP target gene expression and reducing lipid and cholesterol levels (123). LXRs function as cholesterol sensors to enhance reverse cholesterol transport, a process by which cholesterol is excreted into bile. SIRT1 positively regulated LXR by deacetylation at Lys-432 (124), resulting in the homeostasis of cholesterol and triglycerides. FXR is a critical regulator of lipid metabolism. Acetylation of FXR enhanced its stability but inhibited its transactivation activity. SIRT1 directly interacted with and deacetylated FXR at Lys-217, increasing its transactivation activity and resulting in ameliorative metabolic outcomes (125). Therefore, SIRT1 modulated lipid metabolism and prevented the progression of kidney diseases related to lipid metabolism disorders. SIRT1 is also involved in insulin signaling pathway. The deacetylation of insulin receptor substrate (IRS)-2 by SIRT1 was critical in insulin-induced IRS-2 tyrosine phosphorylation, which was a vital step in the insulin signaling pathway (126). It may imply the novel role of SIRT1 in the regulation of diabetes and its complications including DN.

Role of SIRT1 in Obstructive Nephropathy

Although SIRT1 has been reported to exert beneficial effects in kidney diseases through multiple pathways, emerging evidence shows that blocking SIRT1 attenuated renal interstitial fibrosis in obstructive nephropathy (127). According to this study, the SIRT1 inhibition-mediated anti-fibrotic effects were associated with dephosphorylation of platelet-derived growth factor receptor- β (PDGFR β), epidermal growth factor receptor (EGFR), signal transducer and activator of transcription 3. However, how SIRT1 inhibition reduces EGFR and PDGFR β phosphorylation remains unclear. Apparently, these results were in stark contrast to previous studies that SIRT1 activators attenuated renal fibrosis. Thus, the role of SIRT1 in renal fibrosis and obstructive nephropathy need further investigation.

REGULATION OF SIRT1 FUNCTION AND EXPRESSION

Numerous studies have showed that SIRT1 deacetylates a wide range of substrates, indicating SIRT1 is in a broad spectrum of biological processes. Therefore, the molecular circuits regulating SIRT1 levels (Figure 2) may provide a new method to accumulate the therapeutic benefit of SIRT1.

Regulation Through NAD⁺

The catalytic activity of SIRT1 depends on the availability of cellular NAD⁺. Although NAD⁺ has many functions, it is best known for its role in redox reactions and energy metabolism. Therefore, SIRT1 activity is intrinsically linked to the energy status of the cell. Changes in energy status and the NAD⁺:NADH ratio could influence the activity of SIRT1. In energy excess conditions such as high-fat diets, SIRT1 activity decreased because of the decreased NAD⁺:NADH ratio (128,129), whereas a low-energy status such as fasting, calorie restriction, nutrient deprivation and exercise could increase SIRT1 activity by increasing the NAD⁺:NADH ratio

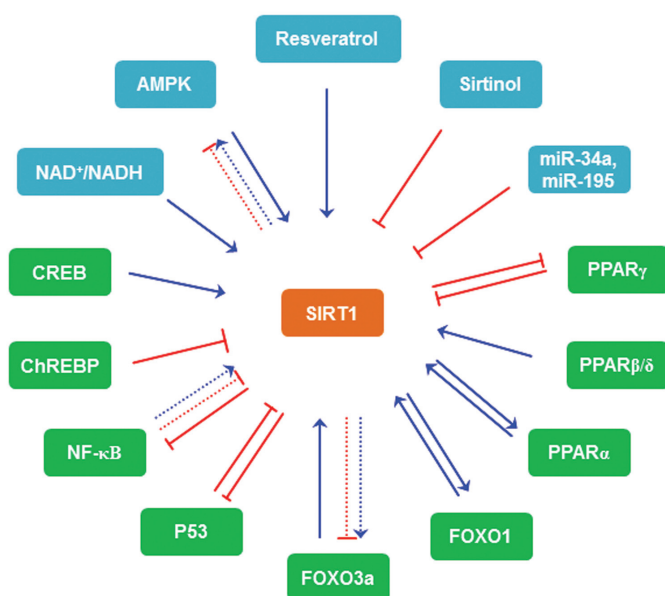


Figure 2. Regulatory mechanisms of SIRT1 function and expression. →, Stimulation; ←, inhibition; ⇨, tentative stimulation; ⇩, tentative inhibition.

(130–132). The levels of NAD^+ not only affected the activity of SIRT1 but also coordinately altered SIRT1 expression levels (133,134).

Regulation by Transcription Factors

Numerous transcription factors can regulate the expression of SIRT1. In response to calorie restriction, cyclic AMP response-element-binding protein (CREB) induced SIRT1 expression by binding to the *SIRT1* gene promoter, whereas the carbohydrate response-element-binding protein (ChREBP) repressed SIRT1 expression by binding to the ChREBP response element within the promoter of the *SIRT1* gene in a high-energy state (134).

Members of the FOXO family can also mediate changes in the expression of SIRT1. FOXO1 increased SIRT1 expression by binding to the FOXO1 response elements located in the *SIRT1* gene promoter (19,62). Interestingly, SIRT1 was reported to deacetylate FOXO1 and increase its transcriptional activity, suggesting the existence of a positive feedback loop between SIRT1 and FOXO1 (19). By contrast, FOXO3a-induced SIRT1 expression was mediated by the interac-

tion with p53. FOXO3a translocated into the nucleus and formed a complex with p53 at the p53-binding sites within the *SIRT1* gene promoter, thereby reducing the inhibitory effects of p53 on *SIRT1* gene expression (62). FOXO3a also served as a target of the SIRT1 deacetylase activity. Unlike FOXO1, SIRT1 can either activate or repress the transcriptional activity of FOXO3a, depending on target genes and environmental stimuli (61,135).

The tumor suppressor p53, which is also a stress-responsive transcription factor, has been shown to affect *SIRT1* gene expression. P53 repressed SIRT1 expression through binding to the p53-binding sites present in the *SIRT1* gene promoter (62), leading to the expression of pro-apoptotic genes. Interestingly, SIRT1 was capable of deacetylating all major p53 acetylation sites and reducing its transcriptional activity (58), suggesting a negative feedback loop between SIRT1 and p53. SIRT1-dependent deacetylation of p53 suppressed apoptosis in response to oxidative stress and DNA damage (56). The antagonistic crosstalk between SIRT1 and p53 is crucial for cell homeostasis.

A number of putative binding sites for NF- κ B were found within the promoter sequences of the *SIRT1* gene (64,136). However, the role of NF- κ B in the regulation of SIRT1 function and expression has been controversial. There was study demonstrating that the p65/RelA subunit of NF- κ B-mediated tumor necrosis factor- α -induced upregulation of SIRT1 (137). Another study showed that the *SIRT1* gene promoter was activated by overexpression of different NF- κ B subunits, followed by enhanced expression of SIRT1 mRNA levels (64). These results implied that NF- κ B could induce SIRT1 expression. On the contrary, there was also evidence indicating that NF- κ B inhibited SIRT1 expression and signaling. Reportedly, NF- κ B could increase the expression of microRNA-34a (miR-34a), which targeted the 3'UTR of SIRT1 and inhibited SIRT1 expression (138–141). SIRT1 even became cleaved in inflammatory status (78,79). In addition, as a target of SIRT1, p65 subunit of NF- κ B could be deacetylated and inactivated by SIRT1 (16).

PPARs that function as transcription factors could also regulate SIRT1 expression. PPAR α induced SIRT1 expression, presumably by binding to the PPAR responsive element within the *SIRT1* gene promoter (133). Interestingly, although there was no evidence that PPAR α was a deacetylation target of SIRT1, SIRT1 increased PPAR α activity through its coactivators, indicating a positive feedback loop between SIRT1 and PPAR α (142). PPAR β/σ could also enhance SIRT1 expression through Sp1 (143). On the contrary, PPAR γ reduced SIRT1 expression, possibly by interacting with the promoter of the *SIRT1* gene (144). Unlike PPAR α and PPAR β/σ , PPAR γ was a deacetylation target of SIRT1 and was repressed by SIRT1, suggesting a negative feedback loop between SIRT1 and PPAR γ (144).

Regulation by AMP-Activated Protein Kinase

AMP-activated protein kinase (AMPK), known as a fuel-sensing en-

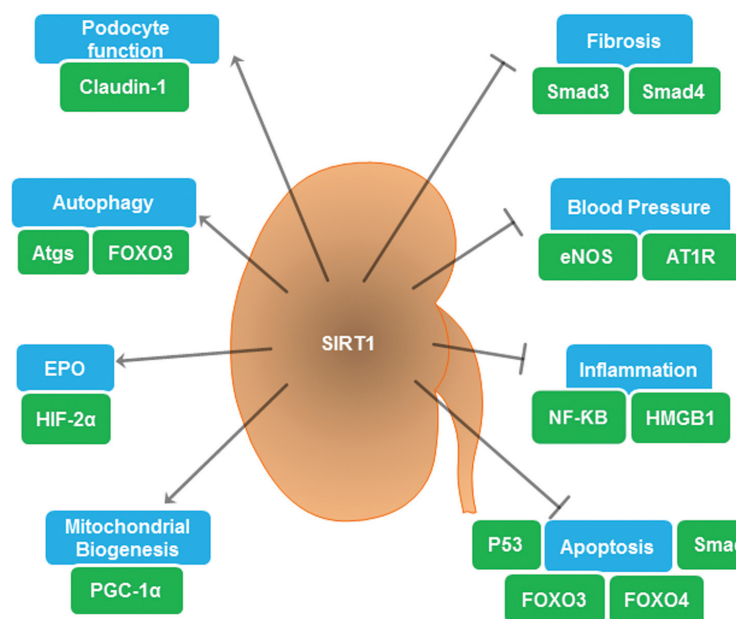


Figure 3. The role of SIRT1 in the kidney. SIRT1 exerts renoprotective effects by preserving podocyte function, reducing fibrosis, inhibiting apoptosis, suppressing inflammation, inducing autophagy and EPO expression, regulating blood pressure and enhancing mitochondrial biogenesis through deacetylation of promoter-bound histones and several target proteins. →, Stimulation; ⊥, inhibition. Furthermore, SIRT1 protects the kidneys from renal diseases derived from diabetes and lipid metabolism disorders by deacetylation of IRS-2, SREBP, LXR and FXR. In addition, although study also showed that blocking SIRT1 attenuated renal interstitial fibrosis in obstructive nephropathy, the direct targets related to these effects remain unknown (see the detailed discussion in the text). Atgs, autophagy-related genes.

zyme, could increase NAD^+ availability that would favor SIRT1 function and expression (145). The alternative mechanisms by which AMPK can stimulate SIRT1 activity were also reported recently. For instance, AMPK could directly phosphorylate SIRT1, resulting in the dissociation of SIRT1 and its negative regulator (146). There were also studies showing that SIRT1 acted upstream of AMPK. Overexpression of SIRT1 stimulated the AMPK phosphorylation (147), whereas shRNA-mediated SIRT1 knockdown reduced AMPK phosphorylation (148). However, these results might need further confirmation because other studies showed that the loss of SIRT1 was associated with increased AMPK (149).

Regulation by microRNAs

SIRT1 expression is also under the control of several miRNAs, including miR-

34a and miR-195. These miRNAs bound SIRT1 mRNAs and reduced their stability or suppressed their translation; consequently, SIRT1 expression was decreased (140,150).

Regulation by Small Chemicals

SIRT1 can be activated or inhibited by small chemicals. As discussed above, SIRT1 activators could protect the kidneys via modulation of target genes and proteins. SIRT1 inhibitors could induce acetylation and activation of p53, making them promising compounds for the treatment of cancer. Resveratrol and sirtinol have been extensively investigated and have been widely referred to as the SIRT1 activator and inhibitor, respectively (151,152). More recently, the synthetic SIRT1 activators with improved bioavailability and sirtinol analogs with improved potency have been developed (153,154).

CONCLUSION

Accumulated evidence has demonstrated the beneficial effects of SIRT1 on (a) suppression of apoptosis, inflammation and fibrosis; (b) induction of autophagy and EPO expression; and (c) regulation of lipid metabolism, glucose homeostasis and blood pressure (Figure 3). Importantly, emerging evidence suggests that SIRT1 can protect the kidneys against DN and reduce albuminuria via modulation of the expression of the tight junction protein claudin-1 in podocytes (12). In this review, we provide an overview of SIRT1-modulated biological processes related to kidney diseases and discuss how SIRT1 protects the kidneys via modulation of target genes and proteins. The general effect of SIRT1 is renoprotection; however, further studies are still needed to develop economical and effective SIRT1 activators and to determine whether these new activators or inhibitors can improve the clinical outcome of kidney diseases.

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DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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