Sirtuins in Renal Health and Disease

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ABSTRACT

Sirtuins belong to an evolutionarily conserved family of NAD^+-dependent deacetylases that share multiple cellular functions related to proliferation, DNA repair, mitochondrial energy homeostasis, and antioxidant activity. Mammalians express seven sirtuins (SIRT1–7) that are localized in different subcellular compartments. Changes in sirtuin expression are critical in several diseases, including metabolic syndrome, diabetes, cancer, and aging. In the kidney, the most widely studied sirtuin is SIRT1, which exerts cytoprotective effects by inhibiting cell apoptosis, inflammation, and fibrosis together with SIRT3, a crucial metabolic sensor that regulates ATP generation and mitochondrial adaptive response to stress. Here, we provide an overview of the biologic effects of sirtuins and the molecular targets thereof regulating renal physiology. This review also details progress made in understanding the effect of sirtuins in the pathophysiology of chronic and acute kidney diseases, highlighting the key role of SIRT1, SIRT3, and now SIRT6 as potential therapeutic targets. In this context, the current pharmacologic approaches to enhancing the activity of SIRT1 and SIRT3 will be discussed.

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Two decades ago, studies on *Saccharomyces cerevisiae* indicated that among the family of silent information regulator (Sir) genes, *Sir2* was essential for transcription silencing and DNA repair. The corresponding protein product Sir2 was identified as a NAD^+-dependent histone deacetylase responsible for chromatin silencing and the regulation of yeast lifespan.[1] Sir2 inactivation translated into a proaging phenotype, whereas its overexpression promoted increased yeast lifespan, which was attributed to the ability of Sir2 to suppress the progressive accumulation of self-replicating extrachromosomal recombinant DNA circles, a major contributor to accelerated aging in yeast.[2] Four and five sirtuins, showing the highest homology with yeast Sir2, were subsequently identified as longevity factors in nematodes[3] and flies,[4] respectively[4]; although controversial results, possibly because of technical disparities between laboratories, have cast doubts on the assumption of the role of sirtuins in longevity in these species.[2]

In mammals, seven sirtuins (SIRT1–SIRT7) constitute an evolutionarily conserved family of enzymes involved in diverse yet interrelated physiologic processes with much broader enzymatic activity than deacetylases, such as ADP-ribosyl-transferases, demalonylase, and desuccinylase, which all require coupling with NAD^+ (Figure 1). Unlike in worms and flies, studies performed in mice to deal with sirtuin's lifespan extension effect have shown promising progress. Sirtuins have emerged as critical modulators of metabolic adaptive responses to stress and their activities have been associated with multiple diseases, including metabolic abnormalities, neurodegenerative disorders, cardiovascular diseases, and cancer, all of which are age-associated conditions.[5,6] The kidney, along with the heart and brain, is one of the main organs susceptible to age-related diseases, translating into increased vulnerability to CKD in the elderly population.[7] In this review, we will focus on the biologic function of various sirtuins and address their role in renal physiology and pathophysiology.

SIRTUIN LOCALIZATION AND MOLECULAR TARGETS

Sirtuins 1–7 are NAD+-dependent deacetylases (Figure 1) that regulate histone proteins at specific lysine residues, promoting post-translational modification that results in chromatin silencing and transcriptional repression.[5,6] Nonhistone proteins are also targets for deacetylation that leads to the modulation of their activity.[5,6] The dependence of sirtuins on the cellular levels of the coenzyme NAD^+ links sirtuin activity to energy metabolism.[8] NAD^+ is produced by two biologically distinct pathways. The *de novo* synthesis uses the essential amino acid tryptophan, supplied by dietary intake, which is metabolized to form biosynthetic precursors generating NAD^+. This cofactor is also recycled by the salvage pathway, where NAD^+ is resynthesized

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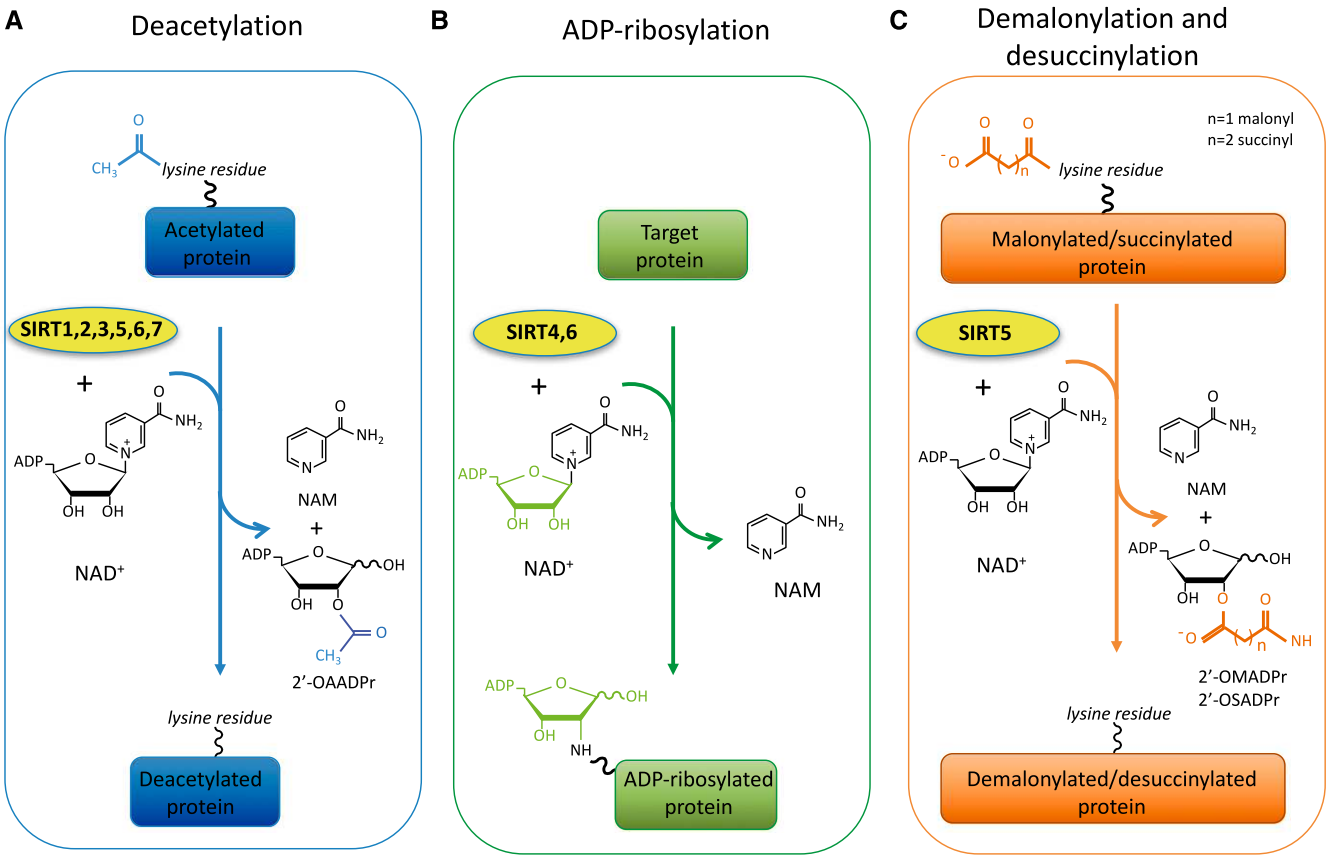

Figure 1. Sirtuins have broad enzymatic activities. (A) SIRT1, 2, 3, 5, 6, and 7 exhibit a lysine deacetylation activity of target proteins, in which the coenzyme NAD^+ is consumed to generate nicotinamide (NAM) and 2′-*O*-acetyl-ADP-ribose (2′-OAADPr). (B) SIRT4 exclusively carries out ADP-ribosyl transferase activity, using NAD^+ as the donor of the ADP-ribose group to the target proteins. ADP-ribosyl transferase activity is shared with SIRT6. (C) SIRT5 uses NAD^+ as a cofactor to demalonylate and desuccinylate target proteins, generating NAM and 2′-*O*-malonyl-ADP-ribose (2′-OMADPr) and 2′-*O*-succinyl-ADP-ribose (2′-OSADPr), respectively.

from nicotinamide by nicotinamide phosphoribosyltransferase (NAMPT).[8] NAD^+ is a hydride acceptor that forms the reduced dinucleotide NADH, and their ratio regulates redox balance in energy production.[8] Furthermore, NAD^+ is the precursor for $NADP^+$ and NADPH, which preserve cells from reactive oxygen species (ROS).[8] As described elegantly in a recent review,[8] after persistent oxidative stress, overactivation of ADP-ribosyltransferases (also named PARPs) consumes NAD^+ to promote the repair of ROS-induced DNA lesions,[9] ultimately reducing sirtuin activity.[10,11] Likewise, the bioavailability of NAD^+ can also be affected by other enzymes, such as ADP-ribosyl cyclases, which hydrolyze NAD^+ to ADP-ribose and nicotinamide.[12]

Despite sharing a common cofactor to boost deacetylase activity, the functional differences between sirtuins are greater than their similarities, as highlighted by their localization in distinct intracellular compartments and their broad range of target proteins.

Nuclear Sirtuins

SIRT1 is the most studied sirtuin, and resides in the nucleus and regulates both nucleosome histone acetylation and the activity of several transcriptional factors.[13] Actually, SIRT1 inhibits TNFα-dependent transactivation of NF-κB, limiting the expression of several proinflammatory genes.[14] After DNA damage and oxidative stress, SIRT1-dependent deacetylation of p53,[15,16] as well as forkhead box type O transcription factors (FoxO),[17] results in reduced cell apoptosis and senescence.[15,16] SIRT1 also regulates the activity and expression of hypoxia-inducible factor-2α, which is responsible for the hypoxic induction of erythropoietin by renal cells.[18] From a metabolic point of view, SIRT1 binds to and represses genes regulated by PPAR-γ after food withdrawal[19] and also controls gluconeogenesis[20] and mitochondria biogenesis by deacetylating/activating PGC-1α.[21]

As for other nuclear sirtuins, SIRT6 deacetylates lysines 9 and 56 of histone H3 to maintain genome stability and telomere function.[22] Recently, it has been shown that SIRT6, in response to oxidative stress, is recruited to the sites of DNA double-strand breaks, promoting its repair *via* ADP-ribosylation.[23] Thus,

the evidence that acetylation of histone H3K56 is increased in multiple types of cancer[24] suggests that SIRT6 plays a role in the process of tumor suppression.

SIRT7 is the only sirtuin located in nucleoli, where its deacetylase activity is required for ribosomal DNA transcription. A recent report proposes there is direct interaction between SIRT7 and chromatin remodeling complexes to regulate RNA polymerase I transcriptional activity.[25] It has been also reported that SIRT7 deacetylates several modulators of nuclear-encoded mitochondrial genes, such as GABPβ1, which favors mitochondrial oxidative phosphorylation,[26] and the nuclear receptors TR4/TAK1, which are involved in lipid metabolism.[27]

Cytoplasmic Sirtuins

SIRT2 is the unique cytoplasmic sirtuin that colocalizes and deacetylates α-tubulin,[28] taking part in the microtubule-related mitotic exit from the cell cycle.[29,30] Moreover, SIRT2, by inhibiting caspase-3 and ROS generation, affects apoptosis and oxidative stress.[31] The involvement of SIRT2 in cell metabolism has been supported by data that SIRT2 is instrumental in AKT activation by insulin,[32] as well as in regulating FOXO1 and PCG-1α deacetylation in adipocytes.[33,34]

Mitochondrial Sirtuins

SIRT3 localizes in the mitochondrial matrix and is the major regulator of the whole organelle acetylome, unlike other mitochondrial sirtuins such as SIRT4 and SIRT5.[35] Within the mitochondrial electron transport chain, SIRT3 directly binds to and regulates complex I, succinate dehydrogenase A of complex II, and ATP synthase (complex V), thus powerfully boosting ATP levels.[36–38] During membrane depolarization, SIRT3 dissociates from complex V and induces rapid deacetylation of specific clusters of matrix proteins to optimize energy production.[39] SIRT3 controls energy production in manifold ways, as it also manages the molecular machinery that governs mitochondrial dynamics[40,41] and permeability.[42] Concomitantly, SIRT3 plays a major-role in the regulation of mitochondrial antioxidant pathways and detoxification through deacetylation and activation of SOD2, favoring superoxide discharge.[43,44] In addition, SIRT3 activates isocitrate dehydrogenase 2, an enzyme that promotes the restoration of antioxidants and catalyzes a key step of the tricarboxylic acid cycle.[45,46] Other metabolic processes directly and indirectly related to the tricarboxylic acid cycle are controlled by SIRT3 *via* the deacetylation of acetyl-CoA synthase 2[47] and glutamate dehydrogenase,[35] involved in glutamate/glutamine metabolism,[48] which fuels the urea cycle. Moreover, SIRT3 promotes β-oxidation by driving long-chain acyl CoA dehydrogenase activity,[49] and ketone body generation by promoting the deacetylation of 3-hydroxy-3-methylglutaryl CoA synthase 2.[50]

Mitochondrial SIRT4 is predominantly an ADP-ribosylase and has the opposite effects to SIRT3, in that it inactivates the enzymes involved in the urea cycle[48] and β-oxidation,[51] but induces lipogenesis through malonyl CoA decarboxylase deacetylation.[51] Notably, that SIRT4 governs the cellular metabolic response to DNA damage *via* glutamine metabolism inhibition would suggest it has a role as a tumor suppressor.[52] More recently, SIRT4 has been shown to play a crucial role in insulin secretion and glucose homeostasis, as demonstrated by the development of glucose intolerance and insulin resistance in SIRT4-deficient mice.[53]

SIRT5 was initially described as a mitochondrial deacetylase that regulates the urea cycle through the direct activation of carbamoyl phosphate synthetase 1.[54] Subsequent studies have revealed that SIRT5 also exhibits demalonylase and desuccinylase activities, through which it controls ketogenesis.[55,56] An important effect of SIRT5 as an inducer of the energetic flux *via* glycolysis has also been shown.[57]

SIRTUINS IN RENAL PHYSIOLOGY

The kidney is one of the main energy-demanding organs in the human body,[58] primarily because of its role in incessantly filtering blood, regulating the balance of electrolytes and acid–base homeostasis, reabsorbing nutrients, and BP control. Given their role as privileged sensors of the metabolic state of the cell, renal sirtuins are involved in the above physiologic processes, supporting the production of sufficient energy throughout the different tubular and glomerular compartments. In terms of activity, proximal tubules reabsorb >80% of the glomerular filtrate, which is supported by active transport mechanisms, and therefore contain more mitochondria than distal tubules and collecting ducts.[59] At the glomerular level, podocytes require energy to adapt their highly interconnected cytoskeletal proteins to environmental changes, thus maintaining an intact glomerular filtration barrier.[60] Below, we discuss the available data on the functional activity of SIRTs 1, 3, 6, and 7 and their specific targets in the different compartments of the kidney (Figure 2).

In the kidney, SIRT1 is widely expressed in tubular cells and podocytes. The abundance of SIRT1 expression, also in aquaporin 2-positive cells in the rat distal nephron, has been taken to suggest that it is possibly involved in sodium and water handling.[61] SIRT1 decreases epithelial sodium reabsorption by interacting with methyl transferase, the disruptor of telomeric silencing-1, ultimately repressing the transcription of the α-subunit of the epithelial sodium channel (ENaC) in cultured inner medullary collecting duct cells.[61] The inhibitory effect of SIRT1 on the promoter of ENaC is independent of its deacetylase activity.[61] The capacity of SIRT1 to regulate sodium and water handling in the kidney might ultimately affect BP. In this context, data are also available to indicate a counterregulatory role of SIRT1 on renin-angiotensin system activation. Overexpression of SIRT1 downregulates angiotensin II type 1 receptor (AT_1R) in vascular smooth muscle cells,[62] whereas the reduced expression of SIRT1 is associated with the increased transcription of AT_1R in podocytes.[63] These findings, together with the evidence that SIRT1 upregulates endothelial nitric oxide synthase, points to SIRT1 as a potential player in BP control.[64]

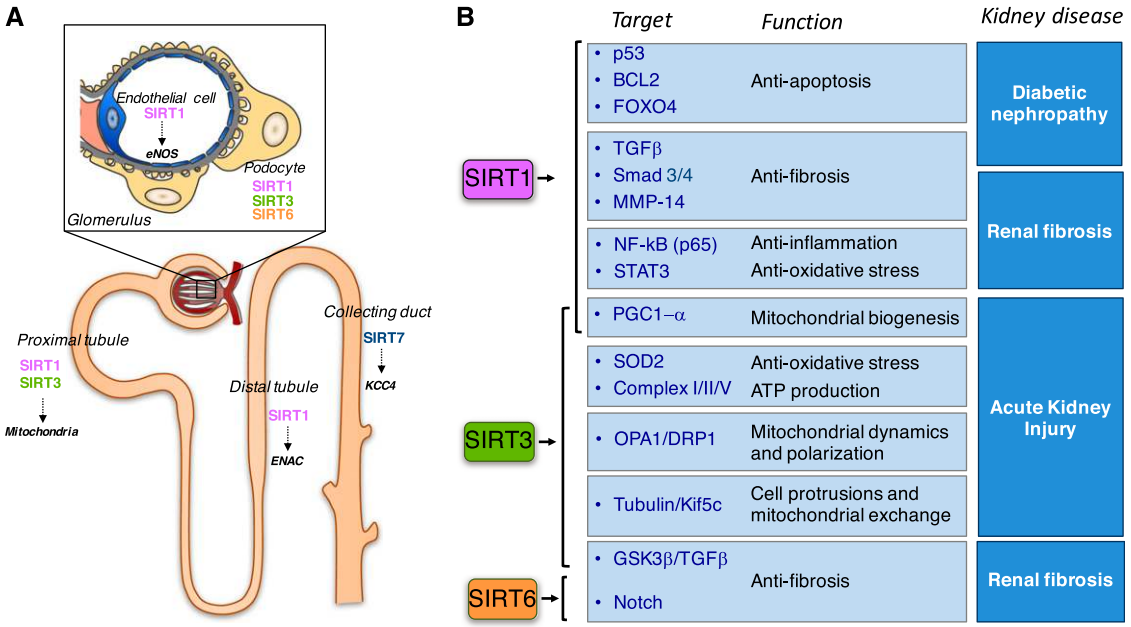

Figure 2. Sirtuins contribute to maintain renal homeostasis and thei downregulation leads to chronic and acute kidney diseases. (A) Sirtuins are expressed throughout the different renal compartments. In the glomerulus (inset), SIRT1, SIRT3, and SIRT6 maintain the structural and functional integrity of podocytes. In close proximity to podocytes, glomerular endothelial cells express SIRT1, which controls systemic BP by regulating endothelial nitric oxide synthase (eNOS). SIRT1 is also ubiquitously expressed throughout all of the nephron segments and participates in sodium balance control and water reabsorption by regulating the α-subunit of the epithelial sodium channel (ENaC) in aquaporin 2-positive cells of the distal nephron. SIRT1 and SIRT3 are highly expressed in the proximal tubule, where they preserve mitochondrial functional integrity. In the collecting duct, SIRT7 controls acid–base and renal electrolyte handling through its ability to deacetylate the K^+/Cl^- cotransporter KCC4. (B) SIRT1, SIRT3, and SIRT6 exerts protective functions by modulating several renal targets (light blue). Downregulation of SIRT1, SIRT3, and SIRT6 favors the development of renal disorders (blue). BCL2, B cell lymphoma 2; DRP1, Dynamin related protein 1; FOXO4, Forkhead box protein O4; GSK3β, glycogen synthase kinase 3β; KIF5c, kinesin family member 5C; MMP-14, matrix metalloproteinase 14; OPA1, Optic atrophy 1; p53, tumor protein 53; PGC1-α, peroxisome proliferative activated receptor γ coactivator 1-α; Smad 3/4, Small mothers against decapentaplegic 3/4; STAT3, signal transducer and activator of transcription 3.

SIRT3 is likely to have a major role in the kidney. Compelling evidence correlates SIRT3 activity with the maintenance of mitochondrial energy homeostasis and antioxidant defense in proximal and distal tubule compartments. Depending on the renal-specific energy demand, mitochondria are able to modify their size, number, and location.[65,66] Mitochondria are highly mobile organelles that exist in a dynamic network whose function relies on complex molecular machinery, finely tuned and balanced between fission and fusion.[40] Fission creates smaller mitochondria that are more susceptible to membrane depolarization and oxidative damage and can easily be removed by mitophagic machinery.[40] Conversely, fusion elicits the generation of a more interconnected mitochondrial network to dilute oxidized proteins and ROS, favoring sustained energy production.[40] In this context, SIRT3 has been described as a crucial regulator of the mitochondrial dynamics in renal cells (Figure 3), tipping the balance toward fusion.[41] More recently, a novel role of SIRT3 in the regulation of proximal tubular cell homeostasis has been documented. SIRT3 has been described as controlling microtubule network-dependent trafficking of functional mitochondria between renal tubular epithelial cells (Figure 3), a process that preserves the proper cellular bioenergetic profile and antioxidant defense.[67]

The contribution of SIRT6 to governing renal homeostasis has recently been demonstrated in *Sirt6*-deficient mice that experience remarkable glomerular injury, specifically in podocytes, consisting of decreased slit diaphragm protein expression and foot process effacement.[68] That SIRT6 is a key enzyme in the maintenance of glomerular permselectivity to plasmatic proteins and podocyte function is also supported by data showing that *Sirt6* deletion accelerates renal hypertrophy and the progression of proteinuria.[68] Finally, it has been reported that SIRT7, through its ability to deacetylate the K^+/Cl^- cotransporter KCC4, expressed at the basolateral membrane of the α-intercalated cells, restores pH balance in the collecting duct compartments during metabolic acidosis.[69] The positive effect of SIRT7 on KCC4 suggests this sirtuin has a role in acid–base and renal electrolyte handling.[69]

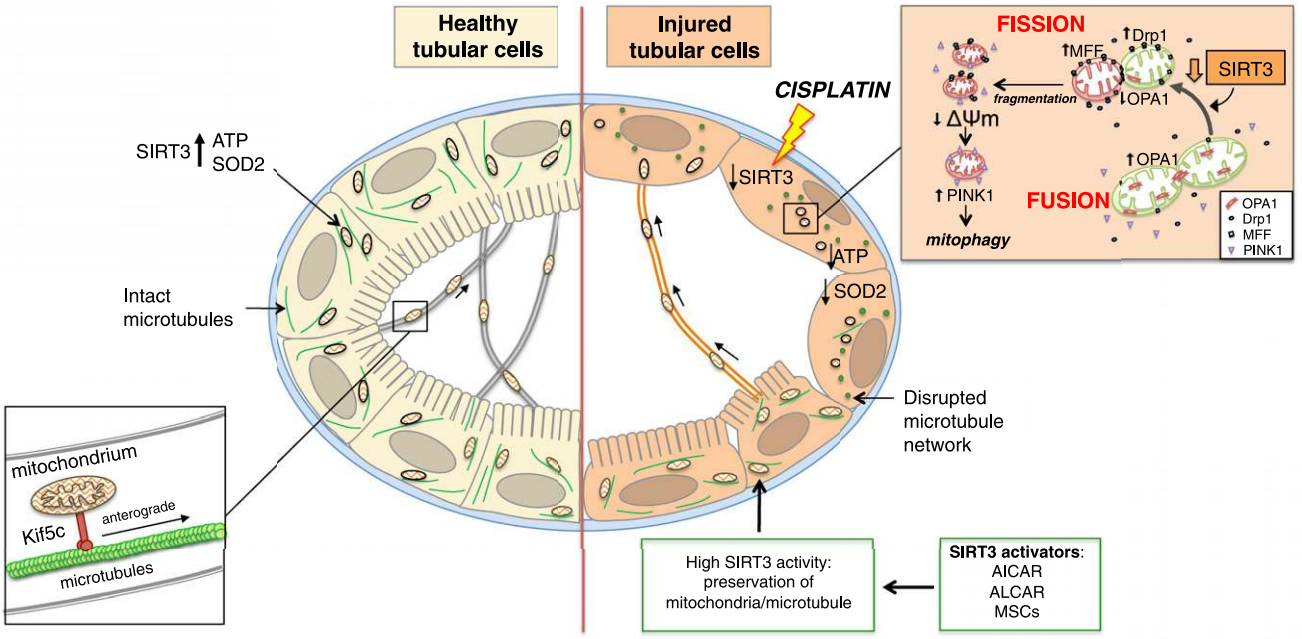

Figure 3. SIRT3 preserves the integrity of mitochondria and their intercellular shuttling between renal cells. Graphic representation depicting the functional activities of SIRT3 in the maintenance of proximal tubular epithelial cell homeostasis. In physiologic conditions (left), SIRT3 controls the global functional and structural integrity of mitochondria by sustaining ATP production and the activity of the antioxidant enzyme SOD2. This enables the constitutive trafficking of healthy organelles along the intact tubulin network *via* the anterograde motor protein Kif5c (left inset). After tubular cell injury (right), SIRT3 downregulation resulted in a remarkable ATP depletion, as well as impairment of SOD2 antioxidant activity. The downregulation of SIRT3 expression and activity also translates into unbalanced mitochondrial dynamics toward fission and fragmentation (right inset) by priming Drp1 recruitment on the mitochondrial outer membrane by binding to its receptor MFF, as well as reducing OPA1 expression. In association with fragmentation, loss of mitochondrial membrane permeability drives the disposal of dysfunctional organelles through PINK1-dependent mitophagy. The upregulation of SIRT3 expression and activity through pharmacologic manipulation with AICAR or ALCAR, as well as cell-based therapy with MSCs, counteracts mitochondrial dysfunction and restores the cell-cell exchange of healthy organelles between injured tubular cells. AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; ALCAR, acetyl-L-carnitine; Drp1, Dynamin related protein 1; Kif5c, kinesin family member 5C; $\Delta\Psi$m, mitochondrial membrane potential; MMF, mitochondrial fission factor; OPA1, Optic atrophy 1; PINK1, PTEN-induced putative kinase 1.

SIRTUINS IN RENAL DISEASES

Given the growing knowledge of the role of sirtuins in renal physiology, several attempts have been made to elucidate the effect they have on the development of renal disorders. Of the seven sirtuins, we will focus mainly on SIRT1 and SIRT3, for which data on both chronic and acute kidney diseases are available. As for SIRT1, which has been described extensively,[70] we will only address the mostly recent discoveries.

AKI

AKI is a public health concern associated with high mortality, the development of long-term CKD and other types of organ dysfunction in a considerable percentage of patients.[71,72] Tubular epithelial cells play a crucial role in AKI after an ischemic or toxic challenge.[71,73] Central to tubular damage is the dysregulation of mitochondria, which shift their dynamic equilibrium toward fission and fragmentation coupled with membrane depolarization and the consequent leakage of proapoptotic factors.[40,74] The impairment of mitochondrial structural integrity ultimately results in ATP breakdown and ROS generation, leading to cytoskeletal changes, the disruption of cell-matrix and cell-cell interactions, and tubular epithelial cell apoptosis and loss.[40,74]

A large body of literature describes the renal protective effects of SIRT1 in AKI, mainly because of its activity on mitochondrial function.[75,76] Tubular cell–targeted SIRT1 overexpression protects mice from cisplatin-induced AKI by enhancing medium chain acyl-CoA dehydrogenase, the rate-limiting enzyme of mitochondrial β-oxidation.[77] Conversely, one-allele genetic depletion of *Sirt1* significantly aggravates renal function decline as well as tubular damage and apoptosis in a model of AKI induced by ischemia–reperfusion injury.[78] Further studies show that SIRT1 activates PGC-1α, an important driver of renoprotection in AKI,[79] which leads to proximal tubule repair by activating mitochondrial biogenesis and respiration *via* oxidative phosphorylation.[80]

In addition to SIRT1, recent studies have also highlighted the renoprotective activity of SIRT3 in counteracting mitochondrial dysfunction in AKI.[41] Mice with cisplatin-induced AKI have severe

mitochondrial damage associated with oxidative stress and decreased levels of SIRT3 in the proximal tubular compartment.[41] Moreover, silencing *Sirt3* in mice administered cisplatin results in more severe AKI and premature death, compared with their wild-type littermates.[41] The preservation of tubular SIRT3 expression and activity by AICAR, an AMPK agonist, or the antioxidant agent acetyl-l-carnitine, protects SIRT3-competent mice from renal function impairment induced by cisplatin, but has no effect in SIRT3-knockout mice.[41] Mechanistically, proximal tubular cell dysfunction induced by cisplatin is conceivably the result of remarkable SIRT3 reduction that primes the recruitment of the fission protein Drp1 on mitochondrial membranes, as well as the downregulation of the pro-fusion dynamin-related protein OPA1, ultimately tipping mitochondrial dynamics toward fission and fragmentation (Figure 3).[41] This process results in mitochondrial membrane permeability loss and the elimination of the organelles through PINK-dependent mitophagy.[41] Further supporting the hypothesis regarding the renoprotective activity of SIRT3, a recent study shows that curcumin, a natural compound that modulates SIRT3 levels, prevents alterations in mitochondrial ultrastructure, energy production, redox balance, and dynamics in mice with AKI.[81] The SIRT3 biologic relevance in AKI has been further proved by the renoprotective effect of potential SIRT3-activator compounds such as honokiol, silybin, resveratrol, and stanniocalcin.[82–85]

The compelling evidence that mesenchymal stromal cells (MSCs) accelerate renal regeneration in mice with AKI has created further interest in investigating whether this effect was mediated by boosting SIRT3-dependent biologic pathways.[67] Treatment with human umbilical cord-derived MSCs in mice with AKI regulates mitochondrial biogenesis in proximal tubules by enhancing PGC-1α expression, NAD^+ biosynthesis, and SIRT3 activity fostering antioxidant defense and ATP production.[67] The mechanism underlying the favorable effect of SIRT3 induced by umbilical cord-derived MSCs rests on the sirtuin's ability to promote the transfer of mitochondria between adjacent tubular cells *via* tubulin-rich protrusions, so as to induce global metabolic reprogramming of damaged cells to sustain the energy supply (Figure 3).[67]

Diabetic Nephropathy

Diabetic nephropathy (DN) is recognized as a leading cause of ESRD worldwide, as well as being an independent risk factor for cardiovascular diseases that contributes to morbidity and mortality in patients with diabeties.[86,87] In search of new therapeutic targets to prevent DN, the attention of the scientific community has turned to the role of sirtuins in diabetic complications.[88] The protective effects of SIRT1 agonists on some metabolic parameters, such as glucose tolerance, fasting blood glucose levels, and insulin resistance resulting in a prolongation of animal lifespan, have been described in several experimental models of diabetes.[89–91] Beside its beneficial effect on the metabolism, SIRT1 has a protective role in limiting podocyte injury in DN. There are data that confirm that the conditional deletion of *Sirt1* in the podocytes of diabetic db/db mice results in acetylation of the p65 subunit of NF-κB and STAT3, which likely translates into increased levels of urinary protein excretion and more severe renal damage compared with db/db mice without the genetic deletion.[92] Consistently, the downregulation of SIRT1 expression is functionally linked to FOXO4 hyperacetylation and the induction of the proapoptotic factor Bcl2L11 in both injured podocytes in culture and glomeruli of db/db mice with DN.[93] It has been suggested that complex functional interplay between proximal tubules and glomeruli coordinated by SIRT1 primes DN.[94] The targeted disruption of SIRT1 in proximal tubules of DN mice results in ectopic expression of the tight junction protein claudin-1 in podocytes, an event that leads to albuminuria and renal function impairment.[94] In search of a potential explanation for such results, the authors provide *in vitro* data showing that proximal tubular cells exposed to high glucose concentration secrete less of the nicotinamide mononucleotide that lowers SIRT1 in podocytes and upregulates claudin-1 expression.[94] The evidence of reduced SIRT1 expression in both tubular cells and glomeruli from patients with DN provides additional clues regarding the potential involvement of SIRT1 in human DN.[95,96]

Concerning SIRT3, there is little data to support the hypothesis that it has a role in DN. Increased expression of SIRT3 antagonizes high glucose–induced cellular senescence *via* the FOXO1 signaling pathway[97] and enhances cellular resistance to oxidative stress damage.[98] Consistently, in mice with DN, the activation of SIRT3 through the G protein–coupled bile acid receptor prevents oxidative stress and lipid accumulation.[99] The restoration of renal SIRT3 protein expression and ketogenesis *via* green tea polyphenols in rats with high fat diet–induced DN have recently been described as limiting early renal oxidative damage.[100]

Fibrosis and Aging

Regardless of the etiology, renal fibrosis is the hallmark of the final outcome of almost all progressive CKDs.[101] The role of SIRT1 in counteracting renal fibrosis has been demonstrated in *Sirt1*-deficient mice with unilateral ureteral obstruction (UUO), which display increased susceptibility to oxidative stress and exuberant renal apoptosis and fibrosis compared with their wild-type littermates.[102] In this model, the use of SIRT1 activators, such as SRT1720[103] and SRT2183,[102] substantially attenuates renal fibrotic processes. Conversely, the sirtuin inhibitor sirtinol, given to mice with UUO-induced renal fibrosis, abolishes the renoprotective effect of losartan, suggesting SIRT1 has a role in mediating the antifibrotic effect of angiotensin II blockers.[104]

Several studies show the inverse relationship between SIRT1 and the TGFβ signaling pathway in renal fibrosis.[105–107] The profibrotic activity of TGFβ is exerted through the acetylation of Smad3 and 4,

in turn promoting the transcription of extracellular matrix proteins and metalloproteinases. In the UUO and 5/6 nephrectomy models, both characterized by robust expression of TGFβ, boosting SIRT1 *via* both resveratrol or its agonist SRT3025 reduced renal inflammation, as well as collagen IV and fibronectin accumulation through the deacetylation of Smad3.[105,106] Furthermore, SIRT1 overexpression in tubular cells halts the progression of AKI to tubulointerstitial fibrosis and the consequent renal accumulation of matrix metalloproteinase-7 *via* deacetylation of Smad4.[107]

An additional mechanism linking SIRT1 to fibrosis is provided by data showing that endothelial *Sirt1* deficiency enhances peritubular capillary rarefaction[108] and perpetrates nephrosclerosis, attributable to the downregulation of matrix metalloproteinase-14.[109] These results, together with the evidence that SIRT1 also exerts its antifibrotic function through PGC-1α,[110] indicate that SIRT1 is a possible therapeutic target in the progression of fibrotic kidney diseases. The finding that SIRT1 mRNA levels are lower in kidney biopsies obtained from patients with focal glomerulosclerosis adds translational relevance of the above data to human fibrosis.[106]

So far, the available evidence points to a protective role of SIRT3 against fibrosis mainly in the heart,[111,112] and there is little data for the kidney.[112] SIRT3-deficient mice develop more heart and renal fibrosis than their aged-matched wild-type littermates as they age.[112] Heart fibrosis in *Sirt3*-deficient animals is the result of the induction of TGFβ expression and the activation of its signaling.[112] Whether this mechanism could also operate in the kidney is currently unknown. A recent study has shown that lack of SIRT3 aggravates hypertension-induced renal fibrosis promoted by angiotensin II infusion, whereas the overexpression of SIRT3 attenuates angiotensin II–induced hypertensive nephropathy.[113] In addition, honokiol, a major bioactive compound isolated from *Magnolia officinalis* that increases SIRT3, suppresses angiotensin-induced renal fibrosis in mice.[113] The mechanism underlying renoprotection has been ascribed to SIRT3's ability to deacetylate KLF15, a negative regulator of extracellular matrix protein synthesis, in cultured podocytes.[113]

Interstitial fibrosis is a unifying pathologic feature of aging across several tissues, contributing to the progressive deterioration of organ functions. The kidney is one of the typical targets affected by age-related diseases, translating to greater susceptibility to CKD in the elderly population.[7] Experimental evidence points to sirtuins as key players in counteracting age-related kidney damage. In this context, decreased SIRT1 activity observed in the kidneys of aged rodents[114,115] is associated with loss of intracellular NAD^+ pool and increased mitochondrial dysfunction.[116] Moreover, mice with podocyte-specific *Sirt1* knockdown exhibit accelerated age-related albuminuria and glomerulosclerosis.[117] Also, SIRT3 expression decreases in kidney specimens of aged mice.[118] Conversely, renal upregulation of SIRT3 and NAMPT, the rate-limiting enzyme in the biosynthesis of NAD^+, as well as the increased number of mitochondria are essential to the longevity phenotype observed in mice lacking *At1r*.[119] More recently, the involvement of SIRT6 has been described as attenuating age-associated renal injury through the inhibition of proinflammatory NF-κB signaling.[120] The activation of sirtuins through caloric restriction,[121] supplementation with the NAD^+ precursor[115] or by a SIRT1 activator[122] are successful strategies for limiting susceptibility to kidney injury.

CONCLUSIONS AND FUTURE PERSPECTIVES

Mammalian sirtuins have emerged as a class of metabolic regulators that link protein acetylation to energy metabolism, exerting renoprotective effects, as discussed in this brief review. Although our understanding of different sirtuin functions at the renal level is still in its early stages, several advances have been made in identifying a broad spectrum of sirtuin targets involved in cell cytoprotective and regenerative mechanisms. The natural extension of these discoveries has been to look for sirtuin-activating compounds (STACs; Table 1). Most STACs belong to the polyphenol family of natural products, of which resveratrol was the first discovered compound capable to increase SIRT1 almost ten-fold.[123,124] Resveratrol is found in red wine and acts as allosteric modulator, causing a conformational change of the substrates, which increases their binding affinity for sirtuins.[124] Although resveratrol's mechanism of activation was quickly disputed,[125] the interest in this compound has not subsided because of its caloric restriction mimetic effect. This has generated several phase one and two clinical trials with encouraging results in diabetes, cardiovascular disease, and neuropathy.[126] Many of these studies are the driving force behind the search for natural compounds that could modulate sirtuins, such as flavonoids, stilbenes, anthocyanidins, and chalcones. These molecules served as templates to guide the computational search and chemical design of more potent and specific synthetic STACs, able to selectively enhance sirtuin deacetylase activity. Such a drug discovery approach has already been undertaken for SIRT1, leading to the synthesis of different agents such as SRT1720,[103] SRT2183,[102] and SRT3025,[106] which have been demonstrated to limit kidney injury. As for SIRT3, honokiol has been shown to exert anti-inflammatory and antioxidant activity in experimental chronic and acute kidney diesases[82,113] by selectively activating SIRT3.[127]

Compounds that boost NAD^+ as nicotinamide riboside and nicotinamide mononucleotide, or exogenous NAD^+ constitute a newer class of STACs that have been found to be beneficial in cardiac and renal diseases because of their ability to restore the redox balance in the setting of disrupted bioenergetics.[8,126] Of great interest for the future would be the development of pharmacologic strategies to target enzymes that regulate NAD^+ biosynthesis, such as NAMPT, as has recently been shown in AKI.[41] In a similar vein, compounds that inhibit NAD^+-depleting enzymes, as shown for the ADP-ribosyl cyclases in multiple aged organs,[128] could be another

Table 1. Therapeutic approaches to enhance expression and activity of sirtuins in kidney diseases

Compound	Target	Biologic Effects	Experimental Models	Reference
Natural STACs				
Resveratrol	SIRT1 SIRT3	Protects renal mitochondrial function by reducing acetylated SOD2 and oxidative stress, and prolongs animal survival	Sepsis-associated AKI	84
Curcumin	SIRT3	Ameliorates renal function and tubular damage, preserving mitochondrial bioenergetics, redox balance and dynamics	Cisplatin-induced AKI	81
Silybin	SIRT3	Improves renal function and reduces tubular necrosis and cell apoptosis, preserving mitochondrial functions	Cisplatin-induced AKI	83
Stanniocalcin	SIRT3	Reduces renal damage by activating AMPK and UCP2	IRI	85
Honokiol	SIRT3	Decreases tubular damage and improves animal survival reducing oxidative stress, NF-κB signaling, and inflammatory cytokines	Sepsis-associated AKI	82
	SIRT3	Attenuates angiotensin II-induced renal function impairment and fibrosis by decreasing KLF15-dependent extracellular matrix protein expression	Hypertensive nephropathy	116
Synthetic STACs				
SRT1720	SIRT1	Inhibits tubular endoplasmic reticulum stress *via* SIRT1-dependent increase of HO-1 and thioredoxin, thus slowing renal fibrosis	UUO	103
SRT2183	SIRT1	Reduces fibrosis and apoptosis in renal medulla	UUO	102
SRT3025	SIRT1	Attenuates proteinuria and GFR decline, thus reducing glomerulosclerosis and tubulointerstitial fibrosis	Remnant kidney	106
NAD+-boosting therapies				
NMN	SIRT1	Protects young and old mice from AKI; preserves renal function and reduces tubular damage and apoptosis by enhancing mitochondrial density	Cisplatin-induced AKI and IRI	115
AICAR	SIRT3	Ameliorates renal function and tubular damage, preserving mitochondrial dynamics through the activation of AMPK signaling, NAMPT, and PGC-1α	Cisplatin-induced AKI	41
Alternative strategies				
CR	SIRT1	Ameliorates renal function and tubular damage by reducing apoptosis and preserving mitochondrial function	Cisplatin-induced AKI	121
MSCs	SIRT3	Stimulates renal tubular repair by preserving functional integrity of mitochondria and their exchange among tubular cells	Cisplatin-induced AKI	67

AMPK, 5′ AMP-activated protein kinase; UCP2, uncoupling protein 2; IRI, ischemia–reperfusion injury; KLF15, Krüppel-like factor 15; HO-1, heme oxygenase 1; NMN, nicotinamide mononucleotide; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1- α; CR, caloric restriction.

potential therapeutic approach. Given that sirtuins can be considered good candidate targets for preventing and treating age-associated disorders, including renal diseases, and possibly for improving the human lifespan, efforts to prove that sirtuin activators are of benefit for patients would have a large impact on clinical and public health.

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DISCLOSURES

None.

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