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Sirtuins and Their Relevance to the Kidney

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Abstract

Sirtuins (silent information regulator 2 [Sir2] proteins) belong to an ancient family of evolutionary conserved nicotinamide adenine dinucleotide $(NAD)^+$-dependent enzymes with deacetylase and/or mono-ADP-ribosyltransferase activity. They regulate DNA repair and recombination, chromosomal stability, and gene transcription, and most importantly mediate the health-promoting effects of caloric restriction (CR), which includes the retardation of aging. At least seven Sir2 homologs, sirtuins (SIRT) 1 to 7 have been identified in mammals. Mammalian SIRT1, the most extensively studied family member, couples protein deacetylation with NAD^+ hydrolysis and links cellular energy and redox state to multiple signaling and survival pathways. Cell-type and context-specific activation of sirtuins increases resistance to metabolic, oxidative, and hypoxic stress in different tissues. In particular, SIRT1 plays a central role in mediating the beneficial effects of CR, and its activation associates with longevity and the attenuation of metabolic disorders. SIRT1 in the kidney is cytoprotective and participates in the regulation of BP and sodium balance. Here, we review sirtuin biology and discuss how CR-triggered sirtuin-dependent pathways affect renal physiology and the pathogenesis of kidney diseases and related disorders.

In 1934, Clive M. McCay and colleagues observed that experimental caloric restriction (CR), without causing malnutrition, increases the life span of rats.[1] This and other health-promoting effects of CR have been demonstrated in a wide range of organisms, including primates,[2–4] and positively affect a wide range of diseases, such as obesity and diabetes, atherosclerosis, neurodegenerative diseases, cancer, and age-associated renal injury.[5–11]

First clues about the molecular pathways triggered by CR that regulate aging come from observations in budding yeast, which serves as a useful model system for discovery of longevity genes. A major cause of aging in yeast is the accumulation of extra-chromosomal

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DISCLOSURES

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rDNA circles (ERCs), which are generated by homologous recombination between ribosomal DNA (rDNA) repeats.[12] Using this model, Guarente and colleagues discovered that Sir2 (silent information regulator 2), the first sirtuin family member, is a suppressor of ERC formation and regulates life span. Increased copy numbers of the *SIR2* gene not only increases life span in yeast but also delays aging in *Caenorhabditis elegans* and *Drosophila melanogaster*.[13–15] These and other findings identify Sir2 and its orthologs as central modulators in the regulation of longevity in both lower and higher organisms. Furthermore, Sir2 and its homologs, Hst1 and Hst2, mediate CR-induced extension of yeast replicative life span,[16,17] which may be different under nondividing conditions, and also appears to involve Sir2-independent pathways.[18–20]

At least seven homologs of Sir2, sirtuin (SIRT) 1 to 7, are present in mammals. SIRT1, the most extensively studied family member, couples protein deacetylation with NAD^+ hydrolysis and integrates cellular energy and redox state with the regulation of multiple signaling and survival pathways. From an evolutionary point of view, SIRT1 has evolved as a universal regulator of a highly conserved cellular defense program that facilitates survival when nutrients are in short supply.[21–23] Although its role in the regulation of longevity in mammals is still unclear, SIRT1 is required and sufficient for the induction of a CR phenotype in rodents.[24–27]

Although the molecular underpinnings of CR are complex and incompletely understood, the notion that pharmacologic targeting of sirtuins, SIRT1 in particular, could potentially revolutionize treatment of age-related disease conditions, such as diabetes, atherosclerosis, cancer, and certain forms of renal disease has been an incentive for major efforts in drug discovery.[28] At least in experimental settings, the health benefits of caloric restriction such as its life-extending, anti-inflammatory, antioxidant, antidiabetic, and cancer-preventive effects are mimicked by the naturally occurring SIRT1 activator, resveratrol (*trans*-3,5,4′-trihydroxystilbene) and its analogs.[29] Because resveratrol is found in foods, such as peanuts, blueberries, and grapes, and is a constituent of red wine, it has received much attention by the public media, although its beneficial effects for humans in naturally occurring amounts are unproven.

In the kidney, CR retards the normal aging process, which associates with structural and functional changes that include glomerulosclerosis and tubulo-interstitial fibrosis, a decrease in GFR and renal blood flow, and progressive loss of multiple tubular transport functions.[30,7,8,31] Recent studies show that SIRT1 is expressed in the kidney and acts as a renal survival factor; however, its role in CR-mediated renoprotection is unclear. Here, we review sirtuin biology and discuss how sirtuin-dependent pathways affect renal physiology and the pathogenesis of kidney diseases and related disorders.

THE SIRTUIN FAMILY OF NAD^+-DEPENDENT DEACETYLASES AND MONO-ADP-RIBOSYLTRANSFERASES: THE ESSENTIAL FACTS

The first sirtuin family member, Sir2, originally known as mating-type regulator 1,[32] was initially discovered as a silencer at mating-type loci in *Saccharomyces cerevisiae*.[33] Later studies showed that Sir2 is also involved in the regulation of rDNA recombination[34] and

telomeric gene repression, which is associated with nucleosomal hypoacetylation.[35,36] Detailed biochemical analyses demonstrate that Sir2 functions as a NAD^+-dependent histone deacetylase,[37,38] which couples deacetylation with hydrolysis of NAD^+, generating nicotinamide (NAM) and 2′-*O*-acetyl-ADP-ribose (Figure 1).[39,40]

Sir2 also has mono-ADP-ribosyltransferase activity (transfer of ADP-ribose to other proteins), which is of minor importance for its biologic function. This is in contrast to two members of the mammalian sirtuins, SIRT4 and SIRT6, which primarily function as mono-ADP-ribosyltransferases. Unlike most other deacetylases, the catalytic activity of sirtuins is absolutely dependent on NAD^+.[41,42] Because the intracellular level of NAD^+ (its ratio to its reduced form, NADH) is dependent on cellular energy and redox state, sirtuins function as molecular sensors of cellular energy balance.[43,22]

In mammals, seven homologs of yeast Sir2, SIRT1 through SIRT7, have been identified. Each sirtuin contains a conserved catalytic core domain of approximately 275 amino acids, which functions as a NAD^+-dependent deacetylase and/or mono-ADP-ribosyltransferase. SIRT1 and SIRT5 primarily target proteins for deacetylation, which include histones, transcriptional regulators (p53, forkhead box O [FOXO] transcription factors, nuclear factor κB [NF-κB], and hypoxia-inducible factor [HIF]-2α), enzymes (acetyl-CoA synthase 1 [AceCS1]), and other signaling molecules such as androgen receptors, whereas SIRT2 and SIRT3 carry out both types of catalytic activity.[23] SIRT4 and SIRT6, however, function as mono-ADP-ribosyltransferases and not as deacetylases.[41,42] SIRT4, for example, mono-ADP-ribosylates glutamate dehydrogenase in pancreatic β cells and thereby inhibits amino acid–stimulated insulin secretion.[42] Mammalian sirtuins differ not only with respect to their catalytic function but also in regard to their sub-cellular localization.[44 – 46] SIRT1, SIRT6, and SIRT7 are primarily located in the nucleus, whereas SIRT2 is found in cytoplasm and SIRT3, SIRT4, and SIRT5 reside in the mitochondria.

REGULATION OF SIRTUIN ACTIVITY

Cellular sirtuin activity is controlled dynamically to meet metabolic and environmental challenges. It depends on protein expression levels, reversible posttranslational modifications, the availability of cosubstrate NAD^+, and the presence or absence of interacting proteins that are capable of modulating sirtuin enzymatic activity. Expression of SIRT1 increases with CR, during starvation and nutrient deprivation, or when cells are acutely exposed to conditions that cause oxidative stress and DNA damage.[47,48] Decreased expression of SIRT1 associates with a high fat diet, insulin resistance, high glucose, and senescence. CR increases the activity at the SIRT1 promoter through the interaction of FOXO3a with p53, whereby FOXO3a removes p53 from the SIRT1 promoter as a negative regulator.[49]

The increase in SIRT1 expression in response to acute stress, such as oxidative stress, is relatively short-lived, and controlled and counterbalanced on multiple regulatory levels. This involves complex regulation at the promoter, mRNA, and protein levels. Hypermethylated-in-cancer 1 and the adenoviral E1A protein-interacting C-terminal binding protein are part of a repressor complex that inhibits *SIRT1* transcription and dissociates in response to

changes in cellular redox state, which results in de-repression at the *SIRT1* locus, increasing transcription in response to oxidative stress.[50] Increased *SIRT1* transcription after oxidative stress and following replicative senescence is counteracted by a reduction in the stability of mRNA encoding *SIRT1*. This results in part from decreased expression of a stabilizing mRNA binding protein, HuR, which maintains steady-state levels of the *SIRT1* mRNA.[51] p53 also induces micro RNA, miR34a, which targets *SIRT1* mRNA and reduces level of SIRT1.[52] An additional level of complexity in the regulation of SIRT1 biologic activity is added by reversible post-translational modifications, which include sumoylation[53] and phosphorylation,[54–56] and through biochemical interaction with inhibiting or activating factors, such as SIRT1 inhibitor DBC1 (deleted in breast cancer)[57] or SIRT1 activator AROS (active regulator of SIRT1).[58] Exposure to ultraviolet radiation or oxidative stress leads to desumoylation of SIRT1, and to increased formation of DBC1-SIRT complexes, both resulting in reduced enzymatic activity.[53,57]

SIRT1 enzymatic activity associates with the consumption of NAD^+ and the production of NAM, which in turn, inhibits its catalytic activity. Recent studies indicate that the NAD^+ salvage pathway plays a critical role in the regulation of SIRT1 enzymatic activity by lowering the concentration of inhibitory NAM and by increasing levels of sirtuin cosubstrate NAD^+ (for a detailed review, see [22]). The first reaction in the NAD^+ salvage pathway is the generation of nicotinamide mononucleotide (NMN) from NAM by the activity of nicotinamide phosphoribosyltransferase (NAMPT), followed by conversion of NMN to NAD^+ by NMN adenylyltransferase (NMNAT) (Figure 2). NAMPT is the rate-limiting enzyme in this pathway and therefore has a key role in regulating sirtuin activity. In cultured cells and in mouse tissues, its level of expression correlates with the cellular level of NAD^+ and with sirtuin activity;[59] that is, during caloric restriction NAMPT and SIRT activity both increase.[21] NAMPT exists in intracellular and extracellular forms (iNAMPT and eNAMPT). eNAMPT, also known as PBEF (pre–B cell colony enhancing factor) or as visfatin (visceral fat–derived hormone),[60,61] is present in plasma, where it synthesizes NMN, making it available for systemic distribution. As a systemic NAD^+ biosynthetic enzyme, eNAMPT also regulates glucose homeostasis.[22]

Interestingly, clinical studies show that serum levels of NAMPT increase in patients with chronic kidney disease.[62,63] Its role in the pathogenesis and progression of chronic kidney disease, however, remains unclear at this point. A potential role for NAMPT in fibrogenesis has been suggested in mesangial cells, where NAMPT expression associates with increased synthesis of profibrotic molecules, such as TGF-β1, plasminogen activator inhibitor-1, and collagen type 1.[64] This however may not involve SIRT1. Although increased NAMPT-mediated NAD^+ biosynthesis enhances sirtuin activity, NAD^+ is consumed by multiple enzymatic reactions that do not involve sirtuins, for example, covalent protein modifications by other ADP-ribosyltransferases.[22]

METABOLIC AND RENOPROTECTIVE EFFECTS OF SIRT1 ACTIVATION: RELEVANCE TO KIDNEY INJURY

Although the molecular underpinnings of CR are complex and understood incompletely, the health benefits of CR are well established. Among those is protection against many age-

associated diseases such as diabetes, cancer, and inflammation. In rodents, caloric restriction or starvation increases SIRT1 levels in multiple tissues including brain, liver, and kidney.[47,48] This response has also been observed in different human cell types, such as mononuclear cells, skeletal muscle, and adipose tissue.[65–67] With regard to the kidney, caloric restriction associates with less injury in age-related and diabetic nephropathy models. This probably results from a combination of systemic and cell type-specific local effects, which include improved glucose and lipid metabolism, decreased accumulation of advanced glycosylation end-products, a reduction in oxidative stress, improved nitric oxide balance, and diminished angiotensin II signaling.[7,8,68,31] Not surprisingly, intermittent fasting in a streptozotocin-induced diabetic nephropathy model is associated with increased renal SIRT1 expression.[68] Although its role in the aging and diabetic kidney is only poorly understood, experimental studies in non-renal settings identify critical sirtuin-dependent signaling pathways that are triggered by CR, some of which are also activated in some renal cells. Without doubt, the metabolic benefits of systemic SIRT1 activation are likely to have a positive effect on the clinical outcome of age-associated or diabetic renal disease.

During fasting, SIRT1 stimulates hepatic glucose output by enhancing gluconeogenesis and by repressing glycolysis in the liver, thus contributing to the maintenance of plasma glucose homeostasis.[48] This seems to occur through deacetylation and activation of peroxisome proliferator–activated receptor-γ coactivator 1α (PGC1-α) and FOXO1.[48,69] Furthermore, SIRT1 promotes fatty acid mobilization in white adipose tissue during fasting by repressing peroxisome proliferator–activated receptor-γ (PPAR-γ) and by quenching its cofactors NCoR (nuclear receptor co-repressor) and SMRT (silencing mediator of retinoid and thyroid hormone receptors).[27] Deletion of one SIRT1 allele in mice is sufficient to minimize this effect, and mice with complete *SIRT1* deficiency fail to adapt to caloric restriction, a finding that underscores the central role of SIRT1 in executing the biologic effects of CR.[25,24] In contrast to caloric restriction, high fat diet or the presence of obesity associates with reduced SIRT1 levels.[70,67] Although it is unclear whether this reduction in SIRT1 is a primary event in the pathogenesis of obesity and its associated metabolic disorders, activation of SIRT1 in this context is beneficial, at least in the experimental setting.

Studies in rodents demonstrate that increasing SIRT1 activity by either pharmacologic or genetic means prolongs the life of obese animals and significantly improves their metabolic parameters, such as glucose tolerance, fasting blood glucose levels, and insulin resistance.[71,72,10,73,26,74] Small-molecule sirtuin activators for the treatment of type 2 diabetes are currently in clinical trials and are likely to improve glucose and insulin homeostasis in humans, which certainly would benefit the kidney as well.

Aside from their positive effects on metabolism, sirtuins regulate pathways in renal cells that control cell viability, as has been shown *in vitro* and *in vivo*. SIRT1 promotes cell survival by modulating the cellular responses to different types of stress, including oxidative, genotoxic, and hypoxic stress.[47,75–78] This survival-promoting role is triggered by CR and is important for the prevention of aging, as aging is associated with increased rates of stress-induced apoptosis.[79,47] SIRT1 activation enhances resistance to apoptosis in human embryonic kidney cells[47] and leads to cytoprotection in heart, brain, and pancreatic islets after ischemic/oxidative or cytokine-mediated injury.[80 – 83] Deacetylation targets, which

mediate these prosurvival effects, include FOXO transcription factors, p53, heat-shock protein-1, NF-κB, Ku70, Smad7, and uncoupling protein-2.[75,84 – 86,76,87– 89]

In the kidney, pretreatment with resveratrol reduces acute ischemia/reperfusion injury in rats.[90,91] In mesangial cells, SIRT1 inhibits oxidative stress–induced apoptosis by deacetylation and inactivation of p53,[92] in HK-2 cells through the activation of FOXO3a and the upregulation of catalase.[93] SIRT1 also protects mesangial cells from TGF-β1–mediated apoptosis by deacetylating Smad7 at lysine residues 60 and 70, which accelerates its degradation by Smad ubiquitination regulatory factor-1.[94]

Recent studies from our laboratory demonstrate that SIRT1 is abundantly expressed in renal medullary interstitial cells, whereas only low levels of SIRT1 are found in the renal cortex by immunohistochemistry (C.M. Hao, unpublished data). *In vitro*, we find that SIRT1 protects primary renal medullary interstitial cells from oxidative stress–induced apoptosis after exposure to hydrogen peroxide. Deletion of one SIRT1 allele worsens apoptosis and fibrosis in the renal medulla after unilateral ureteral obstruction, whereas pharmacologic activation of SIRT1 is beneficial in this model (C.M. Hao, unpublished data). These findings suggest that SIRT1 has a robust cytoprotective role in renal medullary cells. SIRT1 activation could therefore be exploited therapeutically to stimulate potent antioxidant pathways, which promote the survival of cells that normally have to cope with high levels of oxidative stress generated by rapid changes in interstitial tonicity, relatively low blood flow, and low oxygen tension.[95–97] SIRT1 is also expressed in podocytes (C.M. Hao, unpublished data). Whether it is cytoprotective in this cell type is unclear at the moment, and certainly warrants further investigation. For a summary of sirtuin-mediated effects on the kidney, see Figure 2.

SIRT1 IN THE REGULATION OF BP AND HANDLING OF RENAL SODIUM

Strong evidence supports a link between energy metabolism and the regulation of systemic BP,[98,99] as hypertension is frequently clustered with obesity, hyperlipidemia, and hyperinsulinemia, collectively termed metabolic syndrome. CR, however, reduces BP in mildly hypertensive patients or reduces the number of antihypertensive drugs required to control hypertension.[99,100] Several studies suggest that SIRT1 participates in BP regulation.[101–103] Mechanistically, this seems to occur at least on two functional levels, the regulation of vascular tone and the regulation of renal sodium reabsorption in the collecting duct (Figure 2).

Miyazaki and colleagues report that overexpression of SIRT1 reduces angiotensin II AT1 receptor (AT1R) expression in vascular smooth muscle cells, whereas NAM, which inhibits SIRT1, increases vascular smooth muscle cell AT1R expression.[101] Administration of resveratrol in mice not only suppresses AT1R expression in the aorta but also significantly blunts angiotensin II–induced hypertension.[101] SIRT1, furthermore, promotes vasodilation by deacetylating endothelial nitric oxide synthase, thus increasing endothelial nitric oxide (NO) levels.[103] Inhibition of endothelial SIRT1 inhibits vasodilation and decreases NO bioavailability.[103]

In the kidney SIRT1 participates in the regulation of sodium balance by repressing transcription of the α-subunit of the epithelial sodium channel, ENaC, in cultured inner medullary collecting duct cells.[102] Interestingly, the inhibitory effect of SIRT1 on expression of α-ENaC is independent of its deacetylase activity, which is in contrast to most SIRT1 targets. SIRT1 interacts with disruptor of telomeric silencing-1 (Dot1), a methyltransferase that methylates lysine residue 79 in the core domain of histone H3, which associates with the *α-ENaC* 5′-flanking region. The SIRT1/Dot1 interaction results in H3K79 hypermethylation in chromatin along the *α-ENaC* promoter and leads to transcriptional repression of *α-ENaC*.[102] This effect on *α-ENaC* transcription is independent of mineralocorticoid receptor signaling. Interestingly, treatment with aldosterone decreases levels of mRNA encoding *SIRT1*. Because the effects of SIRT1 on *α-ENaC* transcription are independent of its enzymatic activity, changes in NAM levels or the use of SIRT1 activators are unlikely to modulate sodium reabsorption in the collecting duct.

SIRT1 MODULATION OF HYPOXIC RESPONSES: IMPLICATIONS FOR RENAL ERYTHROPOIETIN PRODUCTION

SIRT1 modulates cellular hypoxia responses by interaction with the α-subunit of HIF-2. HIF-2 is an oxygen-sensitive heterodimeric basic helix-loop-helix transcription factor that plays a central role in mediating cellular responses to hypoxic stress. It is responsible for the hypoxic induction of erythropoietin (EPO), vascular endothelial growth factor, and other oxygen-regulated genes.[104] In the kidney, it is expressed in EPO-producing interstitial cells, endothelial, glomerular, and von Hippel-Lindau–deficient renal cancer cells. In nontransformed renal epithelial cells, HIF-2 is not active and hypoxic responses are mediated by HIF-1.[104] SIRT1 stimulates the transcriptional activity of HIF-2, but not HIF-1, by selectively deacetylating HIF-2α under hypoxia.[105] The ability of SIRT1 to modulate the transcriptional activity of HIF-2 under low oxygen conditions is reflected by a blunting of renal EPO responses when SIRT1 levels are reduced genetically.[105] Conversely, SIRT1 activation enhanced renal EPO expression.[105] Whether SIRT1 could become a therapeutic target in the treatment of renal anemia or can be used to stimulate other cytoprotective HIF-2 responses remains unclear.

SUMMARY AND OUTLOOK

In this brief review we provide an overview of sirtuin-modulated biologic processes and discuss how sirtuins could be exploited therapeutically to harness the health-promoting effects of CR. Although a large body of literature exists that deals with sirtuins in different model organisms, current understanding of sirtuin biology in the kidney is comparatively limited. Recent experimental findings, however, suggest that renal sirtuins are involved in the regulation of a wide range of physiologic processes in the kidney, which include oxidative stress responses, EPO production, and sodium homeostasis.

As sensors of redox and energy state, renal sirtuins are likely to integrate nutritional cues with cellular stress and survival responses in the kidney. In this role, renal sirtuins may be essential in protecting the kidney from aging and in mediating the beneficial effects of CR on renal health. Whether renal sirtuins take part in regulating the systemic aging process is

unknown and warrants further investigation. Future studies using pharmacologic or genetic approaches are needed to better understand their role in renal physiology and pathology, and to determine whether they can serve as therapeutic targets to improve the clinical outcome of kidney diseases.

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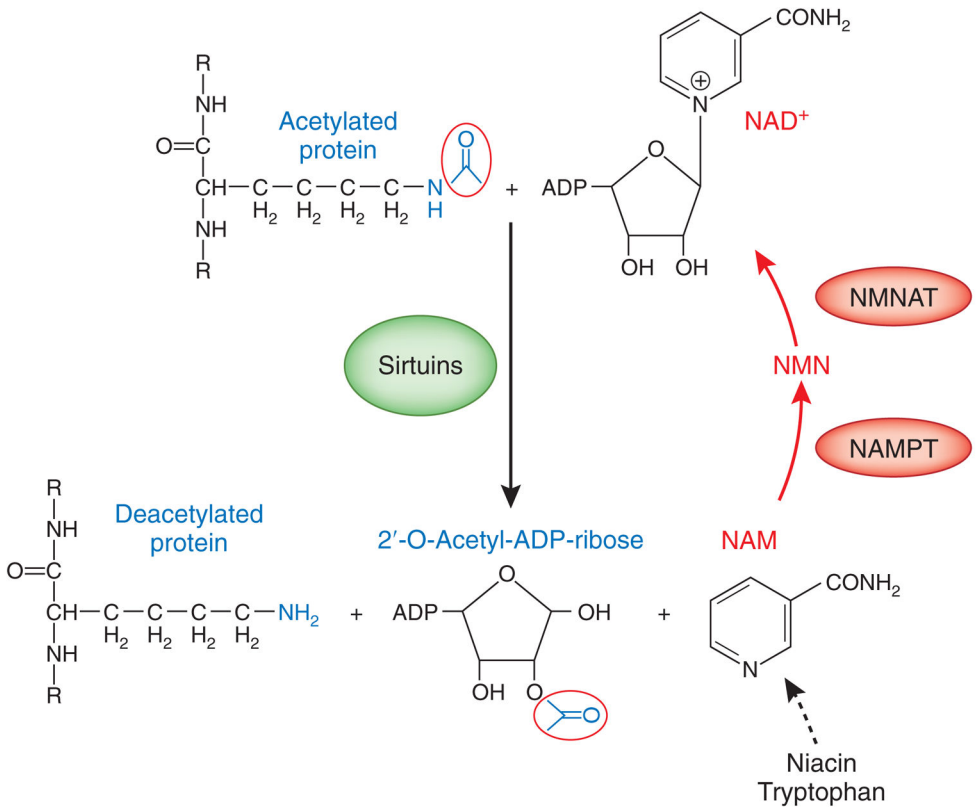

Figure 1.

Sirtuin-mediated protein deacetylation requries NAD^+. Overview of the sirtuin deacetylation reaction and the NAD^+ salvage pathway. Sirtuins deacetylate their target proteins at specific lysine residues. This reaction is dependent on the availability of NAD^+, which serves as a cosubstrate, thereby integrating cellular energy and redox state with multiple signaling and survival pathways. The reaction results in the formation of a deacetylated protein, NAM, and 2′-*O*-acetyl-ADP-ribose, and is inhibited by NAM. The salvage pathway (red arrows) is used to regenerate NAD^+ from NAM. NAMPT, the rate-limiting enzyme in this pathway, converts NAM to NMN, followed by conversion of NMN to NAD^+ by NMNAT.

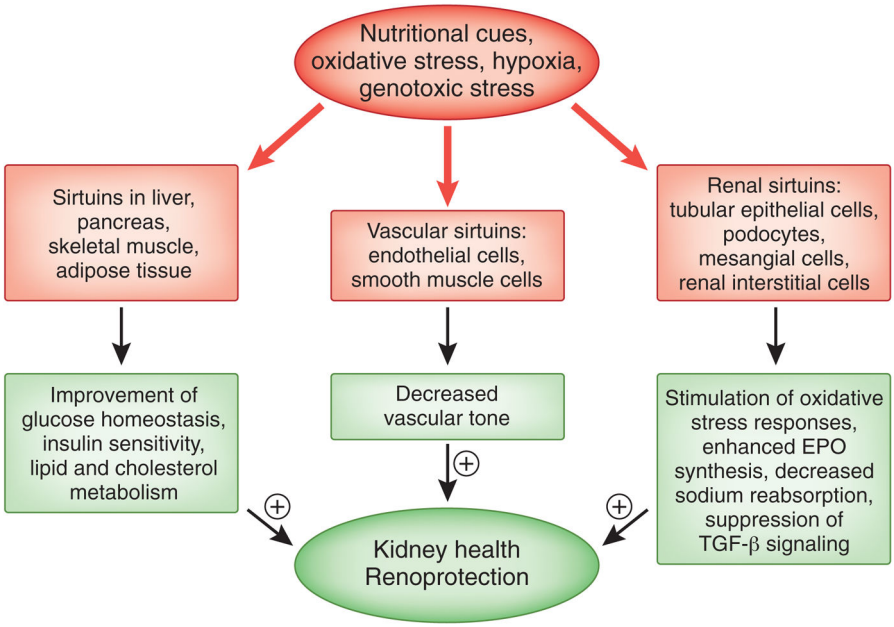

Figure 2.

Sirtuins protect kidney health. Shown is an overview of sirtuin-regulated processes with positive effect on kidney health. Nutritional cues and different forms of stress activate sirtuins in different tissues and cell types. This results in multiple local and systemic effects, which are likely to retard renal aging and result in renoprotection.