REVIEW

Sirtuins play critical and diverse roles in acute kidney injury

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Abstract

Acute kidney injury (AKI) is an extremely common medical affliction affecting both adult and pediatric patients resulting from hypoxic, nephrotoxic, and septic insults affecting approximately 20% of all hospital patients and up to 50% of patients in the intensive care unit. There are currently no therapeutics for patients who suffer AKI. Much recent work has focused on designing and implementing therapeutics for AKI. This review focuses on a family of enzymes known as sirtuins that play critical roles in regulating many cellular and biological functions. There are 7 mammalian sirtuins (SIRT1–7) that play roles in regulating the acylation of a wide variety of pathways. Furthermore, all but one of the mammalian sirtuins have been shown to play critical roles in mediating AKI based on preclinical studies. These diverse enzymes show exciting potential for therapeutic manipulation. This review will focus on the specific roles of each of the investigated sirtuins and the potential for manipulation of the various sirtuins and their effector pathways in mediating kidney injury.

Keywords Acute kidney injury · AKI · Sirtuins · Acylation · Therapy · Metabolism

AKI clinical findings

Acute kidney injury (AKI) is a significant health care concern associated with high morbidity and mortality [1, 2]. Approximately 20% of hospitalized patients have AKI, and 20–60% of adult critically ill patients have AKI [3]. Recent observational studies in pediatric populations including the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE)—critically ill children and Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) studies have shown similar alarming trends related to morbidity and mortality in this population [4]. AKI is characterized by an abrupt decline of kidney function, resulting in an inability to maintain electrolyte, acid-base, and fluid homeostasis [5]. AKI is a complex and multifactorial disease typically occurring as a mixed etiology of ischemia, nephrotoxicity,

and sepsis. Furthermore, a recent landmark study found that COVID-19 patients presented with increased prevalence of AKI and with a distinct pathophysiology, signifying a new risk factor for AKI [6]. Many groups are working to identify the underlying mechanisms involved in AKI, including apoptosis, dysregulation of metabolism, autophagy, inflammation, and the cell cycle [7–11]. However, despite considerable improvements to our understanding of the pathophysiology of AKI, the exact mechanisms are still poorly understood, and no specific therapy exists.

AKI pathophysiology

Multiple models of ischemic and toxic injury to the kidneys show a special susceptibility to injury of the renal tubular epithelial cells (RTECs). The proximal tubular epithelial cells are especially sensitive to injury because they require more active transport mechanisms than other kidney cell types. During AKI, there are 3 major types of changes that are observed and they are related to nuclear/DNA, cytoplasmic, or immune response. These are discussed below.

Nuclear/DNA changes

Significant work in the AKI field has focused on the role of nuclear/DNA alterations including DNA damage which

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directly effects DNA repair, cell cycle arrest, senescence, and/or cell death in RTECs [12]. Much work has also been done related to the role of increased mitosis/proliferative mechanisms and how the proximal tubule has an amazing ability to repair through dedifferentiation and expression of developmental markers followed by redifferentiation [13]. Finally, recent work has characterized how epigenetic changes including deacetylation/acetylation and demethylation/methylation affect the RTECs [14].

Cytoplasmic changes

Cytoplasmic alterations of RTECs during AKI is a growing field with recent studies focusing on many different aspects of cellular homeostasis, such as changes in expression levels of mitochondrial enzymes, protein acylation/deacylation, peroxisomal function, energy utilization (particularly fatty acid oxidation in the mitochondrial rich RTECs), upregulation of pro-apoptotic pathways, elevated pro-oxidative pathways, reactive oxygen species (ROS) accumulation, and cytoskeletal component changes, among others [15].

Immune response

Although intracellular signaling and mechanisms of RTECs play a critical role in driving the injury and repair response, the role of extra-tubular and in particular recruitment of pro-inflammatory, pro-fibrotic, and immune factors following RTEC damage can be paramount to tissue recovery/repair [10]. The ability of the RTECs to mount an extracellular response and recruit in the factors to clean up and repair the damaged cells can make a significant impact upon whether the injury progresses towards a fibrotic response and subsequent future injury that can culminate in chronic kidney disease or whether the injury resolves.

Role of sirtuins in RTECs during AKI

Sirtuins are a multidimensional group of genes that may provide insight into protective mechanisms during AKI. Sirtuins are a family of NAD+-dependent class III histone deacylases. The first identified sirtuin, Sir2, was found in budding yeast *Saccharomyces cerevisiae* and described as a regulator of transcriptional silencing of mating-type loci [16]. The discovery of Sir2's dependence on NAD+ revealed a role for sirtuins as both energy sensors and as transcriptional effectors regulating the acetylation state of histones [17]. Subsequently, many homologs of Sir2 have been discovered across all domains of life, establishing a highly conserved class of enzymes [18–20].

In mammals, there are seven sirtuins, SIRT1–7, which function to regulate metabolism and other diverse physiologic processes through direct enzymatic action on target proteins. Sirtuins act in different cellular compartments and exhibit broad enzymatic activity as deacetylases, mono-ADP ribosyltransferases, demalonylases, deglutarylases, and desuccinylases [21–23]. Apart from the classic role as histone deacetylases, a diverse set of protein targets have also been identified in the cytoplasm and mitochondria [24]. Although sirtuins have notably been studied for their role in caloric restriction and the prevention of aging-related diseases such as cardiovascular disease and diabetes, their diverse substrates and role as sensors of cellular energy balance make them a critical player to restoring cellular homeostasis following injury [25]. The kidney is one organ majorly susceptible to age-related diseases, and sirtuins have been implicated in the pathophysiology of chronic and acute kidney diseases [26, 27].

In this review, we will focus on the functions of mammalian sirtuins and address their role in kidney physiology and AKI.

Sirtuin mechanism of action in the nucleus/DNA of damaged RTECs

There are 3 nuclear sirtuins (SIRT1, 6, and 7) that have been shown to play key roles in AKI. SIRT1 and SIRT6 are found in the nucleus, while SIRT7 is uniquely localized to the nucleolus (Table 1). SIRT1 is the most studied sirtuin. Originally described as a histone deacetylase, it was soon discovered that SIRT1 deacetylates many other proteins [22, 28, 29]. Following DNA damage, SIRT1 deacetylates and represses p53 to reduce cell apoptosis and senescence [31, 32]. Similarly, SIRT1 regulates the acetylation of the forkhead box type O (FOXO) transcription factors to attenuate FOXO-induced apoptosis and cell cycle arrest [33]. SIRT1 also regulates both members of the PGC-1α/ERR-α complex, essential metabolic transcription factors which control mitochondrial biogenesis and gluconeogenesis (Table 1) [34–36]. Mitochondrial dysfunction plays a critical role in the pathogenesis of AKI, particularly in relation to maladaptive induction of apoptosis. When an injury or stress exceeds the mitochondria's ability to sense and respond to changes in nutrient availability, apoptosis is commonly initiated [37]. Apoptosis can activate intrinsically when the mitochondria fragments in response to decreased energy supply or when cytochrome C is released following outer mitochondrial membrane permeabilization [38]. Apoptosis of the tubular epithelial cells is further mediated by a network of factors including tumor suppressor protein p53, BCL2 family proteins, and caspases [39]. Given SIRT1's strong role in regulating apoptosis, it is not surprising there is a wealth of literature describing the renoprotective effects of SIRT1. In its renoprotective capacity, SIRT1 was shown to protect against oxidative stress-induced apoptosis via deacetylation of FOXO3 in proximal tubular epithelial cells

Table 1 Sirtuin expression, enzymatic activity, targets, and function

Sirtuin	Localization	Enzymatic activity	Targets	Function	Citation
Nuclear sirtuins					
SIRT1	Nucleus	Deacetylation	p53￼FOXO3￼PGC-1α	Maintenance of peroxisomes￼Mitochondrial biogenesis￼Mitochondrial homeostasis￼Regulation of apoptosis	[10, 21–34]
SIRT6	Nucleus, cytoplasm	Deacetylation, ADP-ribosylation	ERK1/2￼TNF-α	Maintenance of glomerular function￼Podocyte function￼Apoptosis￼Autophagy	[35–42]
SIRT7	Nucleolus	Deacetylation	NF-κB	Inflammation	[43–49]
Mitochondrial sirtuins					
SIRT3	Mitochondria	Deacetylation	LKB1￼AMPK/mTOR	Mitochondrial dynamics￼Autophagy￼Oxidative stress	[50–58]
SIRT5	Mitochondria	Demalonylation, deglutarylation, desuccinylation	B-oxidation	Fatty acid oxidation￼Energy metabolism	[59–63]
Cytoplasmic Sirtuins					
SIRT2	Nucleolus	Deacetylation, demyristolyation	MAPK-1	Inflammation￼Apoptosis	[64–71]

[40]. Further to this, in proximal tubular-specific SIRT1 transgenic mice, cisplatin-induced injury was attenuated by maintaining peroxisome number with concomitant upregulation of catalase and reduction of renal oxidative stress [41]. In another study, it was shown that SIRT1 activates PGC-1α, resulting in renoprotection by activating mitochondrial biogenesis and improved respiration via oxidative phosphorylation [42]. Finally, SIRT1 also showed a protective effect by regulating apoptosis through deacetylating p53 and inhibiting p53-dependent transcription during cellular stress [43]. Thus, the mechanism of Sirt1 protection is mediated by suppression of apoptosis likely downstream of metabolic signaling pathways (Fig. 1). SIRT6 and SIRT7 primarily have been shown to affect the inflammatory response following AKI and are discussed below.

Sirtuin mechanism of action in cytoplasmic components/mitochondria of damaged RTECs

There are 3 known mitochondrial sirtuins (SIRT3, 4, and 5) (Table 1). While SIRT3 is responsible for global protein deacetylation in mitochondria, SIRT4 exists as a mitochondrial ADP-ribosyltransferase and SIRT5 exhibits enzymatic activities as a deacetylase, desuccinylase, and demalonylase (Table 1). The roles of SIRT3 and SIRT5 have been elucidated in kidney injury and are discussed below, while the role of SIRT4 is currently unknown in this context.

SIRT2 is localized primarily to the cytoplasm, and there is growing evidence for additional roles in the nucleus (Table 1). Like SIRT1, SIRT2 also regulates PGC-1α and FOXO

transcription factors [44, 45]. SIRT2 also deacetylates α-tubulin to affect mitotic progression [46, 47]. During the G2/M transition, nuclear SIRT2 deacetylates histone H4K20 to regulate cell cycle progression and genome stability [48]. Moreover, SIRT2's activity mediates caspase-3 levels to affect apoptosis and oxidative stress (Table 1) [49].

As the major mitochondrial deacetylase, SIRT3 is responsible for the regulation of several metabolic enzymes and components of oxidative phosphorylation. SIRT3 deacetylates and activates mitochondrial acetyl-CoA synthetase (AceCS2), an enzyme involved in acetate utilization [50]. Similarly, SIRT3 has been shown to deacetylate long-chain acyl-CoA dehydrogenase (LCAD) to regulate fatty acid oxidation [51]. SIRT3 has also been demonstrated to deacetylate mitochondrial ribosome subunit MRPL10 to inhibit mitochondrial protein synthesis [52]. In addition, SIRT3 regulates various components of the electron chain, such as complex II and ATP synthase, to enhance ATP levels [53, 54]. These studies reflect only part of SIRT3's wide range of functions in mitochondrial ATP production, fatty acid oxidation, mitochondrial homeostasis, and ROS management (Table 1). SIRT3 plays a significant role in the kidney, especially in the proximal and distal tubular compartments which contain abundant mitochondria. Several studies have described a renoprotective role for SIRT3 due to its role in maintaining mitochondrial dynamics and energy homeostasis. Indeed, *Sirt3* knockout (KO) mice administered cisplatin have more severe AKI and compromised mitochondrial dynamics [55]. SIRT3 overexpression in mice has the effect of promoting autophagy through regulation of the AMPK/mTOR pathway and protecting against a model of sepsis-AKI [56]. SIRT3 also regulates FAO in
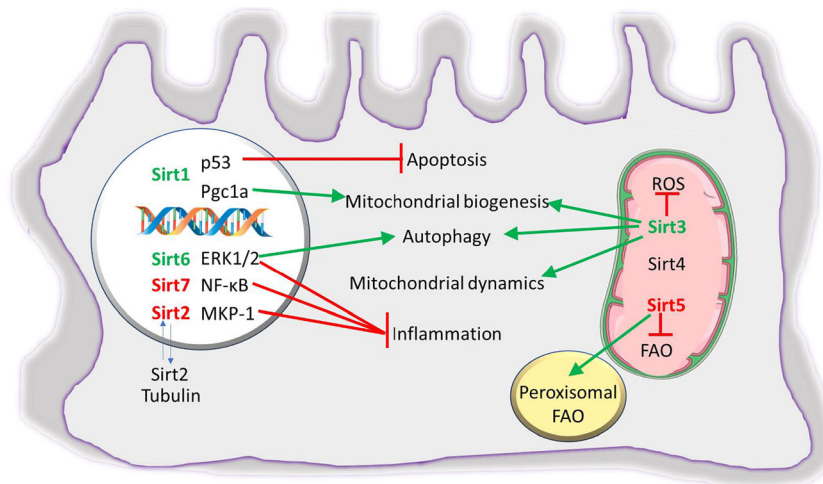
Fig. 1 Sirtuin roles in limiting kidney injury. Sirtuins are expressed in different subcellular compartments and regulate different cellular and biological functions to impact kidney injury. SIRT3 and SIRT5 are mitochondrial sirtuins. SIRT3 maintains mitochondrial dynamics and energy homeostasis and promotes autophagy. SIRT5 is involved in fatty acid oxidation and energy metabolism. SIRT1, SIRT6, and SIRT7 are nuclear sirtuins. SIRT1 has a strong role in maintaining mitochondria as well as in regulating apoptosis. SIRT6 is important for the maintenance of podocyte and glomerular function. SIRT 7 is involved in inflammation through regulation of NF-κB. SIRT2 shuttles between the nucleus and cytoplasm. Nuclear SIRT2 regulates MKP-1 to promote inflammation. Sirtuins in green font are renoprotective, whereas those in red font were renoprotective when deleted. Only Sirt4 has not been studied in the context of kidney injury

mice by deacetylating liver kinase B1 and activating AMPK with the effect of reducing ROS and lipid peroxidation (Fig. 1) [57].

Mitochondrial SIRT5 was initially identified as a deacetylase targeting carbamoyl phosphate synthetase (CPS1) to regulate the urea cycle in liver [58]. However, it has since been discovered that SIRT5 functions as a demalonylase, deglutarylase, and desuccinylase rather than as a deacetylase [59]. SIRT5 has been shown to bind cardiolipin in the inner mitochondrial membrane and desuccinylate electron transport enzymes complex I, complex II, and ATP synthase [60]. SIRT5 desuccinylation targets identified via large-scale profiling studies suggest SIRT5 has a significant role in energy metabolism (Table 1) [61]. Recently, *Sirt5* KO mice were shown to have significantly improved kidney function and less tubular damage following both ischemic and cisplatin challenge [62]. SIRT5 deficiency appears to be protective by reducing mitochondrial-derived ROS and driving peroxisomal FAO. Modifications to this mitochondrial-peroxisomal axis are significant to the pathogenesis of AKI. It is generally accepted that an underlying basis of kidney injury is impaired energetics in the highly metabolically active nephron segments (Fig. 1).

Sirtuin mechanism of action in recruiting inflammatory/ fibrotic factors to damaged RTECs

Several sirtuins (including Sirt2, Sirt3, Sirt6, and SIRT7) have been shown to play roles in the recruitment of inflammatory/ fibrotic factors to the kidney after injury.

Previously, a lack of SIRT2 in mice reduces lipopolysaccharide (LPS)-induced increases in neutrophil gelatinase-associated lipocalin (NGAL) [63]. SIRT2 deficiency also reduced infiltration of renal neutrophils and macrophages and reduced expression of inflammatory chemokines CXCL2 and CCL2 [63]. The same group recently showed that SIRT2 affects mitogen-activated protein kinase-1 (MAPK-1), and *Sirt2* KO mice and *Sirt2* transgenic mice show amelioration and aggravation, respectively, of kidney injury, apoptosis, and inflammation induced by cisplatin (Fig. 1) [64].

SIRT3 overexpression promotes autophagy, upregulates p-AMPK and downregulates p-mTOR in cecal ligation and puncture mice, attenuating sepsis-induced AKI, tubular cell apoptosis, and inflammatory cytokine accumulation in the kidneys [65]. The blockage of autophagy induction largely abolished the protective effect of SIRT3 in sepsis-induced AKI. These findings indicate that SIRT3 protects against sepsis-induced AKI by inducing autophagy through regulation of the AMPK/mTOR pathway.

SIRT6 plays a significant role in genomic DNA stability and repair. Sirt6 knockout mice present with severe progeria and typically only live for 3 months [66]. SIRT6 deacetylates histone H3 at various lysine sites to maintain genome integrity and telomere function [67]. In response to DNA damage, it has been shown that SIRT6 promotes DNA repair under oxidative stress by activating poly[adenosine diphosphate (ADP)-ribose] polymerase 1 (PARP1; Table 1) [68]. In the context of the kidney, SIRT6 appears to be important for podocyte function and maintenance of glomerular function, as *Sirt6* deletion in mice induces podocyte injury and decreased slit diaphragm protein expression [69]. *Sirt6*

overexpression in HK-2 kidney epithelial cells inhibits apoptosis induced by LPS and promotes autophagy while SIRT6 silencing promotes the secretion of cytokines tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) [70]. SIRT6 also deacetylates histone 3 to effectively inhibit extracellular signal-regulated kinase 1/2 (ERK1/2) expression and reduce inflammation and apoptosis caused by cisplatin (Fig. 1) [71].

SIRT7 uniquely activates RNA polymerase I (RNA Pol I) by deacetylating upstream binding factor (UBF) [72]. Others have shown that SIRT7 regulates RNA Pol I transcription by deacetylating PAD53, a component of RNA Pol I (Table 1) [73]. Interestingly, the lack of SIRT7 in mice shows protection against cisplatin-induced AKI. By regulating the nuclear expression of transcription factor nuclear factor kappa B (NF-κB), SIRT7 deficiency ameliorates cisplatin-induced AKI [74]. NF-κB is a potent stimulator of the immune system and the inflammatory response following AKI. Further to this, studies have shown that the inhibition of NF-κB can attenuate the inflammatory response and reduce the amount of injury following AKI [75]. Both the innate and adaptive immune systems are involved in the pathogenesis of AKI and virtually every immune cell has been implicated in AKI [76–79]. The protective phenomenon seen in SIRT7 deficient mice is perhaps due to SIRT7 deficiency reducing the expression of TNF-α, which normally enhances ROS production through the NADPH oxidase complex (Fig. 1) [74].

Potential therapies and clinical implications

The study of sirtuins has revealed a number of protein targets involved in the pathogenesis of AKI, and some sirtuins have been shown to exert strong renoprotective effects. As such, sirtuin-activating compounds (STACS) represent a clinically relevant approach to treat kidney diseases. Considerable efforts have been put towards finding small molecules to modulate the activity of sirtuins for pharmaceutical purposes. Resveratrol was among the first STACs identified in 2003 for its ability to significantly increase SIRT1. However, while in vitro studies indicate resveratrol activates SIRT1 [80], its mechanism was quickly disputed as this effect might instead be a downstream result from its immediate biological targets [81, 82]. Nevertheless, several clinical trials of resveratrol and SRT2104, another SIRT1 activator, have shown promising results in diabetes and cardiovascular disease [83]. NAD+ boosters as sirtuin activators represent another emerging therapeutic area of interest as NAD+ depletion is a major contributor to the pathogenesis of kidney diseases. NAD+ repletion through the pharmacological manipulation of nicotinamide phosphoribosyltransferase (the rate-limiting enzyme in the NAD+ salvage pathway) has been shown to have therapeutic potential as a means

to improve kidney function and decrease tubular injury [55].

Given that deletion of SIRT5 and SIRT7 is renoprotective, another therapeutic avenue exists for selective sirtuin inhibitors. In the case of SIRT5, which uniquely targets succinyl modifications, inhibitors targeting the succinyl substrate are currently under development [84, 85]. The development of either STACs or sirtuin inhibitors holds some risk as sirtuins are involved in myriad pathways, and whether modulating sirtuins will have a beneficial or deleterious effect in humans is unclear. The compromise to this double-edged sword is the development of therapeutics targeting the pathways shown to be regulated by sirtuins rather than the sirtuins themselves.

Conclusion

The study of sirtuins in the kidney has led to impressive advances in our understanding of sirtuin targets involved in renoprotection and in the development of a number of different pharmacological interventions that are effective in ameliorating injury in animal models of AKI. However, the promise of these developments is generally tempered by the results of clinical trials in patients with AKI. Therapies effective in animal models of AKI have translated to little or no effectiveness in humans, and such therapies are yet to be explored in pediatric populations. However, this failing might stem from deficiencies in preclinical models of AKI and an ability to design the clinical trial itself [86]. Although many auspicious sirtuin targets have been identified, the failure to effectively translate animal data to an effective human intervention highlights the importance of studying AKI in multiple model systems. In addition to the multiple in vivo models of AKI available, including the ischemia-reperfusion model, cisplatin-induced AKI, and sepsis-associated AKI, multiple in vitro models are used to study AKI [87, 88]. The mechanistic differences between these various models add to the complexity of AKI pathogenesis, and elucidating the role that sirtuins play in each model will further the understanding and therapeutic application of the sirtuins.

Compliance with ethical standards

Conflict of interest   Not applicable.

Ethics approval   Not applicable.

Consent to participate   Not applicable.

Consent for publication   All authors have reviewed the manuscript and agreed to its publication.

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