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Review article

State of the art – sirtuin 1 in kidney pathology – clinical relevance

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ABSTRACT

Sirtuins represent a group of nicotinamide adenine dinucleotide dependent histone deacetylases, which regulates various biological pathways by promoting chromatin silencing and transcriptional repression. Therefore, they are linked to cellular energy metabolism, mitochondrial biogenesis, stress response, apoptosis, inflammation and fibrosis. Since sirtuin 1 became a promising candidate for targeted therapies of numerous conditions, researchers have been investigating its activator. As for now, natural agents and antidiabetic drug – metformin, have been found to activate sirtuin 1. Sirtuin 1 is able to improve kidney outcomes by direct impact on kidney cells, regulation of non-specific processes generally involved in pathogenesis of age–dependent and metabolic disorders and improvement of the comorbid diseases. This review discusses the state of the art knowledge on the role of sirtuin 1 on kidney pathology.

1. Introduction

Sirtuins (SIRT – silent information regulator) represent a group of nicotinamide adenine dinucleotide dependent histone deacetylases (NAD^+ - dependent HDACs) which regulates various biological pathways by promoting chromatin silencing and transcriptional repression. Therefore, they are linked to cellular energy metabolism, mitochondrial biogenesis, stress response, apoptosis, inflammation and fibrosis [1]. The sirtuin family consists of at least 7 isoforms (SIRT1-SIRT7) [2]. The most extensively studied is SIRT1, also known as a longevity gene. It was identified to be responsible for the positive effect of caloric restriction (CR) on lifespan [1,3,4]. This review discusses the clinical relevance of SIRT1 related to kidney pathology and highly prevalent comorbidities affecting kidney function.

2. Review

2.1. How does SIRT1 influence kidney functions?

The nicotinamide adenine dinucleotide (NAD^+)/reduced nicotinamide adenine dinucleotide (NADH) level represents cellular energy state alternating under physiological processes [5]. Energy restriction caused by dietary regimen or physical exercise increases the NAD^+/NADH ratio and subsequently the SIRT1 activity [6]. On the contrary nutrient overload and high-energy cellular status is associated with low NAD^+ level resulting in diminished SIRT1 activity [7]. It was demonstrated that in mammals under physiological conditions NADH does not reach high enough level to act as a competitive inhibitor of SIRT1 [8], therefore only NAD + and its substrates and derivatives may modulate sirtuins' activity. SIRT1 has impact on metabolism and switches the energy source in relation to oxido-reductive status. The activity of NAD^+/SIRT1 pathway depends on the availability of nicotinamide phosphoribosyltransferase (NAMPT), rate-limiting enzyme for NAD^+ synthesis. Two NAMPT isoforms can be distinguished: intracellular (iNAMPT) and extracellular (eNAMPT) and both were identified to participate in the regulation of NAD^+ biosynthesis [9]. iNAMPT deacetylation by SIRT1 leads to extensive excretion of the protein and affects hypothalamic NAD^+ synthesis. Increased NAD^+ level in hypothalamus augments SIRT1 activation and its downstream pathways which may form feedback loop between adipose tissue and brain.

Aging is the result of mitochondrial dysfunction mainly due to the accumulation of oxidative stress [10]. SIRT1 modulates transcriptional activities of several proteins participating in the oxidative stress response [11], increases mitochondrial number and respiratory function through peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) [12]. As can be seen above, the manipulation of NAMPT/NAD^+/SIRT1 axis might be advantageous for facing the major problem of developed countries, which determines aging of the population and metabolic syndrome secondary to overeating and sedentary lifestyle.

Since SIRT1 became a promising candidate for targeted therapies of

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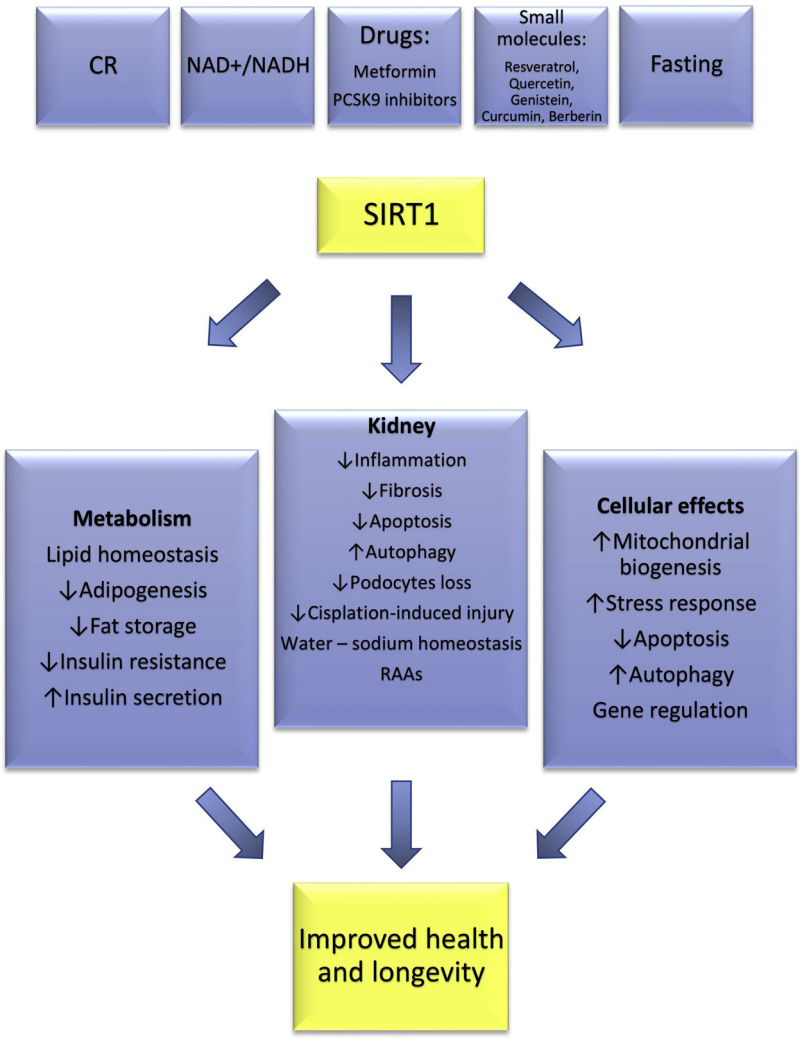

Fig. 1. SIRT1 activity can be modulated by numerous factors including caloric restriction, intracellular redox potential, drugs and small molecules. SIRT1 improves longevity and quality of life participating in wide range of biological pathways affecting intracellular processes, metabolism and organ function.
CR – caloric restriction; RAAs – renin-angiotensin-aldosteron system; NAD^+ – nicotinamide adenine dinucleotide; NADH – reduced nicotinamide adenine dinucleotide.

numerous conditions, researchers have been investigating its activator. The characteristics of SIRT1 activities is similar to pleiotropic effects of most widely prescribed antidiabetic drug - metformin. It was found that metformin's properties are mediated by induction of AMPK/SIRT1 pathway in patients with carotid artery sclerosis [13]. Resveratrol, a natural antioxidant presented in the skin of grapes and red wine, has been reported to mimic the effects of calorie restriction by increasing SIRT1 activity in metabolically-abnormal rodents [14] and humans [15]. Several botanical agents, e.g. quercetin, genistein, berberin, curcumin, piperazine, benzoxazole hydrochloride, puerarin, glycyrrhizic acid serve as SIRT1 activators [16–18]. On the other hand, down-regulation of SIRT1 expression could be elicited by sirtinol, a specific and direct HDACs inhibitor [13].

Due to broad expression and its regulatory role over various proteins activity and gene transcription, SIRT1 is able to improve kidney outcomes at several stages: firstly, in non-specific regulation of processes generally involved in pathogenesis of age–dependent, cardiovascular and metabolic disorders; secondly, in direct impact on kidney cells; thirdly, by improving the course of comorbid diseases and thereby decreasing progression of renal injury. However, those conclusions are extrapolated from preclinical data.

Both direct and indirect impact of SIRT1 on kidney function has a great significance in the development and progression of chronic kidney disease (CKD). Nowadays the leading cause of CKD is diabetes mellitus. It is estimated that the prevalence of diabetes will increase from 425 million worldwide in 2017 to 629 million by 2045 [19], substantially, the percentage of diabetic nephropathy among CKD patients is set to rise markedly. The imbalance of intracellular NAD^+/NADH ratio is involved in pathogenesis of metabolic syndrome [20]. As SIRT1 uses NAD^+ as essential cofactor, it may attract researcher's attention to establish in detail the role of sirtuin family in diabetes mellitus and its macro- and microvascular complications. Recently, some studies [23–25] have raised the issue of SIRT1 gene polymorphism in predisposition to diabetic kidney disease. Previous epidemiological analyses and studies on diabetic nephropathy demonstrated that in some individuals, especially with family history of diabetic kidney disease, even rigid glycaemia control is insufficient to prevent renal complications [21,22]. It has been established that some specific SIRT1 single nucleotide polymorphisms (SNPs) correlate with diabetic nephropathy (rs10823108), while other (rs3818292) have protective character [23–25].

2.2. *SIRT1 preserves podocyte function*

Diabetic nephropathy is morphologically characterized by glomerular hypertrophy, mesangial expansion, thickening of the

glomerular basement membrane and loss of podocyte function, clinically manifesting by albuminuria [26]. Over the past decades, structural changes in glomerular basement were demonstrated to arise from hyperglycaemia–induced pathways. Activated polyol pathway, hexosamine pathway or advanced glycation end products promote oxidative stress, inflammation and modify gene expression [26]. Determining underlying mechanism of podocyte injury would allow to design targeted therapy and halt nephropathy at early stage of development. Recently, autophagy - the process of intracellular degradation - has drawn international attention. An emerging study confirmed the role of autophagy in podocytes under diabetic conditions [27]. Insufficient autophagy resulted in podocytes loss and massive proteinuria in diabetic rodent model and patients with diabetic nephropathy, whereas preserved autophagy function was associated only with minimal proteinuria. SIRT1 induces autophagy through forkhead box O3 (FOXO3) deacetylation in mouse aged kidney model [28]. In line with this, deacetylation of FOXO by SIRT1 increased starvation-induced autophagy in cardiac myocytes [29]. It has been reported that mammalian target of rapamycin complex1 (mTORC1) and adenosine monophosphate – activated protein kinase (AMPK) are also implicated in the impairment of autophagy [30]. SIRT1, mTORC1 and AMPK are components of nutrient-sensing pathways involved in metabolic dysfunctions due to excess nutrition [31]. Therefore, targeting nutrient-sensing pathways may improve outcomes in metabolic conditions, including diabetic nephropathy (Fig. 1).

SIRT1 was found to maintain podocyte function by downregulation of the tight junction protein claudin-1 expression [32]. High level of claudin-1 in podocytes induce their effacement and proteinuria. SIRT1 and claudin-1 are negatively correlated with each other in human specimens with diabetes [32]. Recent studies revealed that SIRT1 has also distinct mechanism of glomerular injury prevention [17,18,33–36]. SIRT1 was found to interact with cortactin, a protein involved in actin polymerization, essential for the maintenance of cytoskeletal integrity. Podocyte-specific SIRT1 knockout mice exhibited severe glomerular injury, podocyte foot process effacement and massive albuminuria [33]. Correspondingly, several smart molecule SIRT1 activators ameliorated diabetic nephropathy via diversified pathways in rodent models [17,34,34,35,36]. An emerging study examined the impact of puerarin - an isoflavonoid derived from traditional medicinal herb, on albuminuria in podocytes culture and rodent model [17,18]. Administration of puerarin contributed to an increase in SIRT1 protein level and mitigation of laboratory and histopathological features of diabetes. The researchers suggest that the improvement is achieved by suppression of NADPH oxidase 4 (NOX4) resulting in oxidative stress mitigation.

Another study focused on novel, more selective SIRT1 activator - BF175 [37]. BF175 was able to restore SIRT1 level in diabetic mice. Moreover, the authors observed accompanying alleviation of podocyte and glomerular impairment, diminished albuminuria and decreased reactive oxygen formation. Of note, a recent study has demonstrated that metformin improves glomerular filtration barrier permeability through independent activation of SIRT1 and AMPK [38]. These findings are in contrast with previous studies, showing that polyphenols activate AMPK via SIRT1 pathway and depletion of SIRT1 diminishes this effect [39]. A great deal of research focused on the ability of both molecules to regulate each other reciprocally [40,41]. Low energy cellular state increases SIRT1 activity, which deacetylates the main activator of AMPK - liver kinase B1 (LKB1), which in turn phosphorylates AMPK [42]. AMPK is able to modulate many cellular processes resulting in an increase in NAD + level and secondary SIRT1 activation [42].

Moreover, anti-inflammatory and anti-apoptotic properties are involved in preserving podocytes function. SIRT1 deacetylates and inactivates master regulator of inflammatory response NF-κβ [43] as well as FOXO4, thus decreases the expression of pro-apoptotic proteins [44]. The anti-apoptotic effects of SIRT1 have been established in podocytes [43], proximal tubular cells [28] and mesangial cells [45]. SIRT1 was shown to reduce cisplatin-induced apoptosis, oxidative stress and increase autophagy by targeting p53, Smad7 and FOXO3 in the above mentioned cells [46].

2.3. The role of SIRT1 in endothelial cells

From the three layers of blood vessels SIRT1 is expressed to the greatest extent in endothelial cells. Some of its major functions are deacetylation and upregulation of eNOS contributing to nitric oxide release [47]. Increased NO production results in several renoprotective activities including vasodilatation, prevention of blood clots formation and antioxidative properties. Further studies revealed anti-inflammatory and antiatherogenic features of SIRT1 relying on a decrease in endothelial adhesion molecules expression, subsequent monocytes migration into arterial wall and foam cell formations [48]. Moreover, SIRT1-KO mice subjected to ischaemic conditions demonstrated impaired neovascularization, suggesting that endothelial SIRT1 is essential for postnatal angiogenesis [49]. Kida et al. [50], found that SIRT1 inhibition effects in the reduction of peritubular capillary (PTC) density through Notch1 signalling pathway. It is supposed that PTC loss leads to insufficient oxygenation in medulla and succeeding hypoxia-induced epithelial-mesenchymal transition initializing fibrogenesis. The process is involved in both gradual CKD progression and kidney function loss after acute kidney injury (AKI). There is an emerging need to evaluate if SIRT1 activation could reduce or withhold PTC rarefaction in kidneys.

2.4. SIRT1 and pathways of CKD

Kidney fibrosis is a central event in CKD progression. TGF-beta1/Smad3 signalling pathway is activated in response to various kidney injury stimuli. The results concerning the role of SIRT1 in fibrogenesis are conflicting. Initially, Li et al. [51] found that resveratrol administration abolished the TGF-beta1/Smad3 induced fibrosis in unilateral ureter obstruction (UUO) model. Kim et al. [52] investigated that losartan - angiotensin II receptor blocker, reduced the endoplasmic reticulum stress and protected against renal fibrosis by upregulating - in a dose-dependent manner - SIRT1 followed by induction of two antioxidant systems heme oxygenase-1 (HO-1) and thioredoxinby suppressing epithelial mesenchymal transition (EMT) – another factor involved in the pathogenesis of tubulointerstitial fibrosis. It has also been documented that treatment with hydrogen rich water has similar effect on EMT and fibrosis in UUO animal model due to SIRT1 mediated response [53]. On the contrary, Ponnusamy et al. [54] have reported that mitigation of renal fibrosis may be achieved due to application of specific SIRT1 inhibitors (sirtinol, EX527). Further studies on resveratrol provided data allowing to explain the contradictory results. Venturelli et al. [55] demonstrated that among four classes of histone deacetylases, resveratrol activates only III class of HDACs (sirtuins), while class I, II and IV is inhibited by the molecule. Taking into account that the inhibition of class I and II HDACs was found to ameliorate fibrosis it could be assumed that the impact of resveratrol on these classes surpasses the impact on the sirtuin family [56,57]. In conclusion, in further studies more specific activators of SIRT1 should be used to fully elucidate its exact function. Beside resveratrol, other SIRT1 activators: SRT1720, SRT2183, SRT1460 were found to have over one hundred off-targets [58], indicating their limited usefulness for investigating SIRT1.

2.5. The relevance of SIRT1 in AKI

AKI is a multifactorial clinical syndrome referring to abrupt decline in kidney function with underlying common pathophysiology. Renal proximal tubular cells are the most vulnerable part of the nephron due to their high metabolic rate [59]. Free fatty acids are the main energy substrate for proximal tubule cells and their metabolism is limited by

NADH, flavin adenine dinucleotide (FADH2) level and reduced oxygen supplementation [60]. Thus, primary causes of AKI including ischemia, hypoxia and nephrotoxins decrease the free fatty acids oxygenation. ATP level becomes insufficient to face cellular demand, which results in structural and functional changes. Renal epithelial cells undergo phenotypic conversion into low–energy demanding mesenchymal cells, which initiate the process of fibrogenesis [59,60].

The protective role of SIRT1 against all common factors inducing AKI was demonstrated in many studies [61,62,65–71]. Regarding hypoxia injury, 2-month-old mice were less sensitive to ischemia caused by clamping renal artery than 4-month-old mice. The severity of renal injury was conversely correlated with SIRT1 expression and mice age [61]. In addition, Guan et al. [62] has shown that not only SIRT1 but also its cofactor NAD^+ level is age–dependent. Pre-treatment with nicotinamide mononucleotide (NMN), a NAD^+ precursor, increased the expression of both components in young and adult mice. Taking into consideration the significance of NAD^+/NADH ratio in AKI pathogenesis, NMN supplementation may play a role in AKI treatment. Ischemic/reperfusion kidney injury is associated with uncontrolled generation of reactive oxygen species [59]. Another study revealed that transgenic SIRT1–deficient mice were more susceptible to oxidative stress in comparison with wild–type mice [63]. Moreover, resveratrol administration restored SIRT1 level and mitigated renal injury.

Acute renal injury is a common dose-dependent side effect of cisplatin, a widely used antineoplastic drug. Cisplatin nephrotoxicity refers to the impairment of peroxisomes and mitochondria in proximal tubular epithelial cells [64]. Decreased antioxidant activity results in free radicals' generation, cell injury and shift into apoptotic pathway. Transgenic mice with overexpression of SIRT1 exhibited resistance to cisplatin–induced AKI, maintaining the amount of peroxisomes and catalase function [65]. Correspondingly, some studies demonstrated reduction of cisplatin-induced apoptosis after SIRT1 activation by resveratrol [66] and curcumin [67]. Additional benefit is obtained by activation of PGC-1 transcription and increase in the number of mitochondria [68]. It is also suggested that modulation of p53 activity and subsequent decreased apoptosis is a mechanism underlying SIRT1 protection against cisplatin nephrotoxicity [66].

Acute renal injury frequently develops during sepsis. Lipopolysaccharide (LPS) – a bacterial endotoxin - is accumulated in the S1 segment of the proximal tubule [69]. The uptake of LPS by toll-like receptor 4 (TLR4) located in cell surface of S1 segment generates oxidative stress in S2 segment, while S1 remains resistant to deleterious impact of free radicals. Up-regulated SIRT1 expression represents autoprotective mechanism in S1 segment of proximal tubule [69]. Sepsis–induced AKI is associated with abundant inflammatory response. In the study by Gao et al. [70], SIRT1 knockout mice developed more severe renal injury accompanied by greater pro-inflammatory cytokines production than the wild type mice. The investigators also confirmed the ability of resveratrol to restore SIRT1 level and attenuate AKI in animal septic model [71].

2.6. SIRT1 significance in renal transplant recipient

For reason of improvement of quality of live and cost-effectiveness, kidney transplantation is the treatment of choice for the end-stage renal disease. Although remarkable progress in transplantology has succeeded, maintaining a balance between optimum immunosuppression, allograft survival and the risk for infectious and oncologic complications is still challenging. There are a few studies on the relevance of SIRT1 in kidney allografts so far [72–75,79]. Sirtuin 1 plays a role in modulation of fibrosis and inflammatory processes, which have been proved to be pathophysiological mechanism of chronic renal allograft dysfunction (CRAD) [72]. Emerging study has demonstrated that in rodent CRAD model SIRT1 expression is significantly lower as compared to control group with unilateral renal resection [73]. Besides, there was a negative correlation between SIRT1 expression and proteinuria, creatinine, TGF-β1, MCP-1, ICAM-1 levels and histological changes in allografts. SIRT1 impact on immune responses was also examined. Foxp3 deacetylation by SIRT1 observed in Treg cells attenuates its suppressive function [74], which determines research direction on SIRT1 gene deletion or pharmacologic inhibition to prevent allograft rejection. Levine et al. [75] showed that SIRT1 lacking allograft recipients developed tolerance and had improved allograft survival. However, the effect of pharmacologic inhibition of SIRT1 was dose-dependent, with toxicity prevailing over benefits at higher dosage. The results should be interpreted with caution due to complexity of immune responses and potential influence on other immune cells. As mentioned above, low levels of SIRT1 augment the pro-inflammatory process, which may result in worse overall renal allograft function.

Although in the aforementioned study [75] mice lacking SIRT1 accepted kidney transplant without immunosuppressive drug, in clinical practise it would be an unreachable perspective. All transplant recipients require permanent immunosuppressive therapy with the risk for side effects. The most widely used immunosuppressant in renal allograft recipients still remains cyclosporine A (CysA) introduced into medical use in 1983 [76]. Treatment with CysA carries the risk for several adverse effects including acute and chronic nephrotoxicity. While acute harmful effect is assigned to constriction of the afferent arteriole, growing evidence suggest the involvement of oxidative stress in chronic CysA nephropathy development [77,78]. Koh et al. [79], examined the impact of D-pinitol, a cyclitol derived from soybean on CysA-induced nephropathy. The results of the study suggest protective effects against tubulointerstitial fibrosis and inflammation achieved by positive regulation of SIRT1 and nuclear erythroid factor 2-related factor 2 (Nrf2) signalling pathway resulting in oxidative stress reduction.

2.7. SIRT1 in renal cell carcinoma

The role of the sirtuin family in carcinogenesis has been widely investigated, but the results remain unclear. The variety of results depends on several factors: type of sirtuin, stage of cancer development, tissue of origin and cellular energy state. Ambivalent effects of SIRT1 on carcinogenesis were documented [80–85]. On one hand, SIRT1 promotes cell survival under stress, by deacetylation of p53 protein resulting in decreased apoptosis. In line with this, overexpression of SIRT1 was demonstrated in prostate [80], pancreatic [81] or liver cancer [82]. On the other hand, prevention of DNA damage by reduced inflammation, promoting DNA repair and genomic stability contribute to antitumor effects. SIRT1 was shown to repress EMT, the critical event initiating cancer metastasis, in lung and oral squamous cell carcinoma [83,84]. However, another study revealed opposing effects on EMT, mediated by distinct signalling pathways [85].

Renal cell carcinoma (RCC) is the most common type of kidney cancer and represents 3% of all malignancies in adults worldwide [86]. Despite the advancement in diagnostic and early surgical treatment, approximately 30% of patients develop metastatic disease [87]. Therefore, deepening the knowledge about molecular biology of RCC and the development of new treatment approaches is of great importance.

Recently, an increasing number of studies focus on microRNAs, which are small, non-coding RNA fragments participating in broad range of biological processes. Growing lines of evidence indicate that some of microRNAs molecules serve as tumour suppressors in RCC, directly targeting SIRT1. Overexpression of microRNA200a and microRNA22 contribute to suppression of cell growth, inhibition of EMT and activation of programmed cell death in RCC cell lines [87,88]. Decreased level of these microRNA molecules was associated with advanced stage of the cancer and metastases.

A retrospective study examined the expression of the sirtuin family in clear cell RCC tissue, adjacent negative surgical margin and its correlation with prognosis [86]. The researchers found that the expression

of SIRT1, SIRT3 and SIRT6 in tumour cells is lower than in normal tissues, but there was no significant correlation with metastases. Interestingly, SIRT3 was found to correlate positively with survival and may become a novel, valuable prognostic marker in RCC. On the contrary, it was demonstrated that SIRT2 expression in RCC is higher as compared to normal kidney and correlates with the resistance to standard chemotherapy [89]. In addition, a study on human species of sporadic papillary RCC has indicated that mutation of SIRT1 increases the expression of protein having a pivotal role in tumour progression [90].

2.8. SIRT1 and autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease resulting from mutation in *pkd1* or *pkd2* gene. It is estimated that ADPKD is responsible for approximately 10% of end-stage renal disease [91]. Currently, there is no effective specific therapy available for the patients. SIRT1 is engaged in renal epithelial cell regeneration after injury. It promotes cell proliferation and growth by inactivation of two tumour suppressor proteins p53 and Rb [92]. Although this may be beneficial in case of kidney damage, in ADPKD it contributes to sustained cyst formation. As an illustration of the above, administration of SIRT1 inhibitor or the enzyme gene deletion in an animal model of ADPKD resulted in delayed cyst formation [92]. Nonetheless, the pathogenesis of continuous cyst formation in ADPKD has been elucidated, there is a need for further investigation to devise efficient therapeutical strategies.

2.9. SIRT1 and lupus nephritis

Systemic lupus erythematosus (SLE) is an autoimmune disease leading to chronic inflammation in several tissues and organs. Lupus nephritis develops as a result of immune complex deposition and may occur in the form of chronic glomerulonephritis, rapid progressive glomerulonephritis, tubulointerstitial nephritis or renal tubular acidosis. Identifying and monitoring renal involvement in the course of the SLE is of great importance due to increased mortality. In routine clinical practise, dsDNA antibodies are widely used to evaluate the risk for lupus nephritis and its activity. An entertaining future perspective provided results of the study on urinary SIRT1 levels in patients with SLE [93]. Patients diagnosed with SLE presented higher SIRT1 levels in comparison to healthy group. Moreover, the authors found a positive correlation between SIRT1 level, clinical disease activity and dsDNA antibodies. It is worth stressing that glomerular proliferative forms of the disease, clinically severe, were associated with higher urinary SIRT 1 level. This data suggest that SIRT1 may become a novel potential biomarker in the assessment of lupus nephritis.

2.10. The role of SIRT1 in blood pressure regulation

Sirtuins participate in regulation of blood pressure, which is closely related to the level of renal decline. Overactivation of renin-angiotensin-aldosterone system (RAAs) signalling mediated by angiotensin type 1 receptor (AT_1R) is involved in pathogenesis of hypertension and CKD. Angiotensin converting enzyme 2 (ACE2) hydrolyses angiotensin II to angiotensin-(1–7), which has the opposite cardiovascular effects. SIRT1 modulates RAAs by activating ACE2 promoter and repressing AT_1R expression [94,95]. SIRT1 is abundantly expressed in distal tubular cells and collecting duct cells what indicates its role in water and sodium metabolism [96]. It has been reported that SIRT1 physiologically acts in opposition to aldosterone by repression of α-ENaC transcription in a mouse collecting duct cells resulting in decreased Na^+ reabsorption [97]. Furthermore, SIRT1 was found to mitigate detrimental effects of angiotensin II on blood vessels in transgenic mice overexpressing SIRT1 in vascular smooth muscle cells [98]. Multidirectional action of SIRT1 on oxidative stress, inflammation and TGF-β, resulted in decrease in vascular remodelling, thereby lowering systolic blood pressure.

Dietary salt restriction has been widely practised in the CKD management and its beneficial effect on CKD progression and cardiovascular risk comes from numerous lines of evidence [99]. A recent study investigated the impact of low-salt diet on renal SIRT1 and ghrelin expression in rats [96]. The researchers demonstrated a significant increase in SIRT1 expression after 7-day low-salt diet (LoS) and CR in the kidneys, brain, heart and muscles. Whereas, a group of rats on high-salt diet (HiS) did not exhibit changes in the level of SIRT1 in the kidneys or in the extra-renal tissues despite similar food intake. This implies that HiS may attenuate the influence of CR on SIRT1 expression. Even though LoS and CR group exhibited a comparable level of SIRT1, only the LoS group presented increased ghrelin expression. Ghrelin increased SIRT1 level in a dose-dependent manner, while inhibiting of the ghrelin receptor repressed SIRT1 expression. Furthermore, ghrelin has been shown to target ENaCs and stimulate Na^+ reabsorption in collecting duct cells [100]. Therefore, it can be expected that there is a local, renal ghrelin - SIRT1 system involved in sodium–water homeostasis and SIRT1 represents a part of negative feedback loop. However, further studies are warranted here.

2.11. SIRT1 and lipid metabolism

Over years researchers have been demonstrating that abnormal lipid metabolism contributes to the development of atherosclerosis and glomerulosclerosis. Pharmacological lipid lowering therapy has shown the effectiveness against cardiovascular risk and renal injury progression [101]. CKD and atherosclerosis are associated with long-term inflammatory stress [102,103], which is responsible for modified lipid homeostasis and adipose tissue redistribution [104]. Lipid redistribution takes place on tissue and intracellular level. Cholesterol from bloodstream is removed by a scavenger receptor located on the surface of vascular smooth muscle cells, macrophages and mesangial cells. Intracellular redistribution refers to lipid accumulation in endoplasmic reticulum, which induces cellular dysfunction eventually leading to programmed cell death [104]. The most important consequence of altered lipid homeostasis in patients with CKD is a lack of correlation between plasma cholesterol levels and cardiovascular risk. Dialyse–-dependent patients present reversed relationship between LDL cholesterol level and cardiovascular mortality. Low plasma LDL concentration is associated with increased all-cause mortality under systemic inflammatory condition [105].

Growing body of evidence indicates that SIRT1 is a prominent regulator of lipid metabolism. Under low-energy conditions it positively regulates PPARα and its coactivator PGC-1α, resulting in fatty acids utilization [106]. SIRT1 inhibits hepatic lipogenesis targeting a major activator of triacylogliceroles synthesis - sterol regulatory element-binding protein (SREBP) [107]. SIRT1 activates liver X receptor (LXR), responsible for reverse cholesterol transport, and reduces expression of the scavenger receptor, which together protect from cellular lipid overload and foam cell formation [108]. SIRT1-KO liver specific mice have increased plasma cholesterol levels due to alteration in the LXR target proteins expression [109]. Surprisingly, unspecific excessive expression of *SIRT1* gene was associated with atherosclerotic plaques formation to a greater extent than a control group [110].

Plasma cholesterol level depends on endogenic synthesis, dietary intake and hepatic uptake by LDL receptor mediated endocytosis. The number of LDL receptors on hepatocytes surface correlates inversely with LDL cholesterol concentration. The principal regulator of LDL receptor expression is proprotein convertase subtilisin/kexin type 9 (PCSK9), which interrupts the recirculation of the receptor and directs it towards lysosomes for degradation. Recently, SIRT1 was found to inhibit the hepatic PCSK9 secretion with subsequent increase in LDL receptor expression [111].

2.12. SIRT1 and obesity

Central body fat distribution triggers a cascade of events which boost glomerulosclerosis [112]. It is well known that adipose tissue is not only a lipid storage site but also a highly active metabolic and endocrine organ. SIRT1 expression in subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) has been shown to have similar levels in normal-weight individuals and decreased levels in obese and diabetic ones. However, the decrease in SIRT1 mRNA level in VAT was not significant in obese humans in contrast to markedly suppressed in subjects with obesity and type 2 diabetes [113].

SIRT1 has multiple regulatory functions in adipose tissue. It suppresses adipocyte differentiation, lipid accumulation and inflammation by inhibition of peroxisome proliferator–activated receptor gamma (PPARγ) [114] and NF-κβ [115]. SIRT1 also regulates adiponectin gene expression, an adipokine which manifests benefits against obesity-related disorders. Fisetin, a plant polyphenol, has been described as promoting adiponectin expression by activation of SIRT1 and PPARγ [116]. Adiponectin has a crucial role in insulin sensitivity and glucose homeostasis, stimulates fatty acid oxidation and suppresses apoptosis in pancreatic beta cells and cardiomiocytes. Moreover, it prevents atherosclerotic vascular disease by enhancement of endothelial nitric oxide bioavailability and suppression of inflammatory responses [117]. Concerning renal pathology, adiponectin has been shown to be conversely correlated with albuminuria in rodents [118] and in obese humans [119]. Reduced podocyte apoptosis after injury and suppressed interstitial fibrosis has been found to contribute to renoprotective effects of adiponectin [120]. In contrast, another adipokines i.e. leptin, TNF-α and Il-6 promote renal damage by exertion of oxidative stress and fibrosis [121]. Adipose SIRT1 has been shown to correlate very strong and positively with adiponectin and has been associated with the same insulin resistance-related metabolic parameters as adiponectin [120]. Taking into consideration the aforementioned, SIRT1 may improve the lipid profile and prevent deleterious abnormal lipid metabolism under stress conditions.

2.13. SIRT1 and cardiovascular disease

The progression of kidney diseases and development of their complications is inseparably associated with cardiovascular disease. Benefits of the sirtuin family on cardiovascular system refer to their pleiotropic target points participating in a wide range of biological processes, age-related and metabolic disorders. *SIRT1* gene polymorphisms have been linked to elevated CV risk, raised blood pressure, high body fat level, diabetic nephropathy, abnormal cholesterol metabolism and coronary calcification [122–125]. In a mouse model, SIRT1 deficiency contributed to increased apoptosis after ischemia reperfusion, while SIRT1 overexpression protected from myocardial injury [126].

SIRT1 is highly expressed in blood vessels, especially in endothelial cells and has a protective role against atherosclerosis, thrombosis, ischemia reperfusion injury due to enhancing nitric oxide synthase (eNOS) activation and stimulating new blood vessels formation [127]. Moreover, it protects endothelial cells from dysfunction by reduction in plasminogen activator inhibitor - 1 (PAI-1). It was demonstrated that PAI-1 is abundantly expressed in senile endothelial cells and correlates with arterial stiffness [128]. In contrast, the role of SIRT1 in vascular smooth cells is associated with their differentiation and proliferative properties. SIRT1 was found to diminish injury-induced neointima formation and counteract angiotensin II induced vascular remodelling [98,129] However, there are some common effects mediated by SIRT1 in both types of cells e.g. prevention of atherosclerotic plaque formation and stability [130–132]. Of note, two more nitric oxide synthases are distinguished: inducible (iNOS) involved in inflammatory responses and neuronal (nNOS) functioning as a neurotransmitter and modulator of muscle responses to changes in calcium concentrations [133]. Interaction between SIRT1 and iNOS may play a key role in the inflammatory responses and insulin resistance in the skeletal muscles [134].

Nonetheless, there is some evidence that SIRT1 is associated with poor cardiac outcomes, especially the role of SIRT1 in cardiac hypertrophy and heart failure remain controversial [127]. The conflicting outcomes may be due to various factors. The type of regulation of gene expression (transient or constitutive) may result in different cellular response. Additionally cardioprotective effects achieved by supplementation of SIRT1 activators may represent the sum of actions of distinct molecular mechanism. It is also speculated that harmful effects of high level SIRT1 protein may be the consequence of non–specific, excessive deacetylation [127].

3. Conclusions

Advances in medicine in the past decades contribute to the improvement of quality and longevity of human life. Consequently, percentage of elderly people and age-dependent diseases have notably risen. At present, modern population predominantly follows sedentary lifestyle resulting in the increasing incidence of obesity and metabolic syndrome. Undoubtedly, strict dietary regimen and systematic physical exercise is challenging for the vast majority of the population. So far, there is no accessible pharmacological treatment for obesity. Age–dependent decline in kidney function can be easily exacerbated by metabolic disorders or even one–time acute kidney injury. The studies providing evidence for sirtuins' beneficial influence against kidney injury and many age-related or metabolic conditions are very encouraging.

It is well known that each stage of CKD is characterized by differing levels of oxidative stress and inflammation as well as varying levels of risk regarding the development of comorbidities such as CVD. In contrast, both those processes influence the development and subsequent progression of CKD. Several studies have shown SIRT1 to be protective against inflammation as well as to regulate oxidative stress. Therapies relying on the modulation of the SIRT1 activity hold a great potential for improving outcomes in patients with kidney and cardiovascular diseases. The prospect of being able to selectively activate SIRT1, serves as a continuous impulse for future research.

Conflict of interests

The authors declare no conflict of interests.

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