Sirtuin Family and Diabetic Kidney Disease

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Diabetes mellitus (DM) is gradually attacking the health and life of people all over the world. Diabetic kidney disease (DKD) is one of the most common chronic microvascular complications of DM, whose mechanism is complex and still lacks research. Sirtuin family is a class III histone deacetylase with highly conserved NAD+ binding domain and catalytic functional domain, while different N-terminal and C-terminal structures enable them to bind different deacetylated substrates to participate in the cellular NAD+ metabolism. The kidney is an organ rich in NAD+ and database exploration of literature shows that the Sirtuin family has different expression localization in renal, cellular, and subcellular structures. With the progress of modern technology, a variety of animal models and reagents for the Sirtuin family and DKD emerged. Machine learning in the literature shows that the Sirtuin family can regulate pathophysiological injury mainly in the glomerular filtration membrane, renal tubular absorption, and immune inflammation through various mechanisms such as epigenetics, multiple signaling pathways, and mitochondrial function. These mechanisms are the key nodes participating in DKD. Thus, it is of great significance for target therapy to study biological functions of the Sirtuin family and DKD regulation mechanism in-depth.

Keywords: Sirtuin (SIRT), diabetes, kidney, NAD+, diabetic kidney disease

1 INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by high blood glucose due to insulin secretion deficiency or biological function impairment (1). According to the International Diabetes Federation (IDF) data, the global adult DM population is over 537 million, 10.5% of the total population and shows a younger trend (2, 3), indicating that DM is gradually attacking the health and life of people all over the world. Therefore, studying the pathogenesis of complications in DM is still an urgent problem to be solved.

Diabetic kidney disease (DKD), also known as diabetic nephropathy (DN) (4) and is one of the most common chronic microvascular complications of DM with a 10%~40% DKD incidence in DM (5–7). The pathological changes are characterized by the continuous and slow development of proteinuria involving a complex pathological process of the glomerulus, renal tubules, microvessels, and other renal structures (8). It is of great significance to understand the pathogenesis of DKD and explore the targeting drugs related to DKD.

Silent information regulator 2-related enzymes (Sirtuin or SIRT) are the first discovered class III histone deacetylases (HDAC) of which NAD+)-Sirtuin pathway is core in the energy metabolism for
aging, cancer, cardiovascular, and cerebrovascular diseases as well as metabolic diseases (9, 10). Recent studies have shown that the Sirtuin family plays an important role in the biological mechanism and pathophysiological changes of DKD.

Thus, the aim of this review is to summarize the role of the Sirtuin family in DKD via displaying renal histological expressions, specific mechanisms, and renal injury of the Sirtuin family in different study models and reagents.

2 PATHOPHYSIOLOGY OF DIABETIC KIDNEY DISEASE

The pathological changes of DKD start from basement membrane thickening in the early stage and gradually spread to the area of the glomerulus, microvessels, and renal tubules with characteristic changes of glomerular hyaline degeneration appearing in the late stage (11). Healthy nephron structures include endothelial cells, basement membrane, parietal cells, mesangial cells, glomerular capillaries, foot processes, podocytes, and renal tubular epithelial cells (12, 13). The pathological changes of DKD are mainly manifested as early glomerular basement membrane thickening, mesangial cell hypertrophy, abnormal hyperplasia, podocyte loss, hypertrophy, foot process disappearance with the later pathological manifestations of tubular epithelial atrophy, collagen deposition, activation of myofibroblasts and stroma, inflammatory cell influx, capillary thinning, and finally, arteriole hyaline degeneration (14–16). These pathological changes lead to persistent and slowly progressing proteinuria, eventually leading to end-stage renal disease (ESRD), which harms people’s health. The specific structure and pathological process are shown in Figure 1. The pathogenesis of DKD is a complex result of multiple factors with great significance to explore the pathogenesis of DKD for clinical diagnosis and treatment. Thus, it is of great significance to study the pathophysiological roles of DKD in different renal structures.

3 SIRTUIN FAMILY AND THEIR BIOLOGICAL FUNCTIONS

Sirtuin family is the first discovered class III HDAC with the recognized family members SIRT1-7, which have different subcellular localizations. SIRT1, SIRT6, and SIRT7 are mainly distributed in the nucleus, while SIRT3, SIRT4, and SIRT5 are mainly located in the mitochondria and SIRT2 is mainly located in the cytoplasm (Table 1 and Figure 2) (17). All of them have highly conserved nicotinamide adenine dinucleotide+ (NAD⁺) binding domain and catalytic functional domain, while different N-terminal and C-terminal structures enable them to bind different substrates (18). SIRT1-SIRT3 have strong deacetylase activity, SIRT4-SIRT7 are considered to be weak or even difficult to detect deacetylase activity and SIRT4 mainly has adenosine diphosphate (ADP)-ribosyltransferase activity (Table 1) (19, 20). Different enzymatic activities may be related to their different pathophysiological functions.

In mammals, NAD⁺ can be composed of four different biological precursors including two forms of niacin (NA), tryptophan, Vitamin B3, nicotinamide (NAM), and nicotinamide nucleoside (NR) synthesized from the daily diet (including milk, meat, nuts, etc.) through three biological ways. The specific mechanism is shown in Figure 2. The enzymatic activity of the Sirtuin family is mainly deacetylase and ADP-ribosyltransferase to remove the acetyl group from the target protein with NAD⁺ transferred into NAM and acetyl-ADP-ribose (22). The main synthetic pathway of NAD⁺ is the Salvage pathway, in which NA, NAM, and NR, as the precursor, are converted to the intermediate nicotinamide mononucleotide.
(NMN), by the rate-limiting enzyme nicotinamide phosphoribose transferase (NAMPT). The intermediate, NMN can be converted into NAD⁺ by nicotinamide mononucleotide adenylate transferase (NMNAT). NAD⁺ produced by this pathway is consumed by a variety of enzymes including Sirtuins to regulate energy metabolism, mitochondrial function, and a variety of cellular responses to produce NAM and reuse it again via the Salvage pathway (23, 24). In the Preiss-Handler pathway, NA obtained from the daily diet can be transformed into mononucleotide nicotinate (NAMN) and nicotinamide adenine dinucleotide (NAAD) by key enzymes such as nicotinate phosphoribosyltransferase (NAPRT) and nicotinate phosphoribosyltransferase (QPRT) and then to NAD⁺ by the rate-limiting enzyme NAD⁺-adenylate transferase (NMNAT). Tryptophan can be converted into NAMN by the quinoline degradation pathway (23, 24). In the Preiss-Handler pathway, NA obtained from the daily diet can be transformed into mononucleotide nicotinate (NAMN) and nicotinamide adenine dinucleotide (NAAD) by key enzymes such as nicotinate phosphoribosyltransferase (NAPRT) and nicotinate phosphoribosyltransferase (QPRT) and then to NAD⁺ by the rate-limiting enzyme NAD⁺-adenylate transferase (NMNAT). Tryptophan can be converted into NAMN by the quinoline degradation pathway (23, 24). In the Preiss-Handler pathway, NA obtained from the daily diet can be transformed into mononucleotide nicotinate (NAMN) and nicotinamide adenine dinucleotide (NAAD) by key enzymes such as nicotinate phosphoribosyltransferase (NAPRT) and nicotinate phosphoribosyltransferase (QPRT) and then to NAD⁺ by the rate-limiting enzyme NAD⁺-adenylate transferase (NMNAT).

### 4 LOCALIZATION OF THE SIRTUIN FAMILY IN KIDNEY

Sirtuins only make action in the presence of coenzyme NAD⁺ in all living cells (23). Based on that, an increasing number of studies suggest that the maintenance of NAD⁺ levels and the corresponding decrease in Sirtuin activity can contribute to normal aging (37, 38). Expression levels of NAD⁺ may be closely related to the localization and expression of the Sirtuin family in renal tissues (21). According to existing studies, SIRT1 is widely expressed in renal tubular cells and podocytes (39), SIRT2 is mainly expressed in proximal epithelial renal tubular cells (40), SIRT3 and SIRT5 are described as key regulators of mitochondrial dynamics in proximal epithelial renal tubular cells (41), while SIRT6 and SIRT7 are strongly related to chromatin repair and transcription activation (36). The different biological functions of the Sirtuin family members may represent their different regulatory effects on DKD.

| Sirtuin family member | Subcellular localization | Substrates | Enzyme function |
|-----------------------|--------------------------|------------|----------------|
| SIRT1 | Nuclear, cytoplasmic | LKB1, p53, NRFb, PGC1α, HIF1α, HIF2α, CTIP2, Tat, p300, LXR, FXR, histone H1, histone H3, histone H4, eNOS, MEF2, Notch1, Ku70, WRN, NBS1, LKB1, hMOF, AceCS1, c-Myc, androgen receptor, cortactin, RAPR1 | Deacetylation, Decrotonylase |
| SIRT2 | Nuclear, cytoplasmic | LKB1, histone H3, histone H4, tubulin, p300, p65, PERK1, FOXO1, FOXO3A, beta-secretase 1, p53, Par-3, CDK9, G6PD, PGAM, HIF1α, ALDH1A1, TUG, SubR1 | Deacetylation, Demalonylase, Decrotonylase |
| SIRT3 | Mitochondrial | AceCS2, HMGCS2, ATP synthase F1, LCAD, SDH, Ku70, SOD2, FOXO3, aconitate 2, GDH, LKB1, MRPL10, LCAD, cyclophilin D, PDH, ALDH, Skp2, OGG1, Hsp10, GOT2, MDH | Deacetylation, Decrotylase, Decrotonylase, Deacetylation, ADP-ribosylation, Lipoylase |
| SIRT4 | Mitochondrial | GDH, MCD, PDH, Hsp60, stress-70 | Deacetylation, Decrotonylase |
| SIRT5 | Mitochondrial | Cytochrome, CPS1, SOD1, urate oxidase, PML, VLCAD, Prx-1, HMGCS2, Hsp70, MCAD | Deacetylation, ADP-ribosylation, Lipoylase |
| SIRT6 | Nuclear | TNFα, histone H3, p70, Kup68, GCN5, KAP1, Ctf1, Parp1, GEN1 | Deacetylation, ADP-ribosylation, Lipoylase |
| SIRT7 | Nuclear | Histone H3, PAF53, DNA-PK, GABPβ1, p53 | Deacetylation |
(Figures 3, 4). Figure 3 indicated that SIRT1 had a similar expression with biomarkers in mesangial and proximal tubular cells, while SIRT2-5 showed a similar distribution similar to biomarkers in proximal tubular cells. SIRT6 and SIRT7 were similar to biomarkers in endothelial cells, while SIRT6 and biomarkers in proximal tubular cells also showed certain similarities. Figure 4 showed that the whole family members had a low correlation to podocyte biomarkers in the filtration membrane system. In the renal tubules, SIRT4 had a higher correlation with proximal tubular cell biomarkers, while SIRT1 and SIRT6 had a lower correlation. The Sirtuin family expression was highly correlated in the thick segment of ascending limb.
The high correlation of SIRT1-5 and low correlation of SIRT6-7 appeared in intercalated cells of the collecting duct and may be due to their different transporters and transport functions. Except for SIRT4, other family members were highly correlated with endothelial cells, fibroblasts, T cells, and macrophages, suggesting the involvement of renal interstitial fibrosis and inflammatory response. Furthermore, other members of the Sirtuin family, except SIRT4, are strongly correlated with plasma biomarkers. Our previous study found that serum SIRT6 decreased with different urinary albumin groups in patients with type 2 DM, which was correlated with urinary albumin excretion rate (47), also confirming their potential as biomarkers in circulation. This database research can partially supplement the defects of previous studies, however, it also has certain contradictions that need further exploration.

The expression of the Sirtuin family in kidneys shown in literature and databases is still contradictory. The reason may be due to the fact that most of Sirtuins’ studies have focused only on a single region of the kidney and have not conducted whole family comparisons at the same level. It is necessary to study the changes of the Sirtuin family in DKD by the spatiotemporal transcriptome sequencing in the whole renal tissues.

### 5 ROLE OF THE SIRTUIN FAMILY IN DIABETIC KIDNEY DISEASE

To explore the role of the Sirtuin family in DKD, previous studies have established different diabetes models, Sirtuin targeting animal models and a series of Sirtuin family targeting reagents. Studies have shown that the Sirtuin family regulates mesangial cell proliferation and hypertrophy, podocytes apoptosis, proximal tubular glucose metabolism, and renal tubular injury under DKD conditions and regulates podocytes mediated renal tubular, endothelial cells, and macrophages crosstalk via epigenetics of deacetylation and dephosphorylation, NAD⁺
involved mitochondrial function and multiple signaling pathway targets.

5.1 Study Models and Specific Reagents

Previous studies have established streptozotocin (STZ) induction, Otsuka-Long-Evans-Tokushima-Fatty (OLETF) rats, Akita mice, OVE26 mice, BTBR ob/ob mice, and endothelial nitric oxide synthase (eNOS)-/- mice as different diabetes models and Sirt1 global, podocyte-specific, and proximal tubule-specific overexpression and knockout mice as Sirtuin targeting animal models, and constructed a series of Sirtuin family targeting reagents represented by Resveratrol, and achieved some results as follows.

The mechanism of the Sirtuin family and DKD is still at the superficial stage and further mechanism exploration is needed. The research results of other pre-renal metabolic diseases (insulin resistance, obesity, non-alcoholic fatty liver disease, hyperuricemia, metabolic syndrome, etc.), renal injury diseases (acute kidney injury, chronic kidney diseases, or acute-chronic process), and post-renal obstructive diseases may have some enlightenment with the research on DKD. Moreover, the adverse pharmacokinetic and/or pharmacodynamic characteristics and uncertain effects may limit clinical application of Sirtuin reagents, which should be treated with caution. It is hoped that DKD therapeutic targets in different kidney tissues can be explored by combining different DKD and specific Sirtuin expressed animal models as well as reagents in the future.

5.1.1 Diabetic Models

The most widely used model for DKD is STZ, which can enter islet cells through glucose transporter 2 (GLUT2) with a toxic effect on insulin, and induce insulin-secreting cells apoptosis. It is a typical model of type 1 or type 2 DM with or without a high-fat diet in rats and mice (48–50). It has a high modeling rate and mild pathological changes in DKD studies but with certain renal toxicity and multiple interventions with low doses. The effect of the Sirtuin family regulating STZ-induced DKD is mostly non-

FIGURE 4 | Correlation of human Sirtuin family transcriptome in renal tissues. The analysis was performed on data from RNA-seq of unfraccionated tissue samples, which contained a mixed cell population. Across the respective sample sets the reference transcripts within each cell type panel correlated highly with each other, but not with those in the other panels. An integrative co-expression analysis was performed to determine the expression profile of each gene; genes highly correlated with all transcripts in only one reference panel were classified as enriched in that cell type.
metabolic damage, mainly manifested as renal damage caused by mitochondrial dysfunction, oxidative stress, and inflammatory reaction, which may be associated with renal toxicity of STZ to some extent (Table 2). The expression of SIRT1, SIRT3, and SIRT6 were all decreased in the STZ-induced DKD model. SIRT1 mainly alleviated renal injury caused by mitochondrial oxidative stress and cellular inflammation through FoxO1, TGFβ1, and NFκB (58, 60, 69). SIRT3 maintained mitochondrial redox balance and regulated the glycolysis in renal tubular epithelial cells through PGC1α and TGFβ1 (101, 106). SIRT6 reduced proteinuria and damage in podocytes and mesangial cells by regulating H3K9ac and H3K36ac epigenetics, affecting nuclear translocation of FoxO1, and stabilizing inflammatory mediators (108, 110, 112, 113).

Another model commonly used to study the Sirtuin family is db/db mice, which are homozygous mutant mice of leptin receptor gene encoded by db genes, with spontaneous hyperglycemia and insulin resistance, and the occurrence of DKD complications at 8-12 weeks and general life of about 10 months. The db/db mice are widely used in obesity and type 2 DM research and are ideal models for studying early DKD lesions. The Sirtuin family’s regulation of db/db mice induced DKD model is mostly metabolic changes, mainly manifested as pre-renal glucolipid metabolism disorders caused by glucotoxicity and lipid peroxidation (shown in Table 2). SIRT1, SIRT3, and SIRT6 were all decreased in this model consistent with STZ-induced DKD. However, SIRT1 can improve glucolipid toxicity and oxidative stress via SREBP1 and GLUT2, thus reducing proteinuria and improving kidney injury (59, 68, 75, 92). SIRT3 reduced oxidative stress and apoptosis of renal tubules by inhibiting BNIP3 (103). SIRT6 regulated renal tubular damage and protected renal function through Smad3 deacetylation (111). In addition, there are no studies on histones regulation by the Sirtuin family in db/db mice, which is worthy of further exploration.

Only a few other models have focused on OLETF rats, Akita mice, OVE26 mice, BTBR ob/ob mice, and eNOS−/− mice. OLETF rats are animals of high appetite induced by loss of rat cholecystokinin A receptor genes. It is similar to the DKD model of human type 2 DM with mild pathological changes, which can better study the whole duration of DKD (114). Studies have shown that inhibition of miRNAs can reduce EMT and renal fibrosis in HK-2 cells of diabetic OLETF rats, and SIRT1 is identified as the target of these two miRNAs (77), speculating that SIRT1 has a regulatory effect on EMT rates DKD model. Akita mice are islets β apoptosis model affecting the normal folding of insulin protein induced by dominant missense mutations of Ins2 genes with the A7 position of insulin changed from cysteine to tyrosine. Its renal lesions are mild and survival is difficult with better usage of early DKD filtration membrane study (115, 116). The study on SIRT3 mentioned Akita mice with DKD development (117), but there was no specific study on Sirtuin family members (101). OVE26 mice are FVB line early-onset type 1 diabetic mice with calmodulin overexpression in islet β cells leading to islet defect. Mice have the characteristics of DKD at 4-6 months, with the irreversible disappearance of podocytes in the later stage and high mortality (118). Studies have shown that both Sirt1 overexpression and exogenous activation reduced podocyte loss and oxidative stress in OVE26 mice (73). BTBR has the characteristics of natural insulin resistance, while ob/ob mice leptin mutant genes lead to loss of satiety and spontaneous obesity in mice. The combination of the two models can establish the DKD model from early to late but with a high price (119, 120). Studies have shown that SIRT3 decreased in BTBR ob/ob mice renal tissues and SIRT3 reduced proteinuria improved glomerular and podocyte damage and had retrograde changes in renal tubular and glomerular (104). The eNOS−/− mice model accelerates renal injury through vascular endothelial dysfunction and hypertension. Its combination with STZ and db/db mice is an ideal model for studying the late stage of DKD but it is difficult for feeding (121, 122). Puerarin treatment increased SIRT1 mRNA and protein in podocytes and significantly alleviated albuminuria and diabetic kidney injury in diabetic eNOS−/− mice (72), thus speculating the relationship between SIRT1 and eNOS−/− mice. These studies of the Sirtuin family are only preliminary and further exploration of pathological changes in different stages of DKD caused by different models is still needed.

5.1.2 Sirtuin Gene Editing Models

The Sirtuin-specific model constructed by gene-editing technology is a supplement to DKD model research (Table 2). Sirt1 overexpression in transgenic mice attenuated ET-1, TGF-β1, microalbuminuria, glucose-induced cell damage markers, and fibrocnict in diabetic renal tissues (66). Podocyte-specific overexpression attenuated the progression of diabetic glomerulopathy and proteinuria (73). Proximal tubule-specific Sirt1 transgenic and knockout mice suggested the occurrence of diabetic glomerular pathological prevention and aggravation, while non-diabetic knockout mice showed proteinuria, suggesting that SIRT1 in proximal tubules affected glomerular function (61). Sirt1 podocyte-specific knockout db/db mice had more proteinuria, renal injury, and acetylation of p65 and STAT3 (63). Sirt6 podocyte-specific knockout intensified podocyte damage and proteinuria (44).

5.1.3 Sirtuin Reagents

In addition, newly developed Sirtuin-related activators and antagonists also have certain applications in DKD research. The SIRT1 activator, Resveratrol, has been widely used in DKD studies (Table 2). In vivo administration of SIRT1 inhibitor, EX-527, for 10 weeks significantly reduced blood glucose and kidney weight in high-fat diet-induced Zucker rats, decreased blood urea nitrogen, serum creatinine, microalbumin, urine excretion, and inhibited the histopathological expansion of the extracellular mesangial matrix and glomerulosclerosis (98). Mechanically, EX-527 regulated the accumulation of extracellular matrix in mesangial cells via the AMPK-PGC1α pathway (94) eliminated the protective effect of Na2S4 in DKD renal tubular cells (93) and inhibited autophagy (86). SIRT1 agonist, BF175, increased PGC1α activation and protected podocyte mitochondria injury induced by high glucose. In vivo BF175 treatment for 6 weeks significantly reduced albuminuria and glomerular injury (73).
### TABLE 2 | Role of Sirtuin family in diabetic kidney diseases.

| Sirtuin family | Animal model | Cell model | Sirtuin related Reagent | Molecular biology | Pathophysiology | References |
|----------------|--------------|------------|-------------------------|-------------------|-----------------|------------|
| SIRT1          | SV40 MES13   | —          | SIRT1 activator, resveratrol | Smad7 deacetylation | attenuate mesangial cell apoptosis | (51)       |
| SIRT1          | STZ-induced Sprague-Dawley rats | — | SIRT1 activator, resveratrol | change histone H3 phosphorylation, MAP kinase p38, SIR2 and p53 expression | — | (52) |
| SIRT1          | HK-2 mouse PTC | SIRT1 activator, resveratrol | activate FoxO3α and catalase | regulate MnSOD activity | release renal tubular cell apoptosis | (53) |
| SIRT1          | db/db C57BLKS mice | mouse PTC | — | FoxO4 deacetylation | ameliorate oxidative stress in proximal tubules | (54) |
| SIRT1          | diabet C57BLKS mice | mouse CIP | — | NFκB deacetylation | prevent podocyte apoptosis | (55) |
| SIRT1          | aldosterone-induced diabetic Wistar fatty and lean rats | MPCK | SIRT1 activator, resveratrol | regulate PGC1α | improve mitochondrial morphology and autophagosomes | (56) |
| SIRT1          | STZ-induced Sprague-Dawley rats | — | SIRT1 activator, resveratrol | activate FoxO1 | regulate oxidative stress and fibrosis | (58) |
| SIRT1          | db/db C57BLKS/J mice | rat MC | SIRT1 activator, resveratrol | activate PGC1α, ERR1α, and SREBP1, decrease P3K, Akt, FoxO3α | ameliorate glomerular matrix expansion and inflammation | (59) |
| SIRT1          | STZ-induced Sprague-Dawley rats | — | SIRT1 activator, resveratrol | activate Nr2/ARE, fibronectin and TGFβ1, increase HO1 | reduce mesangial cell oxidative stress | (60) |
| SIRT1          | kidney- and proximal tubules-specific Sirt1 knockout, STZ-, PK9666–, 5/6 | mouse CIP, HK-2 | — | epigenetically suppress Claudin1 | participate in crosstalk between podocytes and renal tubules: SIRT1 in proximal tubules protects against albuminuria by maintaining NAD+ around glomerulus, thus influencing podocyte function | (61) |
| SIRT1          | STZ-induced Sprague-Dawley rats | mouse CIP, mouse GEC | SIRT1 activator, resveratrol | down-regulate VEGF and VEGFR2 | regulate angiogenesis in podocyte and endothelial cells | (62) |
| SIRT1          | db/db, podocyte-specific Sirt1 knockout mice | human CIP | — | NFκB and STAT3 deacetylation | attenuate proteinuria and podocyte injury | (63) |
| SIRT1          | STZ-induced Sprague-Dawley rats | — | SIRT1 activator, resveratrol | increase HO1, loss FoxO1 | suppress oxidative stress and extracellular matrix deposition | (64) |
| SIRT1          | STZ-induced diabetic spontaneously hypertensive rats | human MC | — | decrease NOX4 and TGFβ1, maintaining PARP1, intracellular NAD+/NADH ratio, AMP/ATP ratio, Smad3 deacetylation | ameliorate mesangial cell extracellular matrix accumulation | (65) |
| SIRT1          | STZ-induced, Sirt1 transgenic C57BL/6J mice | HEK293A | — | regulate p300, ET1 and TGFβ1 | protect from renal injury | (66) |
| SIRT1          | rod MC | SIRT1 activator, resveratrol | inhibit HIF1α | inhibit mesangial cell inflammation and fibrosis | (67) |
| SIRT1          | db/db C57BLKS/J mice | human CIP | SIRT1 activator, resveratrol | decrease FoxO1, FoxO3α, and SREBP1, increase PPARγ, PGC1α, ERR1α, and pACC | ameliorate lipotoxicity, oxidative stress, apoptosis and endothelial cell dysfunction | (68) |
| SIRT1          | STZ-induced Wistar rats | — | SIRT1 activator, resveratrol | normalize TGFβ1, fibronectin, NFκB, Nr2, and FoxO1 | protect renal oxidative damage | (69) |
| SIRT1          | STZ-induced Wistar albinorats | HK-2 | SIRT1 activator, resveratrol | p53 deacetylation | ameliorate renal tubular injury | (70) |
| SIRT1          | STZ-induced Wistar albinorats | — | — | inhibit NFκB | alleviate renal oxidative stress | (71) |
| SIRT1          | STZ-induced eNOS−/− mice | mouse CIP | — | down-regulate NOX4, increase NFκB deacetylation | attenuates podocytes injury | (72) |
| SIRT1          | OVE26 mice, podocyte-specific Sirt1 overexpression mice | human CIP | SIRT1 agonist, BF175 | activate PGC1α | attenuate podocyte loss and glomerular oxidative stress | (73) |
| SIRT1          | db/db C57BL/KsJ mice | mouse MC | — | regulate HIF1α | alleviate mesangial cell proliferation and renal fibrosis | (74) |

(Continued)
| Sirtuin family | Animal model | Cell model | Sirtuin related Reagent | Molecular biology | Pathophysiology | References |
|---------------|--------------|------------|-------------------------|------------------|----------------|------------|
| SIRT1         | db/db C57BL/6 mice | LLC-PK1 porcine renal epithelial cells | — | up-regulate GLUT2, down-regulate SGLT2 | high basolateral glucose in renal tubules increases SGLT2 and decreases SIRT1 and GLUT2 | (75) |
| SIRT1         | — | HK-2 | — | regulate LC3II, ATG5 and ATG7 | regulate autophagy and fibrosis in renal proximal tubules attenuate EMT and proximal tubule cell fibrosis | (76) |
| SIRT1         | OLTF rats | HK-2, HEK293T | — | regulate TGFβ1 | | (77) |
| SIRT1         | STZ-induced diabetic CD-1 mice | mouse CIP | SIRT1 activator, resveratrol | regulate PGC1α, increased MnSOD, inhibit ROS | attenuation of mitochondrial oxidative stress, inhibit podocyte and renal tubular epithelial cell apoptosis | (78) |
| SIRT1         | STZ-induced Sprague-Dawley rats | — | — | up-regulate Nrf2/HO1 | | (79) |
| SIRT1         | STZ-induced C57BL/ 6J mice | — | — | regulate PGC1α | | (80) |
| SIRT1         | STZ-induced diabetic C57BL/6 mice | HK-2, HEK293 | — | down-regulate phosphorylate mTOR | improve kidney fibrosis and mitochondrial biogenesis | (81) |
| SIRT1         | STZ-induced CD1 mice, db/db C57Bl/6 J mice | human CIP, rat GEC, rat MC | — | PGC1α and FoxO1 deacetylation | balance mitochondrial dysfunction, biogenesis, and mitophagy, regulate podocyte injury and proteinuria | (82) |
| SIRT1         | STZ-induced Sprague-Dawley rats | — | — | regulate FoxO1 | | (83) |
| SIRT1         | STZ-induced C57BL/6 mice | — | — | regulate PGC1α, Nrf1, mtTFA, mtDNA copy, and ATP | | (84) |
| SIRT1         | STZ-induced Sprague-Dawley rats with HFD | — | SIRT1 inhibitor, EX527 | regulate FoxO1 | | (85) |
| SIRT1         | STZ-induced C57BL/6 mice | HK-2 | — | — | inhibit NFXB | (86) |
| SIRT1         | STZ-induced Sprague-Dawley rats | — | — | inhibit NLRP3, IL1β, TNFα and NFκB | | (87) |
| SIRT1         | STZ-induced Sprague-Dawley rats with HFD | — | — | activate AMPK/Akt and phosphorylate AMPK | block podocyte oxidative stress and inflammatory responses | (88) |
| SIRT1         | STZ-induced Wistar rats | — | — | inhibit phosphorylate FoxO3α, Claudin1 | suppress renal oxidative stress | (89) |
| SIRT1         | db/db C57BL/6J mice | MPC5, rat MC, GEC, HK-2, NRK-52E, RAW 264.7 | — | activate AMPK-SREBP1 | participate in podocyte lipid metabolism | (90) |
| SIRT1         | STZ-induced C57Bl/6 mice | HK-2 | SIRT1 inhibitor, EX-527 | induce NFXB and STAT3 dephosphorylation and deacetylation | reduce tubular epithelial cell oxidative stress, apoptosis, inflammation response, and EMT ameliorate mesangial cell extracellular matrix accumulation upregulate in diabetic mice kidney | (91) |
| SIRT1         | db/db C57BlKs/J mice | SV40 MES13 | SIRT1 inhibitor, EX527 | compete with PARP1 for NAD+, activate AMPK/PGC1α | oxidative stress increases SIRT2 in kidney cells | (92) |
| SIRT1         | STZ-induced C57BL/6 mice with HFD | — | — | upregulate PGC1α | | (93) |
| SIRT2         | caloric restriction C57Bl/6 mice | HEK293, HEK293T | — | FoxO3α deacetylation, increase FoxO DNA binding, Kip1, MnSOD, and Bim | oxidative stress increases SIRT2 in kidney cells | (94) |
| SIRT1 and SIRT3 | — | rat MC | — | maintaining intracellular NAD+/NADH ratio, blocked Akt, augmented AMPK, prevent mTOR | inhibit mesangial cell hypertrophy | (95) |
| SIRT1 and SIRT3 | Zucker Diabetic Fatty and Rat with HFD | SIRT1 inhibitor, EX527 | — | regulate Claudin1 | revealed expansion of the extracellular mesangial matrix and suppression of glomerulosclerosis | (96) |
| SIRT3         | — | HK-2 | — | regulate Akt/FoxO1 and FoxO3α activity | | (97) |

(Continued)
SIRT3 inhibitor, 3-TYP, inhibited mitochondrial function, apoptosis, and reactive oxygen species (ROS) production in proximal tubular cells under high glucose conditions (103). The research and development, as well as the DKD application of these gene-editing model animals and reagents, play an effective role in the study of the Sirtuin family in DKD.

Sirtuin family targeting reagents, especially Resveratrol, are considered to have high potential in clinical molecular targeted therapy for DKD (123). It is found that its antioxidant and anti-inflammatory properties are associated with diabetes, obesity, cardiovascular diseases, and cancer in related clinical trials (124), however, the adverse pharmacokinetic and/or pharmacodynamic characteristics, such as poor bioavailability, may limit its wide clinical application (125), and even some studies have shown no significant effect on renal function (126). Therefore, these results should be treated with caution before the clinical transformation.

### 5.2 Renal Injury

Early changes of DKD are focused on the glomerular filtration membrane, while renal tubules and other renal areas for the later changes. The Sirtuin family has been widely studied for early filtration membrane injury, including mesangial matrix thickening, abnormal mesangial cell proliferation, and podocytes damage. NAD⁺ is concentrated in renal tubules,
thus, Sirtuin is also closely related to renal tubular injury as well as crosstalk between podocytes and other renal cells.

5.2.1 Glomerular Filtration Membrane

Early changes of DKD are mesangial matrix thickening, abnormal proliferation of mesangial cells, and podocytes changes. The cause of continuous urinary protein changes is mainly focused on abnormal changes in the filtration membrane (11). SIRT1 decreased in renal tubules and glomerulus of diabetic nephropathy patients (127, 128). SIRT6 was detected to decrease in renal biopsy samples of patients with diseases in podocytes including DKD and its expression was correlated with glomerular filtration rates (44). Studies have shown that high glucose reduced SIRT1, SIRT3, SIRT4, and SIRT6 levels in podocytes (83), suggesting that the Sirtuin family can regulate DKD filtration membrane changes.

Abnormal changes in the DKD filtration membrane mainly focus on the structural and functional changes of mesangial cells in the early stage. Our previous studies explored the protective effect of SIRT1 deacetylation modification on DKD mesangial cell injury (84, 129). SIRT1 regulated hypertrophy and proliferation of mesangial cells (74, 84), mesangial matrix deposition (59, 65, 94), oxidative stress (60, 73) and fibrosis (67, 74) in diabetic model. SIRT1 also regulated mesangial cell matrix deposition (97) and mesangial hypertrophy (98) together with SIRT3. Additionally, SIRT6 had an effect on the proliferation, migration, fibrosis, and inflammation in mesangial cells (112).

Major changes in the late stage of DKD are the filtration membrane changes caused by podocytes. Among them, SIRT1 mainly regulated oxidative stress and inflammation in podocytes under high glucose conditions (88, 90) and then slowed down the apoptosis process (55, 78). SIRT1 was also involved in the lipid metabolism of podocytes (92). In addition, SIRT4 and SIRT6 affected proteinuria production by regulating podocyte apoptosis (44, 107, 108). Studying the changes in the filtration membrane is helpful to prove the mechanism of the Sirtuin family regulating proteinuria production through the DKD filtration membrane system (Figure 5).

5.2.2 Renal Tubules

NAD⁺ metabolism is enriched in the proximal tubular area (21), which may be closely related to the localization and expression of the Sirtuin family in renal tissues. Therefore, the pathophysiological role of renal tubules in DKD should not be ignored (130). The main function of diabetic renal tubules is glucose reabsorption and metabolism. Sodium-glucose cotransporter 2 (SGLT2) transports glucose from proximal tubular lumen into proximal tubular cells through active transport in the apical membrane (131, 132). Then glucose easily diffuses into the blood along the concentration gradient through glucose transporter 1/2 (GLUT1/2) after reaching the basement membrane to complete the glucose reabsorption process (133). It was found that high glucose increased SGLT2 in the basement membrane of renal tubules and decreased SIRT1 and GLUT2 (75). SIRT3 in diabetic kidneys was inhibited, showing fibrotic reprogramming related to abnormal renal glycolysis (101). SIRT6 reversed the glucose reabsorption and gluconeogenesis effect (113). These Sirtuin family changes in renal glucose metabolism are of great significance for renal blood glucose regulation.

Except for renal glucose metabolism, late renal changes of DKD mainly include renal tubular epithelial atrophy, collagen deposition, activation of myofibroblast and matrix, inflammatory cell influx, and epithelial-mesenchymal transition (EMT) (134, 135). Studies showed that SIRT1 mainly regulated cell apoptosis induced by renal tubular oxidative stress (54, 78, 79, 93), fibrosis (76, 77) and EMT (77, 93). SIRT3 was mainly related to renal tubular oxidative stress (100, 102, 103). SIRT6 affected basement membrane thickening in renal tubules and collagen deposition (109). These above-noted studies all indicate that the Sirtuin family regulates late DKD pathological changes of oxidative stress, fibrosis, and EMT in renal tubules (Figure 5).

5.2.3 Intercellular Crosstalk

More interestingly, the Sirtuin family is closely related to the regulation of podocytes-mediated renal cell crosstalk in DKD studies. It was found that SIRT1 reduced mitochondrial oxidative stress in DKD renal tissues and inhibited cell apoptosis in podocytes and tubular epithelial cells (78). Proximal tubular SIRT1 affects podocyte function by maintaining periglomerular NAD⁺ concentration (61). The protective effect of SIRT3 on DKD proteinuria and glomerular changes may be due to retrograde tubule-glomerular interaction. Uptregulation of SIRT3 and NAMPT in renal tubules can provide NMN required by diabetic podocytes and other glomerular cells and ultimately provide glomerular NAD⁺ to further increase SIRT3 activity, forming a virtuous cycle (104). The Sirtuin family interaction in podocyte-tubules provides NAD⁺ as energy for various regions of renal tissues and participates in maintaining normal cell metabolism. SIRT1 in podocytes and endothelial cells was also linked, which regulated both podocytes and endothelial angiogenesis (62). In addition, the Sirtuin family also regulated podocyte-macrophage crosstalk. High glucose promoted M1 macrophages transformation, podocyte apoptosis, and decreased SIRT6. SIRT6-overexpressed macrophages could transform into M2 macrophages and protect podocytes from high glucose damage (110). It suggests that podocytes-macrophages crosstalk of the Sirtuin family provides a theoretical basis for protecting against DKD injury (Figure 5).

5.3 Specific Mechanism

Sirtuin is the first discovered class III HDAC with different epigenetic enzyme effects in DKD. Intracellular NAD⁺/NADH ratios maintain the activity of the Sirtuin family for mitochondrial biogenesis. Multiple Sirtuin-related targets found through literature learning and bioinformatics are of great significance to explore the pathogenesis of DKD.

5.3.1 Epigenetics

Epigenetics mainly involves DNA methylation, histone modification, and chromosomal remodeling, among which histone covalent modification includes methylation, acetylation, phosphorylation, and ubiquitination (136–138). Acetylation modifications mainly include “Reader” for specific
recognition of protein lysine, “Writer” as acetyltransferase, and “Eraser” as deacetylation HDACs (139, 140), while Sirtuin is the first discovered class III HDAC. In DKD studies, SIRT1 was involved in the phosphorylation of histone H3 (52) and the acetylation of H3K9 (44, 108). Moreover, SIRT1 has a variety of deacetylase effects. Sirtuin studies on DKD have reported target proteins including Nuclear factor kappa B (NFkB) (56, 63, 72, 93), Smad3 (65), Smad7 (51), Forkhead Box Protein O1 (FoxO1) (83), Forkhead Box Protein O4 (FoxO4) (55), signal transducer and activator of transcription 3 (STAT3) (63, 93), Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1α) (83), p53 (70), and Claudin1 (61). Meanwhile, SIRT1 could make actions for dephosphorylating NFkB and STAT3 (93). In studies of other Sirtuin family members with DKD models, SIRT2 can deacetylate Forkhead Box Protein O3a (FoxO3a) (96), SIRT3 can deacetylate isocitrate dehydrogenase 2 (IDH2) (100), and SIRT6 can deacetylate Smad3 (111). Polydeacetylation and dephosphorylation targets researches of the Sirtuin family are of great significance for DKD function regulation (Figure 5).

5.3.2 Mitochondrial Function

The Sirtuin family participates in various deacetylation for mitochondrial biogenesis, oxidative stress, inflammatory cell apoptosis, and autophagy through cellular NAD⁺ usage. The imbalance of NAD⁺ and NADH is a marker of DM and its chronic complications (141). In the diabetic state, the glycolysis pathway and tricarboxylic acid cycle are activated, NAD⁺ is reduced to NADH, leads to NADH overload and ROS increase, and further leads to oxidative stress. NAD⁺ decrease also results in acetylation of proteins such as PGC1α involved in oxidative stress and mitochondrial biogenesis, ultimately leading to DKD progression (142, 143).

In the mitochondrial function changes, poly ADP-ribose polymerase 1 (PARP1) is a DNA repair and protein...
modification enzyme that competes with NAD⁺ to cause mitochondrial dysfunction (144). Manganese superoxide dismutase (MnSOD) is a key antioxidant enzyme in mitochondria (145). Mitochondrial transcription factor A (mtTFA) is a key regulator for mitochondrial DNA (mtDNA) transcription and replication, maintaining the normal function of mitochondria and preventing mitochondrial damage (146). It was found that NAD⁺ maintained intracellular NAD⁺/NADH ratio as well as SIRT1 and SIRT3 activities (65, 97). SIRT1 phosphorylation mutations from S47 to S47A can regulate podocyte mitochondrial function by reducing ROS and CytC release and increasing ATP (87). SIRT1 can compete with poly ADP-ribose polymerase 1 (PARP1) for NAD⁺ (94) and maintain PARP1, intracellular NAD⁺/NADH ratio, AMP/ATP ratio (65), MnSOD activity (54), mtTFA and mtDNA copy number (85). SIRT2 can increase MnSOD activity (96), while SIRT3 can restore intracellular NAD⁺/NADH ratios (100, 105). In conclusion, SIRT1-3 reduces oxidative stress by improving energy metabolism and plays an important role in regulating mitochondrial function in DKD (Figure 5).

5.3.3 Signaling Pathway
Moreover, we conducted machine learning for all the literature on the Sirtuin family and the wording of the Sirtuin family signaling pathway in DKD was visualized (Figure 5). The wordscount with the top highest frequency were PGC1α, NfκB, FoxO1, FoxO3a, transforming growth factor-β1 (TGFβ1), and AMPK, suggesting a close relationship of Sirtuin family and these pathway factors.

PGC1α plays a role in energy metabolism processes including adaptive thermogenesis, mitochondrial biosynthesis, liver glycogenesis, and fatty acid β oxidation. Therefore, changes of PGC1α occur the most in the DKD process of the Sirtuin family, which is closely related to mitochondrial oxidative stress and energy metabolism (57, 68, 73, 78, 80, 82, 83, 85, 94, 104, 106). PGC1α can regulate the non-ligand-dependent orphan receptor, estrogen-related receptor α (ERRα), and regulation of the Sirtuin family in DKD is also accompanied by changes of ERRα (59, 68). Meanwhile, the regulation of PGC1α by the Sirtuin family is also accompanied by the changes of FoxO transcription factors (59, 68, 83) due to the same mitochondrial energy regulation.

NfκB is involved in the immune and inflammatory response to external stimuli. It mainly plays a role in mitochondrial oxidative stress in DKD regulation of Sirtuin family (56, 69, 71, 72, 88–90) and STAT3-mediated inflammatory regulation (63, 88–90, 93).

FoxO transcription factor family plays an important role in aging and longevity. They mainly involved in the regulation of Sirtuin family in the oxidative stress response in various regions of DKD kidney (53, 58, 64, 68, 69, 86, 91, 96, 102). Our previous studies have found that SIRT1 alleviated oxidative stress and enhanced autophagy in renal tissues of diabetic rats by regulating FoxO1 phosphorylation, which also confirms the main role of Sirtuin (84). The Akt signaling pathway can regulate the changes of the FoxO transcription factor, thus the regulation of SIRT3/FoxOs in DKD always involves the Akt participation (59, 99, 102). In addition, changes of PGC1α often happen in the regulation of Sirtuin-FoxOs in DKD, which may be related to their common energy regulation function (59, 68, 83).

TGFβ1 is a key molecule of renal fibrosis. SIRT1 induces glomerular extracellular matrix proliferation and changes of Collagen type IV (ET-1), Collagen 1α, and non-collagenous glycoprotein, Fibronectin, via TGFβ1/Smad pathway in early DKD (65, 66, 69, 77). Endogenous antioxidant stress results in renal fibrosis and changes of nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant responsive element (ARE) pathway (60, 69). Our previous research also indicates that SIRT1 regulates DKD oxidative stress and fibrosis in diabetic rats through HIF1α and TGFβ1/Smad3 signaling pathway (129). Additionally, SIRT3 in the DKD model was associated with TGFβ1-mediated renal fibrosis (101). Therefore, regulation of the Sirtuin family in DKD via TGFβ1 is mainly related to extracellular matrix accumulation at the early stage leading to renal fibrosis.

AMPK is a key molecule in the regulation of biological energy metabolism. Our previous research found that SIRT6 regulated sterol regulatory element-binding protein 1 mediated glucolipid metabolism in the liver and pancreas through AMPKα-mTORC1 (147). In the DKD study, SIRT1 regulated podocyte fatty acid synthesis via AMPK-SREBP1 (92), podocyte inflammation by AMPK-NFκB (90), glucolipid metabolism, and mitochondrial function by AMPK-PGC1α (82), fibronectin in mesangial matrix deposition (94), and protein synthesis and mesangial cell hypertrophy through AMPK-mTOR (97). In addition, we found that SIRT1 activated by metformin could regulate DKD progression in mesangial cells (84). All the above suggests that SIRT1-AMPK induced glucolipid metabolism of the Sirtuin family plays a key role in DKD mesangial cells and podocytes.

6 CONCLUSION
The Sirtuin family is a deacetylase with NAD⁺ binding domains. SIRT1-7, as members of the Sirtuin family, have different subcellular localization and catalytic enzyme activities, which consume NAD⁺ to regulate energy metabolism, mitochondrial function, redox, and other cellular reactions. Studies have shown that the Sirtuin family regulates mesangial cell proliferation and hypertrophy, podocytes apoptosis, proximal tubular glucose metabolism, and renal tubular injury under DKD conditions. Meanwhile, the Sirtuin family is closely related to the regulation of podocytes mediated renal tubular, endothelial cells, and macrophages crosstalk. These pathophysiological changes are regulated by epigenetics of deacetylation and dephosphorylation, NAD⁺ involved mitochondrial function changes and multiple signaling pathway targets. However, literature and databases still show contradicitions in the renal expression of the Sirtuin family, which needs further exploration. The mechanism of the Sirtuin family and DKD is still at the superficial stage. The research results of other pre-renal metabolic diseases, renal injury diseases, and post-renal obstructive diseases may have some enlightenment with the research on DKD. With the rapid development of modern science and technology, different
gene-specific expression animals and DKD models, as well as reagents, have been discovered. The Sirtuin family is expected to become an important therapeutic target of DKD by regulating different regions of renal tissues.

**AUTHOR CONTRIBUTIONS**

CB: searched data, drafted and revised the manuscript. HR: inspiration, edited and critically revised the manuscript. BL: searched data, drafted and revised the manuscript. CB: searched data, drafted and revised the manuscript. HR: inspiration, edited and critically revised the manuscript.

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