Kidney Diseases

Review Article

Kidney Dis
DOI: 10.1159/000530344

Received: February 14, 2023
Accepted: March 18, 2023
Published online: March 28, 2023

Therapeutic Potential Targeting Podocyte Mitochondrial Dysfunction in Focal Segmental Glomerulosclerosis

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Keywords
Mitochondria · Podocyte · Focal segmental glomerulosclerosis

Abstract
Background: Podocytes are essential components of the glomerular filtration barrier and essential for the proper filtration function of the glomerulus. Podocyte injury under various stress conditions is the primary pathogenesis and key determinant of focal segmental glomerulosclerosis (FSGS) with prominent clinical manifestations of proteinuria or nephrotic syndrome. ***Summary:*** Under physiological conditions, a highly coordinated mitochondrial quality control system, including antioxidant defenses, mitochondrial dynamics (fusion, fission, and mitophagy), and mitochondrial biogenesis, guarantees the sophisticated structure and various functions of podocytes. However, under FSGS pathological conditions, mitochondria encounter oxidative stress, dynamics disturbances, and defective mitochondrial biogenesis. Moreover, mutations in mitochondrial DNA and mitochondria-related genes are also strongly associated with FSGS. Based on these pieces of evidence, bioactive agents that function to relieve mitochondrial oxidative stress and promote mitochondrial biogenesis have been proven effective in preclinical FSGS models. Targeting the mitochondrial network is expected to provide new therapeutic strategies for the treatment of FSGS and delay its progression to end-stage renal disease. ***Key Messages:*** Mitochondrial dysfunction plays a key role in podocyte injury and FSGS progression. This review summarized recent advances in the study of mitochondrial homeostatic imbalance and dysfunction in FSGS and discussed the potential of mitochondria-targeted therapeutics in improving FSGS and retarding its progression to end-stage renal disease.

Introduction

Focal segmental glomerulosclerosis (FSGS) is a common clinicopathological syndrome with prominent clinical manifestations of proteinuria or nephrotic syndrome. The pathology is characterized by the obstruction of glomerular capillary loops by sclerotic material, and the glomerular sclerosis lesions are

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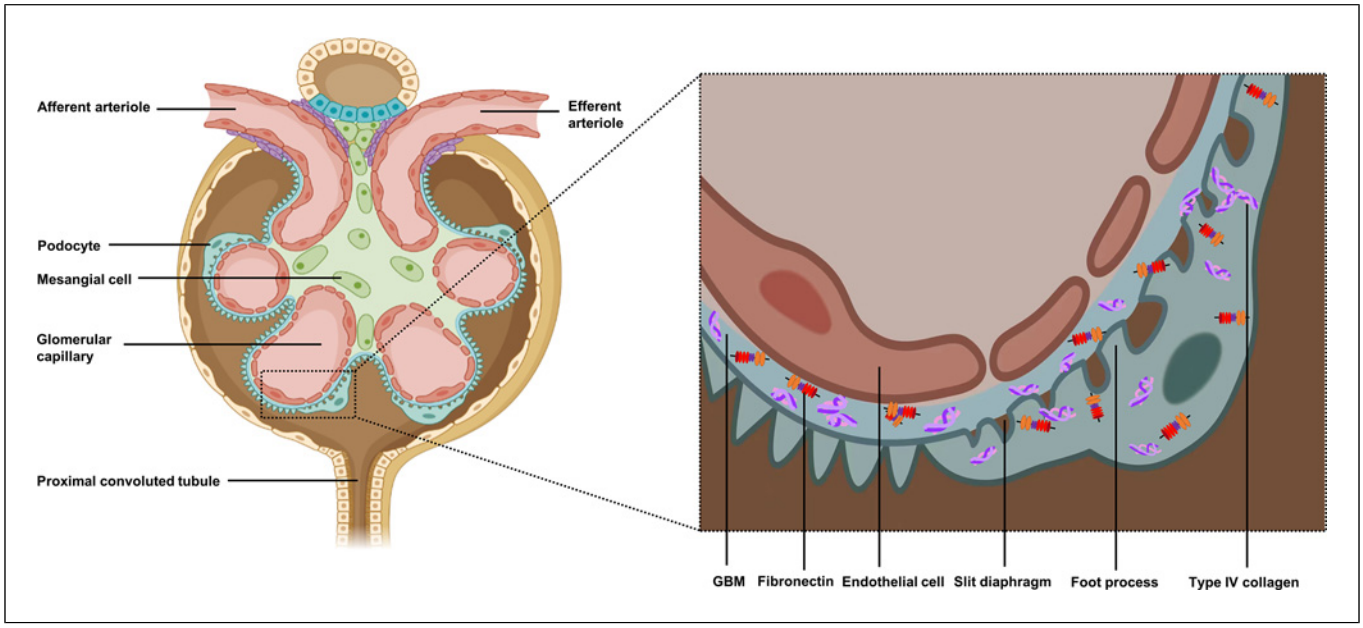

Fig. 1. Basic structure and function of podocytes. Podocytes, together with capillary endothelial cells and GBM, form the basic structure of the glomerular filtration barrier. The crisscrossing foot processes of the podocytes and the slit diaphragm connection between adjacent foot processes are essential for the normal filtration function of the glomerulus. Moreover, podocytes secrete type IV collagen and fibronectin to form the GBM and perform an important role in the metabolic homeostasis of the GBM.

typically focal (less than 50% glomerular involvement) and segmental (less than 50% glomerular tuft involvement) [1]. It is also accompanied by effacement or loss of foot processes due to podocyte degeneration, as seen under electron microscopy [2]. As an important cause of end-stage renal disease worldwide, the incidence of FSGS is gradually increasing; however, treatments using steroids and immunosuppressive agents remain unsatisfactory. Moreover, even after kidney transplantation, FSGS can still recur in some cases [3]. Therefore, it is urgent to explore novel therapeutic targets and effective treatment strategies to attenuate renal injury in FSGS.

Regardless of the etiology of FSGS, a common feature is that the initial event occurs in podocytes [4]. Podocytes are highly differentiated epithelial cells with limited regenerative capacity. Under physiological conditions, the interdigitated foot processes of adjacent podocytes, connected by slit diaphragms, are essential for the proper filtration function of the glomerulus. Podocytes also play an important role in the metabolic balance of the glomerular basement membrane (GBM) by secreting type IV collagen and fibronectin for GBM formation, as well as matrix metalloproteinases and histone proteases for GBM degradation [5] (shown in Fig. 1). However, in the face of genetic defects, immune factors, infection, metabolic stress, and hemodynamic damage, irreversible loss of podocytes occurs [5]. Critical data suggest that podocyte depletion above 20% mediated the development of FSGS, and when depletion exceeded 40%, further development of glomerulosclerosis was triggered [6]. On the basis of this, both classical FSGS animal models using renal ablation or direct podocyte toxins, such as puromycin aminonucleoside (PAN) or adriamycin (ADR), and newly developed genetic animal models, such as *PDSS2*$^{kd/kd}$ mice, have been specially constructed by directly and indirectly, causing podocyte damage [7].

As a type of cell with a sophisticated structure and various functions, a podocyte relies on a substantial energy supply to maintain its function [8]. Podocytes rely on both glycolysis and mitochondrial metabolism to produce energy [9, 10]. In addition to supplying energy, mitochondria also play a pivotal role in regulating reactive oxygen species (ROS), intracellular calcium homeostasis, cell proliferation, and various forms of cell death (apoptosis, necrosis, necroptosis, pyroptosis, and ferroptosis) [11–16]. This review focuses on the recent

advances in the study of mitochondrial abnormalities in podocyte injury and their contribution to FSGS. Based on this, we discussed the potential of mitochondria-targeted therapeutics in FSGS treatment.

Mitochondrial Abnormalities in FSGS

The sophisticated structure of podocytes and the maintenance of various cellular functions, including regulation and organization of the actin cytoskeleton and extracellular matrix proteins, depend on a high energy supply provided by a sufficient number of properly functioning mitochondria [17]. Under physiological conditions, a highly coordinated quality control system, including antioxidant defenses, mitochondrial dynamics (fusion, fission, and mitophagy), mitochondrial biogenesis, protein quality control, and mitochondrial DNA (mtDNA) repair, guarantees the structural and functional homeostasis of mitochondria in podocytes and counteracts stress to a certain extent so that cells can avoid mitochondrial damage. However, under severe stress conditions, the dysregulation of mitochondrial quality control mechanisms may lead to structural damage and dysfunction of mitochondria, triggering podocyte injury. Due to the limited repair and regeneration capacity of podocytes, the damage is usually irreversible, resulting in permanent podocyte loss and ultimately causing irreversible renal damage [5, 18].

Mitochondrial Oxidative Stress

In podocytes, ROS are produced mainly through two pathways – the mitochondrial respiration chain and NADPH oxidase (NOX) [10, 16]. The mitochondrial respiration chain consists of four protein complexes embedded in the inner mitochondrial membrane (complex I–IV) as well as cytochrome c (Cyt C) and quinone [16]. Mitochondrial ROS production is a tightly controlled process. Classical enzymatic antioxidants, including glutathione peroxidase (GPX), catalase (CAT), superoxide dismutase, thioredoxin reductase, and non-enzymatic antioxidants, including glutathione, glucose autoxidation, glycation products, ascorbic acid/vitamin C, α-tocopherol/vitamin E, flavonoids, and carotenoids, which together form an antioxidant defense system in vivo to restrain the excessive generation of ROS [19, 20]. Under physiological conditions, the mitochondrial antioxidant system can effectively maintain ROS at a low level, thus avoiding oxidative stress (OS)-induced damages in podocytes [16]. However, under pathological conditions or when an inherent defect occurs in the podocyte, the imbalance between increased levels of ROS production and decreased capacity of the cellular antioxidant system leads to OS, contributing to podocyte oxidative damage and cell death [12, 21].

Mitochondrial respiratory chain dysfunction leads to an increased mitochondrial ROS level. In both PAN and ADR nephropathy animal models, decreased levels of mitochondrial respiratory chain components were observed [22–24]. In addition to mitochondrial respiratory chain dysfunction, high activity of NOX also accounts for increased ROS levels. Recently, a study in FSGS patients showed that steroid-resistant FSGS patients had higher NOX4 levels as well as higher ROS levels in isolated glomeruli compared to steroid-sensitive nephrotic syndrome patients [25]. By antagonizing the upregulation of NOX expression and downregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) expression, angiotensin II receptor blockers exhibited a therapeutic effect, improving OS and inflammation in spontaneous FSGS Imai rats [26] (shown in Fig. 2).

Evidence of an impaired antioxidant defense system in FSGS has also been demonstrated. Deman et al. [27] captured key evidence of reduced activities of key enzymes of the antioxidant defense system, GPX, CAT, and superoxide dismutase, in an ADR-induced FSGS mouse model. Another similar study found that plasma, urine, and glomerular GPX levels were significantly lower in FSGS patients compared with minimal change disease patients and healthy controls [28]. Intriguingly, others have further demonstrated in ADR-induced FSGS mouse models that *CAT* knockout mice exhibited more severe pathological changes and clinical manifestations of FSGS and accelerated the progression of glomerulosclerosis compared to wild-type mice [29] (shown in Fig. 2).

The unbalanced OS and antioxidant defense system lead to OS within podocytes. High levels of ROS were shown to induce mitochondrial permeability transition pore opening and increase Cyt C release, leading to mitochondrial dysfunction, organelle swelling, and cell apoptosis and death [13, 30]. Mitochondrial damage also leads to mtDNA leakage, which in turn overactivates the cyclic GMP-AMP synthase-stimulator of interferon genes pathway to cause podocyte injury [31]. Sustained high mtROS levels also damage macromolecules, such as DNA, proteins, and lipids. Due to the lack of histone protection and incomplete repair, mtDNA is extremely vulnerable to ROS damage, which may result in mtDNA mutations or invoke more ROS generation [30]. Oxidative alteration of proteins results in an increase of advanced oxidation protein products (AOPPs) [32]. Zhou et al. [33] demonstrated that increased AOPPs in the serum of patients with chronic

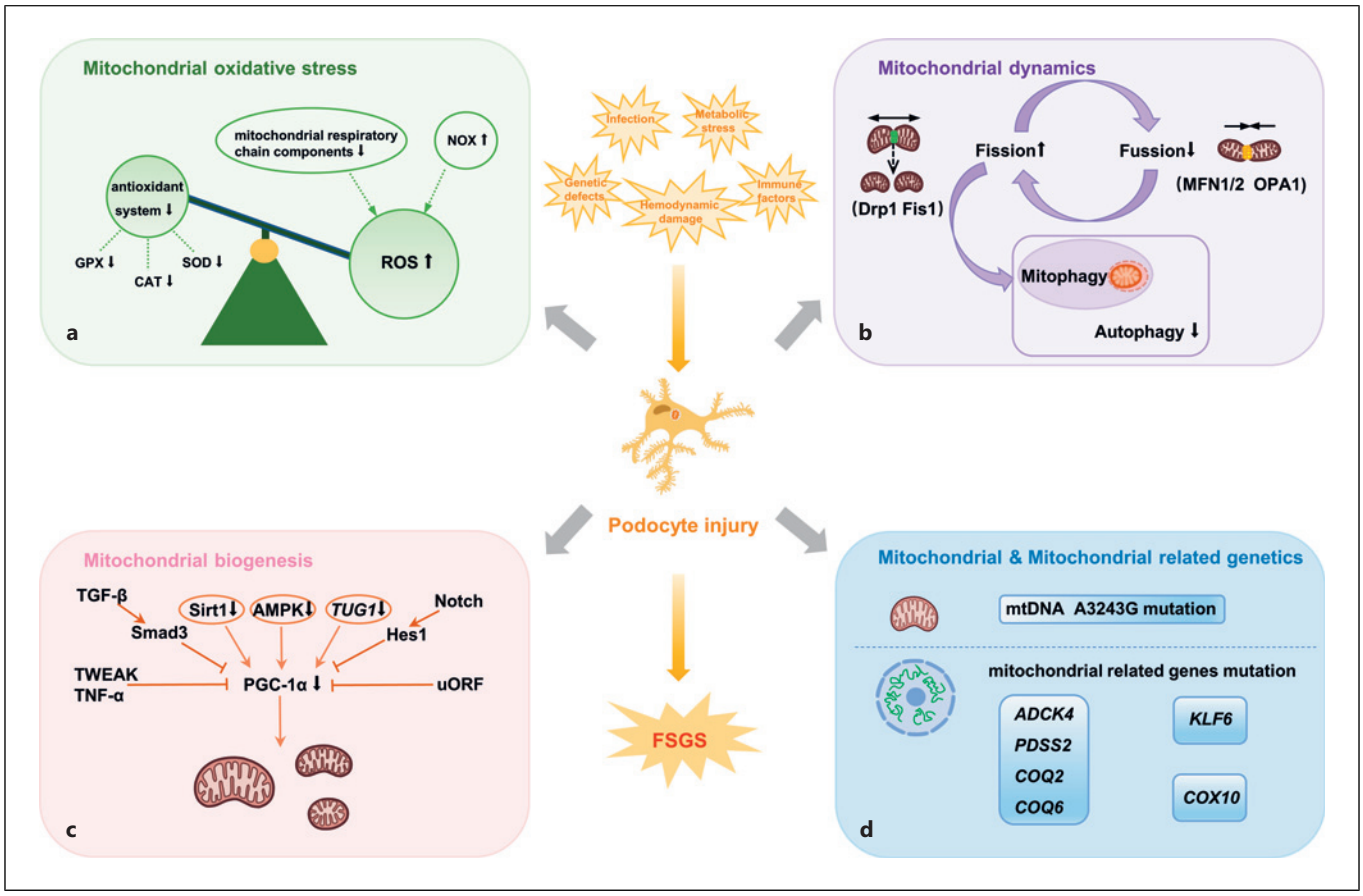

Fig. 2. Mitochondrial homeostatic imbalance and dysfunction of podocytes in FSGS. While under physiological conditions, well-balanced mitochondrial homeostasis is essential for the maintenance of podocyte structure and function. In the face of various deleterious stimuli, such as infection, genetic defects, immune factors, metabolic stress, and hemodynamic damage, irreversible loss of podocytes occurs which in turn further mediates the development of FSGS. **a** In FSGS, the balance between ROS production and clearance in podocytes is disrupted. Impaired mitochondrial respiratory chain and high levels of NOX lead to elevated ROS production. Meanwhile, reduced levels/activities of key antioxidant enzymes system (GPX, CAT, and SOD) represent a decreased ROS clearance ability. **b** In FSGS, the balance of mitochondrial dynamics in podocytes is also disrupted, which includes increased mitochondrial fission mediated by Drp1, Fis1, inhibited mitochondrial fusion mediated by MFN1/2, OPA1, and impaired autophagy. **c** PGC-1α is a master regulator of mitochondrial biogenesis in podocytes and can be positively regulated by Sirt1, AMPK, *TUG1* and negatively regulated by two pro-fibrotic pathways (TGF-β/Smad3, Notch/Hes1), inflammatory factors (TWEAK and TNF-α), and uORF in the 5′ untranslated region of *PPARGC1A* gene. In FSGS, the expressions of PGC-1α, Sirt1, AMPK, and *TUG1* were significantly suppressed, leading to impaired mitochondrial biogenesis. **d** Mutations in mtDNA and mitochondria-related genes also mediated the development of FSGS. SOD, superoxide dismutase.

kidney disease perform a pivotal role in the mobilization of the Wnt/β-catenin pathway, which in turn is engaged in OS-induced podocyte injury. Since activating Wnt/β-catenin pathway promoted cellular senescence in kidney tubular epithelial cells and lung epithelial cells, we might confer that AOPPs-induced Wnt/β-catenin pathway may also induce podocyte loss via inducing cellular senescence [34–37]. ROS also targets lipids, leading to lipid peroxidation and ferroptosis [14]. Recently, Wu and colleagues demonstrated that lipid peroxidation and ferroptosis accounted for high fructose-induced glomerular podocyte injury [38]. These studies suggest that a mitochondrial oxidant and antioxidant imbalance plays an important role in podocyte injury and the pathogenesis of FSGS, and use of mitochondria-targeted antioxidants may exert podocyte protective effects (shown in Fig. 3).

Mitochondrial Dynamics Disturbances

Mitochondria are highly dynamic organelles that combine damaged parts with healthy mitochondria

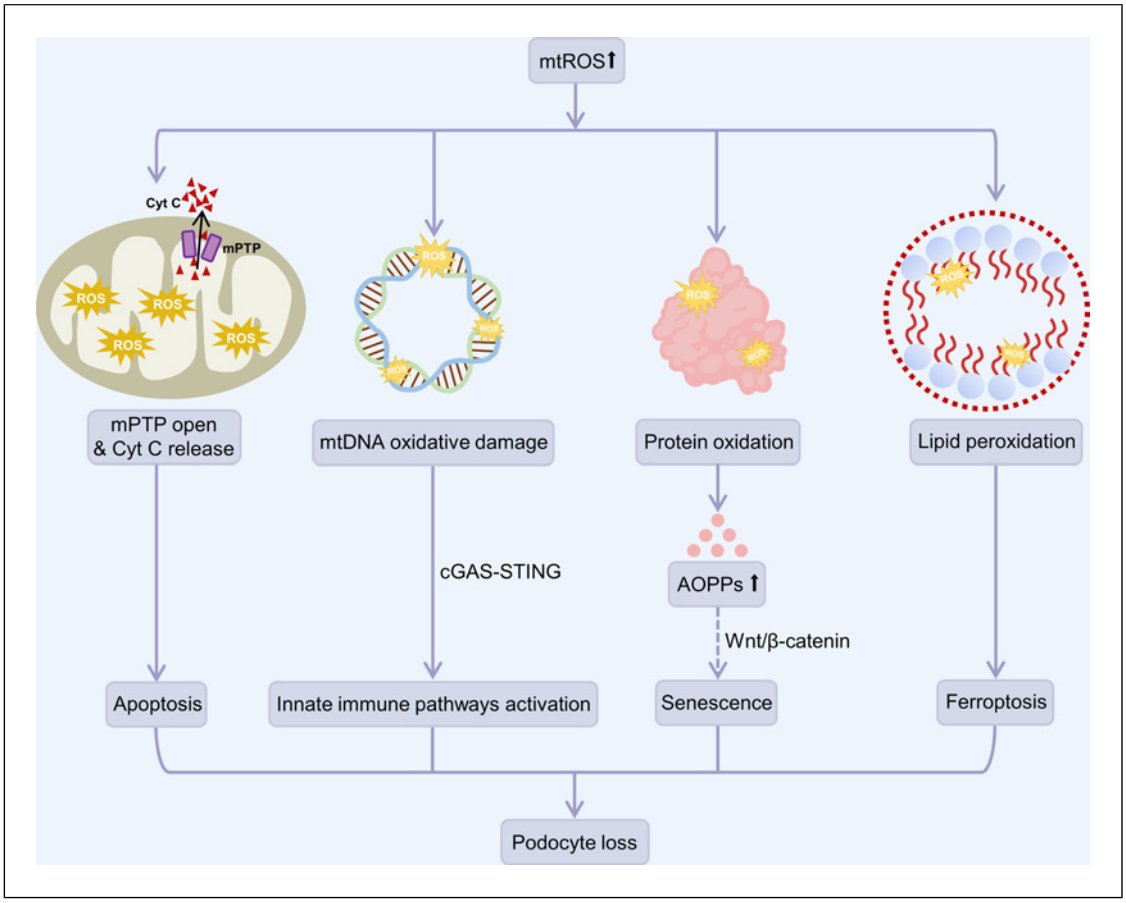

Fig. 3. High levels of mtROS mediate podocyte loss. High levels of mtROS induce mPTP opening and Cyt C release from the mitochondria intermembrane space to the cytosol, ultimately leading to podocyte apoptosis. Sustained high mtROS levels also damage macromolecules, such as DNA, proteins, and lipids. Damaged mtDNA due to oxidation mediates podocyte loss by stimulating the cGAS-STING pathway, which in turn activates a series of innate immune pathways. AOPPs, the products of oxidative proteins, possibly induce podocyte senescence by activating the Wnt/β-catenin pathway. mtROS also targets lipids, resulting in lipid peroxidation and ferroptosis. mPTP, mitochondrial permeability transition pore.

through fusion, and they also separate and eliminate damaged parts of organelles through fission, thus continuously remodeling to meet cellular energy requirements, which is essential to initiate rapid repair of damaged mitochondria [32]. Mitochondrial fission and fusion are also accompanied by mitophagy. Specifically, mitochondrial fission has a surveillance role of identifying malfunctioning daughter organelles that exhibit reduced mitochondrial membrane potential, and they are then restored by fusion or degraded by mitophagy [39]. Research has shown that mitochondrial fission is considered a central process required for mitophagy to occur, while mitochondrial fusion inhibits mitophagy [40]. As a consequence, a network-like mode of action exists between the three processes, which facilitates the maintenance of cellular function and survival under physiological and pathological conditions. Imbalance between mitochondrial fusion, fission, and mitophagy leads to disruption of mitochondrial dynamics, which in turn leads to mitochondrial dysfunction.

Mitochondrial dynamics are regulated by specific proteins: the members of the dynamin superfamily GTPases, in which dynamin-related protein 1 (Drp1) and mitochondrial fission protein 1 (Fis1) are the main mediators of mitochondrial fission; mitofusin 1 (MFN1) and mitofusin 2 (MFN2), which regulate mitochondrial outer membrane fusion; and optic atrophy 1 (OPA1), which regulates mitochondrial inner membrane fusion. In PAN- and ADR-induced podocyte injury models, PAN and ADR were found to induce mitochondrial fission in podocytes by inhibiting MFN1, while the use of the mitochondrial fission inhibitor Mdivi

inhibited the production of caspase-3 in podocytes, thereby preventing PAN-induced podocyte apoptosis [41]. Analogously, knockdown of *Drp1* in vitro reduced aldosterone-induced mitochondrial fragmentation and podocyte damage [42] (shown in Fig. 2).

Autophagy is a lysosomal degradation pathway that not only removes and reuses disintegrated cytoplasmic components through massive degradation of cytosol in a non-selective manner but also selectively removes specific organelles [43]. It is reported that podocytes maintain high basal levels of autophagy to preserve the normal function of long-lived podocytes [44]. Mitophagy is one of the classic representatives of selective autophagy, and it maintains the stability of the intracellular environment and is relatively active in podocytes. Through ubiquitin-dependent (PINK1-Parkin) and ubiquitin-independent (receptor mediated) pathways, damaged mitochondria are selectively phagocytized and cleared by autophagosomes and then degraded by lysosomes [45]. Knockout of the key autophagy genes *Atg5* and *Atg7* in mice resulted in disruption of normal autophagic pathways, leading to typical FSGS pathology in 4-month-old mice and renal failure in 6-month-old mice [46]. Research showed that glomeruli, especially podocytes, had lower levels of Beclin 1-mediated autophagic activity in FSGS patients compared to minimal change disease patients [47]. Moreover, down-regulation of signal regulatory protein α (SIRPα), which is strongly expressed in podocytes and promotes autophagy, was observed in FSGS patients and experimental mice models induced by PAN, and ADR, and the level of SIRPα in podocytes was negatively correlated with the severity of podocyte damage and proteinuria [48]. Recently, Yildirim et al. [49] also found critical evidence of impaired FSGS autophagy in the 5/6 nephrectomy and ADR-induced FSGS rat models (shown in Fig. 2).

Defective Mitochondrial Biogenesis

Mitochondrial biogenesis is a complex and multi-step process referring to the coordinated synthesis of proteins (which are encoded by nuclear and mitochondrial genomes), mitochondrial membranes, and the replication of mtDNA [50]. New functional mitochondria are produced through mitochondrial biogenesis, which helps replace defective mitochondria and provide reserves for increased ATP production [51, 52]. Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) is a transcriptional coactivator that acts as a primary regulator of mitochondrial biogenesis in a variety of cells, including podocytes. One of the principal downstream effects of PGC-1α is the activation of transcription factors Nrf1 and Nrf2, followed by direct transcription of mitochondrial proteins encoded by the nucleus, as well as regulatory factors required for mtDNA transcription and translation, primarily mitochondrial transcription factor A (TFAM), thereby promoting mitochondrial biogenesis [10].

Sirtuin 1 (Sirt1) and AMP-activated protein kinase (AMPK) are the main positive regulators of PGC-1α, which activate PGC-1α by deacetylation and phosphorylation, respectively [10, 50, 53]. We and other researchers have previously demonstrated repressed PGC-1α, Sirt1, and AMPK activation in ADR-induced FSGS models [54–56]. Overexpression of PGC-1α provided a protective effect against ADR-induced podocyte injury [54]. Similarly, 14 days of continuous treatment with nicotinamide mononucleotide attenuated ADR-induced proteinuria and glomerulosclerosis in mice by upregulating kidney expression of Sirt1 [56]. Conversely, podocyte-specific knockdown of *Sirt1* decreased PGC-1α expression and increased susceptibility to ADR nephropathy and glomerular injury [57]. Activating AMPK also restricted podocyte loss and decelerated the progression to FSGS in unilateral and 5/6 nephrectomy mice models [55]. In addition to Sirt1 and AMPK, long non-coding RNA taurine upregulated gene 1 (*TUG1*) was also found to be a positive regulator of mitochondrial biogenesis [58]. A more recent study innovatively found significantly reduced or absent expression of *TUG1* in the urine of FSGS patients, highlighting the potential diagnostic potential of this long non-coding RNA for assessing podocytopathy [59] (shown in Fig. 2).

In contrast, some studies demonstrated that several pro-fibrotic and inflammatory mediators inhibited PGC-1α expression. Transforming growth factor β (TGF-β), a well-known pro-fibrotic cytokine, negatively regulated PGC-1α levels through epigenetic downregulation of Smad3 [60]. Another pro-fibrotic transcription factor, hairy and enhancer of split 1 (Hes1), a target gene of Notch signaling that also has an indispensable role in the development of renal fibrosis, was found to directly bind to the promoter region of *PGC-1α* and repress the expression of PGC-1α [61]. At the same time, inflammatory mediators such as tumor necrosis factor-like weak inducer of apoptosis (TWEAK) or TNF-α rely on the activation of nuclear factor-κB (NF-κB) and epigenetic regulation to negatively regulate PGC-1α [50, 62]. In a recent published paper, PGC-1α translation was also found to be negatively regulated by an upstream open reading frame in the 5′ untranslated region of its gene (*PPARGC1A*) [63]. The current research on the negative regulatory factors of PGC-1α in FSGS is still in its infancy, and further exploration is urgently needed (shown in Fig. 2).

However, a surprising study showed that podocyte-specific overexpression of PGC-1α in mice contributed to

the formation of giant mitochondria and induced proliferation and dedifferentiation of podocytes, exhibiting histological damage similar to collapsing FSGS [64]. This led us to ponder strategies that cause overexpression of PGC-1α or target its upstream and downstream molecules and consider that within a safe range, these strategies may exert a protective effect against podocyte injury in FSGS. Importantly, the degree of podocyte tolerance to PGC-1α still needs to be taken into account, and exceeding its safety limit may have irreparable consequences. Therefore, future investigations are still needed to iteratively validate and explore this potentially narrow therapeutic window of safety in different in vitro and in vivo models.

Mutations in mtDNA and Mitochondria-Related Genes

Owing to the advances in medical science, more than 50 genes have been identified relating to podocytopathies and nephrotic syndrome (mainly FSGS) [65]. The pathogenic gene mutations that have been widely reported to be present in hereditary FSGS include *WT1*, *NPHS1*, *NPHS2*, *TRPC6*, *ACTN4*, and *INF2* [65–67]. In addition to these well-known gene mutations, mutations in mtDNA and mitochondria-related genes are also reported to mediate the development of FSGS. Numerous clinical cases have revealed that an A to G transition mutation at position 3243 (A3243G) of the mtDNA is strongly related to FSGS and proteinuria in patients with mitochondrial cell disease [68, 69]. Intriguingly, Hall et al. [70] conducted a urinary proteomic analysis in 117 adult patients with mitochondrial disease and identified that this mutation occurred in 75 of them (64.1%). These data support the idea that adult patients with mitochondrial disease are prone to kidney involvement (shown in Fig. 2).

Coenzyme Q10 (CoQ10) not only serves as two crucial electron carriers in the respiratory chain together with Cyt C but also has antioxidant activity. Mutations in the aarF domain-containing kinase 4 (*ADCK4*) gene, which encodes a mitochondrial respiratory chain protein expressed in podocytes and participates in CoQ10 biosynthesis, have been reported in patients with steroid-resistant nephrotic syndrome, which is characterized by FSGS and mitochondrial abnormalities in podocytes [71, 72]. Likewise, Saiki et al. [73] found that homozygous mice with mutations in the prenyl diphosphate synthase subunit 2 (*PDSS2*), which is also indispensable for the synthesis of CoQ10, developed proteinuria and interstitial nephritis and eventually died of end-stage renal disease. Gasser et al. [74] further showed that *PDSS2* mutations led to a significantly increased risk of FSGS and collapsing glomerulopathy in humans. Other genes critical for CoQ10 biosynthesis, such as *COQ2* and *COQ6*, are also correlated with steroid-resistant FSGS and collapsing glomerulopathy [75–80]. In patients and animal models with CoQ10 biosynthesis-related gene mutations, supplementation with CoQ10 or its precursor analogs showed prominent therapeutic efficiency [71, 72, 73, 77, 79, 80, 81, 82, 83] (shown in Fig. 2).

Krüppel-like factor 6 (*KLF6*) is a zinc finger domain transcription factor that also works as an early inducible damage response gene that regulates complex IV expression. Decreased *KLF6* expression was discovered in renal biopsies from FSGS patients and HIV-associated nephropathy, and podocyte-specific *KLF6* gene deletion exacerbated ADR-induced FSGS and podocyte injury in mice [84]. Also, mice with a loss-of-function deletion mutation in the mitochondrial complex IV cofactor heme A: farnesyltransferase (*COX10*) developed severe early onset FSGS and died prematurely owing to renal exhaustion [85] (shown in Fig. 2).

Mitochondria-Targeted Therapy

In recent years, with the progressive understanding of mitochondria in FSGS, several mitochondria-targeted strategies have been found beneficial in treating FSGS and other models of podocyte injury in vitro and in vivo. Mitoquinone, a mitochondria-targeted antioxidant, has been confirmed to diminish podocyte dysfunction and OS in podocytes, alleviate glomerulosclerosis, and minimize podocyte injury and apoptosis in a mouse model of angiotensin II-induced podocyte damage [86]. Two clinical trials evaluating the effect of mitoquinone in chronic kidney disease (NCT02364648, NCT03960073) are currently underway. Exogenous dietary supplementation with the antioxidant vitamin E exhibited a level of protective efficacy in an ADR-induced kidney impairment model in rats [87]. In parallel, MitoTEMPO, taurine, and SS-31 (a mitochondria-targeted antioxidant peptide) also displayed positive efficacy in reducing podocyte damage in PAN-induced minimal-change nephrotic syndrome and renal ischemia-reperfusion injury rat models due to their powerful antioxidant effects [88–90].

It has also been demonstrated that in rats with ADR-induced nephropathy, the administration of the mitochondrial permeability transition pore inhibitor cyclosporine reduced OS and exerted a sufficient podocyte protective function [91]. Nevertheless, the safe range of the drug must be closely monitored and controlled during clinical application since it has already been reported that high doses of cyclosporine may excert nephrotoxicity [92]. Resveratrol, a natural

polyphenol found to be a Sirt1 activator, also attenuated aldosterone-induced podocyte injury and mitochondrial dysfunction through upregulation of PGC-1α both in vitro and in vivo [93]. Formoterol, an FDA-approved, classic, long-acting, and specific β2-adrenoceptor agonist, has been reported to promote mitochondrial biogenesis [94]. The mechanism is that formoterol first promotes Akt phosphorylation in a Gβγ-PI3K-dependent manner, leading to increased phosphorylation of its downstream target eNOS, which in turn further activates sGC to increase cGMP production, thereby promoting PGC-1α expression [95]. In ADR-induced FSGS and acute nephrotoxic serum nephritis mice models, treatment with formoterol agonized β2-adrenergic receptors on podocyte membranes and improved renal pathology, diminished proteinuria, and hastened glomerular functional recovery by promoting PGC-1α-dependent mitochondrial biogenesis [96]. Excitingly, novel polymeric nanoparticles that efficiently encapsulate and target formoterol to the kidney have been successfully designed and developed to promote renal mitochondrial biogenesis and reduce cardiovascular side effects, providing a promising therapeutic platform for future treatment in FSGS [97]. Recently, GDC-0879, a novel compound targeting Braf/Mapk, has been reported to ameliorate renal damage associated with global CoQ10 deficiency in *PDSS2*$^{kd/kd}$ mice [98].

The benefit of bioactive components of traditional Chinese medicine in ameliorating podocyte injury has gained increasing attention in recent years. Previous studies in our group have demonstrated that Huaier reversed mitochondrial dysfunction by upregulating PGC-1α expression and relieved ADR-induced podocyte toxicity in animal and in vitro models [99]. Hyperoside, an integral component of the Chinese herb forsythia, was also shown to inhibit mitochondrial fission, promote restoration of mitochondrial function, and improve proteinuria and podocyte damage in an ADR-induced FSGS mouse model [100]. Additionally, it has been suggested that apigenin (a bioactive plant flavone that is widely distributed in vegetables and fruits) and Shenkangning exerted nephroprotective effects by inhibiting OS injury in an ADR-induced FSGS mouse model [101, 102].

Conclusion

As an important component of the glomerular filtration barrier, damage and loss of podocytes under various stresses can lead to proteinuria, and they are important determinants in the progression of FSGS. Podocytes are highly differentiated epithelial cells packed with mitochondria. Under physiological conditions, a fine-tune balance between mitochondrial oxidants and antioxidants, fusion and fission, mitophagy and mitochondrial biogenesis maintains normal podocyte homeostasis and function, whereas under pathological conditions of FSGS, mitochondrial injury and dysfunction occurs, which mediates podocyte lesions and renal dysfunction. Favorable preclinical data have been achieved by targeting mitochondria and the key molecules of mitochondria-related signaling pathways in retarding FSGS development. However, there is still a long way to go for the clinical approval of mitochondria-targeted therapeutics in FSGS.

Although the current findings are promising, many issues remain to be further explored. First, the exact role and mechanisms of mitochondria in FSGS have not been fully elucidated; for example, studies on mitochondrial dynamics disorders in FSGS are still in the preliminary phase. More diverse and improved models of FSGS and more adequate individual studies are required to discover more specific and novel therapeutic targets targeting mitochondria in the future. Second, the pathogenesis of FSGS and podocyte injury is complex and multifactorial, with a variety of immune, infectious, metabolic, hemodynamic, and genetic elements that can be involved. For example, the activation of the Janus kinase-signal transducer/activator of transcription protein pathway, a major transducer of inflammatory signaling, was recently identified in the kidney of FSGS patients [103]. This undoubtedly adds more complexity to future studies. Third, the mechanisms of synergy and crosstalk between podocytes and other cells (such as renal tubular epithelial cells), mitochondria and other organelles (e.g., endoplasmic reticulum), and various links in the mitochondrial network warrant further exploration. Finally, future studies on the heritability of FSGS should be conducted with attention to the possible variability of mitochondrial genes and inheritance patterns between the different age groups of children and adults.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

This work was supported by National Natural Science Foundation Grants (82090022; 81830020); Medical Research Project from Jiangsu Health and Health Commission (Z2022071); and Outstanding Youth Project from Nanjing Health and Health Commission (JQX22010).

Author Contributions

Y.L. and J.F. organized and wrote the first draft of the manuscript. W.Z. and Y.N. wrote sections of the manuscript. M.W. designed the study, revised the manuscript, and provided financial support for this work. A.Z. contributed to the conception and design of the study and provided financial support for this work. All authors approved the submitted version.

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