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Review

Mitochondrial dysfunction in diabetic kidney disease

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ABSTRACT

Although diabetic kidney disease (DKD) is the most common cause of end-stage kidney disease worldwide, the pathogenic mechanisms are poorly understood. There is increasing evidence that mitochondrial dysfunction contributes to the development and progression of DKD. Because the kidney is the organ with the second highest oxygen consumption in our body, it is distinctly sensitive to mitochondrial dysfunction. Mitochondrial dysfunction contributes to the progression of chronic kidney disease irrespective of underlying cause. More importantly, high plasma glucose directly damages renal tubular cells, resulting in a wide range of metabolic and cellular dysfunction. Overproduction of reactive oxygen species (ROS), activation of apoptotic pathway, and defective mitophagy are interlinked mechanisms that play pivotal roles in the progression of DKD. Although renal tubular cells have the highest mitochondrial content, podocytes, mesangial cells, and glomerular endothelial cells may all be affected by diabetes-induced mitochondrial injury. Urinary mitochondrial DNA (mtDNA) is readily detectable and may serve as a marker of mitochondrial damage in DKD. Unfortunately, pharmacologic modulation of mitochondrial dysfunction for the treatment of DKD is still in its infancy. Nonetheless, understanding the pathobiology of mitochondrial dysfunction in DKD would facilitate the development of novel therapeutic strategies.

1. Introduction

The prevalence of diabetes mellitus is high and continues to increase in almost every country, largely as a result of the global epidemic of obesity and the extensive adoption of unhealthy lifestyles. The estimated worldwide population of diabetes was 451 million in 2017, and is expected to rise to 693 million by 2045 [1]. In 2017, approximately 5 million deaths were attributed to diabetes, and about USD 850 million was paid in the healthcare system worldwide [1]. The excessive morbidity, mortality, and financial burden caused by diabetes make this disease an urgent and important public health concern.

Hyperglycemia, or elevated blood glucose level, is the principal biochemical feature of diabetes. Insulin is the key hormone that regulates blood glucose level in human body. Diabetes occurs when the pancreas does not produce enough insulin, or when the body is resistant to the insulin being produced – two scenarios that correspond to type 1 and type 2 diabetes, respectively. In clinical practice, type 2 diabetes accounts for over 85% of all cases. However, it is important to realize that many patients with type 2 diabetes develop insulin deficiency in the latter phase of their disease.

Abbreviations: AGE, advanced glycation end-product; AKI, acute kidney injury; AMPK, adenosine monophosphate activated protein kinase; ARE, antioxidant-responsive element; ATF5, Activating Transcription Factor 5; ATFS-1, activating transcription factor associated with stress-1; Atg5, autophagy-related 5; ATP, adenosine triphosphate; CKD, chronic kidney disease; DAG, diacyl glycerol; DNA, deoxyribonucleic acid; EMT, epithelial-mesenchymal transition; ESKD, end stage kidney disease; FADH2, flavin adenine dinucleotide; FoxO1, forkhead-box class O1; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GFR, glomerular filtration rate; GPX, glutathione peroxidase; GSH, glutathione; GSSG, glutathione disulfide; MA-5, mitochonic acid 5; MELAS, *M*yopathy, *E*ncephalopathy, *L*actic *A*cidosis and *S*troke-like episodes; MGO, methylglyoxal; MIDD, maternally inherited diabetes and deafness; MIOX, myo-inositol oxygenase; mtDNA, mitochondrial DNA; mTOR, mechanistic target of rapamycin; mtUPR, mitochondrial unfolded protein response; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; NRF2, nuclear factor erythroid 2-related factor 2; O-GlcNAc, O-linked β-*N*-acetyl glucosamine; p.m.f., proton-motive force; PARP, poly-ADP-ribose polymerase; PGC-1α, Peroxisome proliferator-activated receptor-γ coactivator-1α; PINK1, phosphatase and tensin homolog (PTEN)-induced putative kinase 1; PKC, protein kinase C; PPAR-γ, peroxisome proliferator-activated receptor gamma; pro–IL-18, pro-interleukin-18; pro–IL-1β, pro-interleukin-1-beta; ROS, reactive oxygen species; RT-QPCR, real time quantitative polymerase chain reaction; SOD2, superoxide dismutase 2; SS, Szeto–Schiller; TNF-α, tumor necrosis factor-alpha; tRNA, transfer ribonucleic acid; UCP2, uncoupling protein 2

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Prolonged elevation of blood glucose level leads to the damage of multiple organs, especially the nerves and blood vessels. Diabetic kidney disease, formerly referred to as diabetic nephropathy, is a clinical syndrome characterized by persistent albuminuria (over 300 mg/24 h or 200 μg/min), nodular glomerular lesions, and a progressive decline in the glomerular filtration rate (GFR). Given the prevalence of diabetes has been increasing rapidly in recent decades, diabetic kidney disease is now the most common cause of end stage kidney disease (ESKD) in the world [2,3]. In Hong Kong and many other parts of the world, diabetic kidney disease now accounts for around 50% of new dialysis patients [4]. Moreover, the presence of diabetes is also consistently associated with a markedly elevated risk of cardiovascular disease and death in dialysis patients. With the epidemic of obesity and metabolic syndrome, it is expected that the incidence of diabetic kidney disease would continue to increase in the coming decades [1,5].

2. Pathogenesis of diabetic kidney disease

The pathogenic mechanisms of diabetic kidney disease are complex [6–8]. Hyperglycemia is the initiating factor and causes structural and functional damages to multiple organs, including the kidney. Traditionally, hyperglycemia results in intra-renal hemodynamic changes in the early stage, with the end result of glomerular hyperfiltration. Hyperglycemia causes increases in proximal tubular reabsorption, partly secondary to induction of tubular growth with associated increases in sodium/glucose cotransport [9]. Increase in proximal tubular reabsorption leads to a decrease in sodium delivery to the macula densa and distal nephron, down-regulation of the tubulo-glomerular feedback stimuli, and therefore increase in single-nephron GFR [10,11].

In addition to the hemodynamic alterations, glucose serves as a power substrate in cells. Hyperglycemia leads to the activation of many metabolic pathways [12,13]. Specifically, the polyol pathway [14,15], hexosamine pathway [16,17], pentose phosphate pathway [18], de novo synthesis of diacyl glycerol (DAG) [19,20], and the non-enzymatic glycosylation of circulating and structural proteins [21] are particularly important in the pathogenesis of diabetic kidney disease. From a molecular point of view, hyperglycemia leads to the production of electron donors nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2) by the Krebs' cycle, which surpasses the capacity of mitochondrial electron transport chain [22]. The excess electrons are transferred to oxygen, giving rise to superoxide and other reactive oxygen species (ROS), which induces DNA breaks and the subsequent activation of the DNA repair enzyme poly-ADP-ribose polymerase (PARP), which in turn inactivates the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Inactivation of GAPDH results in accumulation of upstream glycolytic products, which are diverted to other noxious metabolic pathways that have been linked to hyperfiltration, endothelial injury, microvascular disease, and albuminuria [23,24]. For example, increased glucose flux to polyol pathway depletes the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), which is required for the reduction of the antioxidant glutathione. The result is a vicious cycle of further increase in the oxidative stress. Increased conversion of fructose 6-phosphate to DAG activates protein kinase C (PKC). Fructose 6-phosphate is also diverted to the hexosamine pathway, resulting in the generation of O-linked β-*N*-acetyl glucosamine (O-GlcNAc), which is utilized by O-GlcNAc transferase to cause modification of various enzymes and transcription factors. Accumulation of glyceraldehyde 3-phosphate also ends up in the production of methylglyoxal (MGO), which gives rise to advanced glycation end-products (AGEs). In the aggregate, these pathways lead to glomerular podocyte loss, mesangial matrix expansion, and progressive glomerulosclerosis [25–27].

Although glomerular pathology is traditionally regarded as the primary site of diabetic injury [28], it is now recognized that tubulointerstitial injury plays a critical role in the progression of diabetic kidney disease [29]. High plasma glucose directly damage renal tubular cells, resulting in a wide range of metabolic and cellular dysfunctions. Three cardinal and inter-related pathways are triggered by hyperglycemia and lead to the progression of diabetic kidney disease: overproduction of ROS, activation of apoptotic pathway, and initiation of autophagy [30–34]. Hyperglycemia reduces the production of nitric oxide (NO), resulting in endothelial dysfunction, enhanced oxidative stress, increased production of inflammatory factors, abnormal angiogenesis, and impaired endothelial repair, all of which contribute to the development of endothelial dysfunction [35,36]. Mitochondria, the powerhouse of all cells, are now recognized as the center of these events.

3. Assessment of mitochondrial dysfunction

Mitochondria play an essential role for the survival of all eukaryotic cells except mature erythrocytes. As the powerhouse in cells, mitochondria produce adenosine triphosphate (ATP) through oxidative phosphorylation, and are responsible for over 90% of energy production in human body.

Traditionally, mitochondrial dysfunction refers to the alteration in the canonical role of ATP synthesis by oxidative phosphorylation. Mitochondrial dysfunction, however, could also be loosely regarded as any abnormal biological processes of mitochondria. The latter concept is widely employed in the studies of bioenergetics and cell biology, and the precise definition of each study depends on the specific goal of the corresponding experiment.

Measurements of mitochondrial dysfunction in early studies focused on the oxidative phosphorylation process by studying isolated mitochondria, cells, or tissue samples in vivo. Since the mitochondrial proton circuit is crucial to the physiological function of mitochondria, the core electron transport complexes serve as target of mitochondrial dysfunction assessment [37]. A simple electrical circuit is a useful conceptual analogy of the proton circuit, and the integrity of which could be determined by measuring the voltage, current and resistance in proton circuit [38]. Mitochondrial respiratory control is the best general measure of mitochondrial function in isolated mitochondria [39]. The classic oxygen electrode experiment that determines mitochondrial bioenergetics function was not very accurate, but quantitative measurement of both proton current and proton-motive force (p.m.f.) enables a modular kinetic analysis and allows a full and quantitative description of any change in mitochondrial function [40]. Concentrations and activities of target complexes and enzymes are alternative methods of measurement. Permeabilized cells or skinned muscle fiber preparations can be considered as a packed collection of isolated mitochondria. In theory, measurement of mitochondrial function in vivo is better than in vitro testing.

Since traditional measurement of mitochondrial dysfunction is complicated, simple and reliable methods are needed to determine mitochondrial dysfunction. For example, it is recognized that damaged mitochondria release their content, including mitochondrial DNA (mtDNA), into the extracellular space and then the systemic circulation [41,42]. The mtDNA fragments in the systemic circulation are then filtered through the glomeruli and actively secreted into the urine. As a result, cell-free mtDNA is detectable in blood, urine, and other tissue. Extracellular mtDNA level may therefore serve as a surrogate marker of mitochondrial dysfunction and sublethal tissue damage. The amount mtDNA in body fluid is readily being quantified. The usual technique is real time quantitative polymerase chain reaction (RT-QPCR), which determines the mtDNA copy number [43]. Possible samples include blood, serum, and urine, but other body fluids could also serve as substrate for this technique. On the other hand, Eleftheriadis [44] reported that measuring the concentration of cytochrome C can indirectly determine mtDNA level in body fluid. More recently, complete metabolomic profiling is also applied for the determination of mitochondrial function. Alterations in the cellular levels of various metabolites

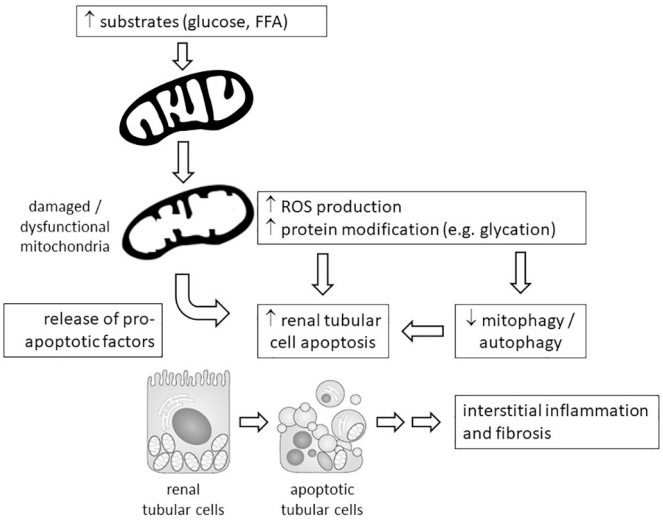

Fig. 1. Schematic representation for the interplay between overproduction of reactive oxygen species (ROS), activation of apoptotic pathway, and initiation of autophagy in the pathogenesis of mitochondrial dysfunction and diabetic kidney disease. [a]ROS encompasses oxygen free radicals, which includes superoxide anion radical ($O2^{\cdot -}$), hydroxyl radical (·OH), and non-radical oxidants, which include hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$). [b]Post-translational protein modifications include acetylation, advanced glycation, nitrosylation, carbamylation and ubiquitination. [c]Apoptosis can be induced by release of mitochondrial proteins including cytochrome *c*, apoptosis-inducing factor (AIF), second mitochondria-derived activator of caspase (SMAC), HtrA serine peptidase 2, and endonuclease G. FFA, free fatty acid.

directly represent mitochondrial dysfunction and give insight to the disturbance of individual metabolic pathway [45].

4. Mitochondrial dysfunction in diabetic kidney disease

Diabetic kidney disease is the most common cause of chronic kidney disease (CKD) [2–5] and mitochondrial dysfunction plays many specific role in its pathogenesis [23]. As mentioned above, the pathogenesis of diabetic complications is linked to four metabolic pathways related to glucose metabolism and inflammatory mediators: increased activity in the polyol pathway, increased production of advanced glycation end-product precursors, protein kinase-C activation, and increased hexosamine pathway activity [46,47]. In the kidney, high plasma glucose directly damage renal tubular cells, resulting in a wide range of metabolic and cellular dysfunctions. Three cardinal and interrelated pathways are triggered by hyperglycemia and lead to the progression of diabetic kidney disease (Fig. 1): overproduction of ROS, activation of apoptotic pathway, and defective mitophagy [30–34]. Mitochondria, the powerhouse of all cells, are the center of these events [23,48]. A number of pathways that are involved in mitochondrial dynamics are affected by diabetes. Mitochondrial biogenesis is increased in the early phase of diabetes, but the level of mitochondrial biogenesis declines following the progression of diabetic kidney disease [49].

The importance of mitochondria in the pathogenesis of diabetic kidney disease attracts further attention in recent years because of the appreciation of a tubulo-centric view [23]. Specifically, adenine nucleotides, especially ATP, are important metabolic regulators of tubuloglomerular feedback in the kidney and hence impact renal blood flow and oxygen delivery [50,51]. ATP production and utilization by the proximal tubular cells is balanced by kidney blood flow, oxygen and metabolite reabsorption, delivery and consumption. This balance is now believed to the principal mechanism for maintaining kidney function in diabetes [7,52]. Extracellular ATP binds to type 2 purinergic receptors on the surface of renal cells. In the diabetic kidney, changes in extracellular ATP signaling via type 2 purinergic receptors have been reported early in disease progression and can initiate tubulointerstitial fibrosis [53,54].

In addition to renal tubular cells, there is emerging evidence that mitochondrial injury to glomerular endothelial cells and podocytes is important for the development of diabetic kidney disease [55,56]. Glomerular damage could modify blood flow and oxygen delivery to other parts of the kidney in the setting of diabetes. Specifically, increased metabolic demand at the medulla or corticomedullary junction could not be met, which creates a vicious cycle of mitochondrial damage in the renal tubules [23].

4.1. Insight from hereditary mitochondrial diseases

The central energy-providing function of mitochondria has many ramifications. Mitochondrial dysfunction is a common finding in many pathological processes, and an increasing number of diseases are being linked to mitochondrial dysfunction [57]. Classically, large-scale partial deletions and duplications of the mitochondrial genome could result in sporadic or maternally-inherited forms of Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia (weakness/exercise intolerance, ptosis, and ophthalmoplegia), and Pearson's syndrome (sideroblastic anemia and exocrine pancreatic dysfunction) [58,59]. Mutations of several genes that are encoded by the genomic DNA but are expressed exclusively within the mitochondria also cause syndromes with variable combinations of ophthalmoplegia, optic atrophy, cardiomyopathy, encephalopathy, and other neurological complications [58].

There is a growing body of evidence indicating that mutations of the mitochondrial genome also result in extensive metabolic dysfunction. The MELAS syndrome (*M*yopathy, *E*ncephalopathy, *L*actic *A*cidosis and *S*troke-like episodes) is the most well-known example. A point mutation in mtDNA (m.3243 A > G) causes maternally inherited diabetes and deafness (MIDD) [60]. The mutation is related to mitochondrial transfer RNA (tRNA) that results in deficient activities of complex 1 and 4 of the respiratory chain [61]. Mutations with large-scale partial deletions of the mitochondrial genome also cause a sporadic syndrome of diabetes and deafness [62].

Since kidney is the organ with the second highest oxygen consumption in our body, it is logical to expect that many mitochondrial diseases have remarkable renal manifestations unrelated to diabetes [58,59]. Specifically, metabolically intense reabsorption and excretion processes take place in the renal tubules. Mitochondria are highly abundant in renal tubular cells, particularly the proximal tubule and the ascending loop of Henle [63]. It is therefore not surprising that many kidney-related mitochondrial disorders are characterized by tubular dysfunction. Mitochondrial diseases that involve the kidney may manifest as various forms of tubulopathies, tubulointerstitial nephritis, or cystic renal disease, while glomerular diseases are uncommon [64,65]. Nonetheless, many clinical manifestations of tubular dysfunction are subtle and often overshadowed by the dramatic concomitant neurological symptoms [58,59].

4.2. Reactive oxygen species

There are several sources of ROS in human cell, but mitochondria are responsible for the generation of a large proportion of ROS via the respiratory chain. Hyperglycemia causes increased oxidative stress, which is an important pathway for the pathogenesis of diabetic complications. Electron escape during mitochondrial electron transport at complexes I and III generates superoxide anions in both the intermembrane space and matrix [66]. Hyperglycemia results in an increased ROS levels in both glomerular mesangial cells and proximal tubular cells [67,68]. In both cell types, hyperglycemia increased the level of ROS, which induces protein modifications, lipid peroxidation and mtDNA damage, ultimately results in mitochondrial dysfunction

[67,68]. In the early phase of pathogenesis, over-production of ROS by mitochondria probably plays a role in the regulation of various metabolic pathways in response to hyperglycemia. However, since mtDNA encodes important genes for oxidative phosphorylation, ROS-induced mutations in mtDNA eventually promote further production of ROS through the impairment of oxidative phosphorylation [9]. Excessive vascular damage by superoxide develops, as observed in animal and cell models in the setting of diabetes, which supports the notion that ROS plays a critical role in initiating diabetic injury [69,70]. The generation of ROS at levels that exceed local antioxidant capacity is a biomarker of mitochondrial dysfunction in the diabetic kidney [23]. Although tubular epithelial cells are mitochondrial rich, mitochondrial dysfunction and ROS-induced damage is also well reported in glomerular podocyte, which has limited capability of regeneration and may represent the major mechanism of progressive renal damage. Specifically, mitochondrial electron transport chain is now known to be the major non-enzymatic source of diabetes-induced ROS in podocyte, which are believed to cause the onset of albuminuria followed by progression to renal damage through podocyte depletion [71].

Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), the master regulator of mitochondrial biogenesis, drives the process by co-activating transcription factors whose target genes increase biogenesis, oxidative phosphorylation, and fatty acid oxidation [66]. PGC-1α has been shown to be the key modulator of ROS pathway in the pathogenesis of diabetic kidney disease [70,72,73]. PGC-1α ameliorates kidney fibrosis in mice with diabetic kidney disease through an anti-oxidative mechanism in podocyte and mesangial cells [74]. Resveratrol ameliorates podocyte damage in diabetic mice via SIRT1 / PGC-1α mediated attenuation of mitochondrial oxidative stress [75]. However, the result has not been consistent between different studies, and alleviating ROS production does not consistently retard the progression of diabetic kidney disease in clinical studies [76,77]. An alternative theory is that mitochondrial function is downregulated in diabetes, and restoration of normal mitochondrial function would alleviate the problem [78].

ROS generation by mitochondria triggers other downstream inflammatory cascades. Specifically, oxidized cardiolipin on the outer mitochondrial membrane can serve as a docking station for NLRP3 inflammasome assembly, which activates caspase-1 to cleave pro-interleukin-1-beta (pro–IL-1β) and pro-interleukin-18 (pro–IL-18) to cause chronic inflammation and tissue remodeling. More importantly, production of ROS causes breaks in mtDNA and damage lipids and proteins [24]. Damaged mtDNA leads to the production of aberrant mitochondrial proteins and prevents mitochondrial protein synthesis. Furthermore, damaged lipids and proteins result in impaired mitochondrial function, leading to a vicious cycle of further mitochondrial ROS generation. From a therapeutic point of view, luteolin, a natural flavonoid in a variety of fruits and vegetables, attenuates high glucose-induced podocyte injury via suppressing NLRP3 inflammasome pathway [79].

Another key mediator of ROS-induced mitochondrial damage is activating transcription factor associated with stress-1 (ATFS-1) [80]. In response to mitochondrial dysfunction such as respiratory chain dysfunction, high levels of ROS, or mitochondrial protein folding stress, mitochondrial import of ATFS-1 is reduced, causing cytosolic accumulation, followed by nuclear translocation. Once in the nucleus, ATFS-1 promotes a transcriptional response that attempts to restore homeostasis by upregulating a host of mitochondrial chaperones and proteases, as well as genes involved in mitochondrial protein importation and ROS metabolism [81]. Activating Transcription Factor 5 (ATF5), the mammalian orthologue of ATFS-1, rescues mitochondrial unfolded protein response (mtUPR) activation in *C. elegans* lacking ATFS-1 [82]. During mitochondrial stress, ATF5 is required for the induction of several mitochondrial chaperone and protease genes, indicating an essential role of ATF5 in cell survival during mitochondrial stress [82].

There are intrinsic mechanisms within mitochondria to protect against ROS damage [20]. For quality control of mitochondria and the maintenance of their activity against oxidative stress, mitochondria employ several stress responses mechanisms to maintain protein homeostasis, such as the mtUPR and mitophagy [83–86]. In addition, ROS activates nuclear factor erythroid 2-related factor 2 (NRF2), which translocates to the nucleus and binds to antioxidant-responsive elements (AREs) to activate the transcription of genes encoding oxidant-neutralizing enzymes, such as mitochondrial superoxide dismutase 2 (SOD2), glutathione peroxidase (GPX) and catalase. These enzymes reduce superoxide anions and hydrogen peroxide. GPX also oxidizes glutathione (GSH), resulting in glutathione disulfide (GSSG). Within mitochondria, GSSG is converted back to GSH by glutathione reductase in a process that requires NADPH. In addition, the activity of the mitochondrial uncoupling protein 2 (UCP2) is increased, which helps to dissipate the proton motive force and reduce ROS production [24].

4.3. Apoptosis

Mitochondrial dysfunction and ROS generation trigger a series of detrimental consequences to the cell [87]. Excessive ROS and causes cardiolipin peroxidation. Oxidized cardiolipin can signal a number of cellular events. First, oxidized cardiolipin damages cristae curvatures, which decreases substrate concentration and delivery of NADH and FADH2 to the respiratory complexes. If oxidative stress is mild, oxidized cardiolipin can translocate to the outer mitochondrial membrane, where it triggers mitophagy (see below). Oxidized cardiolipin on the outer mitochondrial membrane can also recruit Bax to trigger mitochondrial permeability transition, which releases cytochrome *c* from mitochondria to initiate apoptosome activation, activation of caspase-3, and apoptosis. Cells undergo necrosis following profound ATP depletion, and danger molecules released from necrotic cells induces further inflammasome activation.

Hyperglycemia activates several key pro-apoptotic factors, which may contribute to the pathogenesis of diabetic kidney disease. Mitochondrial fragmentation and swelling is observed in early diabetic kidney disease, leading to an increase in fission and the production of ROS. The correlations between increased mitochondrial fragmentation and decreased ATP, and between ROS production and decreased ATP, are interdependent. The bottom line is decreases in mitochondrial energetics that are caused by changes in mitochondrial morphology and hyperglycemia lead to apoptosis in kidney disease [24]. Mitochondria participate in this apoptotic process via various molecular mechanisms in response to cellular stress. In essence, mitochondria toxicity results in the release of pro-apoptotic factors, which activate latent forms of caspases, resulting in cell apoptosis [88,89]. Notably, oxidative stress induced by hyperglycemia could result in activation of the caspase cascade, which triggers the release of tumor necrosis factor-alpha (TNF-α), with the end result of activating the mitochondria-dependent apoptotic pathway [90].

Sirtuins (silent information regulator 2 proteins), an ancient family of evolutionary conserved NAD^+-dependent enzymes with deacetylase or mono-ADP-ribosyl transferase activity [91], probably plays a critical role in this process. Sirtuins regulate DNA repair, recombination, chromosomal stability, and gene transcription, and mediate the health-promoting effects of caloric restriction [91]. At least 7 sirtuins (1 to 7) have been identified in mammals, and sirtuin 3, 4 and 5 are specifically located within the mitochondria [91]. Notably, sirtuin-3 is involved in the regulation of life span and aging-related disorders [92]. More recently, sirtuin-3 is reported to protect hyperglycemia-induced apoptosis in renal tubular cells [30], and pharmacological manipulations that increase sirtuin-3 markedly limit renal injury and accelerate functional recovery of experimental acute kidney injury (AKI) [93]. On the other hand, sirtuin-4 and sirtuin-6 are probably relevant for the hyperglycemia-induced damage in glomerular podocyte. Sirtui-4 overexpression protects against diabetic nephropathy by inhibiting podocyte apoptosis [94], while sirtuin-6 suppresses high glucose-induced mitochondrial

dysfunction and apoptosis in podocytes through adenosine monophosphate activated protein kinase (AMPK) activation [95].

4.4. Mitophagy

One of the principal downstream effects of mitochondrial damage induced by hyperglycemia is the activation of autophagy [96,97], and if the process targets the damaged mitochondria, it is called mitophagy [98,99]. In short, mitophagy selectively eliminates damaged mitochondria, which are enveloped by endoplasmic reticulum membranes to form autophagosomes, fused with lysosomes to form autophagolysosomes that degrade mitochondrial content. Mitochondria are highly dynamic organelles that respond to intra-cellular energy demand and undergo corresponding adaptions [23]. Fusion and fission of mitochondria are the major adaptive mechanisms by facilitating ATP production. The contents of mitochondria are mixed together during fusion. New healthy mitochondria are then formed by fission, while defective parts are segregated and recycled via mitophagy. If the mitophagy machinery is damaged and the defective mitochondria remain uncleared, cytochrome *c* will be released to the cytosol, resulting in cellular apoptosis.

With the accumulation of misfolded proteins or loss of membrane potential, the mtUPR up-regulates a host of mitochondrial proteases that degrade aberrant proteins. However, when the damage becomes excessive within an individual mitochondrion, the entire organelle would be removed by mitophagy. It is now recognized that mtUPR and mitophagy are complementary responses: mtUPR acts as a first line of defense to combat insults to mitochondrial proteostasis, whereas mitophagy removes the unsalvageable mitochondria [100]. Several pathways contribute to the regulation of the latter process, but the one best studied is the Parkin pathway. In essence, PINK1 accumulates on the outer membrane of depolarized mitochondria and recruits Parkin, a E3 ubiquitin ligase, which leads to the ubiquitination of mitochondrial protein for proteasomal degradation and engulfment of mitochondria by autophagosomes [23], which plays a critical role in eliminating defective mitochondria. Recent studies suggest that hyperglycemia increases renal tubular cell expression of myo-inositol oxygenase (MIOX), which leads to mitochondrial fragmentation and defective mitophagy [69].

In the diabetic kidney, mitochondrial fusion and fission are increased, but mitochondrial recycling via mitophagy is impaired [23,49,101,102]. This disturbance prevents the elimination of damaged mitochondria and exacerbates intra-renal ATP deficits. With the disruption of autophagy machinery in diabetic kidneys [103], oxidative phosphorylation complex is affected by preventing increases in autophagy to assist in meeting metabolic demands. However, as kidney damage progresses in diabetes, mitochondrial membrane potential decreases in the proximal tubule [104], endothelial cells [55] and podocytes [56]. Loss of membrane potential in turn provides a signal to initiate the process of mitophagy in the damaged mitochondria. Notably, podocytes exhibit an high level of constitutive autophagy.

Although podocytes have a lower cellular mitochondrial content than tubular epithelial cells, defective mitophagy in podocyte is increasingly being recognized as an important mechanism of kidney damage in diabetes. Defective quality control by mitophagy contributes to the altered bioenergetics of podocytes, and podocyte-specific deletion of autophagy-related 5 (Atg5), the key protein involved in the extension of the phagophoric membrane in autophagic vesicles, led to progressive podocyte loss, proteinuria and glomerular damage [105]. Forkhead-box class O1 (FoxO1) activation protects against high glucose-induced injury by preventing mitochondrial dysfunction in the rat kidney cortex [106]. Specifically, decreased mitophagy via reduced phosphatase / tensin homolog on chromosome 10-induced PINK1 / Parkin-dependent signaling, while FoxO1 upregulation and PINK1 / Parkin pathway activation restore injured podocytes in mice with experimental diabetes [102].

Irrespective to the type of cell being affected, to complete a vicious cycle, damaged mitochondria release pro-apoptotic factors and have increased ROS production, leading to the propagation of cell injury, and autophagy or mitophagy is regarded as being cytoprotective [88,98]. Recent studies show that autophagy attenuates diabetic glomerular damage through protection of hyperglycemia-induced podocyte injury [107]. Autophagy may be interrupted due to high glucose induced unmitigated stress, and the defective autophagy may accelerate the progression of diabetic kidney disease [107]. In the kidney, MIOX is a tubular-specific enzyme that catabolizes myo-inositol to D-glucuronate [69]. Increased MIOX expression in renal tubular cells leads to mitochondrial fragmentation and is associated with defective autophagy, which probably contributes to the pathogenesis of diabetic kidney disease [69]. On the other hand, sirtuin-3 facilitates diabetic kidney disease repair by amniotic fluid stem cells through the modulation of mitophagy [108].

In addition to the above-mentioned mechanisms, recent evidence show that renal tubular cells release DNA fragments of the dysfunctional mitochondria to extracellular space – a process that probably mediate the progressive tubulointerstitial damage [109,110]. Taken together, there is good evidence that dysfunctional mitochondria in the kidney are a key pathological mediator of diabetic kidney disease [23].

5. Mitochondrial dysfunction in non-diabetic CKD

Although the above discussion focus on diabetic kidney disease, many of the pathological processes are generic for all kinds of kidney damage. Kidneys with non-diabetic CKD show increased ROS production, upregulation of mitochondrial complex I and IV expression, and inactivation of complex IV, irrespective to the underlying etiology [66,111,112]. Moreover, there is a close relation between mitochondrial dysfunction and CKD progression irrespective to the underlying renal diagnosis [66,111,112].

The pathogenic relation between mitochondrial dysfunction and CKD is not completely understood. Proteinuria caused by any primary insult to the kidney induces oxidative stress on renal tubular cells, resulting in mitochondrial dysfunction [113–115]. This process further triggers cellular damage by ROS generation and epithelial-mesenchymal transition (EMT) [116,117]. In experimental models of CKD, aborting mitochondrial dysfunction prevents renal tubular cell EMT and renal fibrosis [113,118]. In addition to renal tubular cells, mitochondrial dysfunction in podocyte may also contribute to CKD. A recent report indicates that selective mtDNA mutation in podocytes results in focal glomerulosclerosis and progressive renal failure [119].

6. Pharmacological modulation of mitochondrial function

There are several pharmacological agents that could modulate mitochondrial function and are being developed for the treatment of kidney diseases. For example, compounds known to specifically promote mitochondrial biogenesis or FA oxidation have been explored [87]. Triphenylphosphonium ion conjugated to lipophilic antioxidant molecules, such as coenzyme-Q (MitoQ), have been tried. The positive charge drives the transport of these lipophilic molecules into the mitochondrial matrix in a potential-dependent manner [120]. However, the requirement of mitochondrial potential for uptake limits their use in dysfunctional mitochondria, and lipophilic cations can depolarize mitochondria, inhibit oxidative phosphorylation, or become pro-oxidants, and their efficacy diminished with high dose treatment [121,122].

Mitochondrial damage in diabetes has been reported to be repaired by pharmacological means, which leads to improvement in kidney function [23,78,123]. In Ins2(+/)$^{-}$(AkitaJ) mice, MitoQ treatment for 12 weeks attenuated glomerular basement membrane thickening, mesangial expansion, interstitial fibrosis, and albuminuria [124]. In db/db mice, MitoQ also ameliorated glomerular hypertrophy and mesangial expansion, and partially reversed mitochondrial fragmentation

in tubular cells [125]. On the other hand, cardiolipin-targeting peptides that protect mitochondrial cristae structure have also been developed. Notably, the Szeto–Schiller (SS) peptides are cell permeable tetrapeptides that selectively target mitochondria but concentrate on the inner mitochondrial membrane rather than penetrate into the mitochondrial matrix [126]. One specific compound, SS-31, has been shown to repair damaged mitochondria and restore mitochondria structure in mouse models of chronic kidney disease. Treatment with SS-31 for 2 months restored cristae structure in podocytes of aged mice, decreased senescent markers, and reduced glomerulosclerosis [127]. In mice receiving a high-fat diet, SS-31 treatment protects mitochondria structure and prevents intracellular lipid accumulation [123]. In this metabolic kidney model, SS-31 alleviates glomerular endothelial and podocyte loss, and reduces inflammation, mesangial expansion, and glomerulosclerosis [123]. More importantly, SS-31 significantly reduces glomerular hypertrophy, mesangial expansion, and apoptosis in mice with streptozotocin-induced diabetes [128]. Further studies are needed to determine the effect of MitoQ and SS-31 in human diabetic kidney disease.

Other experimental approaches have also been tested, with a variable degree of success. For example, mitochonic acid 5 (MA-5), which targets the mitochondrial protein mitofilin/Mic60 at the cristae junction of the inner mitochondrial membrane, has been shown to reduce tubular cell necrosis and improve kidney function in a mouse model of acute kidney injury [129]. The compound 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside, which is an AMPK activator, increases fatty acid oxidation and reduced lipid accumulation and renal pathology in mice [130]. These agents, however, remain in their early phase of exploration.

New therapeutic benefit has also been explored in readily available agents. Specifically, mitochondria can adapt to different metabolic conditions via the regulation of mechanistic target of rapamycin (mTOR) and AMPK nutrient sensing pathways, for maintaining a healthy population of mitochondria [24]. Metformin, the first line medication for type 2 diabetes. is now recognized to reduce cellular energy status by activating AMP kinase and inhibiting respiratory-chain complex 1 activity in mitochondria [131]. Salicylate affects the mitochondrial function and reduces circulating free fatty acid level [132]. Similarly, agonists of peroxisome proliferator-activated receptor gamma (PPAR-γ) reduce circulating free fatty acid level and also stimulate mitochondrial biogenesis [133]. Pioglitazone, a PPAR-γ agonist, activates PGC-1α and ameliorates age-related renal injury [134]. Glucagon-like peptide-1, an important target of treatment for diabetes, protects mouse podocytes against high glucose-induced apoptosis, and suppresses reactive oxygen species production and pro-inflammatory cytokine secretion, through sirtuin 1 activation in vitro [135]. Formoterol, a β2-adrenergic receptor agonist, also stimulates PGC-1α expression and mitochondrial respiration in proximal renal tubular cells and mouse renal cortex [136], but the effect on human kidney has not been explored. On the other hand, fenofibrate, improves hyperglycemia, insulin resistance, albuminuria, and glomerular lesions in db/db mice [137]. In streptozotocin-induced model of diabetic kidney disease, fenofibrate significantly reduces serum creatinine, kidney-body weight ratio, and albuminuria [138]. In a randomized control trial, long-term fenofibrate therapy was associated with less albuminuria progression [139], but the study did not have the sufficient statistical power to determine a beneficial effect on kidney function.

Another novel therapeutic target is the autophagy-mitophagy pathway, which plays an important role in pathological processes of mitochondrial dysfunction [140,141]. Sirolimus, an inhibitor of mTOR, attenuates autophagy and protects against renal hypertrophy, glomerulosclerosis and proteinuria in animal model of diabetes [142,143]. Drp1 inhibitor, mdivi-1, suppresses ischemia-induced mitochondrial fragmentation in proximal tubular cells, resulting in reduction of serum creatinine and blood urea nitrogen [144,145]. Nonetheless, more studies are required to confirm the beneficial effects of this treatment.

7. Perspective

Our understanding on mitochondrial dysfunction in kidney disease has dramatically increased in the past decade. However, there are several challenges to researchers in this area. Specifically, the method of assessment mitochondrial dysfunction is not completely standardized. Since mitochondria severe multiple functions in the cellular metabolism, it seems unlikely that a single test is sufficient. There are probably substantial overlap but also interesting differences in the mitochondrial dysfunctions between diabetic and non-diabetic chronic kidney disease. Delineation of such similarities and differences may facilitate the development of novel therapeutic strategies for both problems.

8. Conclusions

Kidney is an organ with high energy consumption. Recent studies show that mitochondrial dysfunction is involved in many kidney diseases. Mitochondrial function is altered in diabetes, which contributes to the pathogenesis of many diabetic complications, notably diabetic kidney disease. Measurement of mitochondrial function may shed light on the pathogenesis of diabetic kidney disease, and may identify valuable targets for its treatment and monitoring.

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