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REVIEW

Control of Mitochondrial Quality: A Promising Target for Diabetic Kidney Disease Treatment

Qi Li[1], Jin Shang[1,2] and Reiko Inagi[1]

[1]Division of Chronic Kidney Disease Pathophysiology, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan; and [2]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD), affecting over 40% of patients with diabetes. DKD progression involves fibrosis and damage to glomerular and tubulointerstitial regions, with mitochondrial dysfunction playing a critical role. Impaired mitochondria lead to reduced adenosine triphosphate (ATP) production, damaged mitochondria accumulation, and increased reactive oxygen species (ROS), contributing to renal deterioration. Maintaining mitochondrial quality control (MQC) is essential for preventing cell death, tissue injury, and kidney failure. Recent clinical trials show that enhancing MQC can alleviate DKD. However, current treatments cannot halt kidney function decline, underscoring the need for new therapeutic strategies. Mitochondrial-targeted drugs show potential; however, challenges remain because of adverse effects and unclear mechanisms. Future research should aim to comprehensively explore therapeutic potential of MQC in DKD. This review highlights the significance of MQC in DKD treatment, emphasizing the need to maintain mitochondrial quality for developing new therapies.

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Globally, DKD is the primary contributor to ESRD, impacting over 40% of individuals diagnosed with diabetes.[1] Diabetes complicated by kidney disease has the highest mortality rates compared with other microvascular complications, with a 10-year cumulative mortality rate of up to 31.1%.[2,3] The clinical presentation of DKD is heterogeneous. Most patients experience gradual progression of albuminuria to renal failure. In contrast, many patients initially show increased serum creatinine at the beginning without significant levels of albuminuria. The histological profile of these patients remains only partially understood.[4] The primary pathological hallmark of DKD is fibrosis, which results in damage to both glomerular and tubulointerstitial regions.[5] However, clarification of the pathological mechanisms involved in the development and progression of DKD awaits further research.

Mitochondria are double-membrane organelles which act as the powerhouse of cells. Mitochondria produce ATP through oxidative phosphorylation, and account for more than 90% of human energy production.[6] Given their role as central hubs that coordinate signaling cascades and regulate cell survival and cell death pathways, the quality of mitochondria is of vital importance for cell survival. Recently, research has focused on the role of mitochondria in the development and progression of kidney diseases, especially DKD.[7] Maintenance of mitochondrial homeostasis is essential to ensuring a healthy and optimally functioning kidney, and the potential contribution of mitochondrial malfunction to the onset and progression of DKD has been widely investigated.[8] In DKD, impaired mitochondrial function leads to diminished mitochondrial DNA (mtDNA) and ATP levels, the buildup of damaged mitochondria, and increased production of ROS. These changes are implicated in the deterioration of glomeruli, renal tubules, blood vessels, and interstitium, all of which are associated with the progression of DKD.[9] Control of mitochondrial quality is therefore critical to avoiding mitochondrial dysfunction, which leads to cell death, tissue injury, and even kidney failure.[10–12]

In the past years, multiple clinical trials of drugs for treating DKD have yielded promising results, and

Correspondence: Reiko Inagi, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan. E-mail: inagi-r@m.u-tokyo.ac.jp
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many investigators have noted that pharmacological approaches improve mitochondrial function by regulating MQC and alleviating DKD.[13-16] However, although a series of treatment interventions have yielded some positive results in the management of DKD, these treatments are still unable to halt a decline in kidney function,[17] and new prospective approaches to the treatment of DKD are still urgently required.

Here, we provide an overview of current research offering unique insights into MQC in DKD and highlight the importance of MQC as a potential promising target for DKD treatment.

PATHOPHYSIOLOGICAL CHARACTERISTICS OF DKD

Mitochondrial dysfunction plays many specific roles in the pathogenesis of DKD.[18] Understanding the pathological process of DKD requires an understanding of the pathophysiological changes that occur in the kidneys because of diabetic hyperglycemia.[19] As a hallmark of diabetes, hyperglycemia primarily triggers 3 fundamental and interrelated pathways that contribute to the progression of DKD: excessive ROS production, activation of apoptotic mechanisms, and the onset of autophagy.[6] Hyperglycemia causes an excessive influx of glucose into the kidney, particularly proximal tubular (PT) cells, which leads to metabolic reprograming from the tricarboxylic acid cycle and oxidative phosphorylation to glycolysis.[20] This shift overloads the capacity of the mitochondrial electron transport chain, resulting in the transfer of excess electrons to oxygen and the subsequent formation of superoxide and other ROS.[21] These metabolic changes can worsen immune-mediated kidney injury, creating a feedback loop that sustains a glycolytic preference in kidney cells.[20] This cycle perpetuates inflammation and oxidative stress, which contributes to further cellular damage and the progression of kidney disease. Hyperglycemia thereby leads to intrarenal hemodynamic changes in the early stages, and ultimately causes glomerular hyperfiltration to compensate for the gradual decline in nephron count. This heightened glomerular filtration in the remaining individual nephrons in turn hastens the deterioration of kidney function toward ESRD. Among patients with DKD, those with type 1 diabetes mellitus predominantly exhibit diabetic glomerulopathy as the primary hyperglycemia-induced kidney lesion. This condition is believed to progress from normoalbuminuria to moderate and then severe albuminuria in an approximately linear pattern, eventually leading to decreased glomerular filtration.[22,23] However, in individuals with type 2 diabetes mellitus (T2DM), the pathophysiological manifestations of DKD are characterized by significant heterogeneity, and the condition presents a more complex clinical picture.[24] In patients with T2DM, the development of albuminuria and renal impairment are not entirely linked.[25] Indeed, a large proportion of patients with T2DM experience renal function decline without exhibiting proteinuria beforehand.[26]

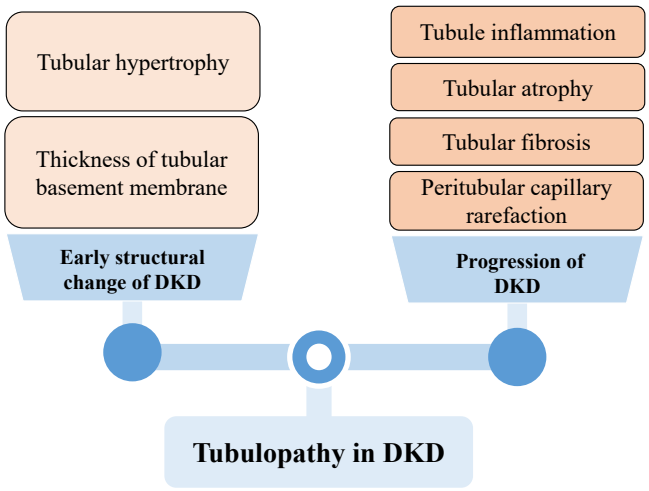

Figure 1. Pathologic changes of tubulopathy in DKD. The severity of renal dysfunction shows a close correlation with tubulopathy during DKD progression. Tubular hypertrophy and thickness of the tubular basement membrane are reported to be an early structural change, which indicates the severity of DKD. In addition, inflammation of the tubules, tubular atrophy, tubular fibrosis, and peritubular capillary rarefaction are also important pathologic changes during the progression of DKD. DKD, diabetic kidney disease.

In addition, PT cells comprise the most abundant resident population in the kidney. Increased PT reabsorption appears to occur partly as a result of tubular growth and the corresponding increase in sodium-glucose cotransport.[27] DKD disrupts the balance of ATP production and utilization in PT cells, under the influence of kidney blood flow, oxygen levels, reabsorption and delivery of metabolites, and their consumption.[28] Hyperglycemia may cause acute tubular necrosis or apoptosis directly, and thereby trigger epithelial-mesenchymal transition and promote extracellular matrix deposition.[29] The severity of renal dysfunction reportedly shows a closer correlation with tubulopathy than a change in glomerular damage during DKD progression.[28] The changes in the tubulointerstitial region are regarded as the primary determinants of the decline in renal function and exacerbation toward ESRD. In addition to tubular hypertrophy and the thickness of the tubular basement membrane, which are reported as early structural changes indicating the severity of DKD,[30] other pathologic changes during the progression of DKD include tubule inflammation, tubular atrophy, peritubular capillary rarefaction, and fibrosis[29] (Figure 1).

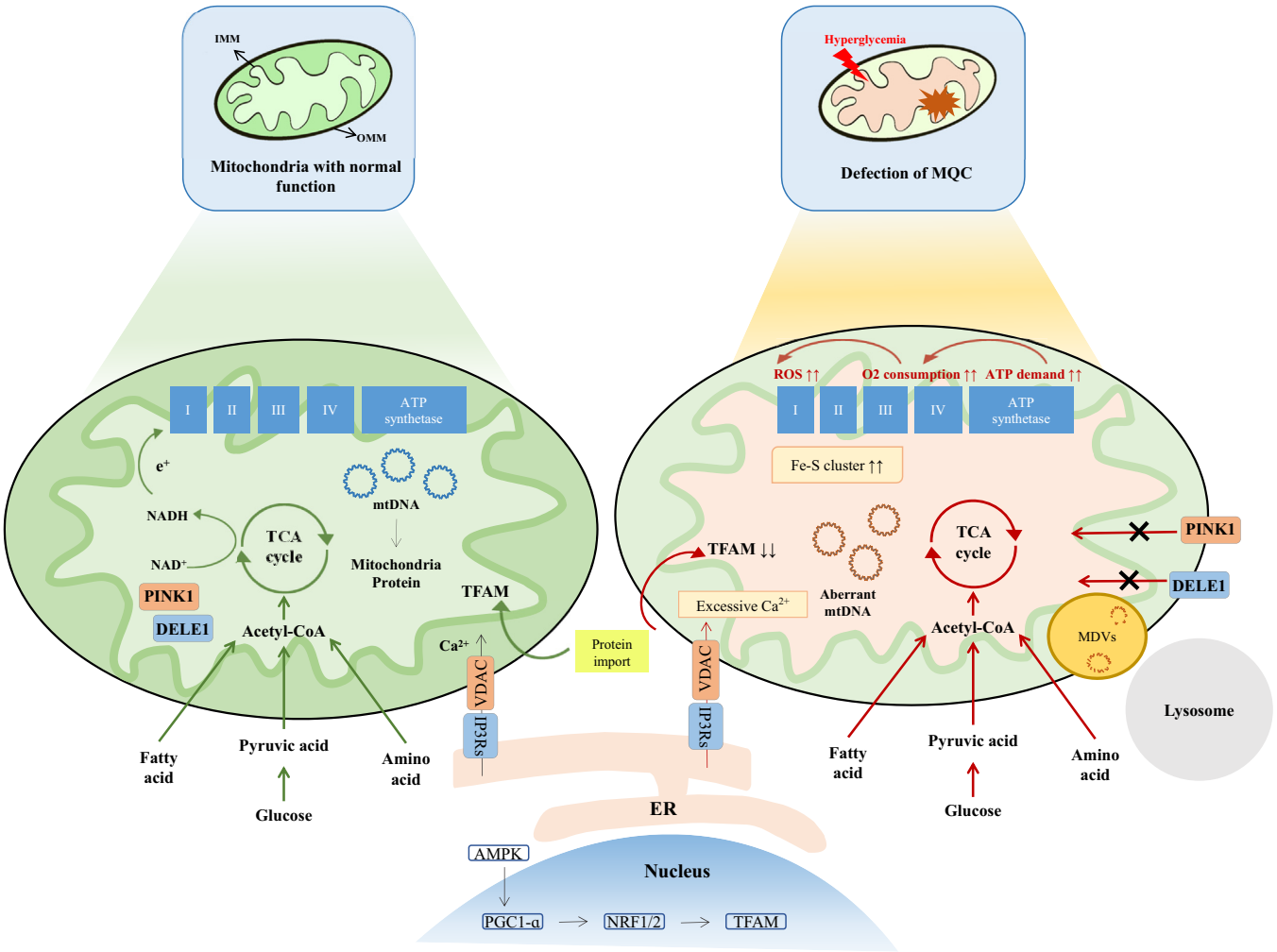

Figure 2. Mitochondrial Quality Control (MQC) in DKD. Accurate mtDNA expression, protein synthesis, effective interorganelle communication, precise protein import, and efficient ion transport are essential for maintaining mitochondrial health. However, under hyperglycemia, defects in MQC lead to increased mitochondrial respiration to support glucose reabsorption, resulting in renal hypoxia and excessive ROS production. Simultaneously, high glucose conditions impair protein import, such as decrease of TFAM, PINK1, and DELE1 fails to be imported to the IMM and instead stabilizes on the OMM, resulting in mitophagy activation, exacerbate mtDNA mutation, cause Ca^{2+} overloading, and lead to Fe-S cluster accumulation, further deteriorating mitochondrial function. AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; Ca^{2+}, calcium ion; ER, endoplasmic reticulum; DKD, diabetic kidney disease; Fe-S cluster, iron-sulfur cluster; I/II/III/IV, mitochondrial complex I/II/III/IV; IMM, mitochondria inner membranes; IP3Rs, inositol trisphosphate receptors; MDVs, mitochondrial-derived vesicles; mtDNA, mitochondrial DNA; NAD+, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; Nrf1, nuclear factor erythroid 2-related factor 1; OMM, mitochondria outer membranes; PGC1-α, peroxisome proliferator-activated receptor γ coactivator 1-α; PINK1, phosphatase and tensin homolog (PTEN)-induced kinase 1; ROS, reactive oxygen species; TCA cycle, tricarboxylic acid cycle; TFAM, mitochondrial transcription factor A; VDAC, voltage-dependent anion channel.

These findings emphasize the critical importance of a close focus on the mechanisms of DKD and identification of early interventions to preventing or treating chronic kidney disease (CKD) in patients with T2DM, particularly in early kidney injury before the onset of microalbuminuria.[31]

MQC IN DKD

Mitochondria, the central hubs for energy production, metabolism, and cellular signal transduction, consist of 2 bilayer lipid membranes, termed the mitochondria outer membranes and mitochondria inner membranes (IMM). Mitochondria also possess systems to transport the numerous metabolites and ions they require to function.[32] Normal function reportedly depends on multiple conditions: precise assembly of mitochondrial resident proteins, appropriate interaction with other organelles, accurate ion transportation, efficient mtDNA repair, and the specific composition of membrane lipids, among others[11,33-35] (Figure 2). The kidney has one of the highest resting metabolic rates in the body with abundant mitochondrial content and a high oxygen consumption rate. Ensuring optimal mitochondrial quality is essential for maintaining balanced glomerular-tubular function. The inability to maintain

adequate MQC is critical in oxidative stress and the resulting injury to tubular cells, and contributes to the progression of DKD.[36]

MQC: mtDNA

Accurate mtDNA expression is crucial for the organelle to function as a metabolic and signaling hub within the cell. Compared with nuclear DNA, mtDNA is more susceptible to damage, because there is no physical barrier separating transcription or translation or evidence of active quality control pathways that prevent translation of defective mRNA transcripts within mitochondria.[37] Selective mitophagy in the cytosol can eliminate mtDNA with harmful mutations, thereby reducing intracellular mitochondrial variation. Conversely, a high load of aberrant mtDNA within the cell can reduce cellular fitness by lowering ATP levels.[38] Therefore, precise maintenance of mtDNA is crucial for the maintenance of good health. Nevertheless, mtDNA repair mechanisms remain much less understood than nuclear DNA repair mechanisms.[39]

Variations in mtDNA and nuclear-encoded mitochondrial genes contribute to susceptibility to kidney disease.[40] In recent DKD-related research, use of high glucose (HG)-stimulated podocyte and diabetic models established using streptozocin has allowed the establishment of a decrease in mtDNA content, accompanied by a decrease in ATP synthesis.[41] Both increased mitochondrial ROS and decreased mitochondrial transcription factor A expression have been independently shown to induce mtDNA oxidative injury.[42] Furthermore, mtDNA mutation was reported that, upregulated in the db/db mouse model, accompanied by increased accumulation of 8-hydroxy-2′-deoxyguanosineand deletion mutations in the D-17 region, indicate mtDNA oxidative damage.[43,44] The elevated mtDNA deletion levels may indicate the accumulation of deleterious mtDNA variants, which could lower mitochondrial membrane potential across the entire network and compromise mitochondrial function, once the level of a certain threshold in DKD is exceeded.[38,45,46] These findings indicate that maintaining a balance between mtDNA quality and mitophagy is essential for preserving the health of kidney cells.

Moreover, aberrant mtDNA could serve as a biomarker for DKD. mtDNA is detectable in urinary supernatant and kidney tissue. In diabetic conditions, the excessive filtration of mtDNA through the kidneys may contribute to chronic renal inflammation.[47] Levels of mtDNA in urinary supernatant and within the kidneys both showed significant correlations with estimated glomerular filtration rate and the severity of interstitial fibrosis, suggesting they serve as markers for renal scarring in diabetic nephropathy (DN).[48] These findings indicate that mtDNA may have potential as a biomarker in early disease detection or as a promising therapeutic target in DKD. Nevertheless, the relationship between mtDNA and DKD remains to be fully understood.

MQC: Protein Synthesis

The controlled expression of mitochondrial-encoded proteins is intricately integrated into the quality control network that sustains cellular viability.[49] There are 13 hydrophobic proteins encoded by mtDNA that require cotranslational insertion into the IMM and help maintain the integrity of the IMM. The proteins are synthesized by mitochondrial ribosomes and form core subunits of complexes I, III, and IV of the respiratory chain. These are the catalytic cores of the oxidative phosphorylationmachinery.[50] In the kidney, approximately 90% of renal energy is derived from oxidative phosphorylation within the mitochondria, and the activity of complexes I, III, and IV is decreased in the diabetic kidney.[51] Damage to the protein synthesis process leads to the production of defective mitochondrial proteins, which in turn perpetuate the production of mitochondria ROS under diabetic conditions in the kidney,[52,53] with compromised ATP production and resulting tissue oxygenation.[54,55] A key pathological mechanism of diabetic tubulopathy in DKD is the imbalance between a reduced fuel supply and an elevated mitochondrial oxygen demand in renal tubules.[56]

Protein synthesis defects can arise naturally via a variety of processes, including mtDNA replication, transcription, posttranscriptional processing errors, and irregular mitochondrial ribosomes and translation errors.[37] Peroxisome proliferator-activated receptor γ coactivator 1-α (PGC1-α) is identified as a nutrient sensor in the kidney, plays a pivotal role in orchestrating mitochondrial biogenesis to maintain the delicate balance between mitochondrial structure and function.[57] PGC1-α–induced stimulation of nuclear factor erythroid 2-related factor (Nrf) 1 and 2promotes the expression of mitochondrial transcription factor A, which is itself considered a link between the nucleus and mitochondria which drives the transcription and replication of mtDNA.[58,59] A significant reduction in PGC-1α level in the kidneys has been observed under HG conditions, particularly in the context of activation of the serine–threonine liver kinase B1–AMP-activated protein kinase (AMPK) axis. This pathway plays critical roles in regulating mitochondrial biogenesis, energy homeostasis, and oxidative metabolism in DN.[60] Further, experimental diabetic mice with reduced expression of Nrf2 and mitochondrial transcription factor A displayed significant renal injury and mitochondrial disorder.[41]

Conversely, normal processing function is also dependent on accurate posttranslational modification and precise assembly with other proteins of mitochondrial respiratory chain complexes. Recently, an accessory subunit of mitochondrial complex I (CI) has been identified, named Ndufs4 which regulates mitochondria cristae remodeling and mitochondrial function in podocytes. Reduced *Ndufs4* expression impairs mitochondrial complex I and respiratory supercomplex formation, negatively affecting podocyte bioenergetics, cristae integrity, and mitochondrial morphology, thereby promoting DKD. Conversely, forced *Ndufs4* expression in podocytes under diabetic conditions enhances respiratory supercomplex assembly, improves cristae structure, and preserves mitochondrial morphology, alleviating DKD progression.[61] In addition, cytochrome c oxidase is a protein which is essential for the biogenesis and assembly of the subunits required to form functional respiratory complex IV of electron transport chain. Stress conditions, such as diabetes, can mimic the p53-mediated induction of cytochrome c oxidase expression, leading to increased ROS production and apoptosis.[62] The loss of functional cytochrome c oxidase was demonstrated to attenuate glomerular injury and lead to a reduction in excess ROS production in glomerular endothelial cells under diabetic conditions.[63] These results emphasize the importance of electron transport chain integrity in slowing the progression of DKD.

MQC: Protein Import

More than 99% of the mitochondrial proteome is synthesized in the cytosol and subsequently imported into mitochondria through diverse import pathways, frequently employing a mitochondrial targeting signal-dependent mechanism.[50,64] The integrity of mitochondrial protein import largely reflects the overall mitochondrial state, making it a crucial process to monitor for MQC.[65] Disruption of mitochondrial protein import activates multiple regulators, including mitophagy, mitochondrial-derived vesicles, the mitochondrial unfolded protein response (UPRmt), and the integrated stress response.[65]

Mammalian Translocase of Inner Mitochondrial Membrane 44

Increased expression of mammalian translocase of inner mitochondrial membrane 44, which facilitates the import of antioxidative enzymes into mitochondria -such as superoxide dismutase and glutathione peroxidase- and helps normalize the electrochemical gradient difference, has been observed in diabetic mouse kidneys.[66] Delivery of the mammalian translocase of inner mitochondrial membrane 44 gene shows promise in preserving mitochondrial function by suppressing ROS production and regulate ROS-related biological responses, offering a new therapeutic strategy for DN.[66]

Phosphatase and Tensin Homolog (PTEN)–Induced Kinase 1 (PINK1)

PINK1 plays crucial roles in maintaining mitochondrial function and cellular homeostasis by mediating protein import. With impaired protein import, PINK1 fails to be imported to the IMM and instead stabilizes on the mitochondria outer membranes, resulting in mitophagy activation.[65] In the development of DKD, PINK1 is present in major kidney cells. Recent evidence suggests that PINK1-mediated MQC is implicated in diabetic tubular injury.[67] It has been reported that hyperglycemia suppresses the expression of PINK1 and that the mitochondrial profusion protein, Mfn2 conversely enhances the expression of the mitochondrial fission proteins Drp1 and Fis1 in renal PT cells.[68]

UPRmt-Related Protein

The UPRmt also links impaired mitochondrial import to stress responses. The UPRmt is triggered by mild mitochondrial stress and serves as an adaptive mechanism which is capable of promoting the repair and functional improvement of mitochondria.[69] It has been demonstrated that the UPRmt can be continuously activated by activating transcription factor 5, which translocate from the cytoplasm to the nucleus and induces transcription of the UPRmt gene cluster in response to mitochondrial stress, in the kidney under sustained HG exposure, to thereby result in increased interstitial fibrosis and tubular atrophy.[70,71]

DELE1

DELE1 is a little-characterized protein that is associated with the IMM and normally localizes to mitochondria. However, under mitochondria stress, it has been identified as transmitting mitochondrial disturbances to the cytosol and acting as a substrate for the stress-activated mitochondrial protease, OMA1.[72] Mitochondrial stress activates OMA1, leading to cleavage of DELE1 and subsequent accumulation of DELE1 in the cytosol. The integrated stress response is a cellular pathway responsive to various stresses and plays a significant role in addressing mitochondrial stress.[73] DELE1 interacts with integrated stress response kinase, HRI in the cytosol, resulting in ATF4 translation and subsequent eIF2alpha phosphorylation.[74,75] The OMA1-DELE1-HRI pathway is seen as a potentially promising therapeutic target for selectively blocking ATF4 activation in cells experiencing mitochondrial dysfunction without globally suppressing the integrated stress response across all cells; nevertheless, related studies in kidney diseases or diabetes have not been conducted.

MQC: Organelle Networking

Recent studies have highlighted that organelles can communicate with each other to maintain their homeostasis, thereby influencing the overall structure and function of the cell. Mitochondrial organelle networking is also a key research area for understanding the pathophysiological of MQC.

Endoplasmic Reticulum

The part of the endoplasmic reticulum (ER) that is directly connected to mitochondria is termed the mitochondria-associated ER membrane (MAM). Disruption of MAM integrity induces a collapse in cellular homeostasis.[76] The MAM facilitates direct communication and exchange of lipids, calcium ions (Ca^{2+}) and other molecules between the mitochondria and ER. The number, length, and width of the contact zone are critical parameters that determine the involvement of the MAM in cellular processes.[77] Research indicates that the MAM serves as a crucial hub for maintaining glucose homeostasis, and that its disruption can lead to mitochondrial dysfunction, thereby contributing to insulin resistance in diabetic conditions.[78,79] In the kidneys, MAM has been observed to decrease gradually across various stages of DN. This reduction is negatively correlated with serum lipid levels and associated with lipid deposition and renal damage.[80] Although chronic HG exposure can lead to ER stress and mitochondrial dysfunction because of the depletion of ER Ca^{2+} stores, phosphofurin acidic cluster sorting protein 2, an anchor protein at the MAM interface, has been shown to protect diabetic kidneys and HG-treated HK-2 cells from renal tubular impairment by preserving ER-mitochondrial interactions and affect the transmission of calcium signals.[81]

Ribosomes

Ribosomes in the proximity of mitochondria are involved in the MQC of localized translation components, including tRNA, mRNA, and the proteins they encode, and participate in the removal of damaged mitochondria by mitophagy.[82] These ribosomes respond to cues arising from changes in mitochondrial physiology and the local environment in several ways. Proteins located at the outer mitochondrial membrane may transmit these signals and modulate ribosomal activity.[82] PINK1-mediated local translation is also crucial for detecting mitochondrial deterioration and initiating mitophagy via the ribosome quality control process. PINK1 functions as a potent activator of mitochondria fission by indirectly regulating Drp1 activity through the A-kinase anchoring protein 1 (AKAP1)-protein kinase A axis.[83] A-kinase anchoring protein 1 is localized to the mitochondria outer membranes where it functions as a regulator and facilitator of mitochondrial signaling and can spatially regulate the translation of mRNAs crucial for mitochondrial metabolism and function.[84] It has been demonstrated that the elevated expression of A-kinase anchoring protein 1 under HG conditions, could recruit Drp1 to promote mitochondrial fission. Knocking down A-kinase anchoring protein 1 expression under HG conditions rescues impaired mtDNA replication, preserves mitochondrial function, and mitigates podocyte injury by promoting the phosphorylation of Larp1, a novel RNA-binding protein that regulates mitochondrial protein translation, via PKC signaling activation.[45]

Mitochondrial-Derived Vesicles

Mitochondrial-Derived Vesicles (MDVs), the small vesicular structures released from mitochondria, are sent to the lysosome and play a crucial role in MQC by eliminating damaged mitochondrial components.[85] Recent advances have illustrated the growing functional importance of MDV release *in vivo*[86] and revealed that mtDNA nucleoids or DNA fragments can be cargo within MDVs under specific stimuli.[87,88] Interest in the functional impact of mitochondrial content secreted from tissues across multiple disease paradigms is growing, which has in turn led to insights into the roles of MDV transport in neurodegenerative disease, heart metabolism, and aging, among others. Nevertheless, no related studies in nephrology have yet appeared.

MQC: Ion Transportation

Ca^{2+}

Mitochondrial Ca^{2+} concentration is crucial for maintaining mitochondrial function and cell survival. Several lines of evidence suggest that Ca^{2+} could also indirectly regulate MQC through the modulation of various MQC pathways.[89] Ca^{2+} flux is regulated by mitochondrial transcription factor A through mitochondria-ER interactions and signals to the nucleus, resulting in the alleviation of metabolic disorders.[90] Ca^{2+} is transported from the ER to mitochondria via inositol trisphosphate receptors (IP3Rs) and voltage-dependent anion channel on the MAM.[91] The IP3R1–glucose-regulated protein 75–voltage-dependent anion channel 1 multiprotein complex, located at the MAM interface, facilitates the transfer of Ca^{2+} flux from the ER to mitochondria.[76] Maintaining balance in mitochondrial calcium levels is crucial. Properly regulated calcium flux between the ER and mitochondria supports energy production and cellular signaling; however, excessive or unregulated calcium flux can lead to mitochondrial dysfunction, ROS production, and cell death, ultimately harming cellular health.

Transient fluctuations in mitochondrial Ca^{2+} levels can disrupt the delicate balance of cellular metabolism,

because the physiological range for maintaining mitochondrial Ca^{2+} concentration is extremely narrow. Both excessively low and high Ca^{2+} levels may result in mitochondrial dysfunction, potentially contributing to pathological conditions by impairing energy production and triggering stress responses.[92] In DKD, transforming growth factor-β was reported to be involved in mediating the vascular dysfunction caused by DKD via its effects on IP3R.[93] After treatment with HG, there were notable reductions in interactions between IP3R1–voltage-dependent anion channel 1 and glucose-regulated protein 75–voltage-dependent anion channel 1, accompanied by ER stress, mitochondrial dysfunction, and apoptosis. This reduction indicates that glucotoxicity induces a decrease in the delivery of Ca^{2+} to mitochondria, and triggers cell death and kidney tubular injury.[81] However, there are 3 isoforms of IP3R—IP3R1, IP3R2, and IP3R3—and the different isoforms may dominate Ca^{2+} transfer in various cell types and diseases, with each isoform exhibiting distinct functions. However, research in DKD regarding these aspects is currently lacking.

Iron

Mitochondria play a crucial role in iron utilization. Iron is transported into mitochondria across both the mitochondria outer membranes and IMM by endosomes and mitoferrins in the cytoplasm, and serves as a substrate for the synthesis of various iron-containing proteins.[94] Important mitochondrial iron-containing proteins include iron-sulfur cluster-containing proteins, which play crucial roles in respiratory chain function.[94] Iron accumulation and ROS generation are accelerated by the ferroptosis inducer, erastin, which inhibit system Xc− and lead to decreased cystine uptake depletion of glutathione (i.e., GSH) and increased nicotinamide adenine dinucleotidephosphate oxidation.[95] It was demonstrated that iron content was increased in DN mice and that the ferroptosis inducer, erastin or RSL3 could induce renal tubular cell death, while iron and high acyl-CoA synthetase long chain family member 4 (ACSL4) levels sensitized ferroptosis.[96]

MQC: Morphology

The morphology of the mitochondrial network is primarily regulated by 2 processes: membrane fusion, mediated mainly by mitofusin 1 and mitofusin 2 (MFN1 and MFN2); and fission, mediated by dynamin-related protein 1 (DRP1) and fission protein 1. DRP1 is recruited from the cytosol to the mitochondrial surface to facilitate fission events.[97] Dysregulation in mitochondrial fusion leads to uncontrolled fission events, causing fragmentation of the network. Conversely, disruption to the fission machinery results in a hyperfused network because of continuous fusion events.[98] In DKD, mitophagy occurs pathologically in almost all types of kidney cells, accelerating the progression of the disease.[9] Mitochondrial fragmentation is a key mechanism in HG-induced mitophagy, triggered by increased mitochondrial depolarization, ROS production, and the accumulation of misfolded proteins, among other factors.[99,100] The imbalance between mitochondrial fusion and fission processes is a critical contributor to the initiation and progression of DKD, and precedes the development of albuminuria and renal histological changes[101] (Figure 3). Inhibitors of DRP1 have been shown to decrease albuminuria and improve mesangial matrix expansion and podocyte morphology, thereby rescuing key pathological features of DN.[102,103] Conversely, induced in HG-1 is a conserved mitochondrial protein that interacts with key mediators of mitochondrial fusion, including MFN

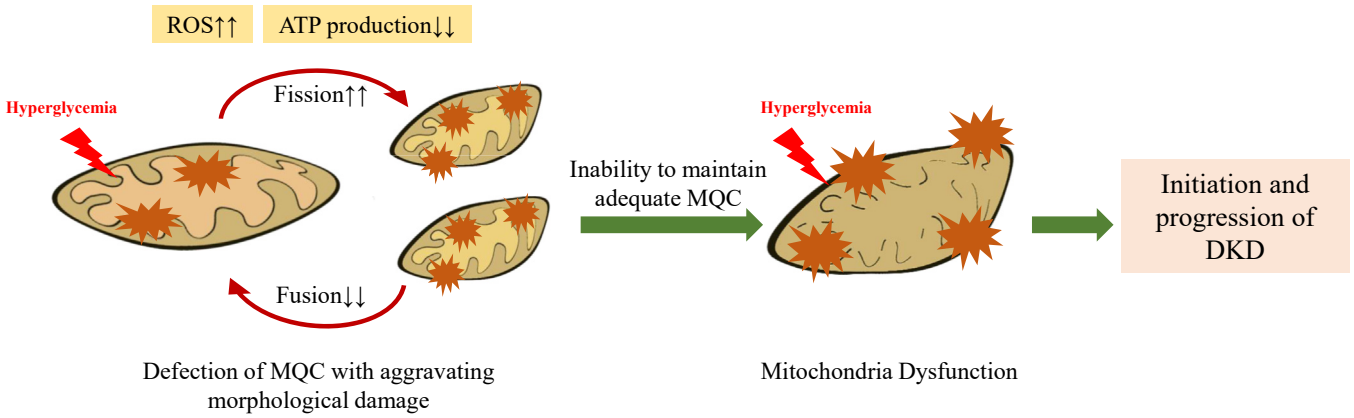

Figure 3. Defection of MQC causes mitochondrial dysfunction leading to the initiation and progression of DKD. Persistent high-glucose stimulation and excessive reactive oxygen species (ROS) production impair the OXPHOS and decrease ATP production. This exacerbates the imbalance in mitochondrial fission and fusion, disrupts MQC and causes mitochondrial morphological damage, ultimately leading to irreversible mitochondrial dysfunction and contributing to the initiation and progression of DKD. ATP, adenosine triphosphate; DKD, diabetic kidney disease; MQC, mitochondrial quality control; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species.

1 and 2, and enhances the GTP-binding capacity of Mfn2. This protein is implicated in DN, where it amplifies profibrotic transforming growth factor-β 1 signaling and promotes mitochondrial biogenesis.[104]

MQC-INVOLVED THERAPY STRATEGIES FOR DKD

Clinical Drugs

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors are recommended for most patients with T2DM and CKD with an estimated glomerular filtration rate $\geq$ 20 ml/min per 1.73 m^2, regardless of hemoglobin A1c level or the necessity for additional glucose-lowering therapy.[105] Increasing evidence supports the protective effects of SGLT2 inhibition on the kidneys, underscoring its critical role in mitigating tubular damage.[106] This is particularly significant because SGLT2 is exclusively localized in proximal tubules. Canagliflozin, dapagliflozin, and empagliflozin, recently approved for treating T2DM, all originated from the natural compound phlorizin.[107] At concentrations measured in human plasma during clinical trials, canagliflozin caused activation of AMPK by inhibiting complex I of the respiratory chain, thereby increasing cellular AMP or ADP levels.[107] Further, dapagliflozin reduced urinary kidney injury molecule 1, interleukin-1β, and mtDNA copy number in patients with CKD after 6 months of treatment.[108] Empagliflozin, as a pharmacological intervention that also targets SGLT2, has been widely adopted as a new treatment option for diabetes. Empagliflozin restores Sirtuin 3 (SIRT3) expression in PT cells, lowers HIF-α levels, and prevents the shift from fatty acid oxidation to abnormal glycolysis. This helps prevent epithelial-to-mesenchymal transition in TECs and may reduce renal fibrosis by restoring mitochondrial metabolism.[109] Further, empagliflozin alleviates DKD by improving renal tubular injury through the suppression of mitochondrial fission via the AMPK/specificity protein1 (SP1)/ phosphoglycerate mutase family member 5 pathway, and phosphoglycerate mutase family member 5 facilitates mitochondrial fission by dephosphorylating DRP1 at Ser637, promoting its translocation to mitochondria.[110] These findings highlight the connection between SGLT2 inhibition and mitochondrial function. Although these insights improve our understanding of SGLT2 inhibitors' role in cellular energy balance, more research is needed to clarify the detailed molecular mechanisms.[111] Among SGLT2 inhibitors, a large-scale real-world dataset was used to compare kidney outcomes in patients with diabetes mellitus who were newly treated with different SGLT2 inhibitors. The results showed no significant difference in the annual estimated glomerular filtration rate decline slopes between patients taking different SGLT2 inhibitors.[112]

Glucagon-Like Peptide-1 (GLP-1)-related drugs

Both GLP-1 receptor Agonists (GLP-1RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, which increase circulating GLP-1, exert vasotropic effects and reduce diabetes-induced oxidative stress in the glomerulus, thereby ameliorating DKD.[113,114] Although GLP-1 receptors are suggested to be absent from glomeruli, GLP-1RAs has been shown to improve mitochondrial function in the kidney.[15] GLP-1RAs improve mitochondrial function by restoring mitophagy; enhancing mitochondrial biogenesis through upregulating AMPK, SIRT1, and PGC-1α; and stabilizing mitochondrial membrane potential. They also reduce ROS production by inducing superoxide dismutase 1 expression, effectively mitigating oxidative stress and protecting mitochondrial health.[115-118] GLP-1RAs treatment was reported to protect kidney tubules in diabetes by suppressing ferroptosis, which involves reducing iron overload, oxidative stress, ACSL4-driven lipid peroxidation, and decreasing GPX4 expression and GSH content.[119] These multifaceted effects highlight the potential of GLP-1RAs in protecting renal mitochondrial function.

Conversely, several clinical trials and studies have explored the effects of DPP-4 inhibitors on DKD and CKD and suggest that DPP-4 inhibitors may provide renal protection in both diabetic and nondiabetic patients with CKD. DPP-4 inhibitors are regarded as safe and effective treatment options for patients with DKD alongside SGLT2 inhibitors and GLP-1RA.[120] These medications may reduce albuminuria and slow disease progression, offering potential benefits in kidney function preservation. Studies on the effects of DPP-4 inhibitors on mitochondrial function remain limited. It is promising to explore their potential impact on mitochondrial biogenesis, dynamics, and related pathways, which may contribute to kidney protection in DKD.[121]

Blockers of the Renin-Angiotensin-Aldosterone System

Blockers of the renin-angiotensin-aldosterone system remain the cornerstone for reducing albuminuria and slowing the decline in renal function in both patients with type 1 diabetes mellitus and T2DM with DKD.[122] Angiotensin II type 2 receptor antagonists were found to reverse the downregulation of PGC1-α, which led to speculation that telmisartan's renoprotective effect may be partly because of its role in stabilizing PGC1-α.[57] Overexpression of angiotensin II type 2 receptor in tubular epithelial cells inhibited all diabetes-induced renal changes, including decreased mitochondrial

bioenergetic efficiency, increased mitochondrial superoxide production, metabolic reprograming, and enhanced proliferation.[123]

Metformin

Metformin, one of the most widely used medications for managing T2DM, has been shown to activate AMPK.[124,125] This activation leads to improved mitochondrial function and enhanced energy regulation, playing a critical role in mitigating metabolic dysfunctions associated with diabetes.[126] Metformin improves insulin sensitivity and reduces oxidative stress, helping to maintain cellular energy balance and support mitochondrial health in patients with T2DM.[127] It alleviated glycolipid metabolism disorders, renal injury, and abnormal cell proliferation in diabetic rats and HG-cultured mesangial cells through the AMPK/SIRT1-FoxO1 pathway.[128] In addition, metformin reduced renal oxidative stress and tubulointerstitial fibrosis in HFD/streptozocin-induced diabetic mice by activating mitophagy via the p-AMPK-Pink1-Parkin pathway.[129] Conversely, metformin reversed the decrease in protein levels of the mitochondrial fusion proteins MFN1, MFN2, and optic atrophy 1, and increased the expression levels of fission protein 1 and DRP1 induced by T2DM. This improvement in mitochondrial dysfunction and regulation of mitochondrial dynamics benefits patients with T2DM.[130]

Imeglimin

Imeglimin, a novel oral antidiabetic drug belonging to the "glimin" class of tetrahydrotriazine-containing molecules, is currently under investigation following the completion of 3 pivotal phase 3 clinical trials in Japan.[131] This agent shows promise in significantly improving treatment outcomes for many individuals for whom previous therapies have failed or are contraindicated.[132] Imeglimin has been reported to increase mtDNA content without altering PGC1-α expression and to improve mitochondrial density and function.[133] Its beneficial effects on glucose homeostasis, particularly insulin sensitivity, stem from improvements in hepatic mitochondrial function, which lead to increased lipid oxidation and reduced production of ROS.[133] Long-term (90-day) imeglimin treatment resulted in reduced kidney damage and improved kidney function, as evidenced by decreased glomerular injury, decreased albuminuria, and reductions in both interstitial inflammation and fibrosis in a rat model of metabolic syndrome.[134] This finding supports the potential systemic benefits of imeglimin in individuals with T2DM, extending beyond glycemic control alone, which are increasingly recognized as essential properties of effective therapies for T2DM[132]

Preclinical or Prospective Treatment Targets

PGC1-α

PGC1-α plays a pivotal role in maintaining the structural and functional stability of mitochondria. Activation of PGC1-α has shown significant renal protective effects in DKD models, emphasizing its potential utility in diagnostics, therapeutics, and prognosis in the context of DKD.[57] In DKD, significant suppression of PGC1-α expression in the kidney leads to increased oxidative stress, disrupted fatty acid oxidation, and impaired energy metabolism, contributing to structural and functional kidney damage and thereby exacerbating DKD pathology.[57] The downregulation of PGC-1α has been shown that promotes mitochondrial fragmentation and disrupts the mitochondrial network structure by increasing the expression of DRP1, which supports the notion that the protective role of PGC-1α in DN is associated with its ability to mitigate ROS production through the remodeling of mitochondrial dynamics.[135] Activation of PGC1-α has demonstrated significant renal protective effects in DKD models. However, exploration of the optimal therapeutic window in targeting PGC1-α is still urgently required, together with rigorous evaluation of the diagnostic and therapeutic capabilities of this approach in patients with DKD.

SIRTs

SIRTs comprises 7 highly conserved regulatory enzymes that play key roles in metabolism, antioxidant defense, and cell cycle regulation. Their dynamic interaction plays a vital role in regulating PGC-1α expression and preserving mitochondrial homeostasis.[57] In the kidney, they extensively express in both the glomerular and tubular compartments and require nicotinamide adenine dinucleotide (NAD^+) for their activity.[136,137] SIRTs regulate cellular metabolism by performing NAD^+-dependent deacetylation or deacylation of various proteins, including histones; transcription factors; and coactivators such as p53, nuclear factor-kappa B, PGC-1α; as well as signaling regulators such as protein kinase A, AMPK, and mechanistic target of rapamycin (mTOR).[138] Notably, enhancing NAD^+ metabolism has been shown to reduce inflammation and slow the progression of DKD, highlighting the critical role of SIRTs in kidney health.[139]

SIRT1, SIRT3, and SIRT6 agonists have all shown a protective role in DKD.[140-142] Within the glomerulus, SIRT1 and SIRT6 are known to uphold the structural and functional integrity of podocytes, and SIRT1 and SIRT3 play crucial roles in regulating endothelial cell functions.[143] SIRT1 is present in both the cytoplasm and mitochondria, regulates lipid accumulation, reduces fibrosis, and slows renal disease progression. It also protects against vascular injury and aging-related

kidney vulnerability.[144] Resveratrol was reported to activate the SIRT1/PGC-1α axis, enhancing nitric oxide synthase synthesis and vascular function in DKD-affected glomerular endothelial cells.[145] SIRT3 is mainly localized in the mitochondria and has been described as the main regulator of mitochondrial global protein deacetylation. Restoring SIRT3 activity through improvements in the intracellular NAD+/NADH ratio ameliorated mitochondrial oxidative stress in HG condition.[146] SIRT3 depends on NAD+ availability to enhance mitochondrial functions, including restoring fatty acid oxidation as a critical step in reversing kidney injury.[139] Further, SIRT6 protected podocytes from the reduced expression of AMPK dephosphorylation and mitochondrial morphological abnormalities observed in diabetic mice.[147] These findings emphasize the significant role of mitochondrial homeostasis in the regulation of DKD by SIRTs agonists. In the future, molecular modeling tools are critical to identify more promising SIRT candidates and efforts should also focus on improving the bioavailability and retention time of sirtuin modulators.[148]

Nuclear Regulatory Factor 2

Nrf2, a transcription factor which is crucial for defensive responses to oxidative stress, is considered a promising target for DKD because of its role in mitigating oxidative stress and inflammation.[42,149] It supports mitochondrial health by regulating antioxidant enzyme expression and promoting mitophagy, which helps remove damaged mitochondria and maintain cellular function. Inactivation of Nrf2 contributes to oxidative stress and diabetic kidney injury.[150] Emerging treatments that target the Nrf2 pathway show promise for future therapeutic advancements.[111] Recent research has highlighted Nrf2's role in countering HG-induced ferroptosis.[151-153] Bardoxolone methyl is an activator of Nrf2 and a direct inhibitor of nuclear factor-kappa B. It has been suggested that bardoxolone methyl may induce albuminuria by inhibiting the activity of inhibitor of nuclear factor kappa B kinase subunit β.[154] Further, in a phase 2 study in patients with CKD and T2DM (the TSUBAKI Study), bardoxolone methyl induced a significant increase in measured estimated glomerular filtration rate and has shown no serious side effects to date.[155] However, because of the short duration and small sample size of the TSUBAKI study, the evaluation of bardoxolone methyl's safety and efficacy was limited. Therefore, the ongoing AYAME study, a large-scale long-term phase 3 trial, aims to assess its efficacy and safety in patients with DKD.[156] Overall, enhancing Nrf2 activity and its downstream pathways holds potential to slow, halt, or even reverse the progression of kidney function decline.[157]

MAM-Related Protein

In recent years, the importance of the MAM in the development of DKD has been increasingly recognized and valued. Recent studies have shown that MAM integrity is disrupted in kidneys with DKD.[158,159] Findings strongly support the idea of MAM as a potential therapeutic target for the treatment of DKD.[160] For instance, PACS-2, an important mitochondrial-ER tether protein, plays a role in regulating the extent of mitochondrial contact with the ER. It has been demonstrated that PACS-2 ameliorates tubular injury in DN by preserving MAM integrity, regulating mitochondrial dynamics, and promoting mitophagy.[81,161] Studies in DKD have also indicated that inhibiting MAPK1 increases PACS-2 expression, which in turn protects against the loss of MAM integrity and mitochondrial fragmentation.[162]

Vitamin D receptor

Conventionally, the binding of vitamin D to vitamin D receptor (VDR) either represses or enhances the transcription of numerous genes by modifying the activity of their respective promoters.[163] However, emerging evidence shows that vitamin D/VDR exerts a broad and effective regulatory influence on mitochondrial function and cellular health and is involved in various renal diseases.[163,164] Activated VDR might contribute to the restoration of mitophagy through the Mfn2-MAMs-FUN14 Domain Containing 1 (Fundc1) pathway in renal tubular cells. VDR could induce a recovery in mitochondrial ATP, complex V activity, and MAMs integrity, and inhibit mitochondrial fission and the generation of mitochondrial ROS.[165]

Melatonin

Melatonin, a pineal hormone associated with circadian rhythms, plays a role in regulating mitochondrial homeostasis by inducing rapid generation of ROS at the antimycin-A-sensitive site of mitochondrial complex III in DKD.[166-168] Recently, it was found out that melatonin promotes AMPK phosphorylation and accelerates the translocation of PINK1 and Parkin to the mitochondria. This activation of mitophagy helps reduce oxidative stress and inhibit inflammation, ultimately contributing to its renal protective effects.[169]

CONCLUSIONS AND PERSPECTIVES

In recent years, research on MQC has gained momentum as a promising therapeutic target in various diseases. In nephrology, although mitochondrial dysfunction is increasingly recognized as playing a critical role in renal diseases, there remains a scarcity of impactful studies specifically focusing on MQC, particularly in DKD.

Given its central role in CKD, concerted efforts are needed to generate new insights and robust evidence on MQC. This will hopefully serve to advance diagnostic and therapeutic strategies for DKD, where current interventions such as blood glucose control are insufficient to completely eliminate albuminuria or slow a decline in renal function, leading many patients to progress to ESRD.[122] Therefore, an urgent need to explore new prospective treatment strategies aimed at better controlling disease progression and preserving kidney function remains, with a clear focus on MQC as a promising area of investigation.

This review provides an innovative summary of recent promising research and offers unique insights into the importance of MQC in DKD. By highlighting MQC as a significant target for treatment in DKD research, it brings attention to its pivotal role. Drugs already used in clinical treatment are closely associated with improving MQC to mitigate the damage caused by diabetes or DKD, emphasizing the critical role of MQC regulation. These effects in turn underscore the importance of MQC modulation and highlight the preservation of mitochondrial quality as a key focus in developing new treatments for DKD. Nevertheless, the application of mitochondrial-targeted drugs to the treatment of DKD remains a significant challenge. This is due not only to their potential adverse effects and unclear mechanisms of action but also to the unclear mitochondrial biology and pathology under this condition. It is crucial to note that MQC mechanisms operate through an integrated hierarchical network of pathways, which are interconnected and mutually supportive.[10] Changes in any one of these can impact others and consequently affect the entire system. Future research efforts should therefore include comprehensive laboratory and clinical investigations to explore the therapeutic potential of targeting MQC in DKD.

DISCLOSURE

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