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TFAM and Mitochondrial Protection in Diabetic Kidney Disease

Siming Yu[1,2], Xinxin Lu[2], Chunsheng Li[2], Zehui Han[2], Yue Li[2], Xianlong Zhang[3], Dandan Guo[2,4]

[1]The First Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, Harbin, People's Republic of China; [2]Heilongjiang University of Traditional Chinese Medicine, Harbin, China; [3]The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, People's Republic of China; [4]The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, Harbin, People's Republic of China

Correspondence: Dandan Guo, The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, Harbin, People's Republic of China, Email guodandan@hljucm.edu.cn; Xianlong Zhang The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, People's Republic of China, Email zhangxianlong853@163.com

Abstract: Diabetic kidney disease (DKD) is a significant complication of diabetes and a major cause of end-stage renal disease. Affecting around 40% of diabetic patients, DKD poses substantial economic burdens due to its prevalence worldwide. The primary clinical features of DKD include the leakage of proteins into the urine, altered glomerular filtration, and an increased risk of cardiovascular diseases. Current treatments focus on managing hypertension and hyperglycemia to slow the progression of DKD. These include the use of SGLT2 inhibitors to control blood sugar and ACE inhibitors to reduce blood pressure. Despite these measures, current treatments do not cure DKD and fail to address its underlying causes. Emerging research highlights mitochondrial dysfunction as a pivotal factor in DKD progression. The kidneys' high energy requirements make them particularly susceptible to disturbances in mitochondrial function. In DKD, mitochondrial damage leads to reduced energy production and increased oxidative stress, exacerbating tissue damage. Mitochondrial DNA (mtDNA) damage is a key aspect of this dysfunction, with studies suggesting that changes in mtDNA copy number can serve as biomarkers for the progression of the disease. Efforts to target mitochondrial dysfunction are gaining traction as a potential therapeutic strategy. This includes promoting mitochondrial health through pharmacological and lifestyle interventions aimed at enhancing mitochondrial function and reducing oxidative stress. Such approaches could lead to more effective treatments that directly address the DKD.

Keywords: diabetic kidney disease, TFAM, mitochondrial dysfunction, mitochondrial DNA, oxidative stress

Introduction

Diabetic kidney disease (DKD) is a prevalent microvascular complication among diabetes patients and a primary cause of end-stage renal disease.[1] Epidemiological studies indicate that nearly 40% of individuals with diabetes are affected by DKD, with its prevalence remaining relatively stable.[2] However, due to the vast number of people with diabetic nephropathy worldwide, DKD has escalated into a significant public health issue, imposing substantial economic burdens on both society and healthcare systems. Clinical manifestations of DKD include the leakage of albumin, metabolites, and ions into the urine, alterations in glomerular filtration rate, and an increased risk of cardiovascular disease and stroke.[3] Current pharmacological strategies for managing DKD primarily target hypertension and hyperglycemia, aiming to slow disease progression.[4] Medications such as SGLT2 inhibitors are used to control blood glucose levels, while ACE inhibitors and angiotensin receptor blockers target the renin-angiotensin system. These medications lower glomerular pressure, dilate small renal efferent arterioles, and reduce albumin excretion, with the goal of slowing the progression of DKD and preventing cardiovascular complications. However, these treatments do not address the underlying causes of DKD. Lifestyle modifications, including weight management, reducing salt intake, regular exercise, and dietary changes, have also proven beneficial in managing DKD by lowering blood pressure and reducing proteinuria. Despite the comprehensive application of these interventions, current treatment approaches cannot completely halt or reverse the progression of DKD. Thus, there is a critical need for the development of more effective and targeted therapies to

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overcome the clinical limitations of existing DKD treatments.[4] To address the challenge posed by DKD, targeting mitochondrial dysfunction has recently emerged as a promising strategy to halt disease progression. Mitochondria are the primary organelles responsible for energy production in the kidneys, whether in a healthy state or during DKD. The substantial energy and oxygen requirements of the kidneys create a strong link between mitochondrial function and renal health.[5–9] Research has demonstrated that in DKD, the mitochondrial membrane potential in kidney cells is diminished, leading to impaired mitochondrial function and an inability to produce energy effectively.[10,11] Due to the substantial metabolic needs of the kidney, which depend on mitochondrial ATP production for normal function, any impairment in mitochondrial activity undermines their operational efficiency, markedly elevating the risk of disease.[9] Thus, dysfunctional mitochondria are increasingly recognized as central to the onset and advancement of DKD. Recent research indicates that mitochondrial transcription factor A (TFAM) is vital for preserving mitochondrial function and is emerging as a potential therapeutic target for diabetic kidney disease (DKD).[12–14] However, the process of sustaining mitochondrial function via TFAM is complex and multifaceted. To advance our understanding, We provides a comprehensive overview of the occurrence and progression of mitochondrial dysfunction in DKD, along with potential mechanisms through which TFAM may confer mitochondrial protection. Based on these insights, we propose therapeutic strategies focused on TFAM that could potentially slow the progression of DKD.

Mitochondrial Dysfunction in DKD

Vulnerability of mtDNA to Oxidative Damage

Mitochondria are crucial organelles involved in various cellular functions including energy regulation, cell death, calcium flux homeostasis, and the synthesis of lipids, amino acids, and heme. Unlike the nuclear genome, mitochondria possess their own distinct genome. Mitochondrial DNA (mtDNA) is a multi-copy, circular genome that encodes 37 genes. Among these, 13 genes code for the core protein subunits of complexes I, III, IV, and V of the electron transport chain; 22 for tRNAs; and 2 for rRNAs essential for the synthesis of these protein subunits.[15] These proteins are integral to oxidative phosphorylation and critical for ATP production during cellular respiration.[16] The mtDNA is composed of a guanine-rich heavy strand and a light strand, with its double-stranded structure rendering it particularly vulnerable to oxidative damage.[10] The replication of mtDNA involves asymmetric pathways that often leave the heavy strand single-stranded for extended periods, increasing susceptibility to spontaneous nucleotide deamidation.[17] Moreover, mitochondrial DNA is more prone to damage from lower concentrations of reactive oxygen species (ROS) than genomic DNA; under sustained oxidative stress, its repair rate lags behind that of genomic DNA.[18] Damage to mtDNA and compromised mitochondrial genome integrity are crucial in the onset of severe early-age and chronic aging-related diseases.[18] Increasing evidence suggests that persistent minor mtDNA damage is not only linked with aging but also closely associated with diabetes and its complications.[19]

Excessive ROS Production as a Potential Driver of Mitochondrial Dysfunction in Diabetic Kidney Disease

As renal injury advances in diabetic patients, the mitochondrial membrane potential diminishes in proximal renal tubules, endothelial cells, and podocytes.[20–24] This reduction in mitochondrial functionality is analogous to that observed in various other diseases that cause renal mitochondrial dysfunction.[21,25–27] Key features of mitochondrial dysfunction include ROS overproduction, mtDNA disruption, abnormal mitochondrial dynamics, reduced adenosine triphosphate (ATP) production and mitochondrial membrane potential (MMP), and disrupted mitochondrial autophagy.[3,28,29] ROS overproduction appears to initiate mitochondrial dysfunction, particularly in diabetic kidney disease DK. In DKD, sustained hyperglycemia enhances electron transport chain (ETC) activity by generating NADH and FADH2 through the TCA cycle. Leaking electrons from the respiratory chain bind directly to molecular oxygen, forming superoxide and leading to increased ROS production in the ETC. Due to its proximity to the site of ROS production in the mitochondrial membrane, mtDNA is highly vulnerable to oxidative damage.[20,30] Unfortunately, mtDNA repair is slow and cannot quickly restore normal function.[18,31] Moreover, high blood glucose promotes the release of mtDNA into the extracellular compartment.[31] Studies have shown that alterations in mtDNA copy number in blood and urine reflect the severity of mitochondrial dysfunction and DKD. Changes in mtDNA copy number in peripheral blood can predict DKD, with

reductions in mtDNA copy number negatively correlated with albuminuria and positively correlated with the estimated glomerular filtration rate.[10] Therefore, monitoring mtDNA changes is recommended for diabetic patients to assess the progression of DKD.

Influence of ROS and DNA Damage on Mitochondrial Division and Fusion

Mitochondria, dynamic organelles, adjust to cellular energy requirements and preserve their structural integrity via division and fusion processes. Mitochondrial division is facilitated by dynein-associated protein 1 (DRP1), while fusion is driven by optic atrophy 1 (OPA1) and mitochondrial fusion proteins 1 (MFN1) and 2 (MFN2).[32] Typically, mitochondrial fusion mitigates damage by acquiring healthy proteins like enzymes. When mitochondrial DNA anomalies are identified, mitochondria may merge to enable the synthesis of protein 2, encoded by distinct mitochondrial genomes.[33]

During the fusion process, mitochondrial contents intermingle. Subsequently, fission generates new, healthy mitochondria, while defective ones are discarded and recycled via mitochondrial autophagy. Mitochondrial fission impairs ATP production by diminishing mitochondrial membrane potential.[34] In this phase, mtDNA and other components replicate, and binary fission results in two new mitochondria. Numerous pathways linked to mitochondrial dynamics are influenced by diabetes. Initially, mitochondrial biogenesis intensifies, but as diabetic nephropathy progresses, biogenesis levels decrease significantly.[35,36] The dynamics of fusion, fission, and recycling in diabetic kidneys are disrupted, hindering the removal of damaged mitochondria and exacerbating ATP shortages.[3] Furthermore, mitochondrial DNA damage and ROS production impair mitochondrial division and fusion processes. Elevated ROS levels heighten oxidative stress, suppress the expression of mitochondrial fusion proteins (such as OPA1 and MFN), and activate mitochondrial fission proteins (like DRP1). This imbalance promotes mitochondrial division, which ultimately reduces mitochondrial autophagy. If damaged mitochondria are not efficiently recycled, cytochrome c (Cyt c) may be released into the cytoplasm at levels high enough to trigger renal cell apoptosis[3] (Figure 1).

TFAM Mediated Mitochondrial Function in DKD

TFAM (mitochondrial transcription factor A) is a protein essential for maintaining mitochondrial function and integrity. Synthesized in the cell's nucleus, TFAM is transported to the mitochondria to regulate their function. TFAM regulates the transcription of 13 genes encoding electron transport chain proteins, 22 transfer RNA genes, and 2 mtDNA-encoded ribosomal RNA genes.[37,38] Under normal physiological conditions, TFAM binds to mtDNA, enhancing transcription

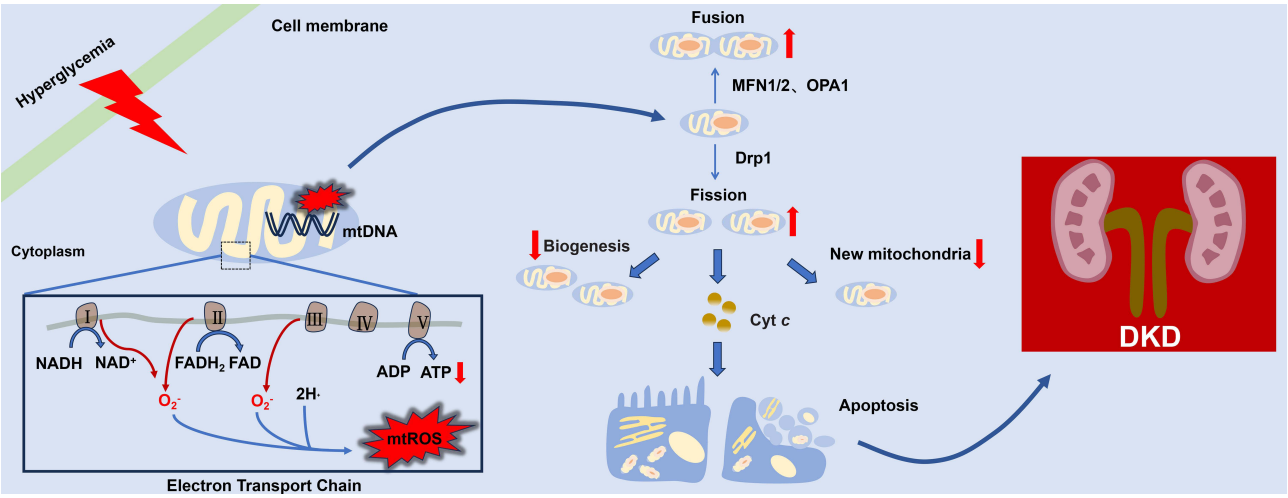

Figure 1 Schematic overview of mitochondrial dysfunction in diabetic nephropathy. In DKD, prolonged hyperglycemia increases NADH and FADH2 production via the tricarboxylic acid cycle, enhancing the ETC. This leads to electron leakage and the formation of superoxide, increasing ROS and damaging mtDNA. The process disrupts mitochondrial fusion and function, despite increased expression of fusion proteins like MFN1 and OPA1, causing mitochondrial fragmentation. Concurrent mtDNA damage and ROS production further impair mitochondrial dynamics, increasing oxidative stress, suppressing fusion protein expression, and boosting fission protein activity (eg, DRP1). This promotes cellular apoptosis, reduces mitochondrial autophagy, and may trigger extensive cytochrome c release, leading to apoptosis in renal cells.

associated with mitochondrial RNA polymerase and mitochondrial transcription factors B1 (TFB1M) or B2 (TFB2M).[15] In addition to binding specific promoter regions, TFAM also binds non-specifically, promoting mitochondrial chromosome stabilization and maintenance and regulating mtDNA copy number.[39–42] TFAM is also involved in mitochondrial functions such as reducing ROS through enhanced antioxidant activity, activating 5′ adenosine monophosphate-activated protein kinase (AMPK), mitochondrial uncoupling, and regulating membrane potential.[43] Consequently, the communication between mitochondria and the nucleus is closely regulated in response to sudden cellular energy challenges, and TFAM plays a significant role in this interaction.

The Critical Role of TFAM in Diabetic Kidney Disease: From mtDNA Stability to Mitochondrial Dysfunction

TFAM is an essential packaging protein vital for mtDNA replication and transcription.[44] As a direct regulator of mtDNA content, TFAM is pivotal in sustaining mtDNA stability, mitochondrial biogenesis, and signaling pathways in response to energy demands and stimuli.[45,46] Under pathological conditions, TFAM destruction can cause mitochondrial DNA depletion and bioenergetic deficiency.[44,47,48] TFAM and mtDNA maintain stability through their binding, allowing mtDNA to exist stably within mitochondria in a nucleus-like structure. Unbound DNA and free TFAM in mitochondria are unstable and susceptible to rapid degradation.[49] In the progression of DKD, a reduction in TFAM levels may impair the interaction between TFAM and mtDNA, decrease ribosomal cores, and foster the formation of abnormal clusters. Consequently, this leads to mtDNA depletion, inhibited mitochondrial transcription, and compromised mitochondrial energy metabolism and renal function.[12,50,51]

TFAM primarily maintains mtDNA copy number and functionality by regulating its replication and transcription, a crucial mechanism for cells and mitochondria to address the metabolic demands of hyperglycemia. TFAM protects mtDNA by binding to specific areas, such as the D-loop region, and forming a nucleoprotein complex that not only safeguards mtDNA but also regulates its replication.[52] This contributes to cellular homeostasis by reducing mtDNA damage and cytoplasmic release, thereby minimizing mitochondrial damage and inflammatory responses.[12] However, in DKD, diminished TFAM expression[12] may expose mtDNA to ROS, resulting in mtDNA leakage into the cytoplasm. This cytoplasmic mtDNA is then recognized by the cGAS-STING pathway, activating NF-κB and increasing the expression of inflammatory factors such as TNF-α, IL-1β, and IL-6.[53–55] Consequently, inflammation may be a significant contributor to metabolic dysfunction in DKD (Figure 2).

Low levels of TFAM were detected in numerous microdissected human renal tubular samples from chronic kidney disease patients, correlating with the degree of fibrosis. This suggests that TFAM is a critical regulator of mitochondrial and metabolic functions.[53] Kidney-specific TFAM knockout mice exhibit severe renal disease, characterized by collagenous tubular atrophy and immune cell infiltration, along with mitochondrial loss, OXPHOS and FAO defects, and reduced ATP levels. These conditions are indicative of significant renal functional impairments, similar to those observed in acute kidney injury.[53,56] TFAM deficiency-induced mitochondrial dysfunction not only disrupts metabolism but also triggers cytokine and chemokine release and immune cell activation. Mechanistically, the cytoplasmic translocation of mtDNA activates NF-κB through the cGAS-STING pathway, linking metabolic deficiencies to increased inflammation (Figure 2). Previous studies have shown that TFAM deficiency leads to aberrant mtDNA packaging and cGAS-STING-dependent IRF3 activation, enhancing the antiviral innate immune response in mouse embryonic fibroblasts.[57] In tfam-deficient renal tubular epithelial cells, similar defects in mtDNA packaging activated the cGAS-STING signaling pathway, though the expression of IRF3-targeted antiviral genes was only slightly elevated. Considering that cytoplasmic mtDNA can also activate NF-κB via the cGAS-STING pathway,[58] the inhibition of STING significantly reduced TFAM-deficiency-induced NF-κB activation and cytokine expression, underscoring the importance of NF-κB-dependent inflammatory signaling in kidney disease development.[53]

Increased mtDNA replication is linked to mitochondrial biosynthesis and may serve as a compensatory mechanism to counteract DKD-induced mitochondrial damage, responding to diminished mitochondrial function as the disease progresses. This adaptation potentially helps maintain or augment the mitochondrial count, thereby supporting the energy demands of the affected kidney. However, merely enhancing mtDNA replication does not necessarily enhance overall mitochondrial function,

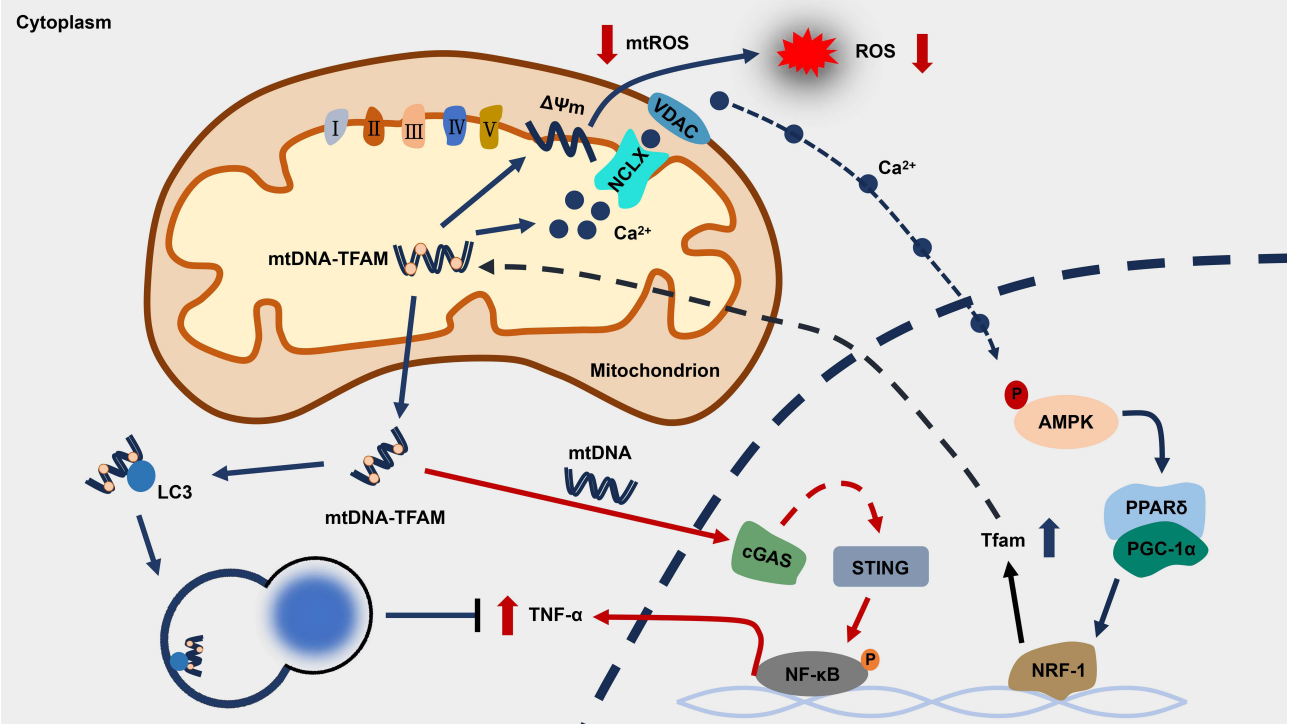

Figure 2 The mechanism by which TFAM improves mitochondrial dysfunction. Firstly, TFAM binds to the D-loop of mtDNA, safeguarding it from leaking into the cytoplasm. In DKD, leaked mtDNA activates the cGAS-STING pathway, resulting in NF-κB activation and increased production of inflammatory cytokines such as TNF-α, which ultimately leads to cellular damage. However, when mtDNA leaks into the cytoplasm, TFAM can facilitate mtDNA degradation via autophagy by interacting with LC3, particularly through its second LC3 interaction motif, which is essential in preventing inflammation. Moreover, TFAM-driven ΔΨm facilitates the transmission of Ca^{2+} signals to the nucleus through NCLX/VDAC, regulating calcium ion flux and controlling mitochondrial Ca^{2+} efflux, thus maintaining mitochondrial Ca^{2+} homeostasis. This Ca^{2+} signaling activates pathways such as AMPK and PGC-1α in the nucleus, promoting energy metabolism, preserving cellular function, and preventing inflammation and metabolic disorders.

as mitochondrial quality control—encompassing autophagy and fusion/fission processes—is also crucial. Thus, while increased mtDNA replication might boost the number of mitochondria, it may not effectively ameliorate DKD pathology if the newly formed mitochondria are also dysfunctional or damaged.[3]

Furthermore, TFAM deficiency results in mitochondrial dysfunction, leading to the escape of mtDNA into the cytoplasm and activation of the cGAS-STING DNA-sensing pathway. This activation triggers pro-inflammatory cytokine expression in renal tubular epithelial cells through STING-dependent NF-κB activation, mediated by mtDNA translocation. Additionally, TFAM deficiency contributes to metabolic abnormalities, tubular atrophy, and pro-fibrotic collagen deposition, ultimately culminating in renal failure and chronic kidney disease.

TFAM Limits Inflammatory Response by Promoting Autophagy

Mitochondrial autophagy, a selective form of macroautophagy targeting damaged mitochondria, has been shown to occur at higher rates in the kidneys, constituting a crucial aspect of mitochondrial homeostasis.[59] Currently, the dominant perspective holds that mitochondrial phagocytosis exerts a protective effect against DKD.[60,61] Conversely, a deficiency in mitochondrial phagocytosis not only correlates with senescence in renal tubular cells but also contributes to the progression of renal diseases.[62,63]

Autophagy sustains material functioning and homeostasis in animal cells.[64] Numerous mitochondrial phagocytic receptors, including the ATPase family with FUNDC1 structural domain, BCL2-interacting proteins 3 (BNIP3) and BNIP3-like (BNIP3L/NIX), prohibitin-2 (PHB2), and ATAD3B with a AAA structural domain, contribute to the degradation of damaged mitochondria.[65–70] Mitochondrial stress triggers phagocytosis through two primary pathways: the PTEN-induced kinase 1/parkin-dependent pathway and a receptor-mediated pathway.[65,71,72] All these receptors share the LIR motif, which collaborates with LC3 to enable mitochondrial phagocytosis.[73,74] These receptors are situated on

the outer mitochondrial membrane (FUNDC1, BNIP3, and BNIP3L/NIX) and the inner mitochondrial membrane (PHB2 and ATAD3B).[65,68] A recent study revealed that under inflammatory or oxidative stress, TFAM and mtDNA are expelled into the cytoplasm where TFAM facilitates the elimination of mtDNA as an autophagy receptor.[75] Historically, research on mtDNA degradation focused on its extraction from the mitochondrial matrix and the removal of binding proteins to the cytoplasm.[68,76,77] TREX1, a cytoplasmic 3′ DNA exonuclease, is recognized as a key mechanism for mtDNA degradation, preventing autoactivation of the cGAS-STING pathway by degrading extracellular mtDNA.[78,79] However, the resistance of oxidized DNA to TREX1-mediated degradation suggests alternative mechanisms may exist,[80] especially since oxidized mtDNA, unlike other TREX1-sensitive DNAs, can mislocalize and activate cGAS in the absence of TFAM, indicating a complex role for TREX1 overexpression in mitigating cytoplasmic mtDNA levels.

TFAM-mediated autophagy, akin to nucleophagy, involves TFAM acting as a selective autophagy receptor. It binds to LC3 and facilitates the transport of mitochondrial-secreted mtDNA to autophagic lysosomes for degradation. Notably, TFAM features two LC3-interacting region (LIR) motifs, with LIR2 playing a crucial role in the TFAM-LC3B interaction that promotes the breakdown of mtDNA protein complexes in autophagy lysosomes. This pathway serves as a cellular defense against the inflammatory effects triggered by mtDNA accumulation[75] (Figure 2). In DKD, mtDNA escapes from mitochondria into the cytoplasm where it can initiate inflammatory responses. Thus, removing cytoplasmic mtDNA is imperative. The elucidation of the TFAM-mediated autophagy pathway offers a promising therapeutic avenue for managing DKD.

TFAM Ameliorates DKD Mitochondrial Disorders by Regulating Ca^{2+}

Ca^{2+} signaling and fluxes regulate numerous cellular physiological processes, including neuronal excitability, muscle contraction, nuclear gene expression, and mitochondrial integrity, function, and dynamics.[81] Under basal conditions, mitochondrial Ca^{2+} content is low but increases in response to various stimuli such as nutrients, hormones, and neurotransmitters, elevating cytoplasmic free Ca^{2+} levels. Elevated mitochondrial Ca^{2+} levels enhance tricarboxylic acid (TCA) cycle dehydrogenase activity,[82,83] thereby boosting oxidative metabolism and increasing the supply of redox cofactors like NADH and FADH2 to drive the electron transport chain (ETC) and ATP synthesis. Under normal conditions, mitochondria receive metabolic state signals and use calcium ions to communicate with the nucleus or endoplasmic reticulum (ER) for appropriate cellular responses. Dysregulated calcium signaling in mitochondria or to the nucleus and ER can increase the risk of metabolic diseases, including insulin resistance and type 2 diabetes mellitus (T2DM).[84,85] Research has revealed that excessive activation of calcium ion channels in high-glucose environments can cause significant podocyte damage. Maintaining calcium ion balance within podocytes is essential for preserving their structure and function. Overactivation of SOCE and other Orai1-mediated channels can lead to calcium overload, triggering pathways such as the activation of the calcium-dependent protease calpain, which contributes to podocyte injury. This injury is characterized by cytoskeletal disarray and a decrease in podocyte marker proteins, including nephrin, ultimately compromising podocyte structure and function.[86] In addition, Chronic perturbation of Ca^{2+} flux in the ER is a key mediator of renal tissue damage, including in diabetic patients.[87–89]

Several studies have indicated that Ca^{2+} overload in T2DM model animals may be linked to mitochondria's inability to maintain intracellular Ca^{2+} homeostasis.[90,91] Mitochondrial regulation of Ca^{2+} homeostasis is directly tied to mitochondrial bioenergetics. Mitochondria cannot uptake Ca^{2+} efficiently when there is a deficiency in the mitochondrial membrane potential ($\Delta\Psi m$), and defects in the respiratory chain are associated with a reduced capacity to pump Ca^{2+}. The proton electrochemical gradient induced by $\Delta\Psi m$ and the pH gradient is essential for ATP production.[92] Hence, $\Delta\Psi m$ maintains mitochondrial Ca^{2+} uptake and physiological functions.[93,94] When $\Delta\Psi m$ is depolarized, mitochondrial Ca^{2+} uptake is inhibited, elevating cytoplasmic Ca^{2+} levels, leading to retrograde mitochondrial signaling into the nucleus and activating Ca^{2+}-mediated transcriptional mechanisms such as calmodulin neurophosphatase and Ca^{2+}/calmodulin-dependent protein kinase (CaMK).[93,94] Importantly, $\Delta\Psi m$ depolarization enhances ROS production.[95–97] However, overexpression of human TFAM (hTFAM) prevents $\Delta\Psi m$ depolarization and blocks ROS production.[43] Furthermore, hTFAM-induced mild $\Delta\Psi m$ uncoupling increases glucose uptake in skeletal muscle and ameliorates high-fat diet-induced insulin resistance.[43] In fact, TFAM-mediated regulation of $\Delta\Psi m$ prevents high-fat diet-induced oxidative stress and insulin resistance by enhancing cytosolic GLUT4, PGC-1α, and PPARδ expression. $\Delta\Psi m$ depolarization or mtDNA deletion inhibits mitochondrial Ca^{2+} uptake and raises cytoplasmic Ca^{2+} levels, leading to mitochondrial retrograde signaling into the nucleus, activating Ca^{2+}-mediated transcriptional mechanisms involved in

calmodulin neurophosphatase and CaMK.[93,94] Since TFAM deficiency can mediate Ca^{2+} overload in the cytoplasm, it induces retrograde signaling in the nucleus, increases ROS, and promotes apoptosis.[94] ROS produced by the lack of TFAM in cells may result from Ca^{2+} overload;[94] however, hTFAM overexpression reduces ROS and oxidative stress in tissues with mildly uncoupled ΔΨm.[43] Thus, TFAM may mediate mild uncoupling of ΔΨm, regulating retrograde Ca^{2+} signaling and tightly controlling cellular ROS (Figure 2).

On the other hand, TFAM regulates calcium ion flux via Na+/Ca^{2+} exchangers (NCLX). NCLX, located in the inner mitochondrial membrane (IMM), is crucial for controlling Ca^{2+} efflux from mitochondria and maintaining mitochondrial Ca^{2+} homeostasis. Its function can be modulated by the ΔΨm flux, which is regulated by TFAM. Consequently, TFAM-driven ΔΨm can relay Ca^{2+} signals to the nucleus through NCLX/voltage-dependent anion channels (VDAC). This signaling cascade enhances the phosphorylation of AMPK. AMPK serves as a central regulator of cellular energy metabolism. Its activation not only increases the expression of peroxisome proliferator-activated receptor delta (PPARδ), which facilitates glucose transport, but also stimulates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), driving mitochondrial biogenesis and enhancing energy metabolism. PGC-1α is a pivotal factor in mitochondrial biogenesis and metabolic regulation. It regulates the expression of nuclear respiratory factor 1 (NRF-1) and PPARδ, playing a critical role in energy metabolism and the prevention of metabolic diseases. NRF-1 can also bind to and activate the TFAM promoter, initiating TFAM transcription, with the newly synthesized TFAM returning to the mitochondria from the nucleus, thereby establishing a feedback loop.[84,98] Together, these effects underscore the vital role of calcium ions and TFAM in regulating energy balance and preventing metabolic disorders.

In summary, TFAM is involved in regulating Ca^{2+} fluxes through mitochondria-ER interactions, which signal to the nucleus and ultimately mitigate metabolic disturbances. Mitochondria interact with the ER to regulate cellular Ca^{2+} fluxes, affecting mitochondrial TCA cycling and oxidative phosphorylation. TFAM plays a crucial role in these processes, attenuating metabolic disturbances through its regulation of Ca^{2+} fluxes and mitochondrial-ER interactions.[84]

Conclusion and Perspectives

DKD remains a formidable challenge in diabetes management, owing to its intricate pathophysiology and substantial impact on global health. This review highlights the pivotal role of mitochondrial dysfunction in DKD progression. Characterized by compromised mitochondrial DNA integrity and altered mitochondrial dynamics, mitochondrial damage significantly affects renal pathology by undermining cellular energy metabolism and exacerbating oxidative stress. Our findings underscore the significance of mitochondrial health in maintaining renal function and propose that therapeutic approaches focused on preserving mitochondrial function may open new pathways for more effective DKD management.

One promising approach is the exploration of anti-microRNA strategies. MicroRNAs (miRNAs) are a class of small non-coding RNA molecules that primarily bind to target mRNAs, inhibiting their translation or promoting their degradation, thus reducing the expression levels of specific proteins. This presents exciting potential for preventing or reversing mitochondrial dysfunction by targeting specific microRNAs to regulate TFAM gene expression, alleviate mtDNA damage, enhance mitochondrial function, and reduce oxidative stress, thereby safeguarding mitochondrial integrity. Such strategies may play a crucial role in the treatment of DKD.[99,100]

In summary, future research should prioritize the therapeutic applications of TFAM and related mitochondrial interventions, with an emphasis on translating these findings into clinical practice. For example, large-scale clinical sample analyses could assess the effectiveness of specific TFAMs as biomarkers, validating their use in early diagnosis, prognosis assessment, and monitoring treatment responses in DKD. Additionally, pharmacological experiments should be conducted to evaluate the safety and efficacy of TFAM-related therapies, potentially incorporating miRNA inhibitors for treatment. This approach could significantly deepen our understanding of mitochondrial function in DKD, providing new hope for effective treatments that address the root causes of these diseases.

Abbreviations

ACE, Angiotensin-Converting Enzyme; ATP, Adenosine Triphosphate; DKD, Diabetic Kidney Disease; DRP1, Dynamin-Related Protein 1; ETC - Electron Transport Chain; MFN1, Mitofusin 1; MFN2, Mitofusin 2; MMP, Mitochondrial Membrane Potential; mtDNA, Mitochondrial DNA; OPA1, Optic Atrophy 1; PINK1, PTEN Induced Putative Kinase 1; ROS, Reactive

Oxygen Species; SGLT2, Sodium-Glucose Transport Protein 2; TCA, Tricarboxylic Acid; TFAM, Transcription Factor A, Mitochondrial; TFB1M, Transcription Factor B1, Mitochondrial.

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Disclosure

The authors report no conflicts of interest in this work.

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