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Unraveling Diabetic Kidney Disease: The Roles of Mitochondrial Dysfunction and Immunometabolism

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Mitochondria are essential for cellular energy production and are implicated in numerous diseases, including diabetic kidney disease (DKD). Current evidence indicates that mitochondrial dysfunction results in alterations in several metabolic pathways within kidney cells, thereby contributing to the progression of DKD. Furthermore, mitochondrial dysfunction can engender an inflammatory milieu, leading to the activation and recruitment of immune cells to the kidney tissue, potentially perturbing intrarenal metabolism. In addition, this inflammatory microenvironment has the potential to modify immune cell metabolism, which may further accentuate the immune-mediated kidney injury. This understanding has led to the emerging field of immunometabolism, which views DKD as not just a metabolic disorder caused by hyperglycemia but also one with significant immune contributions. Targeting mitochondrial function and immunometabolism may offer protective effects for the kidneys, complementing current therapies and potentially mitigating the risk of DKD progression. This comprehensive review examines the impact of mitochondrial dysfunction and the potential role of immunometabolism in DKD. We also discuss tools for investigating these mechanisms and propose avenues for integrating this research with existing therapies. These insights underscore the modulation of mitochondrial function and immunometabolism as a critical strategy for decelerating DKD progression.

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DKD significantly contributes to the global burden of chronic kidney disease, affecting approximately 30% of individuals with type 1 diabetes (T1D) and 40% of those with type 2 diabetes (T2D).[1,2] This condition can lead to kidney failure treated with dialysis or kidney transplantation, and markedly increases risks of cardiovascular disease and mortality.[3,4] Current evidence suggests that DKD is initiated by diabetes-induced disturbances in glucose metabolism, which subsequently activate a cascade of metabolic, hemodynamic, inflammatory, and fibrotic pathways driving disease progression.[5] Notably, achieving glycemic control alone is insufficient to completely halt the progression of DKD.[6] Despite the introduction of novel therapeutic agents, the primary goal of current clinical management of DKD is to reduce decline of kidney function rather than arrest it, leaving a significant residual risk for progression to kidney failure.[7] This limited therapeutic efficacy underscores the significant gaps in our understanding of the pathophysiological

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mechanisms underpinning DKD, highlighting the urgent need for more detailed mechanistic studies to guide the development of more effective therapeutic interventions.

This review aims to synthesize the current understanding of mitochondrial activity and metabolism, as well as the role of immunometabolism in the initiation and progression of DKD. By integrating these insights, we seek to provide a robust foundation for the development of more efficacious therapeutic strategies.

Energy Production in the Kidneys

The kidneys, as the second most oxygen-consuming organs at rest per gram of tissue, require substantial energy for their physiological functions.[8] This energy is primarily generated in mitochondria through oxidative phosphorylation (OXPHOS) by metabolizing various substrates, including glucose, fatty acids, amino acids, ketones, and lactate, which differ by kidney segment.[9] Each substrate follows a distinct metabolic pathway, with glucose undergoing glycolysis, amino acids undergoing transamination or deamination, and fatty acids undergoing beta-oxidation (FAO). These processes produce acetyl-CoA, which subsequently enters the tricarboxylic acid (TCA) or Krebs cycle to generate adenosine triphosphate (ATP). OXPHOS involves 5 inner membrane-bound protein complexes (I–V) comprising the electron transport chain,[10] where electrons carried by NADH and FADH2, intermediates from the TCA cycle and beta-oxidation, are transferred through complexes I to IV, creating a gradient used by complex V (ATP synthase) to synthesize ATP.[11]

Kidney cells exhibit distinct metabolic preferences tailored to their specific energy requirements. Glomerular endothelial cells, mesangial cells, and podocytes predominantly rely on glucose oxidation via glycolysis and OXPHOS.[12-15] Conversely, proximal tubular cells (PTCs), characterized by high energy demands, primarily utilize FAO due to its superior ATP yield.[15,16] In DKD, especially in PTCs, these metabolic processes undergo significant changes from their normal states, a phenomenon known as metabolic reprogramming. In Figure 1, we demonstrate energy production in the kidneys and the metabolic reprogramming of various kidney cells in the diabetes milieu.

Mechanism in DKD

Progression of Perturbation in TCA Cycle and OXPHOS Across the Course of DKD

Mitochondrial dysfunction in diabetes is multifaceted, characterized by reduced ATP production, decreased mitochondrial membrane potential, altered morphology toward a spherical shape, and increased mitochondrial reactive oxygen species (ROS). These changes are driven by hyperglycemia-induced stress, oxidative damage, and altered mitochondrial dynamics, significantly impacting kidney structure and function.[17-19]

In diabetes, particularly the upregulation of sodium-glucose cotransporter-2 (SGLT2) alters kidney glucose handling and leads to excessive glucose reabsorption and disruption of tubuloglomerular feedback, causing glomerular hyperfiltration, an early hallmark of DKD.[20] This process heightens kidney metabolism, leading to an increase in the TCA cycle, which in turn elevates NADH and FADH2 levels, driving increased OXPHOS, oxygen consumption, and ATP production to meet the higher energy demand.[21] Consistent with these processes, previous studies have demonstrated that the oxygen consumption rate, an indicator of overall mitochondrial fitness, is increased in the renal cortex and PTCs.[22,23] In addition, transcriptomic and metabolomic analyses from murine models of diabetes have shown the upregulation of the TCA cycle.[24] As DKD progresses, OXPHOS and TCA cycle activities decline, as demonstrated by reduced electron transport chain complex I, III, and IV activities.[25-27] This decline is also evidenced by the progressive reduction of urinary TCA cycle intermediates observed during follow-up with patients with DKD, despite elevated levels at baseline.[24] Alongside the disruptions in OXPHOS and the TCA cycle, there is a compensatory increase in aerobic glycolysis, commonly referred to as the Warburg effect.[28] This metabolic shift accelerates energy production to offset the deficits in OXPHOS and TCA cycle activities.[29] Consistent with this phenomenon, transcriptomic, metabolomic, and flux analyses by Sas *et al.*[24] revealed significantly elevated levels of key glycolytic enzyme transcripts, such as hexokinase, phosphofructokinase, and pyruvate kinase, accompanied by a marked decline in mitochondrial function in a T2D mouse model. Although considerable evidence exists regarding alterations in the TCA cycle, OXPHOS, and glycolysis, most of it is derived from murine models. Evidence from human studies remains limited and warrants further investigation. In Figure 2, we demonstrate alterations in the TCA cycle and OXPHOS throughout the course of DKD.

Adaptation and Perturbation in the TCA Cycle and OXPHOS (Causes vs. Contributors)

Disruptions in the TCA cycle and OXPHOS within PTCs are fundamental to the pathogenesis of DKD. These disruptions impair energy production and increase oxidative stress, contributing to cellular dysfunction and injury.[21] These metabolic disturbances are precipitated by several interrelated factors, including hyperglycemia, lipid metabolism

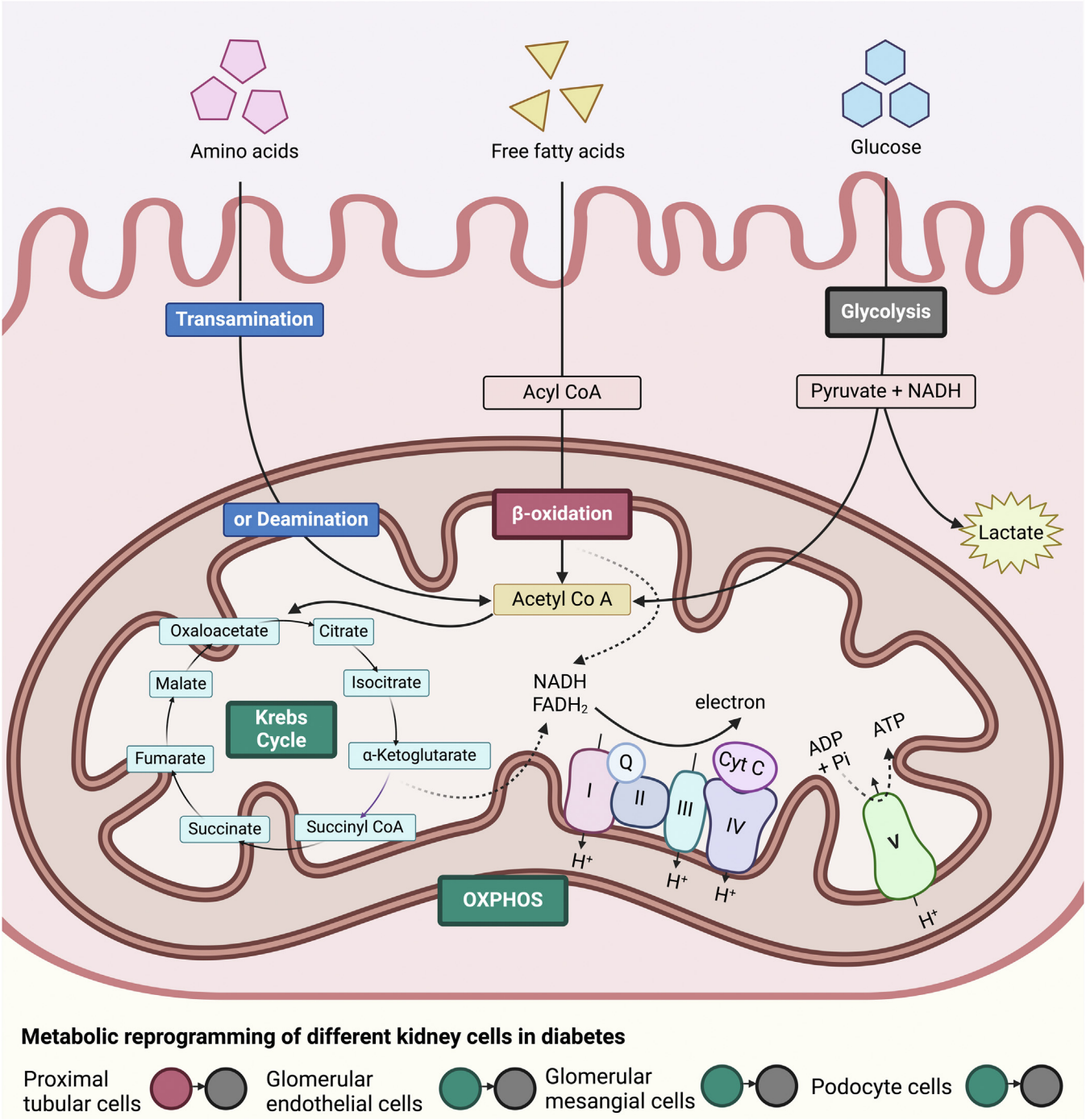

Figure 1. Energy production and metabolic reprogramming in kidney cells in diabetes. The kidneys, highly oxygen-consuming organs, generate energy primarily through OXPHOS in mitochondria by metabolizing glucose, fatty acids, and amino acids. Glucose undergoes glycolysis, amino acids undergo transamination or deamination, and fatty acids undergo beta-oxidation, producing acetyl-CoA, which enters the TCA cycle to generate ATP. OXPHOS involves the electron transport chain, where electrons from NADH and FADH2 are transferred through complexes I to IV, creating a gradient used by complex V (ATP synthase) to synthesize ATP. Glomerular endothelial cells, mesangial cells, and podocytes rely on glucose oxidation via glycolysis and OXPHOS, whereas PTCs primarily utilize FAO. In DKD, these metabolic processes undergo reprogramming, shifting to glycolysis. ATP, adenosine triphosphate; Cyt C, cytochrome C; DKD, diabetic kidney disease; FAO, fatty acids undergoing beta-oxidation; OXPHOS, oxidative phosphorylation; PTC, proximal tubular cells; TCA, tricarboxylic acid.

dysregulation, chronic hypoxia, and genetic predisposition.[21,30] Hyperglycemia, a hallmark of diabetes, leads to an excessive influx of glucose into the kidney, particularly PTCs. This shift causes metabolic reprogramming from the TCA cycle and OXPHOS to glycolysis and is hypothesized to result from increased fructose production mediated by aldose reductase, which converts glucose to fructose.[31,32] The fructose is subsequently metabolized by fructokinase to generate fructose 1-phosphate. Concurrently, fructose

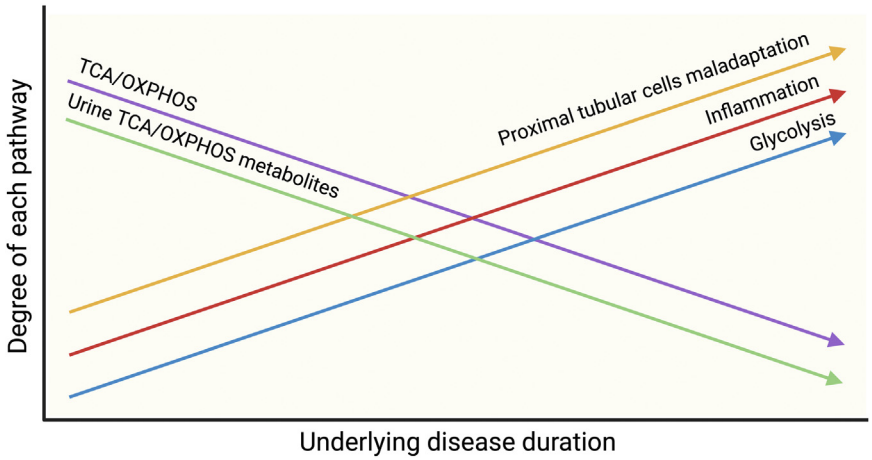

Figure 2. Adaptation and perturbation in TCA cycle and OXPHOS pathways in DKD. The figure illustrates the dynamic changes in various metabolic pathways and cellular response throughout duration of DKD. The decline in TCA/OXPHOS pathways (purple line) indicates the diminishing efficiency of mitochondrial OXPHOS and the associated energy production impairments. Urine TCA/OXPHOS metabolite levels (green line) change in the same direction as the degree of TCA/OXPHOS, implying potential biomarkers of TCA/OXPHOS efficacy. PTCs maladaptation (yellow line) increases as the disease progresses, reflecting cellular dysfunction due to prolonged metabolic stress. Inflammation (red line) and glycolysis (blue line) show a gradual rise, signifying the shift from metabolic reprogramming and the chronic inflammatory state that accompanies DKD progression. DKD, diabetic kidney disease; OXPHOS, oxidative phosphorylation; PTC, proximal tubular cells; TCA, tricarboxylic acid.

metabolism produces uric acid, which inhibits aconitase, redirecting fructose 1-phosphate from the TCA cycle to glycolysis and culminating in lactate production.[33] Evidence from Akita-ReninTG mice, which phenotypically resemble human DKD, shows increased expression of lactate dehydrogenase A, the enzyme responsible for converting pyruvate to lactate in PTCs, supporting an increase in glycolytic flux.[29] Lipid metabolism dysregulation in DKD is marked by enhanced fatty acid absorption coupled with impaired fatty acid utilization, leading to lipid accumulation.[15,34] This pathological process is substantiated by the upregulation of CD36, a cell surface receptor and transporter protein involved in fatty acid uptake, and the activation of hypoxia-inducible factor 1-alpha.[35] The activation of hypoxia-inducible factor 1-alpha subsequently inhibits peroxisome proliferator-activated receptor alpha, thereby attenuating FAO.[36,37] Consequently, these metabolic perturbations shift the metabolic profile of PTC from FAO to glycolysis.[24,38] The increase in glycolytic flux, driven by both glucose and lipid metabolism, leads to the production of ROS, further impairing mitochondrial function. In addition, the intracellular accumulation of glucose and lipid intermediates suppresses adenosine monophosphate-activated protein kinase and activates the mechanistic target of rapamycin complex 1.[26,39] These changes in metabolic regulation can cause chronic impairment of TCA cycle turnover and OXPHOS, culminating in kidney injury.[40-50]

Chronic hypoxia, a persistent state of low oxygen levels in tissues, is increasingly recognized as a crucial factor in the progression of DKD.[51] The hypoxic milieu within the kidney microenvironment results from a disparity between oxygen delivery, which is attributable to compromised renal blood flow and elevated oxygen demands.[52] This disequilibrium detrimentally affects the electron transport chain, precipitating a shift from OXPHOS to glycolysis. The interplay between chronic hypoxia and mitochondrial dysfunction exacerbates kidney fibrosis and inflammation, thereby undermining the overall energy capacity of kidney cells. Furthermore, genetic predispositions can heighten the risk of mitochondrial dysfunction, thereby augmenting susceptibility to metabolic perturbations under diabetic conditions.[21] Data from patients with T1D demonstrate that specific single nucleotide polymorphisms in nuclear genes that influence mitochondrial function are associated with an increased risk of DKD.[53]

Whereas the primary causes of mitochondrial dysfunction set the stage for metabolic perturbations, several secondary factors exacerbate these disruptions, worsening the condition. Oxidative stress is a significant contributor, where elevated ROS levels derived from both mitochondrial and extramitochondrial sources, further damage mitochondrial DNA, proteins, and lipids, resulting in impairment of both the TCA cycle and OXPHOS.[21] Chronic inflammation, driven by proinflammatory cytokines such as tumor necrosis factor-alpha and IL-6, exacerbates mitochondrial dysfunction.[54] An increase of mitochondrial fission and a concordant reduction of fusion leads to fragmented and inefficient mitochondria.[18] The impairment in the

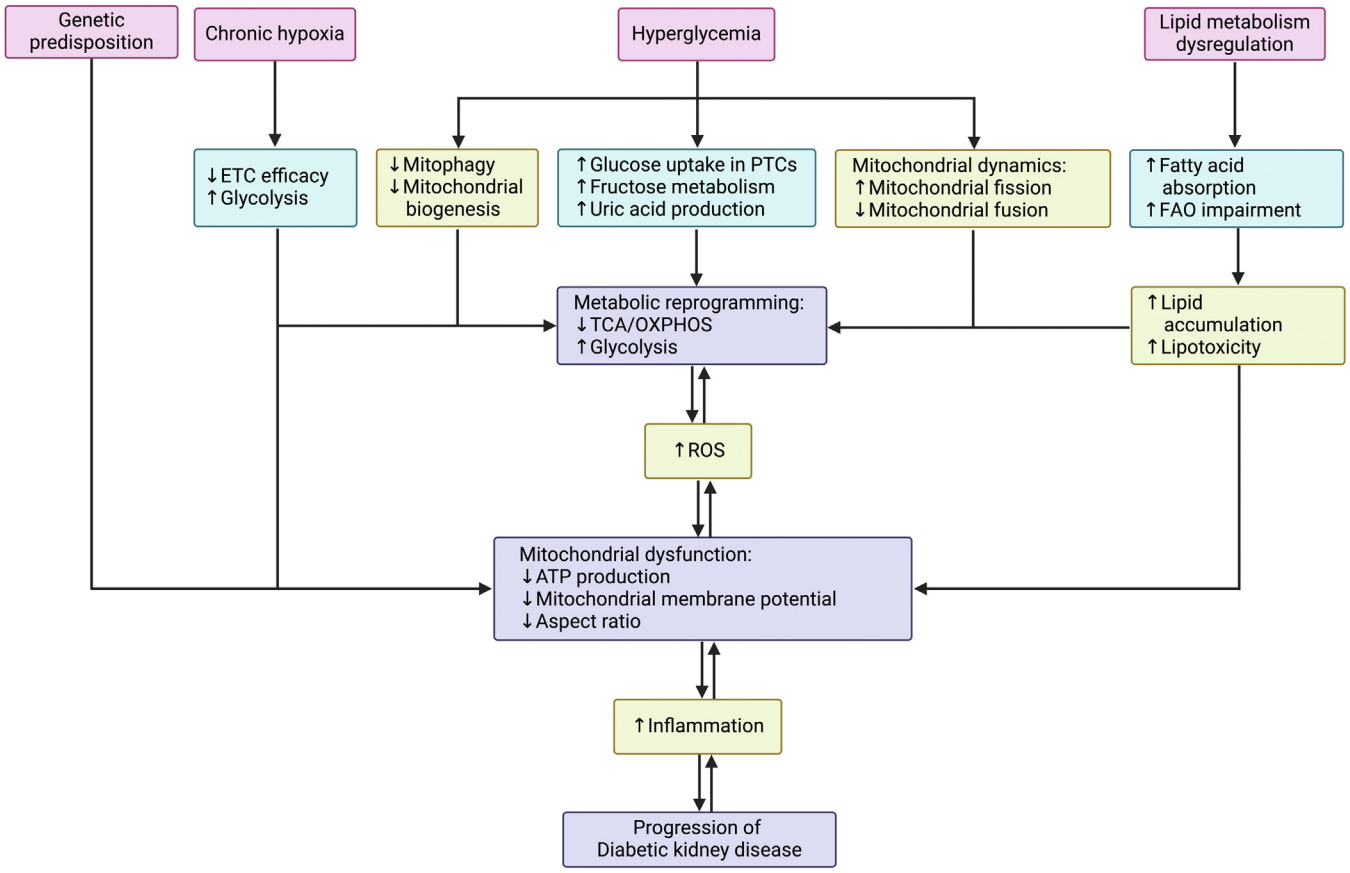

Figure 3. Causes and contributors to adaptation and perturbation in the TCA cycle and OXPHOS, as well as mitochondrial dysfunction in DKD. Adaptations and perturbations within the TCA cycle and OXPHOS are central to the pathogenesis of DKD. Critical factors such as hyperglycemia, lipid metabolism dysregulation, genetic predisposition, and chronic hypoxia converge to disrupt these metabolic pathways, leading to metabolic reprogramming. These metabolic disturbances result in elevated production of ROS, exacerbating mitochondrial dysfunction. This mitochondrial impairment drives inflammation and further metabolic reprogramming, creating a vicious cycle of cellular damage. The interrelated nature of these pathways underscores the complexity of DKD progression, where disruptions in one domain can amplify dysfunction in another, thereby perpetuating kidney injury. DKD, diabetic kidney disease; ETC, electron transport chain; PTC, proximal tubular cells; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TCA, tricarboxylic acid.

targeted breakdown of damaged mitochondria leads to the buildup of dysfunctional mitochondria.[18] Similarly, the downregulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha, results in reduced production of new mitochondria, thereby exacerbating the decline in mitochondrial function.[55] In Figure 3, we illustrate the causes and contributors to adaptation and perturbation in the TCA cycle and OXPHOS, as well as mitochondrial dysfunction in DKD.

The Role of Immune Metabolism in DKD Pathogenesis

Emerging evidence highlights that metabolic pathways significantly influence immune cell behavior, and the converse is also true. This bidirectional interaction has given rise to the research field known as immunometabolism. Traditionally, DKD has been viewed as a nonimmune, metabolic, or hemodynamic glomerular disorder driven primarily by hyperglycemia. However, recent studies have pointed to the involvement of immune cells in DKD. For example, certain white blood cell fractions correlate with DKD lesions and predict the loss of kidney function in T2D.[56] In addition, recent research demonstrates that the pathogenesis and progression of DKD are intricately connected with altered immunometabolism, involving both innate and adaptive immunity.[57]

It has been reported that macrophages, key players in the innate immune system, infiltrate the kidneys in DKD, contributing to kidney injury and serving as significant predictors of declining kidney function.[58–62] In streptozotocin-induced T1D rat models, the quantity of interstitial macrophages is directly proportional to the severity of proteinuria.[60,63] Recent advancements in transcriptomic analysis have significantly deepened our understanding of macrophage populations.[64,65] This technology enables a more detailed exploration beyond the traditional M1 (proinflammatory) and M2 (anti-inflammatory) classifications, which relied on only a few biomarkers.[66] Among the identified macrophage

subsets, TREM2-high macrophages are particularly noteworthy for their protective role against kidney injury.[67] These macrophages exhibit an expansion in DKD in both high fat diet-fed murine models and in patients with obesity and diabetes.[67] Notably, this subset is characterized by increased expression of lipid-associated genes, highlighting the dysregulated lipid metabolism in the kidneys that may drive this macrophage phenotype.[67]

In the adaptive immune system, accumulation of various T cell subtypes may be key players for the underlying mechanism related to DKD progression. A previous study indicated a notable increase in both glomerular and interstitial T cells in diabetic mice compared to nondiabetic controls.[63] In streptozotocin-induced diabetic RAG1 knockout mice, which have mature T and B cell deficiencies, the absence of lymphocytes was associated with preserved podocytes and reduced albuminuria.[68] In patients with T1D, higher levels of circulating activated T cells are observed in those with proteinuria relative to those without proteinuria.[69,70] Furthermore, there is a correlation between T cell accumulation and increased albumin excretion rates.[70] Recent findings suggest that the presence of CD4 + T cells in the kidney interstitium of patients with T2D is associated with the severity of proteinuria.[71] These findings collectively suggest that immune cells, particularly macrophages and T cells, play a significant role in the pathogenesis of DKD.

The pathophysiological mechanism linking immune cells to DKD is characterized by the upregulation of immune adhesive molecules and alterations in immunometabolism. In DKD, metabolic reprogramming shifts cellular energy production from OXPHOS to glycolysis, resulting in increased lactate production.[72] This metabolic shift impairs the efficiency of OXPHOS, exacerbating mitochondrial dysfunction and inflammation.[72] Consequently, these processes lead to an increased expression of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1.[73] These surface glycoproteins are present primarily in the endothelium and in various kidney structures, including the glomeruli, interstitium, and PTCs.[74] The upregulation of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 facilitates the adhesion of lymphocytes and macrophages. In T2D mouse model, genetic deficiency of intercellular adhesion molecule 1 or the pharmaceutical blockade of the interaction between intercellular adhesion molecule 1 on glomerular endothelial cells and lymphocyte function-associated antigen 1 on monocytes results in reduced monocyte recruitment and macrophage accumulation within the glomeruli and improved kidney disease.[75,76] Concurrently, high blood glucose levels and the presence of advanced glycation end products cause kidney cell injury, leading to the production of proinflammatory cytokines and chemokines such as tumor necrosis factor-alpha and monocyte chemoattractant protein-1.[73] The synergistic elevation of immune chemoattractants and adhesion molecules facilitates the activation and subsequent infiltration of immune cells into the kidney, potentially driving the transition of particularly PTCs from adaptive to maladaptive states. This transition leads to disrupted intrarenal metabolism, thereby further exacerbating metabolic reprogramming. Simultaneously, the altered kidney microenvironment, characterized by increased glucose flux, may modulate immune cell metabolism by shifting from OXPHOS toward glycolysis.[77] This shift occurs because activated immune cells are inherently glycolytic and express elevated levels of facilitative glucose transporters.[78,79] These metabolic alterations may exacerbate immune-mediated kidney injury, perpetuating a vicious cycle that maintains the glycolytic preference in kidney cells. Collectively, metabolic reprogramming and altered immunometabolism are likely to contribute to the accelerated progression of DKD. In Figure 4, we demonstrate the interplay between mitochondrial dysfunction and immunometabolism in DKD.

Investigation of Metabolic Reprogramming and Mitochondrial Dysfunction in DKD

Despite the limited evidence on the perturbation of mitochondrial function and immunometabolism in diabetes in humans, recent advancements in investigative techniques are promising. The use of multiomics approaches, advanced imaging, metabolic flux analysis, and mitochondrial morphometrics and functional assessment are providing nuanced insights into the connections between mitochondrial activity, metabolic alterations, and immunometabolism in DKD.

Multiomics Approaches

The kidney's complex cellular architecture comprises over 40 distinct cell types.[80] Understanding this composition and its role in normal and abnormal kidney function is crucial. Multiomics technologies facilitate comprehensive analyses of mitochondrial function and identification of biomarkers indicative of dysfunction. High-throughput genomics methods, including whole-genome, single-cell, and single-nuclear RNA sequencing, uncover gene expression at the single-cell level, highlighting cellular heterogeneity and the specific roles of kidney and immune cells in DKD.[67,81] Both single-cell RNA sequencing and single-nuclear RNA sequencing can identify various genes involved in regulatory networks, reveal the heterogeneity of kidney mitochondrial damage, facilitate

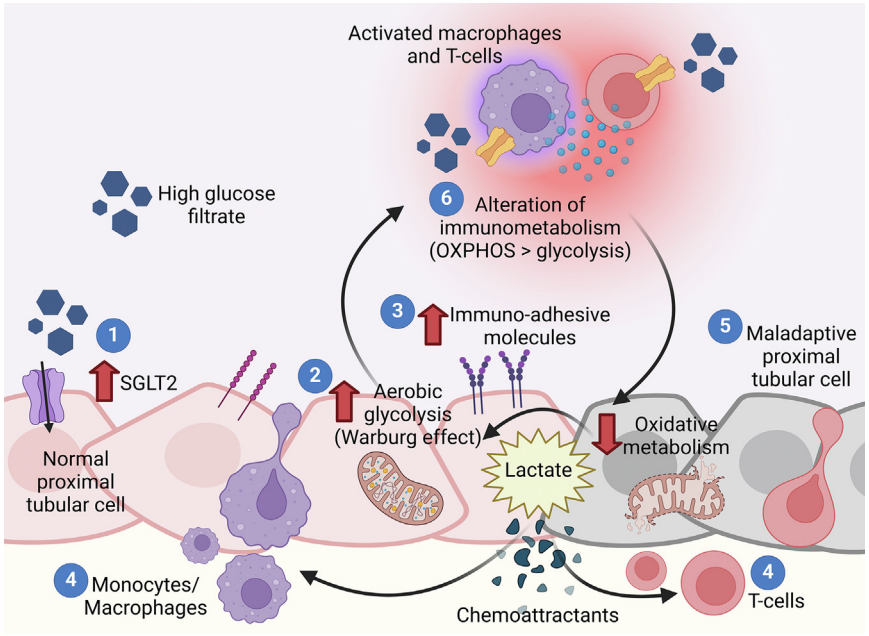

Figure 4. Interplay between mitochondrial dysfunction and immunometabolism in DKD. (1) Hyperglycemia increases glucose reabsorption in the kidney filtrate via SGLT2 transporters. (2) This glucose uptake shift induces metabolic reprogramming in PTCs toward aerobic glycolysis (Warburg effect) for energy production. (3) Elevated glycolysis results in increased lactate production and kidney cell injury, which upregulates immune-adhesive molecules and chemoattractants. (4) The rise in chemoattractants and adhesion molecules promotes the activation and infiltration of immune cells, particularly macrophages and T cells, into the kidney. (5) Activated macrophages and T cells drive PTCs from an adaptive to a maladaptive state, further disrupting intrarenal metabolism and reinforcing glycolytic reprogramming. (6) The inflammatory kidney microenvironment and elevated glucose flux modulate immune cell metabolism, shifting from OXPHOS to glycolysis, leading to more activated immune cells. These metabolic alterations exacerbate immune-mediated kidney injury, perpetuating a vicious cycle that maintains the glycolytic preference in kidney cells. DKD, diabetic kidney disease; OXPHOS, oxidative phosphorylation; PTC, proximal tubular cells; SGLT2, sodium-glucose cotransporter-2; TCA, tricarboxylic acid.

extensive cell type discovery, and identify both adaptive and maladaptive states within each cell type.[81,82] Integrating these techniques with advanced bioinformatics analyses such as conducting trajectory analyses of specific genes in different cell types or states can significantly enhance our understanding of the temporal mapping of perturbations in metabolic reprogramming across various cell types in the context of DKD.[83]

Epigenetic and epitranscriptomic modifications introduce complexity to the elucidation of mitochondrial involvement in DKD by regulating gene expression.[84–86] Both modifications are crucial in DKD pathogenesis, and are influenced by environmental and metabolic factors.[87] Swan *et al.*[88] demonstrated that distinct methylation patterns in genes affecting mitochondrial function are associated with kidney disease in patients with T1D, emphasizing the critical impact of epigenetic changes on mitochondrial function and DKD progression. Tischner *et al.*[89] reported that perturbations in tRNA modifications affecting mitochondrial-encoded proteins can cause tissue-specific abnormalities in OXPHOS complexes, impairing mitochondrial function, particularly in high energy-demand tissues, suggesting the necessity for further investigation in the kidney. Integrating epigenetic and epitranscriptomic data with other multiomics datasets potentially enhance our understanding of their influence on mitochondrial function and metabolic reprogramming in DKD.

Proteomics and metabolomics offer significant benefits in studying mitochondrial function, OXPHOS, and the TCA cycle in DKD. Utilizing mass spectrometry, proteomics enables the comprehensive quantification and identification of mitochondrial proteins, providing insights into the complex protein networks that regulate mitochondrial function. This approach allows for precise measurement of protein abundance and post-translational modifications, which are critical for understanding how proteins involved in OXPHOS, and the TCA cycle are altered in DKD. For example, Mise K. *et al.*[90] identified NDUFS4, a subunit of electron transport chain complex I, through proteomic profiling in diabetic podocytes, demonstrating its role in mitochondrial function. Metabolomics, involving the comprehensive analysis of metabolites within a biological system, offers a detailed view of the metabolic alterations associated with DKD. This technique can identify changes in the levels of metabolites involved in mitochondrial function, revealing how metabolic

pathways are reprogrammed in response to diabetic stress.[91]

Spatial transcriptomics, proteomics, and metabolomics represent advanced methodologies. These techniques offer a comprehensive understanding of tissue-specific processes, revealing the spatial organization and interactions of cells within their native environments. Spatial omics approaches can elucidate the heterogeneity of cell populations and their metabolic states in DKD, providing insights into how different regions of the kidney are differentially affected by the disease, offering a comprehensive understanding of tissue-specific processes.[92]

Advanced Imaging: Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) Imaging

MRI has become instrumental in advancing our understanding of mitochondrial function and the pathophysiology of DKD.[93] Techniques such as blood oxygen level-dependent MRI measure tissue oxygenation by assessing deoxyhemoglobin's paramagnetic properties, enabling precise evaluation of kidney hypoxia linked to mitochondrial dysfunction. Diffusion-weighted imaging MRI evaluates kidney microstructures and fibrosis levels by analyzing the movement of water molecules.[94] Multiparametric MRI combines various techniques, including blood oxygen level-dependent MRI, diffusion-weighted imaging MRI, and T1/T2 mapping, within a single session for comprehensive insights into kidney function, perfusion, and metabolic status.[95] However, MRI's sensitivity to detect cellular metabolic changes is limited, often providing indirect assessments and requiring sophisticated equipment and expertise, making it costly and technically demanding.

PET imaging, in contrast, utilizes radiolabeled tracers to directly visualize and quantify metabolic processes with high sensitivity.[96,97] PET is particularly useful for studying mitochondrial function and metabolic state of kidney tissues, because it delivers detailed information on processes such as glucose metabolism, FAO, and amino acid utilization. For example,[18] F-fluorodeoxyglucose is utilized to highlight glucose metabolism pathways,[98] and ^{11}C-acetate is utilized to assess kidney oxygen consumption.[99] These tracers allow for detailed visualization and quantification of various metabolic and functional alterations in the kidneys, making them invaluable in studying conditions such as DKD. Despite its benefits, PET imaging has limitations such as nonspecific uptake, short tracer half-lives requiring onsite cyclotrons, and radiation exposure, which must be considered in study design and interpretation.[97,100] Collectively, the integration of MRI and PET imaging harnesses the complementary strengths of both modalities. Further research incorporating both MRI and PET imaging is warranted to advance our understanding of DKD mechanisms.

Flux Study

Metabolic flux analysis is a complementary technique that enhances our understanding of mitochondrial function in DKD. By tracing the pathways of metabolites through metabolic networks, flux analysis provides detailed information on the rates of metabolic reactions. This approach elucidates how alterations in the TCA cycle and OXPHOS impact overall cellular metabolism.[101]

Positional isotopomer nuclear magnetic resonance tracer analysis represents a cutting-edge, noninvasive method for assessing mitochondrial function by analyzing plasma following labeled substrates infusion.[102] This technique has been validated in both rodent models and humans, demonstrating its capability to measure mitochondrial fluxes accurately. Notably, positional isotopomer nuclear magnetic resonance tracer analysis has shown excellent correlation with traditional *ex vivo* nuclear magnetic resonance methods, establishing it as a reliable measure of hepatic mitochondrial fluxes across various physiological and pathological states.[102]

Proton and phosphorus (^{1}H and ^{31}P) magnetic resonance spectroscopy also makes substantial contributions to flux studies by enabling *in vivo* assessment of metabolic fluxes.[103,104] Magnetic resonance spectroscopy can directly measure the rates of OXPHOS and TCA cycle activity in tissues such as the liver and muscle.[105,106] Previous studies have leveraged magnetic resonance spectroscopy to gain critical insights into mitochondrial dysfunction in metabolic diseases, highlighting its utility in noninvasively tracking metabolic changes and offering real-time insights into mitochondrial function.[107] Although evidence specifically utilizing positional isotopomer nuclear magnetic resonance tracer analysis and magnetic resonance spectroscopy in DKD remains limited, the potential of these advanced techniques is considerable. They may provide a nuanced understanding of the metabolic reprogramming in DKD, allowing precise quantification of metabolic fluxes and identification of potential therapeutic targets. Ultimately, these methodologies hold promise for improving patient outcomes by addressing kidney mitochondrial damage and metabolic dysregulation inherent in diabetic conditions.

Mitochondrial Morphometrics and Functional Assessment

Investigating mitochondrial morphology and function is pivotal in elucidating their role in DKD. Assessing

mitochondrial size, shape, and quantity uncovers significant structural alterations associated with DKD.[106,108] Advanced imaging modalities, such as electron microscopy and super-resolution microscopy, enable the precise measurement of these morphometric changes. The integration of expansion microscopy with lattice light sheet microscopy further enhances these techniques, permitting high resolution imaging of mitochondrial structures within intact cells and tissues.[109,110]

To evaluate mitochondrial function, various techniques are employed. Fluorescent probes and genetically encoded sensors are extensively utilized to measure mitochondrial membrane potential, ATP production, and ROS levels. Genetically encoded indicators such as A-team facilitate real-time imaging of ATP levels within mitochondria, whereas probes such as TMRM and JC-1 assess mitochondrial membrane potential.[108,111-113] Recent advancements in imaging techniques, including super-resolution microscopy, provide detailed visualization of mitochondrial ultrastructure and dynamics.[108] These methodologies correlate structural abnormalities with functional impairments, offering a holistic view of mitochondrial health and function.[108] Furthermore, fluorescent sensors and techniques such as Förster resonance energy transfer offer in-depth insights into mitochondrial signaling.[114] Live-cell imaging with fluorescently tagged mitochondrial proteins allows for real-time observation of mitochondrial dynamics, encompassing fission, fusion, and mitophagy.

Integrating structural and functional assessments is indispensable for comprehending the pathophysiology of DKD. These evaluations elucidate how mitochondrial dysfunction contributes to cellular energy deficits and kidney injury in patients with diabetes, aiding in potentially identifying therapeutic targets and improving clinical outcomes in DKD.

Therapeutic Interventions Targeting Mitochondrial Function

Non-Pharmacological Therapy: Lifestyle Modification

Lifestyle modifications, including exercise and weight control, are pivotal for improving mitochondrial function and metabolic health in DKD. Recent studies have found that exercise can activate peroxisome proliferator-activated receptor gamma coactivator 1-alpha in skeletal muscle cells, which can stimulate adenosine monophosphate-activated protein kinase signaling, and subsequently reduces nuclear factor kappa B in the kidney.[115] This leads to improved mitochondrial function, resulting in reduced albuminuria, glomerular hypertrophy, and kidney inflammatory markers in aerobic exercise DKD rat models.[115] Moreover, exercise has shown benefits for kidney function in T2D db/db mice, demonstrating that exercise can lower serum creatinine levels, through the improvement of mitochondria function as evidenced by increased citrate synthase and mitochondrial complex I activity.[25]

Weight reduction is crucial because obesity is a major DKD risk factor. Studies on murine models of DKD and metabolic syndrome have demonstrated that mitochondrial dysfunction plays a critical role in obesity-related kidney injury.[116,117] Although the mechanisms by which weight reduction affects kidney function are not fully understood, weight loss is believed to improve kidney outcomes, including reducing proteinuria,[118] potentially through the modulation of mitochondrial function.

Despite the potential benefits of lifestyle modifications on mitochondrial function, the multifactorial nature of DKD's initiation and progression requires a more comprehensive approach.

Pharmacological Therapies

Recent pharmacological treatments for diabetes are designed to offer pleiotropic effects, extending beyond glycemic control to address diabetic complications comprehensively. Agents such as metformin and simvastatin may influence mitochondrial function; however, their specific impact on kidney mitochondrial function and clinical kidney outcomes remain controversial.[119-121] Conversely, therapies such as renin-angiotensin-aldosterone system inhibitors, SGLT2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and nonsteroidal mineralocorticoid receptor antagonists have shown significant benefits in DKD in numerous clinical trials.[122-128] Nonetheless, the precise mechanisms, particularly their effects on mitochondrial function and immunometabolism in DKD, are still not fully understood.

Renin-Angiotensin-Aldosterone System Inhibitors. Renin-angiotensin-aldosterone system modulation is essential for DKD treatment due to its renoprotective effects.[124,125] Both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have shown clinical benefits in DKD; however, the molecular mechanisms affecting mitochondrial function remain limited.[129] Studies in diabetic murine models suggest that angiotensin-converting enzyme inhibitors may offer more kidney benefits than angiotensin II receptor blockers.[130] This advantage is potentially linked to angiotensin-converting enzyme inhibitors modulation of the endogenous tetrapeptide *N*-acetylserinyl-aspartyl-lysinyl-proline, which can restore metabolic

reprogramming by modulating the SIRT3 protein, mitochondrial FAO, and suppressing abnormal glucose metabolism.[130] These findings indicate a possible distinct advantage of angiotensin-converting enzyme inhibitors in influencing mitochondrial function and metabolic pathways in DKD.

SGLT2i. SGLT2i exhibit renoprotective effects in both DKD and non-DKD through receptor-dependent and independent mechanisms.[122,123] Single-cell RNA sequencing of kidney biopsies of patients with youth-onset T2D in early DKD stages reveals that SGLT2i treatment induces significant transcriptional changes across nearly all kidney tubular segments.[131] In PTCs, SGLT2i treatment suppresses elevated transcriptional profiles associated with glycolysis, gluconeogenesis, the TCA cycle, FAO, and glutathione conjugation, thereby shifting these profiles toward healthy controls. These effects are notably associated with the reduction of mechanistic target of rapamycin complex 1 signaling.[131] These findings, consistent with murine models, suggest that SGLT2i may decrease trans-epithelial glucose uptake, leading to various metabolic changes and potential suppression of the mechanistic target of rapamycin complex 1 pathway.[131] *In vitro* studies utilizing human PTCs under diabetic conditions indicate that SGLT2i can enhance mitochondrial fusion and reduce mitochondrial fission.[132] Furthermore, SGLT2i improve mitochondrial function, autophagy, and biogenesis while concurrently attenuating apoptosis and tubular injury.[132] These findings highlight another potential renoprotective mechanism of SGLT2i in DKD through the amelioration of mitochondrial abnormalities.

GLP-1 RAs. GLP-1 RAs exhibit diverse biological effects, including glycemic regulation, enhanced lipid metabolism, blood pressure reduction, and weight loss.[133] Recent studies have focused on the kidney effects of GLP-1, examining aspects such as electrolyte excretion, diuresis, tubular reabsorption, glomerular filtration rate, and renin-angiotensin-aldosterone system inhibition.[2,134-136] However, the mechanisms remain largely unexplored. *In vitro* studies reveal that GLP-1 RAs improve mesangial cell viability, reduce apoptosis, decrease mitochondrial fission, boost antioxidant activity, and enhance TCA cycle efficiency under high-fat, high-glucose conditions.[137] These effects are consistent with *in vivo* studies in diabetic rats and clinical investigations in patients with T2D, where GLP-1 RAs confer mitochondrial protection by reducing mitochondrial ROS, enhancing mitochondrial membrane potential, and improving oxygen consumption rate.[137] In addition, GLP-1 RAs lower proinflammatory cytokines (IL-6, IL-12, and tumor necrosis factor-alpha), while increasing IL-10, a cytokine that drives macrophage polarization toward the anti-inflammatory M2 phenotype.[137] In models of sterile inflammation in diabetic mice, GLP-1 RAs significantly decreased kidney monocyte chemoattractant protein-1, reduced nuclear factor kappa B activity, and promoted IL-10 production.[138] Remarkably, GLP-1 RAs also reduced myelopoiesis in the bone marrow, affecting macrophage and common myeloid progenitors.[138] Gene network analyses revealed that genes involved in inflammation resolution were predominantly expressed in a GLP-1 RA-treated diabetes group compared to an untreated diabetes group. Notably, transcript levels of Slc11a1, Txnip, and Slc6a19, which are associated with macrophage function, inflammatory response, and amino acid metabolism, respectively, are reduced in macrophage populations following GLP-1 RA treatment.[138] These findings collectively suggest that the kidney protective effects of GLP-1 RAs are potentially mediated through improvements in mitochondrial function and immunometabolic regulation.

Nonsteroidal Mineralocorticoid Receptor Antagonists. Nonsteroidal mineralocorticoid receptor antagonists have emerged as therapeutic options for patients with T2D and chronic kidney disease due to their benefits in slowing DKD progression and improving cardiovascular outcomes, as evidenced by the FIDELIO-DKD and FIGARO-DKD trials.[127,128] Preclinical studies indicate that nonsteroidal mineralocorticoid receptor antagonists, particularly finerenone, exhibit anti-inflammatory, antioxidant, and anti-fibrotic properties, and can reverse metabolic abnormalities in DKD.[139-141] These properties implies a possibly positive impact on several contributors of metabolic reprogramming in DKD, which potentially reverse those processes thus improving mitochondrial function. Notably, several proinflammatory cytokines, including monocyte chemoattractant protein-1, are reduced in response to finerenone.[142] These findings suggest that the renoprotective effects of finerenone may be linked to its ability to modulate mitochondrial activity and regulate immunometabolic pathways.

Promising Therapies

Acetyl-CoA Carboxylases 2 (ACC2) Inhibition. ACC2 is an enzyme that catalyzes the conversion of acetyl-CoA to malonyl-CoA. Malonyl-CoA subsequently inhibits carnitine palmitoyltransferase I, an enzyme involved in transporting acyl-CoA molecules into the mitochondria for FAO.[143] Studies in ACC2 knockout mice demonstrate weight reduction, increased FAO, and enhanced acetyl-CoA-related metabolism, including the TCA cycle. These changes are accompanied by decreased

intramyocellular lipid accumulation in skeletal muscle cells and improved insulin sensitivity.[144] Similarly, humans with ACC2 missense mutations have a favorable metabolic phenotype, evidenced by lower body mass index, reduced triglycerides, lower low-density lipoprotein cholesterol, and higher high-density lipoprotein cholesterol.[145] Although direct evidence of ACC2 inhibition affecting kidney outcomes is limited, its potential effects on restoring FAO, reducing weight, and improving insulin sensitivity could benefit DKD and warrant further human studies.

Mitochondrial Protonophores. Mitochondrial protonophores are compounds that disrupt the proton gradient across the mitochondrial inner membrane, which is essential for producing ATP through OXPHOS. By breaking down this gradient, protonophores separate the process of electron transport from ATP synthesis. This uncoupling leads to the release of energy as heat instead of its storage as ATP, resulting in an increased metabolic rate.[146]

In high-fat-fed mice, niclosamide ethanolamine, a mitochondrial protonophore, increased liver metabolism, reduced liver lipid accumulation, decreased body weight, and improved glycemic control.[147] In addition, TLC-6740, a potent liver-targeted protonophore, demonstrated an increase in TCA cycle flux in a diabetic fatty rat model.[148] However, niclosamide ethanolamine did not prevent microvascular complications of T2D, including DKD, in BKS-db/db mice.[149] This discrepancy suggests that mitochondrial protonophores may have organ-specific effects, necessitating further research and caution when using them in DKD, as they might impair TCA cycle and OXPHOS efficacy, potentially worsening kidney function.

Alpha-Amino-Beta-Carboxy-Muconate-Semialdehyde Decarboxylase (ACMSD) Inhibition. ACMSD is a pivotal enzyme in tryptophan metabolism, predominantly expressed in the kidney and liver. It intersects with pathways critical for nicotinamide adenine dinucleotide synthesis by inhibiting *de novo* nicotinamide adenine dinucleotide production.[150] Recent research underscores the role of nicotinamide adenine dinucleotide in energy metabolism, mitochondrial function, and cellular redox balance.[151] Studies involving genetic knockout or pharmacological inhibition of ACMSD show increased nicotinamide adenine dinucleotide levels and improved mitochondrial function, as evidenced by enhanced oxygen consumption rate and ATP production.[152] ACMSD inhibition also protects against acute kidney injury in models induced by cisplatin and ischemia-reperfusion, normalizing OXPHOS complex expression in the kidneys.[152] This promising mechanism of ACMSD counters the mitochondrial-centric aspects of DKD pathogenesis. Further studies in patients with DKD are warranted to explore this potential therapeutic approach.

Future Directions

Recent advancements in investigating TCA cycle and OXPHOS have significantly enhanced our understanding of cellular metabolism, particularly within complex tissues such as the kidney. One notable innovation is the use of kidney organoids 3-dimensional, multicellular structures derived from stem cells that mimic the architecture and function of human kidneys.[153] These organoids provide a more physiologically relevant model compared to traditional 2-dimensional cell cultures, allowing for a more accurate interrogation of metabolic processes. High-resolution respirometry and advanced mass spectrometry techniques are now employed to measure oxygen consumption rate and metabolite fluxes within these organoids, offering detailed insights into TCA cycle and OXPHOS functionality. In addition, genetically encoded biosensors and advanced imaging technologies, such as fluorescence lifetime imaging microscopy, enable real-time monitoring of metabolite levels and enzyme activities within living organoids.[154] These novel methods facilitate monitoring of precise manipulation and analysis of metabolic genes; when combined with CRISPR/Cas9 gene editing, they can provide deeper insights into mitochondrial function and roles in kidney physiology and pathology.[154] Together, these improved techniques represent a significant leap forward in metabolic research, offering powerful tools to unravel the complexities of mitochondrial function in health and disease.

Immunomodulation is another promising area in DKD research, with potential for developing new therapies. Investigating cytokines, macrophage polarization, T cell subtypes, and regulatory pathways in DKD pathogenesis will be crucial. Future research directions may emphasize the identification and validation of biomarkers for predicting disease onset and therapeutic response, thereby enabling personalized immunomodulatory treatments.

Conclusion

DKD remains a global health challenge, with current treatments primarily aiming to stabilize rather than reverse disease progression. Recent evidence has identified mitochondrial dysfunction and immune responses as central components in the pathogenesis of DKD. Advances in multiomics, imaging, metabolic research, and mitochondrial studies offer valuable insights. Targeted interventions that enhance mitochondrial function and modulate immunometabolic

pathways show potential for better DKD management. Personalized treatment strategies are crucial, tailored to the specific mitochondrial and immunometabolic profiles of each patient. This includes using verified biomarkers to identify those who would benefit most and developing individualized treatment plans based on unique metabolic and genetic characteristics. Ongoing research is vital to develop more effective and personalized therapeutic options, aiming to manage and reverse DKD progression.

DISCLOSURE

PB reports serving or having served as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli-Lilly, LG Chemistry, Sanofi, Novo Nordisk, and Horizon Pharma. PB also serves or has served on the advisory boards and/or steering committees of AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and XORTX. All the other authors declared no competing interests.

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