

Progress in the correlation of mitochondrial dysfunction and diabetic kidney disease

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Abstract: Diabetic kidney disease (DKD) is the most common complication of diabetes prevalence rate increased year by year, kidney as one of the body organs consumption, need to provide enough mitochondria ATP to maintain the normal physiological function, sustained high blood sugar levels induced by activating multiple pathways mitochondria damage, cause the energy imbalance, ATP production, to its negative effects, in recent years, Mitochondrial dysfunction has been concerned in the occurrence and development of kidney diseases, and is considered to be a key factor involved in the pathogenesis of diabetic kidney disease. In this paper, the role of mitochondrial structure and dysfunction in the progression of DKD is described, providing a theoretical basis for controlling the progression of DKD.

Keywords: Mitochondrial structure; mitochondrial dysfunction; diabetic kidney disease

1. Introduction

Diabetic kidney disease (DKD) is a common and frequently-occurring disease in the world, which has gradually developed into the main cause of ESRD in developed countries and become the primary cause of ESRD in middle-aged and elderly people in China^[1] About 30%~40% of ESRD worldwide is caused by DKD,^[2] According to survey statistics^[3], About 21.3% of patients with diabetes have chronic kidney disease, and the number can reach 24 million. DKD is characterized by increased excretion rate of persistent albuminuria and/or progressive decline of glomerular filtration rate (GFR). The pathological changes were characterized by early glomerular hyperplasia, thickening of basement membrane, proliferation of mesangial cells, broadening of mesangial matrix, K-W nodular formation, renal tubule and interstitial fibrosis, and eventually nodular or diffuse glomerulosclerosis. The pathogenesis was complex. It is traditionally believed that renal hemodynamic abnormalities, metabolic disorders, oxidative stress, overexpression of inflammatory factors and genetic susceptibility are involved in the occurrence and development of DKD^[4]. Kidney is second only to heart in terms of oxygen consumption and mitochondrial abundance. When stimulated by various physical and chemical factors such as external hyperglycemia and drug toxicity, the body's energy balance is out of balance and mitochondrial function is affected. In recent years, mitochondrial dysfunction is considered to be a key link in the development of DKD. These include mitochondrial oxidative stress, mitochondrial dynamics disorder, mitochondrial DNA damage and mitochondrial autophagy abnormality. This paper will focus on the pathophysiological role of mitochondrial structure and dysfunction in DKD.

2. Mitochondrial structure and biological function

Mitochondria are highly dynamic organelles, which are successively divided into outer membrane, intermembrane, inner membrane and matrix from the outside to the inside. The mitochondrial matrix has a high protein density of up to 500 mg/ml and is the site for DNA replication, transcription and protein biosynthesis of organelles. The inner membrane contains many enzymes, such as: Adenosine triphosphate (ATP) synthetase, adenosine diphosphate (ADP)/ATP translocation enzyme, is one of the main parts of eukaryotic energy conversion^[5]. The endometrium is highly invagination in the matrix to form cristae, increasing the area of the endometrium and ensuring the stability of mitochondrial energy generation to the maximum extent. There are 5 compounds (complex I-V) involved in oxidative phosphorylation between the endometrium and the cristae membrane. Except for complex II, other compounds are located in the mitochondrial endometrium to participate in ATP synthesis. Complex I

has been shown to be involved in the production of oxygen radicals (ROS)^[6]. The membrane gap is about 20 nm between the outer membrane and the inner membrane, which is involved in the input of mitochondrial proteins, the initiation of apoptosis cascade, the regulation of signaling pathways in the metabolic process, and the control of mitochondrial morphogenesis^[7]. The outer membrane contains more pores formed by membrane proteins, which allow the passage of uncharged small molecules. Proteins larger than 5000Da need to enter the mitochondria with the help of special mitochondrial translocation enzymes and protein complexes^[8]. The outer membrane provides a dynamic platform for cell signal transmission, and participates in regulating the morphology and ion exchange of organelles by forming membrane contact points with other suborganelles.^[9] Therefore, mitochondria play a key regulatory role in many important cellular activities.

3. The mechanism of mitochondrial dysfunction involved in DKD

3.1 Mitochondrial oxidative stress and DKD

Oxidative stress (OS) refers to the body reactive oxygen species (ROS) generation increased, and its antioxidant protection system dysfunction caused by a metabolic disorder, not only including cardiovascular disease, cancer and other disease plays an important role, and in diseases associated with metabolic regulation plays an important role in ^[10]. ROS release has harmful effects on mitochondrial components such as mitochondrial DNA(mtDNA), mitochondrial membrane and respiratory chain proteins, leading to mitochondrial dysfunction ^[11]. Reactive oxygen species (ROS) can be eliminated by antioxidant enzymes such as SOD, GSH, peroxiredoxins and controlled within a safe concentration range. Chronic high blood glucose levels in DKD patients lead to glucose autooxidation, protein glycosylation, activation of polyols and other pathways, resulting in increased production of oxygen free radicals. According to previous research results, increased production of ROS is an early event of diabetes complications. Through some signaling pathways, such as protein kinase C and transcription factor NF-κB, the expression of various growth factors and cytokines is promoted to affect the normal operation of target organs ^[12]. Based on PCR detection results, it was found that mitochondrial intermembrane translocase 44 (TIM44) can promote the infiltration of antioxidant enzymes such as SUPEROxide dismutase (SOD) into mitochondria, regulate the production of ROS, improve renal tissue proliferation, and inhibit renal cell apoptosis^[13]. Shahzad K et al.^[14] Activation of inflammasome was found in glomerular endothelial cells and podocytes of diabetic patients, which mediated and inhibited mitochondrial FAO through CD36, resulting in excessive formation of mitochondrial ROS.

In glomerular endothelial cells of diabetic mice found that mitochondrial dysfunction and glomerular endothelin - 1 type A receptor (EDNAR) and circulating endothelin - 1 (EDN - 1) increase in the number of expression, selective blocking EDNAR or clear the mitochondrial targeting aerobic active species, can inhibit oxidative stress of glomerular endothelial cells, so as to alleviate the caused by high blood sugar Endothelial damage, podocyte loss, and glomerulosclerosis^[15]. The upregulation and over-activation of NADPH oxidase (Nox) can serve as the main source of reactive oxygen species (ROS) in the kidney. When stimulated by external high glucose, Nox can be activated, resulting in the increase of renal ROS level, podal cell damage and thickening of mesangial matrix, and inducing the occurrence of DKD^[16]. Sirtuin3(Sirt3) is a protein deacetylase of nicotinamide adenopyrimidine dinucleotide (NAD) located in mitochondria, and its mechanism of action is to regulate the generation of reactive oxygen species in mitochondria. Some literatures pointed out that^[17] The expression of Sirt3 and ROS production in HK-2 cells were decreased and the degree of apoptosis was increased in HK-2 cells induced by high glucose. A recent study showed that succinate produced by peroxisome in diabetic patients, as a pathological molecule, induces the accumulation of lipids and ROS in kidney and participates in the progression of DKD^[18]. In summary, NADPH oxidase and mitochondrial electron transport chain, as the main sources of ROS, trigger various signaling pathways and activate some signaling molecules to cause irreversible pathological changes in cells and tissues, thus leading to renal function damage.

3.2 Mitochondrial dynamics and DKD

In general, mitochondria maintain a dynamic balance through continuous division and fusion, which depends on the coordination of mitochondria-related proteins in the outer and inner membranes and participate in mitochondrial lipid synthesis, calcium homeostasis, ATP synthesis and apoptosis^[19]. Fusion regulators 1 and 2 (MFN1/2) and optic nerve atrophy protein 1 (Opa1) at the outer membrane are involved in mitochondrial fusion. Fission regulator 1 (Drp1) and fission protein 1 (Fis1) promote

mitochondrial fission^[20]. In the process of cell damage or stress, mitochondria are dynamically transformed into fission, which promotes mitochondrial damage and cell apoptosis. Long-term hyperglycemic stimulation leads to glomerulosclerosis and interstitial fibrosis, and every pathological change in the process is affected by changes in mitochondrial dynamic balance, Sun Let al.^[21] Observed as early as 2008 in renal tubular cells treated with high glucose, mitochondrial fragments condensed and cytochrome C was released to induce apoptosis. By specific knockout of Drp1 gene in diabetic mice, renal mesangial matrix expansion and podocyte morphology were improved to a certain extent^[22]. In addition, continuous high blood glucose levels promoted Drp1 phosphorylation by stimulating increased expression of group 4A member 1 of the nuclear receptor subfamily (NR4A1)^[23]. It selectively stimulates mitochondrial fission, causes mitochondrial oxidative stress, opens the mitochondrial membrane transmembrane transfer pore (mPTP), and induces the leakage of pro-apoptotic proteins into the cytoplasm, leading to mitochondria-dependent apoptosis. Pgc-1 α is a major regulator of antioxidant metabolism and mitochondrial biosynthesis, and pgC-1 α overexpression improves glomerular mesangial cell damage under hyperglycemia, which is related to regulating Drp1 mediated mitochondrial dynamic remodeling and inhibiting ROS production^[24]. The expression of mitochondrial fission factor Drp1 decreased and fusion factor Mfn1 increased in pgC-1 α agonist treated renal tubular cells with high glucose^[25]. Ihg-1 is a highly conserved protein located in mitochondria. Long-term hyperglycemic stimulation leads to overexpression of IHG-1. It maintains mitochondrial function by coordinating stability of PGC-1A protein and increasing respiratory capacity, mitochondrial biogenesis and fusion, and protects cells from oxidative stress damage. However, it also increased the pro-fibrotic response of TGF- β ^[26]. A recent study found that^[27] under high glucose stimulation, the expression of disulfide bond A REDOX enzyme like protein (DSBA-L) in renal tubular cells decreased, and the production of mitochondrial ROS increased, aggravating mitochondrial fragmentation, increasing the expression of MFF through the JNK pathway, and improving the ability of DRP1 to recruit into mitochondria. Therefore, mitochondria maintain the balance of mitochondrial membrane potential through continuous division and fusion, and play a certain advantage in preventing oxidative stress and apoptosis.

3.3 Mitochondrial DNA and DKD

Mitochondrial DNA (mtDNA) is a 16,569bp circular molecule that encodes 13 peptides in oxidative phosphorylation complexes (OXPHOS). Seven transcription factors (mtTFA), RNA processing enzyme RNase MRP and Transcription termination factor (mTERF) drive the oxidative respiratory chain and produce ATP^[28]. As the main genetic material regulating mitochondrial replication and transcription, mtDNA is not protected by histones and has an imperfect DNA repair mechanism, adjacent to the oxidative respiration chain, which is highly susceptible to ROS. Moreover, the repair rate of mitochondrial DNA damage is slower than that of genomic DNA. Long-term oxidative stress caused by endogenous ROS generation overload, mitochondrial membrane permeability increased, mitochondrial DNA (mtDNA), peptide and lipid material from being released into the cytoplasm in the mitochondrial membrane, among them, the mtDNA as injury related molecular mode, cause the drop of the mitochondrial membrane potential damage of mitochondrial DNA is released into the cytoplasm, Trigger downstream toll-like receptor 9 (TLR9), CGAS-STING pathway and NLRP inflammasome signaling pathways to induce cell damage^[29]. As a result of renal tubule in heavy absorption process needs to consume a large amount of oxygen to produce ATP, this also need enough mitochondria participate in energy supply, DKD patients of high blood sugar after kidney renal tubular filter can be directly after the injury, leading to the decrease in the number of mitochondrial DNA in cells, increase mitochondrial DNA damage, make Nox4 protein involved in mitochondrial function, The expressions of Bax and cytochromic C in the tubules are increased, and the increased NOX4 leads to increased production of reactive oxygen species (ROS) in the tubules, apoptosis activation and mitochondrial membrane potential loss, resulting in extensive metabolic disorders and dysfunction in renal cell tissues^[30]. It was found in renal mesangial cells (HMC) cultured with high glucose that mitochondrial fragmentation occurred and TLR9 pathway was activated. Initially, changes in mtDNA content and integrity could still meet the energy requirements of the cells, but one week later, mitochondrial activity was affected, ATP production was insufficient, and cellular metabolism was weakened^[31]. In building diabetes mice kidney endothelial cells and the expression level of mitochondrial DNA in the cell, promote the mitochondrial DNA is released into the circulation, after kidney filtration, cause chronic kidney inflammation, which associated with increased glomerular endothelial EDNRA expression^[32], after treatment, with the antioxidant drug in the kidney of mice mitochondrial DNA copy number down, ROS production decreased, TGF- β and NF- κ B expression decreased, and the degree of apoptosis decreased^[33]. Jiang Hong et al.^[34] found in the study of

mitochondrial targeted metabolism that damaged mtDNA leads to increased generation of reactive oxygen species (ROS), and the increased ROS will further increase the damage to mitochondrial DNA. The mitochondrial DNA copy number found in urine of DKD patients can reflect the level of mitochondrial DNA in kidney, and renal tissue biopsy further confirmed that mtDNA in urinary supernatant can be used as a potential indicator of the severity of interstitial fibrosis in patients with PATHologically diagnosed DN^[35].

3.4 Mitochondrial autophagy and DKD

Mitochondrial autophagy refers to the selective phagocytosis of mitochondria and elimination of mitochondrial fragments in dysfunction to ensure the stability of their quality, which plays a key role in maintaining the stability of the environment in the glomerulus and renal tubules. Pink1/Parkin pathway is a key pathway of mitochondrial autophagy. The loss of membrane potential during mitochondrial damage promotes the accumulation of Pink1 in mitochondrial outer membrane, activates phosphorylation of downstream substrate Parkin at Ser65 residues in its N-terminal ubiquitin like domain, and induces Parkin to aggregate on damaged mitochondria. At the same time, phosphorylation of Pink1 at Ser65 initiates mitochondrial autophagy by activating Parkin E3 ligase^[36]. In addition, FUNDC1 protein and BNIP3 /NIX pathway still co-regulate the occurrence of mitochondrial autophagy. DKD patients high oxidative stress status and dysfunction caused by chronic inflammation state mitochondrial autophagy, the decrease in the number of mitochondria, affecting its normal function, in recent years, research has shown that both DKD animal models or clinical patients, as a large number of mitochondria in renal tissue debris accumulation, which prompts DKD mitochondria to remove impaired ability. Lower levels of mitochondrial autophagy were observed in STZ-induced rat kidneys, and intracellular mitochondrial swelling and crest reduction were observed under electron microscopy^[37]. At the same time, the epithelial cells of renal tubule TRX protein interactions (TXNIP) express, impaired mitochondrial autophagy, increased renal fibrosis^[38], depending on the neuropeptide (OPTN), as the key part of mitochondrial autophagy receptors in HK - 2 expression in cells induced by high sugar, affect mitochondrial autophagy, by activating downstream NLRP3 inflammatory corpuscle, Further aggravating kidney injury^[39]. Similarly, IN HFD/ STZ-induced diabetic mice, AMPK agonists were found to activate mitochondrial autophagy via the Pink1/Parkin pathway to improve renal oxidative stress and renal tubulointerstitial fibrosis^[40]. DUSP1 is a phosphatase with double specificity that has been discovered in recent years. It participates in the inactivation of MAPK family isomers and regulates cell proliferation and apoptosis. At first, DUSP1 was thought to play a certain advantage in anti-inflammatory. It has a certain protective effect in DKD^[41]. Recent studies have shown that mitochondrial autophagy is involved in cell apoptosis^[42]. Tipe1 is one of the cell necrotizing apoptosis factors. After specific Tipe1 knockout of renal tubular epithelial cells (RTECs), mitochondrial autophagy is enhanced, and PINK1 and Parkin expressions are increased. Through its interaction with mitochondrial autophagy receptor statin 2 (PHB2), it promotes PHB2 ubiquitination and proteasome degradation, and alleviates renal tubule damage. The above mechanism shows that mitochondrial autophagy is involved in the progress of DKD in many aspects, and affects mitochondrial morphological change and mass balance by causing accumulation of mitochondrial fragments. As for the molecular mechanism of mitochondrial autophagy, it is necessary to further explore its role in DKD.

4. Conclusion

Mitochondrial dysfunction in the influence and mechanism of the occurrence and development of diabetic kidney disease is complex, its influence the occurrence of some functions may involve damage to another function, for example, mitochondrial ROS generation overload lead to mitochondrial DNA damage and impaired mitochondrial dynamics and causes mitochondrial debris removal obstacle, affect the mitochondrial function of autophagy, The mutual infiltration between mechanism, to promote the progress of the disease, therefore, the protection of mitochondrial function, alleviate the mitochondrial damage degree, may help to slow down the progress of diabetic kidney disease to end-stage renal disease, the prevention of diabetic kidney disease, clinical study has the vital significance, such as at present, for mitochondrial targeted drugs are also emerge in endlessly, Explore the role of mitochondrial function mechanisms in DKD progress can provide certain theoretical guidance for treatment of late, we believe that the future for mitochondrial dysfunction in other kidney diseases except DKD pathological mechanism of exploration is of great value, thought that kidney disease diagnosis and provide new prospects and future direction.

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