Mitochondrion and Its Role in Diabetic Nephropathy

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Diabetic nephropathy is a major cause of end-stage renal disease throughout the world. Elevated oxidative stress in diabetic patients results from overproduction of reactive oxygen species and decreased efficiency of antioxidant defenses. Moreover, diabetes-associated metabolic disorders impair activities of enzymes of the mitochondrial respiratory chain complex. Therefore, oxidative stress is closely related to mitochondrial dysfunction. This paper reviews studies of mitochondrial dysfunction in diabetic nephropathy.

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Review

INTRODUCTION

Mitochondrion is the main energy-producing organelle in cells. It is a membrane-enclosed structure found in most eukaryotic cells.[1] The word mitochondrion comes from Greek, *mitos*, which means "thread," and chondrion, which means "granule." The organelle is composed of compartments that carry out specialized functions. These compartments include the outer membrane, the intermembrane space, the inner membrane, and the cristae. These organelles are sometimes described as "cellular power plants" because they generate most of the cell's supply of adenosine triphosphate, used as a source of chemical energy.[2] Mitochondria are involved in other tasks such as control of the cell cycle, cell growth, and differentiation, as well as cell death.[3] Mitochondria have been implicated in several human diseases, including mitochondrial disorders.

Protein complexes in the inner membrane are used to pump protons into the intermembrane space. This process is efficient, but a small percentage of electrons may prematurely reduce oxygen, forming reactive oxygen species (ROS) such as superoxide.[4] This can cause oxidative stress in the mitochondria.

MITOCHONDRIAL FISSION AND FUSION

Mitochondria are highly dynamic, constantly undergoing fission and fusion. Fission results in the production of short mitochondrial rods or spheres. In contrast, fusion promotes a long filamentous morphology of mitochondria (Figure 1).[5,6] Severe damage to the mitochondria, however, in the form of permeabilization of inner or outer membranes of the organelles, can further lead to cell death.[7] A few proteins regulate mitochondrial fission and fusion including dynamin-related protein 1, mitochondrial fission 1 protein, mitofusin 1, mitofusin 2, and optic atrophy 1.

Dynamin-related Protein 1

Dynamin-related protein 1 (DRP1) is a large guanosine triphosphatase of the dynamin superfamily that has an essential role in mitochondrial fission in mammalian cells (Figure 1). Brooks and colleagues showed a striking morphological change of mitochondria in experimental model of renal reperfusion injury.[8] This change contributed to mitochondrial outer membrane permeabilization, release of apoptogenic factors, and consequent apoptosis. Following adenosine triphosphate depletion of rat renal tubular cells, mitochondrial fragmentation was observed prior to cytochrome c release and apoptosis. Dynamin-related protein 1 translocated to mitochondria early during tubular cell injury. Knockdowning of Drp1 in rodent models attenuated mitochondrial fragmentation, cytochrome c release, and apoptosis. Notably, both tubular cell apoptosis and acute kidney injury were attenuated by mdivi-1, a newly identified pharmacological inhibitor of Drp1. This study on animals demonstrates a rapid regulation of mitochondrial dynamics during acute kidney injury and identifies mitochondrial fragmentation as a novel mechanism contributing to mitochondrial damage and apoptosis.[8]

Mitochondrial Fission 1 Protein

Mitochondrial fission 1 protein (FIS1) is another key component of the mitochondrial fission machinery in mammalian cells (Figure 1). In one study, mitochondrial fragmentation and increased expression of FIS1 were observed in venous endothelial cells freshly isolated from patients with diabetes mellitus.[9] In cultured human aortic endothelial cells exposed to high glucose, the authors observed a similar loss of mitochondrial networks and increased expression of FIS1 and DRP1 required for mitochondrial fission. Altered mitochondrial dynamics was associated with increased mitochondrial ROS production. Silencing FIS1 or DRP1 expression with small interfering RNA blunted high glucose-induced ROS production, suggesting that increased mitochondrial fission may impair endothelial function via increased ROS.[9]

Mitofusin 1, Mitofusin 2, and Optic Atrophy 1

Components of the mitochondrial fusion machinery include mitofusin 1, mitofusin 2 (MFN2), and optic atrophy 1 (Figure 1). It is known that the dysfunctional fragmentation may be a combined result of the activation of fission and the suppression of fusion. B-cell leukemia/lymphoma-2 family proteins also take part in the regulation of mitochondrial dynamics. They include Bax and Bak and their interactions with the key proteins in the mitochondrial fission-fusion machinery.

MITOCHONDRIA AND DIABETIC NEPHROPATHY

Diabetic nephropathy (DN) is a major complication of diabetes and is the single largest cause of end-stage renal disease.[10] Pathophysiology of DN has intensively been studied. Inflammation and oxidative stress are among the best known of them.[11-16] Mitochondrial ROS play an important role in diabetes complications, including DN.[17]

Yu and coworkers showed that in cells cultured with high glucose, mitochondria underwent rapid fragmentation, which induced the ROS production.[18]

Figure 1. Dynamin-related protein 1 (DRP1) induces fission. Mitofusin 1 (MFN1), mitofusin 2 (MFN2), and optic atrophy 1 (OPA1) induce fusion.

Importantly, inhibition of the mitochondrial fragmentation prevented ROS production under this condition, supporting a critical role for the alterations of mitochondrial dynamics in ROS production.[18]

Insulin influences the biogenesis of mitochondria by upregulating MFN2.[19] As mentioned earlier, MFN2 regulates mitochondrial morphology and signaling. It was demonstrated that endogenous MFN2 expression decreases with time in DN. On the other hand, overexpression of MFN2 decreases kidney weight relative to body weight, reduces proteinuria and albumin-creatinine ratio, and improves pathological changes typical of the diabetic kidney, including enlargement of glomeruli, accumulation of extracellular matrix, and thickening of the basement membrane. In addition, MFN2 overexpression inhibits accumulation of ROS, prevents mitochondrial dysfunction, and reduces synthesis of collagen IV. Generally, Mfn2 overexpression can attenuate pathological changes in the kidneys of diabetic rats.[20]

Rho-associated Protein Kinase

RhoA, a small guanosine triphosphatase protein and its immediate downstream target, Rho-associated protein kinase (ROCK), control a wide variety of signal transduction pathways. Rho-associated protein kinases have been showed to contribute to several pathophysiological pathways that are led by hyperglycemia. A couple of animal experiments demonstrated that inhibition of either Rho or ROCK attenuated cardiomyopathy in diabetes and improved myocardial compliance.[21,22] Therefore, a Rho/ROCK inhibitor would be a good candidate for treating diabetes mellitus and its complications.[23,24]

Wang and coworkers examined the role of rho-associated coiled-coil-containing protein kinase 1 (ROCK1) on mitochondrial dynamics. Their study showed that ROCK1 mediates hyperglycemia-induced mitochondrial fission by promoting DRP1 recruitment to the mitochondria. On the other hand, deletion of *ROCK1* in diabetic mice inhibited mitochondrial fission (Figure 1).[25]

Human Studies

Previous studies have found deficient mitochondrial oxidative phosphorylation and decreased MFN2 expression in patients with type 2 diabetes and obesity,[26-28] whereas exercise and weight loss increased MFN2 expression.[29-30]

In diabetic patients, insulin improves the mitochondrial structure.[31]

Novel Approaches to Treatment

Fasudil. Fasudil, a Rho/ROCK inhibitor, has been studied widely and applied in clinical practice. Kolavennu and coworkers showed that the kidney cortexes of untreated db/db mice display increased ROCK activity and the fasudil-treated mice exhibited a significant reduction in ROCK activity, albuminuria, and glomerular collagen IV accumulation compared with untreated diabetic mice (Figure 2).[32] According to these results, they proposed that Rho/ROCK blockade constitutes a novel approach to the treatment of DN.[32]

Coenzyme Q10. Coenzyme Q10, also known as ubiquinone, abbreviated at times to CoQ10, where Q refers to the quinone chemical group, and 10 refers to the number of isoprenyl chemical subunits in its tail (Figure 3). This oil-soluble vitamin-like substance is present in most eukaryotic cells, primarily in the mitochondria. It is a component of the electron transport chain and participates in aerobic cellular respiration, generating energy in the form of adenosine triphosphate. Ninety-five percent of the human body's energy is generated this way.[33] Coenzyme Q10 prevents altered mitochondrial function and morphology, glomerular hyperfiltration, and proteinuria in diabetic mice, highlighting the role of mitochondria in the pathogenesis of DN and the benefits of preventing increased oxidative stress.[34] However, its effect on preventing glomerulosclerosis is controversial.[35,36]

Figure 2. Fasudil reduces Rho-associated protein kinase (ROCK) activity. DRP1 indicates dynamin-related protein 1.

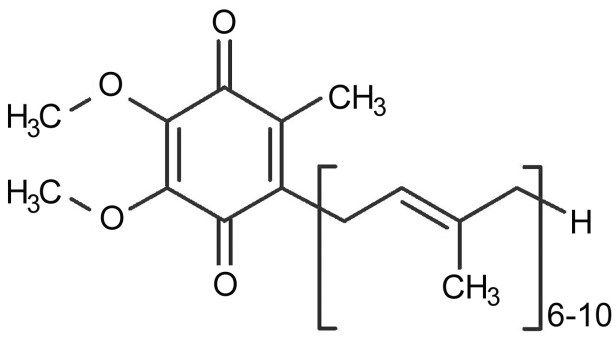

Figure 3. Molecular structure of coenzyme Q10.

Lipoic Acid. Yi and colleagues showed lipoic acid synthase (Lias) deficiency in diabetic mice induces overt DN, including microalbuminuria, glomerular basement thickening, mesangial matrix expansion, and hypertension compared with diabetic controls without Lias deficiency.[37] Wang and colleagues, on the other hand, treated diabetic rats with α-lipoic acid.[38] Their study showed that in the serum and renal cortex of α-lipoic acid group, the content of malondialdehyde and the activities of superoxide dismutase were both significantly decreased. Compared to the diabetic group, the mitochondrial membrane potential in the α-lipoic acid group was significantly increased and mitochondrial swelling was reduced.

CONCLUSIONS

Mitochondrial ROS production plays an important role in pathophysiology of DN. Mitochondrial fission and fusion regulates ROS production, so a couple of studies have been focused on modulating this process in order to decreasing ROS production. Fasudil, coenzyme Q10, and lipoic acid are among the well-studied modulators.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Henze K, Martin W. Evolutionary biology: essence of mitochondria. Nature. 2003;426:127-8.
2. Campbell NA, Williamson B, Heyden RJ. Biology: exploring life. Boston, Massachusetts: Pearson Prentice Hall. 2006.
3. McBride HM, Neuspiel M, Wasiak S. Mitochondria: more than just a powerhouse. Curr Biol. 2006;16:R551-R560.
4. Voet D, Voet JG, Pratt CW. Fundamentals of biochemistry. 2nd ed. John Wiley and Sons; p. 547.
5. Westermann B. Mitochondrial fusion and fission in cell life and death. Nat Rev Mol Cell Biol. 2010;11:872-84.
6. Liesa M, Palacin M, Zorzano A. Mitochondrial dynamics in mammalian health and disease. Physiol Rev. 2009;89:799-845.
7. Zhan M, Brooks C, Liu F, Sun L, Dong Z. Mitochondrial dynamics: regulatory mechanisms and emerging role in renal pathophysiology. Kidney Int. 2013;83:568-81.
8. Brooks C, Wei Q, Cho SG, Dong Z. Regulation of mitochondrial dynamics in acute kidney injury in cell culture and rodent models. J Clin Invest. 2009;119:1275-85.
9. Shenouda SM, Widlansky ME, Chen K, et al. Altered mitochondrial dynamics contributes to endothelial dysfunction in diabetes mellitus. Circulation. 2011;124:444-53.

10. Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States Renal Data System. J Am Soc Nephrol. 2007;18:2644-8.
11. Rashtchizadeh N, Argani H, Ghorbanihaghjo A, Nezami N, Safa J, Montazer-Saheb S. C-reactive protein level following treatment and withdrawal of lovastatin in diabetic nephropathy. Iran J Kidney Dis. 2009;3:93-8.
12. Choudhary N, Ahlawat RS. Interleukin-6 and C-reactive protein in pathogenesis of diabetic nephropathy: new evidence linking inflammation, glycemic control, and microalbuminuria. Iran J Kidney Dis. 2008;2:72-9.
13. Mojahedi MJ, Bonakdaran S, Hami M, Sheikhian MR, Shakeri MT, Aiatollahi H. Elevated serum C-reactive protein level and microalbuminuria in patients with type 2 diabetes mellitus. Iran J Kidney Dis. 2009;3:12-6.
14. Kazemi AM. Interleukin-4 gene polymorphisms in type 2 diabetic patients with nephropathy. Iran J Kidney Dis. 2010;4:302-6.
15. Sheela N, Jose MA, Sathyamurthy D, Kumar BN. Effect of silymarin on streptozotocin-nicotinamide-induced type 2 diabetic nephropathy in rats. Iran J Kidney Dis. 2013;7:117-23.
16. Nasri H, Baradaran A, Ardalan MR, Mardani S, Momeni A, Rafieian-Kopaei M. Bright renoprotective properties of metformin: beyond blood glucose regulatory effects. Iran J Kidney Dis. 2013;7:423-8.
17. Hwang I, Lee J, Huh JY, et al. Catalase deficiency accelerates diabetic renal injury through peroxisomal dysfunction. Diabetes. 2012;61:728-38.
18. Yu T, Sheu SS, Robotham JL, Yoon Y. Mitochondrial fission mediates high glucose-induced cell death through elevated production of reactive oxygen species. Cardiovasc Res. 2008;79:341-51.
19. Pawlikowska P, Gajkowska B, Orzechowski A. Mitofusin 2 (Mfn2): a key player in insulin-dependent myogenesis in vitro. Cell Tissue Res. 2007;327:571-81.
20. Tang WX, Wu WH, Zeng XX, Bo H, Huang SM. Early protective effect of mitofusion 2 overexpression in STZ-induced diabetic rat kidney. Endocrine. 2012;41:236-47.
21. Kizub IV, Pavlova OO, Johnson CD, Soloviev AI, Zholos AV. Rho kinase and protein kinase C involvement in vascular smooth muscle myofilament calcium sensitization in arteries from diabetic rats. Br J Pharmacol. 2010;159:1724-31.
22. Bach LA. Rho kinase inhibition: a new approach for treating diabetic nephropathy? Diabetes. 2008;57:532-3.
23. Guan SJ, Ma ZH, Wu YL, et al. Long-term administration of fasudil improves cardiomyopathy in streptozotocin-induced diabetic rats. Food Chem Toxicol. 2012;50:1874-82.
24. Komers R. Rho kinase inhibition in diabetic nephropathy. Curr Opin Nephrol Hypertens. 2011;20:77-83.
25. Wang W, Wang Y, Long J, et al. Mitochondrial fission triggered by hyperglycemia is mediated by ROCK1 activation in podocytes and endothelial cells. Cell Metab. 2012;15:186-200.
26. Bach D, Pich S, Soriano FX, et al. Mitofusin-2 determines mitochondrial network architecture and mitochondrial metabolism. A novel regulatory mechanism altered in obesity. J Biol Chem. 2003;278:17190-7.
27. Pich S, Bach D, Briones P, et al. The Charcot-Marie-Tooth type 2A gene product, Mfn2, up-regulates fuel oxidation through expression of OXPHOS system. Hum Mol Genet. 2005;14:1405-15.
28. Bach D, Naon D, Pich S, et al. Expression of Mfn2, the Charcot-Marie-Tooth neuropathy type 2A gene, in human skeletal muscle: effects of type 2 diabetes, obesity, weight loss, and the regulatory role of tumor necrosis factor alpha and interleukin-6. Diabetes. 2005;54:2685-93.
29. Cartoni R, Leger B, Hock MB, et al. Mitofusins 1/2 and ERRalpha expression are increased in human skeletal muscle after physical exercise. J Physiol. 2005;567:349-58.
30. Mingrone G, Manco M, Calvani M, Castagneto M, Naon D, Zorzano A. Could the low level of expression of the gene encoding skeletal muscle mitofusin-2 account for the metabolic inflexibility of obesity? Diabetologia. 2005;48:2108-14.
31. Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van den Berghe G. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. Lancet. 2005;365:53-9.
32. Kolavennu V, Zeng L, Peng H, Wang Y, Danesh FR. Targeting of RhoA/ROCK signaling ameliorates progression of diabetic nephropathy independent of glucose control. Diabetes. 2008;57:714-23.
33. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta. 1995;1271:195-204.
34. Persson MF, Franzen S, Catrina SB, et al. Coenzyme Q10 prevents GDP-sensitive mitochondrial uncoupling, glomerular hyperfiltration and proteinuria in kidneys from db/db mice as a model of type 2 diabetes. Diabetologia. 2012;55:1535-43.
35. Ahmadvand H, Tavafi M, Khosrowbeygi A. Amelioration of altered antioxidant enzymes activity and glomerulosclerosis by coenzyme Q10 in alloxan-induced diabetic rats. J Diabetes Complications. 2012;26:476-82.
36. Sourris KC, Harcourt BE, Tang PH, et al. Ubiquinone (coenzyme Q10) prevents renal mitochondrial dysfunction in an experimental model of type 2 diabetes. Free Radic Biol Med. 2012;52:716-23.
37. Yi X, Xu L, Hiller S, et al. Reduced expression of lipoic acid synthase accelerates diabetic nephropathy. J Am Soc Nephrol. 2012;23:103-11.
38. Wang L, Wu CG, Fang CQ, et al. The protective effect of alpha-Lipoic acid on mitochondria in the kidney of diabetic rats. Int J Clin Exp Med. 2013;6:90-7.

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