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Quality Control and Functional Change of Mitochondria in Diabetic Kidney Disease

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Description

As described in our recent review article, mitochondrial dysfunction has been revealed to play an important role in Diabetic Kidney Disease (DKD) and the perspective of mitochondrial dysfunction continues to develop [1]. In this commentary, we focus on mitochondrial dysfunction in DKD in terms of the quality control and the central function of mitochondria, which is energy metabolism including its byproduct, reactive oxygen species.

Mitochondria maintain their quality with three mutually affecting mechanisms is biogenesis, fission and fusion and mitophagy. New and functional mitochondria are produced with biogenesis, in which mitochondrial DKD is duplicated followed by binary fission of mitochondria. In DKD, mitochondrial biogenesis is suppressed at least at its later stage as a result of decreased activity of peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1 α). Mitochondria dynamically change their shape through fission and fusion. Although the significance of the change in shape including whether mitochondrial shape is the cause of mitochondrial dysfunction or it merely reflects the result of it has not fully elucidated yet, it is demonstrated repeatedly that mitochondria are fragmented in DKD in consequence of increased fission and decreased fusion. Mitophagy is a mechanism to remove dysfunctional mitochondria. Mitophagy is shown to be suppressed in podocytes and proximal tubular cells in DKD, and high glucose causes the down regulation of the phosphatase and tensin homolog-induced Putative Kinase 1 (PINK1), a major participant in mitophagy. Decreased biogenesis, fragmented shape and decreased mitophagy seem to contribute to failure in keeping good quality of mitochondria.

In 2000, Brownlee and colleagues published that increased mitochondrial ROS production due to substrate increase was the unifying mechanism causing the injury from hyperglycemia. Based on this hypothesis and promising results from preclinical experiments, clinical trials for various antioxidants were conducted but ended in disappointing results [2]. The failure could be attributed to difference in ROS depending on its origin (mitochondria, endoplasmic reticulum or enzyme systems) or versatile roles of ROS, which are not limited to detrimental ones, such as in cell signaling pathway. As the measures of detecting ROS develop, even the very core issue whether mitochondrial ROS is increased or decreased in DKD has become controversial. Some argue that mitochondrial ROS is decreased because of suppressed activity in Electron Transport Chain (ETC). Then what causes the suppression of ETC in the first place? It is caused by the metabolic shift from mitochondrial Oxidative Phosphorylation (OXPHOS) to aerobic glycolysis, in which lactate is produced as in anaerobic glycolysis even with the presence of oxygen. This phenomenon is well known in cancer and called Warburg effect. Recently it has been demonstrated that Warburg effect also takes place in DKD. We introduced several mechanisms presented as the cause: low Pyruvate Kinase M2 (PKM2) activity, sphingomyelin and NADPH oxidase 4 (Nox4)/fumarate/hypoxia inducible factor 1 α (HIF1 α) axis. PKM2 is demonstrated to be increased and activated in diabetic patients protected from kidney disease, and its down regulation observed in patients with DKD contributes to DKD exacerbation [3]. A specific sphingomyelin species (SM (d18:1/16:0)) is demonstrated to be increased in DKD glomeruli and it caused glycolysis activation in mesangial cells [4]. Nox4 is linked to DKD and its induction in podocytes caused fumarate accumulation and DKD-like phenotype *in vivo* [5]. Fumarate stabilizes HIF1 α, which orchestrates glycolysis-related genes and is a major player in cancer Warburg effect. These mechanisms may replace mitochondrial ROS as new targets to DKD treatment. Mitochondrial dysfunction can be a new therapeutic target of DKD. Further investigation elucidating its role in ameliorating DKD is awaited.

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