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Mitochondrial fatty acid metabolism in acute kidney injury

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Abstract Mitochondrial injury in renal tubule has been recognized as a major contributor in acute kidney injury (AKI) pathogenesis. Ischemic insult, nephrotoxin, endotoxin and contrast medium destroy mitochondrial structure and function as well as their biogenesis and dynamics, especially in renal proximal tubule, to elicit ATP depletion. Mitochondrial fatty acid β-oxidation (FAO) is the preferred source of ATP in the kidney, and its impairment is a critical factor in AKI pathogenesis. This review explores current knowledge of mitochondrial dysfunction and energy depletion in AKI and prospective views on developing therapeutic strategies targeting mitochondrial dysfunction in AKI.

Key words: Mitochondria, Energy metabolism, Fatty acid oxidation, ATP, Mitochondrial dysfunction, Ischemia/reperfusion injury, Nephrotoxin, Sepsis, Acute kidney injury

INTRODUCTION

Acute kidney injury (AKI) is characterized by rapid disruption of renal function that occurs in diverse insults, including sepsis, nephrotoxins and ischemia/reperfusion injury that may occur during organ transplantation and cardiothoracic, vascular and general surgery.[1)] AKI occurs in approximately 30% of all patients admitted to intensive care units and is associated with high mortality and morbidity.[2,3)] Further, a number of recent experimental and clinical studies indicate that AKI is an independent risk factor for onset and deterioration of chronic kidney disease.[4-6)] Currently, AKI remains a significant health burden with its undefined pathogenesis and is a major unmet medical need without any pharmacological treatments.[7,8)]

Kidney is an organ with high metabolic demand due to active transport of glucose, ions and nutrients. Thus, renal tubular mitochondrial dysfunction and ATP depletion are critical factors inducing AKI.[9,10)] Proximal tubules require more active transport mechanisms than other tubule types because they reabsorb 70% of the glomerular filtrate. Proximal tubule, particularly the S3 segment residing in the outer medullary region, is highly vulnerable to hypoxic condition like ischemia/reperfusion injury (IRI), since this region is exposed to the lowest oxygen pressure (tissue oxygen tension 10∼20 mmHg) with only 5∼10% of total renal blood flow.[11)] Therefore, sufficient energy supply from fatty acid β-oxidation (FAO) is critical to the normal function of proximal tubule.[12)] Regardless of the etiology, AKI induces mitochondrial dysfunction in proximal tubule.[13,14)] Pathological signals like elevated levels of intracellular and mitochondrial Ca^{2+}, increased production of reactive oxygen species (ROS), mitochondrial membrane permeabilization and depolarization, and loss of ATP are hallmarks of mitochondrial dysfunction.[13)] Given that proximal tubule is highly sensitive to depletion of ATP, mitochondria is a potential therapeutic target for preventing renal tubular cell death.[12,15)] Here, we review the current findings regarding molecular mechanism of mitochondrial dysfunction, primarily focused on impaired fatty acid metabolism and ATP depletion, and recent developments in mitochondria-targeted therapeutic strategies in AKI.

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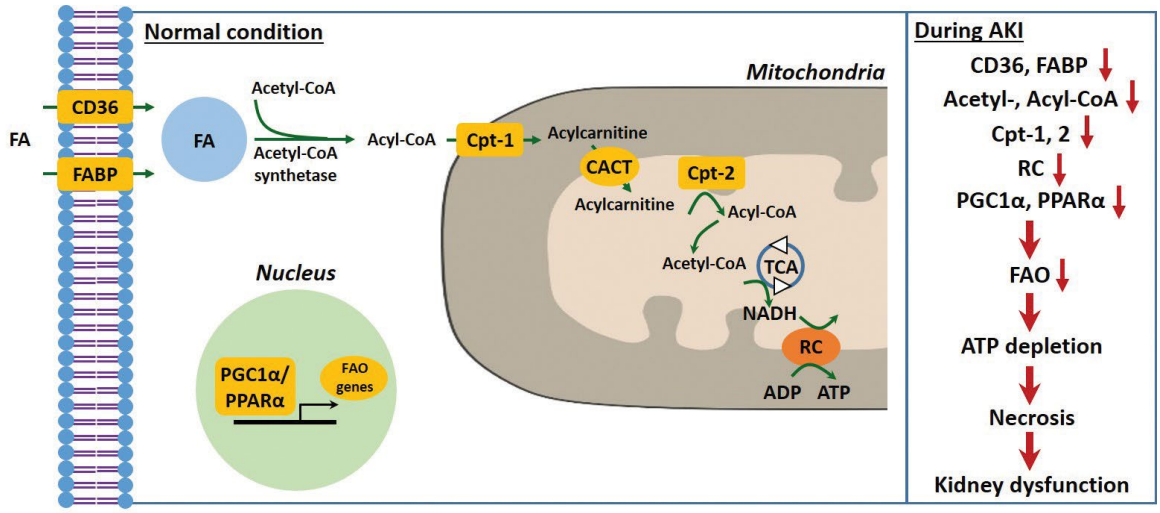

Figure 1. Mitochondrial fatty acid metabolism in AKI. FA enters into cytosol of renal proximal tubule cell (PTC) via FABP or CD36. In the cytosol, FA are transformed from acetyl-CoA to acyl-CoA by addition of acetyl-CoA through acetyl-CoA synthetase and then transferred to mitochondrial matrix by carnitine shuttle, Cpt-1, CACT and Cpt-2, step by step. Acyl-CoA undergo β-oxidation to produce acetyl-CoA for TCA. NADH generated by TCA is used as an electron donor for RC. During AKI, inhibition of genes related to fatty acid oxidation occurs to impair fatty acid oxidation and that in turn deplete ATP, resulting in PTC necrosis and kidney dysfunction. FA, fatty acid; FAO, fatty acid β-oxidation; Cpt, carnitine Opalmitoyltransferase; CACT, carnitine-acylcarnitine translocase; TCA, tricarboxylic acid cycle; RC, respiratory chain.[12,13,18,20,21,25,26,29,31,32]

Mitochondrial energetics

Mitochondria are highly dynamic intracellular organelles and have a network with other organelles, including endoplasmic reticulum and nucleus. Mitochondria can undergo physical changes like fusion, fission, and movement, and serve as a power plant generating cellular energy.[16] The magnitude of generation of ATP is dependent on energy demand of the cell, based on their requirement for passive or active transport of ion, glucose, and nutrients. The principle role of mitochondria is to generate cellular energy via electron transport and oxidative phosphorylation, as well as calcium homeostasis and ROS generation. Kidney uses 95~99% of energy derived from mitochondrial oxidative metabolism.[17] Oxidative phosphorylation is more efficient by generation of 36 ATP per glucose, compared to 2 ATP by glycolysis. On the other hand, one fatty acid (FA) is more effective as it can generate 106 ATP via FAO. The proximal tubule has low glycolytic capacity, and prefers FAO for generation of its high ATP demand.[18,19] Although FAO is the most efficient mechanism for producing ATP in proximal tubules, it is important to note that due to the high consumption of oxygen by proximal tubules, they are more susceptible than other cell types to changes in oxygen levels.[19] The distal tubule, on the other hand, has higher glycolytic metabolism and could switch to anaerobic metabolism in AKI, and may explain why it is relatively resistant to AKI.[19]

Mitochondrial fatty acid metabolism in AKI

FA uptake, oxidation and synthesis are tightly balanced to achieve lipid homeostasis and to prevent lipid accumulation in various disease conditions. In the ischemic kidney, defects in the transport and oxidation of fatty acids can result in accumulation of fatty acids in the cytoplasm which may contribute to the decrease in ATP production and mitochondrial energetics.[12] FA are taken up in proximal tubule cells via specialized transport proteins on the plasma membrane, such as CD36, and also by retrieval from the glomerular filtrate by receptor-mediated albumin endocytosis.[18,20] Since FA is impermeable to outer mitochondrial membrane (OMM), FAs are activated to acyl-CoA by acyl-CoA synthetases in the cytosol. Carnitine palmitoyltransferase-1 (CPT-1), the rate-limiting enzyme of carnitine shuttle on OMM, catalyzes the conversion of acyl-CoA to acylcarnitine, thus facilitating its passage through inner mitochondrial membrane (IMM) by carnitine-acylcarnitine translocase (CPT-2).[18,20,21] CPT-2 on the IMM reconverts the acylcarnitine into an acyl-CoA. The acyl-CoAs undergo FAO to generate acetyl-CoA, to fuel the tricarboxylic acid cycle and production of NADH and $FADH_2$, that serve as electron donors to the electron transport chain for ATP production.[20] Deficiency of CPT-1 results in energy failure and diverse kidney diseases including diabetic nephropathy and chronic kidney disease.[18,20] In the ischemic kidney, the activity of CPT1 is

attenuated, resulting in reduced transport of FAs into the mitochondria, decreased β-oxidation and consequent lipid deposition.[22,23]

Although the causal relationship is unclear, a number of reports suggest that lipid accumulation in certain tissue and cell could be harmful, and is referred to as lipotoxicity.[24,25] Accumulation of triglyceride, which is produced by dysregulated glycerol and non-esterified fatty acid (NEFA) presumably derived from impaired FA transport and/or FAO in cytoplasm causes lipotoxicity, contributing to decreased production of ATP and mitochondrial energy metabolism.[25,26] NEFA triggers mitochondrial dysfunction as a cause of energetic failure of proximal tubules during hypoxia/reoxygenation, and intracellular accumulation of NEFA and triglycerides with downregulation of mitochondrial FAO.[25] Accumulation of triglycerides is observed in tubule injured by ischemic, glycerol-induced and septic AKI, as well as in *in vitro* damaged proximal tubule cell.[26] Lipid accumulation in ischemic proximal tubule may result in persistent energy depletion with NEFA-induced mitochondrial dysfunction.[25] It is still under debate whether FA or triglyceride *per se* is toxic, but it is clear that intrarenal lipid accumulation, by as of yet undefined mechanisms, can represent characteristics of diseased status.[24,25,27] Some data show that, in two chronic kidney disease (CKD) mice models (diabetic nephropathy and folic acid nephropathy), cell-specific lipid accumulation by overexpression of CD36 in tubular epithelial cells did not generate renal fibrosis.[28] It is proposed that mitochondrial defects in energy production are more detrimental than the lipid accumulation in the cytoplasm. Further studies to define the causal relationship between lipid accumulation and energy depletion and the effect of lipotoxicity during AKI are warranted.

PGC1-PPARα axis is well described as a master regulator of FAO genes in diverse tissues, including kidney and its modulation affects the outcome of AKI.[18,29,30] Studies by Portilla et al.[31-34] have demonstrated persisting disturbances of mitochondrial and peroxisomal FAO during both ischemic and cisplatin-induced AKI. These changes are proposed to be driven by downregulation of gene transcription and decreased DNA binding activity of PPARα and decreased expression of its coactivator, peroxisome proliferator activated receptor-gamma coactivator-1 (PGC-1). Activation of PPARα by fibrates and other PPARα ligands led to improvement of renal function and prevention of necrotic and apoptotic tubule cell death in cisplatin nephrotoxicity.[35] Importantly, the PPARα ligand effects were not seen in PPARα null mice,[36] supporting specific mediation by this pathway in cisplatin nephrotoxicity. However, the mechanisms that may lead to inhibition of PPARα signaling pathways in AKI are not defined. Moreover, PPARα activation through selective stimulation of FAO seems to eliminate potential toxic metabolites, such as ceramides, which are derived from impaired FAO, contributing to lipotoxicity.[18,25,37] In addition to its role in FAO, PGC-1 has been recognized as a master regulator of mitochondrial biogenesis and its metabolic switch to FAO to glycolysis.[14] Mitochondrial biogenesis and its regulatory mechanism were reviewed in detail elsewhere.[12,30]

Targeting mitochondrial dysfunction in AKI

Experimental and clinical studies were done or is ongoing for targeting mitochondrial dysfunction in both AKI and CKD.[20] Strategies improving mitochondrial FAO is effective in suppression of albuminuria in type 2 diabetic patients, even though unwanted effects are seen in some renal diseases.[38,39] In addition, mitochondrial targeting for treatment of AKI is still attractive, since drugs, such as SS-31 (Szeto-Schiller 31) and MitoQ, in early clinical trials have shown beneficial effect in renal diseases.[20] SS-31, which is a cell-permeable tetrapeptide targeting mitochondria, has a beneficial effect for preventing disruption of mitochondrial matrix and accelerating ATP recovery in experimental IRI model. MitoQ is a mitochondria-targeted lipophilic antioxidant and is shown to protect mitochondrial respiratory complex in septic AKI. However, it has potential side effects including, inhibition of oxidative phosphorylation and potential role as a pro-oxidant by its characteristics of a lipophilic cation. Indirect activation of CPT-1 by carnitine and 5-aminoimidazole-4-carboxyamide ribonucleoside (AICAR; activator of AMPK) protect ischemic AKI in mice.[40] Similarly, propionyl L-carnitine also have a beneficial effect to prevent IRI through mitigation of oxidative stress and neutrophil infiltration.[41]

Despite the fact that strategies are developed to preserve or restore mitochondrial function and FAO in AKI, major obstacles remain. Since mitochondria is a major organelle to generate ROS, maladaptive mitochondria might increase oxidative stress. Moreover, before attempting mitochondrial therapies, it is required to have a comprehensive understanding of mitochondrial energy metabolism, as well as redox status, in *in vivo* tubular cells and in diseased tissue.[14]

CONCLUSION

Disruption of mitochondrial homeostasis, which is critical to ATP production, is associated with mitochondrial dysfunction and AKI pathogenesis. Persistent inhibition of FAO promotes ATP depletion and subsequent inflammation in AKI, resulting in lipotoxicity and CKD progression after AKI. A better understanding to mitochondrial energy metabolism in the setting of AKI may lead to development of effective therapeutics for prevention of ATP depletion and treatment of AKI.

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