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The Frailty of Advanced Kidney Disease: The Role of Mitochondria

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ABSTRACT

Uremic toxins contribute to the impairment of mitochondrial function that subsequently could result in organ failure. Mitochondrial dysfunction also plays an essential role in the pathogenesis of sarcopenia in chronic kidney disease patients. It may be feasible to assess the effect of mitochondrial-targeted drugs to treat sarcopenia in patients with chronic kidney disease.

Keywords: Chronic kidney disease, mitochondria, muscles

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INTRODUCTION

The Sherpas, who have lived on the high plateau of the Himalayas at an average altitude of more than 14 700 feet, are famous for their speed-climbing records reflective of their muscle strength, which is much higher than the general population. The muscle biopsy findings in these people indicated that their mitochondria were more functional than that of other people who live at lower altitudes, indicating the critical role of mitochondria in muscle function.[1] In contrast, frailty and sarcopenia are commonly present in patients with moderate to advanced chronic kidney disease (CKD) reflective of their muscle strength that is much lower than the general population. The mitochondria of patients with end-stage kidney disease (ESKD) have been reported to be less functional.[2] In essence, these 2 extreme populations reflect the crucial role of mitochondrial function on muscle strength, sarcopenia, and frailty.

Abnormalities in muscle structure and function are frequent findings in patients with CKD, especially in ones on maintenance dialysis. These abnormalities are evidenced by increased frailty, weakness, and a decrease in the quality of life, mostly observed once the estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m^2 and gradually becomes more prominent as kidney failure progresses.[3,4] Most notably, symptoms related to muscle wasting and dysfunction are reported in two-thirds of patients at the initiation of dialysis. Given the central role of mitochondria in producing adenosine triphosphate (ATP) as the primary energy source, these symptoms are prominent when ATP is intensely used and potentially reflect the extent of the mitochondrial abnormalities.

MITOCHONDRIAL FUNCTION

Mitochondria began to live inside the cell due to merging a single-celled organism like rickettsia with the archaeal cell approximately 2 billion years ago.[5] In essence, mitochondria are ultimately a domesticated bacterium that can stimulate the immune system under suitable environmental conditions, just like exogenous bacteria.[6] In addition to its role as the primary site for cellular ATP production, which is the energy currency of all living

organisms, mitochondria also regulate apoptosis, buffering of cytoplasmic calcium, and production of reactive oxygen species (ROS).[6,7]

Mitochondrial protein synthesis is controlled by nuclear and mitochondrial DNA (mtDNA). These proteins build up the mitochondrial skeleton and are involved in the citric acid cycle and the electron transport chain responsible for ATP synthesis. The mtDNA, which is free of histone proteins, is in contact with the inner membrane where oxidant substances are synthesized and are vulnerable to ROS-related damage due to the lack of histone protein.[6] Normally, moderate levels of mitochondrial ROS play a role in signal transduction to the nucleus and control protein synthesis. However, abnormally functioning mitochondria lead to a decrease in ATP synthesis, increase in ROS production, and release of cytochrome C, which stimulates apoptosis (Figure 1).[8]

Mitochondria can either split (fission) or join together with adjacent mitochondria (fusion). A significant increase in the number of mitochondria in distal tubules after chronic loop diuretic use is a typical example of mitochondrial fission.[9] Deficiencies in mitochondrial fusion and fission have substantial negative effects on skeletal muscle function.[2] When mitochondria become dysfunctional because of pathological processes, it is removed by specific autophagy called mitophagy. Mitochondrial turnover by mitophagy is a critical process to clear the dysfunctional mitochondria.[6] The mitochondria control the intrinsic apoptotic pathway by releasing soluble proteins, such as cytochrome C, from the intermembrane space to activate caspase in the cytosol. When mitochondrial membrane integrity is compromised, cytochrome C quickly passes to the cytoplasm and triggers an intrinsic apoptotic pathway.[6,7]

KIDNEY AND MITOCHONDRIA

Mitochondria have critical functions in the kidneys, where a substantial amount of energy is required for its metabolic, clearance, and filtration functions. The proximal tubule and loop of Henle, where an enormous amount of reabsorption occurs, are rich in mitochondria.[10] Recent studies have demonstrated the critical roles of mitochondria in the onset and recovery of acute kidney injury.[11] When tubule cells are exposed to exogenous or endogenous toxic substances, nephron segments rich in mitochondria, such as the proximal tubule, appear to be more susceptible to damage.

Several studies have shown that patients with CKD display skeletal muscle mitochondrial dysfunction compared to healthy individuals. Studies on muscle biopsies from patients on maintenance hemodialysis exhibit various abnormalities in skeletal muscle mitochondria, including the signs of fragmentation, cristae swelling, presence of autophagosomes, and increased lipofuscin pigment, indicative of oxidative damage,[12] worsening kidney function, and longer dialysis vintage have been found to be correlated with the extent of skeletal muscle mass loss.[4] Although protein-energy wasting, which is mediated by insulin resistance and inflammation, is the primary mechanism underlying muscle wasting in these patients,[13] mitochondrial dysfunction may also be an important factor underlying insulin resistance and inflammation.

CHRONIC KIDNEY DISEASE AND MUSCLE MITOCHONDRIAL FUNCTION

As stated above, abnormalities in muscle structure and function along with relatively decreased muscle mass are hallmarks of advanced kidney disease, which is shown to be associated with the degree of loss of kidney function.[3,13,14] Changes in mitochondrial morphology have been reported in patients with CKD. Recent studies have also shed light on the molecular mechanisms of these changes.[2] Oxidative stress, the most important marker of mitochondrial dysfunction, has been shown to increase as the CKD stage increases. Fragmentation and fission, a mitochondrial adaptation to noxious stimuli, have been

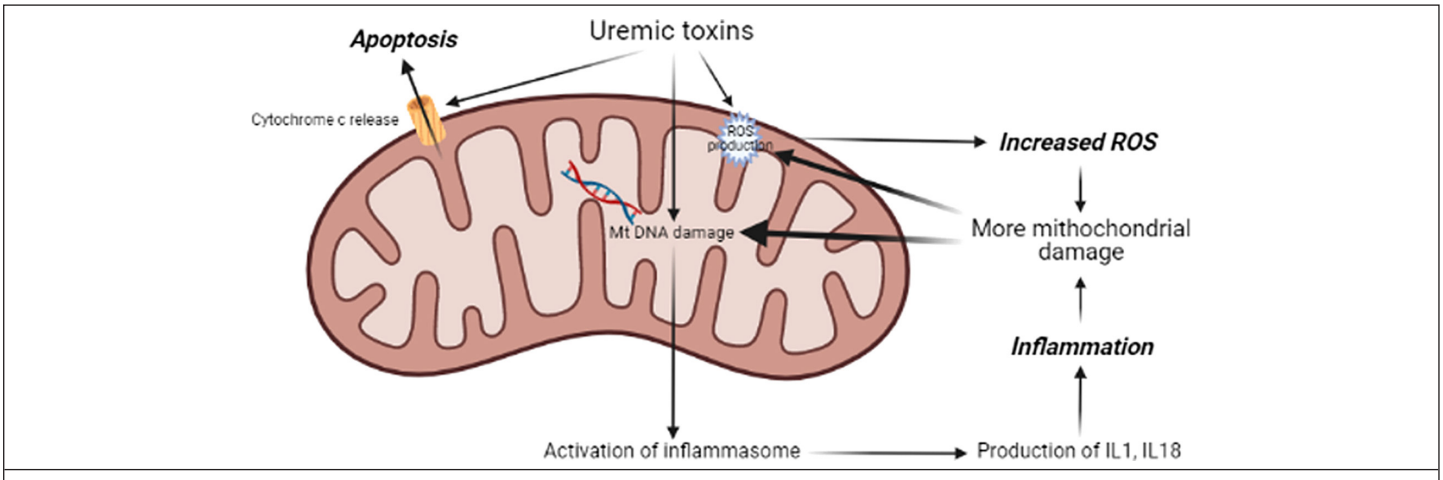

Figure 1. Dysfunctional mitochondria in patients with chronic kidney disease.

demonstrated in muscle biopsies of patients with advanced kidney disease.[4] Mitochondrial fragmentation may trigger cell death.[11] Mitophagy is ROS-dependent, which is heavily regulated by cellular redox activity. We have shown that BNIP3, a marker of mitophagy, is increased in skeletal muscle in patients with CKD stage 5. Fission reaction takes place in mitochondria before mitophagy. Our data suggest that mitophagy severity is correlated with oxidative stress and CKD stage.[2,4,15] Mitochondrial volume is also smaller in The authors declared that this study has received no financial support. patients compared to healthy control, another sign of mitophagy. Decreased mitochondrial DNA copy number is also an indicator of increased mitophagy in CKD patients. Activation of mitophagy is known in the case of protein malnutrition, hypoxia, and membrane potential dissipation.

Inflammation, oxidative stress, and insulin resistance are proposed to be the primary mechanisms underlying CKD-related muscle loss.[6,7] These pathological processes that develop due to advanced kidney disease can directly affect the mitochondria leading to the emergence of dysfunctional mitochondria, which are also shown to be a primary source of production of ROS and inflammation. Reactive oxygen species not only harms molecules inside the cell but also triggers inflammation. Reactive oxygen species has been shown to activate hypoxia-inducible factor 1α, the NLRP3-inflammasome pathway, innate immune response, and the transforming growth factor-β pathway that has pro-fibrotic effects in disease conditions.[9]

Fat accumulation outside of the muscle fibers, called intermuscular adipose tissue (IMAT), is associated with decreased physical activity and low muscle quality. Chronic kidney disease patients with frailty have increased levels of IMAT.[4] Since mitochondria are the main organelle in lipid metabolism, increased fat density may be indicative of mitochondrial dysfunction. However, it is proposed that IMAT causes mitochondrial dysfunction directly and results in decreased physical performance and sarcopenia.[17] Mitochondrial damage in obese and insulin-resistant patients is attributed to lipid toxicity. In studies evaluating IMAT in stages 3-5 CKD patients, IMAT accumulation was significantly increased in stage 5 patients compared to the patients in stages 3-5. There was also a significant association between impaired mitochondrial function and IMAT levels, as assessed by dynamic tests.[4]

CONCLUSION

Mitochondrial function deteriorates with the progression of kidney disease and associated loss of kidney function. The uremic environment causes the generation of free radicals, stimulates an inflammatory milieu, and activates apoptotic and mitophagy pathways leading to the loss of mitochondria. Furthermore, uremia changes mitochondrial shape, fission, and fusion dynamics. Changes in mitochondria function and morphology may lead to muscle wasting, sarcopenia, and frailty. Mitochondria-targeted agents could potentially improve patients' nutritional and metabolic status with moderate to advanced CKD.

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