

Chronic Kidney Illness, Acute Kidney Damage, and Mitochondrial Cytopathies of the Renal System All Include Mitochondrial DNA-Mediated Inflammation

Abstract

Adenosine triphosphate synthesis, metabolic control, the formation of reactive oxygen species, the preservation of intracellular calcium homeostasis, and the management of apoptosis are only a few of the important functions performed by mitochondria, which are key intracellular organelles. Both healthy and pathological situations frequently result in the change of mitochondria. The function of mitochondria in the kidneys is directly tied to their form and structure, and illnesses associated with mitochondrial malfunction have been found. "Mitochondrial cytopathies" refer to illnesses caused by mitochondrial malfunction. Evidence suggests that the two primary paths of end-stage renal disease, chronic kidney disease (CKD), and acute kidney injury, include mitochondrial dysfunction in their aetiology (AKI). Kidney mitochondrial cytopathies primarily present as cystic kidney disorders, localised segmental glomerular sclerosis, and tubular abnormalities. Mutations in the mtDNA and nDNA genes are responsible for the problems. Because the proximal tubular cells are more susceptible to oxidative stress, they are more likely to develop respiratory chain abnormalities, which can result in low-molecular-weight proteins or an electrolyte loss. Myoclonic epilepsy, ragged red muscle fibres (MERRF), and Pearson's, Kearns-Sayre, and Leigh syndromes are common in patients with mitochondrial tubulopathy. The bulk of mtDNA fragment deletions found in these disorders are genetic mutations. Studies have demonstrated the close relationship between mitochondrial dysfunction and the development of CKD by demonstrating significantly increased ROS production, upregulation of COX I and IV expression, and inactivation of complex IV in peripheral blood mononuclear cells of patients with stage IV-V CKD. With the ultimate objective of finding mitochondrial targets to enhance therapy of patients with chronic renal illnesses, it is also explored how cellular signals and demands translate into mitochondrial remodelling and cellular damage, including the impact of microRNAs and lncRNAs [1].

For healthy kidney physiology, mitochondria's integrity and functionality are crucial. Since its anomalies have the potential to impair aerobic respiration, cause cellular malfunction, and even cause cell death, mitochondrial DNA (mtDNA) has received a great deal of attention in recent years. Urinary mtDNA-CN has the potential to be a useful marker for clinical diagnosis and evaluation of kidney function. In particular, aberrant mtDNA copy number (mtDNA-CN) is related with the onset of acute renal damage and chronic kidney disease. According to a number of lines of research, mtDNA may also activate innate immunity, causing inflammation and fibrosis in the kidneys. Under conditions of cell stress, mtDNA can be released into the cytoplasm and detected by a variety of DNA-sensing systems, such as Toll-like receptor 9 (TLR9), cytosolic cGAS-stimulator of interferon genes (STING) signalling, and inflammasome activation. These systems then control subsequent inflammatory cascades. The characteristics of these mtDNA-sensing pathways mediating inflammatory responses are outlined in this review, along with their significance in the pathophysiology of acute kidney injury, nondiabetic chronic kidney disease, and diabetic

Griffith Gilbert*

National Institutes of Health, Bethesda, Maryland, US.

*Author for correspondence:
gilbertgriffith@yahoo.com

Received: 01-Oct-2022, Manuscript No. OAIN-22-77368; **Editor assigned:** 03-Oct-2022, PreQC No. OAIN-22-77368 (PQ); **Reviewed:** 17-Oct-2022, QC No. OAIN-22-77368; **Revised:** 22-Oct-2022, Manuscript No. OAIN-22-77368 (R); **Published:** 29-Oct-2022; DOI: 10.47532/oain.2022.5(5).49-52

kidney disease. We also emphasise the unique treatment target for these kidney disorders, mtDNA-mediated inflammatory pathways [2].

Keywords: Mitochondrial cytopathies • renal • glomerular

Introduction

The double-membraned cell organelles known as mitochondria, or the “power house” of the cell, are in charge of transforming the energy from oxidative phosphorylation into “fuel” in the form of adenosine triphosphate (ATP). These are also important in cell signalling, metabolism, and apoptosis control, as well as calcium storage. Since an organ’s energy need is directly correlated with the amount of mitochondria it contains, the heart has the most mitochondria, followed by the kidneys. For the energy-intensive duty of reabsorbing the bulk of the glomerular filtrate, the kidneys’ renal tubular cells are the richest in mitochondria. The interaction of several cell types, such as endothelial cells, podocytes, mesangial cells, and tubulointerstitial cells, is essential for renal function, which is both energy-demanding and dependent on mitochondrial activity. Renal dysfunction is a complex condition that develops as a result of a short-term or long-term injury to the organ. Recent research has suggested a connection between mitochondrial structural and functional changes and renal inflammation and tissue damage during acute kidney injury (AKI) and chronic kidney disease (CKD).

The double membrane-bound organelle known as mitochondria may be found in almost all eukaryotic cells. In addition to producing adenosine triphosphate (ATP), mitochondria also play a role in the creation of heat, redox equilibrium, calcium signalling, the cell growth and death pathway, and antimicrobial immunity. The integrity and correct operation of mitochondria are vital for the regular function of cells, especially in organs that require a lot of energy, such the heart and kidney, because of their essential role in supplying energy. When the mitochondria are damaged, a number of mitochondrial components are released into the cytoplasm or extracellular environment, where they are recognised as damage-associated molecular patterns (DAMPs) by pattern recognition receptor (PRRs), which in turn triggers proinflammatory reactions downstream. We concentrate on mitochondrial DNA (mtDNA)

in this study despite the fact that several other mitochondrial components, including N-formyl peptides, ATP, and cardiolipin, can function as mitochondrial DAMPs [3].

mtDNA has a double-strand circular structure that is 16.5 kb long and originates from an ancient bacterial genome. The range of mtDNA copies is between 100 to 10,000, depending on the kind of cell. 11 messenger RNAs from mammalian mtDNA can be translated into 13 proteins, resulting in the formation of four oxidative phosphorylation (OXPHOS) complexes. Because of its subcellular location near the electron transport chain where ROS are produced and the absence of protective histones, mtDNA is more susceptible to oxidative damage than nuclear DNA, despite the fact that a delicate quality control system has evolved to maintain mitochondrial homeostasis. Damage to or mutations in the mitochondrial genome can cause problems with aerobic respiration, cellular malfunction, and even cell death. Evidence is mounting that mtDNA may have a role in the innate immune response’s activation, which is a key step in the aetiology of many illnesses [4].

Rapid loss in kidney function is a hallmark of acute kidney injury (AKI), which can lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD). Due of its high mortality and morbidity, it continues to be a global concern. Nephrotoxicity, sepsis, and renal ischemia are the three primary causes of AKI. Although a critical role for prolonged or severe inflammation has long been understood, the aetiology of AKI and CKD is largely unknown. Damage to tubular epithelial cells has been determined to be essential for starting the inflammatory response because it activates local immune cells like macrophages and leukocytes that infiltrate the kidney and release inflammatory mediators to intensify the cascades. Additionally, recent research has shown that the aetiology of AKI and the development of CKD were both affected by mtDNA-associated inflammatory responses [5].

Mechanism of mitochondrial cytopathies

A set of diseases known as mitochondrial

cytopathies are defined by mitochondrial or nuclear DNA abnormalities in the genes that code for mitochondrial proteins. Ageing and, essentially, all chronic illnesses are characterised by mitochondrial dysfunction, which is defined by a reduction in the production of high-energy molecules like adenosine-5'-triphosphate (ATP) and a loss of efficiency in the electron transport chain. An insufficient number of mitochondria, an inability to supply them with the substrates they require, or a problem with their electron transport chain or ATP synthesis machinery are all causes of mitochondrial failure.

As many nuclear genes are important for the normal maintenance of mtDNA, inherited types of mitochondrial cytopathies are associated with a sizable number of mutations in mitochondrial DNA (mtDNA). Renal impairment results from mutations in these genes that result in both quantitative (mtDNA depletion) and qualitative abnormalities (mtDNA deletions) in mtDNA. The swelling and disintegration of mitochondrial structure happens sooner than the rise in blood creatinine, which is a common indicator of kidney damage. These modifications also suggest a direct relationship between declining mitochondrial metabolism and declining renal function [6].

According to several studies, problems with the control of the mitochondrial electron transport chain, proton gradient, and membrane potential can lead to mitochondrial malfunction. Adenosine triphosphate (ATP) concentration is decreased as a result of these disruptions, and reactive oxygen species produced by the mitochondria are produced more often (mROS). These reactive oxygen species encourage inflammation and kidney damage [7].

Mitophagy

Mitophagy is an autophagic mechanism used to selectively remove unhealthy or unnecessary mitochondria. Defective mitophagy has been linked to a number of human disorders, including ageing, cancer, cardiovascular disease, and several kidney diseases. Acute kidney damage, diabetic kidney disease, and lupus nephritis all have a pathophysiology that is attributed to altered mitophagy-related pathways. Initiation, preparation of the mitochondria for identification by autophagy machinery, formation of the autophagosome,

lysosomal sequestration, and hydrolytic destruction are all steps in the process.

According to Palikaras, there are three different forms of mitophagy: basic, planned, and stress-induced. A constant, steady-state process called basal mitophagy is in charge of destroying and recycling mitochondria that are deteriorated and old. There is a tissue-specific distribution of this kind of mitophagy, with low levels in the thymus and high levels in the heart and kidneys. In order to mediate metabolic responses to environmental constraints, stress-induced mitophagy aids mitochondrial quality management [8].

The PINK1/Parkin route or receptors are the two molecular mechanisms that mediate mitophagy, which is substantially described by these pathways. The outer and inner mitochondrial membranes include mitophagy receptors that can really cause mitophagy to occur. FUN14 domain-containing protein 1, BNIP3 and BCL2 interacting protein 3, and FKBP prolyl isomerase 8 are proteins that encourage mitophagy. In general, it is thought that mitophagy malfunction causes mitochondrial dysfunction and the gradual buildup of faulty organelles, which causes cell death and tissue damage. Blocking mitophagy causes damaged mitochondria to build up and produce ROS, which activates the NLRP3 inflammasome.

Kidney diseases and mtDNA

AKI and mtDNA. It has long been known how important mitochondrial health and function are for maintaining appropriate renal function. mtDNA copy number (mtDNA-CN) anomalies have been often seen with the onset of AKI in both animal models and human studies, serving as a crucial marker of mitochondrial function. The mtDNA-CN of whole cell lysates decreased in the murine model of LPS-induced kidney injury, whereas the mtDNA-CN of cytoplasmic extracts increased, likely indicating that under cell stress, mtDNA replication was constrained but that preexisting mtDNA was still released from the mitochondria to the cytosol. In both the bilateral ureteral obstruction (BUO) and ischemia-reperfusion models in mice, analysis of circulating mtDNA-CN showed that the concentration of mtDNA in plasma tended to rise, but not considerably. Due to its accessibility, association with renal function, and prognostic significance for the kidneys, urine mtDNA-CN (UmtDNA-CN) has a larger potential as an excellent indication

for AKI than circulating mtDNA-CN. Increased circulating mtDNA was not linked to renal function, according to a case-control study on systemic inflammatory response syndrome (SIRS), while the amount of UmtDNA was associated with the severity of AKI. The research also showed that tubular epithelial cells responded to mtDNA interference by expressing pro-inflammatory cytokines [9].

Therapeutic Targets and Future Perspectives

The mitochondrial quality control system is a collection of internal processes that cooperate to maintain mitochondrial homeostasis. These processes include mitophagy, mtDNA repair, mt-ROS scavenging, and mitochondrial synthesis. Since mtDNA destruction or release frequently serves as the first step in mtDNA-sensing pathways influencing inflammatory responses, it has been hypothesised that preventative measures specific to mtDNA or mitochondria may be preferable options for the treatment of kidney injury. First, it has been demonstrated that a number of antioxidants that target mitochondria, such as mitoquinol mesylate (MitoQ), SS-31, or plastoquinol decylrhodamine 19 (SkQR1), may effectively reduce ROS generation and kidney damage while promoting the restoration of kidney function. MitoTEMPO, a specialised scavenger of mitochondrial superoxide, reduced mitochondrial damage and inflammation in IR-induced AKI, in part by reversing the drop in TFAM transcription and mtDNA depletion brought on by too much mt-ROS. Treatment with the mitochondrial KATP channel opener diazoxide was also observed to lessen ROS buildup and mtDNA oxidation, which helped to lessen renal ischemia damage. Through the processes of mitophagy, which destroys the old or damaged mitochondria, and mitochondrial biogenesis, which creates new, functioning mitochondria, mitochondria are continuously regenerated [10].

The primary regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor gamma coactivator (PGC-1), is

extensively expressed in the kidney, making it a potential therapeutic target for several kidney disorders. Following IR-induced AKI in mice, treatment with formoterol, a particular 2-adrenergic agonist, increased mitochondrial biogenesis and aided the restoration of renal function via activation of PGC1. AKI also affected the expression of mitochondrial proteins and mtDNA-CN, however agonism of 5-hydroxytryptamine 1F (5-HT1F) receptors boosted PGC1- transcript levels and corrected this.

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