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Mitochondrial dysfunction in kidney injury: potential therapeutic approaches

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Mitochondria are unique organelles that are essential for a variety of cellular functions, including ATP synthesis, calcium homeostasis, cell survival, and cell death. Mitochondria are an important source of energy production in eukaryotic cells and also play an important role in the production of lipids, nucleic acids, and amino acids. Mitochondria are vulnerable to oxidative stress. The main sources of ROS synthesis in cells are mitochondria and NADPH oxidase (NOX). In mitochondria, ROS is produced during the respiratory chain, while in NOX it is produced along the membranes of neutrophils and phagosomes. Under certain conditions, the production of free radicals such as $OH^{\bullet-}$, and $O_2^{\bullet-}$ will result in vulnerabilities. ROS which is produced by mitochondria has many targets, including lipids, proteins, DNA, RNA, and mitochondrial DNA (mtDNA), which become a vulnerable target for oxidative stress due to the lack of histones. Impaired mtDNA and disrupted mitochondrial genome integrity have main roles in the development of severe early-onset and chronic aging-related diseases. It is becoming increasingly clear that long-term, tiny mtDNA damage is not only related to the aging process but may also be closely related to diabetes and nephropathies. Mitochondrial dysfunction has the main role in renal diseases. Epigenetic alterations and interactions between mtDNA, ROS, and inflammatory factors affect nephrons. Alterations of mtDNA affect the development and progression of chronic kidney disease. Alteration of mtDNA also has a significant role in nephropathies monitoring. Evidence suggests that modification in several mtDNA copies in the circulation and urine reflects mitochondrial dysfunction and kidney disease severity. This review will describe mitochondrial antioxidants in nephropathies therapy. Targeted mitochondrial antioxidants will become a new insight in nephropathies therapy. mtDNA can also be a therapeutic target.

Keywords: *Mitochondrial, renal disease, mtDNA, oxidative stress*

INTRODUCTION

The kidney is a dynamic structure and has various physiological functions to maintain homeostasis. This dynamic structure is always affected by internal and external damage, which might impair the innate function of the kidney. But the same injury activates endogenous mechanisms to eliminate the injury, repair, and restore normal function. Lack of timely activation of renorestorative mechanisms or insufficient strength of these mechanisms leads to the accumulation of destructive factors and further tissue damage and the formation of a defective cycle in kidney function.

As the vicious cycle continues and more damage occurs over time, the normal function of the kidneys gradually decreases, and eventually disappears. To prevent and treat kidney damage, four

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points are important. The first is to know the macroscopic and microscopic structure of the kidney, the second is to understand the physiological and pathological mechanisms at the cell, organelle, and molecular levels, the third is to understand the restorative mechanisms and the fourth is the rapid therapeutic response. Time is an important factor in repairing, regeneration, and prevention of disease progression.

Mitochondrial structure

Mitochondria include an outer mitochondrial membrane (OMM) and an inner mitochondrial membrane (IMM), an intramembrane space (IMS), and a matrix (space between cristae). The matrix contains abundant proteins, mitochondrial DNA (mtDNA), and three types of RNA. Human mtDNA is a circular molecule with 16,569 pairs of bases. This molecule encodes 13 respiratory chain proteins, 2 rRNA molecules, and 22 tRNA molecules used to translate mitochondrial mRNA. All mtDNA transcripts and their translation products remain in the mitochondria, and all proteins encoded by mtDNA are made on mitochondrial ribosomes, and most proteins are located in the mitochondria (such as mtRNA polymerase) are made on cytoplasmic ribosomes (Kühlbrandt, 2015).

In addition to mtDNA replication, RNA and protein synthesis also occurs in mitochondria. This process is carried out by enzymes and molecules inside the organelle. The mtDNA locates in the mitochondrial matrix and is sometimes attached to IMM. The mitochondrial genome is about 510 times smaller than the nuclear genome. Mutations in mtDNA accumulate throughout the life of an organism, and the accumulation of mutations in mitochondrial genes over several decades might result in aging, degenerative disorders, and tumorogenesis (Falkenberg, 2018).

Respiratory chains are the major source of reactive oxygen species (ROS) in cells, so the contents of mitochondria (mainly the mitochondrial genome) are most exposed to ROS and its damage. In addition, the mtDNA replication system is less effective than the nuclear system in correcting errors resulting from replication and repair of mtDNA damage. As a result, these two factors create defects in mtDNA over time. According to one theory, this gradual accumulation of defects with age is the main cause of many signs of aging (such as decreased GFR). With an increasing percentage of defective mitochondria, energy production capacity decreases, and as cellular respiration rate drops, not only does energy production decrease but also the possibility of ROS production increases (Guo et al., 2018). Mitochondria fulfill a variety of functions in the cell, including the well-known energy production via oxidative phosphorylation. For this reason, the failure of mitochondria to operate correctly is associated with a wide spectrum of genetic disorders.

Energy production and maintenance of mitochondrial membrane potential

ATP is formed by the mechanism of oxidative phosphorylation in the respiratory chain of mitochondrial, which contains 5 protein complexes residing in IMM. The electrons produced during the oxidation of acetyl-CoA in the Krebs cycle are transferred to the intermediate molecules and then to the electron transfer chain in the IMM. As the electron passes through the electron transfer chain (ETC), the proton ions are pumped to the IMS and the electrochemical gradient of the proton ions from the IMS to the matrix is generated. Subsequently, ATP synthase phosphorylates ADP to form ATP by energy from the transfer of proton ions in the electrochemical gradient from IMS to the matrix (Cantó et al., 2015).

Respiratory chain function and ATP production depend on the integrity and stability of the IMM. The cardiolipin phospholipid in IMM has a crucial role in the formation of cristae, the proper curvature of the IMM, and the organization and placement of electron transfer chain complexes. Cytochrome C (Cyt C) as an electron carrier in the ETC is closely related to cardiolipin. When ROS increases, Cyt C acts as a peroxidase enzyme and oxidizes cardiolipin, which in turn leads to the disruption of SIMM integrity. Overproduction of ROS by impairing the integrity and stability of IMM reduces ATP production, opening the mitochondrial permeability transition pore (mPTP), the release of Cyt C (as an activator of mitochondrial apoptosis), and loss of mitochondrial membrane potential ($\Delta\Psi m$) and (Ascenzi et al., 2015).

MPV17 protein as an IMM resident protein has significant physiological effects on mitochon-

drial homeostasis. This protein, as a selective cation channel, controls the mitochondrial membrane potential (ΔΨm) as well as the passage of small molecules such as deoxynucleotides triphosphates (dNTPs). dNTPs are the building blocks of mtDNA. Genetic and structural abnormalities in the MPV17 protein prevent mtDNA repair and synthesis due to the reduction of dNTPs in mitochondria, which is directly related to mitochondrial biogenesis (Antonenkov et al., 2015; Dalla Rosa et al., 2016). MPV-like proteins are involved in ROS metabolism and modulation of apoptosis through functional and binding interaction with serine mitochondrial proteinases (Krick et al., 2008).

Mitochondrial Permeability Transition Pore (mPTPS) is a non-specific channel for the transmission of signals, materials, and ions. These channels regulate the potential of the mitochondrial membrane. CypD is an important regulator of mPTPS. Disruption of these channels leads to impaired ATP production and oxidative stress. mPTPS are physiologically open based on cellular requirements, but under pathological conditions they remain open for a long time, allowing the transfer of various substances (ions, proteins, and water). The mitochondrial membrane potential and ATP production capacity are lost through mPTPS due to unregulated discharge of substances (enzymes, electron transporters, ATP, and ADP), and also the mitochondria burst due to material entry and water osmosis (Kalani et al., 2018).

VDACsare the main carriers on OMM that cause bilateral salts to move between the cytoplasm and mitochondria. VDACs improve renal morphology and renal function by increasing mitochondrial respiratory capacity, reducing mitochondrial fission, improving mitochondrial function and dynamics, and increasing cell survival after acute renal injury (AKI) (Nowak et al., 2020). Mitochondrial outer membrane permeability, release of pro-apoptotic BCl-2 family proteins, loss of mitochondrial inner membrane potential, mitochondrial swelling, and disruption of mitochondrial structure leading to eventual lysis of mitochondria.

Role of mitochondria in oxidative stress

The oxygen molecule is the final electron receptor in the mitochondrial electron transfer chain. In the ETC, 2 water molecules are made by giving 4 electrons to an oxygen molecule and adding 4 protons to it. Mitochondria are the source of energy (ATP) production in the cell. In the process of oxidative phosphorylation, the oxygen molecule is reduced by receiving 4 electrons and producing water. Meanwhile, about 0.4 to 4% of the oxygen molecule is not reduced. So the oxygen molecule is incompletely reduced by taking an electron and becomes an oxygen radical called superoxide anion (O_2●-). Although superoxide anion has a short half-life and is an unstable molecule, it is a strong oxidizing agent and can oxidize all molecules (lipids, proteins, and nucleic acids) in the cell. The superoxide anion (enzymatically and non-enzymatically) is converted to a peroxide anion ($O_2^{\bullet 2-}$) by taking another electron, which is slightly more stable. The peroxide anion is converted to hydrogen peroxide (H2O2) by taking 2 protons. Under physiological conditions, superoxide anions are converted to peroxide anion or hydrogen peroxide (H_2O_2) by the enzyme superoxide dismutase (SOD). Subsequently, H_2O_2 is converted to water by the enzyme catalase and glutathione peroxidases (GPX) (Kirkham and Rahman, 2006).

Under pathological conditions, hydrogen peroxide produces one electron, one hydroxyl radical (OH●-), and one hydroxyl anion (OH-). The hydroxyl radical is a strong oxidant and can oxidize any organic matter in the cell, and the hydroxyl anion in the liquid is converted to water by taking a proton. The superoxide anion reacts with nitric oxide (NO) to generate the peroxynitrite radical (ONOO-), and the hydroxyl radical can react with the chlorine anion (Cl-) to form hypochlorous acid (HOCl), which is also a strong oxidizer. Molecules formed by the placement of an unpaired electron in an oxygen molecule are called oxygen-free radicals. Superoxide anion, peroxide anion, hydrogen peroxide, peroxynitrite, and hypochlorous acid are oxygen free radicals and are highly reactive molecules, hence they are called reactive oxygen species (ROS) (McBride et al., 2006).

Physiologically, in various cellular processes, free radicals or oxidants are produced, each of which has a specific physiological function, and on the other hand, their excess amounts are neutralized by the endogenous antioxidant system. So in the body, there is a real balance between the oxidant system and the antioxidant. Under pathologi-

cal conditions, the production of oxidants increases, and there is not enough antioxidant power to neutralize them. Because of this, oxidants cause a lot of damage to various systems in the body and cause various diseases such as kidney disease (Turrens, 2003).

The most important part of the oxidative system in the body is ROS. An imbalance between the oxidant and antioxidant systems is called oxidative stress, and it is the pressure that oxidants exert on the body. Antioxidant systems or agents contain compounds that can protect the body against the harmful effects of oxidative stress (active oxygen and nitrogen species). Antioxidants play an important role in inhibiting the active species of oxygen and nitrogen and preventing their formation. Endogenous antioxidants are divided into three categories: 1) enzymatic systems such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, 2) small molecules such as vitamin C, uric acid, glutathione, and vitamin E, and 3) Proteins such as albumin, transferrin, ceruloplasmin, and metallothioneins (Valko et al., 2007). Endogenous non-enzymatic antioxidants include: thioredoxin (Trx), glutathione (GSH), α-Lipoic acid (1,2-dithiolane-3-pentanoic acid), melatonin (N-acetyl-5-methoxytryptamine), and coenzyme Q10 and exogenous non-enzymatic antioxidants include: vitamin C, curcumin, resveratrol, quercetin, vitamin E, lycopene, polyphenols, carotenoids, epigallocatechin-3-gallate (EGCG), flavonoids, organic sulfur compounds and several minerals (selenium, copper, zinc, and manganese) (Mailloux, 2018; Sharifi-Rad et al., 2020). Oxidants are always produced in the body and must always be eliminated, so continuous use of antioxidants is recommended.

In pathological conditions, with increasing ROS and decreasing antioxidant factors, ROS accumulates in the mitochondria and directly damages its structure and components. Also, due to the increased permeability of the mitochondrial membrane caused by ROS, ROS leaks into the cytoplasm and in addition to direct damage to cellular structures, activates inflammation, apoptosis, and harmful signaling pathways. Inhibition of mitochondrial oxidants with antioxidant and renoprotective agents is a specific goal in preventing mitochondrial damage and subsequent prevention of injury and progression of kidney disease (Irazabal and Torres, 2020).

Various experimental models showed that with increasing oxidant factors, endogenous antioxidant factors decrease. Therefore, by using exogenous antioxidants, the destructive effects of oxidative stress can be neutralized. These studies showed that the mitochondrial antioxidant defense system is disrupted before the onset of kidney damage. Therefore, by increasing the antioxidant power and maintaining the proper mitochondrial function, further tissue damage can be prevented and the healing process of kidney disease can be accelerated.

Mitochondrial antioxidants include Szeto-Schiller peptide (SSP), MitoQ, and plastoquinone analogs (SkQ1/SkQR1), which accumulate in the mitochondrial matrix and interact with cardiolipin. Cardiolipin is the main constituent of IMM and plays a major role in maintaining the potential of the mitochondrial membrane (Birk, Chao, et al. 2015). SSPs enhance ATP synthesis, decrease electron leakage and ROS formation, prevent cardiolipin peroxidation, and prevent the consequences of mitochondrial impairment, including inflammation apoptosis, (Szeto 2017). In particular, SSP, MitoQ, MitoTEMPO, and SkQR1 protect against kidney damage in experimental models by reducing oxidative damage and inflammation (Xiao et al., 2017).

Mitochondrial biogenesis

The number and content of mitochondria are determined by the metabolic needs of the cell. The defective mitochondria are selectively removed and new mitochondria are created by fusion and fission mechanisms. The molecular mechanism of mitochondrial biogenesis needs a close relationship between mitochondria and the nucleus. The regulatory factors of biogenesis are peroxisome proliferator-activated receptor (PPAR), PPARγ coactivator 1α (PGC-1α), sirtuin-1 and 3 (SIRT1/3) family deacetylase, AMP-activated protein kinase (AMPK), and nuclear respiratory factors 1 and 2 (NRF1 and NRF2) (Quirós et al., 2016). The action of PGC-1α (as an abiogenesis stimulant) is regulated by AMPK-induced phosphorylation and SIRT1-induced deacetylation (Tran et al., 2016). PGC-1α activates the expression of genes and pro-

teins involved in mtDNA replication and transcription, electron transfer chain, and oxidative phosphorylation mechanism by modulating the expression of nuclear transcription factors NRF1 and NRF2 (Zoja et al., 2014).

Lack of oxygen and metabolic disorders activate the transcription factor FOXO3 by inducing stress in renal tubular epithelial cells. Activated FOXO3 reduces cell damage and increases cell survival by stimulating autophagy and neutralizing ROS in renal tubular cells. FOXO3 induces autophagy by enhancing the expression of Atg proteins and neutralizing ROS by increasing the expression of antioxidant factors. Prolyl hydroxylase (PrH) by hydroxylation degrades FOXO3 through the proteasomal pathway of ubiquitin. Hypoxia and metabolic disorders inhibit the action of PrH hydroxylation on FOXO3 (Lin, 2020; Quan et al., 2020).

Under physiological conditions, mitochondrial biogenesis takes two forms: fission and fusion. In infusion mode, two mitochondria join together to form larger mitochondria with larger content. But in the case of fission, one mitochondrion turns into two smaller mitochondria with a smaller volume and lower content. Over time and according to metabolic needs, the internal content of mitochondria increases.

In pathophysiological and abnormal conditions, mitochondrial biogenesis occurs mainly in the form of fission, and over time and with the disorder, the mitochondrial content does not increase. Unfortunately, the new mitochondria cannot produce enough energy and will also act as a hub for ROS production.

Two points are important in the production of new mitochondria. First, the production of new mitochondria should be accompanied by a surge in enzyme content to increase metabolic activity, and second, the production of new mitochondria should be accompanied by an increase in protective content to counteract the activity of oxidants. Therefore, mitochondria without sufficient content (metabolic enzymes and antioxidants) will not be able to produce energy, and also the lack of antioxidants along with the production of oxidants will cause more oxidative damage.

Mitochondrial dynamics

The constant change in the number, size, location, and protein content of mitochondria based on the energy needs of the cell is called mitochondrial dynamics. This dynamic is essential for size, morphology, function, energy production, maintenance of homeostasis, and cell survival (Liesa and Shirihai, 2013). Mitochondrial dynamics control proteins include fission proteins (the large GTPase, dynamin-related protein 1 (DRP1), and mitochondrial fission protein (Fis1)), and fusion proteins (mitofusins 1 and 2 (Mfn1, Mfn2) and optical atrophy 1 (OPA1)) (Zhan et al., 2013).

Sirtuin deacetylases (SIRT1/3) regulate mitochondrial dynamics and function. Matrix-dwelling sirtuins activate the fusion process by deacetylation of fusion proteins and improve mitochondrial function in acute kidney disease (AKI) (Morigi, Perico, et al. 2015). Disruption of mitochondrial dynamics causes tissue damage and renal disease (Benigni et al., 2016).

In the physiological state, Dynamin-related protein 1 (DRP1) controls mitochondrial function by having GTPase as a fission agent. But DRP1 is activated in response to a decrease in ATP or damage to the epithelial cells of the renal tubule and accumulates in the mitochondria, leading to mitochondrial fission and apoptosis. In experimental models, the removal of Drp1 and the use of DRP1 inhibitor (mdivi-1) protect the kidney against kidney damage and improve its function (Perry et al., 2018). And also the interaction between mitofusin 2 (Mfn-2) in the endoplasmic reticulum and Mfn-1 or Mfn-2 in OMM regulates the relationship between the two organelles (Xia et al., 2019).

Mitochondrial mitophagy

The destruction of organs and defective cellular material by lysosomes is called autophagy. In this process, by forming an autophagosome, the contents of the cytoplasm, damaged organs, and dysfunctional proteins are broken down and used as nutrients in the cell. Physiological autophagy in starvation conditions is necessary for ATP production, amino acid recycling, and protein synthesis, and also in these situations, autophagy is a key mechanism in the removal of toxic cellular substances, defective organelles, and the formation of

damage-free cells. Mitophagy is a type of autophagy in which disturbed mitochondria are removed from the cell. Injured mitochondria are encapsulated in autophagosomes and decompose in autolysosomes by losing the potential of the inner membrane (Higgins and Coughlan, 2014).

Mitophagy is a complex mechanism controlled by several signaling pathways, kinase proteins, and mitochondrial proteins that regulate dynamics and transmission. Pathological mitophagy is dependent on ROS and is activated under oxidative stress. Disorders of mitophagy mechanisms lead to kidney disease (Duann et al., 2016).

Mitochondria and cell death

The two main mechanisms of cell death are apoptosis and necrosis, which differ in the type of operation. Apoptosis is a physiological and/or pathological cell death that occurs during certain stimuli. Necrosis, on the other hand, is merely pathological cell death and occurs during severe cell injury such as hypoxia and external toxins. Necrosis is a passive process and occurs in the absence of ATP, while apoptosis is an active process and is dependent on ATP energy.

The process of apoptosis occurs through two internal and external cellular pathways. The external pathway begins with the binding of important ligands such as TNFα and Fas to death-inducing membrane receptors. While the internal pathway (mitochondrial pathway), the main pathway of apoptosis, is associated with alteration in mPTP and liberation of apoptotic agents.

Elevated permeability of the OMM in response to cell death signals releases proapoptotic molecules from the IMS into the cytoplasm, such as apoptosis-inducing factor (AIF) and Smac/DIABLO. The latter has an antagonistic effect on the inhibitors of caspase. AIF normally plays an antioxidant role in mitochondria. AIF released from mitochondria during the process of apoptosis causes damage to nuclear DNA in a caspase-independent pathway. Release of cytochrome c is a common occurrence in apoptosis due to the opening of the mitochondrial permeability transition pore, the presence of a channel-specific for cytochrome c in the outer mitochondrial membrane, swelling, and rupture of the outer mitochondrial membrane (Galluzzi et al., 2018).

However, from the molecular point of view, apoptosis is mainly determined by the balance between the specific regulatory proteins of pre-apoptosis and anti-apoptosis. These include Bax and Bcl- 2 proteins, which are involved as major proteins in the formation of mitochondrial apoptosis. Bax protein releases apoptotic agents such as cytochrome c from the IMS into the cytosol by decreasing the stability and increasing the permeability of the outer mitochondrial membrane. In contrast, Bcl-2 protein preserves the integrity of the mitochondrial membrane by counteracting the apoptotic activity of Bax proteins. In the endogenous or mitochondrial pathway, caspase-9 is an initiator of caspase and also the common denominator of all apoptotic pathways is ultimately the stimulation of caspase-3 and the breakdown of vital cell proteins (Havasi and Borkan, 2011).

Under physiological conditions, Cytochrome C (Cyt C) is freely present in the matrix or binds to them by attaching to cardiolipin and acting as an electron carrier between respiratory complexes III and IV of the ETC. ETC With mitochondrial damage, production, and accumulation of ROS lead to the conversion of cytochrome c to peroxidase, which oxidizes cardiolipin and releases Cyt C from the matrix to the cytosol. Which eventually activates caspase and apoptosis (Wan et al., 2019).

Mitochondria and cell proliferation and differentiation

Cellular proliferation and differentiation upon damages are considered important repair mechanisms. Dynamic changes in morphology as well as in mitochondrial content play an essential role in mediating cell cycle events. During the transition from phase G1 to phase S of the cell cycle, mitochondria form an extensive network of interactions with different cell components. By reducing the potential of the mitochondrial membrane, the progression of phase G1 to phase S can be prevented. By using an uncoupling agent (carbonyl cyanide-4-phenylhydrazone) in rat renal epithelial cells, cell cycle progression can be prevented by reducing the mitochondrial membrane potential. DRP1 is the major regulator of mitochondrial fission and by inhibiting it; the cell cycle in the S phase is stopped (Mitra et al. 2009).

Mitophagy and mitochondrial clearance appear to be crucial for cell differentiation and cell proliferation along with changes in energy production from oxidative phosphorylation to anaerobic metabolism. In the repair of renal tubules after ischemia-reperfusion injury (IRI), the glycolytic capacity of the cell increases by decreasing the number of mitochondria (Pennock et al., 2015).

Energy production and mtROS formation mainly control mitochondrial-related cell proliferation and differentiation. During the transition from phase G1 to phase S due to DNA replication and energy requirements, energy production by mitochondria increases but in the transition from phase G2 to phase M due to a compensatory increase in Glycolysis or reduction of energy demand, the number of mitochondria of the cell is reduced by degradation (Thomasova and Anders, 2014).

In the repair process, the amount of ROS in the cell is inversely related to cell proliferation and differentiation. Thus, ROS enhances cell proliferation and differentiation at physiological concentrations and inhibits at pathological concentrations. ROS in physiological concentrations modulates cell proliferation and differentiation by regulating many transcription factors such as nuclear factor-kB, hypoxia-1 inducing factor, and different protein kinases. Also, ROS in pathological concentrations causes apoptosis and cell death by activating apoptotic pathways and stopping the cell cycle by p53 (Hamanaka and Chandel, 2010; Antico Arciuch et al., 2012).

The cyclin B1/Cdk1 protein complex plays a fundamental role in regulating cell division and mitochondrial activity. This complex is an excellent target for controlling cellular energy production that can promote progress in restorative therapies. The cyclin B1/Cdk1 protein controls the G2 phase of the cell cycle. As the cell cycle continues to mitosis, the cyclin B1/Cdk1 complex migrates from the nucleus to the mitochondria, increasing energy production by phosphorylating mitochondrial proteins (Wang, Fan, et al. 2014). Cdk1 is also activated by pro-apoptotic proteins (Bax and Bak). Activated Cdk1 migrates to mitochondria and induces apoptotic cell death in mitochondria by phosphorylation of anti-apoptotic proteins (Bcl-2 and Bcl-xL) (Darweesh et al., 2021).

Mitochondria and inflammatory response

Inflammation has evolved as a set of complex mechanisms overtime to maintain homeostasis and is a defensive process that protects the body against internal and external pathogens. Excessive strengthening of inflammatory mechanisms in physiological and pathological conditions is harmful and damages the body.

Table 1. Therapeutic targeting of the cyclic GMP–AMP synthase (cGAS) and stimulator of interferon genes (STING) pathway

cGAS inhibitor compounds		**STING inhibitor compound**	
Catalytic site inhibitors	PF-06928215, RU.365, RU.521, G 150, Compound S3,	STING antagonists targeting the CDN-binding site	Tetrahydroisoquinolines (Screening hit Compound 1, Compound 18)
			Astin C
Inhibitors that disrupt DNA binding	Antimalarial drugs (Hydroxychloroquine, Quinacrine, X6)	Targeting STING palmitoylation sites	Nitrofurans (C-176 and C-178, C-170 and C-171)
			Indole ureas (H-151)
	Suramin		Nitro fatty acids (NO2-cLA and NO2-A)
	Suppressive oligodeoxynucleotides (A151)		Acrylamides (BPK-21and BPK-25)
Compounds with the undetermined mechanism of action	CU-76	Inhibitors of unknown mechanism	Compound 13

Under normal circumstances, the inflammatory process is critical for tissue repair after injury. Nevertheless, persistent and prolonged inflammation exists in a range of chronic disorders including diabetes and CKD. Mitochondria is tightly connected with the regulation of inflammation during kidney injury and act as a proinflammatory signaling center. mtROS is an activator of inflammation and increases the expression of proinflammatory genes. Various molecular forms associated with mitochondrial damage, such as formyl peptides and mtDNA, can bind to Toll-like receptors or NOD-like receptors and lead to inflammation (West et al., 2011).

Mitochondrial damage in renal tubular cells by mtDNA leakage through BAX-activated pores in OMM to the cytosol by activating the cGAS-STING pathway (As a sensor sensitive to cytosolic DNA) causes inflammation of the kidney and AKI progress. Inherently, this pathway can detect viral and bacterial DNA and induce immune and inflammatory responses in infected cells, so the prohibition of the cGAS-STING pathway could be an effective therapeutic target in mitochondrial injury and inflammatory kidney disease (Table 1) (Maekawa et al., 2019; Decout et al., 2021). However, activation of this pathway is especially important in resistance and elimination of external pathogens by activating inflammation.

Mitochondria and kidney damage and/or repair

The kidney plays a crucial role in maintaining the homeostasis of the internal environment. Physiological function of the kidney involves three mechanisms: glomerular filtration, reabsorption, and tubular secretion. Through these three mechanisms, the kidneys excrete metabolic wastes and retain nutrients, water, and electrolytes, and regulate osmolality, pH, and arterial blood pressure (Suliman and Piantadosi, 2016).

Active reabsorption of nutrients for the body leads to high energy demand for the kidneys, which is provided only by mitochondrial oxidative metabolism. Active reabsorption occurs mostly in the proximal tubules. These tubules have limited capacity for glycolysis and the main mechanism of ATP production in them is oxidative-phospho-rylation (aerobic respiration) (Lan et al., 2016).

Proximal tubules have many mitochondria, and maintenance of mitochondrial function and homeostasis is essential for physiological renal function. AKI is characterized by a sudden decline in kidney function, often caused by stress, ischemia-reperfusion (IR), sepsis, or nephrotoxins.

AKI is related to high mortality and significantly promotes the development of CKD (5). The results of empirical and clinical studies showed that improper repair after AKI leads to interstitial tubular fibrosis and eventually to CKD. On the other hand, one of the causes of the pathogenesis of kidney damage in AKI and CKD is mitochondrial damage or dysfunction (See et al., 2019).

After the injury, the surviving tubular cells proliferate and migrate to the affected area. The cells in the affected area differentiate and become fully mature tubular cells, and then the process of repairing the damaged renal tubules begins. Mild damage in kidney disease heals quickly by activating nonrestorative processes. While severe and progressive damage in kidney disease with a defective repair process leads to the destruction of nephrons and the development of kidney diseases such as interstitial tubular fibrosis and advanced CKD (Nath et al., 1998).

Transient receptor potential ankyrin 1 (TRPA1) is expressed in renal tubular epithelial cells. In experimental models, TRPA1 increases mitochondrial homeostasis and reduces renal damage by inhibiting fission, inducing fusion, and reducing oxidative stress, and inflammation (Zhu et al., 2018). TRPA1 is elevated in the renal tubules of patients with acute tubular necrosis (ATN) and its tubular expression is directly related to the severity of tubular and renal damage. Tubular TRPA1 is therefore a risk factor for improving renal function in acute tubular necrosis (Dembla et al., 2016; Wu et al., 2019). These effects probably suggest that TRPA1 does not play an independent role in the development of kidney disease but is an intermediary of major mechanisms involved in renal injuries such as increased oxidative stress and inflammation.

The mechanisms involved in kidney damage and repair are complex and consist of several different factors including vascular, tubular, and inflammatory factors as well as different signaling pathways. Understanding how these factors interact is a turning point in repairing and rehabilitating a damaged kidney.

Table 2. Targeting mitochondrial mechanisms for the tre tment of kidney disease

Therapeutics	Chemicals	Action mechanisms
Antioxidants		
MitoQ, MitoTEMPO, MitoE, Mito-CP, plastoquinone analogs (SkQ1/SkQR1), Szeto–Schiller (SS) peptides	Mitoquinone	Accumulation of anti-oxidants at matrix in a ΔΨm-dependent manner; ROS scavenger
Biogenesis inducers		
Resveratrol (SRT501)	Small peptides	AMPK/SIRT-1/PGC-1α axis activator
AICAR		SIRT3 activator, an AMPK agonist
Formoterol		β2-adrenoceptor agonist, enhancing PGC-1α synthesis
ROS metabolism and bioenergetics		
Mitochonic acid (MA-5)	Synthetic compound	OXPHOS-independent increase of ATP synthesis, reduce ROS
Cardiolipin protection		
Bendavia (SS-31)	Szeto-Schiller tetrapeptide	Protect cardiolipin from peroxidation; increase ATP and reduce ROS
		Prevent cyt C transformation into the peroxidase
mPTP inhibitor		
cyclosporin A (CsA)	Small molecule	Interact with cyclophilin D (an mPTP structural protein)
TDZD-8		mPTP inhibitors, GSK3β inhibitor
Fission inhibitor		
Mdivil	Small molecule	Inhibitor of mitochondrial division; induce mitochondria fusion
		Block DRP1 assembly and translocation
K_{ATP} channel opener		
Simdax (Levosimendan)	Small molecule	Calcium sensitizer, K_{ATP} channel opener
cyt C assembly		
KLF6	DNA-binding zinc finger transcriptional regulator	enhance cyt C assembly

Abbreviation: Mitochondrial inner membrane potential (ΔΨm), oxidative phosphorylation (OXPHOS), AMP-activated protein kinase (AMPK), mitochondrial permeability transition pore (mPTP), Glycogen synthase kinase 3β (GSK3β), Dynamin related protein 1 (DRP1)

Kidney damage may alter mitochondrial structure and function in a variety of ways, including changes in calcium homeostasis, membrane integrity, ROS formation, mitochondrial transport, biogenesis, dynamics (fusion/fission), and mitophagy. disruption of mitochondrial homeostasis might in turn cause further kidney damage and cause a detrimental feedback loop (Brooks, Wei, et al. 2009).

Henle ascending thick tubular cells and proximal medullary cells have high mitochondrial due to high energy demand for reabsorption of salts and substances necessary for the body (Weidemann and Krebs, 1969). The main source of energy in tubular cells is ATP production from fatty acid β-oxidation (FAO) in the mitochondria, which is mediated by carnitine palmitoyl-transferase 1 (CPT1) as a restriction enzyme. Therefore, tubular cells are very sensitive to kidney damage due to a lack of energy (ischemic injury and oxidative stress) (Wang and Youle 2009).

Mitochondria is an important factor in various cellular processes such as regulating catabolism and anabolism, maintaining calcium homeostasis and redox potential, and regulating signaling pathways for cell survival and death. Therefore, maintaining the integrity and physiological functions of mitochondria is vital for cellular homeostasis. Mitochondria and their mechanisms have evolved to make the cell and its organs resistant to injury and stress. These mechanisms operate at three different cellular, organelle, and molecular levels and include antioxidant resistance, control of metabolites and messenger molecules, transcription and repair of mtDNA, mitochondrial dynamics (fusion and fission), and mitochondrial biogenesis, and mitophagy (Bhargava and Schnellmann, 2017). Injury and dysfunction of mitochondria lead to cell death, tissue damage, and failure.

Mitochondria play a key role in the mechanisms involved in kidney damage and repair. Mi-

tochondrial pathological changes are evident before and after renal dysfunction. Protecting and improving mitochondrial function before the onset of kidney injury and dysfunction is an important goal in preventing further injury and treating primary injuries. Protecting and restoring mitochondrial function under stress and disease by using genetic or pharmacological renoprotective agents prevents damage and disease progression (Perry et al., 2018).

Mitochondrial damage is typically caused by AKI by sepsis, IRI, and renal toxicity in experimental models mitochondrial damage in AKI is in connection with mitochondrial fragmentation, decreased mitochondrial mass, mitochondrial swelling, and cristae dysfunction, apoptosis, and generally mitochondrial dysfunction (Heidari et al., 2018).

Mitochondria and subsequent renal injury can be treated by increasing mitochondrial function by improving ETC function, biogenesis, and increasing FAO, or by reducing the cellular effects of mitochondrial dysfunction by reducing ROS formation, inflammation, apoptosis, pyroptosis, and autophagy (Tábara et al., 2014).

Renal cancer

Cell culture and in vivo experiments demonstrated that mitochondrial dysfunction is responsible for increased survival of renal cancer cells and cancer metastasis. Bisulfite sequencing analysis revealed that the downregulation may occur by DNA hypermethylation of CpG islands in the promoter regions in renal cancer cells. Taken together, these findings suggested that renal cancer cells acquire additional anti-apoptotic ability through the DNA methylation during the interactions with renal microenvironment, which may in turn lead to the cancer progression and metastasis.

CONCLUSION

Kidney diseases are one of the health problems of the world community and many people are affected by them. The kidney is an active and dynamic organ and is very prone to damage. AKI is caused by infection, toxic substances, and dehydration. If these acute injuries are not repaired and treated, it can lead to deteriorating kidney function and health. As kidney disease progresses, the acute condition may become chronic and lead to CKD. Chronic diseases reduce kidney function over time by creating a vicious-positive cycle. Severe acute injuries and prolonged chronic injuries cause complete loss of kidney function and the final stage of kidney disease, which has no treatment other than dialysis and new kidney transplantation.

For the treatment of kidney injuries, different parts and mechanisms of the kidney at the cellular, organelle, and molecular level can be selected as targets. One of the selected targets is mitochondria, which is the most important center of energy production in the cell. Because cells need enough energy to maintain homeostasis, survive, and prevent injury, targeting the components and mitochondrial signaling pathways can be an appropriate treatment for kidney disease. Interestingly, before the symptoms of kidney disease appear, mitochondrial lesions and disorders appear on an electron microscopic level.

Although it is important to discover the processes and mechanisms that cause kidney disease, it seems that the best treatment in experimental studies is the use of combination therapies. Because tissue damage is widespread in the disease and affects different parts of the cell. Focusing on one cell part and one mechanism may not be very helpful in discovering new therapies.

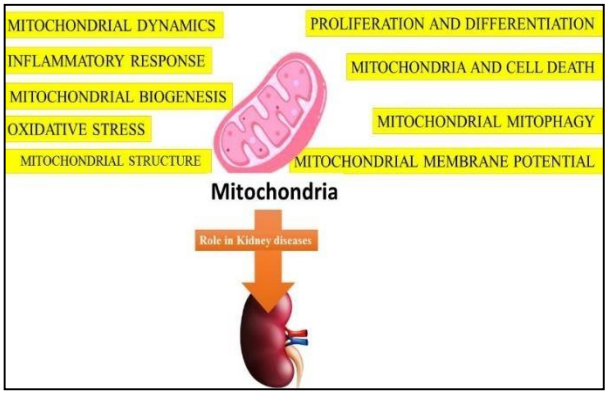

Fig. various factors can be used to inhibit destructive processes.

For example, in the treatment of acute kidney disease, in addition to reducing voluntary activities to reduce kidney function and reduce the need for energy production in the mitochondria, various

factors can be used to inhibit destructive processes (such as oxidative stress, signaling pathways of inflammation and cell death) and stimulate repair processes (e.g. Biogenesis, survival, and repair signaling pathways) (see: Figure). So far, many renoprotective and renorestorative agents have been discovered, but it will take a long time to introduce an effective treatment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Böyrək zədələnməsində mitoxondrial disfunksiya: potensial terapevtik yanaşmalar

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Mitoxondriyalar ATF sintezi, kalsium homeostazı, hüceyrənin sağ qalması və hüceyrə ölümü daxil olmaqla müxtəlif hüceyrə funksiyaları üçün vacib olan unikal orqanellalardır. Mitoxondriya eukariotik hüceyrələrdə mühüm enerji istehsalı mənbəyi olmaqla, həmçinin lipidlər, nuklein turşuları və amin turşularının sintezində də əhəmiyyətli rol oynayır. Mitoxondriya oksidləşdirici stresə həssasdır. Hüceyrələrdə oksigenin reaktiv formalarının (ORF) sintezinin əsas mənbələri mitoxondriya və NADPH oksidazadır (NOX). Mitoxondriyada ORF tənəffüs zəncirində, NOX vasitəsilə isə neytrofillərin və faqosomların membranları boyunca istehsal olunur. Müəyyən şərtlər altında OH●- və O_2●- kimi sərbəst radikalların istehsalı zəifliklərlə nəticələnir. Mitoxondriya tərəfindən istehsal olunan ORF, histonların olmaması səbəbindən oksidləşdirici stress üçün həssas bir hədəfə çevrilən lipidlər, zülallar, DNT, RNT və mitoxondrial DNT (mtDNT) daxil olmaqla bir çox molekullara təsir edir. Zədələnmiş mtDNT və pozulmuş mitoxondrial genom bütövlüyü qocalma ilə əlaqəli xroniki və ağır erkən xəstəliklərin inkişafında əsas rola malikdir. Getdikcə daha aydın olur ki, mtDNT-nin uzunmüddətli kiçik zədələnməsi təkcə qocalma prosesi ilə deyil, həm də diabet və nefropatiyalarla sıx əlaqəli ola bilər. Böyrək xəstəliklərində mitoxondrial disfunksiya əsas rol oynayır. mtDNT, ORF və iltihab faktorları arasında epigenetik dəyişikliklər və qarşılıqlı təsirlər nefronlara təsir göstərir. mtDNT-dəki dəyişikliklər xroniki böyrək xəstəliyinin yaranmasına və inkişafına təsir göstərir. mtDNT-nin dəyişikliyi həmçinin nefropatiyaların monitorinqində də əhəmiyyətli rola malikdir. Sübut olunub ki, qan dövranında və sidikdə mtDNT-nin bir neçə nüsxəsinin modifikasiyasının aşkarlanması mitoxondrial disfunksiyanı və böyrək xəstəliyinin şiddətini əks etdirir. Bu məqalədə nefropatiyaların müalicəsində mitoxondrial antioksidantlar haqqında məlumat verilir. Məqsədli mitoxondrial antioksidantlardan istifadə nefropatiyaların müalicəsində yeni bir fikir olacaq. mtDNT də terapevtik hədəf ola bilər.

Keywords: *mitoxondrial; böyrək xəstəliyi; mtDNT; oksidləşdirici stres*

Митохондриальная дисфункция при повреждении почек: потенциальные терапевтические подходы

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Митохондрии являются уникальными органеллами, которые выполняют различные клеточные функции, включая синтез АТФ, гомеостаз кальция, выживание клеток и их гибель. Митохондрии являются важным источником производства энергии в эукариотических клетках, а также играют существенную роль в синтезе липидов, нуклеиновых кислот и аминокислот. Митохондрии чувствительны к окислительному стрессу. Основными источниками синтеза АФК в клетках являются митохондрии и НАДФН-оксидаза (NOX). В митохондриях АФК продуцируются в дыхательной цепи, а посредством NOX – вдоль мембран нейтрофилов и фагосом. При определенных условиях производство свободных радикалов, таких как OH●- и O_2●-, приводит к уязвимости. АФК, продуцируемые митохондриями, вследствие отсутствия гистонов имеют множество уязвимых для окислительного стресса мишеней, включая липиды, белки, ДНК, РНК и митохондриальную ДНК (мтДНК). Нарушения мтДНК и целостности митохондриального генома играют главную роль в развитии тяжелых ранних и хронических заболеваний, связанных со старением. Становится все более очевидным, что долгосрочные крошечные повреждения мтДНК связаны не только с процессом старения, но также могут быть тесно связаны с диабетом и нефропатиями. Митохондриальная дисфункция играет основную роль в развитии почечных заболеваний. Эпигенетические изменения и взаимодействия между мтДНК, АФК и воспалительными факторами влияют на нефроны. Изменения мтДНК влияют на развитие и прогрессирование хронической болезни почек. Изменение мтДНК также играет важную роль в мониторинге нефропатий. Имеющиеся данные свидетельствуют о том, что модификация нескольких копий мтДНК в кровотоке и моче отражает дисфункцию митохондрий и тяжесть заболевания почек. В этом обзоре описаны митохондриальные антиоксиданты, используемые в терапии нефропатий. Целевые митохондриальные антиоксиданты станут новой точкой зрения в терапии нефропатий. мтДНК также может выступать в качестве терапевтической мишени.

Ключевые слова: *Митохондриальный, почечная болезнь, мтДН, окислительный стресс*