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Review

Disruption of mitochondrial homeostasis in chronic kidney disease: a mini-review

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Summary. Chronic kidney disease (CKD) is recognized as a worldwide health problem. Progression of CKD may lead to many serious complications, which are associated with increased morbidity and mortality. Presently, there is no satisfactory treatment. Thus, targeted therapies are urgently needed. The kidneys are second to the heart in terms of mitochondrial abundance and oxygen consumption. Thus, it is not surprising that mitochondrial homeostasis is absolutely essential for the normal function of the kidney. In fact, a number of reports indicate that mitochondria are involved in the progression of CKD. In this review, we summarize our current knowledge on mitochondrial homeostasis in CKD. We also provide an update on recent developments in the field of mitochondria-targeting therapeutic approaches against CKD.

Key words: Chronic kidney disease, Mitochondrial homeostasis, Treatment

Introduction

Chronic kidney disease (CKD) is defined as a reduced glomerular filtration rate and/or increased urinary albumin excretion for a period longer than 3 months (Jha et al., 2013). Even in the early stages, CKD is associated with accelerated cardiovascular disease and increased mortality (Levin et al., 2013). The main goals of the therapy are to slow the decline in kidney function and limit extrarenal complications (Nasrallah et al., 2014). Although current intervention strategies targeting control of the main risk markers, such as high blood pressure, glucose and albuminuria, can slow the development, the progression to end-stage renal disease (ESRD) is still inevitable (Lambers Heerspink and de Zeeuw, 2013; Sharaf El Din et al., 2016). Moreover, numerous mechanisms have been proposed to explain the pathogenic basis of CKD and identify new therapeutic targets, but successful clinical translation is relatively limited (Liu et al., 2017).

Mitochondria are vital organelles for every nucleated cell and are responsible for cellular ATP production via oxidative phosphorylation. Also, mitochondria are crucial for regulating other cellular events including steroid and heme biosynthesis, calcium signaling, apoptosis, reactive oxygen species (ROS) generation, innate immunity and others (Suarez-Rivero et al., 2016). Mitochondria contain their own circular DNA (mtDNA) and transcription/translation machinery. Maintenance of mitochondrial homeostasis depends on the balance of mitochondrial turnover, mitochondrial dynamics through fission and fusion, transport, generation of new mitochondria via mitochondrial biogenesis and removal of impaired mitochondria or associated mitochondrial components via mitophagy. Moreover, mitochondria have their own protein quality control system in which mitochondrial proteases are critical players in protein maintenance and elimination of oxidized and misfolded proteins (Hamon et al., 2015). In addition to the proteases localized in mitochondria, there is also a role

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for the ubiquitin-proteasome system (UPS) which removes proteins from the outer mitochondrial membranes (Baker et al., 2014). Disruptions of mitochondrial homeostasis and integrity due to perturbation of any of these regulatory systems lead to severe pathophysiological consequences and the onset of diseases (Bohovych et al., 2015).

Although a large body of evidence shows that mitochondrial dysfunction participates in the development and progression of a variety of kidney diseases leading to CKD (Che et al., 2014), a more detailed and comprehensive understanding of mitochondrial function maintenance systems in CKD remains limited. This review will concentrate on mitochondrial homeostasis and its potential role in CKD. More specifically, new compounds capable of regulating mitochondrial homeostasis have shown potentials for the treatment of CKD.

Mitochondrial homeostasis in CKD

Mitochondrial biogenesis in CKD

Mitochondrial biogenesis is defined as the process via which cells replace or increase their mitochondria through the proliferation of pre-existing organelles (Suliman and Piantadosi, 2016). This process is regulated by multiple transcription factors, such as the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial transcription factor A (TFAM) (Kelly and Scarpulla, 2004).

PGC-1 is a main regulator of mitochondrial biogenesis and function in the heart, adipose tissue, skeletal muscle and other organs which are rich in mitochondria (Puigserver et al., 1998). The PGC-1 family consists of PGC-1α, PGC-1β as well as PGC-1 related coactivator, of which the PGC-1α is widely studied (Lynch et al., 2018). PGC-1α can interact with transcriptional co-activators which are called nuclear receptor transcription factors (NRFs) including peroxisome proliferator-activated receptors (PPARs) and estrogen-related receptors (ERRs), and provoke mitochondrial biogenesis (Bhargava and Schnellmann, 2017). Kim et al. observed that the activation of the AMPK-SIRT1-PGC-1α pathway could polish renal lipotoxicity and mesangial cell damage by decreasing apoptosis and oxidative stress in db/db mice (Kim et al., 2013). Kumar Sharma et al. found the mRNA level of PGC-1α was reduced in patients with diabetic kidney disease (Sharma et al., 2013). However, Li reported increasing PGC-1α in podocytes by using podocyte-specific inducible PGC1α-transgenic mice resulted in collapsing glomerulopathy, suggesting that the beneficial therapeutic window for PGC-1α levels in podocytes is narrow (Li et al., 2017a).

TFAM, as a member of a high mobility group protein family, is a nuclear-encoded protein that binds upstream of mtDNA and regulates the transcription of mtDNA (Larsson et al., 1998; Kanki et al., 2004; Uchiumi and Kang, 2012; Kukat et al., 2015). The overexpression of TFAM increased mtDNA while the RNA interference targeting TFAM decreased the amount of mtDNA (Kanki et al., 2004). Su et al. discovered the expression of TFAM was decreased in aldosterone-induced podocyte injury. In addition, the vector-mediated overexpression of TFAM prevented podocytes from aldosterone-induced injury by the restoration of mitochondrial function (Su et al., 2013). In high glucose-treated podocytes, the mRNA expression of TFAM was markedly reduced (Cai et al., 2016).

Mitochondrial dynamics in CKD

Mitochondria are dynamic organelles in the dynamic equilibrium of fission and fusion (Westermann, 2010). The mitochondrial fission is regulated by the dynamin-related protein 1 (Drp1) and four mitochondrial receptor proteins including fission 1 (Fis1), mitochondria fission factor (Mff), mitochondrial dynamics protein of 49 kDa (MID49) and MID51 (Ni et al., 2015). These four proteins, which are located in the mitochondrial outer membrane (MOM), can recruit Drp1 from cytosol to mitochondria and lead to mitochondria dividing into two separate organelles (Losón et al., 2013; Ni et al., 2015). The outer mitochondria membrane fusion depends on the fusion proteins mitofusin 1 and 2 (Mfn1 and Mfn2), which tether adjacent mitochondria and lead to outer membrane fusion. Meanwhile, the fusion in the mitochondrial inner membrane relies on optic atrophy 1 (OPA1) (Ni et al., 2015; Formosa and Ryan, 2016). Mitochondrial fission results in the separation of damaged mitochondria while mitochondrial fusion leads to the exchange of materials between healthy and damaged mitochondria, which ensure the mitochondrial network's integrity (Wu et al., 2016). Wang et al. observed Fis1 and Drp1 were increased in 5/6 nephrectomized rats while the expression of Mfn2 was decreased (Wang et al., 2017). Li et al. showed puromycin aminonucleoside (PAN) or adriamycin (ADR) reduced Mfn1 expression and induced mitochondrial fission in podocytes (Li et al., 2014). In diabetic nephropathy mice, the target deletion of Drp1 in podocytes reduced albuminuria and pathological damage (Ayanga et al., 2016). Moreover, our group found that in aldosterone-induced podocyte injury, aldosterone increased p53 expression, which activated Drp1 and mitochondrial fission, leading to mitochondria dysfunction (Yuan et al., 2018).

Mitochondrial ROS in CKD

Reactive oxygen species (ROS) is influential in cellular signaling, host defense, hormone biosynthesis and so on (Paravicini and Touyz, 2008). ROS is an intermediate product during oxidative phosphorylation (Wu et al., 2016). The electrons escape from the electron transporting chain and combine with O_2 to form ROS

(He et al., 2017). The moderate concentration of ROS functions as second messengers to regulate the signal pathway (Daenen et al., 2019). Under pathological circumstances, the excessive production of ROS and damage of the antioxidant system can cause mitochondrial dysfunction (Angelova and Abramov, 2018). The levels of ROS were increased in animal models of leukocyte-dependent glomerulonephritis, minimal-change disease, membranous nephropathy and diabetic nephropathy (Shah et al., 2007). It was reported that high glucose induced the production of ROS, which was associated with the development of diabetic nephropathy (Lambeth, 2007). Also, Wang et al. discovered ROS played an important role in PAN-induced podocyte injury via interacting with TRPC6-mediated Ca^{2+} signaling both *in vitro* and *in vivo* (Wang et al., 2009).

Mitochondrial DNA in CKD

Mammalian mitochondrial DNA is a closed-circular molecule of approximately 16 kb, which encodes 2 rRNAs, 22 tRNAs as well as 13 polypeptides of the OXPHOS complexes including complexes I, III, IV, and V (Boore, 1999; Kelly and Scarpulla, 2004). The majority of mitochondrial proteins (approximately 1000-2000) are encoded in the nucleus and synthesized in the cytosol (Müller et al., 2015). Nucleus-encoded proteins are subsequently imported into the mitochondria by specific translocation machinery (Neupert and Herrmann, 2007). Compared with patients on CKD stage 3-4, mitochondrial DNA copy number in peripheral blood mononuclear cells was decreased in patients with CKD stage 5 (Gamboa et al., 2016). Xu et al. observed that SNPs in the D-loop of mitochondrial DNA were independent prognostic markers for CKD patients (Xu et al., 2015). Furthermore, Tin et al. reported that higher mtDNA copy number in peripheral blood was relevant to a lower risk of CKD (Tin et al., 2016). Xiao et al. demonstrated mtDNA copy numbers were decreased in db/db mice (Xiao et al., 2017). Chen et al. found the mtDNA copy numbers were reduced in kidney cortexes of 5/6 nephrectomized rats (Chen et al., 2013). In addition, ADR nephropathy could result in the depletion of mtDNA (Papeta et al., 2010).

Mitochondrial trafficking in CKD

Mitochondria are dynamic organelles that are constantly adjusting their shape, size, and location according to cellular and environmental cues (Ito and Di Polo, 2017). Mitochondria transport on cytoskeletal microtubules through motor proteins. According to the structural similarities, the motor proteins are divided into three types, including kinesin, dynein and myosin (Saxton and Hollenbeck, 2012). The dynein transports cargo towards the minus end and the kinesin moves towards the plus end (Saxton and Hollenbeck, 2012; Ni et al., 2015). Milton serves as the adaptor to link Miro to kinesin and dynein (Lin and Sheng, 2015). Miro is anchored to the mitochondrial outer membrane, which has two GTPases and Ca^{2+}-binding EF hands (Schwarz, 2013). In the nervous system, Sheng et al. reported defects in mitochondrial trafficking lead to neurodegenerative disorders owing to failure to produce ATP and buffer local Ca^{2+} rises (Sheng and Cai, 2012). Nguyen et al. observed that the loss of Miro1 caused motor neuron dysfunction most likely due to mitochondrial distribution defects in neuron-specific Miro1 KO mice (Nguyen et al., 2014). The role of mitochondrial trafficking in CKD is still unclear. Glomerular podocytes contain neuron-like functional synaptic vesicles. Thus, we hypothesized that mitochondrial trafficking might also play an important role in CKD by affecting the distribution of mitochondria and energy supply in the kidney.

Mitophagy in CKD

Mitophagy is a type of selective autophagy which can eliminate damaged mitochondria (Ashrafi and Schwarz, 2013). The PINK1 (PTEN-induced kinase 1)/Parkin (E3 ubiquitin ligase PARK2) pathway is the most recognized molecular mechanism that mediates the mitophagy process in mammalian cells (Tang et al., 2015). In healthy mitochondria, PINK1 is normally imported into inner mitochondria membrane via the translocase of the outer membrane (TOM) complex and then rapidly degraded by the mitochondrial rhomboid protease PARL to maintain PINK1 at a low level (Jin et al., 2010). When mitochondrial membrane potential is dissipated, the import of PINK1 into inner mitochondria membrane is inhibited. The stabilization of PINK1 on the outer mitochondria membrane recruits Parkin to the impaired mitochondria (Youle and Narendra, 2011; Ding and Yin, 2012; Anding and Baehrecke, 2017). Once activated, Parkin ubiquitinates the proteins on outer mitochondria membrane including Mfn1/2, Miro, TOMM20 and voltage-dependent anion channel (VDAC) to promote mitophagy (Gegg et al., 2010; Geisler et al., 2010; Ni et al., 2015). The activated Parkin can also recruit autophagy receptors, including p62, optineurin and NDP52 (nuclear dot protein 52 kDa), and then package ubiquitinated cargo into autophagosomes (Wong and Holzbaur, 2014; Lazarou et al., 2015; Bhujabal et al., 2017). Apart from PINK1/Parkin pathway, BNIP3 (Bcl-2/adenovirus E1B 19-kDa-interacting protein 3), Nip3-like protein X (NIX) and FUNDC1 (FUN14 domain-containing protein 1) can mediate mitophagy by directly interacting with LC3 (microtubule-associated protein light chain 3) (Mazure and Pouysségur, 2009; Novak et al., 2010; Liu et al., 2012). In terms of the kidney, the studies of mitophagy mainly focus on AKI. Our previous study found enhanced mitophagy could protect against cisplatin-induced acute kidney injury, the overexpression of PINK1/Parkin promoted cisplatin-induced mitophagy while the knock-down of PINK1/Parkin played the

opposite role (Zhao et al., 2017). Ishihara et al. observed mitophagy was induced in an I/R AKI model by the p53-sestrin-2 and hypoxia-inducible factor 1 (HIF-1)-BNIP3 pathways (Ishihara et al., 2013). Recently, more attention has been shifted to CKD. Li et al. demonstrated the expressions of PINK1 and Parkin were decreased in db/db mice, HK-2 cells and podocytes subjected to high glucose exposure (Li et al., 2017b; Xiao et al., 2017).

Mitochondrial proteases in CKD

Mitochondria has its own protease system that can prevent mitochondria from heat stress and degrade damaged polypeptides (Rugarli and Langer, 2012). The protease system can be classified into three types: processing peptidases, ATP dependent proteases and oligopeptidases (Koppen and Langer, 2007). The processing peptidases mainly cleave off N-terminal presequences of precursor proteins. Mitochondrial processing peptidase (MPP) and mitochondrial intermediate peptidase (MIP) are located in the matrix. When the presequences arrive in the matrix, MPP cleaves the majority of them and MIP exclusively cleaves presequences after initial processing by MPP. Inner membrane peptidase (IMP) is situated in the inner membrane and processes precursor proteins encoded by nuclear or mitochondria (Mossmann et al., 2012; Teixeira and Glaser, 2013). The ATP dependent proteases include AAA proteolytic complexes, Lon and ClpXP (Koppen and Langer, 2007). In the inner mitochondrial membrane, two AAA proteolytic complexes play important roles in protein quality control. According to the different region of active site faces, they are designated as m-AAA which faces the matrix and i-AAA that is active on the intermembrane space side (Koppen and Langer, 2007). They can degrade non-native proteins to peptides (Gerdes et al., 2012). Lon can degrade misfolded and oxidatively damaged proteins in the matrix space to contribute to protein quality control (Matsushima et al., 2010). ClpXP consists of two components ClpP subunits and ClpX subunits (Fishovitz et al., 2011). ClpX binds and partially unfolds the substrates by specific recognition motifs and delivers it to ClpP for degradation (Al-Furoukh et al., 2015). Oligopeptidases can completely degrade polypeptides into amino acids within mitochondria (Koppen and Langer, 2007). Furthermore, OMA1 is an ATP-independent peptidase in the inner membrane, which mediates OPA1 processing in the deficiency of m-AAA proteases or the condition that mitochondrial activities are damaged (Ehses et al., 2009). In IR mice model, Xiao et al. suggested OPA1 proteolysis occurred in coincidence with the loss of renal function, while OMA1 knockout decreased OPA1 proteolysis and ameliorated renal function (Xiao et al., 2014). These findings raised the possibility that mitochondrial proteases may be unrecognized contributors to mitochondrial injury in CKD.

Novel mitochondrial-targeted drugs for CKD therapy

SS-31

Arg-2,6-dimethyltyrosine-Lys-Phe-NH2 (SS-31) is a tetrapeptide which specifically targets inner mitochondrial membrane. It can reduce ROS and promote the production of ATP. However, the main mechanism of SS-31 is unclear. The increased ROS trigger the opening of mitochondrial permeability transition (MPT) pore, resulting in mitochondria depolarization, uncoupling of the oxidative respiratory chain and outer mitochondrial membrane rupture, which further causes cytochrome c to be released into the cytosol and activate caspase cascade. SS-31 can decrease ROS and apoptosis (Thomas et al., 2007). Szeto et al. found SS-31 protected mitochondrial structure and function in early reperfusion of rat ischemia-reperfusion model. In addition, SS-31 expedited the recovery of ATP and inhibited inflammation (Szeto et al., 2011). Moreover, SS-31 could inhibit cardiolipin peroxidation and prevented mitochondrial swelling and helped to preserve cristae membranes in rat ischemia-reperfusion model (Birk et al., 2013). Recently, it was reported that SS-31 also played an important role in CKD. In the experimental model of AKI-CKD transition, SS-31 reduced the level of inflammatory factors, restored the structure of podocytes and prevented glomerulosclerosis and interstitial fibrosis (Szeto et al., 2017).

Mitochonic acid 5 (MA-5)

Mitochonic Acid 5 (MA-5) is a new synthetic derivative of indole acetic acid (IAA), which is a plant hormone auxin. Suzuki et al. reported that MA-5 targeted mitofilin, a part of the mitochondrial inner membrane organizing system (MINOS) complex, promoting ATP production and rescuing renal mitochondrial respiration (Suzuki et al., 2016). MA-5 can increase the level of ATP production and raise the survival of fibroblasts among patients with mitochondrial disease (Suzuki et al., 2015). Matsuhashi et al. recruited 25 patients with mitochondrial disease and found that MA-5 had a protective effect on 24 cases of them. They also proposed that MA-5 promoted the oligomerization of ATP synthase which is essential for the maintenance of cristae junctions (Matsuhashi et al., 2017).

Hyperoside

Hyperoside is the active ingredient of hypericum perforatum, which is widely used in traditional Chinese Medicine. Recently, hyperoside was reported to have a protective effect on many diseases, such as chronic liver fibrosis (Zou et al., 2017), cancer, cerebral ischemic injury and rheumatoid arthritis (Jin et al., 2016). It works mainly by the mechanisms of anti-oxidation, anti-

apoptosis, and anti-inflammation (Zeng et al., 2011; Li et al., 2016). In the kidney, hyperoside might prevent nephrolithiasis formation (Zhu et al., 2014). In addition, Chao et al. reported hyperoside alleviated cisplatin-induced acute renal injury by NRF2 signaling pathway (Chao et al., 2016). On the part of CKD, Zhang et al. found that hyperoside reduced urinary albumin and pathological changes in DN mice (Zhang et al., 2016). Hyperoside also ameliorated glomerular basement membrane damage and podocyte apoptosis in diabetic nephropathy (Zhou et al., 2012; An et al., 2017). Furthermore, our study showed that hyperoside inhibited mitochondrial fission and promoted mitochondrial fusion in adriamycin-induced podocyte injury both *in vivo* and *in vitro* (Chen et al., 2017).

Conclusions

The study of mitochondria mainly focuses on cardiology, neurology and oncology. Recently, there is growing evidence that mitochondrial homeostasis plays an important role in the development of CKD. Mitochondria may be a promising target for the treatment of CKD. More efforts should be made to investigate the drugs that can restore mitochondrial function as a new therapeutic strategy for CKD.

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