ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted versión will be made available at final publication

HISTOLOGY AND HISTOPATHOLOGY

ISSN: 0213-3911
e-ISSN: 1699-5848

Submit your article to this Journal (http://www.hh.um.es/Instructions.htm)

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

Authors: Qing Li, Aihua Zhang, Changying Xing and Yanggang Yuan

DOI: 10.14670/HH-18-101
Article type: REVIEW
Accepted: 2019-03-20
Epub ahead of print: 2019-03-20

This article has been peer reviewed and published immdediately upon acceptance.
Articles in "Histology and Histopathology" are listed in Pubmed.
Pre-print author´s version

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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

Qing Li[1], Aihua Zhang[2], Changying Xing[1] and Yanggang Yuan[1]

[1]Department of Nephrology, the First Affiliated Hospital of Nanjing Medical University, Nanjing Medical University, Nanjing, China

[2]Department of Nephrology, Nanjing Children's Hospital, Nanjing Medical University, Nanjing, China

Correspondence to: Yanggang Yuan, M.D., Ph.D., Department of Nephrology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, 300 Guangzhou Road, Nanjing 210029, Jiangsu Province, P. R. of China, Tel: 0086-25-6830-6462, Fax: 0086-25-6830-6462, Email: ygyuan@njmu.edu.cn

Co-correspondence to Changying Xing, cyxing1962@163.com

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

Abstract

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.

Keywords chronic kidney disease, mitochondrial homeostasis, treatment

HISTOLOGY AND HISTOPATHOLOGY
(non-edited manuscript)

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

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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 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

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial transcription factor A (TFAM) (Kelly and Scarpulla, 2004b).

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, Park*, et al.*, 2017).

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

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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.*, 2018). 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

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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, 2004a). 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

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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.

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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, Du*, et al.*, 2017; 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.*,

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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.

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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 promoted ATP

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

production, decreased ROS and increased cytochrome c oxidase activity through the formation of ATP synthase dimer and mitochondrial inner membrane organizing system (MINOS) complex in IR and cisplatin-induced nephropathy model (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

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

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.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (No. 81870469, 81670628, 81300573, 81530023), the Natural Science Foundation of Jiangsu Province (No. BK20131030), the China Scholarship Council (CSC, File No. 201608320124), Chinese Society of Nephrology (17010060675), the Clinic Research Center of Jiangsu Province (No. BL2014080) and the Priority Academic Program Development (PAPD) of Jiangsu Higher Education Institution.

Disclosure Statement

The authors have no conflicts of interest to disclose.

HISTOLOGY AND HISTOPATHOLOGY (non-edited manuscript)

References

Al-Furoukh N., Ianni A., Nolte H., Hölper S., Krüger M., Wanrooij S. and Braun T. (2015). Clpx stimulates the mitochondrial unfolded protein response (uprmt) in mammalian cells. Biochim. Biophys. Acta 1853, 2580-2591.

An X., Zhang L., Yuan Y., Wang B., Yao Q., Li L., Zhang J., He M. and Zhang J. (2017). Hyperoside pre-treatment prevents glomerular basement membrane damage in diabetic nephropathy by inhibiting podocyte heparanase expression. Scientific reports 7, 6413.

Anding A. and Baehrecke E. (2017). Cleaning house: Selective autophagy of organelles. Dev. Cell 41, 10-22.

Angelova P. and Abramov A. (2018). Role of mitochondrial ros in the brain: From physiology to neurodegeneration. FEBS Lett. 592, 692-702.

Ashrafi G. and Schwarz T. (2013). The pathways of mitophagy for quality control and clearance of mitochondria. Cell Death Differ. 20, 31-42.

Ayanga B., Badal S., Wang Y., Galvan D., Chang B., Schumacker P. and Danesh F. (2016). Dynamin-related protein 1 deficiency improves mitochondrial fitness and protects against progression of diabetic nephropathy. J. Am. Soc. Nephrol. 27, 2733-2747.

Baker M.J., Palmer C.S. and Stojanovski D. (2014). Mitochondrial protein quality control in health and disease. Br. J. Pharmacol. 171, 1870-1889.

Bhargava P. and Schnellmann R. (2017). Mitochondrial energetics in the kidney. Nat. Rev. Nephrol. 13, 629-646.

Bhujabal Z., Birgisdottir Å., Sjøttem E., Brenne H., Øvervatn A., Habisov S., Kirkin V., Lamark T. and Johansen T. (2017). Fkbp8 recruits lc3a to mediate parkin-independent mitophagy. EMBO Rep. 18, 947-961.

Birk A., Liu S., Soong Y., Mills W., Singh P., Warren J., Seshan S., Pardee J. and Szeto H. (2013). The mitochondrial-targeted compound ss-31 re-energizes ischemic mitochondria by interacting with cardiolipin. J. Am. Soc. Nephrol. 24, 1250-1261.

Bohovych I., Chan S.S. and Khalimonchuk O. (2015). Mitochondrial protein quality control: The mechanisms guarding mitochondrial health. Antioxid. Redox Signal 22, 977-994.

Boore J. (1999). Animal mitochondrial genomes. Nucleic Acids Res. 27, 1767-1780.

Cai X., Bao L., Ren J., Li Y. and Zhang Z. (2016). Grape seed procyanidin b2 protects podocytes from high glucose-induced mitochondrial dysfunction and apoptosis via the ampk-sirt1-pgc-1α axis in vitro. Food Funct 7, 805-815.

Chao C., Tsai C., Chang Y., Chen J., Chin H. and Yang S. (2016). Hyperin inhibits nuclear factor kappa b and activates nuclear factor e2-related factor-2 signaling pathways in cisplatin-induced acute kidney injury in mice. Int. Immunopharmacol. 40, 517-523.

Che R., Yuan Y., Huang S. and Zhang A. (2014). Mitochondrial dysfunction in the pathophysiology of renal diseases. Am. J. Physiol. Renal Physiol. 306, F367-378.

Chen J., Liu H., Ni H., Lv L., Zhang M., Zhang A., Tang R., Chen P. and Liu B. (2013). Improved mitochondrial function underlies the protective effect of pirfenidone against tubulointerstitial fibrosis in 5/6 nephrectomized rats. PLoS ONE 8, e83593.

Chen Z., An X., Liu X., Qi J., Ding D., Zhao M., Duan S., Huang Z., Zhang C., Wu L., Zhang B., Zhang A., Yuan Y. and Xing C. (2017). Hyperoside alleviates adriamycin-induced podocyte injury via inhibiting mitochondrial fission. Oncotarget 8, 88792-88803.

HISTOLOGY AND HISTOPATHOLOGY (non-corrected manuscript)

Daenen K., Andries A., Mekahli D., Van Schepdael A., Jouret F. and Bammens B. (2018). Oxidative stress in chronic kidney disease. Pediatr. Nephrol.

Ding W. and Yin X. (2012). Mitophagy: Mechanisms, pathophysiological roles, and analysis. Biol. Chem. 393, 547-564.

Ehses S., Raschke I., Mancuso G., Bernacchia A., Geimer S., Tondera D., Martinou J., Westermann B., Rugarli E. and Langer T. (2009). Regulation of opa1 processing and mitochondrial fusion by m-aaa protease isoenzymes and oma1. J. Cell Biol. 187, 1023-1036.

Fishovitz J., Li M., Frase H., Hudak J., Craig S., Ko K., Berdis A., Suzuki C. and Lee I. (2011). Active-site-directed chemical tools for profiling mitochondrial lon protease. ACS Chem. Biol. 6, 781-788.

Formosa L. and Ryan M. (2016). Mitochondrial fusion: Reaching the end of mitofusin's tether. J. Cell Biol. 215, 597-598.

Gamboa J., Billings F., Bojanowski M., Gilliam L., Yu C., Roshanravan B., Roberts L., Himmelfarb J., Ikizler T. and Brown N. (2016). Mitochondrial dysfunction and oxidative stress in patients with chronic kidney disease. Physiol. Rep. 4.

Gegg M., Cooper J., Chau K., Rojo M., Schapira A. and Taanman J. (2010). Mitofusin 1 and mitofusin 2 are ubiquitinated in a pink1/parkin-dependent manner upon induction of mitophagy. Hum. Mol. Genet. 19, 4861-4870.

Geisler S., Holmström K., Skujat D., Fiesel F., Rothfuss O., Kahle P. and Springer W. (2010). Pink1/parkin-mediated mitophagy is dependent on vdac1 and p62/sqstm1. Nat. Cell Biol. 12, 119-131.

Gerdes F., Tatsuta T. and Langer T. (2012). Mitochondrial aaa proteases--towards a molecular understanding of membrane-bound proteolytic machines. Biochim. Biophys. Acta 1823, 49-55.

Hamon M.P., Bulteau A.L. and Friguet B. (2015). Mitochondrial proteases and protein quality control in ageing and longevity. Ageing Res. Rev. 23, 56-66.

He L., He T., Farrar S., Ji L., Liu T. and Ma X. (2017). Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. Cell. Physiol. Biochem. 44, 532-553.

Ishihara M., Urushido M., Hamada K., Matsumoto T., Shimamura Y., Ogata K., Inoue K., Taniguchi Y., Horino T., Fujieda M., Fujimoto S. and Terada Y. (2013). Sestrin-2 and bnip3 regulate autophagy and mitophagy in renal tubular cells in acute kidney injury. American journal of physiology. Renal physiology 305, F495-509.

Ito Y. and Di Polo A. (2017). Mitochondrial dynamics, transport, and quality control: A bottleneck for retinal ganglion cell viability in optic neuropathies. Mitochondrion 36, 186-192.

Jha V., Garcia-Garcia G., Iseki K., Li Z., Naicker S., Plattner B., Saran R., Wang A.Y. and Yang C.W. (2013). Chronic kidney disease: Global dimension and perspectives. Lancet 382, 260-272.

Jin S., Lazarou M., Wang C., Kane L., Narendra D. and Youle R. (2010). Mitochondrial membrane potential regulates pink1 import and proteolytic destabilization by parl. J. Cell Biol. 191, 933-942.

Jin X., Yan E., Wang H., Sui H., Liu Z., Gao W. and Jin Y. (2016). Hyperoside exerts anti-inflammatory and anti-arthritic effects in lps-stimulated human fibroblast-like synoviocytes in vitro and in mice with collagen-induced arthritis. Acta Pharmacol. Sin. 37, 674-686.

Kanki T., Ohgaki K., Gaspari M., Gustafsson C., Fukuoh A., Sasaki N., Hamasaki N. and Kang D. (2004). Architectural role of mitochondrial transcription factor a in maintenance of human

HISTOLOGY AND HISTOPATHOLOGY
(Corrected manuscript)

mitochondrial DNA. Mol. Cell. Biol. 24, 9823-9834.
Kelly D. and Scarpulla R. (2004a). Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. Genes Dev. 18, 357-368.
Kelly D.P. and Scarpulla R.C. (2004b). Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. Genes Dev. 18, 357-368.
Kim M., Lim J., Youn H., Hong Y., Yang K., Park H., Chung S., Ko S., Koh S., Shin S., Choi B., Kim H., Kim Y., Lee J., Chang Y. and Park C. (2013). Resveratrol prevents renal lipotoxicity and inhibits mesangial cell glucotoxicity in a manner dependent on the ampk-sirt1-pgc1α axis in db/db mice. Diabetologia 56, 204-217.
Koppen M. and Langer T. (2007). Protein degradation within mitochondria: Versatile activities of aaa proteases and other peptidases. Crit. Rev. Biochem. Mol. Biol. 42, 221-242.
Kukat C., Davies K., Wurm C., Spåhr H., Bonekamp N., Kühl I., Joos F., Polosa P., Park C., Posse V., Falkenberg M., Jakobs S., Kühlbrandt W. and Larsson N. (2015). Cross-strand binding of tfam to a single mtdna molecule forms the mitochondrial nucleoid. Proc. Natl. Acad. Sci. USA 112, 11288-11293.
Lambers Heerspink H.J. and de Zeeuw D. (2013). Novel drugs and intervention strategies for the treatment of chronic kidney disease. Br J Clin Pharmacol 76, 536-550.
Lambeth J. (2007). Nox enzymes, ros, and chronic disease: An example of antagonistic pleiotropy. Free Radic. Biol. Med. 43, 332-347.
Larsson N., Wang J., Wilhelmsson H., Oldfors A., Rustin P., Lewandoski M., Barsh G. and Clayton D. (1998). Mitochondrial transcription factor a is necessary for mtdna maintenance and embryogenesis in mice. Nat. Genet. 18, 231-236.
Lazarou M., Sliter D., Kane L., Sarraf S., Wang C., Burman J., Sideris D., Fogel A. and Youle R. (2015). The ubiquitin kinase pink1 recruits autophagy receptors to induce mitophagy. Nature 524, 309-314.
Levin A., Rigatto C., Brendan B., Madore F., Muirhead N., Holmes D., Clase C.M., Tang M., Djurdjev O. and Can P.i. (2013). Cohort profile: Canadian study of prediction of death, dialysis and interim cardiovascular events (canpreddict). BMC Nephrol 14, 121.
Li S., Park J., Qiu C., Han S., Palmer M., Arany Z. and Susztak K. (2017). Increasing the level of peroxisome proliferator-activated receptor γ coactivator-1α in podocytes results in collapsing glomerulopathy. JCI Insight 2.
Li W., Du M., Wang Q., Ma X., Wu L., Guo F., Ji H., Huang F. and Qin G. (2017). Foxo1 promotes mitophagy in the podocytes of diabetic male mice via the pink1/parkin pathway. Endocrinology 158, 2155-2167.
Li X., Tao H., Xie K., Ni Z., Yan Y., Wei K., Chuang P., He J. and Gu L. (2014). Camp signaling prevents podocyte apoptosis via activation of protein kinase a and mitochondrial fusion. PLoS ONE 9, e92003.
Li Y., Wang Y., Li L., Kong R., Pan S., Ji L., Liu H., Chen H. and Sun B. (2016). Hyperoside induces apoptosis and inhibits growth in pancreatic cancer via bcl-2 family and nf-κb signaling pathway both in vitro and in vivo. Tumour Biol. 37, 7345-7355.
Lin M. and Sheng Z. (2015). Regulation of mitochondrial transport in neurons. Exp. Cell Res. 334, 35-44.
Liu L., Feng D., Chen G., Chen M., Zheng Q., Song P., Ma Q., Zhu C., Wang R., Qi W., Huang L., Xue P., Li B., Wang X., Jin H., Wang J., Yang F., Liu P., Zhu Y., Sui S. and Chen Q. (2012). Mitochondrial

HISTOLOGY AND HISTOPATHOLOGY (Non-edited manuscript)

outer-membrane protein fundc1 mediates hypoxia-induced mitophagy in mammalian cells. Nat. Cell Biol. 14, 177-185.

Liu Z.Z., Bullen A., Li Y. and Singh P. (2017). Renal oxygenation in the pathophysiology of chronic kidney disease. Front Physiol. 8, 385.

Losón O., Song Z., Chen H. and Chan D. (2013). Fis1, mff, mid49, and mid51 mediate drp1 recruitment in mitochondrial fission. Mol. Biol. Cell 24, 659-667.

Lynch M., Tran M. and Parikh S. (2018). Pgc1α in the kidney. Am. J. Physiol. Renal Physiol. 314, F1-F8.

Müller M., Lu K. and Reichert A. (2015). Mitophagy and mitochondrial dynamics in saccharomyces cerevisiae. Biochim. Biophys. Acta 1853, 2766-2774.

Matsuhashi T., Sato T., Kanno S., Suzuki T., Matsuo A., Oba Y., Kikusato M., Ogasawara E., Kudo T., Suzuki K., Ohara O., Shimbo H., Nanto F., Yamaguchi H., Saigusa D., Mukaiyama Y., Watabe A., Kikuchi K., Shima H., Mishima E., Akiyama Y., Oikawa Y., Hsin-Jung H., Akiyama Y., Suzuki C., Uematsu M., Ogata M., Kumagai N., Toyomizu M., Hozawa A., Mano N., Owada Y., Aiba S., Yanagisawa T., Tomioka Y., Kure S., Ito S., Nakada K., Hayashi K., Osaka H. and Abe T. (2017). Mitochonic acid 5 (ma-5) facilitates atp synthase oligomerization and cell survival in various mitochondrial diseases. EBioMedicine 20, 27-38.

Matsushima Y., Goto Y. and Kaguni L. (2010). Mitochondrial lon protease regulates mitochondrial DNA copy number and transcription by selective degradation of mitochondrial transcription factor a (tfam). Proc. Natl. Acad. Sci. USA 107, 18410-18415.

Mazure N. and Pouysségur J. (2009). Atypical bh3-domains of bnip3 and bnip3l lead to autophagy in hypoxia. Autophagy 5, 868-869.

Mossmann D., Meisinger C. and Vögtle F. (2012). Processing of mitochondrial presequences. Biochim. Biophys. Acta 1819, 1098-1106.

Nasrallah R., Hassouneh R. and Hebert R.L. (2014). Chronic kidney disease: Targeting prostaglandin e2 receptors. American journal of physiology. Renal physiology 307, F243-250.

Neupert W. and Herrmann J. (2007). Translocation of proteins into mitochondria. Annu. Rev. Biochem. 76, 723-749.

Nguyen T.T., Oh S.S., Weaver D., Lewandowska A., Maxfield D., Schuler M.H., Smith N.K., Macfarlane J., Saunders G., Palmer C.A., Debattisti V., Koshiba T., Pulst S., Feldman E.L., Hajnoczky G. and Shaw J.M. (2014). Loss of miro1-directed mitochondrial movement results in a novel murine model for neuron disease. Proc. Natl. Acad. Sci. USA 111, E3631-3640.

Ni H., Williams J. and Ding W. (2015). Mitochondrial dynamics and mitochondrial quality control. Redox Biol. 4, 6-13.

Novak I., Kirkin V., McEwan D., Zhang J., Wild P., Rozenknop A., Rogov V., Löhr F., Popovic D., Occhipinti A., Reichert A., Terzic J., Dötsch V., Ney P. and Dikic I. (2010). Nix is a selective autophagy receptor for mitochondrial clearance. EMBO Rep. 11, 45-51.

Papeta N., Zheng Z., Schon E., Brosel S., Altintas M., Nasr S., Reiser J., D'Agati V. and Gharavi A. (2010). Prkdc participates in mitochondrial genome maintenance and prevents adriamycin-induced nephropathy in mice. J. Clin. Invest. 120, 4055-4064.

Paravicini T. and Touyz R. (2008). Nadph oxidases, reactive oxygen species, and hypertension: Clinical implications and therapeutic possibilities. Diabetes Care 31 Suppl 2, S170-180.

Puigserver P., Wu Z., Park C., Graves R., Wright M. and Spiegelman B. (1998). A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell 92, 829-839.

Rugarli E. and Langer T. (2012). Mitochondrial quality control: A matter of life and death for neurons.

HISTOLOGY AND HISTOPATHOLOGY (not edited manuscript)

EMBO J. 31, 1336-1349.

Saxton W. and Hollenbeck P. (2012). The axonal transport of mitochondria. J. Cell. Sci. 125, 2095-2104.

Schwarz T. (2013). Mitochondrial trafficking in neurons. Cold Spring Harb Perspect Biol 5.

Shah S., Baliga R., Rajapurkar M. and Fonseca V. (2007). Oxidants in chronic kidney disease. J. Am. Soc. Nephrol. 18, 16-28.

Sharaf El Din U.A., Salem M.M. and Abdulazim D.O. (2016). Stop chronic kidney disease progression: Time is approaching. World J. Nephrol. 5, 258-273.

Sharma K., Karl B., Mathew A., Gangoiti J., Wassel C., Saito R., Pu M., Sharma S., You Y., Wang L., Diamond-Stanic M., Lindenmeyer M., Forsblom C., Wu W., Ix J., Ideker T., Kopp J., Nigam S., Cohen C., Groop P., Barshop B., Natarajan L., Nyhan W. and Naviaux R. (2013). Metabolomics reveals signature of mitochondrial dysfunction in diabetic kidney disease. J. Am. Soc. Nephrol. 24, 1901-1912.

Sheng Z.H. and Cai Q. (2012). Mitochondrial transport in neurons: Impact on synaptic homeostasis and neurodegeneration. Nature reviews. Neuroscience 13, 77-93.

Su M., Dhoopun A., Yuan Y., Huang S., Zhu C., Ding G., Liu B., Yang T. and Zhang A. (2013). Mitochondrial dysfunction is an early event in aldosterone-induced podocyte injury. Am. J. Physiol. Renal Physiol. 305, F520-531.

Suarez-Rivero J.M., Villanueva-Paz M., de la Cruz-Ojeda P., de la Mata M., Cotan D., Oropesa-Avila M., de Lavera I., Alvarez-Cordoba M., Luzon-Hidalgo R. and Sanchez-Alcazar J.A. (2016). Mitochondrial dynamics in mitochondrial diseases. Diseases 5.

Suliman H.B. and Piantadosi C.A. (2016). Mitochondrial quality control as a therapeutic target. Pharmacol. Rev. 68, 20-48.

Suzuki T., Yamaguchi H., Kikusato M., Matsuhashi T., Matsuo A., Sato T., Oba Y., Watanabe S., Minaki D., Saigusa D., Shimbo H., Mori N., Mishima E., Shima H., Akiyama Y., Takeuchi Y., Yuri A., Kikuchi K., Toyohara T., Suzuki C., Kohzuki M., Anzai J., Mano N., Kure S., Yanagisawa T., Tomioka Y., Toyomizu M., Ito S., Osaka H., Hayashi K. and Abe T. (2015). Mitochonic acid 5 (ma-5), a derivative of the plant hormone indole-3-acetic acid, improves survival of fibroblasts from patients with mitochondrial diseases. Tohoku J. Exp. Med. 236, 225-232.

Suzuki T., Yamaguchi H., Kikusato M., Hashizume O., Nagatoishi S., Matsuo A., Sato T., Kudo T., Matsuhashi T., Murayama K., Ohba Y., Watanabe S., Kanno S., Minaki D., Saigusa D., Shinbo H., Mori N., Yuri A., Yokoro M., Mishima E., Shima H., Akiyama Y., Takeuchi Y., Kikuchi K., Toyohara T., Suzuki C., Ichimura T., Anzai J., Kohzuki M., Mano N., Kure S., Yanagisawa T., Tomioka Y., Toyomizu M., Tsumoto K., Nakada K., Bonventre J., Ito S., Osaka H., Hayashi K. and Abe T. (2016). Mitochonic acid 5 binds mitochondria and ameliorates renal tubular and cardiac myocyte damage. J. Am. Soc. Nephrol. 27, 1925-1932.

Szeto H., Liu S., Soong Y., Seshan S., Cohen-Gould L., Manichev V., Feldman L. and Gustafsson T. (2017). Mitochondria protection after acute ischemia prevents prolonged upregulation of il-1 and il-18 and arrests ckd. J. Am. Soc. Nephrol. 28, 1437-1449.

Szeto H., Liu S., Soong Y., Wu D., Darrah S., Cheng F., Zhao Z., Ganger M., Tow C. and Seshan S. (2011). Mitochondria-targeted peptide accelerates atp recovery and reduces ischemic kidney injury. J. Am. Soc. Nephrol. 22, 1041-1052.

Tang C., He L., Liu J. and Dong Z. (2015). Mitophagy: Basic mechanism and potential role in kidney diseases. Kidney diseases 1, 71-79.

Teixeira P. and Glaser E. (2013). Processing peptidases in mitochondria and chloroplasts. Biochim.

HISTOLOGY AND HISTOPATHOLOGY (Cell Biology manuscript)

Biophys. Acta 1833, 360-370.

Thomas D., Stauffer C., Zhao K., Yang H., Sharma V., Szeto H. and Suthanthiran M. (2007). Mitochondrial targeting with antioxidant peptide ss-31 prevents mitochondrial depolarization, reduces islet cell apoptosis, increases islet cell yield, and improves posttransplantation function. J. Am. Soc. Nephrol. 18, 213-222.

Tin A., Grams M., Ashar F., Lane J., Rosenberg A., Grove M., Boerwinkle E., Selvin E., Coresh J., Pankratz N. and Arking D. (2016). Association between mitochondrial DNA copy number in peripheral blood and incident ckd in the atherosclerosis risk in communities study. J. Am. Soc. Nephrol. 27, 2467-2473.

Uchiumi T. and Kang D. (2012). The role of tfam-associated proteins in mitochondrial rna metabolism. Biochim. Biophys. Acta 1820, 565-570.

Wang D., Chen J., Liu X., Zheng P., Song G., Yi T. and Li S. (2017). A chinese herbal formula, jian-pi-yi-shen decoction, improves muscle atrophy via regulating mitochondrial quality control process in 5/6 nephrectomised rats. Scientific reports 7, 9253.

Wang Z., Wei X., Zhang Y., Ma X., Li B., Zhang S., Du P., Zhang X. and Yi F. (2009). Nadph oxidase-derived ros contributes to upregulation of trpc6 expression in puromycin aminonucleoside-induced podocyte injury. Cell. Physiol. Biochem. 24, 619-626.

Westermann B. (2010). Mitochondrial fusion and fission in cell life and death. Nat. Rev. Mol. Cell Biol. 11, 872-884.

Wong Y. and Holzbaur E. (2014). Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an als-linked mutation. Proc. Natl. Acad. Sci. USA 111, E4439-4448.

Wu H., Wei H., Sehgal S., Liu L. and Chen Q. (2016). Mitophagy receptors sense stress signals and couple mitochondrial dynamic machinery for mitochondrial quality control. Free Radic. Biol. Med. 100, 199-209.

Xiao L., Xu X., Zhang F., Wang M., Xu Y., Tang D., Wang J., Qin Y., Liu Y., Tang C., He L., Greka A., Zhou Z., Liu F., Dong Z. and Sun L. (2017). The mitochondria-targeted antioxidant mitoq ameliorated tubular injury mediated by mitophagy in diabetic kidney disease via nrf2/pink1. Redox Biol. 11, 297-311.

Xiao X., Hu Y., Quiros P.M., Wei Q., Lopez-Otin C. and Dong Z. (2014). Oma1 mediates opa1 proteolysis and mitochondrial fragmentation in experimental models of ischemic kidney injury. American journal of physiology. Renal physiology 306, F1318-1326.

Xu J., Guo Z., Bai Y., Zhang J., Cui L., Zhang H., Zhang S. and Ai X. (2015). Single nucleotide polymorphisms in the d-loop region of mitochondrial DNA is associated with the kidney survival time in chronic kidney disease patients. Ren. Fail 37, 108-112.

Youle R. and Narendra D. (2011). Mechanisms of mitophagy. Nat. Rev. Mol. Cell Biol. 12, 9-14.

Yuan Y., Zhang A., Qi J., Wang H., Liu X., Zhao M., Duan S., Huang Z., Zhang C., Wu L., Zhang B., Zhang A. and Xing C. (2018). P53/drp1-dependent mitochondrial fission mediates aldosterone-induced podocyte injury and mitochondrial dysfunction. Am. J. Physiol. Renal Physiol. 314, F798-F808.

Zeng K., Wang X., Ko H., Kwon H., Cha J. and Yang H. (2011). Hyperoside protects primary rat cortical neurons from neurotoxicity induced by amyloid β-protein via the pi3k/akt/bad/bcl(xl)-regulated mitochondrial apoptotic pathway. Eur. J. Pharmacol. 672, 45-55.

HISTOLOGY AND HISTOPATHOLOGY (Pre-edited manuscript)

Zhang J., Fu H., Xu Y., Niu Y. and An X. (2016). Hyperoside reduces albuminuria in diabetic nephropathy at the early stage through ameliorating renal damage and podocyte injury. J. Nat. Med. 70, 740-748.

Zhao C., Chen Z., Xu X., An X., Duan S., Huang Z., Zhang C., Wu L., Zhang B., Zhang A., Xing C. and Yuan Y. (2017). Pink1/parkin-mediated mitophagy play a protective role in cisplatin induced renal tubular epithelial cells injury. Experimental cell Res. 350, 390-397.

Zhou L., An X., Teng S., Liu J., Shang W., Zhang A., Yuan Y. and Yu J. (2012). Pretreatment with the total flavone glycosides of flos abelmoschus manihot and hyperoside prevents glomerular podocyte apoptosis in streptozotocin-induced diabetic nephropathy. J. Med. Food 15, 461-468.

Zhu W., Xu Y., Feng Y., Peng B., Che J., Liu M. and Zheng J. (2014). Prophylactic effects of quercetin and hyperoside in a calcium oxalate stone forming rat model. Urolithiasis 42, 519-526.

Zou L., Chen S., Li L. and Wu T. (2017). The protective effect of hyperoside on carbon tetrachloride-induced chronic liver fibrosis in mice via upregulation of nrf2. Exp. Toxicol. Pathol. 69, 451-460.

HISTOLOGY AND HISTOPATHOLOGY
(non-edited manuscript)