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Mitochondrial Cytopathies of the Renal System

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Abstract

Mitochondria are major intracellular organelles with a variety of critical roles like adenosine triphosphate production, metabolic modulation, generation of reactive oxygen species, maintenance of intracellular calcium homeostasis, and the regulation of apoptosis. Mitochondria often undergo transformation in both physiological and pathological conditions. New concepts point that mitochondrial shape and structure are intimately linked with their function in the kidneys and diseases related to mitochondrial dysfunction have been identified. Diseases associated with mitochondrial dysfunction are termed as “mitochondrial cytopathies”. Evidence support that there is a role of mitochondrial dysfunction in the pathogenesis of two common pathways of end-stage kidney disease, namely, chronic kidney disease (CKD) and acute kidney injury (AKI). Mitochondrial cytopathies in kidneys mainly manifest as focal segmental glomerular sclerosis, tubular defects, and as cystic kidney diseases. The defects implicated are mutations in mtDNA and nDNA. The proximal tubular cells are relatively vulnerable to oxidative stress and are therefore apt to suffer from respiratory chain defects and manifest as either loss of electrolyte or low-molecular-weight proteins. Patients with mitochondrial tubulopathy are usually accompanied by myoclonic epilepsy and ragged red muscle fibers (MERRF), and Pearson’s, Kearns-Sayre, and Leigh syndromes. The majority of genetic mutations detected in these diseases are fragment deletions of mtDNA. Studies have shown significantly increased ROS production, upregulation of COX I and IV expressions, and inactivation of complex IV in peripheral blood mononuclear cells of patients with stage IV–V CKD, thereby demonstrating the close association between mitochondrial dysfunction and progression to CKD. Furthermore, the mechanisms that translate cellular cues and demands into mitochondrial remodeling and cellular damage, including the role of microRNAs and lncRNAs, are examined with the final goal of identifying mitochondrial targets to improve treatment of patients with chronic kidney diseases.

Keywords: mitochondrial cytopathies, renal, glomerular, mitophagy, fission, fusion

1. Introduction

Mitochondria, also called as the “power house” of the cell, are double membraned cell organelles involved with converting the energy derived from oxidative phosphorylation into a “fuel” in the form of adenosine triphosphate (ATP) [1, 2]. These also are involved in calcium storage, regulation of metabolism and apoptosis, and cell signaling. The energy demand of an organ is directly proportional to the number of mitochondria present in the organ, so heart is the organ with maximum number of mitochondria followed by kidneys [3, 4]. In the kidneys, renal tubular cells are richest in mitochondria, so as to facilitate the energy-consuming task of reabsorption of the majority of the glomerular filtrate. The renal function depends on interplay between multiple cell types, including endothelial cells, podocytes, mesangial cells, and tubulointerstitial cells, and is energetically demanding and relying on mitochondrial function [5].

Renal dysfunction is a multifactorial entity and manifests as a sequel to an acute or chronic insult to the organ. Recently it has been proposed that renal inflammation and tissue damage during acute kidney injury (AKI) and chronic kidney disease (CKD) have been linked to mitochondrial structural and functional alterations [4, 6].

2. Definition

Diseases related to mitochondrial alterations are known as ‘mitochondrial cytopathies’ (MC) and encompass a group of disorders characterized by mutations either in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) genes that encode for mitochondrial proteins [6]. Mitochondrial cytopathies affecting the kidneys are broadly classified as [6, 7]:

1. Inherited mitochondrial cytopathies
2. Acquired mitochondrial cytopathies

Mitochondrial cytopathies can also present as:

1. Tubular defects affecting the:
 - a. Proximal tubules
 - b. Distal tubules.
2. Non-tubular include:
 - a. Glomerular diseases
 - b. Tubulointerstitial nephritis
 - c. Renal cystic diseases
 - d. Neoplasia

3. Mechanism of mitochondrial cytopathies

Various studies indicate that mitochondrial dysfunction can arise due to disturbances in the regulation of the mitochondrial electron transport chain, proton gradient, and membrane potential [4, 7]. These disturbances lead to reduction in concentration of adenosine triphosphate (ATP) and increase in production of mitochondrial-derived reactive oxygen species (mROS). These reactive oxygen species promote kidney injury and inflammation [4, 7, 8].

Structural changes of mitochondrial swelling and fragmentation occur earlier than rise in serum creatinine which is largely used as a marker for kidney injury. These changes also indicate that impaired mitochondrial metabolism is directly linked to the deterioration of kidney function [4–9].

Inherited forms of mitochondrial cytopathies are associated with a fair number of mutations with mitochondrial DNA (mtDNA) as many nuclear genes are responsible for proper maintenance of mtDNA. Mutations in these genes cause quantitative (mtDNA depletion) and qualitative defects (mtDNA deletions) in mtDNA leading to renal impairment [10].

The equilibrium between mitochondrial fusion and fission maintains the healthy mitochondrial structure and functions [4, 11]. Disruption of this balance leads to mitochondrial fragmentation, loss of mitochondrial DNA (mtDNA) integrity, and cell death [12, 13].

Mitochondrial cytopathies encompass a group of disorders characterized by mitochondrial or nuclear DNA mutations in genes encoding for mitochondrial proteins [7]. Mitochondrial dysfunction, characterized by a loss of efficiency in the electron transport chain and reductions in the synthesis of high-energy molecules, such as adenosine-5'-triphosphate (ATP), is characteristic of aging, and essentially, of all chronic diseases [1–4]. Mitochondrial dysfunction arises from an inadequate number of mitochondria, an inability to provide necessary substrates to mitochondria, or a dysfunction in their electron transport and ATP-synthesis machinery [10, 11].

The number and functional status of mitochondria in a cell can be changed by [10, 12, 14].

1. Fusion of partially dysfunctional mitochondria and mixing of their undamaged components to improve overall function,
2. The generation of entirely new mitochondria (fission), and,
3. The removal and complete degradation of dysfunctional mitochondria (mitophagy).

3.1 Fission and fusion

The mitochondrial homeostasis is maintained because of the balance between fission and fusion. Fission leads to production of short rods or spheres whereas fusion leads to production of long and filamentous mitochondria. The balance between the two processes is disrupted under stress that leads to mitochondrial fragmentation. The both two processes are mediated by following factors: [15–19]

1. Fission: Fis1(Fission protein 1), Drp1 (Drosophila 1), Bif-1.
2. Fusion: Mfn 1 and Mfn 2 (Mitochondrial fusion protein 1 & 2), Optic atrophy factor 1 (OPA1).

3.2 The process of fission

Fission is regulated by two main mediators: Drp1 and Fis1. The Drp1 is a GTPase of dynamin superfamily and is mainly present in the cytoplasm and later localizes to the outer membrane of the mitochondria. It has been seen that this shuffling of Drp1 is regulated by phosphorylation, ubiquitination and sumoylation.

Fis1 is a small membrane protein anchored at the outer mitochondrial membrane and overexpression of Fis1 promoted mitochondrial fission causes fragmentation of the mitochondria.

3.3 The process of fusion

Mitochondrial fusion is mediated by mitofusin 1 (Mfn1), mitofusin 2 (Mfn2) and optic atrophy factor 1 (OPA1). All three proteins are GTPases belonging to dynamin superfamily like Drp1. Mfn1 and Mfn2 are also localized to outer mitochondrial membrane whereas OPA1 is present on the inner mitochondrial membrane.

3.4 Mitophagy

Mitophagy, an autophagy process by which dysfunctional or superfluous mitochondria are selectively eliminated. Defective mitophagy has been implicated in various human diseases, such as aging, neurodegenerative disease, cardiovascular disease, cancers and many other renal diseases. Altered mitophagy related mechanisms are implicated in the pathogenesis of acute kidney injury, diabetic kidney disease, and lupus nephritis. The process includes initiation, priming of mitochondria for recognition by autophagy machinery, formation of the autophagosome, followed by lysosomal sequestration and hydrolytic degradation [17–19].

Mitophagy as described by Palikaras, can be described as three types: basal, programmed and stress-induced. Basal mitophagy is a steady-state, continuous, process responsible for elimination and recycling of aged and damaged mitochondria. This type of mitophagy exhibits tissue-specific distribution, with low levels in the thymus and high levels in the heart and kidneys [20, 21]. Stress induced mitophagy facilitates mitochondrial quality control to mediate metabolic adjustments to external challenges [20, 21].

Mitophagy is largely explained by molecular pathways and is mediated by either PINK1/Parkin-pathway or via the receptors. Mitophagy receptors are localized in the outer and inner mitochondrial membranes, and can directly induce mitophagy. Proteins that promote mitophagy are FUN14 domain-containing protein 1, BNIP3 and BCL2 interacting protein 3 like, and FKBP prolyl isomerase 8 [22–24].

Recently it was described that BNIP3/NIX, atypical members of the pro-apoptotic BCL2 family, contain an atypical BH3 domain which under hypoxic stress, get upregulated by hypoxia-inducible factor 1 (HIF-1). This in turn causes initiation of LC3-dependent mitophagy and overproduction of mtROS overproduction [4, 6, 9, 20, 23].

Overall, it is believed that impairment of mitophagy is responsible for mitochondrial dysfunction and progressive accumulation of defective organelles, leading to cell

death and tissue damage. Blockade of mitophagy leads to the accumulation of damaged, ROS-generating mitochondria which activate the NLRP3 inflammasome [25].

Thus, mitochondrial cytopathies result due to disturbances in the process related to mitophagy or due to imbalance between the processes of fusion and fission.

4. Mitochondrial dysfunction and kidney injury

In this section we will discuss about the diseases that affect the kidney due to mitochondrial dysfunction. As described before renal mitochondrial cytopathies can manifest either as glomerular or tubular diseases, or as renal cysts or neoplasia.

4.1 Glomerular involvement in renal mitochondrial cytopathies

4.1.1 Diabetic nephropathy

Diabetic nephropathy results from microvascular complications, leading to chronic kidney disease that develops in approximately 30% of patients with type 1 diabetes mellitus (DM1) and approximately 40% of patients with type 2 diabetes mellitus (DM2) [26–28]. Various mitochondrial defects seen include impaired respiratory chain functions, structural and networking abnormalities, disrupted cellular signaling and increased reactive oxygen species generation [4, 29].

Coughlan et al. demonstrated that a deficiency in apoptosis inducing factor (AIF) results in changes in mitochondrial function, networking, and production of reactive oxygen species that precipitate renal disease. Along with the diabetic milieu, switch from mitochondrial fusion to fission, impaired OXPHOS, and a depleted mitochondrial ATP pool, all accelerate towards a more advanced renal injury [30].

Studies have implicated impaired mitophagy as the cause of mitochondrial dysfunction in diabetic kidneys and also showed that with progression of disease, concomitant accumulation of fragmented and swollen mitochondria occurs [22, 30, 31].

Experimental studies have shown that there is decrease in PINK1 and Parkin in the tubules of diabetic mice [32]. In study on streptozotocin-induced diabetic rat models, the authors demonstrated that in early stages of diabetes there is increase in expression of PINK1 in the renal cortex. This provided an evidence that mitophagy could be activated to clear dysfunctional mitochondria from the kidney during early diabetes and as the disease progresses there is accumulation of fragmented mitochondria and induction of cell death [4]. Thioredoxin-interacting protein (TXNIP) - dependent activation of the mammalian target of rapamycin (mTOR) signaling pathway contributes to dysfunctional mitophagy in the diabetic kidney [4, 30, 33, 34].

Studies have evaluated presence of cell-free mtDNA in urine in patients of diabetic nephropathy and reported an inverse relationship in levels of urinary mtDNA and intra-renal mtDNA leading to increase in interstitial fibrosis and reduction in estimated glomerular filtration rate (eGFR) [35].

It has also been demonstrated that damaged mitochondria generate excess mitochondrial superoxide, and glycation of mitochondrial proteins also contributes to mROS generation. Advanced glycation end products as well as the receptors for these, play a vital role in generation of ROS that contribute in progression of diabetic nephropathy [33, 36].

4.1.2 IgA nephropathy (IgAN)

IgAN is one of the most common glomerulonephritis and a leading cause of CKD that can progress to ESRD. Kidney biopsy from a patient with IgAN may show varied morphological affection ranging from mesangial proliferation to focal segmental mesangial sclerosis, crescents with dominant mesangial IgA deposition [4, 37]. The disease is characterized by presence of circulating and glomerular immune complexes comprised of galactose-deficient IgA1, an IgG autoantibody directed against the hinge region O-glycans, and C3 [38]. Nishida et al. demonstrated an increased number of abnormal mitochondria in the proximal tubular epithelial cells and an elevated urinary mtDNA levels in patients with IgAN. An association between five common single-nucleotide polymorphisms and ESRD, suggests that mitochondrial defects have an essential role in the progression to CKD in patients with IgAN [4, 39]. Interestingly, higher expression and interaction between the mitochondrial protein induced in high glucose-1 (IHG-1) and cold shock protein Y-box binding protein-1 are associated with renal inflammation, tubulointerstitial inflammation, and glomerulosclerosis in IgAN. Defects in the mitochondrial genome and functions play a critical role in worsening glomerular inflammation and disease progression [40].

4.1.3 Polycystic kidney disease

Autosomal dominant PKD (ADPKD), is characterized by presence of multiple cysts in the renal parenchyma and is associated with mutations in the genes PKD1 and PKD2, which encode polycystin 1 (PC1) and PC2, respectively [41]. The PC1-PC2 complex modulates mitochondrial Ca^{2+} uptake and directly regulate oxidative phosphorylation and indirectly affect mitochondrial function by maintaining the mtDNA copy number and mitochondrial morphology [42]. Mutations in PKD1 and PKD2 lead to mitochondrial dysfunction and metabolic imbalance. Proinflammatory cytokine $\text{TNF}\alpha$ promote cyst formation, increased MCP-1 in cyst-lining cells and excretion of urinary MCP-1, and renal profibrotic macrophages in experimental ARPKD which might be associated with defects in mitophagy are also reported in patients with ADPKD. Loss of PC2 enhanced mitochondrial Ca^{2+} uptake, mitochondrial bioenergetics, and mitochondrial-ER tethering associated with increased Mfn2, and knock-down of Mfn2 rescued ER-dependent mitochondrial Ca^{2+} signaling are associated with reduced cyst proliferation [4]. Mitochondria of cyst-lining cells in the kidney of a mouse model of ADPKD display morphological abnormalities and decreased mtDNA. There is reduced peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α), which regulates mitochondrial biogenesis. Functional mitochondrial abnormalities and increased mROS production indicate that mitochondrial dysfunction plays a functional role in cystogenesis [4, 43].

4.1.4 Lupus nephritis

Renal involvement in systemic lupus erythematosus (SLE) occurs in 40–50% of adult patients, and results in end stage renal disease (ESRD) about 10% of patients despite modifications in therapeutic strategies [44]. LN is the most common severe manifestation of systemic lupus erythematosus. The pathogenesis of LN is multifactorial, and includes aberrant T-cell and B-cell signaling, autoantibody production, and deregulated cytokine secretion. Various genetic as well as environmental factors also contribute [45, 46]. The T-cells of SLE show increased mitochondrial mass

(megamitochondria), mitochondrial hyper-polarization, and ATP depletion which lead to aberrant activation and enhanced necrosis of T-cells. This leads to release of extracellular mitochondria and their components and are recognized as damage-associated molecular patterns (DAMPs) that initiate innate and adaptive immune responses to elicit an inflammatory response that triggers organ damage [47]. Nitric oxide (NO)-dependent mitochondrial biogenesis could account for megamitochondria leading to sustained T-cell activation. On the other hand, increased T-cell mitochondria in SLE have also been attributed to insufficient mitophagy. Sequestration and successful clearance of damaged mitochondria by mitophagy suppresses mtROS accumulation, prevents inflammation and generation of autoantigens by intracellular oxidation suggesting that mitophagy is a potential therapeutic target for SLE and LN [46–48].

Gkirtzimanaki et al. observed that IFN α damages mitochondrial metabolism and mediates lysosomal dysfunction, impeding mitochondrial clearance and leading to cytosolic accumulation of mtDNA in monocytes [49]. Caspase-1 gets activated in the podocytes of both lupus nephritis patients and lupus-prone mice and inhibit mitophagy and amplify mitochondrial damage, mediated by cleavage of the key mitophagy regulator Parkin in lipopolysaccharide (LPS)-primed bone-marrow-derived macrophages [50].

Drp1, fusion mediator of mitochondria, is reduced in T cells from SLE patients and lupus-prone mice, concomitant with the accumulation of mitochondria.

Mitochondrial hyperpolarization and reactive oxygen intermediates production have been detected in peripheral blood T-lymphocytes from SLE patients, together with diminished levels of intracellular ATP, indicating dysfunction in mitochondria of T-cells in patients with lupus nephritis. CD4 β T cells from SLE exhibit an increased mitochondrial mass and size due to increased mitochondrial biogenesis and defective mitophagy [51].

4.1.5 Membranous nephropathy & focal and segmental glomerulosclerosis

Membranous nephropathy (MN) is a most common cause of adult nephrotic syndrome. Various podocytic autoantigens have been implicated in the pathogenesis of the disease. Phospholipase A2 receptor (PLA2R) is the major autoantigen on podocytes in primary MN, whereas thrombospondin type-I domain-containing 7A (THSD7A) is the minor antigen, the antibodies to which are predominantly of the IgG4 subclass [52].

Cultured podocytes when exposed to sera from patients with MN revealed mitochondrial fragmentation, loss of membrane potential, and mROS production [53]. Patients with MN also show increased glomerular mitochondrial fission proteins, DRP1, phosphorylated-DRP1 (Ser-616), and FIS1. The observation of these studies show that podocytic injury in MN is secondary to mitochondrial dysfunction [53].

Focal segmental glomerular sclerosis (FSGS), also a common cause of nephrotic syndrome in pediatric as well as adults, is one of the major renal complication of mitochondrial cytopathies.

The mitochondrial DNA (mtDNA) encodes for 13 structural genes of OXPHOS enzymes, two ribosomal RNAs, and 22 transfer RNAs. Glomerular involvement of an A-to-G transition at mtDNA position 3243 in the gene for tRNA^{Leu}(UUR) has been implicated in FSGS. Recent studied with a mouse model carrying mutant mtDNA with a 4696-bp deletion, developed focal and segmental glomerulosclerosis and died within 6 months due to renal failure [54, 55].

Puromycin aminonucleoside nephrosis (PAN) model to study FSGS reveals reduction of respiratory chain enzymatic activities, oxygen consumption, and the swelling of renal tubular mitochondria [56]. Reduction of the intraglomerular mtDNA-encoded protein, COX I, suggests that there is either an induction of mtDNA damage or a reduction in mtDNA copy number during the progression of PAN. Several studies have described mitochondrial dysfunction and/or mtDNA changes in glomerular diseases like accumulation of oxidative damage of mtDNA in the kidney of streptozotocin-induced diabetes rats, and downregulation of respiratory chain complex in patients with the congenital nephrotic syndrome of the Finnish type [57].

MCs comprise one of the causes of primary FSGS, among which mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes (MELAS) syndrome account for a large proportion. MELAS syndrome is mainly caused by point mutations in the *MTTL1* gene, encoding mitochondrial tRNA^{LEU}. Renal biopsies from patients with coexistence of MELAS and FSGS often manifest with numerous dysmorphic mitochondria in podocytes and effacement of foot processes [58].

4.1.6 Tubular defects and role of mitochondria

Renal tubules comprise one of the major victims of MCs, of which the most frequently reported is proximal tubular defects. Proximal tubular cells are relatively vulnerable to oxidative stress and are therefore apt to suffer from respiratory chain defects. Renal tubule defects mainly manifest as loss of electrolytes and low-molecular-weight proteins, which are frequently characterized as Fanconi syndrome and Bartter-like syndrome. Patients with mitochondrial tubulopathy are usually accompanied by myoclonic epilepsy and ragged red muscle fibers (MERRF), and Pearson's, Kearns-Sayre, and Leigh syndromes. The majority of genetic mutations detected in these diseases are fragment deletions of mtDNA [6, 7, 59–61].

4.1.7 Acute kidney injury (AKI)

AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). AKI is common (8–16% of hospital admissions) and many aspects of its natural history remain uncertain [62]. Classification of AKI includes pre-renal AKI, acute post-renal obstructive nephropathy and intrinsic acute kidney diseases. Of these, only 'intrinsic' AKI represents true kidney disease, and the most common etiologies are toxins, ischemia, sepsis and obstructive injury [63]. Disruption of mitochondrial integrity in renal tubular cells is considered as the common findings in all forms of AKI [64]. In AKI, mitochondrial damage contributes critically to sublethal and lethal injury of kidney tubules, and the consequent loss of renal function. In various models of AKI, mitochondrial dynamics are disrupted, resulting in mitochondrial fragmentation, membrane permeabilization, mitochondrial dysfunction, energetic failure, and ROS production [9]. There is decreased antioxidant defenses, injured mitochondrial respiration, intrarenal inflammatory response and oxidative stress along with downregulation of protein expression during mitochondrial metabolism and decreased oxygen are seen [65]. Elevated mitochondrial DNA levels in the urine has been considered as a novel non-invasive biomarker for detecting mitochondrial dysfunction. Eirin et al. revealed that increased urinary mtDNA (UmtDNA) in hypertensive patients correlated with other biomarkers of renal dysfunction and glomerular hyperfiltration [66, 67]. Derangements of mitochondrial integrity may be associated with the

detectable release of UmtDNA in sepsis-induced AKI has never been determined. Sepsis activates several pathological mechanisms linked to mitochondria, including hypoperfusion, oxidative stress, and the inflammatory response. Ultrastructural changes observed in the kidney tubular cells include mitochondrial impairment, swelling and cellular death. Disruption of mitochondrial integrity in the renal tubular epithelial cells leads to release of mitochondrial DAMPs into the urine which can be used as a surrogate biomarker of renal mitochondrial damage [68].

Expression of genes involved in oxidative phosphorylation are reduced as demonstrated by Parikh et al [69]. There is proportional decrease in expression of PGC-1 α expression with reduction of renal function. Activation of PGC-1 α promotes recovery from AKI caused by sepsis. cGAS–STING pathway activation is involved in autoimmune and inflammatory reactions, that activate by self-genomic DNA damage. Cyclic GMP–AMP synthase (cGAS) is a pattern recognition receptor that recognizes double-stranded DNA in the cytoplasm and then binds to the trans-membrane protein, a stimulator of interferon genes (STING) localized on the endoplasmic reticulum (ER). A relationship between mitochondrial damage and induction of cGAS–STING pathway in inflamed proximal tubular cells has been postulated in Cisplatin induced AKI. In ischemic and cisplatin nephrotoxic AKI, the fusion-fission mitochondrial dynamics in proximal tubules reveal that mitochondrial fission initiated by Drp1 occurs immediately after the injury [69–72].

4.1.7.1 Mitophagy and acute kidney injury

Recent literature suggests that mitophagy is involved in the pathophysiological processes of AKI. PINK1/Parkin-mediated mitophagy has a protective role for mitochondrial quality control in the context of tubular cell survival and function. Tang et al. demonstrated both PINK1 and Parkin are upregulated in renal tubular epithelial cells during ischemic AKI *in vitro* and *in vivo*, PINK1 and/or Parkin deficiency results in increased mitochondrial damage, ROS production, and inflammation causing increased tubular damage and aggravated AKI [73]. Boston University mouse proximal tubular cell line (BUPMT cells) show upregulation of BNIP3 following oxygen–glucose deprivation-reperfusion, and in kidney tissues of mouse models. BNIP3-deficient mice renal tubular epithelial cells show accumulation of damaged mitochondria, increased ROS production, enhanced cell apoptosis, and inflammation. These findings strongly support the involvement of multiple mitophagy regulatory pathways in the pathogenesis of AKI [74].

Wang et al. stated that Bax inhibitor-1 (BI1) promotes mitochondrial retention of PHB2 and improves mitophagy, preserving mitochondrial homeostasis in a murine AKI model. He also demonstrated that renal functional loss, tissue damage, and apoptosis are aggravated in cisplatin-treated *Pink1*–/– and *Parkin*–/– mice relative to cisplatin-treated wild-type mice, suggesting that activation of PINK1/Parkin-mediated mitophagy plays a protective role against cisplatin nephrotoxicity [3]. A recent study by Zhu et al. demonstrated that trehalose administration attenuates mitochondrial dysfunction through activating transcriptional factor EB (TFEB)-mediated autophagy and mitophagy in cisplatin-induced AKI *in vitro* and *in vivo*. The study sheds lights on the roles of TFEB on mitophagy and provides a novel promising therapeutic target for AKI [75].

Notably, preservation of mitochondrial dynamics, prevention of mitochondrial membrane permeabilization, and/or promotion of mitochondrial biogenesis can protect kidney tubular cells and tissues in AKI.

4.1.8 Tubulointerstitial fibrosis

Tubulointerstitial fibrosis follows following aberrant kidney repair following AKI, eventually progressing to CKD. Suppression of the proinflammatory cytokines interleukin (IL)-18 and IL-1 β and nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation, inhibits progression to CKD following prolonged ischemia. Studies indicate that mitochondrial dysfunction plays a role in inflammation leading to tubulointerstitial fibrosis and development of end-stage renal disease. Analysis of genome-wide transcriptome-based analyses revealed that human fibrotic kidneys have lower expression of various mitochondrial enzymes and regulators of fatty acid oxidation along with higher intracellular lipid deposition. Fibrosis is mediated by monocyte chemoattractant protein 1 (MCP-1), a chemokine that promotes the infiltration of monocytes, inflammation, and fibrosis, the levels of which are increased with decreased renal expression of mitophagy regulators (PINK1, MFN2, and Parkin) in experimental and human kidney fibrosis. Mitophagy impairment led to an accumulation of abnormal mitochondria, augmented macrophage induced fibrotic response, superoxide production, and reduced ATP synthesis. Deficiency of mitophagy by Pink1 or Park2 gene deletion markedly increased mROS production and mitochondrial damage, which worsened renal fibrosis. These effects were rescued by a mitochondria-targeted antioxidant. Defective mitochondrial metabolism and reduced expression of mitophagy regulators have been shown to enhance the renal inflammatory and fibrotic responses and mediate the progression of CKD [4, 76–78].

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