



Review

Mitochondrial bioenergetics, redox state, dynamics and turnover alterations in renal mass reduction models of chronic kidney diseases and their possible implications in the progression of this illness



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Malate (CID 525)
Succinate (CID 1110)
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ABSTRACT

Nowadays, chronic kidney disease (CKD) is considered a worldwide public health problem. CKD is a term used to describe a set of pathologies that structurally and functionally affect the kidney, it is mostly characterized by the progressive loss of kidney function. Current therapeutic approaches are insufficient to avoid the development of this disease, which highlights the necessity of developing new strategies to reverse or at least delay CKD progression. Kidney is highly dependent on mitochondrial homeostasis and function, consequently, the idea that mitochondrial pathologies could play a pivotal role in the genesis and development of kidney diseases has risen. Although many research groups have recently published studies of mitochondrial function in acute kidney disease models, the existing information about CKD is still limited, especially in renal mass reduction (RMR) models. This paper focuses on reviewing current experimental information about the bioenergetics, dynamics (fission and fusion processes), turnover (mitophagy and biogenesis) and redox mitochondrial alterations in RMR, to discuss and integrate the mitochondrial changes triggered by nephron loss, as well as its relationship with loss of kidney function in CKD, in these models. Understanding these mechanisms would allow us to design new therapies that target these mitochondrial alterations.

1. Introduction: renal mitochondria and its importance in the development of new therapies to prevent the CKD progression

The term chronic kidney disease (CKD) is used to include a broad range of disorders characterized by progressive nephron loss, glomerular filtration rate (GFR) reduced to less than 60 ml/min/1.73 m² for at least 3 months and increased renal damage markers (such as blood creatinine and blood urea nitrogen, BUN) [1]. CKD can be developed by a series of acute insults, such as ischemic episodes or by exposure to nephrotoxic agents, which generate the initial nephron loss. In an attempt to adapt this nephron loss, the kidney triggers hemodynamic, vascular and inflammatory changes [2,3] (see Taal & Brenner [3] for more details), which lead to further nephron loss, thus promoting progressive deterioration of renal function. Within the last

decades, the number of patients with CKD has increased dramatically, moving from the 27th (in 1990) to the 18th place (in 2014) in the list of worldwide death causes and its death rate is expected to continue increasing [4,5]. In addition, its medical treatment cost is high, since patients with CKD usually have other complications, such as cardiovascular diseases, hypertension, obesity and diabetes [1,2]. Therefore, there is an urgent need for the development of new treatments and strategies to prevent or at least delay CKD progression.

In the kidney, ATP production is predominantly sustained by oxidative phosphorylation (OXPHOS) of fatty acids β -oxidation [6], although other substrates like lactic acid and ketone bodies are also oxidized [7]. Due to the different energy requirements along the nephron, each nephron segment has different mitochondrial abundance [6–8]. So, the nephron shows a higher mitochondrial density in the

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most energy demanding segments [6,8], such as the proximal convoluted tubule (PCT) and the thick ascending loop of Henle (TAL) [8], because mitochondria is responsible of the maintenance of high reabsorption rates in these segments [6]. Mitochondrial membrane potential ($\Delta\Psi_m$) also changes along the nephron, multiphotonic excitatory confocal microscopy studies in anesthetized mice demonstrated a notably higher $\Delta\Psi_m$ in proximal tubule (PT) and TAL [9,10]. Additionally, in pathologic states (like hypoxia), $\Delta\Psi_m$ alterations are different along the tubular segments, which is consistent with the poor PT capacity for obtaining energy from anaerobic glycolysis.

Since renal function highly depends on mitochondrial ATP production and, hence, on the balance between the processes that regulate mitochondrial dynamics (fission and fusion) and turnover (biogenesis and mitophagy) [6,11] mitochondrial alterations have been related to the development of kidney pathologies and have been considered as a therapeutic target [12]. In the case of acute kidney disease (AKD) there is a correlation between tubular damage and mitochondrial alterations in models of cisplatin [13], ischemia / reperfusion [9], gentamicin [14], dichromate [15] and maleate [16]. In addition, the excessive increase in mitochondrial reactive oxygen species (ROS) production leads to the loss of integrity of mitochondrial membrane, inducing its permeability and the release of pro-apoptotic proteins [17], thus contributing to cell death in these models. Furthermore, mitochondrial alterations are related to tubular defects in patients with renal pathologies, such as Fanconi syndrome, Bartter-like syndrome and cystic renal disease, among others [17,18]. In the case of CKD, many evidences suggest that mitochondrial dysfunction may be involved in the pathophysiology of these diseases, although the precise role of mitochondria in those changes, especially in non-diabetic conditions, is largely unknown [12]. It is believed that, after the original damage, an increase in the metabolism rate and ATP consumption generate mitochondria bioenergetics stress, which together with the increase in ROS production [3,19,20] contribute to CKD progression. However, nowadays there is not a theory that describes, in a temporal course way, the changes that occur in the mitochondria along CKD progression [12].

Renal mass reduction (RMR) models, like uninephrectomy, 3/4 nephrectomy, and 5/6 nephrectomy (5/6Nx) models are widely used techniques for studying CKD progression [3,21]. This procedure induces nephron hypertrophy and hyperfunction and an increase in single nephron GFR (snGFR), however, it leads to a higher injury in the remnant renal mass, decreasing total GFR and producing a circle of progressive deterioration in the kidney, which emulates clinical CKD [3,21]. Therefore, RMR models are powerful tools for studying the mechanisms involved in CKD progression [3,21].

Since RMR models are powerful tools for studying the mechanisms involved in CKD progression in a non-diabetic context [3,21], in this review, we will first analyze the current information about mitochondrial bioenergetics alterations triggered by nephron loss in these models. Then, we will discuss the current information of mitochondrial oxidative stress and mitochondrial dynamics and turnover alterations in these models, to discuss and try to integrate along time the mitochondrial changes, as well as their relationship with the illness development. This would suggest possible mitochondrial proteins or mechanisms that may be used as targets to develop new therapies to prevent CKD progression.

2. Mitochondrial bioenergetics alterations in RMR models

According to the unified theory postulated by Taal & Brenner [3], in CKD (as well as in the RMR models), the progression is linear with respect to time and it results from a set of common mechanisms, which include hemodynamic, oxidative stress, hypertrophy and bioenergetics changes [3]. In RMR models, hemodynamic alterations appear immediately after the renal mass loss, which include an early increase in renal vascular resistance and glomerular capillaries pressure, as well as a decrease in plasma blood flow [22,23]. Together these changes lead to

an increase in snGFR, which peaks between the first and fourth week after the damage (depending of the magnitude of the renal mass loss) [3].

Hypertrophy processes and biomacromolecular synthesis rise also appear in early stages of the disease [3]. Hypertrophy triggers DNA, mRNA, rRNA and lipid synthesis, especially in PT. Further, pro-apoptotic genes are suppressed and growth factors levels rise in the first days [24–26]. During the first 24 h after RMR, the elevated snGFR leads to higher solute reabsorption rates and an increase in Na^+/K^+ ATPase activity, which further drives the basolateral membrane growth, particularly in PT. These changes, together with the dramatic molecular biosynthesis increase, lead to a higher energy expenditure [27,28]. Moreover, vasoactive and tropic factors such as aldosterone, vascular endothelial growth factor and insulin-like growth factor-1, lead to a further kidney growth which could persist until the 2nd or 3rd month [3,22,25,26,29]. Briefly, in the first period after nephrectomy, the increase in snGFR and solute reabsorption together with the biosynthetic rise and hypertrophy process generate an excessive energy demand in the tubular segment of the nephron, especially in PT. It has been hypothesized that this hypermetabolic state in the remnant renal mass induces stress in ATP sources, especially in mitochondria [3,30,31].

In RMR models, there is an early increase in mitochondrial volume per cell, which persists until the 14th day [30,32]. This increase in the mitochondrial volume was associated with higher size (mitochondrial hypertrophy) but not with mitochondrial proliferation, since an increase in mitochondrial DNA (mtDNA) or in expression of nuclear-encoded mitochondrial genes [with exception of glutathione (GSH)/glutathione disulfide (GSSG) transporter] was not observed in this interval [30,32–34]. However, as we will be discussing later, the current evidence suggests that mitochondrial fusion has a pivotal role in the mitochondrial hypertrophy, associated with a failed compensatory response to the higher kidney energy demand [32], since inorganic phosphate accumulation, increase in oxygen uptake and sodium transport alterations have been observed in PT [23,35,36]. This suggests that in the early stage after RMR, bioenergetics imbalance is particularly greater in PT.

These changes also occur in patients with CKD, where it has been proposed that mitochondria is not able to maintain the ATP production in PT and TAL segments [37,38]. These observations have led to the hypothesis that the increase in energy demand triggers mitochondria stressful hypermetabolic state along all the tubular segments. Moreover, since PT segment is not able to obtain energy by non-mitochondrial pathway [33], this segment is particularly more vulnerable to mitochondrial dysfunction.

In accordance with this, recently, our research group has demonstrated important bioenergetics mitochondrial alterations at 24 h after 5/6Nx. We confirmed that isolated mitochondria from remnant kidney tissue have decreased respiratory state 3 (S3) and ADP/oxygen (ADP/O) ratio and increased respiratory state 4 (S4), which leads to a reduction in the respiratory control index ($\text{RCI} = \text{S3}/\text{S4}$) in complex I-linked respiration (malate-glutamate feeding). The activities of complex I (CI) and ATP synthase also decrease, however, no changes in the subunit protein levels of these complexes were observed [30]. On the other hand, Lash et al. [33] observed an increase in S3 in complex II (CII)-linked respiration (using succinate) at 10 days post-nephrectomy; however, they were not able to observe changes in any other bioenergetics parameters. This contrasts with a recent work made by Thomas et al. [39] at 1 week, that reported a slight increase in S3, S4 and uncoupled respiration (badly called by them S3u) in the respirations fed by malate-glutamate, pyruvate-malate and succinate + rotenone, without changes in RCI or in the mitochondrial ATP production. These findings need to be interpreted with caution. It is true that the increase in energy demand drives an increase in OXPHOS capacity, higher values of S3, mitochondria coupling, respiration leak decrease [40,41] and mitochondrial biogenesis [42] in a physiologic context, such as during exercise. However, in RMR models, the energy demand increase

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