Mitochondrial Biogenesis in Kidney Disease

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ABSTRACT

The transcriptional regulation of mitochondrial biogenesis by normal metabolic adaptation or injury has been clarified over the past decade. Mitochondrial biogenesis and its attendant processes enhance metabolic pathways such as fatty acid oxidation and increase antioxidant defense mechanisms that ameliorate injury from aging, tissue hypoxia, and glucose or fatty acid overload, all of which contribute to the pathogenesis of acute and chronic kidney disease. There has been considerable interest in peroxisome proliferator-activated receptors (PPAR) in the kidney, which affect multiple processes in addition to mitochondrial biogenesis. As yet there is relatively little information focused specifically on mitochondrial biogenesis and its regulation by PPARγ coactivators and their modulators such as SIRT1. The available data indicate that these pathways will be fruitful areas for study in the modification of renal disease.


Interest in mitochondrial biogenesis has been fueled by the involvement of lipid-sensing peroxisome proliferator-activated receptors (PPARs) and the disease-modifying effects of fibrates and thiazolidinediones that target them,1–3 the discovery of the PPARγ coactivator (PGC) family as master regulators of this biogenesis,4 and the recognition that modification of biogenesis and its signaling are pathogenically important in skeletal muscle insulin resistance associated with increased cellular lipids, in adipocyte function and obesity, and during aging.4–9 Moreover, PGC activation and biogenesis are major effects of calorie restriction and SIRT1-activating polyphenols.5–7 Mitochondrial biogenesis increases net mitochondrial mass and functional capacity or helps preserve it by compensating for loss of damaged mitochondria by autophagy (mitophagy).10–12

Mitochondria have their own small genome of circular double-stranded DNA (mtDNA), which is considered a remnant of their endosymbiotic origin from an ancestral α-proteobacterium that incorporated into eukaryotic cells early in evolution. Its 16,000 bp encode 37 genes, of which 13 are essential protein subunits for the oxidative phosphorylation apparatus, and the rest are the transfer RNA and ribosomal RNA needed for synthesis of those proteins. The remainder of the approximately 1100 mitochondrial proteins, including the three transcription factors that control the expression of mtDNA genes, TFAM, TFB1M, and TFB2M, are encoded by the nucleus. Although ubiquitous transcription factors also participate, the strongest regulation of gene expression for the many nuclear encoded proteins is mainly through three families of transcription factors (Figure 1). Nuclear respiratory factor 1 (NRF-1) and GA-binding protein α (also commonly referred to as nuclear respiratory factor 2) direct gene expression for oxidative phosphorylation proteins, mitochondrial import proteins, and the mtDNA transcription factors. PPARα and PPARδ promote expression of fatty acid oxidation (FAO) and uncoupling protein 2 genes. Estrogen-related receptor-α (ERRα) up-regulates the entire gene network necessary for biogenesis, including the genes controlled by the nuclear respiratory factors and PPARs. In contrast to ERRα, PPARs and the nuclear respiratory factors are not sufficient by themselves to fully induce biogenesis.13–15

PPARγ, the third member of the PPAR family, and its agonists, regulate expression of the fatty acid synthetic machinery and uncoupling protein 1 in adipocytes, modulate ion transporters, perhaps leading to fluid retention,16–18 attenuate the renal effects of aging,9 and generally promote mitochondrial biogenesis by inducing PGC-1α.14,17 The discovery in 1999 of PGC-1α, on the basis of a yeast two-hybrid screen for binding partners of PPARγ, and subsequent identification of two other PGC family members, PGC-1β and PGC-1-related coactivator, as coactivators for all of the transcription factors required for biogenesis set the stage for the explosion of information in this field over the last decade.4 Among the other PPARs, there is also evidence for activation of PGC-1α gene expression by PPARδ.19
In addition to PPARs, multiple signals arising from normal metabolic perturbations as well as exaggerated signaling from injury and stress control activity and expression of PGC-1α (Figure 1), consistent with its role in mitochondrial biogenesis in normal metabolic adaptation or in response to pathologic perturbations. Both ATP depletion and increased reactive oxygen species (ROS) induce PGC-1α. Mitochondrial biogenesis is increased after cerebral hypoxia and ischemia. Oxygen and nutrient deprivation individually and synergistically increase PGC-1α expression in myocytes and multiple other cell types. Hepatic mitochondrial biogenesis and increases in PGC-1α, NRF-1, GA-binding protein α, and TFAM occur in response to sepsis.

Although PGC-1α-null mice and some muscle-specific overexpression models in vivo display complex and frequently paradoxical phenotypes, studies that induce milder, likely more physiologic increases in vivo and in isolated cells have reported the effects of PGC-1α and biogenesis to increase insulin sensitivity and fatty acid metabolism in skeletal muscle, preserve skeletal muscle mass and metabolic function during aging, improve mitochondrial myopathy, and protect neuronal and endothelial cells against oxidant injury.

Mitochondria are major intracellular sources of ROS, which cause local damage to them and initiate dysfunctional signaling that contributes to the development of pathologic inflammatory phenotypes in many diseases. A more reduced state of the mitochondrial electron transport chain such as produced by increased cellular glucose loads in diabetes favors ROS production. Increased mitochondrial mass resulting from biogenesis can alleviate this process by distributing oxidation of a fixed excess carbohydrate or lipid substrate load among more mitochondria, thus decreasing the average degree of reduction of the electron transport chain in each, and thereby attenuate ROS production.

Additionally, and potentially of even greater importance for amelioration of ROS toxicity, mitochondrial biogenesis is accompanied by increased expression of antioxidant genes mediated in part by interaction of PGC-1α with the transcription factor Foxo3. The NRF-1 promoter has four antioxidant response elements for NF-E2-related factor, the transcription factor that up-regulates multiple antioxidant enzymes as the main cellular protective response to electrophiles and ROS.

The foregoing overview of the regulation of mitochondrial biogenesis is largely derived from a literature that has been developed for skeletal muscle and from related data on adipocytes and hepatocytes. Both the patterns of regulation and their consequences for overall biogenesis will vary by cell and tissue type. At present only a limited number of observations have been made in kidney and in most studies the role of biogenesis per se as compared with other events evoked by experimental probes that elicit it has not been studied specifically. Nonetheless, this is a potentially fruitful area of research that will become increasingly active because of its effect on the processes of tissue hypoxia, cellular lipid and glucose overload, and aging that are highly relevant to kidney disease. In the remainder of this discussion I will summarize recent data on the role of PGC-1α, aspects of the extensive literature on renal effects of PPARs and their agonists.
that bear most directly on biogenesis and events closely related to it, as well as emerging studies on the role of SIRT1.34

PGC-1α is highly expressed in kidney.4,35 Global knockout of the gene encoding PGC-1α does not affect kidney size,36,37 but there are no detailed studies of structure or function or the response to injury in kidneys of these mice. Interestingly, however, endothelial nitric oxide synthase null mice, which have strongly downregulated PGC-1α because of decreases of nitric oxide-mediated, cGMP-induced PGC-1α expression, show large decreases of mitochondrial antioxidant enzymes as well as of cytochrome c and the mitochondrial FAO enzyme, medium-chain acyl dehydrogenase (MCAD), in multiple tissues including prominent changes in the kidney.38 Endothelial nitric-oxide synthase deficiency strongly promotes development of glomerulopathy in mouse diabetes models.39,40

There are differences in mitochondrial function along the nephron that may affect the location or degree of injury41,42; proximal tubules, for example, are more oxidized than distal tubules. Varying degrees of mitochondrial damage, although they are not the only cellular target,48 PGC-1α protein increases 12-fold during reversible injury produced by tBHP through signaling that decreases of PDGF-B and angiopoietin. The decreases that occur afterwards.45 Varying degrees of mitochondrial antioxidant enzymes as well as of cytochrome c and the mitochondrial FAO enzyme, medium-chain acyl dehydrogenase (MCAD), in multiple tissues including prominent changes in the kidney.38 Endothelial nitric-oxide synthase deficiency strongly promotes development of glomerulopathy in mouse diabetes models.39,40

In contrast to the limited data available for PGC-1α, there is much literature documenting the importance of PPARs and their agonists in the modification of acute and chronic kidney injury through effects on both glomerular and tubular cells.2,3 However, there has not been any work addressing the specific role of mitochondrial biogenesis in these effects, and sorting this out will be complex because of the multiple effects of these transcription factors and their agonists on both local and systemic metabolism as well as their actions to directly inhibit anti-inflammatory pathways, including strong antagonism of the nuclear factor-kB2,3,49

A priori, mitochondrial biogenesis may not necessarily be beneficial during renal injury despite promotion of fatty acid metabolism and antioxidant mechanisms if it aggravates tubulointerstitial hypoxia, which contributes importantly to progression during CKD.1,50–52 In isolated myotubes, PGC-1α-induced biogenesis produces intracellular hypoxia and induction of HIF-1α target genes.53 In vivo overexpression of PGC-1α in skeletal muscle induces VEGF by HIF-1α-independent mechanisms involving coactivation of ERRα alone or coordinately through increases of PDGF-B and angiopoietin. The result is protective against an ischemic insult to the muscle.23 However, in chronic tubulointerstitial injury with pre-existing loss of the peritubular microvasculature that precludes vascular repair,31 increased oxygen consumption as a result of biogenesis could conceivably worsen tissue hypoxia or aggravate progression under some conditions.

PPARs does not by itself increase biogenesis,18,15 but instead more selectively stimulates FAO, which removes potentially toxic lipids that contribute to both acute and chronic kidney injury by increasing their mitochondrial metabolism.34 PPARγ also promotes peroxisome proliferation with the potential for ameliorating injury on that basis.55 Portilla and coworkers have comprehensively documented impairment of PPARγ signaling during both cisplatin and ischemia/reperfusion-induced acute kidney injury (AKI) and benefit from PPARγ agonists.56–60 Most recently they show strong attenuation of both insults by inducible, selective, proximal tubular up-regulation of PPARγ.61

In the latter work, induction of PPARγ does not change levels of mitochondrial FAO enzymes before AKI but prevents the decreases that occur afterwards.

The relative importance of metabolic versus anti-inflammatory pathway modification through this signaling has yet been reported, and the fact that FAO enzymes are not increased before insult could mean that other cellular effects of increased PPARγ contribute to protection with the observed preservation of mitochondrial enzymes, reflecting at least in part less overall cell injury. PPARα and PPARδ agonists are also strongly protective in models of AKI,62,63 but their primary targets and any involvement of biogenesis in these effects are not understood. Interestingly, both PPARα and PPARγ increase the expression of heme oxygenase 1,64,65 a potent protective factor in multiple acute and chronic insults to the kidney.66

The NAD acetylase SIRT11 prominently targets PGC-1α among the processes that it affects, and increases of SIRT1, PGC-1α, and mitochondrial biogenesis are implicated in the beneficial effects of calorie restriction during aging.5,67 Funk et al.43 have shown that treatment of primary cultures of rabbit proximal tubules with a SIRT1 activator, SRT1720, produces increased PGC-1α and mitochondrial biogenesis that are dependent on SIRT1 deacetylase activity but not apparently on AMP-acti-
vated protein kinase (AMPK), another important modulator of PGC-1α activity during metabolic stress that acts in coordination with SIRT1. Like PGC-1α overexpression, SIRT1720 treatment after an oxidant insult by tBHP promotes mitochondrial recovery. The effects of pre-treatment were not described.

Hasegawa et al.55 have recently reported modification of cisplatin-induced AKI by transgenic overexpression of SIRT1 in S1 and S2 segment proximal tubules using the sodium-phosphate cotransporter IIa promoter. Under control conditions, SIRT1 transgenic mice do not show differences in numbers of mitochondria or MCAD. Overexpression also does not affect the number of peroxisomes or the levels of the peroxisomal enzymes, catalase, or acyl CoA oxidase. During cisplatin injury, which strongly affected S2 segments in these mice, there are substantial decreases in peroxisome number, catalase, and acyl CoA oxidase that attenuate in the transgenic phenotype, which also has less functional changes or cell death. Mitochondrial number is only minimally decreased after cisplatin and is not affected in the transgenics; however, large decreases of MCAD after cisplatin are ameliorated in the transgenic cohorts. Cisplatin-induced decreases in PGC-1α are not attenuated in the transgenics. On the basis of the more prominent changes seen in peroxisomes, including preservation of the antioxidant, catalase, they appear as the major mediators of the benefit seen. The increases of both peroxisomes and mitochondrial FAO enzymes suggest that SIRT1 effects are mediated through PPARα (Figure 1). SIRT1 overexpression does not affect ischemia/reperfusion injury, but in these transgenics SIRT1 is not increased in S3 segments, where ischemia-reperfusion injury predominates. Calorie restriction was also assessed in this study, but extensive data were developed supporting a pathway involving SIRT1-mediated deacetylation of Foxo3, leading to protective increases of Bnip3 (BCL2 adenovirus E1B 19-kd interacting protein 3)-mediated mitophagy and increases in the cyclin-dependent kinase inhibitor p27kip1 to account for the SIRT1-mediated beneficial effects of calorie restriction. Similar behavior is seen during acute hypoxic injury of cultured tubule cells.10

Calorie restriction led to increases of kidney SIRT1 in both the Hasegawa et al.55 and Kume et al.10 studies, and Hasegawa et al.55 show that these increases occur prominently in the proximal tubule. However, the strongest SIRT1 expression in young mice on a normal diet was found by He et al.69 to be in medullary interstitial cells, where it contributes to protection from oxidative stress and limits injury produced by ureteral obstruction at least in part by increasing interstitial cell expression of cyclooxygenase-2. These recent studies by Hasegawa et al.55 Kume et al.,10 and He et al.69 emphasize the multiple pathways potentially engaged by SIRT1 modification, including major effects in medullary interstitial cells where oxidative metabolism is limited.69 Interestingly, SIRT1 overexpression in uninjured proximal tubules does not increase mitochondrial number.55

In summary, work in skeletal muscle and other tissues shows that mitochondrial biogenesis and its attendant processes enhance metabolic pathways such as fatty acid oxidation and decrease mitochondrial ROS production to ameliorate injury from tissue hypoxia, glucose and fatty acid overload, and aging. Benefits from maneuvers that promote mitochondrial biogenesis can also derive from concomitant enhancement of other protective pathways such as increases of extramitochondrial antioxidants, heme oxygenase 1, Bnip3, and cyclooxygenase-2 that are elicited by the same coactivators and transcription factors. A caveat with respect to kidney pathology is the possibility of worsening tissue hypoxia in some settings caused by increased oxidative metabolism. Additionally, recent work describes aggravation of tubule cell injury when mitochondrial biogenesis is induced before an oxidant insult, in contrast to benefit that is observed using the same system by induction during recovery. Although currently available information about the effects of mitochondrial biogenesis on kidney pathogenesis is limited, it will be subject to increasing attention given its ability to modify major pathogenic processes contributing to acute and chronic kidney disease.

DISCLOSURES
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