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The role of Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 α (PGC-1 α) in kidney disease

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Abstract

Peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) is a key transcriptional regulator of mitochondrial biogenesis and function. Several recent studies evaluated the role of PGC-1 α in various renal cell types in healthy and disease conditions.

Renal-tubule cells mostly depend on mitochondrial fatty acid oxidation (FAO) for energy generation. A decrease in PGC-1 α expression and FAO is commonly observed in patient samples and mouse models with acute and chronic kidney disease. Conversely, increasing PGC-1 α expression in renal-tubule cells restores energy deficit and has been shown to protect from acute and chronic kidney disease.

Other kidney cells, such as podocytes and endothelial cells, are less metabolically active and have a narrow PGC-1 α tolerance. Increasing PGC-1 α levels in podocytes induces podocyte proliferation and collapsing glomerulopathy development, while increasing PGC-1 α in endothelial cells alters endothelial function and causes microangiopathy, thus highlighting the cell-type-specific role of PGC-1 α in the kidney.

Keywords

PGC-1 α ; mitochondria; podocyte; tubular cells; Notch

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PGC-1 α and mitochondria

Mitochondria are the power plants of cells. They contain proteins encoded both by nuclear and the mitochondrial genomes; coordinated regulation of these two genomes governs mitochondrial biogenesis and function, such as oxidative phosphorylation.

The peroxisome proliferator-activated receptor (PPAR) γ coactivator-1 α (PGC-1 α) has been identified as the main inducible upstream transcriptional regulator of mitochondrial biogenesis and function (7, 8). PGC-1 α is generally considered a coactivator as it binds and works together with other transcription factors, including peroxisome proliferator-activated receptor (PPAR) α/β , Nuclear Respiratory Factor (NRF) 1 and 2, and estrogen-related receptor (ERR)(9, 10). Increasing cellular PGC-1 α level will increase mitochondrial biogenesis. Increasing mitochondrial number and oxidative phosphorylation, on the other hand, can also increase reactive oxygen (ROS) byproduct generation. To avoid the increase of toxic ROS, PGC-1 α also regulates the expression of several ROS-detoxifying enzymes' transcription (SOD2, GPX1, UCP2) (11, 12), such that cells can benefit from increased respiration and ATP production without suffering from oxidative damage. The binding of PGC-1 α to other co-transcription factors such as PPAR will enhance fatty acid oxidation and increase nutrient supply via increasing angiogenesis and vascular endothelial growth factor levels (13). In summary, PGC-1 α coordinates a complex network of nutrient availability, mitochondria biogenesis, and FAO. (Figure 1)

Decreased PGC-1 α expression, mitochondrial loss, and defective mitochondrial function have been shown to contribute to various metabolic diseases including renal failure (8, 14), diabetes, and Parkinson disease (15). In this review, we will discuss the latest findings on the role of PGC-1 α in kidney disease development.

Metabolism in different cell types of the kidney

The kidney is a highly metabolically active organ. It uses 20% of the cardiac output despite comprising less than 1% of the body mass. Renal tubular epithelial cells (RTEC) represent 90% of the kidney mass. Proximal tubules and collecting duct cells have some of the highest mitochondrial content in human body. They actively reabsorb large amounts of water, electrolytes, and other small molecules from the primary filtrate, which is highly energy demanding. Like most highly metabolic cells, the preferred energy fuel for tubule cells is fatty acid (1). Fatty acids are oxidized by the mitochondria via oxidative phosphorylation. The energy yield of FAO is about 106 ATP per equivalents per fatty acid, as opposed to 38 ATP during carbohydrate oxidation.

Kidney endothelial cells line the interior surface of the glomerular and intertubular capillaries. Endothelial cells have a relatively low mitochondrial content and rely primarily on glycolysis, far exceeding the products of glucose oxidation(2). Aerobic glycolysis can preserve the maximal amounts of oxygen to transfer to the perivascular tissues. Glycolytic endothelial cells can grow in hypoxic environment by adapting to the hypoxic surroundings and can shunt glucose into glycolysis side branches which is advantageous for macromolecule synthesis (3).

Podocytes are cells in the Bowman's capsule that wrap around glomerular capillaries. Their interdigitating pedicles are the last barrier to restrict the passage of large serum molecules into urine. While the preferential energy fuel of podocytes is less known, most studies indicate that they can use glucose as their energy source (4), (5, 6). Both 2 deoxyglucose and electron transport chain inhibitors can block ATP generation in podocytes, suggesting they metabolize glucose by glycolysis and by mitochondrial oxidative phosphorylation. Ozawa et al described that glycolysis is responsible for providing ATP for the peripheral regions (foot processes), while mitochondria respiration is the energy source for the central cell body such as around the nucleus (6).

PGC-1 α in acute kidney injury

Acute kidney injury (AKI) refers to rapid loss of kidney function occurring within 1–2 days. AKI mostly affects hospitalized patients and develops as a result of oxygen or nutrient deficit in the renal tubule cells. The corticomedullary junction is particularly sensitive to hypoxia because it has the lowest local oxygen concentration due to its limited blood vessel density, though it is one of the highest energy consuming segments. As oxygen is the terminal electron acceptor in oxidative phosphorylation, hypoxia should decrease FAO and NAD⁺/NADH ratio, which is consistent with the published literature. During reperfusion, oxygen tension will rise, which in theory should immediately restore FAO. However, studies indicate that FAO enzymes remain suppressed during the reperfusion phase (16) and lipid droplets accumulate (17).

In endotoxin-induced sepsis AKI models, PGC-1 α levels are decreased and correlate with the degree of renal impairment (17, 18). To test the casual relationship between low PGC-1 α level and AKI, Trai *et al* performed a sepsis-induced AKI model in control and in PGC-1 α knock-out mice. They found that mice with global or tubule-specific PGC-1 α deletion failed to recover from kidney injury following sepsis (18), suggesting that renal tubule epithelial PGC-1 α is essential for renal recovery after sepsis-induced AKI. Similar results were obtained in models of renal ischemia reperfusion injury. To prove the causal role of PGC-1 α in renal recovery, they showed that tubular-epithelial-specific transgenic expression of PGC-1 α attenuated pathological changes and was associated with improved renal function after ischemia (19). Together, these data indicate that re-expression of PGC-1 α or its functional effect is necessary for recovery from AKI.

PGC-1 α in chronic kidney disease and fibrosis

Similar to acute kidney injury, decreased PGC-1 α and lipid droplet accumulation have been repeatedly observed in kidneys of patients with CKD and mouse models of CKD. Incubating cultured tubule cells in long-chain-fatty-acid-containing medium will result in an inflammatory response including ER stress, NF κ B activation, and oxidative stress (20, 21), a phenomenon described as “lipotoxicity”. “Lipoid nephrosis” and “lipotoxicity” have been proposed as key mechanisms for kidney fibrosis. To test whether lipid overload is causally related to renal fibrosis, we have expressed the long chain fatty acid transporter CD36 on renal tubule cells. As expected, CD36 expression resulted in long chain fatty acid and lipid droplet accumulation. On the other hand, lipid accumulation did not result in kidney disease

or fibrosis development. We did not observe increased susceptibility to acute or chronic kidney disease in these animals (1), indicating that lipid accumulation *in vivo* does not necessarily cause kidney fibrosis.

Gene expression analysis of a large collection of microdissected human kidney tubule samples indicated that genes with metabolic function comprise the largest dysregulated gene group in kidney fibrosis. Expression of PPAR α , PGC1 α , and enzymes involved in FAO such as Cpt1 and Acox1 were consistently reduced in diabetic and non-diabetic CKD and animal models of CKD. To test the role of altered metabolism and FAO in CKD, we have generated animal models with transgenic-inducible expression of PGC-1 α and found that these animals were protected from fibrosis development. On the mechanistic level, we showed that TEC exclusively rely on FAO and they are unable to switch to glycolysis so pharmacological inhibition of Cpt1 results in ATP depletion, cell death, and dedifferentiation (1). The effect of PGC-1 α is mostly mediated by improving FAO as PPAR- α agonists fenofibrate or a Cpt1 agonist have also been associated with improved outcomes in different models of kidney disease (22–24), indicating that FAO, but not total mitochondrial density or PGC-1 α level, is the key determinant of CKD development. To further support this claim, it is important to point out that the PGC-1 α knock-out mice (or the PPAR- α knock-out animals) do not present with renal malfunction or structural abnormalities at baseline. These studies indicate that PGC-1 α and PPAR- α are dispensable for basal metabolism, and increasing their expression or their activity is associated with a protective phenotype, mostly because their effect on FAO. These correlations do not necessarily indicate that these transcription factors, but rather FAO are the cause of kidney fibrosis. We believe that it is very likely that another metabolic transcription factors are responsible for the FAO and metabolic alterations.

The effect of PPAR- α agonists such as fibrates have been studied in patients with CKD and diabetic kidney disease. These studies, however, have been complicated by the fact that fibrates interfere with creatinine secretion, which alters creatinine-based eGFR estimations. Both the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (25) and the Action to Control Cardiovascular Risk in Diabetes ACCORD (26) studies indicated statistical improvement in urinary albuminuria in patients with diabetic kidney disease who were treated with fenofibrate. These studies also indicated a small but significant reduction in GFR; however, the GFR effect seems smaller in patients than in animal models.

These data indicate that low PGC-1 α expression and defective fatty acid utilization are common pathological mechanisms of chronic kidney disease, and restoring FAO by PGC-1 α or other means therefore could be a potential therapeutic strategy for chronic kidney disease. (Figure 2)

Regulation of PGC-1 α in kidney cells

Given the key role of PGC-1 α and metabolism in renal tubule cells, it is important to understand the upstream regulatory mechanism of PGC-1 α expression. As PGC-1 α is almost ubiquitously expressed, its regulation by AMPK, Sirt1, p38MAPK, and CaMKII (28) is well described. To understand the regulation of PGC-1 α , first we mapped its regulatory regions, such as promoter and enhancer regions in kidney cells. We used genome-wide

chromatin immunoprecipitation data (ChIP) and sequencing to achieve this goal. As expected, an active PGC-1 α promoter can be detected in most analyzed cells and tissues, on the other hand we detected several cell- and tissue-specific enhancer regions.

Examining transcription factors that can bind to PGC-1 α regulatory regions, we have identified that, in addition to classic metabolic regulators, developmental and profibrotic transcription factors such as Hes1 or Smad3 can also bind to PGC-1 α .

The interaction of metabolic signals such as PGC-1 α and developmental signals such as Notch have been particularly exciting. Notch signaling is a critical regulator of kidney development. While it is expressed at low level in healthy adult kidneys (29), Notch reactivation appears to be both necessary and sufficient for renal fibrosis development (30). Although the critical role of Notch in kidney fibrosis is well established, the mechanisms for this are undetermined. Recently, our group identified that Hes1, a downstream target of Notch signaling, can directly bind on *Ppargc1a* promoter region and inhibit PGC-1 α expression. More importantly, overexpression of PGC-1 α in tubular cells can almost totally prevent Notch-induced renal fibrosis *in-vivo* (31). This result strongly suggests Notch-induced fibrosis is mostly mediated by a metabolic dysfunction in RTEC. Of interest, the interactions between PGC-1 α and Notch seem to be cell-type specific. For example, endothelial PGC-1 α can induce Notch signaling to blunt the activation of Rac/Akt/eNOS signaling, which renders endothelial cells unresponsive to angiogenic factors (32).

TGF- β is one of the best known pro-fibrotic cytokines. TGF- β can induce renal fibrosis via activation of both canonical (Smad-mediated) and non-canonical (non-Smad-mediated) signaling pathways. TGF- β can suppress FAO through epigenetic downregulation of PGC-1 α and PPAR- α . Chromatin immunoprecipitation studies revealed that Smad3, a downstream effector of TGF- β , can directly bind to the enhancer of PGC-1 α gene and inhibit PGC-1 α expression in many cell types (33), including RTEC (1).

In summary, our systemic analysis indicates that diverse signals can regulate PGC-1 α expression in the kidney including signals such as Notch and TGF- β that are involved in maintaining cell differentiation. These results could indicate that metabolic signals are in balance with cell differentiation signals to match energy production with cellular function (and energy needs).

PGC-1 α in glomerular disease

Altered PGC-1 α expression and mitochondrial loss have also been observed in podocytes in different glomerular diseases including diabetic nephropathy, adriamycin- and aldosterone-induced glomerulosclerosis (36–39). However, the contribution of decreased PGC-1 α levels to glomerular disease or podocyte dysfunction remains a bit controversial.

Recently, Long *et al.* described that a long non-coding RNA taurine-upregulated gene 1 (Tug1) is downregulated in diabetic glomeruli, and podocyte-specific Tug1 overexpression mice are protected from diabetic nephropathy. Further analysis revealed Tug1 overexpression alters the expression profile of several distinct biological pathways including metabolic regulation. Tug1 can rescue the expression of PGC-1 α and its transcriptional

targets in diabetic nephropathy. Mechanistically, they propose that Tug1 can loop PGC-1 α enhancer and promotor and therefore positively regulates PGC-1 α transcription, (40, 41). In agreement with this observation, another group found that PGC-1 α can attenuate mitochondrial dysfunction, restore slit diaphragm protein expression, and reduce apoptotic response in podocytes after ADR treatment in-vitro (38). These findings suggest increasing PGC-1 α levels in podocytes could be beneficial in glomerular diseases.

To address this issue, our group has decided to study the role of PGC-1 α in podocytes using a podocyte-specific transgenic approach. To our surprise, transgenic animals developed severe proteinuria, renal failure, and histological changes consistent with collapsing glomerulopathy. We found changes in mitochondrial properties including mitochondrial fusion and electron transport chain composition changes, which likely resulted in increased podocyte proliferation (4), indicating that podocytes have a narrow tolerance for PGC-1 α levels. In this aspect, podocytes are similar to endothelial cells as PGC-1 α is increased in diabetic mice and humans. Genetic overexpression of PGC-1 α in endothelial cells resulted in increased Notch expression, downstream endothelial dysfunction, and a condition that mimicked diabetic vasculopathy phenotypes in mice. Conversely, endothelial PGC-1 α knockout mice are protected from diabetes-induced vascular complications (32) (Figure 3).

Summary and Outlook

The kidney is a highly active metabolic organ and consumes a large amount of energy to maintain fluid and electrolyte homeostasis. Renal tubular epithelial cells have a very high mitochondrial density and use fatty acid as their energy source to match the physiological energy demand. In the setting of acute and chronic kidney injury, the PGC-1 α mitochondrial, FAO axis is suppressed, as cells cannot switch to alternative fuel, it results in energy depletion. Cells initially adjust to energy depletion by dedifferentiation as decreasing the expression of various high energy transport mechanisms likely reduce the cell's energy requirement. Severe energy depletion will eventually result in cell death. Reactivation of PGC-1 α pathway therefore could provide a potential intervention strategy; however, endothelial cells and podocytes have narrow PGC-1 α tolerance. PGC-1 α can interact with Notch leading to endothelial dysfunction, and excessive PGC-1 α can induce podocyte proliferation and collapsing glomerulopathy.

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Figure 1. Biological function of PGC-1α

PGC-1α co-activates transcription factors such as estrogen-related receptors (ERRs), Retinoid X receptors (RXRs), peroxisome proliferator-activated receptors (PPARs), Mitochondrial transcription factor A (Tfam), and nuclear respiratory factors (NRFs), known to regulate different aspects of energy metabolism including angiogenesis, fatty acid oxidation, antioxidant, and mitochondrial biogenesis.

Figure 2. Energetic alterations in renal tubule epithelial cells and renal fibrosis

Renal tubule epithelial cells use fatty acids to produce ATP. Kidney injury directly induces mitochondrial damage and suppresses PGC-1 α expression, hence blocking PPAR α activity, mitochondrial biosynthesis and NAD synthesis. All these changes lead to fatty acid oxidation failure. Defective fatty acid oxidation results in lipid accumulation, tubule epithelial cell dedifferentiation, and apoptosis.

Figure 3. Potential contributions of excessive PGC-1α to the development of collapsing glomerulopathy

Podocytes use glucose as energy fuel. In certain circumstances, drug-induced and other mitochondrial injuries cause podocyte ATP deficiency. PGC-1α is therefore upregulated to compensate depleted cell energy, but podocytes have a narrow PGC-1α tolerance. Excessive PGC-1α changes podocyte mitochondrial intrinsic properties and cell fate, leading to collapsing glomerulopathy.