The Role of Peroxisome Proliferator-Activated Receptor γ Coactivator 1α (PGC-1α) in Kidney Disease

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Summary: Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) is a key transcriptional regulator of mitochondrial biogenesis and function. Several recent studies have evaluated the role of PGC-1α in various renal cell types in healthy and disease conditions. Renal tubule cells mostly depend on mitochondrial fatty acid oxidation for energy generation. A decrease in PGC-1α expression and fatty acid oxidation is commonly observed in patient samples and mouse models with acute and chronic kidney disease. Conversely, increasing PGC-1α 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-1α tolerance. Increasing PGC-1α levels in podocytes induces podocyte proliferation and collapsing glomerulopathy development, while increasing PGC1-α in endothelial cells alters endothelial function and causes microangiopathy, thus highlighting the cell-type–specific role of PGC-1α in different kidney cells.

Keywords: PGC-1α, mitochondria, podocyte, tubular cells, Notch

Mitochondria are the power plants of cells. They contain proteins encoded both by nuclear and 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-1α (PGC-1α) has been identified as the main inducible upstream transcriptional regulator of mitochondrial biogenesis and function.[1,2] PGC-1α is considered a coactivator because it binds and works together with other transcription factors, including PPARα/β, nuclear respiratory factors 1 and 2, and estrogen-related receptor.[3,4] Increasing the cellular PGC-1α 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-1α also regulates the expression of several ROS-detoxifying enzymes (SOD2, GPX1, UCP2),[5,6] such that cells can benefit from increased respiration and adenosine triphosphate (ATP) production without suffering from oxidative damage. The binding of PGC-1α 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.[7] In summary, PGC-1α coordinates a complex network of nutrient availability including mitochondrial biogenesis and fatty acid oxidation (FAO) (Fig. 1).

Decreased PGC-1α expression, mitochondrial loss, and defective mitochondrial function have been shown to contribute to various metabolic diseases including renal failure,[2,8] diabetes, and Parkinson disease.[9] In this review, we discuss the latest findings on the role of PGC-1α in kidney disease development.

THE METABOLISM IS CELL-TYPE SPECIFIC

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 (RTECs) represent 90% of the kidney mass. Proximal tubules and collecting duct cells have some of the highest mitochondrial content in the human body. They actively reabsorb large amounts of water, electrolytes, and other small molecules from the primary filtrate, which is a highly energy-demanding process. Similar to most highly metabolic cells, the preferred energy fuel for tubule cells is fatty acids.[10] Fatty acids are oxidized by the mitochondria via

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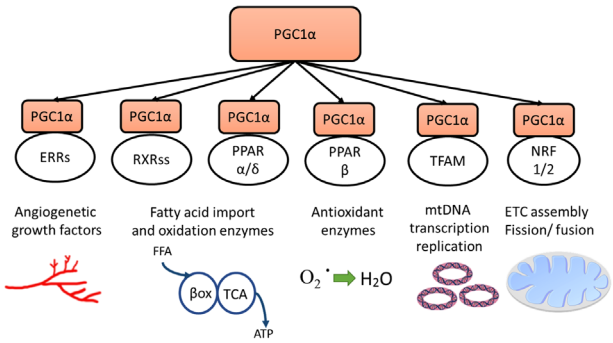

Figure 1. The various functions of PGC-1α. PGC-1α works together with transcription factors such as estrogen-related receptors (ERRs), retinoid X receptors (RXRs), PPARs, mitochondrial transcription factor A (Tfam), and nuclear respiratory factors (NRFs), known to regulate different aspects of energy metabolism including angiogenesis, fatty acid oxidation, antioxidant, and mitochondrial biogenesis. ETC, Electron transport chain; FFA, free fatty acid; mtDNA, mitochondrial DNA; TCA, tricarboxylic acid cycle.

oxidative phosphorylation. The energy yield of FAO is greater than 106 ATP per equivalents per fatty acid, as opposed to 38 ATP during carbohydrate oxidation.

Endothelial cells line the interior surface of the glomerular and intertubular capillaries. Endothelial cells have relatively low mitochondrial content and rely primarily on glycolysis.[11] Aerobic glycolysis can preserve the maximal amounts of oxygen to transfer to the perivascular tissues. Glycolytic endothelial cells can grow in a hypoxic environment by adapting to the hypoxic surroundings and can shunt glucose into glycolysis side branches, which is advantageous for macromolecule synthesis.[12]

Podocytes are cells in 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. Although the preferential energy fuel of podocytes is less well known, most studies indicate that they can use glucose as their energy source.[13–15] Both 2 deoxyglucose and electron transport chain inhibitors can block ATP generation in podocytes, suggesting that they metabolize glucose by glycolysis and by mitochondrial oxidative phosphorylation. Ozawa et al[15] described that glycolysis is responsible for providing ATP for the peripheral regions (foot processes), while mitochondrial respiration is the energy source for the central cell body such as around the nucleus.

PGC-1α IN ACUTE KIDNEY INJURY

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

In endotoxin-induced sepsis AKI models, PGC-1α level is decreased and its level correlate with the degree of renal impairment.[17,18] To test the casual relationship between low PGC-1α level and AKI, Tran et al[18] developed a sepsis-induced AKI model in control and in PGC-1α knock-out mice. They found that mice with global or tubule-specific PGC-1α deletion failed to recover from kidney injury after sepsis, suggesting that renal tubule epithelial PGC-1α 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-1α in renal recovery, they showed that tubular-epithelial–specific transgenic expression of PGC-1α attenuated pathologic changes and was associated with improved renal function after ischemia.[19] Together, these data indicate that re-expression of PGC-1α or its functional effect is necessary for recovery from AKI.

PGC-1α IN CHRONIC KIDNEY DISEASE AND FIBROSIS

Similar to acute kidney injury, decreased PGC-1α and lipid droplet accumulation have been observed repeatedly in kidneys of patients with chronic kidney disease (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, nuclear factor-κβ activation, and oxidative stress,[20,21] a phenomenon described as "lipotoxicity." "Lipoid nephrosis" and "lipotoxicity" have been proposed as key mechanisms of kidney fibrosis.[22] 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 induce kidney disease or fibrosis development. We did not observe increased susceptibility to acute or chronic kidney disease in these animals,[10] 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