



Exploring Renal Pyruvate Metabolism as a Therapeutic Avenue for Diabetic Kidney Injury

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Acute kidney injury (AKI) involves sudden deterioration in kidney function, and multiple circumstances, including diabetes, have been identified as risk factors. Although AKI frequently leads to death, a poor understanding of its detailed mechanisms impedes the development of effective treatment. During AKI, ischemia-reperfusion (IR) injury, as well as subsequent increases in reactive oxygen species (ROS) and inflammation, occur and are thought to play a critical role [1].

The mitochondria generate a large amount of ROS, and their dysfunction leads to a variety of metabolic disorders. The mitochondria are the primary intracellular organelles that generate cellular energy, and pyruvate metabolism is a key event in the mitochondria. Pyruvate, produced by glycolysis in the cytoplasm, is further metabolized within the mitochondria to produce adenosine triphosphate (ATP) under aerobic conditions. During this process, pyruvate is converted into acetyl-coenzyme A (CoA), which can be utilized to generate ATP or free fatty acids. The pyruvate dehydrogenase (PDH) complex mediates the conversion of pyruvate to acetyl-CoA, which is allosterically inhibited by ATP, acetyl-CoA, and NADH (nicotinamide adenine dinucleotide [NAD]⁺+hydrogen [H]), as well as by PDH phosphorylation by pyruvate dehydrogenase kinases (PDK1-4). In contrast, adenosine monophosphate, CoA, and NAD⁺ allosterically increase PDH action, as does PDH dephosphorylation by pyruvate dehydrogenase phosphatases (PDP1 and PDP2) [2,3].

Recent studies spearheaded by In-Kyu Lee's group at Kyungpook National University, Korea, proposed that pyruvate me-

tabolism centered on PDK is critical in a variety of metabolic syndromes. Global or adipose-tissue-specific depletion of PDK2 in mice prevented diet-induced obesity [4]. Under streptozotocin (STZ)-induced diabetic conditions, PDK2 in hypothalamic astrocytes has been demonstrated to mediate neuroinflammation while also modulating food intake and blood glucose levels [5]. Additionally, muscle PDK4 has been shown to elevate endoplasmic reticulum-mitochondria contact and attenuate muscle insulin signaling during obesity [6], while hepatic PDK2 and PDK4 have been documented to regulate liver glucose metabolism via insulin and glucagon signaling [7,8]. Also, the PDK inhibitor dichloroacetate (DCA) was found to reduce vascular inflammation and atherogenesis in an apolipoprotein E (APOE) knockout mouse model [9].

A recent publication in *Diabetes & Metabolism Journal* by Khang et al. [10] revealed that diabetic kidney injury induced by STZ treatment and IR resulted in elevated levels of PDK4 but not its other isoforms. Phosphorylation of PDH E1 α (PDHE1 α), which is the canonical target of PDK, increased concurrently. Furthermore, when the authors suppressed PDK activity with DCA, the treatment alleviated the pathological phenotypes of diabetic AKI mouse models, such as cell death, oxidative stress, and inflammation. These *in vivo* phenotypes, including cell death and inflammation, were also mitigated by DCA treatment or gene silencing of PDK4 in their *in vitro* experiments utilizing kidney epithelial normal rat kidney (NRK)-52E cells and mouse primary tubular cells subjected to high glucose and hypoxia/reoxygenation conditions.

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In-Kyu Lee's group had previously demonstrated that PDK4 was involved in cisplatin-induced or non-diabetic IR-induced AKI [11,12]. In non-diabetic IR-induced AKI, proximal tubule cell-specific PDK4 deletion ameliorated kidney damage by lowering succinate levels, which may also influence diabetic AKI. In the observed outcomes by Khang et al. [10], the authors newly reported PDK4's crucial involvement in diabetic AKI, supporting PDK4 as therapeutically beneficial. Given that mitochondrial dysfunction is also a hallmark of chronic kidney disease (CKD) in addition to AKI [13], additional research into the role of PDK4 in CKD will provide mechanistic and therapeutic insight into whether pyruvate metabolism centered on PDK4 also plays an important role in CKD pathogenesis. Indeed, CKD patients' muscle samples showed decreased PDH activity and concomitantly increased PDK4 protein levels [14].

CONFLICTS OF INTEREST

Jaemin Lee has been associate editor of the *Diabetes & Metabolism Journal* since 2024. He was not involved in the review process of this article. Otherwise, there was no conflict of interest.

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