Tetsuhiro Tanaka, J Nephrol Ther 2018, Volume 8
DOI: 10.4172/2161-0959-C7-068

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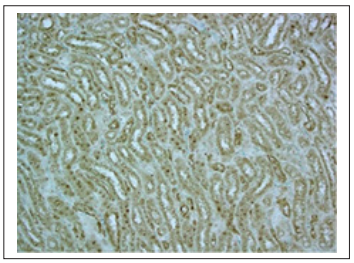
A role of hypoxia-signaling in diabetic kidney disease



Pathophysiology of Diabetic Kidney Disease (DKD) is complex. In addition to high glucose-induced inflammation, oxidative stress and activation of the renin-angiotensin system, the pathogenic role of chronic hypoxia in the tubulointerstitium is increasingly recognized. Beginning from the early stage of DKD, an increase in oxygen consumption secondary to mitochondrial uncoupling reduces local oxygenation, and together with loss of peritubular capillaries and impaired oxygen diffusion, negatively influences the balance of injury and repair in tubular epithelial cells and serves as a final common pathway leading to fibrosis. Studies on Erythropoietin (EPO) transcription led to the identification of Hypoxia Inducible Factors (HIFs) and their key regulators, Prolyl Hydroxylases (PHDs). Inhibition of PHD leads to HIF stabilization irrespective of oxygen content and up-regulates EPO, as well as other 100-200 target genes involved in processes such as angiogenesis and anaerobic metabolism necessary for cellular hypoxic adaptation. Based on this, several small molecule PHD inhibitors are currently under human clinical trials for the treatment of anemia in CKD. Application of PHD inhibitors has several potential implications beyond anemia treatment. Because HIF drives the expression of genes essential to adaptation to hypoxia, there is a promising view that activation of HIF using PHD inhibitors might protect against DKD. Besides, animal and human clinical studies even suggest that PHD inhibitors may improve glucose and lipid metabolism, which may also orchestrate protection against DKD progression.

Biography

Tetsuhiro Tanaka is a currently working at the Division of Nephrology and Endocrinology, the University of Tokyo, School of Medicine. His major research interest is the role of chronic hypoxia and hypoxia-inducible gene transcription in the pathogenesis of CKD. He has completed his Graduation from the University of Tokyo, School of Medicine in 1997 and has obtained his PhD degree at the University of Tokyo Graduate, School of Medicine in 2005. He has received the Young Investigator Award of the Japanese Society of Nephrology in 2014. He is currently serving as an editorial board member of Kidney International and Clinical and Experimental Nephrology.

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