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Hypoxic memory in the ischemic kidney injury

Tetsuhiro Tanaka

University of Tokyo Hospital, Japan

Tubulointerstitial hypoxia plays an essential role as the final common pathway to end-stage renal disease. Hypoxia-Inducible Factor (HIF) is a master transcriptional factor responsible for tissues to adapt to the environment of reduced oxygen concentration. Such mechanisms include regulation of downstream target genes involved in angiogenesis, erythropoiesis and anaerobic metabolism. In some pathophysiological contexts, hypoxia may be recorded as epigenetic changes (“hypoxic memory”) and be responsible for progression of the kidney disease in the long term. In this regard, we performed genome-wide analysis of HIF-1 binding sites using high-throughput sequencers and found novel downstream targets relevant to epithelial cell behavior. By simultaneously checking histone modification marks, we identified novel roles of HIF-1 in histone modification which enhances its target gene expression. Furthermore, microarray analysis and RNA-seq in cultured tubular cells exposed to hypoxia demonstrated the expression of several novel long non-coding RNA (lncRNA), including aspartyl-tRNA synthase anti-sense 1 (DARS-AS1), which was most strongly induced by hypoxia and suggested to play anti-apoptotic roles. In an AKI to CKD transition model of ischemia-reperfusion injury in vivo, we observed that pharmacological targeting of histone modifications was effective in ameliorating fibrosis. In summary, HIF is responsible for a variety of epigenetic changes and may ultimately determine the consequences of the disease phenotypes.

Biography

Tetsuhiro Tanaka is 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 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*.

tetsu-ky@umin.ac.jp

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