Oxidative stress and hypoxia as novel therapeutic targets in kidney disease

Masaomi Nangaku
The University of Tokyo Graduate School of Medicine, Japan

Oxidative stress and hypoxia serve as final common pathways to end-stage kidney disease. Oxidative stress is a harmful process that negatively affects cellular structures, such as membranes, lipids, proteins, and nucleic acids. Oxidative stress in the kidney leads to vascular and tubular injury, which results in the loss of peritubular capillaries. Interstitial fibrosis impairs oxygen diffusion and supply to tubular cells. Hypoxia of tubular cells exacerbates fibrosis of the kidney and subsequent chronic hypoxia, setting in train a vicious cycle. In addition to hyperoxia, hypoxia also induces oxidative stress, and abnormal oxygen metabolism is a focus of intensive researches. Therapeutic approaches that target oxidative stress and hypoxia should be effective against a broad range of kidney diseases. Cells are endowed with a defensive mechanism against oxidative stress, and Nrf2 is a master regulator of this defense. Similarly, hypoxia-inducible factor (HIF) is a master regulator of defense against hypoxia. Clinical trials utilizing small compounds to activate Nrf2 or HIF are on-going. HIF activators increase erythropoietin and will be available at the bedside as a new therapeutic modality against anemia in CKD. Results of phase 2 studies of Nrf2 activators showed improvement of GFR in patients and seem promising.