Oxygen biology in the CKD patients

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In celebration of the 60th Anniversary of the International Society of Nephrology (ISN) two years ago, the ISN published a series "Breakthrough Discoveries". Among the 60 historical discoveries of significant impact in nephrology, this publication included studies about hypoxia-inducible factors (HIF) and hypoxia of the kidney, which are involved in numerous pathophysiological processes, including chronic kidney disease (CKD).
Gregg Semenza was the first to elucidate the mechanism of regulation of erythropoietin (EPO) and disclosed HIF as an important transcription factor that regulates EPO expression. Sir Peter J. Ratcliffe later discovered that HIF Prolyl Hydroxylases (HIF-PHs) play an essential role in the regulation of HIF in an oxygen-dependent manner, and William Kaelin Jr. demonstrated the essential role of von Hippel-Lindau (VHL) E3 ligase in proteolysis of hydroxylated HIF- α subunit. These three discoveries, which together identified molecular machinery that regulates the activity of genes in response to varying levels of oxygen, were awarded the Nobel Prize in 2019, paving the way for extensive future research.

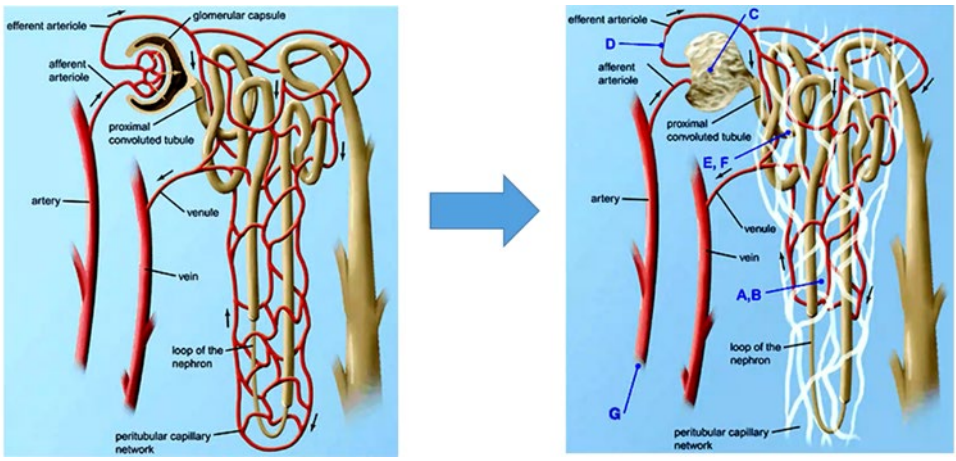

Figure 1. Hypoxia as the final common pathway to ESKD

Oxygen biology in chronic kidney disease and animal models

At an advanced stage of kidney disease tissue fibrosis results in the loss of peripheral capillaries, as well as a decrease in oxygen and diffusion efficiency. Thus, hypoxia is the final common pathway to end-stage kidney disease throughout the disease course. Exploring oxygen biology in the kidney required methodology to quantitatively assess the oxygen tension in the organs. Tanaka et al. created transgenic hypoxia-sensing rats that express reporter genes under the control of HIF. These animals were used in a variety of animal models to demonstrate that hypoxia begins from the early stages of renal illness. A similar concept inspired William Kaelin Jr. to develop hypoxia-sensing transgenic mice. He used a sophisticated IVIS technique to visualize the expression of the reporter gene in live mice. When the transgenic mice were kept in hypoxic conditions, the oxygen tension in the brain was normal, while oxygen tension in the kidney decreased dramatically, proving that the kidneys are susceptible to hypoxia. Research led by Yosuke Hirakawa established the new intravital phosphorescence lifetime

imaging microscopy (PLIM) technique for visualizing and estimating oxygen tension within the cells at the resolution of tubular cells. Surprisingly, the oxygen tension of individual tubules differed markedly, even in the adjacent ones. In human patients, Pruijm et al. used blood oxygenation level-dependent magnetic resonance imaging (BOLD-MRI) to assess tissue oxygenation by measuring deoxyhemoglobin. The study showed that the decrease in oxygen tension of the kidney predicts a progressive decline of kidney function in patients with chronic kidney disease (CKD) and diabetic kidney disease.

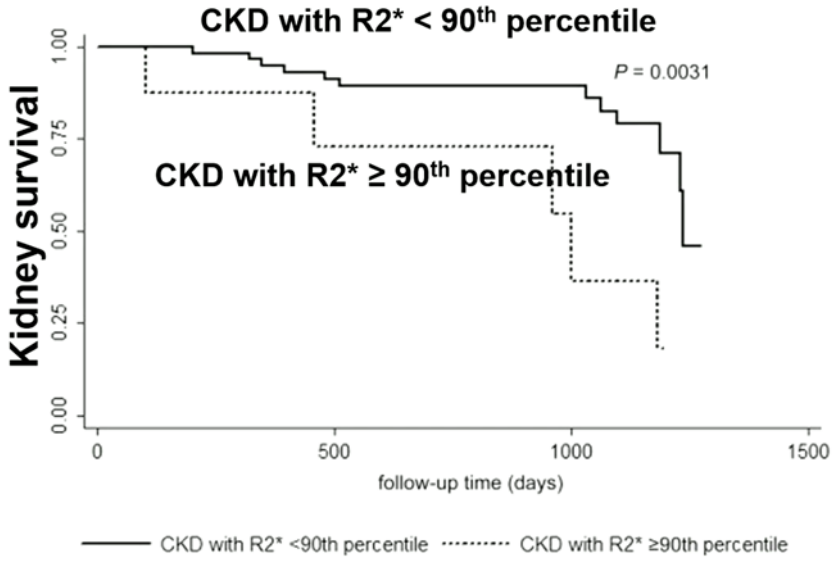

Figure 2. Reduced cortical oxygenation predicts a progressive decline of renal function in CKD

Oxygen biology in acute kidney injury

Acute kidney injury (AKI) is a transient phenomenon in which hypoxia plays an important role. Even though many AKI patients temporarily regain renal function, epidemiological research shows that many of them develop chronic and end-stage kidney disease (ESKD) over time. Mimura et al. revealed that epigenetic changes induced by hypoxia, such as changes in histone modifications, can explain the mechanism of AKI to CKD transition. These epigenetic alterations are memorized in cells as hypoxic memory and lead to long-term changes in gene expression. Pharmacological HIF activation has a renoprotective effect in various animal models such as AKI animal models and a model of diabetic kidney disease. Also, experimental studies confirmed that treatment with a pharmacological HIF activator reduces oxidative stress and protects both the heart and the kidney.

HIF activation also affects cell metabolism. In renal tubular cells, pharmacological activation of HIF resulted in glycogen accumulation, which is then utilized as an energy source and protects the tubular cells against hypoxia and ischemia. Furthermore, HIF activation improves metabolic disturbances in the model of diabetic kidney disease. Treatment with HIF-PH inhibitor in BTBR ob/ob–type 2 diabetic mice resulted in lower body weight, reduced blood glucose levels with improved insulin sensitivity, lower total cholesterol levels, higher adiponectin levels, and less adipose tissue, as well as a tendency for lower macrophage infiltration. The subject animals also exhibited reduced albuminuria and amelioration of glomerular epithelial and endothelial damage. Nevertheless, these organ-protective effects of HIF activation were so far only observed in animal models.

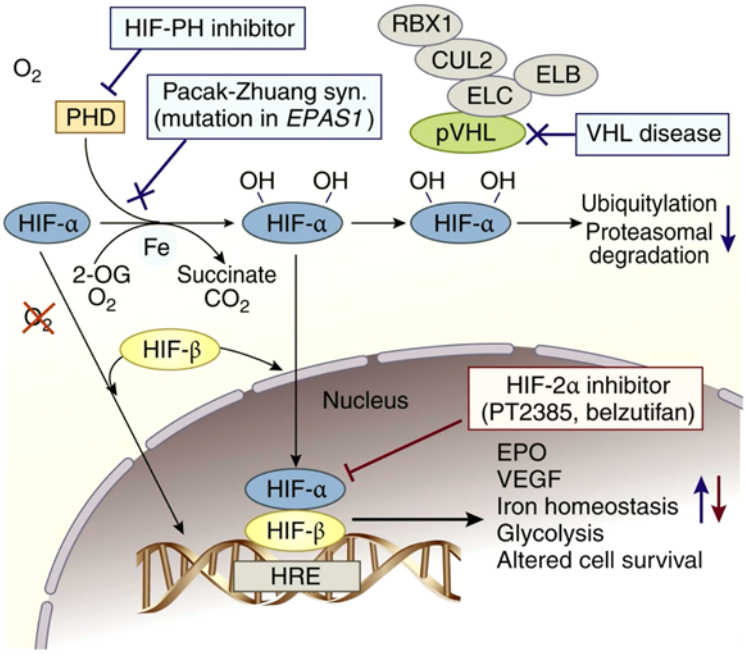

Figure 3. The therapeutic effects of the HIF2α inhibitor

HIF inhibitors in the treatment of CKD-related anemia

HIF-PH Inhibitors have recently been approved as a new treatment for anemia in CKD patients. Clinical trials showed that these agents improve anemia in non-dialysis-dependent CKD, HD, and PD patients. However, there are certain theoretical concerns about HIF-PH inhibition, one of which is thrombosis. Thrombosis induced by HIF-PH inhibitors can be explained by a decrease in serum iron because HIF-PH inhibitors improve iron utilization. Iron deficiency upregulates transferrin to induce hypercoagulability and is associated with platelet and plasma P-selectin expression with pro-thrombotic tendency. Another theoretical concern with HIF activation is the incitement of HIF2α mutation which is associated with autosomal dominant erythrocytosis and pulmonary hypertension. Namely, inhibition of HIF2α reversed polycythemia and pulmonary hypertension in mouse models. HIF does not exhibit oncogenic properties and its activation should not induce the development of new cancer. However, since HIF activation can induce VEGF expression and angiogenesis, it may result in the aggravation of occult malignancy.

The results of the pooled analysis of three phase 3 clinical trials of daprodustat in Japan show no increase in the rate of thromboembolic events, cardiovascular events, retinal events, and cancer-related mortality. However, due to the insufficient duration of follow-up, and the fact that the analysis did not include patients with serious retinal diseases and cancer patients, caution should be employed with long-term treatment with HIF PH inhibitors.

Key points

1. Hypoxia is the final common pathway to end-stage kidney disease throughout the course of CKD.
2. Hypoxia plays an important role in AKI to CKD transition. Epigenetic changes induced by hypoxia, such as changes in histone modifications, can explain the mechanism of AKI to CKD transition.
3. Research on experimental models demonstrated the renoprotective effects of pharmacological HIF activation.
4. Clinical trials showed that HIF inhibitors improved anemia in non-dialysis-dependent CKD, HD, and PD patients. However, there are certain theoretical concerns about HIF PH inhibition, one of which is thrombosis.
5. Since HIF activation can induce VEGF expression and angiogenesis, it may result in the aggravation of occult malignancies requiring a cautious approach in high-risk patients.

Further reading

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