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The role of HIF stabilizers in kidney fibrosis

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HIF is a master regulator of responses against hypoxia, and its stability and activity is regulated by prolyl hdroxylase (PHD) in an oxygen tension-dependent manner. Representative HIF target genes include erythropoietin and VEGF, and recently a number of companies are running clinical trials of PHD inhibitors (HIF stabilizers) as a new therapeutic modality against anemia in CKD. Chronic hypoxia in the tubulointerstitial region and subsequent development of fibrosis is a final common pathway to end stage kidney disease. Fibrosis aggravates local hypoxia by decreasing the number of peritubular capillaries and reducing oxygen diffusion efficiency. Theoretically HIF stabilization can protect the kidney by increasing resistance of resident kidney cells and improving oxygen supply to kidney cells. Some studies utilizing genetically engineered mice showed that HIF stabilization may paradoxically aggravate kidney fibrosis, but these results were observed by supra-physiological activation of HIF by gene knockout. HIF activation can also induce long-term effects on the kidney by inducing a variety of epigenetic changes including changes of histone modifications. Oxygen biology of HIF and PHD is so important, and discovery of these molecules was applauded with the Albert Lasker award in 2016. This is a hot and relevant topic, and we will soon utilze HIF stabilizers at the bed side to treat amenia in CKD and hopefully fibrosis of the kdiney.