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Pathophysiological Aspects of Hypoxia-Inducible Factors in Renal Disorders

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Keywords: Acute kidney injury; chronic kidney diseases; End-stage renal disease; Hypoxia-inducible factors; Prolyl hydroxylase; Renal ischemia/reperfusion injury

Abbreviations: AKI: acute kidney injury; ccRCC: clear cell renal cell carcinoma; CKDs: chronic kidney diseases; CVD: cardiovascular diseases; EPO: erythropoietin; ESRD: end-stage renal disease; FIH: factor inhibiting HIF;GEO: Gene Expression Omnibus;GLP-1: glucagon-like peptide-1;GLUTs: glucose transporters; HIFs: Hypoxia-inducible factors; HO-1: heme oxygenase-1; NF-kB: nuclear factor kappa-B; PHDs: Prolyl hydroxylase domain enzymes; RCC: Renal cell carcinoma; TGF-β1: transforming growth factor-beta1; VEGF: vascular endothelial growth factor; VHL: von Hippel-Lindau

Introduction

The kidneys are sensitive to changes in oxygen homeostasis. It has been established that hypoxia contributes to both acute and chronic kidney diseases (CKDs). Vascular damage, tubular injury, and fibrosis are the main pathologies associated with hypoxia [1].

Hypoxia-Inducible Factors (HIFs) are oxygen-sensing transcription factors that mediate metabolic reprogramming to enable cellular adaptation under hypoxic conditions [2]. HIFs are heterodimers composed of HIF-α and HIF-β. HIF-α is classified into HIF-1α, which participates in the acute phase, and HIF-2α and HIF-3α, which are more involved in chronic hypoxia [3]. It has been reported that HIFs can regulate the expression of genes involved in iron homeostasis, glycolysis, cell survival, erythropoiesis, apoptosis, and angiogenesis [4].

Under normoxic conditions, HIF is hydroxylated by Prolyl Hydroxylase Domain Enzymes (PHDs), which promotes ubiquitination by the von Hippel-Lindau (VHL) ubiquitin ligase and subsequent proteasomal degradation [5]. HIF-1 is regulated by another HIF-1 hydroxylase factor known as factor inhibiting HIF (FIH). In addition, HIF is regulated at the transcriptional and translational levels by many cytokines, heat shock proteins, protein kinase C, growth factor signaling pathways, and certain exosomes [6].

In hypoxia, PHD activity is inhibited, allowing HIF-α to accumulate in the cytoplasm, translocate to the nucleus, and, together with HIF-β, bind to hypoxia-response elements in the promoters of target genes to regulate gene transcription. The physiological functions of HIFs depend on the activation of their target genes. HIFs can stimulate the transcription of multiple genes, including erythropoietin (EPO), glucose transporters (GLUTs), vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1), and heme oxygenase-1 (HO-1). These genes can protect against renal injury during hypoxia by facilitating angiogenesis, regulating the inflammatory response, promoting glycolysis, and maintaining mitochondrial function [7].

Hypoxia has been documented as a critical factor in the pathogenesis of acute kidney injury (AKI), especially renal ischemia/reperfusion injury (RIRI). Increased HIF-1 has been identified as a hallmark change in RIR. Bioinformatic analysis of the Gene Expression Omnibus (GEO) dataset, together with integration of gene expression profiles from a rat model of renal IRI, identified HIF-1α signaling [8]. HIF-1α is believed to play a protective role in RIRI by increasing the expression of HIF-1α-target genes involved in the transition from glucose metabolism to glycolysis, scavenging reactive oxygen species (ROS), and regulating cell survival [9]. Recently, Kang & Cheng demonstrated

that targeting HIF-1α is a promising therapeutic strategy for AKI, particularly through HIF prolyl hydroxylase inhibitors, which offer novel avenues for both prevention and treatment [10].

Recent evidence indicates that hypoxia plays a significant role in the pathogenesis of CKD and its complications, including anemia, cardiovascular events, and sarcopenia [11]. In renal chronic hypoxia, in addition to glycolysis being the primary energy source, hypoxia also alters gene expression patterns [12]. Diabetic nephropathy (DN) is one of the most common forms of CKD and the leading cause of end-stage renal disease (ESRD). Studies have demonstrated that hypoxia participates in the early stages of DN and in its progression in experimental DN rat models, and that HIF-1α expression in diabetic kidneys is significantly higher than in control rat kidneys and in normal human kidneys [13].

CKD-related complications, including anemia, cardiovascular diseases (CVD), and sarcopenia, are strongly associated with hypoxia [14]. Insufficient EPO production is a major cause of anemia in patients with CKD. Hypoxia is the primary stimulator of EPO production, and targeting HIF is effective and well-tolerated for correcting anemia in CKD [15].

CVD is the leading cause of death in patients with CKD, and hypoxia is also a contributing factor. Under hypoxic conditions, HIF signaling influences the progression, metabolic response, atherosclerosis, and ischemia of heart disease in multiple ways. In addition, HIF-1α plays a major protective role in heart disease [16].

Sarcopenia is a complication in patients with CKD. Skeletal muscle hypoxia is thought to be responsible for muscle weakness and atrophy, and HIF-1α has been found to contribute to sarcopenia through the glucagon-like peptide-1 (GLP-1) and nuclear factor kappa-B (NF-kB) catabolic pathways [17].

Renal transplantation is the only available therapy for end-stage renal disease. Reperfusion after renal transplantation may trigger inflammation and renal injury. Pre-activation of HIF before renal transplantation has been reported to improve both short-term and long-term prognosis [18].

Renal cell carcinoma (RCC) is the third most common urologic cancer, after prostate and bladder cancers. Most clear cell renal cell carcinoma (ccRCC) cases are associated with loss of von Hippel-Lindau tumor suppressor function and dysregulation of the hypoxia pathway. Inactivation of VHL leads to accumulation of the HIF-1α and HIF-2α transcription factors. Genomic analyses of renal tumors have identified deletions in a region of chromosome 14 that harbors the HIF-1α gene as a common feature of ccRCC [19]. It has been reported that HIF-1α is an inhibitor and HIF-2α a promoter of aggressive tumor behaviors [20].

In conclusion, the role of hypoxia and HIF in kidney diseases has become a focus of attention for nephrologists. Although hypoxia and HIF activation are documented in several scenarios of renal diseases, further studies are necessary to clarify whether intervening with the HIF pathway is beneficial across different pathological contexts..

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