NOVEL THERAPEUTIC APPROACH TARGETING THE HIF-HRE SYSTEM IN THE KIDNEY

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Abstract: Recent studies emphasize the role of chronic hypoxia in the tubulo-interstitium as a final common pathway to end-stage renal disease. Therefore, therapeutic approaches which target the chronic hypoxia should prove effective against a broad range of renal diseases.

Many of hypoxia-triggered protective mechanisms are hypoxia inducible factor (HIF)-dependent. Although HIF-1α and HIF-2α share both structural and functional similarity, they have different localization and can contribute in a non-redundant manner. While gene transfer of constitutively active HIF has been shown effective, pharmacological approaches to activate HIF are more desirable. Oxygen-dependent activation of prolyl hydroxylases (PHD) regulates the amount of HIF by degradation of this transcription factor. Therefore, PHD inhibitors have been the focus of recent studies on novel strategies to stabilize HIF. Cobalt is one of the inhibitors of PHD, and stimulation of HIF with cobalt is effective in a variety of kidney disease models. Furthermore, crystal structures of the catalytic domain of human prolyl hydroxylase 2 have been clarified recently. The structure aids in the design of PHD selective inhibitors for the treatment of hypoxic tissue injury.

Current advance has elucidated the detailed mechanism of hypoxia-induced transcription, giving hope for the development of novel therapeutic approaches against hypoxia.

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1. INTRODUCTION

Recent studies emphasize the role of chronic hypoxia in the tubulointerstitium as a final common pathway to end-stage renal failure. Hypoxia in the kidney has been demonstrated in a variety of disease models utilizing pimonidazole staining, a Clark-type electrode, blood oxygen level dependent (BOLD)-MRI, and transgenic animals expressing a hypoxia-sensing reporter vector.

Chronic hypoxia of the kidney occurs via several mechanisms acting in concert. When advanced, tubulointerstitial damage is associated with the loss of peritubular capillaries. Associated interstitial fibrosis impairs oxygen diffusion and supply to tubular and interstitial cells. In addition, a number of mechanisms that induce tubulointerstitial hypoxia at an early stage have been identified. Glomerular injury and vasoconstriction of efferent arterioles due to imbalances in vasoactive substances decrease post-glomerular peritubular capillary blood flow. Oxidative stress also hampers the efficient utilization of oxygen in tubular cells, leading to reduced renal oxygen tension. Relative hypoxia in the kidney also results from increased metabolic demand in tubular cells. Further, renal anemia hinders oxygen delivery. These factors can affect the kidney before the appearance of significant pathological changes in the vasculature and predispose the kidney to tubulointerstitial injury.

Therefore, therapeutic approaches which target the chronic hypoxia should prove effective against a broad range of renal diseases. At the center of the cellular response to hypoxia is hypoxia-inducible factor, HIF, and activation of this “master gene” switch results in a broad and coordinated downstream reaction to protect organs against hypoxia.

2. HIF IN THE KIDNEY

HIF is composed of two subunits, an oxygen-sensitive HIF-α subunit and a constitutively expressed HIF-β subunit (also known as ARNT, the aryl hydrocarbon receptor nuclear translocator). Both HIF-1α and HIF-1β are members of the basic helix-loop-helix PER/ARNT/SIM (HLH-PAS) family of transcription factors. HIF binds to the HRE in the cis-regulatory regions of its target genes, and transcriptionally activates various genes encoding proteins that mediate adaptive responses to reduced oxygen availability. Under normoxic conditions, two conserved proline residues within the central oxygen-dependent degradation domains of the HIF proteins are hydroxylated by the protein products “prolyl hydroxylase domain containing” (PHDs). This promotes binding of the von Hippel Lindau tumor suppressor protein (pVHL), part of a ubiquitin ligase complex, resulting in polyubiquitylation and rapid degradation. Similarly, a conserved asparagine residue in the carboxyl-terminal transactivation domain (CAD) of the HIF proteins is hydroxylated in normoxia by factor inhibiting HIF (FIH), preventing recruitment of the p300/CREB transcriptional co-activators and thus leading to transcriptional repression. Under hypoxia, oxygen is lacking as an essential substrate for the hydroxylation reaction, and the unmodified HIF proteins avoid degradation but rather heterodimerize with HIF-β and up-regulate the transcription of target genes.

HIF-α subunits have different isoforms, and a biological role of each isoform remains to be elucidated. HIF-1α is expressed in most cell types, whereas HIF-2α shows a more restricted pattern of expression. In the adult kidney, HIF-2α is expressed in peritubular endothelial cells and fibroblasts as well as glomerular endothelial cells,