Role of Endothelial Prolyl-4-Hydroxylase Domain Protein/Hypoxia-Inducible Factor Axis in Acute Kidney Injury

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Keywords

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Abstract

Ischemia reperfusion injury (IRI) results from a cessation or restriction of blood supply to an organ followed by reestablishment of perfusion and reoxygenation. In the kidney, IRI due to transplantation, cardiac surgery with cardiopulmonary bypass, and other major vascular surgeries contributes to acute kidney injury (AKI), a clinical condition associated with significant morbidity and mortality in hospitalized patients. In the postischemic kidney, endothelial damage promotes inflammatory responses and leads to persistent hypoxia of the renal tubular epithelium. Like other cell types, endothelial cells respond to low oxygen tension by multiple hypoxic signaling mechanisms. Key mediators of adaptation to hypoxia are hypoxia-inducible factors (HIF)-1 and -2, transcription factors whose activity is negatively regulated by prolyl-hydroxylase domain proteins 1 to 3 (PHD1 to PHD3). The PHD/HIF axis controls several processes determining injury outcome, including ATP generation, cell survival, proliferation, and angiogenesis. Here, we discuss recent advances in our understanding of the endothelial-derived PHD/HIF signaling and its effects on postischemic AKI.

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PHD/HIF Axis Regulates Vascular Responses

Endothelial cells play a major role in maintaining nutrient and oxygen supply to all tissues in the body by regulating vascular tone, inflammatory responses, hemostasis, and angiogenesis. Being the first cell layer in direct contact with the blood, endothelial cells cope with all alterations occurring within the blood. Among these alterations is the reduction in the oxygen tension, which can arise in the context of systemic or regional hypoxia. Cells respond to oxygen deprivation through multiple mecha-

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nisms, including the hypoxia-inducible factor (HIF), a “master” regulator of the hypoxic response.

HIF-1 and HIF-2 belong to the basic helix loop helix-PER/ARNT/SIM family of proteins and consist of an oxygen-sensitive α -subunit and a constitutively expressed β -subunit, also known as ARNT [1]. Both transcription factors promote cellular adaptation to hypoxia by regulating genes that control processes involved in oxygen homeostasis, including anaerobic glucose metabolism, angiogenesis, and erythrocyte production. Under normoxic conditions, HIF-1 α and HIF-2 α undergo prolyl-hydroxylation by 3 Fe (II)- and 2-oxoglutarate-dependent prolyl-4-hydroxylase domain (PHD) proteins, PHD1, 2, and 3 (also known as EGLN2, EGLN1, and EGLN3, respectively), which act as oxygen sensors [2]. HIF- α prolyl-hydroxylation promotes targeting for ubiquitination by the von Hippel-Lindau (pVHL)-E3-ubiquitin ligase complex and rapid proteasomal degradation. Hypoxia inhibits the catalytic activity of PHD enzymes, leading to HIF stabilization and transcriptional activation of ~200 hypoxia-regulated genes [1, 2].

In humans, VHL inactivation due to somatic mutations is frequent in nonhereditary kidney cancers while germline *VHL* mutations cause VHL disease, which is characterized by the development of angiogenic tumors such as hemangioblastomas, renal cell cancer, and pheochromocytomas [2]. Notably, germline homozygosity for a hypomorphic *VHL* allele results in polycythemia, thrombosis, and vascular abnormalities [3]. Genetic studies performed on rodents also support a critical role for the PHD/HIF/VHL axis in vascular development and cardiovascular diseases. Global ablation of either ARNT (HIF- β) or HIF-1 α subunit results in lethality due to abnormal embryonic vascularization [4]. HIF-2 α deficiency results in variable phenotypes between genetic backgrounds, but defective cardiovascular and pulmonary function is a common feature shared by all the mutants [4]. Studies exploring the contribution of endothelial cell-derived HIF signaling in these vascular abnormalities have yielded conflicting results probably due to spatiotemporal differences in *Cre*-recombinase activity between the different endothelial transgenic approaches employed. Specifically, partial neonatal lethality and vascular defects including cardiac hemorrhage and impaired hepatic vasculature were observed when ARNT was deleted in endothelial cells by the *Tie2-Cre* transgene [5]. Furthermore, inhibition of HIF-mediated transcription by a dominant-negative HIF mutant expressed in endothelial cells from the promoter/enhancer regions of the *kinase insert domain protein receptor (Kdr)* gene resulted

in early embryonic lethality and multiple cardiovascular defects [6]. On the other hand, we found no apparent pathology following the *Cdh5-Cre*-driven endothelial inactivation of both HIF-1 α and HIF-2 α [7].

Vascular pathology has been reported because of activation of HIF signaling by PHD2 deficiency. Specifically, germline inactivation of PHD2 caused embryonic demise between embryonic days 12.5 and 14.5 due to placental and heart defects [8], whereas inducible global PHD2 deletion resulted in excessive vascular growth and angiectasis in multiple organs [9]. Recently, we found that loss of endothelial PHD2 induced pulmonary arterial hypertension and vascular remodeling in a HIF-2 α -dependent and not HIF-1 α -dependent fashion. Furthermore, endothelial HIF-2 α was required for the development of hypoxia-induced pulmonary hypertension [10]. Therefore, current evidence suggests a critical role for hypoxia signaling in vascular homeostasis, and given the significant endothelial cell heterogeneity, the function of the PHD/HIF axis in different vascular beds requires further investigation.

HIF Activation Protects against Acute Kidney Injury

The kidney operates within a narrow range of tissue oxygenation; cortical PO₂ is 15–50 mm Hg, while medullary PO₂ is lower (5–25 mm Hg) based on measurements performed by Clark oxygen microelectrodes [11]. High oxygen utilization due to energy-demanding transport processes in conjunction with changes in local perfusion and arterial-to-venous oxygen shunting makes the kidney vulnerable to hypoxic injury, particularly the outer medulla [12]. Indeed, among several clinical conditions leading to AKI, kidney hypoxia has emerged as a key driver contributing to cell death and injury. In the context of systemic or regional hypoxia, activation of the HIF pathway is a central mechanism by which kidney cells respond and adapt to changes in renal oxygenation. Under acute hypoxia, HIF-1 α has been detected in tubular and glomerular epithelial cells, whereas HIF-2 α was found in glomerular cells, peritubular endothelial cells, and interstitial fibroblast-like cells [13]. In the ischemic kidney, HIF-2 α showed similar pattern of expression, and HIF-1 α was predominantly induced in tubular cells localized to the corticomedullary junction and renal papilla [13]. Because the endogenous response to ischemia appears submaximal, several groups have examined the cytoprotective potential of approaches boosting HIF activation prior to ischemic injury. Indeed, it has been consistently demonstrated that systemic HIF activation by PHD inhibition pri-

Table 1. Summary of in vivo studies examining the role of the PHD/HIF axis in acute kidney injury

AKI model	Experimental approach	AKI outcome	Ref
IRI (rats)	Cobalt chloride induced PHD inhibition before IRI	Kidney injury ↓	[14]
IRI (rats)	Carbon monoxide induced systemic hypoxia or FG-4487 induced PHD inhibition before IRI	Kidney injury ↓	[15]
IRI (mice)	DMOG/L-mimosine induced PHD inhibition before IRI → Genetic inactivation of HIF-1α: IRI in <i>Hif1a</i> ^{+/-} mice → Genetic inactivation of HIF-2α: IRI in <i>Hif2a</i> ^{+/-} mice →	Kidney injury ↓ Kidney injury ↑ Kidney injury ↑	[16]
IRI (mice)	GSK1002083A induced PHD inhibition before IRI → GSK1002083A induced PHD inhibition after IRI →	Kidney injury ↓ No effect	[17]
IRI (rats)	ICA induced PHD inhibition before IRI → ICA induced PHD inhibition after IRI →	Kidney injury ↓ No effect	[18]
IRI (mice)	Inducible genetic inactivation of <i>Vhl</i> 1 week before IRI: HIF-1α ↑, HIF-2α ↑	Kidney injury ↓	[19]
IRI (mice)	Xenon induced HIF-1α before IRI	Kidney injury ↓	[20]
IRI (mice)	Nanoparticle targeted delivery of <i>Phd2</i> siRNA in kidney before IRI	Kidney injury ↓	[21]
IRI (mice)	<i>Vhl</i> inactivation in thick ascending limb: HIF-1α ↑	Kidney injury ↓	[22]
IRI (rats)	TRC160334 induced PHD inhibition before IRI → TRC160334 induced PHD inhibition after IRI →	Kidney injury ↓ Kidney injury ↓	[29]
IRI (mice)	Genetic inactivation of HIF-2α: IRI in <i>Hif2akd</i> mice → Genetic restoration of EC- HIF-2α in <i>Hif2akd</i> mice →	Kidney injury ↑ Kidney injury ↓	[30]
IRI (mice)	EC- <i>Hif1a</i> ^{-/-} → EC- <i>Hif2a</i> ^{-/-} → EC- <i>Hif1aHif2a</i> ^{-/-} →	No effect Kidney injury ↑ Kidney injury ↑	[7]
IRI (mice)	EC- <i>Phd2</i> ^{-/-} → EC- <i>Phd2Hif1a</i> ^{-/-} → EC- <i>Phd2Hif2a</i> ^{-/-} →	Kidney injury ↓ No effect Kidney injury ↓	[32]
Cisplatin-induced AKI (rats)	Cobalt chloride induced PHD inhibition before AKI	Kidney injury ↓	[23]
Cisplatin-induced AKI (rats)	Carbon monoxide induced systemic hypoxia before AKI	Kidney injury ↓	[24]
Allogenic kidney transplant (rats)	FG-4497 induced PHD inhibition in donors: HIF-1α ↑, HIF-2α ↑	Improved graft function Early mortality ↓ Long-term survival ↑	[25]
Gentamicin-induced AKI (rats)	Cobalt induced PHD inhibition along with gentamicin-induced AKI	Kidney injury ↓	[26]
Sepsis-induced AKI (mice)	3,4-Dihydroxybenzoate induced PHD inhibition before sepsis	Kidney injury ↓	[28]
Rhabdomyolysis-induced AKI (mice)	Inducible genetic inactivation of <i>Vhl</i> in renal tubules before rhabdomyolysis-induced AKI	Kidney injury ↓	[27]

PHD, prolyl-hydroxylase domain; DMOG, dimethyloxallyl glycine; ICA, 2-(1-chloro-4-hydroxyisoquinoline-3-carboxamido) acetate; EC, endothelial cell.

or to injury attenuates ischemic kidney injury (Table 1) [14–18]. While the concerted transcriptional activation of genes involved in cellular energy metabolism, antioxidant responses, antiapoptotic pathways, and immunity appears

to have a central role in PHD/HIF-mediated renoprotection, significant complexity arises from cell type-, isoform-, and context-specific responses. Both HIF-α isoforms have been implicated in dictating AKI outcomes as heterozygos-

ity for either HIF-1 α or HIF-2 α exacerbated renal IRI [16]. Furthermore, systemic HIF activation by VHL loss or xenon-mediated enhanced translation ameliorated AKI [19, 20]. HIF activation limited to the kidney by nanoparticle-based targeted delivery of PHD2 siRNA was sufficient to protect against IRI [21]. Accordingly, VHL deletion restricted to the thick ascending limb conveyed substantial protection against ischemic kidney injury elucidating the importance of this nephron segment [22]. Besides renal IRI, HIF activation has been shown to induce robust renoprotection in other AKI models, including kidney transplantation, sepsis, and cisplatin-induced nephrotoxicity (Table 1) [23–28]. However, in contrast to the consistent protection observed when HIF is activated prior to insults, the effects of postischemic HIF-PHD inhibition remain controversial. One study showed that administration of the PHD inhibitor TRC160334 at 2 h, 6 h, and 10 h after kidney ischemia ameliorated postischemic AKI [29], but two other studies found no renoprotection when the PHD inhibitor was given 1 min prior to reperfusion [18] or 2 and 4 days after IRI [15]. Therefore, for potential clinical translation of PHD inhibition in AKI, careful investigation of the factors determining the therapeutic window is needed; timing, dosing, and potency of inhibition against specific PHD isoforms may have critical roles in dictating outcomes.

The Role of Endothelial Hypoxic Signaling in Acute Kidney Injury

Among the different cellular compartments explored as sources for HIF-induced cytoprotection, the endothelium has received particular attention because restoration of HIF-2 α expression specifically in endothelial cells was sufficient to reverse the susceptibility to IRI due to systemic HIF-2 α knockdown [30]. Remarkably, inactivation of endothelial HIF-2 α , but not endothelial HIF-1 α , impaired recovery after kidney IRI leading to increased tubulointerstitial injury, peritubular capillary rarefaction, and inflammation [7, 31]. Treatment with inhibitory monoclonal antibodies against Vascular Cell Adhesion Molecule-1 (VCAM1) and its ligand -Very Late -Antigen-4 (VLA-4) reversed renal injury associated with endothelial HIF-2 α deletion suggesting a critical role for the endothelial HIF-VCAM1 axis in regulating postischemic kidney injury [7]. To investigate the role of the endothelial PHD2/HIF axis in postischemic kidney injury, we inactivated PHD2 individually or concurrently with either HIF-1 α or HIF-2 α by Cre-loxP-mediated recombination [32]. Mice lacking endothelial PHD2 demonstrated im-

proved early and late outcomes following ischemic kidney injury with preserved kidney function and reduced fibrotic response. Using mice concomitantly deficient for either PHD2 and HIF-1 α (*EC-Phd2Hif1*) or PHD2 and HIF-2 α (*EC-Phd2Hif2*), we found that PHD2 activity in endothelial cells regulated postischemic renal IRI in a manner dependent on HIF-1 α , but not HIF-2 α . Furthermore, our studies showed that the endothelial PHD2/HIF-1 axis attenuated postischemic leukocyte recruitment by regulating endothelial adhesion molecules and chemotactic factors. Surprisingly, there was no evidence of HIF stabilization in the kidneys of mice lacking endothelial PHD2 at baseline conditions and following IRI, an observation which indicates decreased responsiveness of the kidney endothelium to PHD2 deficiency. Interestingly, differential expression analysis of the three *Phd* isoforms in mouse kidney tissues subjected to single-cell RNA sequencing demonstrated low expression for *Phd2* and *Phd3* in kidney endothelial cells, whereas *Phd1* showed the highest expression. Given the lack of detectable HIF-1 α activation in the kidneys of mutant mice deficient for endothelial PHD2, we hypothesized that extrarenal PHD2-responsive vascular beds may generate HIF-1 α -dependent anti-inflammatory signals through the release of a humoral factor. To test this hypothesis, we examined whether serum isolated from *EC-Phd2Hif2*, *EC-Phd2Hif1* mutants, and their controls modulates the proinflammatory responses of endothelial cells exposed to hypoxia/reoxygenation (H/R) and TNF- α . Notably, serum from mice lacking both endothelial PHD2 and HIF-2 α but not HIF-1 α was sufficient to suppress the induction of Interferon Regulatory Factor 1 (*IRF1*) and VCAM1 mRNA levels by H/R and TNF- α treatment [32]. Interestingly, humoral factors have also been implicated in the hyperactive angiogenesis induced by PHD2 inhibition even in organs with inefficient PHD2 disruption [9].

Clinical Studies

Activation of hypoxia signaling has been implicated in mediating remote ischemic preconditioning (RIPC), in which ischemia to one organ protects distant organs. While prior randomized trials have shown renal protection [33, 34] when RIPC was applied, two recent multicenter, randomized trials, the Remote Ischemic Preconditioning for Heart Surgery (RIPHeart) Study [35] and the Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Graft Surgery (ERICCA) trial [36], found no reno-

Fig. 1. A schematic depicting the role of endothelial hypoxic signaling in postischemic kidney injury. Under endothelial PHD2-competent conditions, endothelial HIF-2 regulates IRI-induced kidney injury and inflammation by a mechanism that involves suppression of VCAM1. On the other hand, in the context of endothelial PHD2 inactivation, endothelial HIF-1 signaling probably derived from an extrarenal vascular bed generates renoprotective and anti-inflammatory effects through the release of humoral factors. PHD, prolyl-hydroxylase domain; HIF, hypoxia-inducible factor; IRI, ischemia reperfusion injury; WT, wild type; EC, endothelial cell; PHI, PHD inhibitor; 2OG, 2-oxoglutarate.

protection by RIPc in patients who underwent cardiac surgery. Both negative trials used propofol as the primary anesthetic agent, which has been shown to inhibit HIF activity, an action that could blunt the effects of preconditioning [37]. In fact, a meta-analysis of randomized trials showed that propofol-based anesthesia, as compared with halogenated agents, doubled mortality among patients who underwent cardiac surgery [38]. Furthermore, it is likely that common comorbidities in patients included in these trials such as diabetes and old age may interfere with the response to preconditioning.

PHD inhibitors activate HIF, and late-stage clinical trials have established their efficacy in stimulating erythropoiesis in patients with renal anemia. Beyond erythropoiesis, the use of PHD inhibitors against human AKI

remains unexplored. At the time of writing this review, a phase II clinical trial (NCT01920594) using the PHD inhibitor GSK1278863 found no reduction of ischemic complications in patients undergoing thoracic aortic aneurysm repair. Given the promise of PHD inhibitors as cytoprotective agents in AKI, intense clinical investigation is anticipated in this field. In this regard, the challenges in translating RIPc to humans should inform the design of AKI trials using PHD inhibitors, with particular emphasis on factors such as the patient populations included, comorbidities, and concomitant medications.

Conclusion and Future Directions

Recent studies elucidated a critical role for endothelial-derived PHD/HIF signaling in regulating postischemic kidney injury and inflammation with potential implications that extend to other ischemic injuries. Under PHD-competent conditions, endothelial HIF-2 α appears to be the major regulator of postischemic AKI outcomes, whereas in the context of endothelial PHD2 deficiency, HIF-1 α drives the renoprotective and anti-inflammatory effects against postischemic AKI (Fig. 1). Nevertheless, the role of different endothelial PHD isoforms in the pathophysiology of AKI is not well defined and warrants further investigation. With the first generation of PHD inhibitors being in late-phase clinical trials for patients with renal anemia, O₂ sensing-based cytoprotective therapies exhibit a promising potential against ischemic AKI. Because activation of HIF signaling has several adverse effects including pulmonary hypertension, tumor progression, and angiogenesis, understanding of its context-specific pathophysiological function is needed for the successful translation to therapies.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Both co-authors wrote, edited and approved the manuscript.

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