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Hypoxia as a key player in the AKI-to-CKD transition

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Tanaka S, Tanaka T, Nangaku M. Hypoxia as a key player in the AKI-to-CKD transition. Am J Physiol Renal Physiol 307: F1187–F1195, 2014. First published October 1, 2014; doi:10.1152/ajprenal.00425.2014.—Recent clinical and animal studies have shown that acute kidney injury (AKI), even if followed by complete recovery of renal function, can eventually result in chronic kidney disease (CKD). Renal hypoxia is emerging as a key player in the pathophysiology of the AKI-to-CKD transition. Capillary rarefaction after AKI episodes induces renal hypoxia, which can in turn profoundly affect tubular epithelial cells, (myo)fibroblasts, and inflammatory cells, culminating in tubulointerstitial fibrosis, i.e., progression to CKD. Damaged tubular epithelial cells that fail to redifferentiate might supply a decreased amount of vascular endothelial growth factor and contribute to capillary rarefaction, thus aggravating hypoxia and forming a vicious cycle. Mounting evidence also shows that epigenetic changes are closely related to renal hypoxia in the pathophysiology of CKD progression. Animal experiments suggest that targeting hypoxia is a promising strategy to block the transition from AKI to CKD. However, the precise mechanisms by which hypoxia induces the AKI-to-CKD transition and by which hypoxia-inducible factor activation can exert a protective effect in this context should be clarified in further studies.

hypoxia; hypoxia-inducible factor; acute kidney injury; chronic kidney disease; AKI-to-CKD transition

It was generally held that most patients who survive an episode of acute kidney injury (AKI) regain complete renal function with excellent long-term prognoses. However, over the past 5 yr, data from epidemiological studies (2, 51, 79, 130, 131) and a meta-analysis (25) have shown a strong correlation between AKI episodes and subsequent development of chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Follow-up data from children undergoing AKI also suggest a correlation between AKI episodes and CKD development (5, 35, 81). A correlation between AKI and subsequent CKD was observed even among the population that regained normal renal function after experiencing AKI episodes (19, 58). However, caution should be exercised because normalization of serum creatinine does not always truly indicate complete recovery from AKI; the possibility remains that intact nephrons compensate and muscle mass is reduced during acute illness. Importantly, the severity of AKI (21, 50) and the number of AKI episodes (127) predict subsequent development of CKD. These compelling epidemiological data, together with the findings of many animal studies in which the pathways underlying the development of CKD from AKI have been clarified (22), suggest a causal relationship between AKI episodes and subsequent development of CKD (13, 45). However, proving this causality is challenging because of several issues including residual confounding, e.g., an overlap of risk factors (103).

The mechanism by which AKI leads to CKD is still unclear, especially in humans. However, several mechanisms have been proposed, such as nephron loss that is followed by glomerular hypertrophy, inflammation, endothelial injury with vascular rarefaction and hypoxia, as well as epigenetic changes and cell cycle arrest in epithelial cells (4, 7, 8, 12, 20, 22, 44a, 137). These mechanisms are intricately linked and appear to work both upstream and downstream during pathogenesis. In the present article, we review the biological findings that support a causal relationship between renal hypoxia and the AKI-to-CKD transition.

Renal Oxygenation and Chronic Hypoxia Hypothesis

Some regions of the kidney are physiologically hypoxic despite the large amount of blood the organ receives, which is as much as 20% of cardiac output in humans. The partial pressure of oxygen in various animals was reported as 20–60 mmHg in the cortex and 10–30 mmHg in the medulla (16, 17, 56, 77, 93, 113, 134). A recent study using rats showed that the partial pressure of oxygen in the cortex, corticomedullary junction, and outer medulla was 11.9, 4.1, and 7.9 mmHg, respectively (135). Oxygen tensions within normal kidney cells are expected to be much lower, because these measurements should be an average of oxygen partial pressures in the blood, interstitial space, and cells (37). The hypoxic status of the kidney is primarily the result of an arterial-venous diffusional oxygen shunt (75, 94, 113, 134) that permits the kidney to extract no more than 10% of the oxygen delivered by the renal artery. A study using hypoxia-sensing transgenic mice elegantly demonstrated that the kidney tends to show lower oxygen levels compared with other parts of the body, both under normoxic and hypoxic conditions (109). Moreover, the supply of oxygen to the kidney, especially the cortex, can change dramatically depending on the status of renal perfusion. Such inefficiency in oxygen utilization and variability in oxygen levels predisposes the kidney to hypoxic damage.

On the basis of these characteristics of the kidney, Fine et al. (32) proposed that chronic hypoxia in the tubulointerstitium is the final common pathway in the development of ESKD. This theory has been validated by numerous studies (28, 29, 42, 90, 97). Chronic hypoxia is currently broadly recognized as being intricately linked to other factors such as oxidative stress and inflammation and as leading to the development of ESKD (98, 104). Thus determining the effect of renal hypoxia on the progression of CKD has been difficult. Recently, Palm and colleagues (34) administered dinitrophenol, a mitochondrial
uncoupler that increases oxygen consumption, to rats for 30 days. Dinitrophenol treatment successfully decreased kidney oxygen tension in both the cortex and medulla without affecting markers of oxidative stress. It also induced vimentin expression and inflammatory cell infiltration in the kidney as well as increased urinary protein excretion. Although there remains a possibility of nonspecific toxic effects of dinitrophenol, these results suggest the importance of hypoxia in the progression of CKD.

**Hypoxia-Inducible Factor in the Kidney**

Hypoxia-inducible factor (HIF) is a major contributor in cellular adaptation to hypoxia. It upregulates the transcription of >100 target genes controlling hematopoiesis (e.g., erythropoietin), angiogenesis [e.g., vascular endothelial growth factor (VEGF)], and anaerobic metabolism (e.g., glucose transporters and glycolytic enzymes) (88). HIF is a heterodimeric transcription factor consisting of alpha (HIF-α) and beta (HIF-β), also referred to as aryl hydrocarbon receptor nuclear translocator (ARNT). HIF-α is a major regulator of erythropoietin expression and positive staining for pimonidazole, a marker of deep tissue hypoxia, whereas HIF-2α is a major regulator of erythropoietin expression and positive staining for pimonidazole, a marker of deep tissue hypoxia.

HIF-α has two major active isoforms, HIF-1α and HIF-2α. In the hypoxic kidney, HIF-1α is expressed predominantly in tubular epithelial cells and works as a master regulator of hypoxic stress, whereas HIF-2α is expressed predominantly in interstitial cells (107, 136). Accumulating evidence shows that HIF activation is highly dependent on oxygen levels.

In the hypoxic kidney, HIF dimers bind to hypoxia response elements in the regulatory domain-containing proteins (PHDs). Hydroxylated HIF-α is recognized by von Hippel-Lindau tumor suppressor protein (VHL), resulting in immediate proteasomal degradation via polyubiquitination (52, 54). In contrast, under hypoxic conditions, PHDs cannot hydroxylate HIF-α, thus leaving HIF-α intact. HIF-α is then able to translocate to the nucleus where it binds and forms a heterodimer with HIF-β, which is constitutively expressed irrespective of oxygen tension. HIF heterodimers bind to hypoxia response elements in the regulatory regions of target genes, resulting in transactivation (91). In brief, the main regulatory mechanism of HIF-α expression involves the hydroxylation of conserved residues, a process that is highly dependent on oxygen levels.

HIF-1α has two major active isoforms, HIF-1α and HIF-2α. In the hypoxic kidney, HIF-1α is expressed predominantly in tubular epithelial cells and works as a master regulator of hypoxic stress, whereas HIF-2α is expressed mainly in endothelial and interstitial cells (107, 136). Accumulating evidence shows that HIF-2α is a major regulator of erythropoietin expression (41, 119, 121). HIF is not expressed in the normal renal medulla (107), where the partial pressure of oxygen is physiologically low. This interesting finding suggests that different cell types likely have their own unique threshold for accumulation, owing to their distinct metabolic characteristics and PHD isoform (PHD1–3) expression patterns (110a).

**Does Hypoxia Occur in AKI Animal Models or Human AKI?**

Traditionally, AKI models have been divided into two groups: ischemic and nonischemic models. However, tissue hypoxia and HIF expression are not limited to the acute phase of ischemic AKI; they are much more frequently observed in multiple contexts. In addition to ischemia with or without reperfusion (26, 43, 44, 107), radiocontrast agents (106), cisplatin (123), and rhabdomyolysis (105) induce HIF activation and positive staining for pimonidazole, a marker of deep tissue hypoxia (oxygen tension <10 mmHg) (40). HIF staining disappears 24 h after AKI induction (26, 106). Interestingly, HIF reappeared between days 3 and 7 after AKI induction in a warm ischemia–reperfusion (I/R) model (26). These time-dependent changes in HIF activation may suggest that the oxygen-consuming processes occurring during cell regeneration lead to the recurrence of tissue hypoxia (92). Similar delays in HIF activation are also observed in transplanted human kidneys (108). Marked HIF upregulation is detected in renal allograft biopsies just after engraftment as well as at 10–14 days but not at 3 mo after engraftment. These data may also indicate that tissue repair after renal transplantation causes hypoxia. Therefore, renal hypoxia can occur not only during the acute phase of AKI but also during the recovery phase.

In contrast, evidence of hypoxia occurring in human AKI is scarce, reflecting limitations in the methodology available to evaluate renal hypoxia in humans. Blood oxygen level dependent-magnetic resonance imaging (BOLD-MRI) can be used to visualize tissue oxygen status by determining deoxyhemoglobin levels, and it has been increasingly utilized as a noninvasive method to detect tissue hypoxia in vivo. With the use of BOLD-MRI, a correlation between renal oxygenation levels and estimated glomerular filtration rate (eGFR) has been observed in CKD patients (49, 138) but not in AKI patients (49). These findings might be attributable to the inaccurate assumption of renal function in AKI patients, based on eGFR, as well as the varying etiology of AKI. In contrast, Redfors et al. (102) showed that AKI patients have impaired renal oxygenation, which was estimated based on increased renal oxygen extraction (i.e., oxygen consumption over oxygen delivery), after undergoing cardiac surgery. Although GFR and sodium reabsorption were lower in AKI patients compared with normal controls, their renal oxygen consumptions were similar, suggesting that AKI patients have decreased oxygen utilization efficiency. Unchanged oxygen consumption and decreased renal blood flow (oxygen delivery) caused by increased renal vascular resistance result in increased renal oxygen extraction in AKI patients.

**Capillary Rarefaction Leads to Renal Hypoxia in AKI**

What then is the mechanism underlying renal hypoxia development in AKI? Substantial evidence suggests that capillary rarefaction can cause renal hypoxia (6, 33, 72, 90, 125). Basile et al. (8) showed that increased urinary protein excretion and tubulointerstitial fibrosis occur 40 wk after bilateral renal I/R in rats and are accompanied by reductions in microvascular density, which becomes evident at as early as 4 wk. Hypoxia has also been detected in the outer medullary region by pimonidazole staining 5 wk after I/R injury in rats (9). Administration of L-arginine increased renal blood flow in these rats, albeit not affecting vessel density, resulting in decreased pimonidazole staining and protection from chronic renal damage, including tubulointerstitial fibrosis. These results indicate that capillary rarefaction due to I/R injury likely leads to renal hypoxia, which may in turn contribute to the progression to CKD. Similar decreases in microvascular density have been observed in mouse kidneys in response to I/R injury (44a), folic acid nephropathy (140), and nitric oxide synthase inhibition (96). Recently, Humphreys and colleagues (68) described the precise changes in capillary perfusion that occur after AKI in a mouse I/R injury model. They used fluorescence microangiography (1), which enabled them to obtain higher resolution images than those obtained previously using Microfil (8, 73). They showed that the reduction in the total perfused areas in
the cortex and medulla after I/R-induced AKI was the result of reductions in capillary number as well as individual capillary caliber and area. In addition, a comparison between fluorescence microangiography and CD31 staining suggested that some capillaries express the endothelial marker CD31 following AKI but lack perfusion and are nonfunctional.

Although the regenerative ability of vascular endothelial cells seems to be more limited than that of tubular epithelial cells (6, 7, 11, 22, 47, 69), the precise mechanisms by which capillary loss occurs after AKI remain unknown. Loss of angiogenic factors, particularly VEGF, is thought to play an important role in the development of capillary rarefaction. In normal kidneys, VEGF is expressed mainly in podocytes and tubular epithelial cells (18, 39, 116, 117), whereas VEGF receptors (VEGFRs) are detected in the endothelium of glomeruli and peritubular capillaries (39, 117, 118). Normal VEGF signaling is essential for the maintenance of vascular architecture in the kidney (84, 111, 124). For example, bevacizumab, which is a monoclonal antibody against VEGF and is used for the treatment of malignancy, has been reported to cause glomerular thrombotic microangiopathy (31). Kamba et al. (60) found significant reductions in peritubular and glomerular capillaries (30 and 10%, respectively) in the kidneys of mice treated with a small-molecule VEGFR tyrosine kinase inhibitor. Reductions in VEGF expression were found to occur during an early phase of renal I/R injury (10), and administration of VEGF-121 can ameliorate capillary rarefaction and subsequent tubulointerstitial fibrosis after I/R injury (11, 74). Therefore, a decreased VEGF level is associated with capillary rarefaction following I/R injury. In contrast, a recent study by Duffield and colleagues (23, 64, 76, 112) proposed that pericyte detachment from adjacent capillary endothelial cells is the mechanism that underlies capillary rarefaction. By blocking VEGFR2 signaling in endothelial cells, they showed that circulating soluble receptor ectodomains ameliorate pericyte detachment from endothelial cells, capillary rarefaction, and tubulointerstitial fibrosis in mouse unilateral ureteral obstruction and I/R injury models (76). Further studies are warranted to determine the precise mechanism by which the loss of capillary density occurs after AKI.

Sustained Renal Hypoxia in the Pathophysiology of the AKI-to-CKD Transition

Failed redifferentiation of regenerating tubular epithelial cells after AKI has been suggested to result in sustained production of profibrotic peptides and play an important role in subsequent CKD progression (15, 36, 70, 129) (Fig. 1). However, the mechanisms underlying failed redifferentiation remain unclear. A recent study by Polichnowski et al. (100) suggests that hypoxia is a key player in failed redifferentiation. They performed renal I/R in rats with varying degrees of renal mass reduction and observed strong correlations among vimentin positivity, a marker of tubular epithelial cell dedifferentiation, reduced tubular VEGF expression, peritubular capillary rarefaction, and tubulointerstitial fibrosis 4 wk after injury. Therefore, local hypoxia induced by the loss of capillaries potentially prevents regenerating tubules from redifferentiation. This supports the hypothesis that tubular damage and hypoxia form a vicious cycle, leading to subsequent fibrosis. In addition, many in vitro studies have shown that hypoxia has a deleterious effect on tubular epithelial cells. Hypoxic damage to cultured tubular epithelial cells can induce cellular apoptosis (63, 122) or convert cells to a myofibroblast phenotype (82), although recent studies have undermined the contribution of epithelial-mesenchymal transition to tubulointerstitial fibrosis in vivo (3, 46, 71).

Inflammatory cells have also been suggested to contribute to the AKI-to-CKD transition (4, 7, 8, 12, 20, 22, 44a, 137), and the AKI is closely linked to inflammation (30, 67, 101). An in vitro study suggested that hypoxia induces leukocyte adhesion to endothelial cells through the activation of β2-integrin (67). Palm and colleagues (34) showed that dinitrophenol-induced renal hypoxia caused the accumulation of macrophages in the kidney, suggesting that hypoxia alone is capable of inducing an immune response. The recruited inflammatory cells can produce profibrotic cytokines, such as transforming growth factor-β (TGF-β), and activate fibroblasts. Moreover, human renal fibroblasts were shown to increase the production of collagen and tissue inhibitor of metalloproteinase 1 and decrease collagenase expression under hypoxic conditions (95).

Tubulointerstitial fibrosis, in turn, aggravates hypoxia because fibrosis increases the distance between capillaries and tubular epithelial cells, leading to reduced oxygen diffusion efficiency (86). Therefore, hypoxia and tubulointerstitial fibrosis form a vicious cycle, resulting in the progression to CKD.

Possible Roles of Epigenetic Changes

Hypoxia and epigenetic changes are likely linked phenomena that contribute to the pathophysiology of the AKI-to-CKD transition. Technological advances in the field of epigenetics have been rapid and huge, making studies to clarify a pathophysiological role for epigenetic changes in the AKI-to-CKD transition feasible (85). Accumulating data have shown that
hypoxia-induced epigenetic changes promote proinflammatory and profibrotic gene expression (87). Three weeks after I/R injury in mouse kidneys, the expression of proinflammatory and profibrotic genes, such as monocyte chemotactic protein-1, TGF-β1, and collagen III, increases significantly. This increase in expression is accompanied by an increased level of gene-activating histone modification (e.g., H3K4m3 or H3K9/14ac) and increased binding of chromatin-remodeling enzymes, such as Brahma-related gene 1, to the promoters of those genes (89, 142, 144). Although little is known about what drives such epigenetic changes during AKI, an in vitro study using hepatoma-derived cells showed that hypoxia induces gene-activating histone modifications (H3K4m3 and H3K14ac) (57). Recently, Zager et al. (143) showed that I/R injury upregulates endothelin-1 (ET-1) and increases levels of gene-activating histone modifications near the transcriptional start site of the ET-1 gene, which may exaggerate renal hypoxia by causing vasoconstriction (141).

HIF Activation as a Treatment for AKI

Treatments that successfully decrease the severity of AKI should be reasonable strategies to block the transition from AKI to CKD, because AKI severity has been shown to be associated with subsequent development of CKD in both epidemiological (21, 50) and animal studies (68, 137). Given that hypoxia and HIF activation, as mentioned above, occur in the kidney during AKI and HIF is generally regarded as essential for adaptive responses to hypoxia, HIF activation can serve as a therapeutic target for AKI. Recent studies that show suboptimal HIF activation under uremic conditions also emphasize the potential value of a therapeutic strategy to induce HIF activation in patients with kidney disease (126).

A growing body of evidence shows that blocking HIF leads to poorer outcomes in a warm I/R injury model. Because HIF-1α knockout mice die during embryonic development (53) and HIF-2α knockout in mice is embryonic lethal or causes multiple critical disorders (99, 115, 128), Hill et al. (44) used mice heterozygous for Hif1α and Hif2α. Mice with these heterozygous genotypes appeared normal. More severe renal injury was observed after I/R in Hif1α–/+ and Hif2α–/+ mice, compared with the injuries seen in wild-type littermates. Similar results were obtained for HIF-2α knockout mice (65), endothelial HIF-2α knockout mice (62), and in vivo HIF-2α siRNA (26). These data show that intrinsic HIF has a critical role during AKI pathogenesis and suggest that augmentation of the HIF response may ameliorate renal damage. In fact, the AKI outcome in a cisplatin-induced nephropathy and warm I/R injury model was improved by carbon monoxide (14, 133), which leads to tissue hypoxia secondary to functional anemia; by xenon, which induces HIF activation through an unknown mechanism (80); and by various pharmacological approaches to PHD inhibition (14, 44, 83, 123). Schley et al. (110) showed that the deletion of VHL in the thick ascending limb resulted in strong HIF-1α expression in the thick ascending limb and attenuated renal damage following I/R.

The problem, however, is that all of these approaches are preventive strategies, in which HIF is activated before the onset of AKI. A therapeutic strategy, in which HIF is activated after AKI occurs, would be more clinically relevant. However, such strategies have yielded contradictory results (55, 132). Moreover, AKI patients carrying a HIF-1α genetic variant that is known to enhance transactivation experienced more severe AKI and adverse outcomes (66). Because little is known about which HIF target genes actually have a protective role in AKI, significant progress must be made before AKI patients can be treated using a HIF augmentation strategy.

Hypoxia-Targeting Strategy to Block the AKI-to-CKD Transition

Some studies have shown that effective treatment of AKI suppressed CKD progression (59, 78), whereas other recent studies have shown that successful AKI interventions do not necessarily block the AKI-to-CKD transition. In a study using a rat I/R injury model, erythropoietin administered at the time of reperfusion successfully led to functional and structural improvements of the kidney injury at 4 days post-I/R. However, after 28 days, erythropoietin treatment was associated with greater tubulointerstitial fibrosis (38). In another study, the effect of pifithrin-α (p53 inhibitor) was investigated in a rat I/R injury model (27). Although pifithrin-α showed acute protective effects on renal function and tubular epithelial cell apoptosis, treatment with pifithrin-α for 2 days following ischemia did not affect the degree of tubulointerstitial fibrosis at 8 wk postinjury. Moreover, treatment with pifithrin-α for 7 days following ischemia worsened fibrosis after 8 wk. These results indicate that some effective AKI treatment strategies do not necessarily prevent the AKI-to-CKD transition and may even promote progression to CKD in some cases.

In recent years, an increasing number of studies have reported that interventions targeting hypoxia during AKI successfully suppressed subsequent progression to CKD with or without the amelioration of AKI itself. Those reports are of great importance because they reinforce the causal relationship between hypoxia and subsequent progression from AKI to CKD. Treatment with VEGF-121 was reported to be effective in suppressing the AKI-to-CKD transition in a rat I/R injury model (74). Although VEGF-121 did not affect acute kidney damage, the loss of peritubular capillaries in the cortex and outer stripe of the outer medulla was significantly attenuated by VEGF-121 administration 5 wk after injury. These rats were then fed a high-salt diet to promote CKD progression (120). Nine weeks after I/R injury, tubulointerstitial fibrosis was significantly milder in VEGF-121-treated animals. Notably, this protective effect of VEGF-121 against the AKI-to-CKD transition was observed only when VEGF-121 was administered early during injury. Delayed treatment with VEGF-121 had no effect. Another angiogenic factor, angiopoietin-1 (Ang1), was also shown to be effective in blocking the AKI-to-CKD transition. Jung et al. (59) utilized cartilage oligomeric matrix protein Ang1 (COMP-Ang1), an engineered variant of native Ang1 with higher activity (24). Treatment with COMP-Ang1 adenovirus 3 days before I/R injury in mice was associated with better renal function, preserved peritubular capillaries, and higher renal blood flow during the acute phase of I/R-induced AKI. In addition, milder tubulointerstitial fibrosis was observed 30 days after injury in the COMP-Ang1 treatment group. These results suggest that the preservation of peritubular capillaries early in the AKI process leads to the maintenance of oxygen levels in the kidney, protecting the kidney from the AKI-to-CKD transition.
Kapitsinou et al. (61) examined the effect of HIF activation on the prevention of the AKI-to-CKD transition using a PHD inhibitor. The PHD inhibitor was administered to mice 48 and 6 h before bilateral renal I/R. Preconditioning with the PHD inhibitor significantly improved renal function from day 1 to day 21. Reduced fibrosis was observed in both the cortex and medulla at day 21 in the treatment group. Importantly, they performed a subgroup analysis in which they selected mice with comparable blood urea nitrogen elevations at day 1 from the treatment and vehicle groups. The group pretreated with the PHD inhibitor showed less fibrosis at day 21 than the vehicle-treated group, according to the subgroup analysis. These results indicate that PHD inhibition not only reduces the severity of I/R-induced AKI, which should effectively suppress the AKI-to-CKD transition, but also blocks the mechanisms of the AKI-to-CKD transition itself, probably by promoting repair of renal I/R injury. This group also administered the PHD inhibitor to mice on days 2 and 4 post-I/R to investigate the effect of PHD inhibition after injury. In contrast to pre ischemic administration, post-I/R PHD inhibition did not affect blood urea nitrogen levels or fibrosis on day 21. The importance of the timing of HIF activation was also seen in a rat remnant kidney model (139), in which renal fibrosis worsened or was ameliorated depending on the timing of PHD inhibition.

Summary

Currently, renal hypoxia is broadly accepted as a key player in AKI pathophysiology and the progression of CKD to ESKD. In the present review, we illustrate that renal hypoxia also likely plays an important role in the AKI-to-CKD transition. Capillary rarefaction, which is probably induced by decreased expression of vascular factors, such as VEGF in tubular cells, or is associated with pericyte detachment, is observed during the early stage of AKI and causes renal hypoxia. Hypoxia not only damages tubular epithelial cells, which might then prevent the redifferentiation of regenerating tubular cells, but also activates fibroblasts and induces inflammatory reactions, all of which are critical components leading to tubulointerstitial fibrosis. Epigenetic changes in the kidney are intricately associated with hypoxia in the pathophysiology of the AKI-to-CKD transition. Therapeutic strategies targeting hypoxia, such as HIF activation, have been shown to be effective in blocking the transition. Therapeutic strategies targeting hypoxia, such as inhibited PHD, have been shown to be effective in blocking the transition.

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Hypoxia in the AKI-to-CKD Transition

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