Hypoxia-Inducible Factor-1 (HIF-1) and Renal Obstruction Literature Review

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Abstract: Hypoxia-inducible factors (HIFs) are transcription factors that respond to changes in available oxygen in the cellular environment - to decreases in oxygen, or hypoxia. The HIF signaling cascade mediates the effects of hypoxia in the cells. Hypoxia keeps cells from differentiating, but it promotes the formation of blood vessels and is important for the formation of a vascular system in embryos and cancer tumors. In mammals, deletion of the HIF-1 genes results in perinatal death. HIF-1 has been shown to be vital to chondrocyte survival, allowing the cells to adapt to low-oxygen conditions within the growth plates of bones. HIF plays a central role in the regulation of human metabolism. Obstructive uropathy is a condition in which the flow of urine is blocked. This causes the urine to back up and injure one or both kidneys. Obstructive uropathy occurs when urine cannot drain through a ureter. Urine backs up into the kidney and causes it to become hydronephrosis. It can occur suddenly, or be a long-term problem.
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1. Introduction

Hypoxia-inducible factors (HIFs) are transcription factors that respond to changes in available oxygen in the cellular environment - to decreases in oxygen, or hypoxia. The HIF signaling cascade mediates the effects of hypoxia in the cells. Hypoxia keeps cells from differentiating, but it promotes the formation of blood vessels and is important for the formation of a vascular system in embryos and cancer tumors.

In mammals, deletion of the HIF-1 genes results in perinatal death. HIF-1 has been shown to be vital to chondrocyte survival, allowing the cells to adapt to low-oxygen conditions within the growth plates of bones. HIF plays a central role in the regulation of human metabolism.

The alpha subunits of HIF are hydroxylated at conserved proline residues by HIF prolyl-hydroxylases, allowing their recognition and ubiquitination by the VHL E3 ubiquitin ligase, which labels them for rapid degradation by the proteasome. This occurs only in normoxic conditions. In hypoxic conditions, HIF prolyl-hydroxylase is inhibited, since it utilizes oxygen as a cosubstrate. Inhibition of electron transfer in the succinate dehydrogenase complex due to mutations in the SDHB or SDHD genes can cause a build-up of succinate that inhibits HIF prolyl-hydroxylase, stabilizing HIF-1α. This is termed pseudohypoxia. HIF-1, when stabilized by hypoxic conditions, upregulates several genes to promote survival in low-oxygen conditions. These include glycolysis enzymes, which allow ATP synthesis in an oxygen-independent manner, and vascular endothelial growth factor (VEGF), which promotes angiogenesis. HIF-1 acts by binding to HIF-responsive elements (HREs) in promoters that contain the sequence NCGTG. It has been shown that muscle A kinase–anchoring protein (mAKAP) organized E3 ubiquitin ligases, affecting stability and positioning of HIF-1 inside its action site in the nucleus. Depletion of mAKAP or disruption of its targeting to the perinuclear (in cardiomyocytes) region altered the stability of HIF-1 and transcriptional activation of genes associated with hypoxia. Thus, "compartmentalization" of oxygen-sensitive signaling components may influence the hypoxic response.

The advanced knowledge of the molecular regulatory mechanisms of HIF1 activity under hypoxic conditions contrast sharply with the paucity of information on the mechanistic and functional aspects governing NF-κB-mediated HIF1 regulation under normoxic conditions. It is shown that, when endogenous NF-κB is induced by TNFα (tumour necrosis factor α) treatment, HIF-1α levels also change in an NF-κB-dependent manner. HIF-1 and HIF-2 have different physiological roles. HIF-2 regulates erythropoietin production in adult life.

In other scenarios and in contrast to the therapy outlined above, recent research suggests that HIF induction in normoxia is likely to have serious consequences in disease settings with a chronic inflammatory component. It has also been shown that chronic inflammation is self-perpetuating and that it distorts the microenvironment as a result of aberrantly active transcription factors. As a consequence, alterations in growth factor, chemokine, cytokine, and ROS balance occur within the cellular milieu that in turn provide the axis of growth and survival needed for de novo development of cancer and metastasis. The results of a recently published study have numerous implications for a number of pathologies where NF-κB

and HIF-1 are deregulated, including rheumatoid arthritis and cancer. Therefore, it is thought that understanding the cross-talk between these two key transcription factors, NF-κB and HIF, will greatly enhance the process of drug development. HIF activity is involved in angiogenesis required for cancer tumor growth, so HIF inhibitors such as phenethyl isothiocyanate and Acriflavine are under investigation for anti-cancer effects.

Obstructive uropathy is a condition in which the flow of urine is blocked. This causes the urine to back up and injure one or both kidneys. Obstructive uropathy occurs when urine cannot drain through a ureter. Urine backs up into the kidney and causes it to become hydronephrosis. It can occur suddenly, or be a long-term problem. If the blockage comes on suddenly, kidney damage is less likely if the problem is detected and treated promptly, and the damage to the kidneys goes away normally. Long-term damage to the kidneys may occur if the blockage has been present for a long time. If the problem is caused by a blockage in the bladder, the bladder may have long-term damage, which may lead to problems emptying the bladder or leakage of urine.

The following introduces recent reports as references in the related studies.

Chade, A. R., X. Zhu, et al. "Simvastatin promotes angiogenesis and prevents microvascular remodeling in chronic renal ischemia." FASEB J. 2006 Aug;20(10):1706-8. Epub 2006 Jun 21.

Chade et al tested the hypothesis that statins would decrease renal injury in renal artery stenosis (RAS) by restoring angiogenesis and attenuating intrarenal microvascular (IMV) remodeling. Single-kidney hemodynamics and function were quantified using electron-beam-computed tomography (CT) in normocholesterolemic pigs after 12 wk of experimental RAS, RAS supplemented with simvastatin (RAS+simvastatin), and normal controls. Renal circulation was also studied in vivo using angiography and ex vivo using a unique 3D micro-CT imaging technique. Angiogenic and remodeling pathways were subsequently explored in renal tissue. Blood pressure and the degree of stenosis were similarly increased in RAS groups. Simvastatin in RAS enhanced both intrarenal angiogenesis and peri-stenosis arteriogenesis and increased the expression of angiogenic growth factors and hypoxia-inducible factor-1alpha. Furthermore, simvastatin decreased tissue-transglutaminase expression and IMV inward remodeling, restored IMV endothelial function, decreased fibrogenic activity, and improved renal function. Chronic simvastatin supplementation promoted angiogenesis in vivo, decreased ischemia-induced IMV remodeling, and improved IMV function in the stenotic kidney, independent of lipid lowering. These novel renoprotective effects suggest a role for simvastatin in preserving the ischemic kidney in chronic RAS.

Chen, H., T. Davidson, et al. "Nickel decreases cellular iron level and converts cytosolic aconitase to iron-regulatory protein 1 in A549 cells." Toxicol Appl Pharmacol. 2005 Aug 15;206(3):275-87. Epub 2004 Dec 25.

Nickel (Ni) compounds are well-established carcinogens and are known to initiate a hypoxic response in cells via the stabilization and transactivation of hypoxia-inducible factor-1 alpha (HIF-1alpha). This change may be the consequence of nickel's interference with the function of several Fe(II)-dependent enzymes. In this study, the effects of soluble nickel exposure on cellular iron homeostasis were investigated. Nickel treatment decreased both mitochondrial and cytosolic aconitase (c-aconitase) activity in A549 cells. Cytosolic aconitase was converted to iron-regulatory protein 1, a form critical for the regulation of cellular iron homeostasis. The increased activity of iron-regulatory protein 1 after nickel exposure stabilized and increased transferrin receptor (Tfr) mRNA and antagonized the iron-induced ferritin light chain protein synthesis. The decrease of aconitase activity after nickel treatment reflected neither direct interference with aconitase function nor obstruction of [4Fe-4S] cluster reconstitution by nickel. Exposure of A549 cells to soluble nickel decreased total cellular iron by about 40%, a decrease that likely caused the observed decrease in aconitase activity and the increase of iron-regulatory protein 1 activity. Iron treatment reversed the effect of nickel on cytosolic aconitase and iron-regulatory protein 1. To assess the mechanism for the observed effects, human embryonic kidney (HEK) cells over expressing divalent metal transporter-1 (DMT1) were compared to A549 cells expressing only endogenous transporters for inhibition of iron uptake by nickel. The inhibition data suggest that nickel can enter via DMT1 and compete with iron for entry into the cell. This disturbance of cellular iron homeostasis by nickel may have a great impact on the ability of the cell to regulate a variety of cell functions, as well as create a state of hypoxia in cells under normal oxygen tension. These effects may be very important in how nickel exerts phenotypic selection pressure to convert a normal initiated cell into a cancer cell.

Ebrahimi, B., A. Eirin, et al. "Mesenchymal stem cells improve medullary inflammation and fibrosis after revascularization of swine atherosclerotic renal artery

stenosis." PLoS One. 2013 Jul 3;8(7):e67474. doi: 10.1371/journal.pone.0067474. Print 2013.

Atherosclerotic renal artery stenosis (ARAS) raises blood pressure and can reduce kidney function. Revascularization of the stenotic renal artery alone does not restore renal medullary structure and function. This study tested the hypothesis that addition of mesenchymal stem cells (MSC) to percutaneous transluminal renal angioplasty (PTRA) can restore stenotic-kidney medullary tubular transport function and attenuate its remodeling. Twenty-seven swine were divided into three ARAS (high-cholesterol diet and renal artery stenosis) and a normal control group. Six weeks after ARAS induction, two groups were treated with PTRA alone or PTRA supplemented with adipose-tissue-derived MSC (10 x 10(6) cells intra-renal). Multi-detector computed tomography and blood-oxygenation-level-dependent (BOLD) MRI studies were performed 4 weeks later to assess kidney hemodynamics and function, and tissue collected a few days later for histology and micro-CT imaging. PTRA effectively decreased blood pressure, yet medullary vascular density remained low. Addition of MSC improved medullary vascularization in ARAS+PTRA+MSC and increased angiogenic signaling, including protein expression of vascular endothelial growth-factor, its receptor (FLK-1), and hypoxia-inducible factor-1alpha. ARAS+PTRA+MSC also showed attenuated inflammation, although oxidative-stress remained elevated. BOLD-MRI indicated that MSC normalized oxygen-dependent tubular response to furosemide (-4.3 +/- 0.9, -0.1 +/- 0.4, -1.6 +/- 0.9 and -3.6 +/- 1.0 s(-1) in Normal, ARAS, ARAS+PTRA and ARAS+PTRA+MSC, respectively, $p<0.05$), which correlated with a decrease in medullary tubular injury score ($R(2) = 0.33$, $p = 0.02$). Therefore, adjunctive MSC delivery in addition to PTRA reduces inflammation, fibrogenesis and vascular remodeling, and restores oxygen-dependent tubular function in the stenotic-kidney medulla, although additional interventions might be required to reduce oxidative-stress. This study supports development of cell-based strategies for renal protection in ARAS.

Ebrahimi, B., Z. Li, et al. "Addition of endothelial progenitor cells to renal revascularization restores medullary tubular oxygen consumption in swine renal artery stenosis." Am J Physiol Renal Physiol. 2012 Jun 1;302(11):F1478-85. doi: 10.1152/ajprenal.00563.2011. Epub 2012 Mar 14.

Renal artery stenosis (RAS) promotes microvascular rarefaction and fibrogenesis, which may eventuate in irreversible kidney injury. Ebrahimi et al showed that percutaneous transluminal renal angioplasty (PTRA) or endothelial progenitor cells (EPC) improve renal cortical hemodynamics and function in the poststenotic kidney. The renal medulla is particularly sensitive to hypoxia, yet little is known about reversibility of medullary injury on restoration of renal blood flow. This study was designed to test the hypothesis that PTRA, with or without adjunct EPC delivery to the stenotic kidney, may improve medullary remodeling and tubular function. RAS was induced in 21 pigs using implantation of irritant coils, while another group served as normal controls (n = 7 each). Two RAS groups were then treated 6 wk later with PTRA or both PTRA and EPC. Four weeks later, medullary hemodynamics, microvascular architecture, and oxygen-dependent tubular function of the stenotic kidneys were examined using multidetector computed tomography, microcomputed tomography, and blood oxygenation level-dependent MRI, respectively. Medullary protein expression of vascular endothelial growth factor, endothelial nitric oxide synthase, hypoxia-inducible factor-1alpha, and NAD(P)H oxidase p47 were determined. All RAS groups showed decreased medullary vascular density and blood flow. However, in RAS+PTRA+EPC animals, EPC were engrafted in tubular structures, oxygen-dependent tubular function was normalized, and fibrosis attenuated, despite elevated expression of hypoxia-inducible factor-1alpha and sustained downregulation of vascular endothelial growth factor. In conclusion, EPC delivery, in addition to PTRA, restores medullary oxygen-dependent tubular function, despite impaired medullary blood and oxygen supply. These results support further development of cell-based therapy as an adjunct to revascularization of RAS.

Haase, V. H. "Pathophysiological Consequences of HIF Activation: HIF as a modulator of fibrosis." Ann N Y Acad Sci. 2009 Oct;1177:57-65. doi: 10.1111/j.1749-6632.2009.05030.x.

Tissue fibrosis is associated with structural and functional changes that limit blood flow and oxygen availability. In the kidney, tubulointerstitial fibrosis, which leads to progressive destruction of renal tissue and irreversible loss of kidney function, is associated with reduced tissue oxygen levels and activation of hypoxia-inducible factor (HIF) signaling. Although cytoprotective in acute injury models, HIF-1 was found to promote fibrosis in an experimental model of chronic renal injury following unilateral ureteral obstruction. Pharmacological inhibition of lysyl oxidases phenocopied the effects of genetic HIF-1 ablation on cell motility in vitro and on fibrogenesis in vivo, suggesting that lysyl oxidases are important mediators of profibrotic HIF signaling. These findings support the notion that HIF-mediated cellular responses differ under conditions of acute and chronic oxygen deprivation. Under certain conditions, these

responses may lead to further tissue destruction by promoting fibrogenesis.

Higgins, D. F., K. Kimura, et al. "Hypoxia promotes fibrogenesis in vivo via HIF-1 stimulation of epithelial-to-mesenchymal transition." J Clin Invest. 2007 Dec;117(12):3810-20.

Hypoxia has been proposed as an important microenvironmental factor in the development of tissue fibrosis; however, the underlying mechanisms are not well defined. To examine the role of hypoxia-inducible factor-1 (HIF-1), a key mediator of cellular adaptation to hypoxia, in the development of fibrosis in mice, we inactivated Hif-1alpha in primary renal epithelial cells and in proximal tubules of kidneys subjected to unilateral ureteral obstruction (UUO) using Cre-loxP-mediated gene targeting. Higgins, et al found that Hif-1alpha enhanced epithelial-to-mesenchymal transition (EMT) in vitro and induced epithelial cell migration through upregulation of lysyl oxidase genes. Genetic ablation of epithelial Hif-1alpha inhibited the development of tubulointerstitial fibrosis in UUO kidneys, which was associated with decreased interstitial collagen deposition, decreased inflammatory cell infiltration, and a reduction in the number of fibroblast-specific protein-1-expressing (FSP-1-expressing) interstitial cells. Higgins, et al demonstrate that increased renal HIF-1alpha expression is associated with tubulointerstitial injury in patients with chronic kidney disease. Higgins, et al provide clinical and genetic evidence that activation of HIF-1 signaling in renal epithelial cells is associated with the development of chronic renal disease and may promote fibrogenesis by increasing expression of extracellular matrix-modifying factors and lysyl oxidase genes and by facilitating EMT.

Iguchi, N., A. Hou, et al. "Partial bladder outlet obstruction in mice may cause E-cadherin repression through hypoxia induced pathway." J Urol. 2014 Sep;192(3):964-72. doi: 10.1016/j.juro.2014.03.037. Epub 2014 Mar 16.

Posterior urethral valves are the most common cause of partial bladder outlet obstruction in the pediatric population. Posterior urethral valves is a devastating clinical problem that ultimately results in urinary incontinence, neurogenic bladder and renal impairment. Despite improvements in medical and surgical management at least a third of patients with this condition progress to end stage renal disease and half will have problems with urinary incontinence. To achieve better understanding of the mechanism associated with clinical events Iguchi et al generated partial bladder outlet obstruction in male mice. In this model Iguchi et al investigated pathological consequences and underlying molecular mechanisms secondary to partial bladder outlet obstruction. 5 to 8-week-old male C57BL/6 mice were divided into a surgical obstruction group and a sham operated group that served as controls. Bladders and kidneys were harvested from each group 1, 2, 3, 5 and 7 days postoperatively, respectively. Aiguchi et al examined histological and biochemical alterations, and further investigated our hypothesis that partial bladder outlet obstruction induces hypoxia activated profibrotic signaling and changes in gene expression in the bladder. Mice with partial bladder outlet obstruction demonstrated significant increases in bladder mass and urinary retention compared to sham operated mice. Obstruction caused fibrosis in the bladder and induced up-regulation of profibrotic genes, hypoxia-inducible factors and epithelial-mesenchymal transition-inducing transcription factors, resulting in E-cadherin down-regulation. As the conclusion, obstruction induced significant histological and molecular alterations, including activation of the hypoxia-inducible factors pathway in the mouse bladder. Activation of epithelial-mesenchymal transition-inducing transcription factors by hypoxia-inducible factors might have an important role in the pathogenesis of partial bladder outlet obstruction.

Kapitsinou, P. P., H. Sano, et al. "Endothelial HIF-2 mediates protection and recovery from ischemic kidney injury." J Clin Invest. 2014 Jun;124(6):2396-409. doi: 10.1172/JCI69073. Epub 2014 May 1.

The hypoxia-inducible transcription factors HIF-1 and HIF-2 mediate key cellular adaptions to hypoxia and contribute to renal homeostasis and pathophysiology; however, little is known about the cell type-specific functions of HIF-1 and HIF-2 in response to ischemic kidney injury. Here, Kapitsinou, et al used a genetic approach to specifically dissect the roles of endothelial HIF-1 and HIF-2 in murine models of hypoxic kidney injury induced by ischemia reperfusion or ureteral obstruction. In both models, inactivation of endothelial HIF increased injury-associated renal inflammation and fibrosis. Specifically, inactivation of endothelial HIF-2alpha, but not endothelial HIF-1alpha, resulted in increased expression of renal injury markers and inflammatory cell infiltration in the postischemic kidney, which was reversed by blockade of vascular cell adhesion molecule-1 (VCAM1) and very late antigen-4 (VLA4) using monoclonal antibodies. In contrast, pharmacologic or genetic activation of HIF via HIF prolyl-hydroxylase inhibition protected wild-type animals from ischemic kidney injury and inflammation; however, these same protective effects were not observed in HIF prolyl-hydroxylase inhibitor-treated animals lacking endothelial HIF-2. Taken together, our data indicate that endothelial HIF-

2 protects from hypoxia-induced renal damage and represents a potential therapeutic target for renoprotection and prevention of fibrosis following acute ischemic injury.

Kimura, K., M. Iwano, et al. "Stable expression of HIF-1alpha in tubular epithelial cells promotes interstitial fibrosis." Am J Physiol Renal Physiol. 2008 Oct;295(4):F1023-9. doi: 10.1152/ajprenal.90209.2008. Epub 2008 Jul 30.

Chronic hypoxia accelerates renal fibrosis. The chief mediator of the hypoxic response is hypoxia-inducible factor 1 (HIF-1) and its oxygen-sensitive component HIF-1alpha. HIF-1 regulates a wide variety of genes, some of which are closely associated with tissue fibrosis. To determine the specific role of HIF-1 in renal fibrosis, we generated a knockout mouse in which tubular epithelial expression of von Hippel-Lindau tumor suppressor (VHL), which acts as a ubiquitin ligase to promote proteolysis of HIF-1alpha, was targeted. We investigated the effect of VHL deletion (i.e., stable expression of HIF-1alpha) histologically and used the anti-HIF-1alpha agent [3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole] (YC-1) to test whether inhibition of HIF-1alpha could represent a novel approach to treating renal fibrosis. The area of renal fibrosis was significantly increased in a 5/6 renal ablation model of VHL-/- mice and in all VHL-/- mice at least 60 wk of age. Injection of YC-1 inhibited the progression of renal fibrosis in unilateral ureteral obstruction model mice. In conclusion, HIF-1alpha appears to be a critical contributor to the progression of renal fibrosis and could be a useful target for its treatment.

Kobayashi, H., V. Gilbert, et al. "Myeloid cell-derived hypoxia-inducible factor attenuates inflammation in unilateral ureteral obstruction-induced kidney injury." J Immunol. 2012 May 15;188(10):5106-15. doi: 10.4049/jimmunol.1103377. Epub 2012 Apr 6.

Renal fibrosis and inflammation are associated with hypoxia, and tissue pO(2) plays a central role in modulating the progression of chronic kidney disease. Key mediators of cellular adaptation to hypoxia are hypoxia-inducible factor (HIF)-1 and -2. In the kidney, they are expressed in a cell type-specific manner; to what degree activation of each homolog modulates renal fibrogenesis and inflammation has not been established. To address this issue, we used Cre-loxP recombination to activate or to delete both Hif-1 and Hif-2 either globally or cell type specifically in myeloid cells. Global activation of Hif suppressed inflammation and fibrogenesis in mice subjected to unilateral ureteral obstruction, whereas activation of Hif in myeloid cells suppressed inflammation only. Suppression of inflammatory cell infiltration was associated with downregulation of CC chemokine receptors in renal macrophages. Conversely, global deletion or myeloid-specific inactivation of Hif promoted inflammation. Furthermore, prolonged hypoxia suppressed the expression of multiple inflammatory molecules in noninjured kidneys. Collectively, we provide experimental evidence that hypoxia and/or myeloid cell-specific HIF activation attenuates renal inflammation associated with chronic kidney injury.

Lv, Y., P. Liu, et al. "Oxidative stress and hypoxia observed in the kidneys of mice after a 13-week oral administration of melamine and cyanuric acid combination." Res Vet Sci. 2013 Dec;95(3):1100-6. doi: 10.1016/j.rvsc.2013.10.001. Epub 2013 Oct 10.

Both melamine and cyanuric acid have low toxicity, but together they may cause serious lesions to the kidney, via an unknown mechanism. This study was aimed to estimate whether lesions to the kidney were relative to oxidative damage and hypoxia in the kidney after mice exposed to 1mg/kg/day, 5mg/kg/day or 25mg/kg/day of a mixture of melamine and cyanuric acid for 13 weeks. Pathological changes to the kidneys, oxidative stress and energy parameters and hypoxia-inducible factor-1alpha (HIF-1alpha) change in the kidneys were evaluated. Pathological changes were found in the distal tubules of kidneys, such as crystals, proteinaceous casts and compensatory expansion, indicating that the mixture induced toxicity to the kidney. The activities of total antioxidant capacity (TAC) and superoxide dismutase (SOD) and the concentration of glutathione (GSH) decreased, while the concentrations of lipid peroxidation (MDA) and protein carbonyl groups (PC) increased after exposure to the mixture, demonstrating that the mixture resulted in imbalance of antioxidant and reactive oxygen species (ROS) and excessive ROS induced oxidant damage to lipid and proteins in kidneys. The activities of malate dehydrogenase (MDH) and succinate dehyrogenase (SDH) decreased, however, the activity of lactic dehydrogenase (LDH) and the concentration of HIF-1alpha increased after exposure to the mixture. Accordingly, it was concluded that the mixture resulted in a hypoxic state in kidneys and that both oxidative stress and hypoxia contributed to the lesion of kidneys. The exact cause of oxidative damage and hypoxia is not clear, it might be caused by either a direct effect or by an indirect effect, which is secondary to substantial renal damage caused by tubular obstruction due to crystal formation.

Ma, Y. Y., D. Sun, et al. "Transplantation of endothelial progenitor cells alleviates renal interstitial fibrosis in a mouse model of unilateral ureteral obstruction." Life Sci. 2010 May 22;86(21-22):798-

807. doi: 10.1016/j.lfs.2010.03.013. Epub 2010 Mar 20.

AIMS: The present study investigated whether transplantation of bone marrow-derived endothelial progenitor cells (BM-EPCs) in renal capillary network improves renal interstitial fibrosis in unilateral ureteral obstruction (UUO) model in mice. MAIN METHODS: Ex vivo generated, characterized, and cultivated mice BM-EPCs were identified by their vasculogenic properties in vitro. BM-EPCs were labelled with carboxyfluorescein diacetate succinimidyl ester (CFDA-SE) before transplantation. The animal models of UUO were used. Histological changes in renal tubular interstitium were observed with HE and Masson staining. The protein levels of vascular endothelial growth factor(VEGF), hypoxia inducible factor-1alpha (HIF-1alpha) and connective tissue growth factor (CTGF) were analyzed by western blotting and immunohistochemistry. Transforming growth factor-beta1 (TGF-beta1) was detected by immunohistochemistry. Peritubular capillary (PTC) density was determined by CD31 immunostaining. KEY FINDINGS: Transplanted BM-EPCs were successfully incorporated into the capillary network in the obstructed kidney in vivo. UUO induced a significant decrease in VEGF levels and PTC density in the kidney tissue, which was accompanied by a significant increase in HIF-1alpha, CTGF and TGF-beta1. Transplantation of BM-EPCs increased PTC density, VEGF expression and alleviated the development of renal interstitial fibrosis in UUO mice. No significant pathological changes were found in control mice. SIGNIFICANCE: The reduction of PTC density and up-regulation of HIF-1alpha are the important mechanisms of interstitial fibrosis in UUO mice. BM-EPCs transplantation may increase the number of capillary density and alleviate the development of renal fibrosis in obstructive nephropathy in mice.

Nlandu Khodo, S., E. Dizin, et al. "NADPH-oxidase 4 protects against kidney fibrosis during chronic renal injury." J Am Soc Nephrol. 2012 Dec;23(12):1967-76. doi: 10.1681/ASN.2012040373. Epub 2012 Oct 25.

NADPH oxidases synthesize reactive oxygen species that may participate in fibrosis progression. NOX4 and NOX2 are NADPH oxidases expressed in the kidneys, with the former being the major renal isoform, but their contribution to renal disease is not well understood. Here, we used the unilateral urinary obstruction model of chronic renal injury to decipher the role of these enzymes using wild-type, NOX4-, NOX2-, and NOX4/NOX2-deficient mice. Compared with wild-type mice, NOX4-deficient mice exhibited more interstitial fibrosis and tubular apoptosis after obstruction, with lower interstitial capillary density and reduced expression of hypoxia-inducible factor-1alpha and vascular endothelial growth factor in obstructed kidneys. Furthermore, NOX4-deficient kidneys exhibited increased oxidative stress. With NOX4 deficiency, renal expression of other NOX isoforms was not altered but NRF2 protein expression was reduced under both basal and obstructed conditions. Concomitant deficiency of NOX2 did not modify the phenotype exhibited by NOX4-deficient mice after obstruction. NOX4 silencing in a mouse collecting duct (mCCD(cl1)) cell line increased TGF-beta1-induced apoptosis and decreased NRF2 protein along with expression of its target genes. In addition, NOX4 silencing decreased hypoxia-inducible factor-1alpha and expression of its target genes in response to hypoxia. In summary, these results demonstrate that the absence of NOX4 promotes kidney fibrosis, independent of NOX2, through enhanced tubular cell apoptosis, decreased microvascularization, and enhanced oxidative stress. Thus, NOX4 is crucial for the survival of kidney tubular cells under injurious conditions.

Norregaard, R., T. Bodker, et al. "Increased renal adrenomedullin expression in rats with ureteral obstruction." Am J Physiol Regul Integr Comp Physiol. 2009 Jan;296(1):R185-92. doi: 10.1152/ajpregu.00170.2008. Epub 2008 Oct 22.

Ureteral obstruction is characterized by decreased renal blood flow that is associated with hypoxia within the kidney. Adrenomedullin (AM) is a peptide hormone with tissue-protective capacity that is stimulated through hypoxia. We tested the hypothesis that ureteral obstruction stimulates expression of AM and hypoxia-inducible factor-1 (HIF-1alpha) in kidneys. Rats were exposed to bilateral ureteral obstruction (BUO) for 2, 6, 12, and 24 h or sham operation and compared with unilateral obstruction (UUO). AM mRNA expression was measured by quantitative PCR in cortex and outer medulla (C+OM) and inner medulla (IM). AM and HIF-1alpha protein abundance and localization were determined in rats subjected to 24-h BUO. AM mRNA expression in C+OM increased significantly after 12-h BUO and further increased after 24 h. In IM, AM mRNA expression increased significantly in response to BUO for 6 h and further increased after 24 h. AM peptide abundance was enhanced in C+OM and IM after 24-h BUO. Immunohistochemical labeling of kidneys showed a wider distribution and more intense AM signal in 24-h BUO compared with Sham. In UUO rats, AM mRNA expression increased significantly in IM of the obstructed kidney compared with nonobstructed and Sham kidney whereas AM peptide increased in IM compared with Sham. HIF-1alpha protein abundance increased significantly in IM after

24-h BUO compared with Sham and HIF-1alpha immunoreactive protein colocalized with AM. In summary, AM and HIF-1alpha expression increases in response to ureteral obstruction in agreement with expected oxygen gradients. Hypoxia acting through HIF-1alpha accumulation may be an important pathway for the renal response to ureteral obstruction.

Ruiz-Deya, G., S. C. Sikka, et al. "Potential role for the nuclear transcription factor NF-kappa B in the pathogenesis of ureteropelvic junction obstruction." J Endourol. 2002 Oct;16(8):611-5.

In an effort to better understand the pathophysiology of ureteropelvic junction (UPJ) obstruction and to determine possible predisposing factors for endopyelotomy failures, we compared the activation of the nuclear factor NF-kappa B and proinflammatory cytokines in patients who failed endopyelotomy and post-primary pyeloplasty patients. We hypothesized that an imbalance toward proinflammatory cytokines may promote fibrosis prior to and after endopyelotomy in patients with severe hydronephrosis. The charts of patients who underwent open pyeloplasty at our institution were reviewed. Group I was the control group, consisting of 10 patients who had undergone radical nephrectomy for renal-cell carcinoma without involvement of the renal pelvis. Group II was the endopyelotomy failure group and included 11 patients over the age of 15 years treated for symptomatic UPJ obstruction. Group III included six patients who underwent primary pyeloplasty. Paraffin-embedded blocks of UPJ segments from each of these patients were obtained, and immunohistochemical detection of NF-kappa B activation, interleukin (IL)-6, and hypoxia-inducing factor (HIF) was performed. As an in-vitro model, activation of NF-kappa B and cytokine gene expression were also monitored in human bladder T24 urothelial cells 24 hours after exposure to hypoxia (1% O(2)) in the presence and absence of NF-kappa B inhibitor. The activation of NF-kappa B was determined by immunocytochemical analysis, whereas cytokine gene expression was measured using reverse transcriptase-polymerase chain reaction. Immunoreactivity to NF-kappa B was observed in the nuclei of the urothelium and muscle layer in all patients in group II. Such immunostaining suggests increased nuclear translocation and activation of this transcription factor. Those patients with increased expression of NF-kappa B demonstrated increases in IL-6 expression as well. Hypoxia-inducing factor was identified in all the tissue samples tested in group II. Stimulation of the human urothelial cells by hypoxia, known to activate NF-kappa B, resulted in an increase in the levels of IL-1 and IL-6 transcripts compared with hypoxia-exposed cells in the presence of NF-kappa B inhibitors. The NF-kappa B factor was upregulated and proinflammatory cytokines were activated in patients with UPJ obstruction who failed endopyelotomy. Proinflammatory cytokines upregulated by this nuclear factor can result in fibrosis and affect healing after endopyelotomy. Hypoxia appears to activate this nuclear factor. Further studies correlating the degree of hydronephrosis with the activation of HIF are necessary to clarify the role of severe hydronephrosis and its management in UPJ obstruction.

Sun, D., L. Bu, et al. "Therapeutic effects of human amniotic fluid-derived stem cells on renal interstitial fibrosis in a murine model of unilateral ureteral obstruction." PLoS One. 2013 May 28;8(5):e65042. doi: 10.1371/journal.pone.0065042. Print 2013.

Interstitial fibrosis is regarded as the main pathway for the progression of chronic kidney disease (CKD) and is often associated with severe renal dysfunction. Stem cell-based therapies may provide alternative approaches for the treatment of CKD. Human amniotic fluid-derived stem cells (hAFSCs) are a novel stem cell population, which exhibit both embryonic and mesenchymal stem cell characteristics. Herein, the present study investigated whether the transplantation of hAFSCs into renal tissues could improve renal interstitial fibrosis in a murine model of unilateral ureteral obstruction (UUO). We showed that hAFSCs provided a protective effect and alleviated interstitial fibrosis as reflected by an increase in microvascular density; additionally, hAFSCs treatment beneficially modulated protein levels of vascular endothelial growth factor (VEGF), hypoxia inducible factor-1alpha (HIF-1alpha) and transforming growth factor-beta1 (TGF-beta1). Therefore, we hypothesize that hAFSCs could represent an alternative, readily available source of stem cells that can be applied for the treatment of renal interstitial fibrosis.

Sun, D., Y. Ma, et al. "Thrombospondin-1 short hairpin RNA suppresses tubulointerstitial fibrosis in the kidney of ureteral obstruction by ameliorating peritubular capillary injury." Kidney Blood Press Res. 2012;35(1):35-47. doi: 10.1159/000330718. Epub 2011 Aug 19.

Thrombospondin-1 (TSP-1), a naturally occurring inhibitor of angiogenesis, is an important mediator of renal fibrosis in clinical and experimental kidney disease. Increasing evidence shows that the microvasculature plays a critical role in progressive renal disease. The present study was undertaken to investigate whether interstitial fibrosis could be prevented by abolishing TSP-1 function in unilateral ureteral obstruction (UUO)-induced renal fibrosis. A short hairpin RNA vector, designated Thbs-1,

significantly suppressed TSP-1 in both transcriptional and translational levels in in vitro-cultured cells and in vivo fibrosis-induced mouse kidney. Furthermore, TSP-1 RNA interference increased the protein level of vascular endothelial growth factor (VEGF) and the density of peritubular capillaries (PTCs), reduced the expression of hypoxia-inducible factor-1alpha in tubulointerstitial cells, and collagen III and the connective tissue growth factor expression were markedly reduced from day 7 after UUO-induced fibrosis, but un- or vector-treated mice maintained their expression. TSP-1 shRNA suppressed the protein level of TSP-1, increased VEGF expression and PTC density and alleviated the development of renal interstitial fibrosis in UUO mice. These data suggest that inhibition of TSP-1 expression prevented tubulointerstitial fibrosis through ameliorating PTC injury.

Sun, D., Y. Wang, et al. "Effects of nitric oxide on renal interstitial fibrosis in rats with unilateral ureteral obstruction." Life Sci. 2012 Jun 14;90(23-24):900-9. doi: 10.1016/j.lfs.2012.04.018. Epub 2012 Apr 30.

It is well recognized that microvascular injury is a major determinant of renal fibrosis. Mounting evidence shows that nitric oxide (NO) plays an important role in angiogenesis. Therefore, we investigated to the effects of NO on kidney angiogenesis and renal fibrosis. METHODS: In the present study, a unilateral ureteral obstruction (UUO) model was established with L-arginine (L-Arg, 1 g/dl) and N-nitro-L-arginine methyl ester (L-NAME, 5 mg/dl) serving as interference factors. We investigated the alteration of NO concentration with spectrophotometry, peritubular capillary (PTC) density with aminopeptidase P (JG12) immunohistochemical staining, and the expression of vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS), hypoxia inducible factor-1alpha (HIF-1alpha) and transforming growth factor-beta1 (TGF-beta1) with immunohistochemical staining and Western blotting at weeks 2, 3 and 4. KEY FINDINGS: Our findings showed that the expressions of VEGF, eNOS and PTC density were significantly decreased in rats with UUO, which was accompanied by a progressive increase in HIF-1alpha, TGF-beta1 and an area of renal interstitial fibrosis. The administration of L-Arg promoted the synthesis of NO and significantly elevated the expressions of VEGF, eNOS and PTC density with the conspicuous loss of HIF-1alpha and TGF-beta1 expressions and ultimately ameliorated renal fibrosis, which was markedly aggravated by L-NAME administration. SIGNIFICANCE: These findings demonstrate that NO appears to play an important role in kidney angiogenesis and in slowing the progression of renal interstitial fibrosis, which suggests that NO may serve as a novel therapeutic strategy for preventing renal fibrosis as well as fibrosis in other organs.

Tateishi, Y., M. Osada-Oka, et al. "Myeloid HIF-1 attenuates the progression of renal fibrosis in murine obstructive nephropathy." J Pharmacol Sci. 2015 Feb;127(2):181-9. doi: 10.1016/j.jphs.2014.12.011. Epub 2014 Dec 27.

Hypoxia-inducible factors (HIFs) play an important role in the pathogenesis of renal fibrosis. Although the role of macrophage infiltration in the progression of renal fibrosis is well known, the role of macrophage HIF-1 remains to be revealed. To address this question, myeloid specific conditional HIF-1 knock out mice were subjected to unilateral ureteral obstruction (UUO). Renal interstitial deposition of collagen and mRNA expressions of collagen and collagen were markedly increased at 7 days after UUO and myeloid HIF-1 depletion significantly accelerated these increases. Immunohistochemistry and flow cytometric analysis revealed that renal infiltrating macrophages were increased with duration of UUO but myeloid HIF-1 depletion did not affect these changes. Myeloid HIF-1 depletion did not affect M1 and M2 macrophage phenotype polarization in obstructed kidneys. Renal connective tissue growth factor (CTGF) expression was markedly increased and myeloid HIF-1 depletion further enhanced this increase. Immunomagnetic separation of renal cells revealed that renal CTGF was expressed predominantly in renal cells other than macrophages. It is suggested that myeloid HIF-1 attenuates the progression of renal fibrosis in murine obstructive kidney. Alteration of CTGF expression in renal cells other than macrophages is one of possible mechanisms by which myeloid HIF-1 protected renal fibrosis.

Urbieta-Caceres, V. H., X. Y. Zhu, et al. "Reversal of experimental renovascular hypertension restores coronary microvascular function and architecture." Am J Hypertens. 2011 Apr;24(4):458-65. doi: 10.1038/ajh.2010.259. Epub 2011 Jan 13.

Hypertension (HTN) may lead to left ventricular hypertrophy and vascular dysfunction, which are independent factors for adverse cardiovascular outcomes. We hypothesized that decreased blood pressure by percutaneous transluminal renal angioplasty (PTRA) would improve the function and architecture of coronary microvessels, in association with decreased inflammation and fibrosis. Three groups of pigs were studied: normal, HTN, and HTN+PTRA. After 6 weeks of renovascular HTN, induced by placing a local-irritant coil in the renal artery, pigs underwent PTRA or sham. Four weeks later multidetector-computed tomography (CT) was

used to assess systolic, diastolic, and microvascular function, and responses to adenosine. Microvascular architecture, oxygen sensors, inflammation, and fibrosis were then explored in cardiac tissue. RESULTS: PTRA successfully decreased blood pressure and left ventricular hypertrophy. Basal fractional vascular volume (FVV) was similar among the groups, but its response to adenosine was significantly attenuated in HTN, whereas microvascular permeability (MP) and response to adenosine were greater than normal. Both were restored by PTRA. These were accompanied by increased myocardial expression of hypoxia-inducible factor (HIF)-1alpha, inflammation, and microvascular remodeling, including increased density of epicardial microvessels (20-200 microm), as well as cardiac diastolic dysfunction, all of which improved by reversal of HTN. However, PTRA only partially decreased myocardial fibrosis. Reversal of early renovascular HTN improved coronary microvascular function and architecture and reversed myocardial hypertrophy and diastolic dysfunction, in association with decreased levels of myocardial ischemia and inflammation markers, underscoring the benefits of blood pressure normalization for preservation of cardiovascular function and structure.

Zhang, S., C. H. Han, et al. "Transient ureteral obstruction prevents against kidney ischemia/reperfusion injury via hypoxia-inducible factor (HIF)-2alpha activation." PLoS One. 2012;7(1):e29876. doi: 10.1371/journal.pone.0029876. Epub 2012 Jan 25.

Although the protective effect of transient ureteral obstruction (UO) prior to ischemia on subsequent renal ischemia/reperfusion (I/R) injury has been documented, the underlying molecular mechanism remains to be understood. We showed in the current study that 24 h of UO led to renal tubular hypoxia in the ipsilateral kidney in mice, with the accumulation of hypoxia-inducible factor (HIF)-2alpha, which lasted for a week after the release of UO. To address the functions of HIF-2alpha in UO-mediated protection of renal IRI, we utilized the Mx-Cre/loxP recombination system to knock out target genes. Inactivation of HIF-2alpha, but not HIF-1alpha blunted the renal protective effects of UO, as demonstrated by much higher serum creatinine level and severer histological damage. UO failed to prevent postischemic neutrophil infiltration and apoptosis induction in HIF-2alpha knockout mice, which also diminished the postobstructive up-regulation of the protective molecule, heat shock protein (HSP)-27. The renal protective effects of UO were associated with the improvement of the postischemic recovery of intra-renal microvascular blood flow, which was also dependent on the activation of HIF-2alpha. Our results demonstrated that UO protected the kidney via activation of HIF-2alpha, which reduced tubular damages via preservation of adequate renal microvascular perfusion after ischemia. Thus, preconditional HIF-2alpha activation might serve as a novel therapeutic strategy for the treatment of ischemic acute renal failure.

Zhu, X. Y., A. R. Chade, et al. "Cortical microvascular remodeling in the stenotic kidney: role of increased oxidative stress." Arterioscler Thromb Vasc Biol. 2004 Oct;24(10):1854-9. Epub 2004 Aug 12.

Mechanisms of renal injury distal to renal artery stenosis (RAS) remain unclear. We tested the hypothesis that it involves microvascular remodeling consequent to increased oxidative stress. Three groups of pigs (n=6 each) were studied after 12 weeks of RAS, RAS+antioxidant supplementation (100 IU/kg vitamin E and 1 g vitamin C daily), or controls. The spatial density and tortuousity of renal microvessels (<500 microm) were tomographically determined by 3D microcomputed tomography. The in situ production of superoxide anion and the expression of vascular endothelial growth factor (VEGF), its receptor VEGFR-2, hypoxia-inducible-factor (HIF)-1alpha, von Hippel-Lindau (VHL) protein, and NAD(P)H oxidase (p47phox and p67phox subunits) were determined in cortical tissue. RAS and RAS+antioxidant groups had similar degrees of stenosis and hypertension. The RAS group showed a decrease in spatial density of cortical microvessels, which was normalized in the RAS+antioxidant group, as was arteriolar tortuousity. RAS kidneys also showed tissue fibrosis, increased superoxide anion abundance, NAD(P)H oxidase, VHL protein, and HIF-1alpha mRNA expression. In contrast, expression of HIF-1alpha, VEGF, and VEGFR-2 protein was downregulated. These were all significantly improved by antioxidant intervention. Increased oxidative stress in the stenotic kidney alters growth factor activity and plays an important role in renal microvascular remodeling, which can be prevented by chronic antioxidant intervention.

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