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Review

Hypoxia: The Force that Drives Chronic Kidney Disease

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In the United States the prevalence of end-stage renal disease (ESRD) reached epidemic proportions in 2012 with over 600,000 patients being treated. The rates of ESRD among the elderly are disproportionally high. Consequently, as life expectancy increases and the baby-boom generation reaches retirement age, the already heavy burden imposed by ESRD on the US health care system is set to increase dramatically. ESRD represents the terminal stage of chronic kidney disease (CKD). A large body of evidence indicating that CKD is driven by renal tissue hypoxia has led to the development of therapeutic strategies that increase kidney oxygenation and the contention that chronic hypoxia is the final common pathway to end-stage renal failure. Numerous studies have demonstrated that one of the most potent means by which hypoxic conditions within the kidney produce CKD is by inducing a sustained inflammatory attack by infiltrating leukocytes. Indispensable to this attack is the acquisition by leukocytes of an adhesive phenotype. It was thought that this process resulted exclusively from leukocytes responding to cytokines released from ischemic renal endothelium. However, recently it has been demonstrated that leukocytes also become activated independent of the hypoxic response of endothelial cells. It was found that this endothelium-independent mechanism involves leukocytes directly sensing hypoxia and responding by transcriptional induction of the genes that encode the β2-integrin family of adhesion molecules. This induction likely maintains the long-term inflammation by which hypoxia drives the pathogenesis of CKD. Consequently, targeting these transcriptional mechanisms would appear to represent a promising new therapeutic strategy.

Keywords: Hypoxia; Kidney disease; Leukocyte adhesion; CD43; CD45; β2-integrins; Gene transcription

Since the beginning of renal replacement therapy for end stage renal disease (ESRD) through dialysis or transplantation, the number of patients treated for terminal kidney failure worldwide has continued to grow at an annual rate of approximately 7%.[1-3] This is far in excess of the annual 1% growth rate of the world population in general. In 2012, a survey of 7 billion people spanning over 230 countries was undertaken.[1] This survey found that 3,010,000 patients were being treated for ESRD. Of these, 652,000 were living with a donor organ, and 2,358,000 were on dialysis treatment.

In 2011, the United States spent over 49 billion dollars treating nearly eleven times more ESRD patients than in 1980.[4] This trend shows no sign of slowing down.[4] In 2003, the prevalence of chronic kidney disease (CKD) in the US adult population was 11% (19.2 million). Of these patients, an estimated 5.9 million individuals had stage 1; 5.3 million had stage 2; 7.6 million had stage 3; 400,000 individuals had stage 4; and 300,000 individuals had stage 5, or kidney failure.[5]

The incidence of ESRD has already reached epidemic proportions in the United States. Furthermore, the rates of ESRD among the elderly are disproportionably high. Consequently, as life expectancy increases and baby-boomers retire, the already heavy burden imposed by ESRD on the US health care system is predicted to increase dramatically.

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The main cause of ESRD is CKD. This in turn is driven by a constellation of interlinked risk factors. Primary amongst these factors are anemia,[6-9] diabetic hyperglycemia,[10-12] hypertension,[13-17] hypercholesterolemia,[18-20] cigarette smoking,[21-27] air pollution,[28-42] atherosclerosis,[43-52] repeated episodes of acute kidney injury,[53-70] and sleep apnea.[71-87] All the risk factors associated with CKD produce inappropriately low oxygen tensions within the kidney. On the basis of this association, Fine et al[88] proposed in 2000 that chronic hypoxia is the final common pathway that leads to the development of end-stage renal failure. Subsequently, this theory has been validated by numerous studies.[89-99] Particularly informative have been recent experiments where kidney oxygen tension has been reduced with dinitrophenol without affecting markers of oxidative stress. Under these circumstances urinary protein excretion, inflammatory cell infiltration into the kidney, and renal epithelial-to-mesenchymal transition were all increased.[100,101] Consequently, there appears to be a direct link between hypoxia and the progression of CKD.

Causes of Kidney Hypoxia

In relation to their weight, the kidneys are the best-perfused organs of the body.[102] Paradoxically, however, oxygenation of the renal parenchyma is poor, with oxygen tensions in the renal cortex averaging 30 mm Hg and those in the renal medulla being below 10 mm Hg.[103,104] The reason for this dramatic contrast between oxygen supply and oxygenation is due both to the way the kidney is built and to the function it performs. With regard to kidney structure, arterial and venous pre-glomerular and post-glomerular vessels run strictly parallel and in close contact to one another over long distances. This parallel architecture drives the diffusion of oxygen from arterioles to the post-capillary venous system before it can enter the capillary bed.[104,105] Compounding the problem of oxygen delivery is that the rate of regional blood inflow to the inner and outer medulla is lower than that to the renal cortex.[106] Furthermore, the acute angle between the interlobular artery and the afferent arterioles supplying juxtamedullary glomeruli causes the capillary hematocrit in the medulla to be dramatically lower than that in the cortex. This is due to a phenomenon termed plasma skimming, in which erythrocytes that are primarily in the center of vessels continue to flow in the interlobular artery towards the superficial cortex, while the plasma in the periphery of the capillary is captured by the juxtamedullary afferent arterioles and ultimately flows into vasa recta.[107,108] In addition to the architecture of the kidney limiting oxygenation, kidney tubules are characterized by a limited ability to generate energy under anaerobic conditions, causing oxygen to be consumed rapidly in the metabolic processes involved in active salt reabsorption. Consequently, the twin constrains of low oxygen supply dictated by renal structure and high oxygen demand dictated by renal function conspire to make the kidney particularly vulnerable to physiologic and environmental stresses that cause ischemia.

Anemia

Anemia has long been known to be an independent physiologic risk factor for the development of CKD.[6-9] The obvious way in which anemia impacts unfavorably on renal oxygenation is that it is characterized by fewer erythrocytes in the circulation and consequently blood with a reduced oxygen-carrying capacity. The Epo-TAg^{h} transgenic mouse has severe anemia caused by targeted disruption of the gene encoding erythropoietin (EPO).[109] Consistent with the connection of anemia to the development of CKD, the Epo-TAg^{h} mouse mimics CKD pathology by exhibiting renal hypoxia.[9,109] In addition, EPO administration has been shown not only to correct anemia but also protect against ischemia-induced kidney damage.[110-112] This protective effect could clearly stem from enhanced delivery of oxygen by an increased mass of erythrocytes. However, the renoprotective ability of EPO also appears to be due to mechanisms independent of its ability to increase red blood cell production.[113,114] Here EPO binds a heterodimer on the surface of renal cells composed of the EPO receptor and CD131.[115] This binding then elicits a cascade of intracellular signaling events involving the dephosphorylation of p38 mitogen-activated protein kinase and the phosphorylation of Janus kinase 2, signal transducer and activator of transcription 5, serine/threonine protein kinase B, serum and glucocorticoid-regulated kinase 1 and glycogen synthase kinase 3β.[113,114,116,117] The net result of these events is that apoptosis is inhibited through reduced expression of pro-apoptopic nuclear factor-κB and Bcl-2-like protein 4 and increased expression of the anti-apoptopic molecules B-cell lymphoma 2, B-cell lymphoma extra-large and X-linked inhibitor of apoptosis protein.[113,114,118-122] In addition, EPO effects renoprotection by ameliorating oxidative stress through increased expression of glutathione peroxidase, superoxide dismutase and endothelial nitric oxide synthase.[113,123] EPO also down-regulates the ability of renal tissue to produce increased levels of intercellular adhesion molecule 1 and proinflammatory cytokines and chemokines in response to ischemia. As a consequence, renal tissue is less susceptible to attack by neutrophils and macrophages.[121,122]

Hyperglycemia

Diabetic patients with poorly controlled blood glucose levels are at high risk of developing renal dysfunction, and diabetes-induced renal complications are a major cause of morbidity and mortality.[124,125] Diabetes is associated with decreased renal oxygen tension.[11] Several mechanisms have been implicated in driving this process. Hyperglycemia induces the formation of reactive oxygen species by renal mitochondria, nicotinamide adenine dinucleotide phosphate oxidase, and uncoupled nitric oxide synthase.[10] The reactive oxygen species superoxide then directly interacts with nitric oxide, forming peroxynitrite and, thus, reducing nitric oxide bioavailability. A process independent of reactive oxygen species decreases L-arginine, further reducing the bioavailability of nitric oxide.[11] Reduced nitric oxide and increased reactive oxygen species independently both lead to increased oxygen consumption.[11]

In addition, reduced nitric oxide causes vasoconstriction that limits renal blood perfusion and, therefore, oxygen delivery.[12] Hyperglycemia also limits renal perfusion by narrowing the diameter of arterioles within the glomerulus through inducing extracellular collagen accumulation and the proliferation of mesangial, distal tubular epithelial, and vascular smooth muscle cells.[126-129] The molecular mechanism by which this is achieved involves hyperglycemia producing sustained activation of protein kinase C and nuclear factor kappa-light-chain-enhancer of activated B cells that in turn stimulates the release of osteopontin.[129-134] This growth factor then binds and activates its β3-integrin receptor that signals to induce the synthesis of both DNA and collagen.[129,135] An additional consequence of hyperglycemia inducing protein kinase C is that this increases expression of intercellular adhesion molecule 1 by mesangial cells, thus promoting glomerular damage effected by infiltrating mononuclear cells.[133] The link between hyperglycemia, renal hypoxia, and the development of CKD is further evidenced by analysis of the obese db/db mouse model of diabetic nephropathy.[136] This model exhibits hyperglycemia, increased production of reactive oxygen species, loss of capillaries, arteriolar constriction, and a decrease in resting and maximum blood flow.[136-139] Consistent with these characteristics causing kidney damage through hypoxia, the db/db mouse shows increased glomerular expression of hypoxia-inducible factor 1 (HIF-1) and other genes involved in oxidative stress.[140]

Hypertension

The hallmark of systemic hypertension is chronic induction of multiple vasoconstrictors including the renin-angiotensin-aldosterone system, constrictor prostaglandins and endothelin.[141-143] Constriction of blood vessels limits blood flow and consequently reduces oxygen delivery to the kidney.[14-17] In addition, hypertension leads the kidney to consume approximately twice as much oxygen as normal to transport a given amount of sodium.[16] Consequently, the combination of reduced oxygen delivery caused by vasoconstriction and increased oxygen demand caused by aberrant metabolism results in lower renal oxygenation. Specifically, the oxygen tension of the kidney cortex and medulla has been shown to be approximately 10 mm Hg lower than normal in spontaneously hypertensive rats and other models of hypertension as well as in hypertensive patients.[15,89,144-146] The role of hypertension in the progression of CKD was first described in 1914 by Volhard and Fahr.[13] Subsequently, it was appreciated that hypertension predisposes to kidney failure by inducing renal hypoxia.[147,148] The detrimental effects of hypoxia are exacerbated by hypertension also inducing kidney tissue to generate elevated levels of reactive oxygen species such as superoxide, hydrogen peroxide, peroxynitrite, and hydroxyl radicals.[149] These species are formed by elevated intrarenal angiotensin II binding type 1 angiotensin II receptors that then transduce signals to activate the pro-oxidant enzyme nicotinamide adenine dinucleotide phosphate-oxidase.[150,151] The generation of reactive oxygen species is further augmented by decreased expression of the anti-oxidant enzymes superoxide dismutase 1 and 3 and isoforms of nitric oxide synthase.[151] The reactive oxygen produced as a consequence of hypertension acts in the same way as that generated during hyperglycemia to drive renal hypoxia. That renal hypoxia caused by hypertension directly contributes to the development of CKD is demonstrated by angiotensin receptor blockers, angiotensin-converting enzymes, and the anti-oxidant tempol all normalizing renal oxygenation and function in hypertensive rats.[15, 16, 148, 152-154]

Hypercholesterolemia

High cholesterol levels have been shown to correlate with reduced renal oxygenation and increased kidney damage in response to ischemia.[155-157] One mechanism by which cholesterol likely drives these processes is through its role in determining the physical properties of the cell surface. Cholesterol constitutes the non-polar, hydrophobic lipid of the enveloping layer of the erythrocyte membrane. This cholesterol is in equilibrium with the concentration of plasma cholesterol. Consequently, as the concentration of plasma cholesterol increases so does the cholesterol content of the erythrocyte membrane. Under such circumstances the fluidity of the membrane decreases and the lipid shell stiffens. This produces a greater barrier to oxygen diffusion that both delays oxygen entry into the erythrocyte during saturation and delays oxygen release during desaturation.[18-20] Indeed, the percentage change in blood oxygen diffusion has been found to be inversely proportional to plasma cholesterol concentration.[18] Consequently, cholesterol contributes to renal hypoxia by reducing the erythrocyte capacity to both load and release oxygen. Hypercholesterolemia also results in lipid deposition in kidney tissue.[158] Thus, oxygen delivery by diffusion is again compromised. Furthermore, lipid deposition in renal arteries increases their stiffness and reduces their ability to dilate and deliver an augmented blood flow when oxygen tensions are low.[159,160] Besides contributing to renal hypoxia through its physical properties, cholesterol also likely contributes through its metabolism. Resistance to hypoxia-induced kidney damage has been shown to be mediated by increased de novo synthesis of esterified cholesterol and the cholesterol transport protein 18 KDa translocator protein.[161-163] However, chronically high cholesterol levels repress expression of both these molecules, so compromising cytoprotection during ischemia.[164-167]

Cigarette Smoking

Both active and passive cigarette smoking have been found to be independent risk factors for the de novo development of CKD in healthy subjects.[168-176] Cigarette smoking is also a major risk factor for the initial development or worsening of preexisting CKD in patients with human immunodeficiency virus infection, chronic obstructive pulmonary disease, diabetes, diabetic nephropathy, hypertension, autosomal polycystic kidney disease, primary glomerulopathies, lupus nephritis, and those who are obese or who have undergone a lung transplant.[177-187] In addition, smoking by either the donor

or recipient has been shown to adversely influence the function and survival of transplanted kidneys and overall patient survival.[170,171,188,189] Allograft survival and function both worsen with increasing pack-years smoked. The number of cigarettes smoked correlates directly with the severity of renal dysfunction and the likelihood that either CKD will develop or a kidney allograft will fail.[24,168,170,181,190] Conversely, smoking cessation reduces the risk of developing CKD and is of benefit to patients where the condition pre-exists.[176,190,191] Mainstream cigarette smoke has been said to contain 4,000 or more constituents.[22-24,192] Some of these, like cadmium and lead, are directly nephrotoxic.[193,194] Other constituents like tar, carbon monoxide, nicotine, and reactive oxygen species, effect kidney damage by compromising oxygenation. The accumulation of tar in the lung results in a physical barrier that impairs gas exchange within alveoli. Consequently, carbon dioxide is less effectively released and oxygen less effectively acquired by erythrocytes. In addition, tar further reduces oxygen availability to erythrocytes by inducing inflammatory reactions that demand increased oxygen consumption.[22] The carbon monoxide in cigarette smoke reversibly binds various heme-containing proteins within the body. These proteins include hemoglobin, myoglobin, cytochrome P450, and cytochrome oxidase that are responsible for oxygen transport. Since the bond formed between heme and carbon monoxide is less dissociable than the heme-oxygen bond, severe disruption of normal oxygen transport can occur.[26,27] The nicotine of cigarette smoke induces degradation of nitric oxide and stimulates parasympathetic nerves. Both these processes constrict the vasculature, so limiting blood flow and oxygen delivery to the kidney.[21,25] In addition, nicotine binds a range of nicotinic acetylcholine receptors expressed by mesangial, endothelial, vascular smooth muscle, and renal proximal and distal tubule cells.[195-198] These receptors are expressed under normoxic conditions but are induced by both transient and chronic hypoxia.[199,200] Upon nicotine binding, receptors mediate activation of protein kinase C that in turn activates nicotinamide adenine dinucleotide phosphate-oxidase to produce reactive oxygen species.[195,196,201-204] Stable compounds within cigarette smoke, such as acrolein, also induce endothelial production of reactive oxygen species through activation of nicotinamide adenine dinucleotide phosphate-oxidase.[205] These oxygen species then act in the same way as those generated through hypertension and hyperglycemia to drive renal hypoxia and kidney damage. In addition, the reactive oxygen species produced in response to nicotine also induces mesangial cell proliferation and extracellular matrix deposition through pathways that involve increased expression of cyclooxygenase 2-derived prostaglandins and increased phosphorylation of extracellular signal-regulated protein kinases 1 and 2, c-Jun N-terminal kinases, activator protein 1, and protein kinase B.[195,196,204,206-210] This aberrant proliferation and deposition mirrors the protein kinase C dependent processes by which hyperglycemia constricts glomerular arterioles to limit blood flow and, hence, oxygen delivery to the kidney. In an additional mirror of hyperglycemia, nicotine also promotes hypoxia by facilitating oxygen-consuming inflammation. This occurs through increased expression of unphosphorylated signal transducer and activator of transcription 3 that induces renal proximal tubule cells to secrete the pro-inflammatory cytokine transforming growth factor β1 and the pro-inflammatory chemokine monocyte chemotactic protein 1.[210] Finally, with a higher daily number of cigarettes smoked or a longer duration of smoking the risk of developing hypertension increases.[211-213] Consequently, it is logical to assume that beyond its own specific mechanisms of inducing hypoxia-mediated CDK, cigarette smoking also utilizes those manifest in hypertension.

Air Pollution

The ready access of the lungs and blood stream makes them unusually susceptible to the deleterious effects of airborne pollutants.[28,29] Carbon monoxide breathed passively from second-hand smoke or atmospheric pollution can produce hypoxic affects similar to those produced by active cigarette smoking.[27] Nitrogen dioxide and sulphur dioxide may render hemoglobin useless for oxygen transport by driving its conversion to methemoglobin or sulfhemoglobin.[29] Lead and arsine can damage the erythrocyte membrane resulting in anemia.[29] Ozone is formed for the most part by the interaction between solar radiation and nitric oxides, carbon monoxide, and volatile hydrocarbons. These are the primary pollutants of traffic exhaust fumes. Ozone causes acute arterial vasoconstriction, reducing blood flow and limiting oxygen delivery.[30] Ultrafine particles of aerodynamic diameter 0.1μM are emitted by diesel engines and can pass directly into the blood circulation, limiting oxygen delivery by inducing vasoconstriction, vascular inflammation, and increasing blood viscosity.[30-32] Fine particles of 2.5 μM emitted by diesels accumulate within the pulmonary alveoli and cause an inflammatory reaction of the lung that is related both to their physical parameters and the oxidative stress generated by the organic and metallic compounds adsorbed onto their surface.[33] These compounds trigger the local production by macrophages and activated alveolar cells of inflammatory cytokines such as interleukin 6 and tumor necrosis factor α and the potent vasoconstrictor endothelin 1.[30,32,33] As with diesel particles and cigarette tar, the dust produced from coal, silica, wheat, flax, and rice and the fibers originating from cotton, silk, fiberglass, and asbestos can build up in the lungs, limiting gas exchange and inducing oxygen-consuming inflammation.[34-40] Furthermore, dusts originating from agricultural products such as flax, cotton, rice, wheat, and wood are loaded with gram-negative bacterial endotoxin. Exposure to such endotoxin elicits chronic inflammation within the lungs that drives a long-term decline in their function.[36-40] In summary, air pollution can reduce renal oxygenation through a host of mechanisms. These include the induction of oxygen-consuming inflammation, that reduces the ability of the lungs to effect gas exchange, and anemia, vasoconstriction, and hemoglobin conversion that reduces the oxygen delivery capacity of the blood stream. That air pollution does indeed compromise kidney function is supported by the finding that

glomerular filtration is compromised by breathing heavy metals from copper smelters and by living in close proximity to major roadways.[41,42] In addition, rats exposed to either the asbestos group member amosite or to passive smoking develop significant glomerulosclerosis and tubulinterstitial fibrosis, and occupational exposure to silica, fiberglass, or solvents has been linked to an increased risk of developing ESRD.[35,214]

Atherosclerosis

Approximately six million Americans have combined atherosclerosis and kidney disease.[47] The development of atherosclerosis stems from multiple interactions among injurious stimuli and the healing or reparative responses of the arterial wall.[48] After endothelial injury, direct cell-cell interaction and the secretion of chemotactic and growth factors induce recruitment of monocytes to subintimal regions, smooth muscle proliferation and increased synthesis of matrix proteins. The recruited monocytes differentiate into macrophages, accumulate lipid and ultimately become foam cells. Together with accompanying T-lymphocytes, these changes represent the fatty streak, an early histopathological change indicating atherosclerosis. Progression of this atherosclerotic lesion is marked by the accumulation of alternating layers of smooth muscle cells and lipid-laden macrophages. The advanced lesions of atherosclerosis compromise the lumen diameter, reducing the blood flow in arteries and thus limiting kidney oxygenation.[44-46,49-52] In the early stages of atherosclerotic renal artery stenosis progressive decreases in blood flow are accompanied by compensatory changes in arteriovenous shunting, and decreases in glomerular filtration rate and tubular reabsorption of sodium, that either increase oxygen availability or reduce its consumption. Within the whole kidney these adaptive mechanisms appear to maintain appropriate oxygenation.[215] However, direct measurements of intra-renal tissue oxygenation demonstrate the induction of regional hypoxia in the cortex, but especially the medulla.[216-218] This heterogenous pattern of intra-renal hypoxia likely results from inherent differences in the physiology and vasculature of the renal cortex and medulla.[219] These cause stenosis to induce localized microvascular dysfunction and rarefaction, inflammation, oxidative stress, and/or fibrosis.[219-223] While reductions in oxygen consumption can maintain whole-kidney oxygenation when renal artery stenosis is moderate, this compensatory mechanism becomes overwhelmed when vascular occlusion reaches between 70% and 80%. Under these circumstances cortical hypoxia is overt, leading to activation of the renin-angiotensin-aldosterone system, loss of kidney function, rarefaction of small renal vessels, kidney fibrosis, atrophy, and end stage kidney disease designated "ischemic nephropathy".[221,223,224-228] The connection between atherosclerosis-driven renal hypoxia and CKD is underscored by the finding that the preservation of microvascular architecture by intra-renal administration of vascular endothelial growth factor decreases renal fibrosis and maintains renal hemodynamics and function in an experimental model of renal artery stenosis.[224] In addition, when femoropopliteal angioplasty restores the lumen diameter in patients with generalized atherosclerosis, the incidence of renal disease is dramatically reduced.[43] Furthermore, several clinical trials have validated renal angioplasty and stenting in treating renal artery stenosis, especially in high-risk patients with recurrent flash pulmonary edema.[229-231] Controversy exists as to whether kidney reoxygenation through this surgery is superior to that induced by medical therapy. Nevertheless, the goal of both strategies is to correct renal hypoxia. A goal reinforced by the practice guidelines of the American Heart Association and the American College of Cardiology Foundation that state the preferred treatment for hemodynamically significant renal artery stenosis is improved kidney oxygenation.[49]

Repeated Episodes of Acute Kidney Injury

Acute kidney injury (AKI) is the generic term for an abrupt and sustained decrease in renal function that can be reversible if treated promptly and appropriately.[53] Most major causes of AKI produce conditions of hypoxia within the kidney. These include sepsis that induces renal vasoconstriction through the release of endothelin and the use of radiocontrast imaging dyes that increase oxygen consumption for solute reabsorption and reduce regional inner medullary blood flow.[54-61] More generalized reductions in blood flow represent another major cause of AKI. These can result from hemorrhage, decompensated liver cirrhosis, treatment with non-steroidal anti-inflammatory drugs, congestive heart failure, and renal artery occlusion or stenosis.[53] In addition, many forms of surgery where blood flow is inadvertently or deliberately reduced carry an inherent risk for the development of AKI.[62-70] Inadvertent surgical reductions in blood flow can be caused by voluminous blood loss such as often occurs during major hepatic resections.[64,69] Deliberate blood flow reduction is caused by the clamping of major blood vessels such as occurs during organ transplantation, cardiopulmonary bypass, and thoracoabdominal aneurysm surgery.[63,65,66,70] Meta-analysis, epidemiological, and clinical follow-up studies have all shown a strong correlation between AKI episodes and subsequent development of CKD.[232-236] This correlation is observed even in patients who regained normal renal function after AKI.[237] Strikingly, both the severity and the number of AKI episodes are predictive of CKD development.[238,239] These data, along with animal studies, have established a causal relationship between AKI and the subsequent development of CKD.[240-242] Induction of AKI in animals by ischemia, radiocontrast agents, cisplatin, or rhabdomyolysis all induce oxygen tensions below 10 mm Hg deep within kidney tissue.[95,243-247] In addition, impaired renal oxygenation has also been observed in human AKI.[248] Importantly, renal hypoxia is found not only during the acute phase of AKI but also up to 5 weeks later, after the recovery phase.[243,249,250] This sustained hypoxia results in the kidney down-regulating pro-angiogenic isoform 164 and up-regulating dys-angiogenic isoforms 120 and 188 of vascular endothelial growth factor A (VEGF-A).[251,252] As a consequence, the vascular architecture

of the kidney fails to be maintained with reductions in capillary number as well as individual capillary caliber and area.[252-255] Thus, the initial hypoxia insult caused by an episode of AKI is consolidated by subsequent capillary rarefaction that reduces oxygen delivery. This chronic hypoxia then induces a slew of pathological processes in tubular epithelial cells including apoptosis, the prevention of redifferentiation after regeneration and conversion to myofibrolasts.[256-260] Hypoxia also induces monocytes to express the β2 integrin family of adhesion molecules and kidney cells to express vascular cell adhesion molecule 1 and intracellular adhesion molecule 1 as well as the monocyte chemo-attractants C-C motif ligand 2 and C-X3-C motif ligand 1.[252,261-264] These hypoxia-dependent changes in gene expression appear mediated in part by chromatin-remodeling, histone modification and the transcription factors HIF-1 and purine-rich binding protein alpha (Purα).[261-265] Therefore, by inducing pro-inflammatory adhesion molecules and chemokines, hypoxia causes the accumulation of macrophages in the kidney that produce profibrotic cytokines such as

Table 1. Targeting renal hypoxia: current and potential future treatments for chronic kidney disease

Hypoxia pathology	Therapeutic strategy
Systemic hypo-oxygenation	Erythropoiesis induction[110-112]
	Continuous positive airway pressure (CPAP)[81,83,87,377]
	Hyperbaric oxygen therapy (HBOT)[378]
Vasoconstriction	Renal angioplasty and/or stenting[49]
	Vasopressin v2 receptor inhibition[379]
	Renin inhibition[380]
	Angiotensin II type 1 receptor inhibition[381]
	Angiotensin-converting enzyme inhibition[381]
	Voltage-dependent calcium channel inhibition[382]
	Endothelin receptor inhibition[268,383]
	L-arginine vasodilation[155,250]
	Kallikrein vasodilation[298]
Microvascular rarefaction	Platelet-derived growth factor receptor β inhibition[252]
	Vascular endothelial growth factor receptor 2 inhibition[252]
	Vascular endothelial growth factor 121 administration[400]
	Angiopoietin 1 administration[401]
	3-hydroxy-3-methyl-glutaryl-CoA reductase inhibition[223]
	MicroRNA 93 vascular endothelial growth factor inhibitor inhibition[402]
Oxidative stress	Bendavia mitochondria protection[403]
	Pirfenidone mitochondrial protection[404]
	Mammalian target of rapamycin inhibition[405]
	Antioxidant administration[406]
	Nuclear factor erythroid 2-related factor 2 mild induction[407]
	Uncoupling protein 2 inhibition[408]
	Hemeoxygenase 1 induction[409]
	Semicarbazide-sensitive amine oxidase inhibition[410]
	AMP-activated protein kinase activation[411]
	Nitric oxide induction[412]
	Phosphodiesterase inhibition[413]
	Soluble epoxide hydrolase inhibition[414]
	Nicotinamide adenine dinucleotide phosphate oxidase inhibition[415]
	Transforming growth factor β type I receptor inhibition[416]
	Cyclooxygenase 2 inhibition[417]
Leukocyte recruitment	Stem cell administration[418]
	Hypoxia-inducible factor 1α inhibition in leukocytes[262]
	Purine-rich binding protein α inhibition in leukocytes[262]
	Dipeptidyl peptidase 4 inhibition[419]
	Palmitoylethanolamide administration[420]
	D-series resolvin administration[421]
	Protectin D1 administration[421]
	Herbal astragalus administration[422]
	Mothers against decapentaplegic homolog 7 administration[423]
	C-C chemokine receptor type 1 inhibition[424]
	C-C chemokine receptor type 2 inhibition[425]

Table 1 Continued.

Fibrosis	Aldosterone inhibition[304] Kinin B1 receptor inhibition[426] Chemokine C-C motif ligand 2 inhibition[427] Angiotensin II inhibition[428] A2B adenosine receptor inhibition[429] Connective tissue growth factor inhibition[430] Epidermal growth factor receptor inhibition[431] Platelet-derived growth factor inhibition[432] β-catenin inhibition[433] Protein kinase C inhibition[434] Potassium calcium-activated channel protein $K_{Ca}3.1$ inhibition[435] Stromal cell derived factor 1α administration[436] Hepatocyte growth factor administration[437] Inosine monophosphate dehydrogenase inhibition[438] Bone morphogenic protein 7 administration[439] Collagen synthesis inhibition[440] Tumor necrosis factor α inhibition[441] Notch intracellular signaling inhibition[442] p38 mitogen-activated protein kinase inhibition[443] Homeo-domain interacting protein kinase 2 inhibition[444] Cardiac myocyte-derived follistatin-like 1 administration[445] Transforming growth factor β inhibition[446] Pro-fibrotic metalloproteinase inhibition[447] Anti-fibrotic metalloproteinase activation[447]
Destabilization of renal hypoxia-inducible factor	Remote ischemic pre-conditioning[384-390] Prolyl hydroxylase inhibition[244,448] von Hippel-Lindau protein inhibition[449]

transforming growth factor β and activate renal fibrobalsts.[100,101,253] Hypoxia also activates fibroblasts directly to increase extracellular matrix deposition by increasing production of collagen and tissue inhibitor of metalloproteinase I and decreasing expression of collagenase.[266] This activation of fibroblasts, along with the recruitment of inflammatory cells and the damage done to tubular epithelial cells, all lead to tubulointerstitial fibrosis. This fibrosis, in turn, aggravates hypoxia by increasing the distance between capillaries and tubular epithelial cells, leading to reduced oxygen diffusion efficiency.[97] Consequently, hypoxia and tubulointerstitial fibrosis form a pathologic cycle that results in the progression of CKD (figure 1).[242] The cycle is exacerbated by hypoxia-inducing gene-activating histone modifications that up-regulate expression of endothelin 1, thus, reducing oxygen delivery to the kidney by vasoconstriction.[267,268]

Sleep Apnea

Sleep apnea occurs in approximately 60% of patients with CKD.[74-76] This prevalence is much higher than the 20% rate found in the general population.[269] There are two main types of sleep apnea, termed obstructive and central.[71-73] Obstructive sleep apnea is characterized by abnormal collapse of the pharyngeal airway, while central sleep apnea is characterized by a chronic lack of drive to breath. Sleep apneas are very common, affecting about 16% of men and 5% of women between 30 and 65 years-of-age. Cross-sectional cohort studies have demonstrated a significant direct association between the severity of sleep apnea and the severity of renal dysfunction.[270-276] In addition, cohort studies of the longitudinal relationship between sleep apnea and kidney function show that apnea is independently associated with an increased risk of accelerated loss of kidney function.[277,278] Conversely, as kidney function declines, the prevalence of sleep apnea and nocturnal hypoxia increases.[272] Furthermore, aggressive dialysis has been found to improve obstructive sleep apnea. These findings have led to the contention that sleep apnea and CKD have a bidirectional relationship with both diseases being a risk factor for the other.[279] CKD may lead to sleep apnea by autonomic nerve damage, effected by generalized uremic neuropathy, interfering with baroreceptor activity, pharyngeal narrowing due to fluid overload, and accumulation of uremic toxins.[279-284] Sleep apnea likely causes CKD through numerous mechanisms that promote renal hypoxia.[285,286] The most obvious mechanism is that apnea causes insufficient or absent ventilation, compromised gas exchange, and, thus, intermittent nocturnal hypoxia.[77-81,83-86] Long-term exposure to these recurrent episodes of hypoxia-reoxygenation activate nicotinamide adenine dinucleotide phosphate-oxidase 2 that consumes oxygen through its generation of reactive oxygen species.[287-291] Tissue damage effected by these species is augmented by intermittent hypoxia reducing renal expression of antioxidants.[292] In addition, intermittent hypoxia induces the sympathetic nervous system to increase vascular resistance, down-regulates expression of the kallikrein-kallistatin vasodilator

pathway, and activates the renal renin-angiotensin-aldosterone system to cause vasoconstriction.[293-299] Together these processes conspire to produce renal fibrosis and sustained hypertension and their associated means of reducing renal oxygenation (figure 1).[82,300-304] Oxygenation is further compromised by nocturnal hypoxia altering parasympathetic control of heart rate and inducing left ventricular hypertrophy.[305,306] An additional consequence of sleep apnea is that it activates nuclear factor κB, initiating a cascade of events that include increased production of tumor necrosis factor α, interleukin 6, interleukin 8, interleukin 18, C-reactive protein, and C-C motif ligand 2.[307-309] The resulting systemic inflammation, together with apnea-induced reactive oxygen species, hypertension, and platelet aggregability, drives the development of atherosclerosis and its mechanisms of generating renal hypoxia (figure 1). Indeed, chronic intermittent hypoxia linked with a high-fat diet has been shown to cause the de novo generation of atherosclerotic plaques.[310] The profound consequences of atherosclerosis induced by sleep apnea are evident by it being an independent risk factor for cardiovascular mortality both in the general population and in patients with ESRD.[76,84,311-316] Renal

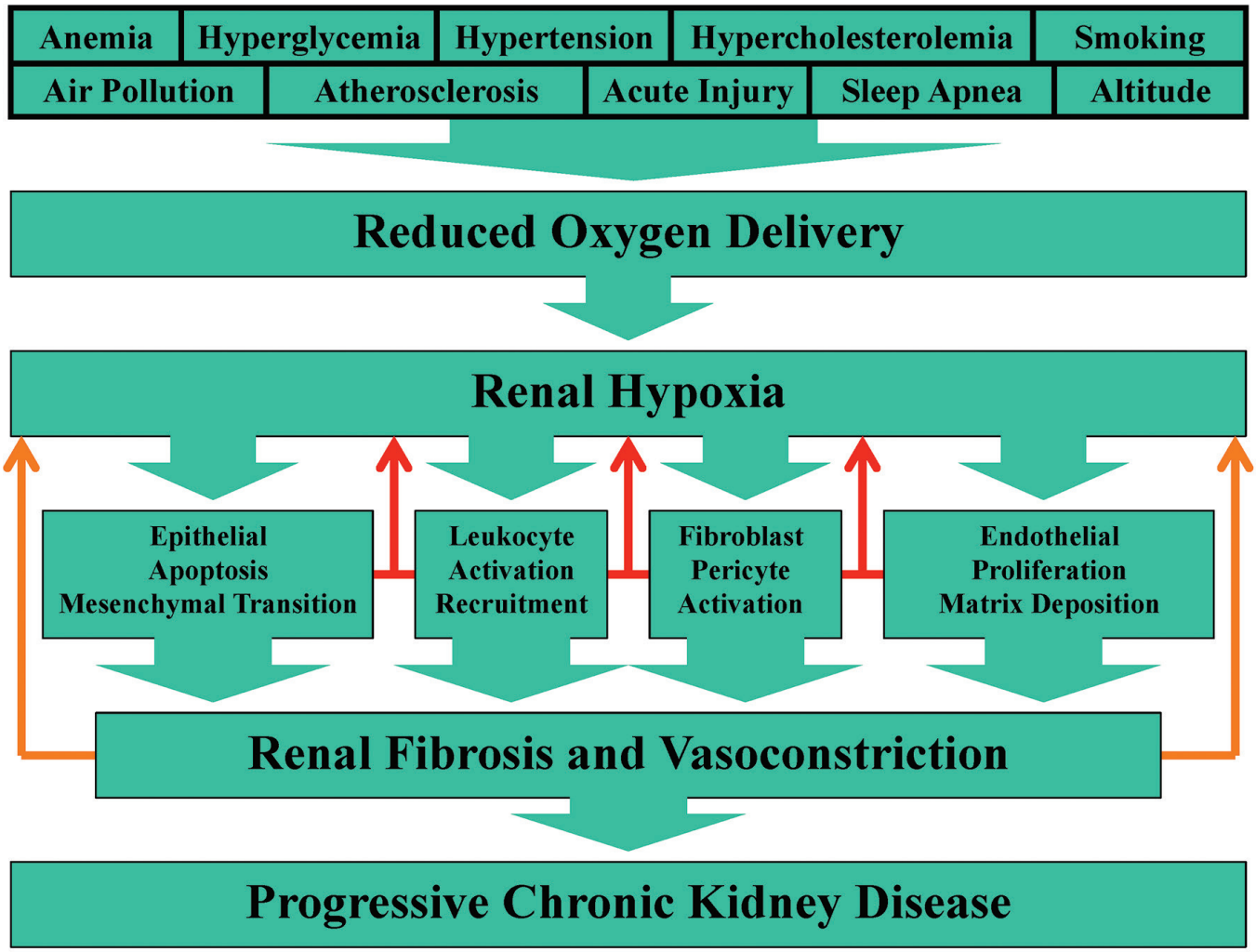

Figure 1. The hypoxia cycle driving chronic kidney disease. A constellation of environmental, behavioral, and physiologic risk factors reduce systemic oxygenation. In many cases these conditions exacerbate one another. Due to its vascular architecture and physiologic function, the kidney is particularly vulnerable to lowered oxygen tensions. This vulnerability is counteracted by defense mechanisms centered around activation of hypoxia-inducible factor. While these defense mechanisms are effective when periods of hypoxia are brief, they are overwhelmed when risk factors cause prolonged hypoxia. Under these circumstances a range of pathological cellular processes are activated, all of which aggravate renal hypoxia by metabolically consuming oxygen (red arrows). In addition, these processes cause renal fibrosis and vasoconstriction further aggravating hypoxia by limiting oxygen diffusion and reducing erythrocyte access (orange arrows). The net result is that a self-reinforcing cycle is established in which hypoxia causes cellular pathologies that themselves compromise renal oxygenation. The inevitable consequence of this cycle is progressive chronic kidney disease.

oxygenation is significantly improved by the treatment of sleep apnea with continuous positive airway pressure.[81] This treatment also ameliorates glomerular hyperfiltration, improves endothelial function and survival, reduces the production of reactive oxygen species, C-reactive protein and interleukin 6, increases vasodilator levels, and decreases the levels of vasoconstrictors.[81,83,87,317-322] That re-oxygenation has such a dramatic beneficial influence on renal function further underscores the intimate connection between renal hypoxia and the pathogenesis of CKD.

The Hypoxia Death Cycle

Environmental, behavioral, and pathophysiological risk factors each, in their own way, reduce systemic oxygenation or the specific oxygenation of the kidney. Many of these risk factors are inter-related, with one being a risk factor for the development of another. Consequently, a perfect storm of conditions can develop that pushes the pre-existing condition of low oxygen tension in the kidney into the realm of hypoxia (figure 1). When this occurs, renal cells initially respond with protective mechanisms that center around the phosphorylation of extracellular signal-regulated protein kinases 1 and 2 and the resulting stabilization of both HIF-1α and HIF-2α.[94-96,292,323-325] These protective mechanisms include the up-regulation of pro-angiogenic factors such as isoform 164 of VEGF-A that protect against capillary rarefaction, and increased expression of matrix metalloproteinases that effect repair and protect against fibrosis by degrading extracellular matrix.[326,327] In addition, short-term exposure to hypoxia leads to increased renal expression of antioxidants such as nuclear factor erythroid 2-related factor 2, hemeoxygenase 1, and metallothionein I that protect against fibrosis and inflammation induced by reactive oxygen species.[94,292,328-330] However, when hypoxia is prolonged, there is an up-regulation of natural antisense HIF-1α that decreases HIF-1α expression by destabilizing its mRNA.[331] In addition, increasing levels of reactive oxygen species target the HIF-1α protein for degradation through the ubiquitin-proteosome system.[332,333] The expression of HIF-2α is unaffected by prolonged hypoxia, thus, there is a shift in the quanlitative nature of HIF away from subunit 1α and towards subunit 2α.[331] This shift in HIF expression likely underlies the observation that under conditions of prolonged hypoxia the initial protective mechanisms of the kidney either fail to be engaged or are down-regulated.[292,334,335] Thus, the expression of pro-angiogenic factors such as VEGF-A isoform 164 is repressed, and the expression of dys-angiogenic factors such as VEGF-A isoforms 120 and 188 is increased, causing capillary rarefaction.[221,223,251,252] Fibrosis is driven by decreased expression of metalloproteinases and increased expression of their inhibitors and extracellular matrix proteins.[336,337] Expression of antioxidants either fails to be induced or is decreased, allowing increased expression of reactive oxygen species to affect tubulointerstitial fibrosis through necrosis, apoptosis, activation of interstitial fibroblasts and pericytes, proliferation of endothelial cells, and epithelial-mesenchyme transition (figure 1).[109-113,259,292,336-343] In addition, prolonged hypoxia causes renal endothelium to produce pro-inflammatory adhesion molecules, cytokines, and chemokines that activate macrophages already resident within the kidney and also recruit additional inflammatory cells from the circulation.[344] Activated macrophages exacerbate the inflammatory process by producing additional cytokines such as tumor necrosis factor 1α and interleukin 6.[345] Furthermore, they destroy renal tissue by phagocytosis and promote fibrosis by producing pro-fibrotic cytokines, such as transforming growth factor β1.[346-348] The net result of prolonged hypoxia is that a vicious pathological cycle is initiated in which fibroblast and inflammatory cell activation combine with apoptosis, endothelial proliferation, and epithelial-mesenchymal transition to cause tubulointerstitial fibrosis. This fibrosis then further drives renal hypoxia by limiting oxygen diffusion. In addition, prolonged hypoxia also induces the renal cortex to up-regulate expression of the potent vasoconstrictor endothelin 1 and its type A receptor.[268] Consequently, the kidney is further "suffocated" to CKD (Figure 1).[97]

A New Hypoxia Paradigm

The recruitment of inflammatory cells into the hypoxic kidney is driven by increased inter-cellular adhesion. This is totally dependent upon increased function of adhesion molecules expressed both on the surface of inflammatory cells and on the surface of kidney tissue.[349] Critical adhesion molecules on the surface of renal tissue include the selectin and intercellular adhesion molecule families.[350,351] Particularly critical on the leukocyte surface are the anti-adhesion molecules CD43 and CD45 and the β2-integrin family of pro-adhesion molecules.[352-355] When leukocytes are not activated, they are maintained in the circulation by CD43 and CD45, which cover one-third of their surface and extend 45 nm and 55 nm, respectively, into the extracellular space.[356,357] The extracellular domains of both CD43 and CD45 are heavily decorated with O-linked and N-linked carbohydrate moieties that often terminate in sialic acid.[358] The strong negative charge conferred by this sialic acid, coupled with abundance and length, allow CD43 and CD45 to prevent leukocyte adhesion. When leukocytes are activated, there is a down-regulation of CD43 and CD45 along with a reduction in their sialylation and a concomitant up-regulation of the pro-adhesive β2-integrin family.[358-363] The induction of this reciprocal expression of anti-adhesion and pro-adhesion forces results in leukocytes acquiring an adhesive phenotype capable of extravasation and infiltration into organs such as the kidney (figure 2).

The β2-integrin family comprises four heterodimers, composed of a common beta subunit encoded by the CD18 gene linked with one of four distinct alpha subunits encoded by the CD11a, CD11b, CD11c and CD11d genes.[352,353] The CD11a/CD18 heterodimer is present on the surface of virtually all leukocytes, while CD11d/CD18 is expressed predominantly on myelomonocytic cells. CD11b/CD18 is expressed on natural killer and mature myeloid cells, and

CD11c/CD18 expression mirrors that of CD11b/CD18, but also extends to dendritic cells, some cytotoxic T-lymphocyte clones, and some activated B and T-lymphocytes. Since the CD18 gene is active in all leukocytes, it is the more selective expression of the CD11 genes that dictates the specific cell-types on which the different CD11/CD18 heterodimers are present. The pattern of CD11 and CD18 production dictates that during activation macrophages exhibit induced expression of all four heterodimers that comprise the β2-integrin family.

The increase in β2-integrin function that occurs during leukocyte activation is caused by a number of mechanisms. The most rapid increase in function is caused by increased

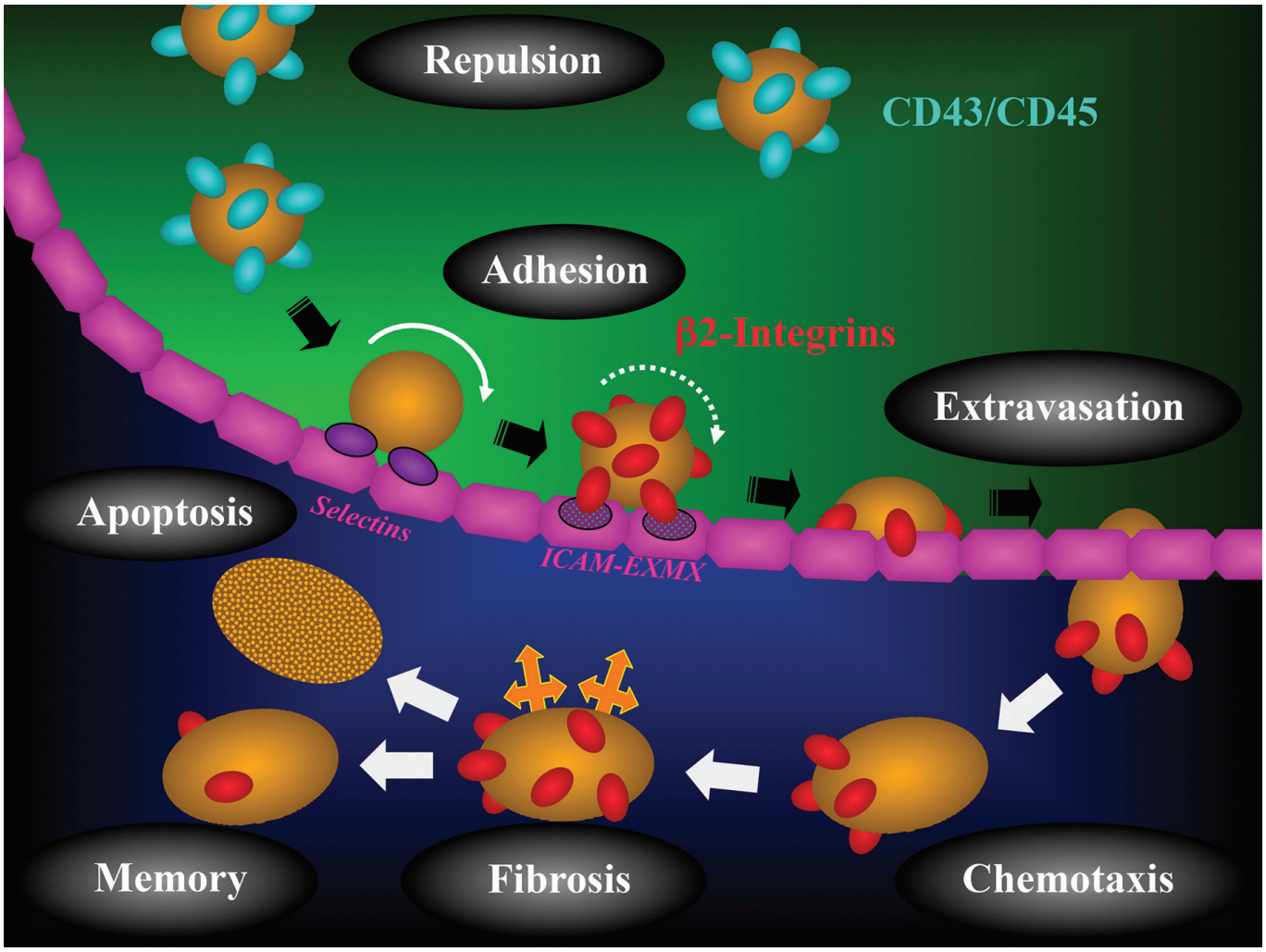

Figure 2. Recruitment of inflammatory leukocytes into renal tissue. When leukocytes (orange spheres) are non-activated they are maintained in the circulation by repulsive forces conferred by CD43 and CD45 (blue ellipsoids) expressed on their surface. Leukocytes are activated by hypoxia either directly or indirectly as a result of responding to chemokines and cytokines released from hypoxic kidney tissue. The initial consequence of this activation is that the expression of anti-adhesive CD43 and CD45 is reduced allowing leukocytes to engage in fast-rolling along arterial cell walls (pink octahedrons) tethered by endothelial selectins (purple ellipsoids) binding leukocyte carbohydrate moieties. Fast-rolling is first slowed and then halted by β2-integrins (red ellipsoids) being induced on the leukocyte surface and binding endothelial extracellular matrix and intercellular adhesion molecules (ICAM-EXMX) (speckled purple ellipsoids). The β2-integrins subsequently mediate extravasation and chemotaxis through the traction they impart at the leukocyte leading-surface. Once embedded within renal tissue activated leukocytes drive fibrosis through phagocytosis, self-inflicted apoptosis and the release of cytokines and chemokines (orange arrowed-crosses) that induce the activation or apoptosis of surrounding cells and recruit additional inflammatory cells from the circulation. The vast majority of infiltrating inflammatory leukocytes eventually undergo apoptosis. However, a small proportion can remain resident with reduced β2-integrin expression and "memory" that allows rapid re-activation.

affinity and avidity of β2-integrin molecules already at the leukocyte surface.[364] The next wave of increased function results from the mobilization to the leukocyte surface of pre-made pools of the β2-integrins.[365] Finally, in order that leukocyte adhesion can be sustained, there is transcriptional induction of the β2-integrin genes.[360]

Since transcriptional induction of β2-integrin gene expression plays a vital role in macrophage function, work was undertaken to identify the causative molecular mechanisms.[366-371] Using transfection analyses and phorbol myristate acetate, it was established for each β2-integrin gene that the proximal promoter region is sufficient to drive a pattern of inducible expression in vitro which mimics that of the endogenous gene in vivo.[360] In subsequent studies it was determined that GA-binding proteins alpha and beta mediate induction of the CD18 gene,[369] activator protein 1, specificity protein 1 and Purα mediate induction of the CD11c gene,[368,371] myeloid specificity 2 and Purα mediate induction of the CD11a and CD11b genes,[262,370] and Purα mediates induction of the CD11d gene.[262]

Despite β2-integrin expression being regulated at the transcriptional level, accepted dogma held that changes in β2-integrin expression relevant to leukocyte function occur almost exclusively after protein translation.[364,365] This dogma was challenged by demonstrating that during hypoxia, transcription of the β2-integrin genes is absolutely required for leukocytes to exhibit increased adhesion to endothelium.[261,262] A second dogma in the field of leukocyte function was that hypoxia induces their adhesion not as a consequence of their sensing oxygen deprivation directly but only indirectly as a consequence of sensing inflammatory cytokines released by hypoxic tissue.[344-346] Again, this dogma was challenged by demonstrating that during hypoxia leukocytes exhibit an intrinsic increase in β2-integrin gene expression.[261,262]

Following activation by hypoxia, recent evidence indicates that leukocytes exacerbate the inflammatory microenvironment. Specifically, it has been demonstrated that during acute inflammatory disease, infiltrating neutrophils mold the tissue microenvironment in ways that significantly promote the stabilization of HIF.[372] Microarray analysis of epithelial cells following β2-integrin-dependent neutrophil transmigration identified the induction of a prominent cohort of HIF target genes. These studies revealed that transmigrating neutrophils rapidly deplete the local environment of molecular oxygen and "transcriptionally imprint" the surrounding tissue to induce HIF target genes.

Taken together, recent studies establish a new paradigm in which leukocytes can sense hypoxia directly and respond by HIF-1 and Purα inducing transcription of the β2-integrin genes.[261,262] Under normoxic conditions Purα has been shown to repress transcription of the CD43 gene.[361,362] Consequently, this transcription factor appears to act as a master regulator, coordinating the reciprocal expression of anti-adhesion and pro-adhesion molecules to drive leukocyte adhesion. While hypoxia utilizes Purα to induce β2-integrin expression, it remains to be determined whether hypoxia represses expression of either CD43 or CD45, and if it does, whether Purα is involved. However, it is intriguing to note that the expression of both CD43 and CD45 is repressed under contitions of oxidative stress.[373,374]

Future Directions

It has been demonstrated experimentally that intrarenal hypoxia, per se, without confounding factors such as hyperglycemia and oxidative stress, can induce nephropathy.[100,101] In addition, populations such as the Navajo Nation and Tibetans who live at high altitudes exhibit increased risk of developing CKD independent of glycemic control and lipidemia status.[375,376] These findings, along with a host of other studies, argue strongly in favor of a causal relationship between hypoxia and CKD.[88-101] As a consequence, there is increasing interest in the development of therapeutic strategies that target hypoxia and its dependent processes. Proof-of-principle of these strategies ranges from experiments performed in vitro, to testing in animals, to deployment in the clinic. The most evolved methodologies are those aimed at improving overall body oxygenation and counteracting artery narrowing. Systemic oxygenation strategies include the administration of erythropoietin to increase hematocrit levels, apparatus to effect continuous positive airway pressure, and whole-body chambers to produce an environment of 100% oxygen.[81,83,87,110-112,377,378] Artery narrowing is already routinely counteracted by renal angioplasty with or without stenting and the administration of vasoconstriction inhibitors that target the renin-angiotensin-aldosterone system.[49,379-381] The targeting of vasoconstriction pathways controlled through vasopressin, endothelin, and voltage dependent calcium channels are in their infancy, as is the use of vasodilators such as arginine and kallikrein.[155,250,268,298,379,382,383] Beyond systemic hyperoxygenation and vasoconstriction, the hypoxia-dependent processes of microvascular rarefaction, oxidative stress, leukocyte recruitment, and fibrosis all contribute to the development of CKD. A host of potential therapeutic targets exists within these areas (Table 1). However, efficacy remains proven predominantly only in vitro or in animals. A notable exception is in efforts to stabilize the expression of HIF-1α. During periods of brief hypoxia, this factor is induced and is renoprotective. Only when hypoxia is prolonged does HIF-1α become destabilized, leading to kidney damage. This phenomenon has been harnessed in the surgical setting by the development of the technique of remote ischemic preconditioning.[384] Here repeated brief episodes of hypoxia are induced by artery clamping, stent balloon inflation, or applying a tourniquet or over-inflated blood-pressure cuff to an arm or lower limb. This procedure stabilizes HIF-1α in the kidney, thereby conferring protection against a subsequent period of prolonged hypoxia.[385] Pre-conditioning by having cobalt chloride in drinking water or by breathing xenon, carbon monoxide, or isoflurane gas also stabilizes HIF-1α and confers

renoprotection.[386-390] The clear limitation of ischemic preconditioning is that it can only be deployed against a defined episode of acute hypoxia known to be imminent, such as occurs after artery clamping in transplant surgery, or the injection of radiocontrast medium. Consequently, effort has been applied to develop pharmacological stabilizers of HIF-1α that can be used to treat conditions characterized by prolonged chronic hypoxia. Dominant amongst these efforts has been the development of agents that work by inhibiting HIF-1α prolyl hydrolases (PHD).[391] This family of three enzymes naturally down-regulate HIF-1α in a manner that is dependent upon 2-oxoglutarate. Pharmacological inactivation of the PHD enzymes by 2-oxoglutarate analogues is sufficient to stabilize HIF-1α, but it is nonspecific for individual PHD isoforms.[392] Studies performed in vitro suggest these isoforms exhibit some significant differences in substrate specificity. PHD3, for example, does not hydroxylate proline 402 within the oxygen-dependent degradation domain of HIF-1α, while PHD1 and 2 do so efficiently.[393,394] Such observations have generated significant interest in identifying PHD-modifying therapeutics, and a number of PHD inhibitors have been described. These include antagonists of alpha-keto-glutarate, analogs of naturally occurring cyclic hydroxamates, and direct inhibitors of the prolyl hydroxylases.[392,395] The most mature work in this area is the development of the PHD inhibitor FG-4592.[396] This agent stabilizes HIF-1α and is currently in phase 2 and 3 clinical trials for the treatment of anemia in patients with ESRD. The challenge for the future is to develop the full range of hypoxia targets that have demonstrated therapeutic potential in the laboratory (Table 1). Some that are already in clinical use are being applied in combination, such as dual inhibition of angiotensin receptors and angiotensin-converting enzyme.[397] In addition, triple blockade of the aldosterone receptor, angiotensin-converting enzyme, and angiotensin receptors is also being evaluated.[398] Other combinations, such as the simultaneous inhibition of angiotensin receptors and C-C chemokine receptor type 2, have proven more effective than monotherapy in animal models.[399] Consequently, a future appears at hand when deployment of a personalized battery of therapeutics will deprive CKD of the hypoxia-driven forces that ferment its progression.

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