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Invited Commentary

Erythrocyte metabolism, oxygen delivery, and hypertensive kidney disease

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A recent study by Xie et al. [1] suggests that metabolic adjustments in erythrocytes affect progression of hypertensive kidney disease by regulating tissue oxygen delivery. The study provides novel mechanisms in the pathogenesis of renal disease and potential treatment targets. Given the substantial energy demand of tubular solute reabsorption, the kidneys are highly metabolically active organs consuming around 7% of the oxygen taken up by the body. While comprising no more than 2% of body mass, the kidneys receive approximately 22% of resting cardiac output. Despite this apparent luxury perfusion - oxygen extraction is lower than in many other organs - kidneys show a steep oxygen gradient with decreasing oxygen partial pressure from cortical towards medullary portions. Indeed, local tissue oxygen partial pressures may be as low as 10 mmHg in the renal medulla [2]. In contrast, other vital organs, like the heart, the liver and the brain, operate at tissue oxygen partial pressures above 30 mmHg [3].

Further reductions in renal oxygen tension can cause acute renal failure. In fact, highly trained and healthy mountaineers may experience reductions in kidney function and albuminuria, the so-called high altitude renal syndrome (HARS), at altitudes above 7000 m [2]. Renal tubular cells, well-endowed with energy consuming Na^+/K^+ pumps, are prone to hypoxic damage. Moreover, hypoxia promotes transition from acute to chronic kidney disease [4]. Renal tubular cells respond to sustained oxygen shortage with epithelial-mesenchymal transdifferentiation into myofibroblasts [5]. Hypoxia also activates fibroblasts and may change extracellular matrix characteristics. The resulting renal tubulointerstitial fibrosis, a hallmark of chronic kidney disease, drives further renal function loss including reduced erythropoietin release with subsequent anemia [6]. Renal microvascular rarefication and glomerular sclerosis foster renal hypoxia with advancing age [7]. Avoiding renal tissue hypoxia could conceivably ameliorate fibrogenesis and slow the decline in kidney function.

Theoretically, oxygen consumption and oxygen supply could be tweaked to improve renal oxygenation. In fact, mechanisms regulation renal oxygen consumption have been an important scientific focus in recent years. For example, worsened renal energy efficiency through mitochondrial uncoupling has been observed in diabetic kidney disease [8]. Conversely, more efficient mitochondria convey renal hypoxia tolerance in animals [9]. In many organs, increased perfusion is the prime mechanism matching oxygen supply to increased oxygen demand. In the kidney, however, increased perfusion results in concomitant increases in glomerular solute filtration. Filtered solutes have to be reclaimed through energy-dependent tubular reabsorption such that oxygen demand increases with increasing perfusion. Alternatively, the amount of oxygen released at a given perfusion rate could increase. A recent study in mountaineers suggested that sphingosine-1-phosphate signaling in erythrocytes protects against tissue hypoxia at high altitude by improving oxygen release [10].

Xie et al. [1] generated mice with erythrocyte lineage-specific ablation of the gene encoding sphingosine kinase 1, which produces sphingosine-1-phosphate. Chronic angiotensin II infusion elicited a more pronounced increase in blood pressure, renal damage, and renal hypoxia in mice with erythrocyte lineage-specific sphingosine kinase 1 knockout compared to wildtype mice. The differential response was not explained by differences in erythropoiesis secondary to renal disease. In knockout animals, erythrocyte sphingosine-1-phosphate concentrations were low and did not respond to angiotensin II infusion. In contrast, erythrocyte sphingosine-1-phosphate concentrations were much higher in wildtype animals and increased further with angiotensin II infusion likely through sphingosine kinase 1 induction. Together, these observations suggest that sphingosine-1-phosphate generation in erythrocytes protects the kidney from hypoxia associated damage elicited through angiotensin II.

Next, Xie et al. [1] identified metabolites and metabolic pathways in erythrocytes differentially affected by angiotensin II. The glycolysis pathway was significantly affected in knockout mice with angiotensin II infusion compared to wildtype mice. Among glycolytic intermediates, 2, 3-bisphosphoglycerate was particularly strongly induced by angiotensin II in wildtype mice. The response was obliterated in knockout mice. Over decades, physiology professors have touted that 2,3-bisphosphoglycerate modulates hemoglobin oxygen binding such that oxygen delivery in peripheral tissues is improved. Here is a useful application. Detailed metabolic analyses utilizing labeled metabolites among other tools showed that angiotensin II induces bisphosphoglycerate mutase, the enzyme generating 2,3-bisphosphoglycerate, in wildtype but not in knockout mice. AMP-activated protein kinase and protein phosphatase 2A appear to be involved. Indeed, pharmacological AMP-activated protein kinase activation and protein phosphatase 2A inhibition rescued the chronic kidney disease phenotype in knockout animals. Clinicians may find it intriguing that metformin also activates AMP-activated protein kinase. Finally, preliminary studies in erythrocytes obtained from patients with chronic kidney disease reproduced some of the findings in mice.

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Overall, the study focusses our attention on the interaction between metabolic programming and hypoxia on kidney disease progression. The idea that the sphingosine-1-phosphate mechanism could be engaged through hypoxia acclimatization [10] is intriguing. Sphingosine-1-phosphate may also convey endothelial protection during intermittent hypoxia [11]. Yet, systemic intermittent hypoxia has also been implicated in the progression of chronic kidney disease in patients with chronic obstructive pulmonary disease [12]. We dare to speculate that while too much hypoxia may damage the kidney, individualized hypoxia training could have utility in ameliorating kidney disease.

Metabolic programing may also affect target organ tolerance to hypoxia. A shift towards fructose metabolism is a highly conserved evolutionary mammalian mechanism protecting tissues against hypoxia among other stresses [13]. Naked mole rats survive prolonged anoxia by switching their metabolism to fructose based energy generation [14]. In a rodent model for kidney transplantation, fructose-1,6-diphosphate increased the viability of kidney grafts during cold ischemia [15]. Furthermore, in patients undergoing cardiac bypass surgery, intravenous fructose-1-6-diphosphate infusion was associated with reduced likelihood of experiencing postoperative myocardial infarction and better cardiac function [16]. Finally, hypoxia may affect tissue regeneration. A functioning hypoxia – hypoxia-inducible-factor – von-Hipple-Lindau-gene axis is mandatory for the differentiation of nephron progenitor cells [17]. The regenerative capacity of many adult tissues including the kidneys is limited. The phenomenon may be explained in part by oxidative stress-induced activation of the DNA damage response resulting in cell cycle arrest [18]. In mice, myocardial regeneration can be rescued by severe sustained hypoxia [19]. Overall, we suggest that recognition of the mechanisms orchestrating the interaction between hypoxia and the kidney may pave the way to novel therapies ameliorating kidney disease. The sphingosine-1-phosphate mechanism in erythrocytes is not the only pathway worth pursuing.

Declaration of competing interest

None.

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