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ANAEMIA

Regulation of renal erythropoietin via HIF

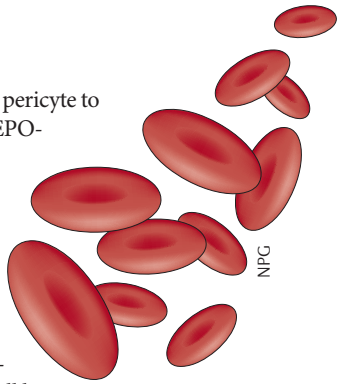
A study from Volker Haase and colleagues shows that non-erythropoietin (EPO)-producing renal epithelial cells can regulate the production of EPO in other renal cell types. After generating pan-epithelial von Hippel-Lindau (*Vhl*)/*Epo* double knockout mice, the researchers found that this effect was negatively modulated by the activation of hypoxia inducible factor (HIF).

The researchers first showed that inactivation of *Vhl* in murine renal epithelial cells resulted in stabilization of HIF, but the animals developed polycythaemia due to constitutive EPO induction in the liver. To circumvent the confounds of hepatic EPO production, they created *Vhl/Epo* double knockout mice under the control of paired box 8 (*P8; Vhl*$^{fl/fl}$ *Epo*$^{fl/fl}$), which prevented hepatic EPO production whilst not inactivating the *Epo* gene in renal interstitial cells. Surprisingly, these mice rapidly developed anaemia without loss of renal function.

> “activation of HIF in renal epithelial cells regulates induction of EPO in perivascular fibroblasts”

Next, the researchers investigated the metabolic consequences of HIF activation in renal epithelial cells and found that the *P8; Vhl*$^{fl/fl}$ *Epo*$^{fl/fl}$ mice exhibited increased glucose uptake, glycolysis, and renal tissue partial pressure of oxygen (pO_2) and reduced mitochondrial mass and oxygen consumption. Further analyses indicated that constitutive activation of HIF in the proximal nephron led to a reduction in the number of EPO-producing renal interstitial cells and suppression of renal EPO production.

“A fascinating finding is that the activation of HIF in renal epithelial cells regulates the induction of EPO in perivascular fibroblasts and pericytes, which are the physiologic source of EPO in the kidney”, says Haase. “Given the close proximity of these cell types, we believe that intercellular crosstalk — at a metabolic level through the regulation of renal tissue pO_2 and via oxygen-independent mechanisms — regulates the ability of a perivascular fibroblast or pericyte to become an EPO-producing cell.” The researchers propose that the inability to generate a renal EPO-producing cell line over the past 30 years may be because these intercellular interactions have been lost, and they consider that epithelial HIF activation can also disrupt these cellular interactions.



Haase and colleagues now plan to define the epithelium-derived signals that modulate renal pericyte function and regulate the conversion of renal pericytes and perivascular fibroblasts into EPO-producing cells. They hope that such future studies will lead to a better understanding of the pathogenesis of renal anaemia.

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ORIGINAL ARTICLE Farsijani N. M. *et al.* Renal epithelium regulates erythropoiesis via HIF-dependent suppression or erythropoietin. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI74997