Activation of Epo-producing cells by HIF stabilizers in the kidney and beyond

Thomas Knöpfel, Olga M. Lempke, Stana M. Burger, Małgorzata Wilk, Patrick Spielmann and Roland H. Wenger

Institute of Physiology, University of Zurich, Zurich, Switzerland

During kidney disease, erythropoietin (Epo) expression ceases by an ill-defined mechanism. The lack of Epo production eventually causes renal anemia that needs treatment with recombinant Epo or the recently approved inhibitors of HIF prolyl-4-hydroxylases (PHIs). However, it is not clear to what extent various organs and cell types respond to PHIs. To address this question, we developed a reporter mouse that allows for the permanent labelling of active Epo-producing cells and the subsequent fate tracing. We found that tagged renal Epo-producing (REP) cells are a long lasting, clearly defined novel cell type even in the absence of Epo expression. Treatment with the PHI FG-4592 (roxadustat) stimulated Epo expression in REP cells in a similar spatial pattern like systemic hypoxia. In an unilateral model of fibrotic renal tissue remodeling, tagged REP cells halt to produce Epo. However, FG-4592 rapidly reactivated Epo expression in REP cells of the damaged kidney to a similar extent as in the contralateral healthy kidney, consistent with a model of microenvironmental relative hyperoxia causing Epo loss in renal anemia. Whereas FG-4592 was unable to stimulate hepatic Epo expression, the novel PHI TP0463518 caused a massive induction of Epo exclusively in the liver. Circulating Epo levels matched those obtained with FG-4592. Furthermore, tagged cells in the liver did not show a hypoxia-like cell pattern and were located in the well oxygenated periportal area. In contrast, the rare, tagged cells in the liver from control and FG-4592 treated mice were also found around the less oxygenated central vein. Depending on the degree of kidney disease, a liver specific PHI will provide a valuable tool to tackle renal anemia.