The molecular identity of erythropoietin-producing cells in healthy, fibrotic and PHI-treated mice

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A decrease in blood oxygen content following anaemia or hypoxaemia causes a hypoxic microenvironment around "interstitial" renal erythropoietin (Epo)-producing (REP) cells, leading to hypoxia-inducible factor (HIF)-mediated transient transcriptional bursts of Epo mRNA. During kidney disease progression, interstitial tissue remodelling blocks Epo expression by an ill-defined mechanism. The lack of Epo production eventually causes renal anaemia that is treated with recombinant Epo or the inhibitors of oxygen sensing HIF prolyl-4-hydroxylases (PHIs) such as roxadustat. However, despite the physiological importance, little is known about the cellular identity of REP cells, and hence the exact mechanism underlying Epo loss and its rescue by roxadustat remains unknown. Using an Epo reporter mouse model, we recently described the transcriptional identity of "Norn" cells, a new interstitial cell type that represents the main, if not sole, source of renal Epo. Importantly, several potential markers and putatively crucial transcription factors were identified in Norn cells. This newly obtained information is currently used by us in spatial recognition of Norn cells in spatial transcriptomic data derived from healthy, hypoxic and diseased mouse models. The detailed characterization of Norn cell biology will be essential to understand and optimize the function of small molecule drugs for the treatment of renal anaemia.

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