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Role of HIF-PH inhibitors in physiological erythropoiesis

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Relatively disordered erythropoietin (EPO) production has been thought to be the main cause of anemia in patients with chronic kidney disease (CKD). However, decreased EPO production capacity as well as suppressed erythropoiesis, shortened red blood cell survival time, and dysregulated iron metabolism might cause anemia in patients with CKD. We demonstrated that hepcidin and tumor necrosis factor (TNF)-α induced iron sequestration in cells and caused dysregulation of iron metabolism in CKD patients (T. Kuragano et al. Am J Nephrol, 2010). In mice with adenine-induced CKD, we found that dysregulation of iron metabolism, rather than EPO deficiency, might cause anemia in CKD (Kimura T et al Int J Hematol. 2019). Furthermore, in an observational study over 3 years, we revealed that dysregulation of iron metabolism was significantly associated with risk of cardiocerebral vascular disease and death in hemodialysis patients (T Kuragano et al. Plos one. 2020). Thus, we hypothesized that physiological erythropoiesis, which attenuates dysregulation of iron metabolism, might reduce adverse events or premature death in CKD patients. A recently developed HIF (hypoxia inducible factor)-PH (prolyl hydroxylase) inhibitor that increases endogenous EPO production and iron bioavailability for erythropoiesis maintains target Hb levels in patients with inflammation or hyporesponsiveness to ESA who are suspected to have dysregulated iron metabolism. In this section, I will discuss the role of HIF-PH inhibitors in the dysregulated iron metabolism in CKD patients.