Erythropoietin-driven dynamic proteome adaptations during erythropoiesis prevent iron overload in the developing embryo.

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Autoren

S. Chakraborty G. Andrieux P. Kastl L. Adlung S. Altamura M. E. Boehm L. E. Schwarzmuller Y. Abdullah M. C. Wagner B. Helm H. J. Grone W. D. Lehmann M. Boerries H. Busch M. U. Muckenthaler M. Schilling **U. Klingmuller**

Abstract

Erythropoietin (Epo) ensures survival and proliferation of colony-forming unit erythroid (CFU-E) progenitor cells and their differentiation to hemoglobin-containing mature erythrocytes. A lack of Epo-induced responses causes embryonic lethality, but mechanisms regulating the dynamic communication of cellular alterations to the organismal level remain unresolved. By time-resolved transcriptomics and proteomics, we show that Epo induces in CFU-E cells a gradual transition from proliferation signature proteins to proteins indicative for differentiation, including heme-synthesis enzymes. In the absence of the Epo receptor (EpoR) in embryos, we observe a lack of hemoglobin in CFU-E cells and massive iron overload of the fetal liver pointing to a miscommunication between liver and placenta. A reduction of iron-sulfur cluster-containing proteins involved in oxidative phosphorylation in these embryos leads to a metabolic shift toward glycolysis. This link connecting erythropoiesis with the regulation of iron homeostasis and metabolic reprogramming suggests that balancing these interactions is crucial for protection from iron intoxication and for survival.