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IRP1 regulates erythropoiesis and systemic iron homeostasis by controlling HIF2α mRNA translation

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HIF2α transcriptionally activates several genes in response to hypoxia. Under normoxic conditions it undergoes oxygen-dependent degradation by the PHD/VHL system. The presence of an iron responsive element (IRE) within the 5′ UTR of HIF2α mRNA suggests a further iron- and oxygen-dependent mechanism for translational regulation of its expression via iron regulatory proteins, IRP1 and IRP2. We show here that the disruption of mouse IRP1, but not IRP2, leads to profound HIF2α-dependent abnormalities in erythropoiesis and systemic iron metabolism. Thus, 4-6 week old IRP1-/- mice exhibit splenomegaly and extramedullary hematopoiesis, which is corrected in older animals. These erythropoietic abnormalities are caused by translational de-repression of HIF2α mRNA and subsequent accumulation of HIF2α, which induces expression of erythropoietin (Epo). Increased levels of circulating Epo lead to reticulocytosis, polycythemia and suppression of hepatic hepcidin mRNA. This in turn promotes hyperferremia and iron depletion in splenic macrophages due to unrestricted expression of ferroportin. Our data demonstrate that IRP1 is the principal regulator of HIF2α mRNA translation in vivo and provide evidence that translational control of HIF2α expression dominates over PHD/VHL-mediated regulation of HIF2α stability in juvenile IRP1-/- mice.

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