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Heme and stress regulation of protein synthesis, gene transcription and metabolism in erythropoiesis and erythroid cell disorders

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Heme-regulated eIF2 α kinase (HRI) is necessary for regulation of protein synthesis under stress conditions in erythroid precursors. HRI controls protein synthesis by phosphorylating the α -subunit of eukaryotic initiation factor 2 (eIF2 α). Phosphorylation of eIF2 impairs the recycling of eIF2 for the purpose of translational initiation and results in the cessation of protein synthesis. Heme serves as the prosthetic group of hemoglobin, the predominant protein in red blood cells (RBCs) and late erythroid precursors. Under conditions of heme, or iron deficiency, HRI is activated and is essential for translational regulation of α and β globins to balance heme and globin synthesis. HRI is also essential for the survival of erythroid progenitors and is responsible for the physiological adaptation that produces hypochromic, microcytic erythrocytes in iron deficiency.

In addition to heme-deficiency, HRI is activated by arsenite-induced oxidative stress, osmotic shock and heat shock. HRI is the only eIF2 α kinase activated by arsenite and is the major eIF2 α kinase responsive to heat shock in erythroid cells. Thus, HRI may protect erythroid cells against stress in general and may play a role in the physiological response to intrinsic disorders of red blood cells. Indeed, HRI deficiency in mice adversely modifies the phenotype: HRI deficiency exacerbates erythropoietic protoporphyria and renders β -thalassemia embryonically lethal. This finding suggests that HRI may be a significant modifier of many red cell disorders in humans. These results also demonstrate

that translational regulation could play a critical role in the clinical manifestation of red cell diseases.

Besides general inhibition of protein synthesis, phosphorylation of eIF2 α by HRI also leads to specific increase of translation of ATF4 mRNA in erythroid precursors and the subsequent induction of gene transcription for the adaptation to stress. HRI is necessary for the adaptive gene expression in chronic iron deficiency. The number of genes with expression affected more than 2-fold increased from 213 in iron deficiency and 73 in HRI deficiency to 3,135 in combined iron and HRI deficiencies. Many of these genes are regulated by Gata1 and Fog1. Gata1 expression in developing erythroid precursors is decreased in iron deficiency, and is decreased further in combined iron and HRI deficiencies. Additionally, Fog1 expression is decreased in combined deficiencies, but not in iron or HRI deficiency alone. These results indicate that HRI confers adaptive gene expression in developing erythroblasts during iron deficiency through maintaining Gata1/Fog1 expression.

Beyond the erythroid lineage, the novel function of HRI in macrophages is discovered recently. HRI protein is expressed in macrophages, albeit at a lower level than in erythroid precursors. HRI deficiency impairs the maturation of macrophages and *Hri*^{-/-} mice exhibit a weaker anti-inflammatory response with reduced cytokine production upon lipopolysaccharide challenge. Furthermore, there is an impairment of erythrophagocytosis by *Hri*^{-/-} macrophages both *in vitro* and *in vivo* under chronic hemolytic anemia, providing evidence for the role of HRI in iron recycling from senescent red blood cells.