Response of EIF2AK1 (HRI) to heme deficiency

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 79

This document contains 1 pathway and 20 reactions (see Table of Contents)
Response of EIF2AK1 (HRI) to heme deficiency

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The kinases of the integrated stress response phosphorylate EIF2S1 (eIF2-alpha) to regulate cellular translation. The kinases comprise PERK (also called EIF2AK3), which responds to unfolded protein in the endoplasmic reticulum; EIF2AK2 (also called PKR), which responds to cytosolic double-stranded RNA; EIF2AK4 (also called GCN2), which responds to amino acid deficiency; and EIF2AK1 (also called heme-regulated inhibitor, HRI, and heme-controlled repressor, HCR), which responds to heme deficiency and cytosolic unfolded protein. Each molecule of EIF2AK1 binds two molecules of heme, one bound near the N-terminus and one bound at the kinase insert (KI) domain that inhibits the kinase activity of EIF2AK1 (inferred from the rabbit homolog in Chefalo et al. 1998, Rafie-Kolpin et al. 2000, inferred from the mouse homolog in Misanova et al. 2006, Hirai et al. 2007, Igarashi et al. 2008). Dissociation of heme from the KI domain activates the kinase activity of EIF2AK1, which autophosphorylates (inferred from the mouse homolog in Bauer et al. 2001, Rafie-Kolpin et al. 2003, Igarashi et al. 2011) and then phosphorylates EIF2S1 (Bhavnani et al. 2018, inferred from the rabbit homologs in Chefalo et al. 1998, Rafie-Kolpin et al. 2000, inferred from the mouse homologs in Lu et al. 2001, Rafie-Kolpin et al. 2003, Igarashi et al. 2011).

Phosphorylated EIFS1 causes a reduction in general cellular translation and thereby coordinates globin synthesis with heme availability during erythropoiesis (inferred from mouse knockout in Han et al. 2001, reviewed in Chen et al. 2014). Translation of mitochondrial and cytosolic ribosomal proteins is most severely reduced, causing a decrease in cellular protein synthesis (inferred from mouse homologs in Zhang et al. 2019). Lack of EIF2AK1 causes accumulation of unfolded globins devoid of heme and consequent anemia in iron-deficient mice (inferred from mouse knockout in Han et al. 2001). Activation of the cytoplasmic unfolded protein response and impaired mitochondrial respiration are also observed in HRI deficiency (inferred from mouse homologs in Zhang et al. 2019).

Phosphorylation of EIFS1 activates translation of certain mRNAs such as ATF4, ATF5, and DDIT3 (CHOP)
that have upstream ORFs (inferred from mouse homologs in Harding et al. 2000). ATF4 in turn activates programs of gene expression that ameliorate effects of the stress to maintain mitochondrial function, redox homeostasis, and erythroid differentiation (inferred from mouse homologs in Zhang et al. 2019). Unresolved stress, however, can eventually lead to apoptosis regulated by DDIT3. EIF2AK1 also represses mTORC1 (mechanistic target of mechanistic target of rapamycin complex 1) signaling via ATF4-mediated induction of GRB10 as a feedback mechanism to attenuate erythropoietin-mTORC1-stimulated ineffective erythropoiesis in iron deficiency anemia (inferred from mouse homologs in Zhang et al. 2018 and Zhang et al. 2019).

EIF2AK1 is also activated by heat shock, arsenite (oxidative stress), and osmotic stress (inferred from mouse homologs in Lu et al. 2001). The mechanisms by which these stresses act on EIF2AK1 are independent of heme but are not yet fully elucidated. Furthermore, EIF2AK1 is involved in the production of human fetal hemoglobin, and EIF2AK1-mediated stress response has emerged as a potential therapeutic target for hemoglobinopathies (reviewed in Chen and Zhang 2019).

In addition to regulation of erythropoiesis, EIF2AK1 shows effects outside of the erythroid lineage, including requirement for the maturation and functions of macrophages (inferred from mouse homologs in Liu et al. 2007), reduction in endoplasmic reticulum stress in hepatocytes, activation of hepatic expression of fibroblast growth factor, and mediation of translation of GRIN2B (GluN2B, a subunit of the NMDA receptor) and BACE1 in the nervous system (reviewed in Burwick and Aktas 2017). HRI-integrated stress response is activated in human cancer cell lines and primary multiple myeloma cells, and has emerged as a molecular target of anticancer agents (reviewed in Burwick and Aktas 2017; reviewed in Chen and Zhang 2019).

**Literature references**


Han, AP., Rafie-Kolpin, M., Chen, JJ. (2003). Autophosphorylation of threonine 485 in the activation loop is essential for attaining eIF2alpha kinase activity of HRI. *Biochemistry, 42*, 6536-44.


**Editions**

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Ferriheme dissociates from p-T-EIF2AK1:2xferriheme dimer

Location: Response of EIF2AK1 (HRI) to heme deficiency

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