Response of EIF2AK1 (HRI) to heme deficiency

Bruhat, A., Chen, JJ., D'Eustachio, P., Gillespie, ME., Matthews, L., May, B., Staschke, KA., Urano, F.

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02/09/2020
**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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

**Literature references**


Reactome database release: 73

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

Stable identifier: R-HSA-9648895

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**


**Editions**

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

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-9648880

**Type:** dissociation

**Compartments:** cytosol

**Inferred from:** Ferriheme dissociates from p-T-Eif2ak1:2xferriheme dimer (Mus musculus), Ferriheme dissociates from p-T-EIF2AK1:2xferriheme dimer (Oryctolagus cuniculus)

One molecule of hemin (ferriheme b chloride) tightly binds the N-terminal domain of EIF2AK1 (HRI) and one molecule of hemin loosely binds the kinase insert (KI) domain of EIF2AK1 (Bhavnani et al. 2018, and inferred from rabbit and mouse homologs). When cytosolic heme concentrations are low, heme dissociates from the KI domain, resulting in activation of the kinase activity of EIF2AK1 (inferred from rabbit and mouse homologs).

**Followed by:** p-T-EIF2AK1:ferriheme dimer autophosphorylates

**Literature references**


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p-T-EIF2AK1:ferriheme dimer autophosphorylates

Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9648883

Type: transition

Compartments: cytosol

Inferred from: p-T-Eif2ak1:ferriheme dimer autophosphorylates (Mus musculus)

During heme deficiency, EIF2AK1 (HRI) autophosphorylates, notably on threonine residues in the activation loop (inferred from the mouse homolog). EIF2AK1 also has many phosphorylated residues prior to activation in response to heme deficiency (inferred from the mouse homolog). Autophosphorylation of threonine-488 (threonine-485 in the mouse homolog) is essential for kinase activity of EIF2AK1 acting on EIF2S1 (eIF2-alpha) in response to heme deficiency and oxidative stress by arsenite (inferred from the mouse homolog).

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

Followed by: p-T,T486,T488-EIF2AK1 phosphorylates EIF2S1 (eIF2-alpha)

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**p-T,T486,T488(EIF2AK1) phosphorylates EIF2S1 (eIF2-alpha)**

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-9648888

**Type:** transition

**Compartments:** cytosol

**Inferred from:** p-T-Eif2ak1 phosphorylates Eif2s1 (eIF2-alpha) (Mus musculus), p-T(EIF2AK1) phosphorylates EIF2S1 (eIF2-alpha) (Oryctolagus cuniculus)

Phosphorylated EIF2AK1 phosphorylates EIF2S1 (eIF2-alpha) on serine-52 (homologous to serine-51 of the rabbit homologue) (inferred from rabbit and mouse homologs). Phosphothreonine 488 (homologous to phosphothreonine-485 of the mouse homolog) of EIF2AK1 is required for kinase activity of EIF2AK1 acting on EIF2S1 (inferred from mouse homologs). Phosphorylated EIF2S1 in the EIF2alpha complex causes the complex to bind more tightly to the GTP exchange factor EIF2B, which inhibits exchange of GDP for GTP, and hence inhibits recycling of EIF2alpha to the active (GTP-bound) state. The result is a general decrease of translation in the cell, with a few mRNAs, such as ATF4, that possess upstream ORFs exhibiting increased translation. The decrease in translation of globin mRNAs in particular helps to maintain a 1:1 balance of heme and globin in erythropoiesis during heme deficiency.

**Preceded by:** p-T(EIF2AK1):ferriheme dimer autophosphorylates

**Followed by:** Translation of PPP1R15A, Translation of ATF5, Translation of DDIT3, Translation of ATF4

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**Translation of ATF4**

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-381128

**Type:** omitted

**Compartments:** cytosol, nucleoplasm

**Inferred from:** Translation of Atf4 (Mus musculus)

ATF4 mRNA is translated to yield ATF4 protein, which then transits to the nucleus (Blais et al. 2004, Ross et al. 2018). The mRNA of ATF4 contains 2 upstream ORFs (uORFs) (Ross et al. 2018 and inferred from the mouse homolog). The second uORF overlaps the ORF encoding ATF4 and thus prevents translation of ATF4. When EIF2S1 (eIF2-alpha) is phosphorylated, translation initiation is decreased overall, translation of the uORFs is suppressed, and translation of the ORF encoding ATF4 is increased (Blais et al. 2004, Ross et al. 2018, and inferred from mouse homologs).

**Preceded by:** p-T,T486,T488(EIF2AK1 phosphorylates EIF2S1 (eIF2-alpha))

**Followed by:** Expression of GRB10, ATF4, CEBPB, and ATF3 bind the CHAC1 promoter, ATF4 binds the DDIT3 promoter, ATF4 binds the PPP1R15A (GADD34) promoter, ATF4 and a CEBP protein bind the ATF5 promoter, Expression of ASNS (Asparagine Synthetase), ATF4 and CEBPB,CEBPB bind the ASNS gene, ATF4 and a CEBP protein bind the TRIB3 promoter

**Literature references**


Ross, JA., Bressler, KR., Thakor, N. (2018). Eukaryotic Initiation Factor 5B (eIF5B) Cooperates with eIF1A and eIF5 to Facilitate uORF2-Mediated Repression of ATF4 Translation. *Int J Mol Sci, 19*.
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Translation of DDIT3

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-9650722

**Type:** omitted

**Compartments:** cytosol, nucleoplasm

**Inferred from:** Translation of Ddit3 (Mus musculus)

The DDIT3 mRNA is translated to yield DDIT3 (CHOP) protein (Jousse et al. 2001, and inferred from the mouse homolog), which is then imported into the nucleus. The mRNA of DDIT3 contains an upstream ORF (uORF) which has a start codon in an unfavorable context (Jousse et al. 2001, and inferred from the mouse homolog), resulting in low expression of the downstream DDIT3 coding region. When EIF2S1 (eIF2-alpha) is phosphorylated in response to stress, translation of the uORF is suppressed and translation of DDIT3 is increased (inferred from the mouse homolog).

**Preceded by:** p-T,T486,T488-EIF2AK1 phosphorylates EIF2S1 (eIF2-alpha)

**Followed by:** ATF4 and a CEBP protein bind the ATF5 promoter

**Literature references**


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https://reactome.org
The PPP1R15A (GADD34) mRNA is translated to yield PPP1R15A protein which then associates with the cytosolic faces of the endoplasmic reticulum membrane and the mitochondrial outer membrane (inferred from the mouse homolog). The PPP1R15A mRNA contains 2 upstream ORFs (uORFs) that limit translation of the downstream PPP1R15A coding region (inferred from the mouse homolog). During certain stresses, EIF2S1 (eIF2-alpha) is phosphorylated, causing a reduction in initiation at the uORFs and increased translation of the PPP1R15A coding region (inferred from mouse homologs).

**Preceded by:** p-T,T486,T488-EIF2AK1 phosphorylates EIF2S1 (eIF2-alpha)

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Translation of ATF5

Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9653745

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: Translation of Atf5 (Mus musculus)

The ATF5 mRNA is translated to yield ATF5 protein (Watatani et al. 2008, and inferred from the mouse homolog) which is then imported into the nucleus. The ATF5 mRNA contains 2 upstream ORFs (uORFs) which inhibit translation of the downstream ATF5 coding region (Watatani et al. 2008). Translation of uORF2 also targets the mRNA for nonsense-mediated decay (Hatano et al. 2013). During stresses such as amino acid limitation and arsenite-induced oxidative stress, EIF2S1 (eIF2-alpha) is phosphorylated, decreasing translation initiation at the uORFs and increasing translation of ATF5 (Watatani et al. 2008, and inferred from the mouse homolog).

Preceded by: p-T,T486,T488-EIF2AK1 phosphorylates EIF2S1 (eIF2-alpha), Transcription of ATF5

Literature references


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Chen, JJ.
ATF4 binds the DDIT3 promoter

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-9655086

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Atf4 binds the Ddit3 promoter (Rattus norvegicus)

ATF4 binds a composite CEBP-ATF element in the promoter of the DDIT3 (CHOP, GADD153) gene in response to oxidative stress caused by arsenite (inferred from rat homologs) and amino acid deficiency (Bruhat et al. 2000, Averous et al. 2004, Bruhat et al. 2007, Cherasse et al. 2007). Both arsenite and heme deficiency regulate DDIT3 via EIF2AK1 (HRI) therefore heme deficiency is inferred to produce similar regulation of DDIT3 by ATF4. (Amino acid deficiency regulates DDIT3 via EIF2AK4.) The CEBP binding partner of ATF4 at the CEBP-ATF4 site is unknown. Phosphorylated ATF2 together with ATF4 activate DDIT3 in response to amino acid deficiency (Bruhat et al. 2000, Averous et al. 2004, Bruhat et al. 2007), however the role of ATF2 in heme deficiency is unknown.

**Preceded by:** Translation of ATF4

**Followed by:** Transcription of DDIT3 (CHOP, GADD153) in response to heme deficiency

**Literature references**


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Transcription of DDIT3 (CHOP, GADD153) in response to heme deficiency

Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9655071

Type: uncertain

Compartments: nucleoplasm

Inferred from: Expression of Ddit3 (Rattus norvegicus), Expression of DDIT3 (Cricetulus griseus), Transcription of Ddit3 (Mus musculus)

The DDIT3 gene is transcribed to yield mRNA. Transcription of DDIT3 is activated by ATF4 in response to heme deficiency, which activates ATF4 expression via the integrated stress kinase EIF2AK1 (HRI) (inferred from the mouse, rat, and hamster homologs).

Preceded by: ATF4 binds the DDIT3 promoter

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ATF4 and a CEBP protein bind the ATF5 promoter

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-9653742

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Atf4 and a Cebp protein bind the Atf5 gene (Mus musculus)

ATF4 and a member of the CEBP family of transcription factors (CEBPB, CEBPG, or DDIT3, also known as CHOP) bind as a heterodimer to a composite CEBP-ATF element in the promoter of the ATF5 gene (inferred from mouse homologs).

**Preceded by:** Translation of ATF4, Translation of DDIT3

**Followed by:** Transcription of ATF5

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Transcription of ATF5

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-9653724

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Transcription of Atf5 (Mus musculus)

The ATF5 gene is transcribed to yield mRNA (Watatani et al. 2007, Wei et al. 2010, and inferred from the mouse homolog). Transcription of ATF5 is activated by a heterodimer of ATF4 and a CEBP factor in response to proteasome inhibition, heme deficiency, endoplasmic reticulum stress, and amino acid deficiency (inferred from mouse homologs).

**Preceded by:** ATF4 and a CEBP protein bind the ATF5 promoter

**Followed by:** Translation of ATF5

**Literature references**


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ATF4, CEBPB, and ATF3 bind the CHAC1 promoter

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-9653893

**Type:** binding

**Compartments:** nucleoplasm

ATF4 binds the ATF/CRE element and the ACM elements in the promoter of the CHAC1 gene. ATF3 and CEBPB bind the ATF/CRE element (Crawford et al. 2015). The stoichiometry and interaction between the transcription factors at the promoter is unknown.

**Preceded by:** Translation of ATF4

**Followed by:** Expression of CHAC1

**Literature references**


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The CHAC1 gene is transcribed to yield mRNA and the mRNA is translated to yield CHAC1 protein (Crawford et al. 2015, and inferred from the mouse homolog). The transcription factors ATF4, ATF3, and CEBPB (full length) bind ATF/CRE and ACM elements in the CHAC1 promoter and activate transcription of CHAC1 in response to endoplasmic reticulum stress (Crawford et al. 2015). Expression of CHAC1 is also activated by heme deficiency (inferred from the mouse homolog). TRIB3 binds the CHAC1 promoter and represses transcription of CHAC1 which leads to decreased cell death during oxidative stress (inferred from mouse homologs).

**Preceded by:** ATF4, CEBPB, and ATF3 bind the CHAC1 promoter

**Literature references**

ATF4 and a CEBP protein bind the TRIB3 promoter

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-9635927

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Atf4 and Cebpg bind the Trib3 gene (Mus musculus)

ATF4 binds composite CEBP-ATF elements located in three 33-bp tandem repeats in the promoter of the TRIB3 (TRB3, NIPK) gene (Ohoka et al. 2005, Ord and Ord 2005). ATF4 cooperates with DDIT3 to activate TRIB3 promoter activity (Ohoka et al. 2005). ATF4 also appears to bind as a heterodimer with CEBPB or CEBPG, which is required for full response to amino acid deficiency (inferred from mouse homologs).

**Preceded by:** Translation of ATF4

**Followed by:** Expression of TRIB3 in response to stress

**Literature references**


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Expression of TRIB3 in response to stress

Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9635912

Type: omitted

Compartments: nucleoplasm

Inferred from: Expression of Trib3 (Mus musculus)


Preceded by: ATF4 and a CEBP protein bind the TRIB3 promoter

Literature references


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ATF4 binds the PPP1R15A (GADD34) promoter

Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9654752

Type: binding

Compartments: nucleoplasm

Inferred from: Atf4 binds the Ppp1r15a (Gadd34) promoter (Mus musculus)

ATF4 binds a conserved site in the promoter of the PPP1R15A (GADD34) gene in response to endoplasmic reticulum stress and traumatic brain injury (inferred from mouse homologs). ATF4 forms homodimers and heterodimers with other bZip proteins, however the binding partner of ATF4 at the PPP1R15A promoter is unknown. EIF2AK1 activates transcription of PPP1R15A via ATF4 in response to heme deficiency (inferred from mouse homologs).

Preceded by: Translation of ATF4

Followed by: Transcription of PPP1R15A

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**Transcription of PPP1R15A**

**Location:** Response of EIF2AK1 (HRI) to heme deficiency

**Stable identifier:** R-HSA-9654774

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Transcription of Ppp1r15a (Mus musculus)

The PPP1R15A (GADD34) gene is transcribed to yield mRNA (Hollander et al. 1997, Hollander et al. 2001, Oh-Hashi et al. 2001, and inferred from the mouse homolog). Transcription of PPP1R15A is activated by ATF4, which binds the PPP1R15A promoter in response to certain stresses such as endoplasmic reticulum stress, traumatic brain injury, and heme deficiency (inferred from mouse homologs).

**Preceded by:** ATF4 binds the PPP1R15A (GADD34) promoter

**Literature references**


**Editions**

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ATF4 and CEBPB, CEBPG bind the ASNS gene

Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9635915

Type: binding

Compartments: nucleoplasm

Inferred from: Atf4 and Cebpg bind the Asns gene (Mus musculus)

ATF4 and CEBPB or CEBPG bind a CEBP-ATF regulatory element (CARE) in the promoter of the ASNS gene (Siu et al 2001, Chen et al. 2004, inferred from mouse homologs). ATF4 binds rapidly during the first 2 hours after amino acid deprivation (Chen et al. 2004). ATF3 and CEBPB accumulate on the ASNS promoter more slowly and appear to correlate with decreasing transcription of ASNS (Chen et al. 2004). EIF2AK1 acts via ATF4 to activate transcription of ASNS in response to heme deficiency (inferred from mouse homologs).

Preceded by: Translation of ATF4

Followed by: Expression of ASNS (Asparagine Synthetase)

Literature references


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The Asparagine Synthetase (ASNS) gene is transcribed to yield mRNA and the mRNA is translated to yield protein (Chen et al. 2004, Lee et al. 2008, Gjymishka et al. 2009, Sikalidis et al. 2011, Balasubramanian et al. 2013, inferred from the mouse homolog). Transcription of ASNS is activated by the unfolded protein response (Gjymishka et al. 2009), amino acid deficiency (Chen et al. 2004, Lee et al. 2008, Sikalidis et al. 2011, Balasubramanian et al. 2013, inferred from the mouse homolog), and heme deficiency (inferred from the mouse homolog).

**Preceded by:** Translation of ATF4, ATF4 and CEBPB, CEBPG bind the ASNS gene

**Literature references**


## Editions

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Expression of GRB10

Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9654792

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Grb10 (Mus musculus)

The GRB10 gene is transcribed to yield mRNA and the mRNA is translated to yield GRB10 protein (inferred from the mouse homolog). Expression of GRB10 is activated by ATF4 in response to endoplasmic reticulum stress and heme deficiency (inferred from the mouse homolog).

Preceded by: Translation of ATF4

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