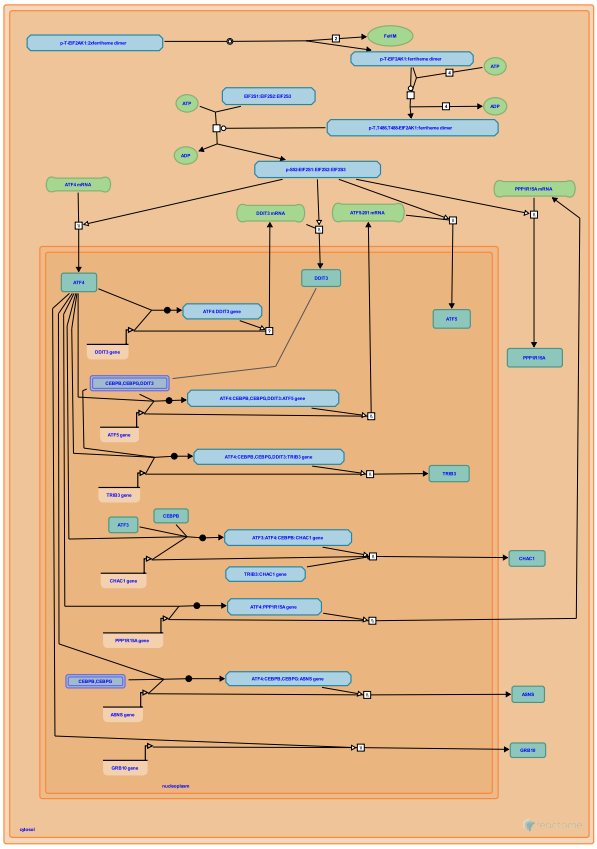
Response of EIF2AK1 (HRI) to heme deficiency



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

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

20/04/2024

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

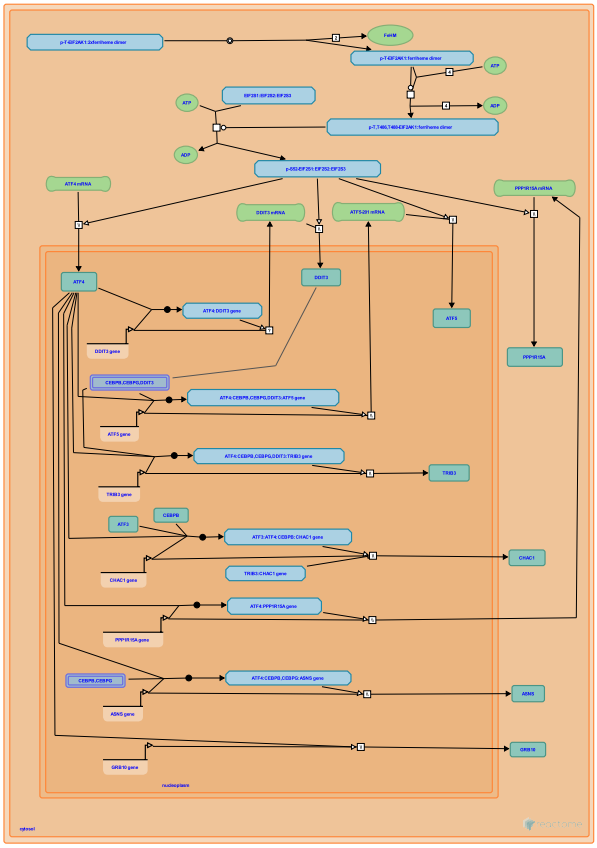
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

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

Kaufman, RJ., Macias-Garcia, A., Paltrinieri, E., Zhang, S., Velazquez, J., Chen, JJ. (2018). HRI coordinates translation by eIF2αP and mTORC1 to mitigate ineffective erythropoiesis in mice during iron deficiency. *Blood, 131*, 450-461. ↗

Chen, JJ. (2014). Translational control by heme-regulated eIF2α kinase during erythropoiesis. *Curr. Opin. Hematol., 21*, 172-8. ↗

Rafie-Kolpin, M., Lu, L., Chen, JJ., Bauer, BN., Han, A. (2001). Multiple autophosphorylation is essential for the formation of the active and stable homodimer of heme-regulated eIF2alpha kinase. *Biochemistry, 40*, 11543-51. ↗

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. ↗

Han, AP., Lu, L., Chen, JJ. (2001). Translation initiation control by heme-regulated eukaryotic initiation factor 2alpha kinase in erythroid cells under cytoplasmic stresses. *Mol. Cell. Biol., 21*, 7971-80. ↗

Editions

2019-06-10	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

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

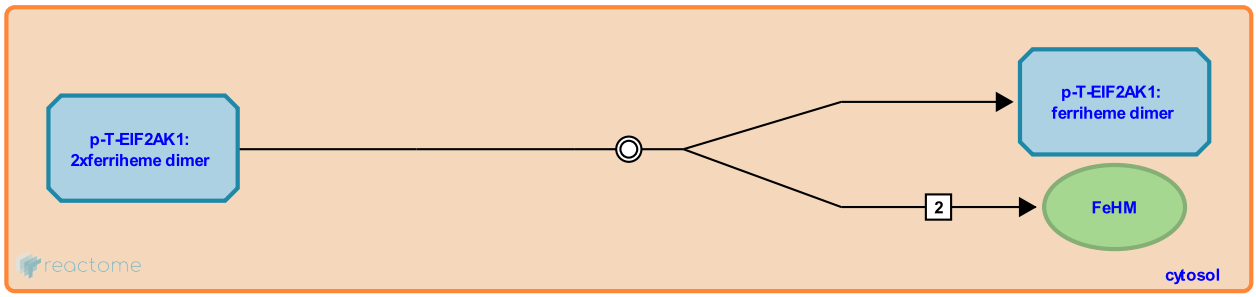
Location: Response of EIF2AK1 (HRI) to heme deficiency

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

Pal, J., Bhavnani, V., Panigrahi, P., Kaviraj, S., Yapara, S., Suresh, CG. (2018). Elucidation of molecular mechanism of stability of the heme-regulated eIF2α kinase upon binding of its ligand, hemin in its catalytic kinase domain. *J. Biomol. Struct. Dyn., 36*, 2845-2861. ↗

Editions

2019-06-10	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

p-T-EIF2AK1:ferriheme dimer autophosphorylates ↗

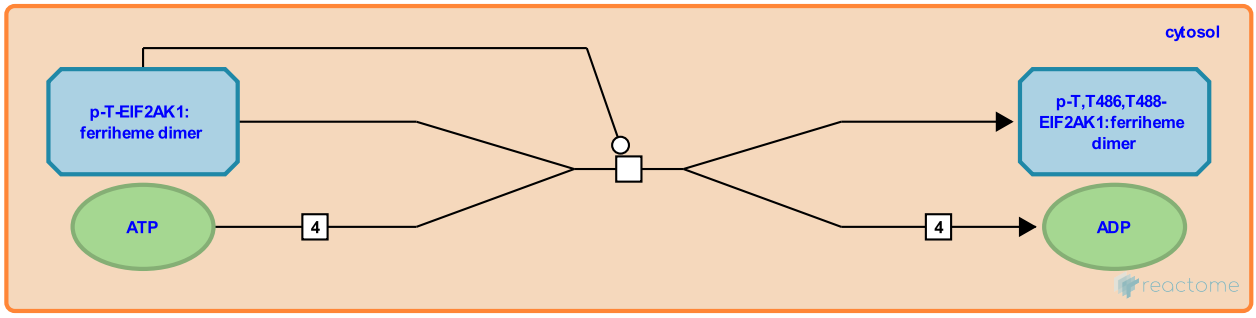
Location: Response of EIF2AK1 (HRI) to heme deficiency

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)

Editions

2019-06-10	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

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

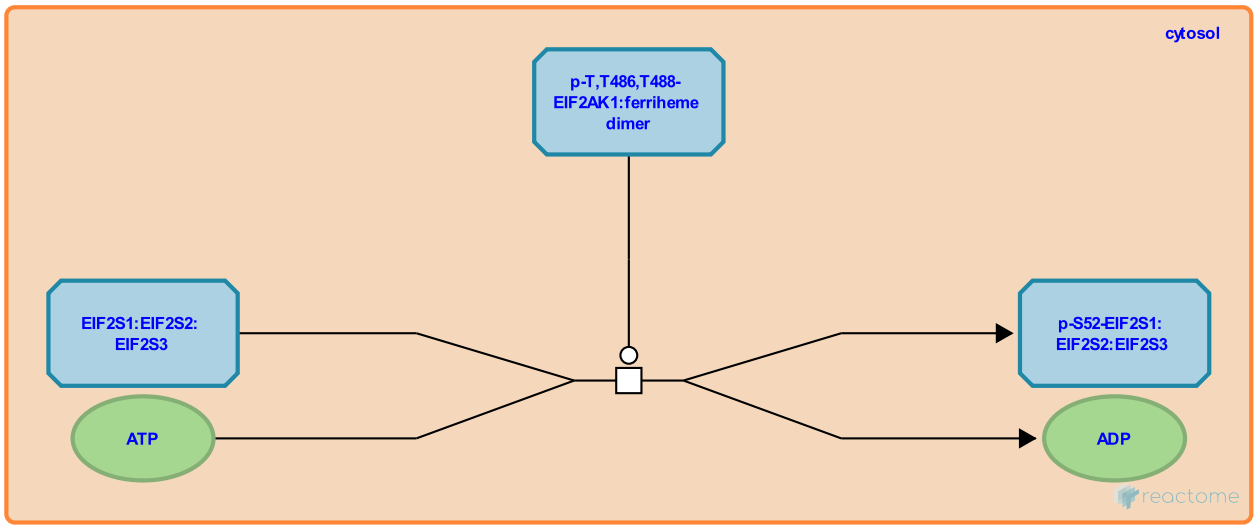
Location: Response of EIF2AK1 (HRI) to heme deficiency

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

Editions

2019-06-10	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

Translation of ATF4 ↗

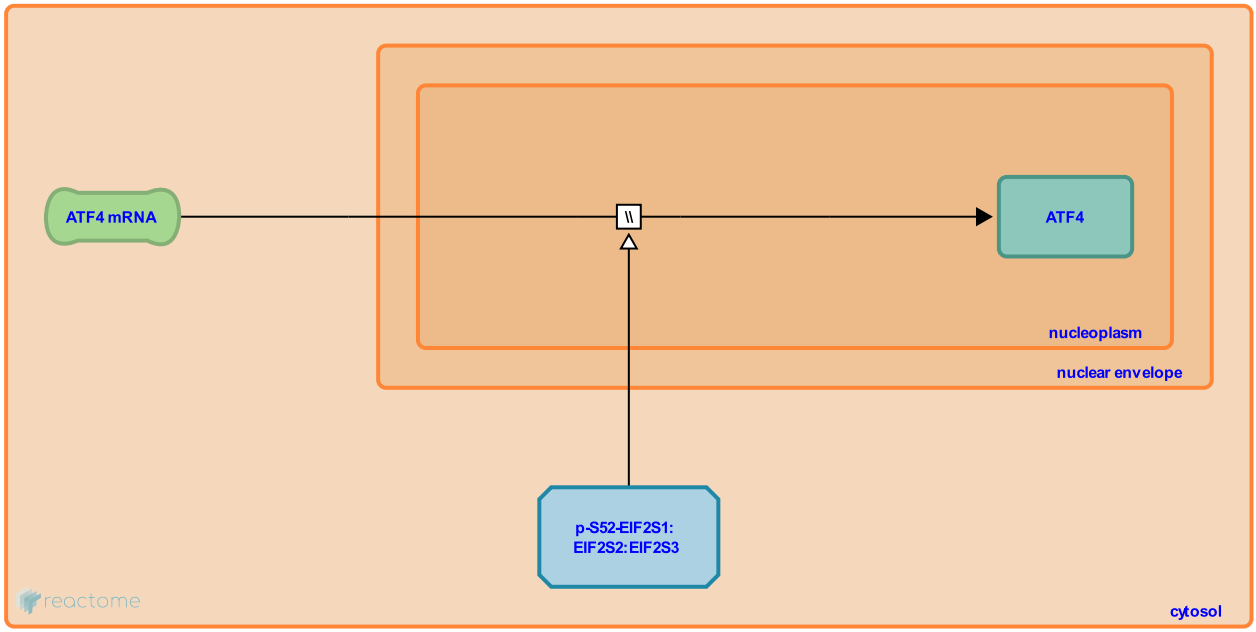
Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-381128

Type: omitted

Compartments: nucleoplasm, cytosol

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,CEBPG bind the ASNS gene, ATF4 and a CEBP protein bind the TRIB3 promoter

Literature references

Ron, D., Blais, JD., Wouters, BG., Harding, HP., Bi, M., Koumenis, C. et al. (2004). Activating transcription factor 4 is translationally regulated by hypoxic stress. *Mol Cell Biol, 24*, 7469-82. ↗

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

Editions

2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.
2009-06-02	Authored, Edited	May, B.
2010-04-30	Reviewed	Urano, F.
2019-09-15	Reviewed	Bruhat, A.
2019-10-22	Reviewed	Chen, JJ.
2019-11-20	Reviewed	Staschke, KA.

Translation of DDIT3 ↗

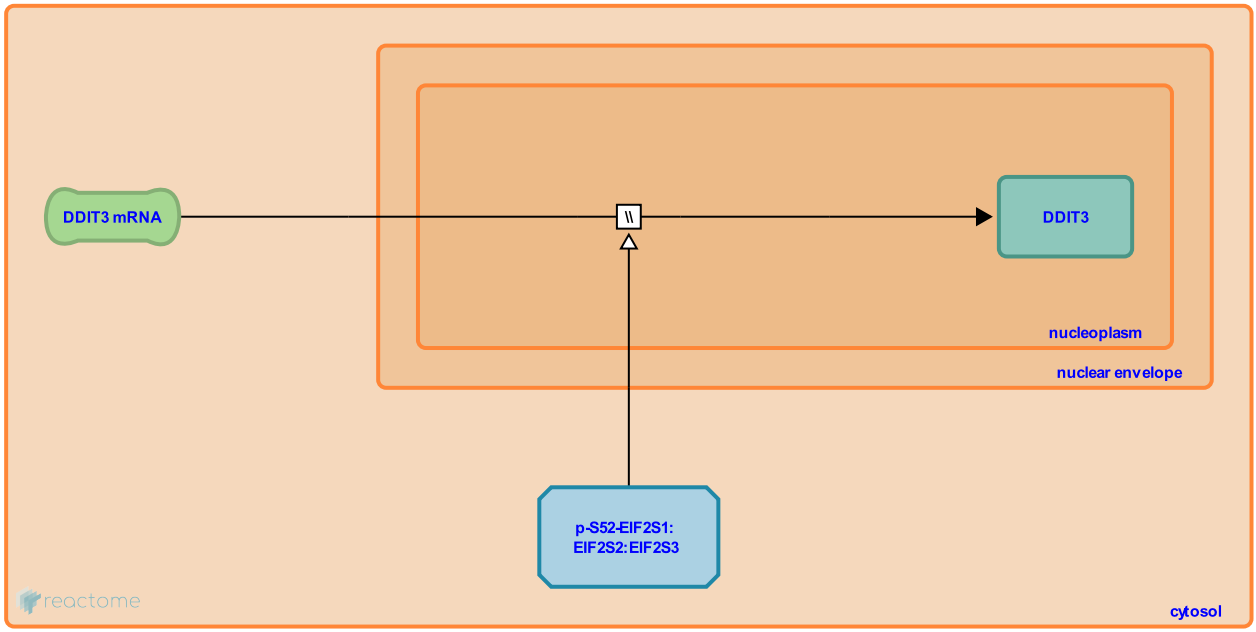
Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9650722

Type: omitted

Compartments: nucleoplasm, cytosol

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

Ferrara, M., Carraro, V., Ron, D., Urano, F., Bruhat, A., Fafournoux, P. et al. (2001). Inhibition of CHOP translation by a peptide encoded by an open reading frame localized in the chop 5'UTR. *Nucleic Acids Res., 29*, 4341-51. ↗

Editions

2019-06-15	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-10-22	Reviewed	Chen, JJ.
2019-11-20	Reviewed	Staschke, KA.

Translation of PPP1R15A ↗

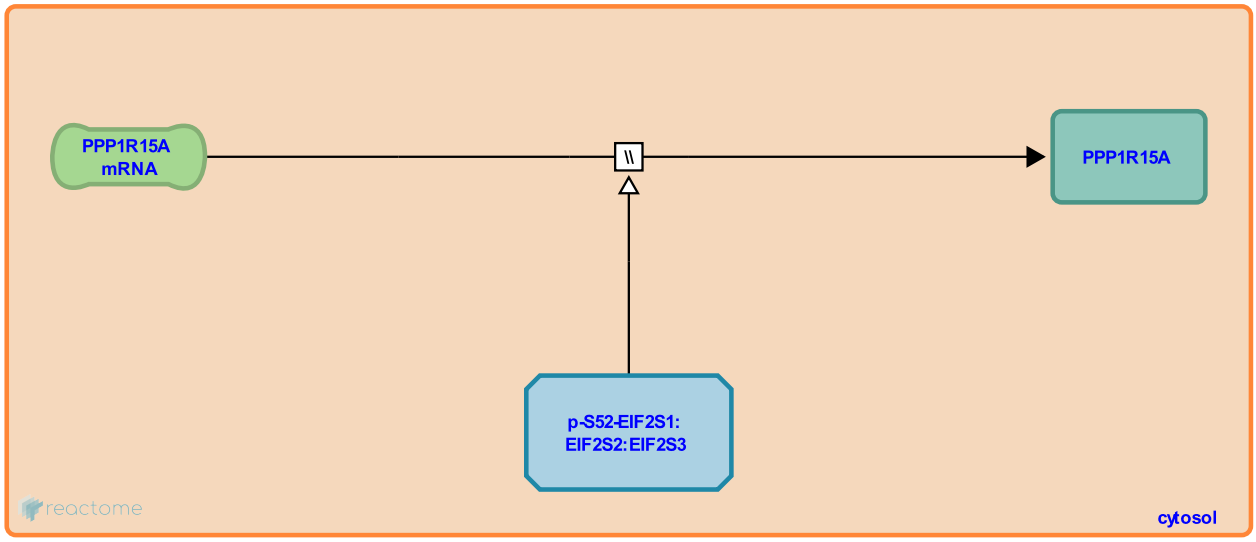
Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9650710

Type: omitted

Compartments: cytosol

Inferred from: Translation of Ppp1r15a (Mus musculus)



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)

Editions

2019-06-15	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

Translation of ATF5

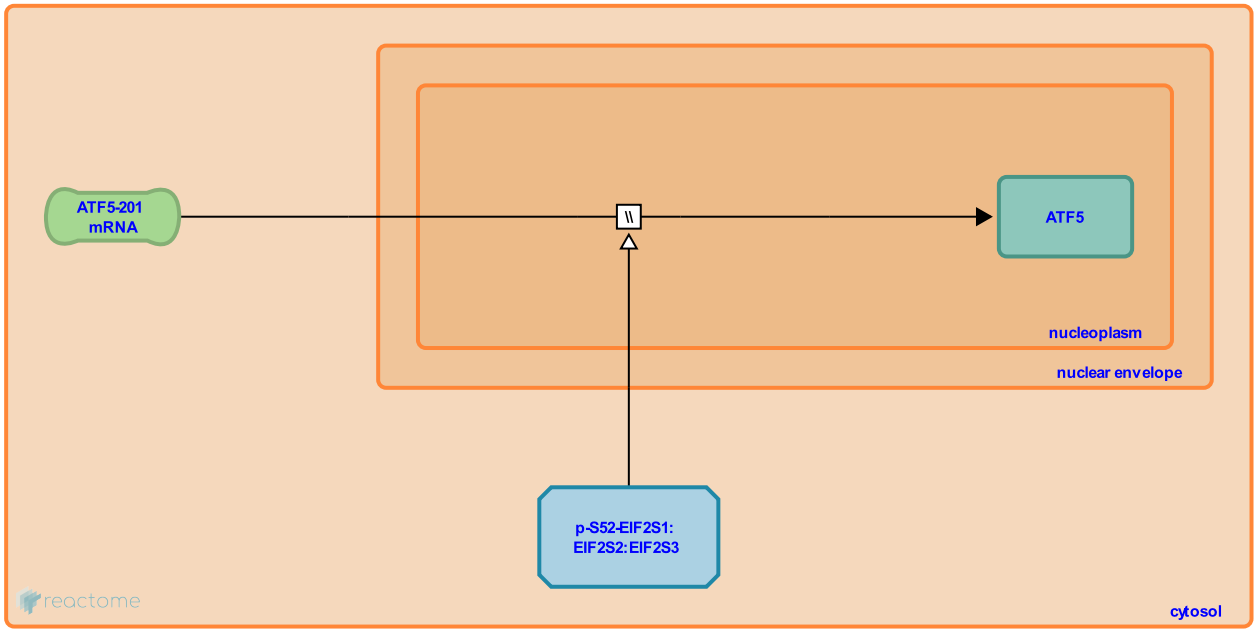
Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9653745

Type: omitted

Compartments: nucleoplasm, cytosol

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

Literature references

Yamazaki, T., Takahashi, S., Takeda, H., Hatano, M., Umemura, M., Takahashi, Y. et al. (2013). The 5'-untranslated region regulates ATF5 mRNA stability via nonsense-mediated mRNA decay in response to environmental stress. *FEBS J., 280*, 4693-707.

Takahashi, S., Takeda, H., Ichikawa, K., Nakanishi, N., Hirose, H., Takahashi, Y. et al. (2008). Stress-induced translation of ATF5 mRNA is regulated by the 5'-untranslated region. *J. Biol. Chem., 283*, 2543-53.

Editions

2019-07-14	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

ATF4 binds the DDIT3 promoter ↗

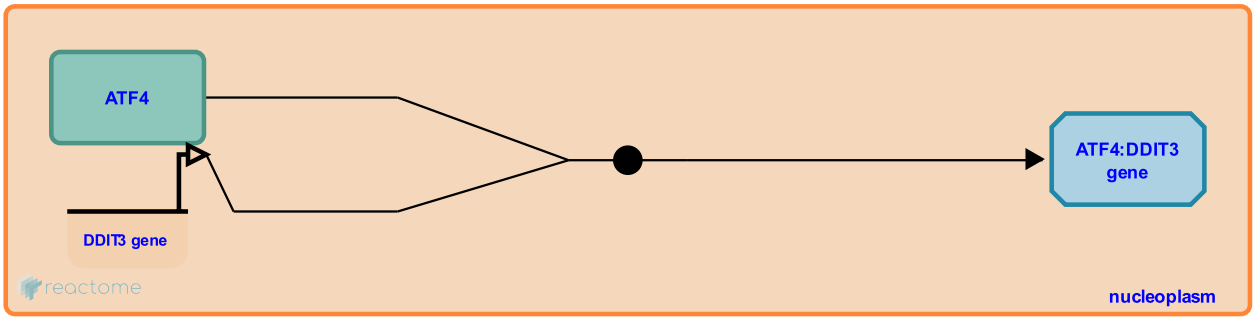
Location: Response of EIF2AK1 (HRI) to heme deficiency

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

Bruhat, A., Cherasse, Y., Fafournoux, P., Jousse, C., Jones, N., Maurin, AC. et al. (2007). ATF2 is required for amino acid-regulated transcription by orchestrating specific histone acetylation. *Nucleic Acids Res., 35*, 1312-21. ↗

Jousse, C., Carraro, V., Fafournoux, P., Averous, J., Thiel, G., Bruhat, A. (2004). Induction of CHOP expression by amino acid limitation requires both ATF4 expression and ATF2 phosphorylation. *J Biol Chem, 279*, 5288-97. ↗

Bruhat, A., Cherasse, Y., Fafournoux, P., Chambon, C., Carraro, V., Chaveroux, C. et al. (2007). The p300/CBP-associated factor (PCAF) is a cofactor of ATF4 for amino acid-regulated transcription of CHOP. *Nucleic Acids Res., 35*, 5954-65. ↗

Ferrara, M., Carraro, V., Bruhat, A., Fafournoux, P., Jousse, C., Reimold, AM. (2000). Amino acids control mammalian gene transcription: activating transcription factor 2 is essential for the amino acid responsiveness of the CHOP promoter. *Mol. Cell. Biol., 20*, 7192-204. ↗

Editions

2019-07-23	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

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

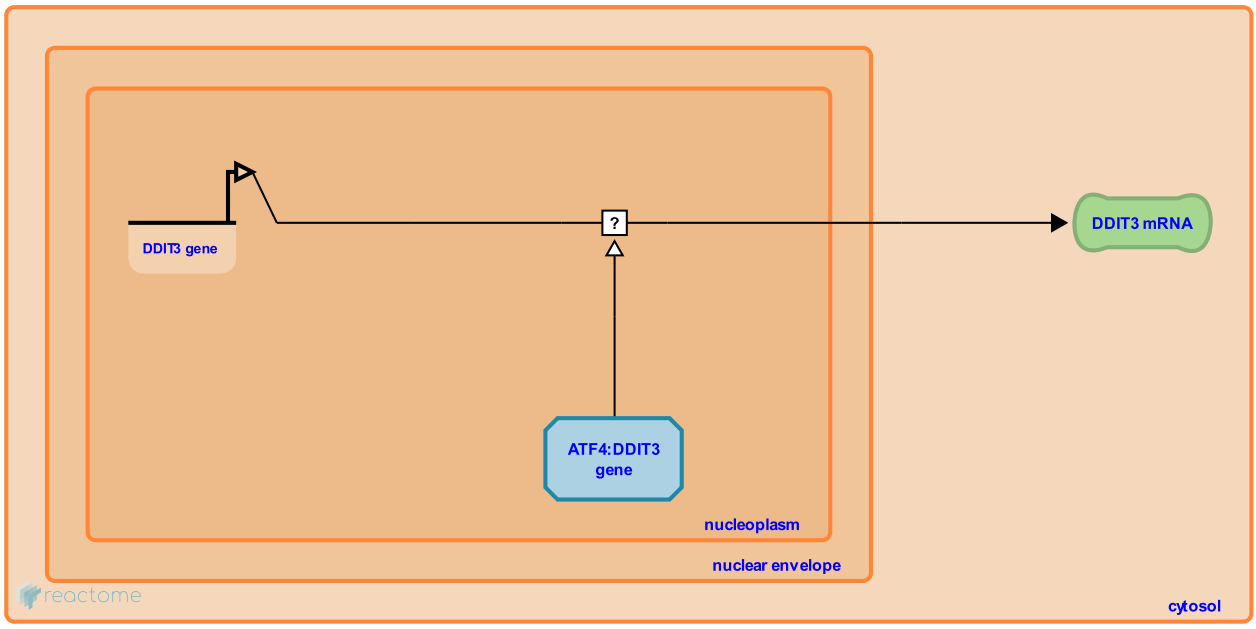
Location: Response of EIF2AK1 (HRI) to heme deficiency

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). In mouse, expression of Ddit3 is activated by DNA damage and by NF-Y and Atf4 in response to endoplasmic reticulum stress.

Preceded by: ATF4 binds the DDIT3 promoter

Editions

2019-07-23	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

ATF4 and a CEBP protein bind the ATF5 promoter ↗

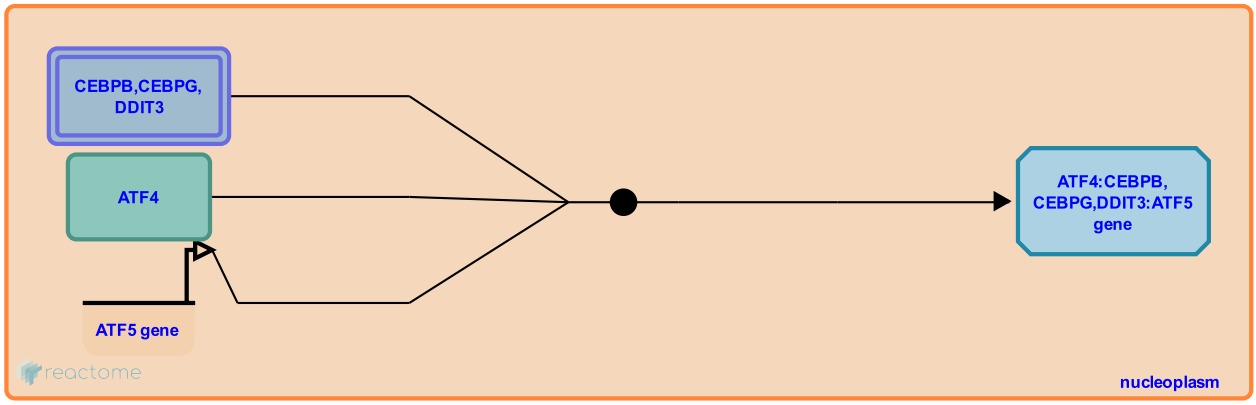
Location: Response of EIF2AK1 (HRI) to heme deficiency

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

Editions

2019-07-14	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

Transcription of ATF5

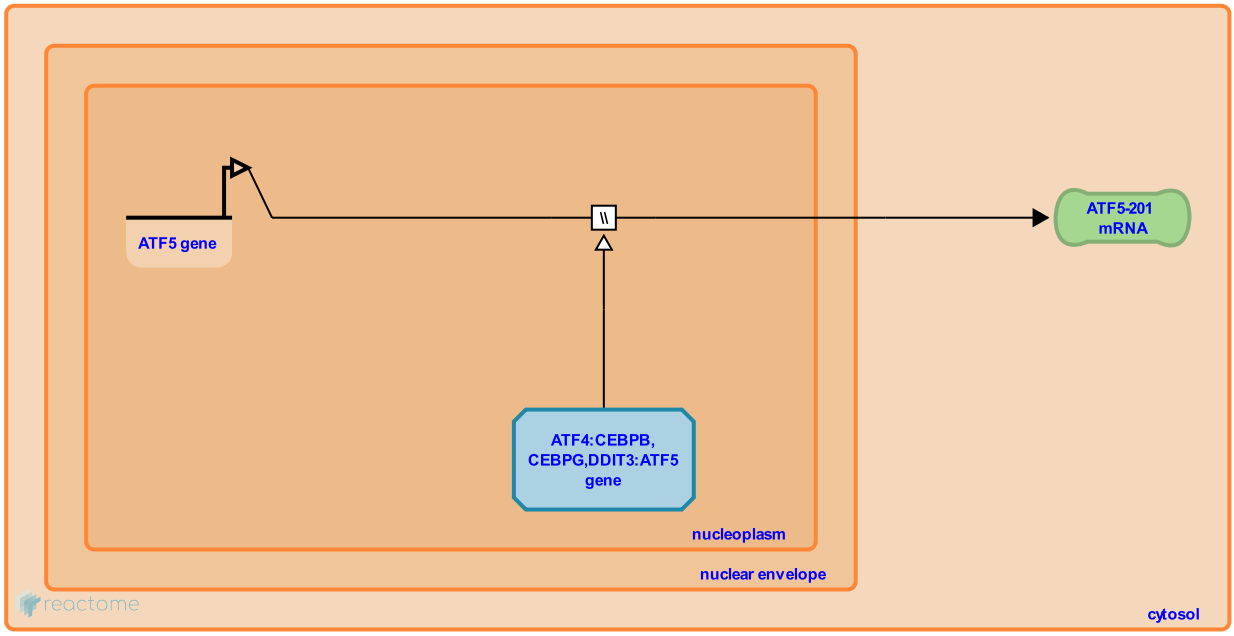
Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9653724

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Transcription of Atf5 (Mus musculus)



ATF4 and DDIT3 (CHOP) bind an CARE element in the promoter of the ATF5 gene and enhance transcription (inferred from mouse homologs).
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

Wei, Y., Ge, Y., Jiang, J., Wu, G., Liu, D., Chen, H. et al. (2010). Identification and characterization of the promoter of human ATF5 gene. *J. Biochem., 148*, 171-8.

Akiyama, I., Takahashi, S., Shimizu, YI., Hirose, H., Takahashi, Y., Kimura, N. et al. (2007). Amino acid limitation induces expression of ATF5 mRNA at the post-transcriptional level. *Life Sci., 80*, 879-85.

Editions

2019-07-14	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

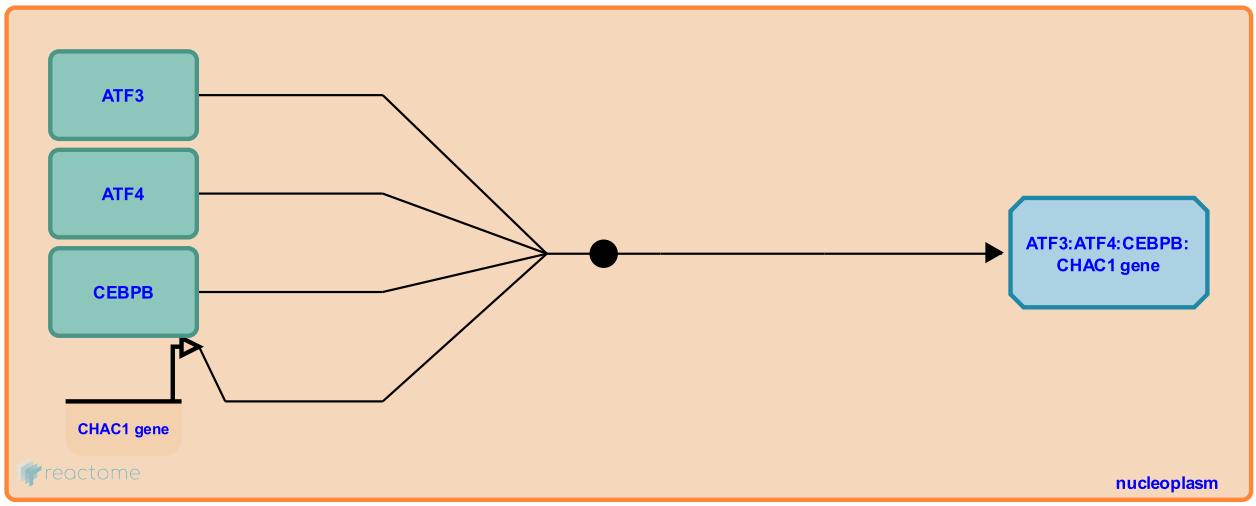
ATF4, CEBPB, and ATF3 bind the CHAC1 promoter ↗

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

Mungrue, IN., Kilberg, MS., Shan, J., Sylvester, CF., Higdon, AN., Crawford, RR. et al. (2015). Human CHAC1 Protein Degrades Glutathione, and mRNA Induction Is Regulated by the Transcription Factors ATF4 and ATF3 and a Bipartite ATF/CRE Regulatory Element. *J. Biol. Chem., 290*, 15878-91. ↗

Editions

2019-07-15	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

Expression of CHAC1 ↗

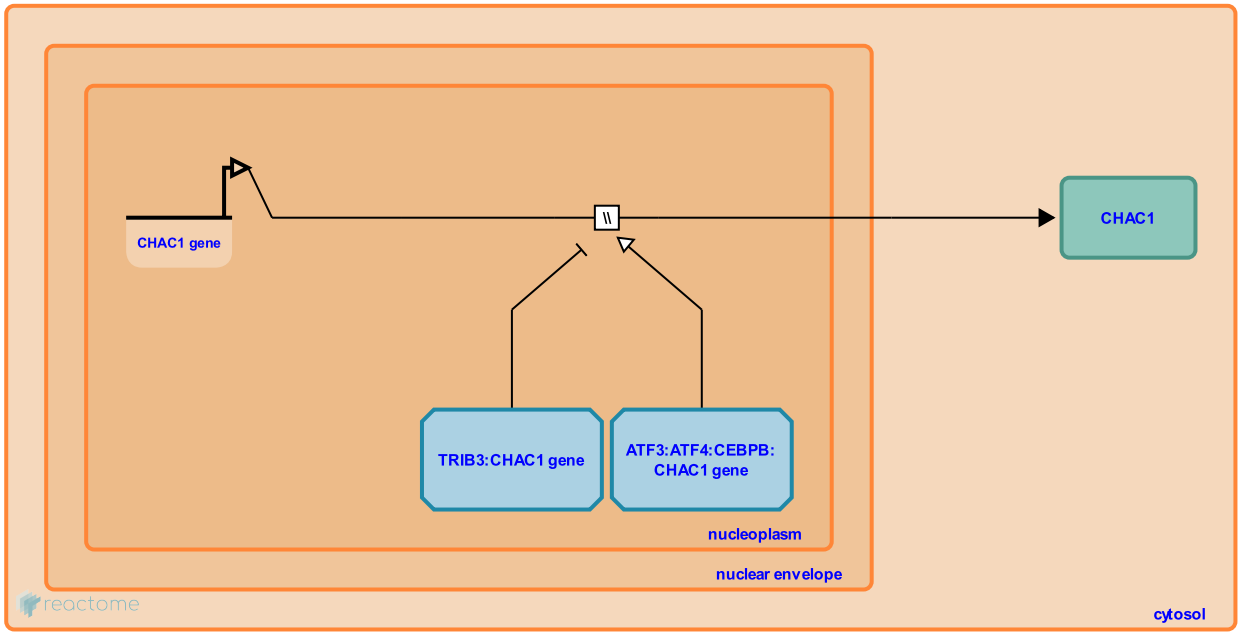
Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9653894

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Chac1 (Mus musculus)



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 via EIF2AK1 (HRI) and ATF4 (inferred from the mouse homologs). 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

Mungrue, IN., Kilberg, MS., Shan, J., Sylvester, CF., Higdon, AN., Crawford, RR. et al. (2015). Human CHAC1 Protein Degrades Glutathione, and mRNA Induction Is Regulated by the Transcription Factors ATF4 and ATF3 and a Bipartite ATF/CRE Regulatory Element. *J. Biol. Chem., 290*, 15878-91. ↗

Editions

2019-07-15	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

ATF4 and a CEBP protein bind the TRIB3 promoter ↗

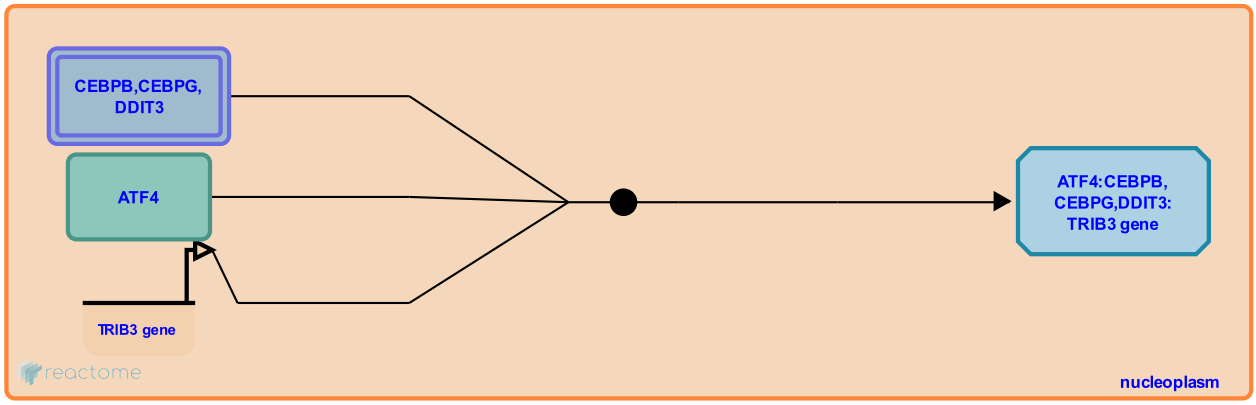
Location: Response of EIF2AK1 (HRI) to heme deficiency

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

Ord, T., Ord, D. (2005). Characterization of human NIPK (TRB3, SKIP3) gene activation in stressful conditions. *Biochem. Biophys. Res. Commun., 330*, 210-8. ↗

Yoshii, S., Hattori, T., Onozaki, K., Ohoka, N., Hayashi, H. (2005). TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death. *EMBO J., 24*, 1243-55. ↗

Editions

2019-02-09	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-10-22	Reviewed	Chen, JJ.
2019-11-20	Reviewed	Staschke, KA.

Expression of TRIB3 in response to stress ↗

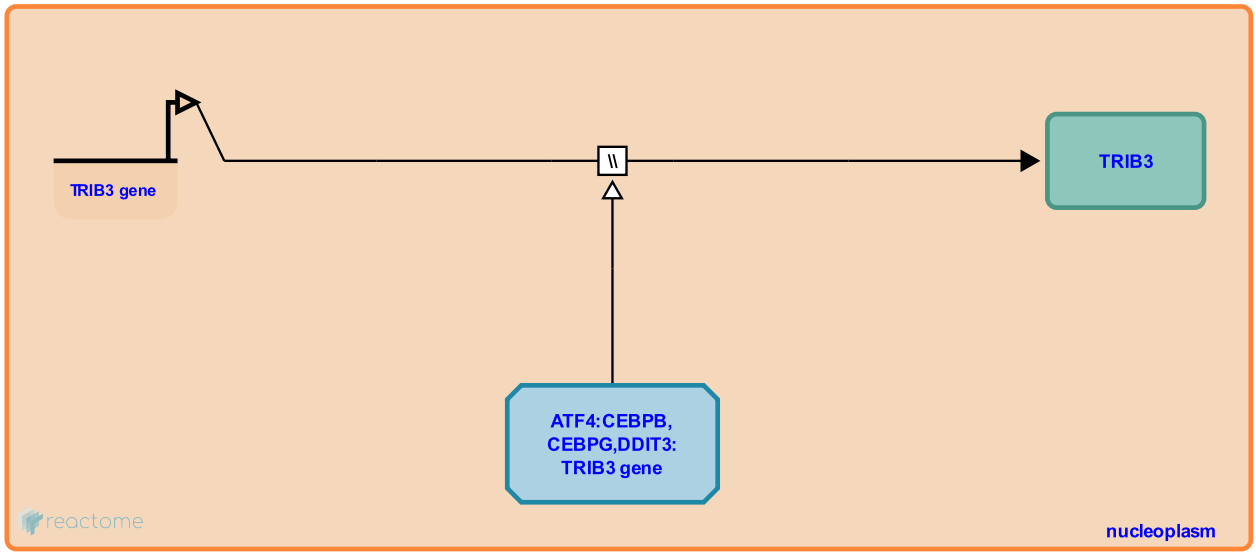
Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-9635912

Type: omitted

Compartments: nucleoplasm

Inferred from: Expression of Trib3 (Mus musculus)



The TRIB3 (TRB3, NIPK) gene is transcribed to yield mRNA and the mRNA is translated to yield TRIB3 protein (Ohoka et al. 2005, Ord and Ord 2005, Lee et al. 2008, Sikalidis et al. 2011, Ord et al. 2016, and inferred from the mouse homolog). Transcription of TRIB3 is enhanced in response to amino acid deficiency (Lee et al. 2008, Sikalidis et al. 2011, and inferred from mouse homologs), endoplasmic reticulum stress (Ohoka et al. 2005, Ord and Ord 2005), oxidative stress (Ord and Ord 2005, Ord et al. 2016) and heme deficiency (inferred from mouse homologs). ATF4 bound with a CEBP family protein to the promoter of TRIB3 (NIPK, TRB3) enhances transcription of TRIB3 (Ohoka et al. 2005, Ord and Ord 2005, Lee et al. 2008, Sikalidis et al. 2011, Ord et al. 2016, and inferred from mouse homologs).

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

Literature references

Örd, T., Biene, T., Ord, T., Ord, D. (2016). TRIB3 increases cell resistance to arsenite toxicity by limiting the expression of the glutathione-degrading enzyme CHAC1. *Biochim. Biophys. Acta, 1863*, 2668-2680. ↗

Dominy, JE., Sikalidis, AK., Lee, JI., Stipanuk, MH., Hirschberger, LL., Wang, W. (2008). HepG2/C3A cells respond to cysteine deprivation by induction of the amino acid deprivation/integrated stress response pathway. *Physiol. Genomics, 33*, 218-29. ↗

Ord, T., Ord, D. (2005). Characterization of human NIPK (TRB3, SKIP3) gene activation in stressful conditions. *Biochem. Biophys. Res. Commun., 330*, 210-8. ↗

Sikalidis, AK., Lee, JI., Stipanuk, MH. (2011). Gene expression and integrated stress response in HepG2/C3A cells cultured in amino acid deficient medium. *Amino Acids, 41*, 159-71. ↗

Yoshii, S., Hattori, T., Onozaki, K., Ohoka, N., Hayashi, H. (2005). TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death. *EMBO J., 24*, 1243-55. ↗

Editions

2019-02-09	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-10-22	Reviewed	Chen, JJ.
2019-11-20	Reviewed	Staschke, KA.

ATF4 binds the PPP1R15A (GADD34) promoter ↗

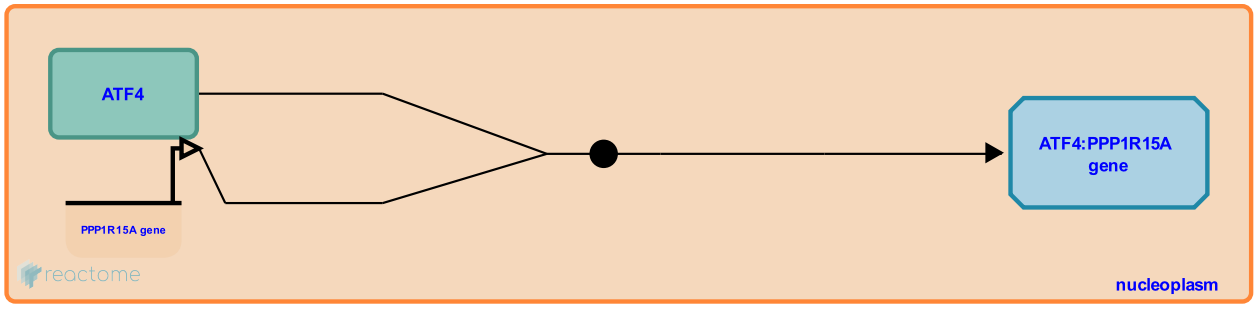
Location: Response of EIF2AK1 (HRI) to heme deficiency

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

Editions

2019-07-18	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

Transcription of PPP1R15A ↗

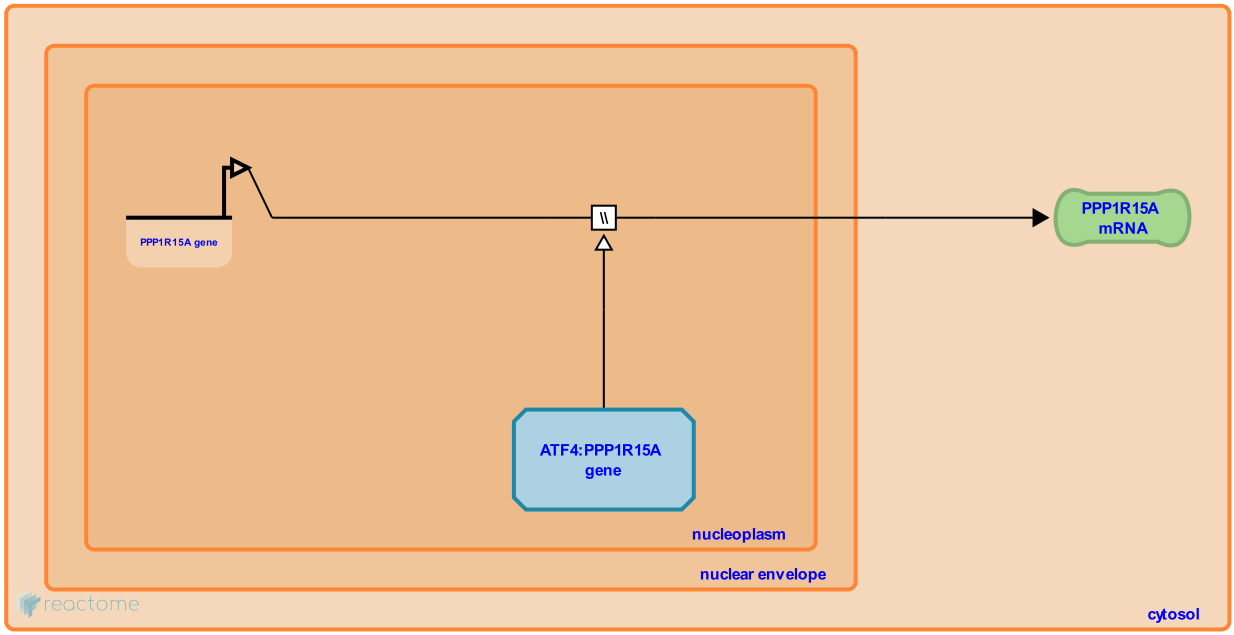
Location: Response of EIF2AK1 (HRI) to heme deficiency

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

Iglesias, M., Zhan, Q., Yu, K., Fornace, AJ., Sheikh, MS., Woodworth, C. et al. (2001). Activation of Gadd34 by diverse apoptotic signals and suppression of its growth inhibitory effects by apoptotic inhibitors. *Int. J. Cancer, 96*, 22-31. ↗

Zhan, Q., Fornace, AJ., Bae, I., Hollander, MC. (1997). Mammalian GADD34, an apoptosis- and DNA damage-inducible gene. *J. Biol. Chem., 272*, 13731-7. ↗

Oh-Hashi, K., Isobe, K., Maruyama, W. (2001). Peroxynitrite induces GADD34, 45, and 153 VIA p38 MAPK in human neuroblastoma SH-SY5Y cells. *Free Radic. Biol. Med., 30*, 213-21. ↗

Editions

2019-07-18	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

ATF4 and CEBPB,CEBPG bind the ASNS gene ↗

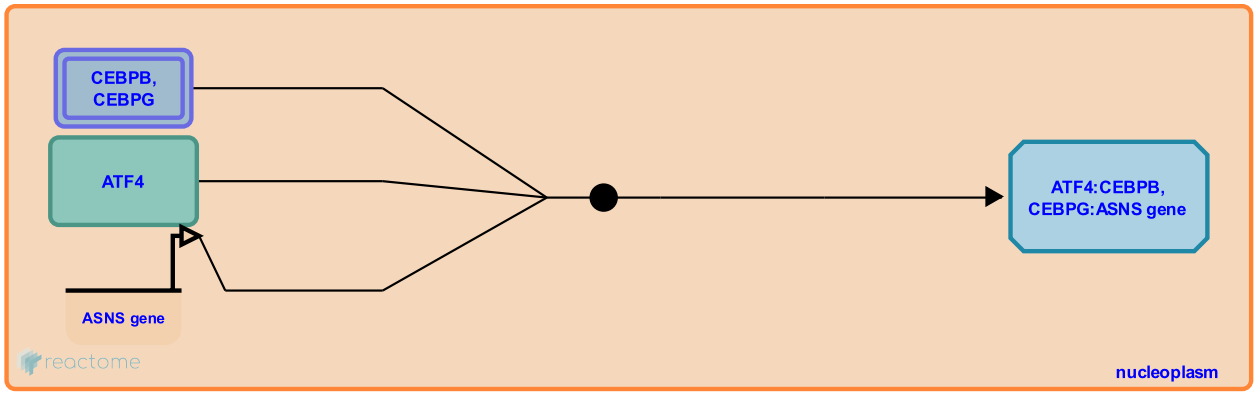
Location: Response of EIF2AK1 (HRI) to heme deficiency

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

Kilberg, MS., Zhong, C., Chen, C., Siu, F. (2001). CCAAT/enhancer-binding protein-beta is a mediator of the nutrient-sensing response pathway that activates the human asparagine synthetase gene. *J. Biol. Chem., 276*, 48100-7. ↗

Kilberg, MS., Pan, YX., Chen, H., Dudenhausen, EE. (2004). Amino acid deprivation induces the transcription rate of the human asparagine synthetase gene through a timed program of expression and promoter binding of nutrient-responsive basic region/leucine zipper transcription factors as well as localized histone acetylation. *J. Biol. Chem., 279*, 50829-39. ↗

Editions

2019-02-09	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-10-22	Reviewed	Chen, JJ.
2019-11-20	Reviewed	Staschke, KA.

Expression of ASNS (Asparagine Synthetase) ↗

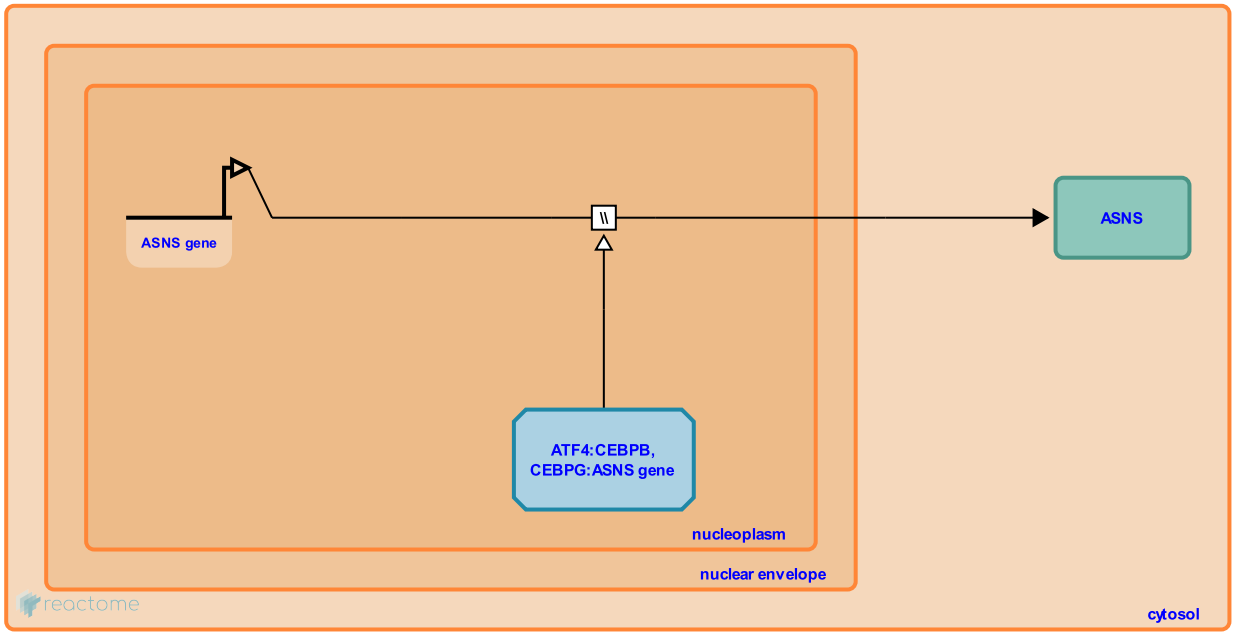
Location: Response of EIF2AK1 (HRI) to heme deficiency

Stable identifier: R-HSA-1791118

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Asns (Mus musculus)



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

Dominy, JE., Sikalidis, AK., Lee, JI., Stipanuk, MH., Hirschberger, LL., Wang, W. (2008). HepG2/C3A cells respond to cysteine deprivation by induction of the amino acid deprivation/integrated stress response pathway. *Physiol. Genomics, 33*, 218-29. ↗

Sikalidis, AK., Lee, JI., Stipanuk, MH. (2011). Gene expression and integrated stress response in HepG2/C3A cells cultured in amino acid deficient medium. *Amino Acids, 41*, 159-71. ↗

Kilberg, MS., Pan, YX., Chen, H., Dudenhausen, EE. (2004). Amino acid deprivation induces the transcription rate of the human asparagine synthetase gene through a timed program of expression and promoter binding of nutrient-responsive basic region/leucine zipper transcription factors as well as localized histone acetylation. *J. Biol. Chem., 279*, 50829-39. ↗

Kilberg, MS., Shan, J., Balasubramanian, MN. (2013). Dynamic changes in genomic histone association and modification during activation of the ASNS and ATF3 genes by amino acid limitation. *Biochem. J., 449*, 219-29. ↗

Kilberg, MS., Su, N., Gjymishka, A. (2009). Transcriptional induction of the human asparagine synthetase gene during the unfolded protein response does not require the ATF6 and IRE1/XBP1 arms of the pathway. *Biochem J, 417*, 695-703. ↗

Editions

2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.
2010-04-30	Reviewed	Urano, F.
2011-10-13	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-10-22	Reviewed	Chen, JJ.
2019-11-20	Reviewed	Staschke, KA.

Expression of GRB10 ↗

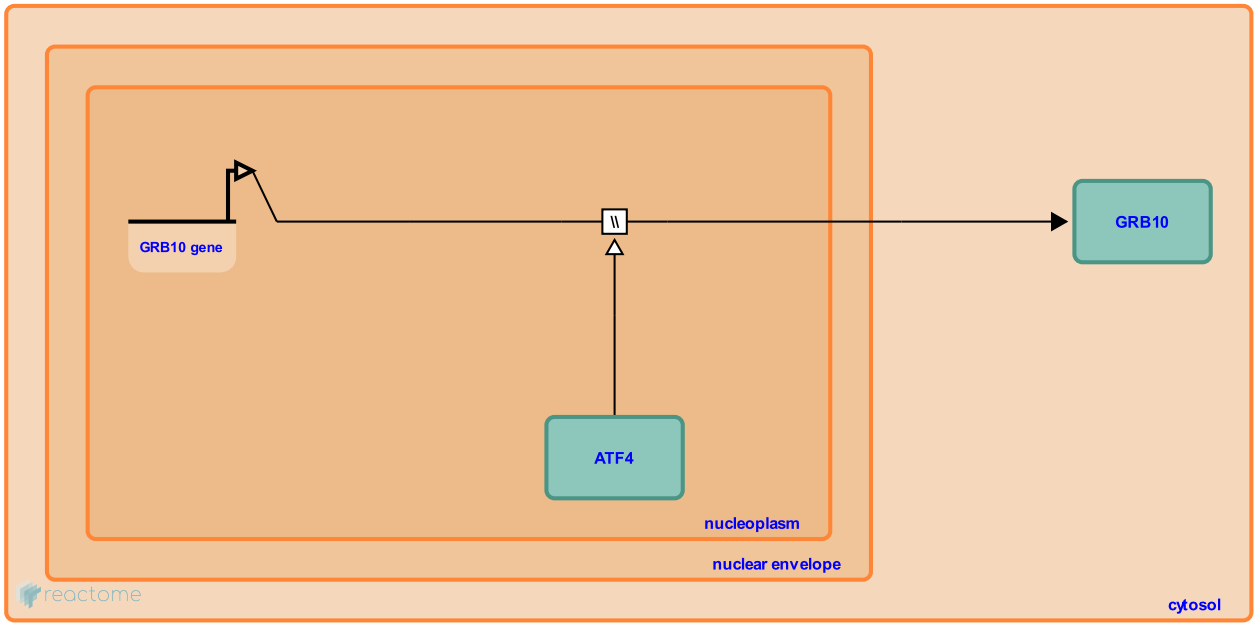
Location: Response of EIF2AK1 (HRI) to heme deficiency

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

Editions

2019-07-19	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

Table of Contents