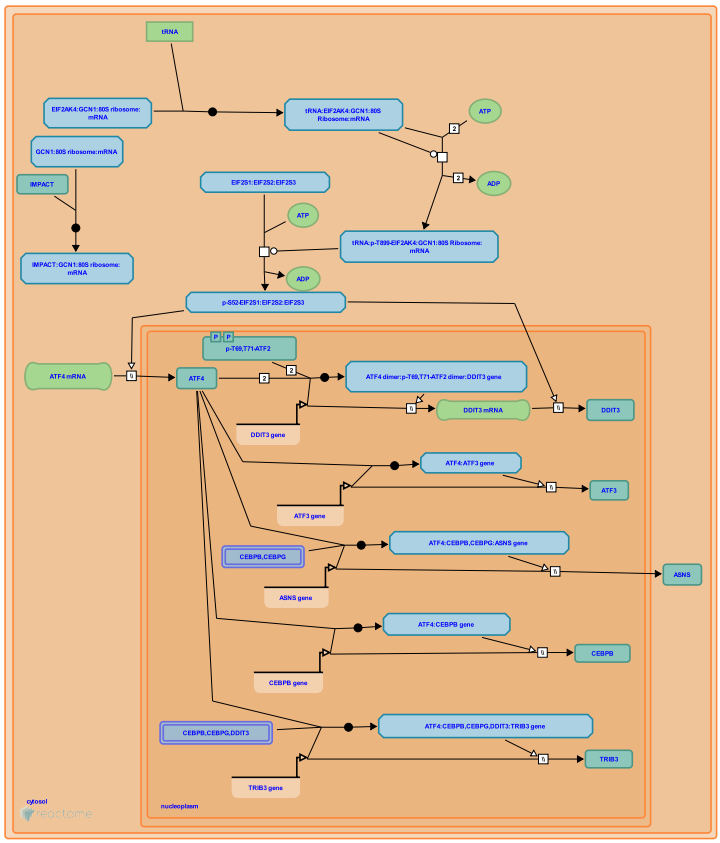
Response of EIF2AK4 (GCN2) to amino acid deficiency



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.

23/04/2024

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. ↗

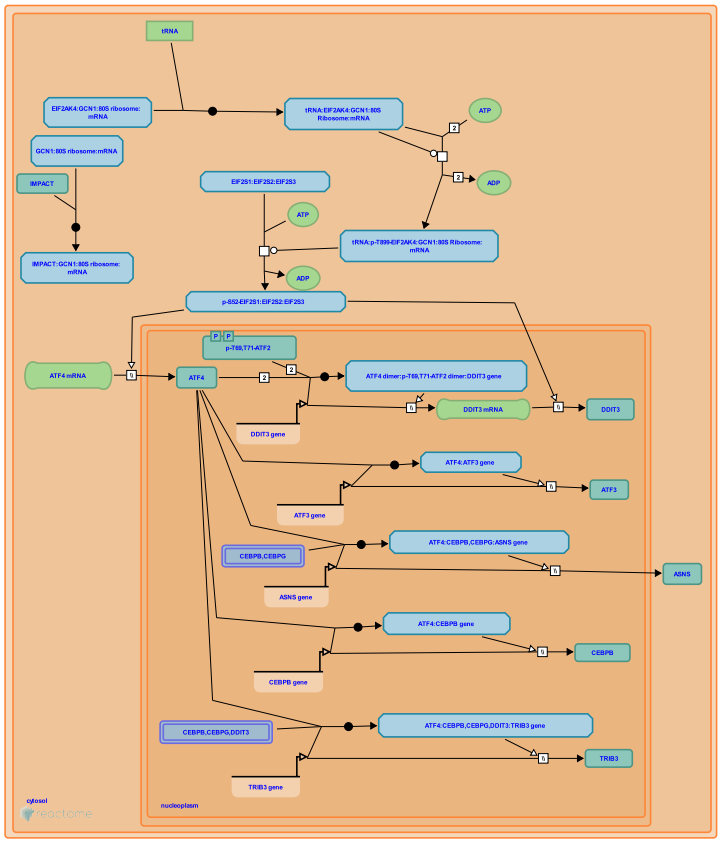
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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 EIF2AK4 (GCN2) to amino acid deficiency ↗

Stable identifier: R-HSA-9633012



EIF2AK4 (GCN2) senses amino acid deficiency by binding uncharged tRNAs near the ribosome and responds by phosphorylating EIF2S1, the alpha subunit of the translation initiation factor EIF2 (inferred from yeast homologs and mouse homologs, reviewed in Chaveroux et al. 2010, Castilho et al. 2014, Gallinetti et al. 2013, Bröer and Bröer 2017, Wek 2018). Phosphorylated EIF2S1 reduces translation of most mRNAs but increases translation of downstream ORFs in mRNAs such as ATF4 that contain upstream ORFs (inferred from mouse homologs in Vattem and Wek 2004, reviewed in Hinnebusch et al. 2016, Sonenberg and Hinnebusch 2009). ATF4, in turn, activates expression of genes involved in responding to amino acid deficiency such as DDIT3 (CHOP), ASNS (asparagine synthetase), CEBPB, and ATF3 (reviewed in Kilberg et al. 2012, Wortel et al. 2017). In mice, EIF2AK4 in the brain may responsible for avoidance of diets lacking essential amino acids (Hao et al. 2005, Maurin et al. 2005, see also Leib and Knight 2015, Gietzen et al. 2016, reviewed in Dever and Hinnebusch 2005).
EIF2AK4 is bound to both the ribosome and GCN1, which is required for activation of EIF2AK4 and may act by shuttling uncharged tRNAs from the A site of the ribosome to EIF2AK4. Upon binding tRNA, EIF2AK4 trans-autophosphorylates. Phosphorylated EIF2AK4 then phosphorylates EIF2S1 on serine-52, the same serine residue phosphorylated by other kinases of the integrated stress response: EIF2AK1 (HRI, activated by heme deficiency and other stresses), EIF2AK2 (PKR, activated by double-stranded RNA), and EIF2AK3 (PERK, activated by unfolded proteins) (reviewed in Hinnebusch 1994, Wek et al. 2006, Donnelly et al. 2013, Pakos-Zebrucka et al. 2016, Wek 2018),

Literature references

Koryga, I., Pakos-Zebrucka, K., Gorman, AM., Samali, A., Mnich, K., Ljujic, M. (2016). The integrated stress response . *EMBO Rep., 17*, 1374-1395. ↗

McGrath, BC., Ross-Inta, CM., Hao, S., Koehnle, TJ., McDaniel, BJ., Sharp, JW. et al. (2005). Uncharged tRNA and sensing of amino acid deficiency in mammalian piriform cortex. *Science, 307*, 1776-8. ↗

Leib, DE., Knight, ZA. (2015). Re-examination of Dietary Amino Acid Sensing Reveals a GCN2-Independent Mechanism. *Cell Rep, 13*, 1081-1089. ↗

Shanmugam, R., Himme, BM., Sattlegger, E., Silva, RC., Ramesh, R., Castilho, BA. (2014). Keeping the eIF2 alpha kinase Gcn2 in check. *Biochim. Biophys. Acta, 1843*, 1948-68. ↗

Mitchell, JR., Gallinetti, J., Harputlugil, E. (2013). Amino acid sensing in dietary-restriction-mediated longevity: roles of signal-transducing kinases GCN2 and TOR. *Biochem. J., 449*, 1-10. ↗

Editions

2018-12-28	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-11-20	Reviewed	Staschke, KA.

EIF2AK4 (GCN2) binds tRNA ↗

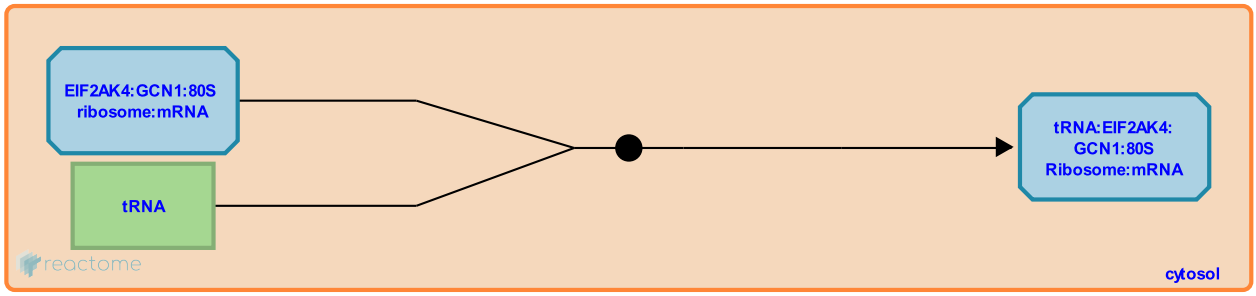
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-9633005

Type: binding

Compartments: cytosol

Inferred from: Eif2ak4 binds tRNA (Mus musculus), GCN2 binds tRNA (Saccharomyces cerevisiae)



The histidyl-tRNA synthetase-like domain of EIF2AK4 (GCN2) binds uncharged tRNA, resulting in activation of the protein kinase domain of EIF2AK4 (Inglis et al. 2019 and inferred from yeast homologs and mouse homologs). In the absence of tRNA, EIF2AK4 appears to exist in an equilibrium between antiparallel and parallel dimers. Upon binding tRNA, the parallel dimer is stabilized and the C-terminal domain shifts away from the protein kinase domain, resulting in activation of the kinase activity of EIF2AK4 (inferred from GCN2, the yeast homolog).
EIF2AK4 interacts with GCN1 and the P-stalk of ribosomes (Inglis et al. 2019), though the interaction between mammalian EIF2AK4 and ribosomes is not as stable as the interaction between yeast GCN2 and ribosomes (inferred from yeast homologs and mouse homologs). By such transient interactions, a population of EIF2AK4 may sample a larger population of ribosomes for uncharged tRNAs. The interaction between EIF2AK4 and GCN1 is required for efficient phosphorylation of EIF2S1 by EIF2AK4 and GCN1 may act to transfer uncharged tRNAs from the A site of the ribosome to EIF2AK4 (inferred from yeast homologs and mouse homologs).

Followed by: EIF2AK4 (GCN2) dimer autophosphorylates

Literature references

Hegde, RS., Perisic, O., Masson, GR., Inglis, AJ., Shao, S., McLaughlin, SH. et al. (2019). Activation of GCN2 by the ribosomal P-stalk. *Proc. Natl. Acad. Sci. U.S.A., 116*, 4946-4954. ↗

Editions

2018-12-28	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-11-20	Reviewed	Staschke, KA.

EIF2AK4 (GCN2) dimer autophosphorylates ↗

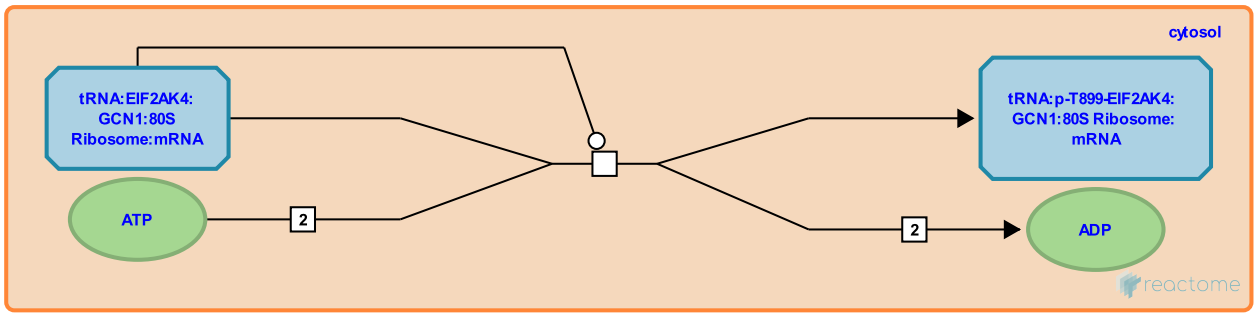
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-9633742

Type: transition

Compartments: cytosol

Inferred from: GCN2 dimer autophosphorylates (Saccharomyces cerevisiae), Eif2ak4 dimer autophosphorylates (Mus musculus)



After binding uncharged tRNA, the EIF2AK4 (GCN2) dimer trans-autophosphorylates on threonine-899, resulting in activation of the kinase domain of EIF2AK4 (Harding et al. 2000, Deng et al. 2002, Cambiaghi et al. 2014, and inferred from mouse homologs and yeast homologs).

Preceded by: EIF2AK4 (GCN2) binds tRNA

Editions

2018-12-29	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-11-20	Reviewed	Staschke, KA.

p-T899-EIF2AK4 (GCN2) phosphorylates EIF2AS1 ↗

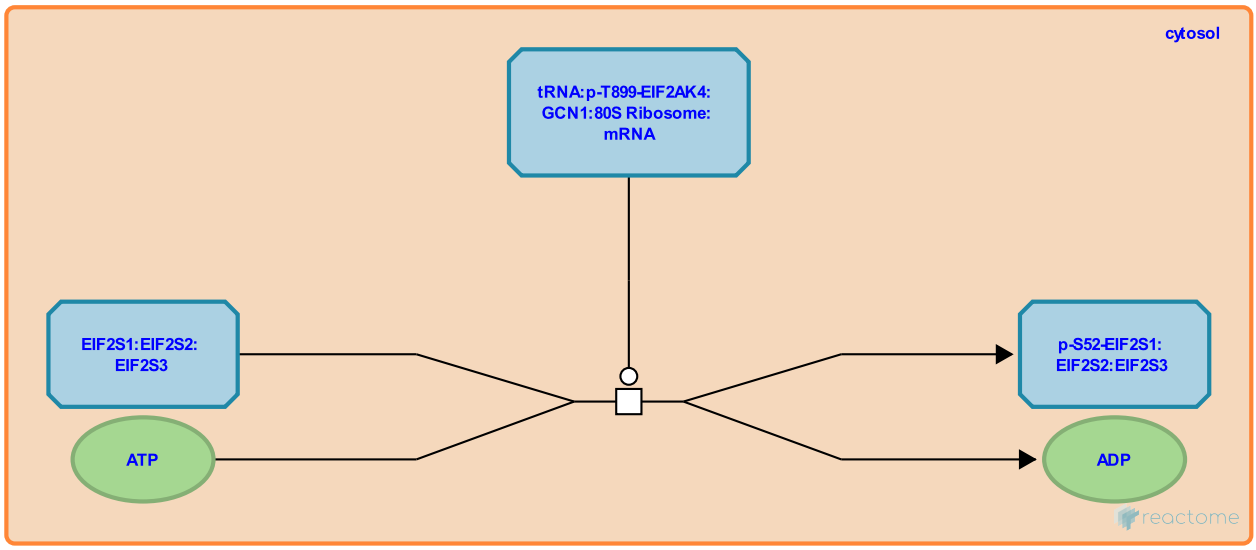
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-9633008

Type: transition

Compartments: cytosol

Inferred from: GCN2 phosphorylates SUI2 (Saccharomyces cerevisiae), Eif2ak4 phosphorylates Eif2s1 (Mus musculus)



After binding uncharged tRNA and autophosphorylating, EIF2AK4 (GCN2) phosphorylates EIF2S1 (eIF2 alpha subunit) on serine-52 (serine-51 in the rabbit homolog, inferred from mouse homologs and yeast homologs), which inhibits the guanine nucleotide exchange factor eIF2B, impairs exchange of GDP for GTP, and reduces recycling of EIF2 for initiation of translation. This causes downregulation of translation of most mRNAs, however translation of certain mRNAs possessing upstream ORFs, such as ATF4, is upregulated (inferred from mouse homologs and yeast homologs).

Followed by: Translation of DDIT3, Translation of ATF4

Editions

2018-12-28	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-11-20	Reviewed	Staschke, KA.

Translation of ATF4

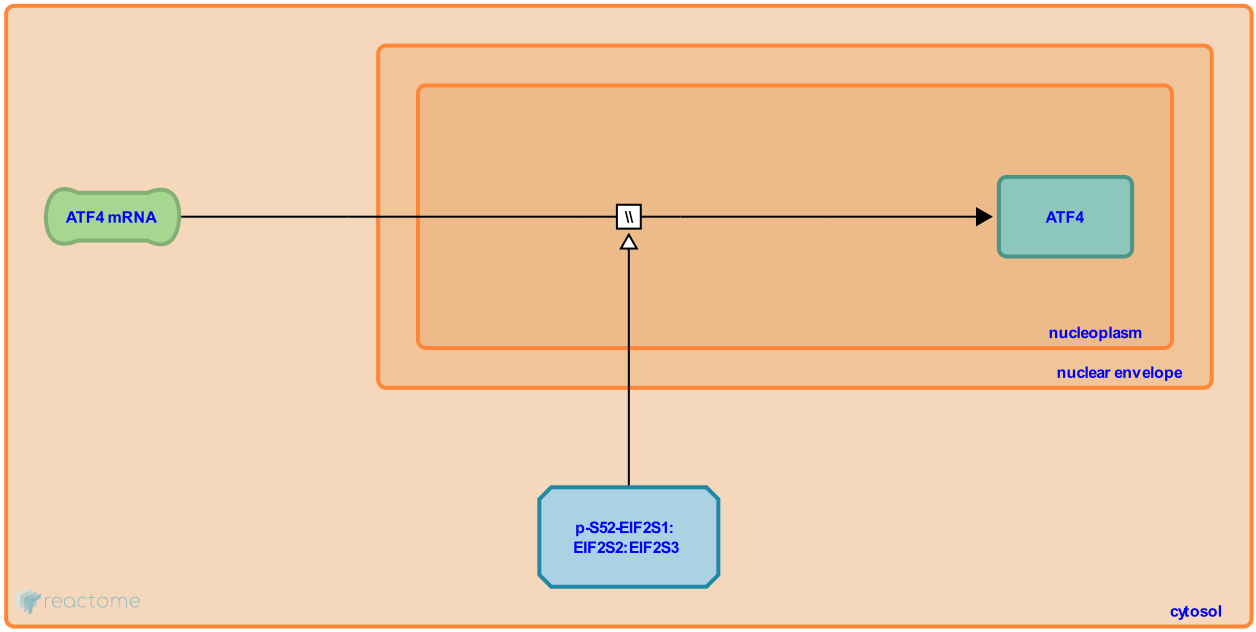
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

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-T899-EIF2AK4 (GCN2) phosphorylates EIF2AS1

Followed by: Expression of ATF3, Expression of ASNS (Asparagine Synthetase), ATF4 and CEBPB,CEBPG bind the ASNS gene, ATF4 binds the CEBPB gene, ATF4 and phospho-ATF2 bind the DDIT3 promoter, ATF4 binds the ATF3 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 ↗

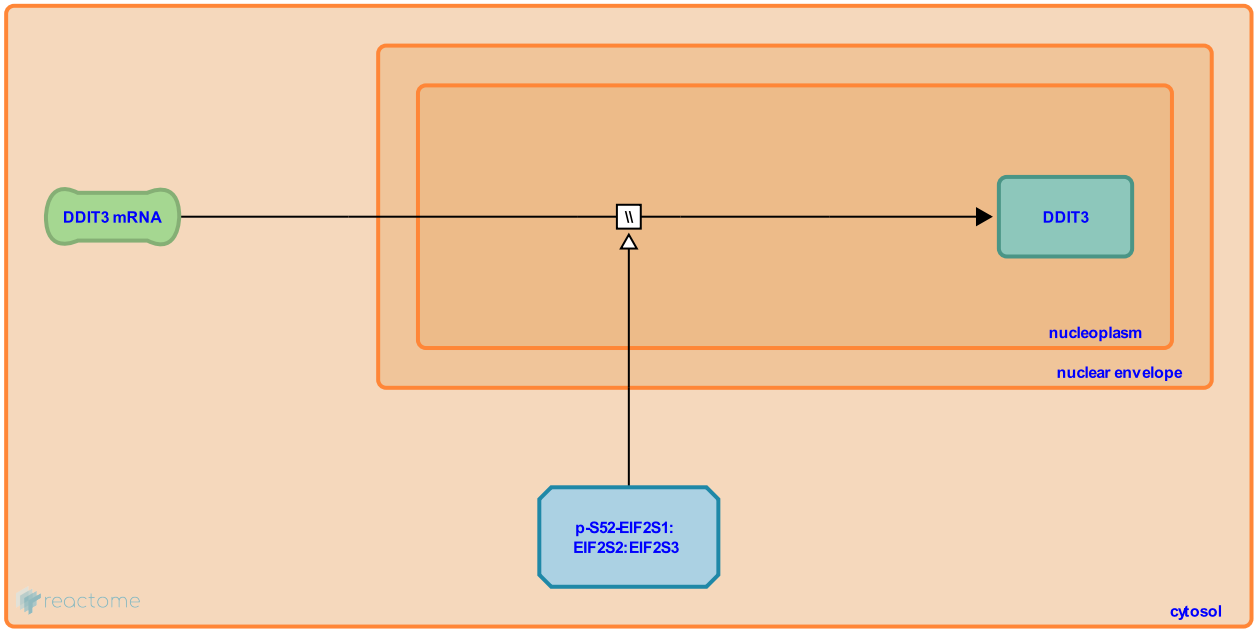
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

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: Transcription of DDIT3 (CHOP, GADD153) in response to amino acid deficiency, p-T899-EIF2AK4 (GCN2) phosphorylates EIF2AS1

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.

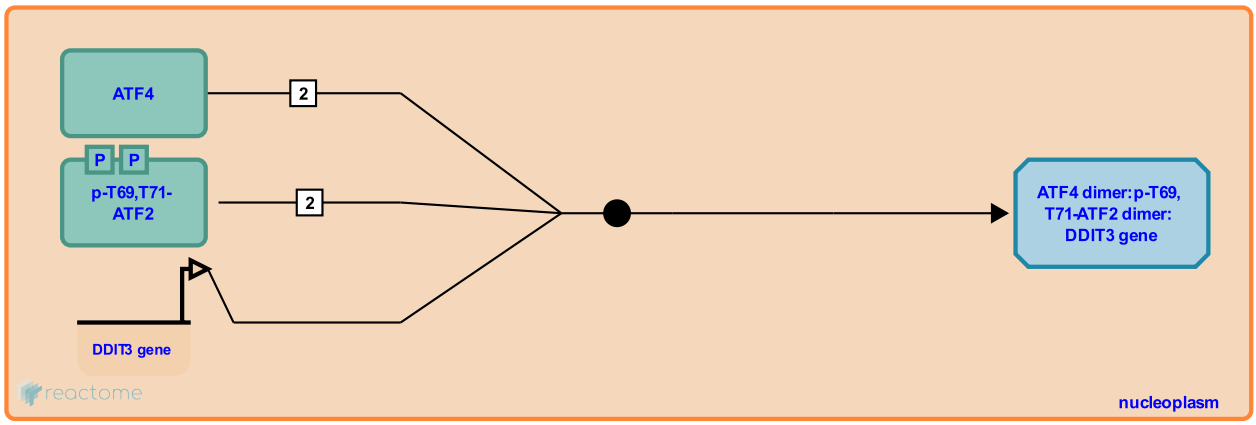
ATF4 and phospho-ATF2 bind the DDIT3 promoter ↗

Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-9635804

Type: binding

Compartments: nucleoplasm



The promoter of the DDIT3 (CHOP) gene contains an Amino Acid Response Element (AARE) that binds ATF4 and ATF2. ATF2 and ATF4 are required for full activation of gene transcription in response to amino acid deprivation (Bruhat et al. 2000, Averous et al. 2004). Phospho-ATF2 is essential in the acetylation of histone H4 and H2B (Bruhat et al. 2007). ATF4 recruits PCAF to enhance transcription (Chérasse et al. 2007). ATF4 appears to be a monomer in the absence of DNA and a dimer after binding DNA (Podust et al. 2001).

Preceded by: Translation of ATF4

Followed by: Transcription of DDIT3 (CHOP, GADD153) in response to amino acid 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. ↗

Kim, Y., Krezel, AM., Podust, LM. (2001). Crystal structure of the CCAAT box/enhancer-binding protein beta activating transcription factor-4 basic leucine zipper heterodimer in the absence of DNA. *J. Biol. Chem., 276*, 505-13. ↗

Editions

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

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

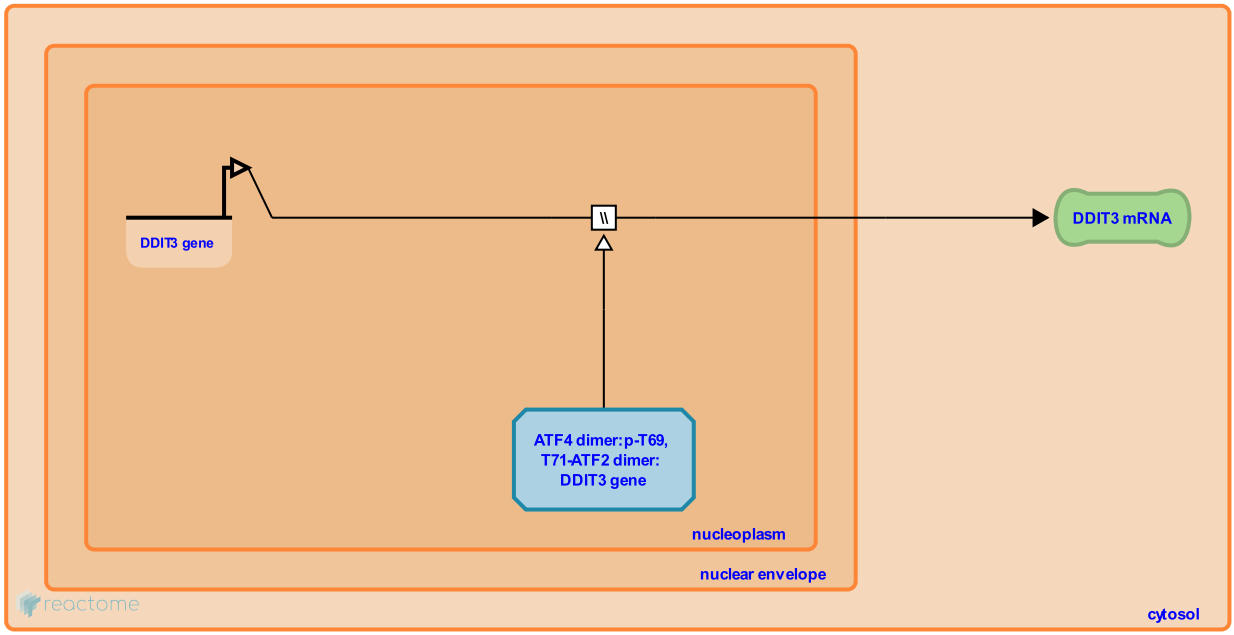
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-9644926

Type: omitted

Compartments: nucleoplasm

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



The DDIT3 (CHOP) gene is transcribed to yield mRNA and the mRNA is translated to yield protein (Bartlett et al. 1992, Carlson et al. 1993, Bruhat et al. 1997, Yoshida et al. 2000, Lee et al. 2008, Sikalidis et al. 2011). In response to amino acid starvation, transcription of DDIT3 s enhanced by ATF4 and phosphorylated ATF2 (Bruhat et al. 2000, Averous et al. 2004, Bruhat et al. 2007). 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 and phospho-ATF2 bind the DDIT3 promoter

Followed by: Translation of DDIT3

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. ↗

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. ↗

Holbrook, NJ., Carlson, SG., Luethy, JD., Sollott, SJ., Bartlett, JD. (1992). Calcium ionophore A23187 induces expression of the growth arrest and DNA damage inducible CCAAT/enhancer-binding protein (C/EBP)-related gene, gadd153. Ca2+ increases transcriptional activity and mRNA stability. *J. Biol. Chem., 267*, 20465-70. ↗

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. ↗

Editions

2019-04-28	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
2019-11-20	Reviewed	Staschke, KA.

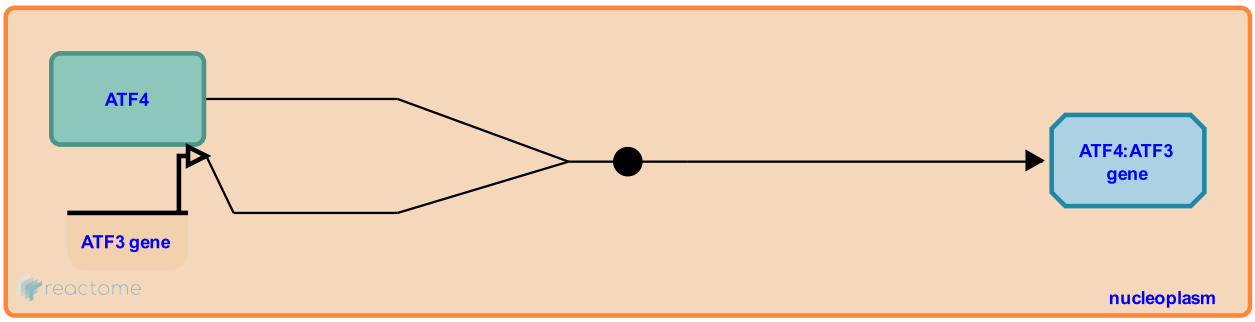
ATF4 binds the ATF3 gene ↗

Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-9635892

Type: binding

Compartments: nucleoplasm



ATF4 binds an amino acid response element (AARE) in the promoter of the ATF3 gene (Chen et al. 2004, Pan et al. 2007, Fu and Kilberg 2013, Hayner et al. 2018). ATF4 initially binds the ATF3 promoter with phosphorylated ATF2, then with JUN (c-Jun), then with CEBPB (Fu and Kilberg 2013, Hayner et al. 2018). ATF3 and CEBPB bind later and correlate with reduced expression of ATF3 (Pan et al. 2007, Fu and Kilberg 2013, Hayner et al. 2018).

Preceded by: Translation of ATF4

Followed by: Expression of ATF3

Literature references

Kilberg, MS., Fu, L. (2013). Elevated cJUN expression and an ATF/CRE site within the ATF3 promoter contribute to activation of ATF3 transcription by the amino acid response. *Physiol. Genomics, 45*, 127-37. ↗

Kilberg, MS., Pan, YX., Chen, H., Thiaville, MM. (2007). Activation of the ATF3 gene through a co-ordinated amino acid-sensing response programme that controls transcriptional regulation of responsive genes following amino acid limitation. *Biochem. J., 401*, 299-307. ↗

Kilberg, MS., Hayner, JN., Shan, J. (2018). Regulation of the ATF3 gene by a single promoter in response to amino acid availability and endoplasmic reticulum stress in human primary hepatocytes and hepatoma cells. *Biochim Biophys Acta Gene Regul Mech, 1861*, 72-79. ↗

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.
2019-11-20	Reviewed	Staschke, KA.

Expression of ATF3

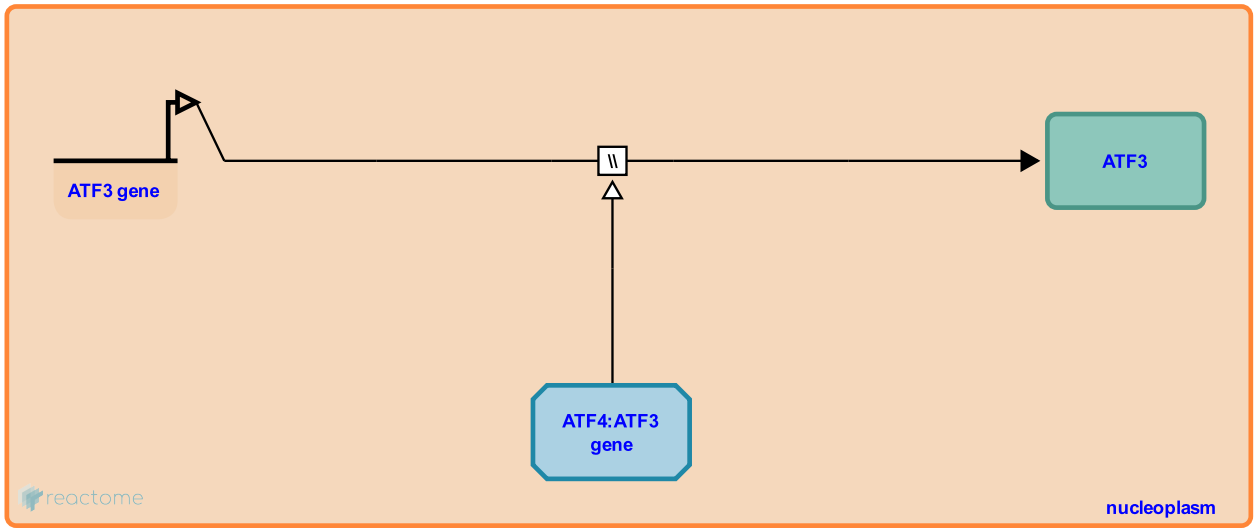
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-1791173

Type: omitted

Compartments: nucleoplasm

Inferred from: Expression of Atf3 (Mus musculus)



The ATF3 gene is transcribed to yield mRNA and the mRNA is translated to yield protein (Chen et al. 2004, Pan et al. 2007, Lee et al. 2008, Armstrong et al. 2010, Sikalidis et al. 2011, Fu and Kilberg 2013, Lee et al. 2013, Hayner et al. 2018). Transcription of ATF3 is enhanced in response to amino acid deficiency (Chen et al. 2004, Pan et al. 2007, Lee et al. 2008, Sikaldis et al. 2011, Fu and Kilberg 2013, Hayner et al. 2018). ATF4 binds a CEBP-ATF response element (CARE) and an additional upstream element in the promoter of the ATF3 gene, resulting in enhanced transcription (Pan et al. 2007, Armstrong et al. 2010, Fu and Kilberg 2013, Lee et al. 2013, Hayner et al. 2018, and inferred from mouse homologs). CEBPB and ATF3 bind later and correlate with reduced expression of ATF4 (Pan et al. 2007)

Preceded by: Translation of ATF4 , ATF4 binds the ATF3 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.

Kilberg, MS., Fu, L. (2013). Elevated cJUN expression and an ATF/CRE site within the ATF3 promoter contribute to activation of ATF3 transcription by the amino acid response. *Physiol. Genomics, 45*, 127-37.

Kilberg, MS., Pan, YX., Chen, H., Thiaville, MM. (2007). Activation of the ATF3 gene through a co-ordinated amino acid-sensing response programme that controls transcriptional regulation of responsive genes following amino acid limitation. *Biochem. J., 401*, 299-307.

Lovat, PE., Veal, GJ., Redfern, CP., Armstrong, JL., Flockhart, R. (2010). Regulation of Endoplasmic Reticulum Stress-induced Cell Death by ATF4 in Neuroectodermal Tumor Cells. *J Biol Chem, 285*, 6091-100.

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.

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.
2019-11-20	Reviewed	Staschke, KA.

ATF4 and CEBPB,CEBPG bind the ASNS gene ↗

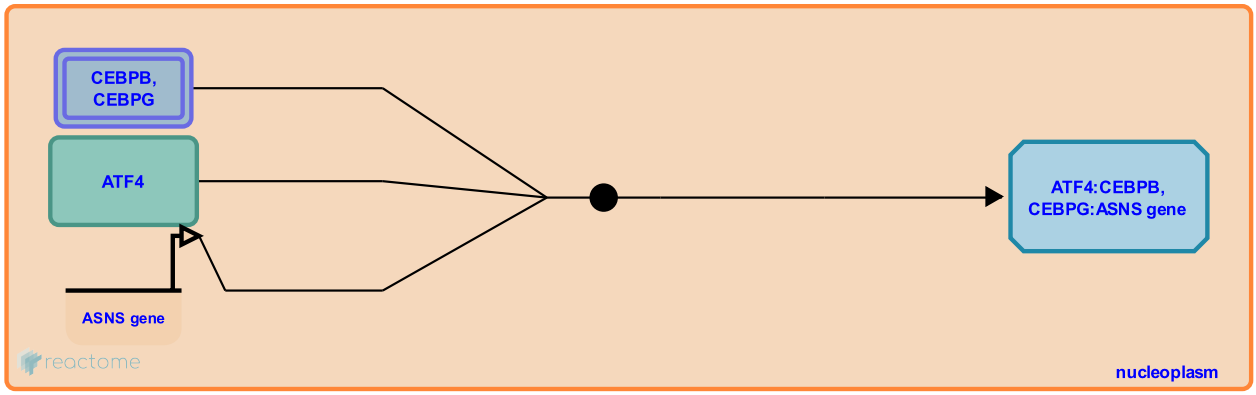
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

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.
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2019-11-20	Reviewed	Staschke, KA.

Expression of ASNS (Asparagine Synthetase)

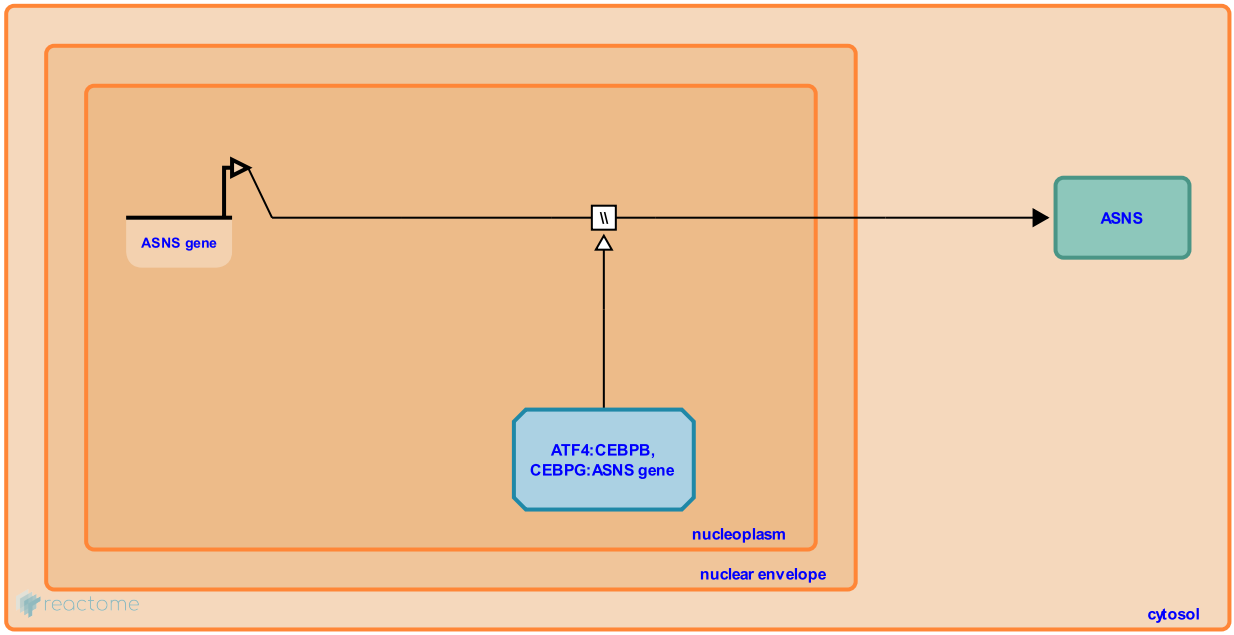
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

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.
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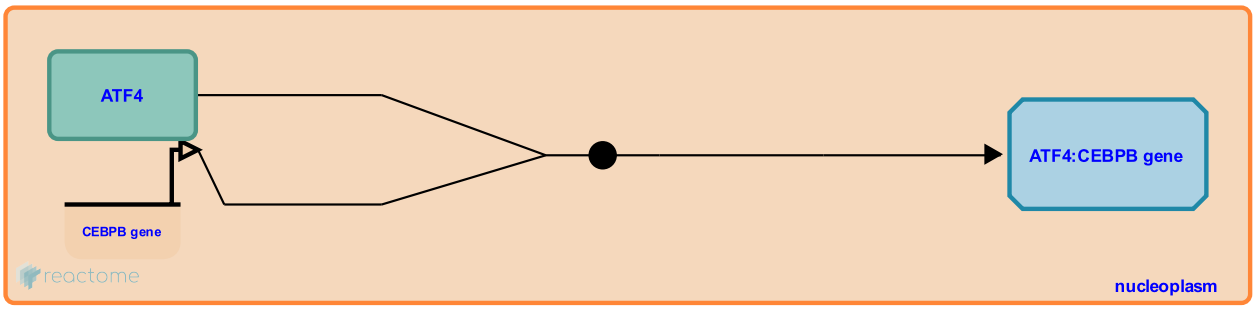
ATF4 binds the CEBPB gene ↗

Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-9635936

Type: binding

Compartments: nucleoplasm



ATF4 binds an enhancer downstream of the protein coding region of the CEBPB gene (Chen et al. 2005). The binding site resembles a composite CEBP-ATF element. Therefore ATF4 may form a heterodimer with a CEBP protein at the element (Chen et al. 2005).

Preceded by: Translation of ATF4

Followed by: Expression of CEBPB in response to stress

Literature references

Kilberg, MS., Gjymishka, A., Pan, YX., Dudenhausen, E., Chen, C., Chen, H. (2005). Amino-acid limitation induces transcription from the human C/EBPbeta gene via an enhancer activity located downstream of the protein coding sequence. *Biochem. J., 391*, 649-58. ↗

Editions

2019-02-09	Authored, Edited	May, B.
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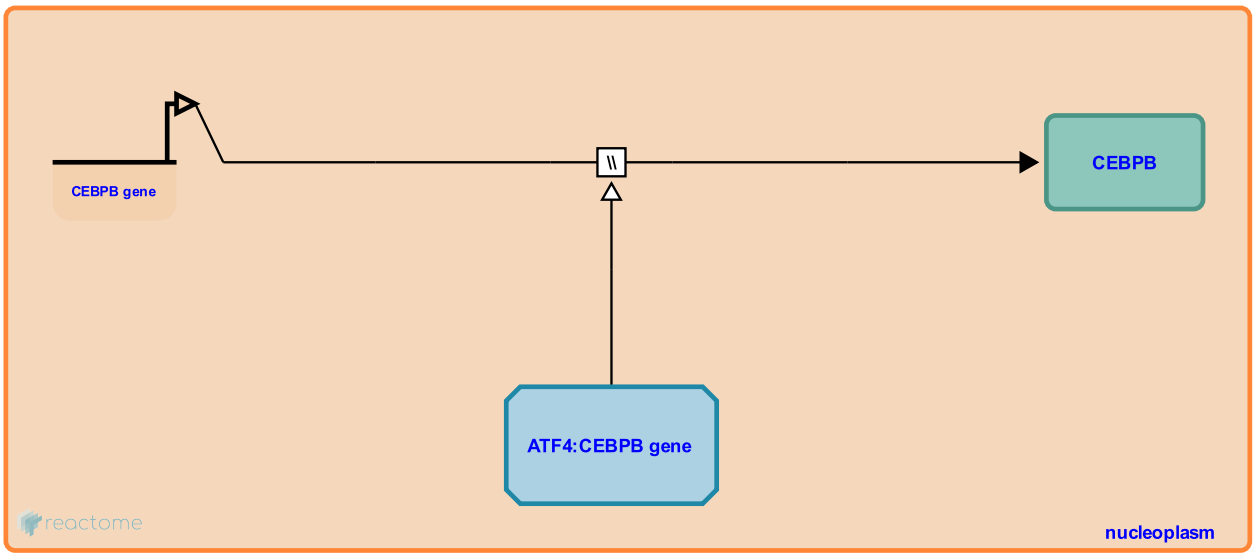
Expression of CEBPB in response to stress ↗

Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-9635918

Type: omitted

Compartments: nucleoplasm



The CEBPB gene is transcribed to yield mRNA and the mRNA is translated to yield protein (Chen et al. 2005, Lee et al. 2008, Sikalidis et al. 2011). Transcription of CEBPB is activated in response to amino acid deficiency (Chen et al. 2005, Lee et al. 2008, Sikalidis et al. 2011). ATF4 bound to an enhancer downstream of the CEBPB coding region (Chen et al. 2005) increases transcription of CEBPB approximately 4-fold (Chen et al. 2005, Lee et al. 2008, Sikalidis et al. 2011).

Preceded by: ATF4 binds the CEBPB 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. ↗

Kilberg, MS., Gjymishka, A., Pan, YX., Dudenhausen, E., Chen, C., Chen, H. (2005). Amino-acid limitation induces transcription from the human C/EBPbeta gene via an enhancer activity located downstream of the protein coding sequence. *Biochem. J., 391*, 649-58. ↗

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. ↗

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ATF4 and a CEBP protein bind the TRIB3 promoter ↗

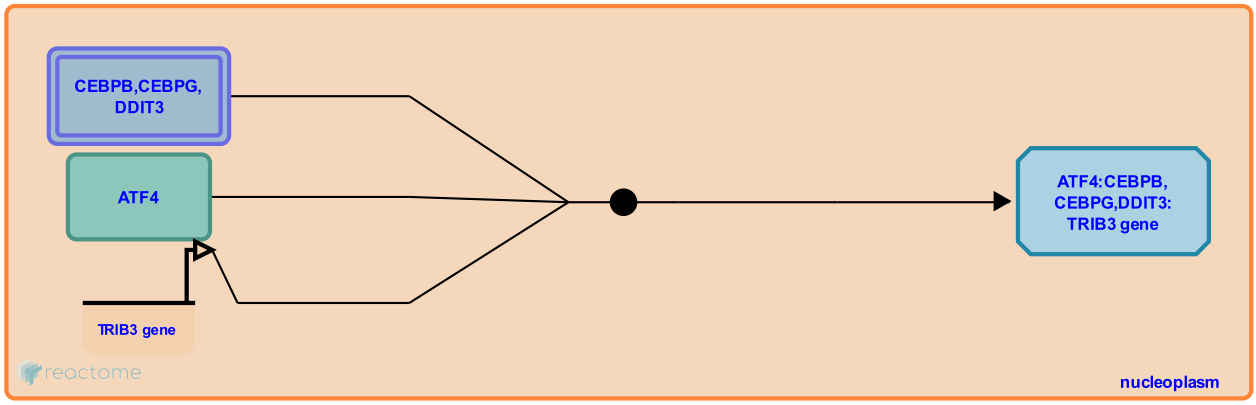
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

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. ↗

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2019-02-09	Authored, Edited	May, B.
2019-09-15	Reviewed	Bruhat, A.
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Expression of TRIB3 in response to stress ↗

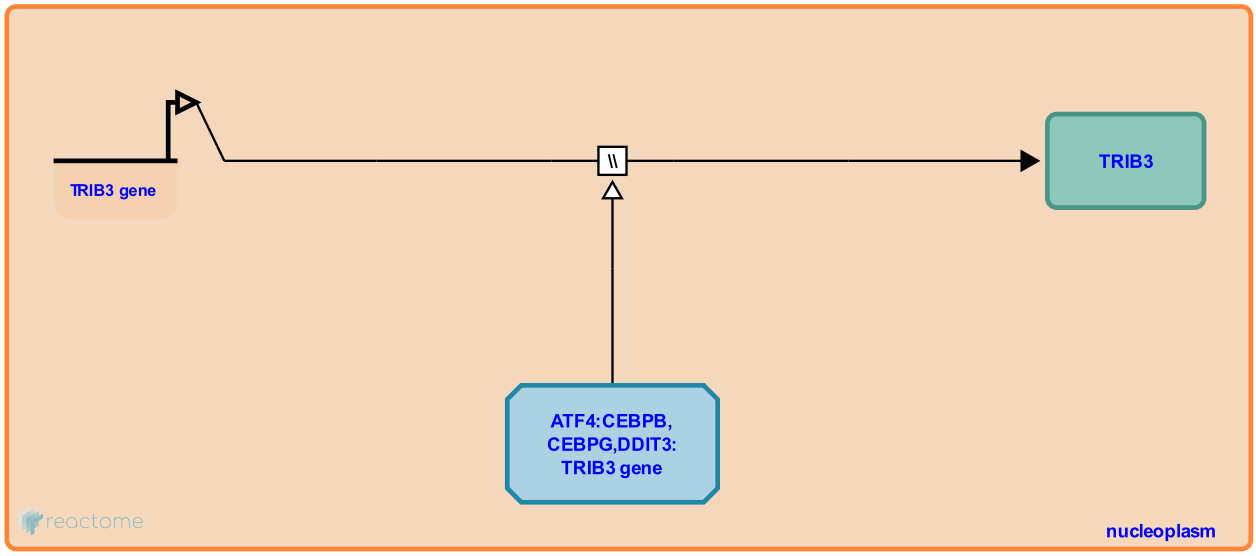
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

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. ↗

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2019-02-09	Authored, Edited	May, B.
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IMPACT binds GCN1 ↗

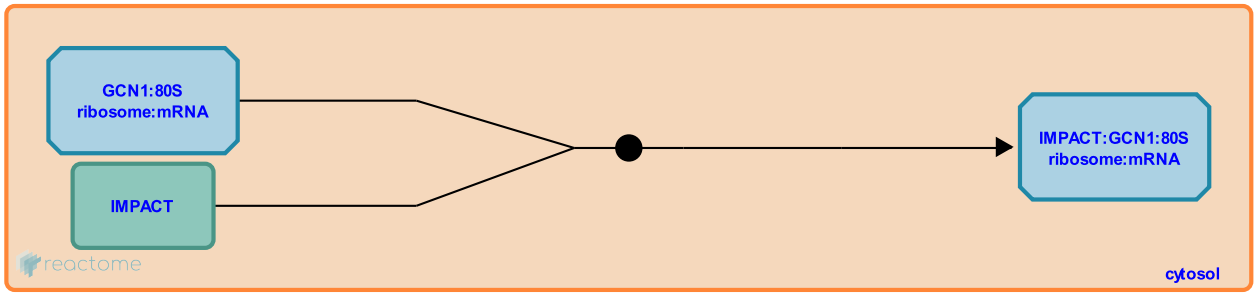
Location: Response of EIF2AK4 (GCN2) to amino acid deficiency

Stable identifier: R-HSA-9634669

Type: binding

Compartments: cytosol

Inferred from: Impact binds Gcn1 (Mus musculus)



IMPACT, a mammalian homolog of yeast YIH1, competes with EIF2AK4 (GCN2) for binding to GCN1, which is required for activation of EIF2AK4 and may act by transferring unacylated tRNAs from the ribosome to EIF2AK4 (inferred from mouse homologs). IMPACT thereby inhibits phosphorylation of EIF2A by EIF2AK4 in response to amino acid deficiency (inferred from mouse homologs). IMPACT is preferentially expressed in neurons, associates with translating ribosomes, enhances translation initiation, and promotes neuritogenesis (inferred from mouse homologs).

Editions

2019-01-12	Authored, Edited	May, B.
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Table of Contents