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.

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06/07/2020
Introduction

Reactome is an 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 16 reactions (see Table of Contents)
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


**Editions**

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**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

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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

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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

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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


**Translation of DDIT3**

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

**Literature references**


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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

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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)


**Preceded by:** ATF4 and phospho-ATF2 bind the DDIT3 promoter

**Followed by:** Translation of DDIT3

**Literature references**


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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**


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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)


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

Literature references


Fu, L., Kilberg, MS. (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.

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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**


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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**


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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**


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Preceded by: ATF4 binds the CEBPB gene

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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**


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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)


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

Literature references


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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).

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