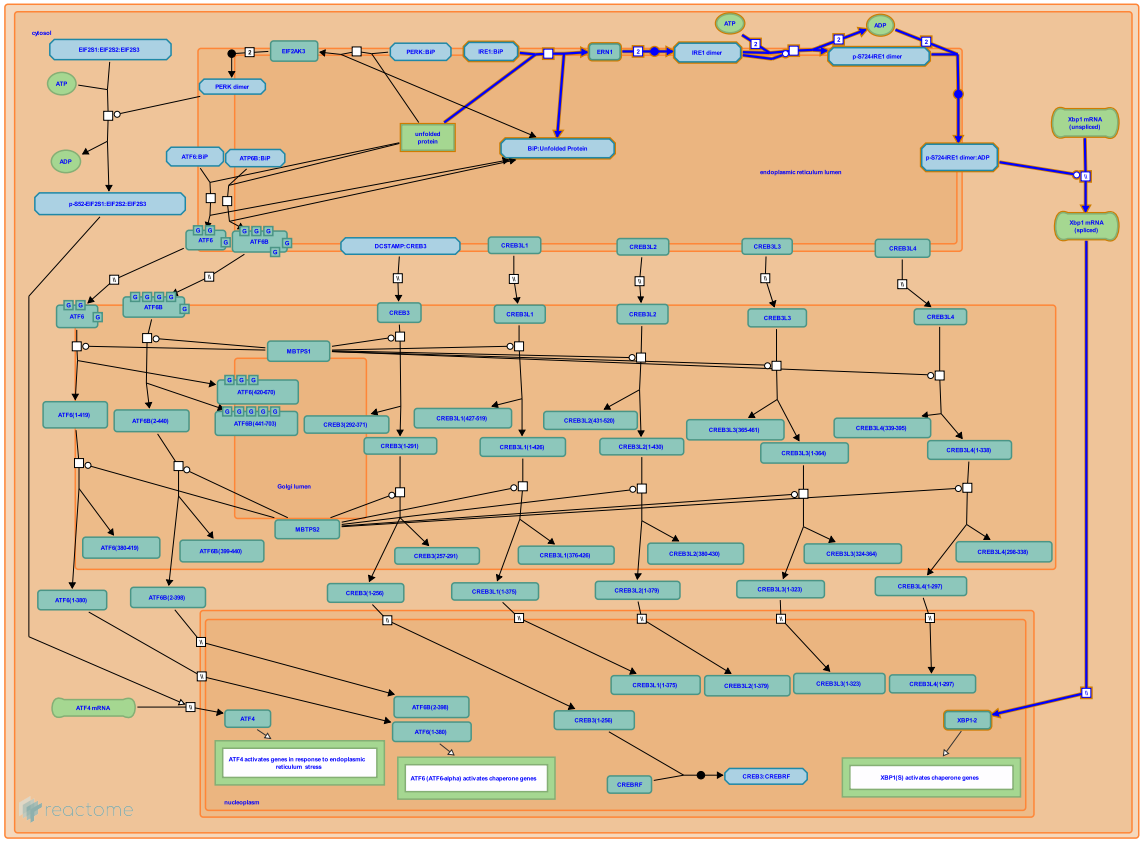
IRE1alpha activates chaperones



D'Eustachio, P., Gillespie, ME., Gopinathrao, G., Matthews, L., May, B., Urano, F.

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01/05/2024

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. ↗

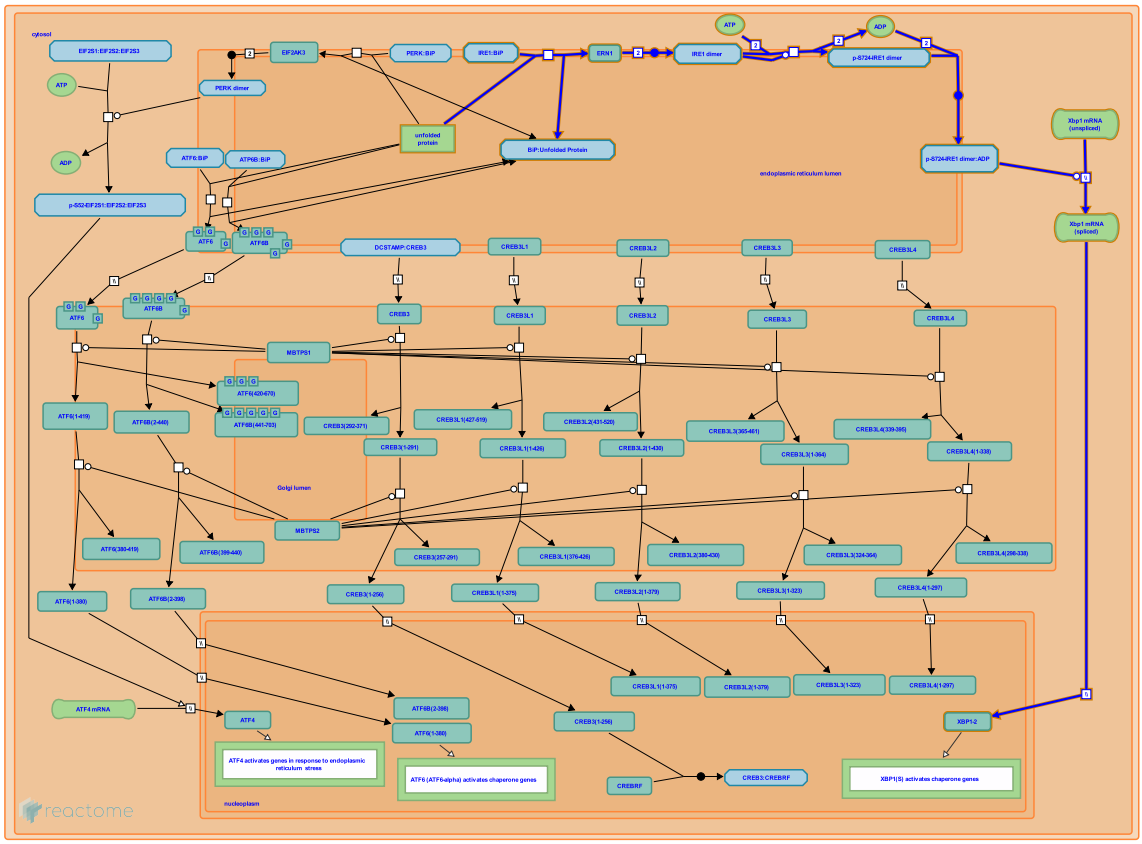
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

IRE1alpha activates chaperones ↗

Stable identifier: R-HSA-381070

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane, cytosol, nucleoplasm



IRE1-alpha is a single-pass transmembrane protein that resides in the endoplasmic reticulum (ER) membrane. The C-terminus of IRE1-alpha is located in the cytosol; the N-terminus is located in the ER lumen. In unstressed cells IRE1-alpha exists in an inactive heterodimeric complex with BiP such that BiP in the ER lumen binds the N-terminal region of IRE1-alpha. Upon accumulation of unfolded proteins in the ER, BiP binds the unfolded protein and the IRE1-alpha:BiP complex dissociates. The dissociated IRE1-alpha then forms homodimers. Initially the luminal N-terminal regions pair. This is followed by trans-autophosphorylation of IRE1-alpha at Ser724 in the cytosolic C-terminal region. The phosphorylation causes a conformational change that allows the dimer to bind ADP, causing a further conformational change to yield back-to-back pairing of the cytosolic C-terminal regions of IRE1-alpha. The fully paired IRE1-alpha homodimer has endoribonuclease activity and cleaves the mRNA encoding Xbp-1. A 26 residue polyribonucleotide is released and the 5' and 3' fragments of the original Xbp-1 mRNA are rejoined. The spliced Xbp-1 message encodes Xbp-1 (S), a potent activator of transcription. Xbp-1 (S) together with the ubiquitous transcription factor NF-Y bind the ER Stress Responsive Element (ERSE) in a number of genes encoding chaperones. Recent data suggest that the IRE1-alpha homodimer can also cleave specific subsets of mRNAs, including the insulin (INS) mRNA in pancreatic beta cells.

Literature references

Cardozo, AK., Eizirik, DL., Cnop, M. (2008). The role for endoplasmic reticulum stress in diabetes mellitus. *Endocr Rev, 29*, 42-61. ↗

Schröder, M. (2008). Endoplasmic reticulum stress responses. *Cell Mol Life Sci, 65*, 862-94. ↗

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Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.
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2010-04-30	Reviewed	Urano, F.

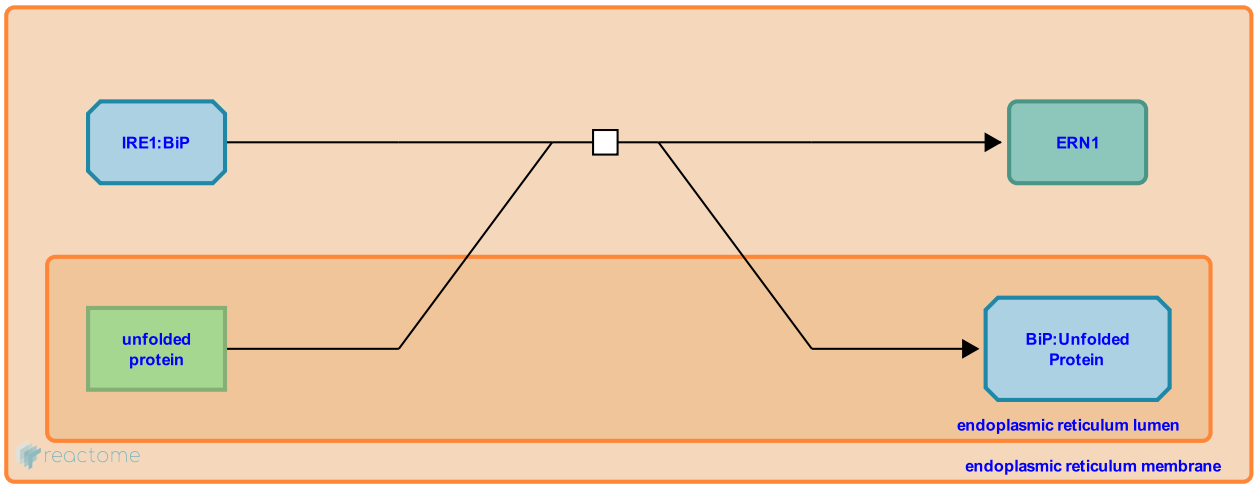
IRE1:BiP dissociates in response to unfolded protein ↗

Location: IRE1alpha activates chaperones

Stable identifier: R-HSA-381217

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



IRE1-alpha is a single-pass transmembrane protein with a luminal N-terminus and a cytoplasmic C-terminus. IRE1-alpha is maintained in an inactive state in the Endoplasmic Reticulum (ER) membrane by interaction between the luminal domain of IRE1-alpha and the ATPase domain of BiP within the ER.
BiP is a general chaperone that also binds unfolded proteins within the ER. Thus BiP dissociates from IRE1-alpha when chaperone activity is overwhelmed by unfolded proteins in the ER.

Followed by: IRE1 binds IRE1 forming dimer

Literature references

Kimata, Y., Iwawaki, T., Oikawa, D., Kohno, K. (2009). Activation of mammalian IRE1alpha upon ER stress depends on dissociation of BiP rather than on direct interaction with unfolded proteins. *Exp Cell Res, 315*, 2496-504. ↗

Back, SH., Liu, CY., Kaufman, RJ., Peisach, D., Zhou, J., Xu, Z. et al. (2006). The crystal structure of human IRE1 luminal domain reveals a conserved dimerization interface required for activation of the unfolded protein response. *Proc Natl Acad Sci U S A, 103*, 14343-8. ↗

Wong, HN., Liu, CY., Kaufman, RJ., Schauerte, JA. (2002). The protein kinase/endoribonuclease IRE1alpha that signals the unfolded protein response has a luminal N-terminal ligand-independent dimerization domain. *J Biol Chem, 277*, 18346-56. ↗

Editions

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2009-06-02	Authored, Edited	May, B.
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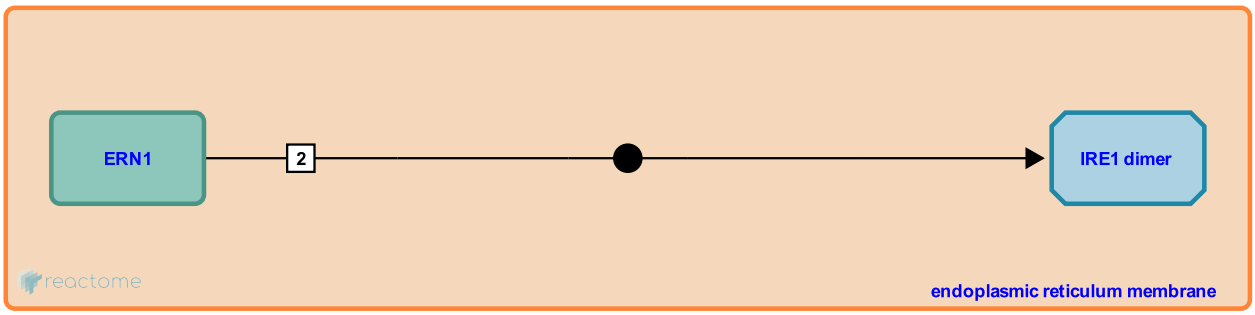
IRE1 binds IRE1 forming dimer ↗

Location: IRE1alpha activates chaperones

Stable identifier: R-HSA-381109

Type: binding

Compartments: endoplasmic reticulum membrane



The dissociation of the IRE1-alpha:BiP heterodimer liberates IRE1-alpha, which forms homodimers. Dimer formation is initiated by interaction between the N-terminal, luminal domains.

Preceded by: IRE1:BiP dissociates in response to unfolded protein

Followed by: IRE1 dimer autophosphorylates

Literature references

Liu, CY., Schröder, M., Kaufman, RJ. (2000). Ligand-independent dimerization activates the stress response kinases IRE1 and PERK in the lumen of the endoplasmic reticulum. *J Biol Chem, 275*, 24881-5. ↗

Back, SH., Liu, CY., Kaufman, RJ., Peisach, D., Zhou, J., Xu, Z. et al. (2006). The crystal structure of human IRE1 luminal domain reveals a conserved dimerization interface required for activation of the unfolded protein response. *Proc Natl Acad Sci U S A, 103*, 14343-8. ↗

Wong, HN., Liu, CY., Kaufman, RJ., Schauerte, JA. (2002). The protein kinase/endoribonuclease IRE1alpha that signals the unfolded protein response has a luminal N-terminal ligand-independent dimerization domain. *J Biol Chem, 277*, 18346-56. ↗

Lee, K., Kaufman, RJ., Callaghan, B., Welihinda, A., Tirasophon, W. (2000). The endoribonuclease activity of mammalian IRE1 autoregulates its mRNA and is required for the unfolded protein response. *Genes Dev, 14*, 2725-36. ↗

Editions

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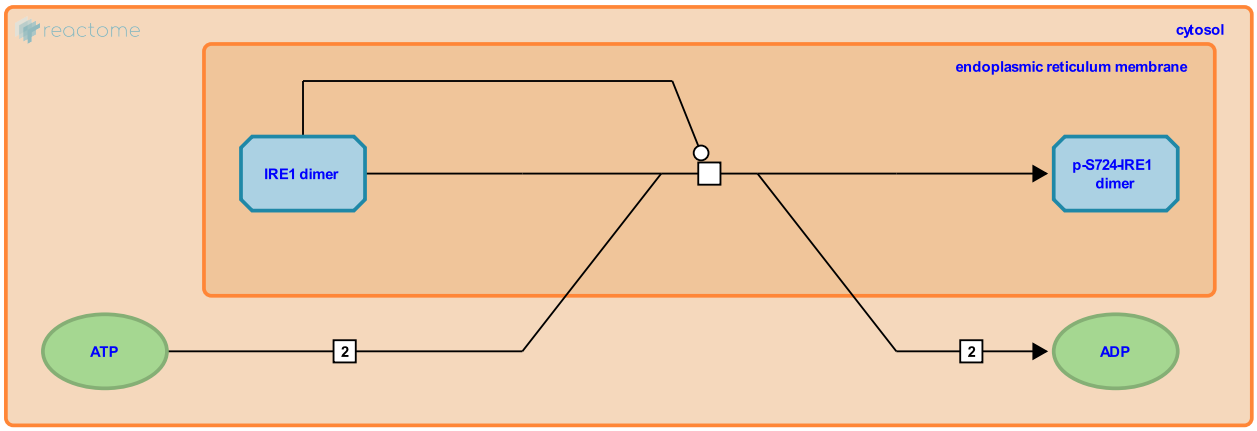
IRE1 dimer autophosphorylates ↗

Location: IRE1alpha activates chaperones

Stable identifier: R-HSA-381091

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Dimerization of the N-terminal luminal regions of IRE1-alpha brings the cytosolic C-terminal regions in proximity. The C-terminal region possesses kinase activity and the homodimer trans-autophosphorylates. From homology with Saccharomyces IRE1-alpha the phosphorylation of human IRE1-alpha is believed to be at Ser724.

Preceded by: IRE1 binds IRE1 forming dimer

Followed by: Phosphorylated IRE1 dimer binds ADP

Literature references

Back, SH., Liu, CY., Kaufman, RJ., Peisach, D., Zhou, J., Xu, Z. et al. (2006). The crystal structure of human IRE1 luminal domain reveals a conserved dimerization interface required for activation of the unfolded protein response. *Proc Natl Acad Sci U S A, 103*, 14343-8. ↗

Lee, K., Kaufman, RJ., Callaghan, B., Welihinda, A., Tirasophon, W. (2000). The endoribonuclease activity of mammalian IRE1 autoregulates its mRNA and is required for the unfolded protein response. *Genes Dev, 14*, 2725-36. ↗

Kaufman, RJ., Welihinda, AA., Tirasophon, W. (1998). A stress response pathway from the endoplasmic reticulum to the nucleus requires a novel bifunctional protein kinase/endoribonuclease (Ire1p) in mammalian cells. *Genes Dev , 12*, 1812-24. ↗

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.

Phosphorylated IRE1 dimer binds ADP ↗

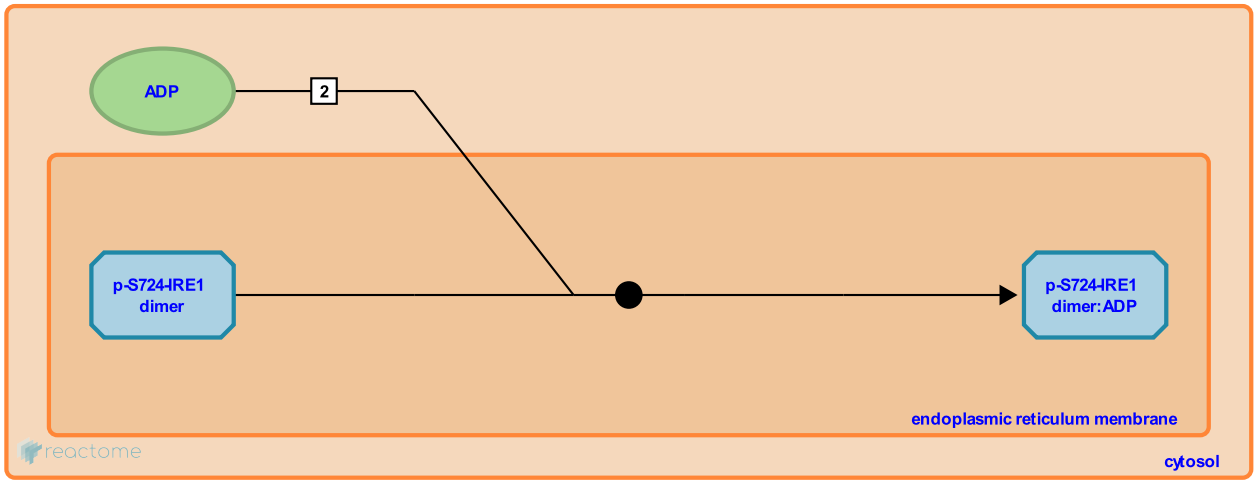
Location: IRE1alpha activates chaperones

Stable identifier: R-HSA-381116

Type: binding

Compartments: endoplasmic reticulum membrane, cytosol

Inferred from: Phosphorylated Ire1 Dimer Binds ADP (Saccharomyces cerevisiae)



Phosphorylation of the C-terminal region causes a loop in the C-terminus to change position, enabling access to an ADP-binding pocket. Phosphorylated IRE1-alpha dimers bind ADP in preference to ATP.

Preceded by: IRE1 dimer autophosphorylates

Followed by: IRE1alpha hydrolyzes Xbp1 mRNA and Xbp1 mRNA is spliced

Editions

2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.
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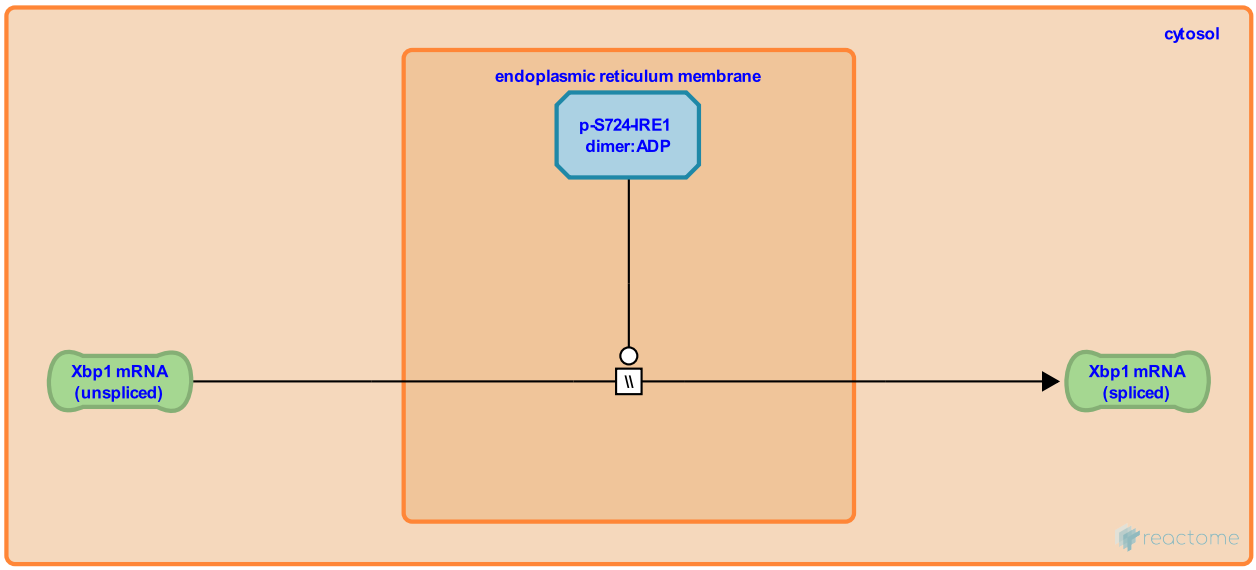
IRE1alpha hydrolyzes Xbp1 mRNA and Xbp1 mRNA is spliced ↗

Location: IRE1alpha activates chaperones

Stable identifier: R-HSA-425923

Type: omitted

Compartments: endoplasmic reticulum membrane, cytosol



Phosphorylated IRE1-alpha homodimers with bound ADP have endoribonuclease activity in their C-terminal (cytosolic) regions. The IRE1-alpha homodimers cleave an internal 26 nucleotide segment out of the Xbp-1 mRNA. In yeast the resulting RNAs are ligated by a tRNA ligase but the corresponding human ligase has not been identified. The cleavage and ligation leads to a frameshift in the Xbp-1 mRNA which results in a longer ORF that encodes Xbp-1 (S), the active form of the Xbp-1 transcription factor

Preceded by: Phosphorylated IRE1 dimer binds ADP

Followed by: XBP(S) mRNA is translated and XBP1(S) translocates to the nucleus

Literature references

Mori, K., Yamamoto, A., Yoshida, H., Matsui, T., Okada, T. (2001). XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell, 107*, 881-91. ↗

Iwawaki, T., Akai, R. (2006). Analysis of the XBP1 splicing mechanism using endoplasmic reticulum stress-indicators . *Biochem Biophys Res Commun, 350*, 709-15. ↗

Hosoda, A., Sasaka, S., Imagawa, Y., Tsuru, A., Kohno, K. (2008). RNase domains determine the functional difference between IRE1alpha and IRE1beta. *FEBS Lett, 582*, 656-60. ↗

Mori, K., Yoshida, H., Oku, M., Uemura, A. (2009). Unconventional splicing of XBP1 mRNA occurs in the cytoplasm during the mammalian unfolded protein response. *J Cell Sci, 122*, 2877-86. ↗

Editions

2008-12-02	Reviewed	Gillespie, ME., D'Eustachio, P., Matthews, L.
2009-06-04	Authored, Edited	May, B.
2010-04-30	Reviewed	Urano, F.

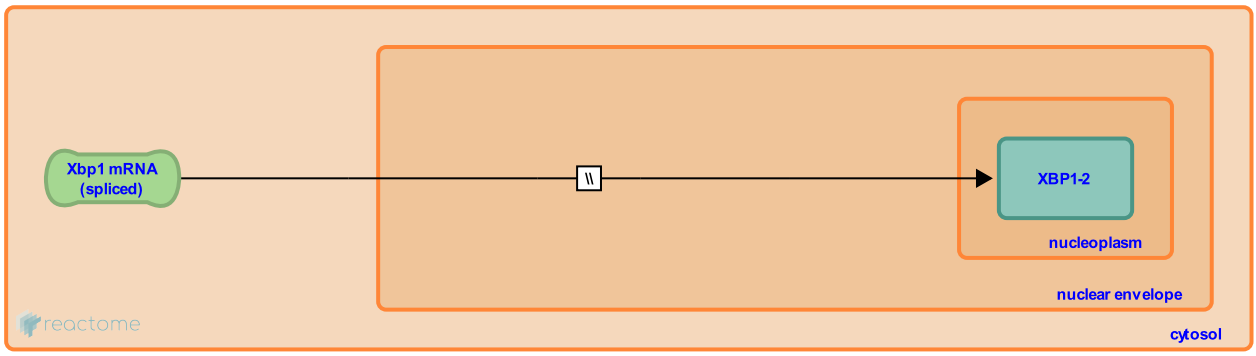
XBP(S) mRNA is translated and XBP1(S) translocates to the nucleus ↗

Location: IRE1alpha activates chaperones

Stable identifier: R-HSA-381203

Type: omitted

Compartments: nuclear envelope



Phosphorylated IRE1-alpha homodimers with bound ADP have endoribonuclease activity in their C-terminal (cytosolic) regions. In particular, the homodimers cleave an internal 26 nucleotide segment out of the Xbp-1 mRNA. In yeast the resulting RNAs are ligated by a tRNA ligase but the corresponding human enzyme has not been identified. The cleavage and ligation leads to a frameshift which results in a longer ORF that encodes Xbp-1 (S), the active form of the Xbp-1 transcription factor.
The ribonuclease activity of IRE1-alpha also degrades subsets of mRNAs in the vicinity of the ER membrane, thereby reducing the amount of protein entering the ER.
Xbp-1 mRNA that has been cleaved by IRE1-alpha encodes a 40 kd protein designated Xbp-1 (S). Xbp-1 (S) is a potent bZIP transcription factor that transits from the cytosol to the nucleus and binds the sequence CCACG in the ER Stress Responsive Element (ERSE).

Preceded by: IRE1alpha hydrolyzes Xbp1 mRNA and Xbp1 mRNA is spliced

Literature references

Clauss, IM., Glimcher, LH., Chu, M., Zhao, JL. (1996). The basic domain/leucine zipper protein hXBP-1 preferentially binds to and transactivates CRE-like sequences containing an ACGT core. *Nucleic Acids Res, 24*, 1855-64. ↗

Mori, K., Yoshida, H., Suzuki, M., Oku, M. (2006). pXBP1(U) encoded in XBP1 pre-mRNA negatively regulates unfolded protein response activator pXBP1(S) in mammalian ER stress response. *J Cell Biol, 172*, 565-75. ↗

Mori, K., Yamamoto, A., Yoshida, H., Matsui, T., Okada, T. (2001). XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell, 107*, 881-91. ↗

Editions

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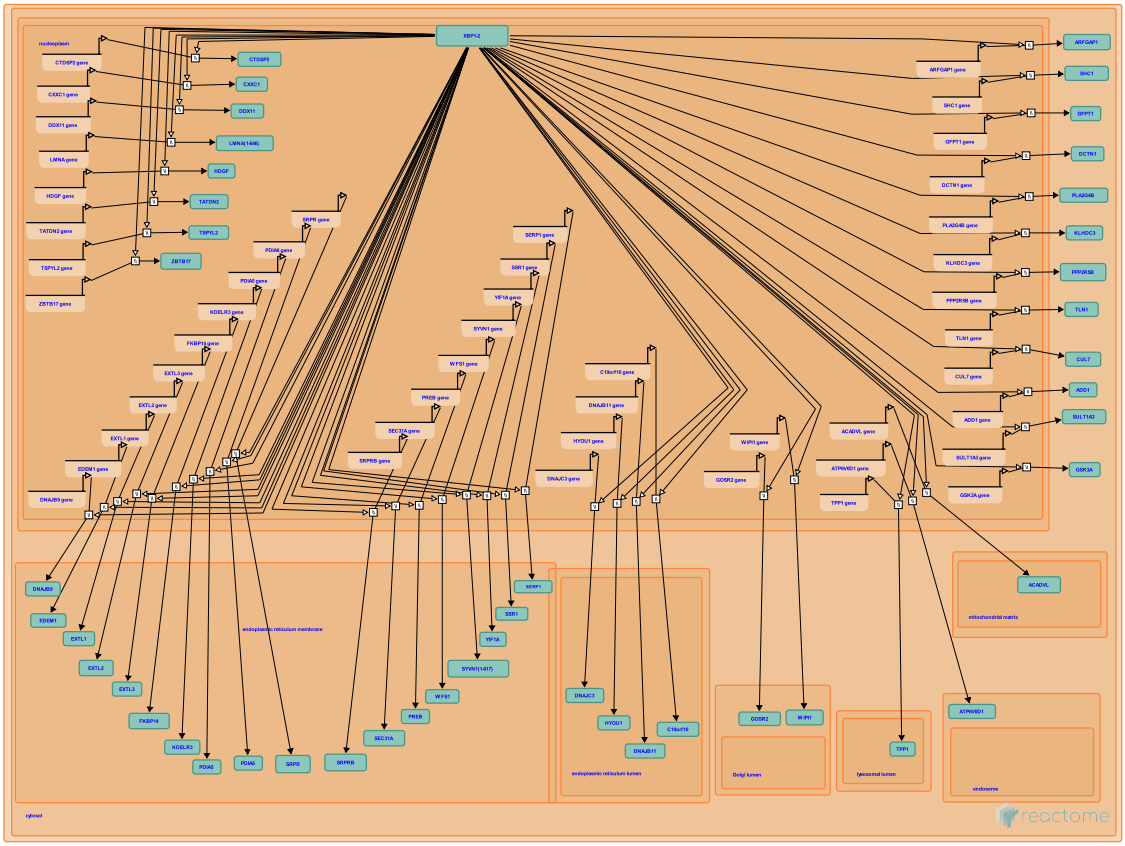
XBP1(S) activates chaperone genes ↗

Location: IRE1alpha activates chaperones

Stable identifier: R-HSA-381038

Compartments: endoplasmic reticulum membrane, nucleoplasm, cytosol, endoplasmic reticulum lumen



Xbp-1 (S) binds the sequence CCACG in ER Stress Responsive Elements (ERSE, consensus sequence CCAAT (N)9 CCACG) located upstream from many genes. The ubiquitous transcription factor NF-Y, a heterotrimer, binds the CCAAT portion of the ERSE and together the IRE1-alpha: NF-Y complex activates transcription of a set of chaperone genes including DNAJB9, EDEM, RAMP4, p58IPK, and others. This results in an increase in protein folding activity in the ER.

Literature references

Mori, K., Yoshida, H., Kaufman, RJ., Wada, T., Okada, T., Suzuki, N. et al. (2008). Human HRD1 promoter carries a functional unfolded protein response element to which XBP1 but not ATF6 directly binds. *J Biochem, 144*, 477-86. ↗

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Zhou, Y., Tsikitis, M., Dynlacht, BD., Lents, NH., Blais, A., Arias, C. et al. (2007). XBP1 controls diverse cell type- and condition-specific transcriptional regulatory networks. *Mol Cell, 27*, 53-66. ↗

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Kato, T., Ishiwata, M., Hayashi, A., Kakiuchi, C. (2006). XBP1 induces WFS1 through an endoplasmic reticulum stress response element-like motif in SH-SY5Y cells. *J Neurochem, 97*, 545-55. ↗

Editions

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2010-04-30	Reviewed	Urano, F.

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