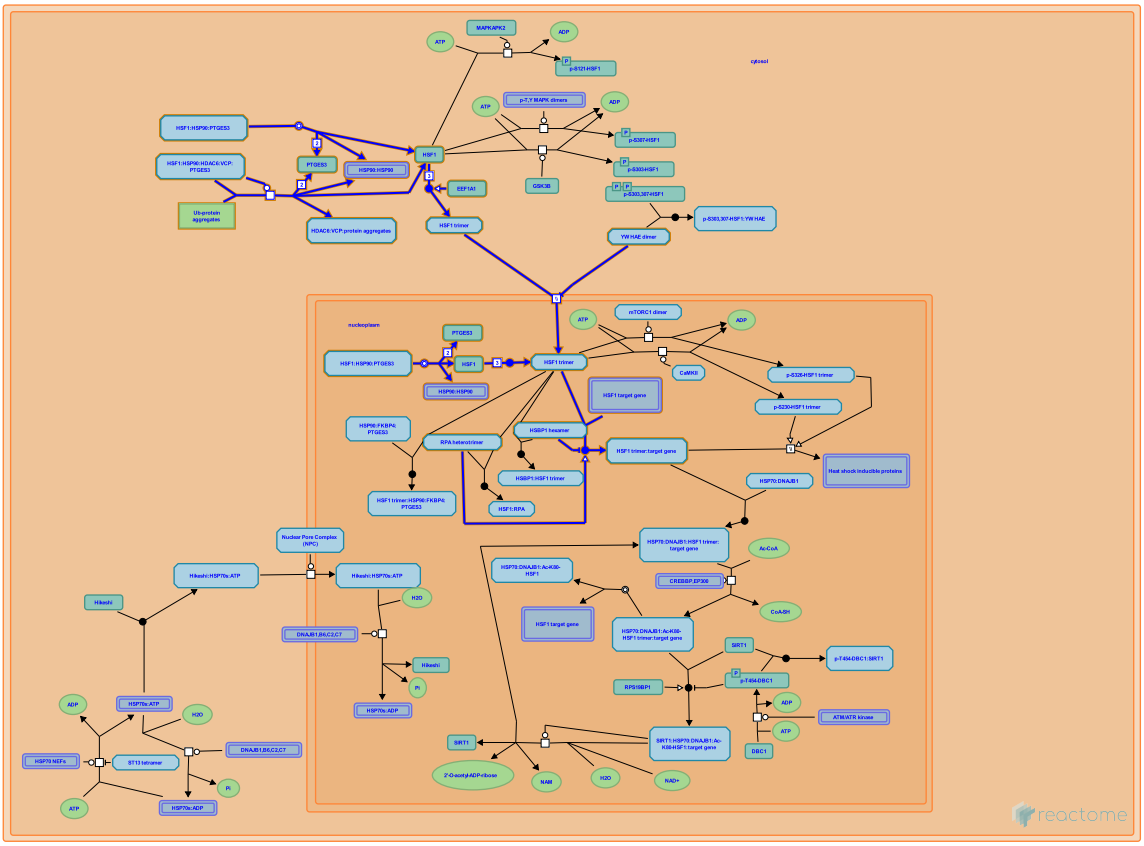
HSF1 activation



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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.

03/05/2024

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. ↗

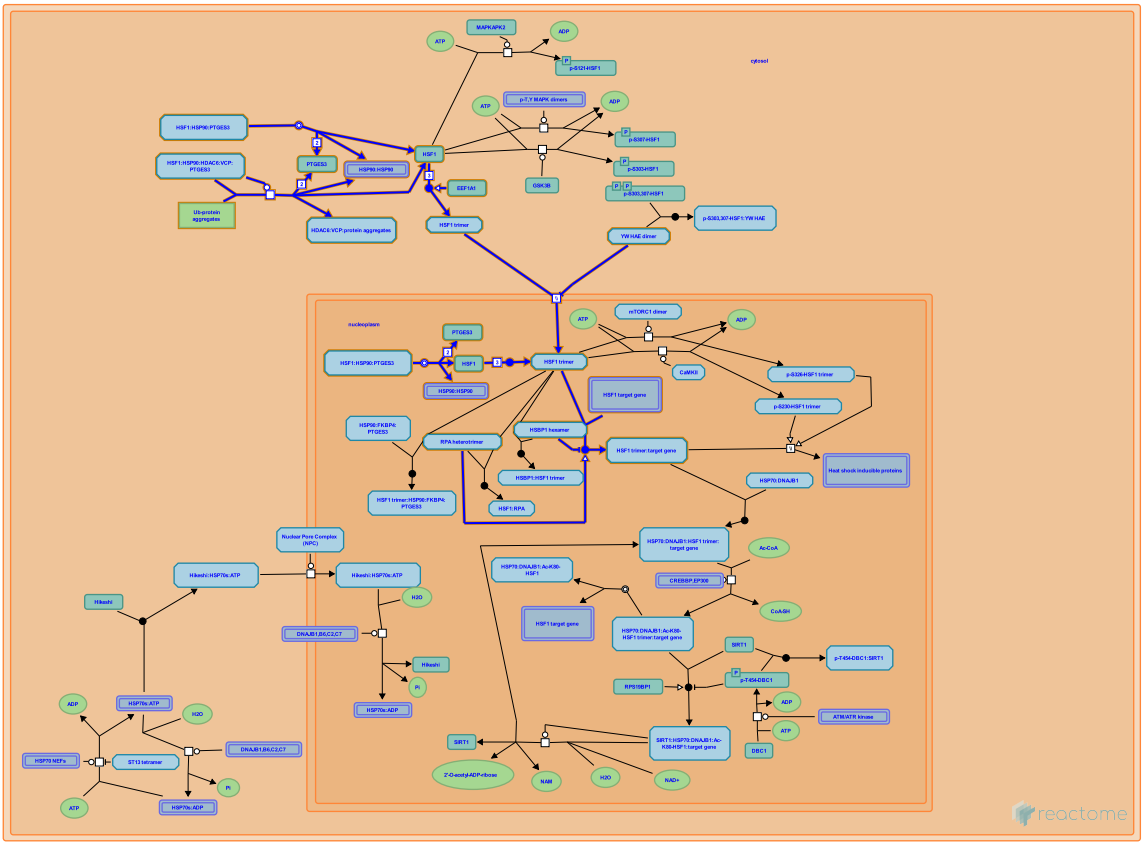
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

HSF1 activation ↗

Stable identifier: R-HSA-3371511



Heat shock factor 1 (HSF1) is a transcription factor that activates gene expression in response to a variety of stresses, including heat shock, oxidative stress, as well as inflammation and infection (Shamovsky I and Nudler E 2008; Akerfelt et al. 2010; Bjork and Sistonen 2010; Anckar and Sistonen 2011).

HSF1 is constitutively present in the cell. In the absence of stress HSF1 is found in both the cytoplasm and the nucleus as an inactive monomer (Sarge KD et al. 1993; Mercier PA et al. 1999; Vujanac M et al. 2005). A physical or chemical proteotoxic stress rapidly induces HSF1 activation, which occurs through a multi?step process, involving HSF1 monomer-to-homotrimer transition, nuclear accumulation, and binding to a promoter element, called the heat shock element (HSE), which leads to the increase in the stress-inducible gene expression (Sarge KD et al. 1993; Baler R et al. 1998; Sonna LA et al. 2002; Shamovsky I and Nudler E 2008; Sakurai H and Enoki Y 2010; Herbomel G et al. 2013). Depending on the type of stress stimulus, the multiple events associated with HSF1 activation might be affected differently (Holmberg CI et al 2000; Bjork and Sistonen 2010).

Literature references

Morimoto, RI., Kline, M., Cotto, JJ. (1996). Activation of heat shock factor 1 DNA binding precedes stress-induced serine phosphorylation. Evidence for a multistep pathway of regulation. *J. Biol. Chem., 271*, 3355-8. ↗

Rungger, D., Voellmy, R., Zuo, J. (1995). Multiple layers of regulation of human heat shock transcription factor 1. *Mol. Cell. Biol., 15*, 4319-30. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
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2014-02-17	Edited	Shamovsky, V.

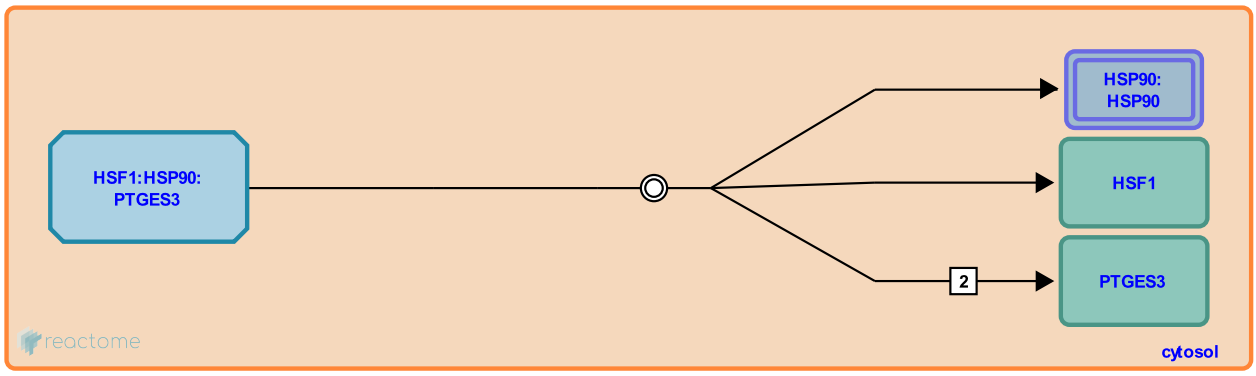
Dissociation of cytosolic HSF1:HSP90 complex ↗

Location: HSF1 activation

Stable identifier: R-HSA-3371586

Type: dissociation

Compartments: cytosol



In the absence of stress HSF1 is predominantly monomeric and is thought to be repressed in its inactive monomeric state by the following mechanisms:

- interaction with chaperone proteins such as HSP90 (Zou J et al.1998; Guo Y et al. 2001)
- intramolecular coiled-coil interactions between a hydrophobic leucine zipper domain in the carboxyl-terminus of the protein and three amino-terminal leucine zippers, which are required for homotrimerization and transcriptional activation (Rabindran SK et al. 1993; Zuo J et al. 1995)
- post-translation modifications that include protein acetylation, sumoylation and phosphorylation may also contribute to HSF1 repression (Knauf U et al. 1996; Hietakangas V et al. 2003; Batista-Nascimento L et al. 2011)

The accumulation of misfolded proteins upon proteotoxic stresses leads to the release of HSF1 from the HSP90-containing multichaperone complex and results in HSF1 self-association to form homotrimers (Baler R et al. 1993). There is also evidence showing that HDAC6 senses the accumulation of misfolded, ubiquitinated protein aggregates in cells and induces dissociation of a repressive HDAC6:HSF1:HSP90 complex and subsequent HSF1 activation (Boyault C et al. 2007).

Followed by: Trimerization of cytosolic HSF1

Literature references

Voellmy, R., Smith, DF., Guettouche, T., Guo, Y., Zou, J. (1998). Repression of heat shock transcription factor HSF1 activation by HSP90 (HSP90 complex) that forms a stress-sensitive complex with HSF1. *Cell, 94*, 471-80. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

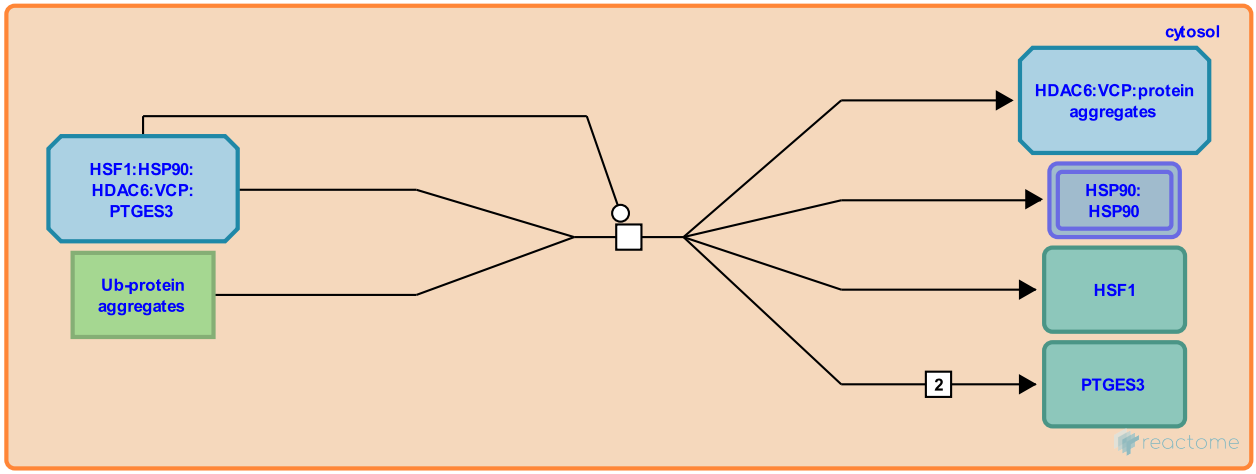
Dissociation of cytosolic HSF1:HSP90:HDAC6:PTGES3 upon sensing protein aggregates ↗

Location: HSF1 activation

Stable identifier: R-HSA-5324632

Type: transition

Compartments: cytosol



Proteotoxic stress results in an accumulation of misfolded proteins which tend to form insoluble protein aggregates. Histone deacetylase 6 (HDAC6) binds to ubiquitinated protein aggregates to regulate their degradation (Boyault C et al. 2006). HDAC6 was also found to interact with HSP90 and to regulate HSP90 chaperone complex activity via deacetylation of HSP90 (Kovacs JJ et al. 2005; Boyault C et al. 2007). Binding of HDAC6 to polyubiquitinted proteins triggers the dissociation of the HDAC6:HSP90:HSF1 complex resulting in the activation of HSF1 (Boyault C et al. 2007).

In the absence of stress HSF1 is predominantly monomeric and is thought to be repressed in its inactive monomeric state by the following mechanisms:

- interaction with chaperone proteins such as HSP90 (Zou J et al.1998; Guo Y et al. 2001)
- intramolecular coiled-coil interactions between a hydrophobic leucine zipper domain in the carboxyl-terminus of the protein and three amino-terminal leucine zippers, which are required for homotrimerization and transcriptional activation (Rabindran SK et al. 1993; Zuo J et al. 1995)
- post-translation modifications that include protein acetylation, sumoylation and phosphorylation may also contribute to HSF1 repression (Knauf U et al. 1996; Hietakangas V et al. 2003; Batista-Nascimento L et al. 2011)

Followed by: Trimerization of cytosolic HSF1

Literature references

Garrido, C., Gilquin, B., Zhang, Y., Khochbin, S., Vourc'h, C., Matthias, P. et al. (2007). HDAC6 controls major cell response pathways to cytotoxic accumulation of protein aggregates. *Genes Dev., 21*, 2172-81. ↗

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2014-02-17	Edited	Shamovsky, V.

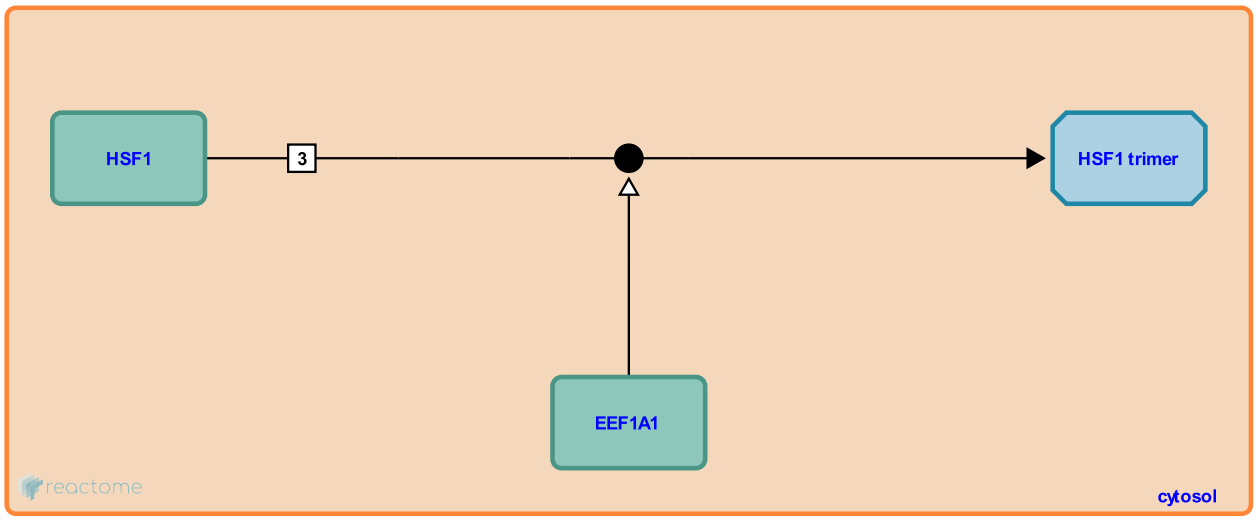
Trimerization of cytosolic HSF1 ↗

Location: HSF1 activation

Stable identifier: R-HSA-3371591

Type: binding

Compartments: cytosol



Accumulation of non-native or misfolded proteins upon cellular stress is believed to release monomeric HSF1 from chaperon regulatory proteins (Guo Y et al. 2001). The released HSF1 monomer is rapidly converted to a homotrimer (Baler R et al. 1993; Herbomel G et al 2013). Upon trimerization HSF1 undergoes significant conformational changes resulting in an assembly of a stable triple-stranded alpha-helical coiled-coil structure with the amino-terminal hydrophobic domains from individual monomeric units (Rabindran SK et al. 1993; Zuo J et al. 1994, 1995; Neef DW et al. 2013). Biochemical and structural analysis strongly suggest that the monomer-to-trimer transition is tightly regulated at several interdependent levels. Thus, HSPs and cofactors bind HSF1 monomers preventing trimerization (Zou J et al.1998; Guo Y et al. 2001). In addition, leucine zippers (LZ) in the trimerization domain (LZ1-LZ3) are thought to retain HSF1 in its inactive monomeric form by intramolecular coiled-coil interactions with LZ4 in the carboxyl-terminus of HSF1, while LZ interactions between trimerization domains of individual monomeric units facilitate homotrimerization (Rabindran SK et al. 1993; Zuo J et al. 1994, 1995; Neef DW et al. 2013). HSF1 flexible linker region between DNA binding domain and first LZ of the trimerization domain was also found to modulate the monomer-trimer equilibrium (Liu PCC and Thiele DJ 1999). Furthermore, intermolecular disulfide bonds between cysteine residues 36 and 103 were reported to stabilize HSF1 trimer, while intramolecular disulfide crosslink inhibited HSF1 oligomerization (Lu M et al. 2008, 2009). Moreover, redox regulatory mechanisms were shown to regulate thiol-disulfide exchange and the conformation and activity of mammalian HSF1 in response to stress (Manalo DJ et al. 2002; Ahn SG and Thiele DJ 2003).

A ribonucleoprotein complex containing translation elongation factor EEF1A1 (eEF1A) and a long non-coding RNA, HSR1 (heat shock RNA-1) was shown to mediate trimerization of HSF1 (Shamovsky I et al. 2006).

Preceded by: Dissociation of cytosolic HSF1:HSP90:HDAC6:PTGES3 upon sensing protein aggregates, Dissociation of cytosolic HSF1:HSP90 complex

Followed by: HSF1 trimer translocates to the nucleus

Literature references

Voellmy, R., Baler, R., Dahl, G. (1993). Activation of human heat shock genes is accompanied by oligomerization, modification, and rapid translocation of heat shock transcription factor HSF1. *Mol. Cell. Biol., 13*, 2486-96. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

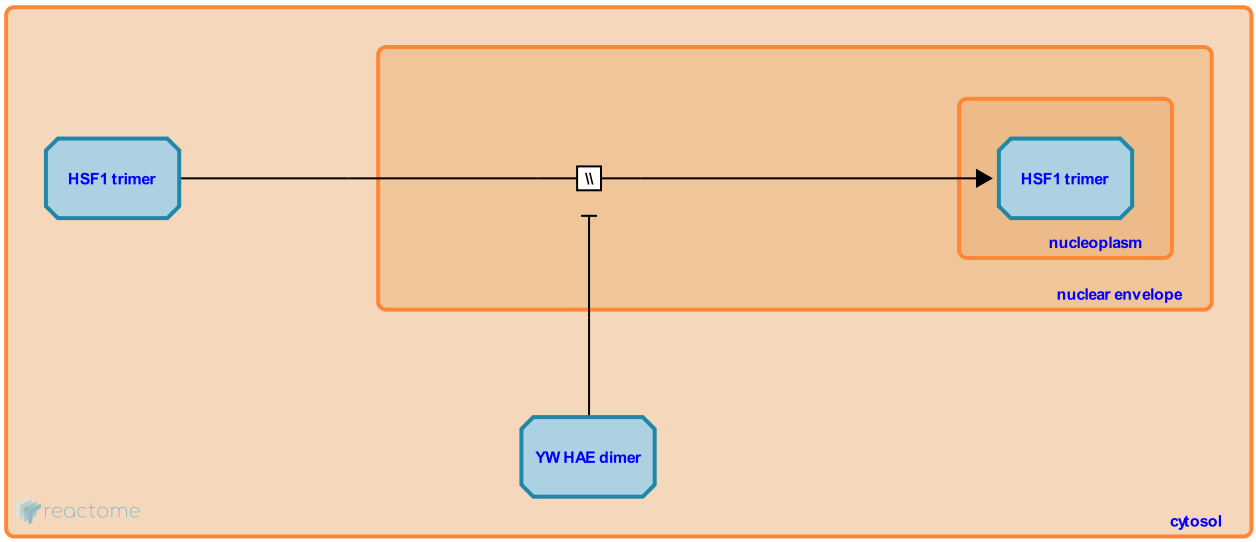
HSF1 trimer translocates to the nucleus ↗

Location: HSF1 activation

Stable identifier: R-HSA-3371527

Type: omitted

Compartments: nuclear envelope, nucleoplasm, cytosol



There is no consensus on whether inactive HSF1 monomers localize in the nucleus or in the cytosol (Sarge KD et al. 1993; Zuo J et al. 1995; Mercier PA et al. 1999; Vujanac M et al. 2005). Moreover, inactive HSF1 was reported to constitutively shuttle between the nucleus and the cytoplasm in mammalian cells (Vujanac M et al. 2005). However, active HSF1 trimers were shown to rapidly accumulate in the nucleus where they bind to heat shock elements (HSE) present within promoters of hsp genes (Wang Y and Morgan WD 1994; Herbomel G et al. 2013).

Heat shock response in human and monkey cells (but not rodent cells) is also associated with the stress-induced relocalization of HSF1 within the nucleus not only on hsp gene promoters but also into specific subnuclear organelles termed nuclear stress bodies (nSBs, also known as HSF1 granules) (Sarge KD et a. 1993; Cotto JJ et al. 1997; Jolly C et al. 1999). nSBs are rarely detectable in unstressed cells but their number drastically increases after heat shock. Formation of nSBs is initiated by the interaction between HSF1 and pericentric tandem repeats of satellite III sequences on chromosome 9, where sat III repeats are transcribed by RNA polymerase II in an HSF1-dependent manner. (Jolly C et al. 2002, 2004). HSF1 can also bind to DNA regions enriched in sat II and sat III repeated sequences detected on other human chromosomes (Eymery A et al. 2010). The functional relevance of HSF1 granules and their transcripts remains an open question.

Preceded by: Trimerization of cytosolic HSF1

Followed by: HSF1 trimer binds HSE on the target gene

Literature references

Vujanac, M., Zimarino, V., Fenaroli, A. (2005). Constitutive nuclear import and stress-regulated nucleocytoplasmic shuttling of mammalian heat-shock factor 1. *Traffic, 6*, 214-29. ↗

Voellmy, R., Baler, R., Dahl, G. (1993). Activation of human heat shock genes is accompanied by oligomerization, modification, and rapid translocation of heat shock transcription factor HSF1. *Mol. Cell. Biol., 13*, 2486-96. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

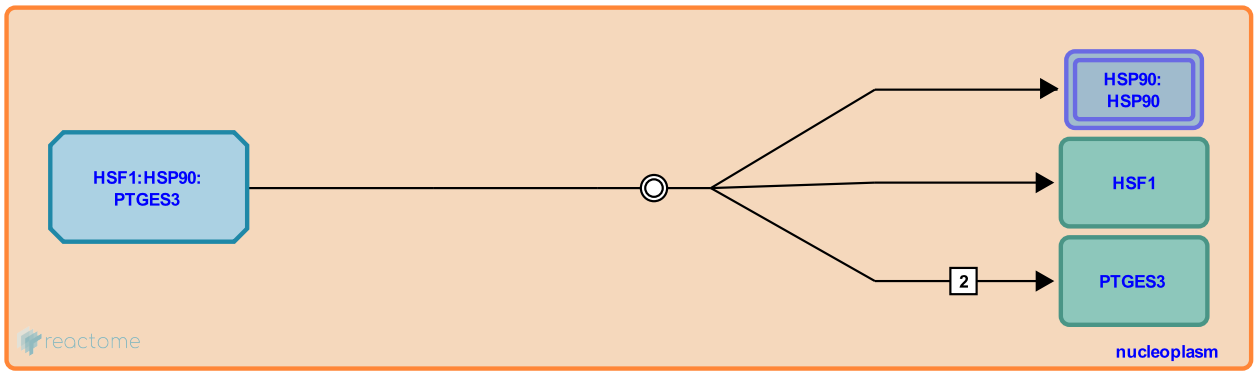
Dissociation of HSF1:HSP90 complex in the nucleus ↗

Location: HSF1 activation

Stable identifier: R-HSA-5082409

Type: dissociation

Compartments: nucleoplasm



The inactive HSF1 was reported to constitutively shuttle between the nucleus and the cytoplasm in mammalian cells (Vujanac M et al. 2005). There is no consensus on whether inactive HSF1 monomers localize in the nucleus or in the cytosol (Sarge KD et al. 1993; Zuo J et al. 1995; Mercier PA et al. 1999; Vujanac M et al. 2005). This event shows stress-induced activation of HSF1 in the nucleus.

In the absence of stress HSF1 is predominantly monomeric and is thought to be repressed in its inactive monomeric state by the following mechanisms:

- interaction with chaperone proteins such as HSP90 (Zou J et al.1998; Guo Y et al. 2001)
- intramolecular coiled-coil interactions between a hydrophobic leucine zipper domain in the carboxyl-terminus of the protein and three amino-terminal leucine zippers, which are required for homotrimerization and transcriptional activation (Rabindran SK et al. 1993; Zuo J et al. 1995)
- post-translation modifications that include protein acetylation, sumoylation and phosphorylation may also contribute to HSF1 repression (Knauf U et al. 1996; Hietakangas V et al. 2003; Batista-Nascimento L et al. 2011)

The accumulation of misfolded proteins upon proteotoxic stresses leads to the release of HSF1 from the HSP90-containing multichaperone complex and results in HSF1 self-association to form homotrimers (Baler R et al. 1993).

Followed by: Trimerization of HSF1 in the nucleus

Literature references

Voellmy, R., Smith, DF., Guettouche, T., Guo, Y., Zou, J. (1998). Repression of heat shock transcription factor HSF1 activation by HSP90 (HSP90 complex) that forms a stress-sensitive complex with HSF1. *Cell, 94*, 471-80. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
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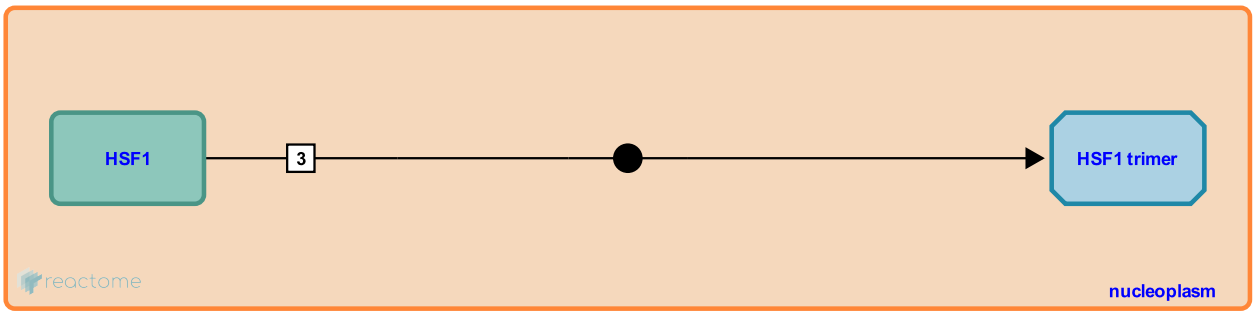
Trimerization of HSF1 in the nucleus ↗

Location: HSF1 activation

Stable identifier: R-HSA-5082391

Type: binding

Compartments: nucleoplasm



Accumulation of non-native or misfolded proteins upon cellular stress is believed to release monomeric HSF1 from chaperon regulatory proteins (Guo Y et al. 2001). The released HSF1 monomer is rapidly converted to a homotrimer (Baler R et al. 1993; Herbomel G et al 2013). Upon trimerization HSF1 undergoes significant conformational changes resulting in an assembly of a stable triple-stranded alpha-helical coiled-coil structure with the amino-terminal hydrophobic domains from individual monomeric units (Rabindran SK et al. 1993; Zuo J et al. 1994, 1995; Neef DW et al. 2013). Biochemical and structural analysis strongly suggest that the monomer-to-trimer transition is tightly regulated at several interdependent levels. Thus, HSPs and cofactors bind HSF1 monomers preventing trimerization (Zou J et al.1998; Guo Y et al. 2001). In addition, leucine zippers (LZ) in the trimerization domain (LZ1-LZ3) are thought to retain HSF1 in its inactive monomeric form by intramolecular coiled-coil interactions with LZ4 in the carboxyl-terminus of HSF1, while LZ interactions between trimerization domains of individual monomeric units facilitate homotrimerization (Rabindran SK et al. 1993; Zuo J et al. 1994, 1995; Neef DW et al. 2013). HSF1 flexible linker region between DNA binding domain and first LZ of the trimerization domain was also found to modulate the monomer-trimer equilibrium (Liu PCC and Thiele DJ 1999). Furthermore, intermolecular disulfide bonds between cysteine residues 36 and 103 were reported to stabilize HSF1 trimer, while intramolecular disulfide crosslink inhibited HSF1 oligomerization (Lu M et al. 2008, 2009). Moreover, redox regulatory mechanisms were shown to regulate thiol-disulfide exchange and the conformation and activity of mammalian HSF1 in response to stress (Manalo DJ et al. 2002; Ahn SG and Thiele DJ 2003).

A ribonucleoprotein complex containing translation elongation factor EEF1A1 (eEF1A) and a long non-coding RNA, HSR1 (heat shock RNA-1) was shown to mediate trimerization of HSF1 (Shamovsky I et al. 2006).

Preceded by: Dissociation of HSF1:HSP90 complex in the nucleus

Followed by: HSF1 trimer binds HSE on the target gene

Literature references

Voellmy, R., Baler, R., Dahl, G. (1993). Activation of human heat shock genes is accompanied by oligomerization, modification, and rapid translocation of heat shock transcription factor HSF1. *Mol. Cell. Biol., 13*, 2486-96. ↗

Editions

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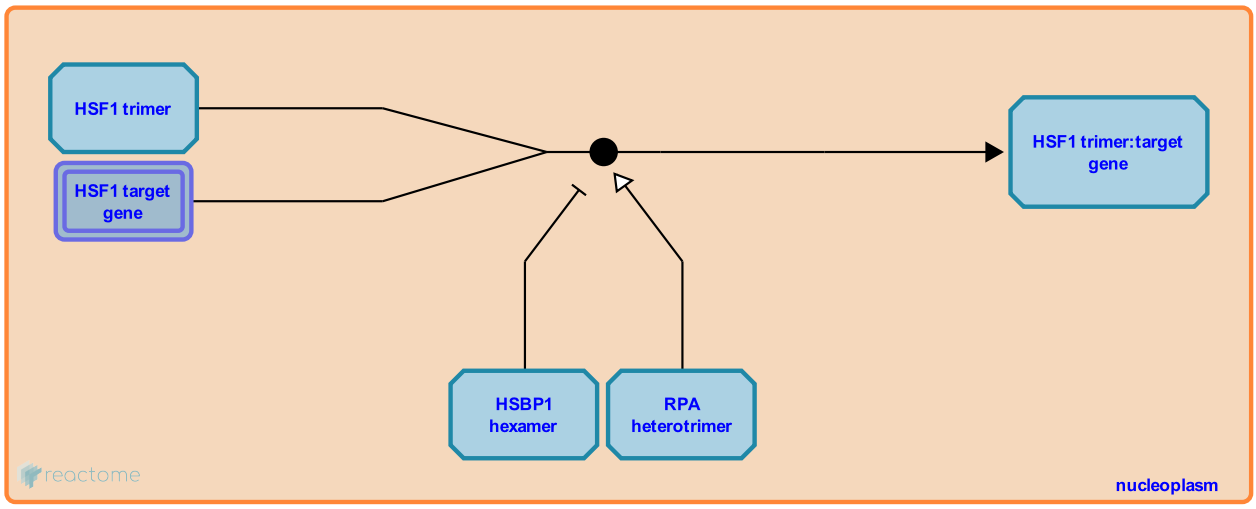
HSF1 trimer binds HSE on the target gene ↗

Location: HSF1 activation

Stable identifier: R-HSA-4793819

Type: binding

Compartments: nucleoplasm



Stress-induced HSF1 trimerization results in the increased affinity of HSF1 for the heat shock elements (HSE) usually located within promoters of HSF1 target genes (Sarge KD et al. 1993; Wang Y and Morgan WD 1994; Herbomel G et al. 2013). HSEs are highly conserved and consist of contiguous inverted repeats of pentameric sequence nGAAn (i.e., nGAAnnTTCnnGAAn) (Abravaya K et al. 1991; Sarge KD et al. 1993; Cunniff NFA & Morgan WD 1993). The promoters of HSF target genes can contain more than one HSE, suggesting that the HSF1-HSE interaction may occur in cooperative manner when the binding of HSF trimer to HSE facilitates binding of the next HSF1 trimer (Wang Y and Morgan WD 1994).

Replication protein A (RPA), which is involved in DNA metabolism, was shown to support transcription factor access to nucleosomal DNA as a scaffold for HSF1 and a histone chaperone, FACT (Fujimoto M et al. 2012).

Mutagenesis analysis revealed that DNA binding domain of human HSF1 is required for HSF1 binding to HSE and for nuclear stress bodies (nSBs) formation (Westerheide SD et al. 2009; Herbomel G et al. 2013).

While HSF1 can bind to promoters of many genes targets with or without inducing their transcription, it is best known for stress-induced regulatory functions on certain chaperone genes, such as HSPA1A/HSP70, HSPC/HSP90, HSPB1/HSP27, and DNAJB1/HSP40 (Mosser DD et al. 1988; Trinklein ND et al. 2004a,b; Page TG et al. 2006). At the same time, however, the constitutive expression of hsp70, hsp60, BiP/GRP78, and hsp27 in cultured embryonic murine cells was unaffected by the disruption of the hsf1 gene (McMillan et al. 1998). This is additionally supported by findings that the production of HSP70 was not induced after transfection of HSF1 into human epidermoid A431 cells despite the fact that HSF1 was found to bind HSE on hsp70 gene. While HSP70 production was not altered in unstressed cells, the treatment with phorbol 12-myristate 13-acetate (PMA) increased the HSP70 level in A431 cells and reached even higher expression level in HSF1-transfected A431 cells (Ding XZ et al. 1997). Thus, HSF1 is required for stress-induced upregulation of hsp genes while may not be involved in their basal expression (as was shown in higher eukaryotes).

Preceded by: Trimerization of HSF1 in the nucleus, HSF1 trimer translocates to the nucleus

Literature references

Morgan, WD., Wang, Y. (1994). Cooperative interaction of human HSF1 heat shock transcription factor with promoter DNA. *Nucleic Acids Res., 22,* 3113-8. ↗

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Table of Contents