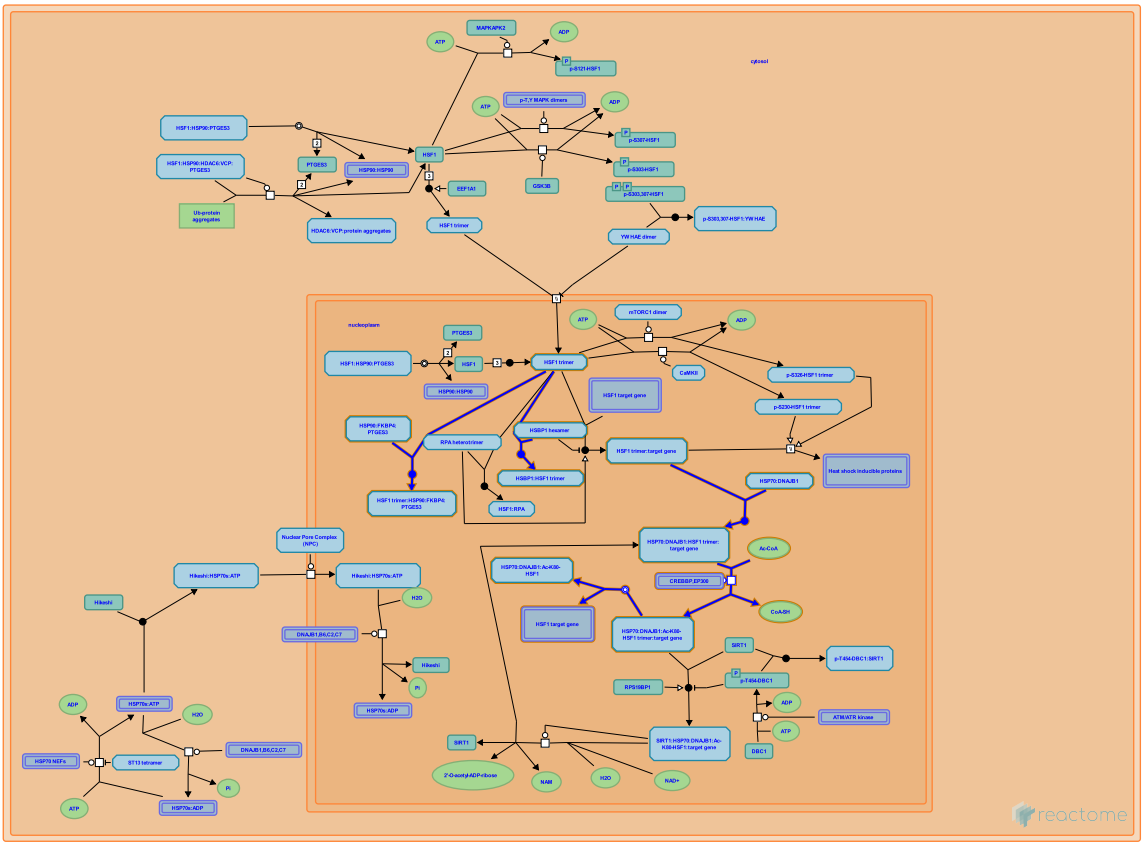
Attenuation phase



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04/05/2024

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. ↗

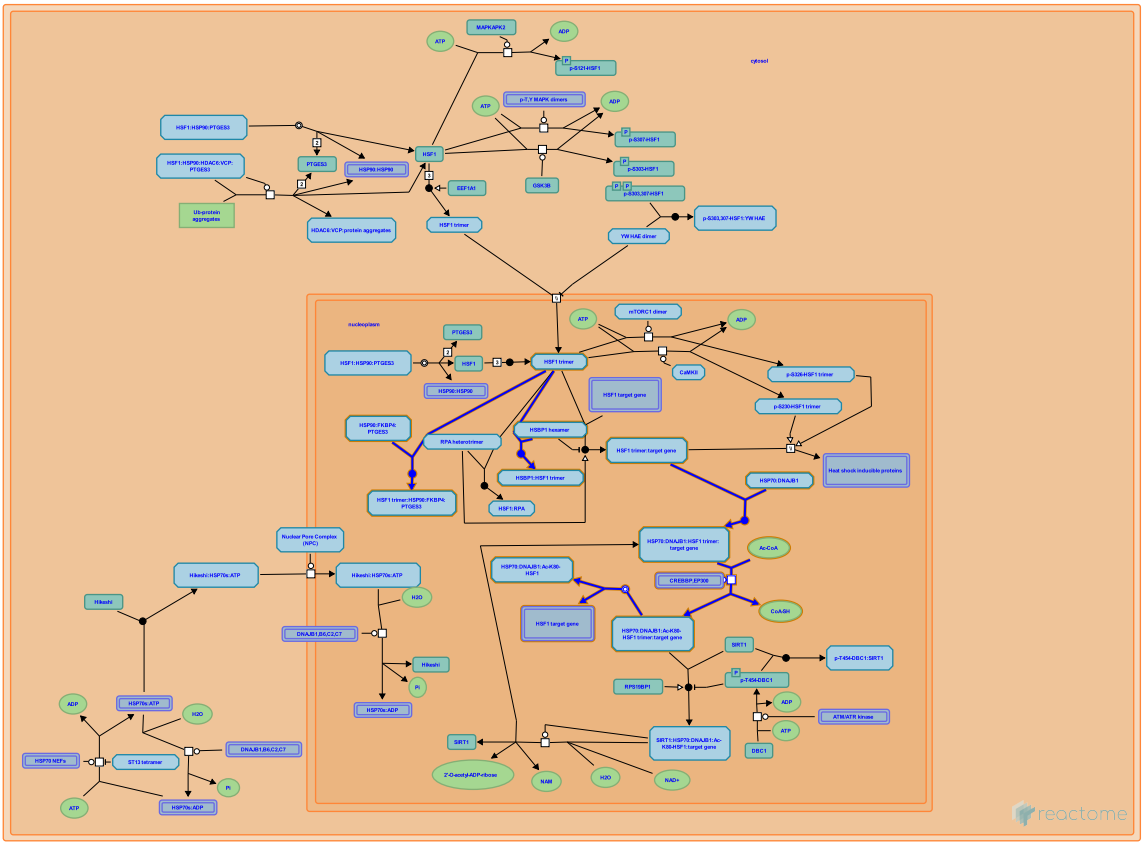
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Attenuation phase ↗

Stable identifier: R-HSA-3371568



Attenuation of the heat shock transcriptional response occurs during continuous exposure to intermediate heat shock conditions or upon recovery from stress (Abravaya et al. 1991). The attenuation phase of HSF1 cycle involves the transcriptional silencing of HSF1 bound to HSE, the release of HSF1 trimers from HSE and dissociation of HSF1 trimers to monomers. HSF1-driven heat stress associated transcription was shown to depend on inducible and reversible acetylation of HSF1 at Lys80, which negatively regulates DNA binding activity of HSF1 (Westerheide SD et al. 2009). In addition, the attenuation of HSF1 activation takes place when enough HSP70/HSP40 is produced to saturate exposed hydrophobic regions of proteins damaged as a result of heat exposure. The excess HSP70/HSP40 binds to HSF1 trimer, which leads to its dissociation from the promoter and conversion to the inactive monomeric form (Abravaya et al. 1991; Shi Y et al. 1998). Interaction of HSP70 with the transcriptional corepressor repressor element 1-silencing transcription factor corepressor (CoREST) assists in terminating heat-shock response (Gomez AV et al. 2008). HSF1 DNA-binding and transactivation activity were also inhibited upon interaction of HSF1-binding protein (HSBP1) with active trimeric HSF1(Satyal SH et al. 1998).

Literature references

Morimoto, RI., Abravaya, K., Phillips, B. (1991). Attenuation of the heat shock response in HeLa cells is mediated by the release of bound heat shock transcription factor and is modulated by changes in growth and in heat shock temperatures. *Genes Dev., 5*, 2117-27. ↗

Editions

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

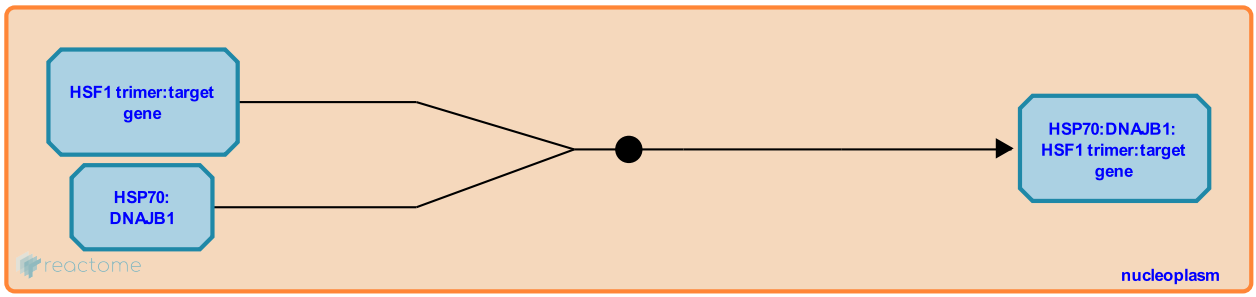
HSP70:DNAJB1 binds HSF1 ↗

Location: Attenuation phase

Stable identifier: R-HSA-5082384

Type: binding

Compartments: nucleoplasm



During attenuation and recovery from heat shock, increased levels of HSP70 and HDJ1 (HSP40) were found to associate with the HSF1 activation domain, repressing its transcriptional activity (Shi Y et al. 1998)

Literature references

Voellmy, R., Welch, WJ., Baler, R. (1992). Heat shock gene regulation by nascent polypeptides and denatured proteins: hsp70 as a potential autoregulatory factor. *J. Cell Biol., 117*, 1151-9. ↗

Murphy, SP., Morimoto, RI., Abravaya, K., Myers, MP. (1992). The human heat shock protein hsp70 interacts with HSF, the transcription factor that regulates heat shock gene expression. *Genes Dev., 6*, 1153-64. ↗

Shi, Y., Morimoto, RI., Mosser, DD. (1998). Molecular chaperones as HSF1-specific transcriptional repressors. *Genes Dev., 12*, 654-66. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
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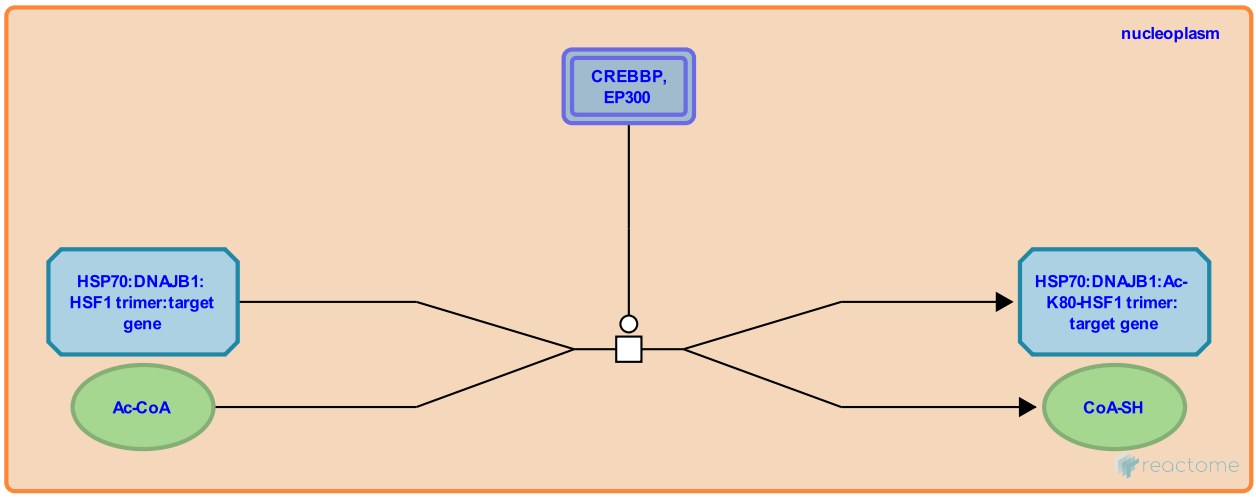
HSF1 acetylation at Lys80 ↗

Location: Attenuation phase

Stable identifier: R-HSA-3371554

Type: transition

Compartments: nucleoplasm



Acetylated HSF1 was detected in lysates of human embryonic kidney 293T cells which were transfected with vectors encoding a Flag-HSF1 fusion and p300 proteins and exposed to various stress conditions (Westerheide SD et al. 2012). No acetylation was found in lysates of unstressed cells. Acetylation of HSF1 may occurs on multiple lysines, such as Lys80 within the DNA binding domain. Mutation of Lys80 disrupted the DNA-binding ability of recombinant HSF1, indicating that the acetylation at Lys80 caused the regulated release of the HSF1 trimers from DNA and thus represents a regulatory step in the attenuation of the heat shock responce (Westerheide SD et al. 2009; Herbomel G et al 2013).

Followed by: Acetylated HSF1 dissociates from DNA

Literature references

Sistonen, L., Morimoto, RI., Westerheide, SD., Anckar, J., Stevens, SM. (2009). Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. *Science, 323*, 1063-6. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
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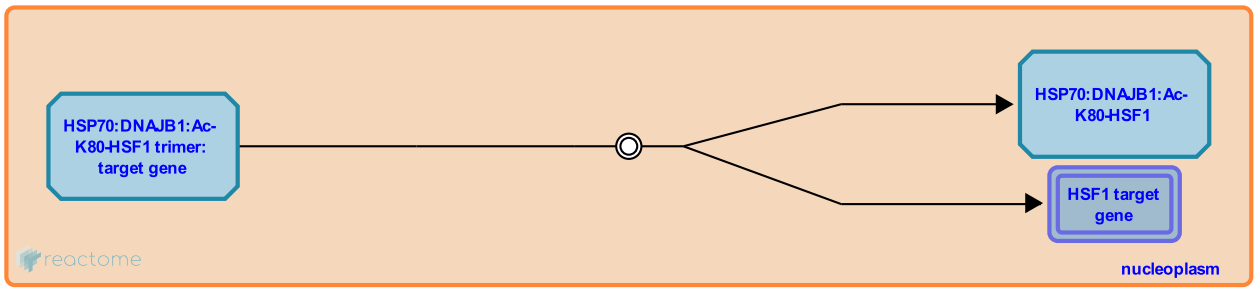
Acetylated HSF1 dissociates from DNA ↗

Location: Attenuation phase

Stable identifier: R-HSA-5082369

Type: dissociation

Compartments: nucleoplasm



Inducible acetylation of HSF1 at Lys80 within the DNA binding domain results in the disrupted DNA-binding ability thus causing the regulated release of the HSF1 trimers from DNA (Westerheide SD et al. 2009). This acetylation is reversible. Activation of the deacetylase and longevity factor SIRT1 was shown to prolong HSF1 binding to the heat shock promoter of hsp70 gene by maintaining HSF1 in a deacetylated state (Westerheide SD et al. 2009). Thus, the balance between deacetylase activity of SIRT1 and acetyltransferase activity of p300 determine the DNA-binding competent state of HSF1.

Preceded by: HSF1 acetylation at Lys80

Literature references

Sistonen, L., Morimoto, RI., Westerheide, SD., Anckar, J., Stevens, SM. (2009). Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. *Science, 323*, 1063-6. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
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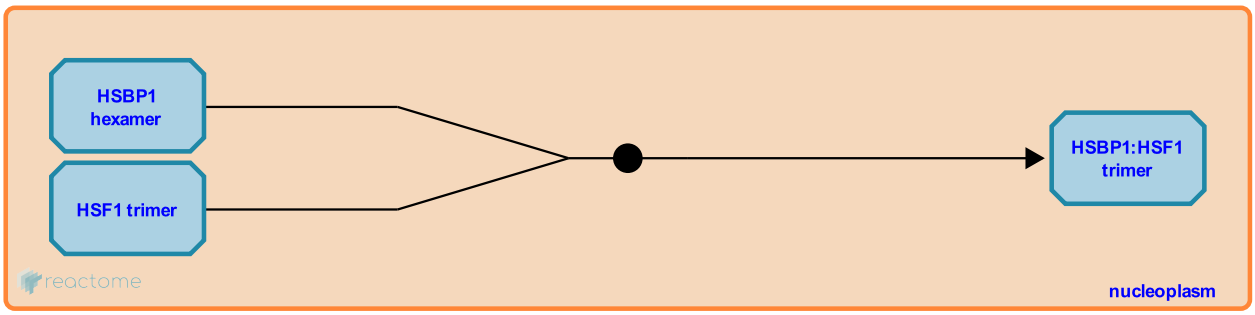
HSBP1 binds HSF1 trimer ↗

Location: Attenuation phase

Stable identifier: R-HSA-3371582

Type: binding

Compartments: nucleoplasm



Heat shock factor binding protein 1 (HSBP1) is a nuclear localized hydrophobic repeat-containing protein, which interacts with trimerization domain of HSF1 and negatively regulates DNA-binding activity of HSF1. Overexpression of HSBP1 in mammalian cells represses the transactivation activity of HSF1 (Satyal SH et al. 1998).

Literature references

Fox, SG., Morimoto, RI., Kramer, JM., Chen, D., Satyal, SH. (1998). Negative regulation of the heat shock transcriptional response by HSBP1. *Genes Dev., 12*, 1962-74. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
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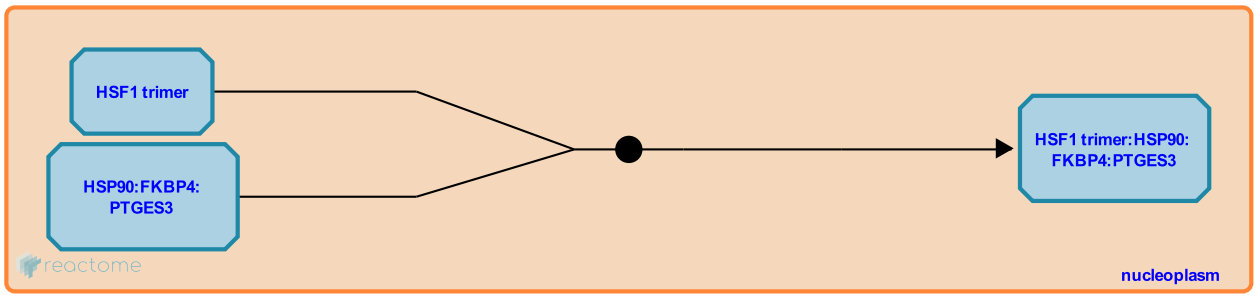
HSP90:FKBP4:PTGES3 binds HSF1 trimer ↗

Location: Attenuation phase

Stable identifier: R-HSA-5324617

Type: binding

Compartments: nucleoplasm



Under non-stress conditions monomeric HSF1 is sequestered in a HSP90-containing heterocomplex. FKBP4 (immunophilin) is one of the components of HSP90-chaperone machinery which was found to associate with trimeric, but not monomeric form of HSF1 (Guo Y et al. 2001). Multichaperone complex of HSP90:FKBP4:PKGES3 has been shown to associate with HSF1 trimer through its regulatory domain, and this is thought to repress HSF1 transcriptional activity (Guo Y et al. 2001).

Literature references

Voellmy, R., Pratt, WB., Smith, DF., Toft, DO., Guettouche, T., Guo, Y. et al. (2001). Evidence for a mechanism of repression of heat shock factor 1 transcriptional activity by a multichaperone complex. *J. Biol. Chem., 276*, 45791-9. ↗

Hjermstad, S., Rimerman, RA., Smith, DF., Nair, SC., Toran, EJ., Smithgall, TE. (1996). A pathway of multi-chaperone interactions common to diverse regulatory proteins: estrogen receptor, Fes tyrosine kinase, heat shock transcription factor Hsf1, and the aryl hydrocarbon receptor. *Cell Stress Chaperones, 1*, 237-50. ↗

Editions

2013-11-19	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
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