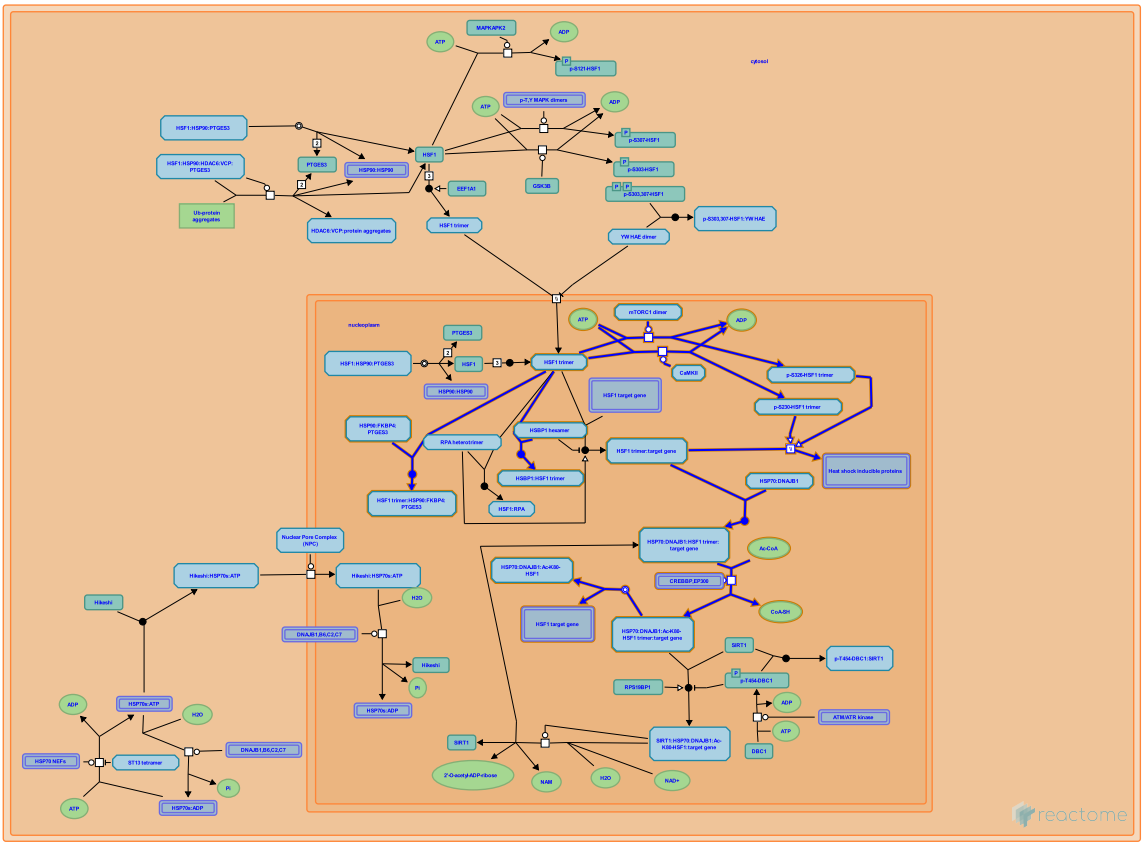
HSF1-dependent transactivation



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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.
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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. ↗

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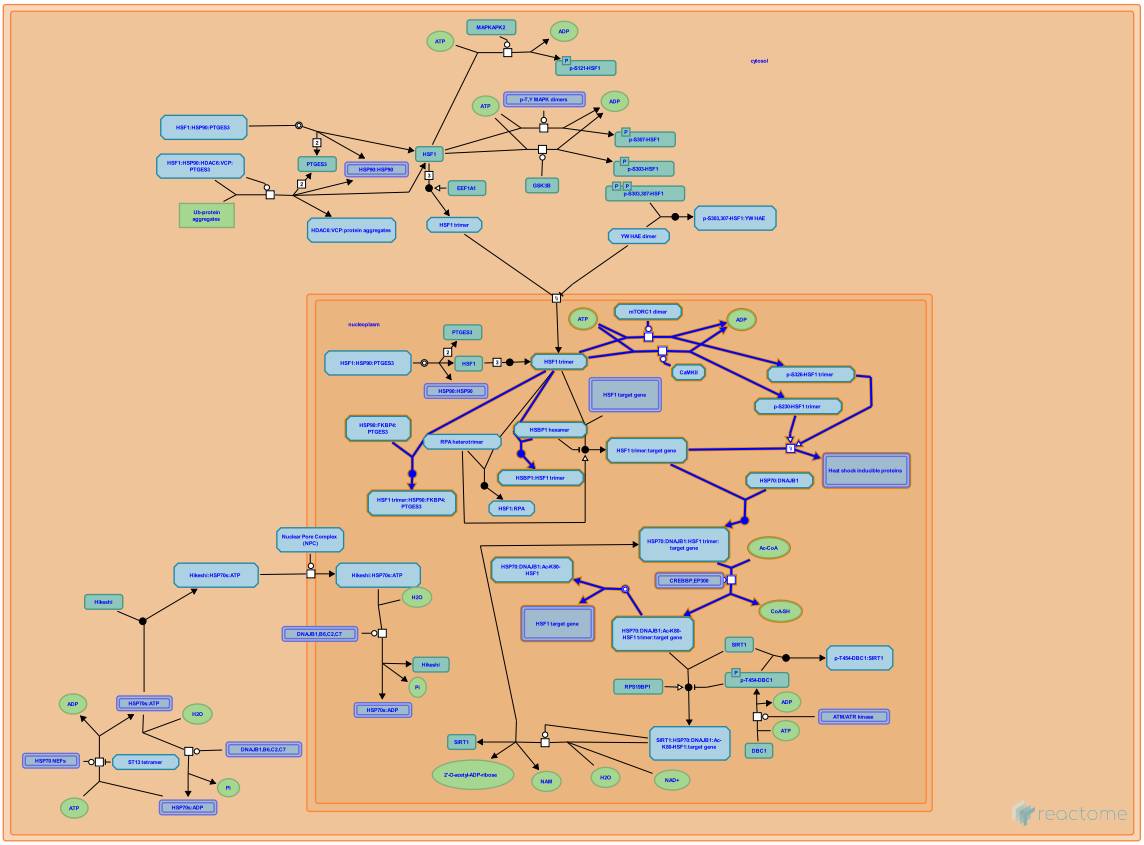
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

HSF1-dependent transactivation ↗

Stable identifier: R-HSA-3371571



Acquisition of DNA binding activity by HSF1 is necessary but insufficient for transcriptional activation (Cotto JJ et al. 1996; Trinklein ND et al. 2004). In addition to having a sequence-specific DNA binding domain, HSF1 contains a C-terminal region which is involved in activating the transcription of the target genes (Green M et al. 1995). However, the transactivating ability of the transactivation domain itself is not stress sensitive. Rather, it's controled by a regulatory domain of HSF1 (amino acids 221-310), which represses the transactivating ability under normal physiological conditions (Green M et al. 1995; Zuo J et al. 1995; Newton EM et al. 1996). The HSF1 transactivation domain can be divided into two distinct regions, activation domain 1 (AD1) and activation domain 2 (AD2) (Brown SA et al. 1998). AD1 and AD2 each contain residues that are important for both transcriptional initiation and elongation. Mutations in acidic residues in both AD1 and AD2 preferentially affect the ability of HSF1 to stimulate transcriptional initiation, while mutations in phenylalanine residues preferentially affect stimulation of elongation (Brown SA et al. 1998).

Activation of the DNA-bound but transcriptionally incompetent HSF1 is thought to occur upon stress induced HSF1 phosphorylation at several serine residues (Ding XZ et al. 1997; Holmberg CI et al. 2001; Guettouche T et al. 2005). In cells exposed to heat, acquisition of HSE DNA-binding activity was observed to precede phosphorylation of HSF1 (Cotto JJ et al. 1996; Kline MP & Morimoto RI 1997). While there is a sufficient evidence to suggest that phosphorylation of HSF1 is essential to modulate HSF1 transactiviting capacity, mechanisms behind stress stimuli and kinases/phosphatases involved have not been clearly established.

Literature references

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

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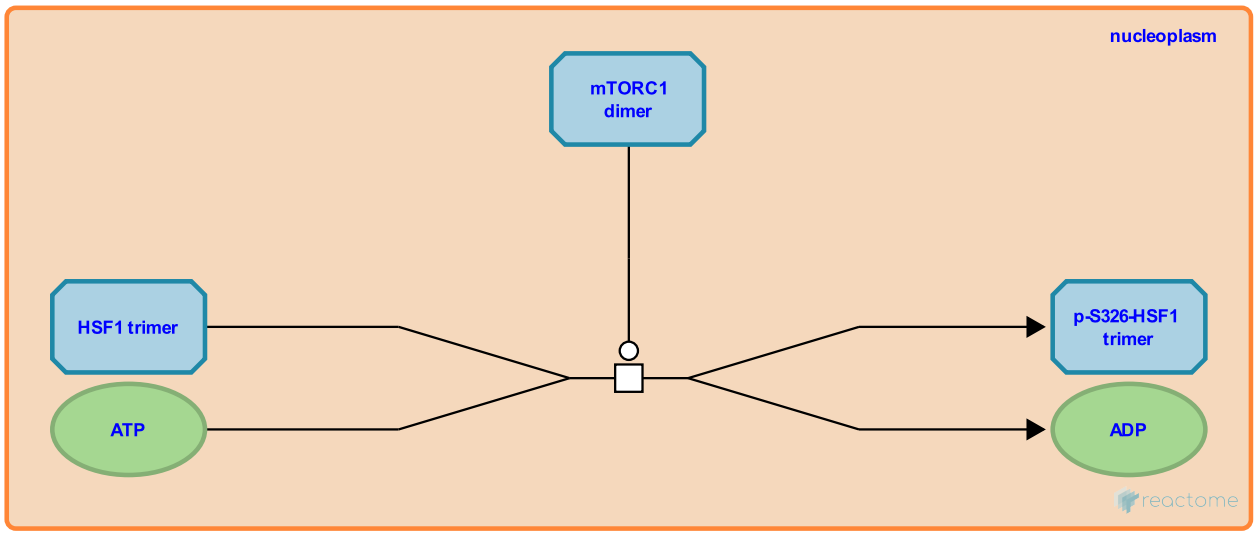
Phosphorylation of HSF1 at Ser326 induces transactivation ↗

Location: HSF1-dependent transactivation

Stable identifier: R-HSA-5082405

Type: transition

Compartments: nucleoplasm



Mutagenesis experiments and functional studies suggest that phosphorylation of HSF1 residue Ser326 promotes induction of the HSF1 transcriptional competence in response to heat and other cell stressors including proteasome inhibitors and sodium arsenite (Guettouche T et al. 2005; Chou SD et al. 2012).

The mammalian target of rapamycin complex 1 (mTORC1) has been implicated in sensing intracellular protein misfolding (Qian SB et al. 2010; Chou SD et al. 2012). RNA interference?mediated repression of mTOR kinase activity in human HeLa cells was found to increase sensitivity to heat shock. Moreover, inhibition of HSF1 phosphorylation on Ser326 by rapamycin suggests that this site in HSF1 is a target for the mTORC1complex (Chou SD et al. 2012).

Literature references

Prince, T., Chou, SD., Gong, J., Calderwood, SK. (2012). mTOR is essential for the proteotoxic stress response, HSF1 activation and heat shock protein synthesis. *PLoS ONE, 7*, e39679. ↗

Lane, WS., Voellmy, R., Guettouche, T., Boellmann, F. (2005). Analysis of phosphorylation of human heat shock factor 1 in cells experiencing a stress. *BMC Biochem., 6*, 4. ↗

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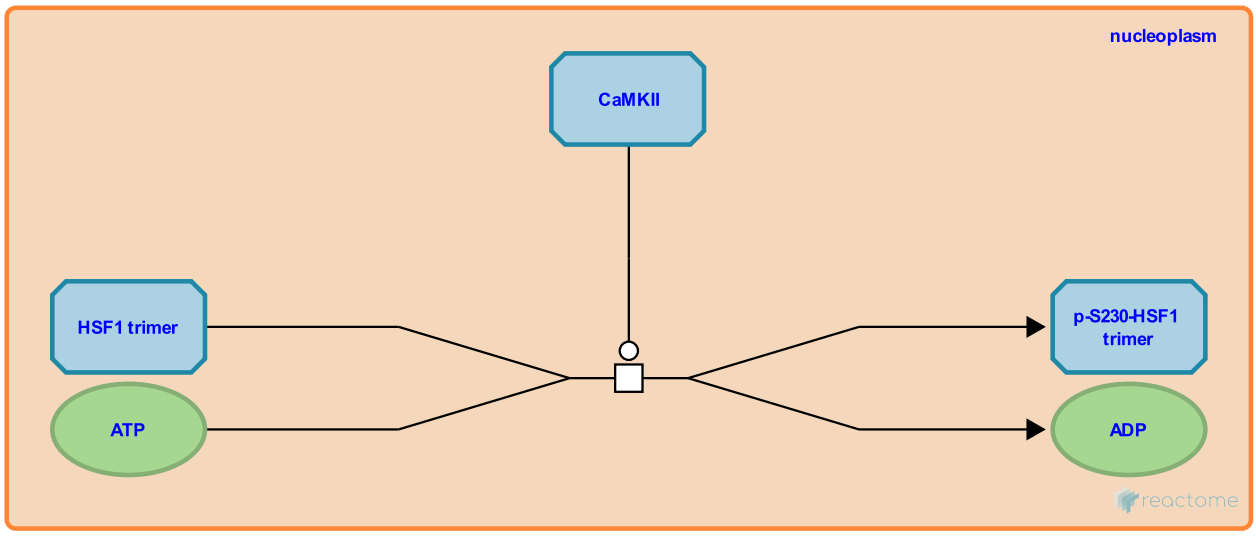
Phosphorylation of HSF1 at Ser230 induces transactivation ↗

Location: HSF1-dependent transactivation

Stable identifier: R-HSA-5082387

Type: transition

Compartments: nucleoplasm



The transcriptional activity of HSF1 has been shown to be controlled by the regulatory domain composed of amino acids 221-310 (Green M et al. 1995; Zuo J et al. 1995; Newton EM et al., 1996). Ser230 is located in this regulatory domain of HSF1 and is constitutively and stress-inducibly phosphorylated (Holmberg CI et al. 2001). Analyses with phosphopeptide-specific antibody and site-directed mutagenesis revealed that phosphorylation at Ser230 enhanced the inducible HSF1 transcriptional activity in heat-shocked human K562 erythroleukemia and HeLa cells (Holmberg CI et al 2001). Active calcium/calmodulin-dependent protein kinase II (CaMKII) was shown to phosphorylate HSF1 at Ser230 in vitro. Moreover, CaMKII enhanced heat-induced tranactivating capacity of HSF1 and the level of endogenous Ser230 phosphorylation in K562 cells transfected with active CaMKII together with a CAT reporter plasmid containing the proximal HSE of human hsp70 promoter. Thus, CaMKII signaling may be involved in the positive regulation of HSF1-mediated transactivation. However, the possibility that other protein kinases might also phosphorylate Ser230 in vivo should not be excluded (Holmberg CI et al 2001).

Literature references

Lane, WS., Voellmy, R., Guettouche, T., Boellmann, F. (2005). Analysis of phosphorylation of human heat shock factor 1 in cells experiencing a stress. *BMC Biochem., 6*, 4. ↗

Rantanen, JO., Holmberg, CI., Sistonen, L., Meinander, A., Morrice, N., Morimoto, RI. et al. (2001). Phosphorylation of serine 230 promotes inducible transcriptional activity of heat shock factor 1. *EMBO J., 20*, 3800-10. ↗

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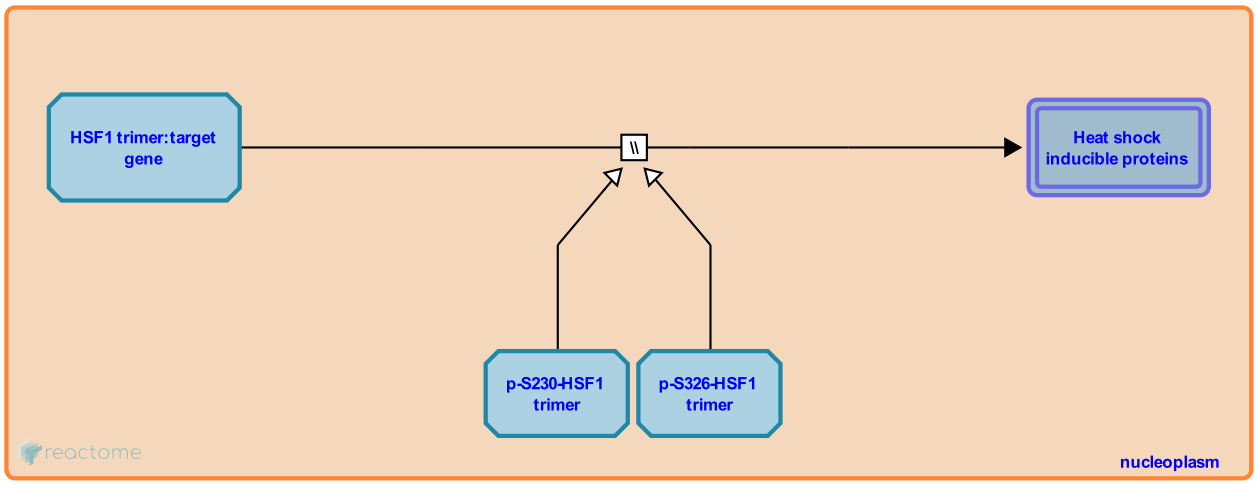
HSF1-mediated gene expression ↗

Location: HSF1-dependent transactivation

Stable identifier: R-HSA-5082356

Type: omitted

Compartments: nucleoplasm



Combination of chromatin immunoprecipitation (ChIP) microarray analysis and time course gene expression microarray analysis with and without siRNA-mediated inhibition of HSF1 showed that human HSF1 can induce the expression of different sets of target genes to maintain a wide range of biological processes (e.g., anti-apoptosis, RNA splicing, ubiquitination)(Page TG et al. 2006; Vihervaara A. et al. 2013). However, HSF1 is best known for rapid stress-induced upregulation of certain genes related to protein folding, 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; Vihervaara A. et al. 2013).

In the nucleus acetylation of Histone H3 is linked to the function of the Elongator complex in transcription (Kim JH et al. 2002). Elongator complex protein 3 (ELP3), a catalytic acetyltransferase subunit of the Elongator complex, has been reported to regulate the transcription of HSP70 gene, and the histone acetyltransferase (HAT) domain of ELP3 is essential for this function (Han Q et al. 2007; Li F et al. 2001).

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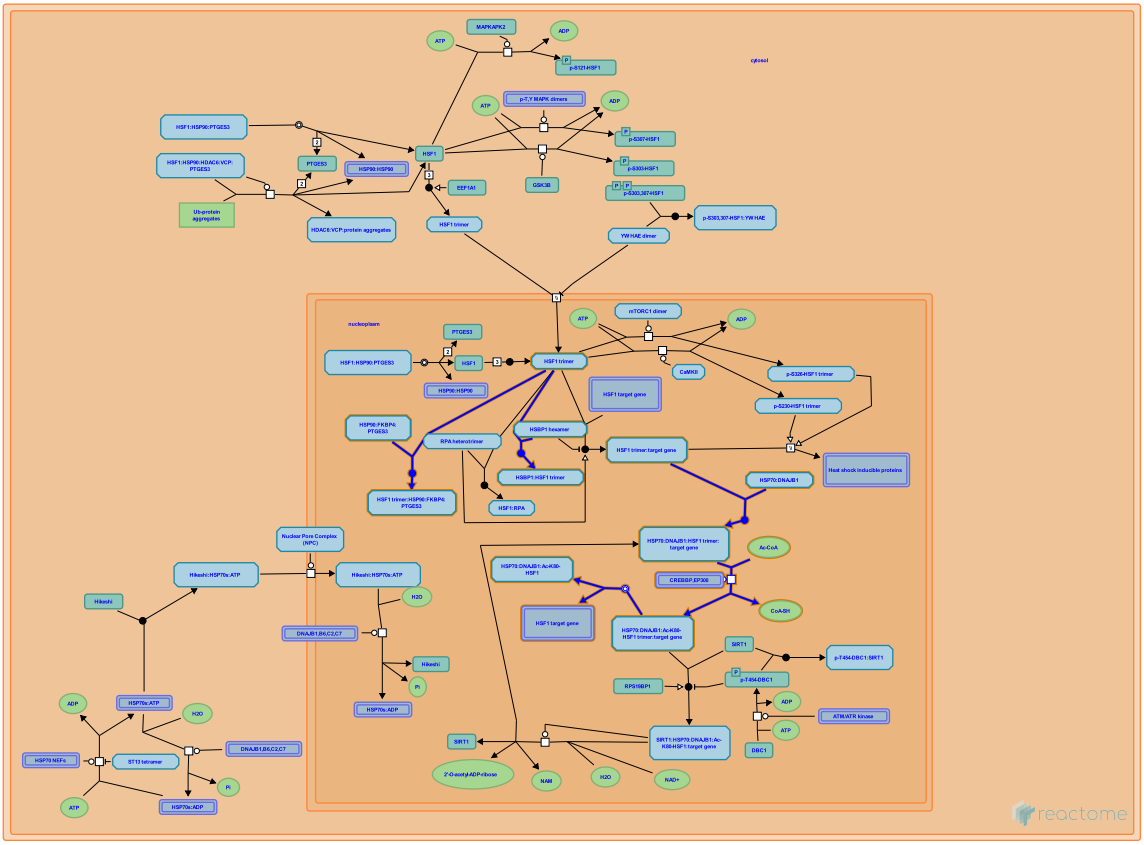
Attenuation phase ↗

Location: HSF1-dependent transactivation

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. ↗

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