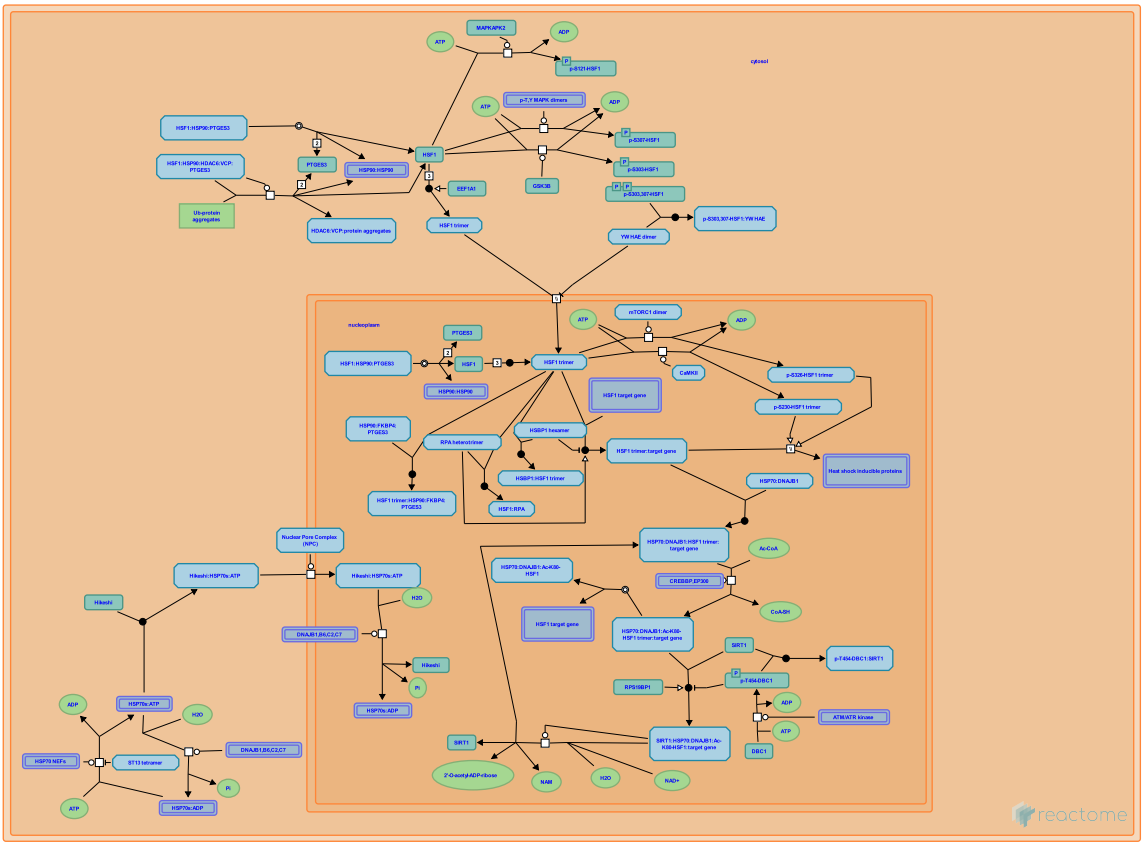
Cellular response to heat stress



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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.

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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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Cellular response to heat stress ↗

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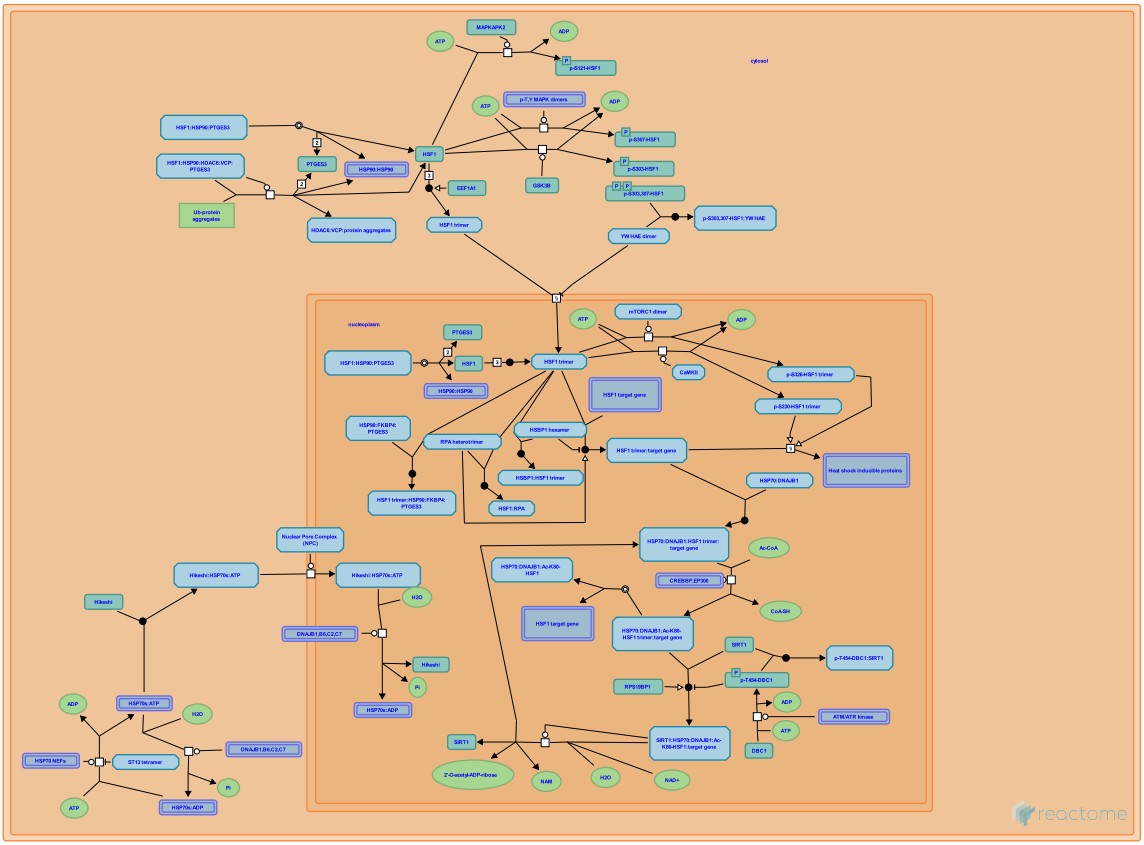

In response to exposure to elevated temperature and certain other proteotoxic stimuli (e.g., hypoxia, free radicals) cells activate a number of cytoprotective mechanisms known collectively as "heat shock response". Major aspects of the heat shock response (HSR) are evolutionarily conserved events that allow cells to recover from protein damage induced by stress (Liu XD et al. 1997; Voellmy R & Boellmann F 2007; Shamovsky I & Nudler E 2008; Anckar J & Sistonen L 2011). The main hallmark of HSR is the dramatic alteration of the gene expression pattern. A diverse group of protein genes is induced by the exposure to temperatures 3-5 degrees higher than physiological. Functionally, most of these genes are molecular chaperones that ensure proper protein folding and quality control to maintain cell proteostasis.

At the same time, heat shock-induced phosphorylation of translation initiation factor eIF2alpha leads to the shutdown of the nascent polypeptide synthesis reducing the burden on the chaperone system that has to deal with the increased amount of misfolded and thermally denatured proteins (Duncan RF & Hershey JWB 1989; Sarkar A et al. 2002; Spriggs KA et al. 2010).

The induction of HS gene expression primarily occurs at the level of transcription and is mediated by heat shock transcription factor HSF1(Sarge KD et al. 1993; Baler R et al. 1993). Human cells express five members of HSF protein family: HSF1, HSF2, HSF4, HSFX and HSFY. HSF1 is the master regulator of the heat inducible gene expression (Zuo J et al. 1995; Akerfelt M et al. 2010). HSF2 is activated in response to certain developmental stimuli in addition to being co-activated with HSF1 to provide promoter-specific fine-tuning of the HS response by forming heterotrimers with HSF1 (Ostling P et al. 2007; Sandqvist A et al. 2009). HSF4 lacks the transcription activation domain and acts as a repressor of certain genes during HS (Nakai A et al. 1997; Tanabe M et al. 1999; Kim SA et al. 2012). Two additional family members HSFX and HSFY, which are located on the X and Y chromosomes respectively, remain to be characterized (Bhowmick BK et al. 2006; Shinka T et al. 2004; Kichine E et al. 2012).

Under normal conditions HSF1 is present in both cytoplasm and nucleus in the form of an inactive monomer. The monomeric state of HSF1 is maintained by an intricate network of protein-protein interactions that include the association with HSP90 multichaperone complex, HSP70/HSP40 chaperone machinery, as well as intramolecular interaction of two conserved hydrophobic repeat regions. Monomeric HSF1 is constitutively phosphorylated on Ser303 and Ser 307 by (Zou J et al. 1998; Knauf U et al. 1996; Kline MP & Moromoto RI 1997; Guettouche T et al. 2005). This phosphorylation plays an essential role in ensuring cytoplasmic localization of at least a subpopulation of HSF1 molecules under normal conditions (Wang X et al. 2004).

Exposure to heat and other proteotoxic stimuli results in the release of HSF1 from the inhibitory complex with chaperones and its subsequent trimerization, which is promoted by its interaction with translation elongation factor eEF1A1 (Baler R et al. 1993; Shamovsky I et al. 2006; Herbomel G et al 2013). The trimerization is believed to involve intermolecular interaction between hydrophobic repeats 1-3 leading to the formation of a triple coil structure. Additional stabilization of the HSF1 trimer is provided by the formation of intermolecular S-S bonds between Cys residues in the DNA binding domain (Lu M et al.2008). Trimeric HSF1 is predominantly localized in the nucleus where it binds the specific sequence in the promoter of hsp genes (Sarge KD et al. 1993; Wang Y and Morgan WD 1994). The binding sequence for HSF1 (HSE, heat shock element) contains series of inverted repeats nGAAn in head-to-tail orientation, with at least three elements being required for the high affinity binding. Binding of the HSF1 trimer to the promoter is not sufficient to induce transcription of the gene (Cotto J et al. 1996). In order to do so, HSF1 needs to undergo inducible phosphorylation on specific Ser residues such as Ser230, Ser326. This phosphorylated form of HSF1 trimer is capable of increasing the promoter initiation rate. HSF1 bound to DNA promotes recruiting components of the transcription mediator complex and relieving promoter-proximal pause of RNA polymerase II through its interaction with TFIIH transcription factor (Yuan CX & Gurley WB 2000).

HSF1 activation is regulated in a precise and tight manner at multiple levels (Zuo J et al. 1995; Cotto J et al. 1996). This allows fast and robust activation of HS response to minimize proteotoxic effects of the stress. The exact set of HSF1 inducible genes is probably cell type specific. Moreover, cells in different pathophysiological states will display different but overlapping profile of HS inducible genes.

Literature references

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2013-10-29	Authored	Shamovsky, V.
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HSF1 activation ↗

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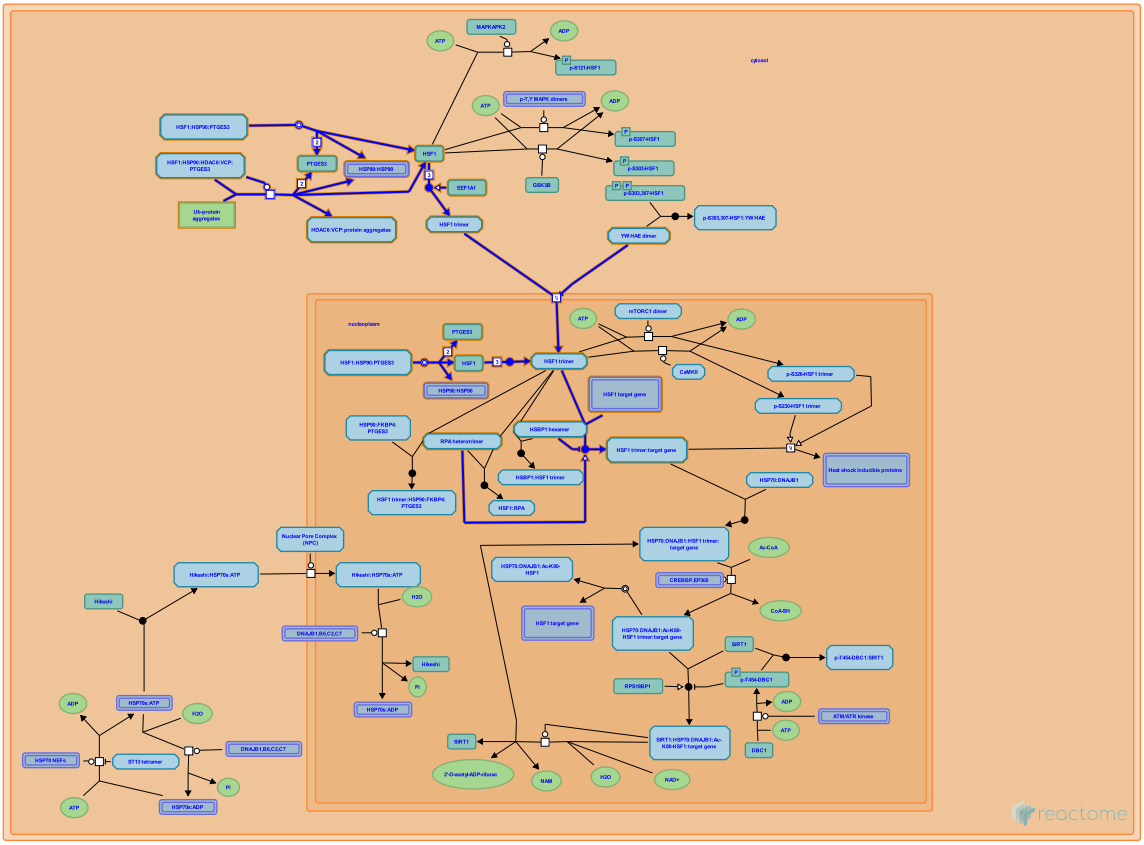

Heat shock factor 1 (HSF1) is a transcription factor that activates gene expression in response to a variety of stresses, including heat shock, oxidative stress, as well as inflammation and infection (Shamovsky I and Nudler E 2008; Akerfelt et al. 2010; Bjork and Sistonen 2010; Anckar and Sistonen 2011).

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).

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HSF1-dependent transactivation ↗

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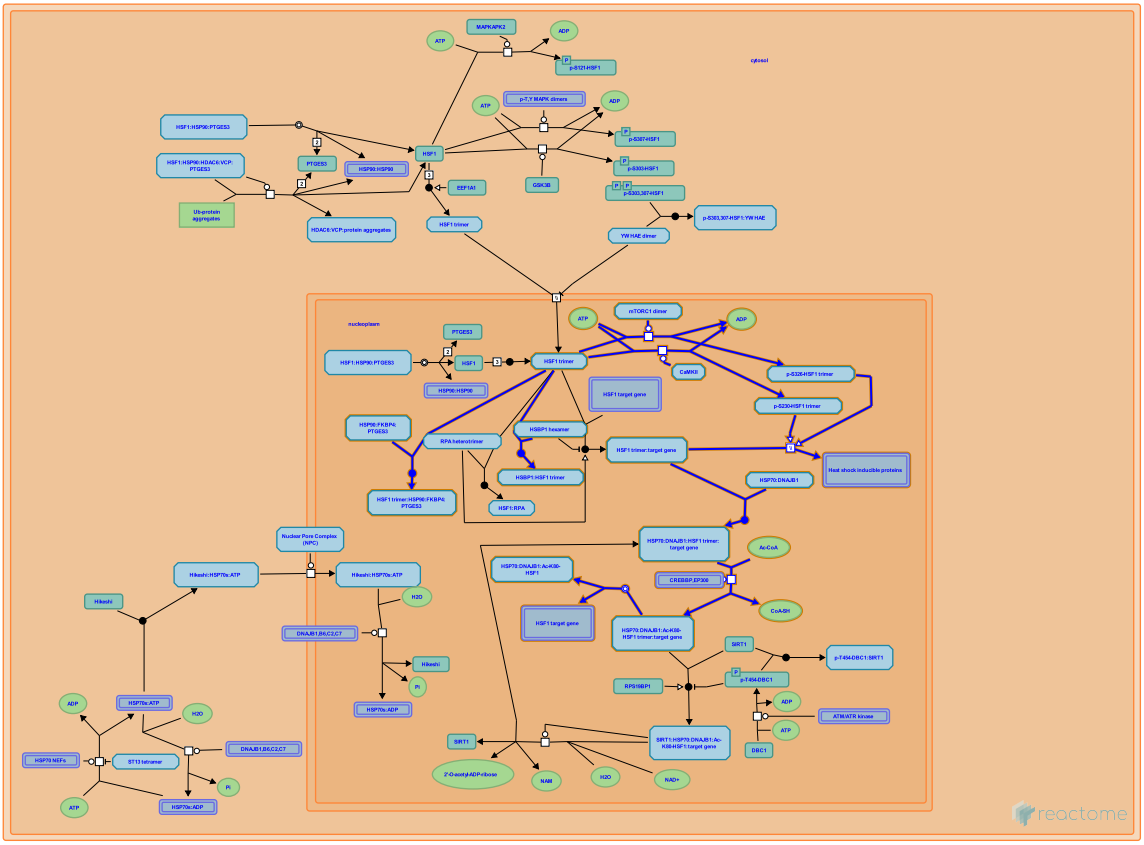

Acquisition of DNA binding activity by HSF1 is necessary but insufficient for transcriptional activation (Cotto JJ et al. 1996; Trinklein ND et al. 2004). In addition to having a sequence-specific DNA binding domain, HSF1 contains a C-terminal region which is involved in activating the transcription 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.

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Regulation of HSF1-mediated heat shock response ↗

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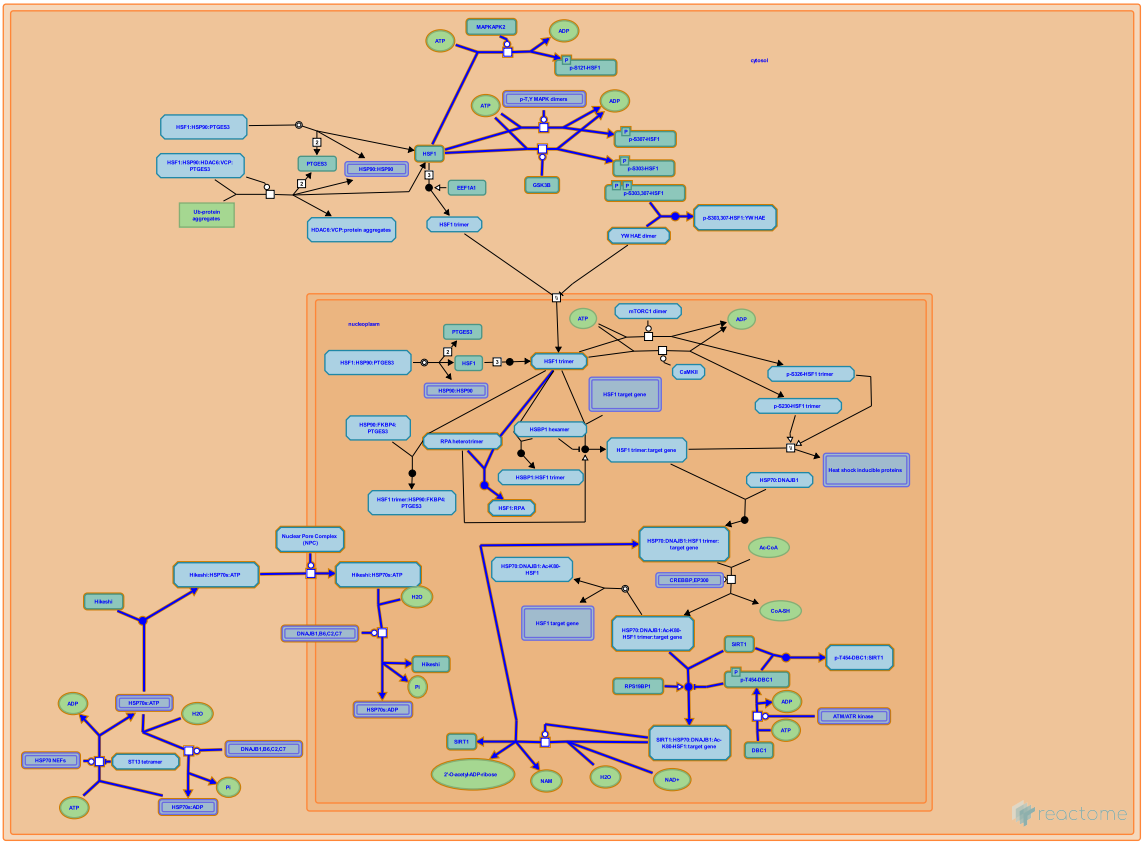

The ability of HSF1 to respond to cellular stresses is under negative regulation by chaperones, modulation of nucleocytoplasmic shuttling, post-translational modifications and transition from monomeric to trimeric state.

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

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