Chapter 3
Regulation of HSF Activation and Repression

Eiichi Takaki and Akira Nakai

Abstract Heat shock response (HSR) is characterized by robust induction of heat shock proteins (HSPs) during heat shock and is regulated mainly at the level of transcription by heat shock factor (HSF). Preexisting inert HSF monomers undergo conformational change to form trimers that bind to DNA and to acquire transcriptional activity during heat shock and other stimuli. These two steps are separated processes and are induced by release from feedback repression by HSPs, direct effects of stimuli, posttranslational modifications, and others. Basal activity of HSF is also regulated in unstressed conditions. In this chapter, we review molecular mechanisms of activation and repression of HSF and describe stimuli that activate HSF by controlling these mechanisms.

Keywords Conformational change • Feedback repression • Posttranslational modification • Small compound • Transcriptional activity • Trimerization

3.1 Introduction

Eukaryotic cells respond to elevated temperatures by a rapid increase in the synthesis of heat shock proteins (HSPs) that facilitate protein folding and non-HSP proteins with diverse functions including protein degradation (Lindquist 1986; Richter et al. 2010). This adaptive response called as the heat shock response (HSR) is regulated mainly at the transcriptional level by heat shock factor (HSF), which is conserved in all eukaryotic species (Wu 1995; Morimoto 1998). HSF preexists mostly as an inert state in unstressed cells and is converted quickly to an active state to induce the heat shock genes including *HSP* genes during heat shock. HSF is also activated at different levels by a variety of environmental and pathophysiological stresses. Thus, regulation of HSF activity plays a pivotal role in controlling proteostasis capacity in a cell (Balch et al. 2008; Morimoto 2011; Wolff et al. 2014; Hipp et al. 2014).

E. Takaki • A. Nakai (✉)
Department of Biochemistry and Molecular Biology, Yamaguchi University School of Medicine, Ube, Japan
e-mail: anakai@yamaguchi-u.ac.jp

A. Nakai (ed.), *Heat Shock Factor*, DOI 10.1007/978-4-431-55852-1_3

A single HSF exists in yeast, fly, and worm, while vertebrate cells possess four HSFs (HSF1 to HSF4). Among them, HSF1 is a master regulator of the HSP expression during heat shock in mammalian cells (Akerfelt et al. 2010; Fujimoto and Nakai 2010). In this chapter, we principally describe molecular mechanisms of activation and repression of orthologs of mammalian HSF1 and summarize stimuli that activate them.

3.2 Trimer Formation and the Acquisition of Transcriptional Activity

HSF in budding yeasts constitutively forms a trimer that binds to the HSE (Sorger et al. 1987). Heat shock induces extensive phosphorylation of HSF, which is correlated with the transcriptional activation of *HSP* genes (Sorger and Pelham 1988). It turned out that this hyperphosphorylation serves as a regulatory mechanism to deactivate HSF, rather than being involved in its activation (Høj and Jakobsen 1994). However, these observations indicate that the trimerized HSF should be modified to acquire potent transcriptional activity during heat shock.

Mammalian HSF1 and HSF in fission yeast *Schizosaccharomyces pombe* and *Drosophila* stay mostly as an inactive monomer and are converted to a DNA-binding trimer upon heat shock (Gallo et al. 1991; Clos et al. 1990; Sarge et al. 1991, 1993; Baler et al. 1993). However, the acquisition of the DNA-binding activity is not sufficient for HSF1 to activate *HSP70* gene in some cell lines such as murine erythroleukemia (MEL) and human Y79 retinoblastoma cells (Hensold et al. 1990; Mathur et al. 1994). Furthermore, treatment of human cells with sodium salicylate, an anti-inflammatory agent, induces the DNA-binding activity of HSF1 and its occupancy on HSP70 promoter in vivo. Nevertheless, sodium salicylate does not induce the transcription of *HSP70* gene (Jurivich et al. 1992, 1995). It also induces the DNA binding of *Drosophila* HSF and puff formation in the polytene chromosomes, but does not induce the transcription of *HSP70* gene (Winegarden et al. 1996). These observations indicate that the trimer formation of HSF1 and its acquisition of transcriptional activity are separated processes (Fig. 3.1).

Mammalian HSF1, like yeast HSF, is hyperphosphorylated upon heat shock. Human HSF1 isolated from heat-shocked cells is more extensively phosphorylated than HSF1 activated in vitro, suggesting that the hyperphosphorylation is associated with transcriptional activity of HSF1 (Larson et al. 1988). However, it is dispensable for the acquisition of the transcriptional activity (Newton et al. 1996; Budzyński et al. 2015). Rather, specific residues in HSF1 are covalently modified by thiol oxidation, sumoylation, and acetylation as well as phosphorylation (Björk and Sistonen 2010). Therefore, HSF1 activation including the acquisition of transcriptional activity should be regulated multistep modifications as described below (see Sect. 3.5).

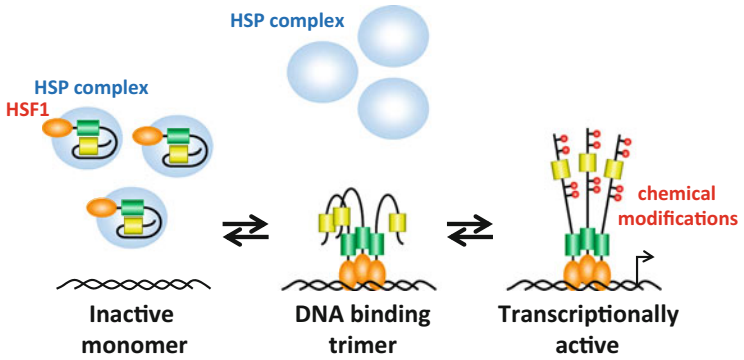

Fig. 3.1 HSF1 activation involves two distinct steps. Metazoan HSF1 stays as an inactive monomer by binding to chaperone machineries (*HSP complex*). It is converted to a DNA-binding trimer upon heat shock and then acquires transcriptional activity by unmasking the activation domain. DNA-binding domain (*orange circle*) and hydrophobic heptad repeats, HR-A/B (*green box*) and HR-C (*yellow box*), are shown (see Chap. 2). Chemical modifications are indicated by flags (*red*)

3.3 Release from Feedback Repression by HSPs

HSR or the accumulation of HSPs is quantitatively related to the degree of heat stress such as heating temperature and duration. How do cells sense these changes in the severity of temperature upshift? The concept that the free pool of HSP70 and other chaperones serves as a cellular sensor or a thermometer that regulates the HSR has been proposed for a long time (Craig and Gross 1991). Lindquist group originally showed that HSP70 expression was proportional to the degree of stress in *Drosophila* cells, and the elevated expression of HSP70 continued when the accumulation of functional HSP70 is blocked (DiDomenico et al. 1982). The bacterium *E. coli* harboring DnaK (HSP70 homolog) mutation failed to turn off the HSR (Tilly et al. 1983). Furthermore, yeast *S. cerevisiae* expressed a high level of HSP90 or activity of the heat shock element (HSE)-driven reporter at normal growth temperature when two *HSP70* genes were mutated (Craig and Jacobsen 1984; Boorstein and Craig 1990). These observations suggest that HSP70 acts as a negative regulator of the HSR.

In *E. coli*, *HSP* genes are under the control of the σ^{32} transcription factor, whose level and activity increase during heat shock (Straus et al. 1989; Tilly et al. 1989). DnaK functions as molecular chaperone in cooperation with DnaJ (HSP40 homolog) and GrpE (HSP110 homolog, a nucleotide exchange factor). As was expected, strains carrying mutations in DnaJ and GrpE as well as DnaK enhanced the synthesis of HSPs at normal growth temperature and failed to shut off the HSR, in part by increased synthesis and stabilization of σ^{32} (Straus et al. 1990). Furthermore, the overexpression of DnaK and DnaJ reduced not only the level of σ^{32} but

also its activity in response to heat shock (Tomoyasu et al. 1998). Thus, the amount of functional DnaK (HSP70) chaperone machinery provides tight control of the level and activity of the σ^{32} transcription factor. The GroEL/S chaperonin also controls the σ^{32} and HSR (Guisbert et al. 2004, 2008).

In mammalian cells, the activity of HSF1 and transcription level of *HSP70* gene are linked to the accumulation of proteins denatured by heat shock. When human HeLa cells grown at 37 °C were exposed to continued heat shocked at 42 °C, HSF1 was modestly activated and attenuated soon. In contrast, the high level of HSF1 activation continued when cells were heat shocked at 43 °C (Abravaya et al. 1991). Furthermore, the threshold temperature for HSF1 activation was decreased when cells were treated with an inhibitor of the synthesis of nascent polypeptides, which consist of major nonfolded proteins present in cells (Baler et al. 1992). Taken together with the fact that HSF1 interacted with HSP70, a product of its target gene, it was suggested that HSP70 acts as an autoregulatory factor of the HSR (Abravaya et al. 1992; Baler et al. 1992).

To understand molecular mechanisms of the autoregulation by HSP70, profiles of HSF1 activation and deactivation were monitored in cells overexpressing HSP70. The acquisition of the DNA-binding activity of HSF1 during heat shock was reduced in human T-cell leukemia cell line by the overexpression of HSP70 (Mosser et al. 1993), whereas it was not affected in rat fibroblasts at all (Rabindran et al. 1994; Kim et al. 1995). Rather, the shutdown of the DNA-binding activity during recovery period was accelerated in common in these cells. Morimoto group analyzed the mechanism in more detail and revealed that HSP70 and HSP40 (HDJ1) interact with the C-terminal activation domain of HSF1 and negatively regulate its transcriptional activity in vivo during attenuation of the HSR (Shi et al. 1998). HSP90 also interacts with HSF1 (Nadeau et al. 1993; Nair et al. 1996), suggesting its inhibitory role in the HSR. Using in vitro HSF1 activation system, Voellmy group found that the treatment of cells with geldanamycin, an inhibitor of HSP90, induced the DNA-binding activity of HSF1 in vitro and demonstrated that HSP90 inhibited the acquisition of the DNA-binding activity in vitro, but HSP70 did not (Zou et al. 1998a). It is proposed later that the HSP90 chaperone machinery including p23 and FKBP52 binds to the regulatory domain of HSF1 and negatively regulates both the monomer-to-trimer transition of HSF1 and its transcriptional activity (Ali et al. 1998; Duina et al. 1998; Bharadwaj et al. 1999; Guo et al. 2001). Analysis in *Drosophila* cells further shows that the synergistic interaction of HSP70 and HSP90 chaperone machineries modulates HSF activity by feedback repression (Marchler and Wu 2001) (Fig. 3.2). Moreover, TRiC/CCT chaperonin complex also interacts and represses the activity of HSF1 (Neef et al. 2014). Taken together, HSF1 is activated by the release from feedback repression by chaperone machineries during heat shock, and the activated HSF1 is subsequently repressed by the increased free pool of chaperones during recovery period.

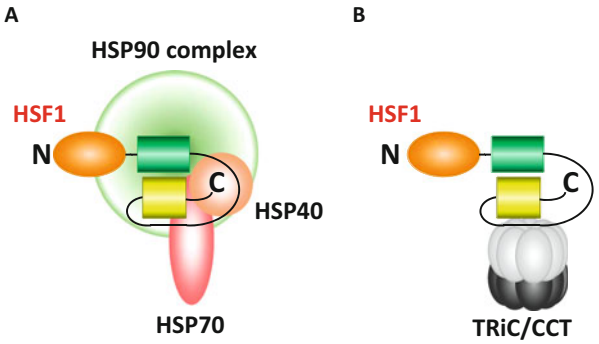

Fig. 3.2 HSF1 is maintained as an inactivate state by chaperone machineries. (**a**) HSP90 chaperone machinery including p23 and FKBP52 binds to the regulatory domain of HSF1, while HSP70 chaperone machinery containing HSP40 interacts with the C-terminal activation domain. These chaperone machineries may cooperatively inhibit the trimerization of HSF1 and suppress its transcriptional activity. (**b**) Chaperonin TRiC/CCT also binds to HSF1 and represses its activity

3.4 HSF Directly Senses Heat and Stimuli

After the development of a cell-free system that exhibits heat-induced activation of human HSF1 in vitro (Larson et al. 1988), signaling pathways that induce the DNA-binding activity have been extensively studied. The DNA-binding activity of human HSF1 in unstressed HeLa cytoplasmic extract was induced in vitro not only by heat shock but also by low pH (pH 6.0), Nonidet P-40, and urea, which affected protein conformation (Mosser et al. 1990). The in vitro HSF1 activation by these reagents was inhibited by glycerol, which stabilized protein structure. Furthermore, the treatment of *Drosophila* SL2 cytoplasmic extract with polyclonal antiserum against *Drosophila* HSF also induced the HSF DNA-binding activity in vitro (Zimarino et al. 1990). These observations suggest that HSF1 or HSF can be activated directly by undergoing a conformational change, without a covalent modification of protein.

Does purified HSF undergo a conformational change in response to heat? Kingston group purified in vitro heat-activated human HSF1 in the HeLa cytoplasmic extract by using an HSE oligonucleotide affinity column and deactivated it by denaturation using guanidine and subsequent renaturation (Larson et al. 1995). They showed that the DNA-binding activity of purified HSF1 was induced by heat shock, and the acquisition of its DNA-binding activity is accompanied with a monomer-to-trimer transition of oligomeric structure, like that in heat-shocked HeLa cells. Mouse HSF1 synthesized in *E. coli* was purified, and its DNA-binding activity was also induced in vitro by heat shock (Goodson and Sarge 1995; Farkas et al. 1998). These observations demonstrate that HSF1 can directly sense temperature upshift. Wu group carefully analyzed kinetics of the dissociation of

Drosophila HSF trimer (Zhong et al. 1998). They infected a baculovirus overexpressing *Drosophila* HSF into insect Sf9 cells and purified it (bac-HSF). A high concentration of bac-HSF solution contained predominantly trimers, which dissociated to monomers when the solution was diluted. The population of trimers reversed upon reconcentration. Furthermore, the dissociation of bac-HSF trimers was inhibited by heat, H_2O_2, and low pH, but not by 2,4-dinitrophenol, ethanol, arsenite, indomethacin, and salicylate, which induce HSF trimerization in intact cells (Zhong et al. 1998, 1999). Thus, some inducers of the HSR act directly to HSF, while others do indirectly.

3.5 Posttranslational Modifications

3.5.1 Phosphorylation

When cells are heat shocked, an apparent molecular weight of mammalian HSF1 on SDS-polyacrylamide gel dramatically increases due to multisite phosphorylation, which is called as hyperphosphorylation (Sorger et al. 1987; Larson et al. 1988; Sarge et al. 1993; Baler et al. 1993). HSF1 becomes hyperphosphorylated by heat shock, heavy metals, and amino acid analogs, but not by anti-inflammatory drugs that induce trimerization but not transcriptional activity (Cotto et al. 1996). Thus, the acquisition of transcriptional activity of HSF1 is generally correlated with its hyperphosphorylation. However, mutation analyses of multi-phosphorylation sites in HSF1 show that the hyperphosphorylation is not necessary for HSF1 to acquire full transcriptional activity during heat shock (Newton et al. 1996; Budzyński et al. 2015). It would be possible that the hyperphosphorylation facilitates dissociation of active HSF1 trimers during recovery period (Xia and Voellmy 1997).

Is there a specific phosphorylation site that promotes HSF1 transcriptional activity? Sistonen group identified that Ser230 was constitutively and stress-inducibly phosphorylated by calcium/calmodulin-dependent protein kinase II (CaMKII) (Holmberg et al. 2001) (Fig. 3.3). Phosphorylation of Ser230 and CaMKII enhanced HSF1 transcriptional activity in response heat shock. Voellmy group carried out an alanine scan of all serines, threonines, and tyrosines in human HSF1 using a reporter assay and also identified phosphorylation sites of exogenously expressed HSF1 in HeLa cells (Guettouche et al. 2005). They found that phosphorylation of only Ser326 contributed to HSF1 activation during heat shock. Phosphorylation on Ser326 increased rapidly during heat shock. It promoted the transcriptional activity of HSF1, but did not affect the DNA-binding activity. It turned out that Ser326 is phosphorylated by ERK1/2, and its phosphorylation promotes carcinogenesis (Dai et al. 2007, 2012). HSF1 activity may also be enhanced by polo-like kinase 1 (PLK1) and protein kinase A (PKA) during heat shock through phosphorylation of Ser216/419 and Ser320, respectively (Kim et al. 2005; Lee et al. 2008; Murshid et al. 2010).

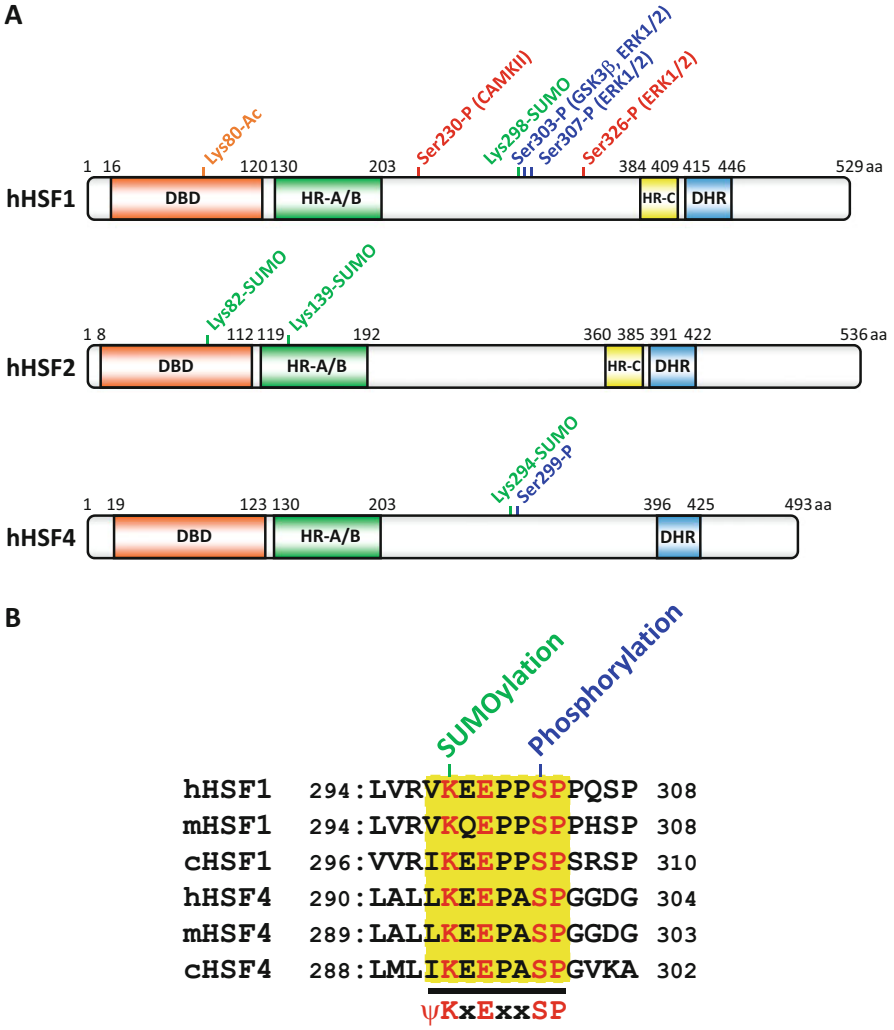

Fig. 3.3 Posttranslational modification of HSF family members. (**a**) Major phosphorylation sites that activate HSF1 are shown in *red*, and those repress it are in *blue*. Protein kinases that phosphorylate each amino acid are indicated in parentheses. Acetylation sites (*orange*) and sumoylation sites (*green*) are also shown. (**b**) Phosphorylation-dependent sumoylation motif (PDSM) in HSF1 and HSF4. Amino acid sequences containing the PDSM motif (*yellow box*) in human, mouse, and chicken HSF1 and HSF4 are aligned, and a consensus sequence is indicated (ψ is acceptable for all hydrophobic amino acids). Numbers indicate position of amino acids

In unstressed condition, the regulatory domain represses activity of the C-terminal transcriptional activation domain of human HSF1 (a.a. 221–310) (Green et al. 1995). Ser303 and Ser307 in the regulatory domain of human HSF1 are constitutively phosphorylated, and phosphorylation of these sites is required for

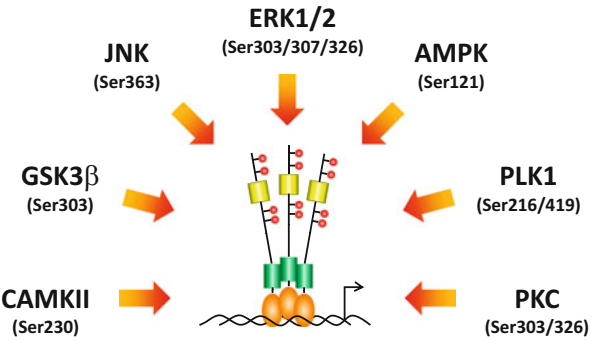

Fig. 3.4 HSF1 is phosphorylated by various kinases. Protein kinases that phosphorylate HSF1 and phosphorylation sites of each kinase are indicated (see text)

the repression of HSF1 transcriptional activity at control temperature (Knauf et al. 1996; Chu et al. 1996; Kline and Morimoto 1997). Ser307 is first phosphorylated by ERK1/2, and this modification is required for phosphorylation of Ser303 by glycogen synthase kinase 3 (GSK3) (Knauf et al. 1996; Chu et al. 1996). Ser303/307 not only regulates the transcriptional activity but also stability of HSF1. Phosphorylated Ser303/307 is recognized by an FBXW7α ubiquitin ligase, which results in degradation of HSF1 (Kourtis et al. 2015). Regulation of Ser303/307 phosphorylation could modulate HSF1 activity in response to growth control signals.

Effects of protein kinases on HSF1 activity in unstressed condition are complex. GSK3 represses not only transcriptional activity of HSF1 but also the trimer formation by unknown mechanisms (Xavier et al. 2000). ERK1/2 represses the activity of HSF1 through phosphorylation of Ser307, but activates it through that of Ser326 as described above. Protein kinase C (PKC) and c-Jun N-terminal kinase (JNK) repress HSF1 activity through Ser363 phosphorylation (Chu et al. 1998; Dai et al. 2000), and AMP-activated protein kinase (AMPK) does so through Ser121 phosphorylation (Dai et al. 2015) (Fig. 3.4).

3.5.2 Sumoylation

Sarge group first found that HSF2, another member of the HSF family, interacted with the SUMO-conjugating (E2) enzyme Ubc9 (Goodson et al. 2001). They showed that HSF2 was constitutively modified by SUMO-1 at Lys82 in the DNA-binding domain, whereas HSF1 underwent heat shock-inducible SUMO-1 modification at Lys298 in the regulatory domain (Hong et al. 2001) (Fig. 3.3). Sistonen group further studied roles of sumoylation in HSF1 function and showed that phosphorylation of Ser303 was prerequisite for the sumoylation of Lys298 (Hietakangas et al. 2003). Phosphorylation of Ser303 in HSF1 is markedly induced during heat shock, which allows Lys298 to be inducibly modified by sumoylation. A motif combining a SUMO consensus site to an adjacent proline-directed

phosphorylation site is generally conserved in other factors including HSF4, GATA1, and MEF2 (Hietakangas et al. 2006) (Fig. 3.3). Sumoylation of Lys298 of HSF1 and Lys294 of HSF4 represses the transcriptional activity of these factors. Effects of sumoylation on the DNA-binding activity are unclear (Goodson et al. 2001; Hong et al. 2001; Anckar et al. 2006), but structural analysis at least demonstrates that SUMO attachment at Lys82 of HSF2 negatively modulates the formation of protein-DNA complex (Tateishi et al. 2009).

3.5.3 *Acetylation*

Stress resistance and metabolic regulation are coupled to protein homeostasis, and key regulatory factors for these mechanisms including HSF1 and a NAD^+-dependent lysine deacetylase SIRT1 are involved in lifespan extension in *C. elegans* (Hsu et al. 2003; Morley and Morimoto 2004). Therefore, Morimoto group examined the regulation of HSF1 by SIRT1 and found that HSF1 was inducible acetylated at Lys80 by p300 during heat shock, whereas it was deacetylated by SIRT1 (Westerheide et al. 2009) (Fig. 3.3). The HSF1-DNA complex dissociates by the acetylation of Lys80. Thus, SIRT1 inhibits the attenuation of the HSR, and p300 promotes it (Fig. 3.5). SIRT1 modulators also regulate HSF1 activity (Raynes

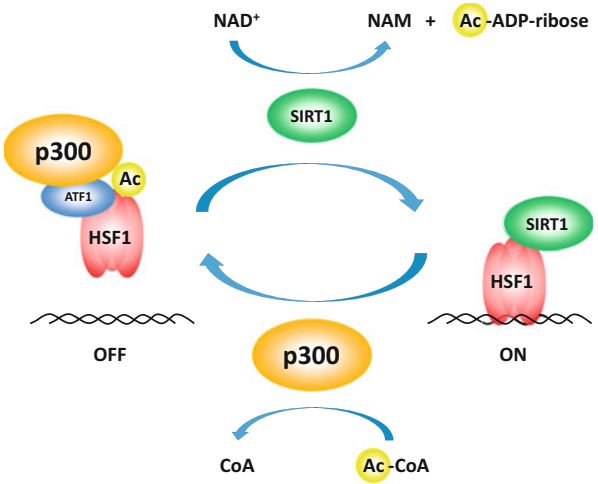

Fig. 3.5 Acetylation and deacetylation of HSF1. HSF1 is largely deacetylated by SIRT1 in unstressed condition. SIRT1 cleaves NAD^+ and produces nicotinamide (*NAM*). Simultaneously, the acetyl group is transferred from HSF1 to the ADP-ribose moiety of NAD^+ to generate O-acetyl-ADP ribose. In response to heat shock, HSF1 binds to the DNA and recruits p300 in a manner that is dependent on ATF1. p300 acetylates HSF1 by transferring an acetyl group from acetyl CoA. Acetylated HSF1 dissociates from the DNA

et al. 2013). In some condition, acetylation by p300 may also control stability of HSF1 through proteasomal degradation (Raychaudhuri et al. 2014).

In general, chromatin-modifying enzymes such as lysine acetyltransferases are enriched in active genes and are correlated with gene expression in the whole genome (Wang et al. 2009). Previous studies suggested that p300, one of histone acetyltransferases, might promote heat-inducible HSP70 expression in *Xenopus* oocytes and mammalian cells (Li et al. 1998; Xu et al. 2008). Does p300 enhance heat shock-inducible expression of HSP70 or inhibit it by deactivating HSF1? Nakai group found that the HSF1-ATF1 complex promoted the recruitment of p300 to the HSP70 promoter during heat shock (Takii et al. 2015). Inhibition of p300 accumulation by disconnecting the interaction delayed the shutdown of HSF1 DNA-binding activity during recovery period, but did not affect histone acetylation on HSP70 promoter in MEF cells. Depletion of a *Drosophila* ortholog of p300 also inhibited only the shutdown of the HSR during recovery period (Ghosh et al. 2011). These observations indicate that p300 negatively regulates the HSR by inhibiting HSF1 activity through acetylation.

3.5.4 Thiol Oxidation

Human and mouse HSF1 possesses five cysteine residues, and redox-dependent regulation of HSF1 activity through these residues has been analyzed. Liu group first showed that trimerization of human HSF1 in the cytoplasmic extracts from HeLa cells during in vitro heat shock was inhibited by diamide, a reagent that promotes disulfide bond formation (Manalo and Liu 2001). Mutation of Cys36 and Cys103 in the DNA-binding domain did not affect sensitivity to diamide, while HSF1 having mutated Cys153 in the HR-A/B domain or Cys373/378 just upstream of the HR-C domain was insensitive to diamide (Manalo et al. 2002). They proposed from these in vitro studies that disulfide bond formation between Cys153 and Cys373 or Cys378 in HSF1 inhibited the trimerization during in vitro heat shock. Thiele group showed another mechanism of redox regulation. They showed that a purified mouse HSF1 underwent a monomer-to-trimer transition by heat and hydrogen peroxide (Ahn and Thiele 2003), like *Drosophila* HSF (Zhong et al. 1998). Mutation of Cys35 and Cys105 (Cys36 and Cys103 in human HSF1, respectively) in the DNA-binding domain inhibited the trimerization and acquisition of DNA-binding activity in vitro by heat shock and hydrogen peroxide. Furthermore, these HSF1 mutants were defective in heat-inducible trimerization and activation of *HSP* genes in vivo in cells (Ahn and Thiele 2003). The heat-induced bonding between Cys36 and Cys103 in human HSF1 may form an intermolecular disulfide bond and is required for trimerization (Lu et al. 2008).

3.6 Other Regulations

Many studies have been conducted to identify proteins interacting HSF1 and regulate its activity. Many of these proteins are involved in regulation of chromatin and HSF1 transcription complexes (see Chap. 4) and in feedback repression and chemical modifications as described above (see Sects. 3.3 and 3.5). We here explain roles of some other factors that regulate the trimerization and DNA-binding activity of HSF1.

CHIP (C-terminus of HSP70-interacting protein) is one of the co-chaperones for HSP70 chaperone machinery and also has ubiquitin ligase activity (Murata et al. 2003). It turned out that overexpression of CHIP, but not other co-chaperones, uniquely induced the HSF1 DNA-binding activity and expression of HSP70 (Dai et al. 2003). Furthermore, CHIP was required for maximal HSP70 induction in cells and tissues. CHIP seems to affect complex formation of HSF1 with chaperone machineries.

HSF1 activity is repressed by DAF-2 or an insulin/IGF-1-like signaling (ILS), which is one of the major regulatory pathways for longevity in *C. elegans* (Hsu et al. 2003; Morley and Morimoto 2004). DDL-1 and DDL-2 are also involved in longevity pathways and form a complex that interacts with and stabilizes HSF1 monomers (Chiang et al. 2012). Increased ILS signaling promotes the formation of this complex, whereas reduction of this signaling results in disruption of the complex and increase in the trimerization of HSF1.

Remarkably, it is proposed that a noncoding RNA regulates the trimerization and DNA-binding activity of HSF1. Nudler group identified a translation elongation factor eEF1A as one of HSF1-interacting proteins (Shamovsky et al. 2006). eEF1A induced the HSF1 DNA-binding activity by recruiting noncoding RNA consisting of ~600 nucleotides, termed as heat shock RNA-1 (HSR1). Both eEF1A and HSR1 were required for induction of the HSF1 DNA-binding activity in vitro and in vivo and for the expression of HSP70. eEF1A also promoted the HSR in part by enhancing the transcriptional activity of HSF1 and by binding to and stabilizing HSP70 mRNA (Vera et al. 2014).

3.7 HSF Activation by Diverse Stresses

3.7.1 Environmental Stimuli

HSR was originally detected as heat-induced puffs in *Drosophila*, and an identical set of puffs could be induced by other agents (Ritossa 1962). Inducers of the heat-induced puffs are inhibitors of oxidative phosphorylation and electron transport (azide, dinitrophenol, rotenone, valinomycin); an inducer of reactive oxygen species (ROS) (menadione), anoxia, and a thiol-reactive reagent (arsenite); and an inhibitor of the synthesis of inflammatory mediators (salicylate) (Ashburner and

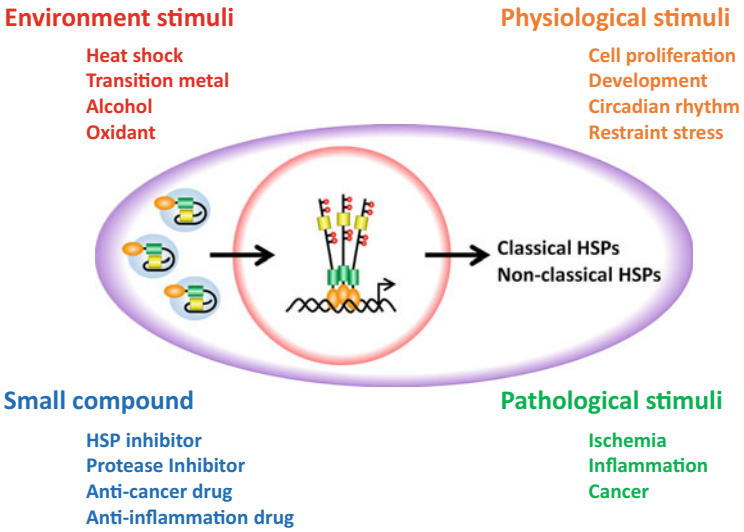

Fig. 3.6 HSF1 can be activated by diverse stimuli. Activity of HSF1 can be induced by environmental, physiological, and pathological stimuli or by the treatment with small compounds, which results in enhanced synthesis of HSPs

Bonner 1979). However, the synthesis of HSPs is not always induced in *Drosophila* and other species by these induces including oxidants and inhibitors of respiration. In mammalian and avian cells, the synthesis of HSPs is strongly induced by environmental stimuli such as heat shock, transition metals (copper, cadmium, zinc, and mercury), arsenite, and ethanol (Levinson et al. 1980; Johnston et al. 1980; Li 1983), which activate HSF1 (Fig. 3.6).

3.7.2 Physiological Stimuli

Activity of HSF1 is regulated during development. In *Drosophila*, the expression of HSPs is induced during development (Zimmerman et al. 1983) and is tightly correlated with the nuclear localization of HSF (Wang and Lindquist 1998). Regulation of HSF activity is complex in mammals because members of HSF family are involved in development (Abane and Mezger 2010) (see Chaps. 6, 7 and 8). Correlation between HSF1 activation and the induction of HSP expression during organogenesis have been shown. DNA-binding activity of HSF1 and the expression of HSPs were markedly induced in the pubertal olfactory epithelium, and HSF1 deficiency resulted in decreased expression of HSPs and impaired olfactory neurogenesis (Takaki et al. 2006). In response to the immunization of mice with sheep red blood cells, B cells proliferate in germinal center in the spleen. Simultaneously, HSF1 was activated and elevated the expression of HSPs (Inouye

et al. 2004). HSF1 deficiency impaired the proliferation of B cells in the germinal center. Mechanisms of HSF1 activation during early development and organogenesis are not known.

HSF1 is one of circadian transcription factors. Activated HSF1 induces the expression of HSPs at the onset of dark phase in mice, when they start to be behaviorally active (Reinke et al. 2008) (see Chap. 10). HSF1 is also activated in vivo by neurohormonal stimuli. Restraint stress or immobilization stress induced the HSP70 expression in the rat adrenal by activating HSF1 (Blake et al. 1991; Fawcett et al. 1994). Hypophysectomy prevented HSF1 activation, and administration of adrenocorticotropic hormone (ACTH) to hypophysectomized rats induced it. Thus, activity of HSF1 is under hormonal control in vivo.

3.7.3 Pathological Stimuli

The expression of HSPs in a tissue is markedly elevated under pathological conditions such as ischemia, trauma, and inflammation. It was shown that HSF1 in the cerebral neocortex was activated in vivo by focal cerebral ischemia, which was produced by occluding the middle cerebral and common carotid arteries in rats (Higashi et al. 1995). A high DNA-binding activity of HSF1 appeared soon after the ischemic treatment and then gradually decreased. HSF1 activation by ischemia and reperfusion was further monitored in isolated rat hearts (Nishizawa et al. 1996). Rat hearts were isolated and perfused with a buffer by the Langendorff method. In the ischemia/reperfusion experiments, isolated hearts were subjected to global ischemia by clamping the aortic cannula and then reperfused. HSF1 was slightly activated at 10 min and quickly attenuated, and reperfusion activated HSF1 again. Furthermore, repetitive ischemia/reperfusion induced a robust activation of HSF1, while its effect was inhibited in the presence of scavengers of reactive oxygen species (ROSs) (Nishizawa et al. 1999). Thus, ROSs may play an important role in the activation of HSF1 in organs by the ischemia/reperfusion injury.

Inflammation is caused by physical, chemical, infectious, and some immunological agents and is associated with increased production of various kinds of mediators (Polla et al. 1998) (see Chap. 9). Among them, proinflammatory cytokines including TNF-α, IL-1α, and IL-6 activated HSF1 in synovial fibroblast-like cells (Schett et al. 1998). HSF1 activation by TNF-α may be in part due to the TNF-α-mediated induction of ROSs (Goossens et al. 1995). HSF1 is also activated by cyclopentenone prostaglandins (PGs) including PGA_1, PGA_2, and PGJ_2, which possess anti-inflammatory, antitumor, and antiviral activities (Holbrook et al. 1992; Amici et al. 1992). These PGs exert biological effects in part through its reaction with cysteine residues of many cellular proteins (Straus and Glass 2001), which could then activate HSF1 (Santagata et al. 2012). Furthermore, a prostaglandin precursor, arachidonic acid, also activates HSF1 and induces the expression of HSPs (Jurivich et al. 1994).

HSF1 facilitates malignant transformation and cancer cell survival (Dai et al. 2007; Min et al. 2007). Protein level of HSF1 is elevated in some cancer cells (Hoang et al. 2000), and high levels of HSF1 is associated with poor prognosis in various cancers originating from the breast, colon, lung, prostate, and pancreas (Santagata et al. 2011; Mendillo et al. 2012). The upregulation of HSF1 in cancer cells is in part due to activation of mitogen-activated protein kinase (MAPK) signaling, which phosphorylates HSF1-Ser326 (Dai et al. 2012; Chuma et al. 2014) (see Chap. 13).

HSF1 inhibits progression of aging and age-related protein misfolding disease models (Hsu et al. 2003; Morley and Morimoto 2004; Fujimoto et al. 2005; Hayashida et al. 2010) (see Chap. 11). However, it is still unclear whether HSF1 is activated by the accumulation of misfolded proteins in the brain of protein misfolding diseases including polyglutamine diseases. HSF1 was not activated by aggregation-prone, polyglutamine-expanded fragments even in cells selected for the highest expression levels (Bersuker et al. 2013).

3.7.4 Small Compounds

HSF1 is activated by a variety of small compounds. Because HSF1 is usually repressed by chaperone machineries, compounds that inhibit chaperone activity may release HSF1 from the feedback repression. In fact, HSF1 is robustly activated when cells are treated with geldanamycin, a benzoquinone ansamycin antibiotic, that inhibits HSP90 function by binding to its ADP/ATP-binding pocket (Zou et al. 1998a, b). Geldanamycin and its derivatives including 17-allylamino-17-demethoxygeldanamycin (17-AAG) could be candidates of therapeutic drug for neurodegenerative disease and cancer (see Chap. 14). Geranylgeranylacetone (GGA), an acyclic polyisoprenoid, is known as an antiulcer drug and also induces the HSR (Hirakawa et al. 1996), in part by binding to HSP70 and disrupting the HSF1-HSP70 interaction (Otaka et al. 2007). Furthermore, HSF1 is activated by proteasome inhibitors including lactacystin and MG132 and amino acid analogs, azetidine, and canavanine (proline and arginine analogs, respectively), by inducing the accumulation of misfolded proteins in cells (Kelley and Schlesinger 1978; Kawazoe et al. 1998; Mathew et al. 1998; Pirkkala et al. 2000). Moreover, a lot of thiol-reactive compounds including natural product celastrol, a quinone methide triterpene, also activate HSF1 probably through modification of cysteines in cellular target proteins (Westerheide et al. 2004; Trott et al. 2008; Santagata et al. 2012). Bimoclomol, a nontoxic hydroxylamine derivative, is a co-inducer of HSPs that elevates levels of HSPs under stress conditions (Vígh et al. 1997; Kieran et al. 2004), in part by binding to HSF1 complex directly (Hargitai et al. 2003). Furthermore, HSF1 is activated by anticancer drugs including 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) (an alkylating drug), vincristine (a microtubule-damaging drug), and bleomycin (a DNA-damaging drug) by unknown mechanisms (Kroes et al. 1991; Kim et al. 1999). BCNU strongly induces

the HSR, while the latter two drugs induce only the expression of mitochondrial HSPs. Moreover, anti-inflammatory drugs, sodium salicylate and indomethacin, induce the HSF1 DNA-binding activity without upregulation of the HSP expression (Jurivich et al. 1992; Lee et al. 1995).

3.8 Future Perspectives

In response to proteotoxic stresses including heat shock and proteasome inhibition, the activation of HSF1 is triggered by the rapid elevation of misfolded proteins within cells, which leads the release from feedback repression of HSF1 by HSPs. Heat shock also promotes the monomer-to-trimer transition of HSF1 directly. Furthermore, the activation and shutdown of HSF1 activity are associated with posttranslational modifications including phosphorylation and acetylation. Because these posttranslational modifications are complex, impact of each modification on the regulation of HSF1 activity in response to a specific proteotoxic stress is not well understood. Furthermore, it is still unclear whether is there any other factor than HSPs that directly regulates HSF1 activation during proteotoxic stress.

It is proposed that each cell possesses a unique proteostasis capacity or a buffering capacity against protein misfolding, which is determined by the balance of protein synthesis, folding, and degradation (Gidalevitz et al. 2010). Not only the status of protein folding and degradation but also that of protein synthesis regulates HSF1 activity (Santagata et al. 2013), indicating a tight link between the proteostasis capacity and HSF1 activity even in unstressed conditions. The basal HSF1 activity is required for maintenance of the proteostasis capacity in unstressed conditions and delays physiological aging and the progression of a model of misfolding diseases (Hsu et al. 2003; Morley and Morimoto 2004; Hayashida et al. 2010). Thus, regulation of the basal HSF1 activity may modulate aging and age-related protein misfolding diseases. It should be clarified how HSF1 activity is strictly regulated by metabolic signaling pathways under physiological conditions in future.

References

Abane R, Mezger V (2010) Roles of heat shock factors in gametogenesis and development. FEBS J 277:4150–4172

Abravaya K, Phillips B, Morimoto RI (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 5:2117–2127

Abravaya K, Myers MP, Murphy SP et al (1992) The human heat shock protein hsp70 interacts with HSF, the transcription factor that regulates heat shock gene expression. Genes Dev 6:1153–1164

Ahn SG, Thiele DJ (2003) Redox regulation of mammalian heat shock factor 1 is essential for Hsp gene activation and protection from stress. Genes Dev 17:516–528
Akerfelt M, Morimoto RI, Sistonen L (2010) Heat shock factors: integrators of cell stress, development and lifespan. Nat Rev Mol Cell Biol 11:545–555
Ali A, Bharadwaj S, O'Carroll R et al (1998) HSP90 interacts with and regulates the activity of heat shock factor 1 in Xenopus oocytes. Mol Cell Biol 18:4949–4960
Amici C, Sistonen L, Santoro MG et al (1992) Antiproliferative prostaglandins activate heat shock transcription factor. Proc Natl Acad Sci USA 89:6227–6231
Anckar J, Hietakangas V, Denessiouk K et al (2006) Inhibition of DNA binding by differential sumoylation of heat shock factors. Mol Cell Biol 26:955–964
Ashburner M, Bonner JJ (1979) The induction of gene activity in drosophila by heat shock. Cell 17:241–254
Balch WE, Morimoto RI, Dillin A et al (2008) Adapting proteostasis for disease intervention. Science 319:916–919
Baler R, Welch WJ, Voellmy R (1992) Heat shock gene regulation by nascent polypeptides and denatured proteins: hsp70 as a potential autoregulatory factor. J Cell Biol 117:1151–1159
Baler R, Dahl G, Voellmy R (1993) Activation of human heat shock genes is accompanied by oligomerization, modification, and rapid translocation of heat shock transcription factor HSF1. Mol Cell Biol 13:2486–2496
Bersuker K, Hipp MS, Calamini B et al (2013) Heat shock response activation exacerbates inclusion body formation in a cellular model of Huntington disease. J Biol Chem 288:23633–23638
Bharadwaj S, Ali A, Ovsenek N (1999) Multiple components of the HSP90 chaperone complex function in regulation of heat shock factor 1 in vivo. Mol Cell Biol 19:8033–8041
Björk JK, Sistonen L (2010) Regulation of the members of the mammalian heat shock factor family. FEBS J 277:4126–4139
Blake MJ, Udelsman R, Feulner GJ et al (1991) Stress-induced heat shock protein 70 expression in adrenal cortex: an adrenocorticotropic hormone-sensitive, age-dependent response. Proc Natl Acad Sci USA 88:9873–9877
Boorstein WR, Craig EA (1990) Transcriptional regulation of SSA3, an HSP70 gene from *Saccharomyces cerevisiae*. Mol Cell Biol 10:3262–3267
Budzyński MA, Puustinen MC, Joutsen J et al (2015) Uncoupling stress-inducible phosphorylation of heat shock factor 1 from its activation. Mol Cell Biol 35:2530–2540
Chiang WC, Ching TT, Lee HC et al (2012) HSF-1 regulators DDL-1/2 link insulin-like signaling to heat-shock responses and modulation of longevity. Cell 148:322–334
Chu B, Soncin F, Price BD et al (1996) Sequential phosphorylation by mitogen-activated protein kinase and glycogen synthase kinase 3 represses transcriptional activation by heat shock factor-1. J Biol Chem 271:30847–30857
Chu B, Zhong R, Soncin F et al (1998) Transcriptional activity of heat shock factor 1 at 37° C is repressed through phosphorylation on two distinct serine residues by glycogen synthase kinase 3 and protein kinases Calpha and Czeta. J Biol Chem 273:18640–18646
Chuma M, Sakamoto N, Nakai A et al (2014) Heat shock factor 1 accelerates hepatocellular carcinoma development by activating nuclear factor-κB/mitogen-activated protein kinase. Carcinogenesis 35:272–281
Clos J, Westwood JT, Becker PB et al (1990) Molecular cloning and expression of a hexameric Drosophila heat shock factor subject to a negative regulation. Cell 63:1085–1097
Cotto JJ, Kline M, Morimoto RI (1996) Activation of heat shock factor 1 DNA binding precedes stress-induced serine phosphorylation. Evidence for a multistep pathway of regulation. J Biol Chem 271:3355–3358
Craig EA, Gross CA (1991) Is hsp70 the cellular thermometer? Trends Biochem Sci 16:135–140
Craig EA, Jacobsen K (1984) Mutations of the heat inducible 70 kilodalton genes of yeast confer temperature sensitive growth. Cell 38:841–849

Dai R, Frejtag W, He B et al (2000) c-Jun NH2-terminal kinase targeting and phosphorylation of heat shock factor-1 suppress its transcriptional activity. J Biol Chem 275:18210–18218
Dai Q, Zhang C, Wu Y et al (2003) CHIP activates HSF1 and confers protection against apoptosis and cellular stress. EMBO J 22:5446–5458
Dai C, Whitesell L, Rogers AB et al (2007) Heat shock factor 1 is a powerful multifaceted modifier of carcinogenesis. Cell 130:1005–1018
Dai C, Santagata S, Tang Z et al (2012) Loss of tumor suppressor NF1 activates HSF1 to promote carcinogenesis. J Clin Invest 122:3742–3754
Dai S, Tang Z, Cao J et al (2015) Suppression of the HSF1-mediated proteotoxic stress response by the metabolic stress sensor AMPK. EMBO J 34:275–293
DiDomenico BJ, Bugaisky GE, Lindquist S (1982) The heat shock response is self-regulated at both the transcriptional and posttranscriptional levels. Cell 31:593–603
Duina AA, Kalton HM, Gaber RF (1998) Requirement for Hsp90 and a CyP-40-type cyclophilin in negative regulation of the heat shock response. J Biol Chem 273:18974–18978
Farkas T, Kutskova YA, Zimarino V (1998) Intramolecular repression of mouse heat shock factor 1. Mol Cell Biol 18:906–918
Fawcett TW, Sylvester SL, Sarge KD et al (1994) Effects of neurohormonal stress and aging on the activation of mammalian heat shock factor 1. J Biol Chem 269:32272–32278
Fujimoto M, Nakai A (2010) The heat shock factor family and adaptation to proteotoxic stress. FEBS J 277:4112–4125
Fujimoto M, Takaki E, Hayashi T et al (2005) Active HSF1 significantly suppresses polyglutamine aggregate formation in cellular and mouse models. J Biol Chem 280:34908–34916
Gallo GJ, Schuetz TJ, Kingston RE (1991) Regulation of heat shock factor in *Schizosaccharomyces pombe* more closely resembles regulation in mammals than in Saccharomyces cerevisiae. Mol Cell Biol 11:281–288
Ghosh SK, Missra A, Gilmour DS (2011) Negative elongation factor accelerates the rate at which heat shock genes are shut off by facilitating dissociation of heat shock factor. Mol Cell Biol 31:4232–4243
Gidalevitz T, Kikis EA, Morimoto RI (2010) A cellular perspective on conformational disease: the role of genetic background and proteostasis networks. Curr Opin Struct Biol 20:23–32
Goodson ML, Sarge KD (1995) Heat-inducible DNA binding of purified heat shock transcription factor 1. J Biol Chem 270:2447–2450
Goodson ML, Hong Y, Rogers R et al (2001) Sumo-1 modification regulates the DNA binding activity of heat shock transcription factor 2, a promyelocytic leukemia nuclear body associated transcription factor. J Biol Chem 276:18513–18518
Goossens V, Grooten J, De Vos K et al (1995) Direct evidence for tumor necrosis factor-induced mitochondrial reactive oxygen intermediates and their involvement in cytotoxicity. Proc Natl Acad Sci USA 92:8115–8119
Green M, Schuetz TJ, Sullivan EK et al (1995) A heat shock-responsive domain of human HSF1 that regulates transcription activation domain function. Mol Cell Biol 15:3354–3362
Guettouche T, Boellmann F, Lane WS et al (2005) Analysis of phosphorylation of human heat shock factor 1 in cells experiencing a stress. BMC Biochem 6:4
Guisbert E, Herman C, Lu CZ et al (2004) A chaperone network controls the heat shock response in *E. coli*. Genes Dev 18:2812–2821
Guisbert E, Yura T, Rhodius VA et al (2008) Convergence of molecular, modeling, and systems approaches for an understanding of the *Escherichia coli* heat shock response. Microbiol Mol Biol Rev 72:545–554
Guo Y, Guettouche T, Fenna M et al (2001) Evidence for a mechanism of repression of heat shock factor 1 transcriptional activity by a multichaperone complex. J Biol Chem 276:45791–45799
Hargitai J, Lewis H, Boros I et al (2003) Bimoclomol, a heat shock protein co-inducer, acts by the prolonged activation of heat shock factor-1. Biochem Biophys Res Commun 307:689–695
Hayashida N, Fujimoto M, Tan K et al (2010) Heat shock factor 1 ameliorates proteotoxicity in cooperation with the transcription factor NFAT. EMBO J 29:3459–3469

Hensold JO, Hunt CR, Calderwood SK et al (1990) DNA binding of heat shock factor to the heat shock element is insufficient for transcriptional activation in murine erythroleukemia cells. Mol Cell Biol 10:1600–1608
Hietakangas V, Ahlskog JK, Jakobsson AM et al (2003) Phosphorylation of serine 303 is a prerequisite for the stress-inducible SUMO modification of heat shock factor 1. Mol Cell Biol 23:2953–2968
Hietakangas V, Anckar J, Blomster HA et al (2006) PDSM, a motif for phosphorylation-dependent SUMO modification. Proc Natl Acad Sci USA 103:45–50
Higashi T, Nakai A, Uemura Y et al (1995) Activation of heat shock factor 1 in rat brain during cerebral ischemia or after heat shock. Brain Res Mol Brain Res 34:262–270
Hipp MS, Park SH, Hartl FU (2014) Proteostasis impairment in protein-misfolding and -aggregation diseases. Trends Cell Biol 24:506–514
Hirakawa T, Rokutan K, Nikawa T et al (1996) Geranylgeranylacetone induces heat shock proteins in cultured guinea pig gastric mucosal cells and rat gastric mucosa. Gastroenterology 111:345–357
Hoang AT, Huang J, Rudra-Ganguly N et al (2000) A novel association between the human heat shock transcription factor 1 (HSF1) and prostate adenocarcinoma. Am J Pathol 156:857–864
Høj A, Jakobsen BK (1994) A short element required for turning off heat shock transcription factor: evidence that phosphorylation enhances deactivation. EMBO J 13:2617–2624
Holbrook NJ, Carlson SG, Choi AM et al (1992) Induction of HSP70 gene expression by the antiproliferative prostaglandin PGA2: a growth-dependent response mediated by activation of heat shock transcription factor. Mol Cell Biol 12:1528–1534
Holmberg CI, Hietakangas V, Mikhailov A et al (2001) Phosphorylation of serine 230 promotes inducible transcriptional activity of heat shock factor 1. EMBO J 20:3800–3810
Hong Y, Rogers R, Matunis MJ et al (2001) Regulation of heat shock transcription factor 1 by stress-induced SUMO-1 modification. J Biol Chem 276:40263–40267
Hsu AL, Murphy CT, Kenyon C (2003) Regulation of aging and age-related disease by DAF-16 and heat-shock factor. Science 300:1142–1145
Inouye S, Izu H, Takaki E et al (2004) Impaired IgG production in mice deficient for heat shock transcription factor 1. J Biol Chem 279:38701–38709
Johnston D, Oppermann H, Jackson J et al (1980) Induction of four proteins in chick embryo cells by sodium arsenite. J Biol Chem 255:6975–6980
Jurivich DA, Sistonen L, Kroes RA et al (1992) Effect of sodium salicylate on the human heat shock response. Science 255:1243–1245
Jurivich DA, Sistonen L, Sarge KD et al (1994) Arachidonate is a potent modulator of human heat shock gene transcription. Proc Natl Acad Sci USA 91:2280–2284
Jurivich DA, Pachetti C, Qiu L et al (1995) Salicylate triggers heat shock factor differently than heat. J Biol Chem 270:24489–24495
Kawazoe Y, Nakai A, Tanabe M et al (1998) Proteasome inhibition leads to the activation of all members of the heat-shock-factor family. Eur J Biochem 255:356–362
Kelley PM, Schlesinger MJ (1978) The effect of amino acid analogues and heat shock on gene expression in chicken embryo fibroblasts. Cell 15:1277–1286
Kieran D, Kalmar B, Dick JR et al (2004) Treatment with arimoclomol, a coinducer of heat shock proteins, delays disease progression in ALS mice. Nat Med 10:402–405
Kim D, Ouyang H, Li GC (1995) Heat shock protein hsp70 accelerates the recovery of heat-shocked mammalian cells through its modulation of heat shock transcription factor HSF1. Proc Natl Acad Sci USA 92:2126–2130
Kim SH, Kim D, Jung GS et al (1999) Involvement of c-Jun NH(2)-terminal kinase pathway in differential regulation of heat shock proteins by anticancer drugs. Biochem Biophys Res Commun 262:516–522
Kim SA, Yoon JH, Lee SH et al (2005) Polo-like kinase 1 phosphorylates heat shock transcription factor 1 and mediates its nuclear translocation during heat stress. J Biol Chem 280:12653–12657

Kline MP, Morimoto RI (1997) Repression of the heat shock factor 1 transcriptional activation domain is modulated by constitutive phosphorylation. Mol Cell Biol 17:2107–2115
Knauf U, Newton EM, Kyriakis J et al (1996) Repression of human heat shock factor 1 activity at control temperature by phosphorylation. Genes Dev 10:2782–2793
Kourtis N, Moubarak RS, Aranda-Orgilles B et al (2015) FBXW7 modulates cellular stress response and metastatic potential through HSF1 post-translational modification. Nat Cell Biol 17:322–332
Kroes RA, Abravaya K, Seidenfeld J et al (1991) Selective activation of human heat shock gene transcription by nitrosourea antitumor drugs mediated by isocyanate-induced damage and activation of heat shock transcription factor. Proc Natl Acad Sci USA 88:4825–4829
Larson JS, Schuetz TJ, Kingston RE (1988) Activation in vitro of sequence-specific DNA binding by a human regulatory factor. Nature 335:372–375
Larson JS, Schuetz TJ, Kingston RE (1995) In vitro activation of purified human heat shock factor by heat. Biochemistry 34:1902–1911
Lee BS, Chen J, Angelidis C et al (1995) Pharmacological modulation of heat shock factor 1 by antiinflammatory drugs results in protection against stress-induced cellular damage. Proc Natl Acad Sci USA 92:7207–7211
Lee YJ, Kim EH, Lee JS et al (2008) HSF1 as a mitotic regulator: phosphorylation of HSF1 by Plk1 is essential for mitotic progression. Cancer Res 68:7550–7560
Levinson W, Oppermann H, Jackson J (1980) Transition series metals and sulfhydryl reagents induce the synthesis of four proteins in eukaryotic cells. Biochim Biophys Acta 606:170–180
Li GC (1983) Induction of thermotolerance and enhanced heat shock protein synthesis in Chinese hamster fibroblasts by sodium arsenite and by ethanol. J Cell Physiol 115:116–122
Li Q, Herrler M, Landsberger N et al (1998) Xenopus NF-Y pre-sets chromatin to potentiate p300 and acetylation-responsive transcription from the Xenopus hsp70 promoter in vivo. EMBO J 17:6300–6315
Lindquist S (1986) The heat-shock response. Annu Rev Biochem 55:1151–1191
Lu M, Kim HE, Li CR et al (2008) Two distinct disulfide bonds formed in human heat shock transcription factor 1 act in opposition to regulate its DNA binding activity. Biochemistry 47:6007–6015
Manalo DJ, Liu AY (2001) Resolution, detection, and characterization of redox conformers of human HSF1. J Biol Chem 276:23554–23561
Manalo DJ, Lin Z, Liu AY (2002) Redox-dependent regulation of the conformation and function of human heat shock factor 1. Biochemistry 41:2580–2588
Marchler G, Wu C (2001) Modulation of Drosophila heat shock transcription factor activity by the molecular chaperone DROJ1. EMBO J 20:499–509
Mathew A, Mathur SK, Morimoto RI (1998) Heat shock response and protein degradation: regulation of HSF2 by the ubiquitin-proteasome pathway. Mol Cell Biol 18:5091–5098
Mathur SK, Sistonen L, Brown IR et al (1994) Deficient induction of human hsp70 heat shock gene transcription in Y79 retinoblastoma cells despite activation of heat shock factor 1. Proc Natl Acad Sci USA 91:8695–8699
Mendillo ML, Santagata S, Koeva M et al (2012) HSF1 drives a transcriptional program distinct from heat shock to support highly malignant human cancers. Cell 150:549–562
Min JN, Huang L, Zimonjic DB et al (2007) Selective suppression of lymphomas by functional loss of Hsf1 in a p53-deficient mouse model for spontaneous tumors. Oncogene 26:5086–5097
Morimoto RI (1998) Regulation of the heat shock transcriptional response: cross talk between a family of heat shock factors, molecular chaperones, and negative regulators. Genes Dev 12:3788–3796
Morimoto RI (2011) The heat shock response: systems biology of proteotoxic stress in aging and disease. Cold Spring Harb Symp Quant Biol 76:91–99
Morley JF, Morimoto RI (2004) Regulation of longevity in *Caenorhabditis elegans* by heat shock factor and molecular chaperones. Mol Biol Cell 15:657–664

Mosser DD, Kotzbauer PT, Sarge KD et al (1990) In vitro activation of heat shock transcription factor DNA-binding by calcium and biochemical conditions that affect protein conformation. Proc Natl Acad Sci USA 87:3748–3752

Mosser DD, Duchaine J, Massie B (1993) The DNA-binding activity of the human heat shock transcription factor is regulated in vivo by hsp70. Mol Cell Biol 13:5427–5438

Murata S, Chiba T, Tanaka K (2003) CHIP: a quality-control E3 ligase collaborating with molecular chaperones. Int J Biochem Cell Biol 35:572–578

Murshid A, Chou SD, Prince T et al (2010) Protein kinase a binds and activates heat shock factor 1. PLoS One 5:e13830

Nadeau K, Das A, Walsh CT (1993) Hsp90 chaperonins possess ATPase activity and bind heat shock transcription factors and peptidyl prolyl isomerases. J Biol Chem 268:1479–1487

Nair SC, Toran EJ, Rimerman RA et al (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 1:237–250

Neef DW, Jaeger AM, Gomez-Pastor R et al (2014) A direct regulatory interaction between chaperonin TRiC and stress-responsive transcription factor HSF1. Cell Rep 9:955–966

Newton EM, Knauf U, Green M et al (1996) The regulatory domain of human heat shock factor 1 is sufficient to sense heat stress. Mol Cell Biol 16:839–846

Nishizawa J, Nakai A, Higashi T et al (1996) Reperfusion causes significant activation of heat shock transcription factor 1 in ischemic rat heart. Circulation 94:2185–2192

Nishizawa J, Nakai A, Matsuda K et al (1999) Reactive oxygen species play an important role in the activation of heat shock factor 1 in ischemic-reperfused heart. Circulation 99:934–941

Otaka M, Yamamoto S, Ogasawara K et al (2007) The induction mechanism of the molecular chaperone HSP70 in the gastric mucosa by Geranylgeranylacetone (HSP-inducer). Biochem Biophys Res Commun 353:399–404

Pirkkala L, Alastalo TP, Zuo X et al (2000) Disruption of heat shock factor 1 reveals an essential role in the ubiquitin proteolytic pathway. Mol Cell Biol 20:2670–2675

Polla BS, Bachelet M, Elia G et al (1998) Stress proteins in inflammation. Ann NY Acad Sci 851:75–85

Rabindran SK, Wisniewski J, Li L et al (1994) Interaction between heat shock factor and hsp70 is insufficient to suppress induction of DNA-binding activity in vivo. Mol Cell Biol 14:6552–6560

Raychaudhuri S, Loew C, Körner R et al (2014) Interplay of acetyltransferase EP300 and the proteasome system in regulating heat shock transcription factor 1. Cell 156:975–985

Raynes R, Pombier KM, Nguyen K et al (2013) The SIRT1 modulators AROS and DBC1 regulate HSF1 activity and the heat shock response. PLoS One 8:e54364

Reinke H, Saini C, Fleury-Olela F et al (2008) Differential display of DNA-binding proteins reveals heat-shock factor 1 as a circadian transcription factor. Genes Dev 22:331–345

Richter K, Haslbeck KM, Buchner J (2010) The heat shock response: life on the verge of death. Mol Cell 40:253–266

Ritossa F (1962) A new puffing pattern induced by temperature shock and DNP in Drosophila. Experientia 18:571–573

Santagata S, Hu R, Lin NU et al (2011) High levels of nuclear heat-shock factor 1 (HSF1) are associated with poor prognosis in breast cancer. Proc Natl Acad Sci USA 108:18378–18383

Santagata S, Xu YM, Wijeratne EM et al (2012) Using the heat-shock response to discover anticancer compounds that target protein homeostasis. ACS Chem Biol 7:340–349

Santagata S, Mendillo ML, Tang YC et al (2013) Tight coordination of protein translation and HSF1 activation supports the anabolic malignant state. Science 341:1238303

Sarge KD, Zimarino V, Holm K et al (1991) Cloning and characterization of two mouse heat shock factors with distinct inducible and constitutive DNA-binding ability. Genes Dev 5:1902–1911

Sarge KD, Murphy SP, Morimoto RI (1993) Activation of heat shock gene transcription by heat shock factor 1 involves oligomerization, acquisition of DNA-binding activity, and nuclear localization and can occur in the absence of stress. Mol Cell Biol 13:1392–1407

Schett G, Redlich K, Xu Q et al (1998) Enhanced expression of heat shock protein 70 (hsp70) and heat shock factor 1 (HSF1) activation in rheumatoid arthritis synovial tissue. J Clin Invest 102:302–311

Shamovsky I, Ivannikov M, Kandel ES (2006) RNA-mediated response to heat shock in mammalian cells. Nature 440:556–560

Shi Y, Mosser DD, Morimoto RI (1998) Molecular chaperones as HSF1-specific transcriptional repressors. Genes Dev 12:654–666

Sorger PK, Pelham HR (1988) Yeast heat shock factor is an essential DNA-binding protein that exhibits temperature-dependent phosphorylation. Cell 54:855–864

Sorger PK, Lewis MJ, Pelham HR (1987) Heat shock factor is regulated differently in yeast and HeLa cells. Nature 329:81–84

Straus DS, Glass CK (2001) Cyclopentenone prostaglandins: new insights on biological activities and cellular targets. Med Res Rev 21:185–210

Straus DB, Walter WA, Gross CA (1989) The activity of sigma 32 is reduced under conditions of excess heat shock protein production in *Escherichia coli*. Genes Dev 3:2003–2310

Straus D, Walter W, Gross CA (1990) DnaK, DnaJ & GrpE heat shock proteins negatively regulate heat shock gene expression by controlling the synthesis and stability of sigma 32. Genes Dev 4:2202–2209

Takaki E, Fujimoto M, Sugahara K et al (2006) Maintenance of olfactory neurogenesis requires HSF1, a major heat shock transcription factor in mice. J Biol Chem 281:4931–4937

Takii R, Fujimoto M, Tan K et al (2015) ATF1 modulates the heat shock response by regulating the stress-inducible heat shock factor 1 transcription complex. Mol Cell Biol 35:11–25

Tateishi Y, Ariyoshi M, Igarashi R et al (2009) Molecular basis for SUMOylation-dependent regulation of DNA binding activity of heat shock factor 2. J Biol Chem 284:2435–2447

Tilly K, McKittrick N, Zylicz M et al (1983) The dnaK protein modulates the heat-shock response of *Escherichia coli*. Cell 34:641–646

Tilly K, Spence J, Georgopoulos C (1989) Modulation of stability of the *Escherichia coli* heat shock regulatory factor cr32. J Bacteriol 171:1585–1589

Tomoyasu T, Ogura T, Tatsuta T et al (1998) Levels of DnaK and DnaJ provide tight control of heat shock gene expression and protein repair in *Escherichia coli*. Mol Microbiol 30:567–581

Trott A, West JD, Klaić L et al (2008) Activation of heat shock and antioxidant responses by the natural product celastrol: transcriptional signatures of a thiol-targeted molecule. Mol Biol Cell 19:1104–1112

Vera M, Pani B, Griffiths LA et al (2014) The translation elongation factor eEF1A1 couples transcription to translation during heat shock response. Elife 16:3e03164

Vígh L, Literáti PN, Horváth I et al (1997) Bimoclomol: a nontoxic, hydroxylamine derivative with stress protein-inducing activity and cytoprotective effects. Nat Med 3:1150–1154

Wang Z, Lindquist S (1998) Developmentally regulated nuclear transport of transcription factors in Drosophila embryos enable the heat shock response. Development 125:4841–4850

Wang Z, Zang C, Cui K et al (2009) Genome-wide mapping of HATs and HDACs reveals distinct functions in active and inactive genes. Cell 138:1019–1031

Westerheide SD, Bosman JD, Mbadugha BN et al (2004) Celastrols as inducers of the heat shock response and cytoprotection. J Biol Chem 279:56053–56060

Westerheide SD, Anckar J, Stevens SM Jr et al (2009) Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. Science 323:1063–1066

Winegarden NA, Wong KS, Sopta M et al (1996) Sodium salicylate decreases intracellular ATP, induces both heat shock factor binding and chromosomal puffing, but does not induce hsp 70 gene transcription in Drosophila. J Biol Chem 271:26971–26980

Wolff S, Weissman JS, Dillin A (2014) Differential scales of protein quality control. Cell 157:52–64

Wu C (1995) Heat shock transcription factors: structure and regulation. Annu Rev Cell Dev Biol 11:441–469

Xavier IJ, Mercier PA, McLoughlin CM et al (2000) Glycogen synthase kinase 3beta negatively regulates both DNA-binding and transcriptional activities of heat shock factor 1. J Biol Chem 275:29147–29152

Xia W, Voellmy R (1997) Hyperphosphorylation of heat shock transcription factor 1 is correlated with transcriptional competence and slow dissociation of active factor trimers. J Biol Chem 272:4094–4102

Xu D, Zalmas LP, La Thangue NB (2008) A transcription cofactor required for the heat-shock response. EMBO Rep 9:662–669

Zhong M, Orosz A, Wu C (1998) Direct sensing of heat and oxidation by Drosophila heat shock transcription factor. Mol Cell 2:101–108

Zhong M, Kim SJ, Wu C (1999) Sensitivity of Drosophila heat shock transcription factor to low pH. J Biol Chem 274:3135–3140

Zimarino V, Wilson S, Wu C (1990) Antibody-mediated activation of Drosophila heat shock factor in vitro. Science 249:546–549

Zimmerman JL, Petri W, Meselson M (1983) Accumulation of a specific subset of *D. melanogaster* heat shock mRNAs in normal development without heat shock. Cell 32:1161–1170

Zou J, Guo Y, Guettouche T et al (1998a) Repression of heat shock transcription factor HSF1 activation by HSP90 (HSP90 complex) that forms a stress-sensitive complex with HSF1. Cell 94:471–480

Zou J, Salminen WF, Roberts SM et al (1998b) Correlation between glutathione oxidation and trimerization of heat shock factor 1, an early step in stress induction of the Hsp response. Cell Stress Chaperones 3:130–141