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Review

Roles of Heat Shock Factor 1 (HSF1) beyond the heat shock response

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Abstract

Various stress factors leading to protein damage induce the activation of an evolutionarily conserved cell protective mechanism, the heat shock response (HSR), to maintain protein homeostasis in virtually all eukaryotic cells. Heat shock factor 1 (HSF1) plays a central role in the HSR. HSF1 was initially known as a transcription factor that upregulates genes encoding heat shock proteins (HSPs), also called molecular chaperones, which assist in refolding or degrading injured intracellular proteins. However, recent accumulating evidence indicates multiple additional functions for HSF1 beyond the activation of HSPs. Here we present a nearly comprehensive list of non-HSP-related target genes of HSF1 identified so far. Through controlling these targets, HSF1 acts in diverse stress-induced cellular processes and molecular mechanisms, including the endoplasmic reticulum unfolded protein response and ubiquitin-proteasome system, multidrug resistance, autophagy, apoptosis, immune response, cell growth arrest, differentiation underlying developmental diapause, cancer development and ageing. Hence, HSF1 emerges as a major orchestrator of cellular stress response pathways.

Key words: ageing, apoptosis, autophagy, cancer, cell cycle, circadian rhythm, development, differentiation, heat shock factor 1, heat shock proteins, heat shock response, immune response, multidrug resistance, oxidative stress, proteasome, unfolded protein response

The heat shock response

Intracellular proteins have been evolutionarily optimized to function in a relatively tight temperature range. Even a small scale but long-acting change in the ambient temperature can severely perturb protein homeostasis (proteostasis), thereby compromising cellular processes and leading to accelerated ageing and the incidence of various proteotoxicity-triggered disorders. In humans, such pathologies include diverse neurodegenerative diseases, heart failure, cancer, diabetes, tissue atrophy and fibrosis, and immune deficiency [1-7]. Heat shock and other cellular stress factors such as oxidizing agents, toxins, heavy metals and infective microbes, can induce a conserved cell defence mechanism, the heat shock response (HSR), to maintain proteostasis in eukaryotic cells [8]. The HSR primarily involves the expression of heat shock proteins (HSPs), also termed molecular chaperones, which facilitate the synthesis and ensure the structural stability of other intracellular proteins. HSPs can also mediate the refolding or degradation of damaged intracellular proteins. This cell protective mechanism enables the cell to survive under harsh environmental conditions, predominantly at elevated temperatures. The activation of HSPs is mainly achieved by the heat shock transcription factor HSF1. Hence, HSF1 functions as a central regulator of the HSR.

HSF1 controls the HSR

HSF1 is an evolutionarily conserved transcription factor that is known to be primarily activated in response to heat stress. When triggered, HSF1 becomes trimerised and phosphorylated, and then translocated into the nucleus where it binds to conserved heat shock responsive DNA elements (HSEs) to upregulate genes coding for HSPs. HSEs are generally located in the upstream untranslated region of HSF1 target genes. As each DNA-binding

domain of the HSF1 homotrimer recognises a nGAAn pentameric sequence motif (where "n" indicates any nucleotide), a stable association of HSF1 to its binding element requires 3 pentameric sequences with alternating orientation, TTCnnGAAnnTTC [9-11]. Both *in vitro* and *in vivo* studies have shown that HSF1 prefers HSEs with tandem, properly orientated repeats [10]. At the same time, a ChIP-seq (chromatin-immunoprecipitation associated with deep sequencing) analysis on *Drosophila* has revealed that HSF1 can bind only a subset of its potential HSEs *in vivo*, and in the surroundings of these binding elements active chromatin marks are located [12].

HSF1 activation is accomplished at the level of protein-protein interaction and posttranslational modification [8]. Certain HSF1-induced HSPs, such as Hsp70 (HSPA1A), Hsp72 (HSPA1A) and Hsp90 (HSPC1), directly inhibits HSF1 via binding to its trimerisation domain. In addition, a cytoplasmic histone deacetylase (HDAC6) and a valosin-containing protein (VCP, a highly conserved member of the AAA – ATPases associated with a variety of cellular activities – family proteins) participates in the repressing HSF1-HSP complex [13]. This negative autoregulatory feedback loop ensures that HSF1-mediated stress response occurs precisely according to the actual level of protein damage [14]. HSF1 activity is also influenced by the phosphorylation, sumoylation or acetylation status of certain amino acids of the protein [8, 15, 16].

In both nematodes (*Caenorhabditis elegans*) and mammals, HSF1 activity can be modified by certain stress-induced kinases that represent components of conserved signal transduction systems including the insulin/IGF1 (insulin-like growth factor receptor 1) and cyclic guanosine monophosphate-mediated (cGMP) pathways [17, 18]. Some of these kinases like p38-Map (p38 mitogen-activated protein kinase), c-Jun (Jun proto-oncogene), Gsk3 (glycogen synthase kinase 3) and Erk1 (extracellular signal-regulated kinase 1) inhibit, while others

including PI3K (phosphatidylinositol 3-kinase), Akt (Akt serine/threonine kinase) and cAMP-dependent PKA (protein kinase A) trigger HSF1 activity [1, 8, 19, 20].

HSPs have multiple roles in eukaryotic cells. For example, Hsp90 binds damaged proteins and transmits them to Hsp60 (HSPD1) and Hsp70 for further processing [21, 22]. It also plays a diverse role in the functioning of signal transduction systems [23-25].

HSF1 is an essential gene in yeast, flies and nematodes [26-28]. The lethal phenotype of *HSF1(-)* mutant yeast cells can be suppressed by constitutively co-expressing Hsp70 and Hsp90 [29]. In mammals, however, HSF1 is not essential for viability and dispensable for the basal expression of molecular chaperones [30]. This may be due to the fact that in these organisms the basal expression of molecular chaperones is also influenced by other transcription factors including STAT1 (signal transducer and activator of transcription), STAT3 and NF-IL6 (nuclear factor for interleukin-6 expression) [31].

While most invertebrate genomes contain only a single *HSF1* gene, at least 9 HSF paralogues have been identified in vertebrates, HSF1-5, Hsfx1/2 and Hsfy1/2 [8]. It is possible that the expression of mammalian *Hsp* genes is controlled redundantly by HSF paralogues. In humans, for example, HSF1 coordinates the HSR, but HSF2 and HSF4 also participate in *Hsp* activation. Due to the functional diversity of HSF proteins, distinguishing between the HSP-dependent and -independent functions of HSF1 is quite difficult in mammals. Therefore, a systematic identification of HSF1 target genes in divergent genetic model systems appears to be particularly important in understanding how HSF1 integrates various stress response pathways.

Roles of HSF1 beyond the HSR

Until the beginning of this century, HSF1 was generally considered a heat shock-induced transcription factor that regulates the expression of HSPs (**Table S1**). Since then however HSF1 has also been revealed to influence numerous developmental events and cellular processes, and to be implicated in various molecular stress-induced pathologies [1-8]. In the last 15 years, several single gene-based and genome-scale studies were conducted to identify novel targets of HSF1 in genetic model organisms and cell cultures [32-38]. Based on these works it has become clear that following heat stress several genes become up- or downregulated independently of HSF1, and that HSF1 controls the transcription of numerous genes encoding proteins others than HSPs, largely in a temperature-independent manner. These so-called *non-HSP target genes* of HSF1 are implicated in various physiological and stress-induced cellular processes and molecular mechanisms including metabolism, protein modification and degradation, cell cycle, programmed cell death, ageing, the endoplasmic reticulum (ER) unfolded protein response (UPR), multidrug resistance and immune function. It is intriguing that HSF1 can play a role in controlling gene expression even in the absence of heat shock [33], and that the presence of a conserved HSE does not necessarily accompany a HSF1-dependent transcriptional control [31]. Moreover, the transcriptional activity of several HSF1 targets is repressed by the transcription factor, and this negative regulatory interaction occurs independently of temperature. For example, in *C. elegans* HSF-1 influences the transcription of genes encoding collagens involved in cuticle formation [33]. These data imply that the functional spectrum of HSF1 is much broader than previously assumed.

HSF1 in stress-induced cellular processes and molecular mechanisms

HSF1 and the endoplasmic reticulum unfolded protein response

The accumulation of un- and misfolded proteins in the lumen of ER, where newly translated proteins are stored and become modified, causes ER stress, which leads to the activation of genes encoding ER-resident proteins required for protein folding [39]. This molecular information is transmitted from the ER lumen to the nucleus by a conserved intracellular signalling pathway, the UPR. The UPR actually consists of three parallel intracellular signal transduction systems; the first is mediated by IRE1α/XBP1s (inositol-requiring protein 1α/spliced X box-binding protein 1) proteins, the second involves PERK/ATF4 (protein kinase RNA-like endoplasmic reticulum kinase/activating transcription factor 4) proteins, while the third relies on ATF6/ATF6f (activating transcription factor 6/cytosolic domain fragment of ATF6) proteins. These molecular machineries function to reduce the damaging effect of harmful proteins through restoring protein folding capacity in the affected cell. Together with the HSR, the UPR protects eukaryotic cells from the damaging effect of proteotoxicity. These two highly conserved protein stress-response systems, the HSR and UPR, are activated in the cytosol and ER, respectively.

In yeast, the expression of an HSE-containing reporter system is significantly increased in response to ER stress, and this transcriptional upregulation depends on Ire1/IRE1 and Hac1/XBP1 activity [40]. Thus, it is possible that ER stress triggers – via IRE1 and XBP1 proteins – HSF1 to participate in the UPR. Consistent with these results, a constitutively active HSF1 increases ER stress tolerance in both wild-type and *ire1(-)* mutant yeast cells [41, 42]. Indeed, a genome-wide gene expression analysis revealed that HSF1 activates both ER resident and cytosolic chaperones [42].

In human cells, HSF1-regulated chaperones are implicated in the control of UPR [43]. For example, Hsp90 was shown to interact with and stabilize the cytosolic domain of IRE1α, thereby influencing the UPR. Hsp72 is expressed at basal levels under physiological conditions. In cells constitutively overexpressing Hsp72, this chaperone activates the

IRE1α/XBP1 branch of the UPR through forming a stable complex with the cytoplasmic domain of IRE1α [44]. In addition to ER stress, heat shock also leads to an UPR-like response, in which ER-associated chaperones and their regulatory transcription factors are triggered simultaneously [45]. By using a dominant negative *HSF1* mutation, transcript levels of certain ER resident chaperones, such as BiP (HSPA5) and DNAJB9, were shown to become elevated following heat shock. Thus, genes encoding these chaperones do not serve as targets for HSF1. Vertebrate genomes however code for multiple HSF1 paralogues, which certainly function redundantly with HSF1. This suggests that the role of specific HSF paralogues cannot be excluded from the heat shock-induced UPR.

The yeast *ERO1* gene encodes an ER oxidoreductin, which is required for the formation of protein disulphide bonds [46]. *ERO1* was shown to be upregulated by HSF1 in response to various stress factors (**Tables 1** and **S1**) [47]. This regulatory interaction is particularly interesting because *ERO1* transcription is also activated by the bZIP (basic-leucine zipper) transcription factor Hac1 involved in the UPR. Hac1, the metazoan orthologue of which is Xbp1, binds the UPR (an XBP1 responsive *cis*-regulatory) element in the promoter of UPR-regulated genes [48]. Therefore, *ERO1* serves as a genetic factor where HSF1 and the UPR directly interact with each other. In other words, HSF1 may directly activate the UPR by controlling *ERO1* under conditions of proteotoxicity.

HSF1 and oxidative stress

Besides heat shock, the potent oxidizing agent hydrogen peroxide (H_2O_2) also evokes HSF1 homotrimerisation [37]. Two Cys residues, Cys35 and Cys105, were identified in the DNA-binding domain of HSF1, the transformation of which to Ser inhibits the ability of the protein to become homotrimerised and to bind DNA. Moreover, unlike in wild-type cells, C35S and C105S mutant HSF1 proteins remain in the cytoplasm following oxidative stress. Based on

these results, it can be concluded that HSF1, through these Cys residues, is able to directly sense the cellular redox state, which greatly influences the structure and function of intracellular proteins. Indeed, misfolded proteins accumulate following oxidative stress. In model organisms, *HSP* genes become upregulated in response to oxidative stress [49, 50]. In yeast exposed to H_2O_2, Hsf1 binds to the promoter of *CUP1*, *BTN2*, *SIS1*, *HSP1*, *SGT2* and *SSA3* genes, and upregulates their transcriptional activity (**Tables 1** and **S1**) [51]. A proteomic analysis has also indicated that menadion provoking oxidative stress induces the activation of various proteins, including metabolic enzymes, antioxidant enzymes, as well as chaperones and their cofactors in a Hsf1-dependent manner [52]. Thus, HSF1 is capable of inducing several cell protective mechanisms in response to oxidative stress.

Nrf2 (Nf E2-related factor 2) acts as a key regulator of cellular response to oxidative stress, and controls the transcription of genes that function to attenuate the effect of cellular stress caused by reactive oxygen species (ROS) [53]. HSF1 and Nrf2 share several target genes, including *HMOX1* (hemoxigenase) and *SQSTM1* (sequestosome)*/p62*, [54-56], *Atf3* (activating transcription factor) [57, 58], *Hsp70* and *Hsp25/27 (HSPB1)* [59]. This implies that the two stress-induced transcription factors collaborate with each other under certain circumstances. Furthermore, certain small HSPs (sHSPs), such as Hsp25 and αB-crystallin (HSPB5), are known to participate in maintaining cellular redox state, thereby reducing the level of oxidative damage. Due to the overexpression of these sHSPs, the concentration of the antioxidant glutathione (GSH) increases, together with glucose-6-phosphate-dehydrogenase (G6PD) activity, which contributes to the reduced state of GSH [59].

At physiological temperatures, the expression of *sHSPs* also relies on HSF1 [60]. In $HSF1^{-/-}$ mutant mice, Hsp25 and αB-crystallin levels are significantly lowered, as compared with wild-type ($HSF1^{+/+}$) mice. In this mutant background, the GSH/GSSG (glutathione

disulphide) ratio is considerably decreased, and heart muscle cells contain higher levels of ROS as a consequence of reduced G6PD activity.

HSF1 can trigger autophagy

Autophagy (cellular self-eating) is a highly regulated self-degradation process of eukaryotic cells, during which parts of the cytoplasm are delivered into the lysosomal compartment for enzymatic breakdown. The autophagic process plays a fundamental role in maintaining cellular proteostasis and organellar integrity through ensuring normal macromolecule and organelle turnover and the elimination (degradation) of damaged, largely toxic proteins [61, 62]. It was demonstrated in several mammalian cell lines and genetic models that autophagy is induced following heat shock [63, 64]. Surprisingly, a constitutively active HSF1 mutant was shown to inhibit both heat shock-induced and basal autophagy, and in the absence of HSF1 activity starvation- and rapamycin-induced autophagy become elevated [63, 65]. Another study however reported that the treatment of tumorous cells with the chemotherapeutic agent carboplatin leads to an increased amount of autophagic structures, and this change fails to occur when HSF1 is silenced [66]. These data suggest that HSF1 and the HSR may also play a role in the regulation of autophagy under certain conditions. Indeed, HSF1 is triggered by carboplatin, and able to bind to a HSE found in the regulatory region of the autophagy gene *Atg7* (**Tables 1** and **S1**). This way HSF1 may directly induce autophagy at the transcriptional level by upregulating certain key *Atg* genes.

In plants, HsfA1a plays an orthologous function to HSF1 [67]. In tomato, HsfA1a was shown to confer tolerance to drought by inducing autophagy through directly promoting the expression of at least two *Atg* genes, *Atg10* and *Atg18* [68]. Their expression and the formation of autophagic structures were elevated in plants overexpressing HsfA1a, but were compromised in plants defective for HsfA1a.

SQSMT1/p62, which encodes a specific receptor for selective autophagy (the protein actually delivers substrates for autophagy and also participates in autophagosome nucleation), was also identified as a HSF1 target gene in MCF-7 cells [55]. In this experimental paradigm, HSF1 conferred resistance to inhibitors of Hsp90, which plays an important role in various types of cancer, by promoting *SQSMT1/p62* expression and the autophagic flux. Another study also showed that HSF1 can induce the autophagic clearance of protein aggregates via regulating *SQSMT1/p62* activity [56]. According to this analysis, HSF1 inhibition blocked autophagosome formation and hence the elimination of damaged proteins.

Unlike severe stress, which is almost always harmful to the organism, mild stress can be favourable for health and survival. This phenomenon is called hormesis. In *C. elegans*, *Atg* genes were demonstrated recently to be required for longevity and increased thermotolerance caused by hormetic heat stress or HSF-1 overexpression [69]. Although direct regulatory interaction was not examined, mild heat stress could induce the expression of multiple *Atg* genes including those involved in the formation of autophagic structures and lysosomal breakdown [70-72]. Many of these *Atg* genes contain at least one putative HSE in their upstream regulatory sequences. In good accordance with these observations, HSF-1 overexpression was also capable of inducing the amount of autophagic structures and the expression of these *Atg* genes [69]. According to a recent ChIP-seq analysis performed on *C. elegans*, HSF-1 directly represses certain autophagy-related genes including *lgg-1/Atg8*, *lgg-2/Atg8* and *epg-9* during larval development under physiological conditions (**Tables 1** and **S1)** **[**38]**.**

Interaction between HSF1 and the ubiquitin-proteasome system

Beside autophagy, the ubiquitin-proteasome system (UPS) can also participate in the degradation of intracellular proteins. The UPS target proteins are first labelled by

ubiquitination, *that is*, conjugated with the small, highly conserved protein ubiquitin, then transferred into the 26S proteasome complex, in which they are digested by enzymatic proteolysis to oligopeptides. The primary role of UPS is to control protein activity, but compromised and toxic proteins can also be eliminated by this molecular machinery. Defects in the UPS can lead to HSF1 and HSF2 overactivation, which in turn elevates *HSP* expression [73-77]. These data support an intimate relationship between HSF1 and the UPS in eliminating misfolded cytoplasmic proteins. It may seem reasonable that HSF1 directly upregulates certain UPS genes. Indeed, a strong correlation was shown between HSF2 deficiency and the transcriptional activity of two ubiquitin genes, *Ubb* and *Ubc* in mouse embryonic fibroblasts cells [75]. In addition, the expression of several components of the 20S and 19S proteasome subunits was also lowered in an HSF2 defective genetic background.

A ChIP-seq analysis on human cell lines has also revealed that both HSF1 and HSF2 are capable of binding the regulatory region of *Ubb* and *Ubc*, and this molecular interaction causes a significant transcriptional upregulation of these targets (**Tables 1** and **S1**) [78]. By another study, *Ubb* gene was also identified as a direct HSF1 target in HepG2 cells [79]. The authors have found that the anti-inflammatory pyrrolidine dithiocarbamate promotes HSF1 binding to the *Ubb* promoter. Based on these results, it can be assumed that in response to proteotoxicity, HSF proteins ensure the increased levels of ubiquitin and proteasomal proteins required for the effective operation of the UPS.

Co-activation of HSF1 and the UPS can also be observed during development. For instance, in *C. elegans* males an apoptosis-independent programmed cell death process eliminates the so-called linker cells, and during this process HSF1 increases the transcription of three UPS-related genes, *ubi-1* (ubiquitin), *rpn-3* (a proteasome subunit), and *let-70* (E2 ligase) [80]. In this paradigm HSF1 contributes to cell death rather than protecting cells from undergoing demise.

HSF1 in multidrug resistance

In cancer therapy, a significant problem of treatment effectiveness often results from the development of drug resistance that tumorous cells acquire against the chemical agent applied. This phenomenon is mainly caused by the activity of ABC (ATP-binding cassette) transmembrane proteins that pump the drug out from the cell at the expense of ATP hydrolysis. Behind drug resistance, there are some underlying mechanisms of chemoresistance, including those influencing the passage of drugs into the target cell, the efflux of drugs from the target cell, drug metabolism, and the loss of the affected cell by apoptosis. HSF1 can influence chemoresistance in multiple ways. One of them results from its anti-apoptotic (cell protective) effect, which is mainly achieved through HSP upregulation [81]. In addition, the role of HSF1 was also shown in the regulation of a specific ABC transporter [82-85]. HSF1 overexpression leads to an increased activity of ABCB1 (also called MDR1 or P-pg), which causes resistance against the chemotherapeutic agent doxorubicin [82-84]. However, another study reported ABCB1 hyperactivity under condition of HSF1 deficiency [85]. Thus, the regulatory interplay between HSF1 and ABCB1 is far from being clear. HSF1 may directly activate *ABCB6* expression [83], or the regulation of *ABCB1* by HSF1 may occur at the posttranscriptional level [82]. The latter alternative was supported by the finding that ABCB1 activation can happen even in an HSF1 mutant background defective for the transactivation domain of the protein [84]. It is possible that the effect of HSF1 on ABCB1 activity depends on cell type or transcription factors by which HSF interacts, or that HSF1 simply maintains an open chromatin state at the *ABCB1* promoter in order to enable the recruitment of other transcription factors to this particular regulatory sequence. A similar role for HSF1 was previously reported. Accordingly, HSF1 binds the *IL-6* (interleukin 6) promoter, allowing the recruitment of specific enhancers and inhibitors to this locus [86].

HSF1 in non-coding RNA transcription and chromatin remodelling

In primates, following proteotoxic stress electrodense structures, also called nuclear stress bodies (nSBs), become apparent in the nucleus [87, 88]. In addition to ribonucleoproteins and RNAs, HSF1 represents a major component of nSBs. In humans, nSBs are localised to specific loci on chromosomes 9, 12 and 15, where HSF1 and HSF2 attach to pericentric satellite III (Sat III) repeats [89-91]. At this specific heterochromatic region, the two transcription factors promote the expression of long, non-coding RNAs (**Tables 1** and **S1**) [92, 93]. The exact role of nSBs in the heat shock response remains unclear. Since nSBs contain several splicing factors and RNA-processing enzymes, it is possible that these proteins are stored in inactive forms in these compartments during stress [94, 95]. It has been recently shown that Sat III transcripts recruit essential factors required for transcription in nSBs. This suggests that nSBs contribute to the inhibition of transcription under proteotoxic stress [96].

Accumulating evidence indicates that the expression of non-coding RNAs of telomeric origin also increases under heat stress [97-99]. Telomeric repeat-containing RNAs (TERRA) are chromosome-specific, long non-coding RNAs transcribed in the subtelomeric regions of chromosomes [98, 100]. Telomeres also become shortened (damaged) upon heat stress [97, 101]. Following TRF2 (telomeric repeat-binding factor 2) depletion elevated TERRA transcription may play a key role in DNA damage response protecting naked telomeric sequences [102]. Furthermore, several HSEs have been identified in TERRA promoters. In accordance with these results, HSF1 is shown to directly induce the transcription of certain TERRAs (3p and 10p -18p), thereby lowering the level of telomere damage under condition of heat stress (**Tables 1** and **S1**) [103]. Together, HSF1 participates in protecting telomere structure.

Numerous publications have reported that HSF1 influences stress-induced HSP transcription in collaboration with chromatin remodelling factors [104-111]. Such factors may promote the transition of HSEs into accessible (open) chromatin regions [12]. In *C. elegans*, for example, E2F/DP transcription factors support HSF1 binding to the promoter of genes that participate in controlling development [38]. In mouse fibroblast cells, HSF1 maintains the open chromatin state in the proximity of *IL-6* gene even in the absence of cellular stress, thereby endorsing the accessibility of other transcription factors to this regulatory region [86]. These results imply that HSF1 is also involved in the regulation of chromatin state.

HSF1 and apoptosis

Genomics studies have revealed that HSF1 is able to upregulate several genes with an inhibitory effect on apoptosis [32-36]. The anti-apoptotic function of HSF1 contributes to the survival of hyperproliferating cells. In tumorous cells, this role of HSF1 is mainly achieved by upregulating Hsp27 and Hsp70. These HSPs negatively interact with members, such as death receptors, caspases and mitochondrial factors, of the apoptotic cell death pathway [10, 112-116]. Furthermore, HSF1 was shown to induce directly the transcriptional activity of *BAG3*, which encodes a co-chaperone of Hsp70 [117, 118]. In Sca-1^+ (stem cell antigen) stem cells, it also binds the promoter region and represses the expression of *MiR-34a* gene (HSF1 actually increases H3K27me3 levels at this locus), which in turn blocks Hsp70 [119]. These data imply that HSF1 can prevent normal and tumorous cells from undergoing apoptosis.

In contrast, both heat stress and HSF1 overexpression can trigger the apoptotic cell death program through modulating the Fas pathway [120, 121]. Fas is a death receptor that becomes activated upon ligand binding to trigger the extrinsic part of the apoptotic pathway. In germline cells of male mice, HSF1 directly associates with the regulatory region of *Tdag51* (T-cell death associated gene) to activate its transcription in response to heat stress [122].

Tdag51 codes for a pleckstrin homology domain protein that induces apoptosis in T-lymphocytes and neurons, and triggers the activity of the pro-apoptotic *Fas* gene in T-cell hybridoma cells [123]. At high temperatures HSF1 hence can induce apoptosis through activating the Fas-mediated pathway in a Tdag-51-dependent manner.

Later, human *FAS1* was identified as a direct transcriptional target of HSF1 (**Tables 1** and **S1**) [124]. The death-associated protein kinase DAPK exerts a pro-apoptotic effect, and its transcription is elevated by certain cytokines such as Fas and TNFα (tumour necrosis factor alpha) [125, 126]. During mild TNFα-mediated inflammatory stress, HSF1 directly upregulates *DAPK* which leads to the apoptotic loss of colorectal tumour cells [127]. Together, these data show that under certain circumstances HSF1 is capable of inducing the extrinsic part of the apoptotic cell death pathway.

HSF1 also play a regulatory role in p53-induced gene expression. Indeed, HSF1 is required for p53-mediated cell cycle arrest and apoptosis [128], and its activity is essential for the expression of several p53 target genes under both normal and genotoxic stress-induced conditions. HSF1 may operate as a p53 cofactor. First, according to ChIP experiments the parallel binding of HSF1 and p53 is detectable on the promoter of certain p53 target genes such as *p21* and *gadd45* (**Tables 1** and **S1**). Second, the silencing of HSF1 significantly reduces p53 binding to its targets, as compared with the control genetic background. Other studies have raised the possibility that HSF1 also participates in controlling nuclear translocation of p53 [8, 129]. Based on these data one may conclude that HSF1 can trigger apoptotic cell death through promoting p53-induced gene expression.

HSF-1 in cell growth and proliferation

Above physiological temperatures, the cell cycle process can become blocked. Several regulatory proteins involved in cell cycle control are stabilized by molecular chaperones. As

an example, Cdc2 (cyclin-dependent kinase) forms a complex with Hsp90 to mediate cell signal transduction [130-132]. Thus, HSF1 may control cell cycle and proliferation via inducing HSP chaperones. Indeed, double knockout of *HSF1* and *HSF3* leads to a decreased expression of Hsp90a in chicken DT40 cells even under physiological conditions. This causes Cdc2 instability, and the affected cell sticks in the G2 phase upon heat stress. Hyper-activation of Hsp90a can rescue normal cell cycle progression even in the presence of HSF1/3 deficiency. In this context HSF1 deficiency suppresses RAS oncogene- and p53 tumour suppressor mutation-induced tumour development in mice [133].

AP-1 (activator protein) complex consists of a Jun and a Fos family member. The complex controls the expression of numerous genes implicated in cell cycle regulation, as well as cell migration and death. Upon proteotoxicity, HFS1 binds to an HSE located in the *Fos1* promoter, and *Fos1* expression is increased in a HFS1-dependent manner, (**Tables 1** and **S1**) [134, 135]. HSF2 also activates *Fos1* transcription [136]. In HeLa cells exposed to stress, HSF1 interacts with the proto-oncogene *Jun* regulatory sequences and promotes transcription (**Tables 1** and **S1**) [137]. FoxM1 (Forkhead box M1) transcription factor acts as a master regulator of cell cycle, and its dysregulation is strongly linked to tumour development and progression. FoxM1 is required for the survival of cells exposed to heat stress and for the G2/M transition. Its direct transcriptional targets include the cell cycle genes *Cdc20*, *Cdc2* and *Cdc25B* [138, 139]. In response to proteolytic stress, HSF1 binds *FoxM1* promoter to stimulate expression [140]. Therefore, HSF1 controls the cell cycle in both direct and indirect ways.

HSF1 also directly controls the transcriptional activity of *FUT4* (Fucosyltransferase IV), which plays an important regulatory role in cell division (**Tables 1** and **S1**) [141]. The serum- and growth factor-induced *IER5* (immediate early response gene) is also under the control of HSF1 (**Tables 1** and **S1**) [142]. Based on these data one can conclude that HSF1 plays a key

role in the control of cell growth and proliferation, and, accordingly, it serves as an important drug target in cancer therapy.

HIF1 (hypoxia-inducible factor) mediates the effect of low oxygen concentration (hypoxia) on cell growth and proliferation. Its translation is mediated by the mRNA-binding protein HuR (human antigen R), the transcription of which in turn directly relies on HSF1 activity [143]. Therefore, HSF1 promotes tumour growth in an oxygen-depleted environment by triggering angiogenesis. HuR also interacts with the long non-coding RNA lincRNA-p21, a major mediator of p53-dependent apoptosis, which inhibits the translation of *CTNNB1* mRNA encoding beta catenin, a key regulator of cell division [144].

In addition to regulating gene expression, HSF1 can control cell growth and proliferation via other mechanisms. For example, it influences translation and cell growth by modulating the JNK-mTOR (c-Jun N-terminal kinase-mammalian target of rapamycin) pathway [145]. HSF1 is likely to promote mTOR-mediated protein synthesis by inhibiting JNK at the posttranscriptional level. It also directly binds the upstream regulatory region of *Hgf* gene encoding hepatocyte growth factor (**Tables 1** and **S1**). Furthermore, in case of elevated mTOR activity *HSF1* translation and *HSP* transcription become markedly increased. HSF1 is therefore capable of controlling proteotoxic stress response at the level of both transcription and translation.

HSF1 in cancer

Since HSF1 is implicated in controlling cell growth and proliferation, as well as in apoptosis (see chapters above), its potential effect in the development of cancer should also be discussed briefly. Through upregulating its target genes, HSF1 modulates several cellular processes and molecular mechanisms (*e.g.* autophagy, the UPR, oxidative stress response and multidrug resistance) that are involved in the survival of terminally differentiated cells. HFS1 primarily

supports cell survival by increasing their stress tolerance. It also elevates the ability of cancer cells to resist against various stress factors. Accordingly, increased HSF1 activity has been detected in numerous types of cancer [6, 7, 146, 147]. Several oncoproteins, such as ERBB2/HER2, c-MET, CYCLIND1, CDK4, BRAF, AKT and TP53, require HSF1 for maintaining their structural stability. On the other hand, signalling system involved in cell growth and proliferation are also affected by HSF1. The best examples include the RAS/RAF/MEK (Ras/rapidly accelerated fibrosarcoma/MAPK-ERK kinase), TGFβ (transforming growth factor-beta) and PI3K/AKT/mTOR (phosphatidylinositol 3-kinase) signalling pathways [18, 148]. Cancer cells are also frequently exposed to hypoxia. HIF1 is an important factor in tumour growth and metastasis [149]. HSF1 promotes HIF1 translation and hence tumour angiogenesis by inducing the transcription of the mRNA-binding protein HuR (human antigen R) [143]. Thus, HSF1 influences both tumour genesis and growth, and has a complex role in tumour development.

HFS-1 controls stress-induced developmental diapause

Grown under normal conditions, the hatched *C. elegans* embryo develops into a reproductive adult through four larval stages, L1-L4, which are separated by moults. However, under harsh environmental conditions such as starvation, high temperatures and elevated population density (crowding), the L1 larva develops into a highly stress-resistant dauer larval stage, which is a non-ageing developmental diapause [150]. On exposure to normal conditions, the animal exits from the dauer stage and resumes development. Mutations causing constitutive dauer larval development even under normal conditions confer increased stress resistance to the adult animal and significantly extend its lifespan. Concentration of the *C. elegans* dauer pheromone is proportional with population density as each animal secretes a nearly equal amount of substance to the environment. The crowding pheromone encoded by *daf-22* (dauer formation defective), together with its ligand DAF-6, inhibits the guanylate cyclase DAF-11

and HSP90-like DAF-21 proteins, which in turn activate DAF-7, a TGFβ-like ligand. High levels of DAF-22 thereby hamper TGFβ signalling required for normal reproductive growth, and promotes dauer development. HSF-1 has been shown to mediate the stimulatory effect of DAF-11 and DAF-21 on *daf-7* transcription [17]. DAF-11 and DAF-21 inhibits HSF-1, while HSF-1 directly represses *daf-7* (**Tables 1** and **S1**). This molecular interaction shows how HSF-1 becomes activated by a hormonal cue, the dauer pheromone, and how it promotes a stress-induced developmental event, the decision to form dauer larvae instead of reproductive adults. Moreover, HSF-1 upregulates directly another key component of the TGFβ signalling pathway, *daf-9*, which encodes a cytochrome P450, thereby fine-tuning the decision between dauer development vs. reproductive growth [17]. These results demonstrate that HSF-1 can sense and respond to at least three different stress factors, food deprivation, elevated temperatures and crowding (**Fig. 1**).

The insulin/IGF-1 (insulin-like growth factor receptor 1) signalling (IIS) pathway, which similarly affects metabolism, development, stress resistance and lifespan, also lowers HSF-1 activity [18]. In nematodes defective for the IIS receptor DAF-2, *daf-7* transcript levels are decreased in a HSF-1-dependent manner, as compared with the wild type [17]. DAF-2 deficiency attenuates *daf-7* expression, while in *daf-2(-); hsf-1(-)* double mutant animals *daf-7* is expressed at nearly normal levels. This implies that HSF-1 influences development, metabolism, lifespan and stress resistance through intertwining three signal transduction systems, cGMP/GC (cyclic guanosine monophosphate/guanylate cyclase), insulin/IGF-1 and TGFβ signalling (**Fig. 1**).

The influence of HSF-1 on stress-induced dauer development is further supported by the fact that its several target genes are involved in the synthesis of ascaroside pheromones, also called daumones. *acox-1* (acyl-coenzime A oxidase), *dhs-28* (dehydrogenases), *maoc-1* (mao-c-like dehydratase) and *daf-22* expression are each controlled by HSF-1 (**Tables 1** and **S1**)

[151]. Accordingly, under condition of heat stress, dauer pheromone extracts isolated from wild-type animals trigger dauer development more effectively than those isolated from *hsf-1(-)* mutants. Hence, dauer pheromone synthesis at higher temperatures is regulated by HSF-1.

HSF1 and ageing

During the lifespan of an organism, damaged macromolecules, in particular misfolded, aggregated and oxidized proteins, progressively accumulate in the cytoplasm, which leads to massive levels of cell death, and eventually a tissue dysfunction, at advanced ages [61, 152-156]. In ageing cells, proteostasis becomes gradually compromised, implying that molecular pathways ensuring protein homeostasis also participate in the ageing process. Indeed, the capacity of cellular stress-response (maintenance and repair) mechanisms including the HSR, UPR and autophagy, markedly declines as the organism ages [157-161]. By inducing these mechanisms and pathways, HSF1 preserves proteostasis at advanced ages and hence promotes longevity [162-165].

In *C. elegans*, elevated dosages of HSF-1 increase both stress tolerance and lifespan [166, 167]. Furthermore, worms depleted for HSF-1 live significantly shorter than untreated control [168]. These studies have shown that HSF1 activity is required for longevity in *daf-2(-)* mutant nematodes defective for IIS. The FOXO (Forkhead box O) transcription factor DAF-16, the terminal effector of IIS, regulates several genes in collaboration with HSF-1. These targets include *sHSP* genes [166], *sip-1* (stress-induced protein) and *cyp-35B1/dod-13* (cytochrome P450 family) [169], encoding a cytochrome P450 that is also involved in controlling lipid storage (**Tables 1** and **S1**). HSF-1 also affects certain TGFβ pathway components including *daf-7/TGFβ* and *daf-9/p450*, which inhibit dauer larval development [17]. These results demonstrate that HSF-1 controls the ageing process at least in part through functioning downstream of IIS.

In *Drosophila*, overexpressing mitochondrial Hsp22 promotes longevity [170]. Mice mutant for a co-chaperone (CHIP) exhibit a faster rate of the ageing process, while in long-lived mutant mouse strains certain *Hsp* genes become upregulated [171]. Together, the effect of HSF1 on ageing is established in a complex manner; first, through the upregulation of *HSP* genes, second, via modulating other stress/repair pathways that determine lifespan (*e.g*. autophagy), and, third, by influencing signalling systems (*e.g*. IIS) that affect the rate at which the cells age.

HSF1 in immune response

Studies on invertebrate and vertebrate genetic systems have demonstrated that HSF1 enables the normal function of the immune system [172-175]. In *C. elegans*, for example, HSF-1 is required for tolerance against several pathogenic agents, while in mice defective for HSF1 IgG generation is also compromised.

Certain cytokines promoting fever and inflammation are inhibited by HSF1. The interaction between HSF1 and *TNFα* (tumour necrosis factor alpha) appears to be direct as HSF1 binds to its regulatory region [176]. The expression of other cytokine- or cytokine receptor-encoding genes, such as *IL-6*, *c-fms* (colony-stimulating factor-1 receptor) and *m-scf* (macrophage colony-stimulating factor*), G-CSF* (granulocyte-colony stimulating factor), and *IL-1b* (interleukin 1 beta), is also repressed by HSF1 (**Tables 1** and **S1**) [58, 173, 176-179]. In case of IL-6, it has been noted that HSF1 binds the promoter region and maintains its open chromatin state in order to recruit transcription factors with inhibitory (*e.g.* ATF3) or stimulatory (*e.g.* NF-κB; nuclear factor kappa B) effects. These cytokines play a role in provoking inflammation. In addition, the regulatory role of HSF1 was shown in the activity of several other cytokines such as CXCL1, 2, 5, and 8 (chemokine ligand), as well as IL-10 [180,

181]. HSF1 also stimulates the transcription of *COX-2* (cyclooxygenase), a key regulator of inflammatory processes [182].

HSF1 regulates the hypothalamic-specific expression of the heat-inducible ion channel gene *TRPV1* (transient receptor potential vanilloid) [183] Since this protein plays an important role in the control of body temperature, HSF1 has a protective effect during fever. It inhibits certain cytokines to reduce fever and to protect against chronic inflammation. Consistent with the potential anti-inflammatory effect of HSF1, treatment with heat shock can lower the level of death caused by sepsis [184].

The function of HSF1 was also revealed in haematopoiesis [185]. It directly controls the expression of SPI1/PU.1 (PU-box) transcription factor, which influences macrophage differentiation. As a competitive inhibitor for NF-IL-6, HSF1 blocks *G-CSF* (granulocyte colony stimulating factor) transcription, thereby promoting myeloid differentiation [176].

During acute viral infection, HSPs are generally induced. Following infection by HIV, Hsp27, Hsp40 (DNAJB1) and Hsp70 expression becomes rapidly elevated [186, 187]. Consistent with this change, the activity of HSF1 also increases, and it directly binds HIV-1LTR promoter to trigger expression [188].

HFS1 in development and physiology

Among the HSF1 targets identified so far, several genes are involved in the control of normal developmental events (**Tables 1** and **S1**). This suggests that HSF1 functions, contrary to its name “heat shock”, not only under stress-induced circumstances, but also in normal biological processes.

Larval development

In *C. elegans*, a strong *hsf-1(-)* mutation, the deletional allele *ok600* affecting both regulatory and transactivation domains of the encoded protein, arrests development at the L2/L3 larval stages [27, 38]. Another *hsf-1* allele, the nonsense mutation *sy441* altering the transactivation domain at the C-terminus, enables the organism to develop into adulthood under stress-free conditions [189]. In *hsf-1(sy441)* mutants, HSP induction is also compromised. Thus, larval development and reproductive growth in nematodes rely on HSF-1 activity. Indeed, a recent ChIP-seq analysis has identified around 70 target genes for HSF-1 which mediate larval development in this organism (**Tables 1** and **S1**) [38]. The promoter of the development-related HSF1 targets often contains a partial HSE and a GC-rich motif (**Tables 1** and **S1**). This raises the possibility that HSF1 binds partial HSEs with the help of a cofactor; numerous developmental genes are coordinately regulated by HSF1 and the E2F/DP coactivator complex [38].

In *Drosophila,* larval development also requires HSF1 function; flies defective for HSF1 arrest development at the late L2 to early L3 larval stages [26]. Using a conditional (thermosensitive) *hsf1* mutant, it has been revealed that HSF1 deficiency from the onset of the L2 larval stage allows the animal to develop as adult. Moreover, HSF1 plays a role in oogenesis as its defects cause maternal effect sterility. HSF1 probably affects larval development independently of HSPs (under stress-free conditions the expression levels of *HSPs* do not significantly differ between HSF1 mutants and wild-type animals) [26].

Neuronal development

In mice, HSF1 participates in the development of the central nervous system. The absence of HSF1 activity can lead to impaired hippocampal spino- and neurogenesis, and severe perturbations in behaviour, such as depression and aggressivity [190]. It has been revealed

that HSF1 directly controls the expression of two polysialytransferase genes, *St8siaII* and *St8siaIV*, in the hippocampus, thereby influencing levels of PSA-NCAM (polysalylated-neural cell adhesion molecule), which is essential for synapse development [190]. Moreover, HSF1 displays a cell protective role during neuronal development via upregulating *Syt1* and *Vamp2* genes in response to cellular insults (**Table S1**) [191, 192]. *Dp71* gene encoding dystrophin was also identified as a direct target of HSF1 [193]. As dystrophin has a key role in the development of the nervous system, particularly that of hippocampus, it is possible that reduced expression of *Dp71* contributes to behavioural abnormalities in mice deficient in HSF1 function.

In the mouse neuroepithelium, proliferation and differentiation of sensory neurons are regulated by several cytokines. One of them is called LIF1 (leukaemia inhibitory factor), the expression of which is promoted by HSF1, but inhibited by HSF4 [194]. LIF1 overexpression triggered by HSF4 deficiency may contribute to neuroepithelial atrophy and smell disorders.

HSF1 and HSF4 also operate antagonistically in regulating the differentiation of eye lens epithelial cells [195]. As demonstrated, HSF4 hampers fibroblast growth factor (*FGF*) genes, such as *FGF1*, *4* and *7*, which drive this differentiation event. *FGF7* was identified as a direct HSF4 target gene. Unlike HSF4, HSF1 activates these targets (**Table S1**). In good accordance with these results, the *HSF1*; *HSF4* double mutant genotype allows a nearly normal development of the lens epithelium of mice.

Gamete differentiation

HSF1 has a dual role in spermatogenesis. First, it prevents immature germ cell from undergoing death [196]. Second, it participates in the elimination of defective spermatocytes during meiotic prophase (pachiten checkpoint) [197]. Although the above roles of HSF1 occur through HSP regulation, in mice, HSF1 and HSF2 directly control several sex chromosome-

specific multicopy genes in meiotic spermatocytes and postmitotic haploid round spermatids [129]. These genes located on chromosome X or Y are required for the proper packaging of DNA into the sperm.

HSF1 is also essential for oocyte meiosis in *Drosophila* [26]. In *HSF1* knockout mice, oocytes do not develop further, early development being arrested at phase I or II of meiosis [198]. Presumably, lowered Hsp90 levels are responsible for this phenomenon because in the absence of HSF1 Hsp90 becomes downregulated, and Hsp90-specific inhibitors cause a very similar phenotype. Using a comparative transcriptome analysis of wild-type and HSF1 defective mouse oocytes, it has been demonstrated that HSF1 influences the transcription of several genes during oocyte meiosis [199]. In *HSF1-/-* mutant oocytes, the synaptonemal complex, recombination nodules and DNA repair are all compromised. Thus, HSF1 may function as an important meiotic transcription factor as well.

C*ircadian rhythm*

Circadian rhythm is the endogenous oscillation of biological processes of about 24 hours. Cells have an inner circadian clock driving this 24-hour rhythm, which rapidly becomes desynchronized when cells are maintained in cultures [200]. Certain stimuli, such as temperature, however are capable of resetting and synchronizing this clock, rhythmic alternations of temperature lead to rhythmic changes of clock genes [128, 201]. The core clock gene *Per2* can be induced by heat shock, and its promoter contains functional HSEs [202, 203]. Moreover, both nuclear localization and phosphorylation levels of HSF1 display a circadian rhythm, which are likely to be driven by changes in temperature [204]. In chicken epiphysis, for example, HSF1 activity is triggered by light [205].

Conclusions

Results from the last two decades have clearly indicated that the roles of HSF1 are not limited to the HSR control. Through influencing the transcriptional activity of target genes encoding diverse proteins other than HSPs, this transcription factor influences basic cellular maintenance processes and molecular mechanisms like autophagy, the UPR and UPS, multidrug resistance, programmed cell death, cell cycle arrest, chromatin structure, and immune response (**Fig. 2**). These functions of HSF1 are often achieved in a complex manner. For instance, HSF1 affects cell growth and proliferation by directly regulating specific target genes involved in these processes (**Tables 1** and **S1**), via influencing (an)other intermediate process(es) (*e.g*. autophagy [133, 206]), or through upregulating *HSP* genes that participate in that particular processes (**Fig. 2**). Another expressive example is the ageing process that is driven by the progressive, life-long accumulation of unrepaired cellular damage, and the rate at which cells age is also modulated by HSF1 (**Fig. 2**). In *C. elegans*, HSF-1 controls several DAF-16 target genes (DAF-16 acts an effector of IIS playing a key regulatory role in lifespan determination), among them certain *Hsp* genes [166], and specific *Atg* genes [69] required for normal lifespan [206]. HSF1 similarly affects various developmental events including decision between normal reproductive growth and dauer larval formation (in nematodes), gamete differentiation (in vertebrates), generation of various immune factors (in organisms ranging from nematodes to mammals), and synapse formation (in mammals) (**Fig. 2**). Besides *HSPs*, direct transcriptional targets of HSF1 include genes that encode for example signalling components, ABC transporters, immune proteins, Atg proteins and substrates, as well as proteasome proteins (**Tables 1** and **S1**). These data imply that HSF1 is able to sense and respond to diverse cellular stress factors leading to proteotoxicity, such as high temperatures, starvation, crowding, chemical agents (toxins, heavy metals) and adverse metabolic factors

(ROS). These data imply that HSF1 functions as a major orchestrator of cellular stress response mechanisms.

Accumulating evidence indicates that during development HSF1 also controls a transcriptional program distinct from the HSR. For example, in *C. elegans* it interacts with E2F and DP transcription factors to regulate larval development [38]. It is intriguing that even in the absence of transactivation domain, HSF1 can mediate development and thermotolerance by upregulating various *non-HSP* target genes [207]. In murine neuroblastoma HT22 cells, overexpressing HSF1 lacking trimerisation and transactivation domains exerts a neuroprotective effect, as the mutant protein is not able to bind to classical HSEs [208]. Thus, the neuroprotective effect of HSF1 does not rely on HSP induction. An important issue in this field will certainly be uncovering the mechanisms whereby HSF1 influences these processes. It is possible for instance that HSF1 can interact with other transcription factors through its trimerisation domain. Alternatively, it can open local chromatin structures to recruit other transcription factors to target genes, or function as a co-factor for other transcription factors. Addressing this question may open new avenues in HSF1 biology.

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Tables

Table 1. Selected list of HSF1 target genes identified so far. Non-HSP-related targets involved in cellular stress response are shown only. For a comprehensive list of HSF1 target genes, see Table S1.

Supplementary Table S1. A comprehensive list of HSF1 target genes identified so far. The organism, gene function and relevant citation are indicated.

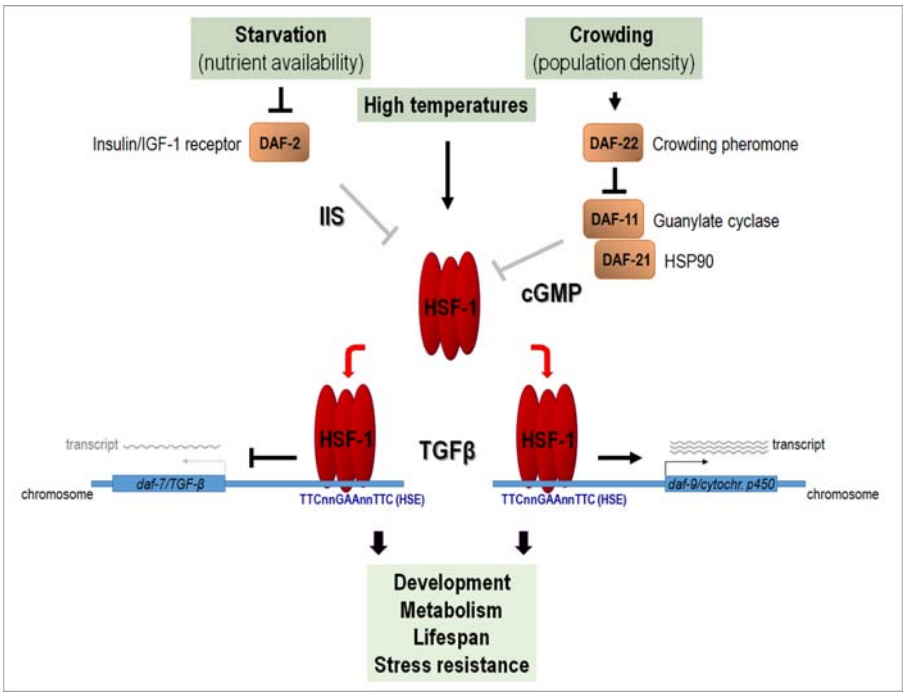

Figure 1. Signal integration by HSF-1 in response to various stress factors in *C. elegans*. HSF-1 is activated by diverse environmental stress factors, including starvation, high temperatures and crowding. This activation is mediated by the insulin/IGF-1 (IIS) and cyclic guanosine monophosphate (cGMP) signalling pathways. HSF-1 activity then influences the expression of key components (*daf-7* and *daf-9*) of transforming growth factor-beta (TGFβ) signalling, which regulates development, metabolism, ageing and stress resistance in this organism. This way, HSF-1 intertwines the insulin/IGF-1, cGMP and TGFβ signalling systems in orchestrating cellular stress response. Arrows indicate activation, bars represent inhibitory interactions.

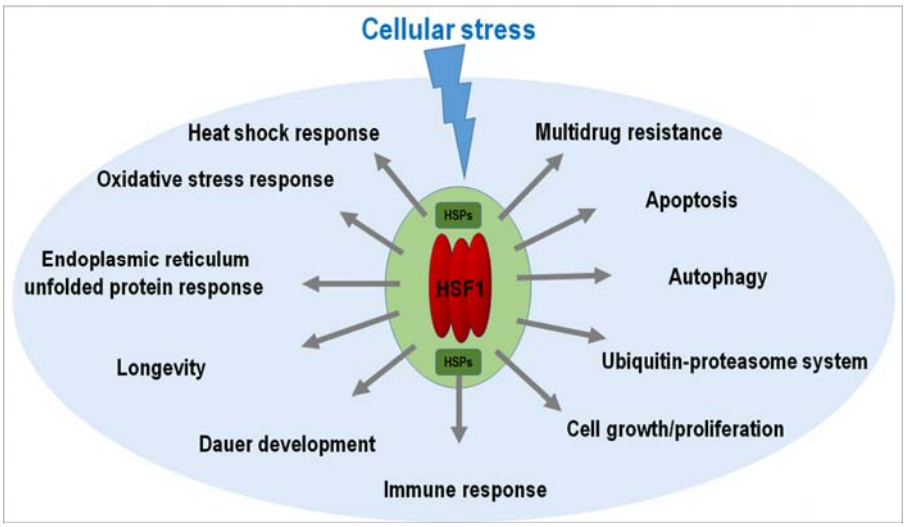

Figure 2. Co-regulation of cellular stress response mechanisms and processes by HSF1. HSF1 is activated by various cellular stress factors (represented by the blue swallow). HSF1 activity then upregulates key components of diverse stress response pathways and processes. Thus, HSF1 acts as a major orchestrator of cellular stress response pathways and processes.

Supplementary Table S1. A comprehensive list of HSF1 target genes identified so far. The organism, gene function and relevant citations are indicated.

Target gene	Organism/ Cell culture	Function	Direct interaction	Regulation	References
hsa-miR-432	HeLa cells	gene regulation	Yes	up	(Das and Bhattacharyya, 2014a)
SERF2	HeLa cells	?	Yes	up	(Das and Bhattacharyya, 2016)
chp-1	embryonic fibroblasts	?	?	up	(Hahn, 2005)
pat-10	*C. elegans*	actin cytoskeleton	?	up	(Baird et al., 2014)
TauT	spinal motor neurons in ALS mice and human	taurine transporter: Amyotrophic lateral sclerosis (ALS)	Yes	up	(Jung et al., 2013)
BAG3	HeLa	chaperones	Yes	up	(Franceschelli et al., 2008)
	HeLa	chaperones	Yes	up	(Du et al., 2009)
	HepG3	chaperones	Yes	up	(Abramova et al., 2010)
Fas	A549 cells	apoptosis	Yes	up	(Shunmei et al., 2010)
AIRAP	HeLa cells	arsenite-inducible RNA-associated protein	Yes	up	(Rossi et al., 2010)
aip-1	*C. elegans*	arsenite-inducible RNA-associated protein	?	up	(Ferguson et al., 2010)
p62	RKO, A549 and MCF-7 cells	autophagy	?	up	(Samarasinghe et al., 2014)
	C57BL/6J mice HeLa, HEK293 cells	autophagy	?	up	(Watanabe et al., 2017)
ATG10 ATG18f	tomato	autophagy	Yes	up	(Wang et al., 2015)
Atg7	MDA-MB-231 and -436 cells	autophagy	Yes	up	(Desai et al., 2013)
PAI-1	seed human umbilical vein endothelial cells	blood coagulation, thrombosis, diabetes	Yes	up	(Zhao and Shen, 2007)
NAT1	human prostate cancer cell line 22Rv1	cancer, drug metabolism	Yes	up	(Butcher and Minchin, 2010)
Cln-1	Human hepatoma cells	cancer, tight junction	Yes	up	(Lee et al., 2015)

	(SNU-354, SNU-387, SNU-423, SNU-449)				
FUT4	human breast cancer cells (MCF-7, MDA-MB-231)	cell growth, cell cycle	Yes	up	(Yang et al., 2014)
IER5	HeLa cells	cell growth, cell cycle	Yes	up	(Ishikawa and Sakurai, 2015)
JUN	HeLa cells	cell growth, cell cycle	Yes	up	(Sawai et al., 2013)
FoxM1	mouse embryonic fibroblast cells	cell growth, cell cycle	Yes	up	(Dai et al., 2013)
FOS1	human and rodent cells	cell growth, cell cycle	Yes	up	(Ishikawa et al., 1999)
	human and rodent cells	cell growth, cell cycle	Yes	up	(Ishikawa et al., 2000)
Hsp70.3	mice; mouse embryo fibroblasts and bone marrow progenitor cells	chaperones	?	up	(Zhang et al., 2002)
Hsp105	mice; mouse embryo fibroblasts and bone marrow progenitor cells	chaperones	?	up	(Zhang et al., 2002)
Hsp25	mice; mouse embryo fibroblasts and bone marrow progenitor cells	chaperones	?	up	(Zhang et al., 2002)
Hsp72	C6 glioma cells	chaperones	Yes	up	(Seo et al., 2005)
Hsp90	human and other mammalian cells	chaperones	Yes	up	(Prodromou, 2016; Shen et al., 1997; Zhang et al., 1999)
HYPK	HeLa cells	Huntingtin Yeast Partner K: chaperone, neurodegeneration	Yes	up	(Sakurai et al., 2014)
	HeLa and Neuro2A cells	chaperone, neurodegeneration	Yes	up	(Das and Bhattacharyya, 2014b)
Per2	mouse NIH-3T3 fibroblasts	circadian rhythm	Yes	up	(Tamaru et al., 2011)
Hsp47	hepatic stellate cells	collagen, liver fibrosis	?	up	(Park et al., 2013)
G-CSF	mice	cytokine immunity, differentiation	Yes	down	(Zhang et al., 2011)
IL-6	mouse embryo fibroblast (MEF) cells	cytokine immunity, differentiation	Yes	opens up chromatin for activators and repressors	(Inouye et al., 2007)
	mouse embryo fibroblast (MEF) cells	cytokine immunity, differentiation	Yes	opens up chromatin for activators and	(Takii et al., 2010)

				repressors	
	mice spleen cells	cytokine immunity, differentiation	Yes	up	(Inouye et al., 2004)
	C2C12 mouse myoblast cell	cytokine immunity, differentiation	?	up	(Welc et al., 2013)
TNFα	mice	cytokine immunity, differentiation	Yes	down	(Ambade et al., 2012)
	human peripheral blood monocytes	cytokine immunity, differentiation	Yes	down	(Ferat-Osorio et al., 2014)
	mice, murine macrophages	cytokine immunity, differentiation	Yes	down	(Singh et al., 2002)
CXC chemokine genes (CXCL-1, -2, -5, -8)	human pulmonary epithelial-like A549 cells	cytokine immunity, differentiation	Yes	up, down	(Maity et al., 2011)
c-fms	Chinese hamster ovaricytes	cytokine immunity, differentiation	Yes	down	(Xie et al., 2003)
IL-1beta	Chinese hamster ovaricytes	cytokine immunity, differentiation	Yes	down	(Xie et al., 2003)
	human monocyte cell line THP-1	cytokine immunity, differentiation	Yes	up	(Housby et al., 1999)
LIF1	mice	cytokine immunity, neuronal differentiation	Yes	down	(Takaki et al., 2006)
IL-10	RAW264.7 mouse macrophages	cytokine immunity, differentiation	Yes	up	(Zhang et al., 2012)
FGF1	mice	development	Yes	up	(Takaki et al., 2006)
FGF4	mice	development	Yes	up	(Fujimoto et al., 2004)
FGF7	mice	development	Yes	up	(Fujimoto et al., 2004)
	mice	development	Yes	up	(Fujimoto et al., 2004)
crystallin-αB	rat kidney proximal tubular cells	chaperone	?	up	(Lou et al., 2016)
acox-1	*C. elegans*	dauer pheromone synthesis	?	up	(Joo et al., 2016)
dhs-28	*C. elegans*	dauer pheromone synthesis	?	up	(Joo et al., 2016)
maoc-1	*C. elegans*	dauer pheromone synthesis	Yes	up	(Joo et al., 2016)
daf -22	*C. elegans*	dauer pheromone synthesis	Yes	up	(Joo et al., 2016)
PDS	HEK293, mice	pendrin/SLC26A4 Cl−/HCO3− exchanger: electrolyte and water homeostasis	Yes	up	(Rozenfeld et al., 2012)
Tdag51	mice	T□cell death associated gene 51:	Yes	up	(Hayashida et al., 2006)

		heat shock-induced cell death of male germ cells			
HIV-1 LTR promoter, Hsp40	human cell cultures: HEK-293T and Jurkat cells	HIV-1 infection	Yes	up	(Rawat and Mitra, 2011)
Hsp82	?	chaperones	Yes	up	(Wu, 1984)
Hsp70	*D. melanogaster*	chaperones	Yes	up	(Parker and Topol, 1984)
Hsp71	human	chaperones	Yes	up	(Parker and Topol, 1984)
Hsps	MEFs	chaperones	Yes	up	(Zhang et al., 2002)
HSPA1A Hsp72	HepG2	chaperones	Yes	up	(Song et al., 2010)
HSPA1B Hsp71	HepG4	chaperones	Yes	up	(Fulda, 2010)
HOP co-chaperone	human cancer cell lines (HCT116 and H1299)	chaperones	Yes	up	(Ruckova et al., 2012)
Hsp83	*D. melanogaster*	chaperones	Yes	up	(Wu et al., 1987)
Hsp70Ab	*D. melanogaster*	chaperones	Yes	up	(Topol et al., 1985)
FKBP4	HepG5	chaperones	Yes	up	(Kota and Balasubramanian, 2010)
HSP78,	Yeast	chaperones	Yes	up	(Sakurai and Ota, 2011)
MDJ1, SSC1	Yeast	chaperones	Yes	up	(Sakurai and Ota, 2011)
HSC82, HSP82	Yeast	chaperones	Yes	up	(Sakurai and Ota, 2011)
HuR	mice, MCF10A cells	cancer	?	up	(Gabai et al., 2012)
MICA/B	HeLa and HepG2 tumour cell lines	MHC class I-related chain molecules A and B: immunity	Yes	up	(Zhang et al., 2009)
COX-2	primary human umbilical vein endothelial cells	inflammatory response	Yes	up	(Rossi et al., 2012)
cyp-35B1	*C. elegans*	life span, lipid storage	Yes	up	(Iser et al., 2011)
lactate dehydrogenase A	human breast cancer cells	metabolism, glycolysis, cancer	Yes	up	(Zhao et al., 2009)
PGC1α	mice	metabolism, obesity, diabetes	Yes	up	(Ma et al., 2015)
CUP1	yeast	metallothionein	Yes	up	(Kragl et al., 2007)
BTN2	yeast	v-SNARE binding protein	Yes	up	(Kragl et al., 2007)
SIS1	yeast		Yes	up	(Kragl et al., 2007)
HSP10	yeast	chaperone - mitochondrial matrix co-chaperonin	Yes	up	(Kragl et al., 2007)

SGT2	yeast	chaperone - glutamine-rich cytoplasmic cochaperone;	Yes	up	(Kragl et al., 2007)
SSA3	yeast	chaperone - ATPase involved in protein folding and the response to stress;	Yes	up	(Kragl et al., 2007)
HSP10,	yeast	chaperone mitochondrial HSPs	Yes	up	(Sakurai and Ota, 2011)
HSP60	yeast	chaperone mitochondrial HSPs	Yes	up	(Sakurai and Ota, 2011)
ABCB1/MDR	mouse melanoma B16F10 cells	multidrug resistance, cancer	?	up	(Vydra et al., 2013)
	HeLa cells	multidrug resistance, cancer	Yes	up	(Vilaboa et al., 2000)
	U2-OS cells, HepG2	multidrug resistance, cancer	?	up	(Tchenio et al., 2006)
	mice cardiomyocytes	multidrug resistance, cancer	Yes	down	(Krishnamurthy et al., 2012)
St8siaII	mice	neuro-differentiation	Yes	up	(Uchida et al., 2011)
St8siaIV	mice	neuro-differentiation	Yes	up	(Uchida et al., 2011)
Dystrophin Dp71	mice	neuronal differentiation	Yes	up	(Tan et al., 2015)
Sly	mice	sperm meiosis, multicopy genes on sex-chromosomes	Yes	up	(Akerfelt et al., 2010)
Ssty1	mice	sperm meiosis, multicopy genes on sex-chromosomes	Yes	up	(Akerfelt et al., 2010)
Ssty2	mice	sperm meiosis, multicopy genes on sex-chromosomes	Yes	up	(Akerfelt et al., 2010)
Srsy	mice	sperm meiosis, multicopy genes on sex-chromosomes	Yes	up	(Akerfelt et al., 2010)
Slx	mice	sperm meiosis, multicopy genes on sex-chromosomes	Yes	up	(Akerfelt et al., 2010)
Ott	mice	sperm meiosis, multicopy genes on sex-chromosomes	Yes	up	(Akerfelt et al., 2010)
miR-34a	mice, Sca-1^{+} cells	stem cell survival, ichemia	Yes	down	(Feng et al., 2014)
daf-9	*C. elegans*	steroid hormone, aging stress response, development	?	up	(Barna et al., 2012)
VDUP1	human embryonic kidney cell line 293-derived Bosc cells	vitamin D3 up-regulated protein 1: stress	Yes	up	(Kim et al., 2004)
SatIII	HeLa cells	satellite III DNA: stress granule	Yes	up	(Valgardsdottir et al., 2005)
	HeLa cells	satellite III DNA: heat shock-	?	up	(Goenka et al., 2016)

		induced transcriptional repression			
	HeLa cells	satellite III DNA: stress granule	?	up	(Jolly et al., 2004)
HLA-G	human melanoma cell line M8 (HLA-A1, -A2, -B12, and B40/male)	stress-induced immunity	Yes	up	(Ibrahim et al., 2000)
STIP1 p60Hop	HepG6	Stress Induced Phosphoprotein 1	Yes	up	(Biso et al., 2010)
SQR	echiuran worm *Urechis unicinctus*	sulfidequinone oxidoreductase: stress resistance, oxidation of sulfide in mitochondria	Yes	up	(Liu et al., 2016)
NFIX	mammalian cell lines	Nuclear factor 1 family member: Stress response	Yes	up	(Singh et al., 2009)
TTR	mice	Transthyretin: Stress, Alzheimer's disease	Yes	up	(Wang et al., 2014)
PSD95	mice	Stress, Alzheimer's disease, synapsis	?	up	(Chen et al., 2014)
synapsin I	mice	Stress, Alzheimer's disease, synapsis	?	up	(Chen et al., 2014)
synaptophysin	mice	Stress, Alzheimer's disease, synapsis	?	up	(Chen et al., 2014)
daf-7	*C. elegans*	TGFβ, aging stress response, development	Yes	down	(Barna et al., 2012)
TRPV1	rat	thermoregulation	Yes	up	(Fan-xin et al., 2012)
ATF3	MEFs	cytokine immunity, differentiation	Yes	up	(Takii et al., 2010)
SPI1/PU.1	mice and monocyte	cytokine immunity, differentiation	Yes	up	(Jego et al., 2014)
UBB	HepG7	ubiquitin-proteasome system	Yes	up	(Song et al., 2010)
let-70	*C. elegans*	ubiquitin-proteasome system	Yes	up	(Kinet et al., 2016)
ubi-1	*C. elegans*	ubiquitin-proteasome system	?	up	(Kinet et al., 2016)
rpn-3	*C. elegans*	ubiquitin-proteasome system	?	up	(Kinet et al., 2016)
ERO1	yeast	oxidoreductin: unfolded protein response	Yes	up	(Takemori et al., 2006)
BTN2	yeast	v-SNARE binding protein;	Yes	up	(Yamamoto et al., 2007)
HuR	mice cell culture, MCF7, MCF10A, SKBR-3, MDA-MB-231, SK-OV-3	hypoxia, cancer	?	up	(Chou et al., 2015)
DAPK	human colorectal carcinoma tissues	apoptosis	Yes	up	(Benderska et al., 2014)

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