# Chapter 12
# Heat Shock-Induced Transcriptional and Translational Arrest in Mammalian Cells

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**Abstract** The heat shock response is a highly conserved cellular stress response pathway that protects cells against stress-induced damages. The heat shock response is characterized by the activation of the heat shock factor, a transcription factor, which in turn regulate the expression of heat shock proteins which help the cells to recover from the stress-induced damages. While the mechanism behind the activation of heat shock factor and the expression of heat shock proteins are well studied, our understanding on the other aspects of the heat shock response pathway – mainly the global suppression of transcriptional and the translational processes – has been very limited. Thus, this chapter would focus more on the recent studies elucidating the mechanism behind the heat shock-induced transcriptional and post-transcriptional repression of gene expression. Given the importance of the stress response pathways in cell survival, the chapter would focus on the discoveries made in the mammalian systems and their impact on human health and disease.

**Keywords** Chromatin dynamics · Heat shock · Heat shock factor 1 · Non-coding RNA · Stress · Stress granules · Transcription · Translation

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## Abbreviations

| | |
|---|---|
| CREBBP | CREB-binding protein |
| eIF2 | Eukaryotic initiation factor 2 |
| hnRNPs | Heterogeneous nuclear ribonucleoproteins |
| HSF1 | Heat shock factor 1 |
| HSP | Heat shock proteins |
| HSR | Heat shock response |
| IR | Intron retention |
| NMD | Non-sense mediated degradation |
| RBPs | mRNA-binding proteins |
| RNA pol II | RNA polymerase II |
| Sat3 | Satellite III transcripts |
| SGs | Stress granules |
| SINEs | Short interspersed elements |
| SRSF1 | Serine/arginine-rich splicing factor 1 |
| TSS | Transcription start site |

## 12.1 Introduction

Notwithstanding the existence of homeostatic mechanisms, cells forming the organ systems in the complex multicellular organisms such as mammals at times face sudden changes in the cellular environment that are harmful to the cellular physiology. For example, fever or hyperthermia lead to an increased load of misfolded proteins within the cell, which in turn activates a cascade of cellular response pathways which are collectively called as the heat shock response (HSR) (Morimoto 1998). Besides the heat stress, several other stimuli, such as the free radicals, heavy metals, ischemia, and infection, also induce HSR (Morimoto 1998). The heat shock factor – a conserved transcription factor – is thought to activate the HSR, resulting in a global change in the transcriptional, translational and post-translation processes. The HSR in a multicellular organism was first discovered in *Drosophila*, as a "puffing" pattern of the polytene chromosome in response to a heat shock (Lindquist 1986; Lakhotia 1989). Further metabolic labeling studies in flies revealed that while the expression of a majority of proteins was down-regulated, the expression of a set of proteins, known now as heat shock proteins (HSP), are up-regulated upon exposure to a heat shock (Lindquist 1986). HSP, which are molecular chaperones, help the synthesis and folding of other proteins (Lindquist 1986). During a heat shock, the heat shock-induced HSP help to prevent the misfolding of proteins (Powers et al. 2009). Devastating human neurodegenerative disorders, like the Huntington disease, are thought to result from chronic misfolding of proteins, thereby causing an imbalance in the protein homeostasis (Powers et al. 2009). Therefore, activating the heat shock response has been a long sought therapeutic intervention for these diseases (Maheshwari et al. 2014). More than 100 human diseases with protein conformation abnormalities are known in the literature (Westerheide and Morimoto

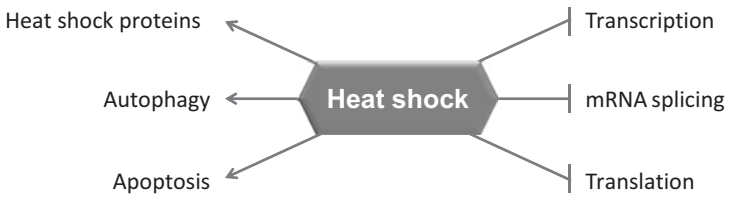


**Fig. 12.1** Schematic diagram showing the positive and negative regulatory roles of heat shock response pathway in cellular physiology. Heat shock induces the expression of heat shock proteins and the autophagic process while a lethal thermal stress can also trigger apoptosis. On the other hand, heat shock response brings about global suppression of transcription, mRNA splicing and translational processes

2005) and the perturbations in the HSR could be playing a potential role in their pathophysiology.

The regulation of the HSR is a well-studied phenomenon and is known to be orchestrated by the transcription factor Heat Shock Factor 1 (HSF1). HSF1 is normally sequestered in the cell in the form of inactive monomers and released when the misfolded protein load increases in the cell for them to trimerize and acquire a site-specific DNA binding activity (Sarge et al. 1993; Westwood and Wu 1993). It then induces the transcription of HSP and other cytoprotective proteins (Sarge et al. 1991). Activation of HSF1 during the heat stress, in turn, is regulated by a ribonucleoprotein complex containing translation elongation factor eEF1A and a non-coding RNA HSR1 (heat shock RNA-1) (Shamovsky et al. 2006). One of the immediate effects of heat shock is translational shut-down and breakdown of the cytoskeleton complex. As a result, there is a free pool of eEF1A which then forms a complex with HSR1 non-coding RNA. Further, the HSR1–eEF1A complexes assist in the HSF1 trimerization and in its subsequent DNA binding activity (Shamovsky et al. 2006).

Since the discovery of genes coding for HSP in *Drosophila* (Lindquist 1986), the mechanism of upregulation of these proteins and their functional significance had been the major interest of study for a long time. However, the impact of heat shock on the cellular physiological processes such as DNA replication and repair, transcription, splicing, and translation had been thoroughly investigated (Velichko et al. 2013; Velichko et al. 2012) (see Fig. 12.1). Some of the early studies which suggested a global transcription repression to occur during heat shock had mostly been performed in *Drosophila* (Lindquist 1986). Interestingly it had been shown that the expression of "high molecular weight" RNA species, such as rRNA and mRNA precursors, were repressed during a heat shock while the expression of the "low molecular weight" RNA species i.e. those produced by RNA Pol III, remain unaffected (Kantidze et al. 2015). Moreover, gene expression data from mammalian cells using oligonucleotide hybridization chips showed several hundred genes to be repressed by more than two-fold during the heat shock (Kantidze et al. 2015). The extent of transcriptional repression is thought to be dependent upon the temperature or the duration of stress and also the cell type exposed to the stress (Kantidze et al. 2015). The possible mechanism of regulation of such repression has been uncovered only recently. Thus, this chapter would focus more on the recent studies elucidating the mechanism behind the heat shock-induced transcriptional and post-transcriptional repression of gene expression.

### 12.1.1 Heat Shock Response and Chromatin Dynamics

The DNA is packed into nucleosomes which in turn are packed into high-order structures. This order of nucleosome packaging in chromatin is crucial to gene expression. During a heat shock the chromatin structure decondenses at the promoter elements of the genes coding for the HSP. The coordinated function of various proteins and protein complexes such as histone variants, histone-modifying enzymes, histone chaperones and chromatin remodeling complexes bring about a change the chromatin structure by allowing the displacement of nucleosomes upon exposure to a heat shock (Li et al. 2007). Such heat shock-induced changes in gene expression are preceded by changes in the promoter chromatin dynamics thereby altering the kinetics of RNA polymerase II-promoter binding (Teves and Henikoff 2013). Binding of the Heat Shock factor 1 (HSF1) to the HSP gene promoters initiates the release of RNA Pol II into the elongation phase of transcription which was initially paused about 30bp downstream of Transcription Start Site (TSS) (Rougvie and Lis 1988). Regulation of gene expression by RNA Pol II pausing is known to occur in up to 30% of the genes in the genome (Levine 2011), including the heat shock genes (Levine 2011). Thus, the RNA Pol II is bound to the gene promoter even when the gene is not being transcribed. The paused Pol II binds to factors that induce pausing (Missra and Gilmour 2010; Wu et al. 2003) including components of the RNAi pathway (Cernilogar et al. 2011). During a heat shock exposure, the active HSF1 binds to the HSP gene promoters and induces the elongation factor P-TEFb kinase to bind to the paused RNA Pol II and relieve the inhibitory factors, thereby facilitating the transcription elongation by RNA Pol II (Peterlin and Price 2006).

Concurrent with the expression of HSP, the HSR is marked by the reduction in the transcriptional, translation and splicing events in the cell which collectively bring about global changes in the gene expression patterns, which eventually help the cell under heat stress by reducing the load of misfolded protein (Shalgi et al. 2014). This is ensued by loss of Pol II from the promoter region of active genes as reported in the salivary glands of *Drosophila* (Jamrich et al. 1977) and in the mammalian systems wherein non-coding RNAs induced upon heat shock inhibit the contacts between Pol II and the promoter DNA (Yakovchuk et al. 2009). Such repression does not operate on the HSP gene promoters since selective RNAse complexes remove the non-coding RNA repressors and facilitate the binding of RNA Pol II (Shamovsky et al. 2006)

### 12.1.2 Heat Shock Response and Transcriptional Regulation

As discussed above, the heat shock response is known to be associated with global transcription repression (Lindquist 1986), however, the mechanism behind such a global change was not understood well for a very long time. Recent studies indicate critical roles for long non-coding RNAs in this process. For example, a class of

human ncRNAs called *Alu* RNA, and its mouse homologue *B2* RNA transcribed from short interspersed elements (SINEs), were shown to regulate different aspects of the heat-induced transcription repression (Allen et al. 2004). *Alu* and *B2* RNAs are known to interact directly with RNA Pol II and occupy the promoter of repressed genes in a complex with RNA Pol II (Yakovchuk et al. 2009). Further, the *Alu* ncRNA prevents pol II from engaging the promoter DNA by preventing appropriate contacts between the polymerase and the promoter, both upstream and downstream of the TATA box during closed complex formation by RNA Pol II in initiating transcription (Mariner et al. 2008). As a result, an inert transcriptional complex is formed at the promoter with the polymerase being trapped in the complex thereby resulting in gene repression. During the heat shock response, transcription of human *Alu* and mouse *B2* RNA increase several folds (Li et al. 1999; Liu et al. 1995). The increased RNA acts as a *trans*-acting repressor of transcription during cellular heat shock response by the above mechanism. Interesting knockdown of the non-coding RNA molecules during heat shock relieves the transcript repression significantly thus establishing the direct role of the RNA in transcription repression (Mariner et al. 2008). A very similar role for another non-coding RNA, known as Satellite III transcripts (Sat3), in HSR was shown in the human cell lines. The Sat3 transcripts which are human specific are synthesized upon heat shock and remain associated with their locus of transcription (Jolly et al. 2004). Intriguingly, these transcripts co-localize with transcription factors such as HSF1 and CREB-binding protein (CREBBP; also known as CBP), RNA polymerase II and RNA-binding proteins such as SRSF1 (serine/arginine-rich splicing factor 1; also known as SF2 or ASF), KHDRBS1 (also known as Sam68), and several heterogeneous nuclear ribonucleoproteins (hnRNPs) (Weighardt et al. 1999; Denegri et al. 2001; Metz et al. 2004; Chiodi et al. 2004; Jolly et al. 2004). A recent study demonstrates that Sat3 transcripts are involved in transcription repression by sequestering the transcription co-activator CREBBP to its locus, thus rendering it less/unavailable for the transcription of its target genes during heat shock (Goenka et al. 2016). Interestingly, knockdown of either the Sat3 RNA or the SRSF1 redistributes CREBBP from the nSBs into the nucleus in the heat-shocked cells (Goenka et al. 2016), reflecting the hierarchy in the cascade from HSF1 to Sat3 to SRSF1 to CREBBP which essentially functions as a co-activator and has more than 400 potential sites in the genome (Zhang et al. 2005); its modulation thus could have cascading effects on secondary and tertiary targets. Thus, the Sat3 RNA mediates the transcriptional repression observed during heat shock suggests a role analogous to the *hsr-omega* transcripts in *Drosophila* (Jolly and Lakhotia 2006).

### *12.1.3 Heat Shock Response and RNA Splicing*

One of the key consequences of the meticulously regulated heat shock response is the altered splicing events or inhibition of splicing as observed during heat stress. A recent study reports a significant inhibition in splicing, particularly by the

mechanism of Intron Retention (IR), during a heat stress (Hussong et al. 2017). Notably, the introns which are perfectly spliced in normal cells were retained in the pre-mRNA during heat shock. As a result, there is a significant reduction in the transcript abundance due to the introduction of premature termination codon and the mis-spliced transcript being degraded through the non-sense mediated degradation (NMD) pathway (Hussong et al. 2017). One of the critical factors that regulate the alternative splicing is an acetylated histone binding protein named BRD4 (bromodomain protein 4). During a heat shock, BRD4 gets recruited to the Sat3-positive nuclear stress bodies in an HSF1-dependent manner, depleting its concentration from gene cassettes thereby resulting in delayed or inhibition of splicing events, leading to the degradation of abnormally processed mRNAs (Hussong et al. 2017).

### *12.1.4 Heat Shock Response and Translational Control*

Translational regulation has a vital role in maintaining cellular homeostasis; for example, in mammals, high temperatures cause an immediate halt of global protein synthesis, which recovers when cells are returned to normal temperature (Banerji et al. 1984; De Benedetti and Baglioni 1984). Heat shock induced translation regulation was first described in *Drosophila* by Storti et al. (Storti et al. 1980) and later in other organisms, cells, and tissues (Spriggs et al. 2010; Richter et al. 2010) and in mammalian cells translation regulation during heat shock was first described in chicken reticulocytes by Banerji et al. (Banerji et al. 1984). One of the most commonly used mechanisms for inhibiting global translation during heat shock in mammalian cells is by phosphorylation of Eukaryotic Initiation Factor 2 (eIF2) (see Fig. 12.2), a critical factor involved in the initiation of translation (Trachsel et al. 1978; Rowlands et al. 1988; De De Benedetti and Baglioni 1986; Dubois et al. 1989). Phosphorylation of eIF2α is regulated by various stress-activated eIF2α kinases (Holcik and Sonenberg 2005). HSP act as a chaperone for eIF2 α -specific kinases and regulates their activation (Matts et al. 1992, 1993). Intriguingly, in response to heat shock, phosphorylation of eIF2a can induce the formation of stress granules (SGs) (see Fig. 12.2). SGs are the dynamic non-membranous cytosolic foci which range in size 0.1 μm to 2 μm in size (Anderson and Kedersha 2006). SGs are primarily composed of un-translated mRNAs, translation initiation components, and other proteins which effects mRNA function like the TDP43 and G3BP1 (Anderson and Kedersha 2006, 2008; Buchan and Parker 2009). SGs are known to recruit various RNA-binding proteins (such as HuR, TIA1, SMN, TDP-43, FUS, hnRNPA1, ATXN2, VCP) (Anderson and Kedersha 2008; Buchan and Parker 2009; Wolozin 2012; McDonald et al. 2011; Bosco et al. 2010), transcription factors (SRC3, Rpb4p) (Yu et al. 2007; Lotan et al. 2005), signaling molecules (dsRNA dependent protein kinase (PKR)) (Reineke and Lloyd 2015), RNA helicases (Dhh1/RCK, Rhau, P54 RNA helicase) (Sheth and Parker 2003; Swisher and Parker 2010; Chalupníková et al. 2008; Zampedri et al. 2016), and nucleases (TSN) (Shao et al. 2017; Weissbach and Scadden 2012). SGs are known to harbor microRNAs,

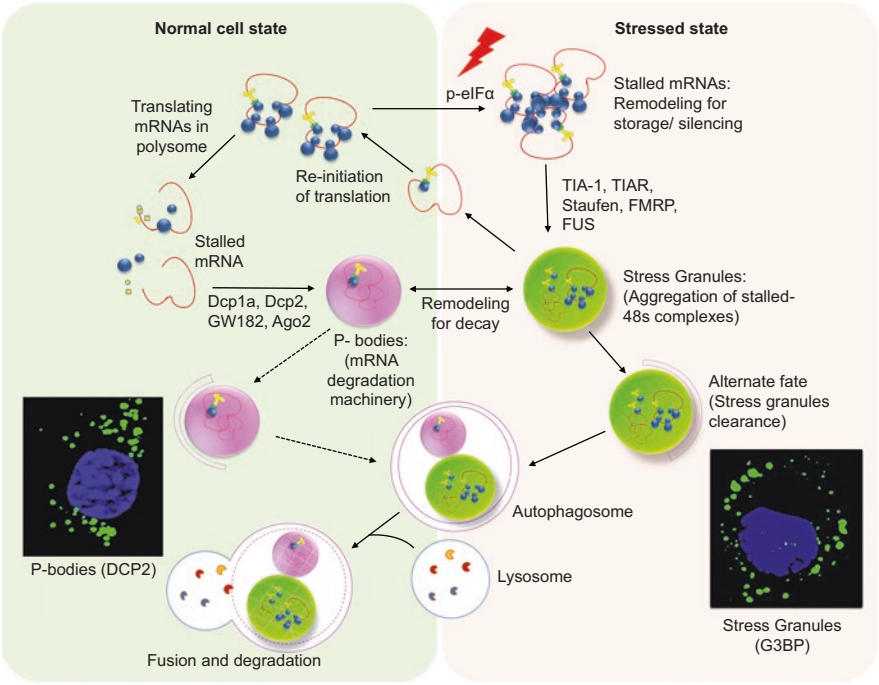


**Fig. 12.2** Schematic diagram showing the fate the mRNA during a normal cell state (*left side*) or during a stressed state (*right side*), as indicated. During the normal state, the translated mRNA might get recruited to the processing bodies (P-bodies). The P-bodies represent a lose assembly of mRNA and P-body specific proteins (such as the Dcp1a, Dcp2, GW182, and Ago2) and are involved in mRNA storage and degradation. The fate P-bodies in the cell are not clear; one line of evidences indicates that they might get degraded via the autophagic process. When the cells are exposed to a stress, such as heat shock, the heat shock response pathway is activated which in turn arrests the translation process. This is done via the formation of a specialized structure called stress granules which recruit the mRNA-ribosome complex. The stress granule-specific proteins, such as TIA-1, TIAR, Staufen, FMRP, and FUS, are thought to arrest the translational process. The mRNA-ribosome complex may resume translation during the recovery phase or the damaged complex may be degraded via the P-bodies or the autophagic process. The fluorescence images shown at the bottom of the schematic visualize the P-bodies (stained for Dcp2; green color) (*left side*) in a normal state or the stress granule (stained for G3BP; green color) (*right side*) upon exposure to a heat shock. The nuclei were visualized by staining with DAPI (blue color)

argonaute proteins, mRNA-editing enzymes, and proteins required for transposon activity (Leung and Sharp 2013). Once formed, the SGs act as the site of mRNA triage to sequester mRNAs for stability or degradation (Anderson and Kedersha 2008). Further, the transcripts are facilitated from stress granules to processing bodies (PBs) for degradation (Anderson and Kedersha 2006; Anderson and Kedersha 2008; also, see below). Processing bodies are the cytoplasmic domains for the RNA decay machinery (Eulalio et al. 2007a). PBs represent a loose assembly of mRNA decay factors (Dcp1/Dcp2, Hedls), and the factors involved in the NMD and decapping machinery (Pérez-Ortín et al. 2013; Eulalio et al. 2007b). The cellular recovery

process from a heat stress is accompanied by the disassembly of SGs. The assembly and disassembly of SGs are dependent on various mRNA-binding proteins (RBPs) (Emde and Hornstein 2014), and thus represent essential components of the cellular stress response mechanism. Abnormal or aberrant functions of SGs are associated with several diseases in humans, including cancer and neurodegenerative disorders (Mahboubi and Stochaj 2017).

### *12.1.5 Heat Shock Response and Proteolytic Pathways*

Besides altering the transcription and translational processes, heat shock also affects the half-life of proteins. Proteins are five times more stable and 900 times more abundant to their corresponding mRNAs that encode them in the mammalian cells (Schwanhäusser et al. 2011). Secondly, since proteins are the tertiary products, perturbations in protein stability and function would have an immediate impact on the cell as compared to the effect of heat shock on RNAs. Heat shock is known to induce unfolding of protein and their aggregations (Parag et al. 1987), thus these aberrant protein forms need to be selectively degraded (Goldberg and St. John 1976; Hershko et al. 1983). Ubiquitin proteasome system is well-known degradation machinery and also thought to be clear heat-denatured proteins in mammalian cells (Hershko et al. 1983; Ciechanover et al. 1984; Bond and Schlesinger 1985; Finley et al. 2004). To reduce the overload of abnormal proteins the heat shock response is also known to activate proteolytic processes (Dokladny et al. 2015). Intriguingly, HSF1, a master of heat shock response is known to regulate autophagy – the bulk degradative pathway in the cell via transcription of an autophagy gene, *Atg*-7 and induces autophagy (Liu et al. 2010). Indeed, a regulatory cooperation between the heat shock response pathway and the autophagy pathway has been proposed and demonstrated (Dokladny et al. 2013; Jain et al. 2017). HSF1 was shown regulate the LC3 lipidation – a critical step in the activation of autophagy (Dokladny et al. 2013), suggesting a well-coordinated interaction between the two homeostatic pathways. Besides the degradation of aberrant proteins, the heat shock-induced autophagy is also known to clear SGs and processing bodies via autophagy (Buchan et al. 2013; Walters et al. 2015; Mateju et al. 2017) (see Fig. 12.2).

### *12.1.6 Heat Shock Response in Infection*

Heat shock response is not limited to exposure to external stress; it can be induced to stimulate the host immune response during an infection including fever (Hasday and Singh 2000). HSF1 serves as an important factor for immunoregulatory signaling and the expression of several pro-inflammatory factors (reviewed in Hasday and Singh 2000). Fever acts as a protective effect in response to the infection in the body either by directly inducing heat shock response in the host or by the activation of

pathogen heat shock proteins (Kluger 1978). A study by Kluger et al showed a significant increase of survival in ectothermic vertebrates during infection with a gram-negative pathogen. Similar findings were observed in goldfish, sockeye salmon, crickets, grasshoppers, rainbow trout followed by experiments in mice model (Kluger 2005). A 2°C increase of the core body temperature of mice infected with a lethal form of herpes simplex virus leads to up to 85% increase in the survival of infected animals (Schmidt and Rasmussen 1960; Bell and Moore 1974;, Jiang et al. 2000). Conversely, blocking fever in animals infected with microbes lead to the poor survival of the host (Bernheim and Kluger 1976; Vaughn et al. 1980; Esposito 1984; Kurosawa et al. 1987). The HSR is thought to protect cells against the fever by preventing the heat-induced protein denaturation and by activating proteolytic processes. A more direct role for HSR in the pro-inflammatory response has also been documented. For example, the HSF1 induced heat shock proteins are known to modulate the activity of NF-κB at different levels (Leite et al. 2016). In general, HSR is a primary defense mechanism that protects cells from apoptosis, by clearing the abnormally misfolded proteins and inhibiting the pro-apoptotic proteins (Stefani and Dobson 2003; Stankiewicz et al. 2005; Lanneau et al. 2008; Ali et al. 2010; Upadhyay et al. 2016). The importance of the proteolytic processes in cell survival has come from the studies on neurodegenerative disorders (Mittal and Ganesh 2010). A majority of these disorders are associated with the accumulation of abnormally folded proteins in the neurons and activation of HSP was shown to protect the neurons from the toxicity of these aggregates (Dong et al. 2005; Kumar et al. 2007; Nagel et al. 2008; Jung et al. 2008; Kalia et al. 2010), indirectly by inhibiting the pro-inflammatory and pro-apoptotic signaling pathways. Thus, the HSR response found in various neurodegenerative disorders, ageing, dementia, and cancer possibly represent a failed attempt by the cellular machinery.

## 12.2 Conclusions

The discovery of heat shock response pathway leads to the thorough characterization of HSF1, its targets and the functional significance of heat shock proteins coded by them. Studies have shown that the activation of HSR is not just limited to heat shock, that it is a conserved pro-survival pathway and is activated by exposure to the variety of stressor, including infection. The HSR is not just limited to the activation of a set of genes coding for HSP. As discussed above, the HSR is accompanied by global changes in the transcriptional, translational and post-translational changes in the cell exposed to a stress. While much advancement has been made in understanding the role of HSF1 in activating the genes coding for the HSP, our understanding of the mechanism behind the HSR in modulating the global changes in the transcription, translation, and post-translational processes have been very limited. Secondly, most of the studies on HSR have restricted the analyses to cellular processes and thus HSR was considered as a cell-autonomous process. Perhaps this is due to the model systems used for the studies – such as cell lines and the yeast

model. Thus there is a greater need for studies on HSR as a systemic response to thermal stress in multicellular organisms. Indeed, the possible involvement of neuronal signaling in cell-non-autonomous mode of heat shock response has been shown in worms (Prahlad et al. 2008), that this may involve serotonergic signaling (Tatum et al. 2015) and that such mechanism could operate for the protein homeostasis processes (Sala et al. 2017). Thus, appropriate genetic screens are required to understand cell-non-autonomous HSRs in mammalian species not only to understand the HSR *per se* but also to relate HSR in disease conditions.

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