

CELL SCIENCE AT A GLANCE

HSF1 at a glance

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ABSTRACT

Heat shock factor 1 (HSF1) is an evolutionarily highly conserved transcription factor that coordinates stress-induced transcription and directs versatile physiological processes in eukaryotes. The central position of HSF1 in cellular homeostasis has been well demonstrated, mainly through its strong effect in transactivating genes that encode heat shock proteins (HSPs). However, recent genome-wide studies have revealed that HSF1 is capable of reprogramming transcription more extensively than previously assumed; it is also involved in a multitude of processes in stressed and non-stressed cells. Consequently, the importance of HSF1 in fundamental physiological events, including metabolism, gametogenesis and aging, has become apparent and its significance in pathologies, such as cancer progression, is now

evident. In this Cell Science at a Glance article, we highlight recent advances in the HSF1 field, discuss the organismal control over HSF1, and present the processes that are mediated by HSF1 in the context of cell type, cell-cycle phase, physiological condition and received stimuli.

KEY WORDS: Cancer progression, Chromatin environment, Heat shock factor, Organismal stress response, Proteostasis, Transcription

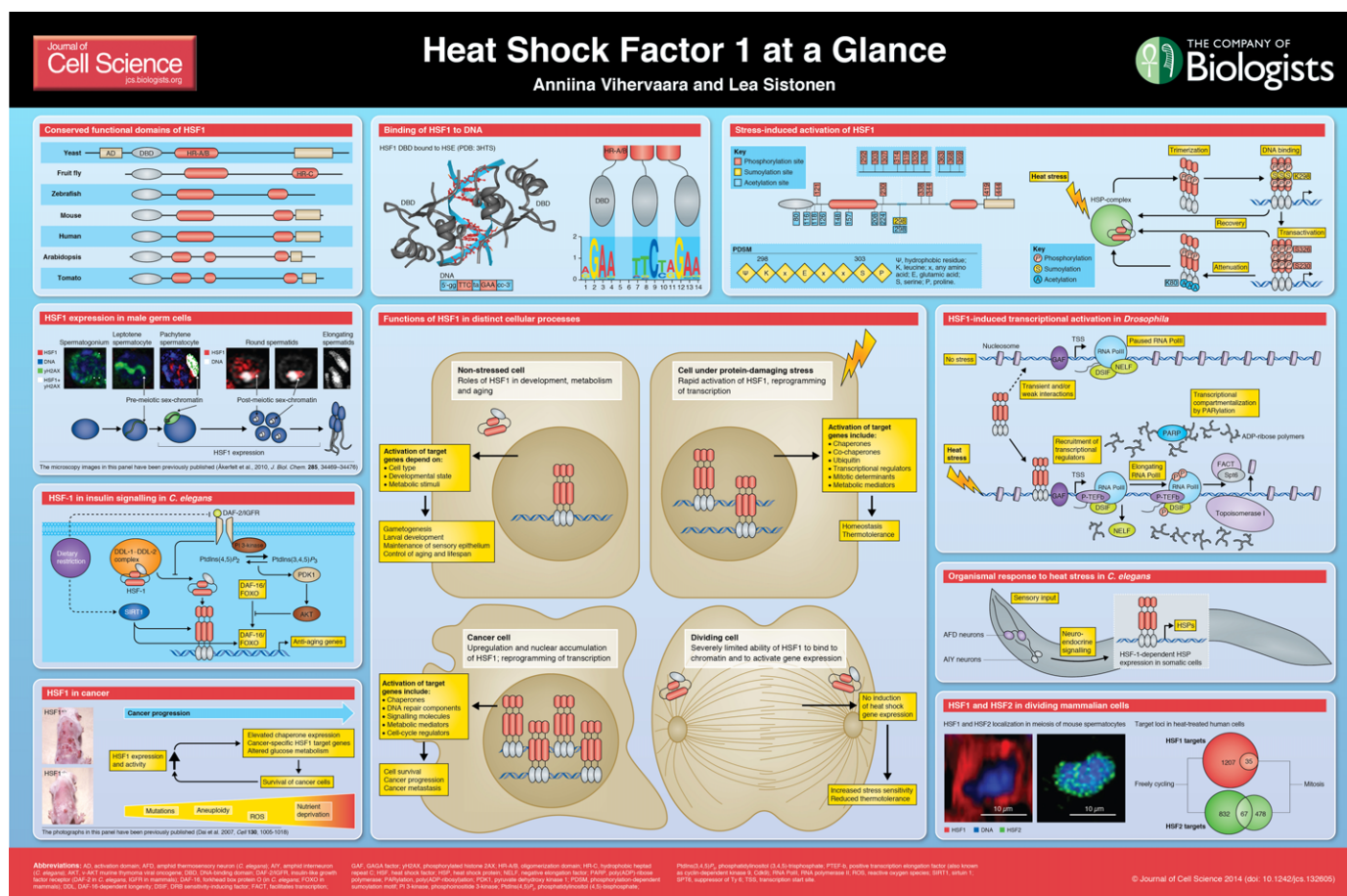
Introduction

Heat shock factor 1 (HSF1) is a prime integrator of transcriptional responses during stress when the overall transcription is silenced, translation halted and progression of the cell cycle stalled. The rapidly induced gene activation in stress has facilitated key findings on transcriptional processes and elucidated survival mechanisms in protein-damaging conditions. Although the main focus has been on HSF1-induced expression of chaperone genes, HSF1 controls a wide set of target loci in stressed cells and directs versatile physiological processes also in non-stressed

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circumstances, including development, metabolism and aging. Its central role in core physiological pathways and the capacity to orchestrate genome-wide transcription has revealed HSF1 as a fundamental director of cellular processes, and advanced our understanding on how gene expression is coordinated in cells, organs and entire animals. This Cell Science at a Glance article provides a focused summary on the structure, activation, transactivation capacity and regulation of HSF1, as well as highlights how it coordinates cellular functions under distinct physiological conditions.

Conserved functional domains of HSF1

The molecular structure of HSF1 is highly conserved in eukaryotic species. HSF1 is characterized by an N-terminal helix–turn–helix DNA-binding domain and an adjacent oligomerization domain that consists of hydrophobic heptad repeats (HR-A/B) (see poster; reviewed in Fujimoto and Nakai, 2010; Nover et al., 2001). Unlike most transcription factors, HSF1 binds to DNA as a trimer and its oligomerization is mediated by coiled-coil interactions between the HR-A/B domains (Peteranderl and Nelson, 1992; Rabindran et al., 1993; Westwood and Wu, 1993). Spontaneous trimerization of HSF1 is allosterically inhibited by a C-terminal heptad repeat (HR-C) that folds back and forms intramolecular contacts with the HR-A/B domain (Rabindran et al., 1993). In most species, HSF1 also contains a transactivation domain that is targeted by several proteins to control the extent of HSF1 activation and to direct HSF1 to specific target genes (Eastmond and Nelson, 2006; reviewed in Anckar and Sistonen, 2011).

Binding of HSF1 to DNA

At the target loci, HSF1 binds to cis-acting elements that are composed of inverted nGAAn pentamers and are collectively called heat shock elements (HSEs) (Amin et al., 1988; Pelham 1982; Sorger and Pelham, 1988). Each DNA-binding domain in an HSF1 trimer recognizes a single nGAAn sequence and, consequently, three alternately oriented pentamers are required for stable HSF1 binding (Gonsalves et al., 2011; Perisic et al., 1989; Xiao et al., 1991). Tail-to-tail (5'-nTTCnnGAAn-3') orientation brings two HSF1 molecules sufficiently close so they fit into one major groove of DNA, but interaction with the third pentamer, that occurs in head-to-head (5'-nGAAnnTTCn-3') orientation, extends to the adjacent major groove (see poster; Bonner et al., 1994; Littlefield and Nelson, 1999). The number and exact nucleotide sequence of nGAAn pentamers vary at distinct target loci and contribute to the affinity of HSF1 to the DNA (Perisic et al., 1989; Xiao et al., 1991). This unusual flexibility of HSF1 to recognize diverse nucleotide compositions in alternate orientations is, intriguingly, accompanied with a striking conservation of the core HSE in various species (Hahn et al., 2004; Guertin and Lis, 2010; Gonsalves et al., 2011; Mendillo et al., 2012; Trinklein et al., 2004; Vihervaara et al., 2013).

HSF1 activation

The activity of HSF1 is under complex and strict regulation through protein–protein interactions and post-translational modifications (see poster; reviewed in Anckar and Sistonen, 2011). Several laboratories have shown that HSF1-induced HSPs can directly inhibit HSF1, thereby providing an autoregulatory mechanism that senses protein folding in the cell and adjusts the extent of stress responses (Abravaya et al., 1992; Guo et al., 2001; Zou et al., 1998). Upon exposure to heat, HSF1 trimerizes, binds

to DNA and is phosphorylated at several amino acids located between the HR-A/B and HR-C domains (see poster). Although hyperphosphorylation of HSF1 is associated with its transactivity, several amino acids are phosphorylated also in the absence of stress and repress HSF1 activation (Chu et al., 1996; Kline and Morimoto, 1997). To date, only phosphorylation of S230 and S326 were shown to increase the transcriptional capacity of HSF1 (Holmberg et al., 2001; Guettouche et al., 2005). Besides controlling activation, post-translational modifications contribute to defining the extent and duration of HSF1-mediated transcription. At a so-called phosphorylation-dependent sumoylation motif (PDSM), phosphorylation of S303 primes HSF1 for sumoylation at K298, leading to the suppression of its transactivating capacity (Hietakangas et al., 2003; Hietakangas et al., 2006). Moreover, the removal of HSF1 from chromatin is facilitated by acetylation of K80, an amino acid residue that directly contacts DNA (Westerheide et al., 2009). By contrast, the duration of the binding of HSF1 to DNA can be prolonged by the nutrient sensor and longevity factor sirtuin 1 (SIRT1), which serves as a deacetylase for HSF1 (Westerheide et al., 2009).

HSF1-mediated transactivation of heat shock genes

Transcriptional regulation is a highly dynamic process that involves a multitude of transient protein–DNA and protein–protein interactions (reviewed in Selth et al., 2010). Upon stress, HSF1 is the key transcriptional activator of chaperones, co-chaperones and ubiquitin, and also coordinates the expression of many transcriptional and translational regulators, signaling molecules and mitotic determinants (Hahn et al., 2004; Mendillo et al., 2012; Trinklein et al., 2004; Vihervaara et al., 2013). Particularly, the rapid and robust expression of HSPs has served as a model for transcriptional responses and fostered many ground-breaking insights into the regulatory mechanisms of gene expression (reviewed by Guertin et al., 2010). Although still incomplete, expression of *HSP70* upon protein-damaging stress provides one of the best-understood models of transcriptional activation. In the fruit fly *Drosophila melanogaster*, the *Hsp70* promoter is primed for activation by GAGA factor (GAF), transcription factor IID (TFIID) and a transcriptionally engaged but paused RNA polymerase II (RNA PolII) (Rasmussen and Lis, 1993; Rougvie and Lis, 1988; Shopland et al., 1995; Weber et al., 1997). Upon exposure to heat, HSF1 rapidly accumulates at the promoter and initiates a cascade of events, including recruitment of the mediator complex and positive transcription elongation factor b (P-TEFb) (Lis et al., 2000; Park et al., 2001). P-TEFb-mediated phosphorylation of DRB-sensitivity-inducing factor (DSIF) and of the C-terminal domain of RNA PolII enables the removal of negative elongation factor (NELF) and the maturation of RNA PolII to its elongation mode (Brès et al., 2008; Marshall et al., 1996; Ni et al., 2008; Wu et al., 2003). Effective RNA PolII elongation along the *Hsp70* gene is eased by nucleosome remodeling complexes, facilitates transcription (FACT, also known as SSRP1) and suppressor of Ty 6 (SPT6, SPT6H in mammals), as well as by topoisomerase I, which relieves DNA coiling (Andrulis et al., 2000; Gilmour et al., 1986; Kaplan et al., 2000). Finally, poly(ADP-ribose) polymerase (PARP) generates a compartment that selectively retains and recycles transcriptional components (see poster; Petesch and Lis, 2008; Zobeck et al., 2010).

Several aspects of heat-induced expression of HSP70 are shared between flies and mammals, including HSF1-mediated

release of paused RNA PolII and the removal of nucleosomes along the gene (Brown et al., 1996; Brown and Kingston, 1997). However, some of the molecular mechanisms that underlie the highly conserved function of HSF1 as a transactivator vary in different species. In *Drosophila*, GAF and nucleosome remodeling factor (NURF) restrict the occupancy of nucleosomes at the *Hsp70* promoter whereas, in mammals, HSF1 itself has been shown to collaborate with replication factor A (RPA) and FACT to maintain the *HSP70* promoter in a highly accessible state (Fujimoto et al., 2012; Tsukiyama and Wu, 1995). Importantly, mammals contain several HSF members (HSF1, HSF2, HSF3, HSF4). Upon acute stress, HSF2 can form heterotrimers with HSF1, localize to more than half of its target sites and modulate HSF1-mediated gene expression (Loison et al., 2006; Östling et al., 2007; Sandqvist et al., 2009; Vihervaara et al., 2013; reviewed in Åkerfelt et al., 2010a).

The role of HSF1 in dividing cells

Transcriptional responses profoundly depend on the phase of the cell cycle (reviewed in Alabert and Groth, 2012). Recently, we established the genome-wide target sites of HSF1 and HSF2 in human cells, and showed their drastically distinct capacities to bind to chromatin that is condensed for division (see poster; Vihervaara et al., 2013). Upon heat shock, HSF1 binds to only 35 target sites in mitotic chromatin, as compared to the 1242 target sites that it occupies in freely cycling cells, and its ability to activate transcription in mitosis is minimal. By contrast, HSF2 avidly interacts with open and condensed chromatin and occupies 545 target loci in stressed mitotic cells (see poster; Vihervaara et al., 2013). HSF2 is, however, a poor transactivator upon stress and cannot compensate for HSF1 in cycling or mitotic cells (Sarge et al., 1993; Vihervaara et al., 2013; Yoshima et al., 1998). Consequently, mitotic cells are unable to induce expression of heat shock genes and are highly susceptible for protein-damaging stress (Martínez-Balbás et al., 2005; Vihervaara et al., 2013). HSF2 has been suggested to ‘bookmark’ promoters of HSPs for rapid HSF1-mediated activation after mitosis (Xing et al., 2005). The genome-wide analysis of HSF2 target loci supports HSF2 as an epigenetic regulator that coordinates gene expression throughout the progression of the cell cycle (Vihervaara et al., 2013). So far, the only gene shown to be bookmarked by HSF2 for rapid activation after mitosis is myeloid/lymphoid or mixed-lineage leukemia (MLL), a trithorax homolog that is involved in the epigenetic maintenance of transcriptional memory (Blobel et al., 2009; Vihervaara et al., 2013). Although, the mechanisms of HSF2 at the condensed chromatin remain to be established, the highly intertwined functions, and the distinct gene regulatory mechanisms of HSF1 and HSF2 suggest their synergistic capacity to steer both the chromatin state and transcriptional activation. This collaboration could be highly influential in the development of cellular memory as well as during differentiation, when the transcriptional profiles and epigenetic characters of the cells are defined.

The role of HSF1 in development

HSF1 exerts vital functions in the absence of stress and is indispensable for growth and viability of yeast, as well as for oogenesis and larval development of *Drosophila* (Gallo et al., 1993; Jedlicka et al., 1997; Sorger and Pelham, 1988). In mice, HSF1 is a maternal factor that is required for gametogenesis and formation of sensory epithelium (Åkerfelt et al., 2010b; Christians et al., 2000; Fujimoto et al., 2004; Le Masson et al., 2011; Metchat et al., 2009; Salmand et al., 2008; Takaki et al.,

2006). Importantly, the developmental functions of HSF1 are mainly executed through target genes that are unrelated to HSPs, and studies in *Drosophila* have shown that HSF1 is activated differently in development as compared to in stressed cells (Åkerfelt et al., 2010b; Fujimoto et al., 2004; Jedlicka et al., 1997; Le Masson et al., 2011; Takaki et al., 2006). In cultured cells, HSF1 is stably expressed but, in the context of entire animals, its expression level and subcellular localization vary depending on the tissue and the developmental state (Fiorenza et al., 1995; Åkerfelt et al., 2010b). For instance, during mouse spermatogenesis, HSF1 is abundantly expressed from pachytene spermatocytes to round spermatids but cannot be detected in spermatogonial stem cells or elongating spermatids (see poster; Åkerfelt et al., 2010b). Although the exact role of HSF1 in specific germ cell types remains unknown, it regulates the post-meiotic expression of X- and Y-chromosomal genes that are required for the correct packing of DNA in the sperm (Åkerfelt et al., 2010b; Touré et al., 2004). The importance of precisely coordinated HSF1 activity is further demonstrated by the spermatogenic defects in *Hsf1*^{−/−} mice (Åkerfelt et al., 2010b; Salmand et al., 2008) and the infertility caused by constitutively active HSF1 (Nakai et al., 2000).

HSF1 in insulin signaling

HSF1 is involved in the metabolism of healthy and malignant cells (Dai et al., 2007; Hahn et al., 2004; Gonsalves et al., 2011; Mendillo et al., 2012; Santagata et al., 2013; Trinklein et al., 2004; Vihervaara et al., 2013). Moreover, metabolic processes have been proposed to regulate HSF1, as the well-conserved insulin pathway inhibits HSF-1 activation in *Caenorhabditis elegans* (Chiang et al., 2012). Insulin signaling is a key component in the sensing of the nutrient status of the organism and reduced insulin levels, e.g. owing to restricted nutrient intake, are coupled to increased lifespan (reviewed in Bishop and Guarente, 2007). Insulin signaling is best characterized in worm, fly and mouse; here, disruption of insulin-like growth factor receptor (DAF-2 in *C. elegans*, IGFR in mammals) or of its downstream phosphatidylinositol 3-kinases, leads to prolonged lifespan and protection from neuronal loss (Blüher et al., 2003; Holzenberger et al., 2003; Kenyon et al., 1993; Tatar et al., 2001). The findings that the prolonged lifespan of DAF-2 mutant worms is dependent on both HSF-1 and forkhead box protein O (DAF-16; FOXO in mammals) (Cohen et al., 2006; Hsu et al., 2003; Morley and Morimoto, 2004), support a current model in which insulin signaling silences HSF-1 and DAF-16, thereby reducing the expression of genes that enhance the lifespan (see poster).

HSF1 drives transcription in cancer cells

Cancer cells are mutation prone, aneuploid and show high activity of HSF1 (Solimini et al., 2007). The ground-breaking study by Dai and colleagues revealed that mice that lack HSF1 are largely protected from carcinogen-induced skin tumors in a p53-compromised background (Dai et al., 2007; see poster). Subsequently, large cohort studies have identified the presence of HSF1 as a main marker for poor prognosis in a wide variety of cancers, and correlated high levels of HSF1 and its nuclear localization to metastasis (Mendillo et al., 2012; Santagata et al., 2011). A commonly held view is that HSF1 facilitates the survival and metastasis of cancer cells by enabling their adaptation to the hostile conditions they experience (see poster). Recently, Mendillo and colleagues (Mendillo et al., 2012) identified the genome-wide target sites of HSF1 in human

breast cancer cell lines with different metastatic capacities, and also showed that HSF1-driven transcription is profoundly different in malignant cells compared with cells that are exposed to heat stress. Cancer cells display increased protein synthesis, which is supported by increased ribosomal biogenesis (Stumpf and Ruggero, 2011; White, 2005 and references therein). Intriguingly, a general block in translation was shown to almost fully abolish the binding of HSF1 to its target genes in cancer cells (Santagata et al., 2013). This direct link between the translation machinery and HSF1 activity illustrates the central position HSF1 has in integrating core cellular processes, and demonstrates that the ability of HSF1 to maintain cancer cells is sensitive to their ribosomal function. Future studies of how cancer cells ‘hijack’ HSF1, and utilize its transactivating potential and central role in homeostasis will certainly provide novel insights into key cellular mechanisms, but might also yield therapeutic tools to fight cancer.

Cellular responses to stress at the organismal level

Our knowledge of stress responses originates mostly from cell and tissue models that are adapted to culture conditions. Therefore, we have yet to learn how distinct cell types and tissues respond to acute and chronic stress, and how these responses are coordinated in the context of the entire animal. Recent studies in *C. elegans* have paved the way for elucidating organismal responses to proteotoxicity and indicate that stress responses are under neuronal control, communicated between tissues and integrated to the metabolic processes of the animal (Baumeister et al., 2006; Durieux et al., 2011; Garcia et al., 2007; van Oosten-Hawle et al., 2013; Prahlad et al., 2008; reviewed in Gidalevitz et al., 2011). In *C. elegans*, the HSF-1-mediated response to heat stress is controlled by two amphid thermosensory neurons (AFDR and AFDL) that sense the increased environmental temperature and relay the signal through interneurons (AIYR and AIYL) and endocrine pathways to the cells of the body (Prahlad et al., 2008; see poster). Neuronal circuitry has also been suggested to distinguish between acute and chronic stresses, implying that the intracellular response to stress is surveyed by intercellular communication (Prahlad and Morimoto, 2011). Intriguingly, the dauer pheromone, which is a potent mediator of growth and metabolism, affects the magnitude of HSF-1-induced HSP expression, which shows that stress responses are adjusted to the metabolic processes of the animal (Prahlad et al., 2008). Moreover, a localised increase in the expression of HSP90 dampens the HSF-1-mediated stress response at the systemic level, suggesting that chronic, tissue-specific proteotoxicity impairs the ability of the animal to cope with severe acute stress (van Oosten-Hawle et al., 2013). A comprehensive view of stress responses in intact animals remains to be elucidated; in particular, whether plants and animals other than *C. elegans* display organismal coordination over cellular stress responses is currently unexplored. Nevertheless, the studies in *C. elegans* have demonstrated that cellular responses can be controlled at organismal level, and highlight the importance of integrating external and internal conditions into a coordinated behavior of the animal.

Perspectives

HSF1 is a prime coordinator of transcription in stressed cells and involved in a multitude of physiological processes. In stressed, freely cycling cells, HSF1 controls the composition of the entire chaperone machinery and, simultaneously, adjusts the expression of ubiquitin to meet the need for protein clearance through the proteasomal pathway (Vihervaara et al., 2013). However, focusing on target genes, whose HSF1-mediated expression increases

several-fold does not fully illustrate the ability of HSF1 to orchestrate complex networks of cellular processes. In stressed cells whose global transcription and translation are silenced, and cell cycle progression is stalled (reviewed in Richter et al., 2010), HSF1 controls genes that encode transcription factors, cell cycle determinants and translational components. This broad effect of HSF1 on transcription suggests that HSF1 is involved in balancing core cellular processes during stress and enables their rapid re-establishment once conditions suitable for proliferation have been restored. Importantly, HSF1 controls a distinct set of target genes in cell stress, development and cancer progression, and has radically limited capacity to bind to condensed chromatin (Åkerfelt et al., 2010b; Le Masson et al., 2011; Mendillo et al., 2012; Vihervaara et al., 2013). These recent findings highlight the plasticity of HSF1 as a transcriptional regulator, and imply that the HSF1-driven transcription strongly depends on the cell type, developmental state, metabolic conditions and the phase of the cell cycle (see poster).

A number of essential aspects of HSF1 remain to be elucidated. Despite extensive efforts, the initial signal that leads to HSF1 activation remains elusive; most probably it is a combination of activating/inhibiting protein assemblies and signaling pathways that act in a cell type specific manner. Recent studies in *C. elegans* have shown that HSF1 is controlled at the organismal level, and that its activation is intimately linked to the metabolic state and lifespan of the animal. However, the mechanisms by which the activity, expression and subcellular localization of HSF1 are controlled remain to be established, both at the cellular and organismal level. HSF1 has been shown to target open chromatin regions (Guertin and Lis, 2010), but it remains unknown how HSF1 chooses its target genes and physically locates to the target loci in distinct cell types and upon different stimuli. Deepening our understanding of HSF1-mediated regulation at the level of chromatin requires the characterization of transcriptional cascades on multiple HSF1 target sites, including protein coding, RNA coding, and intronic and intergenic chromatin regions.

The central role of HSF1 in diverse cellular functions is reflected in pathologies, such as neurodegenerative diseases and cancer, where an imbalanced HSF1 activity facilitates disease onset. Particularly, the recently described ability of cancer cells to harness HSF1 for metastatic progression highlights the plasticity of HSF1 in rewiring transcription and coordinating cellular processes. To this end, fully uncovering the physiological functions and molecular mechanisms of HSF1 will certainly continue to provide paramount insights into the essence of life.

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Competing interests

The authors declare no competing interests.

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