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Heat Shock Factor 1: From Fire Chief to Crowd-Control Specialist

Catherine G. Triandafillou[1] and D. Allan Drummond[1,*]
[1]Department of Biochemistry and Molecular Biology, The University of Chicago, Chicago, IL 60637, USA
*Correspondence: dadrummond@uchicago.edu
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HSF1 is the supposed master regulator of the heat shock response. In this issue of *Molecular Cell*, Solís et al. reveal that it has a much narrower job description: organizing a small team of molecular chaperones that keep the proteome moving.

Crank up the heat on any eukaryotic cell, and you'll witness a spectacular reaction: surges of transcription from dozens of genes; sudden diversion of translation to these new messages to produce emergency workers, who swarm to the scene; and masses of protein and RNA molecules huddling together in dense, seething crowds. Who's in charge of the emergency response? For decades, the answer has been clear: the transcriptional regulator Heat Shock Factor 1 (HSF1), widely known as the master regulator of the heat shock response. But a new study (Solís et al., 2016), along with recent work from Mahat et al. (2016), demolishes the conventional wisdom: HSF1 is not the master regulator of the heat shock response. Instead, in mammalian cells and in budding yeast, HSF1 coordinates a small, elite team of molecular chaperones needed under a wide range of conditions, shedding light on HSF1's roles in processes from stress to aging to cancer. In the new organizational chart, HSF1 isn't the fire chief but is instead the crowd-control manager (Figure 1).

Unlike the six HSF orthologs in the mammalian genome, budding yeast's single HSF1 is essential, hampering progress in this classic model system. In a clever breakthrough, Solís et al. (2016) use the "Anchor Away" (AA) system (Haruki et al., 2008) to inducibly haul HSF1 protein out of the nucleus, away from its DNA targets, in response to rapamycin. By comparing the responses of nuclear-HSF1-depleted cells to untreated cells across an array of assays—transcription, transcript levels, DNA binding, protein aggregation, and so on—a consistent portrait of HSF1's contribution under basal and stress conditions emerged. Most startlingly, despite showing clear signs of HSF loss, rapamycin-treated HSF-AA cells still mount the majority of the transcriptional heat shock response. The authors track regulation of this response to the general stress-responsive transcription factors Msn2/4.

A heat shock response without the master regulator of the heat shock response? That is also precisely what Mahat et al. (2016) recently reported using genome-wide measurements of transcription in mammalian cells, where both HSF1 and its paralog HSF2 can be knocked out. Comparison of *Hsf1*$^{-/-}$ cells to *Hsf1*$^{+/+}$ cells revealed that less than half of the heat-induced genes depended on HSF1, and heat-repressed genes were almost entirely HSF1 independent. (HSF1 mediates a unique and largely repressive transcriptional program in cancer cells [Mendillo et al., 2012], raising the question of how HSF1 acquires its repressive activities during malignant transformation.)

What is HSF1 doing, then? Pulling on the thread exposed by yeast HSF1's essentiality, Solís et al. (2016) identified the genes whose basal transcription, and resulting transcript levels, primarily depended on HSF1; every one of the resulting 18 genes had a promoter bound by HSF1. All but one of these HSF1-dependent genes encode molecular chaperones. Turning their attention to two types of mammalian cells, the authors identify a set of just nine genes dependent on HSF1 for heat-dependent induction in both cell types. (Mahat et al. [2016] identify a larger response, perhaps due to a focus on transcription versus transcript levels.) Again, all but one encodes a molecular chaperone, and the majority of human HSF1-dependent genes are homologous to genes in the yeast set. Which of these HSF1-dependent genes, if any, provide the essential function in budding yeast? Solís et al. (2016) discover that just two chaperones, Hsp70 and Hsp90, suffice to suppress the lethality of HSF1 deprivation.

Molecular chaperones are best known for assisting with protein folding, or dealing with the debris left by folding failures: protein aggregates. During heat stress, yeast cells accumulate protein-dense particles marked by the disaggregase Hsp104, Hsp70, and other chaperones (Cherkasov et al., 2015). Artificially destabilized, misfolding-prone proteins colocalize at these foci, prompting the inference that foci consist largely of misfolded, aggregated proteins in need of triage.

Deprived of nuclear HSF1 without heat shock, yeast also accumulate Hsp104-marked foci containing destabilized reporter proteins, consistent with the depletion of chaperones required to maintain the solubility of some endogenous proteins in the absence of heat stress. HSF1, the authors suggest, manages a tight team of specialists focused on the protein-folding needs of the cell. Take that medical/rescue team off the scene and protein homeostasis collapses, yielding immobile drifts of misfolded cellular citizens.

Recent work suggests a provocative alternate scenario. Formation of heat-induced foci, far from being unique to heat shock, has emerged as just one of many examples of the evolutionarily conserved formation of stress granules: massive protein/RNA assemblies induced

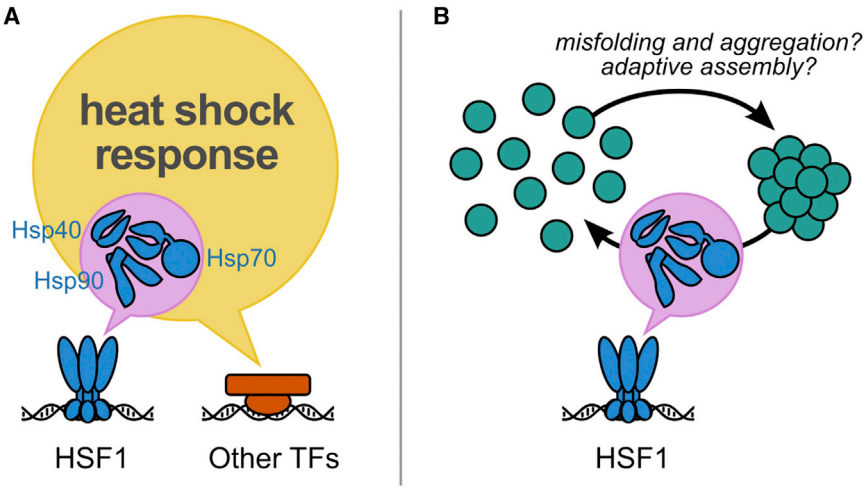

Figure 1. Heat Shock Factor 1 (HSF1) Coordinates a Small Chaperone Team

(A) In yeast and mammalian cells, HSF1 drives a compact transcriptional subprogram of the transcriptional heat shock response, regulating important chaperones. Other transcription factors (TFs), such as Msn2/4 in yeast, regulate the majority of the response.

(B) The major function of HSF1-dependent chaperones—which are essential in unstressed yeast—is remodeling and dispersal of massive protein assemblies; the endogenous substrates of these chaperones, and the physical mechanisms driving their coalescence into large particles, remain incompletely understood.

by starvation, oxidative stress, inhibition of mitochondrial respiration, hypoxia, and other nasty shifts in the environment. Stress granules serve adaptive and regulatory roles, modulating translation and sequestering basally expressed mRNAs during stress (Kedersha and Anderson, 2009). Instead of being triaged, proteins accumulated in heat-induced stress granules fully disperse back to solubility during recovery (Wallace et al., 2015) with the help of Hsp104, Hsp70, and other chaperones (Cherkasov et al., 2013; Kroschwald et al., 2015). Much if not most apparent aggregation during stress may reflect the operation of this adaptive, regulatory molecular assembly process (Wallace et al., 2015).

The tantalizing possibility suggested by Solís et al. (2016)'s results is that in yeast, and possibly in mammals as well, some proteins depend upon molecular chaperones to remain soluble under basal conditions—but not due to misfolding. Instead, these proteins may be primed to form molecular clusters in the absence of stress, just as stress-granule components are primed to cluster adaptively during stress. Both classes of proteins rely on molecular chaperones to regulate their behavior.

What are these endogenous granule-forming proteins? Are any of them essential, and if so, are their essential activities lost in massive assemblies, possibly (at last) illuminating the root cause of HSF1 knockout lethality in yeast? Why do these proteins require chaperones to remain dispersed? What mammalian factors have taken on the role of promoting high basal chaperone levels? Answering these questions will clarify HSF1's regulatory role and will make precise many of the diffuse claims about the activities of its targets, the molecular chaperones. We will learn to what extent HSF1 coordinates a team that facilitates organized (if stressful) meetings in cellular society versus one that merely fights to control unruly, destructive mobs.

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