Phosphorylation is dispensable for Hsf1 activation and the heat shock response

Awardee: David Pincus  
Award: Early Independence Award  
Awardee Institution: Whitehead Institute for Biomedical Research

Heat shock factor (Hsf1) is a transcription factor conserved in all eukaryotes that controls expression of genes encoding chaperone proteins and other adaptive responses to maintain protein-folding homeostasis in the cell. Environmental stress such as heat shock, genetic stress such as cancer and age-related metabolic stress such as oxidative damage all activate Hsf1. Despite its central role in cellular adaptation, stress resistance and disease, the mechanisms that regulate Hsf1 activity remain unclear. A conspicuous feature of Hsf1 that has been maintained over evolution is that it becomes phosphorylated during shock. Individual sites of phosphorylation have been implicated in both transcriptional activation and repression in a stress- and gene-specific manner. Here we provide evidence that in budding yeast, Hsf1 displays condition-specific patterns of phosphorylation and can be phosphorylated on 73 unique sites. Yet, we find no relationship between phosphorylation and either activation or repression. By en masse mutational analysis we show that Hsf1 can tolerate 152 simultaneous point mutations – which remove all phosphorylation – and retain its essential and heat shock inducible activities genome wide and normal attenuation kinetics. However, phosphorylation does destabilize Hsf1 which leads to substantial cell-to-cell variability in Hsp90 levels. In the absence of phosphorylation, decreased cell-to-cell variability translates into reduced acquired resistance to the antifungal drug fluconazole. Phosphorylation is not the switch that activates or deactivates Hsf1 but promotes noise in the heat shock response that enables the evolution of new phenotypes.