Highlight article: Hsf1 phosphorylation generates cell-to-cell variation in Hsp90 levels and promotes phenotypic plasticity

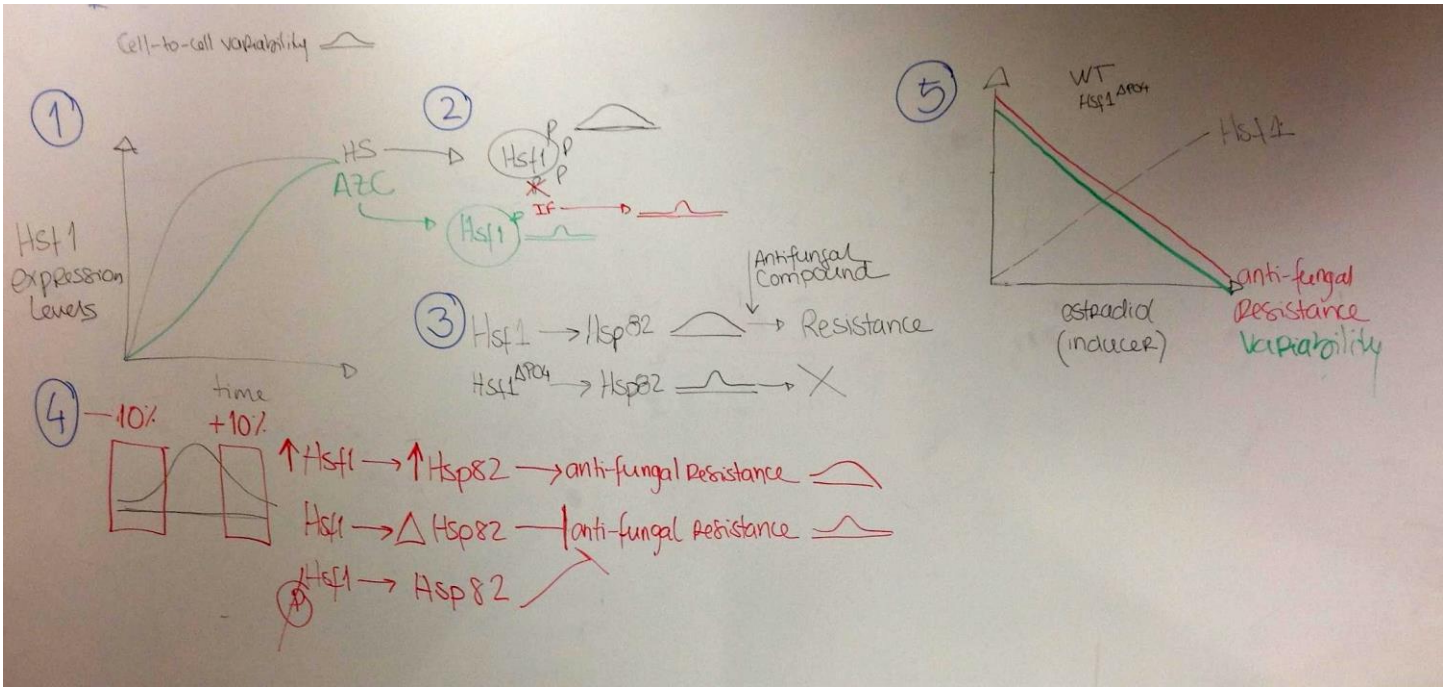
Due to random processes, clonal cells have different gene expression patterns that ultimately lead to cell-to-cell differences in the global protein pattern and homeostasis. These differences can be key to microorganisms' plasticity resulting in adaptability to adverse and fluctuating environments. Zheng et al., aimed to explore the role of a stress induced transcription factor, Hsf1, in generating cell-to-cell variability. Moreover, the authors investigate the role of its target gene, Hsp90 that has been previously associated with resistance to antifungal drugs.

As Hsf1 responds not only to heat shock stress but also to compounds that disrupt protein homeostasis, the first approach was to assess whether Hsf1 activity depends on the type of stress, as heat shock or a protein folding impairing agent (AZC). Hsf1 phosphorylation levels and activity were monitored by electrophoretic mobility and using a fluorescent reporter (HSE-YFP), respectively. Although, Hsf1 is activated by both stresses, cells challenged with AZC displayed a delayed activation kinetics as well as a decreased variation among cells. Moreover, phosphorylation levels are lower compared with heat shocked cells.

In order to unveil if Hsf1 phosphorylation was responsible for the increased variation during a heat shock, wild type (WT) and cells carrying a non-phosphorylated version of Hsf1 ($Hsf1^{\Delta po4}$) were used. During heat shock, $Hsf1^{\Delta po4}$ cells displayed a striking decrease in cell-to-cell variation suggesting that phosphorylation of Hsf1 plays an important role in generating cell-to-cell variation during stress.

Hsp90 is a target of Hsf1 known to play a role in the adaptive capacity of the cells. To understand the role of cell-to-cell variability in Hsf1 activity, the authors look to an Hsp90 paralog that is expressed in response to heat shock (Hsp82). The expression levels were monitored in either WT or $Hsf1^{\Delta po4}$ cells. Hsp82 production has greater variability among WT cells that in cells without Hsf1 phosphorylation. Testing these populations for resistance to the antifungal compound, fluconazole, the authors shown that the population with a higher variability is more resistant to fluconazole than the $Hsf1^{\Delta po4}$ cells. Next, the authors aimed to understand if cells with higher Hsp82 levels have different antifungal resistance than the low expressing cells, by sorting the highest and lowest 10% cells and testing for fluconazole resistance. Indeed, high expressing cells tend to be more resistant to the antifungal drug than the lower expressing cells. Moreover, antifungal resistance is dependent on the presence of the Hsp82 since high producing cells lacking this protein are not able to resist fluconazole. In this sense, the authors next hypothesized whether the total levels of Hsf1 were the driving force behind the antifungal resistance. As such, an estradiol-responsive promoter was used to control the expression of either Hsf1 or $Hsf1^{\Delta po4}$ and both cell-to-cell variation and fluconazole resistance were monitored. In both strains, higher amounts of estradiol led to an induction of Hsf1 while also decreasing cell-to-cell-variation. However, fluconazole resistance was observed for the lower estradiol amounts, suggesting that not the median expression of Hsf1 but rather the cell-to-cell variation in its activity is responsible for cells to acquire fluconazole resistance

In sum, Zheng *et al*. show that variation of Hsf1 phosphorylation and activity leads to phenotypic plasticity, which gives rise to the ability of yeast cells to acquire resistance to antifungal drugs. Globally, this study sheds light in the dynamics of Hsf1 activity which may have multiple implications in cells resistance to adverse environments.



Schematic illustration

URL: https://www.biorxiv.org/content/early/2017/09/07/185934