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## Modelling the regulation of thermal adaptation by Hsf1 and Hsp90 in *Candida albicans*, a major fungal pathogen of humans

The heat shock response is one of the most highly conserved and well studied networks in eukaryotic cells. Upon sensing a sudden temperature upshift, the heat shock transcription factor is rapidly activated, leading to the induction of numerous genes that mediate thermal adaptation, including heat shock genes that encode molecular chaperones. We have shown that the major fungal pathogen of humans, *Candida albicans*, has retained a bona fide heat shock response even though it is obligatorily associated with warm blooded mammals [1]. Furthermore, this thermal adaptation is essential for the virulence of *C. albicans*. We have predicted that interactions between Hsf1 and the essential chaperone Heat shock protein 90 (Hsp90) play critical roles in the regulation of thermal adaptation in *C. albicans* [2]. We have now tested this prediction using a combination of mathematical modelling and experimental dissection. Our model predicts that chronic exposure to heat leads to protein unfolding, which in turn sequesters Hsp90, thereby releasing Hsf1 from inactive Hsp90-Hsf1 complexes. This allows Hsf1 to become activated leading to the transcriptional activation of heat shock genes including *HSP90*. Our model, which predicts the dynamic molecular responses of *C. albicans* with reasonable accuracy, has yielded a number of novel predictions. For example, Hsf1 activation appears to be acutely sensitive to the concentration of unfolded proteins. Also, Hsp90 levels appear to be regulated at post-transcriptional as well as transcriptional levels. Furthermore, our model provides an explanation for the observation that *C. albicans* cells retain a 'molecular memory', rendering them more resistant to subsequent heat shocks. Therefore our mathematical modelling has provided novel insights into the regulation of this evolutionarily conserved environmental response.

### References

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