Coordinated heat-shock response in *C. elegans*

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Exposure to high temperatures has an adverse effect on cellular processes and results in activation of the cellular heat shock response (HSR), a highly conserved program of inducible genes to maintain protein homeostasis. Quantitative studies of the HSR in singe cell organisms have been instrumental to our understanding of the principles of control and adaptation, and exemplify the utility of tools from control theory, dynamical systems, and formal models in molecular systems biology. HSR in multicellular organisms, however, adds another layer of complexity: while different cells may be exposed to different environmental cues and different stability requirements, organismic adaptation requires coordination and corporation among cells and tissues. Here we use time-resolved longitudinal imaging of HSR in *C. elegans* to study its dynamics and coordination. By applying precise spatiotemporal perturbation we show that somatic cells integrate local sensation with systemic signals to control the time and level of response. We describe a robust dynamical pattern of activation and deactivation, and implicate sensory neurons in initiating these dynamics. A distributed modeling approach assigns distinct functionalities to the presumed coupling modes in driving specialized but coordinated response.

***Keywords* — Stress response. Spatiotemporal perturbations. Microfluidics. Time-lapse imaging.**

THE heat-shock response is a highly conserved molecular response to environmental conditions that disrupt protein homeostasis [1,2]. Its major role is to prevent protein misfolding and aggregation, both under normal conditions and under stress. In a multi-cellular organism, this is a major challenge, as the proteome of different cells can be markedly different [3]. Heat-shock response (HSR) therefore provides an opportunity to address a fundamental question about signals and regulation in a multi-cellular organism: How does a regulatory network control a coordinated response while at the same time allowing for different levels of activation which meet the specific needs of individual cells?

The control of HSR at the cellular level is highly similar across organisms, from bacteria to human. Multiple control loops link temperature and load of misfolded proteins with activation of HSR and synthesis of protein chaperones that stabilize the proteome. The impacts of these regulatory modules on the robustness of the HSR and on its dynamics have been studied theoretically in multiple organisms, including bacteria [4], fungi [5] and mammalian cells [6], using tools *e.g.* from control theory and dynamical systems.

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Recent results demonstrate that in *C. elegans* activation of HSR is not cell-autonomous, and involves both local interactions and systemic activation [7,8]. Here we study the activation of the insulin/IGF-1 pathway in *C. elegans* as part of HSR [9,10]. Upon activation, the central regulator of this pathway, the FOXO transcription factor DAF-16, is translocated to cell nuclei. A functional DAF-16::GFP fusion allows us to track this HSR in real time at the single cell level. This is done in a custom microfluidic device [11], which permits durable longitudinal imaging of up to 64 worms at a time as well as precise control of the spatiotemporal temperature profile.

By measuring the dynamics of response to spatiotemporal perturbations we show that information on the overall temperature load across the organism is integrated and transmitted systemically. This signal is necessary but not sufficient for cellular activation of HSR, which required in addition local sensation of heat stress. We find a robust dynamical pattern of activation and deactivation of HSR, and implicate sensory neurons in initiating these dynamics. Together, the integration of systemic and local signals balances between the need for coordination and for fine-tuning the response to the needs of individual cells.

Building on established models of single-cell HSR, we investigate the impact of multiple layers of couplings among cells. We characterize the multi-cellular HSR as a network-of-networks, where cellular HSR networks are coupled at different hierarchical levels to form the organismic network. Our results suggest that different forms of coupling serve different functional role, from synchronization and coordination to local fine-tuning. These results can be used to interpret our recent data, delineating the activation pattern of heat-shock proteins.

REFERENCES

[1] R. M. Vabulas, S. Raychaudhuri, M. Hayer-Hartl, and F. U. Hartl, Cold Spring Harb Perspect Biol **2**, a004390 (2010).
[2] T. Gidalevitz, V. Prahlad, and R. I. Morimoto, Cold Spring Harbor Perspectives in Biology **3**, a009704 (2011).
[3] G. N. Somero, Annual Review of Physiology **57**, 43 (1995).
[4] H. El-Samad, H. Kurata, J. C. Doyle, C. A. Gross, and M. Khammash, PNAS **102**, 2736 (2005).
[5] M. D. Leach, K. M. Tyc, A. J. P. Brown, and E. Klipp, PLoS ONE **7**, e32467 (2012).
[6] T. R. Rieger, R. I. Morimoto, and V. Hatzimanikatis, Biophysical Journal **88**, 1646 (2005).
[7] V. Prahlad, T. Cornelius, and R. I. Morimoto, Science **320**, 811 (2008).
[8] P. van Oosten-Hawle, R. S. Porter, and R. I. Morimoto, Cell **153**, 1366 (2013).
[9] K. Lin, H. Hsin, N. Libina, and C. Kenyon, Nat Genet **28**, 139 (2001).
[10] W.-C. Chiang, T.-T. Ching, H. C. Lee, C. Mousigian, and A.-L. Hsu, Cell **148**, 322 (2012).
[11] R. B. Kopito and E. Levine, Lab Chip **14**, 764 (2014).