Single-cell measurement and control to unravel yeast gene expression heterogeneity

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From microbes to cancer, variability in gene expression can lead to nongenetic phenotypic heterogeneity. This heterogeneity is important in determining how populations of cells grow, survive fluctuating environments, and develop drug resistance. For example, individual yeast cells within isogenic populations show striking heterogeneity in stress tolerance. Though genetic forces (*e.g.* mutation) determining population heterogeneity are well appreciated, non-genetic forces (*e.g.* stochastic gene expression) have been less thoroughly elucidated. Recently, we used single-cell RNA sequencing to quantify transcript heterogeneity in *Saccharomyces cerevisiae* cells treated with and without salt stress to explore population variation and identify cellular covariates that influence the stress-responsive transcriptome [1]. There is significant regulatory variation in individual yeast cells, both before and after stress. Heterogeneity in the expression of transcription factor targets implicated regulatory variability in establishing population-level heterogeneity. Live-cell imaging of cells expressing pairs of fluorescent regulators, including the transcription factor Msn2 with Dot6, Sfp1, or MAP kinase Hog1 revealed coordinated and decoupled nucleocytoplasmic shuttling. The live cell imaging coupled with analysis of the single-cell expression data suggests that cells may filter decoupled bursts of transcription factor activation but mount a stress response upon coordinated regulation, even in a subset of unstressed cells. We have developed an optogenetic toolkit that allows us to construct light-activated transcription factors. Using these transcription factors, we are working to resolve the relationship between bursts of transcription factor activity, burst coordination, and gene expression leading to population-level heterogeneity

References

[1] Gasch, *et al* (2017) Single-cell sequencing reveals intrinsic and extrinsic regulatory heterogeneity in yeast responding to stress *PLOS Biology* **15**(12)

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