

## NEWS AND VIEWS

# Chance and necessity in cellular response to challenge

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Living cells are enormously elaborate and exquisitely fine-tuned molecular machines, and the way they respond to changes in the environment is precisely determined by the iron logic of adaptation. Or so we would like to believe should we stick to the traditional adaptationist paradigm of neo-Darwinism (Dobzhansky 1951; Mayr 1963). Of course, the foundations of neo-Darwinism have been shaken a long time ago by the demonstration that many, if not most, of the mutations that are fixed in populations are neutral (Kimura 1983; Nei 2005), although these neutral changes provide the raw material for subsequent selection (Wagner 2005). However, what about the actual physiology, specifically, the cellular response to environmental challenge; is it primarily adaptive or is there a substantial neutral component even at this level of biology? In a study currently published in *Molecular Systems Biology*, Stern *et al* (2007) offer some of the most compelling evidence so far that the transcriptional response of yeast to a severe challenge is dominated by stochastic noise.

In the last few years, an increasing number of studies examined the global transcriptional response of diverse cells to various kinds of perturbations. Although the often considerable and uncertain amount of technical noise in the microarray data muddies the waters, the emerging consensus seems to be that the typical transcriptional response to stresses and challenges is not highly specific. Indeed, a substantial fraction of the genes in a genome tends to respond by changing their expression level, and only very few of these genes show discernible functional relevance to the particular perturbation (Jelinsky *et al*, 2000; Causton *et al*, 2001; Ideker *et al*, 2001; Liu *et al*, 2003).

The experiments of Stern *et al* (2007) are notable in that they constructed a novel challenge to yeast cells, one to which yeast could not have adapted during evolution, by placing an essential histidine biosynthesis gene (HIS3) under the control of the GAL regulatory network and then transferring the cells from galactose to glucose to repress HIS3. The experimental setup also involved variation in the applied pressure: a high-pressure environment was created by adding, along with repression through the GAL system, an inhibitor of HIS3. Yeast cells readily adapted to the novel challenge, reaching a new steady state (in terms of the expression profile) after 10–20 generations during which transient changes in transcription were observed. The observed transcriptional response showed several interesting features: (i) in each experiment, hundreds of genes, a substantial fraction of the genome, showed a significant (> 2-fold) induction or repression, (ii) the overlap between the sets of genes whose expression significantly

changed was very low between repetitions of the same experiment, typically of the order of 10% (the study, of course, included a careful control for technical noise), (iii) increase of the pressure on the cells through the use of an HIS3 inhibitor led to a substantially increased correlation between repeated experiments, and (iv) beyond the obvious induction of genes for glucose metabolism genes and repression of genes for galactose metabolism, there was very little functional coherence in the induced or repressed gene sets, even under high pressure.

The overall conclusion from the study of Stern and co-workers is that cells readily adapt to a novel challenge but do so via a nonspecific, global response that involves a substantial fraction of the transcriptome. Moreover, and perhaps most interestingly, there seems to be a major stochastic component in this global response as evidenced by the uniqueness of the profiles of induced and repressed genes in repeated experiments. A study on the evolutionary adaptation of *Escherichia coli* to minimal media of different compositions yielded remarkably similar results (Fong *et al*, 2005). However, an independent, extremely thorough analysis revealed nearly identical changes in transcriptional profiles of 12 *E. coli* lines adapting to a glucose-limiting environment (Pelosi *et al*, 2006). The source of these differences remains to be determined, but the key finding of Stern and co-workers, that the transcriptional response becomes more predictable under higher pressure, suggests a possible explanation: the experimental design in the study where a uniform response was observed might result in a particularly strong pressure on the cells. Alternatively, the crucial difference between the experiments of Stern *et al* (2007) and those of Pelosi *et al* (2006) could be that the former study deliberately subjected the cells to a challenge they have never encountered during evolution, whereas Pelosi and co-workers varied concentration of glucose, a 'familiar' situation to which bacteria could be specifically adapted.

The work of Stern and co-workers and related studies suggest a whole new and, perhaps, rather paradoxical perspective on the interplay between the adaptive and neutral components of the cellular response to challenge. Clearly, taken in its entirety, the observed change in the transcriptome is an adaptive reaction. However, the great majority of the changes in the transcription of individual genes have nothing to do with the function of the gene(s) that is directly targeted by the challenge and cannot be considered adaptive. Some of these changes might be truly and completely neutral, just random noise, whereas others might affect the relevant

gene(s) by transmitting the signal through the regulatory network of the cell (Luscombe *et al.*, 2004).

Paradoxical or not, from a purely logical point of view, the stochastic response observed by Stern and co-workers seems to be the only way a cell could successfully confront unknown and unpredictable challenges. Conceivably, the cells respond to such challenges by randomly and substantially perturbing a large portion of the transcriptome. The pressure then acts as a selective factor, favoring adequate variants of the response. The solutions are likely to be numerous for relatively mild challenges but much more difficult to come up with in the cases of a severe pressure.

Thus, a new paradigm of cellular adaptation seems to be emerging, one in which stochasticity and neutrality play a much greater role than previously suspected. Of course, the most interesting and important questions remain. Suffice it to mention two of these questions: (i) are the modes of response to new and 'familiar' challenges, indeed, substantially different, the former dominated by stochasticity and the latter deterministically dictated by adaptation? and (ii) what are the underlying mechanisms of the adaptive transcriptional response, in particular, are there master regulators that mediate the response to diverse cues?

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