Molecular Systems Biology 7; Article number 558; doi:10.1038/msb.2011.92
Citation: *Molecular Systems Biology* 7:558

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molecular systems biology

NEWS AND VIEWS

Winner takes all in a race for cell fate

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Molecular Systems Biology **7**: 558; published online 6 December 2011; doi:10.1038/msb.2011.92

The choice between alternative cell fates is fundamental to biology. The Gram-positive soil bacterium *Bacillus subtilis* can become competent for genetic transformation by external DNA or can form resistant spores. Although decades of work has elucidated much about the complex regulatory pathways that lead to these mutually exclusive fates (Dubnau and Losick, 2006), the decision mechanism that determines whether a cell becomes competent or forms spores has remained elusive. The paper by Kuchina *et al* (2011a), recently published at *Molecular Systems Biology,* asks the following question of this 'simple' prokaryotic system. Is there cross talk between the pathways that gradually diminishes the probability of one fate while enhancing that of the other? Or is decision making the result of a 'molecular race' in which the pathways proceed independently until one or another fate wins out by chance?

Spore formation is dependent on a phosphorylated transcription factor, Spo0A-P (hereafter OA-P), which is known to gradually increase in average concentration as cells approach the decision to sporulate (Fujita and Losick, 2005). Indeed, this gradual increase is essential for successful spore formation as OA-P successively activates a series of promoters, beginning with those for which it has the highest affinities. During the run-up to spore formation, the expression of OA-P is markedly heterogeneous (noisy) when measured across the cell population, so that spore formation is asynchronous (Chastanet *et al*, 2010; Kuchina *et al*, 2011b). Competence on the other hand requires the transcription factor ComK, which is itself dependent for its expression on low concentrations of OA-P. The expression of competence is limited to a minor fraction of the cells in a clonal population and recent work has established that the choice of cells for competence is stochastic and dependent on intrinsic noise in gene expression from the *comK* promoter (Suel *et al*, 2006; Maamar *et al*, 2007; Suel *et al*, 2007).

The study by Kuchina *et al* (2011a) used time-lapse imaging of fluorescent protein reporters fused to competence and sporulation promoters. Cells were studied in a starvation medium that had been optimized for sporulation, although competent cells were readily detected. In initial experiments, a fusion to the *spoIIR* promoter, a marker of commitment to sporulation, was used to detect and align the initiation of spore formation in a population of asynchronously sporulating cells. Reasonably, maximal *spo0A* expression coincided with *spoIIR* expression. Co-expression of promoter fusions to reporters for OA-P and ComK activity then permitted the onsets of competence and sporulation to be detected in individual cells.

The first important conclusion from this work is that the probability of competence remains constant during the approach to spore formation. In other words, no evidence was obtained for a cross-regulation mechanism that decreases the probability of competence during this approach, lending support to the molecular race model. A second conclusion concerns the roles of two proteins thought to cross-regulate competence and sporulation. Before commitment, expression of their cognate genes shows no correlation with the fate of the cells, whereas correlation was detected after commitment. The Kuchina *et al* (2011a) results imply the following scenario. As the concentration of OA-P increases, the probability of sporulation also increases. Along the way, competence can be randomly triggered by noise in *comK* promoter activity. In fact, a nice feature of the molecular race model is its good fit with the stochastic choice of cell fate, a conclusion that has been reached previously for competence. Once a decision has been made to sporulate or become competent, cross-regulation then serves to prevent the alternative fate. An important cautionary implication from these experiments is that the use of gene knockouts in cross-regulatory genes, leading to the elimination of one or another cell fate, can imply the mistaken conclusion that cross-regulation determines cell fate before a decision point.

The molecular race model suggests the existence of cells that have nearly simultaneously initiated both sporulation and competence. It is satisfying that such dual-activity (DA) cells, expressing ComK but proceeding to sporulate, were detected at about the frequency expected from the product of the competence and sporulation probabilities (0.1%). As a further test of the molecular race model, *comK* was expressed from promoters that turned on its expression earlier or later during the sporulation program. As expected, the relative timing of ComK expression was found to be critical for cell fate outcome. For example, expression of *comK* from the *spo0A* promoter increased the probability of competence more than expression from the later stage *spoIIG* promoter.

What is the selective advantage of cell fate determination by a molecular race? The authors plausibly suggest that a cross-regulation strategy operating in all the cells before the decision point would be costly, whereas the burden imposed by the infrequent production of DA cells is minimal. Still unanswered is the question of the generality of this mechanism. Would the molecular race apply under conditions that permit the high-frequency induction of competence? How frequent in biology are independent developmental pathways leading to alter-

native fates? And how does cross-regulation work? Is it symmetric, so that the choice of each fate reduces the chances of the other? Further work will certainly address these issues.

Conflict of interest

The author declares that he has no conflict of interest.

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