

Determination of cell fate during phage lambda infection

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Short Abstract — The lambda lysis-lysogeny decision serves as a paradigm for how extrinsic and intrinsic variability in the timing of molecular events might drive cell fate selection processes. We recently reported that variation in cellular volume, present in natural (asynchronous) populations of bacteria, is a strong extrinsic marker of cell fate. Here, we present unpublished experiments that help elucidate the mechanisms by which the lambda regulatory circuit senses and responds to extrinsic variation.

I. INTRODUCTION

One of the best-studied natural biological systems for exploring cell fate commitment is bacteriophage lambda. In studying the lambda lysis-lysogeny “decision,” a valuable starting observation is that, across many conditions, genetically identical cells grown in the same environment and each infected with a single lambda particle select different cell fates: Some cells lyse whereas other cells become lysogens [1]. Variability in cell fate selection is partly determined by phenotypic cell-cell variation present prior to infection; specifically, variation in cellular volume was found to be a strong predictor of cell fate. For example, a ≈ 2 -fold increase in the size of stationary phase cells can lead to a ≈ 5 -fold decrease (61% to 12.2%) in frequency of lysogeny [2]. Here, we explore the molecular mechanisms by which the lambda regulatory network senses and responds to pre-existing variation in host volume.

II. RESULTS

To build a molecular model in which variation in volume is correlated with cell fate outcomes, we first determined which aspects of host cell physiology, correlated with volume, might impact lambda development. We previously described a “gene dosage” model wherein variation in host volume results in variation in the concentration of phage-encoded genes during infections at constant phage:cell ratios [2]. In an alternative model, the lambda lysis-lysogeny decision may be sensitive to the cell cycle position of its host cell, a parameter tightly correlated with cell volume and other cellular factors. To decouple cell volume and cell cycle position, we considered a bacterial mutant (*ftsZts*) for which cell division is controlled by temperature. In this mutant, inhibition of cell division does not affect progression

through the cell cycle. We found that a 3- to 4-fold increase in cell volume led to a >10 -fold decrease in the frequency of lysogeny (3.9% to $< 0.3\%$). These results are inconsistent with lambda being directly sensitive to cell cycle position, and are not inconsistent with a “gene dosage” model.

We next set out to determine which factors of the lambda regulatory circuit might sense variation in volume, plausibly via variation in the dosage of specific lambda genes. While the main components of the lambda regulatory circuit are known, it is not completely understood which factors are involved in the decision between lysis and lysogeny and which factors carry out the decision. To resolve this issue, we constructed single-cell fluorescent reporters for the activity of two critical lambda regulators, CII and Q [3]. We found that CII and Q activity were predictive of eventual cell fate in more than 95% of infected cells. This suggests that commitment occurs upstream of CII (and Q) activity, and that factors acting downstream of CII – such as CI and Q – may be involved in the execution, rather than the determination, of the cell fate decision. Factors involved in sensing extrinsic variation [4], such as variation in volume or a correlated variable, are therefore likely to act before the activity of CII is determined.

III. CONCLUSION

Lambda’s observed sensitivity to host volume or a related physical variable is unlikely to be predominantly due to variation in cell cycle position, a physiological parameter tightly correlated with volume. Rather, we posit that lambda may sense and respond to “gene dosage” and that this response takes place before the activity of CII, a transcription activator which acts early in infection, is determined. The same network might mediate both the observed responses to variation in volume [2] and phage:cell ratio, or multiplicity of infection [1].

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