Hypothesis: Variations in the rate of DNA replication determine the phenotype of daughter cells

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Abstract

The existence of two identical chromosomes within the same cell in which genes and higher order structures compete for limited resources is a symmetry-breaking situation previously proposed to lead to differentiation. Recent experiments are consistent with an intimate relationship between metabolism and the rate of chromosome replication in bacteria. The process of chromosome replication progressively changes the copy number of genes and sites in a linear order. This raises the possibility that slowing or even pausing replication for different times at different sites in the chromosome might be combined with various mechanisms leading to local cooperation and global competition. If so, such replication-phenotype coupling could produce different patterns of gene expression. Indeed, replication-phenotype coupling may constitute a powerful and fundamental way of generating coherent phenotypes. As a prelude to testing this hypothesis, we discuss some of the parameters that will need to be explored by bench experimentation and computer simulation.

1 Introduction

One of the fundamental problems in biology, highlighted by Kauffman [2], is how cells integrate gene expression and environmental conditions to steer their phenotypes in a coherent, reproducible way through the vast space of possibilities apparently available to them. A possible solution is that the very existence of two chemically identical chromosomes in the same cytoplasm spontaneously leads to different patterns of gene expression and that this underpins differentiation [5]. This is based on the idea that if a gene attracts an RNA polymerase it has a greater chance of attracting a second one and hence, if two identical copies of a gene compete for a limited number of RNA polymerases, one copy is expressed and the other silent. Related ideas about the primordial role of the cell cycle in generating not just diversity but coherent diversity have also been developed [6, 4].

Such ideas need to be updated in the context in which gene expression takes place at the level of hyperstructures which are large, spatially extended assemblies of ions, molecules and macromolecules that are implicated in functions that range from DNA replication and cell division to chemotaxis and secretion [3]. These ideas also require updating due to the discovery that carbon metabolism in *Bacillus subtilis*, and almost certainly other bacteria, affects the enzymes responsible for the elongation step in chromosome replication [1]. In other words, metabolism appears to be exerting a direct control over the way the chromosome is replicated. This suggests to us a reciprocal relationship in which the way the chromosome is replicated determines the phenotype. Here we explore this idea.

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References

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