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Review

Stochasticity of gene expression as a motor of epigenetics in bacteria: from individual to collective behavior

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Abstract

Measuring gene expression at the single cell and single molecule level has recently made possible the quantitative measurement of stochasticity of gene expression. This enables identification of the probable sources and roles of noise. Stochastic gene expression can result in bacterial population heterogeneity, offering specific advantages for fitness and survival in various environments. This trait is therefore selected during the evolution of the species, and is consequently regulated by specific genetic network architecture. Examples exist in stress-response mechanisms, as well as in infection and pathogenicity strategies, pointing to advantages for multicellularity of bacterial populations.

Keywords: Stochasticity; Gene expression; Regulatory networks; Bi-stability; Epigenetics; Behavior; Multicellularity

1. Introduction

For bacteria living in complex communities and fluctuating environments, phenotype heterogeneity, i.e. population variability, can result in improved survival by providing different strategies of adaptation [2]. Phenotype heterogeneity may thus have important consequences for bacterial fitness, adaptation and expansion [28]. Population variability is often associated with differences in gene product abundance and appears to be more than a random consequence of the inherent stochasticity of biological systems. Indeed, phenotypic heterogeneity plays a fundamental role in the regulation of gene expression and as a motor of evolution.

Globally, non-genetic phenotypic heterogeneity, as opposed to genetic variations (due to irreversible mutations or reversible phase variations), can result from the cellular response to random fluctuations in environmental signals, cell aging (e.g. accumulation of intracellular damage and protein aggregation [32,41]) or from intercellular variations in gene expression (Fig. 1). The latter aspect is due to gene expression stochasticity or 'noise'. This corresponds to random fluctuations of the set of reactions controlling the abundance of a gene product. Expression noise results in phenotypic differences between genetically identical cells despite constant environmental conditions.

Phenotypic heterogeneity may also be due to non-homogeneous environmental conditions. It should be noted that environmental heterogeneity may be difficult to detect experimentally when it corresponds to local microvariations, differences in cell to cell interactions or secretion of autocrine and paracrine signals. Furthermore, stochasticity of gene expression can affect the properties of the local environment of the bacteria which, reciprocally, could lead to a change in gene expression noise. Therefore, in some conditions (e.g. stressed populations, biofilms), it may be difficult to precisely determine the cause(s) of phenotypic heterogeneity. This interplay between gene expression stochasticity, environmental fluctuation, genetic variation and aging may reduce

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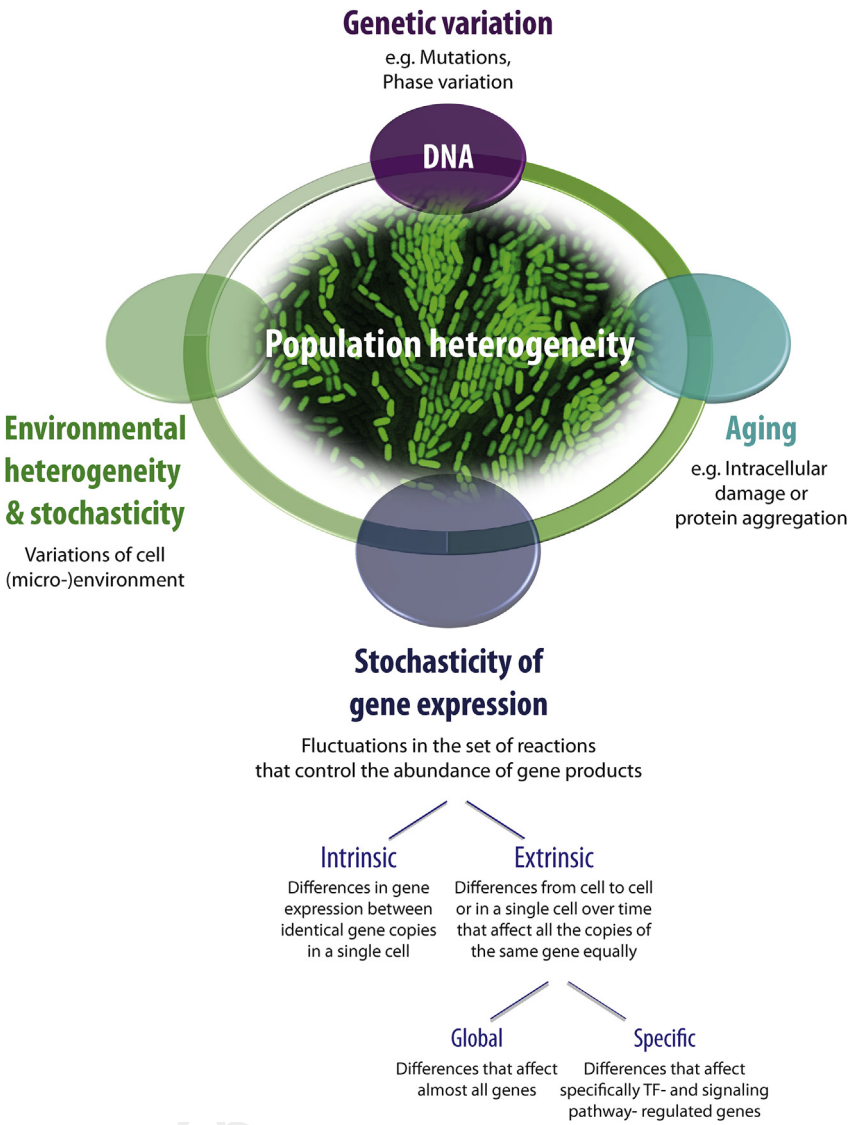

Fig. 1. **The main causes of population heterogeneity**. Genetic variation, environmental condition fluctuations, aging and gene expression stochasticity are the four main causes of population heterogeneity (the sum of genetic and non-genetic heterogeneities). They may influence each other through interactions that modulate the heterogeneity of the resulting population. Stochasticity of gene expression can be further defined as intrinsic, global extrinsic or specific extrinsic depending on the origin of the biological noise (see Fig. 2 and glossary for details). The image shows a clonal population of an enteropathogenic strain of *E. coli* carrying a transcriptional *gfp* reporter under the control of the promoter controlling the expression of the bacterial receptor *tir* (courtesy of H. Leh, LBPA, ENS Paris-Saclay). FT = transcription factor.

or amplify population heterogeneity [26,32]. This is illustrated by the example of DNA repair proteins that need to be expressed at a low level to avoid cell toxicity. Both the resulting stochasticity of gene expression of the proteins detecting and repairing DNA damage and unequal repartition of DNA damage events in the population can lead to genetic heterogeneity that might, in turn, lead to increased population phenotypic heterogeneity [66].

The emerging field of 'biological noise' has led to a paradigm shift from a deterministic to a probabilistic view of gene expression. Probabilistic/stochastic models of gene expression assume that several possible outcomes can occur with different probabilities in the same set of apparently identical initial conditions (elegantly discussed in [61]). The probabilistic view of gene expression was established in bacteria decades ago (e.g. [8,9,47,50,57]). In the early 2000s, the field was rejuvenated by the landmark study of gene expression stochasticity in single *Escherichia coli* cells [30]. Technical advances in single cell and single molecule (mRNA and protein) analysis in synthetic and system biology approaches have provided new opportunities to study stochastic gene expression as a phenotype per se and as an evolvable trait (see below). These analyses also revealed some limitations and misinterpretations resulting from population averaging methods, in particular when subpopulations present several logarithmic differences in gene expression (illustrated in Fig. S1). They also made it possible to gain a better appreciation of the strategies that can be used at the cellular level to create diversity in a population.

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