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Bacterial genomes: from regulatory complexity to engineering

Editorial overview

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Rotem Sorek is an Assistant Professor at the Weizmann Institute of Science. His research utilizes computational genomics tools to study patterns of evolution and novelty in microbial genomes. In particular, Dr. Sorek studies focus on the arms race between bacteria and phages, and on the immune systems that bacteria developed to resist phage predation.

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Luis Serrano is Director of the Centro de Regulacion Genomica (CRG). As a member of the EMBL-CRG Systems Biology program his research is focused on the full quantitative understanding of a model living system (the small bacteria *Mycoplasma pneumonia*), as well as on quantitative modeling of signal transduction pathways in eukaryotes.

In recent years, the field of microbial genomics has undergone a transformative change. Genomes are no longer sequenced just for the sake of sequencing; the accumulation of over 1000 publicly available sequenced genomes now allows progress towards understanding of basic principles in the buildup and regulation of a microbial organism. And so, with these new understandings, we begin to grasp how to engineer a bacterial genome from scratch. This transformation is in the center of this collection of reviews.

Several reviews within this Genomics issue of *Current Opinion in Microbiology* discuss progress in understanding the complexity of the bacterial transcriptome. This field of study had been neglected until several years ago, as the bacterial transcriptome was considered 'simple' as compared to the more complex eukaryotic transcriptome. With the emergence of novel high throughput techniques, it has become feasible to interrogate whole prokaryotic transcriptomes, and studies exploring such transcriptomes now provide evidence for prokaryotic transcriptome plasticity and regulatory complexity exceeding by far what was originally anticipated from previous genetic studies. Not only we are finding features that resemble Eukaryotic transcriptomes, but also we are learning the importance of noise and stochastic variability, and getting some ideas and principles of how to engineer bacterial chromosomes in a rational way. New studies show that to fully understand bacterial regulation we need to consider that bacteria do not live isolated but are part of large communities where genes could be lost or gained and regulatory features could be a response to a network of interactions between organisms. These topics are covered here in an interesting assemblage of reviews.

A review by Filiatrault discusses the recent advances in approaches for studying prokaryotic transcriptomes, and presents exciting emerging applications for transcriptome analyses. These emerging applications include metatranscriptomics, in which transcriptomes of complex communities of bacteria are studied in their natural habitats, allowing for the interrogation of 'community' gene expression without the need to culture each strain separately. Another exciting application is *in vivo* and *in-planta* transcriptome analyses, which can reveal RNA-based regulatory mechanisms driving bacterial pathogenicity. Understanding of the transcriptome of single bacterial cells is crucial for deciphering delicate regulatory mechanisms such as regulation by cis-antisense RNA transcription; very recent advances in this field (Y Kang *et al.*, *Genome Res* 2011) hold a promise for discoveries in the near future.

Regulated RNA processing is another facet of the prokaryotic transcriptome regulatory complexity. In a review by Evguenieva-Hackenberg and Klug, progress in understanding RNA-processing in bacteria is discussed. As the

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authors argue, mRNA turnover determines how long these molecules are functional and constitutes an important step in regulation of gene expression. Moreover, RNA processing serves as a regulatory tool in maturation of regulatory small RNAs, as well as differential processing of different genes in the same operon. Until recently, RNA processing was interrogated based on studies in single genes; with the genomic revolution, studies on RNA processing are now being conducted in a genome-wide manner, and studies from the recent years provide critical advancement in our understanding of the roles of RNA processing in the bacterial cell.

It is clear that cellular transcriptomics are subject to diverse types of noise (intrinsic and extrinsic) and different groups have proposed that noise in some cases could be useful to preadapt cells for future diverse conditions for example. In a very interesting review Collins and coworkers discuss the problem of bacterial persistence which is the fact that in a isogenic bacterial population you could have some cells which will be resistant to antibiotic treatment. They suggest that these persisters could be originated by stochastic fluctuations in gene expression in the population which could result in a homogeneous genetic population, but with heterogeneous physiology. A question that remains to be answered is to what extent these different physiological states are separated from each other by a kind of transition barrier, that is, bistability, or they are extremes of a smooth transition. The former could in principle allow characterization of all possible physiological states, while the second will be much more difficult to analyze. The authors then proceed to elaborate strategies of how to push persisters into antibiotic sensitive cells by external perturbations.

Cloots and Marchal present a nice summary of network based modeling of transcriptomics and metabolism in bacteria. They analyze different modeling and bioinformatic approaches to try to integrate large –OMICS data for a single organism into an integrated network that can be subsequently use for modeling. This is a very coming review at a time when is obvious that large scale studies while providing great insight into an organism are never complete and have a significant degree of false positives and true negatives. Thus it is necessary in many cases to look at different complementary data sets and even other organisms to try to elaborate a curated network. Probably it will not be possible in the near future to obtain a fully accurate reconstruction of a living cell, and perhaps a good reason is that there is not such 'a single cell' but in fact as mentioned in the Collins review many slightly different ones. However, we have now the tools to integrate very different data into coherent networks that could allow us to discern fundamental traits in bacteria that could be used for engineering or treatment.

Another theme in this issue of *Current Opinion in Microbiology* revolves around understanding of basic principles in the design of the bacterial genome, and the usage of these principles for biotechnological applications. The review paper by Hess nicely summarizes the field of cyanobacterial genomics and its biotechnological and ecological implications. Cyanobacteria are photosynthetic microorganisms that perform primary carbon fixation in many marine ecosystems, and thus have fundamental ecological roles in oceanic primary production and global carbon cycling. To date, over 60 cyanobacterial genomes have been sequenced and studied in detail, revealing significant genome flexibility in terms of size, ploidy, and dispensable genes. These genomic understandings now pave the way for several exciting biotechnological applications. First, many useful natural bioactive secondary metabolites, which have pharmaceutical and biotechnology potential, were shown to be produced by such cyanobacteria. Second, some cyanobacterial species whose genome was sequenced are a promising source for compounds of nutritive value such as beta-carotene. Finally, genome engineering of model cyanobacteria holds the promise of turning them into 'biofuel factories' for the production of ethanol, butanol and other biofuels directly from CO_2.

The review paper by Popa and Dagan discusses a crucial factor shaping the microbial genome, which is lateral gene transfer (LGT). LGT enables the extensive exchange of genetic material between microorganisms, and thus has direct implications on health issues such as the spread of antibiotic resistance among bacteria. Popa and Dagan discuss recent progress in the understanding of the frequency of LGT, the mechanisms involved in gene transfer and barriers for transfer, and their implications for phylogenetic reconstructions. One of these exciting advances uses a 'networks approach' to reveal the impact of lateral transfer during genome evolution (Kloesges *et al.*, *Mol Biol Evol* 2011, **28**:1057–1074).

One of the most exciting future steps in microbial genomics is genome engineering. Now that more than 1000 bacterial genomes have been sequenced, the cumulative understanding derived from the analysis of these genomes is expected to enable the design of genomes 'from scratch', thus creating synthetic organisms that would perform biotechnological chores of choice. An insightful paper by Arkin and colleagues presents the engineer point-of-view for rational genome design, and paves a virtual roadmap of the next steps that should be taken by the genomic community before such rational design can take place.

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