Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

Editorial overview: Bacterial cell regulation: from genes to complex environments

Jan-Willem Veening and Rita Tamayo

Current Opinion in Microbiology 2018, **42**:110–114

https://doi.org/10.1016/j.mib.2018.01.005

Jan-Willem Veening[1,2]

[1] Department of Fundamental Microbiology, Faculty of Biology and Medicine, University of Lausanne, Biophore Building, CH-1015 Lausanne, Switzerland
[2] Molecular Genetics Group, Groningen Biomolecular Sciences and Biotechnology Institute, Centre for Synthetic Biology, University of Groningen, Nijenborgh 7, 9747 AG Groningen, The Netherlands
e-mail: Jan-Willem.Veening@unil.ch

Jan-Willem Veening is a professor at the University of Lausanne in the Department of Fundamental Microbiology. His lab uses systems and synthetic biology approaches to study the opportunistic human pathogen *Streptococcus pneumoniae*. A main focus of the research in his lab concerns with DNA replication, chromosome segregation and the role of phenotypic variation for virulence and antibiotic resistance development. For more information visit www.veeninglab.com.

Rita Tamayo

Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
e-mail: rita_tamayo@med.unc.edu

Rita Tamayo is an associate professor at the University of North Carolina at Chapel Hill School of Medicine. Her lab studies the mechanisms underlying the ability of facultative pathogenic bacteria to adapt to changing environmental stimuli. Her research primarily focuses on the regulation of virulence genes by nucleotide second messengers in the intestinal pathogens *Clostridium difficile* and *Vibrio cholerae*.

Scientists, funding agencies, policy makers, and the general public have come to appreciate and embrace the societal and environmental relevance of the microbial world. For instance, in 2014, the first museum dedicated entirely to microbes was opened (https://www.micropia.nl/). Microbiology has become a truly interdisciplinary field, and this, combined with recent technological advances in areas such as DNA sequencing, gene editing, and fluorescence microscopy, is revolutionizing our knowledge of microbial life. Recent work on how bacterial cells regulate basic processes such as DNA replication and division and central metabolism reveal remarkable elegance and sophistication in the control mechanisms involved. In addition to these core functions, bacteria have evolved numerous strategies to make the best of their environment. Consider chemotaxis and bacterial exploration towards new nutrient-rich niches, production of nanotubes to transmit information with others, immune evasion of the host they are feeding off, or killing competitors in their environment. In this issue of Current Opinion in Microbiology, we highlight new insights in bacterial regulation in its broadest sense. New developments in understanding bacterial chromosomal organization to regulation of anti-bacteriophage CRISPR systems are discussed. The latest technologies for studying bacterial life that have made these advances possible, such as single cell (dual) RNA-seq, are also discussed. The overall picture emerging from this collection of reviews is that tremendous progress is being made towards our understanding of the molecular basis of bacterial cell regulation, demonstrating the versatility, flexibility, and exquisite regulation that bacteria employ.

Control of fundamental physiological processes: bacterial chromosome organization and transcription

We begin our introduction on the reviews in this 'Cell regulation' issue with an update on the current state-of-the-art concerning the organization and segregation of the bacterial chromosome. Structural Maintenance of Chromosomes (SMC) complexes are highly conserved and have fundamental roles in chromosome organization and dynamics. The development of techniques such as chromosome conformation capture (Hi-C) has made it possible to build three dimensional maps of bacterial chromosomes and begin to determine the molecular basis of SMC complex function. The review by (Stephan Gruber) highlights recent findings regarding two major classes of SMC complexes in bacteria, Smc-ScpAB and MukBEF. Features that distinguish these SMC complexes, potential models by which they interact with DNA and the roles of protein cofactors, and how they circumvent problems from head-on collisions with other DNA machinery are also discussed.

The first regulated step of gene regulation is transcription. *In vivo* transcriptional errors have been estimated to be in the range of 10^{-4}–10^{-5} [1] while recent studies using nascent elongating transcript sequencing (NET-seq) have shown that up to 3% of all elongation complexes are stalled at one point due to nucleotide misincorporation events in *Escherichia coli* [2]. There are several mechanisms at play to ensure high fidelity of transcription by RNA polymerase (RNAP) and for restarting transcription elongation. Gamba and Zenkin review recent progress made in our understanding of how transcription fidelity is established [3]. Not only was a ribozyme-like mechanism shown to be involved in intrinsic proofreading activity, a new catalytic domain, the Trigger loop, was also recently discovered to help RNA polymerase guide its use of (correct) substrate and hence enhance fidelity [3].

Advances in understanding regulation of gene expression

Another level of gene regulation involves small RNAs (sRNAs) that target mRNAs to post-transcriptionally regulate their translation or stability. The review by Kavita *et al.* describes recent progress in the identification of new Hfq-dependent RNAs, where Hfq binds on those RNAs, and, in some cases, suggesting sRNA-mRNA pairs [4]. These discoveries have been greatly facilitated by the application of modern sequencing techniques such as RNA-seq, CLIP-seq, RIL-seq, and GRIL-seq [5–7]. Interestingly, these approaches have revealed that many sRNAs are encoded within open reading frames, which complicates the ability to distinguish a functional sRNA from an overlapping or parent mRNA. Further, sRNAs can have more than one regulatory function [8] and Hfq itself can be modulated through the action of sRNA 'decoys' or 'sponges' [9,10], can promote or interfere with Rho-dependent termination events, and may regulate translation of mRNAs independent of an sRNA. These findings underscore that we have only scratched the surface of the potential regulatory schemes involving Hfq, sRNAs, and mRNAs in controlling gene expression.

A very new notion of how cells control gene expression is not by sensing and responding to changes in the environment, but rather by sensing and responding to changes in intracellular metabolic fluxes. This emerging field, stimulated by advances in quantitative metabolomics, is covered by Litsios *et al.* [11]. Recent work has shown that key metabolites, such as fructose-1,6-biphosphate, can act as metabolic flux sensors [12] which for instance can drive the entry into bacterial persistence. By interacting with other cellular components such as transcriptional regulators, the concentration of flux-signaling metabolites can relay and control gene regulation, protein activity, or growth [11]. The beauty of using metabolite fluxes as a control mechanism is that it allows cells to respond to the actual metabolic situation inside the cell as opposed to measuring which substrates are available externally. Litsios *et al.* argue that using metabolic flux sensing might also be an excellent way to buffer against noise in gene expression and make regulation more robust.

Rojas and Huang discuss the recent insights that have been made in the century-old concept of growth by osmosis-dependent cell swelling [13]. It turns out that many bacteria make use of the turgor pressure of the membrane against the cell wall to regulate growth and division. For instance, in *Staphylococcus aureus*, cell separation occurs very rapidly, within milliseconds. This process presumably initiates by partial degradation of the cell wall then leading to rapid, turgor-pressure driven splitting of the daughter cells [14,15]. Furthermore, turgor pressure can also drive cell growth and constriction, and Rojas and Huang speculate that there is interplay between turgor and septal cell wall synthesis [13]. Future work will shed light on how important turgor is in general for bacterial growth and regulation.

Controlling type IV pili and CRISPR

Looking outside of the bacterial cell, a major area of intense research is the type IV pilus. Type IV pili are appendages on the outside of bacteria that act as nanomotors to generate motile forces. Such pili are involved in twitching motility in for instance *Myxococcus xanthus* but also in DNA uptake in naturally competent bacteria such as *Neisseria meningitidis* [16]. Mignolet *et al.* discuss how the Tad/Cpa system, a type IV pilus machine in *Caulobacter crescentus* important for biofilm formation, pathogenesis, and adhesion, is controlled [17]. This system is a secretion system that is strictly localized at newborn cell poles and is involved in various processes. Recent work has elucidated how the components are regulated such that the pilus is formed only once per cell cycle, at the cell pole of the newborn cell. It turns out that the Tad/Cpa system is cell-cycle controlled at multiple levels by various factors including transcription factors CtrA, CcrM, and GcrA [17].

Although certain bacteria are infamous for causing infection, bacteria themselves are under heavy predation as well from bacteriophages. To counter bacteriophage infection, bacteria have evolved several defense mechanisms including restriction-modification systems and CRISPR (clustered regularly interspaced short palindromic repeats). A diverse set of CRISPR systems has been described, and they all work by binding and cutting non-host DNA or RNA. Leon *et al.* review recent insights gained on how bacteria obtain immunity against bacteriophages and, just as important, prevent auto-immunity due to cutting of their own DNA or RNA [18]. A special focus is given on the post-translational processes that control CRISPR enzyme activity.