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Editorial overview

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Patrick H Viollier is an associate professor in the Department of Microbiology and Molecular Medicine at the University of Geneva (Faculty of Medicine) located in Switzerland. His research interrogates developmental regulation in bacterial cells with particular emphasis on the molecular mechanisms governing polarity and asymmetry using the Gram-negative bacterium *Caulobacter crescentus* as a model system.

The reviews in this issue sketch out the surprising level of sophistication and plasticity of the molecular mechanisms that prokaryotes use to steer growth and development. They also illustrate that bacteria, though originally deemed (damned?) as trivially simple entities, embody an amazing repertoire of regulatory versatility with mechanisms that resemble in operation and/or molecular design to those in multicellular eukaryotes. Included in this suite are topical mechanisms that influence growth and/or development through intrinsic cues provided by cell polarity or through external signals induced by cell–cell contact, mediated by proteins with structural resemblance to important eukaryotic cytoskeletal players (e.g. tubulin and tropomyosin) or organellar components (YaeT/Omp85), respectively. Topics making recent headlines in the eukaryotic field include the regulation of gene expression at the translational level by small RNAs (sRNAs) or at the epigenetic level by DNA methylation. As detailed below, both mechanisms are also operational in bacterial cells. In hindsight the realization that many principles originally described in eukaryotes are also used for cell regulation in prokaryotes should not come as a surprise. Interrogating the available prokaryotic genome databases, we find an ever-growing list of bacterial proteins that resemble those performing newly discovered regulatory functions in eukaryotes. Since the discovery and illumination of these fundamental biological mechanisms remain the current challenge in biology, might not the power of bacterial genetics and cytology offer formidable avenues in the 21st century towards this goal? The reviews below advocate this point perfectly.

Low and Hayes survey different mechanism of prokaryotic growth control, including that known as CDI that induces growth arrest upon cell contact. A receptor function in CDI was recently attributed to the highly conserved YaeT/Omp85 protein that facilitates the formation of beta barrels in the outer membrane and is also present in eukaryotic organelles. Although the molecular basis of growth inhibition through YaeT/Omp85 is not yet defined, there are many potential ways that CDI could halt growth. The toxin–antitoxin (TA) modules define a well-known and conserved mechanism for growth arrest. As discussed by Low and Hayes, TA systems typically rely on the production of toxic mRNA interferases that are tightly regulated at the level of translation and/or protein stability. Antisense RNAs are known to inhibit translation of some toxins, thus acting essentially as antitoxins. As reviewed by Fröhlich and Vogel, RNAs can act as translation activators, rather than inhibitors. It is certainly conceivable that such translational activation also underlies regulation of TA systems.

A second remarkable illustration of the power of bacterial genetics/cytology is provided by recent molecular insight relating to prokaryotic cell division. Cell division is tightly intertwined with exponential growth of bacterial cells.

It is a precisely regulated process and is currently best understood in the rod-shaped *Escherichia coli* and *Bacillus subtilis* cells that divide by binary fission. The medial constriction machinery (divisome) is assembled that directs: first, the invagination of the envelope; second, the synthesis of the septal cell wall; and third, the fusion of the cell membrane(s). A tubulin-like cytoskeletal protein, FtsZ, binds GTP and organizes the constriction machinery. FtsZ polymerizes into protofilaments that have the ability to hydrolyze GTP and associate into arcs or ribbons, collectively known as the Z-ring, at the cytoplasmic surface of the membrane. The Z-ring provides the support for the assembly of the divisome components, including the constituents of the cell wall biosynthetic machinery, which are recruited in an orderly fashion. The review by Bramkamp and Van Baarle first brings us up to speed with the sophisticated and multifactorial measures of cells to control the positioning and/or integrity of the Z-ring. Subsequently, they outline important new insight on the dynamics and function of an old regulatory factor, Min. It now transpires that Min also acts on a protein(s) other than FtsZ to promote divisome maturation in *B. subtilis*.

The theme of cell division is pursued in McCormick's synopsis, focusing on the role of the division machinery in the sporulating actinobacterium *Streptomyces coelicolor* that exhibits a hyphal (filamentous) growth mode. *S. coelicolor* is the only cell-walled prokaryote that is viable in the absence of FtsZ or any other known divisome component. By contrast, *E. coli* or *B. subtilis* cells depleted of FtsZ fail to divide, eventually forming long multinucleate filaments that lose viability for unknown reasons. Cell death is also manifested with the depletion of most other (but not all) divisome components from *E. coli* or *B. subtilis* cells. In *S. coelicolor* the divisome has evolved to fulfill a specialized, and thus dispensable, developmental function in dissemination rather than growth. Cell wall extension in *S. coelicolor* does not appear to depend on FtsZ function, relying instead on the essential tropomyosin-like protein DivIVA, a protein well known for its role in providing polarity cues in *B. subtilis* development.

As outlined by Sherr and Nguyen, the DivIVA protein appears to direct cell wall extension to polarized sites in actinobacteria, which includes diverse genera such as the industrial workhorse *Corynebacterium glutamicum* and the world's most successful killer bug *Mycobacterium tuberculosis*. While in *M. tuberculosis* and *C. glutamicum*, the sites of DivIVA localization (i.e. the poles) are the products of a previous (FtsZ-dependent) division event, DivIVA assembles into lateral clusters along *S. coelicolor* hyphae, apparently at the point of maximum hyphal bending, consistent with the recent notion that membrane curvature is an important determinant of DivIVA localization (see Bramkamp and van Baarle). These lateral clusters of DivIVA redirect cell wall growth perpendicular to the prevailing axis, resulting in the elaboration of hyphal branches. While polarized DivIVA is subsequently retained at the tips of these branches, FtsZ primarily localizes in sporogenic hyphae in which branching is suppressed (by an unknown mechanism). Despite the distinct morphologies and ecological niches that the two species occupy, it was recently found that some *Mycobacteria* (perhaps all) have the capacity to differentiate into spores. Remarkably, spore-like infectious particles have been detected during latent infections with *M. tuberculosis*, suggesting that conserved developmental pathways have been exploited for dissemination and survival in actinobacteria. As highlighted by Scherr and Nguyen, molecular studies reveal that paralogs of *S. coelicolor* sporulation proteins regulate durability traits in *M. tuberculosis*.

While DivIVA provides an inspiring example of how actinobacteria exploit polarity for growth control, Tomlinsen and Fuqua recapitulate how polarized functions act sequentially in adhesion of the plant pathogen *Agrobacterium tumefaciens* to various surfaces. A novel unipolar adhesive organelle, UPP, was recently discovered at the pole(s) of *A. tumefaciens* that appears to be made up of similar polysaccharide-based constituents as the holdfast organelle that is located at the tip of the stalk in *Caulobacter crescentus*, a dimorphic bacterium that lives a solitary life style and is phylogenetically related to *A. tumefaciens*. *A. tumefaciens* interacts with the host by way of a cell pole and uses a polarly localized extracellular appendage (T-pili) and secretion apparatus to intoxicate and transform the host. Polarity is, therefore, tightly interlaced with the early events of infection, yet the nature of the positional information and the underlying molecular mechanisms for polar localization are not well understood in *A. tumefaciens*. By contrast, a suite of molecular determinants of polarity has been identified and studied in *C. crescentus*. Several sequence homologs of these determinants are also encoded in the *A. tumefaciens* genome, providing a rational starting point for decoding the mechanisms of polarity in *Agrobacteria*.

In C. crescentus polarity is used to implement asymmetric cell division, a mode of reproduction that requires differentiation to be tightly coordinated with the cell division cycle. The review by Thanbichler discusses the recent progress in understanding the molecular pathways and polarity mechanisms that dictate the acquisition of distinct functional and morphological traits in the two cell types. Phospho-based and/or dicyclicnucleotide-based signaling systems, whose components can be localized to the cell poles(s), enable DNA replication initiation to be coordinated with polar differentiation. In addition to these classic signal transduction circuits, the recent identification of novel types of regulatory proteins led to the appreciation that noncanonical regulatory networks coordinate other critical functions in time and space. These networks operate in a polarized fashion to couple

division with development, cell growth, and chromosome segregation. Reciprocally, they also direct the correct placement of the constriction machinery in cells with a duly ordered chromosome.

In addition to this spatial effect, the chromosome can also temporally influence cell cycle events through epigenetic switches that impinge on gene expression. The review by Collier examines regulation by adenine methylation in *C. crescentus* and *E. coli*. The bifunctional DNA replication initiator–transcription factor, DnaA, is expressed from a methylation-sensitive promoter, a special class of promoters whose activity is typically modulated in S-phase. With the duplication of a given locus, hemi-methylated DNA emerges from the DNA replisome, a modification that can either induce or prevent firing of a promoter. Thus, methylation offers an ingenious and elegant way to passively modulate the expression of a gene at the time in the cell cycle when it is duplicated, at least in organisms that have nonoverlapping or synchronous rounds of replication. Interestingly in their review Low and Hayes allude to the possibility that regulation in specialized cellular states, for example the 'persister' cell state, is based on an epigenetic mechanism.

In addition to methylation-based epigenetics, regulation of gene expression by sRNAs is known as a molecular mechanism used primarily by eukaryotes. As detailed by Fröhlich and Vogel, it now transpires that activation of gene expression by sRNAs is not only pervasive in a given cell, but also widespread in bacterial lineages to affect growth under various environmental conditions aided by proteins that trap, degrade, and/or pair RNAs. Recent bioinformatic and genetic analysis reveals that structural and/or functional homologs of such ancillary proteins are encoded in the genomes of different phyologenetic lineages, promising the discovery of new sRNA-controlled functions.

For all these inspiring mechanisms, and likely a plethora of novel ones, we eagerly await the ongoing research, while also anticipating that it will profoundly shape (perhaps change) our still limited understanding and overall perception of bacterial cells.