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# Growth and development The whole picture begins to emerge

Editorial overview

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Current Opinion in Microbiology 2004, 7:561–564

This review comes from a themed issue on  
Growth and development  
Edited by Mike Tyers and Mark J Buttner

Available online 10th November 2004

1369-5274/\$ – see front matter  
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DOI 10.1016/j.mib.2004.10.018

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Mike Tyers investigates cell cycle control in the budding yeast *Saccharomyces cerevisiae*, with emphasis on G1 phase regulation and genome stability, the ubiquitin proteolytic system, transduction of environmental cues, and genome-wide analysis of genetic, chemical-genetic and protein interaction networks. He holds a Canada Research Chair at the Samuel Lunenfeld Research Institute and the Department of Medical Genetics and Microbiology at the University of Toronto

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Mark Buttner has worked for more than 20 years on multiple aspects of the biology of the mycelial, antibiotic-producing genus of bacteria, *Streptomyces*. Most of this work has focused on the genetic and biochemical elucidation of molecular mechanisms involved in the regulation of differentiation (sporulation) and stress responses in the model species, *Streptomyces coelicolor*. He currently works at the John Innes Centre, a BBSRC-funded research institute in Norwich, UK.

## Introduction

This issue focuses on the central biological processes of growth and development. Spurred on in part by comparative genomics, recent efforts in many microbial systems have begun to divulge the high level operating principles that underlie biology, some of which have been enshrouded by the mists of evolutionary time. The ever closer relationships between microbial and metazoan cellular functions have now surpassed even the wildest expectations. As highlighted in several of the reviews in this issue, these similarities now span sub-systems once perceived either as being in the exclusive domain of multicellular organisms, such as apoptosis, now firmly documented in yeast, or in the eukaryotic domain, such as cytoskeletal substructures, now evident as microtubule-, actin- and intermediate filament-like forms in bacterial systems. The study of these processes in genetically powerful models is sure to afford new insights into less tractable metazoan organisms.

Perhaps more importantly, these findings heighten the prospect of elucidating the means whereby the main sub-systems of the cell are interlinked, an area encapsulated in the general rubric of systems biology. The sequenced genomes, powerful molecular genetics, and innovative functional genomic approaches of microbial systems will remain unrivalled for systematic data collection, hypothesis generation and hypothesis testing, particularly when applied to the diverse behavioral repertoire of microbes. These approaches currently rest on proteomics, systematic genetics, metabolomics and a variety of DNA array-based platforms. While these nascent technologies are far from perfect – as noted in various reviews, glaring gaps exist in coverage, dynamics, and predictive power – the methods and associated informatic tools will be inexorably refined. From the perspective of these integrated datasets, we can now reasonably hope to discern the emergent network properties presumed to define living systems [1,2]. Indeed, in the first concrete example of dynamic network analysis, the yeast cell cycle exhibits the properties of an attractor, with a major basin in G1 phase and minor basins at cell cycle checkpoints [3]. Whether diverse biological processes exhibit similar global behaviour should soon become apparent.

## Bacterial systems

Temporal control has long been emphasised by bacteriologists, but the first three reviews in this issue beautifully illustrate the comparatively recent realisation that the regulation of any function in a bacterial cell can only be

appreciated fully when analysed spatially as well as temporally. As recently as 15 years ago, bacterial compartments were thought to be homogenous. As a consequence, proteins could have one of only a very limited number of locations — they were ‘in the cytoplasm’, ‘in the membrane’, or (in Gram-negative bacteria) ‘in the periplasm,’ and even these limited locations could not be assessed in living, single cells, but only through the disruption and fractionation of large populations. The advent of bacterial cytology has led to the realisation that many, and, perhaps, most bacterial proteins have very specific subcellular ‘addresses,’ and that in some cases these addresses can change with astonishing speed during growth [4].

The review by [Grauman](#) gives striking examples of how cell biological methods have profoundly changed our understanding of the ways in which microbial processes are organised and regulated. *ftsZ*, *mreB* and other genes involved in the regulation of bacterial cell morphology and cell division were defined genetically in the 1960s, but only the recent application of cell biological techniques has given insight into how they function. An early milestone in bacterial cell biology was the demonstration that FtsZ marks the site of initiation of cell division by polymerising into a ring-like structure. More recently, MreB-like proteins, which control cell shape in many bacteria, have been shown to assemble into dynamic helical ‘cables’ that extend from pole to pole. Further, the distribution of immature peptidoglycan (localised with fluorescent vancomycin) reflects the helical distribution of Mbl protein around the long axis of the cell, implying that MreB-like proteins control bacterial cell shape by directing, in three dimensions, the synthesis of the rigid cell wall. Another MreB-like protein has been shown to form filaments required for segregation of the plasmid R1. It is now clear that FtsZ is a structural and functional homologue of tubulin, and that MreB and Mbl are structural and functional homologues of actin, overturning the previously held view that the cytoskeleton is unique to eukaryotes. Further, the first intermediate filament protein in bacteria, crescentin, has recently been identified in *Caulobacter*, and is required for this bacterium to maintain its crescent-like asymmetric shape.

The next two reviews address systems involving asymmetric cell division. [Viollier and Shapiro](#) review the control of cell cycle progression, polar morphogenesis and cell division in *Caulobacter crescentus*, and [Piggot and Hilbert](#) review endospore formation in *Bacillus subtilis*. They show how the application of the broadest range of available tools — genetics, biochemistry, transcriptomics, cell biological methods and modelling — by the *Caulobacter* and *Bacillus* communities has led to the most comprehensive understanding of all bacterial developmental systems. In particular, they beautifully illustrate how,

in the bacterial cell, with no characterised directed transport systems, the subcellular localisation of both structural and regulatory proteins can change dynamically, and that in many cases these changes actually direct cell cycle progression, cell division and the formation of new cell types [4]. They also show how the bacterial chromosome can be specifically oriented in the cell such that each section of the chromosome has a specific location, and in *Bacillus* it is already clear that this positioning contributes to the temporal and spatial control of gene expression. A further seminal discovery, from the *Caulobacter* field, is the emergence of cyclic-di-GMP as an important signalling molecule in bacteria.

[Søgaard-Andersen](#) reviews gliding motility and multicellular fruiting body formation in *Myxococcus xanthus*. These bacteria are unicellular but exhibit complex social behaviour, swarming during feeding and, in response to starvation, aggregating to form fruiting bodies in which some cells are fated to form dormant spores and others are fated to undergo developmental lysis. Motility and intercellular signalling therefore play vital roles in the lifecycle of these bacteria, and yet the nature of some of the intercellular signals and the means by which these non-flagellated bacteria move have been controversial. The substantial and exciting recent progress in understanding the nature and regulation of the motility motors and the true identity of the ‘C-signal’ are clearly summarised.

In order to disperse themselves, filamentous bacteria and fungi erect aerial filaments that differentiate into spore-bearing structures. To grow into the air, these aerial filaments have to escape surface tension at the air:water interface, and [Elliot and Talbot](#) discuss the surface-active proteins made by bacteria and fungi that allow this to happen. Although the proteins made by the two groups of microorganisms are not homologous, they are strikingly analogous. There have been substantial recent breakthroughs in this area, with the crystal structure of a fungal hydrophobin and the identification of the chaplins and rodmins in the filamentous bacterium *Streptomyces coelicolor*. In addition, the recent biochemical and genetic characterisation of SapB, a surfactant peptide made by *S. coelicolor*, unexpectedly revealed it to be structurally and biosynthetically related to a major class of peptide antibiotics.

Biofilm formation is a new area in the study of microbial development, from which novel concepts are rapidly emerging. [Fuqua and colleagues](#) review biofilm formation on plant surfaces and its importance in plant–microbe associations. It is striking how the comparatively recent realisation of the importance of biofilms in nature forces us to substantially rethink the list of bacteria we recognise as having a developmental cycle. Many of the themes found in other reviews in this issue, such as social behaviour, intercellular signalling, and the role of nutrient

depletion, also appear as fundamental themes in biofilm formation.

The section on bacterial development concludes with a review by [Bos and Tommassen](#), summarising the recent substantial advances in our understanding of the biogenesis of the Gram-negative outer membrane (OM). Much of this recent progress has been made possible following the unexpected finding that *Neisseria meningitidis* can survive without outer membrane-associated lipopolysaccharide, which was previously thought to be essential in all Gram-negative bacteria. This discovery has facilitated a genetic dissection of the machineries that direct the biogenesis of the different components of the outer membrane. In particular, the mechanism of insertion of outer membrane proteins (OMPs) into the OM has long remained obscure. However, an essential OMP called Omp85 has recently been shown to be part of a complex that has a direct role in OMP assembly. Depletion of Omp85 in an *omp85* conditional mutant leads to accumulation of unfolded OMPs that are not inserted into the OM. Omp85 is conserved in mitochondria where it plays a similar role in OMP assembly.

### Fungal systems

The second part of this issue focuses on the overall processes of fungal growth and division, as partitioned into three main sub-themes. On the topic of biological networks, four reviews elaborate the interconnected pathways that underlie cell wall biogenesis, nutrient sensing, ribosome biogenesis and transcriptional control. [Bussey and colleagues](#) describe recent exciting advances on the regulation of budding yeast cell wall assembly by the Rho GTPases, whose multiple effectors are positioned to couple polysaccharide synthesis to polarity, actin dynamics, secretion and stress responses. [Broach and colleagues](#) develop a lucid overview of the intricate mesh work of signalling events that mediate a broad spectrum of nutrient responses in budding yeast, including interplay between the PKA, Snf1 and TOR kinase pathways. As the details of this network coalesce, it will establish a new benchmark for the analysis of metazoan transduction networks — as noted above, responses to the environment may soon be couched in terms of dynamics and attractors that have non-obvious emergent properties [3]. An immediate downstream target of nutrient signalling is the process of building new ribosomes, a process governed by a labyrinthine network of literally hundreds of assembly factors still being charted by proteomic and genomic approaches, as discussed by [Dez and Tollervey](#). Ribosome biogenesis is emerging as a nexus of cellular regulation, with unforeseen connections to the cell cycle that are only just now becoming evident, in both yeast and mammalian systems. The complexity of the ribosome biogenesis apparatus suggests the potential for vast regulatory emanations. These three reviews on specific networks are buttressed by a comprehensive discussion of

transcriptional network analysis by [Hughes and colleagues](#), who have made a Herculean effort to synopsise the vast extant literature on this topic. While several substantial gaps in experimental and theoretical understanding remain to be bridged, it is obvious that transcriptional networks impinge heavily on most if not all cellular processes. The integration of transcriptional circuits with biochemical and genetic networks to enable meaningful predictions forms a main challenge of systems biology.

Another sub-theme that spontaneously emerged in this issue is the dynamics of cellular state change, as reflected in aspects of four quite different reviews. As in metazoans, single-celled organisms implement complex developmental adaptations, often in direct response to ever-fluctuating environmental conditions. The first of these reviews, by [Laney and Hochstrasser](#), addresses the critical but often under-appreciated issue of disassembly of a pre-existing state, which is of course necessary so as not to interfere with properties of the new state. As discussed by the authors, the genetic tractability of the cell type switching system of budding yeast has yielded insights into the role of the ubiquitin system in developmental reprogramming. Much remains to be discerned about how the cell swaps one identity for another, including the protein substrates, their cognate E3 ubiquitin ligases and the regulation of E3-substrate interactions. In an analogous vein, [Madeo, Frohlich and colleagues](#) review the nascent field of apoptosis in single cell organisms, as focused on early breakthroughs in budding yeast. An apoptotic response to many stimuli entails reprogramming on a population level, presumably to enable better fitness of the colony at the expense of the individual. In a third example of re-programming, [Magee and Magee](#) provide an intriguing evolutionary perspective on how the same overall cellular wiring can be applied to different problems, in this case the mating type system of the pathogen *C. albicans*. Although the *C. albicans* MAT system seems nearly identical in molecular detail to that of the well-studied *S. cerevisiae* system, whether or not mating type switching in *C. albicans* actually occurs in the wild remains controversial. To explain this conundrum, [Magee and Magee](#) field the interesting hypothesis that the cell type specific transcriptional programs have been co-opted to allow the pathogen to adapt to different host environments, in lieu of switching mating type *per se*. In yet another fungal system that resonates on various themes, [Kahmann and colleagues](#) review the role of PKA and MAPK signalling, developmentally regulated transcriptional programs and the cytoskeleton in mating and pathogenesis in the plant pathogen *Ustilago maydis*. Quite propitiously, given its historically important role as a model system for DNA repair and recombination, homologues of the critical human tumour suppressor Brca2 and its associated factor Dss1 have recently been discovered in *Ustilago*, a finding that will undoubtedly speed the elucidation of Brca2 function.

Finally, two reviews focus on the pivotal intertwined problems of genome stability and DNA replication, the understanding of which has been paved largely through intensive efforts in yeast. Beginning from their own seminal findings on the age-dependent onset of genome instability, McMurray and Gottschling, construct a framework that may well guide future studies on loss of heterozygosity (LOH) in cancer cells. That the budding yeast mother cell protects its own genome to the detriment of its progeny genomes has remarkable parallels to the behaviour of the self-renewing stem cell, which underpins development, tissue renewal, and probably many cancers. McMurray and Gottschling postulate a role for the gradual accumulation of oxidatively damaged proteins in this process. A complementary review from Schwob begins from the other side of the equation, namely the mechanics and high fidelity control of DNA replication. The replication problem has long encompassed central yet ineluctable issues: what mechanisms ensure once and only once per cell cycle replication of the genome? How is origin firing linked to cell cycle commitment? What is the purpose of ordered origin firing and how is it established? How do checkpoint

networks sense errors, intercept the replication fork and mediate repair and recovery? Comparative analyses across bacterial, archeal, fungal and metazoan systems are at last converging on the logic and detailed mechanisms that underlie this most crucial of cellular processes.

As the astute reader will notice, the themes we have highlighted above are but a few that tether the various reviews together. Over the next few years, comparative and comprehensive studies of the growth and development of microbial species will provide the first detailed vista of biological systems and the evolutionary processes that built the organisms of today.

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