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Cell structure and dynamics

Editorial overview

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The past 30 years have seen an unprecedented effort, mainly using genetics, to uncover the specific functions of genes involved in various processes in different organisms. Such studies have tended to generate papers describing, for example, that gene X is involved in process Y. This single-gene era is now coming to an end as improved genomic methodology — high-throughput sequencing, bioinformatics, DNA microarrays, RNAi, protein interaction mapping and mass spectroscopy — has led to an industrial revolution in genetics, allowing rapid, comprehensive and standardized identification of gene function. In particular, the standardization of procedures such as mutagenesis methods and phenotypic classification bring the same advantages to gene identification that the standardization of machinery brought to production in the nineteenth century. These types of genome-scale approaches represent the beginning of the development of tools and methods to analyze complex phenomena that depend upon large numbers of genes and their products.

These genome-wide issues are discussed by Gunsalus and Piano, who distinguish between 'screening' approaches (i.e. the discovery of a single gene involved in a process) and 'systems biology' approaches (the identification of all the genes involved in a process). They stress that the development of informatic tools will be essential for the exploration of the huge amount of data that are being generated.

But, can we really hope to understand how hundreds, or even thousands, of gene products interact to produce a complex biological process such as cell division or tissue development? Sorger argues for a smaller-scale 'reductionist' systems biology. Systems biology, in his view, refers to the study of biological processes using a combination of mathematics, computation and empirical observations. This is the classic approach of physiology, but importantly builds up from the molecular level. In his commentary he argues that reaction engineering can be used to create detailed molecular models of smaller-scale protein-interacting modules, whereas multiscale models based on systems theory can bridge from proteins to cells and from cells to organisms. The models can be tested by interfering with the component proteins, either through genetic- or RNAi-based approaches or by using small-molecule inhibitors that are increasingly being discovered using high-throughput 'chemical genetic' screens, reviewed by Hathaway and King.

The review by Kruse and Jülicher on biological oscillations nicely demonstrates the power of the modeling approach. They show that mathematical tools from non-linear dynamics can be used to understand the molecular basis of a diverse range of phenomena, ranging from mechanical oscillations in sensory hair cells to spatiotemporal oscillations of signaling molecules in

bacteria and transcriptional circuits in the developing spinal cord. The models reveal that similar underlying mechanisms operate in widely different organisms and at different levels of organization. Becskei and Mattaj review recent molecular models of the transport of proteins through nuclear pores; they argue that the transit times introduce significant delays that have interesting effects on regulatory networks that involve signals that move between the nuclear and cytoplasmic compartments.

Protein modules can be either well-defined protein complexes, such as ribosomes, or less well-defined entities, such as signaling pathways, the components of which are more loosely associated but combine for a common purpose. Although many of these macromolecular protein complexes exist to do work (e.g. condense chromatin or move chromosomes) and use energy to do so, it is probably wrong to think of them all as machines, in the sense that we think of a car engine. Rather, they assemble as required to perform certain functions and then disassemble when not required, more like a construction crew where the various tradesmen come and go as needed and where one tradesman might be working on several jobs at the same time. Eventually, these modules will be understood in enough detail so that the input and output can be described. For instance, the input of a motor is ATP and the output is movement. The descriptions of these modules will then allow the modeling of cellular behaviour.

Many of the major functions of the cell are mediated by large protein complexes, such as the ribosome or the proteasome. These tend to have more of the hallmarks of macromolecular machines, and they can generally be isolated intact from the cell. One article on the nuclear pore complex, referred to above, and another on the kinetochore, by Kline-Smith *et al.*, illustrate the steps taken today to understand the structure and function of these complex machines.

Loose assemblies of molecules tend to combine to perform signaling functions. Among the most exciting of these are end-binding complexes of microtubules, described here by Akhmanova and Hoogenraad. These complexes assemble on the tips of growing microtubules where they apparently perform complex signaling functions in cell polarity and growth. The tip binding complexes can only form in the context of a growing microtubule and therefore cannot be thought of as a protein complex in the traditional sense of the meaning.

Another example, reviewed by Lin *et al.*, is the modified actin-filled microvillus that forms the hair bundle, the sensory organelle of hair cells. The treadmilling of actin makes this a highly dynamic structure, which nevertheless supports the highly precise and sensitive transduction machinery that confers on us our exquisite sensitivity to sound. Remarkably, microvilli turn over occurs every two days, even though the cells last a lifetime. This work illustrates beautifully the value of studying how specialized cells function in tissues.

The understanding of protein modules is predicated from knowledge of the basic enzymology of the underlying components. We have a pretty good understanding of the mechanisms by which standard enzymes function, as well as the basic signaling pathways. However, the enzymology of the cytoskeleton has been harder to understand. The cytoskeletal filaments, themselves, convert the energy derived from ATP or GTP hydrolysis into work that can be used to build (and demolish) cellular structures; thus the major problem is to translate the enzymology of nucleotide hydrolysis into the physical properties of assembly and disassembly. This is the subject of the reviews by Plastino and Sykes on actin filaments and Dogterom *et al.* on microtubules. The cytoskeleton is an old invention, and Møller-Jensen & Löwe give us an update on the structure of the bacterial cytoskeleton, which, in addition to having filaments composed of tubulin- and actin-related proteins, also contains relatives of intermediate filaments.

The dynamics of the cytoskeleton are regulated by many proteins. An interesting example is mitotic centromere-associated kinesin (MCAK), which is reviewed by Wordeman, a protein in the kinesin-13 family that depolymerizes microtubules. This depolymerase activity can be contrasted with more usual motor proteins that move along the filaments, rather than disassemble them. The physical and chemical mechanisms by which motor proteins — the prototypic molecular machines — move along their filaments is now being understood with unprecedented detail, thanks to the convergence of structural and single-molecule studies. Asbury reviews recent work on how kinesin, the worlds smallest motor, walks along microtubles, and Oiwa and Sakakibara review recent structural and functional work on the largest and least understood motor, dynein. Information about how the motors, cytoskeleton and protein modules interact can then be used for another iteration of the systems biology program.