Trends in Cell Biology

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Review

How Cells Measure Length on Subcellular Scales

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Cells are not just amorphous bags of enzymes, but precise and complex machines. With any machine, it is important that the parts be of the right size, yet our understanding of the mechanisms that control size of cellular structures remains at a rudimentary level in most cases. One problem with studying size control is that many cellular organelles have complex 3D structures that make their size hard to measure. Here we focus on linear structures within cells, for which the problem of size control reduces to the problem of length control. We compare and contrast potential mechanisms for length control to understand how cells solve simple geometry problems.

Trends

The mechanisms that control organelle size are unknown. Length control of linear structures provides a simplified version of the more general organelle size-control problem.

Numerous distinct mechanisms have been proposed for regulating the length of various structures, including molecular rulers, limiting precursor production, balanced assembly/disassembly, and molecular gradients.

While molecular rulers play a prominent role in regulating length in prokaryotes, it is less obvious whether rulers are similarly important in eukaryotic cells.

Organelle size control, as a problem that spans the molecular and cellular scales of organization, is emerging as a key challenge for quantitative cell biology.

Length Control of Cellular Structures: A Paradigm for Organelle Size Regulation

> Tous les problèmes de géométrie se peuvent facilement réduire à tels termes, qu'il n'est besoin par après que de connaître la longueur de quelques lignes droites, pour les construire. (All problems of geometry can be reduced to terms such that it is only necessary to know the length of several straight lines to construct them.)
> René Descartes (1637) La Géométrie

Cells have complex geometries that are directly linked to their function. Where does the information come from that specifies the 3D architecture of cells and how is this information translated into actual structures? Important geometrical properties for cellular components include the length of linear structures and the surface area and volume of membrane-bound organelles. Cells need a way to ensure that their components are of the appropriate sizes, but how exactly does this happen? Many biological regulatory systems, such as pathways that regulate membrane potential or lactose synthesis rates, involve sensors that allow cells to measure the quantity that is being regulated. Here we consider how cells might sense and measure length and distance.

Using Length to Determine Geometry

The most obvious biological role of length measurement is to fix the size of those cellular structures that happen to be essentially linear (Figure 1). Cells carefully control the length of actin filaments in stereocilia [1,2] and sarcomeres [3] to tune mechanical sensitivity and force generation, respectively. In prokaryotes and viruses, the lengths of bacterial injectisomes [4], bacterial flagellar hooks [5], and bacteriophage tails [6] are tightly controlled to a narrow range of lengths, thereby allowing proper biological function. For the injectisome, the optimal length is likely to reflect a trade-off between mechanical stiffness and the ability to reach out to a target cell over some distance. Microtubules in eukaryotic cilia and flagella are set to predefined lengths, presumably to help optimize their mechanical properties for swimming [7], and microtubule bundles in spindle midzones [8] are also regulated to within a narrow length distribution. In each

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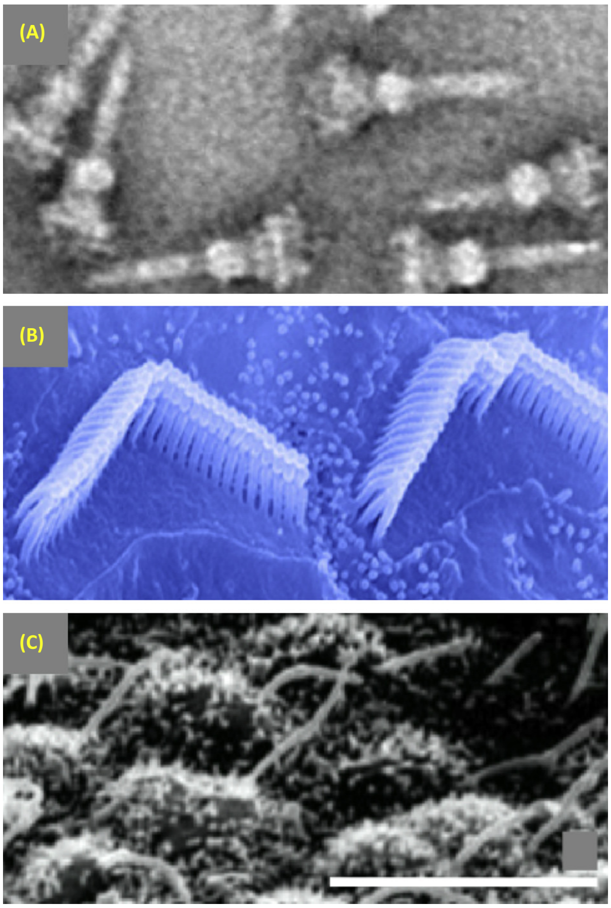

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Figure 1. Examples of Linear Structures with Defined Lengths. (A) Bacterial injection needle [59]. Each needle is approximately 50 nm long. (B) Stereocilia (https://commons.wikimedia.org/wiki/File:Stereocilia.jpg). The image shows two adjacent hair cells from the ear, each possessing an array of actin-based stereocilia. (C) Cilia from the node of a developing mouse embryo [60]. Scale bar, 5 µm. These different structures on different length scales, comprising different molecular building blocks, all show precise length control but employ radically different mechanisms to achieve it.

case, the cell is able to control the length of an essentially polymeric structure, which amounts to controlling the number of monomers that assemble into the polymer. Linear dimensions of more complex structures such as the mitotic spindle [9,10] are also regulated by the cell and these can be considered as cases of length determination although the structures in question may also have to control other geometric features such as cross-sectional area or total volume.

In addition to directly controlling the size of a structure, linear elements of defined size can be used to set distances between other structures. Simple molecular spacers, in the form of coiled-coil domains, are used to set the spacing between layers of the yeast spindle pole body [11] and between the axial elements of the synaptonemal complex of meiotic chromosomes [12]. Within centrioles, the coiled-coil domain of the centriole cartwheel protein Bld10/Cep135 appears to contribute to stabilizing the ninefold symmetry of the cartwheel by setting the length of the cartwheel spokes, thus regulating the diameter of the centriole and hence the number of triplets that can be accommodated around the circumference of the centriole [13,14]. This mechanism appears to act in parallel with the direct self-assembly of ninefold symmetry by the cartwheel protein SAS6 (reviewed in [15]).

At larger spatial scales, such use of linear elements to dictate spacing between structures seems to be relatively uncommon. One clear case occurs in the phototactic unicellular green alga *Chlamydomonas reinhardtii*, in which the length of the rootlet microtubule bundles seems to set the distance between the flagella and the eyespot, a geometrical parameter that is critical for proper