Dispatches

Cellular Allometry: The Spindle in Development and Inheritance

Recent studies have demonstrated a correlation between cell size and the behaviors of the cytoskeletal division machinery during embryogenesis, giving insight into how a core cellular process is modulated over the course of development.

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Cell division is essential for all reproduction and is one of the most basic processes underlying development in multicellular organisms. In eukaryotes, assemblies of cytoskeletal filaments are responsible for the mechanics of division. Cell cleavage is accomplished by a cortical, contractile ring, largely composed of actin filaments, while chromosome segregation is performed by an array of microtubules, called the spindle. The spindle is a dynamic structure that assembles, elongates while transporting the chromosomes to what will become the two daughter cells, and then dissociates. While central aspects of cell division are highly stereotyped, the division machinery must be modulated to properly work in cells with different shapes and sizes, as are found throughout development. A study by Hara and Kimura [1], reported in this issue of *Current Biology*, investigates this phenomenon by examining how the spindle varies during embryogenesis in *Caenorhabditis elegans*. Work such as this may help us understand how core cellular processes are modified to function in different cells.

The basic mechanisms and proteins responsible for cell division are highly conserved [2], and much of our knowledge about the spindle has come from focusing on the similarity between different systems. This approach has been very successful because it has allowed researchers to select organisms that are best suited for their desired method of studying the spindle: yeast for genetics [3], *Xenopus* egg extracts for biochemistry [4], and grasshopper spermatocytes for measuring forces [5]. However, the division of different cells is different. It is not really appropriate to speak about 'the' spindle, as if all spindles were shadows of some ideal archetype, and, despite the underlying conservation, the diversity of mitosis is truly remarkable. Nearly all aspects of cell division in single-celled eukaryotes show great variability: the size and shape of the spindle, the extent and timing of nuclear envelope breakdown, the nature of microtubule-organizing centers at the spindle poles, and the structure and behavior of chromosomes [6]. Closely related species also exhibit a range of differences: a recent study of early embryogenesis of 34 nematode species found variation in every aspect of cell division that was investigated [7]. In fact, it has been known for over one hundred years that there are even differences between spindles from different cells within the same organism [8].

During early development, many organisms undergo multiple rounds of cleavage, rapidly dividing the large embryo into many smaller cells. The cytoskeletal assemblies that perform these divisions must therefore be able to function in cells with different sizes. More generally, the volume of eukaryotic cells spans a vast range, from $\sim 1\ \mu m^3$ in *Micromonas pusilla* [9] to over $10^9\ \mu m^3$ in some eggs, but there is very little known about how cellular organization depends on cell size. This deficiency is surprising because the importance of allometry, the manner in which characters scale with body size, is widely acknowledged [10]. Furthermore, there are strong theoretical reasons to suspect that cell size should have important implications for cellular organization because the speed of mixing by diffusion [11] and the relative efficiency of pulling and pushing by cytoskeletal filaments [12] are size dependent. One aspect of what might be called *cellular* allometry, the scaling of characters with cell size, that has received considerable attention is the variation of nuclear volume with cell volume, which was first noted over one hundred years ago [8] and is still being actively studied [13]. Recent work has started to address how the cytoskeletal machinery responsible for cell division varies with cell size by examining the scaling of spindle size in *Xenopus laevis* development [14] and the scaling of cortical ring contraction dynamics in *C. elegans* development [15].

In the new study, Hara and Kimura [1] investigated the structure and dynamics of spindles throughout *C. elegans* embryogenesis. They found that as the embryo divides into smaller and smaller cells, the spindles within these cells that are responsible for further divisions also reduce in size. Interestingly, spindle length is not proportional to cell length, but instead shows a sub-linear dependence, similar to what was found in *Xenopus laevis* [14]. The amount by which spindles elongate during division decreases as cell size decreases, so that larger cells contain larger spindles which elongate more, but the final length of the spindle also has a sub-linear dependence on cell size. These results show that division in small cells is not just a miniature version of this process in large cells; rather, the relative proportions of the spindle and the cell depend on cell size. However, the *rate* of spindle expansion decreases with decreasing cell size such that the *time* for spindle expansion is approximately independent of cell size. This result is reminiscent of the earlier finding that the time required for cell cleavage does not change during early *C. elegans* development because the speed of contraction of the cortical ring is lower in smaller cells [15].

What processes modulate spindles and cortical rings in different-sized cells during *C. elegans* embryogenesis? Both Hara and Kimura

[1] and Carvalho *et al.* [15] propose what might be called 'confined constant biochemistry' models, in which the microscopic behaviors of proteins remain the same throughout early development, but the organization of these proteins adjusts to the changing size of the cell. Support for this class of model comes from perturbation experiments: the same relationship between cell size and spindle behavior [1] or cortical contraction dynamics [15] holds when embryo size is artificially altered, suggesting that it is really cell size that is important, not development stage. Hara and Kimura [1] account for their data by a model in which spindle elongation is caused by cortical forces pulling on astral spindle microtubules, with some forces being proportional to the square of the microtubule's length, which they claim is an approximate way to represent the effect of a limited number of cortical force generators [16], and some forces being length independent. The authors use computer simulations to argue that this combination of forces naturally reproduces the cell size dependence of spindle elongation, and they use RNAi experiments to suggest a molecular basis for the length-dependent forces.

However, it is still too early to rule out an alternative class of model for how the division machinery changes over the course of embryogenesis: 'developmental regulation' models, in which the activities of cytoskeletal proteins are modified in different cells through post-translational modifications, degradation, selective division, or some other mechanism. After all, at every stage of *C. elegans* development there are large differences between cells which have the same size [17,18], and even though artificially changing cell size can produce corresponding changes in cytoskeletal behaviors, this does not prove that those changes in the cytoskeleton are normally caused by changes in cell size. In addition to the mechanistic question of *how* cell division is modified at different stages of development, it will be equally crucial to ask *why* these changes occur from an evolutionary perspective. Are the spindle and the contractile ring perfectly optimized to function differently in different cell types, and if so, why are these particular scaling relationships optimal? Or, is the observed variation caused by non-adaptive processes [19]? Clearly much work remains, but these recent studies show that understanding the differences in how cells divide is just as interesting and important as understanding the similarities.

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Perceptual Decisions: From Sensory Signals to Behavior

Recent non-invasive studies in humans provide new insights into the timing of perceptual decision making and show that integrated sensory evidence is represented in motor areas well before a behavioral response.

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Imagine you are driving down a road in the evening twilight looking for a certain house number. The darker it gets the longer it takes you to identify the numbers. The correct perceptual decision is relevant for selecting the appropriate behavioral response. What is the time course of processes in the brain leading to the decision? A study reported by Donner *et al.* [1] published in this issue of *Current Biology* provides new insights into the timing of perceptual decision making. Specifically, they demonstrate that the temporally integrated sensory information affects activity in motor areas well before movement onset.

The term 'perceptual decision making' refers to the process of transforming sensory signals into a percept and an appropriate behavioral response. Most of our knowledge about the mechanisms underlying this transformation and their neural substrates stems from seminal studies in monkeys carried out in the somatosensory domain by Romo and coworkers, and in the