Tubular Transformations

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stressors are mostly about challenges to their rank, whereas for omega males, stress comes from the displacement aggression rained on them when high-ranking males are frazzled about something. Does the hypercortisolism of alpha and omega males have different health consequences? Another question concerns the differences in temperament that influence the resiliency and coping mechanisms of alpha males (*10*, *11*). Do individual differences in, say, coping style influence physiology? Furthermore, baboon troops differ in their social milieu [e.g., different rates of aggression and of grooming (*4*)]; does a troop's milieu affect the endocrine differences between alpha and beta males?

The study of Gesquiere *et al*. is thought provoking and prompts considerable future work. Perhaps it suggests that like male baboons, John D. Rockefeller and Andrew Carnegie were much more stressed than their immediate underlings, retreating to those executive bonding sessions in the woods to cope with the strain of their stature.

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DEVELOPMENTAL BIOLOGY

Tubular Transformations

Two studies offer insight into the cellular processes that produce twists and turns in lung and gut tubes.

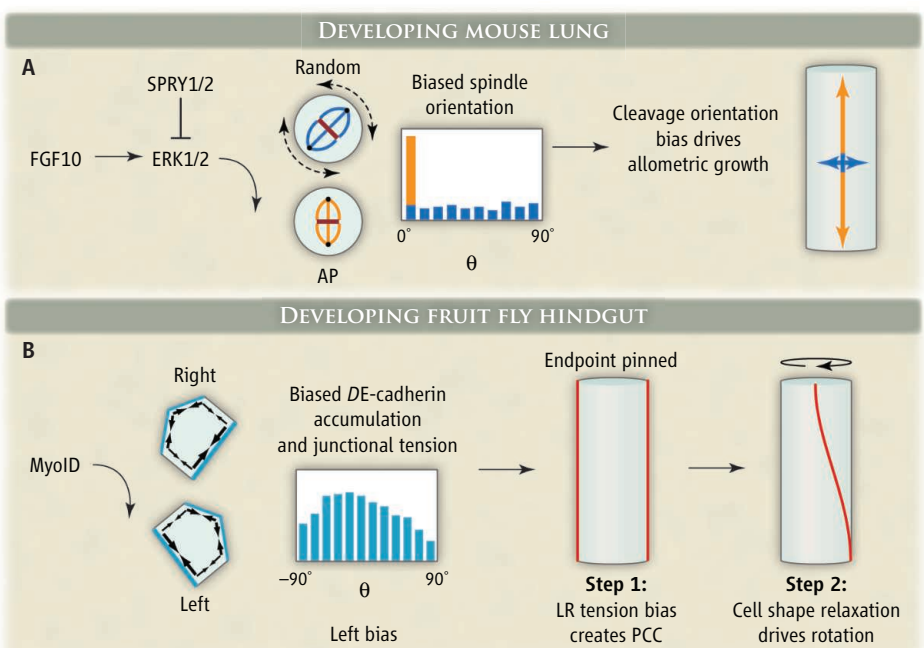
Sally Horne-Badovinac[1] and Edwin Munro[1,2]

Tubes constructed from single-layered sheets of epithelial cells (which line body surfaces and cavities) provide the structural basis for many internal organs (*1*). These tubes assume diverse forms, from the 25-foot-long, highly coiled intestine, to the elaborate branched networks of the lung and kidney. Even the brain and heart arise from simple epithelial tubes. Each tube must attain the precise length and diameter required for its physiological function, and creating tubes that bend, coil, branch, or twist requires additional regulatory mechanisms or modes of cellular force production. A major challenge for developmental biologists studying organ formation in the embryo, and for tissue engineers who aspire to build organs in the lab, is to understand how the molecular-level control of subcellular forces leads to tissue-level control of epithelial tube size and shape. Two papers in this issue, by Tang *et al*. (*2*) on page 342 and by Taniguchi *et al*. (*3*) on page 339, address this challenge. They provide new insight into the cellular processes that make the right tube to fit the job.

Tang *et al*. tackle mechanisms that control airway branch shape during the early stages of mouse lung development. They find that the growth of individual branches is allometric; over time, there is a greater increase in tube length than circumference. Quantitative analysis reveals that ~40% of cell divisions are tightly aligned with the tube's long axis, with other dividing cells randomly oriented with respect to that axis. They further show that hyperactivation of a specific signaling pathway—involving fibroblast growth factor 10 (FGF10), rat sarcoma (RAS) proteins, and extracellular signal–regulated kinases 1 and 2 (Erk1/2)—abolishes the bias toward longitudinal divisions, converting allometric to isometric growth (the ratio between tube length and circumference remains the same over time). Mutations in genes known as sprouty (*Spry*) 1 and 2, which repress Erk signaling (*4*), lead to an analogous effect, suggesting that ERK signaling controls lung branch allometry by "tuning" the proportion of cells that divide with a longitudinal orientation.

The authors then use a simple but elegant mathematical model to show that the measured frequency of longitudinal versus randomly oriented cell divisions is sufficient to predict the measured changes in tube length and circumference. Together, these data show that the fraction of longitudinally oriented cell divisions is the key "dial" that Erk1/2 signaling uses to control lung branch allometry in mice.

Taniguchi *et al*. address a slightly more perplexing question: how to create a tube with a twist. The posterior-most region of



Tube twists and turns. (**A**) In the developing mouse lung, a signaling pathway involving FGF10, SPRY, and ERK appears to control the proportion of dividing cells aligned with an airway tube's axis, leading to allometric growth. (**B**) In the fruit fly hindgut, the protein MyoID appears to influence the arrangement of cell-cell boundaries, creating a bias in the direction of growth and causing a twist to form in the gut tube.

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the fruit fly intestine, the hindgut, starts out as a simple tube along the embryo's midline. Through a process that occurs without cell division, this tube first dips ventrally (toward the fly's "belly"), and then rotates leftward by 90° to create a net rightward bend. Seeking a cellular basis for the rotation, Taniguchi *et al*. make the key observation of a small statistical bias in hindgut cell shapes with respect to the embryo's left-right axis. Cell-cell boundaries that make angles between −90° and 0° with the tube's long axis (left boundaries) appear more frequently than boundaries that make angles between 0° and 90° (right boundaries). The authors call this pattern planar cell-shape chirality (PCC). They identify the cell-cell adhesion molecule *Drosophila* E-cadherin (*D*E-cadherin) as a factor required for both PCC and gut rotation, showing that it is preferentially enriched on left boundaries. Mutations in a motor protein involved in intracellular movement, known as unconventional myosin ID (*MyoID*), reverse the polarity of *D*E-cadherin accumulation and PCC. This is consistent with *MyoID*'s previously identified role in setting the direction of gut rotation (*5*, *6*).

Because mutations in *D*E-cadherin cause all cell boundaries to expand, Taniguchi *et al*. suggest that *D*E-cadherin limits boundary expansion by increasing boundary tension. They propose that left-biased tension is sufficient to produce a leftward tissue rotation. Indeed, computer simulations identify one possible mechanism by which this might work. First, left-biased tension drives cell shape change and rearrangement while the endpoints of the tube remain fixed. Then, rotation occurs in the absence of asymmetric tension, and the tube twists as the cells relax back toward more regular shapes.

Together, Tang *et al*. and Taniguchi *et al*. highlight how statistical differences in cell behavior across a large population can lead to stereotyped, tissue-level morphogenesis. They also highlight several key ways in which mathematical models provide an essential predictive bridge between cell- and tissue-level dynamics. In the mouse lung, it is intuitively clear that biases in cell division orientations could cause differential increases in tube length versus circumference, and previous work had shown that oriented cell divisions can contribute to tube shape (*7*–*10*). A model, however, was essential to show quantitative sufficiency. In the case of the fruit fly hindgut, it is far from obvious how biasing tension on left boundaries will produce a leftward twist. Here, mathematical models step in when intuition fails, and provide plausible testable hypotheses.

For both systems, the mathematical models provide a framework for exploring the molecular mechanisms that control local cell polarity and coordinate its tissue-wide effects. One obvious candidate in both cases is the signaling pathway known as the planar cell polarity (PCP) pathway, which controls cell division orientations and cellular polarities in many other contexts (*11*, *12*). In the experiments conducted by Tang *et al*. and Taniguchi *et al*., however, disrupting PCP function had no effect on these developmental processes, suggesting that other mechanisms are at work.

In the mouse lung, a key question is: How does ERK signaling shape the distribution of cell division angles? The nature of the wild-type distribution suggests that cells partition between two qualitatively distinct orientation states: strictly longitudinal or random. Tang *et al*. hypothesize that the longitudinal state is the default, that ERK signaling overrides this default to randomize division axes, and that *Spry1/2* tune ERK signaling to achieve a balance between longitudinal and random divisions. But how does a graded change in ERK levels control the fraction of cells that inhabit these two states? Does ERK signaling merely gate the response to a longitudinal cue, or does it directly control a transition between distinct phenotypic states?

Likewise, the Taniguchi *et al*. study provides a starting point for thinking about how local left-right asymmetries in force generation could drive chiral rotation, but how do these asymmetries arise? The observation that *MyoID* mutants exhibit reversed PCC and gut rotation implies an intrinsic mechanism for breaking chiral symmetry that can be biased in either direction. The genetic requirements for *D*E-cadherin and MyoID suggest that symmetry breaking occurs shortly before hindgut rotation and requires local interaction across cell-cell boundaries. By contrast, in vertebrates, establishment of left-right asymmetry occurs far in space and time from the organs undergoing chiral morphogenesis, which suggests that it may be easier to identify the mechanisms involved.

These studies signal a growing trend in which classical molecular and genetic approaches merge with quantitative microscopy, image analysis, and modeling to provide new insights into the cellular dynamics of tissue morphogenesis. It is likely, however, that we are seeing just the tip of an iceberg.

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PSYCHOLOGY

Sentence and Word Complexity

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Do humans learn the sentence and sound patterns of natural languages through distinct learning mechanisms?

Our understanding of human learning is increasingly informed by findings from multiple fields—psychology, neuroscience, computer science, linguistics, and education. A convergence of insights is forging a "new science of learning" within cognitive science, which promises to play a key role in developing intelligent machines (*1*, *2*). A long-standing fundamental issue in theories of human learning is whether there are specialized learning mechanisms for certain tasks or spheres of activity (domains). For example, is learning how to open a door (turning the handle before pulling) the same kind of "learning" as putting up and taking down scaffolding (where disassembly must be done in the reverse order of assembly)? Surprisingly, this issue plays out within the domain of human language.

Language perception is organized at different levels, each with its own internal organizing principles: the organization of sounds into words (phonology), the organization of roots and affixes into words (morphology), and the organization of words into phrases into sentences (syntax). Are there any differences among the patterns observed at each level? And if there are, are specialized or

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