Cilia take charge in L–R asymmetry

Left-right asymmetry is determined by the distinct activities of two populations of cilia in the node of the mouse embryo, according to results from James McGrath, Martina Brueckner (Yale University, New Haven, CT), and colleagues. Previous experiments suggested that ciliary movement at the node generates movement of the extracellular fluid surrounding the node, called nodal flow. Nodal flow is critical for establishing L–R asymmetry and requires the motor protein left–right dynein (lrd). But just what kind of signal could be at work in such a situation was unclear. To find out, Brueckner and her team engineered a mouse expressing GFP-tagged lrd under the control of the wild-type lrd promoter. GFP-lrd is expressed in the central cilia in the node, but is absent from a second population of cilia surrounding those expressing lrd. With the use of videomicroscopy, the team finds that the lrd-expressing cilia are motile, whereas many of the cilia in the surrounding population are nonmotile.

Both populations, however, express polycystin-2, a cation channel that acts as a mechanosensor in the kidney, where fluid currents trigger an influx of calcium. When the Yale team looked at calcium signaling in the node, they found that only those cilia to the left of the motile population induce a rise in intracellular calcium. This asymmetric distribution is disrupted in lrd and polycystin-2 mutants, suggesting that nodal flow produced by the central motile cilia induce calcium influx only in cells in the direction of flow.

“The whole nodal flow hypothesis has been somewhat of a difficult sell, because a major developmental process—formation of one of the three primary body axes—is happening in the extraembryonic space,” says Brueckner. “But our model suggests that L–R development is entirely dependent on the physical force created by nodal flow, and its inherent simplicity makes it really satisfying.” The next step is to determine how asymmetrically expressed genes like nodal are regulated by calcium signaling.

Reference: McGrath, J., et al. 2003. Cell. 114:61–73.

Network architecture determines stability

The genomics revolution and modern molecular techniques continue to provide detailed information about many signaling pathways, but a new mathematical model developed by Maximino Aldana and Philippe Cluzel (University of Chicago, Chicago, IL) provides a unique look at the overall architecture of these pathways.

The model is satisfying, says Aldana, because, although it is relatively simple, it accurately reflects a cell’s ability to both remain stable in fluctuating environments and to respond and differentiate when the environment changes sufficiently. “It tells you that very simple dynamics can give you what we observe in living organisms, though most people think they are very complex,” says Aldana.

The standard model for signaling networks in cells was published over 30 years ago (Kauffman 1969), but that model fails to predict the overall stability that is characteristic of many living systems. In that model, genes have only two states: on and off. Although Aldana and Cluzel maintained this trait in their model, they modified how the genes are connected to one another. In Kauffman’s model, all of the nodes are connected to one another in a homogeneous random manner. In the new version, the researchers used scale-free topology, in which most nodes have relatively few connections and only a few nodes are highly connected.

The best part of this new layout, says Aldana, is not only that the model predicts the dynamic stability required of biological systems, but also that the scale-free topology is consistent with the genetic and molecular data pouring in, which indicates that a few genes in any given pathway have a greater-than-average amount of control over the system.

References: Aldana, M., and P. Cluzel. 2003. Proc. Natl. Acad. Sci. USA. 10.1073/pnas.1536783100.
Kauffman, S.A. 1969. J. Theor. Biol. 22:437–467.