Rewiring the cell

Micrographs came before movies, and for systems biologists the transition to a dynamic picture seems even more daunting: assembling a global picture of transcription connections in one state was plenty of work already. But now, Nicholas Luscombe, Mark Gerstein (Yale University, New Haven, CT), Madan Babu (MRC, Cambridge, UK), and colleagues have pooled data on multiple growth conditions in yeast. They find that transcriptional connections vary wildly between the states, suggesting that the cell faces a major task when switching from one state to another.

Half of the active interactions (transcription factor to regulated gene) are replaced for every change in condition, and only 66 of 2,476 interactions are retained across 4 or more conditions. The logic of organization also changes depending on whether the cell is responding to purely intracellular changes or to a signal from outside the cell. The latter response is characterized by pathways that are simpler (less transcription factors per target gene), more decisive (more targets per factor), and more direct (fewer sequential steps in a pathway and fewer connections between pathways). By contrast, endogenous pathways are more cautious; they feature more of the feed-forward motifs that buffer conditions before proceeding.

One prominent feature of previous static pictures was hubs of activity. Hubs were thought of as constant, but most (78%) are now found to be transient. Plenty of transcription factors do stick around for other tasks—the vast majority participate in more than one process and unique regulation relies on combinations.

“This is really a first view,” says Luscombe. He hopes to extend the approach to protein interactions, post-translational modifications, and other organisms with complex developmental programs. More detailed time courses would also illuminate whether there are unique pathways by which cells move from one state to another, hubs that are critical in propagating changes, and particular bottlenecks or vulnerabilities. JCB

Reference: Luscombe, N.M., et al. 2004. Nature. 431:308–312.

Polarization by migration

The direction of cell migration may determine the direction of planar polarization, say Hernán López-Schier, Jim Hudspeth, and colleagues (Rockefeller University, New York, NY).

Planar polarity controls the polarity across epithelial sheets using components distinct from those that determine apical-basal differences. These planar polarity components have been well-studied but all act to interpret rather than generate the planar polarity signal.

Many previous workers studied planar polarity using bristle morphology in flies, but the Rockefeller group set out to study the neuromasts of the lateral line organ in zebrafish—a system where the planar polarity is vital for the biology. Hair cells in the neuromasts must be precisely aligned so they can use polarized stereociliary bundles to detect the direction of water movement.

López-Schier found that the neuromasts migrated posteriorly in two waves from two primordia. Hair cells derived from the first migrating primordium differentiated soon after being deposited and were fixed in this anterior-posterior orientation even after a much later ventral migration. But the second primordium received a ventral migration signal when it was still immature and was fixed in a perpendicular orientation. This allows the fish to detect water movements in two distinct axes.

Disruption of the posterior migration cue in mutants and with misexpression altered both migration and polar polarization in equivalent directions. López-Schier thinks that some of the molecules deposited at the front of migrating cells may favor later polarization events.

Migration may be a factor in other polarization events such as those occurring during gastrulation. Zebrafish offer a system where the migration can be tracked without the need for dissection. The fish also regenerate neuromasts after ablation, and López-Schier wants to know if proper polarity can also be recovered. If regenerated hair cells, originating from resident or externally supplied stem cells, “are not polarized properly it would be a major problem,” he says. In the vestibular organ, for example, randomly oriented hair cells might not work properly and “the animal would feel seasick constantly.” JCB

Reference: López-Schier, H., et al. 2004. Dev. Cell. 7:401–412.