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.

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.
**Flow to the front**

Cortical actomyosin flow carries polarity proteins to the front of the worm embryo, according to Edwin Munro (Center for Cell Dynamics, Friday Harbor, WA), Jeremy Nance, and James Priess (Fred Hutchinson Cancer Research Center, Seattle, WA). Similar flows may set up polarity in many other systems.

The idea that asymmetrical contraction drives cortical flow and the segregation of cell fate determinants has a long and controversial history. Earlier efforts were dogged by the transience of the flow and different results after the use of different fixation methods.

But when Munro finally had GFP-labeled myosin to work with, “the whole story unfolded in front of me,” he says. Contractile, coupled foci of cortical myosin gave way at the posterior when the sperm centrosomes approached the posterior cortex. The actomyosin network then contracted toward the anterior, taking a host of cytoskeletal proteins and anterior determinants with it.

Absence of these anterior determinants allows the PAR-2 determinant to attach to the posterior cortex, where it was needed to prevent a reverse flow of actomyosin back to the posterior. Both the PAR-2 and centrosome signal may somehow weaken or degrade parts of the actomyosin system, although the specific mechanism is a mystery.

Similar flows were seen at the 8-cell stage when cells set up PAR-based apicobasal polarity. In this case, the cue that weakens the actomyosin cortex may be basolateral contact with surrounding cells. “Any time you get differences in contractility you’ll see flows in the cortex,” says Munro. “The mystery is not why do you have flows but how do you prevent flows.”

Reference: Munro, E., et al. 2004. *Dev. Cell.* 7:413–424.

**Immune synapses make a choice**

The immunological synapse between T cells and the antigen-presenting dendritic cells acts as a locus for T cell activation. Now, Roberto Maldonado, Laurie Glimcher (Harvard School of Public Health, Boston, MA), and colleagues find that this synapse also helps the T cells decide between two different activated, differentiated fates based on the extent of colocalization of receptors at the synapse.

The end products of this decision are the bacteria-fighting Th1 cells and the parasite-fighting Th2 cells. Activation of the interferon-γ receptor (IFNGR) or interleukin 4 receptor (IL-4R) is known to favor Th1 production or Th2 production, respectively.

Now, Glimcher’s group shows that the IFNGR but not IL4R colocalizes with the T cell receptor (TCR) at the immunological synapse. The extent of this colocalization is greatest in mice that tend to generate more Th1 cells. IL-4, which favors production of Th2 cells, inhibits the colocalization.

Turning this colocalization correlation into causation will take more experiments. For example, cross-linking of the IFNGR and TCR might generate Th1 cells even in the Th2-favoring presence of IL-4. For now, the group points out that colocalization of the two receptors at the synapse puts the IFNGR near the source of its ligand and may set up a positive feedback between activation and differentiation pathways.

Reference: Maldonado, R.A., et al. 2004. *Nature.* doi:10.1038/nature02916.

**Endocytosis gets squeezed**

A squeeze from myosin may separate incoming endocytic vesicles from the plasma membrane, according to Gudrun Jonsdottir and Rong Li (Harvard Medical School, Boston, MA).

The myosin in question, Myo5, is a class I myosin from budding yeast. The Boston group found that Myo5 had unusual dynamics: it was stationary around the neck of an invaginating vesicle. Li now hopes to determine whether the motor activity of Myo5 is needed for endocytosis and to investigate Myo5 activity in an in vitro endocytosis system.

Myo5 was not previously put into this sequence, but the new results suggest that Myo5 may drive vesicle pinching off (scission). The driving together of two membranes during scission could occur by directed myosin movement or contraction of an actomyosin mesh around the neck of an invaginating vesicle. Li now hopes to determine whether the motor activity of Myo5 is needed for endocytosis and to investigate Myo5 activity in an in vitro endocytosis system.

Reference: Jonsdottir, G.A., and R. Li. 2004. *Curr. Biol.* 14:1604–1609.