Cells’ precise pattern readout

Running from head to tail in a fly embryo, the Bicoid (Bcd) gradient is the blueprint for anterior-posterior development. How cells read the blueprint to give a precise pattern was thought to require multiple mechanisms to smooth out sloppy Bcd input signals. Now, two papers from Thomas Gregor and colleagues (Princeton University, Princeton, NJ) put numbers on the cells’ Bcd readout abilities and show the system to be highly precise—approaching the limits set by the inherent noise in any physical system.

Using live embryos to image the dynamics of the Bcd gradient, the team determined that the gradient was established within ~1 hour after fertilization and that Bcd diffused through the cytoplasm of the syncytial embryo with a diffusion constant of 0.3 μm² per second. But if one assumes that simple diffusion establishes the gradient, Bcd would never reach steady-state within the developmental timeframe. More work is needed to find other mechanisms that are at play.

This first look at a transcription factor’s behavior in a live organism also revealed tightly regulated levels of nuclear Bcd between mitotic cycles. During four syncytial cycles, when nuclei multiply rapidly and get smaller, the Bcd concentration in a given nucleus returned at each interphase to within 10% of its starting concentration, holding the blueprint coordinates steady.

At the midpoint of the embryo—where Bcd levels are at the head-tail borderline—nuclei held ~700 molecules of Bcd.

A bouquet for meiotic spindle

During early meiosis, telomeres gather at the nuclear membrane, forming a structure of mysterious function dubbed the telomere bouquet. Kazunori Tomita and Julia Cooper (Cancer Research UK, London, UK) now report that the bouquet helps form the meiotic spindle and is therefore critical to chromosomal division.

Cooper previously showed that a telomere-binding protein called Taz1 is required for forming bouquets in fission yeast. The taz1 mutants are moderately defective in homologous recombination, which is thought to be the bouquet’s main purpose. But their dominant fault lies in spore formation after meiosis—mutants often have too few spores containing uneven amounts of DNA.

To question why bouquet mutants disrupt meiosis, the team has now followed the dynamics of bouquet formation in live cells. In meiotic prophase of wild-type cells, the bouquet associated with the spindle pole body (SPB)—the yeast microtubule-organizing center. The SPB then dissociated from the telomeres, divided, and set up the bipolar spindle for the meiosis I division. It then divided again and set up the meiosis II spindle.

Deleting taz1 disrupted this prophase telomere–SPB association. As the bouquet mutants progressed through meiosis I, the SPB became disorganized, failed to divide properly, and sometimes even appeared outside the nucleus altogether. The problems resulted in weak, monopolar, or tripolar spindles during one or both meiotic divisions.

Closer inspection of the wild-type telomere–SPB dissociation event revealed “telomere fireworks,” in which the telomere ends simultaneously dissociated from the SPB. Since these fireworks directly preceded the first SPB division and failed in bouquet mutants, Cooper speculates that the event somehow “marks” the SPB for proper division and spindle organization for the rest of meiosis.

A version of Taz1 that cannot bind telomeres did not rescue the SPB or spindle defects, hinting that a connection to chromosome ends is needed, perhaps because a mechanical force must be generated or because bouquet proteins only function in the context of a telomere complex.

Cooper will next investigate the effects of bouquet association and dissociation on the SPB. Because they are highly conserved, bouquets may be critical for mammalian gametogenesis, too. JCB

References: Gregor, T., et al. 2007. Cell. 130:141–152.
Gregor, T., et al. 2007. Cell. 130:153–164.

A burst of dissociation (left to right) of telomeres (green) from the SPB (red) may set up meiotic spindles.
Collective guidance wisdom

Traditionally, cell migration studies focus on the responses of a single cell to guidance signals, but migrations during development and metastasis involve traveling clumps of cells. Pernille Rørth and colleagues (EMBL, Heidelberg, Germany) now show that a collective consciousness can direct the migration of cell clusters.

The team tracked two distinct migration phases—a quick start and a later, slower phase—by the border cell cluster in developing fly egg chambers. They found that the phases required different growth factor–induced signaling pathways; only the latter was controlled by MAPK and PLCγ.

While early signals were restricted to the front of the cluster’s leader, the later MAPK signal was uniform throughout leading cells. How this signal could direct movement puzzled the group until they considered that the cluster might be guided as a unit. Movies revealed that, in the late phase, the cluster slowed to a tumbling, shuffling motion in which the leading cell or two—ones with the most MAPK signaling—often changed identity.

The shuffling means that cells are constantly in competition for who is “seeing” growth factor best at any given moment by being closest to the ligand source and sensing it best. This group mentality, which can assess a larger environment than individual cells, may boost migration precision.

Reference: Bianco, A., et al. 2007. Nature. 448:362–365.

Fluid for a single lumen

All biological tubes consist of a single lumen. According to Michel Bagnat, Didier Stainier, and colleagues (University of California, San Francisco, CA), one way to ensure this singularity is to use fluid pressure.

Too many lumens are found in the gut of Zebrafish larvae lacking the Tcf2 transcription factor. Extra tubes remain because they fail to coalesce normally during development. Bagnat and colleagues guessed that coalescence might be controlled by genes under Tcf2’s control.

DNA microarrays revealed that the gene for an epithelial junction protein, called claudin 15, was down-regulated in tcf2 mutants. Claudins form pores between cells that allow ions to be transported across epithelia down an electrochemical gradient. Tcf2 mutant gut cells also lacked a Na+/K+ ATPase, which probably creates the gradient that drives ions through the pores.

Where ions flow, water is sure to follow, resulting in lumenal fluid build-up. In vitro, Claudin 15 plus ion flow encouraged small neighboring lumens to unite. The authors hypothesize that pressure from the fluid forces lumens to join together, but cell rearrangements must also occur.

Fluid accumulation probably promotes single lumen formation in structures such as the pancreas, which begins with multiple small lumens, and the neural tube, where fluid accumulation is tightly regulated.

Reference: Bagnat, M., et al. 2007. Nat. Cell Biol. doi:10.1038/ncb1621.

SINEs create boundaries

Transcription requires chromatin to be in the unwound, open-access state. Boundary elements create a roadblock to remodeling machinery to prevent euchromatin from improperly converting back to tightly wound heterochromatin, and vice versa. Now, Victoria Lunyak, Geoff Rosenfeld (University of California, San Diego, CA), and colleagues reveal that boundary elements can be created by the transcription of non-coding repeat sequences derived from retrotransposons.

Lunyak et al. were dissecting the unwinding and regulation of the mouse growth hormone gene (GH). They mapped histone modifications that mark the transition to unwound chromatin to a region far upstream of the gene’s enhancer—a spot containing a short interspersed nuclear element (SINE) B2 repeat. SINE B2 repeats are best known as retrotransposon-derived pseudogenes of the tRNA gene that are uniquely transcribed on opposite strands by RNA polymerases II and III.

Enhancer-blocking assays confirmed the sequence’s role as a boundary element. Deleting the short sequence, which is about the length of one nucleosome, left GH in a permanently heterochromatic state.

Most known vertebrate boundary elements recruit proteins that form the chromatin roadblock. It is unknown what triggers the bidirectional transcription of SINE B2, but boundary activity only occurred when both transcription machineries were in play. The authors also found that the boundaries were created by the double transcription, not the transcripts. Lunyak suggests that this boundary strategy might be sprinkled throughout the mouse and human genomes where SINE-type repeats exist.

Reference: Lunyak, V.V., et al. 2007. Science. 317:248–251.

Zebrafish lacking Tcf2 develop multiple lumens (arrows) in the gut.