

Embryo morphogenesis: getting down to cells and molecules

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After the molecular cloning revolution in the 1980s, the field of developmental biology became focused on the regulation of gene expression as a framework for understanding the specification of cell fate. The advent of sequenced genomes and comprehensive microarrays has removed the last obstacle to cataloguing the molecules that orchestrate development, and one challenge for the future will be to put them in their cellular and embryological context. The title of the workshop that took place at the Juan March Institute (Madrid, Spain) in May this year, “The dynamics of morphogenesis: regulation of cell and tissue movements in development”, which was organized by Claudio Stern (UCL, London, UK) and Angela Nieto (Instituto Cajal, Madrid, Spain), exemplifies this change in emphasis. Many of the talks reflected the increasing communication of ideas and techniques between cell and developmental biologists, and the advances in live imaging techniques that have allowed the field to refocus on the cell as the unit of morphogenesis. While developmental biologists clearly have a lot to gain from taking a more cell biological approach, some of the astonishing cell behaviors observed in developing organisms should provide cell biologists with more interesting problems than those presented in a culture dish.

New approaches to studying morphogenesis

Understanding the cellular bases of morphogenetic processes is a prerequisite for the dissection of their underlying molecular genetic mechanisms. Tissue culture studies over the past ten years have established important principles for how single cells move. With these principles in hand, new *in vivo* imaging and fluorescent labeling techniques are now allowing similar questions to be addressed in the tissues of intact organisms. Paul Martin and colleagues (UCL, London, UK) have used time-lapse imaging of embryos expressing GFP-actin to investigate the relative contributions of actin cables, lamellipodia and filopodia to the movement of cell sheets during dorsal closure and wound healing (Jacinto et al., 2002).

An elegant combination of fluorescent transgenesis and lineage tracing has allowed Steve Wilson and collaborators (UCL, London, UK) to trace the development of left-right asymmetry in the zebrafish brain. Within the pineal complex, this asymmetry is reflected in the left placement of the parapineal organ (Concha and Wilson, 2001). As Steve Wilson discussed, the photoactivation of caged fluorescein in transgenic embryos that express GFP in the epithalamus revealed that the unilateral parapineal organ has a bilateral origin from the anterodorso epithalamus, and that some of its precursors migrate across the midline (Fig. 1A-D) (Concha et al., 2003). Scott Fraser (Caltech, Pasadena, CA, USA) demonstrated how

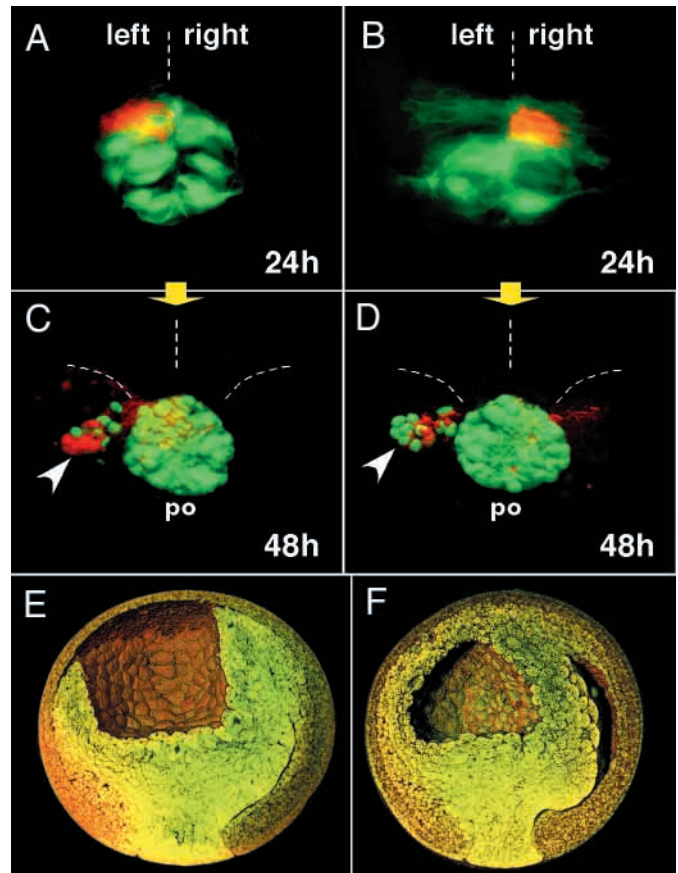


Fig. 1. New imaging techniques provide new insights into morphogenetic processes. (A-D) Fate mapping the origin of the parapineal organ in zebrafish. (A,B) Zebrafish embryos in which caged-fluorescein (pseudo-coloured in red) in the left (A) and right (B) dorsal epithalamus was photo-activated by laser. Images in (C,D) show the presence of the label in both pineal (po) and parapineal organs [images courtesy of Miguel Concha and Steve Wilson, modified, with permission, from Concha et al. (Concha et al., 2003)]. (E,F) Surface imaging microscopy (SIM) in a middle- (E) and late-gastrula (F) frog embryo from a mid-sagittal perspective (images courtesy of Andrew Ewald, John Wallingford and Scott Fraser).

a surface imaging microscopy (SIM) reveals cellular details in the optically opaque *Xenopus* embryo (Fig. 1E,F). In this method, fixed embryos are embedded in plastic and then sectioned. Subsequent optical sectioning of the tissue sections is then used to reconstruct embryonic architecture in 3D (Ewald et al., 2002).

Increasing repertoire of morphogenetic movements

Improved imaging methods continue to uncover novel types of morphogenetic movements, as well as the cellular bases of formerly described morphogenetic processes. Magdalena Zernicka-Goetz (Wellcome Trust/Cancer Research UK Institute, Cambridge, UK) and Jerome Collignon (Monod Institute, Paris, France) presented data that indicate that the early mouse embryo undergoes a global shape change. At 5 days of development, the mouse embryo forms a flattened cup in which its anteroposterior axis, as visualized by the expression of anterior and posterior markers, is aligned with

the short morphological axis of the embryo. Strikingly, at 6.5 days these anterior and posterior markers are aligned with the long morphological axis. Of the three mechanisms that could account for this shift – cell migration, alteration of gene expression or a change in embryo shape – their groups independently obtained evidence for the latter.

Vertebrate gastrulation sculpts the body plan through conserved morphogenetic movements. Germ layers are formed by emboly, whereby mesodermal and endodermal precursors move underneath the prospective ectoderm. Convergence and extension movements narrow the germ layers mediolaterally and elongate them anteroposteriorly. The cell behaviors driving these different movements are best understood in the frog *Xenopus laevis*, but less is known about other vertebrate models. Whether the process of emboly in zebrafish entails involution (the infolding of a tissue layer, as in *Xenopus*) or ingression of individual cells has been a matter of some debate (Kane and Adams, 2002). New studies presented by Miguel Concha

(Universidad de Chile, Santiago, Chile) and his collaborator Richard Adams (University of Cambridge, Cambridge, UK) show that in the zebrafish, mesodermal precursors accumulate into a sheet at the blastoderm margin. Subsequently, the marginal blastomeres change shape and move into a deeper layer as individuals, thus employing an ingression-like movement reminiscent of mesoderm formation in amniote embryos.

Recent studies demonstrate that a similar morphogenetic endpoint can be reached by a variety of cell behaviors (Fig. 2). In the frog, mediolaterally elongated mesodermal cells intercalate between their medial and lateral neighbors to drive the simultaneous convergence and extension of tissue. Studies in Lila Solnica-Krezel's group (Vanderbilt University, Nashville, TN, USA) demonstrated that in the early zebrafish gastrulae, lateral mesoderm cells migrate towards the animal pole without converging dorsally, contributing only to mesoderm extension. Only at later stages do their trajectories turn dorsally, marking the onset of convergence. These slightly

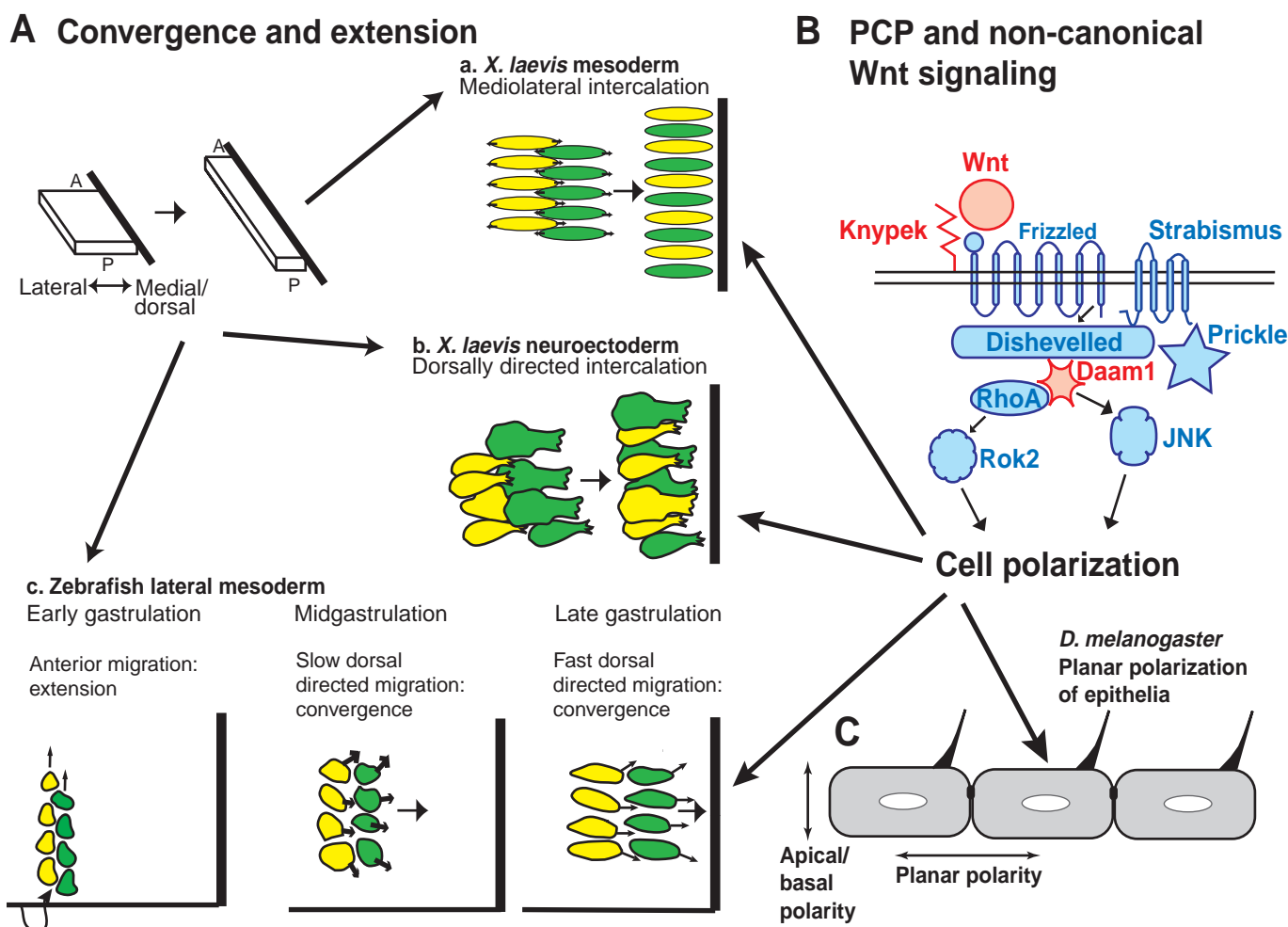


Fig. 2. Evolutionarily conserved planar cell polarity (PCP) signaling pathway controls diverse cellular behaviors during invertebrate and vertebrate development. (A) Convergence and extension can be achieved during gastrulation via distinct cellular activities: (a) in *X. laevis* mesoderm by mediolateral intercalation; (b) in *X. laevis* neuroectoderm by dorsally directed intercalation; and (c) in zebrafish lateral mesoderm by combined anterior and dorsally directed migration. (B) The *D. melanogaster* PCP pathway (shown in blue) mediates cell polarity in the plane of epithelia (epithelial cells also exhibit apical-basal polarization, shown in C). The vertebrate equivalent of this pathway, the non-canonical Wnt signaling pathway (shown in red), is required for the mediolateral elongation of mesenchymal mesodermal and epithelial neuroectodermal cells, which exhibit such diverse behaviors as directed migration, and mediolateral and dorsal intercalation (as shown in A). Modified, with permission, from Myers et al. (Myers et al., 2002).

elongated cells first migrate dorsally along complex trajectories at low net speed. Subsequently, they become elongated mediolaterally, and migrate dorsally along straight trajectories, achieving a high net speed of dorsal convergence. Ray Keller (University of Virginia, Charlottesville, VA, USA) presented evidence that, in frog neuroectoderm, cells develop a dorsally directed protrusive activity and engage in dorsally biased intercalation (Keller, 2002). Taken together, these studies uncover a much more complex repertoire of cell behaviors than was previously imagined to drive gastrulation movements. They predict a corresponding complexity in the molecular genetic mechanisms that regulate these movements.

Guiding cell movements

To achieve the proper architecture of organs and tissues, morphogenetic movements have to be precisely guided. Guidance mechanisms comprise both positive and negative cues, which can take the form of secreted or membrane tethered molecules, or extracellular matrix components. The primordial germ cells (PGCs) of most invertebrate and vertebrate embryos undergo an elaborate voyage from their site of specification, through many embryonic tissues, to the somatic gonad rudiment, where they eventually differentiate into gametes (Starz-Gaiano and Lehmann, 2001). In *Drosophila*, PGCs must penetrate the posterior midgut epithelium, migrate along the midgut, then leave the midgut and move to the mesoderm. Genetic screens in Ruth Lehmann's lab (Skirball Institute, New York, NY, USA) have recently identified a novel G-protein coupled receptor (GPCR), Theseus, the function of which is required in germ cells for them to move through the posterior midgut. Intriguingly, a GPCR, CXCR4, and its cognate SDF1 ligand have been recently implicated in guiding PGC migration in zebrafish (Doitsidou et al., 2002; Knaut et al., 2003), and also in mice (Molyneaux et al., 2003; Ara et al., 2003).

There is a growing appreciation that, within the developing brain, tangential migration of neurons is as common as the more recognized radial migration along the apical-basal axis of the neural tube. The movement of interneurons from the basal telencephalon to the dorsal embryonic cortex is a prominent example of tangential neuronal migration within the forebrain. Oscar Marín (Miguel Hernández University, San Juan, Spain) discussed his embryological analyses that indicate that a repulsive cue in the basal telencephalon and an attractive cue emanating from the cortex guide this movement. Given that Neuregulin ligands are expressed at the appropriate time in the cortex, and that the migrating neurons express the cognate receptor ErbB4, they are excellent candidates for the attractive guidance signal from the cortex.

One of the more spectacular mass migrations during early vertebrate development is that undertaken by hypaxial skeletal muscle precursors, which first delaminate from the paraxial epithelial somites, and then migrate towards the forming limb buds. Carmen Birchmeier (Max Delbrück Center, Berlin, Germany) discussed two systems that act downstream of the Pax3 transcription factor to regulate different steps in the migratory process (Birchmeier and Brohmann, 2000). Met receptor tyrosine kinase (Met RTK), a proto-oncogene, is expressed in the ventral myotome and its activity is required for this delamination. Its ligand, scatter factor/hepatocyte growth factor (SF/HGF) is expressed in the migration target, limb bud mesenchyme. Furthermore, Gab1, a mediator of c-

Met RTK signal transduction, is also essential for this process. By contrast, in mouse embryos harboring an inactive transcription factor, Lbx1, muscle precursor cells delaminate but fail to migrate laterally.

Cell biologists have long studied the mechanisms that give rise to polarized membrane protein distribution in tissue culture cells. Neurons and epithelial cells appear to share some of the sorting mechanisms involved in such membrane polarization, and proteins that move to the apical domain of epithelial cells are often also found enriched in axons. In many cases, endocytosis plays a crucial role in polarizing the apical-basal distribution of membrane proteins. Work from Guy Tear's lab (King's College, London, UK) has uncovered a remarkable role for endocytosis in polarizing a guidance molecule in the axonal membrane. Axons of *Drosophila* neurons that cross the midline to form commissures must alter their sensitivity to cues emitted by midline cells. In order to cross the midline, these axons must ignore inhibitory signals mediated by Slit. However, subsequent re-sensitization to Slit is needed to prevent these axons from re-crossing the midline (Georgiou and Tear, 2002). Guy Tear and his colleagues have found that the Slit receptor Robo is downregulated from the axonal membrane in the commissural region, and then reappears in those regions of axons that have crossed the midline. Robo downregulation depends on an endocytic mechanism involving the combined action of Commissureless and Nedd4; in the absence of these molecules, Robo remains on the plasma membrane and Slit prevents axons from crossing the midline. Endocytic remodeling of the axonal membrane affords rapid and localized changes in membrane composition that are crucial for axon guidance.

Controlling physical cell properties that drive morphogenesis

Understanding the cues that specify the direction of cell movements within embryos is only a small piece of the morphogenesis puzzle. Cells moving in the context of a whole embryo must solve the same problems as migrating cultured cells, and more. Single cell movement in the embryo is likely to involve a motility cycle, whereby a cell makes an actin cytoskeleton-based protrusion at a leading edge that makes an adhesive contact site with the substratum or a neighboring cell. The subsequent actomyosin-based contraction would develop a tension between adhesion sites in the cell, leading to: a translocation of a cell body; cell shape change and/or rearrangement; or extracellular matrix remodeling. However, the repertoire of different types of protrusions made by embryonic cells, their molecular control and their significance to morphogenesis is only poorly understood.

Before the movement is initiated, some cell types have to break away, as individuals, from a multicellular epithelium, in which cells are interconnected by tight junctions. The regulation of adherens junction formation and Cadherin-mediated adhesion has been extensively studied in epithelial tissue culture, where it has been shown that the downregulation of Cadherin complexes at the cell surface can be rapidly mediated by endocytosis. Cell biologists have speculated that the endocytic downregulation of Cadherin might be important for adhesive remodeling, although this is somewhat difficult to investigate outside of an organism. David McClay (Duke University, Durham, NC, USA) presented a striking example of adhesive remodeling during sea urchin gastrulation. At this time, primary mesenchymal cells undergo

an epithelial to mesenchymal transition (EMT) and enter the blastocoel. To do so, they must break contacts with neighboring epithelial cells and alter their affinity for different extracellular matrix molecules. These events appear to be regulated by endocytic and exocytic events more rapidly than would be possible by transcriptional modulation. At ingression, E-Cadherin is internalized and new integrin molecules are exocytosed, suggesting that dramatic membrane turnover accompanies epithelial mesenchymal transition.

Another spectacular example of EMT is observed when neural crest cells that are specified at the boundary of neural tissue within the ectodermal sheet, migrate away to multiple destinations in developing vertebrate embryos. The transcription factors Snail and Slug have a well-established role in mediating the EMT of neural crest, by regulating directly and indirectly several modulators of cell movement, including E-cadherin, fibronectin and Rho GTPases. As discussed by Angela Nieto (Instituto Cajal, Madrid, Spain), Snail might also regulate other properties of migrating cells, such as proliferation and survival. Snail-expressing cells are resistant to cell death as induced by serum withdrawal and TNF α .

Bringing together genetic and cell biological approaches, Denise Montell's lab (Johns Hopkins University, Baltimore, MD, USA) has found a novel role for the JAK/STAT pathway in promoting migratory behaviour. *Drosophila* border cells are a small group of somatic cells that form at the anterior end of the egg chamber (Montell, 2003). Upon their specification, in part by JAK/STAT and Unpaired ligand, the border cells leave the epithelium, invade the chamber, and move on and between nurse cells towards the posteriorly localized oocyte. The control of cell behaviour via the JAK/STAT pathway has been assumed to occur mainly through transcriptional changes; when phosphorylated, STAT translocates to the nucleus and modulates transcription of a variety of target genes. Denise Montell presented intriguing data that the function of Unpaired is also required for sustained migration in this system, independent of cell fate specification. This suggests that JAK/STAT signaling might impact cell movement in a more direct manner than that previously anticipated. Montell's studies with human cancer cell lines support this notion; interfering with STAT3 function, using double-stranded RNA oligonucleotides, blocked the migration of these cells in vitro. Moreover, the phosphorylated (active) form of STAT3 accumulates in focal adhesions where it is thought to interact with known modulators of cell adhesion, such as focal adhesion kinase and paxilin. This raises the possibility that the JAK/STAT pathway modulates cell migration by acting directly on the cytoskeleton and on focal adhesions, in addition to influencing transcription.

Polarization of cell shape, orientation and protrusive activity is a hallmark of cells moving in embryos. Studies from Lila Solnica-Krezel's and Heidi Hamm's laboratories (Vanderbilt University, Nashville, TN, USA) show that heterotrimeric G proteins, G α 12 and G α 13, are required at early zebrafish gastrulation for a moderate elongation of cells undergoing directed dorsal convergence at low net speed. In both *Xenopus* and zebrafish, mediolaterally elongated cells engage during convergence and extension in intercalation and fast migration, in each organism, respectively. In recent years, a non-canonical Wnt signaling pathway that is equivalent to the *Drosophila* planar cell polarity pathway has been shown to mediate this

mediolateral cell polarization (Myers et al., 2002). In this pathway, signaling from activated Frizzled serpentine receptors is transmitted via Dishevelled to small GTPases and their downstream effectors, to modulate cytoskeleton and cell polarization. Masa Tada (UCL, London, UK) implicated the Prickle protein as being a modulator of this pathway that is shared between vertebrates and *Drosophila*; this is consistent with recent reports (Takeuchi et al., 2003; Veeman et al., 2003).

While it is clear that endocytosis contributes to the polarization of proteins along the apical-basal axis of epithelial cells, the Eaton lab (MPI, Dresden, Germany) has found that it may also contribute to planar polarization and tissue organization. In *Drosophila*, coordinating the polarity of hairs, bristles and ommatidia relies on the activity of the tissue polarity genes (Fig. 2B,C). Many of these genes encode apical junctional proteins that undergo a polarized rearrangement to form separate proximal and distal cortical subcellular domains. The polarity of these domains has different readouts in different tissues, serving to orient the polarity of ommatidial rotation, and of hair or bristle outgrowth. The Eaton lab has shown that some of the components of these domains localize not only to the cortex, but also to endosomes, and that perturbing endocytosis prevents their polarization along the planar axis. This raises the possibility that cortical polarity is generated by an endocytic mechanism.

Hyaluronan, an extracellular high molecular weight glycosaminoglycan, has been proposed to stimulate migration of cultured cells, tumor invasiveness and cancer metastasis. Mouse embryos mutant for Hyaluronan synthase 2 (Has2) die in utero; however, the role of Hyaluronan in early morphogenesis has remained unclear. Jeroen Bakkers (MPI, Freiburg, Germany) demonstrated that impairing Has2 function in zebrafish embryo interferes with the ability of cells to form lamellipodial protrusions and to undergo dorsal convergence movements. Both protrusion and gastrulation defects can be partially suppressed by the ectopic expression of the small GTPase Rac, suggesting that, in zebrafish embryos and cell culture, Rac is a key effector of Hyaluronan.

Controlling morphogenetic movements of cell populations

A striking feature of morphogenetic processes in developing embryos is that they are produced by the concerted actions of many cells. How specific morphogenetic cell behaviors, such as shape changes or rearrangements, are coordinated in time and space is an important and challenging question. Scott Fraser (CalTech, Pasadena, CA, USA) raised an interesting possibility that convergence and extension movements are coordinated by calcium waves that sweep through gastrulae (Wallingford et al., 2001). However, it remains to be determined which specific aspect of cell behaviour and signaling pathways are impacted by these calcium waves. Intriguingly, cells intercalating during convergence and extension are imbedded in an extracellular network of fibronectin with which they interact through cell surface integrin receptors. Ray Keller (University of Virginia, Charlottesville, VA, USA) discussed time-lapse studies in *Xenopus* that show that the fibronectin network is carried along by moving cells, rather than providing a fixed substratum for cell movements. Moreover, the disruption of integrin-fibronectin interaction impairs mediolateral cell intercalation

and, consequently, convergence and extension. It is tempting to speculate that this fibronectin-intergrin network is used for cell communication to coordinate the processes of cell polarization and intercalation.

The eversion, migration and fusion of imaginal disc epithelia during *Drosophila* development shares both molecular and morphological features with dorsal closure and wound healing. Using both serial sectioning and live imaging of everting discs, Enrique Martin-Blanco (CSIC, Barcelona, Spain) demonstrated that, before eversion, discs are organized as epithelial sacs, which are connected to the larval epidermis by a stalk. Previous studies had suggested that stalk contraction and the squamous peripodial cells caused the rest of the disc to evert. Martin-Blanco's observations argue that the stalk and peripodial cells partially lose their epithelial integrity, and interdigitate with larval epidermal cells to form a hole through which the disc everts. These cells subsequently form a migratory 'leading edge' and drive the fusion of the different imaginal discs to form the adult epidermis.

Epithelial branching morphogenesis represents a somewhat different topological problem in cell coordination: movement as an epithelial tube rather than as an epithelial sheet. Mark Krasnow's lab (Stanford University, Stanford, CA, USA) has performed screens to identify molecules that control epithelial branching morphogenesis in the tracheal system of *Drosophila*. Previously, his lab had shown that the outgrowth of tracheal branches was guided by the FGF *branchless* (Lubarsky and Krasnow, 2003). Whereas the FGF expression that determines the overall pattern of primary branches is hardwired, the later expression that guides outgrowth of the finer terminal branches occurs in response to low oxygen levels. It turns out that oxygen-starved cells do more than express FGF and wait for a terminal branch to show up. Instead, they send out 'hypoxipodia', long, thin membrane protrusions that appear to capture tracheal branches and actively pull them to where they are needed. As Lewis Wolpert remarked at the end of the meeting, "However clever you think cells are...they're even cleverer".

How do tracheal branches grow towards cells that express FGF? Krasnow's screen has identified a GPI-linked cell adhesion molecule that is expressed in response to FGF signaling and is required for outgrowth. Its name, *tortuous trachea 1*, reflects its overexpression phenotype, which is characterized by the 'tortuosity' of tracheal branches, similar to those observed under extreme hypoxia or in tumor vasculature. How do tracheal cells choose the appropriate source of FGF in the developing embryo? Work from Jordi Casanova's lab (CSIC, Barcelona, Spain) suggests that subsets of tracheal cells express different adhesion molecules that allow them to migrate along different substrates. In particular, those cells that will grow towards the viscera express the integrin PS1, allowing them to travel along their PS2-expressing migratory substrate. The logic of the signaling pathways that determine the pattern of tracheal branching is emerging with some clarity. The fascinating cell biological problems of how epithelial cells organize themselves as tubes, rather than as sheets, and of how tube caliber is controlled, are being addressed by ongoing screens in Krasnow's lab.

Within the past decade, developmental biologists have made remarkable progress in dissecting signaling pathways that specify cell fates during embryogenesis. One surprising conclusion from these studies is that a small number of

evolutionarily conserved signaling pathways is used over and over again to specify embryonic polarity, to induce and pattern germ layers, and to generate thousands of cell types within tissues and organs. The talks presented at this meeting indicate that the more complex and less-well understood problem of morphogenesis is poised for equally rapid progress in the years to come. Intriguingly, again a limited set of signaling pathways might be repeatedly employed to mediate diverse morphogenetic processes by modulating similar sets of cytoskeletal effectors. Hence, a fascinating question at hand is how a limited set of tools can produce such diverse morphogenetic outcomes as gastrulation movements, neurulation, neuronal migration, axon guidance and macrophage migration.

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