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Developmental biology moves forward in the 21st century

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Developmental biology began as experimental embryology: the attempt to derive the rules that control the development from egg to animal or plant by ablation and transplantation. With the revolution in molecular genetics, developmental biology became grounded in genetics and focused on signaling pathways and transcription factors that control cell fate decisions in a few model organisms, with *Drosophila* leading the way.

Now we can begin to sense the directions of 21st century of developmental biology. Classical questions, like the nature of morphogen gradients are being redefined as we learn about the complex mechanisms that control the production and response to morphogen gradients. Cell biology now permeates many aspects of developmental biology, from the production of signaling molecules to the regulation of cell movements. And developmental biology is moving beyond the limitations of a handful of model organisms into the diversity of developmental mechanisms used by other plants and animals.

Morphogen gradients: not just by diffusion

One of the most important concepts in developmental biology has been that of the morphogen, a form generating substance made in one cell type that specifies a series of cell fates at a distance from the source, as a function of distinct concentrations of the morphogen. Three reviews in this issue directly address the distribution and function of morphogens. Constam provides a broad update on the vertebrate morphogen Nodal, discussing recent studies on its role in cell-type specification at gastrulation and left-right patterning, studies of the spread of Nodal through tissues, and the influence of endocytic trafficking on Nodal signaling and movement through tissues. The review by Steinhauer and Treisman provides a thorough overview of lipid modifications of morphogens. Because morphogens are secreted and spread through tissues,

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the original discovery of insoluble lipid modifications on Hedgehog was unexpected, but as the authors explain, lipid modifications have since been identified on several long range signaling molecules. In some cases lipid modification actually appears to be required for long range signaling, apparently because these morphogens move through tissues in association with lipoprotein particles. Steinhauer and Treisman also discuss the progress that has been made on the synthesis of lipid modifications, and the diverse roles they play in modulating the action of different morphogens. The review by Kutejova and Briscoe discusses recent studies that have challenged conventional notions of how tissues respond to morphogens. Rather than a simple read-out of distinct concentrations, cellular responses to morphogens involve more complex temporal responses. These include both dynamic responses to the initial morphogen, and regulatory interactions among downstream targets of morphogen signals. Together, these reviews provide an illustration of the complexity that lies behind the simple concept of a morphogen.

Intracellular trafficking and developmental biology

Traditionally the topic of cell biology, the regulation of intracellular trafficking has become central to a number of central questions in developmental biology. We have already mentioned examples roles of trafficking in controlling the activity of the Nodal ligand (Constam) and the lipid modifications of ligands (Steinhauer and Treisman). Other reviews show the broad importance of intracellular trafficking in signaling and in morphogenesis.

The Notch signaling pathway is frequently employed when cells are choosing between alternative cell fates. This pathway is deceptively simple in that the Notch protein serves as both transmembrane receptor and, after processing, transcriptional co-activator. However, regulation of Notch has turned out to be remarkably complex. Fortini and Bilder discuss the multiple, distinct roles that endocytic trafficking has in regulating the activity of Notch. The diverse requirements for Notch are also reflected in several distinct human genetic diseases associated with mutations in Notch pathway components. Dunwoodie discusses one of these, spondylocostal dysostosis, which can be caused by any one of four different Notch pathway genes. This disease results from defects in the development of the vertebral column, which reflect the requirement for normal Notch signaling during somitogenesis.

Advances in imaging, especially live imaging, have continued to enable developmental biologists to move beyond cell fate specification and to begin to decipher the cellular and molecular details of morphogenetic processes, and to understand the dynamics of cell behavior during morphogenesis. Most developmental biologists have tended to think of cell movements as directed at the single cell level, carried out by motile, mesenchymal cells. However, observations in several model systems have emphasized that cells can move in groups of cells, which can retain characteristics of epithelial cells as they move. This important class of collective cell movements, and the implications of individual versus collective cell migration, are discussed by Gilmour and Revenu. Even the classic movement of the mesodermal cells away from the primitive streak during gastrulation has characteristics of collective migration, as discussed by Weijer and Chuai in a review that describes what live imaging has revealed about cell movements during early chick development.

The review from Wirtz-Peitz and Zallen delves deeper into morphogenetic processes of epithelia, focusing on how remodeling of junctions allows epithelial cells to move relative to one another while maintaining epithelial integrity. Epithelial junctions are surprisingly dynamic, and as Wirtz-Peitz and Zallen discuss, much of this dynamism can be explained by intracellular trafficking of E-cadherin. Finally, Tepass provides a thorough overview of FERM domain containing proteins and their roles in both apical-basal epithelial polarity of epithelia and in the motility of mesenchymal cells.

Beyond the traditional

While the mechanisms that establish patterning along embryonic axes have been the subject of intensive study in a few model systems, a series of reviews tackle new topics in new cell types and new organisms, taking advantage of both new genetic tools and RNAi technology.

In traditional lab organisms, new cell types and new classes of developmental regulators continue to be discovered. Puligilla and Kelley discuss the integration of signaling pathways involved in the remarkable organ responsible for the detection of sound, the ear. Temporal patterning is also crucial during development, and Poethig discusses the importance of miRNAs and other small RNAs in regulating timing during the development of flowering plants. Two reviews focus on novel transcriptional regulators of the PRDM family. These proteins share similar structures with an N-terminal PR domain followed by a variable number of C-terminal Zn finger repeats and are transcriptional repressors that control cell fate choices in vertebrates in ways that are only beginning to be elucidated. First identified for its function in B lymphocytes, Robertson and Bikoff provide an overview of the many tissue-specific roles of Blimp1/Prdm1 in mammalian development. Saitou discusses the critical role of Blimp1 and another family member, Prdm14, in the network of signals and transcriptional regulators that controls the specification of primordial germ cells in the mouse.

The earliest stages of embryonic development are controlled by maternal gene products. This has been well characterized in some invertebrate model organisms, like *Drosophila* and *C. elegans*, but much less is known in vertebrates. Abrams and Mullins discuss the results of maternal effect screens in zebrafish that have identified genes essential for axial patterning, as well as genes required for patterning of the oocyte and control of early cell divisions.

The successful application of RNAi methods has made possible functional analysis of gene function in a wide range of organisms. Unlike in *Drosophila*, posterior fates in most arthropods are established from a posterior growth zone. As discussed by Nunes da Fonseca, Lynch and Roth, comparative analysis of gene expression patterns combined with functional analysis using RNAi, makes it possible to define and compare the strategies for axial patterning and segmentation in different arthropods. Planaria have re-emerged over the last several years as a model system for regeneration, and the review by Forsthoefel and Newmark discusses the regulation and re-establishment of patterning of the body axes in regenerating planaria. Planaria regeneration is initiated by stem cells called neoblasts, which must decipher positional information provided by conserved signaling pathways, including Wnt and Bmp.