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Editorial overview: Developmental mechanisms, patterning and organogenesis

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In this issue of *Current Opinion in Genetics and Development*, we survey the latest insights into organ biology, gleaned from a variety of model organisms including flies, fish, mammals, planaria, plants and worms. Our understanding of the mechanisms regulating organogenesis has flourished due to the increasing availability of gene expression data, the development of markers for many new cell types, and the elaboration of tools for eliminating either specific proteins or specific cell populations. New imaging tools have provided unprecedented temporal and spatial resolution to developmental processes. Biophysicists and engineers, armed with superfast computers and real-time measurements, have brought quantitative approaches to determining the physical properties of cells and tissues, as well as providing insight into the dynamics of signal reception, signal propagation and feedback mechanisms. Here, we highlight a few themes that emerge from studying a vast array of organ systems.

Pattern formation: making, executing, and maintaining cellular decisions

Organ formation originates with early patterning decisions that set up the requisite cell fates, and recent studies have refined our understanding of how these key choices are made and maintained. Lin and Capel discuss how sex determination in mammals, like many developmental events, begins with the simple choice between two alternative cell fates: Sertoli (male) cells or granulosa (female) cells. As with most such decisions, the choice depends on a transcription factor, or two. The male-determining Y-linked Sry transcription factor acts through the related Sox9 transcription factor to initiate the male pathway. Maintaining maleness requires yet another transcription factor — DMRT, which in turn represses expression of FoxL2, the transcription factor required to maintain the female fate. Likewise, studies of cardiopharyngeal lineage decisions in *Ciona*, described by Lionel Christiaen and colleagues, reveal a series of fate decisions based on the differential expression of cross-antagonistic transcription factors. Here, the authors introduce the idea of ‘transcriptional priming’, in which the RNAs for key transcription factors are expressed early and are segregated during asymmetric divisions that produce distinct cell fate outcomes.

The transcription factors that direct initial cell fate decisions are ultimately incorporated into larger molecular networks; early decisions are reinforced and elaborated upon by downstream signaling pathways. The same Sox9 transcription factor required for the choice to form Sertoli cells in the bipotential gonad also plays a key role in digit formation. Sox9 is proposed to control digit patterning by regulating secreted signals with differing reaction–diffusion kinetics that feed back into the regulation of Sox9 expression. Kimberly Cooper discusses how this feedback system fits nicely with the self-organizing model proposed by Turing in the early 1950s and explains the order in which digits first appear in the developing limb autopod.

Integration of antagonistic systems also plays an important part in setting up the exquisite patterning of embryonic blood vessels. As described by Meadows and Cleaver, coordination of both repulsive and attractive guidance cues creates the appropriate contexts to determine where vasculature arises and where and how vessels are remodeled. Importantly, interplay between positive and negative signals also creates specific avascular zones with defined boundaries. A remaining challenge here is to learn how endothelial cells translate perception of opposing cues into the specific cell behaviors that sculpt vascular networks.

Reiterative deployment of key signals in multiple contexts

Plants, planaria and people all seem to use and reuse the same set of signaling pathways while constructing very different organ structures. Indeed, the same signaling pathways are often called into play at multiple stages during the differentiation of even a single organ. Robinson and Roeder describe how three signaling modules make multiple appearances in building five distinct epidermal cell types in plants: trichomes, root hairs, pigment cells, giant cells and bulliform cells. Similar redeployment of a limited set of signaling pathways is used to build and specialize the multiple cell types of the Drosophila ovary, with the same signals inducing proliferation at one developmental stage and terminal differentiation later on. Lilach Gilboa explains the elegant orchestration of Drosophila ovarian development, which requires the formation of at least six mature cell types that are not only present in the correct numbers but are also properly positioned within the tissue and with respect to each other. Kay Schneitz and colleagues discuss recent advances toward understanding similar processes in flower development, in which growth and hormone signals coordinate with patterning genes to yield the huge diversity of floral patterns found in nature.

New roles for mesenchyme in shaping organ morphology

Many aspects of organ development rely upon epithelial morphogenesis: achieving polarity, bending and folding to make evaginations and invaginations, and moving cells within the plane to shape a tissue. Now, a number of recent studies emphasize the interactions between the epithelia and the loosely structured mesenchyme that surrounds them. In the context of salivary gland branching in mammals, Kwon and Larsen highlight the many sources of salivary mesenchyme, including cranial neural crest, Schwann cell precursors to the peripheral nervous system and an endothelial population of unknown origin. These mesenchymal cells provide a variety of signals controlling epithelial behavior, including bud outgrowth, cleft formation, ductal differentiation and lumen formation. Similarly complex

roles for lung mesenchyme have emerged over the past few years, as highlighted by Xin Sun and colleagues. In the developing lung, mesenchymal signals have been implicated in lineage specification, differentiation and maturation, as well as in branching morphogenesis. In addition, mutual antagonism between the mesenchymal precursors that form the cartilage and smooth muscle serve to precisely juxtapose these cell populations to completely encircle the upper respiratory airway.

Kidney development provides a classic example of reciprocal induction between epithelia and mesenchyme: expression of the WT1 transcription factor in the metanephric mesenchyme leads to expression of secreted GDNF, a crucial signal for the outgrowth of the ureteric bud. In turn, the developing ureteric bud provides signals back to the metanephric mesenchyme to induce formation of the renal excretory units. Melissa Little describes how sophisticated whole-organ imaging techniques have brought a new level of resolution to our comprehension of how the interplay between the ureteric bud and its surrounding mesenchyme sets a delicate balance between tissue self-renewal and differentiation. In addition, the establishment of a comprehensive gene expression atlas for the developing kidney has led to a wealth of tools that serve as markers for lineage tracing, for tracking patterns of cell division, and for following the changes in cell shape and arrangement that accompany morphogenesis of this elaborate tubular network.

Mesenchymal cells also play key roles in patterning the developing head, as described by Choe and Crump. Although several key signaling structures in the head form from only ectoderm and endoderm, signals from the surrounding mesenchyme — derived from cranial neural crest and presomitic mesoderm — are essential for establishing epithelial character and movement, as well as controlling cell survival. Indeed, the very localized and distinct patterns of epithelial movement that shape the face are dependent upon signals from the neighboring mesenchyme.

Physical forces, inside and outside of cells, control the mechanics of morphogenesis

The impact of physical forces on organ dimensions is highly evident, and numerous recent approaches promise to unearth the precise biophysical mechanisms driving the dynamics of morphogenesis. Siedlik and Nelson describe how recent advances in imaging, *ex vivo* organ culture and computational strategies have the potential to provide a comprehensive understanding of tissue mechanics. Indeed, quantitative modeling has already shown that minimization of potential energy is a driving force for convergent extension and tissue elongation. Similar modeling approaches are expected to provide insight into how actinomyosin contraction drives apical constriction and lung bifurcation, as well as uncovering the forces fueling collective cell migration and overall changes in 3D organ architecture.

Whereas the roles of actinomyosin contractions in muscle function are very familiar, new investigations also reveal the importance of these forces in building muscles in the first place. The review by Chen and colleagues highlights the roles of factors that mediate actin polymerization, as well as the role of non-muscle myosin, in bringing skeletal muscle

precursor cells in close enough contact for membrane fusion, a process essential for building multinucleated contractile muscle fibers. Work in flies has uncovered mechanisms for muscle cell fusion that are probably shared by all higher organisms, based on related studies in zebrafish and mice. Additional studies have linked actinomyosin cables to a variety of other morphogenetic events, including stabilizing clefts during salivary gland branching (Kwon and Larsen), preventing cell mixing at the margin of the eye field (Stephen Wilson and colleagues), and shaping the worm vulva (Schmid and Hajnal).

In conjunction with intracellular forces, the extracellular matrix (ECM) regulates the mechanical properties of tissues and provides the substrata for cell motility. In the Drosophila germarium, the coordinate migration of follicle cells along the overlying basement membrane causes rotation of the entire tissue, a process linked to the elongation of the developing egg, as discussed by Cetera and Horne-Badovinac. Stephen Wilson and colleagues describe the interactions between the basal lamina of the developing zebrafish eye and its overlying epithelial precursors that establish the apicobasal polarity of the evaginating optic cup. McMillen and Holley discuss important mechanisms through which ECM dynamics drive the elongation of the vertebrate trunk. For example, an ECM composed of collagen, elastin, and laminin forms around the developing notochord and prevents its radial expansion, thus providing the forces for notochord elongation. In addition, interactions between paraxial mesoderm and its Fibronectin-dense matrix contribute to the forces that lengthen the growing trunk.

In addition to the roles of the basal ECM in organ morphogenesis, there is also an apical ECM that provides elastic forces to resist the strain produced by directed apical expansion during elongation of the Drosphila trachea (Dong and Hayashi), showing some reciprocity to the processes that lengthen the vertebrate notochord. An apically secreted ECM is also required to create the hydrostatic pressure that keeps the lumen of the worm vulva open, as described by Schmid and Hajnal. Importantly, the accumulation of fluid and building of hydrostatic pressure has been implicated in shaping the lumen of the zebrafish gut, as described by Navis and Bagnat, as well as inflating the zebrafish otic vesicle, as discussed by Tanya Whitfield.

Applying principles from organ development during organ regeneration

The promise of regenerative medicine to replace injured or aging organs will require a very thorough understanding of all of the factors driving organogenesis, from the transcription factors that make and maintain crucial developmental decisions, to the signaling pathways that underlie patterning, to the forces both within and outside cells that control tissue shapes and sizes. We will also have to overcome the factors that limit regeneration, a problem not encountered by planaria, which possess stem cell populations throughout their remarkably replaceable bodies that are poised and ready to replace anything that goes missing. As discussed by Roberts-Galbraith and Newmark, the regeneration of these missing parts seems to invoke the same set of players as are used during development of other model organisms, from the ‘master regulators’ of eye specification and morphogenesis, to the FoxA transcription factors controlling development of endodermal gut derivatives, to the molecules that mediate excretory cell formation.

Unlike all other solid organs in humans, the liver retains remarkable regenerative potential, with the ability to replace up to two-thirds of itself. Cox and Goessling describe the cellular and molecular events of liver formation in the developing zebrafish as well as growing evidence that the same pathways that function during development come into play during liver regeneration. With the high level of homology between zebrafish and humans, the transparent zebrafish is an excellent model system in which to screen for drugs that could facilitate liver regeneration and block fibrosis, or even protect liver cells from damage in the first place.

As a more comprehensive understanding of organogenesis allows us to move toward the goals of regenerative medicine, we must keep in mind that model organisms really are just models. By highlighting the contrasts between pancreatic islet development in mice and humans, Nair and Hebrok warn us that obtaining information about human development will also be crucial. Although major events in pancreatic development are grossly conserved in these two species, there are multiple differences in the timing of developmental fate decisions, as well as key differences in the arrangement of endocrine cell types and their proximity to the nerves and vasculature. Similar cautions are suggested by the detailed analysis of mammalian kidney development, described by Melissa Little. Fortunately, emerging approaches utilizing iPS-derived organoids should provide numerous exciting opportunities for the study of human organogenesis, allowing future leverage of the many valuable regulatory mechanisms revealed through use of model organisms.

Biographies

Deborah Andrew is a professor of cell biology at the Johns Hopkins University School of Medicine. She received her Ph.D. in 1987 from the University of California, San Diego, where she trained with Bruce Baker. She did her postdoctoral training with Matthew Scott, first at the University of Colorado, Boulder, then at Stanford University. She has been a faculty member at the Johns Hopkins School of Medicine since 1993. Dr. Andrew's laboratory studies the molecules and mechanisms underlying epithelial tube formation using the Drosophila salivary gland and trachea as model systems.

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