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Cellular mechanisms of morphogenesis

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The development and functions of multicellular organisms rely on the local activities of cells and molecules. Advances in microscopy have made it possible to visualize directly dynamic assemblies of cells as they grow, divide, and morph into the recognizable structures that make up a fully formed animal. However, the rules that determine how cells interact, and how these interactions produce the elaborate shapes of different tissues and organs that allow them to carry out their diverse functions in the body, remain to a large degree mysterious.

During development, dynamic movements and interactions between cells cause epithelial sheets to elongate, branch, and fuse to form a variety of structures. Despite constant cell turnover, many of these structures are maintained throughout the lifetime of an animal. The reviews in this issue of *Seminars in Cell and Developmental Biology* highlight how progress in understanding processes of tissue generation, maintenance, and repair has been accelerated by mobilizing interdisciplinary tools to address this problem—tools that include the identification of key molecules, quantitative live imaging, biophysics, and *in silico* modeling.

A unique feature that emerges when cells assemble into tissues is the exchange of mechanical forces between cells that often exist in crowded and highly dynamic *in vivo* environments. In particular, densely packed epithelial monolayers provide the structural foundation for many tissues and organs in the body. Eaton and Jülicher [1] review how epithelial tissues in *Drosophila* elongate through a combination of forces generated by cell rearrangements, cell-shape changes, and cell division. In addition to locally generated forces, long range forces, resulting from interactions between tissues linked by extracellular matrix, can induce global flow patterns that have profound effects on tissue structure. In the review by Kim, Jackson, and Davidson [2], the authors discuss how migratory cells integrate into epithelial monolayers in mesenchymal-to-epithelial transitions. They demonstrate how insights from biophysics can help to explain the distinct mechanical events that drive this process, and they illustrate how these events allow individually and collectively migrating cells to contribute to epithelial structures throughout the body, including the heart and kidney. In the review by Sundaram and Cohen [3], the authors describe another example of tissue remodeling, in which cells form tiny, single-celled seamless tubes. Seamless tubes are common among mammalian blood capillaries, including in humans, and defects in capillary architecture underlie multiple human diseases. The authors highlight recent studies from *C.*

elegans and *Drosophila* that have revealed key insights into how seamless tubes develop. Together, these reviews illustrate a remarkable variety of structures that cells can form.

In addition to generating forces, cells in tissues also respond to forces generated by the cells around them, and these mechanical signals can be translated into biochemical changes that influence tissue structure. In the review by Gudipaty and Rosenblatt [4], the authors describe how epithelial sheets are able to maintain mechanical integrity in order to perform essential barrier functions in developing and adult tissues. Epithelial barrier function is continually threatened by the possibility of gaps in tissue that can occur as a result of cell death, and by local overcrowding that can arise from cell proliferation. The authors highlight how epithelial tissues utilize a combination of chemical and mechanical signals that allow them to extrude dying cells before they disrupt the mechanical integrity of the tissue, and to extrude live cells in overcrowded regions to restore homeostasis. A failure to carry out these functions can lead to several diseases, and pathogens can exploit these processes to traverse epithelial barriers and promote infection. The review by Gilbert and Weaver [5] describes recent progress in understanding how cells respond to mechanical forces generated by the extracellular matrix, which can influence cell fate and behavior. Studies that recapitulate 2D and 3D cell environments in culture have provided insight into the mechanisms that translate mechanical forces into biochemical changes within cells, and are being extended to *in vivo* settings to determine how these mechanisms play out within tissues. These studies support the idea that force-induced signaling mechanisms are important for development and influence tissue aging and disease in the adult.

Recent years have seen a highly successful interplay between *in vivo* experiments and computer modeling. In the review by Yu and Fernandez-Gonzalez [6], the authors provide a primer on the use of vertex models to study epithelial morphogenesis. Mathematical models can help to break down the contributions of individual factors to complex morphogenetic processes, reveal gaps in our understanding, predict the effects of tuning different parameters on the tissue, and infer mechanical properties that are difficult to measure directly. Interpreted cautiously, these models have been invaluable toward obtaining insights into the contributions of short-range and long-range forces to processes of epithelial morphogenesis, such as epithelial closure and wound healing. In the review by Merkel and Manning [7], the authors describe how physical properties of cells have important implications for the behavior of biological tissues. In particular, theoretical frameworks for deducing the mechanical properties of tissues and predicting how they will respond to mechanical forces provide a valuable companion to biological measurements that make it possible to explain complex properties of tissue behavior. In the review by Varner and Nelson [8], the authors describe how different types of modeling, which capture signaling states of cells or tissue-level patterns of branch geometry and mechanical forces, have been used to obtain insight into the mechanisms that produce highly branched multicellular structures. These studies highlight how modeling approaches are able to recapitulate even complex tissue features, such as the elaborately branched tree-like networks of the bronchial network in the mammalian lung.

Together, the review articles in this issue highlight how a combination of experiments and modeling has contributed to a greater understanding of the cellular, molecular, and physical

mechanisms that build tissues. The variety of experimental and modeling approaches presented in the reviews here may well be necessary to capture the broad range of possibilities by which mechanical forces, biochemical signaling pathways, and geometric patterns work together to produce the shapes and functions of multicellular tissues.

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