Preface

Developmental biology 50 years—investigating the emergence of shape

“The word morphogenesis when used strictly should mean the molding of cells and tissues into definite shapes” C.H. Waddington, 1956.

A central mission of developmental biology as a science is to understand how organisms develop from simple fertilized eggs into complex animals and plants of diverse shapes and elaborate internal architecture. This quote from Waddington coincides with the establishment of Developmental Biology as a journal. In celebration of the journal’s 50th anniversary we present the following series of review articles, which address the problem of morphogenesis.

Macroscopic changes in tissue or organ structure result from coordinated changes in the arrangements and shapes of cells. To this end, the pre-molecular era, and the first two decades of this journal, were dominated by studies of descriptive and experimental embryology. The processes that are responsible for the development of animals and plants can be roughly divided into three main categories: cell communication, differentiation and morphogenesis. Morphogenesis is derived from the Greek words meaning the emergence (γεννίσι) of shape (μορφή) —morph. It is therefore only fitting that the study of morphogenesis dates back to an ancient Greek philosopher, Aristotle, who recognized that the egg of an animal had the “potential” to influence its final form.

Over the last three decades, genetic analyses have elucidated the central signaling pathways directing cell communication and differentiation and have shown them to be evolutionarily conserved. This acquisition of information can be viewed as a description of the parts. Indeed many key factors regulating processes like cell division, fate determination and differentiation are encoded by a relatively small number of conserved gene families. Together with an additional level of regulation, afforded by antagonists, activators, as well as posttranscriptional or posttranslational modifiers, a framework of genes and mechanisms controlling development have emerged. In this framework, a cell type results from the activity of multiple genes, and genetic pathways are viewed as parallel information pipelines that converge on the regulatory regions of specific genes.

By contrast, elucidation of the molecular genetic mechanisms of morphogenesis has proven more challenging. Forward genetic approaches in Drosophila melanogaster, Caenorhabditis elegans, plants and zebrafish that netted hundreds of mutations affecting cell fate specification and differentiation, and identified a smaller number of mutations specifically affecting morphogenesis. We learned that early morphogenesis is protected by a large maternal contribution of transcripts and proteins deposited in eggs of invertebrate and some vertebrate model animals. Moreover, a remarkable redundancy of genes regulating and executing morphogenesis ensures robustness of this complex process, making it more resistant to genetic dissection. Therefore, our knowledge of fundamental processes such as gastrulation is still limited. Likewise, despite the physiological importance of many organs, we are only just beginning to understand how their morphogenesis is controlled and how particular shapes influence function. Moreover, if we are to understand development at the molecular level and formulate principles that can be applied across systems, a great deal more needs to be learned about the dynamics of gene expression, cell behaviors and fate, and how they are molecularly determined.

Despite these challenges the rate of discovery in the area of morphogenesis has been accelerating rapidly in the recent decade. Microscopy has always been a central tool in developmental biology and a prerequisite for studying morphogenesis. The recent availability of improved imaging reporters, along with advances in optical imaging modalities have come together to push the envelope of microscopic visualization of cell dynamics. This technology has also spurred the development of computational methods to analyze large-scale multi-dimensional image data. Indeed morphogenesis is a formidable problem to tackle, being four-dimensional (taking place in three dimensions over time) and involving the interactions of cells with one another as well as with substrata.

The past decade has seen increased interest in the formulation of quantitative models of morphogenetic processes at the level of tissue, cells, and molecules. These should facilitate a dynamic understanding of molecular mechanisms underlying changes in the discrete properties and behaviors of individual cells. An exciting prospect for the future is the ability to model and test how different variables can affect cell behavior, and in turn regulate the size, shape and pattern of a particular organ. As we move from the description of the parts that configure biological systems to an analysis of how they are integrated to produce the final form, there is an emerging interest in the quantitative analysis of these events together with the necessity for the development of accurate techniques to accurately measure dynamic cell behaviors and concomitant computational methods and analytical tools that can yield insights into processes with multiple variables.

The collection of reviews in this anniversary volume of Developmental Biology summarizes the progress achieved in our understanding of morphogenetic processes in animals and plants by the combination of forward and reverse genetic approaches in all model systems, notably the mouse model, combined with remarkable advances in imaging and mathematical modeling. This collection is by no means comprehensive, rather it provides a brief glimpse of key and current morphogenetic problems, ranging from cell shape changes, to collective cell behaviors, to the integration of each to produce the final product. The reviews also highlight what is becoming a more
common and exciting development in the field of morphogenesis, a multidisciplinary approach to the problem. Several reviews illustrate the synergistic collaborations between the developmental genetics and cell biology approaches that include biochemical, biophysical and mathematical methods.

The shapes of cells can vary according to differentiation state and environment, and changes in cell shape can directly drive the morphogenesis of tissues. For over a century it has been recognized that shrinking one side of a cell may result in the dramatic bending of a sheet of cells. The review by Bob Goldstein and colleagues focuses on apical constriction, a process that occurs throughout metazoa to drive such diverse morphogenetic events as invagination of mesoderm during gastrulation in many animals or neurulation (Goldstein et al., 2009). Starting off with Rhumbler’s insightful and pioneering studies from a century ago, the authors go on to review physical and chemical perturbations, as well as the genetic pathways and dissection of protein function from studies carried out in diverse systems. They arrive at our current understanding of apical constriction, which results from the integration of molecular mechanisms with an appreciation of force production.

Animals and plants employ many distinct classes of morphogenetic processes. In cases where cell types are specified at distant locations, they must migrate to reach their final destination. Cell migration during development must be coordinated with other basic cell behaviors such as cell growth, proliferation, and shape changes, as well as other concurrent morphogenetic movements. Since cell migration processes are involved in inflammation and are often reactivated during tumor invasion and metasta- sis the studies of these morphogenetic cell movements are clinically relevant. Tatjana Piotrowski and Andy Aman discuss processes of cell migration in diverse model systems, where they compare the similarities and highlight the differences (Aman and Piotrowski, 2009).

The formation of tubes is a unique morphogenetic process driven by novel cellular mechanisms that have to be deciphered. Branched tubular structures are a fundamental tissue across metazoa required for the efficient transport of resources and of waste products. Andy Ewald and Debbie Andrews discuss almost two decades of work that has begun to unravel the mechanisms driving the formation, elongation and branching morphogenesis of epithelial tubes. They describe the series of events starting with tube formation and culminating in branching morphogenesis during various develop- ment processes from tracheal development in Drosophila, to lung and mammary gland development in mice (Andrew and Ewald, 2009). An important and clinically pertinent paradigm of tube formation is the morphogenesis of the vasculature. Markus Affolter, Heinz-Georg Belting and colleagues discuss the cell behaviors and molecular mechanisms that regulate vessel assembly, sprouting, growth and remodeling in vertebrates, and specifically the zebrafish (Ellertsdóttir et al., 2009).

One intriguing mode of morphogenesis is when cells alter their size and shape by fusing with other cells. Cell fusion is exemplified by the formation of the musculature, a process that is phenotypically if not mechanistically conserved across species. Myoblast fusion occurs in both the formation and repair of muscle, and is therefore clinically relevant for regenerative medicine. Mary Baylies, Sudipto Roy and colleagues discuss the sequence of cellular events that are critical for myoblast fusion and the emerging molecular mechanisms regulating them in three model systems, Drosophila, the zebrafish and the mouse (Rochlin et al., 2009).

The coordination of various morphogenetic cell behaviors in time and space is critical for the correct development of organ systems. This is highlighted by what is perhaps the most complex region of the body, the head. Craniofacial development relies on precise three-dimensional patterning and coordinated morphogenetic movements of tissues derived from all three germ layers. Craniofacial defects represent a common developmental disorder in humans. In their review on craniofacial morphogenesis Karen Liu and colleagues highlight studies in three model systems, zebrafish, mouse and human, which have identified novel cell biological mechanisms regulating the growth and morphogenesis of the craniofacial skeleton (Szabo-Rogers et al., 2009).

In contrast to most animals, plants will form new organs, including leaves, stems and floral structures, almost continuously throughout their life. They accomplish this by maintaining a population of stem cells in the meristem structures that were generated during embryogenesis. Aboveground organs are generated by the shoot apical meristem, while belowground organs arise from the root apical meristem. As in animals the placement of new organ primordia must be carefully regulated. As there is little cell rearrangements or movements in plants, the rate and orientation of cell division is the key morphogenetic tool with which plants achieve a correct final form. Two decades ago, the cloning of the first genes involved in apical meristem function opened the door to elucidating the molecular mechanisms regulating the behavior of this precisely controlled stem cell population in several plant models. Kathy Barton provides an overview of these studies and predicts what directions the next two decades of work may steer us (Barton, 2009).

The shape of any flexible body is governed by the second law of thermodynamics, such that an arrangement that minimizes the free energy of the system is favored over any other possible arrangements. Over the past decade has come the realization that mechanical forces play key roles during tissue morphogenesis, and importantly, technological improvements have afforded the means to quantify these forces. Contractile forces generated by the actin–myosin cytoskeleton give rise to various temporal and spatial patterns of force generation that are critical for morphogenesis. However, although the importance of actin and myosin II has been clearly demon- strated the mechanisms by which they drive cell shape changes are still poorly understood. Adam Martin discusses recent studies exploiting live imaging with computational and biophysical approaches to provide new insights into how contractile forces are generated and coordinated between cells and tissue. Intriguingly, studies in several systems report that cycles of actomyosin contrac- tility underly such processes as venral furrow formation and dorsal closure during Drosophila gastrulation, and convergence and exten- sion during Xenopus gastrulation (Martin, 2009).

Finally, it is becoming apparent that the extracellular environment plays as critical a role in morphogenesis as in cell–cell communication. The three-dimensional organization of the extracellular matrix (ECM) impacts several aspects of morphogenesis. ECM is laid down early in development and thereafter is involved in regulating various cell behaviors including growth, survival, signaling and movement. Doug DeSimone and Tania Rozario discuss a range of cell and tissue functions attributed to the ECM—from serving as a dynamic repository for growth factors to facilitating the generation of forces and mechanical signals (Rozario and DeSimone, 2009).

This collection of reviews on morphogenesis helps us celebrate 50 Years of Developmental Biology and sets the stage for the next five decades of investigation. Clearly as the field of morphogenesis enters this new era we are equipped with new technologies and knowledge that afford addressing the problems of morphogenesis with unprece- dented sophistication and purpose. It is now possible to link the movements of entire tissues or cell populations to specific motile behaviors of individual cells. It now becomes feasible to delineate the molecular mechanisms that underlie these specific motile behaviors in terms of properties of cell surface, cytoskeletal elements and other cellular organelles. These efforts are facilitated not only by new technical advances, but also by new interdisciplinary approaches that help address these complex phenomena. As we continue to advance our understanding of how dynamic cell behaviors are driven, and in turn drive tissue morphogenesis, the key challenge for the future is understanding how these behaviors are coordinated with one
another and most intriguingly with concurrent cell fate specification events.

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