# Preface

## Developmental Genetics: An Historical Perspective

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The ability of researchers to answer experimental questions greatly depends on the available technologies. New technologies lead to novel observations and field-changing discoveries, and influence the types of questions that can be asked. Today's recently available technologies include sequencing and analyzing the genomes of human and model organisms, genome-wide expression and epigenetic profiling, and high-throughput screening. The information provided by these approaches enables us to begin to understand the complexity of many biological processes through the elucidation of gene regulatory networks, signaling pathway networks, and epigenetic modifications. This book describes many lines of research that are being impacted by these new technologies, including developmental genetics and the related fields of clinical genetics, birth defects research, stem cell biology, regenerative medicine, and evolutionary biology.

The field of developmental genetics, or the study of how genes influence the developmental processes of an organism, has been influenced by new technologies and by interactions with other fields of study throughout its history. The concept of a genetic basis of development began in "modern" times at the intersection of descriptive embryology and cytology. Modern histological techniques were developed in the mid-19th century, largely by Wilhelm His so that he could study cell division in the neural tube, which enabled visualization of the cell nucleus, chromosomes, and the discrete steps of mitosis. Theodor Boveri cleverly applied these improved microscopic techniques to transparent marine embryos to demonstrate that each parent contributes equivalent groups of chromosomes to the zygote, and that each chromosome is an independently inherited unit. Importantly, he noted that if an embryo contains the incorrect number or improper combination of chromosomes it develops abnormally. However, many early embryologists rejected the idea that development is driven by prepackaged heritable particles because it seemed too similar to the idea of "preformation": the concept that development is driven by predetermined factors or "force" (sometimes described in rather mystical terms).

Wilhelm Roux, an advocate of studying the embryo from a mechanistic point of view, was a leader in manipulating the embryo with microsurgical techniques to elucidate causes and effects between component parts (experimental embryology). By using an animal model whose embryos were large, developed externally to the mother, could be surgically manipulated with sharpened forceps, and cultured in simple salt media (i.e., amphibians), he rejected the role of predetermined factors and demonstrated the importance of external (epigenetic) influences and cell-cell interactions in regulating developmental programs. Experimental embryologists further refined their skills in dissecting small bits of tissue from the embryo, recombining them with other tissues in culture or transplanting them to ectopic regions in the embryo. This work led to the invention of tissue culture by Ross Harrison and the discovery of tissue inductions by Hans Spemann and Hilde Mangold.

While experimental embryology was thriving, T. H. Morgan founded the field of *Drosophila* genetics. Also trained as an embryologist, Morgan was skeptical of Boveri's idea of heritable packets, and directed his studies towards understanding the principles of inheritance. For several decades, the two fields, experimental embryology and genetics, had little impact on one another. Interestingly, however, after a few decades of study of the fruit fly, Morgan's work supported the idea of discrete intracellular particles that directed heritable traits, which he named "genes." Nonetheless, experimental embryology and genetics remained fairly separate fields with distinct goals and points of view. Embryologists were elucidating the interactions that are important for the development of numerous tissues and organs, whereas geneticists were focused on the fundamentals of gene inheritance, regulation of expression, and discovering the genetic code.

Much of this work was carried out in non-mammalian animal models that develop external to the mother, and thus can be manipulated during during development and/or have very short life cycles. Elucidating the genetic basis of vertebrate development was delayed until new technologies in molecular biology and cloning were devised. The techniques for cloning eukaryotic genes and constructing vectors for controlling expression came from the field of bacterial and viral

genetics. The rationale for and techniques of mutagenizing the entire genome and screening for developmental abnormalities came from the classical genetic studies in the fly and nematode. Important regulatory genes were discovered in these invertebrates, and their counterparts have been identified in many other animals, including mammals, by homology cloning approaches that were not common until the 1990s. Thus was born the modern field that we call developmental genetics.

An important advance has been the demonstration that homologues of the genes that regulate developmental processes in invertebrates also have important developmental functions in vertebrates. The wealth of information concerning the molecular genetic processes that regulate development in various animals demonstrates that developmental programs and biological processes are highly conserved, albeit not identical, from yeast to human. Indeed, the Human Genome Project has made it possible to identify the homologues in humans, and to demonstrate that many of these regulatory genes underlie human developmental disorders, birth defects, and aspects of adult diseases in which differentiation processes go awry. Currently, researchers are studying the fundamentals of developmental processes in the appropriate animal model and screening humans for mutations in the genes identified by the basic research to be likely causative candidates. Researchers are mutagenizing vertebrate animal models and screening for mutants that resemble known human syndromes. Stem cell biologists are using the molecular genetic information discovered by from developmental biology researchers to understand how to manipulate cellular differentiation *in vitro* and direct pluripotent cells to desired lineages for tissue replacement therapies. This cross-fertilization of fields is also impacting concepts in evolutionary biology, leading to a better understanding of "ancestral" species and tissue anlage via homologous gene expression profiles.

In recent years there have been significant technological advances in genetic, genomic, epigenetic, and protein expression analyses that are having a major impact on experimental approaches and analytical design. The intersection of developmental biology with these technologies offers a new view of developmental genetics that is only now beginning to be exploited in clinical approaches. It is this new intersection between modern developmental genetic approaches and potential clinical interventions that is the focus of this book. The book is organized into sections focused on different aspects of developmental genetics. Section I discusses the impact of new genetic and genomic technologies on development, stem cell biology, evolutionary biology, and understanding human birth defects. Section II discusses several major events in early embryogenesis, fate determination, and patterning, including cellular determinants (Boveri revisited?), gene cascades regulating embryonic axis formation, signaling molecules and transcription factors that regulate pattern formation, and the induction of the primary germ layers (ectoderm, mesoderm, and endoderm). Section III describes the morphogenetic and cellular movements that underlie the foundation of the organ systems, with a focus on the signaling cascades and transcriptional pathways that regulate organogenesis in representative systems derived from the embryonic ectoderm, mesoderm, and endoderm. These chapters illustrate how embryonic rudiments become organized into adult tissues, and how defects in these processes can result in congenital defects or disease. Each chapter demonstrates the usefulness of studying model organisms and discusses how this information applies to normal human development and clinical disorders. Several of the chapters in this section also discuss the utility of stem cells to repair damaged organs and the application of developmental genetics to the manipulation of stem cells for regenerative medicine. Section IV presents the developmental genetic underpinnings of a few selected clinical problems that commonly face pediatricians.

The goal of this book is to provide a resource for understanding the critical embryonic and prenatal developmental processes that are fundamental to the normal development of animals, including humans. It highlights new technologies to be used, new questions to be answered, and the important roles that invertebrate and vertebrate animal models have had in elucidating the genetic basis of human development and disease. Developmental genetics has re-emerged from its birth a century ago as a nexus of diverse fields that are using the common language of gene sequence and function. This is influencing what questions are posed and how the answers are used. New technologies are making it relatively easy to study gene expression and regulation at single cell, tissue, and embryonic levels. The conservation between the genomes of species that are separated by vast evolutionary time encourages us to more fully utilize animal models to gain important insights into the clinical relevance of the animal model data. It is our hope that this book will stimulate even more cross-fertilization and interactions between evolutionary biology, developmental biology, stem cell biology, basic scientists, and clinical scientists.

I wish to thank all of the authors for contributing such exciting and excellent chapters, and Catherine Van Der Laan for keeping all of us on schedule.

## RECOMMENDED RESOURCES

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