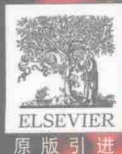




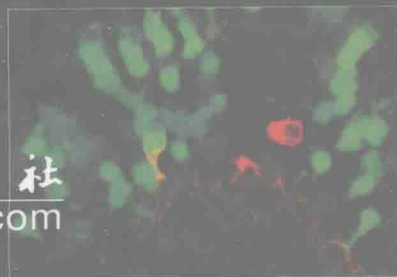
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# Principles of Developmental Genetics 发育遗传学原理

Sally A. Moody



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PRINCIPLES OF  
DEVELOPMENTAL GENETICS

发育遗传学原理

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Sally A. Moody

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# 发育遗传学的重要专著

——评“Principles of Developmental Genetics”（《发育遗传学原理》）

孟安明

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生物个体的发育十分复杂，充满了神秘之感，也吸引着很多科学家投身其中。大约30年之前，对个体发育的研究主要还局限于细胞、组织和个体水平。20世纪70年代DNA重组技术的出现，带动了整个生命科学的快速发展，发育学方面的研究也在分子水平上展开，进入了快车道。特别是最近10年，科学家们已阐明了脊椎动物多个发育过程的分子机理。今天我们已经知道，许多的信号通路、众多的基因按设定的程序执行功能，从而控制着个体逐渐发育；基因功能的异常或信号通路的紊乱会导致人类出生缺陷和疾病。

事实上，分子生物学的出现，逐渐打破了生命科学领域中传统的分支学科间的分隔状态，形成了各学科相互交叉、渗透的新局面。例如，发育生物学与遗传学、细胞生物学、分子生物学、进化生物学等业已存在密不可分的关联，有时就很难将某项研究归入某一学科。发育遗传学就是这样一门交叉学科，它主要研究基因如何控制和调节生物个体的发育。

近年来，我国在发育遗传学领域的研究取得了一批重要成果，整体研究水平提高很快。比如，我国已经建立了小鼠、斑马鱼、果蝇、水稻、拟南芥等模式动植物的遗传资源库和技术平台，发现了一些调控胚胎发育、个体生长的重要基因和机理，成果发表在*Nature*、*Science*等国际顶尖学术刊物上；克隆了一批人类遗传疾病的致病基因；在干细胞生物学、进化遗传学等研究方向上也取得了世界公认的成果。比较遗憾的是，我国目前还没有出版发育遗传学的中文教材或比较系统的专著。

由美国乔治华盛顿大学 Sally A. Moody 主编的《发育遗传学原理》是发育遗传学领域中最新的一本专著，该书由数十位活跃在发育遗传学领域的一流专家参与撰写，内容非常丰富，囊括了各方面的最新研究进展。该书由五篇（四十四章）组成，可以重新归纳为三大部分。第一部分重点介绍当今发育遗传学研究中所用到的新技术、新方法及其成果，同时还介绍了基于基因组表达数据的脊椎动物发育进化，以及常用模式动物及其与人类出生缺陷和疾病研究的相关性。第二、第三部分主要是按照动物胚胎发育的时序和组织器官划分章节。第二部分主要介绍动物胚胎早期发育过程中的细胞命运决定、胚轴确定、胚层的形成和分化、细胞运动与形态构建。第三部分重点介绍外胚层、中胚层和内胚层来源的组织和器官的发生和形成机制。

该书的特点之一是内容丰富。从发育生物学的角度看，该书涉及了主要的发育生物学内容，如生殖细胞发育、胚层诱导、前后轴线和背腹轴线的形成和分化、原肠作用、神经诱导和神经元的分化、神经嵴细胞发育、视网膜发育、内耳发育、牙发育、心血管系统发育、骨骼发育、生殖腺发育、肢体发育、肺系统发育、胰腺发育、肝发育、干细

胞生物学、发育进化等等；从遗传调控角度来看，该书涉及到多种主要的信号通路，如 Wnt、TGF $\beta$ 、BMP、FGF、SHH、Delta-Notch、Ephrin-Eph、视黄酸（RA）等信号通路，还介绍了一些重要的转录调控因子及其调控网络。因此，不仅发育生物学和遗传学领域的工作者可以从书中获取知识，其他许多领域如细胞生物学、肿瘤学等相关领域的研究人员也能够获得有价值的资料。

该书的第二个特点是前沿性。各章节力图从基因调控网络的角度阐述相应组织或器官的发育，整合了大量的最新研究进展，从引用许多 2006 年、2007 年发表的文献即可见一斑。撰写人员是在科研一线工作的研究人员，对前沿把握准确、理解透彻。例如，第五章中，作者总结了 30 余个与染色质重塑相关基因的突变对小鼠发育的影响；一些章节还介绍了非编码小 RNA（microRNA）在发育中的作用。某些器官发育的分子机理迄今所知甚少，在一般的教科书或专著中鲜有详细介绍，但从该书中就可获得相关的最新知识，如牙的发育、内耳的发育、肝脏的发育、肠干细胞生物学等。

该书的第三个特点是注重发育过程和机理的普遍性和特异性。从低等的无脊椎动物到人，一些发育程序是相同或类似的，但不同物种也有一些特殊的发育程序，在发育调控的分子机理上也是如此。该书的各章节相当注意介绍相关发育过程和调控机理在不同物种上的保守性和特异性。

该书的第四个特点是理论与应用的联系。模式动物的最大优势是可以直接对基因组中的基因进行遗传修饰，并进行相应的分子机理研究。该书的许多章节都尽可能地将模式动物上获得的知识与人类出生缺陷和疾病相联系，使得从事基础和临床科学的读者均可受益。

此外，每章正文中涉及的主要内容都标明了引用文献的出处，结尾处列出了这些参考文献，显示了写作的严谨性，也方便读者精读相关文献。许多章的末尾列出了有关的网络资源，方便读者查找信息。每章之后还附有一些专用名词的解释，对读者学习和理解发育遗传学很有帮助。

该书适合作为研究生课程的教科书或参考书，对于从事发育生物学、遗传学、细胞生物学、进化生物学、干细胞生物学、基础医学和临床医学的教学和科研人员都有重要的参考价值。

## 前 言

发育遗传学；或者说在进化、发育、干细胞以及人类出生缺陷和疾病方面，遗传学和基因组学能够告诉我们些什么？

研究人员回答实验疑问的能力主要依赖于所用的技术手段。新的技术产生新的观察结果，导致可颠覆研究领域的发现，影响到提出问题的类型。现今可资利用的技术包括人类和模式生物基因组序列测定和分析、基因组水平的表达分析、高通量的基因组和遗传分析。这些分析方法所提供的信息，能帮助我们阐明基因调控网络、信号转导网络和表观遗传修饰，从而理解许多复杂的生物学过程。本书介绍了正在受到这些技术影响的多方面研究，包括发育遗传学和相关的领域，如临床遗传学、出生缺陷研究、干细胞生物学、再生医学和进化生物学。

新技术及其与相关领域的交叉，影响着发育遗传学领域，或者说是影响着基因调控的生物体发育过程的研究。“现代”发育的遗传基础的概念起始于描述性胚胎学和细胞学的交叉。19世纪中叶，主要由 Wilhelm His 建立了现代组织解剖技术，这使他能够研究神经管中的细胞分裂，看见细胞核、染色体和有丝分裂的不连续阶段。Theodor Boveri 聪明地将这些改进的显微技术用于观察透明的海洋动物胚胎，发现了每个亲本贡献相同数量的染色体给合子，而且每条染色体是一个独立的遗传单元。更重要的是，他注意到含有不正确数量染色体或异常的染色体组合的胚胎不能正常发育。

然而，对于发育是由预先包装的、可遗传的微粒所驱动的观点，许多早期的胚胎学家持否定态度。在他们看来，这一观点与“先成论”太相似了，后者认为发育是由预先确定的因子或“力”（有时用相当神秘的词去描述）所驱动的。Wilhelm Roux 提倡从机理上研究胚胎的发育，他率先利用显微技术操作胚胎，以阐述胚胎各组份之间的因果关系（实验胚胎学）。他以胚体较大并在母体外发育的两栖动物为模式，用尖嘴镊子做外科手术式的操作和在简单的盐溶液中培养的方法，否定了预先确定因子的作用，证明了外在因素（表观遗传）以及细胞-细胞间相互作用调控着发育程序。实验胚胎学家随后进一步改进技术，从而能够从胚胎中切割小块组织，将其与其他组织组合培养，或将其移植到胚胎的其他区域（异位区）。这类实验使 Ross Harrison 发明了组织培养技术，并促使 Hans Spemann 发现了组织诱导作用。

在实验胚胎学蓬勃兴起之际，T. H. Morgan 开创了果蝇遗传学领域。同时，作为胚胎学家，Morgan 对 Boveri 的可遗传微粒的观点持怀疑态度，并致力于理解遗传原理方面的研究。在这几十年中，（胚胎学和遗传学）两个领域之间并无交叉影响。然而有趣的是，经过对果蝇几十年的研究之后，Morgan 的工作支持了存在控制遗传性状的不连续细胞内微粒的观点，他将其命名为“基因”。尽管如此，实验胚胎学和遗传学仍维持相互分割状态，各有不同的目标和观点。胚胎学家致力于阐明对于各种组织和器官发育很重要的相互作用，而遗传学家专注于基因遗传的基本原理、表达的调控和遗传密码的发现。事实上，在发明出分子生物学和克隆新技术之前，对脊椎动物发育的遗传基础的研究进展一直十分迟缓。基于细菌和病毒遗传领域的研究进展，出现了克隆真核基因

和构建控制基因表达载体的新技术。在果蝇和线虫的经典遗传学研究基础上，逐渐形成了全基因组诱变和筛选发育缺陷突变体的理论基础。在这些无脊椎动物上发现了重要的调控基因，通过同源克隆策略可以在其他许多物种上发现这些基因的同源基因。因此，我们将由此诞生的现代领域称之为发育遗传学。

过去十年中一个重要的进展，是证明在无脊椎动物中调控发育过程的基因，在脊椎动物上同样有重要的功能。在各种动物中调控发育的分子遗传过程的大量信息显示，从酵母到人的发育程序和生物学过程尽管不完全相同，然而却是高度保守的。事实上，人类基因组计划使我们可以鉴定人类的同源基因，证明其中许多基因与人类发育缺陷以及分化异常所造成的成年疾病直接相关。目前，研究人员正在利用适当的模式动物研究发育程序的基本规律，根据基础研究中鉴定的基因筛选人类突变，以寻找致病候选基因。研究人员正在对脊椎类的模式动物进行诱变，筛选与已知的人类病症类似的突变体。不同领域的这种异体交叉也正在影响着进化生物学的概念，通过分析基因表达谱，及干细胞生物学中祖细胞可被导向“设计”命运的范式，更好地促进人们对“祖先”物种发育过程的理解。

最近，在遗传、基因组、蛋白表达分析上取得了显著的技术进步，对实验策略和分析设计产生了重大影响。发育生物学和这些技术的交集，提供了发育遗传学的一个新视野，对其探索才刚刚开始。在基因组世纪开始之际的这种新的交叉，正是本书的聚焦点。本书的各个部分聚焦在发育遗传学的不同方面。第一部分讨论了新的遗传和基因组技术对发育、干细胞生物学、进化生物学和了解人类出生缺陷的影响。第二部分讨论了在早期胚胎发育、命运决定、图式形成中的几个重要事件，包括细胞决定子（Boveri理论的再访?）、调控胚轴形成的基因级联、调控图式形成的信号分子和转录因子，以及主要胚层（外胚层、中胚层和内胚层）的诱导。第三部分介绍了胚胎经不同类型的形态发生和细胞运动的重新组织，这些运动导致器官系统原基的产生；讨论了调控这些复杂过程的许多信号分子和黏附分子。最后三部分聚焦在信号通路和转录通路上，在来自于胚胎外胚层、中胚层和内胚层的代表性系统中，它们控制着器官形成。这些章节举例说明胚胎器官原基如何形成成体组织，以及这些过程的异常如何导致出生缺陷和疾病。每一章都说明研究模式生物的益处，讨论相关信息如何应用到正常的人类发育和临床疾病之中。有几章还讨论了干细胞对于修复损伤器官的价值，以及在再生医学方面发育遗传学对于干细胞操作的可应用性。

本书的目的是帮助理解关键的胚胎过程和出生前的发育过程，这些过程对于包括人在内的动物的正常发育是必不可少的。本书突出了要用到的新技术、要回答的新的问题、以及无脊椎动物和脊椎动物模式在阐明人类发育的遗传基础方面的重要作用。发育遗传学产生于一百年前，如今它作为不同领域的纽带重新出现，成为共同利用基因序列和功能为研究手段的不同领域的连接点，正在影响着我们提出什么问题以及如何利用这些问题的答案。新技术的出现，使在单个细胞、组织和胚胎水平上研究基因的表达变得相对容易。在久远的进化时间中被分隔的物种，其基因组所显示的保守性鼓励我们更充分地利用动物模式，研究其数据结果的临床相关性。我们的愿望是本书可以促进进化生物学、发育生物学、干细胞生物学、从事基础研究的科学家和从事临床研究的科学家更多地交叉和相互合作。

我要感谢本书的所有作者贡献了如此令人兴奋和出色的章节，感谢 Pat Gonzalez 使我们能如期完成此书的写作。

Sally A. Moody  
乔治华盛顿大学解剖与细胞生物学系

(孟安明 译)

# PREFACE

## **Developmental Genetics, or What Can Genetics and Genomics Tell Us About Evolution, Development, Stem Cells, Human Birth Defects, and Disease?**

**Sally A. Moody**

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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 profiling, and high-throughput genomic and genetic analyses. The information provided by these approaches is enabling 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 "forces" (sometimes described in rather mystical terms).

Wilhelm Roux, an advocate of studying the embryo from a mechanistic point of view, was a leader in the approach of manipulating the embryo with microsurgical techniques to elucidate cause and effects between component parts (experimental embryology). By using an animal model whose embryos were large, developed external 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 at 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.

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 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, the fields of experimental embryology and genetics remained fairly separate entities 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. Indeed, elucidating the genetic basis of vertebrate development was delayed until new technologies in molecular biology and cloning were devised. From the field of bacterial and viral genetics came the techniques for cloning eukaryotic genes and constructing vectors for controlling expression. From the classical genetic studies in fly and nematode came the rationale for mutagenizing the entire genome and screening for developmental abnormalities. Important regulatory genes were discovered in these invertebrates, and their counterparts were discovered in many other animals by homology cloning approaches. Thus was born the modern field that we call developmental genetics.

An important advance in the past decade is the demonstration that genes that regulate developmental processes in invertebrate species 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 demonstrate that many of these regulatory genes underlie human developmental disorders 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. This cross-fertilization of fields is also impacting concepts in evolutionary biology,

leading to a better understanding of “ancestral” species via gene expression profiles, and paradigms in stem cell biology in which naïve cells may be directed to “designer” lineages.

Most recently, there have been significant technological advances in genetic, genomic, and protein expression analyses that are having a major impact on experimental approaches and analytic design. The intersection of developmental biology with these technologies offers a new view of developmental genetics that is only beginning to be exploited. It is this new intersection at the onset of the genomic era 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 reorganization of the embryo via different types of morphogenetic and cellular movements that result in the foundation of organ systems, and discusses the many signaling and adhesion molecules that are involved in regulating these complex processes. The final three sections 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 chapters 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.

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. 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 Pat Gonzalez for keeping all of us on schedule.

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