国外生命科学优秀教材

Molecular Biology of the Gene

Sixth Edition

基因分子生物学

影印版

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科学出版社
北京

图字：01-2011-3861

内 容 简 介

本书由 6 位生物学界著名专家合作编著，第一作者沃森（1962 年诺贝尔医学或生理学奖获得者）系 DNA 双螺旋结构发现者、分子生物学科奠基人、人类基因组计划的发起者。本书自 1965 年第一版出版以来得到生物学界的广泛关注和认可，迄今已成为分子生物学经典教科书。第六版保持前几版的一贯特色：适用于分子生物学科需求；保持与学科进展的同步性，体现最新、最权威的学科知识。

全书分为 5 大部分，合计 22 章，分别是：I.化学与遗传学（5 章）——孟德尔世界，核酸遗传信息的传递，弱化学相互作用的重要性，高能键的重要性，弱键与强健决定的大分子结构。II.基因组的维系（6 章）——DNA 与 RNA 的结构，基因组结构、染色质与染色体，DNA 复制，DNA 突变与修复，分子水平的同源重组，位点特异性重组和 DNA 移位。III.基因组的表达（4 章）——转录，RNA 剪接，翻译，遗传密码。IV.调控（5 章）——原核生物的转录调控，真核生物的转录调控，RNAs 的调控，发育与进化中的基因调控，基因组学与系统生物学。V.研究方法（2 章）——分子生物学技术，模式生物。

本书适合生命科学相关专业教学选用，也可供从业人员参考使用。

图书在版编目(CIP)数据

基因分子生物学＝Molecular Biology of the Gene：原书第 6 版：英文/(美) 沃森(Watson, J. D.)等著. —影印本. —北京：科学出版社，2011.6

国外生命科学优秀教材

ISBN 978-7-03-031761-2

Ⅰ.①基… Ⅱ.①沃… Ⅲ. ①基因-分子生物学-教材-英文 Ⅳ. ①Q343.1

中国版本图书馆 CIP 数据核字(2011)第 119715 号

责任编辑：单冉东

责任印制：张克忠 / 封面设计：陈 敬

科学出版社出版

北京东黄城根北街16号

邮政编码：100717

http://www.sciencep.com

双青印刷厂 印刷

科学出版社发行 各地新华书店经销

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2011 年 7 月第 一 版 开本：A4(890×1240)

2011 年 7 月第一次印刷 印张：54 3/4

印数：1—3 000 字数：1 500 000

定价：136.00 元

（如有印装质量问题，我社负责调换）

Preface

THREE SIGNIFICANT CHANGES HAVE TAKEN PLACE in molecular biology since the fifth edition of *Molecular Biology of the Gene* appeared four years ago. The first is in the cost and influence of genome sequencing; the second is the explosion in our appreciation of RNA as a regulatory molecule; and the third is the widespread touting of systems biology as the future of our field in the postgenomic era. The influence of all three developments is evident in this, the sixth edition.

Numerous species—together with one of the authors—have had their genomes sequenced in the past four years. And currently each genome can be done at a cost almost 500-fold lower than was possible in 2003. In that year we knew the sequences of the model systems—yeast, worm, *Arabidopsis*, fly, mouse, human—and perhaps two or three other animals. Now we have a much wider representation from the tree of life: we have the chimp, rat, and honeybee genomes; the cat and dog; several more insects; rice; the sea anemone; the opossum; and many others besides. And we have many more representatives of each group: as an example, 13 *Drosophila* species have by now been sequenced. And finally, as noted above, we have entered the era of the individual human genome—as well as James Watson's, Craig Venter's genome has been completely sequenced.

Along with this mushrooming in the amount of sequencing, the *influence* of sequencing is becoming ever more apparent and routine. There are several cases in this new edition where evolutionary and mechanistic arguments are based on the ability to compare genomes—in some cases between closely related species, in others more distantly.

Genome sequences have contributed to the second big development—the growing understanding of all that RNA does. The extent and importance of alternative splicing and the widespread use of regulatory RNAs represent areas where the text has been extensively revised.

Systems biology remains a rather ill-defined term, evoking somewhat different things for different people. For some it reflects high-throughput methodology, for example; for others it reflects mathematical modeling of biological systems. In this edition, we examine one aspect of this emerging field—the one with most obvious and immediate significance to topics covered in this book—namely, the representation and modeling of gene regulatory networks.

Organization of the Book

Although much has changed, many core values and organizing principles of the book have not. Thus, the new edition retains the structure of the last, being divided into five parts.

Part 1 lays the groundwork for what follows—it summarizes the history of genetics and molecular biology and explains the chemical principles that determine the structure and function of macromolecules.

Part 2 covers the organization and maintenance of the genetic material. Beginning with a description of the structures of DNA and RNA, it also covers the organization of genomes in chromosomes and explains DNA replication, recombination, and repair.

Part 3 deals with expression of the genome through transcription, splicing, and translation.

Part 4 is about how the expression of genes within the genome is regulated. This includes mechanisms of transcriptional regulation, the role of regulatory RNAs in controlling gene expression, gene regulation in the control of development, and how changes in regulation underlie much of evolution. Finally, we consider genome-wide studies of gene expression and how gene regulatory networks are modeled and analyzed in the emerging fields of systems and synthetic biology.

Part 5 comprises two chapters: one on the techniques of molecular biology, genomics, proteomics, and bioinformatics and the other on the model organisms whose study has revealed many of the underlying principles of molecular biology.

As well as revision of each chapter, there are significant additions to this edition. Most notably, there are two new chapters and a new range of boxed features.

New Chapters and Boxes

Chapter 18: Regulatory RNAs One of the striking developments since the fifth edition is the extent to which RNAs are found to be regulators of gene expression. In this chapter, we cover everything from riboswitches and small RNAs in bacteria, through RNA interference and microRNAs in eukaryotes, to the role of RNA regulators in X-chromosome inactivation. As well as mechanistic details of how these regulators work, we discuss how they were discovered and how they have afforded us new ways to manipulate gene expression artificially.

Chapter 20: Genome Analysis and Systems Biology The genomes of many animals have been sequenced and found to be strikingly similar. This finding emphasizes that it is largely differences in the regulation, rather than the identity, of the genes within a genome that determine phenotype. Techniques now exist to study genome-wide gene expression patterns; we discuss how these techniques work and what they have revealed. In the second half of the chapter, we learn about the representation of gene regulatory networks as so-called wiring diagrams (an example is shown on the cover of this book as is discussed below). These diagrams emphasize the information flow and types of decision-making steps within such pathways.

Boxes The sixth edition includes an array of new boxes, each assigned to one of four color-coded categories:

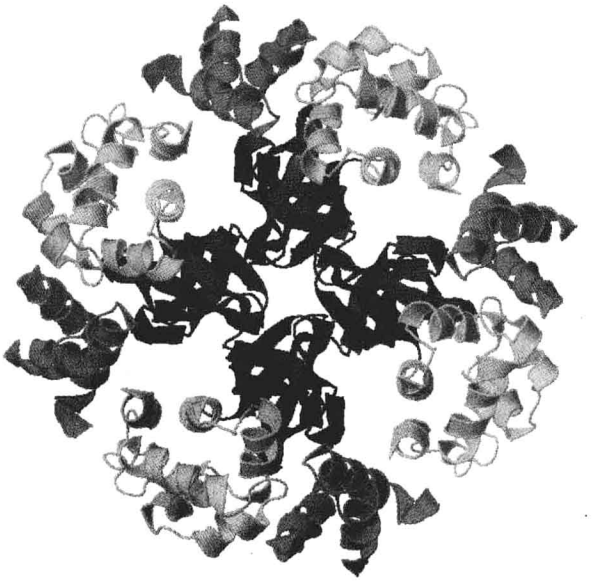
- *KEY EXPERIMENTS* describe critical experiments in each field, ranging from the historical to the very recent. Without disrupting the narrative flow of the main text, they give students insight into how scientific problems are solved.
- *TECHNIQUES* describe techniques of particular relevance to the chapter in question, complementing the more general techniques described in the last two chapters of the book.
- *MEDICAL CONNECTIONS* highlight links between the basic molecular biology described and a variety of human diseases. These boxes emphasize how basic research informs current medical understanding.
- *ADVANCED CONCEPTS* explore selected concepts in more depth to allow students a glimpse of cutting-edge ideas.

As well as being included in the detailed table of contents, there is a separate listing of all the Boxes by topic on page xxxi.

Media Icons New web references and icons within the text direct students to explore the animations and structural tutorials on the companion website.

Supplements

Companion Website www.aw-bc.com/watson
The Companion Website combines the contents from the previous edition's "Student Media" CD-ROM into one fully integrated resource that helps students better understand complex structures and molecular interactions. Two new structural tutorials on Argonaute and RecBCD have been added in the sixth edition in addition to the popular structural media tutorials of the previous edition.



III. RuvA Tetramer-Holliday Junction DNA

In tetrameric RuvA, each monomer is a lobe of the symmetrical tetramer. The domain I beta barrels of each monomer are positioned centrally, and domains II and III are located peripherally.

Examining the charge distribution of atoms over the surface of the RuvA tetramer, it is clear that the DNA binding surface is largely positively charged (basic), whereas the opposite surface is largely negatively charged (acidic). The , orange, and red colors represent relatively negatively charged atoms and the green and blue colors represent more positively charged atoms (red and blue indicate acidic or basic residues). The relative positive charge of the DNA binding surface attracts the negatively charged DNA backbone.

An exception to the mostly basic surface of the DNA binding side of the RuvA tetramer is an eight residue acidic "central pin" containing glutamate[55] and aspartate[56] from each monomer. This negatively charged center may repel the negatively charged oxygens of the DNA backbone, driving the DNA away from the center of the Holliday junction.

A number of residues that interact directly or indirectly (via water molecules) with the DNA backbone line the channels in which Holliday junction DNA is bound.

reset

return to beginning

IV. References

Ariyoshi, M., Nishino, T., Iwasaki, H., Shinagawa, H., Morikawa, K.: Crystal Structure of the Holliday Junction DNA in Complex with a Single Ruva Tetramer. *Proc.Nat.Acad.Sci.* **97**: 8257-8262 (2000).

Hargreaves, D., Rice, D. W., Sedelnikova, S. E., Artymiuk, P. J., Lloyd, R. G., Rafferty, J. B.: Crystal

Glossary
An online glossary defines terms that appear in bold in the text.

Instructor Resource CD-ROM 978-0-3215-2766-0/0-3215-2766-6
This dual-platform CD-ROM contains all art and tables from the book in jpeg and PowerPoint format in high-resolution (150-dpi) files. This CD-ROM also contains the answers to the end-of-chapter Critical Thinking questions posed to students on the Companion Website.

Transparency Acetates 0-3215-3639-8/978-0-3215-3639-6
The transparency package features approximately 300 four-color illustrations from the text selected by the authors.

Cover Design and Part-Opener Photographs

Cover image The cover is a representation from systems biology of a frequently observed motif in the circuitry governing gene expression (see Chapter 20). The motif, known as an incoherent feed-forward loop, consists of two regulatory genes, A and B, and a target gene C whose expression is indicated as the output. In response to an input, gene A is turned on. The gene A product is an activator both of the target gene C and of the second regulatory gene B. The gene B product is a repressor of gene C. The representation "AND" in the figure indicates that the circuit operates with the logic of a so-called AND gate, a term borrowed from electrical engineering, which means that the output requires (in the case shown) the presence of the gene A activator AND the absence of the gene B repressor. Incoherent feed-forward loops have the property of causing target genes to be expressed in a pulse. That is, gene C is turned on by the activator in response to the input and then switched off by the delayed accumulation of the repressor.

The cover design of this, the sixth edition, consciously mimics that of the first edition, published by Benjamin (a forerunner of Benjamin Cummings) in 1965. That cover, together with those of the second through fifth editions, is reproduced on the back cover of this edition. The first edition cover was designed by Bill Prokos, a New York City painter, who in 1965 was working on the art program of another Benjamin book, *Bioenergetics*, by Albert Lehninger. Benjamin saw similarities in the ambition and style of these two books and so gave both essentially the same cover design. The Lehninger book, however, was dominated by a red (rather than a blue) square, and, in place of the turn of DNA double helix seen on *MBoG, Bioenergetics* carried an ATP molecule. Publication of both books was celebrated with a joint party, held in Woods Hole that year.

Cold Spring Harbor Laboratory Photographs As in the previous edition, each part opener includes a few photographs, some newly added to this edition. These pictures, selected from the archives of Cold Spring Harbor Laboratory, were all taken at the lab, the majority during the Symposia hosted there almost every summer since 1933. Captions identify who is in each picture and when it was taken. Many more examples of these historic photos can be found at the CSHL archives website (http://archives.cshl.edu/).

Acknowledgments

Parts of the current edition grew out of an introductory course on molecular biology taught by one of us (RL) at Harvard University, and this author is grateful to Steve Harrison and Jim Wang who contributed to this course in past years and whose influence is reflected in Chapter 6 and elsewhere. We are also particularly grateful to Craig Hunter, who wrote the section on the worm for Chapter 21, and to Rob Martienssen, who wrote the section on the plant *Arabidopsis* for that same chapter.

We have shown sections of the manuscript to various colleagues and their comments have been most useful in ensuring the text and figures reflect current ideas and information. Specifically, we thank Katsura Asano, Jamie Cate, Amy Caudy, Richard Ebright, Mike Eisen, Chris Fromme, Brenton Graveley, Ann Hochschild, Jim Hu, David Jeruzalmi, Leemor Joshua-Tor, Sandy Johnson, Adrian Krainer, Karoline Luger, Julian Lewis, Sue Lovett, Rob Martienssen, Bill McGinnis, Matt Michael, Lily Mirels, Nipam Patel, Mark Ptashne, Danny Reinberg, and Bruce Stillman.

We also thank those who provided us with figures, or the wherewithal to create them: Sean Carroll, Seth Darst, Richard Ebright, Brenton Graveley, Ann Hochschild, Julian Lewis, Bill McGinnis, Phoebe Rice, Dan Rokhsar, Nori Satoh, Matt Scott, Peter Sorger, Tom Steitz, Andrzej Stasiak, Dan Voytas, and Steve West.

We are indebted to Leemor Joshua-Tor who rendered all the structure figures so beautifully. Her skill and patience were much appreciated. We are also grateful to

those who provided their software[1]: Per Kraulis, Robert Esnouf, Ethan Merrit, Barry Honig, and Warren Delano. Coordinates were obtained from the Protein Data Bank (www.rcsb.org/pdb/); and citations to those who solved each structure are included in the figure legends.

Our art program was again executed by a talented team from the Dragonfly Media Group, led by Craig Durant and assisted by Helen Wortham. Denise Weiss and Ed Atkeson produced the cover design. We thank Clare Clark and the CSHL Archive for providing the photos for the part openers and for much help tracking them down.

We thank Susan Winslow at Benjamin Cummings who did much to ensure this new edition happened and even more to make things as easy as possible once it began in earnest. Gary Carlson took over late in the game, and we are grateful to him for letting things continue seamlessly. In overseeing the book's development, Jan Argentine managed endlessly to accommodate our demands, reorganizing our tasks to provide the time and support we needed, while still protecting the sacred schedule. Kaaren Janssen edited our text and redrew our messy sketches, generating momentum with her inexhaustible desire to help, and Inez Sialiano kept organized the resulting drafts and corrections, and Carol Brown the permissions. In production, the patience of Kathleen Bubbeo and Susan Schaefer was as tireless as it needed to be in accommodating the changes we continued to generate even after we were supposed to have finished. And we are grateful to Denise Weiss, who not only oversaw production, but did much herself to make the book look so good from page layout to design. John Inglis kept a watchful eye on proceedings, providing useful advice whenever needed.

And finally we thank our families and friends for again providing strong support, despite having to put up with the demands of the project just as much as we did.

JAMES D. WATSON
TANIA A. BAKER
STEPHEN P. BELL
ALEXANDER GANN
MICHAEL LEVINE
RICHARD LOSICK

[1]Per Kraulis granted permission to use MolScript (Kraulis P.J. 1991. MOLSCRIPT: A program to produce both detailed and schematic plots of protein structures. *J. Appl. Crystallog.* **24:** 946–950). Robert Esnouf gave permission to use BobScript (Esnouf R.M. 1997. An extensively modified version of MolScript that includes greatly enhanced coloring capabilities. *J. Mol. Graph. Model.* **15:** 132–134). In addition, Ethan Merritt gave us use of Raster 3D (Merritt E.A. and Bacon D.J. 1997. Raster3D: Photorealistic molecular graphics. *Methods Enzymol.* **277:** 505–524), and Barry Honig granted permission to use GRASP (Nicholls A., Sharp K.A., and Honig B. 1991. Protein folding and association: Insights from the interfacial and thermodynamic properties of hydrocarbons. *Proteins* **11:** 281–296). Warren DeLano agreed to the use of PyMOL (DeLano W.L. 2002. *The PyMOL Molecular Graphics System*. DeLano Scientific, Palo Alto, California).

About the Authors

JAMES D. WATSON was Director of Cold Spring Harbor Laboratory from 1968 to 1993, was its President from 1994 to 2003, and is now its Chancellor. He spent his undergraduate years at the University of Chicago and received his Ph.D. in 1950 from Indiana University. Between 1950 and 1953, he did postdoctoral research in Copenhagen and Cambridge, England. While at Cambridge, he began the collaboration that resulted in the elucidation of the double-helical structure of DNA in 1953. (For this discovery, Watson, Francis Crick, and Maurice Wilkins were awarded the Nobel Prize in 1962.) Later in 1953, he went to the California Institute of Technology. He moved to Harvard in 1955, where he taught and did research on RNA synthesis and protein synthesis until 1976. He was the first Director of the National Center for Genome Research of the National Institutes of Health from 1989 to 1992, and his own genome was sequenced in 2007. Dr. Watson was sole author of the first, second, and third editions of *Molecular Biology of the Gene*, and a co-author of the fourth and fifth editions. These were published in 1965, 1970, 1976, 1987, and 2003, respectively. He is also a co-author of two other textbooks: *Molecular Biology of the Cell* and *Recombinant DNA*.

TANIA A. BAKER is the Whitehead Professor of Biology at the Massachusetts Institute of Technology and an Investigator of the Howard Hughes Medical Institute. She received a B.S. in biochemistry from the University of Wisconsin, Madison, and a Ph.D. in biochemistry from Stanford University in 1988. Her graduate research was carried out in the laboratory of Professor Arthur Kornberg and focused on mechanisms of initiation of DNA replication. She did postdoctoral research in the laboratory of Dr. Kiyoshi Mizuuchi at the National Institutes of Health, studying the mechanism and regulation of DNA transposition. Her current research explores mechanisms and regulation of genetic recombination, enzyme-catalyzed protein unfolding, and ATP-dependent protein degradation. Professor Baker received the 2001 Eli Lilly Research Award from the American Society of Microbiology and the 2000 MIT School of Science Teaching Prize for Undergraduate Education, is a fellow of the American Academy of Arts and Sciences since 2004, and was elected to the National Academy of Sciences in 2007. She is co-author (with Arthur Kornberg) of the book *DNA Replication*, Second Edition.

STEPHEN P. BELL is a Professor of Biology at the Massachusetts Institute of Technology and an Investigator of the Howard Hughes Medical Institute. He received B.A. degrees from the Department of Biochemistry, Molecular Biology, and Cell Biology and the Integrated Sciences Program at Northwestern University and a Ph.D. in biochemistry at the University of California, Berkeley in 1991. His graduate research was carried out in the laboratory of Dr. Robert Tjian and focused on eukaryotic transcription. He did postdoctoral research in the laboratory of Dr. Bruce Stillman at Cold Spring Harbor Laboratory, working on the initiation of eukaryotic DNA replication. His current research focuses on the mechanisms controlling the duplication of eukaryotic chromosomes. Professor Bell received the 2001 ASBMB–Schering-Plough Scientific Achievement Award, the 1998 Everett Moore Baker Memorial Award for Excellence in Undergraduate Teaching at MIT, and the 2006 MIT School of Science Teaching Award.

ALEXANDER GANN is Editorial Director of Cold Spring Harbor Laboratory Press and a faculty member of the Watson School of Biological Sciences at Cold Spring Harbor Laboratory. He received his B.Sc. in microbiology from University College London and a Ph.D. in molecular biology from The University of Edinburgh in 1989. His graduate research was carried out in the laboratory of Noreen Murray and focused on DNA recognition by restriction enzymes. He did postdoctoral research in the laboratory of Mark Ptashne at Harvard, working on transcriptional regulation, and that of Jeremy Brockes at the Ludwig Institute for Cancer Research at University College London, where he worked on newt limb regeneration. He was a Lecturer at Lancaster University, United Kingdom, from 1996 to 1999, before moving to Cold Spring Harbor Laboratory. He is co-author (with Mark Ptashne) of the book *Genes & Signals* (2002).

MICHAEL LEVINE is a Professor of Molecular and Cell Biology at the University of California, Berkeley, and is also Co-Director of the Center for Integrative Genomics. He received his B.A. from the Department of Genetics at University of California, Berkeley, and his Ph.D. with Alan Garen in the Department of Molecular Biophysics and Biochemistry from Yale University in 1981. As a postdoctoral fellow with Walter Gehring and Gerry Rubin from 1982 to 1984, he studied the molecular genetics of *Drosophila* development. Professor Levine's research group currently studies the gene networks responsible for the gastrulation of the *Drosophila* and *Ciona* (sea squirt) embryos. He holds the F. Williams Chair in Genetics and Development at the University of California, Berkeley. He was awarded the Monsanto Prize in Molecular Biology from the National Academy of Sciences in 1996 and was elected to the American Academy of Arts and Sciences in 1996 and the National Academy of Sciences in 1998.

RICHARD LOSICK is the Maria Moors Cabot Professor of Biology, a Harvard College Professor, and a Howard Hughes Medical Institute Professor in the Faculty of Arts and Sciences at Harvard University. He received his A.B. in chemistry at Princeton University and his Ph.D. in biochemistry at the Massachusetts Institute of Technology. Upon completion of his graduate work, Professor Losick was named a Junior Fellow of the Harvard Society of Fellows when he began his studies on RNA polymerase and the regulation of gene transcription in bacteria. Professor Losick is a past Chairman of the Departments of Cellular and Developmental Biology and Molecular and Cellular Biology at Harvard University. He received the Camille and Henry Dreyfuss Teacher-Scholar Award, is a member of the National Academy of Sciences, a Fellow of the American Academy of Arts and Sciences, a Fellow of the American Association for the Advancement of Science, a Fellow of the American Academy of Microbiology, a member of the American Philosophical Society, and a former Visiting Scholar of the Phi Beta Kappa Society. Professor Losick is the 2007 winner of the Selman A. Waksman Award in Microbiology of the National Academy of Sciences.

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WE WISH TO THANK ALL OF THE INSTRUCTORS for their thoughtful suggestions and comments on versions of many chapters in this book.

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