科爱传播
KE'AI COMMUNICATIONS
·导读版·

Handbook of Epigenetics
The New Molecular and Medical Genetics

表观遗传学手册
新分子遗传学与医学遗传学

Trygve Tollefsbol

ELSEVIER
原版引进

科学出版社

Handbook of Epigenetics

The New Molecular and Medical Genetics

表观遗传学手册

新分子遗传学与医学遗传学

Edited by

Trygve Tollefsbol

Department of Biology

University of Alabama at Birmingham

Birmingham, AL, 35294-1170, USA

科学出版社

北京

图字:01-2011-1552

This is an annotated version of
Handbook of Epigenetics: The New Molecular and Medical Genetics
Edited by Trygve Tollefsbol.

ISBN: 978-0-12-375709-8

图书在版编目(CIP)数据

表观遗传学手册:新分子遗传学与医学遗传学=Handbook of Epigenetics: The New Molecular and Medical Genetics:英文/(美)托勒夫斯波(Tollefsbol,T.)主编.—北京:科学出版社,2011

ISBN 978-7-03-031742-1

Ⅰ.①表… Ⅱ.①托… Ⅲ.①分子遗传学-手册-英文②医学遗传学-手册-英文 Ⅳ.①Q75-62②R394-62

中国版本图书馆 CIP 数据核字(2011)第 121212 号

责任编辑:李小汀/责任印制:钱玉芬/封面设计:耕者设计工作室

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

*

2011 年 7 月第 一 版 开本:787×1092 1/16
2011 年 7 月第一次印刷 印张:42 1/4
印数:1—1 800 字数:1 000 000

定价:168.00 元

(如有印装质量问题,我社负责调换)

导　读

“表观遗传学”的研究对象是一类特殊的**可继承**的生物性状的变化。不同于经典的遗传性状突变，表观遗传性状的变化并非由 DNA 突变造成。而且表观遗传性状的变化既具有可继承性，又有一定程度的可逆性。

在后基因组时代，表观遗传学是生命科学领域的一个前沿和热点。在过去的十余年中，表观遗传学研究突飞猛进，许多经典的表观遗传学现象的分子机制得到了诠释。但是，与近年来表观遗传学领域的迅猛发展以及研究论文的指数式上升所不相称的是表观遗传学领域书籍的相对贫乏。这无疑不利于青年学生和其他领域的科学家对表观遗传学产生兴趣，并加深了解。科学出版社将美国冷泉港实验室出版社 2007 年出版的《表观遗传学》先后影印及翻译出版，部分缓解了国内读者对表观遗传学领域书籍的渴望。然而，四年多来表观遗传学领域又出现了众多突破性研究成果，而且此前出版的《表观遗传学》更侧重生物学机制的阐述，较少涉及到与人类疾病直接相关的医学表观遗传学。因此，科学出版社决定引进 Elsevier 出版集团 2011 年出版的《表观遗传学手册：新分子遗传学与医学遗传学》，并以导读版的形式出版。这无疑是恰逢其时。

《表观遗传学手册：新分子遗传学与医学遗传学》由美国阿拉巴马大学 Trygve Tollefsbol 教授主编，各章节均由活跃在表观遗传学各个领域的科学家撰写。Trygve Tollefsbol 教授是研究表观遗传因素在衰老及癌症发生过程中的作用和机理的科学家，该书在介绍表观遗传学分子机理的同时，用大量的篇幅介绍了表观遗传学相关疾病，以及正在兴起的表观遗传学疗法。

由于此前冷泉港实验室出版社出版的《表观遗传学》用大量的篇幅介绍了表观遗传现象的相关分子机制。因此，Trygve Tollefsbol 教授在主编《表观遗传学手册：新分子遗传学与医学遗传学》时仅用两个章节简单地介绍了表观遗传现象的相关分子机制，但却涵盖了前书未及探讨的表观遗传学领域的两大最新进展：组蛋白去甲基化和 DNA 胞嘧啶的 5-羟甲基化。从而，有助于读者们了解表观遗传学研究的最新前沿。

《表观遗传学手册：新分子遗传学与医学遗传学》的最大特色是强调了表观遗传学机制在发育过程、正常生理状态及病理状态下的作用。这使得更多的读者能够认识到，从经典表观遗传学现象中发现的分子机制，并非仅仅局限于一些特殊的生命现象。相反，这些分子机制还在更多的生命进程中被生物体所利用，并参与正常的发育过程和生理功能。因此，表观遗传因子的异常会导致发育失常并诱发疾病。本书用多个章节介绍了表观遗传学疾病和新兴的表观遗传疗法，因此对于研究型临床医生和药物设计人员，也不失为一本有价值的参考书。

此外，本书系统性地介绍了表观遗传学领域的相关研究技术，为将要涉足表观遗传学研究的青年学生和其他领域的科学家提供了充分的入门介绍。

在介绍本书之余，笔者还希望能藉此机会向读者们介绍一下自己对表观遗传调控体系的认识。表观遗传现象，除了朊粒等极少数个例，归根到底是基因的转录水平调控。

基因的转录水平调控在绝大多数情况下取决于识别特定 DNA 序列的转录因子，例如能够将体细胞诱导成全能性细胞（iPS）的四个 Yamanaka 因子。然而，许多情况下转录因子并不足以改变基因的表达状态，因为它们的靶基因处于“封闭”的异染色质状态，阻碍了转录因子的结合。而染色质结构“封闭”或“开放”状态的形成、维持和转换，正是表观遗传学研究的核心问题。

对于刚刚对表观遗传学产生兴趣的青年学子而言，显而易见的问题是，“我们为什么需要有一个表观遗传调控体系？这一体系与经典的遗传体系的共同点、差异性和互补性又是什么?”显然，本学科的所有科学家都没有这些问题的最终答案。但一个大致的轮廓却可以被勾勒出来。表观遗传调控体系存在的基本意义毋庸置疑是为了实现多细胞复杂生物中不同细胞间功能的分化，换言之，是为了使得“拥有同一个基因组的不同体细胞能拥有不同的表观基因组，从而分别表达其特有的转录组”。因此，经典遗传体系与表观遗传体系的最大区别就在于前者是刚性的，不会发生可逆的变化；而后者则具有一定的可塑性，可以对内在或外在环境的信号作出响应，通过对表观基因组的改变实现转录组的变化。这就使得多细胞生物中不同细胞间功能的分化成为可能。而类似于经典遗传体系的是，表观遗传体系也具有一定的可继承性，从而使细胞在扩增时能够维持其特有的表观基因组和相应的转录组。

过刚易折，过柔则弱。上善若水，刚柔相济。这或许就是表观遗传体系的写照了。

朱冰
北京生命科学研究所
2011 年 6 月于静思湖畔

前　言

表观遗传学被许多人认为是“新遗传学”，因为许多生命进程并非由基因突变所控制，而是被可逆却又可继承的表观遗传现象所控制。这些表观遗传现象涵盖 DNA 甲基化、组蛋白修饰乃至朊粒等。表观遗传进程发生在众多的物种中并且控制大量的生命功能，例如组织/器官再生、X-染色体失活、干细胞分化、基因组印迹和衰老。表观遗传异常会导致各种疾病，包括癌症和免疫系统、内分泌系统、神经系统疾病。上述疾病中的一部分已经有了相应的临床干预手段，更多的表观遗传疗法很可能将在近期出现。

《表观遗传学手册：新分子遗传学与医学遗传学》全面系统地介绍了表观遗传学，并且概括了这一迷人领域的近期研究进展。本书通过阐述表观遗传学的进化、正常生命活动和病理条件下的表观遗传机理以及表观遗传学在研究和治疗中的应用，相信会吸引学生和科研及医药工业研究人员的兴趣。

（朱　冰　译）

目　录

（朱　冰　译）

CONTENTS

CONTRIBUTORS

Masahiko Abematsu
Laboratory of Molecular Neuroscience
Graduate School of Biological Sciences
Nara Institute of Science and Technology
Nara 630-0101, Japan

David W. Anderson
Department of Pathology
St. Luke's Hospital and Health Network
801 Ostrum Street
Bethlehem, PA 18015, USA

Roberta H. Andronikos
Murdoch Childrens Research Institute
Flemington Road
Parkville, Victoria 3052, Australia

Adriana Arita
Nelson Institute of Environmental Medicine
New York University School of Medicine
57 Old Forge Road, New York, NY 10987, USA

Zoya Avramova
School of Biological Sciences, UNL
E-300 Beadle Center
P.O. Box 88066
Lincoln, NE 68588-0666, USA

Autumn J. Bernal
Department of Radiation Oncology
Box 3433
Duke University Medical Center
Durham, NC 27710, USA

Javier Campión
Department of Nutrition and Food Sciences,
Physiology and Toxicology
University of Navarra, 31080 Pamplona
Navarra, Spain

Vince Castranova
PPRB/NIOSH
Basic Pharmaceutical Sciences
West Virginia University
1095 Willowdale Road
Morgantown, WV 26505, USA

Frances A. Champagne
Department of Psychology
Columbia University
Room 406, Schermerhorn Hall
1190 Amsterdam Avenue
New York, NY 10027, USA

Wendy Chao
Department of Ophthalmology
Schepens Eye Research Institute
Harvard Medical School
20 Staniford Street
Boston, MA 02114, USA

Fei Chen
PPRB/NIOSH
Basic Pharmaceutical Sciences
West Virginia University
1095 Willowdale Road
Morgantown, WV 26505, USA

Xiaowei Sylvia Chen
Department of Biochemistry
University of Otago
Dunedin 9054, New Zealand

Xiaodong Cheng
Department of Biochemistry
Emory University School of Medicine
1510 Clifton Road
Atlanta, Georgia 30322, USA

Lesley Collins
Massey Genome Service
Massey University
Palmerston North, New Zealand

Max Costa
Nelson Institute of Environmental Medicine
New York University School of Medicine
57 Old Forge Road, New York, NY 10987, USA

James P. Curley
Department of Psychology
Columbia University
Room 406, Schermerhorn Hall
1190 Amsterdam Avenue
New York, NY 10027, USA

Walter Doerfler
Institute for Virology
Erlangen University Medical School
Schlossgarten 4
D-91054 Erlangen, Germany

Tamar Dvash
Department of Human Genetics
The Eli and Edythe Broad Center for Regenerative
Medicine and Stem Cell Research

David Geffen School of Medicine
University of California Los Angeles
695 Charles E. Young Drive South
Los Angeles, CA 90095, USA

Thomas Eggermann
Institute of Human Genetics
University Hospital
RWTH Aachen, Pauwelsstrasse 30, DE-52074
Aachen, Germany

Guoping Fan
Department of Human Genetics
The Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research
David Geffen School of Medicine
University of California Los Angeles
695 Charles E. Young Drive South
Los Angeles, CA 90095, USA

Tamara B. Franklin
Brain Research Institute
Medical Faculty of the University of Zürich and Department of Biology
Swiss Federal Institute of Technology
Winterthurerstrasse 190
CH-8057 Zürich, Switzerland

Steffen Gay
Center of Experimental Rheumatology
University Hospital and Zurich Center of Integrative Human Physiology (ZIHP)
University Hospital Zürich,
8091, Zürich, Switzerland

Eric Gilson
Laboratory of Biology and Pathology of Genomes CNRS UMR6267/INSERM U998/UNS
28 Avenue Valombrose, Faculte de Medecine
06107 Nice Cedex 2, France

Johannes Gräff
Brain Research Institute
Medical Faculty of the University of Zürich and Department of Biology
Swiss Federal Institute of Technology
Winterthurerstrasse 190
CH-8057 Zürich, Switzerland

Hideharu Hashimoto
Department of Biochemistry
Emory University School of Medicine
1510 Clifton Road
Atlanta, GA 30322, USA

Naoko Hattori
Carcinogenesis Division
National Cancer Center Research Institute
1-1 Tsukiji 5-chome
Chuo-ku, Tokyo 104-0045, Japan

Zdenko Herceg
Epigenetics Group
International Agency for Research on Cancer (IARC)
150 cours Albert Thomas
69372 Lyon cedex 08, France

Norbert Hochstein
QIAGEN
Qiagen Strasse 1
40724, Hilden, Germany

John R. Horton
Department of Biochemistry
Emory University School of Medicine
1510 Clifton Road
Atlanta, GA 30322, USA

Simon H. House
22 Stanley Street
Southsea, Portsmouth, Hants
PO5 2DS, UK

Karolina Janitz
The Ramaciotti Centre for Gene Function Analysis
The University of New South Wales, Sydney
NSW 2052, Australia

Michal Janitz
School of Biotechnology and Biomolecular Sciences
The University of New South Wales, Sydney
NSW 2052, Australia

Randy L. Jirtle
Department of Radiation Oncology
Box 3433
Duke University Medical Center
Durham, NC 27710, USA

Ji-Hoon E. Joo
Murdoch Children's Research Institute
Flemington Road
Parkville, Victoria 3052, Australia

Berry Juliandi
Laboratory of Molecular Neuroscience
Graduate School of Biological Sciences
Nara Institute of Science and Technology
Nara 630-0101, Japan

Astrid Jungel
Center of Experimental Rheumatology
University Hospital and Zurich Center of Integrative Human Physiology (ZIHP)
University Hospital Zürich,
8091, Zürich, Switzerland

Hong Kan
PPRB/NIOSH
Basic Pharmaceutical Sciences
West Virginia University
1095 Willowdale Road
Morgantown, WV 26505, USA

Tae Hoon Kim
Yale University School of Medicine
333 Cedar Street SHM I-142B
New Haven, CT 06520-8005, USA

Yoon Jung Kim
Yale University School of Medicine
333 Cedar Street SHM I-142B
New Haven, CT 06520-8005, USA

Hervé Lalucque
Institut de Genetique et Microbiologie
UMR CNRS 8621
Univ Paris Sud 11
91405 Orsay cedex, France

Sheila C.S. Lima
Epigenetics Group
International Agency for Research on Cancer (IARC)
150 Cours Albert Thomas
Rhone-Alpes, 69008 Lyon, France

Sally A. Litherland
Metabolic Signaling and Disease Program
Diabetes & Obesity Center
Sanford-Burnham Medical Research Center
at Lake Nona
6400 Sanger Road
Orlando, FL 32827, USA

John C. Lucchesi
Department of Biology
Emory University
1510 Clifton Road, Atlanta, GA 30322, USA

Hanna Maciejewska-Rodrigues
Center of Experimental Rheumatology
University Hospital and Zurich Center of
Integrative Human Physiology (ZIHP)
University Hospital Zürich,
8091, Zürich, Switzerland

Frédérique Magdinier
Laboratoire de Génétique Médicale et
Génomique Fonctionnelle
INSERM, UMR S_910/Université de la
Méditerannée
Faculté de Médecine de la Timone
27 Bd Jean Moulin 13385
Marseille cedex05, France

Fabienne Malagnac
Institut de Genetique et Microbiologie
UMR CNRS 8621
Univ Paris Sud 11
91405 Orsay cedex, France

Isabelle M. Mansuy
Brain Research Institute
Medical Faculty of the University of Zürich
and Department of Biology
Swiss Federal Institute of Technology
Winterthurerstrasse 190, CH-8057 Zürich
Switzerland

J. Alfredo Martinez
Department of Nutrition and Food Sciences,
Physiology and Toxicology
University of Navarra, 31080 Pamplona
Navarra, Spain

Rahia Mashoodh
Department of Psychology
Columbia University
Room 406, Schermerhorn Hall
1190 Amsterdam Avenue
New York, NY 10027, USA

Fermin I. Milagro
Department of Nutrition and Food Sciences,
Physiology and Toxicology
University of Navarra, 31080 Pamplona
Navarra, Spain

Ashleigh Miller
Department of Medicine
Division of Hematology and Oncology
University of California-San Francisco
San Francisco, CA 94143, USA

Pamela Munster
Department of Medicine
Division of Hematology and Oncology
University of California-San Francisco
San Francisco, CA 94143, USA

Susan K. Murphy
Department Gynecologic Oncology
Box 91092
Duke University Medical Center
Durham, NC 27710, USA

Rabih Murr
Epigenetics Group
International Agency for Research on
Cancer (IARC)
150 cours Albert Thomas
69372 Lyon cedex 08, France

Kinichi Nakashima
Laboratory of Molecular Neuroscience
Graduate School of Biological Sciences
Nara Institute of Science and Technology
Nara 630-0101, Japan

Anja Naumann
Institute for Virology
Erlangen University Medical School
Schlossgarten 4
D-91054 Erlangen, Germany

Alexandre Ottaviani
Laboratoire de Biologie Moléculaire de la Cellule
CNRS UMR5239, Ecole Normale Supérieure de Lyon
UCBL1, IFR128, 46 allée d'Italie
69364 Lyon Cedex 07, France

Jacob Peedicayil
Department of Pharmacology and Clinical Pharmacology
Christian Medical College
Vellore, India

Gerd P. Pfeifer
Division of Biology
Beckman Research Institute of the City of Hope
1500 East Duarte Road
Duarte, CA 91010, USA

Luis Felipe Ribeiro Pinto
Divisão de Genética — Coordenação de Pesquisa
Instituto Nacional de Câncer
Rua André Cavalcanti, 37, 40 Andar
CEP: 20231-050
Riode Janiero, RJ, Brazil

Vincenzo Pirrotta
Department of Molecular Biology and Biochemistry
Rutgers University
604 Allison Road
Piscataway, NJ 08854, USA

Pier Lorenzo Puri
Istituto Dulbecco Telethon at Istituto Di Ricovero e Cura a Carattere Scientifico
Santa Lucia Fondazione and European Brain Research Institute
64 Via del Fosso di Fiorano
00143 Rome, Italy
The Sanford/Burnham Institute for Medical Research
10901 North Torrey Pines Road
La Jolla, CA 92037-1062, USA

Tibor A. Rauch
Section of Molecular Medicine
Department of Orthopedic Surgery
Rush University Medical Center
Chicago, IL 60612, USA

Lee B. Riley
Department of Oncology,
St. Luke's Hospital and Health Network,
801 Ostrum Street,
Bethlehem, PA 18015, USA

Eric D. Roth
Department of Neurobiology
1825 University Blvd, SHEL 1070
Birmingham, AL 35294, USA

Tania L. Roth
Department of Neurobiology
1825 University Blvd, SHEL 1070
Birmingham, AL 35294, USA

Richard Saffery
Murdoch Childrens Research Institute
Flemington Road
Parkville, Victoria 3052, Australia

Vittorio Sartorelli
Laboratory of Muscle Stem Cells and Gene Regulation
National Institute of Arthritis, Musculoskeletal and Skin Diseases
National Institutes of Health
Bethesda, MD, USA

Caroline Schluth-Bolard
Laboratoire de Biologie Moléculaire de la Cellule
CNRS UMR5239, Ecole Normale Supérieure de Lyon
UCBL1, IFR128, 46 allée d'Italie
69364 Lyon Cedex 07, France

Barbara Schönfeld
Allan Wilson Centre for Molecular Ecology and Evolution
Massey University
Palmerston North, New Zealand

Axel Schumacher
Centre for Addiction and Mental Health,
Toronto, ON M5T 1R8, Canada

Philippe Silar
Institut de Genetique et Microbiologie
UMR CNRS 8621
Univ Paris Sud 11
91405 Orsay cedex, France

Kjetil Søreide
Department of Surgery
Stavanger University Hospital
Armaver Hansenvei 20
POB 8100, N-4068
Stavanger, Norway

J. David Sweatt
Department of Neurobiology
1825 University Blvd, SHEL 1070
Birmingham, AL 35294, USA

Scott Thomas
Department of Medicine
Division of Hematology and Oncology
University of California-San Francisco
San Francisco, CA 94143, USA

Kenneth T. Thurn
Department of Medicine
Division of Hematology and Oncology
University of California-San Francisco
San Francisco, CA 94143, USA

Trygve O. Tollefsbol
Department of Biology
175 Campbell Hall
1300 University Boulevard
University of Alabama at Birmingham
Birmingham, AL 35294-1170, USA

Toshikazu Ushijima
Carcinogenesis Division
National Cancer Center Research Institute
1-1 Tsukiji 5-chome
Chuo-ku, Tokyo 104-0045, Japan

David A. Wacker
Yale University School of Medicine
333 Cedar Street SHM I-142B
New Haven, CT 06520, USA

Stefanie Weber
Institute for Virology
Erlangen University Medical School
Schlossgarten 4
D-91054 Erlangen, Germany

Xing Zhang
Department of Biochemistry
Emory University School of Medicine
1510 Clifton Road
Atlanta, GA 30322, USA

PREFACE

Epigenetics is considered by many to be the "new genetics" because many biological processes are controlled not through gene mutations, but rather through reversible and heritable epigenetic phenomena ranging from DNA methylation to histone modifications to prions. Epigenetic processes occur in diverse organisms and control a vast array of biological functions, such as tissue/organ regeneration, X-chromosome inactivation, stem cell differentiation, genomic imprinting, and aging. Epigenetic aberrations underlie many diseases, including cancer and disorders of the immune, endocrine, and nervous systems; clinical intervention is already in place for some of these disorders and many novel epigenetic therapies are likely on the horizon.

Handbook of Epigenetics: The New Molecular and Medical Genetics is the first comprehensive analysis of epigenetics, and summarizes recent advances in this intriguing field of study. This book will interest students and researchers in both academics and industry by illuminating the evolution of epigenetics, the epigenetic basis of normal and pathological processes, and the practical applications of epigenetics in research and therapeutics.

CHAPTER 1

Epigenetics: The New Science of Genetics

Trygve O. Tollefsbol[1,2,3,4,5]
[1]Department of Biology, University of Alabama at Birmingham, AL 35294
[2]Center for Aging, University of Alabama at Birmingham, AL 35294
[3]Comprehensive Cancer Center, University of Alabama at Birmingham, AL 35294
[4]Nutrition Obesity Research Center, University of Alabama at Birmingham, AL 35294
[5]Comprehensive Diabetes Center, University of Alabama at Birmingham, AL 35294, USA

INTRODUCTION

The term epigenetics was first introduced in 1942 by Conrad Waddington and was defined as the causal interactions between genes and their products that allow for phenotypic expression [1]. This term has now been somewhat redefined and although there are many variants of the definition of this term today, a consensus definition is that epigenetics is the collective heritable changes in phenotype due to processes that arise independent of primary DNA sequence. This heritability of epigenetic information was for many years thought to be limited to cellular divisions. However, it is now apparent that epigenetic processes can be transferred in organisms from one generation to another [2–3]. This phenomenon was first described in plants [4] and has been expanded to include yeast, *Drosophila*, mouse and, possibly, humans [5–7].

THE BASICS OF DNA METHYLATION AND HISTONE MODIFICATIONS

In most eukaryotes DNA methylation, the most studied of epigenetic processes, consists of transfer of a methyl moiety from S-adenosylmethionine (SAM) to the 5-position of cytosines in certain CpG dinucleotides. This important transfer reaction is catalyzed by the DNA methyltransferases (DNMTs). The three major DNMTs are DNMT1, 3A and 3B and DNMT1 catalyzes what is referred to as maintenance methylation that occurs during each cellular replication as the DNA is duplicated. The other major DNMTs, 3A and 3B, are known more for their relatively higher *de novo* methylation activity where new 5-methylcytosines are introduced in the genome at sites that were not previously methylated. The most significant aspect of DNA methylation, which can also influence such processes as X chromosome inactivation and cellular differentiation, is its effects on gene expression. In general, the more methylated a gene regulatory region, the more likely it is that the gene activity will become down-regulated and vice versa although there are some notable exceptions to this dogma [8]. Chapter 2 of this book reviews the mechanisms of DNA methylation, methyl-CpG recognition and demethylation in mammals. Recent advances have highlighted important roles of UHRF1 and DNMT3L that are required for maintenance and *de novo* methylation,

Handbook of Epigenetics: The New Molecular and Medical Genetics. DOI: 10.1016/B978-0-12-375709-8.00001-0