



· 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



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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

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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，笔者还希望能借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。

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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)

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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.

Epigenetics: The New Science of Genetics

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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,