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DNA-蛋白质互作

原理与实验方案（原著第3版）

DNA-Protein Interactions

Principles and Protocols (Third Edition)

Tom Moss and Benoît Leblanc

科学出版社

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基因组时代的 DNA-蛋白质相互作用研究

现代生物学史上最有影响力的事件莫过于人类基因组计划（Human Genome Project）。这项预算 30 亿美元的庞大研究计划有美、英、法、德、日、中、印等国的众多顶尖科学工作者参与，于 1990 年正式启动，2001 年绘出草图，2003 年宣告提前两年完成。其间，私营机构 Celera 于 1998 年加入竞争，对该计划起到了很大的推动作用。令人欣慰的是，这一计划也极大地推动了测序技术的发展，2007 年推出的第二代测序技术（Next Generation Sequencing）测定一个人的全基因组的费用降到了仅数百万美元（是人类基因组计划费用的万分之一），现在正在研发并逐渐推向市场的第三代测序技术更是把目标定在了一千美元。在第二代测序技术面世后推出的千人基因组计划（1000 Genomes Project）预计测定五个大种群共 2500 个个体的全基因组信息（现已大部分完成），是研究种群差异的重要参考。美国的 23andMe 公司更是推出了根据全基因组 SNP 信息（single-nucleotide polymorphism）寻根并预测重大疾病隐患的服务，现在已经将费用降低到 99 美元。可以预见在不久的将来，很多人将拥有自己的全基因组信息，为个体化医疗提供高科技的参考和保证。

人类基因组计划的终极目标是弄清人类基因组上 33 亿碱基对里包含的遗传密码，而全基因组序列的测定只是万里长征走完了第一步，因为序列本身不能告诉我们 2 万 5 千个左右的人类基因的表达是如何被精密调控的。而正是这些精密调控决定了受精卵如何发育成完整的个体，婴幼儿如何一步步成长，以及成人如何逐渐衰老。同样重要的是，人类疾病大多是由基因和环境相互作用造成的，无论是先天的基因变异，还是后天的不良生活环境或习惯，都可能对人体系统的精密调控产生破坏性影响，或急或缓地以疾病形式体现出来。鉴于基因表达调控的重要性，在 2003 年人类基因组计划完成以后，美国又紧接着启动了 ENCODE 计划，意在弄清人类基因组的全部功能单元特别是调控元件。作为对这一计划的加强，美国在 2007 年又启动了 modENCODE 计划，意在弄清代表性模式生物（主要是果蝇和线虫）的系统调控机制，并帮助验证从 ENCODE 计划得到的一些预测。

我们目前所知的调控类型主要包括转录因子对基因表达的直接调控，DNA 甲基化和组蛋白修饰的表观遗传调控，以及 miRNA 在多方面的复杂调控，前两者都是通过 DNA-蛋白质相互作用而实现的，因此研究 DNA-蛋白质相互作用是最终揭示人类遗传密码的必由之路。转录因子对基因表达的调控是一个经典课题，传统上是用低通量的分子生物学实验技术来完成的。在基因组学时代来临以后，由于预计人类基因组包含数千个转录因子以及未知数量的结合位点，传统的低通量技术已经无法适应全基因组的调控机制研究，因而高通量的全基因组分析技术得以蓬勃发展。但是高通量技术往往在体外测定而且都有一定噪声，为了更准确地测定活体内的真实调控机制，科技工作者们又发展了很多在体测量实验技术。另外，由于染色体是三维立体结构，研究核小体在染色体上的分布等三维调控也增加了转录调控研究的复杂度，相关实验技术的难度也大一些。上述这几个方面的实验技术都在本书中有很好的体现。相对于转录因子对基因表达的调控而言，表观遗传调控是一个新兴领域。表观遗传调控主要分为两大类，一类是通过对

DNA 不同程度的甲基化来影响转录起始复合物跟 DNA 序列的结合强度，另一类是通过对染色体上的组蛋白的不同修饰来影响 DNA 的可及性从而间接地影响组蛋白附近基因的表达水平。本书对表观遗传调控的相关实验技术也有很好的描述。

在基因组学时代，我国科技工作者们一直紧跟时代的脉搏。早期参与了人类基因组计划和 HapMap 计划（测定人类基因组 SNP 信息），现在也是千人基因组计划的主要参与国之一，而且北京基因组研究所于 2010 年成功研发了自主知识产权的第二代测序仪并正在加紧研制第三代测序仪。基因组学技术也已经应用在中国生物医学的各个科研领域，包括早期的家猪家鸡水稻基因组测定，以及目前在许多重大疾病包括癌症、糖尿病、神经退行性疾病的发病机理研究和水稻性状研究等方面都取得了可喜的成绩。遗憾的是，我国在对于全基因组系统调控的基础研究上还相对薄弱，这在一定程度上反映了中国科学届比较浮躁、急功近利的现状，希望更多有志青年能投入到揭示生命调控机制的基础研究中去，这也是我推荐本书的原因之一。在这儿值得一提的是国际上很热门的合成生物学，其基本理念是从头设计并合成生物，尽管这牵涉到复杂的伦理学问题，但单纯从科学的角度来看是大势所趋。2010 年，经过十五年的不懈努力，由前 Celera 总裁带领的团队第一个在计算机上设计并完全化学合成的细菌基因组成功实现自我复制，宣告第一个合成生命的诞生（详见 Science 杂志），为解读生命的系统调控密码提供了一个全新的平台。合成生物学在我国刚刚起步，离国际水平相距甚远，非常需要大家的共同努力。

本书由欧美一线的科技工作者参与编写，涵盖了研究 DNA-蛋白质相互作用的绝大多数经典的实验技术，并特别在这一版增加了一些全基因组研究和在体研究的新技术，填补了国内相关参考书的空白，适合相关专业的研究人员、技术人员和研究生参考阅读。当然，由于全基因组研究和在体研究的迅猛发展和书籍编辑的滞后效应，有一些最新的技术还需要从最新文献中去补充学习。最后，衷心希望本书能给读者们的科研工作带来一些帮助。

雷红星

2012 年 1 月

于加州小镇戴维斯

前　言

为了强调 DNA-蛋白质相互作用的重要性，现代分子生物学课堂上经常引用的例子是黑猩猩和人类的基因有 95%是相同的，这种相似程度远远超出 Robert Fitzgerald 和 Samuel Butler 两人的《奥德赛》译本。既然在基因上相似程度如此之高，人类和这种多毛的近亲之间显而易见的差异就需要找到合理的解释。这些差异显然不源于哪些基因是人和黑猩猩都利用的，而是这些基因在什么时候以多大程度被利用。因此，真正的关键之处在于懂得调控蛋白是如何与遗传物质相互作用而导致其正确表达的，不管是以主动还是被动的形式，激活还是抑制的形式。

我们之所以说这个问题至关重要，不仅仅指的是在理论层面上懂得生物界的基本原理的重要性（尽管这本身也是一个值得追求的目标），而是因为我们每个人的生活将依赖于对基因表达越来越精确的了解。二十世纪中叶，随着抗体的发现和广泛使用，以及大规模的疫苗注射消灭了天花并控制了小儿麻痹症和肺结核等古老的瘟疫以后，我们人类在历史上首次摆脱了传染病的长期困扰。接下来我们在健康方面的挑战主要源于寿命延长而引发的诸多问题，即一些在年轻人身上鲜有发生而随着年岁的增长不断出现的问题。Ⅱ型糖尿病、心血管疾病、神经退行性疾病、癌症，这些新疾病成了每次就医时都可能滋扰我们的幽灵。这些疾病都有多重复杂病因，我们在发现其中一些病因并予以治疗上取得了一定成果，包括环境、生活习惯和病原诱发等方面。但从长远来看，我们懂得要彻底消灭这些疾病必须对其分子机理有透彻的理解，包括细胞永生化的机理、神经元凋亡的机理和细胞对胰岛素不敏感的机理等。这个论断也同样适用于一些报道较少的由基因组错误表达引起的一些罕见疾病，对于受这些疾病煎熬的人来说，弄清其机理的重要性跟攻克癌症对于大众的重要性是一样的。

当然，DNA-蛋白质相互作用的重要性不仅仅限于生物学、医学和药理学。与此相似，匈牙利人 Karl Ereky 在 1919 年创造的“生物技术”一词原意是指利用现存的生物材料创造新的产品或服务，但近年来它的意义越来越广了。基因剪切和创造转基因物种已经掀起了一场新的农业革命，这对于一个有大约 70 亿人需要养活的世界来说怎么都算得上是彻底改变生活方式的大事情。现在随着我们对 DNA-蛋白质相互作用的了解与日俱增，相关知识在越来越多的物种里发挥作用，最大化地从自然界获益而同时最少地改变环境的时机已经成熟。不管这一理想目标能否实现，要想发展一套高效而且环保的农业经济模式，更多地懂得这个世界是如何运作的总比胡蒙乱猜要靠谱得多。更进一步的是，人类已经不满足于改造现有的物种，我们已经开始尝试设计新物种来对清除石油泄漏之类的问题提供帮助；这方面的成功也将倚重于我们对基因表达的理解。

这是《DNA-蛋白质互作：原理与实验方案》的第三版。这三个版本之间两两间隔都有 7 年，这么长的间隔足以在这个领域产生令人难以置信的技术革新和应用。每一次版本更新都加入了一些新的方法，有一些是基于传统技术的全新利用，有一些则依赖于新技术的发展，但多数是这两者的结合。这些新的方法让我们能够研究蛋白质在何时何地以何种方式与 DNA 相互作用，并且达到了前所未有的精度和规模。这一版本保留了一些基本技术的更新版，这些经典可靠的技术可能永远也不会过时。但是这一版本的主

要推动力来自于最新发展的席卷这一领域的体内和全基因组的实验技术。经过这么多年的体外实验以后，人们想知道这些体外实验的结果在体内环境下是否相似，因为体内DNA紧密包裹在染色质里，而且有很多的信号通路和蛋白质共同协作来完成的。因此，我们很高兴能增加几个关于免疫共沉淀和其他体内实验技术的章节。再加上拓扑结构研究、光交联、荧光共振能量转移和成像技术等新章节，我们相信这个新版本是对系列丛书的有价值而且实用的补充。同时，遵从明晰的分子生物学方法丛书的格式，每个实验方案都有一些作者认为很重要而又很难在研究论文里附上的注解。在过去，这样的注解也一直是实验方案里我们最钟爱的部分，现在我们很高兴能在阅读注解部分时再次发出惊叹，“原来他们是这样做的”！另外需要提到的是，有些在以前的版本里出现的实验方案在这一版没有收录，一般是因为实验方案没有什么变化或者现在用得较少，但庆幸的是它们在SpringerProtocols. com数据库里仍然保留着。

尽管我们对解析能力的大幅提高引以自豪，但是我们认为在书中所述的最新进展（包括一些惊人的进展）的基础上就声称研究DNA-蛋白质相互作用的时代终于来临未免有失偏颇。我们这样说并非是想贬低那些令人惊叹的技术，比如基于微阵列的基因表达分析、原子力显微镜研究或染色体免疫共沉淀芯片绘图，这些都是该领域量子式的跳跃而且份量都重到足以提到如此高度。但我们不想过分强调技术革新本身，而是要强调技术的迅猛发展让我们可以问一些新的问题并且提供一些新的答案。用摩尔定律做一个类比，我们生活的时代产生DNA-蛋白质相互作用的数据和分析这些数据的能力都在几何式的增长，与此同时相关费用的迅速下降让一些以前只有大实验室能完成的实验现在几乎人人皆可。当然，我们在降低费用上仍有很多路要走，但我们离目标越来越近了。在医学和生物技术领域与日俱增的需求下，科学和工程界的奇思妙想必将带来更令人目瞪口呆的解析技术，我也迫不及待地想读到这卷书的更新的版本。我坚信我将会像这次一样的惊喜连连。

在此我要由衷地感谢我的前任们。如果没有Geoff Kneale第一版的先驱性工作，或第二版Tom Moss的拓展和多样化，就不可能有今天的这一版本。另外，我还要感谢Tom邀我共同主编第三版。

请尽情享受在实验室的时光！

Benoît Leblanc

（雷红星　译）

Preface

It is a rote of modern molecular biology classrooms to stress the importance of DNA–protein interactions by pointing out that species such as the bonobo and the human being share more than 95% of their genes – a level of similitude far exceeding that of, say, the translations of the *Odyssey* by Robert Fitzgerald and by Samuel Butler. The nonnegligible differences between our hirsute cousins and us, the argument goes, must find its explanation not so much in what genes we both use but in when and to what extent they are used. Hence the truly vital importance of understanding how regulatory proteins, be they active or passive, activating or inhibiting, interact with the genetic material to see it expressed in the proper way.

We say vital not only in the strictly intellectual sense of understanding the basic mechanisms of the living world (although that would seem to be a worthwhile goal in itself) but because our lives as individuals may well soon depend on an ever more precise understanding of gene expression. Following the discovery and widespread use of antibiotics in the mid-twentieth century, and the massive campaigns of vaccination that eradicated smallpox and helped control ancient scourges such as polio and tuberculosis, our species has recently become free, for the first time in its history, of the constant and urgent threat of infectious diseases. Next on the list of challenges to our health come problems associated with our recent extended lease on life, problems that are statistically rare in young people but tend to crop up in our later days. Type II diabetes, cardiovascular problems, neurodegeneracy, cancer, these are the new specters that haunt each of our visits to the doctor's office. These diseases have multiple etiologies and we have had some success in identifying and correcting some of their causes (be they environmental, related to our lifestyle or triggered by certain pathogens). In the long run, however, we understand that truly vanquishing them will demand a thorough understanding of the molecular mechanisms that turn cells immortal, that cause neurons to start dying, or that make cells insensitive to insulin. The same will hold true of multiple but less heralded pathological conditions associated with an improperly expressed genome, which are certainly as important to the person enduring them as cancer would be to the population at large.

Of course, the relevance of DNA–protein interactions is not limited to biology, medicine, or pharmacology. The word "biotechnology" coined by the Hungarian Karl Ereky in 1919 originally described the use of preexisting biological material for the creation of products and services but has come to signify much more in recent years. Gene splicing and the creation of transgenic species have fairly revolutionized agriculture, and in a world of roughly 7 billion mouths to feed, that qualifies as a life-altering realization in more ways than one. As we learn more and more about the interaction between DNA and the proteins that see to its proper expression in an ever-increasing number of species, we will be in a position to augment the benefits we reap from nature while at the same time minimizing our footprint on the environment. Whether this goal will be reached or not is another matter, but it is certainly easier to devise more efficient and environmentally friendly agribusiness strategies with a better understanding of how the world actually functions than relying on wild guesses and wishful thinking. Not content with modifying existing species, we have also taken the first steps in devising new life forms that may help,

for example, cleaning up oil spills; the success of such endeavors will rely heavily on our understanding of gene expression.

This is the third edition of *DNA–Protein Interactions: Principles and Protocols.* Each edition is separated from its predecessor by roughly 7 years, a period that appears to be sufficient for the field to come up with wild innovations in technology and its applications. New protocols are added to each successive edition, sometimes based on the novel use of ancient techniques, sometimes relying on new technological advances, but most of the time on some new integration of the two. These new ways to do things allow us to study where, when, and to what extent proteins interact with DNA, and that with an unprecedented precision and on a larger scale than ever. The current edition has retained updated versions of the basic techniques, the old-but-trusted ones that may never go out of fashion, but the impetus for this edition is the recent development of in vivo and genome-wide interaction techniques that have taken the domain by storm. The results obtained by years of in vitro techniques make everyone curious about whether they can be translated to an in vivo context, with DNA packaged in chromatin, and with several signaling cascades and protein actors all acting their part in unison. We are therefore happy to present several chapters on chromatin immunoprecipitation and other in vivo techniques. Along with new chapters on topological studies, photocrosslinking, FRET, and imaging techniques, we believe that this new edition will prove a worthy and practical addition to the series. As always, following the enlightened format of Methods in Molecular Biology, each protocol is rich in notes that authors think are important but which rarely make it into the spartan protocols that accompany most research papers. In the past, such notes were always our favorite part of these protocols, and we are glad to once again be able to exclaim "so that's how they do it" while perusing the notes section. It should be mentioned that some protocols featured in previous editions did not make it this time around, as they were either unchanged or perhaps less frequently used, but they are luckily still available on the SpringerProtocols.com database.

Although rapid progress in analytical capacities is something to be very proud of, we think it would be presumptuous to claim that the study of DNA–protein interactions has "finally come of age" following the recent (and sometimes spectacular) advances described in these pages. That is certainly not meant to belittle such amazing approaches as microarray-based gene expression analysis, atomic force microscopy studies, or ChIP-on-chip cartography, all of which were technological quantum leaps in the field and important enough to warrant the use of that overwrought cliché. It is meant, however, to emphasize the speed at which our fast-evolving technology allows us to ask new questions and to provide new answers. In a sort of biological application of Moore's law, we now live in a world where our ability to generate data on DNA–protein interactions and our ability to analyze it seems to increase exponentially, while the costs involved are getting low enough that experiments that were once the sole purview of big laboratories become available to most everyone. (Granted, we still have some work to do regarding the lowering of costs, but we are getting there.) The ingenuity of the scientific and engineering communities, driven by more and more demands from the medical and biotechnology fields, is bound to give rise to even more startling analytical technologies in the future, and personally I cannot wait to read further editions of this volume. I am sure that I will be as amazed then as I was this time around.

The current edition would not have been possible without the pioneering work of Geoff Kneale on the first edition, or without the expansion and diversification made by Tom Moss in the second edition. Both have my gratitude, and I thank Tom for bringing me aboard as coeditor for this third edition.

Have fun in the laboratory.

Benoît Leblanc

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