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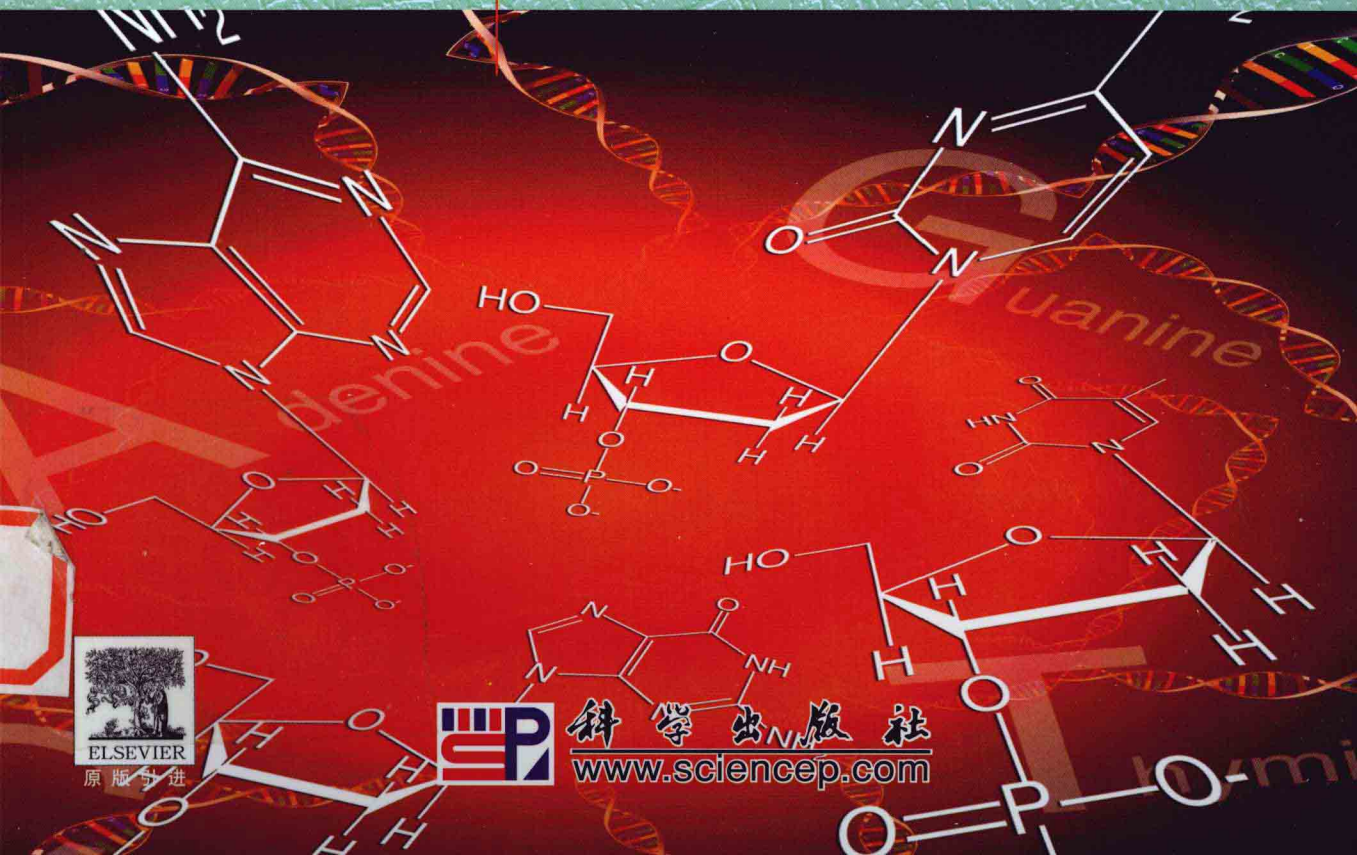
生物技术提高 5

Biotechnology: Applying the Genetic Revolution

遗传缺陷与基因治疗，癌症分子生物学，非传染性疾病，衰老与细胞凋亡

David P. Clark, Nanette J. Pazdernik



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Biotechnology

Applying the Genetic Revolution

生物技术提高⑤

遗传缺陷与基因治疗，癌症分子生物学，非传染性疾病，衰老与细胞凋亡

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生物技术改变了世界，它使许多遗传疾病的病因得到鉴定已成为可能，使人类可以在更高人口密度下生存，因为每公顷土地上能提供更多的食品。现代分子生物学和遗传学的快速发展使我们获得了很多种生物的基因组，包括从病毒和细菌到树和人，这些知识的应用已导致了科学的革命，使其由原来的描述性改变成多种学科，并为人类提供许多新产品，如药物、疫苗和食物。

生物技术为生产具有新功能的蛋白质，甚至具有不同产物的新生化途径开启了大门，有了新的蛋白质和新的生化途径，这就符合逻辑地将这些新功能加入到作物、动物以及患有遗传病的人体中。前不久农学家还主要依赖于绿色指纹获得高产，而今天他们可以利用绿色荧光蛋白来分析转基因作物中的基因表达。产生这些变化的能力将会导致将来更大的变化。生物技术会因为发现了衰老或癌症发展过程中的分子变化而找到长生不老之路吗？这会改变我们治疗疾病的方法吗？会由于发展了新的生物因子而改变战争方式吗？

“生物技术：遗传革命的应用”这本书解释了来自遗传革命的信息如何用于回答上述问题。它告诉读者许多有关生物技术已改变原有研究领域的途径。本书的前几章主要简明扼要地提供了分子生物学基础知识。这些内容在本系列丛书的“分子生物学：遗传革命的领悟”中已作了详细的解释。它使学生回顾基础知识，包括DNA结构、基因表达、蛋白质合成以及大致了解用于生物技术研究的各种生物。接着让学生了解一些用于生物技术研究的基础方法学。第3章（第2分册第1章）解释了核酸是如何分离和克隆到人造的遗传载体，然后引入模式生物作深入分析。接下来的两章更详细讨论了用于研究基因功能的各种技术。第4章（第2分册第2章）侧重于DNA技术，包括体内和体外的DNA合成，以及聚合酶链式反应。第5章（第2分册第3章）侧重于RNA技术，包括反义技术、RNA干扰和核酶。对这几章内容的熟悉是了解本书其他内容的关键。

本书其他各章则是侧重于不同的研究领域，介绍了遗传革命已经彻底改变了这些领域的途径。第6章（第6分册第1章）介绍了产生用作研究和疫苗抗体新技术。第7章（第1分册第3章）则进入了一个不同的领域，即基于纳米尺度的领域。这一章评价了分子生物学将如何会为工作在纳米世界的科学家所改变，如科学家怎样利用新的纳米结构释放药物，原位鉴定生物分子和制造抗菌材料。这一章还展示了纳米生物技术如何将DNA的自组装能力开发成纳米装置，如何用DNA控制蛋白质的形状。这个新的研究领域与分子生物学结合才刚刚开始，在未来的分子生物学课程中将成为重要的内容。

接下来的内容又回到所熟悉的基因组学和蛋白质组学。这些章节强调它们的应用领域和讨论基因组学和蛋白质组学的医学应用进展。蛋白质组学这一章包括了各种分离和鉴定蛋白质的方法，包括新发展起来的质谱技术。蛋白质组学还为下一章作了很好的铺垫，即概述了如何在不同的生物和组培细胞中表达蛋白质来研究它们的功能，接着还介绍了利用蛋白质工程产生具有新特性的蛋白质。

由于单个遗传修饰的蛋白质具有局限性，第12章（第4分册第1章）从实验室转向环境，介绍了新兴起的元基因组学技术。该技术不必像传统方法那样，在实验室里每次从模式生物中只鉴定出一个新基因，而是直接从环境中分离基因组序列，而不必事先鉴定是来自何种生

物。第13章（第4分册第2章）继续介绍新基因功能的研究。这一章介绍了几种利用DNA重组技术改变生化途径的新方法。构建新的蛋白质和新生化途径，只有将它们整合到植物和动物中去才有意义，接下来的两章向学生介绍了转基因植物和动物的最新进展。

接下来的几章侧重于医学领域。第16章（第5分册第1章）介绍了造成遗传缺陷的分子基础，接着进入17章（第5分册第2章）的基因治疗。接下来的几章则分别介绍了癌症的分子基础和非传染性疾病，如勃起功能障碍、糖尿病、肥胖症和衰老。最后，介绍分子生物学在了解细菌病和病毒病方面取得的巨大进展。第21和22章（第6分册第2~3章）使学生知道细菌和病毒是如何使我们的细胞生病，对非同寻常的朊病毒病的最新研究进展也作了介绍，如疯牛病和早老痴呆症。第23章（第6分册第4章）则是基于细菌和病毒致病的知识而对生物战争和生物恐怖进行了概述。

第24章（第6分册第5章）概述了遗传革命如何改变了法医学领域，通过分子生物学鉴定罪犯的方法已不可逆地改变了司法系统。不管是新案、旧案还是未破之案，都可以用DNA测试方法进行鉴定，而且比现有的鉴定方法更准确更可靠。DNA在犯罪侦破中的应用已制作成电视系列片广为传播。作为本书的结尾，第25章（第1分册第4章）介绍了生物伦理学问题。与讨论科学方法不一样的是，本章提出了有关这些方法的社会作用问题。我们是否应该利用遗传革命去克隆人类，创制转基因作物，研究人类干细胞？我们的遗传学证据应该向公众公开吗？

“生物技术：遗传革命的应用”一书展示了技术进步和分子生物学革命融合的许多不同途经。将大量信息的加工与对我们人类和其他生物的无穷小的精确分析能力相结合，已经和将要不断改变我们的社会，伦理和个人环境。本书为学生提供了这些已经发生变化的基础知识，希望他们能将这些知识应用于将来的发展。

（张义正 译）

我们真诚地感谢为本书出版提供资料和建议的个人：Laurie Achenbach, Rubina Ahsan, Phil Cunningham, Donna Mueller, Dan Nickrent, Holly Simmonds, 和 Dave Pazdernik。特别感谢Alex Berezow和Michelle McGehee为本书编写的问题和Karen Fiorino所创作的绝大多数美术作品。

现代生物技术依赖于分子生物学和计算机技术的进步

传统生物技术可以回溯到几千年前，它包括家畜和作物的选择育种，以及酒、牛奶制品、纸、丝绸及其他天然产品的发明。遗传学仅在几个世纪前才作为一个科学研究领域。该领域近来的快速发展，使作物和家畜的育种可以通过精细的遗传操作而不是误差试验来进行。1960－1980年间的绿色革命就是将遗传知识应用到自然育种工作中，特别是在提高粮食产量上取得巨大成功。今天，可以利用遗传工程技术直接改造植物和动物。

目前已构建了几种植物和动物的新变种，有的已在农业中应用。用作人类食物来源的动物和植物正在进行工程改造，使其能适应它们以前不适应的条件。抗病动物和抗虫植物品种也正在开发，以便增加产量和降低成本。这些遗传改造的生物对其他物种和环境的影响是目前争论的问题。

现代生物技术不仅利用了现代遗传学，而且也利用了其他科学领域的进展。例如，处理大量的遗传信息就依赖于计算能力方面的进展。实际上，要是没有更复杂计算机和软件的发展，人类基因组的测序是不可能完成的。有时说我们是处在两个科学革命的中间，一个是信息技术革命，另一个是分子生物学革命。两者都包括处理大量的编码信息，一种是人造的信息，即以任意速率人工编码，其机制是人为的；另一种则是依赖于生命的遗传信息处理。

然而，第三次革命正在发生，即纳米生物技术。这些技术可以观察和操作单个或成小簇的原子，从而为生命系统更精细的分析开启了新途径。纳米技术在生物技术的许多领域正起着重要作用。

这就提出了一个如何精确定义生物技术的问题，对此尚无真正的答案。以前把酿造啤酒和烘焙面包看作是生物技术。今天，现代遗传学或其他相关现代技术的应用常被看作是生物技术的必需过程。因此，生物技术的定义已部分成为一种时尚。在本书中，我们将现代生物技术看作是由传统生物技术与现代遗传学，分子生物学，计算机技术和纳米技术融合而成的技术。

生物技术这个领域的确很大，难于定义。它不仅仅包括农业，它也影响了许多诸如人类健康的医学，如疫苗开发和基因治疗等各个方面。我们已试图提供一种基于遗传信息的融合方法，与此同时，说明生物技术是如何开始扩展到许多人类努力的相关领域，而这种扩展常常是意想不到的。

（张义正　译）

PREFACE

Biotechnology has made the world a different place. Biotechnology has made it possible to identify the genetic causes behind many different inherited diseases. Biotechnology has made it possible for people to survive to a much higher population density by providing more food per acre. The advent of modern molecular biology and genetics has advanced our understanding of the genomes of a wide range of organisms from viruses and bacteria to trees and humans. The application of this knowledge has revolutionized the sciences, changing them from a descriptive nature to a variety of disciplines that provide new products such as drugs, vaccines, and foods.

Biotechnology has opened doors to making proteins with new functions, and even new biochemical pathways with altered products. With new proteins and new biochemical pathways, it seems only logical to find ways to incorporate the new functions into crops, into animals, and, it is hoped, into people with genetically based illnesses. Only a short time ago, agriculturists largely relied on green fingers to get good yields; today they use green fluorescent protein to assess gene expression in transgenic crops. The ability to make such direct changes will result in major changes for the future. Will biotechnology find the proverbial fountain of youth by identifying the molecular changes that cause us to age or develop cancer? Will it change the way we treat diseases? Will the way we wage war change with the development of new biological agents?

Biotechnology: Applying the Genetic Revolution explains how the information from the genetic revolution is being used to answer some of these questions. It informs the reader about the many avenues where biotechnology has changed the original field of study. The first few chapters provide a clear and concise review of the basics of molecular biology. These topics are explained in more detail in the first book of this series, entitled *Molecular Biology: Understanding the Genetic Revolution*. This review will take the student through the basics, including DNA structure, gene expression, and protein synthesis, as well as survey the variety of organisms used in biotechnology research. The student is then presented with the basic methodologies used in biotechnology research. Chapter 3 explains how nucleic acids are isolated, cloned into humanmade genetic vehicles, and then reinserted into one of the model organisms for in-depth analysis. The next two chapters discuss in more detail various techniques that have been developed to investigate the function of genes. Chapter 4 focuses on DNA, dealing with both *in vivo* and *in vitro* synthesis of DNA and the polymerase chain reaction. Chapter 5 focuses on RNA, explaining antisense technology, RNA interference, and ribozymes. Familiarity with these chapters is critical to understanding the rest of the textbook.

The remaining chapters focus on different fields of research, presenting some of the ways the genetic revolution has irreversibly changed these areas. Chapter 6 begins this approach by presenting newer techniques to generate antibodies for genetic research and for creating new vaccines. Chapter 7 delves into a different realm, one based on the nanoscale. This chapter evaluates how molecular biology will be changed by the ability of scientists to work in the nanoscale world. It discusses how scientists are using novel nanoscale structures to deliver drugs, identify biological molecules *in situ*, and manufacture antibacterial materials. The chapter illustrates how nanobiotechnology exploits the self-assembly property of DNA to create nanodevices. It shows how DNA can physically control the shape of proteins. This new field of research is intimately intertwined with molecular biology and will only become a stronger component of molecular biology courses in the future.

The next section returns to the more familiar world of genomics and proteomics. These chapters emphasize the applied aspect of these topics and discuss the medical applications of advances in genomics and proteomics. The proteomics chapter includes a variety of techniques used to isolate and characterize proteins, including the more recent developments in mass spectrometry. Proteomics provides a nice segue to the next chapter, which surveys how proteins are studied by expressing them in various organisms and cultured cells. The creation of proteins with novel properties by protein engineering follows.

Because single genetically modified proteins have their limitations, Chapter 12 moves from the lab to the environment and presents the emerging field of metagenomics. This approach bypasses the traditional method of identifying new genes one at a time from model organisms in the laboratory. Instead, metagenomics skips directly to isolating genomic sequences from the environment without identifying the organism from which they originate. The investigation of novel gene functions continues in Chapter 13. Biochemical pathways may be altered using recombinant DNA technology, and this chapter presents a few of these novel pathways. Construction of novel proteins and biochemical pathways is pointless unless they can be inserted into plants and animals. So the next two chapters present the student with the latest advances in creating transgenic plants and animals.

The next block of chapters focuses on the medical arena. First, in Chapter 16, the molecular basis for inherited defects is examined. This leads into the following chapter on gene therapy. Several chapters then present the molecular basis of cancer, a selection of noninfectious diseases, such as erectile dysfunction, diabetes, and obesity, and then aging. Last, molecular biology has made huge strides in our understanding of bacterial and viral diseases. In Chapter 21 and Chapter 22, the student will learn how bacteria and viruses exploit our cellular machinery to cause disease. The latest research on the unusual prion diseases, such as mad cow disease and Creutzfeldt-Jakob disease, is also covered. Chapter 23 builds on the knowledge of bacterial and viral pathogenesis to present a survey of biowarfare and bioterrorism.

Chapter 24 surveys how the field of forensics has been altered by the genetic revolution. The way criminals are identified via molecular biology has changed the penal system irreversibly. New cases, old cases, and unsolved cases are all now examined with DNA testing which is more accurate and reliable than previous identification methods. The use of DNA in criminal investigation has even spawned popular television series that showcase these advances and their effect on society. As the book comes to a close in Chapter 25, the subject of bioethics is presented. Rather than discussing scientific methodology, this chapter asks questions about the role of these methodologies in society. Should we use the genetic revolution to clone a human, create transgenic crops, do research on human stem cells? Should our genetic identity be open to the public domain?

Biotechnology: Applying the Genetic Revolution demonstrates many different ways in which advances in technology and the revolution in molecular biology have merged. The combined ability to process large volumes of information along with analyzing our bodies and other organisms with infinitesimal precision has and will continue to change our society, our ethics, and our personal surroundings. This book gives the student a basic knowledge of some of those changes that have already occurred, with the hope that they will be able to apply this knowledge toward future advances.

This book is dedicated to Donna. —DPC

This book is dedicated to my children and husband. Their patience and understanding have given me the time and inspiration to research and write this text. —NJP

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MODERN BIOTECHNOLOGY RELIES ON ADVANCES IN MOLECULAR BIOLOGY AND COMPUTER TECHNOLOGY

Traditional biotechnology goes back thousands of years. It includes the selective breeding of livestock and crop plants as well as the invention of alcoholic beverages, dairy products, paper, silk, and other natural products. Only in the past couple of centuries has genetics emerged as a field of scientific study. Recent rapid advances in this area have in turn allowed the breeding of crops and livestock by deliberate genetic manipulation rather than trial and error. The so-called green revolution of the period from 1960 to 1980 applied genetic knowledge to natural breeding and had a massive impact on crop productivity in particular. Today, plants and animals are being directly altered by genetic engineering.

New varieties of several plants and animals have already been made, and some are in agricultural use. Animals and plants used as human food sources are being engineered to adapt them to conditions that were previously unfavorable. Farm animals that are resistant to disease and crop plants that are resistant to pests are being developed in order to increase yields and reduce costs. The impact of these genetically modified organisms on other species and on the environment is presently a controversial issue.

Modern biotechnology applies not only modern genetics but also advances in other sciences. For example, dealing with vast amounts of genetic information depends on advances in computing power. Indeed, the sequencing of the human genome would have been impossible without the development of ever more sophisticated computers and software. It is sometimes claimed that we are in the middle of two scientific revolutions, one in information technology and the other in molecular biology. Both involve handling large amounts of encoded information. In one case the information is humanmade, or at any rate man-encoded, and the mechanisms are artificial; the other case deals with the genetic information that underlies life.

However, there is a third revolution that is just emerging—nanotechnology. The development of techniques to visualize and manipulate atoms individually or in small clusters is opening the way to an ever-finer analysis of living systems. Nanoscale techniques are now beginning to play significant roles in many areas of biotechnology.

This raises the question of what exactly defines biotechnology. To this there is no real answer. A generation ago, brewing and baking would have been viewed as biotechnology. Today, the application of modern genetics or other equivalent modern technology is usually seen as necessary for a process to count as "biotechnology." Thus, the definition of *biotechnology* has become partly a matter of fashion. In this book, we regard (modern) biotechnology as resulting in a broad manner from the merger of classical biotechnology with modern genetics, molecular biology, computer technology, and nanotechnology.

The resulting field is of necessity large and poorly defined. It includes more than just agriculture: it also affects many aspects of human health and medicine, such as vaccine development and gene therapy. We have attempted to provide a unified approach that is based on genetic information while at the same time indicate how biotechnology has begun to sprawl, often rather erratically, into many related fields of human endeavor.

（高　福　译）

CHAPTER 1

Inherited Defects

INTRODUCTION

Genetic defects vary from trivial to life threatening. Although we tend to think of inherited conditions such as diabetes and muscular dystrophy as diseases, we often refer to cleft palates or color blindness as inherited defects. However, they are all the result of mutations in DNA, the genetic material. Not only are some diseases directly caused by mutations, but susceptibility to infectious disease and other damaging environmental factors, such as radiation, is also influenced by a variety of genes.

Precise rates of mutation are difficult to estimate, but for humans and apes, the mutation rate is around 5.0×10^{-8} per kilobase of DNA per generation. For rodents, the rate is some 10-fold less because fewer cell divisions are needed to form gametes from ancestral germ cells. Thus a considerable number of mutations are constantly accumulating in the germline of humans and other animals. Most of these have little or no effect, but a small percentage give rise to serious hereditary defects. A full listing of human hereditary defects, known as OMIM (Online Mendelian Inheritance in Man), is available on the Internet at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM.

Mutations in the human genome are responsible for a wide variety of inherited defects and diseases.

HEREDITARY DEFECTS IN HIGHER ORGANISMS

If the DNA of a single-celled organism is mutated, the mutation will be passed on to all of its descendants when it divides. The situation in multicelled creatures is more complex. In animals, the germline cells are reserved for reproductive purposes and give rise to the eggs and sperm in mature adults. The somatic cells forming the rest of the body are not passed on to the next generation (seeVol. 1 Ch.1). However, mutation of somatic cells is involved in cancer, which is dealt with separately inVol. 5 Ch.3 .

Higher organisms such as animals and plants are normally diploid and have two copies (i.e., two alleles) of each gene. Therefore, if one copy is damaged by a mutation, the other copy can compensate for the loss. Because most mutations are relatively rare, it is unlikely that both alleles of the same gene will carry mutations. Furthermore, most detrimental mutations are recessive to the wild type (Fig. 1.1 and Table 1.1). That is, a single functional allele is sufficient for normal growth and the defective copy has no noticeable effect on the phenotype.

Nonetheless, we humans all have quite a few mutations randomly scattered among our 25,000 genes. Obviously, close relatives tend to share many defects. Individuals share half of their genetic information with their brothers, sisters, father, and mother, although, of course, not the same half with each of them. Therefore, a child from the mating of close relatives (for example, as in brother/sister or father/daughter), has a much increased chance of getting two copies of the same defect, that is of being homozygous for the recessive allele (Fig. 1.2).

Mating between close relatives, even cousins, makes genetic disease more likely. This is because a rare recessive allele present in one ancestor may be passed down both sides of the family and two copies may end up

FIGURE 1.1 Inheritance of Recessive Mutations A defective mutation usually occurs in only one copy of a gene. Therefore, most affected individuals will have one normal copy (A) and one mutated copy (a) of the gene. When two people, both carrying a recessive mutation in the same gene, have children, 25% of the children will inherit both mutant copies and exhibit the disease.