Biological Regulation and Development

Volume 1
Gene Expression

Edited by
Robert F. Goldberger
National Cancer Institute
Bethesda, Maryland

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Contributors

Allan Campbell
Department of Biological Sciences
Stanford University
Stanford, California

Patricia H. Clarke
Department of Biochemistry
University College London
London, England

Riccardo Cortese
Institute of Biological Chemistry
Faculty of Medicine and Surgery
University of Naples
Naples, Italy
Present Address: MRC Laboratory of Molecular Biology
Cambridge, England

Robert F. Goldberger
Laboratory of Biochemistry
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Karl G. Lark
Department of Biology
University of Utah
Salt Lake City, Utah

O. Maaløe
Institute of Microbiology
University of Copenhagen
Copenhagen, Denmark

David Pribnow
Department of Molecular, Cellular, and Developmental Biology
University of Colorado
Boulder, Colorado

Michael A. Savageau
Department of Microbiology
The University of Michigan
Ann Arbor, Michigan

Henry M. Sobell
Department of Chemistry, and Department of Radiation Biology and Biophysics
University of Rochester School of Medicine and Dentistry
Rochester, New York

Dieter G. Söll
Department of Molecular Biophysics and Biochemistry
Yale University
New Haven, Connecticut

Deborah A. Steege
Department of Biochemistry
Duke University Medical Center
Durham, North Carolina

Joan Argetsinger Steitz
Department of Molecular Biophysics and Biochemistry
Yale University
New Haven, Connecticut

Peter H. von Hippel
Institute of Molecular Biology and Department of Chemistry
University of Oregon
Eugene, Oregon

Preface

The motivation for us to produce a treatise on regulation was mainly our conviction that it would be fun, and at the same time productive, to approach the subject in a way that differs from that of other treatises. We had ourselves written reviews for various volumes over the years, most of them bringing together all possible facts relevant to a particular operon, virus, or biosynthetic system. And we were not convinced of the value of such reviews for anyone but the expert in the field reviewed. We thought it might be more interesting and more instructive—for both author and reader—to avoid reviewing topics that any one scientist might work on, but instead to review the various parts of what many different scientists work on. Cutting across the traditional boundaries that have separated the subjects in past volumes on regulation is not an easy thing to do—not because it is difficult to think of what interesting topics should replace the old ones, but because it is difficult to find authors who possess sufficient breadth of knowledge and who are willing to write about areas outside those pursued in their own laboratories. For example, no one scientist works on suppression *per se*. He may study the structure of suppressor tRNAs in *Escherichia coli*, he may study phenotypic suppression of various characters in drosophila, he may study polarity in gene expression, and so on. Anyone who takes on the task of reviewing suppression must be willing to weave together the various parts of the subject, picking up the threads from many different laboratories, and attempt to produce a fabric with a meaningful design. Finding people who are likely to succeed in such tasks was the most difficult part of our job, since the qualifications required are not the same as those by which we are accustomed to evaluating our colleagues. For example, a high degree of productivity as a research scientist is not nearly so important as is the ability to think deeply about scientific issues.

Having determined at least to make a try at accomplishing our goal, we were surprised and gratified to find that we had been sufficiently convincing to enlist the participation of a group of authors we considered truly outstanding for the enterprise. But after getting that far, we were a bit anxious about what the outcome would be; after all, no amount of editing can alter significantly the

substance of what an author has to say. As the manuscripts appeared, we were relieved to find that the authors had taken to heart the charge we had given them. We noted, for example, the high frequency with which the same system was discussed from different points of view by different authors; the multiple instances in which not only a structure or phenomenon was discussed, but also its possible evolution; the willingness of authors to make interesting speculations; and so on. Thus, having gotten what we asked for from our authors, it is we who must take the blame from any reader who is dissatisfied. As for taking credit, we are afraid that it will belong to the authors themselves; although we took an active role in editing, it is only the authors' contributions that can make the basic philosophy of this treatise work.

Robert F. Goldberger
Paul Berg
Leroy E. Hood
Philip Leder
Kivie Moldave
Robert T. Schimke

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Strategies of Genetic Regulation in Prokaryotes

ROBERT F. GOLDBERGER

1 Introduction

One of the most striking characteristics of living systems is that they function in an orderly manner despite their high degree of complexity. One workable definition of regulation, in fact, is the set of mechanisms that allows organisms to maintain this orderly functioning. It is important to realize, however, that regulation was not superimposed upon living systems; orderly processes are simply more successful than are disorderly ones, and therefore tend to be preserved through the evolutionary process by conferring advantages upon organisms that possess them. The thousands of chemical reactions occurring in cells are controlled by regulatory mechanisms that operate at many different levels. This introductory chapter focuses on those that operate at the level of gene expression and will introduce some of the strategies of genetic regulation that have evolved in prokaryotic organisms. Scanning the table of contents of this brief essay should suffice to tell the reader that a very general overview is in store for him. The renaissance in biological research that occurred in the last 25 years has been due mostly to the exciting studies concerning genetic regulation in prokaryotes. I have tried to abstract from those studies the most important basic principles they illustrate and to organize into a few generalizations the enormous body of data they have produced. I believe it is these principles and generalizations with which the reader will need to arm himself before proceeding further into this volume. It is to be hoped that the

ROBERT F. GOLDBERGER • Laboratory of Biochemistry, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

necessarily simplistic view of regulation they provide will be preferable to the bewilderment that so often results from exhaustive reviews that include the details of many specific regulated systems.

2 *The Prokaryotic Chromosome and Its Genes*

Over the past two decades much has been learned about the mechanisms by which a protein is synthesized in accordance with the specifications of a so-called *structural gene.* First, RNA polymerase faithfully transcribes the sequence of deoxyribonucleotides of the gene into the ribonucleotide sequence of a messenger RNA (mRNA) molecule (see Chapters 7 and 8 of this volume). Next, ribosomes, transfer RNA, and amino acids participate, together with various other proteins and small molecules, in translating the nucleotide sequence of the mRNA into the amino acid sequence of a polypeptide chain (see Chapters 9, 10, 11, and 12 of this volume). The work of Anfinsen (1973) and his colleagues has demonstrated that once a polypeptide chain is formed it folds spontaneously, under physiological conditions, to achieve the three-dimensional conformation characteristic of the native protein (see Chapter 3 in Volume 2 of this treatise). Thus, in order to specify the complete and final structure of a native protein, a gene need do no more than specify the linear sequence of its amino acids. A few years ago it seemed clear that genetic information is stored (DNA) and transmitted (mRNA) in linear form and is expressed (protein) in three-dimensional form. More recent insights into the details of the structure and function of the genetic apparatus, however, have revealed a far more complex and interesting picture in which, for example, secondary and higher order structures of nucleic acids play an essential part in the functions of these macromolecules.

The prokaryotic chromosome is a single circular molecule of double-stranded DNA with a molecular weight of about two billion. It contains approximately 4000 genes. From the fact that this molecule is circular, one might make the naive guess that one strand of the DNA is the sense strand (the coding strand) and that transcription of this strand starts at one point on the circle and proceeds all the way around, in a manner similar to that for replication. Such a guess would be not only naive but also entirely incorrect. In fact, in certain parts of the chromosome the strand that runs clockwise is the sense strand and in other parts of the chromosome the strand that runs counterclockwise is the sense strand. Once this fact is appreciated, it becomes obvious that there must be signals in the DNA that direct the transcription apparatus where to begin transcribing. Although the direction of transcription is always 5′ to 3′, the correct strand must be selected for any given gene or group of genes. The fact that each gene or group of genes is transcribed independently is, of course, required if the cell is to be able to regulate the rate at which certain items of genetic information are utilized independently of the rate at which others are utilized. The mechanism by which the correct strand is selected involves the recognition of specific nucleotide sequences in the DNA, known as *promoters,* by the enzyme that carries out the transcription process, RNA polymerase. But it is not sufficient for the RNA polymerase to recognize where to begin transcription; if it is to be prevented from continuing its journey along the