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Biological Regulation and Development

Volume 1 Gene Expression

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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.

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Contents

1 Strategies of Genetic Regulation in Prokaryotes

ROBERT F. GOLDBERGER

1	Introduction	1
2	The Prokaryotic Chromosome and Its Genes	2
3	Gene Clustering and the Operon Concept	3
4	Regulatory Molecules and the Genes with Which They Interact	4
4.1	The Promoter	4
4.2	The Operator and Initiator Genes	4
4.3	Regulatory Proteins and the Small Molecules That Affect Their Activities	5
5	Induction and Repression	6
5.1	Induction	6
5.2	Repression	8
5.3	The Regulon	11
6	Autogenous Regulation	11
7	Integration of Regulatory Mechanisms	12
7.1	Catabolite Repression	13
7.2	Stringency	14
8	Translational Control	14
9	Conclusion	15
	References	17

2 Structure of Complex Operons

ALLAN CAMPBELL

1	Evolution of the Operon Concept	19
2	Types of Complex Operons	21
2.1	Internal Promoters and Multiple Promoters	21
2.2	Antitermination and Antiattenuation	32

2.3	Divergent Transcription	41
2.4	Overlapping Transcription	46
3	Evolution of Complexity	46
4	Methodological Implications for Studies of Genome Organization ..	50
4.1	Use of the Cis/Trans Test	50
4.2	Cis-Acting Proteins	50
	References	51

3 Autogenous and Classical Regulation of Gene Expression: A General Theory and Experimental Evidence

MICHAEL A. SAVAGEAU

1	Introduction	57
2	Repressors and Activators	59
2.1	Inducible Catabolic Systems	60
2.2	Repressible Biosynthetic Systems	63
2.3	Inducible Drug Resistance	64
2.4	Inducible Prophages	65
2.5	Other Systems	66
3	Inducible Systems	66
3.1	Criteria for Functional Effectiveness	67
3.2	Autogenous and Classical Regulation	68
3.3	Predictions	68
3.4	Arabinose	68
3.5	Other Activator-Controlled Inducible Catabolic Systems	70
3.6	Histidine Utilization	71
3.7	Other Repressor-Controlled Inducible Catabolic Systems	72
3.8	Inducible Biosynthetic Systems	74
3.9	Inducible Drug Resistance	75
3.10	Inducible Prophage Lambda	76
4	Repressible Systems	77
4.1	Criteria for Functional Effectiveness	77
4.2	Autogenous and Classical Regulation	79
4.3	Predictions	79
4.4	Tryptophan	79
4.5	Arginine	82
4.6	Histidine	83
4.7	Isoleucine-Valine	84
4.8	Repressible Drug Sensitivity	86
5	Autonomous Systems	88
5.1	Functional Implications and Predictions	88
5.2	Regulator of the Arabinose Operon	89

5.3	Regulator of DNA Replication	89
5.4	6-Phosphogluconate Dehydrogenase	90
5.5	T Antigen	90
5.6	Transcription Termination Factor Rho	91
5.7	RNA Polymerase	92
5.8	Histones	93
5.9	Unwinding Protein	94
5.10	Scaffolding Protein	96
6	Discussion	96
	References	100

4 Regulation of Enzyme Synthesis in the Bacteria: A Comparative and Evolutionary Study

PATRICIA H. CLARKE

1	Introduction	109
2	The Nature of the Evidence	111
2.1	Theories of Regulation of Enzyme Synthesis	111
2.2	Gene Arrangements	114
2.3	The Experimental Approach	117
3	The Molecular Basis of Regulation of Gene Expression	119
3.1	Binding Domains	119
3.2	Origins of Regulatory Genes	121
4	The Biosynthesis of Aromatic Amino Acids	123
4.1	Aromatic Pathway Enzymes and Regulation in <i>Escherichia coli</i>	124
4.2	Aromatic Pathway Enzymes and Regulation in <i>Bacillus</i>	127
4.3	Aromatic Pathway Enzymes and Regulation in Other Genera	129
4.4	Genes and Enzymes of Tryptophan Biosynthesis	130
5	Catabolic Pathways	133
5.1	Induction and Repression	133
5.2	Catabolism of Aromatic Compounds	133
5.3	The β -Ketoadipate Pathway	134
5.4	Meta Pathway Enzymes	141
5.5	Arrangements of Genes of Aromatic Pathway Enzymes	143
5.6	Plasmids and Regulation	144
6	Nitrogen Metabolism and Regulation	145
6.1	Glutamine Synthetase	145
6.2	Nitrogen Regulation in Fungi	148
7	Experimental Evolution	149
7.1	Growth on Novel Substrates	149
7.2	Amidase	150
7.3	Evolved β -Galactosidase	152
7.4	Gene Duplications	153
7.5	New Metabolic Pathways	154

8	Discussion	159
	References	162

5 Importance of Symmetry and Conformational Flexibility in DNA Structure for Understanding Protein–DNA Interactions

HENRY M. SOBELL

1	Introduction	171
2	Symmetry in DNA Structure	172
3	Flexibility in DNA Structure—The Kink	173
4	Detailed Models for Drug–DNA Binding	174
	4.1 Ethidium	178
	4.2 Actinomycin	178
	4.3 Irehdiamine	182
5	Nature of DNA Breathing	184
6	Organization of DNA in Chromatin	185
7	Active Form of DNA in Transcription, Replication, and Recombination	190
8	Operator–Repressor Interactions	192
9	Concluding Remarks	195
	References	196

6 Some Aspects of the Regulation of DNA Replication in *Escherichia coli*

KARL G. LARK

1	Introduction	201
2	DNA Replication in <i>Escherichia coli</i>	201
3	Stoichiometry of DNA Replication	203
4	Regulation Is at the Level of Initiating Chromosome (or Replicon) Replication	204
5	The Replication Complex	205
6	The Destruction of the Replication Complex	208
7	Repair Replication (a Possible Example of Regulative Assembly)	210
8	Regulation of the Quality of DNA Replication	211
9	RNA and the Initiation of Replication	211
10	Conclusion	212
	References	213

7 Genetic Control Signals in DNA

DAVID PRIBNOW

xiii

CONTENTS

1	DNA Control Signals	219
1.1	Introduction	219
1.2	DNA Sequence	221
1.3	Sequence-Specific Protein–DNA Interactions	221
1.4	Genetics of Control Signals	227
1.5	DNA Sequence Analysis	228
1.6	Chemical Probes	229
1.7	General Information in DNA	229
2	Transcription Control Signals	230
2.1	The Transcription Unit	230
2.2	Development versus Maintenance	230
2.3	Control of Transcription	231
3	The Promoter and Its Regulation	231
3.1	The Promoter	231
3.2	Transcription Initiation	232
3.3	The RNA Polymerase	232
3.4	The Basic Promoter	233
3.5	Promoter Function—The Model	233
3.6	Energy–Information Coupling	235
3.7	Binding Energy and Kinetics	236
3.8	Justifying the Model	236
3.9	Promoter Strength	240
3.10	Promoter Activation	242
3.11	Repressors, Operators, and Negative Control	244
3.12	Promoters and Development	248
4	The Terminator and Its Function	250
4.1	Terminators and Rho Factor	250
4.2	Attenuators	251
4.3	Rho-Dependent and Rho-Independent Terminators	251
4.4	Reversing Initiation . . . Somewhat	251
4.5	The Basic Terminator	252
4.6	Polymerase–Terminator DNA Interactions	253
4.7	RNA Structure and Braking	255
4.8	Terminator DNA Melting	257
4.9	RNA Elimination	257
4.10	Concerted Process	258
4.11	Rho-Dependent Termination	258
4.12	Translation and Transcript Termination	260
4.13	Terminator Strength	261
5	Terminator Regulation	261
5.1	Regulation and Rho Factor	261
5.2	The <i>trp</i> Attenuator	262
5.3	Control by Antitermination	264
6	Concluding Remarks	267

6.1	Transcription Regulatory Mechanisms	267
6.2	Adaptive Response versus Development	268
6.3	A Problem in Genetic Design	268
	References	269

8 On the Molecular Bases of the Specificity of Interaction of Transcriptional Proteins with Genome DNA

PETER H. VON HIPPEL

1	Introduction	279
2	Molecular Bases of Protein–Nucleic Acid Interactions	281
	2.1 Protein Structures and Functional Groups	282
	2.2 Nucleic Acid Conformations and Functional Groups	284
3	The Problem of the Other Sites	293
	3.1 Informational Aspects of Regulation	294
	3.2 Thermodynamic Aspects of Recognition	303
	3.3 Methods for Studying Specific and Nonspecific Binding of Proteins to Nucleic Acids and Definitions of Interaction Parameters	306
4	The Lactose Operon of <i>Escherichia coli</i>	308
	4.1 <i>lac</i> Repressor–Operator–Inducer–DNA Interactions	309
	4.2 Repression of the Lactose Operon as an Integrated Control System	319
	4.3 <i>In Vivo</i> Determination of the Thermodynamic Parameters of the <i>lac</i> System	330
	4.4 Kinetics of Intracellular Repressor Transport	332
	4.5 Other Components of the Lactose Operon	336
5	Extension to Other Transcription Regulatory Systems	341
	5.1 Prokaryotic Control Systems	341
	5.2 Eukaryotic Control Systems	342
	References	343

9 Genetic Signals and Nucleotide Sequences in Messenger RNA

JOAN ARGETSINGER STEITZ

1	Introduction	349
2	Ribosome Recognition of Initiation Signals	350
	2.1 A Bit of History	350
	2.2 A Look at Today's Catalog of Ribosome-Binding Sites	352

2.3	mRNA and rRNA Pair during Initiation	353
2.4	Proteins as Determinants in Initiation	358
2.5	RNA versus Proteins in Species Specificity	361
2.6	mRNA Structure and Initiation	363
2.7	Translational Control at the Molecular Level	368
2.8	The Why and Wherefore of Translational Restarts	373
2.9	Mutations in Ribosome-Binding Sites	375
2.10	Perspectives and Problems	377
3	Sequences Directing Elongation of Polypeptide Chains	379
3.1	Selective Codon Usage in Bacteriophage Messengers	380
3.2	Overlapping Genes and Signals in Messenger RNA	383
4	RNA-RNA Interactions in Ribosome Function	384
5	Are Eukaryotic Messengers Different?	387
	References	389

10 The Role of tRNA in Regulation

RICCARDO CORTESE

1	Introduction	401
1.1	Biosynthesis of tRNA	402
1.2	tRNA in Protein Synthesis	403
2	tRNA as a Regulatory Molecule	404
2.1	Stringent Control	405
2.2	Operon-Specific Control	410
3	tRNA as a Target for Regulation	419
3.1	tRNA-Dependent Modulation of Translation: An Evolutionary Equilibrium	419
3.2	tRNA-Dependent Modulation of Translation: A Developmental Regulation	422
4	tRNA Has Other Functions	424
5	Concluding Remarks	426
	References	427

11 Suppression

DEBORAH A. STEEGE AND DIETER G. SÖLL

1	Introduction	433
2	A Short Synopsis of Suppression	435
2.1	How It Started	435
2.2	The Problem of Nomenclature	436
2.3	Nonsense Suppression	436
2.4	Missense Suppression	437
2.5	Frameshift Suppression	437

2.6	Ribosomal Suppression	438
2.7	Polarity Suppression	438
3	Some Topics in Molecular Biology Influenced by Analysis of Genetic Suppression	439
3.1	Phasing of Messenger RNA	439
3.2	UAG, UAA, and UGA in Polypeptide Chain Termination	441
3.3	Effect of tRNA Modification on Codon Specificity	449
3.4	How Specific Is Codon-Anticodon Interaction?	451
3.5	Other Errors in Translation	454
3.6	Polarity and the Coupling of Transcription to Translation in Bacteria	457
3.7	Genetics of tRNA	459
3.8	Biosynthesis of tRNAs	461
3.9	tRNA Structure-Function Relationships: Mischarging Suppressor tRNAs	463
4	Nonsense Mutations in the <i>Escherichia coli lacI</i> Gene	466
4.1	Suppression of Nonsense Mutations Generates Altered <i>lac</i> Repressor Molecules	468
5	Current Developments in Eukaryotic Suppression	469
5.1	tRNA-Mediated Suppression in Yeast	469
5.2	The Search for Nonsense Mutations and Their Suppressors in <i>Drosophila</i> and Mammalian Cells	472
6	Outlook	474
	References	475

12 Regulation of the Protein-Synthesizing Machinery—Ribosomes, tRNA, Factors, and So On

O. MAALØE

1	Introduction	487
2	The Concepts and Elements	488
2.1	Characteristics of Control at the Operon Level	488
2.2	Transcription and the Regulation of the Protein-Synthesizing System	489
2.3	Relations between the Major Synthetic Activities	490
2.4	Parameters Characterizing Steady States of Growth	492
3.	Patterns and Frequencies of Transcription	495
3.1	Protein Synthesis at Medium and High Growth Rates	496
3.2	Protein Synthesis at Low Growth Rates	500
3.3	The Amino Acids—Substrates and Effectors	504
3.4	Transcription and Translation Frequencies	507
3.5	Synopsis	519
4	The Role of ppGpp in Regulation of the Protein-Synthesizing System	520

4.1	ppGpp Concentrations	521
4.2	The Relaxed Syndrome	525
4.3	Ribosome and Protein Synthesis during Shift-Down Transients	527
4.4	The Low Efficiency of Ribosomes at Low Growth Rates	532
4.5	Synopsis	534
5	Ribosome Synthesis during the Cell Cycle	535
6	Afterthoughts	536
	References	537

Index	543
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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

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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