



Genes & Signals

Mark Ptashne
Alexander Gann
Foreword by Tony Pawson

Contents

Preface, xiii
Foreword, xv

Introduction, 1

CHAPTER 1 • Lessons from Bacteria

11

RNA POLYMERASE, 11

REGULATED RECRUITMENT: THE *lac* GENES, 13

Protein-DNA Interactions, 15

Detecting Physiological Signals, 16

Promoter Recognition and Transcription by RNA Polymerase, 17

Switching the Genes On: Activation by CAP, 18

Cooperative Binding of Proteins to DNA, 18

Cooperative Binding and Gene Activation by CAP, 21

Repression by Lac Repressor, 25

Interim Summary and Extension, 25

MORE REGULATED RECRUITMENT: THE BACTERIOPHAGE λ , 26

The Switch, 28

Establishing Lysogeny, 29

Analogies with *lac*, 31

Promoters, 32

Protein-DNA Interactions, 32

Repression, 32

Activation, 32

Detecting Physiological Signals, 33

Making an Efficient Switch, 34

Cooperative Binding of λ Repressor to DNA, 34

Autogenous Control by Repressor, 37

PANEL: Antitermination: *N* and *Q*, 38

Interim Summary and Extensions, 39

Activation: A Closer Look, 39

DNA binding: A Closer Look, 41

Synergy, 41

POLYMERASE ACTIVATION: *glnA* AND RELATED GENES, 42

Promoter Recognition by σ^{54} -containing Polymerase, 43

DNA Binding by NtrC, 43

Detecting the Physiological Signal, 43

Activation by NtrC, 43

Other Activators of σ^{54} Polymerase, 45

Interim Summary, 45

PANEL: Phage T4 Late Genes, 47

PROMOTER ACTIVATION: *merT* AND RELATED GENES, 47

Promoter Recognition, 47

Detecting the Physiological Signal and Activation, 48

Interim Summary, 48

GENERAL SUMMARY, 49

PANEL: More on Repression in Bacteria, 51

FOOTNOTES, 53

BIBLIOGRAPHY, 55

CHAPTER 2 ■ Yeast: A Single-celled Eukaryote

59

RNA POLYMERASE, 60

OTHER PARTS OF THE TRANSCRIPTIONAL MACHINERY, 60

AN OVERVIEW OF ACTIVATION, 63

A MODEL CASE: THE *GAL* GENES, 63

Overview of Regulation of a *GAL* Gene, 64

Specific DNA Binding, 65

Detecting Physiological Signals, 66

HOW Gal4 WORKS, 67

Separate DNA-binding and Activating Regions of Gal4, 67

Activating Region Structure, 71

*Independent Mutations Can Increase Activator Strength Additively
When Combined*, 72

*Activating Regions Work with an Efficiency Proportional
to Their Lengths*, 72

<i>Activating Region–Target Interactions Tolerate Sequence Changes</i> , 73	
<i>New Activating Regions Are Easily Generated</i> , 73	
Squelching, 75	
Recruitment Visualized, 76	
Activator Bypass Experiments, 76	
<i>Activation by a Heterologous Protein-Protein Interaction</i> , 78	
<i>Direct Tethering of the Transcriptional Machinery</i> , 80	
PANEL: Activator Bypass Experiments, 81	
How does Gal4 Recruit Polymerase?, 82	
Nucleosomes and Their Modifiers, 83	
Targets of Gal4: Experiments Performed In Vitro, 84	
Action of Gal4: Experiments Performed In Vivo, 85	
<i>What Is Required for Activation?</i> , 86	
<i>What Appears at the Gene Upon Activation?</i> , 86	
Imposing a Need for Nucleosome Modifiers, 87	
<i>Weakening the Gal4-binding Sites or the Gal4-activating region</i> , 87	
<i>Cell-cycle Stage-dependent Requirement for Nucleosome Modifiers</i> , 89	
Activation: An Interim Summary, 89	
Repression by Mig1, 91	
SIGNAL INTEGRATION AND COMBINATORIAL CONTROL, 92	
Cooperative Binding with Alternative Partners, 93	
Sequential Binding of Activators, 94	
SILENCING, 95	
Heterochromatic Chromosomal Regions, 95	
Compartmentalization, 98	
PANEL: Variegation Visualized, 99	
PANEL: Epigenetics, 100	
DNA LOOPING, 101	
SUMMARY, 103	
FOOTNOTES, 104	
BIBLIOGRAPHY, 110	

CHAPTER 3 ■ Some Notes on Higher Eukaryotes

115

MECHANISM OF ACTIVATION: RECRUITMENT, 116

WHAT IS RECRUITED?, 118

Transcriptional Machinery and Promoters, 118

<i>Activating Region–Target Interactions Tolerate Sequence Changes</i> , 73	
<i>New Activating Regions Are Easily Generated</i> , 73	
Squelching, 75	
Recruitment Visualized, 76	
Activator Bypass Experiments, 76	
<i>Activation by a Heterologous Protein–Protein Interaction</i> , 78	
<i>Direct Tethering of the Transcriptional Machinery</i> , 80	
PANEL: Activator Bypass Experiments, 81	
How does Gal4 Recruit Polymerase?, 82	
Nucleosomes and Their Modifiers, 83	
Targets of Gal4: Experiments Performed In Vitro, 84	
Action of Gal4: Experiments Performed In Vivo, 85	
<i>What Is Required for Activation?</i> , 86	
<i>What Appears at the Gene Upon Activation?</i> , 86	
Imposing a Need for Nucleosome Modifiers, 87	
<i>Weakening the Gal4-binding Sites or the Gal4-activating region</i> , 87	
<i>Cell-cycle Stage-dependent Requirement for Nucleosome Modifiers</i> , 89	
Activation: An Interim Summary, 89	
Repression by Mig1, 91	
SIGNAL INTEGRATION AND COMBINATORIAL CONTROL, 92	
Cooperative Binding with Alternative Partners, 93	
Sequential Binding of Activators, 94	
SILENCING, 95	
Heterochromatic Chromosomal Regions, 95	
Compartmentalization, 98	
PANEL: Variegation Visualized, 99	
PANEL: Epigenetics, 100	
DNA LOOPING, 101	
SUMMARY, 103	
FOOTNOTES, 104	
BIBLIOGRAPHY, 110	

CHAPTER 3 • Some Notes on Higher Eukaryotes

115

MECHANISM OF ACTIVATION: RECRUITMENT, 116

WHAT IS RECRUITED?, 118

Transcriptional Machinery and Promoters, 118

- Nucleosomal Templates, 119
- Targets, 119
- The Human Interferon- β Gene, 121
- The *Drosophila HSP70* Gene, 122
- REPRESSION, 122
- DETECTING AND TRANSMITTING PHYSIOLOGICAL SIGNALS, 123
 - Transport Into and Out of the Nucleus, 123
 - Phosphorylation of Inhibitor or Activator in the Nucleus, 124
- PANEL: Transport-dependent Proteolysis: The Case of SREBP, 125
 - Allosteric Change of DNA-bound Activator, 126
- SIGNAL INTEGRATION, COMBINATORIAL CONTROL, AND ALTERNATIVE ENHANCERS, 126
 - The Human Interferon- β Enhancer, 126
 - The *Drosophila eve* Gene, 128
- ACTION AT A DISTANCE, 129
- DNA METHYLATION, INSULATORS, AND IMPRINTING, 132
- CHROMOSOMAL POSITION AND GENE EXPRESSION, 134
- COMPARTMENTALIZATION, 135
- OVERVIEW, 136
- FOOTNOTES, 137
- BIBLIOGRAPHY, 140

CHAPTER 4 • Enzyme Specificity and Regulation

143

- UBIQUITYLATION AND PROTEOLYSIS, 144
- SPLICING, 146
- IMPOSING SPECIFICITY ON KINASES, 148
 - Cyclin-dependent Kinases, 149
 - Transcriptional Antitermination by TAT, 150
 - Cytokine Receptors and Signaling through STATs, 152
 - Growth Factor Receptors, 154
- INTERIM SUMMARY AND EXTENSIONS, 156
 - Kinases, 157
 - Phosphatases, 158
 - Interpreting Signals, 159
- FURTHER GENERALIZATIONS, 160

Dangers, 160

Interpreting Experiments, 162

Benefits, 163

FOOTNOTES, 167

BIBLIOGRAPHY, 170

Afterword, 173

Appendices, 177

Appendix 1: More on Cooperativity, 177

Appendix 2: Topogenic Sequences, 183

Appendix 3: All-or-none Effects and Levels of Gene Expression, 185

Index, 187