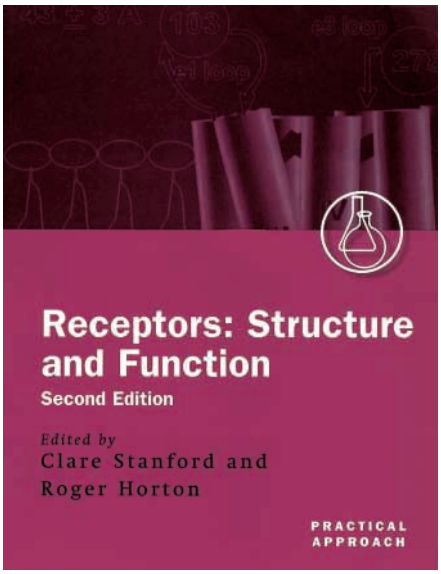
Twelve ways to look at a receptor



Receptors: Structure and Function, 2nd edn (A Practical Approach)

edited by Clare Stanford and Roger Horton

Oxford University Press (2001) 290 pages. ISBN 0-19-963882-9
£35

Receptors act as an informational interface between the cell and its environment: they transduce external signals into internal signals. Receptor structure and function are subjects of great interest in part because they underlie a broad panoply of sensory, developmental and other processes, and in part because receptors are prime targets for drug intervention. Recent genome sequencing projects have revealed the vastness of receptor number and diversity. The human genome, for example, is estimated to contain more than 1500 receptor genes, which would account for more than 5% of human genes (Venter et al., 2001). These receptors are highly divergent in structure and transduce a wide variety of signals.

How do they work? Different classes of receptor operate through different mechanisms, and many receptors have been difficult to study because of their low abundance or because they have been refractory to X-ray structure analysis. The importance of the problem and the difficulty of finding solutions has occasioned a great deal of creativity in seeking new ways to study receptor structure and function.

Twelve ways of studying receptors are presented in the new edition of *Receptors: Structure and Function*, a title in the Practical Approach series published by Oxford University Press. Its twelve chapters explain such topics as how to probe G-protein-coupled receptors (GPCRs) by fluorescence spectroscopy, how to study structure-function relationships by constructing mutant and chimeric receptors, how to investigate receptor stoichiometry and assembly by fluorescence resonance energy transfer (FRET), how to assess receptor function in real time by using a fluorometric imaging plate reader (FLIPR) and how to study turnover kinetics of GPCRs. One particularly appealing chapter, contributed by Thomas Hughes, James Howe and colleagues, concerns the use of receptor-GFP fusion proteins to study the intracellular trafficking of receptors.

The title of this series, *A Practical Approach*, should be taken literally. The emphasis of the volume is on methodology. Chapters explain some of the theory underlying the approaches and then provide a great deal of specific information about how to use each approach. In some chapters the authors convey wisdom accrued through experience; in all chapters they provide protocols containing lists of equipment and reagents, followed by detailed step-by-step instructions. A number of protocols, including one for restriction digestion of DNA and two for plasmid preparation, are widely available elsewhere, and some of the instruction is of most use to the neophyte: "The key to good cell culturing is sterile technique. Wash hands prior to use and wear gloves." However, most chapters convey a good deal of practical advice that could save days or months of effort on the part of seasoned investigators and could make the difference between a revealing discovery and uninterpretable chaos.

This book is not intended for the undergraduate who seeks an introduction to the principles of receptor structure and function; its goal is not to provide an overview of receptor classification, signal transduction or receptor expression. However, it is a fine book for those in search of new experimental approaches to the study of a receptor and for graduate students and postdoctoral fellows who seek a well-marked trail towards a new vista of the receptor of their choice.

Reference

Venter, J. C., Adams, M. D., Myers, E. W., Li, P. W., Mural, R. J., Sutton, G. G., Smith, H. O., Yandell, M., Evans, C. A., Holt, R. A. et al. (2001). The sequence of the human genome. *Science* **291**, 1304-1351.

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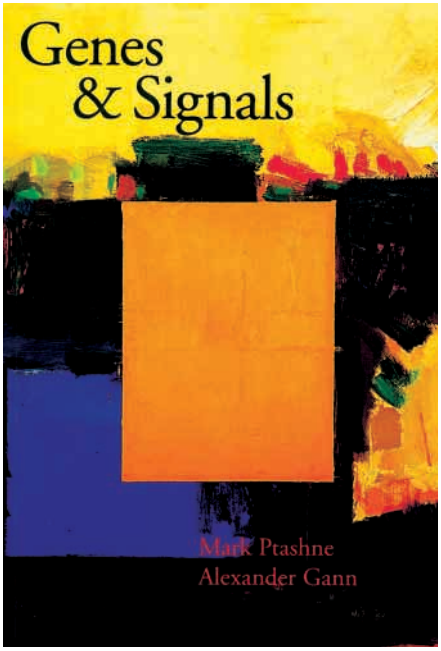
The "glue" that controls transcription



Genes and Signals

by Mark Ptashne and Alexander Gann

Cold Spring Harbor Laboratory Press (2002) 192 pages. ISBN 0-87969-633-8
$39

Guano cormorants flying home to the

rock on which their baby bird is waiting to be fed face a daunting task. They must distinguish their own child from the thousands of other almost identical looking babies waiting on the same rock. How do they accomplish this? Parents and baby are connected by an invisible bond, manifest in the form of a voice signal sent out by the baby to be recognized by the parents. Thereby, the parents are 'recruited' to the baby in order to deliver the food. At the molecular level, enzymes face a similar problem as they scan through various potential substrates to find the right one at the right time, and, in eukaryotes, in the proper cell. One of the most amazing selection processes is performed by DNA-dependent RNA polymerase, which is recruited to one gene out of thousands to create a needed RNA transcript. Which transcripts are needed can vary rapidly over time in response to a wide range of signals. In the book *Genes and Signals* by Mark Ptashne and Alexander Gann, the authors focus on how RNA polymerase solves this selection process, and the resulting text is very successful in its explanations and treatment of the topic. The authors are highly regarded scientists in the transcription field and have also published several highly cited reviews and another separate book (Mark Ptashne (1992) *A Genetic Switch: Phage Lambda and Higher Organisms*, 2nd edn. Blackwell Science) on regulation of gene expression.

Over the last decade, enormous efforts in the transcription field have culminated in the identification of players and mechanisms that control gene expression in prokaryotes and eukaryotes. One major level of control is the regulation of transcription, which depends on complex DNA-protein and protein-protein interactions, which recruit proteins to genes. In *Genes and Signals*, the basic concept of molecular 'recruitment' in the regulation of transcription is introduced and then further described by discussing the signals that control this recruitment and by comparing recruitment in gene expression with that occurring in other enzymatic processes, such as RNA splicing and protein degradation. Molecular recruitment is based on specific protein-protein interactions that mediate, for example, the binding of an enzyme to its substrate. The authors have termed these interactions "adhesive interactions", and they proceed to describe the 'adhesive interactions' that control gene expression and the signals directing these interactions in bacteria, yeast and higher eukaryotes.

The book itself is divided into four chapters. The first chapter opens with a summary of the many elegant pioneer experiments performed in bacteria that provided some of the first models of how gene expression is regulated. The authors proceed to introduce RNA polymerase and use activation of gene expression by CAP and repression by the Lac repressor as a means to present the general terms of transcription. After introducing these basic models, they then focus on bacteriophage λ and the mechanisms that control its fate in bacteria. This section includes how the lambda repressor and other proteins control whether λ integrates into the host genome and enters the lysogenic cycle or enters the lytic cycle and destroys the host. These processes incorporate other basic principles of gene expression, including cooperative DNA binding and 'adhesive' protein-protein interactions. As a contrast to the previous ideas the chapter concludes with transcription processes that do not depend on recruitment but rather on hydrolysis of ATP (NtrC) or DNA twisting (MerR).

In the second chapter, Ptashne and Gann focus on transcriptional regulation in yeast. This begins with an overview of the players mediating regulation of yeast transcription and a comparison with bacteria. This is followed up with a description of the yeast activator Gal4, which is used to guide the reader through basic mechanisms of activation of transcription with a focus on 'recruitment'. This culminates in the model that specific interactions between activators and proteins associated with RNA polymerase II lead to activation of transcription. In addition, the recruitment of multiple protein complexes in a defined order is required to activate gene expression. In the remaining sections of this chapter, Ptashne and Gann describe how gene expression is regulated at the level of chromatin by histone acetylation and chromatin remodeling. This includes treatment of the factors that are involved and the functional importance of this in yeast. The final sections cover the areas of telomeric silencing in yeast involving Sir proteins, an introduction to epigenetics and heterochromatin, and a final bit on compartmentalization, the hypothesis that the eukaryotic nucleus contains different functional compartments that are specialized for a particular function, such as activation of transcription.

The third chapter delves further into the world of eukaryotic gene expression, starting with a comparison of the similarities and differences between factors and mechanisms regulating gene expression in yeast and higher eukaryotes. The authors point out the 'added on' complexity in higher eukaryotes and use models to demonstrate this. This is continued with a description of the signals and mechanisms that control the activity of transcription factors, including phosphorylation, cytoplasmic retention and proteolytic digestion. Further sections focus on signal integration and discuss the mechanisms underlying the fact that, in contrast to yeast DNA, target sites for activators in higher eukaryotes are, in general, thousands of base pairs away from the transcription start site. There is also a description of the functional role of DNA methylation in regulation of transcription, a process not yet detected in yeast, and sections dealing with the function of insulators, which can flank genes and protect them from regulatory signals emanating from surrounding genes. This chapter, like the previous one, also has an end section discussing compartmentalization of the nucleus.

The true highlight of this book is the fourth chapter. While the first three chapters give a comprehensive and up-to-date summary of the mechanisms regulating gene expression, it is the last chapter that puts this information into perspective while focusing on the question "How is the specificity of enzymatic reactions generated?" The first section applies recruitment to other enzymatic processes such as splicing and protein degradation. By adding these elements, the reader can finally gain a

perspective on why the basics were necessary, and then how they can be applied to the wide range of processes occurring in an organism. This chapter closes with a critical discussion of the 'pros and cons' of the recruitment model.

The authors have managed to create a book that is very useful for the novice in this field, while also proving somewhat beneficial to those who have a more detailed background but are looking for a deeper insight into one topic. The novice will be able to walk away with a good and detailed summary of many processes and principles regulating transcriptional initiation in a range of organisms. In particular, the footnotes provided at the end of each section include additions to and further details and explanation of points in the main text, as do the 'panels' providing information on specific topics (e.g. epigenetics), which make this book very 'reader friendly'. Also, the simplistic writing style makes the material easy to follow. For those already familiar with aspects of regulation and gene expression, this book will provide a source of additional information and should prove especially handy for students preparing for exams on the topic. However, one should be aware that this book is not a complete overview of gene expression and rather is more limited to one major mechanism regulating gene expression: the recruitment of proteins to genes by protein-protein interactions to initiate transcription.

The expert reader will either love or despise this book for its simplicity. Some readers will miss certain topics. We miss a more detailed account of histone modifications and epigenetic regulation in higher eukaryotes. In addition, the recruitment model is not new to experts, and the similarities between transcriptional regulation in bacteria and eukaryotes have been widely accepted since the invention of the TET system, which is based on fusion proteins containing prokaryotic and eukaryotic transcription factors. Despite these minor shortcomings, overall *Genes and Signals* is a great summary on initiation of transcription that will be hard to find anywhere else, especially at a price of $39. And the expert reader is invited by the authors to rethink many aspects that have been taken as given. Reading the book will provide inspiration, one way or another. Although we do not share many of the 'adhesive interpretations' made by the authors, the book was nevertheless a fun read.

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