Book Reviews

Transcription Factors and Human Disease. Gregg L. Semenza. Oxford Monographs on Medical Genetics Vol 37. Oxford University Press. 1999. ISBN 0 19 511239 3

One of the most exciting and satisfying areas of human genetics over the past ten years has been the identification of mutations underlying a range of congenital malformation syndromes. In addition to providing abundant new insights into the molecular basis of embryonic development, the fact that many of these mutations affect genes encoding transcriptional regulators has emphasised the fundamental importance of tight transcriptional control of gene activity for normal execution of a wide variety of basic developmental programmes.

This book provides an in-depth survey of this fast-growing field. The book is divided into two parts: Part I is devoted to an overview of transcriptional regulation while Part II explores in detail the relationship between transcription factors and disease. Most of Part II describes the role of germline mutations in inherited disease – mutations in *cis*-acting regulatory elements, tissue-specific DNA binding proteins, their cofactors, and general factors. Two final chapters on cancer and teratogenesis remind us that transcription factors may cause disease by other mechanisms than germline mutation. Part II is enhanced by some fascinating original clinical photographs; in contrast a few of the line diagrams in Part I are somewhat primitive.

This book contains a wealth of detailed information but I felt that its overall usefulness has been compromised by the sheer pace of research in this area. With the most recent reference from late 1997, there is no mention of the role of WT1 in Frasier syndrome or of PAX8 in congenital hypothyroidism to name just two, and there is an ambience throughout the text of 'absent friends'. The author anticipates the surge of data and states in the Preface that his main aim is to communicate the key principles that have emerged in this area. These include the fact that many factors are deployed in multiple developmental contexts so that mutations frequently affect multiple tissues; that the same factors may be used post-natally in the maintenance of tissue identity and control of cell proliferation (which in the latter case means that somatic mutations can cause cancer); and that many of the factors – and the developmental pathways in which they act – are extremely highly conserved in evolutionarily diverse organisms. These are indeed extremely important points, but the fact that they are embedded in a dated text detracts from their impact. I could not help feeling that a better strategy might not have been to focus more on the principles and less on the multiple members of each transcription factor family.

Having said that, the existing layout does draw attention to another general principle – that the DNA binding proteins fall into a relatively small number of classes (zinc finger proteins, homeodomain proteins etc). This holds true despite the large volume of new data which has been generated during the last two years. The ease of identification of novel members of these families from the emerging human genome sequence surely promises great riches in linking many more diseases to their underlying mutations, as well as providing an abundance of new material for the second edition of this book.

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Prokaryotic Gene Expression. Edited by Simon Baumberg, Oxford University Press, 1999. 325 Pages. Price £32.95 (Pbk). ISBN 0-19-963603-6.

Jacob and Monod's analysis of the *Escherichia coli Lac* system in the early 1960s provided a simple model for gene regulation which, it was hoped, might apply to organisms generally. Over the next few years the bacterial paradigm became complicated somewhat – with transcriptional activators as well as repressors and a few easily understandable mechanisms for post-transcriptional regulation – but not to an excessive extent. The following decades saw an increasing shift in emphasis towards the control of gene expression in eukaryotes, and with the help of the new DNA

https://doi.org/10.1017/S0016672300219186 Published online by Cambridge University Press

technology, a picture has emerged of apparently limitless complexity. Those now preoccupied with the avalanche of new information about eukaryotic systems may tend to assume that the proaryotic scene has remained reasonably simple. If so, they are wrong, and Simon Baumberg's compendium should help to put them right.

What this book shows is that prokaryotic gene activity is subject to regulation at every imaginable step. Even at the level of DNA sequence, genes may be switched on and off by controlled segmental inversions (as in the classic case of flagellar antigen switching in *Salmonella*) or by replication slippage within repetitive sequences and consequent protein diversity, a device used by several pathogens to confuse their hosts. Even given a constant DNA sequence, its transcription is controlled in several analysed cases by protein-mediated changes in DNA geometry (bending and supercoiling), and even in one case in *E. coli* by site-specific methylation, something that one had assumed to be a eukaryotic prerogative. More usually, whether or not a gene is transcribed depends on the nature of the available RNA polymerase, a chameleon-like protein complex with various alternative functions determined by its multiple interchangeable *sigma* subunits, and a great range of other specificities, some broad and some narrow, conferred by accessory activating proteins of many kinds. Some of the protein activators are themselves switched between active and inactive forms by phosphorylation/dephosphorylation – indeed, sometimes by a "cascade" of protein phosphorylation, almost as in the eukaryotes. Once synthesized, the messenger RNA is maintained at a high or low level depending on its turnover rate, which itself may be subject to control. And the degree to which the mRNA is effectively translated is controlled in many instances by the level of the end-product, as in the well-investigated type of *attenuation* which helps to control the transcription of operons of amino acid synthesis in *E. coli* and *Salmonella*. Many of these diverse systems of regulation act on each other, so that the whole system is (of course!) a network rather than a large number of parallel chains of causation.

With so much tightly-packed information, this book was never going to be an easy read, but some contributors are more reader-friendly than others. Two of the more enjoyable articles, with the benefit of clarifying diagrams, are by J. R. Saunders, on switch systems, and Michael Yudkin and Keith Chater on sporulation and antibiotic production (the latter featuring phosphorylation cascades and sigma proteins). Perhaps the most demanding is the wide-ranging article on post-transcriptional control by Zhoping Gu and Paul Lovett; here the numerous examples are each dealt with so briefly, without visual aids, that the information might almost have been better presented in a Table. However, these authors do provide a 178-item reference list. Indeed, the access that it provides to most of the relevant literature, at least up to 1997, is one of the best features of the book as a whole.

I learned a good deal from this book, and perhaps I should not carp at the absence of a few topics that I already knew about. One thing that I missed was any detailed explanation of attenuation and how it works. This topic is mentioned in passing by the editor in his introductory and concluding essays, but in a cursory fashion, as if he was assuming that someone else would be covering it. I was also rather surprized not to find a more general discussion of the properties of operons, including, for example, the significance, so far as there is any, of the upstream-downstream positioning of the genes within them.

These quibbles notwithstanding, Professor Baumberg should be congratulated on having assembled this collection of expert articles. The book fills a gap, and will be widely used.

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https://doi.org/10.1017/S0016672300219186 Published online by Cambridge University Press