demethylation and the subsequent screening of demethylated cells using expression arrays. The maintenance methyltransferase Dnmt1 becomes bound to DNA and is inactivated when 5-aza-cytidine is incorporated into CpG sites opposite a methylated CpG site on the template strand, leading to a rapid, passive loss of DNA methylation in cells and to the ectopic expression of genes that depend on Dnmt1 and DNA methylation for silencing.

Much of the gene-specific methylation analysis uses the bisulphite sequencing technique (originally developed by Frommer and colleagues (Frommer et al., 1992; Clark et al., 1994), which leads to the conversion of cytosine residues to uracil residues, but leaves 5-methylcytosine residues unaffected. This technique is comprehensively outlined in Chapter 14. A low-cost assay is also discussed in Chapter 20, which outlines methyl-sensitive restriction digestion in combination with real-time PCR for the quantification of methylation levels at specific sites. Recently, it has been noted that the potential presence of 5hmC in genomic DNA may challenge the interpretation of data using the bisulphite method, and this may need to be kept in mind in the future (Loenarz and Schofield, 2009). The last section contains protocols for analyzing methylated circulating DNA from patients, which might be useful for biomarker research and for subsequent whole genome analysis. Evidence of the speed of technological development is that there are no sections on how deep-sequencing protocols might be incorporated into the assays discussed. Overall, this is a practical book to have on the bench to determine genome and locus-specific DNA methylation levels. But the question remains, what does it all mean?

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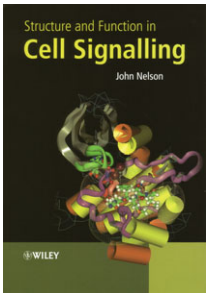
Helpful introduction to signal transduction



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Structure and Function in Cell Signalling

By John Nelson

Wiley (2008) 410 pages
ISBN 978-0-470-02551-2
£34.95 (paperback)

When studying cell signaling, it is easy to get overwhelmed with the complexity of each pathway and with the crosstalk between them. Teaching the basics of cell signaling therefore requires much simplification to make sense out of the chaos of signal transduction maps that, as John Nelson, the author of *Structure and Function in Cell Signalling*, points out, look like "inscrutable electronic circuits". Is it possible to write a book on signaling that embraces the complexity of the topic without overwhelming the reader? One might conclude that almost any effort would deliver something either too simplistic or destined to go quickly out of date. Not so. *Structure and Function in Cell Signalling* is not a collection of chapters written by experts in the field, and I think that this is a saving grace. Rather, this book is written from the perspective of a single author who is both a researcher and a teacher in the field. This gives it a cohesive storyline that links the topics together and provides the reader with much more continuity than is generally achieved in the usual 'edited by' collection of topics.

The history of how the cell signaling field developed is interspersed into the narrative of the book and provides a glimpse into some of the accomplishments of major figures in the early days of the field, such as Krebs, Fischer, Rodbell, Sutherland, Gilman and many others. The readers will enjoy hearing how the experiments of Krebs and Fischer on phosphorylase activation were temporarily stymied when they began to use centrifugation to clear debris instead of filtering cell homogenate through paper. This led them to discover that phosphorylase kinase, the first protein kinase to be identified, required calcium (which was contained in the paper filter), together with ATP, to convert inactive phosphorylase b to active phosphorylase a in the homogenate. The book provides further examples of fortuitous discoveries by keenly observant investigators, proving the point made by Louis Pasteur that "fortune favors the prepared mind" and encouraging students in the field to be alert and open to unexpected results.

The first chapter is devoted to basic concepts and to the historical progression that identified the major components of signaling systems, but the references to history continue throughout the book and provide interesting tidbits that ground our current terminology in the past. The multifunctional serine/threonine protein kinase GSK3, for example, has its name because it phosphorylates a certain residue known as site 3 on rabbit skeletal muscle glycogen synthase, although most students would now think of it primarily in a completely different context, namely as a regulator of β-catenin in the Wnt signaling pathway.

The book is divided into 10 chapters, ranging in subject from protein motifs, G proteins and G protein-coupled receptors, to growth factor and cell cycle signalling. Each chapter is broken up into sections that provide a clear outline of where the author is taking us. The second chapter starts by considering the fundamental properties of enzymes and receptors and then continues

with a very helpful discussion of the modules and motifs involved in signal transduction. Some basic acquaintance with Src homology (SH2, SH3), pleckstrin homology (PH), phosphotyrosine binding (PTB) and PDZ modules is probably a part of every graduate student's education in the molecular life sciences, but this book provides a detailed structural view of these modules and of other, less frequently encountered ones, with numerous sequence comparisons and crystallographic representations. In his preface to the text, the author points out that protein-protein interactions provide the key to understanding cell signaling, as well as most other events in the life of a cell. The protein interaction modules that are shared among a wide variety of proteins thus provide an essential starting point for this analysis. This structural theme is one of the strengths of this book and continues throughout all of the chapters. The author provides instructions in the appendix for downloading protein data bank (PDB) files from the NCBI homepage and for using RasMol, a computer program used to visualize macromolecular structures. References to specific PDB files are included in the legends of all of the structure-oriented figures.

[This book] is not a collection of chapters written by experts in the field, [it] is written from the perspective of a single author who provides the reader with much more continuity than is generally achieved in the usual 'edited by' collection of topics

The basic function of protein kinases is examined in a dedicated chapter, with considerable emphasis on the structural domains that determine ATP binding and the recognition of substrates, and on the requirements for activating phosphorylation events. The prototypical catalytic subunit of protein kinase A is used to illustrate basic structural requirements; subsequently, other examples, including the insulin receptor kinase domain and the cyclin-dependent kinases, are compared with this prototype. The level of detail in the discussion of kinase structure is remarkable and, in this chapter alone, the text is supplemented with 20 figures that depict sequence alignments and structures. This in-depth coverage is perhaps not for the faint of heart, but it makes this a book worth keeping and worth referring back to when new questions about structure and function arise or when one's memory needs to be refreshed.

Another chapter considers G protein-coupled receptors (GPCRs), which are encoded by approximately 5% of all human genes and which are the targets for many of the most frequently prescribed drugs (e.g. opioid analgesics, β-adrenergic antagonists and agonists, and antihistamines). The book summarizes the salient features of this large family of receptors and discusses basic coupling mechanisms and downstream effectors. In order to provide a focus for the discussion of GPCRs, the author chooses to use glycogen metabolism as an example, providing a detailed description of the regulation of glycogen phosphorylase and glycogen synthase. Although this topic might not immediately capture the imagination of most readers, the chapter introduces several of the key questions that are of current interest in the field of cell signaling. I found the discussion of signal scaffolding proteins, such as AKAPs, caveolins and arrestins, to be particularly timely.

Chapters follow that focus on monomeric and trimeric G proteins. Once again, the book benefits from the continuity afforded by having a single author who can compare and contrast the structural elements of monomeric G proteins, using Ras as the prime example, with the alpha subunits of the heterotrimeric G proteins, which are discussed in a separate chapter. Structural domains, protein-protein interactions, scaffolding and intracellular localization dominate the discussion, which, for those who are just becoming familiar with the complexity of these pathways, provides many insights into how such signalling modules function.

One chapter is devoted to growth factor receptors and focuses primarily on the platelet-derived growth factor (PDGF) and the epithelial growth factor (EGF) families of receptors. Brightly colored cartoons depicting the various signaling molecules that associate with context-dependent phosphotyrosine residues are supplemented with structural information when available, and with a narrative that not only summarizes what we currently know, but also points to unresolved questions. The insulin receptor gets treated in a separate chapter, which also includes valuable comparisons with the related receptor for insulin-like growth factor I. Finally, a rather detailed, but very lucid, discussion of cell cycle signaling brings the book to a close.

This book is clearly targeted to graduate students in the life sciences, and it would provide the basis for an excellent course on the principles of signal transduction. I am purchasing a lab copy and am encouraging my students and postdoctoral fellows to read it, but I suspect that many more senior investigators in the field would also benefit, as I did, from this concise review of the basics in the field. New information will certainly extend our understanding of the signaling systems discussed in the book, but the core ideas presented in this readable text are unlikely to go out of date. I was disappointed that cytokine signaling and TGFβ pathways were not included as part of the core material, but I hope to see them in a second edition of this text in a few years' time.

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