Preface

To the non-expert, cell signalling is daunting. Even for a specialist, straying from one area of signalling to an unfamiliar one can be somewhat testing.

The scientific literature now features signal transduction maps that, at first sight, appear to be bewildering collections of coloured blobs connected by circuitous lines and arrows. This is an undeniably efficient way to contain the burgeoning knowledge base, but without an understanding of the underlying fundamentals, such maps are as inscrutable as electronic circuits are to those ignorant of the function of resistors and capacitors. Fortunately, just like electronic circuits, cell signalling pathways are constructed from a limited number of types of components that rely upon a small number of discrete mechanisms of action. Indeed, this is exactly the analogy that Rodbell used when proposing that a 'transducer' (*G protein*) laid between the multiple information 'discriminators' (*receptors*) and the signal 'amplifier' (*effector enzyme*).

My aim is to break signalling down into common elements and activities – the 'nuts and bolts' of cellular information exchange. And, as we shall see, signalling is really just a series of recognition events that lead to either simple binding and conformational change or catalysis.

In order to explore adequately the molecular details of transduction components and their interactions, I have focused on 7-pass and single-pass receptor signalling. Unfortunately, space and time constraints did not permit coverage of neural and visual signalling; similarly, ion channels are not covered in detail, and adhesion- and cytokine signalling are not discussed.

What is in the book...

The book begins with basic principles, including a historical account of key discoveries and their impact, a simplified treatment of classical mathematical methods of quantitation, and a survey of structural domains and linear peptide signatures of the commonest transduction molecules. To give the book a narrative, I have focused on metabolic signalling and the control of cell cycle progression because all the key players (G proteins, 2nd messengers, kinases, adaptors) are present and these pathways, being the longest studied, are relatively well understood. As you shall see, however, understanding of even these venerable pathways and networks is still in a partial state of flux. Finally, I have done my best to clarify the alternative nomenclatures, numberings and terminologies that have emerged from the diverse specialities that now exist within cell signalling.

I have deliberately used the freeware molecular rendering programme RasMol throughout to encourage readers to try it for themselves (simple instructions are in the Appendix). Just remember: successful use of molecular graphics depends upon being able to find your bearings in a (perhaps unfamiliar) linear sequence by relating it to

conserved motifs and known three dimensional structural homologues. Furthermore, one must always bear in mind that the sequence numbering in coordinate files from an X-ray or NMR study is not always the same as the native sequence numbering because proteins are often truncated to aid crystallisation. Lastly, always read the source paper before attempting to examine the structural model.

For the past half century, our understanding of metabolic and signalling pathways has been built from *in vitro* measurements of the activities of individual components isolated from homogenised cells, the behaviour of the entire pathway being inferred mathematically by summation. Recently, however, modern techniques increasingly allow whole pathways to be monitored in single living cells. The familiar paradigms of metabolic pools and 'control point' enzymes (derived, *in vitro*, from kinetic assays of individual glycolytic enzymes) has been challenged by 'metabolic control theory' developed from global analysis of glycolytic flux in living whole cells. Similarly, the paradigm of signal amplification by soluble protein kinase cascades has been modified by the discovery of 'scaffolding proteins', which hold kinases and their downstream kinase substrates in one-to-one cassette-like complexes. New real-time receptor binding assay methodologies (surface plasmon resonance, microcalorimetry) increasingly allow measurements of on- and off-rate constants (k_1 and k_2) of native ligands to be obtained – something previously difficult to measure using labelled ligands.

The 21st century is likely to be dominated by the study of the cell physiological functions of protein-to-protein interactions as they occur in whole cells. Both metabolic and signal transduction research are in a sense coming full circle to the realisation that one only really gets a true picture of how pathways work by looking at them in their entirety *and* in their natural environment: the complex, crowded and elastic milieu of the living cell. We have taken the clock to pieces, now we are putting it back together again.

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