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Signal Transduction

信号转导

Bastien D. Gomperts, Ijsbrand M. Kramer, Peter E. R. Tatham

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前　言

许多人问起这本书是为谁而著，最诚恳的回答是为我们自己而写。我们希望这本书将为各层次的学生和专业人员提供指导性和趣味性。我们希望避免由多个专家撰写的但没有经过仔细编辑的内容，这意味着我们不得不谨慎地处理那些我们不是很擅长的领域。虽然我们涉及了学科的前沿，但是我们也试着纳入一些基本知识，并介绍一些历史背景。当然，我们知道有些重要内容应该放到“信号转导”内，没有把它们纳入会有争议，但是我们认为不可能面面俱到。如调节早期胚胎发育的信号过程和植物的信号转导等内容，就没有出现在本书中。通过此书的写作，我们受益颇丰，当我们知道得越多，我们越有勇气去挑战，至少可以去重新检查一些被公认的教条。我们也学会了尊重我们前人的智慧，正是他们在19世纪和20世纪初期的无所束缚的思想和一些偶然的发现，导致了现代学科的建立，如生理学、药理学、细胞生物学，以及一些相关的临床学科，特别是内分泌学和免疫学。

本书分为两部分。第一部分（第一至九章）介绍所谓“经典”信号转导的基本内容，主要集中在激素及其受体，第二信使的产生及其作用，特别是环核苷酸和钙离子。正是由于此领域的发展，特别是G蛋白的发现，导致了“信号转导”（signal transduction）这一词的使用，虽然“transduction”是从其他地方借用过来的。本书的第二部分，从第十章起，主要介绍生长因子和黏附分子介导的信号转导过程，特别是蛋白质的共价修饰（如磷酸化）和含肌醇的脂类以及它们在细胞内信号级联反应中的作用。此领域研究的一个重要目的是试图了解导致癌症的细胞转化机制，希望能寻找到有效的治疗方法。癌症（cancer）这个词的酝酿已有很长的历史，在词典中均有很好的解释。

在本书的写作过程中，我们受益于许多朋友和同事的建议和想法，他们包括：英国莱斯特大学生化系的Raj Patel和他的同事们，特别是John Challiss，Jonathan Blank和David Crichley，他们阅读了整部书稿；剑桥医学研究理事会（MRC）分子生物学实验室的Leo Lagnado阅读了第一至六章，就视觉信号转导提出建议；Hammersmith医院的帝国大学医学院的Susan Nourshargh对细胞黏着和运输（第十四和十五章）提出了建议；Greta Matthews阅读了整部手稿并提出了许多有价值的建议；耶路撒冷希伯来大学生化系的Alexander Levitzki建议我们舍弃有关G蛋白作用的教条。另外，我们也感谢位于阿姆斯特丹的荷兰癌症研究所的Peter ten Dijke对第十章和十六章的阅读；位于英国卡地夫的Amersham Pharmacia生物技术公司的Fergus McKenzie对第十一、十二和第十七章的阅读，以及第十章中有关细胞周期的描述；伦敦大学医学系的Lodewijk Dekker阅读了第九章，Dundee大学MRC蛋白磷酸化组的Patricia Cohen有关丝氨酸－苏氨酸磷酸化酶的建议和帮助；Bordeaux欧洲化学和生物研究所的Elizabeth Genot在第十二章中有关T细胞激活的建议；牛津大学药理系Steve Watson和伦敦大学生理系的Chris Richards有关钙离子的帮助和建议；Geoffery Strachan把法文和德文译成英文的建议。

还有其他许多人，无法在此一一列出他们的名字，他们的知识使我们受益匪浅。为了感谢他们的贡献，我们引用了1878年的一篇题为“关于皮特尤里（Pituri）”的文章，这篇文章是信号转导的先驱之一所写（见第145页“一种新的第二信使的发现”）。

《关于皮特尤里》作者 Sydney Ringer，M. D. 和 William Murrell，M. R. C. P. 威斯敏斯特医学院应用生理学讲师，皇家胸科医院助理内科医生

不久以前，伦敦大学的一个学生（很遗憾，我们忘记了他的名字）给了我们一小袋皮特尤里（Pituri）的枝叶，这是一种有趣的药物。我们把它给了 Gerard 先生，而他从中提取到了微量的生物碱，并以 1∶20 的比例配成了一些水溶液。在研究了皮特尤里的叶子后，Baron Mueller 认为它是来源于一种名叫 Duboisia Hopwoodii 的灌木。皮特尤里生长在 Darling 河和 Barcoote 至西澳大利亚的沙漠灌丛中。据说当地人在长途跋涉中靠咀嚼它的叶子来增强体质，正像玻利维亚人用可可叶子一样。Bennett 博士在1873年5月新南威尔士医学报上撰文说皮特尤里是一种刺激性麻醉剂，新南威尔士人服用它正像东方人吃槟榔一样，它似乎是烟草的代替品。它一般以干叶子出售，通常被磨成粉，以致看不出它原来是什么样的。

皮特尤里只限于 Mallutha 族的男人们服用。在真正服用之前，他们只咀嚼一匙左右的干叶子，跟一些枝叶烧成的灰混在一起，稍稍咀嚼后就放在耳后（据说这样做可增强它的药效），然后不时地嚼一嚼，直到最后被吞服。在服用后，当地人在谈生意或决斗时就会勇气十足。当服用过量时，它会使人狂怒。对于不习惯服用它的人，皮特尤里会引起严重的头痛。

当然，这篇文章的作者当时根本没听过“信号转导”这个词，它是100年后才在生物学文献中出现的。Ringer 和 Murrell 所描述的生物碱皮特尤里与阿托品的药理特征有一些共性（如增加勇气，引起狂怒、失意、头痛），这些感觉在我们编写此书时并不陌生。然而，我们没有要发怒，甚至从没感到有争执。虽然本书是我们三人所著，我们始终如一的目标是要把本书写成像是出自一人之手。自然，我们三人各有各的兴趣和专长，我们每人各负责一些章节的起草。然后，逐行阅读、推敲、取代、增删和修改，直到最后我们认为整本书已浑然一体。

注释

蛋白质结构数据：我们使用“蛋白数据库”（Protein Data Bank）：Berman，H. M.，Westbrook，J.，Feng，Z. *et al*. The protein data bank. *Nucleic Acid Res*. 2000；28：235—42（http://www.rcsb.org/pdb/）.

化学结构：我们使用 EPSRC 在 Daresbury 的 Chemical Database Service：Fletcher，D. A.，McMeeking，R. F.，Parkin，D. The United Kingdom Chemical Database Service. *J. Chem. Inf. Comput. Sci*. 1996；36：746—9.

蛋白结构使用 Rasmol 和 CHIME：Sayle R.，Milner-White，E. J. RasMol：Bio-

molecular graphics for all. *Trends Biochem. Sci* 1995；20：374.

Martz, E.（University of Massachusetts, Amherst, MA, USA）and MDL Information Systems, Inc.（San Leandro, CA, USA）.

参考资料

我们试图为几乎所有的叙述、所讨论的实验和发现提供原始的文献来源，主要原因是本书所涉及的领域众多，已远远超过我们已有的经验或专长的内容。因此，翔实的文献引用可以确保我们下笔有据，我们所写的并不是简单的凭空想象。另外，因为我们把引用原始的历史材料作为本书的一大特点，所以把现代文献引入也符合逻辑。我们希望这本书能起到有价值的资源作用，任何人想进一步了解的话都能找到基本文献综述。

缩写

此书中主要缩写的定义都能在索引中找到。

基因和基因产物

按惯例，首字母是小写时指基因（如 ras），而首字母是大写时指蛋白产物（Ras）。酵母基因是大写（RAS）。前缀 v-和 c-特指病毒或细胞来源（v-Ras，c-Ras）。

《简明牛津英语词典》第二版（CD）对 translation 一词的定义有如下几条：

1. 下跨或跨过的作用；
2. 转导信号的作用或过程；
3. （微生物学）使用病毒或病毒型颗粒把遗传物质从一个细胞转移到另一个细胞。

（陈晔光　译）

Preface

Many people have asked for whom this book has been written and the most honest answer must be that it has been written for ourselves. It is our hope that it will also be both instructive and entertaining for students and professionals at many levels. We hope it avoids the worst excesses of the skimpily edited multi-author texts written by specialists, but necessarily this means that we have had to tread warily in areas in which none of us has first-hand experience, let alone expertise. Although we have touched the front edges of the subject, we have also endeavoured to provide an elementary basis with some historical background to all the topics covered. There has been no attempt to be comprehensive and we are aware that important topics that well qualify for inclusion in a book having the title *Signal Transduction* are conspicuous only by their absence. An obvious example must be the signalling processes that guide early embryonic development. Another is the field of signal transduction in plants. Throughout the period of writing, we have been the main beneficiaries as students of our own subject. As we learned more, we were encouraged to challenge, or at least to re-examine, some of the well-established dogmas. We have also learned to respect the wisdom of our forebears, whose freedom of thought and sometimes serendipitous discoveries in the 19th and early 20th centuries led to the creation of the modern sciences of physiology, pharmacology and cell biology, and related clinical fields, especially endocrinology and immunology.

The book conveniently divides in two parts. The first half (Chapters 1–9) provides the nuts and bolts of what might be termed 'classical' signal transduction. It concentrates mainly on hormones, their receptors, and the generation and actions of second messengers, particularly cyclic nucleotides and calcium. It was the advances in this area, particularly the discovery of the G-proteins, that originally gave rise to the expression 'signal transduction', although the term 'transduction' was stolen from elsewhere. In the second half of the book, introduced by Chapter 10, attention is concentrated on transduction processes set in action by growth factors and adhesion molecules, particularly the covalent modification of proteins (by phosphorylation) and of inositol-containing lipids and their roles in the initiation of intracellular signalling cascades. An important, though not exclusive, impetus to research in this area has been the quest to understand the cellular transformations underlying cancer, with the

hope of devising effective therapeutic procedures. The gestation of the word 'cancer' has a long history, well revealed by its description in the dictionaries.

In preparing the book, we have had the benefit of advice and opinions given by friends and colleagues. These include Raj Patel (and his colleagues, particularly John Challiss, Jonathan Blank and David Critchley) at the Department of Biochemistry, University of Leicester) who, between them, read the complete script. Leon Lagnado (MRC Laboratory for Molecular Biology, Cambridge) read Chapters 1–6 and advised us particularly on the topic of visual transduction. Sussan Nourshargh (Imperial College School of Medicine at Hammersmith Hospital) advised on matters relating to cell adhesion and trafficking (Chapters 14 and 15). Greta Matthews read the entire script and gave much valuable advice. Alexander Levitzki (Department of Biochemistry, Hebrew University Jerusalem) encouraged us to disregard dogma when discussing the activation of G-proteins. We are also indebted to Peter ten Dijke (Netherlands Cancer Institute, Amsterdam) who read Chapters 10 and 16, Fergus McKenzie (Amersham Pharmacia, Cardiff) who read Chapters 11, 12 and 17, and the essay describing the cell cycle in Chapter 10, Lodewijk Dekker (Department of Medicine, University College London) who read part of Chapter 9, and Patricia Cohen (MRC Protein Phosphorylation Unit, University of Dundee) for her help and advice on the serine–threonine phosphatases. Elizabeth Genot (European Institute of Chemistry and Biology, Bordeaux) provided valuable advice on matters relating to the activation of T cells (Chapter 12). Steve Watson (Department of Pharmacology, University of Oxford) and Chris Richards (Department of Physiology, University College London) gave invaluable support and advice on matters relating to calcium. Geoffery Strachan advised on the translation of French and German texts into contemporary (19th century) English.

Many others, too numerous to name individually, have given us the benefit of their knowledge and understanding. In acknowledgement of their contribution we offer the following quotation from a paper dated 1878, entitled *On Pituri* by one of the pioneers ('A new second messenger is discovered', page 146) of signal transduction.

ON PITURI. By SYDNEY RINGER, M.D., and WILLIAM MURRELL, M.R.C.P., Lecturer on Practical Physiology at the Westminster School of Medicine, and Assistant Physician to the Royal Hospital for Diseases of the Chest

QUITE recently a student of University College, London, whose, name we have unfortunately forgotten, gave us a small packet containing a few twigs and broken leaves of the powerful and interesting drug, Pituri. These we placed in Mr Gerard's hands, and he kindly made first an extract from which he obtained a minute quantity of an alkaloid, and with this he made a solution containing one part of the alkaloid to twenty of water. Baron Mueller, from an examination of the leaves of pituri, is of opinion that it is derived from Duboisia Hopwoodii. Pituri is found growing in desert scrubs from the Darling River and Barcoote to West Australia. The natives, it is said to fortify themselves during their long

foot marches, chew the leaves for the same purpose as Cocoa leaves are used in Bolivia. Dr G Bennett in the New South Wales Medical Gazette, May, 1873, says Pituri is a stimulating, narcotic and is used by the natives of New South Wales in like manner as the Betel of the East. It seems to be a substitute for tobacco. It is generally met with in the form of dry leaves, usually so pulverized that their character cannot be made out.

The use of pituri is confined to the men of a tribe called Mallutha. Before any serious undertaking, they chew these dried leaves, using about a tea-spoonful. A few twigs are burnt and the ashes mixed with the leaves. After a slight mastication the bolus is placed behind the ear (to increase it is supposed its strength), to be again chewed from time to time, the whole being at last swallowed. The native after this process is in a sufficiently courageous state either to transact business or to fight. When indulged in to excess, it is said to induce a condition of infuriation. In persons not accustomed to its use pituri causes severe headache.

Of course, the authors of this paper would themselves never have heard the expression 'signal transduction' and it would be a further 100 years before it made its appearance in the biological literature. The sensations brought about by pituri, an alkaloid that Ringer and Murrell described as sharing some of the pharmacological properties of atropine (courage, infuriation, frustration and headaches), are not dissimilar to those experienced by us in the writing of this book. However, we have never come to blows, never even felt the need to fight. Although it was drafted by three authors, the aim throughout has been to present a book written as if by one mind, one pair of hands. Of course, we all have our own particular fields of interest and (hopefully) expertise and we were individually responsible for the original drafting of particular chapters and sections. However, there is not a line of the book that has not been read, replaced, rewritten, expanded, cut or otherwise altered so that in the end, we hope that the text has a consistent style throughout.

Notes

For protein structural data we have made use of: the Protein Data Bank: Berman, H.M., Westbrook, J., Feng, Z. *et al.* The protein data bank. *Nucleic Acid Res.* 2000; 28: 235–42 (http://www.rcsb.org/pdb/).

For chemical structures we wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury:
Fletcher, D.A., McMeeking, R.F., Parkin, D. The United Kingdom Chemical Database Service. *J. Chem. Inf. Comput. Sci.* 1996; 36: 746–9.

Protein structures have been generated using Rasmol and CHIME:
Sayle R., Milner-White, E.J. RasMol: Biomolecular graphics for all. *Trends Biochem. Sci.* 1995; 20: 374.
Martz, E. (University of Massachusetts, Amherst, MA, USA) and MDL Information Systems, Inc. (San Leandro, CA, USA).

References

We have tried to provide original text sources to nearly all the statements, experiments and discoveries discussed. The main reason for this is that we ourselves have necessarily had to extend the treatment of nearly all the topics presented far beyond the areas of our own experience or expertise. Thus, the comprehensive lists are there to provide us with some sort of reassurance that what we have written has not simply been conjured out of the air. Also, because we have made a particular feature of presenting original historical source material by quotation, which necessarily required referencing, it seemed logical also to include literature references to modern sources as well. Thus we hope that this book may serve as a valuable resource, in the manner of a basic literature review, for anyone wanting to explore further.

Abbreviations

The definitions of all the main abbreviations used in this book can be found in the index.

Genes and gene products

According to convention, acronyms printed in lower case indicate genes (e.g. ras), capitalized acronyms indicate their protein products (Ras). The genes of yeast are printed in upper case (RAS). The prefixes v- and c- indicate viral or cellular origin (v-Ras, c-Ras).

From the Shorter Oxford English Dictionary (3rd edition, 1944, with corrections 1977):

Transduction (trɑnsˌdʊ·kʃən). *rare.* 1656. [ad. L. *tra(ns)ductionem*, *tra(ns)ducere*; see TRADUCE.] The action of leading or bringing across.

Traduce (trădiū·s), *v.* 1533. [ad. L. *traducere* to lead across, etc.; also, to lead along as a spectacle, to bring into disgrace; f. *trans* across + *ducere* to lead.] †1. *trans.* To convey from one place to another; to transport -1678. †b. To translate, render; to alter, modify, reduce -1850. †c. To transfer from one use, sense, ownership, or employment to another -1640. †2. To transmit, esp. by generation -1733. †b. *transf.* To propagate -1711. †c. To derive, deduce, obtain *from* a source -1709. 3. To speak evil of, esp. (now always) falsely or maliciously; to defame, malign, slander, calumniate, misrepresent 1586. †b. To expose (to contempt); to dishonour, disgrace (*rare*) -1661. †4. To falsify, misrepresent, pervert -1674.

1. b. Milton has been traduced into French and overturned into Dutch SOUTHEY. 2. Vertue is not traduced in propagation, nor learning bequeathed by our will, to our heires 1606. 3. The man that dares t., because he can With safety to himself, is not a man COWPER. b. By their own ignoble actions they t., that is, disgrace their ancestors 1661. 4. Who taking Texts .. traduced the Sense thereof 1648. Hence **Tradu·cement**, the, or an, action of traducing; defamation, calumny, slander. **Tradu·cingly** *adv.*

from The Oxford English Dictionary (2nd edition) On Compact Disc:

transduction (tra:ns'd□k ʃ e n, træns-).
[ad. L. *transduction-em* (usually *traductionem*), n. of action f. *tra(ns)dfucere: see* TRADUCE.]

1. **The action of leading or bringing across.** rare.
   1656 BLOUNT *Glossogr., Transduction,* a leading over, a removing from one place to another.
   a1816 BENTHAM *Offic. Apt. Maximized, Introd. View* (1830) 19 In lieu of *adduction,* as the purpose requires, will be subjoined *abduction, transduction,..and* so forth.
2. **The action or process of transducing a signal.**
   1947 Jrnl Acoustical Soc. Amer. XIX. 307/1 It is rather interesting that the direct method of electronic transduction, instead of the indirect method of employing a conventional transducer and then amplifying the output with a vacuum tube, has not been developed.
   1970 J. EARL *Tuners & Amplifiers* iv. 87 Low impedance pickup cartridges using the moving-coil principle of transduction.
   1975 *Nature* 17 Apr. 625/1 The transduction of light energy into neural signals is mediated in all known visual systems by a common type of visual pigment.
3. *Microbiology.* **The transfer of genetic material from one cell to another by a virus or virus-like particle.**
   1952 ZINDER & LEDERBERG in *Jrnl. BacterioL* LXIV. 681 To help the further exposition of our experiments, we shall use the term transduction for genetically unilateral transfer in contrast to the union of equivalent elements in fertilization.
   1960 [see F Ill. 1 l].
   1971 *Nature* 18 June 46611 It has been suggested that transduction of genes by viruses was an important mechanism in evolution for spreading useful mutations between organisms not formally related.
   1977 *Lancet* 9 July 94/2 These were derived by selection of sensitive variants from gentamicin-resistant strains or by transduction of this resistance to sensitive strains.
   Hence
   trans'ductional a., of or pertaining to (genetic) transduction.
   1956 *Genetics* XLI. 845 (*heading*) Linear inheritance in transductional clones.
   1980 *Jrnl. Gen. Microbiol.* CXIX. 51 Transductional analysis revealed that one of the four mutations carried by strain T-693 was responsible for constitutive synthesis of both isoleucine and threonine biosynthetic enzymes.

Figure 1.3 'One hundred and one Netherlandish proverbs', by Pieter Breugel the Elder (1559). It is high summer, though the hayfield seen at the top of the painting is not being harvested. Instead, it is being laid to waste by the pigs. The farmer and all the other villagers are beyond caring. In this hungry month of July, just before the staple crops come to fruition, sustenance is found in the 'bread of dreams', clearly laid out for display on the roof tiles. Containing a rich mixture of alkaloids derived from ergot-infested grains, this was the cause of communal madness and wild manifestations (St Vitus' dance) among the peasantry of the Middle Ages. Several hundred years later, Henry Dale and his colleagues isolated the neurotransmitter acetylcholine from that 'veritable cornucopia' that is ergot. Courtesy of the Gemäldegalerie Staatliche Museen zu Berlin Preußischer Kulturbesitz.

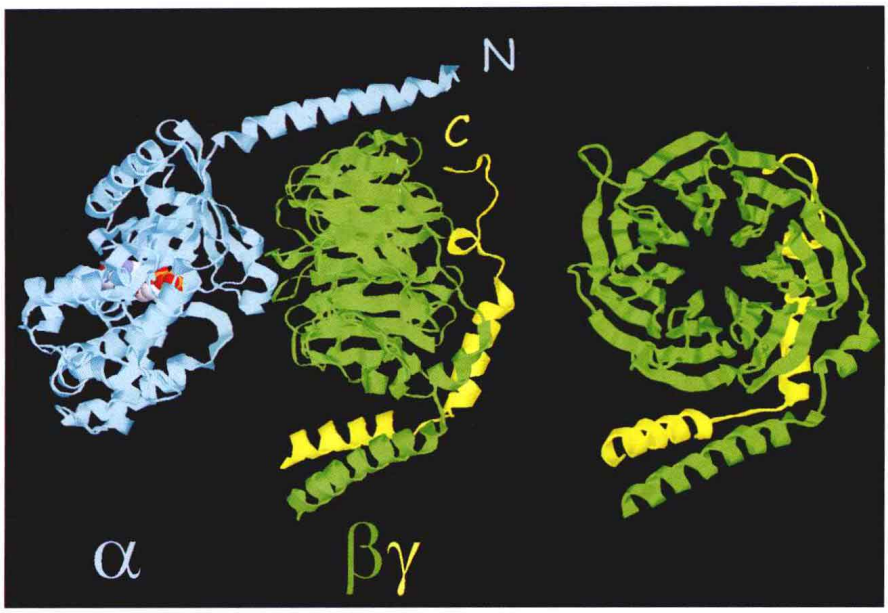

Figure 4.2 Three-dimensional structure of the α- and βγ-subunits of G_i. The α-subunit (left, cyan) has a molecule of GDP bound. The N-terminal helix is at top right. The βγ-subunits (β green, γ yellow) are in close apposition. The surface of the heterotrimeric structure that is in contact with the membrane is at the top of the figure. The hydrophobic attachments that are responsible are not shown. They involve the N-terminal of the α-subunit and the C-terminal of the γ-subunit. The separate βγ-subunit on the right has been rotated about a vertical axis to show the β propeller structure. (Data source: 1gp2.pdb[58]).

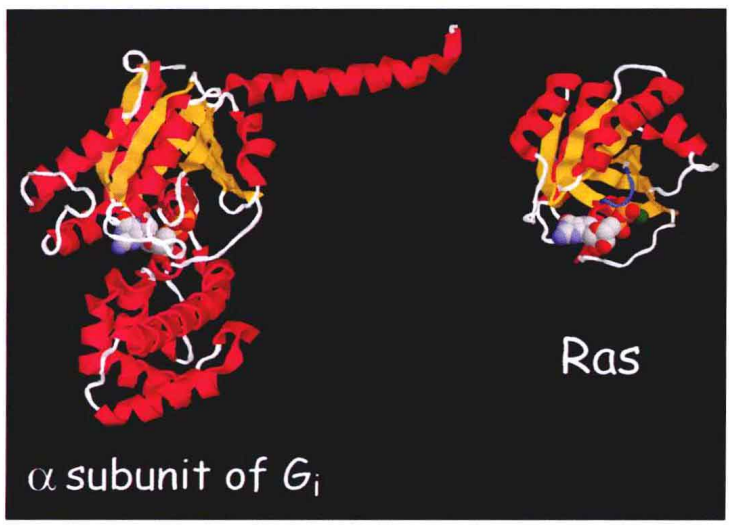

Figure 4.8 The α-subunits of G proteins and the monomeric GTPases exhibit structural similarities. α_i (left) has an rd domain (ras domain, upper half) that resembles the small GTPase Ras (right). The lower half of the α_i structure is the hd domain (helical domain). Each molecule has a bound GDP. (Mg^{2+} is only indicated in the RasGDP structure, green sphere.) Data source: α_i: 1gp2.pdb[58], RasGDP: 4q21.pdb.[125-128]

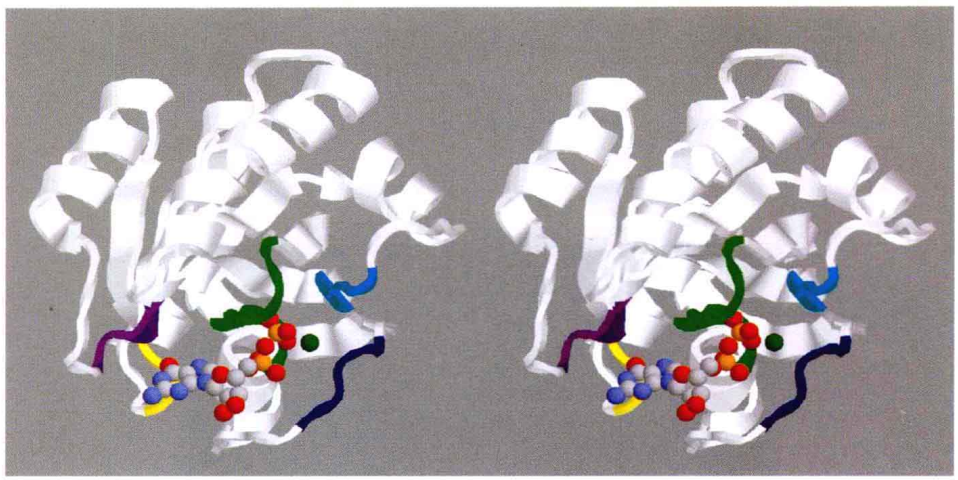

Figure 4.13 Three-dimensional structure of RasGDP. In this stereo image, the conserved motifs G1–G5 that make contact with the nucleotide are depicted in the following colours to match Table 4.4: G1 green, G2 blue, G3 cyan, G4 purple, G5 yellow. GDP is shown in CPK colours. The Mg^{2+} ion is coloured dark green. Instructions for viewing stereo images can be found on page 396. (Data source 4q21.pdb[125–128].)

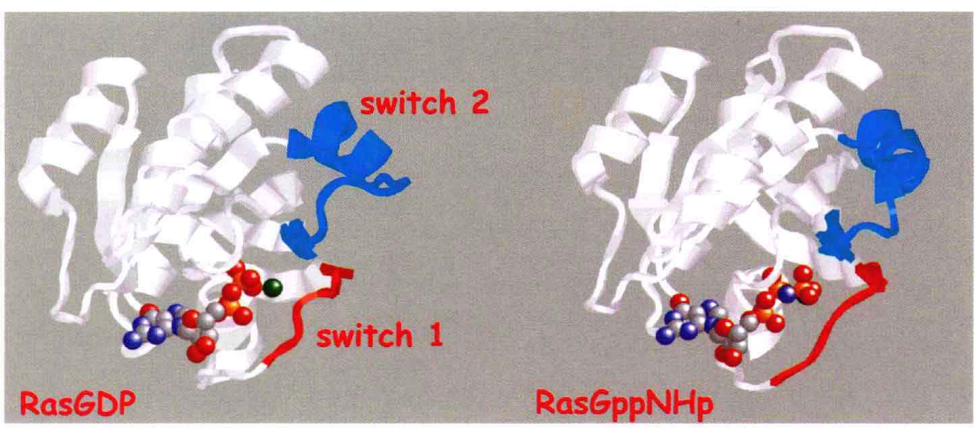

Figure 4.14 Structural differences in the switch regions of GDP- and GTP-bound Ras. Structures of the N-terminal residues of H-Ras complexed with GDP and with GppNHp (an analogue of GTP). The switch regions are indicated. The nucleotides are depicted as ball-and-stick structures. The green atom is Mg^{2+}. (Data sources 4q21.pdb[125–128] and 5p21.pdb[129] respectively.)

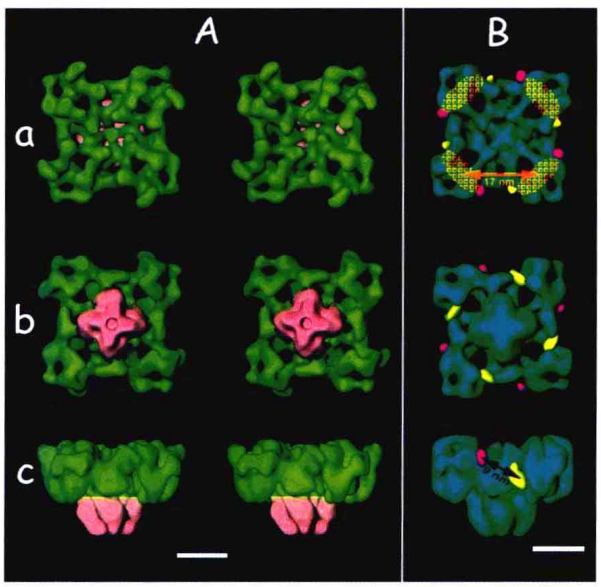

Figure 7.7 Three-dimensional structure of the ryanodine receptor obtained by cryoelectron microscopy: (A) Three-dimensional reconstruction of the ryanodine receptor from skeletal muscle. Stereoscopic views of (a), the surface that faces the T-tubule; (b) that facing the lumen of the SR; (c) a side view. The transmembrane part is pink and the cytoplasmic region is green. Instructions for viewing stereo images can be found on page 396. (B) A depiction of the receptor (cyan) indicating the locations of calmodulin (yellow) and FKBP12 (magenta). The orange shading indicates regions likely to interact with dihydropyridine receptors. The scale bar is 10 nm. Adapted from Malenka *et al.*[21]

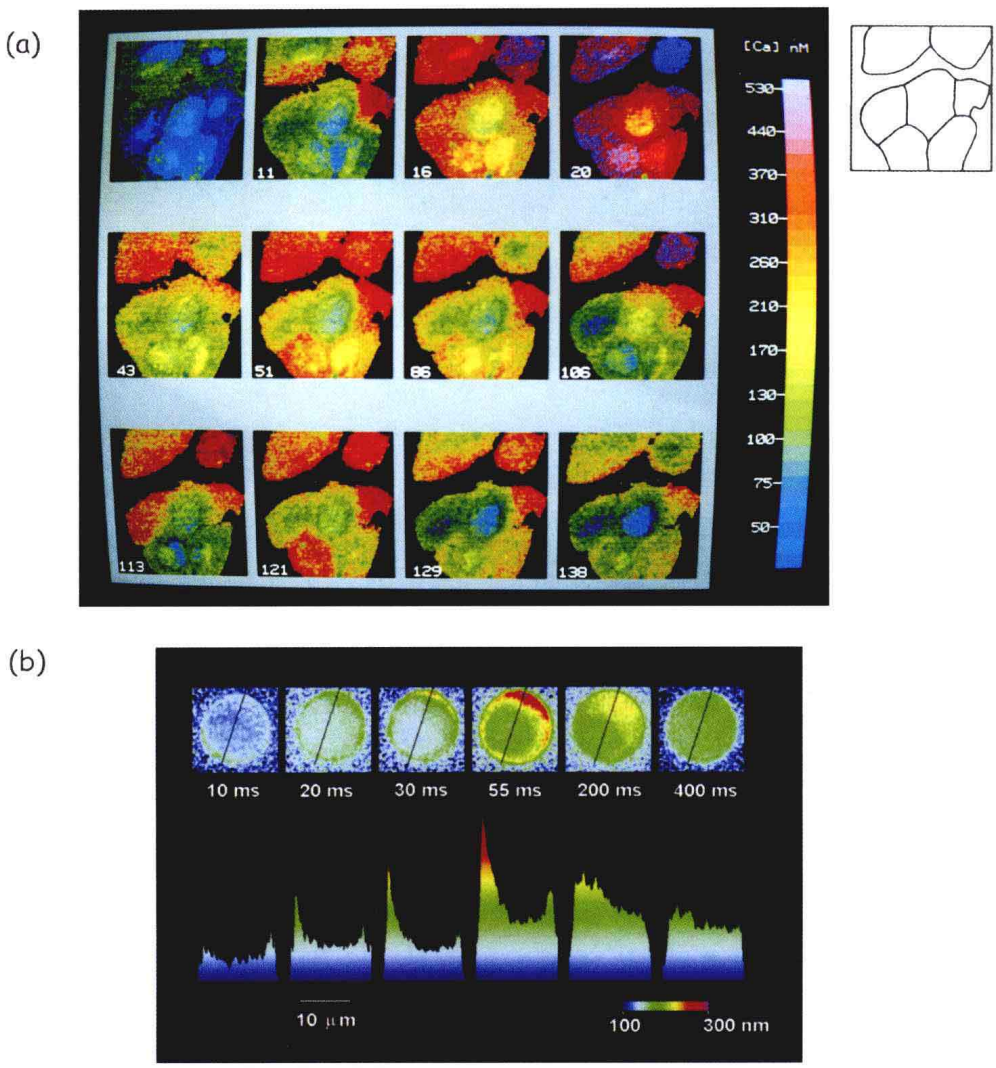

Figure 7.13 Pseudocolour images of Ca^{2+} levels in cells activated by extracellular ligands and by plasma membrane depolarization: (a) Ca^{2+} changes visualized in a confluent layer of human endothelial cells following stimulation with histamine (1 μmol/l). The calibration, on the right, indicates intracellular Ca^{2+} concentration. The map on the extreme right shows the individual cell boundaries. The time, in seconds, after histamine addition is indicated in each frame. There is a complex pattern of spatial and temporal changes in Ca^{2+} level within each cell. (Dye: Fura2.) Courtesy of Ron Jacob.[38] (b) Time course of Ca^{2+} changes in a single chromaffin cell, following membrane depolarization. The cell is voltage clamped in the whole cell configuration (patch pipette not shown). Six fluorescence images of a cell were collected at fixed times after a series of depolarizations, using pulsed laser imaging. The colour-coded images in the top panel show the Ca^{2+} concentration rising mostly in peripheral regions of the cell, especially on one edge (55 ms) and then falling. The bisecting line in each image indicates the region sampled to give the cross-sections shown beneath. (Dye: Rhod2.) Courtesy of Julio Hernandez and Jonathan Monck.[39]