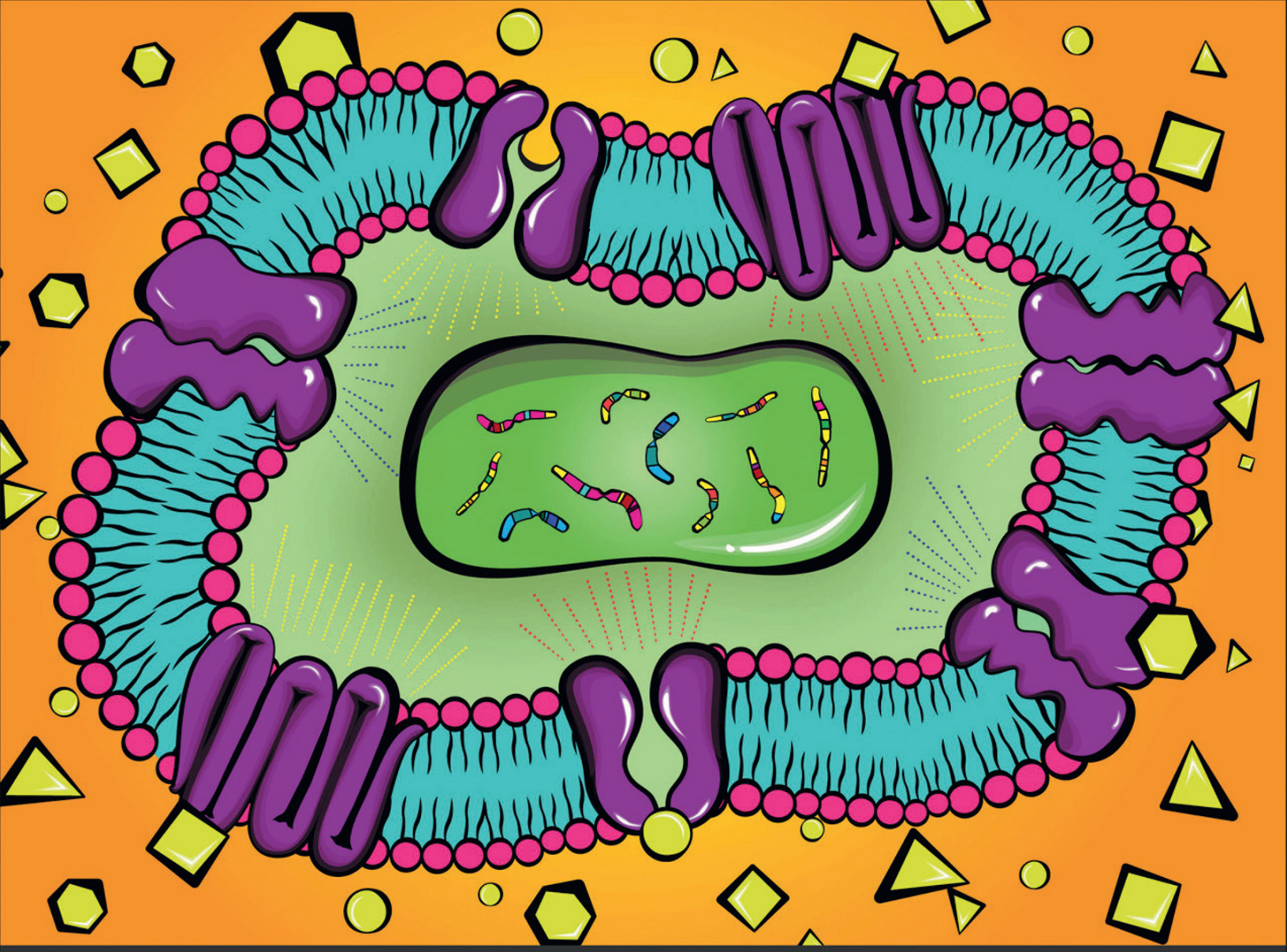

FUNCTIONING OF TRANSMEMBRANE RECEPTORS IN CELL SIGNALING

EDITED BY
RALPH A. BRADSHAW AND EDWARD A. DENNIS

Functioning of Transmembrane Receptors in Cell Signaling

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Functioning of Transmembrane Receptors in Cell Signaling

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Preface

Since cell signaling is a major area of biomedical/biological research and continues to advance at a very rapid pace, scientists at all levels, including researchers, teachers, and advanced students, need to stay current with the latest findings, yet maintain a solid foundation and knowledge of the important developments that underpin the field. Carefully selected articles from the 2nd edition of the *Handbook of Cell Signaling* offer the reader numerous, up-to-date views of intracellular signal processing, including membrane receptors, signal transduction mechanisms, the modulation of gene expression/translation, and cellular/organotypic signal responses in both normal and disease states. In addition to material focusing on recent advances, hallmark papers from historical to cutting-edge publications are cited. These references, included in each article, allow the reader a quick navigation route to the major papers in virtually all areas of cell signaling to further enhance his/her expertise.

The Cell Signaling Collection consists of four independent volumes that focus on *Functioning of Transmembrane Receptors in Cell Signaling, Transduction Mechanisms in Cellular Signaling, Regulation of Organelle and Cell Compartment Signaling,* and *Intercellular Signaling in Development and Disease*. They can be used alone, in various combinations or as a set. In each case, an overview article, adapted from our introductory chapter for the Handbook, has been included. These articles, as they appear in each volume, are deliberately overlapping and provide both historical perspectives and brief summaries of the material in the volume in which they are found. These summary sections are not exhaustively referenced since the material to which they refer is.

The individual volumes should appeal to a wide array of researchers interested in the structural biology, biochemistry, molecular biology, pharmacology, and pathophysiology of cellular effectors. This is the ideal go-to books for individuals at every level looking for a quick reference on key aspects of cell signaling or a means for initiating a more in-depth search. Written by authoritative experts in the field, these papers were chosen by the editors as the most important articles for making the Cell Signaling Collection an easy-to-use reference and teaching tool. It should be noted that these volumes focus mainly on higher organisms, a compromise engendered by space limitations.

We wish to thank our Editorial Advisory Committee consisting of the editors of the Handbook of Cell Signaling, 2nd edition, including Marilyn Farquhar, Tony Hunter, Michael Karin, Murray Korc, Suresh Subramani, Brad Thompson, and Jim Wells, for their advice and consultation on the composition of these volumes. Most importantly, we gratefully acknowledge all of the individual authors of the articles taken from the Handbook of Cell Signaling, who are the 'experts' upon which the credibility of this more focused book rests.

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Section A

Overview

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Chapter 1

Transmembrane Receptors and Their Signaling Properties*

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Cell signaling, which is also often referred to as signal transduction or, in more specialized cases, transmembrane signaling, is the process by which cells communicate with their environment and respond temporally to external cues that they sense there. All cells have the capacity to achieve this to some degree, albeit with a wide variation in purpose, mechanism, and response. At the same time, there is a remarkable degree of similarity over quite a range of species, particularly in the eukaryotic kingdom, and comparative physiology has been a useful tool in the development of this field. The central importance of this general phenomenon (sensing of external stimuli by cells) has been appreciated for a long time, but it has truly become a dominant part of cell and molecular biology research in the past three decades, in part because a description of the dynamic responses of cells to external stimuli is, in essence, a description of the life process itself. This approach lies at the core of the developing fields of proteomics and metabolomics, and its importance to human and animal health is already plainly evident.

ORIGINS OF CELL SIGNALING RESEARCH

Although cells from polycellular organisms derive substantial information from interactions with other cells and extracellular structural components, it was humoral components that first were appreciated to be intercellular messengers. This idea was certainly inherent in the 'internal secretions' initially described by Claude Bernard in 1855 and thereafter, as it became understood that ductless glands, such as the spleen, thyroid, and adrenals, secreted material into the bloodstream. However, Bernard did not directly identify hormones as such. This was left to Bayliss and Starling and their description of secretin in 1902 [1].

Recognizing that it was likely representative of a larger group of chemical messengers, the term *hormone* was introduced by Starling in a Croonian Lecture presented in 1905. The word, derived from the Greek word meaning 'to excite or arouse,' was apparently proposed by a colleague, W. B. Hardy, and was adopted, even though it did not particularly connote the messenger role but rather emphasized the positive effects exerted on target organs via cell signaling (see Wright [2] for a general description of these events). The realization that these substances could also produce inhibitory effects, gave rise to a second designation, 'chalones,' introduced by Schaefer in 1913 [3], for the inhibitory elements of these glandular secretions. The word autocoid was similarly coined for the group as a whole (hormones and chalones). Although the designation chalone has occasionally been applied to some growth factors with respect to certain of their activities (e.g., transforming growth factor β), autocoid has essentially disappeared. Thus, if the description of secretin and the introduction of the term hormone are taken to mark the beginnings of molecular endocrinology and the eventual development of cell signaling, then we have passed the hundredth anniversary of this field.

The origins of endocrinology, as the study of the glands that elaborate hormones and the effect of these entities on target cells, naturally gave rise to a definition of hormones as substances produced in one tissue type that traveled

** Portions of this article were adapted from Bradshaw RA, Dennis EA. Cell signaling: yesterday, today, and tomorrow. In Bradshaw RA, Dennis EA, editors. Handbook of cell signaling. 2nd ed. San Diego, CA: Academic Press; 2008; pp 1–4.*

systemically to another tissue type to exert a characteristic response. Of course, initially these responses were couched in organ and whole animal responses, although they increasingly were defined in terms of metabolic and other chemical changes at the cellular level. The early days of endocrinology were marked by many important discoveries, such as the discovery of insulin [4], to name one, that solidified the definition, and a well-established list of hormones, composed primarily of three chemical classes (polypeptides, steroids, and amino acid derivatives), was eventually developed. Of course, it was appreciated even early on that the responses in the different targets were not the same, particularly with respect to time. For example, adrenalin was known to act very rapidly, while growth hormone required a much longer time frame to exert its full range of effects. However, in the absence of any molecular details of mechanism, the emphasis remained on the distinct nature of the cells of origin versus those responding and on the systemic nature of transport, and this remained the case well into the 1970s. An important shift in endocrinological thinking had its seeds well before that, however, even though it took about 25 years for these 'new' ideas that greatly expanded endocrinology to be enunciated clearly.

Although the discovery of polypeptide growth factors as a new group of biological regulators is generally associated with nerve growth factor (NGF), it can certainly be argued that other members of this broad category were known before NGF. However, NGF was the source of the designation *growth factor* and has been, in many important respects, a Rosetta stone for establishing principles that are now known to underpin much of signal transduction. Thus, considering it to be the progenitor of the field and to be the entity that keyed the expansion of endocrinology, and with it the field of cell signaling, is quite appropriate. The discovery of NGF is well documented [5] as is how this led directly to the identification of epidermal growth factor (EGF) [6], another regulator that has been equally important in providing novel insights into cellular endocrinology, signal transduction, and, more recently, molecular oncology. However, it was not till the sequences of NGF and EGF were determined [7, 8] that the molecular phase of growth factor research began in earnest. Of particular importance was the postulate that NGF and insulin were evolutionarily related entities [9], which suggested a similar molecular action (which, indeed, turned out to be remarkably clairvoyant), and was the first indication that the identified growth factors, which at that time were quite limited in number, were like hormones. This hypothesis led quickly to the identification of receptors for NGF on target neurons, using the tracer binding technology of the time (see Raffioni *et al.* [10] for a summary of these contributions), which further confirmed their hormonal status. Over the next several years, similar observations were recorded for a number of other growth factors, which in turn, led to the redefinition of endocrine mechanisms to include paracrine, autocrine and juxtacrine interactions [11]. These studies were followed by first isolation and molecular characterization using various biophysical methods and then cloning of their cDNAs, initially for the insulin and EGFR receptors [12–14] and then many others. Ultimately, the powerful techniques of molecular biology were applied to all aspects of cell signaling and are largely responsible for the detailed depictions we have today. They have allowed the broad understanding of the myriad of mechanisms and responses employed by cells to assess changes in their environment and to coordinate their functions to be compatible with the other parts of the organism of which they are a part.

TRANSMEMBRANE RECEPTORS

Membranes composed of a lipid bilayer and containing a plethora of proteins that either span or are embedded in it (sometimes by means of lipid anchors), are the structures that allow living cells to organize their intracellular components and organelles and to regulate the passage of molecules and information across it. These membrane-associated proteins constitute upward of one third of the proteins expressed by living organisms and they perform a wide variety of functions. In eukaryotes, they are synthesized on the rough endoplasmic reticulum and are extruded into the lumen of that organelle, where they are variously 'processed.' Some are retained there while the majority are passed through the Golgi apparatus and eventually into vesicles that have various fates, including fusion with the plasma membrane. Those proteins that are found in these bodies but are not associated with the membrane (derived from the ER and Golgi), become part of the secretome (secreted proteins), characteristic of that cell, while those that are embedded in the membrane by one or more transmembrane segments during the extrusion process remain there and become part of the complement of cell surface proteins (as the membrane of the vesicular body becomes part of the plasma membrane as part of the fusion event). The process is similar in prokaryotes, although there is no endoplasmic reticulum or Golgi in these cells. Some organisms also have cell walls in addition to the electrically tight plasma membrane; these also can contain proteins, but they do not serve the same kinds of functions as those found in the lipid-based membranes.

It is in this complex group of proteins inserted into the cellular membrane that are found the receptors and other recognitive molecules that interact with extracellular signals. As with the larger collection of cell surface proteins, this is a diverse group. In it are found various types of receptors for both soluble and membrane-bound ligands, ion channels, and adhesion proteins that participate in junctions of various types with extracellular matrix proteins and other cells. Functionally, these proteins are all involved

in cell signaling but in many different ways. The receptors for hormones and growth factors can be grouped into six main types based on their intracellular signaling systems. These are the receptors that contain a tyrosine kinase as an inherent part of the receptor (termed 'receptor tyrosine kinases' or RTKs), cytokine receptors that utilize soluble tyrosine kinases (JAKs) that associate noncovalently with the receptors, serine/threonine kinase-containing receptors (the transforming growth factor β (TGFβ) receptors), the heptameric or G protein-coupled receptors (GPCRs), the tumor necrosis factor (TNF) receptors, and the guanylyl (or guanylate) cyclase receptors. These receptors interact with a broad spectrum of ligands ranging from small molecules (commonly, the heptameric receptors) to proteins and occasionally other macromolecules such as complex polysaccharides, for example, heparin. In addition, important signaling occurs with adhesion receptors (usually involving integrins), receptors that participate in the immune response and by the activation/inactivation of ion channels (some of which are regulated by heptameric receptors). As depicted schematically in Figure 1.1, all nine groups of transmembrane signaling molecules are discussed in this collection of short reviews.

The different classes of receptors have significantly different types of organizational structures. In general, they are divided into three functional domains: an ecto (or extracellular) domain, a transmembrane domain, and an endo (or intracellular) domain.

The ectodomain is the main basis for recognizing the ligands of that receptor, while the endodomain is chiefly responsible for generating the intracellular signal that will, in most cases, be regulated and amplified by a cascade of succeeding reactions/interactions. The transmembrane segments connect the two and are made up of 20–25 largely hydrophobic amino acid segments that occur in an α-helix. Most of the receptors have one such domain per protomer, but the heptameric GPCRs, as the name implies, contain seven such domains per monomer. Multiple membrane-spanning domain proteins are also commonly found among other functional categories such as ion channels.

The single pass transmembrane protomers can be inserted either as type I (N-terminus on the outside) or type II (N-terminus on the inside) proteins, although type I is clearly the most common orientation. In either case, the ectodomains possess the properties of extracellular proteins (reflecting their origins in the lumen of the ER), which

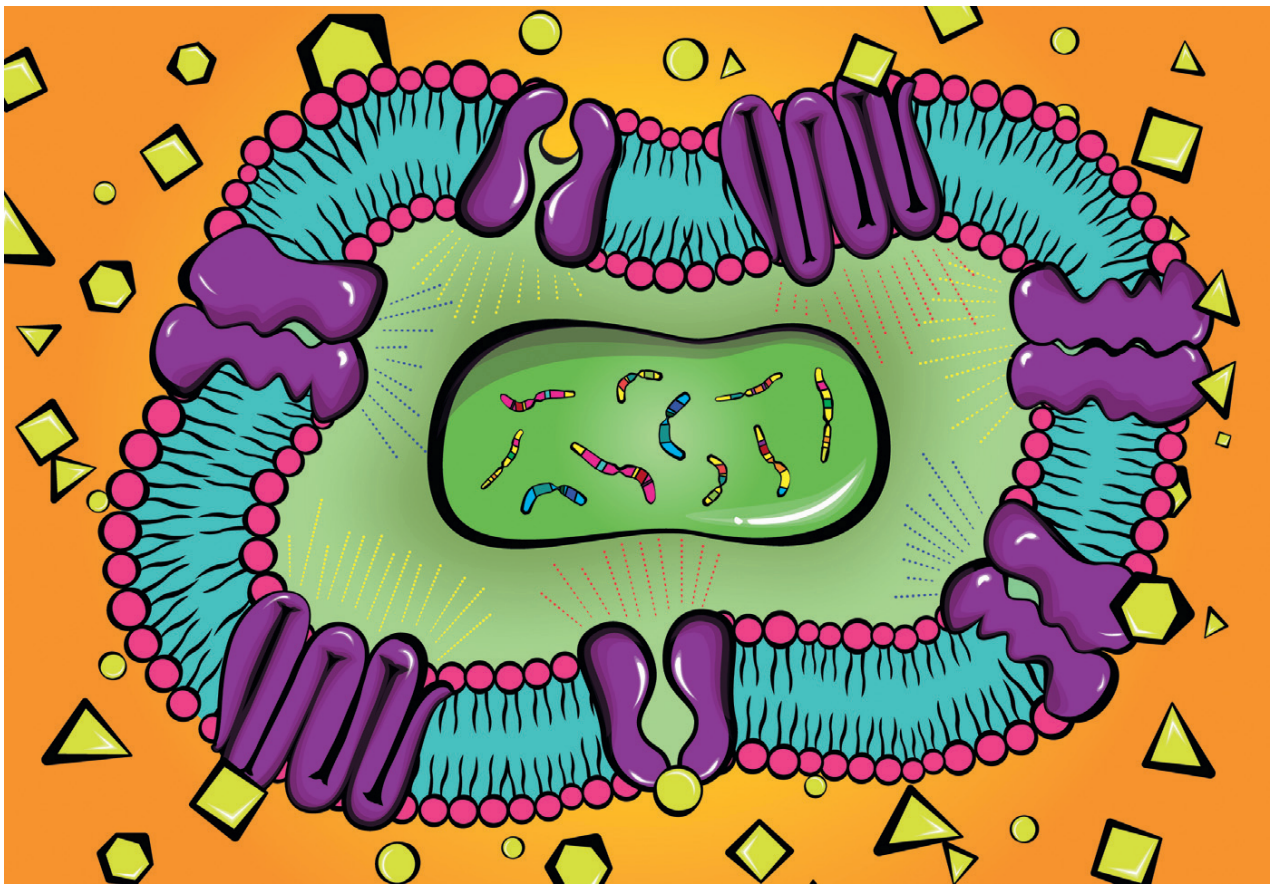

FIGURE 1.1 Schematic representation of nature's wide variety of membrane proteins that interface the cell with its environment, including tyrosine kinase receptors, cytokine receptors, heptameric G-protein coupled receptors, TGFβ receptors, TNF receptors, and guanylyl cyclase receptors as well as adhesion molecules, ion channels, and immunoglobulin receptors.

include complex glycosylation of both the N- and O-linked types and disulfide bonds. In contrast, the endodomains chemically reflect their intracellular origins (this part of the receptor remains in the cytoplasm following extrusion into the ER during translation) and have cysteines (reduced state) and undergo modifications such as phosphorylation and O-GlcNAcylation of serine and threonine residues and, in the former case, tyrosine residues as well, among many others.

Although the cell surface proteins are basically synthesized as single polypeptide chains, various biophysical and modification/mutation experiments have determined that most if not all of the receptor families exist in oligomeric structures in their active states, and a growing body of evidence suggests that these are preformed during biogenesis as opposed to the once strongly prevailing view that the association of the constituent protomers is induced by ligand binding. In the case of the RTKs, these appear to be basically homodimers, and activation (by ligand association) causes a transphosphorylation of several tyrosine residues in the endodomains of each protomer, including those important to stabilize the activation loop of the kinase domain in the open (or active) form. The activation of the kinase domain is apparently achieved by rotational or other conformational movement brought about by ligand binding. Most of the phosphotyrosine residues generated are required for the further perpetration of the intracellular signal. Homodimer (or higher oligomeric structure) formation is also a characteristic of four of the other five classes of receptor families (the exception being the TGFβ family). However, heteromeric complexes are also common in the two subgroups of the cytokine receptors and in the GPCR families. In the latter type, these heteromeric complexes can alter the ligand binding properties such that the heteromeric receptor has a different specificity than either of the two protomers has (when they are in homodimeric forms).

The various families differ in size: the largest (by some margin) is the GPCR family that is composed of over 400 members and potentially contains more than a 1000 members. In contrast, the TGFβ and guanylyl cyclase families have only relatively few. (There are seven guanylyl cyclase transmembrane receptors and five and seven TGFβ type II and type I, respectively). GPCRs are major drug targets, and it has been estimated that upward of 50% of clinically approved pharmaceuticals are so directed with many more targets under active investigation. However, the RTKs, of which there are 58, and the cytokine receptors, of which there are a couple dozen of the two types, collectively, are increasingly the targets for drug development. Both generate tyrosine phosphorylation signals, albeit in different ways. Similar to the cytokine receptors, there are around two dozen members of the TNF receptor superfamily.

The families that comprise the ion channels are much more extensive than most of the transmembrane receptors (with the exception of the GPCRs) and are comparable in number to the full complement of protein kinases (in the human genome) that number in excess of 500. These structures are fundamentally pores that allow the transfer of various ions in or out of cells (thus allowing them to cross the hydrophobic core of the lipid bilayer of the plasma membrane in the process). The resulting changes in ion concentrations control many processes and in the case of calcium ions, is directly connected to other signaling pathways. The kinetics of ion transfer are very rapid and many are, of course, tightly tied to neuronal function, one reason why they have been already extensively investigated even before other forms of signal transduction were appreciated. There are also connections between ion channels and other signaling systems, particularly the GPCRs.

The interaction of cells with other cells, extracellular matrix (ECM), and the substratum are among the most important aspects of cell signaling, particularly as it relates to environmental sensing. Mechanical stress is a major example. The adhesion plaques that form are directly connected to signaling pathways through integrins and other components and involve nonreceptor kinases such as the focal adhesion kinase (or FAK). Similarly, the cadherins, another family of cell surface receptors, participate in the formation of adheren junctions that help in maintaining cell polarity and tissue architecture. The pathways involved link these cell surface molecules to the cytoskeleton and are also active in transcriptional regulation, a hallmark of other cell signaling activities.

Finally, the immune system maintains extensive signaling pathways with receptors that are dedicated to various functions of this essential component of higher vertebrate physiology. The receptors tend to be complex and are involved in both antigen recognition and subsequent antibody generation and in various cell–cell recognition events necessary for immune surveillance and pathogen removal. Key in these interactions, and tying the receptors/ligands involved to other signaling pathways, is the use of the immunoglobin (Ig) superfold that is found throughout recognitive interactions including many of the RTKs, as an example.

FOCUS AND SCOPE OF THIS VOLUME

The chapters of this volume have been selected from a larger collection [15] and have been organized to emphasize the structure and role of cell surface receptors in signaling activities. They have been contributed by recognized experts and they are authoritative to the extent that size limitations allow. It is our intention that this survey will be useful in teaching, particularly in introductory courses, and to more seasoned investigators new to this area.

It is not possible to develop any of the areas covered in this volume in great detail, and expansion of any topic is left to the reader. The references in each chapter provide an excellent starting point, and greater coverage can also be