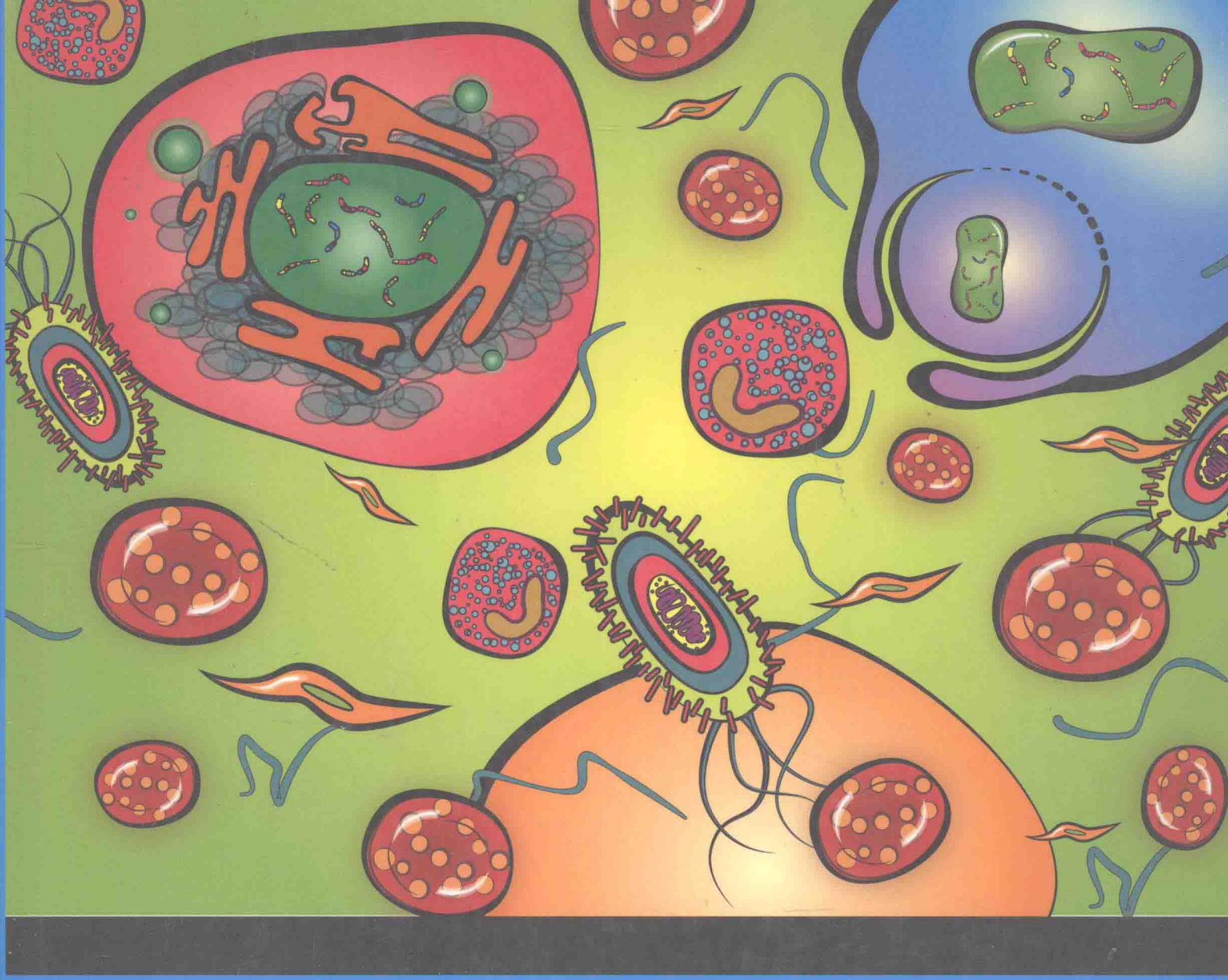

INTERCELLULAR SIGNALING IN DEVELOPMENT AND DISEASE

EDITED BY
EDWARD A. DENNIS AND RALPH A. BRADSHAW

Intercellular Signaling in Development and Disease

Editors-in-Chief

Edward A. Dennis
Department of Chemistry and Biochemistry,
Department of Pharmacology, School of Medicine,
University of California, San Diego,
La Jolla, California

Ralph A. Bradshaw
Department of Pharmaceutical Chemistry,
University of California, San Francisco,
San Francisco, California

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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.

Ralph A. Bradshaw, San Francisco, California
Edward A. Dennis, La Jolla, California
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Contributors

Rexford S. Ahima (45), University of Pennsylvania School of Medicine, Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Philadelphia, Pennsylvania

Daniel A. Albert (50), Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Simon Alford (31), Department of Biological Sciences, University of Illinois at Chicago, Chicago, Illinois

William J. Arendshorst (15), Department of Cell and Molecular Physiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Elsa Bello-Reuss (15), Department of Internal Medicine, Division of Nephrology and Department of Cell Physiology and Molecular Biophysics, Texas Tech University Health Science Center, Lubbock, Texas

Ramji K. Bhandari (14), Center for Reproductive Biology, School of Molecular Biosciences, Washington State University, Pullman, Washington

Trillium Blackmer (31), Department of Biological Sciences, University of Illinois at Chicago, Chicago, Illinois

Lynda F. Bonewald (13), Bone Biology Program, University of Missouri-Kansas City, Kansas City, Missouri

Kanika A. Bowen (12), Department of Surgery, The University of Texas Medical Branch, Galveston, Texas

Ralph A. Bradshaw (1, 2), Department of Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, CA

Matthew H. Brush (48), Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, North Carolina

Paul M. Campbell (38), Drug Discovery Program, H. Lee Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, Florida

Catherine Carrière (42), Departments of Medicine, and Pharmacology and Toxicology, Dartmouth Medical School, Norris Cotton Cancer Center and Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire

Moses V. Chao (33), Molecular Neurobiology Program, Skirball Institute of Biomolecular Medicine, New York University School of Medicine, New York

Jau-Nian Chen (25), Department of Molecular, Cell and Developmental Biology, University of California, Los Angeles, California

Lena Claesson-Welsh (28), Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden

Robert Clarke (40), Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Nicholas O. Deakin (4), Department of Cell and Developmental Biology, State University of New York, Upstate Medical University, Syracuse, New York

Tushar B. Deb (40), Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Lanika DeGraffenreid (38), Departments of Surgery and Pharmacology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Katrin Deinhardt (33), Molecular Neurobiology Program, Skirball Institute of Biomolecular Medicine, New York University School of Medicine, New York

Larry Denner (20), McCoy Stem Cells and Diabetes Mass Spectrometry Research Laboratory, Stark Diabetes Center, Sealy Center for Molecular Medicine, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas

Edward A. Dennis (1), Department of Chemistry and Biochemistry and Department of Pharmacology, School of Medicine, University of California, San Diego, La Jolla, CA, USA

Channing J. Der (38, 39), Departments of Surgery and Pharmacology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, Department of Pharmacology and Curriculum in Genetics and Molecular Biology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Peter N. Devreotes (7), Department of Cell Biology, Johns Hopkins University School of Medicine, Baltimore, Maryland

K.M. Dibb (10), Unit of Cardiac Physiology, University of Manchester, Manchester, England, UK

Robert B. Dickson (40), Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Anna Dimberg (28), Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden

Daniel J. Donoghue (30), Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California, Moores University of California San Diego Cancer Center, La Jolla, California

Thomas Dörner (49), Department of Medicine, Rheumatology, and Clinical Immunology, Charite University Medicine Berlin, Germany

Kristine A. Drafahl (30), Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California

Edward Eivers (23), Howard Hughes Medical Institute and Department of Biological Chemistry, University of California, Los Angeles, California

D.A. Eisner (10), Unit of Cardiac Physiology, University of Manchester, Manchester, England, UK

B. Mark Evers (12), Department of Surgery, The University of Texas Medical Branch, Galveston, Texas

Jonathan Franca-Koh (7), Department of Cell Biology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Robert E. Friesel (8), Center for Molecular Medicine, Maine Medical Center Research Institute, Scarborough, Maine

Luis C. Fuentealba (23), Howard Hughes Medical Institute and Department of Biological Chemistry, University of California, Los Angeles, California

Tatyana Gerachshenko (31), Department of Biological Sciences, University of Illinois at Chicago, Chicago, Illinois

Nicolas Girard (44), Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, New York

Vikas Gupta (17), Department of Medicine, Howard Hughes Medical Institute, University of California, San Francisco, California

Edaeni Hamid (31), Department of Biological Sciences, University of Illinois at Chicago, Chicago, Illinois

Sam Hanash (51), Fred Hutchinson Cancer Research Center, Seattle, Washington

Ariella B. Hanker (39), Curriculum in Genetics and Molecular Biology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Michelle L. Hermiston (17), Department of Pediatrics, Howard Hufghes Medical Institute, University of California, San Francisco, California

Margaret Howe (20), McCoy Stem Cells and Diabetes Mass Spectrometry Research Laboratory, Stark Diabetes Center, Department of Internal Medicine, University of Texas, Galveston, Texas

Marcin Iwanicki (3), Department of Microbiology, University of Virginia Health System, Charlottesville, Virginia

Sophie Jarriault (26), IGBMC (Institut de Génétique et de Biologie Moléculaire et Cellulaire), Department of Cell and Developmental Biology, Illkirch, France; and Université de Strasbourg, Strasbourg, France

Michael D. Johnson (40), Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Louis B. Justement (19), Department of Microbiology, University of Alabama at Birmingham, Birmingham, Alabama

Randal J. Kaufman (47), Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, Michigan, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan, Department of Howard Hughes Medical Institute, University of Michigan Medical School, Ann Arbor, Michigan

Sakari Kauppinen (52), Santaris Pharma, Hørsholm, Denmark, and Wilhelm Johannsen Centre for Functional Genome Research, Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark

Rolf Kemler (21), Department of Molecular Embryology, Max-Planck Institute of Immunobiology, Freiburg, Germany

Rolf König (18), Department of Microbiology and Immunology, The University of Texas Medical Branch, Galveston, Texas

Murray Korc (41, 42, 43), Departments of Medicine, Pharmacology and Toxicology, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, and Dartmouth Medical School, Hanover, New Hampshire

Chulan Kwon (9), Gladstone Institute of Cardiovascular Disease and Departments of Pediatrics and Biochemistry & Biophysics, University of California at San Francisco, San Francisco, California

Adam D. Langenbacher (25), Department of Molecular, Cell and Developmental Biology, University of California, Los Angeles, California

Hojoon X. Lee (23), Howard Hughes Medical Institute and Department of Biological Chemistry, University of California, Los Angeles, California

Lucy Liaw (8), Center for Molecular Medicine, Maine Medical Center Research Institute, Scarborough, Maine

Volkhard Lindner (8), Center for Molecular Medicine, Maine Medical Center Research Institute, Scarborough, Maine

Peter E. Lipsky (49), NIAMS, National Institutes of Health, Bethesda, MD

Karen M. Lyons (29), Department of Molecular, Cell and Developmental Biology, Department of Orthopaedic Surgery, University of California, Los Angeles, California

James P. Madigan (38), Departments of Surgery and Pharmacology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Jyoti D. Malhotra (47), Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, Michigan

Karen H. Martin (3), Department of Microbiology, University of Virginia Health System, Charlottesville, Virginia, Department of Neurobiology and Anatomy, West Virginia University, Morgantown West Virginia

Christopher W. McAndrew (30), Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California

Frank McCormick (37), Cancer Research Institute, University of California Comprehensive Cancer Center, San Francisco, California

Laurens A. van Meeteren (28), Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden

Borna Mehrad (46), Division of Pulmonary and Critical Care Medicine, University of Virginia, Charlottesville, Virginia

Daniel Messerschmidt (21), Department of Molecular Embryology, Max-Planck Institute of Immunobiology, Freiburg, Germany

Guo-li Ming (34), The Salk Institute, La Jolla, California Division of Neurobiology, Department of Molecular and Cell Biology, University of California, Berkeley, California

James T. Nichols (27), Department of Biological Chemistry David Geffen School of Medicine, University of California, Los Angeles, California

Eric E. Nilsson (14), Center for Reproductive Biology, School of Molecular Biosciences, Washington State University, Pullman, Washington

Alixanna Norris (41), Departments of Medicine, Pharmacology and Toxicology, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, and Dartmouth Medical School, Hanover, New Hampshire

Stefan Offermanns (6), Department of Pharmacology, Max-Planck-Institute, Bad Nauheim, Germany

Matthew T. Pankratz (36), Gene Expression Laboratory, The Salk Institute for Biological Studies, La Jolla, California

William Pao (44), Vanderbilt-Ingram Cancer Center, Nashville, Tennessee

J. Thomas Parsons (3), Department of Microbiology, University of Virginia Health System, Charlottesville, Virginia

Samuel L. Pfaff (36), Gene Expression Laboratory, The Salk Institute for Biological Studies, La Jolla, California

Tatjana Piotrowski (22), University of Utah, Department of Neurobiology and Anatomy, Salt Lake City, Utah

Fiona J. Pixley (16), Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, New York, New York, *Current address: School of Medicine and Pharmacology, University of Western Australia, Nedlands, WA, Australia

Mu-ming Poo (34), The Salk Institute, La Jolla, California Division of Neurobiology, Department of Molecular and Cell Biology, University of California, Berkeley, California

Igor Prudovsky (8), Center for Molecular Medicine, Maine Medical Center Research Institute, Scarborough, Maine

Barbara Ranscht (5), Burnham Institute for Medical Research, La Jolla, California

Danica Ramljak (40), Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Kelsey N. Retting (29), Department of Biological Chemistry, University of California, Los Angeles, California

E. M. De Robertis (23), Howard Hughes Medical Institute and Department of Biological Chemistry, University of California, Los Angeles, California

Patrick J. Roberts (38), Departments of Surgery and Pharmacology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Charlotte Rolny (28), Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden

Stefan Rudloff (21), Department of Molecular Embryology, Max-Planck Institute of Immunobiology, Freiburg, Germany

Frederic de Sauvage (24), Department of Molecular Biology, Genentech, Inc., South San Francisco, California

Eric F. Schmidt (35), Department of Neurology and Section of Neurobiology, Yale University School of Medicine, New Haven, Connecticut

Lorenzo F. Sempere (52), Department of Medicine, Norris Cotton Cancer Center, Lebanon, New Hampshire

Shirish Shenolikar (48), Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, North Carolina, Signature Research Program in Neuroscience and Behavioral Disorders, Duke-NUS Graduate Medical School Singapore

Michael K. Skinner (14), Center for Reproductive Biology, School of Molecular Biosciences, Washington State University, Pullman, Washington

Jill K. Slack-Davis (3), Department of Microbiology, University of Virginia Health System, Charlottesville, Virginia

Deepak Srivastava (9), Gladstone Institute of Cardiovascular Disease and Departments of Pediatrics and Biochemistry & Biophysics, University of California at San Francisco, San Francisco, California

E. Richard Stanley (16), Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, New York, New York, *Current address: School of Medicine and Pharmacology, University of Western Australia, Nedlands, WA, Australia

Andrew W. Stoker (32), Neural Development Unit, Institute of Child Health, University College London, London, England, UK

Robert M. Strieter (46), Division of Pulmonary and Critical Care Medicine, University of Virginia, Charlottesville, Virginia

Stephen M. Strittmatter (35), Department of Neurology and Section of Neurobiology, Yale University School of Medicine, New Haven, Connecticut

David B. Talmadge (50), Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

E. Brad Thompson (2), Department of Human Biological Chemistry and Genetics, The University of Texas Medical Branch, Galveston, Texas

Robert W. Tilghman (3), Department of Microbiology, University of Virginia Health System, Charlottesville, Virginia

Hideaki Togashi (35), Department of Neurology and Section of Neurobiology, Yale University School of Medicine, New Haven, Connecticut

A.W. Trafford (10), Unit of Cardiac Physiology, University of Manchester, Manchester, England, UK

Christopher E. Turner (4), Department of Cell and Developmental Biology, State University of New York, Upstate Medical University, Syracuse, New York

Randall J. Urban (20), McCoy Stem Cells and Diabetes Mass Spectrometry Research Laboratory, Stark Diabetes Center

Gladys M. Varela (45), University of Pennsylvania School of Medicine, Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Philadelphia, Pennsylvania

Calvin Vary (8), Center for Molecular Medicine, Maine Medical Center Research Institute, Scarborough, Maine

Gerry Weinmaster (27), Department of Biological Chemistry David Geffen School of Medicine, Molecular Biology Institute, Jonsson Comprehensive Cancer Center; University of California, Los Angeles, California

Arthur Weiss (17), Department of Medicine, Howard Hughes Medical Institute, University of California, San Francisco, California

Chery A. Whipple (43), Departments of Medicine, Pharmacology and Toxicology, and the Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire and Dartmouth Medical School, Hanover, New Hampshire

Stacey Sedore Willard (7), Department of Cell Biology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Susan Wray (11), Physiology Department, School of Biomedical Sciences, University of Liverpool, Liverpool, England, UK

Jen Jen Yeh (38), Departments of Surgery and Pharmacology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Jianxin A. Yu (4), Department of Cell and Developmental Biology, State University of New York, Upstate Medical University, Syracuse, New York

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Section A

Overview

Chapter 1

Signaling in Development and Disease*

Edward A. Dennis[1] and Ralph A. Bradshaw[2]

[1]*Department of Chemistry and Biochemistry and Department of Pharmacology, School of Medicine, University of California, San Diego, La Jolla, CA*

[2]*Department of Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, CA*

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 (see Schaefer [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 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

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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, its role as the progenitor of the field and 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] and how this led directly to 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.

RECEPTORS AND INTRACELLULAR SIGNALING

At the same time that the growth factor field was undergoing rapid development, major advances were also occurring in studies on hormonal mechanisms. In particular, Sutherland and colleagues [15] were redefining hormones as messengers and their ability to produce second messengers. This was, of course, based primarily on the identification of cyclic AMP (cAMP) and its production by a number of classical hormones. However, it also became clear that not all hormones produce this second messenger nor was it stimulated by any of the growth factors known at that time. This enigma remained unresolved for quite a long time until tyrosine kinases were identified [16, 17] and it was shown, first with the EGF receptor [18], that these modifications were responsible for initiating the signal transduction for many of those hormones and growth factors that did not stimulate the production of cAMP.

Aided by the tools of molecular biology, it was a fairly rapid transition to the cloning of most of the receptors for hormones and growth factors and the subsequent development of the main classes of signaling mechanisms. These data allowed the six major classes of cell surface receptors for hormones and growth factors to be defined, which included, in addition to the receptor tyrosine kinases (RTKs) described previosuly, the G-protein coupled receptors (GPCRs) (including the receptors that produce cAMP) that constitute the largest class of cell surface receptors; the cytokine receptors, which recruit the soluble JAK tyrosine kinases and directly activate the STAT family of transcription factors; serine/threonine kinase receptors of the TGFβ superfamily; the tumor necrosis factor (TNF) receptors that activate nuclear factor kappa B (NFκB) via TRAF molecules, among other pathways; and the guanylyl cyclase receptors. Structural biology has not maintained the same pace, and there are still both ligands and receptors for which we do not have three-dimensional information as yet.

In parallel with the development of our understanding of ligand/receptor organization at the plasma membrane, a variety of experimental approaches have also revealed the general mechanisms of transmembrane signal transduction in terms of the major intracellular events that are induced by these various receptor classes. There are three principal means by which intracellular signals are propagated: protein posttranslational modifications (PTMs), lipid messengers, and ion fluxes. There are also additional moieties that play significant roles, such as cyclic nucleotides, but their

effects are generally manifested in downstream PTMs. There is considerable interplay between the three, particularly in the more complex pathways.

By far the most significant of the PTMs is phosphorylation of serine, threonine, and tyrosine residues. Indeed, there are over 500 protein kinases in the human genome with more than 100 phosphatases [19]. Many of these modifications activate various enzymes, which are designated effectors, but it has also become increasingly clear that many PTM additions were inducing new, specific ('docking') sites for protein–protein interactions. These introduced the concept of both adaptors and multisite scaffolds that bound to the sites through specific motifs and as the process is repeated, successively built up multicomponent signaling structures [20]. There has now emerged a significant number of binding motifs, recognizing, in addition to PTMs, phospholipids and proline-rich peptide segments to name a few, that are quite widely scattered through the large repertoire of signaling molecules and that are activated by different types of receptors in a variety of cell types.

Although the intracellular signaling pathways are characterized by a plethora of modifications and interactions that alter existing proteomic and metabolomic landscapes, the major biological responses, such as mitosis, differentiation, and apoptosis, require alterations in the phenotypic profile of the cell, and these require the modulation of transcription and translation. Indeed, signaling can be thought of at two levels: responses (events) that affect (or require) preexisting structures (proteins) and those that depend on generating new proteins. Temporally, rapid responses are perforce of the first type, while longer-term responses generally are of the second. Thus, it may be viewed that the importance of the complex, largely cytoplasmic, machinery, involving receptors, effectors, adaptors, and scaffolds, has two purposes: to generate immediate changes and then to ultimately reprogram the transcriptional activities for more permanent responses.

The process of gene expression in eukaryotes can be considered at several levels: the generation of the primary RNA transcript, its processing, and transport, translation of the mRNA into protein, and finally, its turnover. Since the amount of the potential activity associated with a given protein is fundamentally dependent on both its rate of synthesis and its rate of degradation, the turnover of the protein itself is also critical to signaling processes and is certainly largely, if not completely, affected by signaling events, too. In eukaryotes, transcription and mRNA processing take place in the nucleus; translation and mRNA turnover are cytoplasmic events. All of these processes are controlled or affected by signal transduction pathways.

The effects on transcription occur at a number of levels and usually involve phosphorylation, either of transcription factors or cofactors. In some cases, this occurs in the cytoplasm, and the effect of the modification is to induce transport into the nucleus; in other cases, the modifications affect binding of regulatory cofactors or to the DNA itself. One class of transcription factors, the nuclear receptor family, requires ligand binding before they are functional. Members of this family form the core of signal transduction pathways that regulate gene expression in response to steroid and thyroid hormones, fatty acids, bile acids, cholesterol metabolites, and certain xenobiotic compounds. In fact, this can be viewed as an extension of lipid signaling, as most of the ligands for these receptors are hydrophobic in character. The ligands exert their affects through allosteric regulation, which has a dramatic effect on either the DNA binding or transcriptional activation properties of the transcription factor [21].

Two biological phenomena of critical importance in all organisms are cell generation (cell division or mitosis/meiosis) and cell death (apoptosis and necrosis). Both are extensively regulated and not surprisingly, much of this control is under the aegis of cell signaling events. The progression through the cell cycle and its various checkpoints is a symphony of protein modifications coupled to programmed protein turnover. The key players are a complement of kinases, known as cyclin-dependent kinases (Cdks), whose activation and deactivation are involved in every stage of the cycle. Interaction with cyclins, required for their activity, allows them to cycle in an on–off manner, and the ubiquitin-dependent degradation of the cyclins controls the vectoral nature of the cycle. The cyclin–Cdk complexes can be further regulated by phosphorylation or complexation with other proteins, which also allows for pausing at checkpoints if the cell senses it should not continue with the division process.

There are also feed-forward mechanisms that allow early steps to regulate successive ones. Apoptosis is equally tightly regulated and its progression easily recognized by distinct phenotypic responses (membrane blebbing, cell shrinking, and chromosomal condensation) as the cell progresses to its end. It is predicated on a family of cysteine proteases, called caspases (because they cleave their substrates to the C-terminal side of aspartic acid residues) that are activated in either an extrinsic or intrinsic pathway. The ten caspases generally exist as inactive precursors (zymogens) and can be subclassified into executioner, initiator, and inflammatory types. These have different structural features and different roles in apoptosis. One apoptotic pathway is directly related to the TNF superfamily, transmembrane receptors that contain a death domain. When activated, these lead to the activation of caspases 8, which in turn, activates the executioner caspases 3. Apoptosis is also triggered by cellular stress, and this leads to the involvement of the mitochondria (as noted above). In a complex pathway involving many proteins, an apoptosome is formed which also leads to the eventual

activation of the executioner caspases. Clearly, the connections between these two fundamental processes are of great importance and are closely related to a number of human diseases, notably cancer and neural degeneration.

INTERCELLULAR SIGNALING

All living cells must be able to interact with their environment if they are to remain viable, whether to sense and move to sources of nourishment or to adjust and adapt to changes that may have occurred there. In multicellular organisms, where communication can become quite complex, the effects of cell signaling extend well beyond the intracellular events triggered in the cytoplasm, and these must also be coordinated with those of sister cells to allow higher-level functions, such as exhibited by an organ (see Figure 1.1). External information can be transmitted to a recipient cell by soluble factors, by interactions with the extracellular matrix (ECM), or by cell–cell contacts that can involve a variety of specific and nonspecific interactions, and the types of reactions initiated may be similar or different than those generated by the soluble ligands. Signals received from these sources are essential to direct developmental pathways and can play key roles in the support of some abnormal tissues such as cancers. The cues inherent in these signaling pathways can be tissue-specific or they may be of a general nature. The same signal in two different cell types may lead to very different results. The general appreciation of signaling at this level is not as well-founded as the knowledge of the more detailed events that follow the activation of intracellular signaling pathways, but it will be of great importance for understanding, for example, how stem cells differentiate and what controls their ultimate phenotype. Given the issues surrounding the use of embryonic stem cells and the apparent gains in manufacturing induced pluripotent cells, these will be important targets for signaling research in the future.

There is developing a considerable interest in the role of cell signaling in development. Genetic studies have been enormously valuable in this regard and have pointed to the

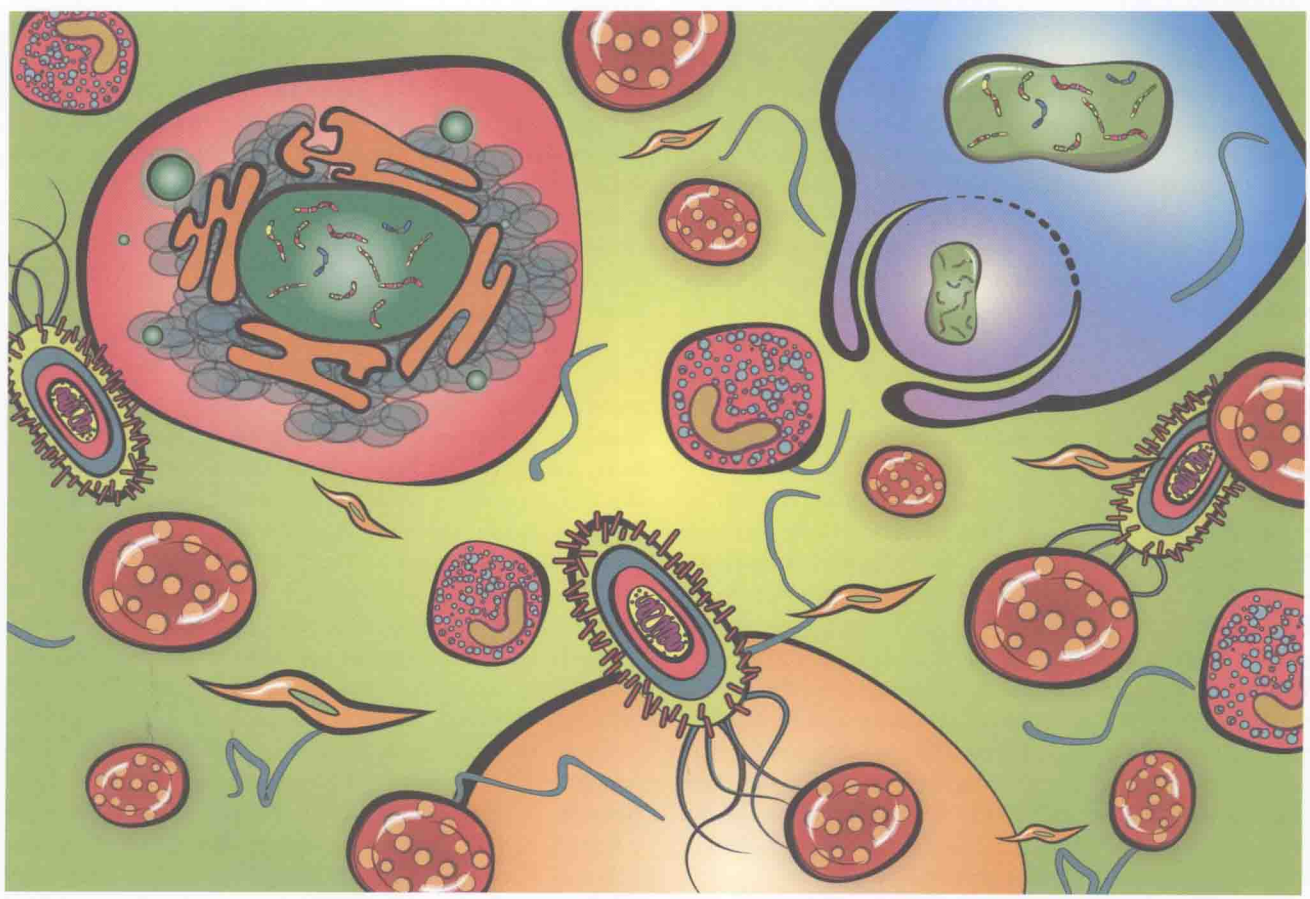

FIGURE 1.1 There are over 200 cell types in the human body, and signaling in individual cells has extracellular manifestations that result from mediators effecting surrounding cells as well as controlling cell–cell interactions. The signaling cascade can extend outward to cause pleiotropic effects on tissues and organs and can, if gone awry, result in significant disease ramifications ranging from metabolic syndrome including insulin sensitivity and obesity to cardiovascular effects, to effects on the CNS, and to numerous forms of cancer throughout the body.