Receptors in Cellular Recognition and Developmental Processes

Edited by

Reginald M. Gorczynski
Ontario Cancer Institute
Toronto, Ontario, Canada

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Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

Robert J. Bloch, Department of Physiology, University of Maryland, School of Medicine, Baltimore, Maryland 21201, (183)

Kimberly E. Dow, Department of Pediatrics (Neonatology), Queen's University, Kingston, Ontario, Canada K7L 3N6, (215)

I. J. Fidler,[1] Department of Cell Biology, The Weizmann Institute of Science, Rehovot 76100, Israel, (287)

Carl G. Gahmberg, Department of Biochemistry, University of Helsinki, 00290 Helsinki 29, Finland, (251)

Scott F. Gilbert, Department of Biology, Swarthmore College, Swarthmore, Pennsylvania 19081, (133)

Reginald M. Gorczynski, Ontario Cancer Institute, Toronto, Ontario, Canada M4X 1K9, (1, 73, 125, 245, 305)

Kimmo K. Karhi, Department of Biochemistry, University of Helsinki, 00290 Helsinki 29, Finland, (251)

David H. Katz, Department of Immunology, Medical Biology Institute, La Jolla, California 92037, (101)

Barry E. Ledford, Department of Biochemistry, Medical University of South Carolina, Charleston, South Carolina 29425, (45)

John J. Marchalonis, Department of Biochemistry, Medical University of South Carolina, Charleston, South Carolina 29425, (45)

A. Raz, Department of Cell Biology, The Weizmann Institute of Science, Rehovot 76100, Israel, (287)

Richard J. Riopelle, Department of Medicine (Neurology), Queen's University, Kingston, Ontario, Canada K7L 3N6, (215)

[1]Present address: Department of Cell Biology, M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Texas 77030.

J. B. Solomon, Immunology Unit, Bacteriology Department, University of Aberdeen, Aberdeen AB9 2ZD, Scotland, (9)

Joe Henry Steinbach, Department of Anesthesiology and Department of Anatomy and Neurobiology, Washington University School of Medicine, Saint Louis, Missouri 63110, (183)

David L. Stocum, Department of Genetics and Development, University of Illinois, Urbana, Illinois 61801, (165)

I. S. Trowbridge, Department of Cancer Biology, The Salk Institute, San Diego, California 92138, (267)

Gerardo R. Vasta, Department of Biochemistry, Medical University of South Carolina, Charleston, South Carolina 29425, (45)

Gregory W. Warr, Department of Biochemistry, Medical University of South Carolina, Charleston, South Carolina 29425, (45)

Preface

The aim of this book is to introduce the reader in a general way to intercellular communication and, in particular, to the evolutionary and ontogenetic role of molecules which allows cells to communicate and/or associate with one another. Communication can occur among cells across a distance as exemplified by neurons and muscle cells at the neuromuscular junction, or it can take place by actual cell contact and association as, for instance, in fertilization and differentiation. In either instance, the macromolecule used by the cells to permit this communication is designated the receptor.

In the past 20 years, rapid developments in fractionation, isolation, and biochemical characterization of both cells and subcellular tissue, coupled with an interest in the molecular biology of the process of cellular differentiation, have led to an expansion of interest in cellular receptors from an earlier relatively restricted pharmacological viewpoint as exemplified by the original studies of Langley in 1878 concerning the inhibition by atropine of the action of pilocarpine. The receptor recognizes (receives) an appropriate specific signal and transduces the information so received to provoke a specific response from the cell concerned. Signal discrimination in a mixed population of cells can be achieved by virtue of the fact that only certain cells will have a receptor capable of binding the stimulator (ligand) at an affinity sufficient to activate subsequent steps in the cascade of biological reactions. Signal transduction is generated by virtue of binding of ligand to the receptor, and generally involves alteration in the activity of some appropriate effector (enzyme, ion channel) in a manner that leads to the requisite physiological response.

If receptors express as their key function the transfer of macromolecular information through impermeable barriers, it can be anticipated that not all such receptors will necessarily be found bridging the cytoplasm of the cell with the external milieu. Thus steroid hormone receptors are found in the cellular cytoplasm, and interaction of these receptors with their specific ligand leads to translocation to the nucleus and specific activation of transcription of parts of the genome. Other receptors such as those for the thyroid hormones tri- and tetraiodothyronine are found within the nucleus itself. Nevertheless, the concern

throughout this volume will be with those receptors present in the plasma membrane of cells. While recent advances have been made in exploring the biochemical mechanisms (enzymatic methylation of membrane phospholipids) whereby receptor triggering leads to signal transduction, there is an advantage to be gained in viewing intercellular communication from a more general perspective.

As organisms increase in complexity from the unicellular through the multicellular to the multiorgan state, there is a need for a concomitant increase in sophistication at the cell surface of those molecules that both recognize and signal the presence of "self" versus "non-self" and lead to the appropriate orientation and organization of the various parts of "self" with one another. Investigation of the phylogeny and ontogeny of receptor molecules and analysis of function of cell surface molecules may enable us to understand the forces operating to conserve receptors during the development of multicellular organisms.

How is their expression controlled (genetically/environmentally)? How do they function in the roles they play? What is the effect of modulation of their expression/function on homeostasis within the whole organism? In what follows, these and other questions will be explored with examples from many disciplines of cell biology. However, it is hoped that underlying each chapter the reader will be able to see a relevance to this guiding theme of intercellular recognition and development.

A volume of this nature could not come to fruition without the concerted effort of a number of people. I would like to thank all of the contributors, who toiled, often I am sure it seemed to them endlessly, yet eventually successfully, to meet the various deadlines I gave them for submissions and updates. My thanks, too, to my many colleagues who on a number of occasions have offered valuable advice on the organization and content of this book—to Gerald Price in particular, who has been a valued collaborator for many years. I absolve them all from any responsibility for what lies within! Without Anne Collins and Maria Boulanger I know these pages would still lie half-typed and uncollated on my desk, awash with a myriad of other unfinished work. Last, and most important of all, I would like to thank Professor Cinader, who first suggested the value of a book of this type and proceeded to support that initiative with many hours of critical review. Without his friendship, wit, and encouragement, this book would never have materialized.

Reginald Gorczynski

Commentary

This book is devoted to the steps toward the Rosetta stone for the current status and future discovery of intercellular communication.

Cell communication is dependent on a series of molecular events involving receptors and ligands that are either cell bound or secreted by one cell and taken up by surface structures—receptors—of another cell. A series of sequential events of molecular interaction at cell and organelle membranes coordinate cell metabolism within the same and between different organs. Receptors can be activated through soluble factors and, hence, at a distance. Receptor–ligand interaction can also occur between membranes of different cell types, i.e., via adhesion molecules that play a role in structural development of organs, exemplified by neural cell adhesion and embryological development under the influence of "master" cells.

Recognition and, thus, receptor–ligand interaction play a role during homing of cells in development, differentiation, and cell migration. In the immune system, macromolecules of the external world cause distortions of internal communication; the resulting change in the balance of molecular communication constitutes the immune response.

Receptor–ligand communication contributes to resistance against infectious disease. Antigen recognition by B and T cells is one component of this process; the ability of a particular parasite to attach to a cell receptor is an example of other facets. In short, interaction of the cellular milieu with external molecular changes occurs through receptors of the lymphoid system and through receptors of other cells that control the ability of parasites to attach to membranes and to reach the interior of cells.

Malfunction of a single step in cell communication results in disease and contributes to neoplastic transformation. Development of neoplastic cells and metastases depends on disappearance or blockage of receptors through which growth and metastatic spread are controlled.

Cell communication is regulated by limitation in the period during which a given stimulus can affect biochemical processes that are activated via a particular receptor. Responses, initiated by ligand–receptor combination, can be termi-

nated by events that lead to cessation of responsiveness after messages have been received for a given time. This limitation is achieved by various processes, including endocytosis, recycling, and affinity changes in receptors, and through disassociation of micromolecular complexes with which the ligand-binding site is associated.

Factors convey signals by combination with receptors. These signals can give rise to the production of other factors and thus to the sentences of the intercellular language; the resulting intercommunication is intense and continuous. There are superfamilies of molecules, corresponding to language families, that play a role in recognition and show homologies in a wide group of animals, from vertebrates to invertebrates. The analysis of this molecular language is a major movement in the biology of the twentieth century.

B. Cinader
Department of Immunology
University of Toronto
Medical Sciences Building
Toronto, Canada M5S 1A8

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I (CHAPTERS 1–4)

Phylogenetic Analysis of Receptors in Development of Immune Recognition

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It seems obvious that the recognition of self must be a property of all cells. In unicellular organisms this avoids iso-phagocytosis, while in pluricellular organisms self-recognition ensures cohesion and collaboration between cellular aggregates. Where the phenomenon has been studied in depth, e.g., in the vertebrate immune system, we can also state that self-recognition is an active process, in which cooperation in the recognition of and reaction to non-self between specialized cells within the same individual is often seen. In part at least, immune responses in vertebrates show evidence for linkage to the polymorphic genes of the major histocompatibility complex (MHC). The evolutionary advantage of this MHC-linked immune responsiveness is unclear, though one popular idea is that given the extensive polymorphism seen at the MHC of most species, linkage of immune-cell recognition to products of genes encoded within the MHC implies capability for increased diversity in immune recognition (Klein, 1980). Clearly a problem with this notion is to explain the adaptive advantage of species showing little MHC polymorphism (e.g., hamster) and the worry that such an interpretation seems to endow the MHC system with "Promethean foresight" (Ohno *et al.*, 1980).

Even in insects, however, the available evidence suggests that distinctions can be made between different types of foreign objects—i.e., graded discrimination is possible. While we shall see that it is by no means clear whether during

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phylogeny recognition is always carried out by cells, or by soluble molecules in collaboration with cells, it is nevertheless possible to imagine one of two mechanisms whereby signal discrimination can occur: (1) graded responses in a recognition system using nonspecific factors, e.g., physiochemical parameters such as surface charge; (2) the development of specific factors which are superimposed upon an already existing nonspecific system.

A review of the nonimmune surface recognition of foreign material common to protozoa and to all cells of multicellular organisms is provided by Solomon in Chapter 1. A feature of such recognition in plants is the interaction between specific saccharides and glycoprotein (lectin) receptors at the cell surface—such an interaction seems to lie at the heart of the cellular adhesion process which is a feature of the agglutination of unicellular amoeba in the aggregation phase of the life cycle of the slime mold (Newell, 1977). Nevertheless, the most primitive of host immune responses in multicellular organisms, phagocytosis, is not seen in higher plants, although encapsulation can occur and phagocytosis is seen in slime molds and algae. Solomon reviews the literature concerning self-/non-self recognition (Boyden, 1962) at the cell surface (in allo- or xenotransplantation reactions) from the sponges through the annelids and mollusks to the chordates. There is convincing evidence for rejection of xeno- as well as allografts, with a growing literature on polymorphism of cell surface histocompatibility molecules in some phyla (Hildenmann *et al.*, 1980). However, the question of whether memory (as witnessed by the phenomenon of second set rejection) exists in allo- or xenotransplants in invertebrates is still unsettled.

Far more detailed investigations have been performed on the humoral factors capable of performing specific recognition functions. It is believed that the recognition and phagocytosis of an implant in the host coelomic cavity occurs by a process similar to that associated with recognition of a transplant at the host surface, and this belief, coupled with the relative ease of experimental manipulation, has led internal phagocytosis to be the response most widely investigated. From mollusks [*Helix pomatia*—differential clearance of erythrocytes bearing different carbohydrate surfaces (Renwrantz, 1981)] to annelids [inhibition of selective uptake of gram-positive/gram-negative bacteria by coelomocytes in the presence of D-(+)-glucose (Fitzgerald and Ratcliffe, 1980)], we find ligand-specific cellular receptors whose recognition function is compromised by the presence of soluble sugars. Despite the fact that soluble hemagglutinins have been found in most invertebrate species studied there is no quantitative or qualitative change in these hemagglutinins following antigen stimulation, nor is there evidence for memory in invertebrate hemagglutinin-mediated anti-self recognition. In this respect then, there does not seem to be a parallel with cell surface receptors on, e.g., mammalian B lymphocytes. It is of interest that the most common reactivity seen in the hemolymph is a lectin-like hemagglutination

reaction—e.g., snail lectin inhibited by methyl-DGalNAc (Hammarstrom and Kabat, 1969)—and indeed mitogen stimulation studies suggest that leukocytes of the earthworm possess a mitogen receptor for concanavalin A (Con A) which is inhibited by methyl D-mannopyranoside (Roch *et al.*, 1975).

With respect to one of the possibilities raised above, then, it does seem that during phylogenetic development within the immune system, a highly discriminatory secondary recognition system has become superimposed upon a primordial nonspecific one. A similar conclusion is reached by Lackie (1981). Let us recognize, however, that we are not attempting here to implicate the immune system, by virtue of its capacity to react with non-self material, in the mechanism of evolution. The teleological nature of this particular argument has been forcefully attacked by Allegretti (1978).

We might now ask, in light of the above, whether there is any evidence which can be adduced for a relationship between molecules with recognition function existing within different members of a species, or a relationship during evolution between these molecules in different species? It is appropriate to investigate evidence for such a "family" of recognition molecules bearing in mind that changes in structure and/or function may occur during evolution from the primitive prototype molecules. This idea of a "superfamily" of recognition molecules showing homology within the vertebrates, chordates and invertebrates is developed further by Marchalonis *et al.* in Chapter 2. Comparison of amino acid composition (Marchalonis and Weltman, 1971) suggests a relatedness between recognition molecules from origins as diverse as the agglutinin of the lamprey, C-reactive protein of vertebrates (specific for phosphorylcholine), mammalian immunoglobulin molecules, and the recently described vertebrate T-lymphocyte receptor. As Marchalonis *et al.* stress in Chapter 2, it is "comparisons with the primitive members of the true immunoglobulin family [which] provide the strongest guidepost of homology."

In the absence of primary protein sequence data to detect sequence homology, and given the disparity in size of the molecules examined, it is probably unwise at this point in time to state the case more strongly. It may be, for instance, that this "superfamily" represents the product of convergent evolution of molecules constrained (by their very function) to evolve within certain geometric limits. However, within individual pairs of molecules where more detailed comparisons can be made (e.g., for T-cell receptors and immunoglobulin molecules) the protein sequence data (Yanagi *et al.*, 1984; Hedrick *et al.*, 1984), the structural resemblance (Marchalonis and Barker, 1984), and the frequent sharing of idiotypic specificities on T cells and B cells expressing a common antigen specificity (Marchalonis and Hunt, 1982) make this suggestion (evolutionary convergence, rather than direct evolutionary relatedness) less likely.

Using a variety of approaches which include the analysis of cell-surface deter-