Cellular Immunology

Selected Readings and Critical Commentary

Compiled by

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and
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Addison-Wesley Publishing Company
Advanced Book Program/World Science Division

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and
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First printing, 1982
Second printing, 1983

Library of Congress Cataloging in Publication Data

Main entry under title:

Cellular immunology.

Bibliography: p.
1. Cellular immunity—Addresses, essays, lectures.
I. Sato, Vicki L. II. Gefter, Malcolm L. [DNLM:
1. Immunity, Cellular—Collected works. QW 568 C3935]
QR185.5.C44 591.2'9 81-12826

ISBN 0-201-10434-2 AACR2

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Advanced Book Program/World Science Division, Reading, Massachusetts, from camera-ready
copy prepared by the office of the editors.

Printed in the United States of America.

BCDEFGHIJ-AL-89876543

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London • Amsterdam • Don Mills, Ontario • Sydney • Tokyo

Preface

Selected Readings represents the combined attempts of one former molecular biologist (MG) and one former plant photobiologist (VS) to grapple with some of the fundamental issues of their new discipline, cellular immunology. We wished to share some of what we have learned, both about cellular immunology and about the flavor of the field, with students of immunology and fellow scientists in other disciplines. Our approach has been to present a series of papers on individual subjects which collectively contributed to some central idea in cellular immunology. This allows the reader to acquaint himself with the nature of immunological experimentation as well as with the ideas being developed. We have included brief editorial analyses which are designed to offer some guidelines and are mostly a reflection of our own views on these subjects. The selected papers are not meant to be a comprehensive survey of a particular topic but were chosen for their contribution to the development of an idea. Unfortunately, constraints of length, reprint permissions, and availability of original papers have added to our inability to include many noteworthy contributions; obviously the number of relevant publications far exceeds the scope of this book. In some instances, we have tried to compensate for our inability to include papers by listing an additional bibliography.

The book inevitably represents the bias of recent but enthusiastic converts to cellular immunology. The field lured us from our respective disciplines because it seemed to offer a fascinating breadth of biological research. The problems of the immune response begin with issues of gene structure and expression, proceed through developmental biology and the questions of biological recognition, and culminate in wide-ranging issues about the nature of information handling and storage. For all of our enthusiasm about this new discipline, our initial encounters with immunology were not without their problems. As we began reading the literature and attending seminars several years ago, we all-too-often found ourselves in a mysterious, jargon-befuddled world that made our goal of understanding the state of the art seem almost unattainable. Confusion was reaching a peak about the time of the Cold Spring Harbor Symposium on Lymphocyte Diversity. We both attended the symposium in 1976 whereupon one of us had the following experience.

> "Applying some of the skills acquired during a scientific career, I sat in the front row of the auditorium between two of the most prominent scientists in immunology. Obviously the hope was that a simultaneous translation from immunology into simple prose would be the key to my successful acquisition of useful information. The experts listened to the speakers with an attentiveness designed to confirm the wisdom of my plan of action, but their solemn concentration discouraged me from

stage-whispering questions during the talks. I held them for the intermission and took copious notes. By the time coffee break came, I had predictably forgotten the questions that I had about the early speakers of the session but had managed to hold on to a few pertaining to the last of the speakers (in actual fact, my notes on the early speakers were sufficiently incomprehensible so that mere recollection of the topic, let alone incisive questions, eluded me). Before I could even ask one question, one of my neighbor-experts asked if I could please decipher the points of interest in the previous session. At that point, I decided it was futile to keep taking notes and directed all my attention to a simple assimilation of as much information as possible in the hope that 'it would all make sense later.' Needless to say, sudden enlightenment was not forthcoming."

Comparing experiences after our return to Cambridge, we decided to try a different approach and teach an introductory course in immunology. Not to venture into the abyss alone each of us sought a buddy. One of us (VS) set out to teach immunobiology at Harvard in collaboration with another traveller down the immunological road, Wally Gilbert, and the other (MG) managed to find a place in the immunology course at MIT taught by Lisa Steiner and Herman Eisen. Staying up all night before class and writing out the entire lecture, after struggling with the literature ourselves, made us barely able to convey the subject matter to the uninitiated. The task during the first semester of teaching was obviously a matter of staying one lecture ahead of the students while keeping just enough information in reserve to intimidate any student sufficiently confident to ask pressing questions.

About this time we each passed through a phase of self-affirmation and decided that surely our difficulties could not lie with us but must lie with the field. Apparently, the study and language of immunology were sufficiently different in style from molecular genetics and bioenergetics that practicing members of the disciplines could not communicate. (This continues to be a general problem. Our colleagues in other biochemical and biological disciplines still bemoan the seminars given by immunologists, and the two of us, ironically enough, have become the simultaneous translators.) In an attempt to break down the barriers, we began to meet once a week to read and discuss a variety of papers, some of which we found useful in teaching. It seemed to us that a collection of some critical papers in cellular immunology would be a useful companion to the numerous introductory texts currently available. Such a collection could serve for undergraduates and graduate students and as a resource for other scientists entranced but a bit intimidated by cellular immunology.

Of course, the more we read, the more we found that fascinating threads of consistency and logic emerged from the morass of often conflicting data, confusing terminology, and vastly different experimental systems. Exhausted but definitely addicted, we emerged from the task pleased to confirm our initial instincts that cellular immunology ranks as one of the most exciting fields in modern biology.

We extend our gratitude to our many colleagues who have helped us in assembling Selected Readings. In particular, we acknowledge Mike Bevan, Herman Eisen, Ed Golub, and Eli Sercarz for helpful discussions; Nancy Basore, John Douhan III, Ann Marshak-Rothstein, Leslie Serunian, and Lisa Shinefeld for reading and criticizing the text; Lisa Steiner for the generous loan of her journals to the publishers; Audrey Childs for her work on the early drafts, and especially Neenyah Ostrom for typing the final copies and offering editorial expertise in the final hectic stages. Special thanks from VS go to the Herzenbergs and from MG to Matthew Scharff for taking us into their laboratories and introducing us to immunology.

Vicki Sato and Malcolm Gefter

ACKNOWLEDGMENTS

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Papers I.5, III.4, VII.2, VII.4, IX.4 were originally published in European Journal of Immunology, Verlag Chemie GMBH.

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Paper I.1 was originally published in The Lancet.

Paper IX.1 was originally published in Annales d'Immunologie, Masson, S.A.

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Chapter I

Early Studies on Cell Cooperation in the Immune Response

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Early Studies on Cell Cooperation in the Immune Response

The essence of immunity lies in the ability to distinguish self from nonself. It is upon the ability to make this distinction that the organism has built a biological defense system geared to fend off pathological invaders. The hallmarks of this defense are its DIVERSITY, its SPECIFICITY, and its MEMORY. The diversity of the immune response is reflected in the organism's apparent ability to recognize and respond to a large universe of intrusive foreign antigens. The fine regulation of that potential diversity results in an extraordinarily specific response--highly restricted elements in the immune system are activated by equally restricted antigenic stimuli. In addition, the immune system displays memory--not only the ability to recall past experiences but also the capability to modify behavior upon a subsequent encounter with the initial antigen.

The workings of one area of the immune system, the humoral response, are conducted by a series of white blood cells, primarily macrophages and lymphocytes. The latter cells come in two forms: thymus-dependent (T) lymphocytes and thymus-independent, bone marrow derived (B) lymphocytes. These three cell types work together in ways that are not yet completely understood to elaborate antibodies that are directed against the challenging antigen. These specific antibodies are released into circulation by antibody-producing plasma cells. The other aspect of immunity does not depend on secreted antibodies but rather through the direct action of antigen-specific lymphocytes. Cell-mediated immune responses seem to rely on direct contact between target cells and effector lymphocytes, the latter usually T cells. The two broad classes of lymphocytes for humoral and cellular immunity are distinguished by a series of cell surface antigens, described in subsequent chapters and also clearly reviewed and catalogued in Katz (1977).

This chapter is concerned first with the initial descriptions by Gowans (paper 1) and Miller (paper 2) that small recirculating lymphocytes are fundamentally important in the immune response, and that at least some of these lymphocytes are dependent upon thymic influence for development. Subsequent papers included here present data that support the notion that the cells responsible for the immune response are heterogeneous, both with regard to function and developmental lineage. Finally the experiments of Claman, Davies, Miller and Mitchell, and Mitchison lay the foundation for the concept of T cell-B cell cooperation in the making of a successful humoral response.

Although much of the pioneering work of Gowans in demonstrating the critical role of the small lymphocyte cannot be included here (Gowans and Knight, 1964), his contribution in laying the foundations of modern cellular immunology cannot be underestimated. It was not until his demonstration in 1962 that depletion of the recirculating pool of small lymphocytes resulted in severe immune deficiency that the fundamental importance of the small lymphocyte was realized. Its apparently

quiescent nature and rather innocuous appearance made it a far less attractive candidate for mediation of host defenses than that of its dramatic, phagocytic macrophage counterpart. Paper 1, which is but one of several important works, demonstrated that an animal could be rendered immunologically compromised by removal of its recirculating lymphocytes and that immunocompetence could be restored by addition of the lymphocytes removed by thoracic duct cannulation. The paper also demonstrates that addition of lymphocytes obtained from an animal rendered immunologically unresponsive (tolerant) to a particular antigen was unable to restore immune competence to an irradiated recipient.

Extirpation experiments, primarily by Glick (1956) and Cooper (1963-1966) in the chicken and by Miller in the mouse (paper 2) extended the observations by Gowans and revealed that not all of the lymphocytes within an individual were functionally equivalent. The logic behind these experiments was admirably straightforward: to assess the contribution of a particular lymphoid organ (and the cells which it produces) by removing it an an early stage in the host's development and determining how the host fared when faced with an immunological challenge.

The results of these experiments in chickens revealed that removal of the Bursa of Fabricius in newborn chickens resulted in severe depression of antibody production with no apparent effect on cell-mediated immune responses like graft rejection. Neonatal thymectomy affected both humoral and cell-mediated immune responses. Miller confirmed that neonatal thymectomy of a mouse seriously compromised its ability to mediate graft rejection. This data is presented in paper 1. Also presented is the demonstration that any delay in thymectomy results in a failure to remove the immunocompetent cells. The implication, then, is that while the thymus is crucial in contributing to the pool of reactive lymphocytes, its influence in this regard decreases with age. That is, immunocompetent cells are generated which are no longer directly dependent upon the thymus for survival or ability to function. Subsequent work by Miller in a paper not included here (1962) extended these observations to show that the neonatally thymectomized animals subsequently challenged with the antigen sheep red blood cells were far less able to make anti-sheep cell antibodies than their sham-thymectomized or untreated fellows.

Thus, the evidence from extirpation experiments led to the following view of the immune system:

a. Depletion of B lymphocytes by bursectomy results in an inability to mount humoral immune responses (i.e., make antibody) without seriously affecting cell-mediated immunity.
b. Depletion of T lymphocytes by neonatal thymectomy results in an inability to mount both humoral and cell-mediated responses.

A simple description of the immune system in which B cells provide humoral immunity, and T cells provide cell-mediated immunity is not sufficient to explain the available data. The remaining papers in this chapter will deal with resolving why humoral responses were affected by removal of either T or B lymphocytes. These papers are concerned with establishing two basic facts in humoral immunity: 1) T and B cells must interact before antibody can be produced in response to a specific antigenic stimulus, and 2) B cells are directly responsible for synthesis and secretion of antibody while T cells provide essential regulatory signals.

The first direct evidence that T and B lymphocytes act synergistically in the humoral response to antigens came from a simple and elegant experiment performed by Henry Claman and coworkers. Taking advantage of the newly developed transfer method of Playfair, Papermaster, and Cole (1965), Claman transferred thymus and/or bone marrow cells from a naive donor into a recipient which had been rendered immunoincompetent by a large dose of radiation. Using this irradiated host essentially as a test tube, Claman introduced thymocytes and bone marrow cells, either alone or in combination, together with an immunizing dose of sheep red blood cells (SRBC) and assessed the ability of the donor cells to produce anti-SRBC antibodies several days later. Briefly summarized, the results indicated that a mixture of bone marrow and thymus cells were able to mount an immune response comparable to