Immune Modulation Agents and Their Mechanisms

edited by

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Preface

Over the past 20 years scientists studying the biological interactions between the tumor and the host, both in laboratory and clinical studies, have acknowledged that biological response modifiers (BRMs) will most likely have a role in cancer treatment. An appreciation of the clinical potential of BRMs has developed slowly. Like chemotherapy in the early 1940s, the usefulness of BRMs was met with skepticism. This was based on the initial clinical responses, with a limited number of BRMs, which resulted in a less significant response than was anticipated.

Biological response modifiers, which have also been referred to as immunomodulators, immunoaugmentors, immunostimulators, and immunorestoratives, are agents which can modify the relationship between the tumor and host by modifying a host's cellular immune response to tumor cells, with resultant therapeutic benefit. The modification can occur by one or several mechanisms: (a) by augmenting antitumor immunity by modulating cellular components of the immune system and inducing or restoring effector cells of immunity, including identifiable subsets of lymphocytes, cells of the monocyte-macrophage lineage, and natural killer cells; or (b) by protecting and/or reconstituting stem cell replication in bone marrow, which would also increase the ability of the host to tolerate damage by cytotoxic modalities of cancer treatment.

The possibility of augmenting the host response through selective modification of various components of the immune response has been demonstrated in animals with various chemicals, natural products, and physiological factors. Therapeutic benefits have been achieved by such an augmentation in tumor-bearing animals. Although similar beneficial effects in man will be necessarily far more difficult to achieve, some encouraging though tentative results have been reported in patients with certain types of cancer. The results with such agents suggest a prolongation of survival (with or without disease) and/or an increase in the remission duration induced by conventional therapy.

The purpose of this book is to provide a critical review of the studies dealing with biological response modifiers and their influence on immune functions and mechanisms through which effector cells are modulated. It will be informative and of interest to physicians, medical students, immunologists, immunopharmacologists, experimental and clinical oncologists, and other health professionals.

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Contents

Preface iii
Contributors v

PART I BIOLOGICAL RESPONSE MODIFIERS
THEIR INFLUENCE ON IMMUNE FUNCTION

Introduction 3
Richard L. Fenichel

SECTION A Defined Organic Immunomodulating Agents

1 Diethyldithiocarbamate (DTC): A Biological Augmenting Agent Specific for T Cells 7
Gérard Renoux and Micheline Renoux

2 Thiazolobenzimidazole and Thiazolobenzothiazole Compounds as Biological Response Modifiers 21
Francis J. Gregory

3 Immunopotentiation by Cyclophosphamide and Other Cytotoxic Agents 39
David Berd, Henry C. Maguire, Jr., and Michael J. Mastrangelo

4 Lentinan 63
Tadao Aoki

5 Immunostimulating Compounds: Isoprinosine and NPT 15396 79
Kwong Yok Tsang, H. Hugh Fudenberg, Fred K. Hoehler, and John W. Hadden

6	Tilorone and Related Analogs *Herbert Megel and John P. Gibson*	97
7	Lipoidal Amines *William W. Hoffman*	121
SECTION B	Natural Products, Extracts, and Lower Molecular Weight Components	
8	Thymosin, Peptidic Moieties, and Related Agents *Teresa L. K. Low and Allan L. Goldstein*	135
9	*Corynebacterium parvum* and Its Fractions *Cecil S. Cummins*	163
10	Cyclosporin A: Current Status Including the Cape Town Experience *Peter Jacobs and Linda Eglin*	191
11	Tuftsin (THR-LYS-PRO-ARG): A Stimulator of All Known Functions of Macrophage *Victor A. Najjar and Nancy J. Bump*	229
SECTION C	Synthetic Polymers	
12	MVE-2: Development of an Immunoadjuvant for Cancer Treatment *Richard A. Carrano, John D. Iuliucci, James K. Luce, James A. Page, and Anthony R. Imondi*	243
13	NED 137: A Low Molecular Weight Polycarboxylate with Immunostimulatory Activity *Julita A. Teodorczyk-Injeyan, Judith A. Falk, Leonard Makowka, Frederick L. Moffat, Leo Filion, and Rudolf E. Falk*	261
SECTION D	Role of Immunomodulating Agents in Autoimmune and Degenerative Diseases	
14	Immunomodulators in the Treatment of Selected Autoimmune Diseases *Bruce Freundlich and Robert B. Zurier*	289
15	Tumor and Metastatic Disease *Gerald J. Elfenbein*	323
PART II	EFFECT OF CHEMICAL AGENTS ON BIOLOGICAL SECRETIONS AND MECHANISMS OF IMMUNE MODULATION	
	Introduction *Michael A. Chirigos*	343
SECTION A	Concepts of Immunomodulation	
16	Immunomodulating Agents *P. Reizenstein and Georges Mathé*	347

17 Modulation of Human Lymphocytotoxicity by Biological Response Modifiers 363
Michael Micksche, Michel Colot, and Atsushi Uchida

SECTION B Effects of Immunomodifiers on Thymus Lymphocytes

18 Levamisole 383
Willem K. Amery and Christian Hörig

19 Lentinan, a T-Cell-Oriented Immunopotentiator: Its Experimental and Clinical Applications and Possible Mechanism of Immune Modulation 409
Junji Hamuro and Goro Chihara

20 Influence of Host-Tumor Relationships on Response to the Biological Response Modifiers, Glucan, and Methyl Palmitate 437
N. R. Di Luzio, Rose B. McNamee, Ernest L. Jones. and David L. Williams

21 Immunopharmacological Properties of 2-Cyanaziridine Derivatives 447
Uwe F. Bicker

22 NPT 15392: A New Chemically Defined Biological Response Modifier 475
Lionel N. Simon, Fred Hoehler, Theodore Ginsberg, and John W. Hadden

SECTION C Induction of Cytotoxicity
Interferon, Natural Killer Cells, and Macrophages

23 Interaction of Interferon and Chemotherapeutic Agents in Modulation of Natural Killer Cell Activity 489
Julie Y. Djeu and Keith M. Ramsey

24 Modulation of the Immune Response by Muramyl Dipeptide 499
William E. Fogler and Isaiah J. Fidler

25 The In Vitro Induction of Colony-Stimulating Factor, Prostaglandin E, and Interferon in Macrophages and Tumor Cells by Biological Response Modifiers 513
Erich Schlick, Klaus Hartung, Mario Piccoli, Anna Bartocci, and Michael A. Chirigos

SECTION D Endocrine Regulation of Immunity

26 Endocrine Regulation of Host Immunity: The Role of Steroids and Thymosin 533
Nicholas R. Hall and Allan L. Goldstein

27 Human Lymphocyte Studies Can Predict Responses to Thymic Factor Therapy 565
Nigel A. Byrom and John R. Hobbs

28 Immunosuppressive Effects of Human Chorionic Gonadotropin on Delayed-Type Hypersensitivity in Mice 597
Anna Bartocci, Roy D. Welker, Mario Piccoli, Erich Schlick, Vasilios Papdemetriou, Klaus Hartung, Michael A. Chirigos, and Bruce C. Nisula

29 The Mode of Action of Imuthiol (Sodium Diethyldithiocarbamate): A New Role for the Brain Neocortex and the Endocrine Liver in the Regulation of the T-Cell Lineage 607
Gérard Renoux

SECTION E Role of Prostaglandins as Regulators of the Immune Response

30 Prostaglandins as Modulators of T- and B-Lymphocyte Function 627
Jan L. Ceuppens and James S. Goodwin

31 Prostaglandins and Cyclooxygenase Inhibitors 649
Joseph Chang and Alan J. Lewis

Index 669

Part I

Biological Response Modifiers
Their Influence on Immune Function

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Biological Response Modifiers
Their Influence on Immune Function

Introduction

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My interest in immunomodulating agents began in 1972 when I read the paper of Stjernsward and co-workers (1) showing the depletion of lymphocte populations in breast cancer patients after radiation treatment and indicating the long recovery time needed for these cells to regain their important functions. The pioneering work of Drs. Gerard and Micheline Renoux with levamisole (2) expressed the concept of immunomodulation of lymphocyte function by a chemical compound and demonstrated its antitumor and antimetastatic activity in murine tumor models. My own research was translated into the origination and initiation of a research program on immunomodulating agents (3,4). Wy-18,251, a thiazolobenzimidazole that emerged from this program, is now in clinical trial.

Part I of this book focuses our attention on defined organic agents—natural products and synthetic polymers that have undergone extensive laboratory investigation. Many of these agents are presently in various phases of clinical trials. The last two summarizing chapters of the section, one on tumors and metastases, the other on autoimmune disease, attempt to put in perspective the role of biological response modifiers in these diverse disease states.

Agents such as diethyldithiocarbamate, thiazolobenzimidazoles, cytoxan, lentinan, isoprinosine, NPT-15,396, tilorone, lipoidal amines, thymosin peptides, *Carynebacter parvum*, cyclosporine, tuftsin, and synthetic polymers MVE-2 and NED 137, are critically examined in this section. Emphasis is placed on the ways they influence the cellular immune system, the correlation of their in vitro with in vivo activities, and their effect on the interrelationship of the cellular immune with the humoral immune systems. The therapeutic implications and applications of these drugs are thoughtfully considered and, where possible, the results of clinical trials are insightfully examined.