Basic and Clinical Aspects of Granulomatous Diseases

Editors: Dov L. Boros and Takeshi Yoshida

Basic and Clinical Aspects of Granulomatous Diseases

Proceedings of the Workshop on Basic and Clinical Aspects of Granulomatous Diseases held June 18-20, 1980 in Bethesda, Maryland

Editors:

DOV L. BOROS, Ph.D.

Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan, U.S.A.

and

TAKESHI YOSHIDA, M.D.

Department of Pathology, University of Connecticut Health Center, Farmington, Connecticut, U.S.A.



Basic and Chrical Aspects of Granulomatous Diseases

Proceedings of the Stockengo on Blase and Climed Aspects of Granntonguing discuss hald bose 18-20, 1980 in Heinerda, Marvins

Contents copyright @ 1980 by Elsevier North Holland, Inc. All rights reserved.

Published by:

Elsevier North Holland, Inc. 52 Vanderbilt Avenue, New York, New York 10017

Sole Distributors outside USA and Canada: Elsevier/North-Holland Biomedical Press 335 Jan van Galenstraat, P.O. Box 211 Amsterdam, The Netherlands

ISBN 0-444-00587-0

Manufactured in the United States of America

Preface Present will plice harmin side effects Thus a being some

Granulomatous tissue responses have been observed and described by pathologists over a century ago. Yet, the function of this chronic inflammatory response remained an enigma in the ensuing decades. In the past fifteen years, thanks to the efforts of the dedicated few, many of whom participated in this Workshop, a great deal of progress has been made. Experimental models succeeded to better delineate the differences which exist between foreign body as opposed to immune-induced granulomatous lesions. The "infectious" hypersensitivity-type granuloma has been conceptually identified as one of the diverse manifestations of the cell-mediated arm of the immune response. The central role of the thymic-derived lymphocyte in the generation, maintenance, and possibly healing of hypersensitivity granuloma has been established. The dual role of the macrophage in antimicrobial resistance and local tissue destruction is now appreciated. The activity of the fibroblast, hitherto a rather neglected component of the lesions, is rapidly gaining the attention of researchers. The program of this Workshop reflects the prevailing trends in granuloma research and points to future approaches. Descriptive histopathology gave way to cellular immunology, molecular biology and immunopharmacology. Interest is focused on cellular subpopulations, cell-cell interactions, cellular receptors, signals carried by mediators and regulatory mechanisms. Though emphasis is placed on the exploration of basic mechanisms active in the various facets of the granulomatous response, the essential goal, an improved handling of granulomatous disorders, should never be lost. Despite efforts, the etiologic agents of several granulomatous diseases are still unknown. Whereas some disorders are benign and may resolve spontaneously, others

forces, prevention of defastition and resonation of the dampers area.

progress to dangerous tissue liquefaction, extensive fibrosis and rarely, to rapid death. Granulomatous inflammations may also be influenced by the genetic background of the diseased individuals. Clinically, granulomatous diseases are treated by broad-action anti-inflammatory drugs such as corticosteroids with often harmful side effects. Thus a better understanding of the cellular and molecular basis of the granulomatous response should help clinicians in at least three major aspects: (a) restoration of the granulomatous response to patients succumbing to disseminating infectious agents; (b) regulation of the intensity of the inflammatory response and (c) curtailment of tissue damage and prevention of irreversible fibrosis.

Granulomata have been compared to a battleground between indigestible agents and macrophages. To extend this metaphor, we'd like to learn more about the battle plan, the generals who lead the fight, the mobilization of infantry and their weaponry, the communication systems of the fighting forces, prevention of devastation and restoration of the damaged area.

The proceedings of this Workshop presented in this book deal with many of these questions. We hope that this book will become a stimulus to the future investigations of basic and clinical researchers in granulomatous inflammation.

Finally, we wish to express our gratitude to the National Institute of Allergy and Infectious Diseases and the National Heart, Lung and Blood Institute for so generously sponsoring this Workshop, thereby helping to realize an ambitious idea and reaffirming that granuloma research has come of age.

July, 1980
Dov. L. Boros at Detroit, Michigan

Takeshi Yoshida at Farmington, Connecticut

finels of the estimionation response the essential goal, an improved

the uticlosic age, of several grands material disease, are still unknown.

Participants

D. O. Adams, M.D., Ph.D.

Department of Pathology, Duke University, Durham, North Carolina 27710

John E. Bennett, M.D.

Clinical Mycology Program, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20205

Dov L. Boros, Ph.D.

Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan 48201

David M. Center, M.D.

Division of Pulmonary Medicine, Boston University Medical Center, Boston, Massachusetts 02118

Stanley Cohen, M.D.

University of Connecticut Health Center, Farmington, Connecticut 060?

Zanvil A. Cohn, M.D.

The Rockefeller University, New York, New York 10021

Frank M. Collins, Ph.D., D.Sc.

Trudeau Institute, Inc., Immunobiological Research Laboratories, Saranac Lake, New York 12983

Ronald Crystal, M.D.

Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20205

Arthur Dannenberg, Jr., M.D., Ph.D.

Experimental Pathology, Department of Environmental Health Sciences, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland 21205

Philip W. Davies, Ph.D.

Department of Immunology, Merck Institute for Therapeutic Research, Rahway, New Jersey 07065

Michael Dunn, M.D.

Uniformed Services University School of Medicine; Liver Section, Department of Gastroenterology, Walter Reed Army Institute of Research, Washington, D.C. 20012

William L. Epstein, M.D.

Department of Dermatology, University of California, San Francisco, School of Medicine, San Francisco, California 94143

Anthony Fauci, M.D.

National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20205

Jordan Fink, M.D.

Veterans Administration Research Service 151B, Milwaukee, Wisconsin 53193

Alfred P. Fishman, M.D.

Cardiovascular-Pulmonary Division, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania 19104

David W. Golde, M.D.

Division of Hematology-Oncology, University of California, Los Angeles, School of Medicine, Los Angeles, California 90024

Siamon Gordon, M.D., Ph.D.

Experimental Pathology, Sir William Dunn School of Pathology, University of Oxford, Oxford, United Kingdom, OX1 3R3

Frank Griffin, Ph.D.

Division of Infectious Diseases, University of Alabama in Birmingham, Birmingham, Alabama 35294

John W. Hadden, M.D.

Sloan Kettering Memorial Institute, New York, New York 10028

Rejane M. Harvey, M.D.

College of Physicians and Surgeons, Columbia University; Pulmonary Division Presbyterian Hospital, New York, New York 10032

Peter Henson, Ph.D.

Department of Pediatrics, National Jewish Hospital and Research Center, Denver, Colorado 80206

Herbert Herscowitz, Ph.D.

Department of Microbiology, Georgetown University School of Medicine and Dentistry, Washington, D.C. 20007

Gary Hunninghake, M.D.

Pulmonary Branch, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20205

Harold L. Israel, M.D.

Thomas Jefferson University, Philadelphia, Pennsylvania 19107

Fred Kantor, M.D.

Yale University School of Medicine, New Haven, Connecticut 06510

Paul Katz, M.D.

Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20205

Stephen Katz, M.D., Ph.D.

Dermatology Branch, National Cancer Institute, Bethesda, Maryland 20205

Donald L. Kreutzer, Ph.D.

Department of Pathology, University of Connecticut Health Center, Farmington, Connecticut 06032

Peter E. Lipsky, M.D.

Department of Internal Medicine, University of Texas Health Science Center at Dallas, Dallas, Texas 75235

Adel Mahmoud, M.D., Ph.D.

Case Western Reserve University School of Medicine, Cleveland, Ohio 44106

Gardner Middlebrook, M.D.

University of Maryland School of Medicine, Baltimore, Maryland 21201

Vernon Moore, Ph.D.

Veterans Administration Hospital, Wood, Wisconsin 53193

Quentin Myrvik, Ph.D.

Department of Microbiology and Immunology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27103

Barbara Nichols

University of California, San Francisco, California 94143

Roy Patterson, M.D.

Northwestern University Medical School, Chicago, Illinois 60611

James E. Pennington, M.D.

Department of Medicine, Peter Bent Brigham Hospital, Boston, Massachusetts 02115

Paul G. Quie, M.D.

University of Minnesota Hospital, Minneapolis, Minnesota 55455

Herbert Y. Reynolds, M.D.

Pulmonary Section, Yale University School of Medicine, New Haven, Connecticut 06510

Milton D. Rossman, M.D.

Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania 19104

John E. Salvaggio, M.D.

Tulane University School of Medicine, New Orleans, Louisiana 70112

Samuel C. Silverstein, M.D.

Rockefeller University, New York, New York 10021

John K. Spitznagel, M.D.

Emory University School of Medicine, Atlanta, Georgia 30322

Peter Stastny, M.D.

University of Texas Southwestern Medical School, Dallas, Texas 75235

J. L. Turk

Department of Pathology, Royal College of Surgeons of England, Institute of Basic Medical Sciences, London WC2 A3PN, United Kingdom

Franz C. von Lichtenberg, M.D.

Harvard University Medical School, Boston, Massachusetts 02115

Byron H. Waksman, M.D.

National Multiple Sclerosis Society, New York, New York 10017

Kenneth Warren, M.D., D. T. M. & H.

Rockefeller Foundation, New York, New York 10036

Takeshi Yoshida, M.D.

University of Connecticut Health Center, Farmington, Connecticut 06032

National Institutes of Health Representatives

Claude Lenfant, M.D.

Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20205

Hugh B. Stamper, Jr., Ph.D.

Division of Lung Diseases, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20205

Richard M. Krause, M.D.

Director, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20205

Sheldon Cohen, M.D.

Director, Immunology, Allergic and Immunologic Diseases Program, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20205

Robert A. Goldstein, M.D., Ph.D.

Chief, Allergy and Clinical Immunology Branch, IAIDP, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20205

Contents

Preface 24 2MFMAHDIM JILATER GUA MORTDINALEIG JILLIGINDS.	ix
List of Participants	хi
The Granulomatous Inflammatory Response: An Overview Discussion Dov L. Boros	1
Annum Certin	
SECTION I: CELLULAR ASPECTS OF GRANULOMATOUS INFLAMMATION Chairman: Zanvil A. Cohn	
Cellular Composition of the Tuberculous (BCG) Granuloma: Local Differentiation and Turnover of Macrophages	
Discussion Arthur M. Dannenberg, Jr., Moritaka Suga, and José E. García-González	21
Development of Blood Monocytes and Alveolar Macrophages Discussion Charlette Gouwerky and David W. Golde	35
Charlotte Gauwerky and David W. Golde	
Macrophage Heterogeneity in BCG-Induced Granulomas	
Discussion	51

Philip W Davis R I Bonney 11 Human and RA Kuelli, in

此为试读,需要完整PDF请访问: www.ertongbook.com

Maria P. McGee, Quentin N. Myrvik, B.Y. Thompson, L.J. Eaton, and J. Ockers

Discussion

Mononuclear Phagocytes: Effectors of Cellular Immunity and Hosts for Facultative Intracellular Pathogens	
Discussion 6	7
Samuel C. Silverstein, Josef Michl, Carl F. Nathan, and Marcus A. Horwitz	'
EMSINO	
SECTION II: LYMPHOCYTE PRODUCTS AND OTHER SMALL	
MOLECULAR SUBSTANCES IN GRANULOMATOUS	
INFLAMMATION	
Chairman: Byron H. Waksman	
Role of Lymphokines in the Induction and Maintenance of the Granuloma	
Discussion 8	1
Takeshi Yoshida	1
Takoni Tonida	
Kinins, Complement Components and Prostaglandins and the Function of	
Mononuclear Phagocytes in Granulomatous Inflammation	
Discussion 9'	7
Philip W. Davies, R.J. Bonney, J.L. Humes, and F.A. Kuehl, Jr.	/
Timp W. Davies, R.J. Domiey, J.D. Humes, and T.A. Ruent, Jr.	
SECTION III: DESTRUCTION AND REPAIR MECHANISMS IN	
GRANULOMATOUS INFLAMMATION	
Chairman: Quentin N. Myrvik	
Macrophage Neutral Proteinases and Lysosomal Hydrolases-Role in Tissue	
Destruction	
Discussion 119)
Siamon Gordon	
Fibrosis in Granulomas	
Discussion 133	3
Michael A. Dunn	
in principal and the result of the company of the c	
SECTION IV: EXPERIMENTAL GRANULOMA MODELS Chairman: Kenneth S. Warren	
Infectious Granulomas as Tools for Studying Macrophage Maturation in Vivo	
Discussion 153	3
D.O. Adams	
Chindren Generally and Decided to state	
Experimental Hypersensitivity Pulmonary Granulomas	

Jordan N. Fink and Vernon L. Moore

Foreign Body Granulomas	
Discussion	181
William L. Epstein objective 25 total total state for a second by	
The product of major than 5 and 5 states of 5	
Diameter Color	
Annu anana i	uvilleasenogyk Discussion
SECTION V: MODULATION AND INTERVENTION IN	
GRANULOMATOUS PROCESSES	
Chairman: Stanley Cohen	
Genetic Control of Granulomatous Inflammation	Boissen if
	201
Vernon L. Moore, Denis J. Schrier, John L. Sternick, and Elizabeth M. Allen	201
Vernon E. Moore, Deins J. Schner, John E. Sternick, and Enzaged W. Anen	
Modulation of Granulomatous Hypersensitivity: Analysis by Adopt	tive Transfer
of Effector and Suppressor T Lymphocytes Involved in Granuloma	
Inflammation in Murine Schistosomiasis	ndex xebri
	210
Discussion Sam R. Wellhausen, Stephen W. Chensue, and Dov L. Boros	219
Sain R. Weilliausen, Stephen W. Chensue, and Dov L. Bolos	
Immunologic Desensitization and Anergy	
Discussion	237
Fred S. Kantor, P.K. Swamy, and H. Scovern	231
Pathophysiologic Consequences of Pharmacologic and Immunologic	ic Intervention
in Granuloma Formation in Vivo	
Discussion	253
Adel A.F. Mahmoud	
Comments on the Pharmacologic Intervention in Granulomatous P.	rocesses
Discussion	265
John W. Hadden	
	*
SECTION VI: CLINICAL ASPECTS OF GRANULOMATOUS DISEAS	ES
Chairman: Ronald Crystal	
Pulmonary Sarcoidosis: Pathogenesis and Therapy	
Discussion	275
Gary W. Hunninghake, Brendan A. Keogh, Bruce R. Line, James E. Gadek, Oich	
Kawanami, Victor Ferrans, and Ronald G. Crystal	
Mycobacterial Diseases	
Discussion	291

John L. Turk, P.Badenoch-Jones, and R.B. Narayanan

Discussion Richard P. Stankus, N.James Doll, and John E. Salvaggio	305
Hypersensitivity Pneumonitis Discussion Roy Patterson, C.Raymond Zeiss, and Paul A. Greenberger	
Clinical Management of Granulomatous Diseases Discussion Paul Katz and Anthony S. Fauci	329
Appendix: Discussion on Defining the Characteristic of the Epithelioid Cell	341
Allector and Supports of Lymphocytes Involved in Granulomanus unmation in Murity wire resonancies 219 Welle Lee Support Course, and Day to Bases	000
THE DESCRIPTION OF THE PROPERTY OF THE PROPERTY OF PRO	
memorated agolom could be an incommon to account the mology intervenium of auditors of account to the mology of the mology of the mology of the mology of the Manager of th	
Leiche die Phytomach gurinder auführen Grandfornstous Processes de sion Weißeiten	ng.
ZIZAZNIG ZANLENGLINANG PROTEZA JADERIO IN DUT	
nouncy Su-roldous: enthorgenesis and Partug cursion Whether glade, Braden A. Koop, Back K. Lac, Sales E. Sales, Orch. Summary, Victor Fernan, and Round G. Grysta.	

The Granulomatous Inflammatory Response: An Overview*

there ? (Metchrikoff, 1891). The stemment made at the dawn of impunctoric

directide all induce foreign body type granulomen, which are morphologically

stating: ... tubercule is composed of a collection of plugocytes mesodernic in criteria which may towards the spot where the bacilli are a sono down. I vod

Department of Immunology and Microbiology, Wayne State University, School of Medicine, Detroit, Michigan

Introduction has now more paving a mi cleab and viscosmol promodestical

The granuloma is a chronic inflammatory reaction to persistent irritants. Granulomatous tissue inflammations have been observed and described by pathologists more than a century ago. Though a great deal of progress has been made since in understanding this complex tissue reaction, basic problems regarding the etiology, clinical management and prevention of these tissue destructive disorders still remain to be solved. The detection and identification of a causative agent which induces the granulomatous condition often poses major difficulties. The dual, protective/destructive role of the granuloma can baffle clinicians who want to develop a uniform strategy of treatment.

Macrophages being the miller emponents of any granulomages response, their

The example of the "classic" granuloma evoked by tubercle bacilli encapsulates the pitfalls, misinterpretations and conceptual difficulties which researchers encountered in the past. Tubercle bacilli have been identified by Koch as the etiologic agents of tuberculosis, which cause granulomatous tissue inflammations and induce a state of hypersensitivity in the infected host. In subsequent decades, these two phenomena have been regarded as separate entities—granulomata being tissue responses to irritating, toxic mycobacterial lipids, whereas dermal reactions to soluble tuberculin represented the "allergic," delayed hypersensitive response of the previously exposed individual. Basically, this assumption was correct because experimentally fractionated lipids or waxes were shown to induce granulomata whereas soluble tuberculin products were ineffective.

Today we recognize that a variety of subcellular fractions of mycobacteria including fatty acids, waxes, cord factor, methanol extraction residue and muramyl

^{*}This work was supported by Grant AI-12913 from the National Institutes of Health.

dipeptide all induce foreign body type granulomata, which are morphologically very similar to lesions induced by intact bacilli. This paradox—the induction of a dual, irritative/immune-inflammatory response by a single infectious agent remained a source of confusion and error till today. The toxic, irritative properties of subcellular mycobacterial products and the florid tissue inflammation which they evoked diverted the attention from the protective role of the granuloma. It is a tribute to Metchnikoff, a pioneer of the discipline of cellular immunology, who alone recognized and defined the protective role of the infectious granuloma by stating: "... tubercule is composed of a collection of phagocytes mesodermic in origin which move towards the spot where the bacilli are situated and englobe them." (Metchnikoff, 1891). This statement made at the dawn of immunologic research is still valid today. During the past decade several attempts were made to classify granulomatous responses. Pathologists believed that the presence of epithelioid cells, (a transformed macrophage) and their organized arrangement within the lesions provides a reliable criterion for distinguishing hypersensitivity from foreign body lesions (Epstein, 1967). This is no more tenable because implanted plastic sheets (van der Rhee et al., 1979) and muramyl dipeptide (Tanaka and Emori, 1980) can also elicit the formation of epithelioid cells in normal animals. Macrophages being the major components of any granulomatous response, their multiplication, longevity and death in a given lesion was taken as a basis for classifying granulomata into active (high) or quiescent (low) turnover lesions. This functional approach unfortunately is applicable mostly to experimental systems and would lump together such widely divergent lesions as the mycobacterial tubercles and the silica granuloma (Spector, 1974). A third approach emphasizes the degree of activation of the macrophages within the granulomata as means of classification (Adams, 1976). The diverse manifestations of the activated macrophage (morphological, membranous, biochemical, microbicidal, secretory, cytotoxic) which can be selectively expressed in some but not other granulomatous lesions makes this classification tenuous. A fourth classification emphasizes the immune, cellmediated or nonimmune foreign body etiology of the lesions (Boros, 1978). This helped to conceptualize the role of the hypersensitivity granuloma within the overall picture of cell-mediated immunity. This classification can be applied to clinical practice only if the state of delayed hypersensitivity of the patient is verifiable by the appropriate reagents and tests.

de, eds. Barre and Chinical Aspects

Though as yet, no satisfactory classification has been devised, advances made in the fields of inflammation and cell-mediated immunity provided important conceptual frameworks for the understanding of the various granulomatous inflammatory responses. This brief review intends to summarize recent advances in the various facets of the chronic granulomatous tissue inflammatory responses.

Granuloma-Inducing Agents

It is generally held, that granuloma-inducing agents persist in the tissues because they are insoluble or poorly degradable (James and Neville, 1977; Adams, 1976; Boros, 1978). The agents may be of microscopic or macroscopic size ready to be ingested or surrounded by macrophages. The intra- or extracellular residence of the irritant may have important influence on the intensity and duration of the ensuing inflammatory response. An additional major factor is the physicochemical properties of the inciting agent. Nonantigenic, inanimate agents such as metal salts, sutures, plastic beads, sponges, etc., would induce a tissue inflammation more limited in intensity, duration and tissue-destructive effect than antigens which initiate a cellmediated immune reaction. A notable exception is the silica granuloma, which though generated by inanimate particles, develops an inflammation of high intensity and is accompanied by pronounced tissue destruction. This indicates that in foreign body type tissue responses the intrinsic cytotoxic properties of the inciting agent(s) may decide whether the lesion will develop into an active or quiescent inflammatory response. Soluble antigens may also induce granuloma formation in specifically sensitized animals provided they are adsorbed or bound to insoluble carriers (bentonite, latex, plastic bead particles) (Boros, 1978) or rendered insoluble by chemical cross-linking (McGee et al., 1978). Naturally forming granulomagenic aggregates are large immune complexes which at equivalence or in antibody excess are insoluble and once ingested by macrophages, may persist intracellularly for long periods of time (Spector and Heesom, 1969). Formation of immune complexes and their deposition in blood vessel walls was shown to cause a variety of clinical disorders known as granulomatous vasculitides, which may be highly destructive (Fauci, 1978). An additional "man-made" granulomatous condition of recent years is the spermatic granuloma which forms around extravasated spermatazoa in the spermatic cord, in a percentage of vasectomized individuals (Alexander and Schmidt, 1977). This type of lesion is of special note, because the condition is induced by ill-resorbed or digested "self" components. It is conceivable that some granulomatous disorders for which no etiologic agent(s) have been yet identified may well have an autoimmune basis. If it is indeed so, then the search for transmissible agents in certain granulomatous disorders of unknown etiology may prove to be futile. That the granulomatous condition is essentially induced and perpetuated by the inability of the macrophage to degrade the ingested material is excellently illustrated by the activity of muramyl dipeptide (MDP). This organic molecule is a water soluble component of the wax D moiety of the mycobacterial cell wall. The compound can substitute as an adjuvant for whole mycobacteria, activates macrophages and the reticuloendothelial system and induces foreign body type epithelioid cell-containing granulomas (Tanaka and Emori, 1980). The biologic activity of the compound derives from its unnatural L-alanyl-D-isoglutamine linkage, which unlike the L-L stereoisomer configuration cannot be broken down by macrophage enzymes (Chedid et al., 1978).

A new dimension added recently to the scope of granuloma research is the genetic background of the granuloma-bearing individual. Though individuals or experimental animals are exposed to the same granuloma-inducing agents, the inclination as to whether to develop a granulomatous response, the intensity of the inflammation and the speed of resolution may all be under genetic control. A tentative genetic influence has been established in humans with leprosy (Hastings, 1977), hypersensitivity pneumonitis (Flaherty et al., 1975), sarcoidosis (James and Neville

此为试读,需要完整PDF请访问: www.ertongbook.com