病毒淋巴细胞对疾病的相互影响意义

Virus-Lymphocyte Interactions:

Implications for Disease

Editor: Max R. Proffitt

Developments in Immunology Volume 7

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, PO Box 211
Amsterdam, The Netherlands

Library of Congress Cataloging in Publication Data

Conference on Immunodynamics, 2d, Cleveland, 1979.
Virus-lymphocyte interactions.
(Developments in immunology; v. 7 ISSN 0163-4921)

Bibliography: p.
Includes indexes.
1. Host-virus relationships—Congresses. 2. Lymphocytes—Congresses. 3. Cell transformation—Congresses. I. Proffitt, Max R. II. Title. III. Series. [DNLM: 1. Viruses—Immunology—Congresses. 2. Lymphocytes—Immunology—Congresses. W1 DE997WM v. 7/QW700 I31v 1979]
QR482.C66 1979 616.07'9 79-19984
ISBN 0-444-00348-7

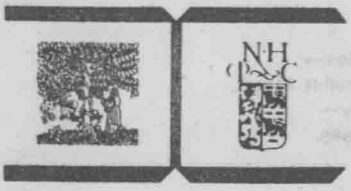
Manufactured in the United States of America

VIRUS-LYMPHOCYTE INTERACTIONS: Implications for Disease

Proceedings of The Second Immunodynamics Conference, The Cleveland Clinic, Cleveland, Ohio, USA, June 18–19, 1979

Editor:

MAX R. PROFFITT
Department of Immunology, Research Division, The Cleveland Clinic, Cleveland, Ohio, USA



ELSEVIER/NORTH-HOLLAND
NEW YORK • AMSTERDAM • OXFORD

DEVELOPMENTS IN IMMUNOLOGY

Volume 1—Genetic Control of Autoimmune Disease, edited by Noel R. Rose, Pierluigi E. Bigazzi and Noel L. Warner, 1978

Volume 2—Immunology of Bacterial Polysaccharides, edited by Jon A. Rudbach and Phillip Baker, 1979

Volume 3—B Lymphocytes in the Immune Response, edited by Max Cooper, Donald E. Mosier, Irwin Scher and Ellen S. Vitetta, 1979

Volume 4—Immunologic Tolerance and Macrophage Function, edited by Peter Baram, Jack R. Battisto and Carl W. Pierce, 1979

Volume 5—Aging and Immunity, edited by S.K. Singhal, N.R. Sinclair and C.R. Stiller, 1979

Volume 6—Immunobiology and Immunotherapy of Cancer, edited by William D. Terry and Yuichi Yamamura, 1979

Volume 7—Virus-Lymphocyte Interactions: Implications for Disease, edited by Max R. Proffitt, 1979

Preface

The hosts of this Second Immunodynamics Conference were the Department of Immunology of the Research Division of The Cleveland Clinic, The Cleveland Clinic Educational Foundation, The Cleveland Clinic Cancer Center and The Cleveland Clinic International Center for Specialty Studies.

"Virus-Lymphocyte Interactions: Implications for Disease" was chosen as the theme for this conference. This was done in recognition of the fact that the fields of immunology and virology are currently experiencing an information explosion that is unparalleled. In reality, the conference encompassed more than virus-lymphocyte interactions. Nevertheless, most of the work reviewed did focus on unique relationships between viruses and cells of the host immune defense system and the potential pathogenic consequences. If the reader finds some of the material provocative, that was intended, for the contributors were encouraged to be provocative and stimulatory. Hopefully some were.

Clearly, the papers collected herein in no way represent an exhaustive compendium of the subject. Representative experts with extensive knowledge of the interactions between various viruses and lymphoreticular cells were invited to contribute with the full realization that we could not have the participation of every colleague we would have wished. Consequently, highly interesting subject areas were left unexplored. This was simply dictated by conflicts with other conferences, the constraints of time and funds, and by our wish to keep the conference small enough to allow an informal, free interchange of ideas. To have enjoyed the participation and significant contributions of all those who have interest or expertise in the subject at hand would have required a conference spanning many days and resulting in several volumes of the collected papers. It is our hope that this conference will serve as a stimulus for future ones having the same theme. If so, it will have served its purpose. It is evident that we only scratched the surface.

Max R. Proffitt, Ph.D.

Acknowledgments

Organizing this Conference and bringing it to fruition required the aid, counsel and encouragement of numerous persons. Among these are Dr. Jack R. Battisto who originally conceived the idea for our Department of Immunology to sponsor a series of Immunodynamics Conferences based upon topical themes of current interest; Dr. F. Merlin Bumpus, Chairman of The Research Division; Drs. Bert C. Del Villano of our Department of Immunology and Anna C. Barker of Battelle Columbus Laboratories; Dr. Penn Skillern and Mr. Phil Gard of The Cleveland Clinic Educational Foundation; the members of the Board of Governors, the Cancer Center Committee and the Committee of the International Center for Specialty Studies at The Cleveland Clinic; the entire staff of the Department of Immunology for help in ways too numerous to mention; my wife Linda for her help in many ways and for her moral support; our secretary, Ms. Maudlyn Wright who was the fulcrum for this endeavor and without whom the Conference would not have been a success. Finally, I am particularly grateful to the following institutions and organizations who generously provided financial aid for the Conference:

Teckmar Company
Microbiological Associates
Merrell-National Laboratories
Cleveland-Cliffs Foundation
Burroughs Wellcome Company
Merck Sharp and Dohme Research Laboratories
Beckman Instruments, Inc.
The Baker Company
The Leukemia Society of America (Nothern Ohio Chapter)
American Cancer Society (Cuyahoga County Unit)
New England Nuclear
Battelle Memorial Institute
The Upjohn Company

Max R. Proffitt, Ph.D.

Participants

Dr. Anna Barker
Battelle, Columbus Laboratories
Columbus, OH

Dr. Samuel Baron
Dept. of Microbiology
University of Texas Medical Branch
Galveston, TX

Dr. William Biddison
National Cancer Institute
National Institutes of Health
Bethesda, MD

Dr. Jan Cerny
Harvard University School of
Public Health
Boston, MA

Dr. Jeffrey Collins
Dept. of Surgery
Duke University Medical Center
Durham, NC

Dr. Syamal Datta
Tufts Cancer Research Center
Tufts University School of Medicine
Boston, MA

Dr. Michael Doyle
Dept. of Immunopathology
Scripps Clinic and Research
Foundation
La Jolla, CA

Dr. Myron Essex
Dept. of Microbiology
Harvard University School of
Public Health
Boston, MA

Dr. Murray Gardner
Dept. of Pathology
University of Southern California
School of Medicine
Los Angeles, CA

Dr. Ronald Glaser
Dept. of Microbiology
College of Medicine
Ohio State University
Columbus, OH

Dr. Esther Hays
University of California
School of Medicine
Los Angeles, CA

Dr. Martin Hirsch
Massachusetts General Hospital &
Harvard Medical School
Boston, MA

Dr. John Huddlestone
Dept. of Immunopathology
Scripps Clinic and Research
Foundation
La Jolla, CA

Dr. Masahiro Imamura
Division of Cancer Biology and
Diagnosis
National Institutes of Health
Bethesda, MD

Dr. Holger Kirchner
Dept. of Virology
University of Heidelberg
Heidelberg, West Germany

Dr. Eva Klein
Dept. of Tumor Biology
Karolinska Institutet
Stockholm, Sweden

Dr. C.J. Lucas
Central Laboratory of the
Netherlands
Red Cross Blood Transfusion Service
Amsterdam, The Netherlands

Dr. Page Morahan
Dept. of Microbiology
Medical College of Virginia
Richmond, VA

Dr. Andrew Neighbour
Dept. of Immunology & Microbiology
Albert Einstein College of Medicine
Bronx, NY

Dr. Harry Openshaw
National Institute of Dental
Research
National Institutes of Health
Bethesda, MD

Dr. Max R. Proffitt
Dept. of Immunology
Cleveland Clinic Foundation
Cleveland, OH

Dr. Charles Rinaldo
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, PA

Dr. Gebhard Schumann
Friedrich Miescher-Institut
Basel, Switzerland

Dr. Vincent Zurawski
Massachusetts General Hospital and
Harvard Medical School
Boston, MA

Contents

Preface ix

Acknowledgments xi

Participants xiii

INTERFERON: ANTIVIRAL, IMMUNOREGULATORY AND ANTICELLULAR ACTIVITIES 1

Samuel Baron, J. Edwin Blalock, Ferdinando Dianzani, Robert Fleischmann, Jerzey Georgiades, Howard Johnson and John Stanton

MACROPHAGE-VIRUS INTERACTIONS 17

Page S. Morahan and Stephen S. Morse

PERSISTENCE OF VIRUS IN LYMPHOCYTES DURING INFECTION 37

Michael V. Doyle and Michael B. A. Oldstone

VIRUSES AS POTENTIAL INITIATORS OF AUTOIMMUNE PHENOMENA AND LYMPHOMA 53

Max R. Proffitt

GENETIC BASIS OF AUTOIMMUNE DISEASE - THE NEW ZEALAND MOUSE MODEL 71

Syamal K. Datta and Robert S. Schwartz

TUMOR ASSOCIATED ALTERATION IN HISTOCOMPATIBILITY ANTIGEN EXPRESSION 83

Masahiro Imamura and W. John Martin

VIRAL ANTIGENS AS TARGETS FOR LEUKEMIA IMMUNOTHERAPY 91

Jeffrey J. Collins, Ralph Snyderman, Eugene V. Genovesi and Fred Sanfilippo

IMMUNOLOGIC EFFECTS OF ENDOGENOUS RETROVIRUS-PRODUCING TUMORS 107

Anthony J. Dennis, Anna D. Barker, John M. Rice, Thomas J. Facklam, Victor S. Moore and Kristi L. Fowler

LYMPHOMAGENIC VIRUSES IN WILD MICE: DISCOVERY OF A NEW MuLV REPRESSOR GENE 123

Murray B. Gardner, Suraiya Rasheed, Bijay K. Pal and John D. Estes

INTERACTION OF MURINE LEUKEMIA VIRUSES (FRIEND AND MOLONEY), WITH LYMPHOCYTE SUBPOPULATIONS. STUDIES ON THE CELLULAR RESTRICTION OF VIRUS REPLICATION, TRANSFORMATION AND ACTIVATION OF ENDOGENOUS VIRUSES 139
Jan Cerny, Dale D. Isaak and Edward A. Hoover

INTERACTIONS OF THYMIC EPITHELIAL CELLS, LYMPHOCYTES AND MURINE LEUKEMIA VIRUSES 157
Esther F. Hays and Terry R. Beardsley

ENDOGENOUS C-TYPE VIRAL GENE PRODUCTS SEEN AS POSSIBLE "SELF STRUCTURES" INVOLVED IN IMMUNE CELL FUNCTION 167
Gebhard Schumann, Jonathan P. Stoye and Christoph Moroni

INTERACTIONS OF FELINE LEUKEMIA VIRUSES WITH LYMPHOID CELLS 179
J. Azocar and M. Essex

PRIMATE TYPE-C ONCOVIRUSES, HUMAN LEUKOCYTES, AND HUMAN DISEASE 191
Martin S. Hirsch, Ann P. Kelly and Paul H. Black

HLA RESTRICTION OF HUMAN INFLUENZA VIRUS-IMMUNE CYTOTOXIC T LYMPHOCYTES 207
William E. Biddison, Stephen Shaw, Susan M. Payne and Gene M. Shearer

PATHOLOGICAL CONSEQUENCES OF EPSTEIN-BARR VIRUS - LYMPHOCYTE INTERACTIONS 213
Eva Klein

THE ASSOCIATION OF THE EPSTEIN-BARR VIRUS WITH NASOPHARYNGEAL CARCINOMA: AN EXPERIMENTAL MODEL 229
Ronald Glaser

LYMPHOCYTES AND MEASLES VIRUS 243
Cornelis J. Lucas, Joachim M. D. Galama and José C. Ubels-Postma

MEASLES VIRUS INFECTION OF T LYMPHOCYTE SUBPOPULATIONS 251
John Huddlestone, Peter Lampert and Michael B. A. Oldstone

INTERACTIONS BETWEEN HERPES SIMPLEX VIRUS AND THE CELLS OF THE IMMUNE SYSTEM 259
H. Kirchner, H. H. Peter and J. Hilfenhaus

INTERACTIONS OF LYMPHOCYTES WITH CYTOMEGALOVIRUS 267
Charles R. Rinaldo, Jr., Myron J. Levin,
Walter P. Carney, Paul H. Black and
Martin S. Hirsch

VIRUSES, INTERFERONS, NATURAL KILLER CELLS, AND MULTIPLE SCLEROSIS 283
P. Andrew Neighbour, Stephen Udem, Grace Ju,
Nagahiro Minato and Barry R. Bloom

LATENCY AND REACTIVATION OF HERPES SIMPLEX VIRUS IN SENSORY GANGLIA OF MICE 301
Harry Openshaw, Alvaro Puga and
Abner Louis Notkins

Author Index 307

Subject Index 309

Published 1979 by Elsevier North Holland, Inc.
Proffitt, ed. Virus-Lymphocyte Interactions: Implications for Disease

INTERFERON: ANTIVIRAL, IMMUNOREGULATORY AND ANTICELLULAR ACTIVITIES

Samuel Baron, J. Edwin Blalock, Ferdinando Dianzani, Robert Fleischmann, Jerzey Georgiades, Howard Johnson, and John Stanton
University of Texas Medical Branch, Galveston, Texas 77550

INTRODUCTION

The intriguing phenomenon by which infection by one virus renders hosts and their cells highly resistant to other superinfecting viruses is termed interference. The most widely occurring cause of interference in nature is the production of a new protein, interferon, by the host cells themselves[1]. Interferon can react with normal, uninfected cells to render them resistant to most types of viruses.

The interferon system is an inducible genetic function of all somatic cells. It can initiate several pathways which in turn can affect not only viral replication, but also the immune response, cell growth, and other cell functions. The study of interferon offers opportunities to elucidate cellular genetic expression, cellular regulation, viral replication, immunoregulation and methods for control of disease. There are a number of reviews available--some of which are listed for additional information[2-13]. Original references for the quoted studies can be obtained from these and the other reviews which are included in the text.

Functions of the interferon system. Interferon as a defense against viral infection is clearly documented by a number of experimental and clinical observations. Generally: 1) in many viral infections a strong correlation has been established between interferon production and natural recovery; 2) inhibition of interferon production or action enhances severity of infection; and 3) treatment with interferon

protects animals against infection by a variety of viruses. In addition the interferon system is the earliest appearing of the known host defenses and it is operative within hours of infection. Clinical trials of interferon and its inducers during viral infections are sufficiently advanced and encouraging so that the first clinical application (e.g., rabies and perhaps serum hepatitis) is indicated.

Although interferon was first recognized as an extraordinarily potent antiviral agent, it was subsequently found to affect other vital cellular and body functions. For example, interferon may enhance phagocytosis, inhibit division of a variety of cells, affect the immune response, affect the expression of cell membrane antigens, and influence the body's response to ionizing radiation[14].

Production and action. Virtually all nucleated cells can produce interferon when the cells are infected by viruses. Figure 1 schematically illustrates the cellular events of interferon induction and action. As shown on the left side of the figure, during the early stages of viral infection some event (probably the presence of foreign viral nucleic acids) derepresses a cellular gene which contains the genetic information for the interferon protein which subsequently is glycosylated.

There are 3 molecularly distinct types of interferon (Table 1). The most common type (fibro-epithelial interferon) is produced by fibroblasts and epithelial cells during viral infection and it functions as a defense against viruses. Another type, leukocyte interferon, is produced by lymphoid cells when induced by certain viruses and foreign or tumor cells[15]. Its functions may be antiviral and cell regulatory.

A third type of interferon is produced by T lymphocytes following antigenic or mitogenic stimulation (immune interferon). Recent studies indicate that its mechanism of action is different from that of the 2 preceeding types of interferon[16]. The first antibody to mouse immune

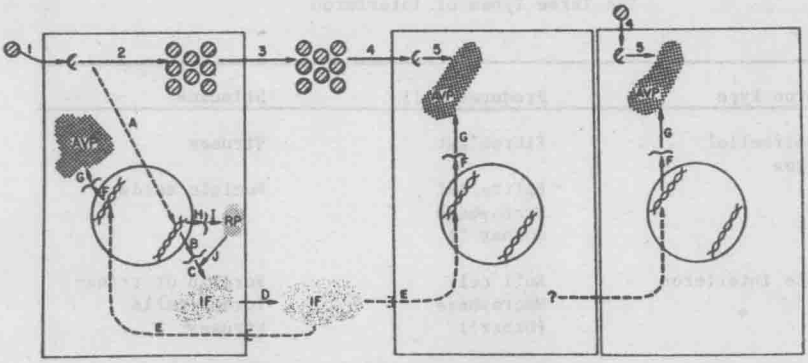


Fig. 1. Cellular events of the induction and action of interferon (IF). Virus comes in contact with the cell (1) and penetrates the cell membrane. The virus then releases its genetic material, and replication of the virus occurs (2). The new virus leaves the cell (3), enters the fluid around the first cell, and some of the replicated virus infects a second cell (4) where the release of the genetic material again takes place (5). During the early stages of infection of the first cell, some event (viral nucleic acid?) stimulates a gene in the DNA which contains the stored genetic information for interferon (A). This leads to the production of a messenger RNA for interferon, which leaves (B) the nucleus, and is translated by the cell's ribosomes (C), into the interferon protein.

Several events now occur more or less simultaneously. Some interferon is secreted by the first cell (D), enters the surrounding fluid, where it comes into contact with and stimulates the second cell (E). The second cell is thereby induced to produce a new messenger RNA (F) which is translated to a new protein(s) (G), the antiviral protein (AVP). This in turn modifies the cell's protein synthesizing machinery, such that cell mRNA is translated into protein, but viral RNA is poorly bound or translated or both. In the first cell processes E, F, and G may, in some instances, also operate to form AVP and thereby reduce the virus yield in the first cell. Shortly after interferon is synthesized in the first cell, another mRNA (H) is believed to be synthesized from the cell's DNA and is translated (I) into a regulatory protein (RP), (hypothesized). This regulatory protein combines with the mRNA for interferon, thereby preventing the further synthesis of more interferon (J). There is recent evidence that the antiviral state may be directly transferred between adjacent cells (from second to third cell at right) by the passage of an unknown (?) inducer of the antiviral protein.

Table 1

The Three Types of Interferon

Interferon Type	Producer Cell	Stimulus
Fibro-epithelial Interferon	Fibroblast	Viruses
	Epithelial Macrophage (Other ?)	Nucleic acids
Leukocyte interferon	Null cell Macrophage (Other?)	Foreign or transformed cells Viruses*
Immune interferon	T (&B?) lymphocyte	Mitogens Antigens

*It remains to be determined whether viruses induce leukocyte interferon directly or indirectly by altering cell membranes.

interferon has been produced in our laboratories recently[17]. Use of this antibody has shown that immune interferon is antigenically distinct from virus-induced and lipopolysaccharide (a B cell mitogen)-induced mouse interferons. Furthermore antigenically indistinguishable immune interferons were induced by various T lymphocyte mitogens in vitro and by antigen injected into sensitized mice[17]. Purification of lymphokine preparations containing immune interferon demonstrated that it could be separated from MIF and lymphotoxin[18,19].

Much slower activation of the antiviral state occurs in cells reacting with immune interferon than with the other 2 interferons[20]. The possibility that this slow action is due to an indirect action has been raised by studies using sequential inhibition of cellular RNA and protein syntheses[16]. The most probable interpretation of the findings is that immune interferon induces cells to synthesize an intermediary protein which then induces the antiviral proteins.

Potentiation of the antiviral action of other interferons may also be an important function of immune interferon. This is suggested by the recent finding that partially purified immune interferon can potentiate the antiviral action of virus-induced interferon by a factor of ten[21]. The functions of immune interferon may be antiviral and cell regulatory.

Production of interferon occurs de novo by cellular protein synthesis. An additional regulatory protein is also produced and it is thought to control interferon production. The 20,000-90,000 MW interferon protein, containing some associated carbohydrate, is actively secreted by the cell into the extracellular fluid. Viral-induced interferon is generally produced at about the same time that the viral progeny is released by the infected cell, thus being able to protect the neighboring cells from the spreading virus.

As shown in the middle of Figure 1 interferon does not directly inactivate virus. Instead, it prevents viral replication in surrounding cells by reacting with the cell membranes to derepress a gene(s) encoded for intracellular antiviral protein(s) which must be synthesized before inhibition of virus replication can occur. The mechanism of the viral inhibition by the antiviral protein is probably by an inhibition of synthesis of essential viral proteins but alternative, and additional, inhibitory mechanisms (transcription and viral release) are still being examined. The inhibition of viral protein synthesis may be caused by cellular changes affecting: a) initiation of protein synthesis, b) polypeptide elongation, and c) composition and configuration of viral mRNA. These changes are being studied and may be mediated directly or indirectly by interferon effects on induction of protein kinases, depletion of specific tRNAs, production of an oligonucleotide which activates an endonuclease, methylation of viral RNA, and a general alteration of cellular RNAs[22-28].