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primary immuno-deficiencies

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PRIMARY IMMUNODEFICIENCIES

Proceedings of the International Symposium on Primary Immunodeficiencies held in Abbaye de Royaumont (France), 18-20 July, 1980.
Sponsored by the Institut National de la Santé et de la Recherche Médicale.

Editors: M. SELIGMANN
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INSERM SYMPOSIUM No. 16

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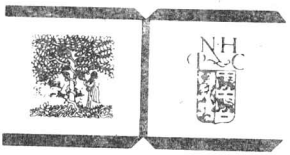

1980
ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS
AMSTERDAM · NEW YORK · OXFORD

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ISBN Series: 0 7204 0653 6
ISBN Volume: 0-444-80296-7

Publishers:
ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS
335 JAN VAN GALENSTRAAT, P.O. BOX 211
AMSTERDAM, THE NETHERLANDS

Sole distributors for the USA and Canada:
ELSEVIER NORTH HOLLAND INC.
52 VANDERBILT AVENUE,
NEW YORK, N.Y. 10017

Library of Congress Cataloging in Publication Data

International Symposium on Primary Immunodeficiences, Abbaye de Royaumont, France, 1980.
Primary immunodeficiences.

(INSERMS symposium ; no. 16)
Bibliography: p.
Includes index.
1. Immunological deficiency syndromes--Congresses. 2. Immunological deficiency syndromes--Animal models--Congresses. I. Séligmann, Maxime, 1927- II. Hitzig, Walter H. III. Institut national de la santé et de la recherche médicale. IV. Title. V. Series: Institut national de la santé et de la recherche medicale. INSERMS symposium ; no. 16.
RC606.I59 1980 616.07'9 80-25785
ISBN 0-444-80296-7

Printed in The Netherlands

FOREWORD

Human primary immunodeficiencies have been, for the past 25 years, one of the most productive areas of of research in clinical immunology. Detailed sutdies of these patients have provided new concepts and important insights into our understanding of the immune system and, conversely, advances in basic immunology have been rapidly applied to clinical investigation. These syndromes represent real experiments of nature and constitute a field par excellence where clinical and basic immunology are closely linked and mutually beneficial.

Two international symposia on primary immunodeficiencies have been prevously held in the United States thanks to the vigorous impulse of R.A. Good and under the auspices of the National Foundation. Together with the attempts at classification of these diseases undertaken by a group of experts appointed by WHO, these meetings have provided valuable opportunities to expand our knowledge. During the recent years, new immunological and clinical findings have accumulated and the biochemical study of the enzymatic defects responsible for some immunodeficiency syndromes has opened a new and important field of investigation. It seemed therefore appropriate to hold a new symposium and to gather basic and clinical immunologists, biochemists and pediatricians devoted to the study of immunodeficiencies. We thought that this meeting should take place in Europe, and we are grateful to INSERM for sponsoring it.

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ONTOGENY AND DIFFERENTIATION OF HUMAN LYMPHOID CELLS IN THE NORMAL AND IN IMMUNODEFICIENT PATIENTS

Primary Immunodeficiencies
INSERM Symposium No. 16
Editors: M. Seligmann and W.H. Hitzig
© 1980 Elsevier/North-Holland Biomedical Press

IgM PRODUCTION: NORMAL DEVELOPMENT AND SELECTIVE DEFICIENCY

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INTRODUCTION

Immunoglobulin molecules possess several characteristics that distinguish them from the vast array of cellular proteins. By virtue of their insertion into the cell membrane of B lymphocytes, they behave as receptor molecules that can relay messages to the internal milieu of a cell. When actively secreted from a plasma cell, they can combine with specific antigens and enact effector functions that neutralize both foreign and self reactivity. Immunoglobulins can also bind passively to immune and non-immune cells via their Fc region and alter the function of such cells. They can bind complement components and amplify the destruction of foreign antigens or cells as well as initiate disease processes in the host organism.

The diversity of immunoglobulin molecules remains one of the most intriguing problems in immunology. It is now well established that most information encoding immunoglobulin chains is present in the genome of germ cells[1-3]. In such cells, genes coding for the variable and constant regions of both heavy and light chains are well separated on different chromosomes. During development, specific recombinatorial events occur that transpose a single V_L or V_H gene into juxtaposition with a specific J(joining) gene (Figure 1). The V-J complexes are then approximated with C_L or C_H genes, forming transcriptional units for complete light and heavy chains, respectively[4,5]. The same V_H J_H genes can then integrate with different constant region genes at various stages of B cell development by a "switch recombination" mechanism[6], thereby providing a mechanism for immunoglobulin class switches.

IgM plays a pivotal role during B cell development and in specific immune responses. It is the first isotype to appear during the ontogeny of B cells[7] and to be synthesized and secreted in large quantities following primary immunization. B cells possessing IgM appear to be the direct progenitors of B lymphocytes producing all other antibody classes[8]. Phylogenetically, IgM may be the

only antibody detectable in primitive species of animals. IgM production persists to a greater extent than synthesis of other isotypes in most immunodeficiency disorders, and deficiency of IgM is usually associated with severe bacterial infections. In this article, we wish to examine briefly the development, structure and function of IgM and its relationship to other immunoglobulin classes. We will also present immunological information on a patient with severe IgM deficiency and speculate on the relationship of this defect with immunodeficiency disorders affecting other immunoglobulin isotypes.

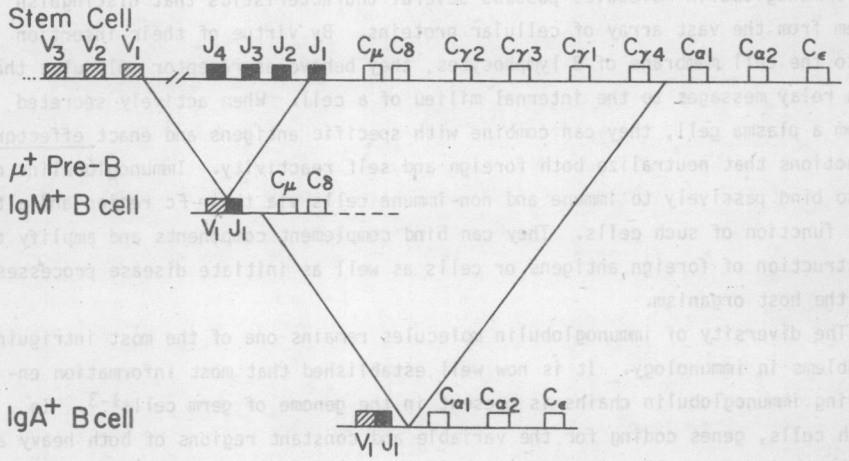

Fig. 1. Sequence of immunoglobulin gene rearrangements in the development of B cell clone. See text for discussion.

DEVELOPMENT OF IgM

Mu chains can be detected prior to all other heavy chain classes during the ontogeny of every mammal examined thus far. These molecules, devoid of light chains, are initially found only in the cytoplasm of cells designated pre-B cells[9,10]. Pre-B cells are sequentially generated in fetal liver and bone marrow, and lack surface μ receptors by functional, immunochemical and immunofluorescent criteria[10,11]. Free μ chains can be released by pre-B cells from both mice and humans, and may be able to modulate events during the early development of the immune system[10].

The absence of functional antibody receptors on pre-B cells may provide an important means for clonal diversification during B cell development. Such cells would not be subject to positive or negative regulation by environmental antigens and pre-B cells expressing a particular V_μ gene could then be rapidly and safely expanded. In these cells, combination of μ chains with randomly selected light chains possessing specific V_L regions would create a diverse array of B lymphocytes derived from a single pre-B cell progenitor.

Following V_L-C_L joining, light chain synthesis is initiated and intact 180,000 dalton IgM molecules soon appear on the surface of B cells. These immature IgM^+ B lymphocytes are the direct progenitors of IgD, IgG, IgA and IgE bearing B cells. Initial evidence for this relationship was derived from ontogenetic analysis of chickens, mice, and humans[12-14] and studies of the suppressive effects of anti-μ antibodies[8]. When neonatal mice or chickens are repeatedly injected with anti-μ antibodies, the development of surface Ig^+ B lymphocytes of all isotypes is inhibited[15,16]. Cessation of anti-μ treatment permits the generation of normal numbers of sIg^+ B cells.

Early in their development, B lymphocytes possessing IgD, IgG or IgA on their surface may also express IgM[13,14]. At a specific point during differentiation, three isotypes may be displayed simultaneously on the surface of a B cell[13], e.g., IgM.IgD.IgG or IgM.IgD.IgA. The persistance of IgM and IgD on such immature cells along with IgG or IgA suggest that long-lived mRNA for μ and δ may exist during certain stages of B cell development.

STRUCTURE OF IgM

Three forms of IgM can be demonstrated during B cell development. Initally pre-B cells synthesize only free μ chains without light chains. B lymphocytes express 180,000 dalton IgM on their surface with two μ and two light chains. Rapidly secreting plasma cells produce 900,000 dalton pentameric antibodies containing 5 IgM monomers that are linked through disulfide bonds by J(joining) chains.

The μ chains synthesized by each of these cells display characteristic structural distinctions. Pre-B μ chains appear smaller than μ chains secreted by plasma cells (65,000 versus 70,000 daltons) and may be relatively poor in carbohydrate[10]. Mu chains found on the surface of B lymphocytes are larger than secreted μ chains and contain a 30-40 amino acid tail enriched in hydrophobic amino acids and lacking carbohydrate side chains[17-19]. Secreted μ chains have a shorter, relatively hydrophilic tail with carbohydrate side chains.

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