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AGING AND IMMUNITY

Proceedings of an International Symposium, London, Ontario, Canada, May 10 and 11, 1979

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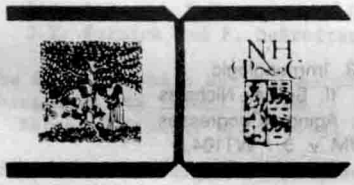

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Preface

Aging cells, organs and organisms undergo a number of changes in metabolic function which tend to decrease their overall capacities compared to those found earlier in their life spans. Many of these changes are considered to be the hallmarks of old age; however, they may be the result of damaging, but correctable pathologic processes commonly associated, but not a part of, the aging process. The separation of events constituting the aging process from correlated changes which are not really part of the aging process requires the analysis of appropriate fundamental models. Areas such as Immunology, Cell Biology, Virology and Pathology contribute to our knowledge concerning the constitutents of the aging process. Many of the contributions in this particular proceedings involve a study of the immune system, a model suitable to the investigation of aging because its components have been defined and because these components are subject to changes during aging. Also, the role which the immune system plays in either conferring resistance or increasing susceptibility to damaging processes during aging represents an important factor determining the overall response of cells, organs or individuals to the passage of time.

The aging process may be interpreted at many levels of scientific thought. These range from the biochemical and physiologic on one hand to the sociological and religious on the other. This book will deal with the biomedical end of this broad spectrum.

In order to contribute to basic knowledge concerning the aging process, an International Symposium on Aging and Immunity was held under the auspices of the University of Western Ontario at London, Ontario, Canada, May 11th and 12th, 1979. The results of that symposium, both the submitted papers as well as transcripts of the informal discussions which occurred after the presentation of papers, are presented in this publication. Contributions came from individuals representing a wide variety of basic and clinical biomedical research. We hope that the results of these two days of deliberations will help others interested in this broad and complex field to formulate ideas and areas in which to pursue their own research.

We wish to extend our great appreciation to all the many investigators who have contributed both their energies and their intellects in making this conference and the publication of these proceedings a worthwhile effort. None of this effort could have been possible without the generous support of a number of organizations. We also wish to extend our appreciation to the Elsevier North Holland Publishing Company for their patience and help in producing a prompt and accurate publication of these proceedings.

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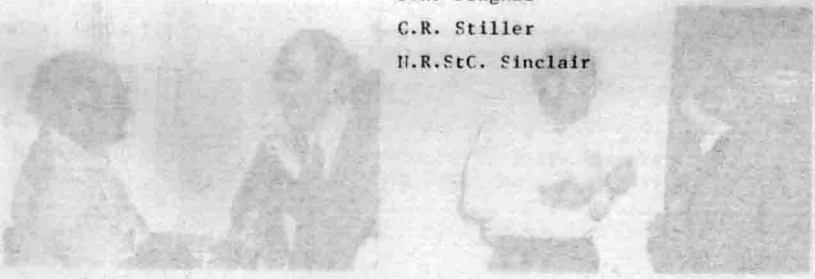

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SESSION 1

Regulation and Genetics of Immune Response

Chairman: T.L. Delovitch
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SESSION I

Regulation and Genetics of Immune Responses

Chairman: T.L. Delovitch
University of Toronto,
Toronto, Ontario

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AUTO-ANTI-IDIOTYPIC IMMUNITY: APPLICATIONS AND PROBLEMS

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INTRODUCTION

The immune system is composed of a variety of celltypes and humoral agents which interact in a positive or negative manner when reacting towards foreign immunogenic substances. Our understanding how the immune response does occur has been greatly helped by the use of inbred strains of animals, the use of serological markers to define subsets of cells and a rapid development of technology allowing the assessment of function of these cells. Several pieces of important information are still lacking, however, before we can safely state that we even know of all the cells involved in the generation of an immune reaction. Our ignorance is even more deeper when it comes to the actual functions of the participating cells in any detail. It is thus obvious that attempts to in a predictive manner manipulate such a complex and largely obscure system will suffer from great inherent difficulties. This manipulation is still a matter of great theoretical and practical interest and we will here discuss approaches attempting to achieve specific decreases or increases of immune reactivity in adult individuals using auto-anti-idiotypic immune reactions.

It has been known since several years that we are not tolerant towards our own antibody molecules, in particular to the antigenic or idiotypic determinants being present on the variable regions of the immunoglobulin molecules[1]. Reactions involving idiotypic and anti-idiotypic determinants have been considered to constitute a maybe major driving force in the actual control of the immune response, where administrations of antigen may only function to perturb an existing equilibrium in a network of idiotypes and anti-idiotypes[2]. Results which support such a concept in a comparatively direct manner have been published[3,4,5]. Likewise, it has gradually become clear over the years that T lymphocytes play a dominating role in the actual control of most specific immune responses. It is thus obvious that before auto-anti-idiotypic approaches are made to control an immune response one must first scrutinize the actual knowledge of idiotypes on immunocompetent T cells.

Idiotypes on T cells

It is by now well established that immunocompetent T cells express their immunocompetence via a display of antigen-specific, idiotypic receptors[6,7]. Such receptors represent the actual product of the cells as shown via internal labelling procedures in combination with specific fractionation procedures to obtain morphologically and functionally distinct subsets of lymphocytes[8]. Idiotypic markers have thus been found on T lymphocytes involved in the initiation of MLC or Graft-versus-Host reactions[9], on helper T cells as well as their suppressor counterparts[7,10,11,12] and on cytolytic T cells at the effector cell stage[13]. Likewise, it has been possible to demonstrate the presence of idiotypic markers of "B cell type" on helper or suppressor T cell factors[14,15]. It would thus seem safe to conclude that antigen-specific receptors present on competent T lymphocytes or their corresponding specific factors are all expressing idiotypic markers.

Idiotypi is a feature of antigenic markers present on the variable region of immunoglobulin molecules and were initially thought to represent unique features of that particular immunoglobulin molecule[16]. Though this has since been shown to be a too restricted definition idiotypic markers do still serve as useful antigenic determinants in the analysis of the genetics of immunoglobulins. There exist in a simplified concept three kinds of idiotypic groups on a classical immunoglobulin molecule: Those requiring the participation of both heavy and light chain variable regions, those determined by the heavy variable region only and those coded for by the variable region of the light chain. Whereas it is clear from the definition that B cells display all three kind of idiotypes within their possible spectrum of idiotopes it has so far only been possible to define V_H-coded idiotypic determinants on the T cell receptors[8,17]. This has been ascertain in several ways: a) By inheritance of T cell carried idiotypes where in no case detectable contribution of light chain immunoglobulin genes were observed. b) By actual immunization procedures using either heavy chain-light chain Ig hybrid molecules as inducers of anti-idiotypic antisera and where only animals immunized with the "correct" heavy but not light chains produced anti-T cell reactive anti-idiotypic sera. Likewise, immunization with purified heavy chains only but not light chains could be shown to induce auto-anti-idiotypic antibodies reactive with the individuals own T cells with the relevant specificity. c) By in vitro inhibition experiments using as target the idiotypic T cells and where binding of the anti-idiotypic antibodies could be blocked by intact idiotypic IgG antibody molecules and with heavy but not light chains produced from such IgG molecules.

The above data in combination with the preliminary findings as to the biochemistry of the T cell receptor polypeptide composition from several groups [18, 19, 20] have suggested that there may indeed be no conventional light chains of Ig type in these receptors. It is in fact not clear if the T cell receptor molecules necessarily is composed of more than one chain of polypeptides at least in the MLC and CTL reactive T cell compartments. Here, it has been found in the rat [8,18] that a polypeptide chain slightly larger than 70.000 daltons may constitute the sole part of the receptor, either in a single or more likely dimeric stage. However, whereas these receptors so far have failed to express a content of additional types of polypeptide chains results with antigen-specific "factors" of T cell origin have indicated the presence of additional chains, most likely carrying serological markers of MHC type[19,21]. Limited data available from the "factor" work does suggest, however, that the larger chain is the antigen-specific chain and there is no evidence as yet to suggest that this additional, hypothetical "MHC" chain is necessary for the creation of antigen-binding specificity of the T cell receptors[21]. It is also possible to consider that the occurrance of an additional, self-MHC chain together with the idiotypic chain may occur for reasons of partial self-reactivity of that chain[22]. Only additional data from cloned immunocompetent T cells or their corresponding T cell hybridomas will probably yield enough clearcut results to finally solve this question. It is, however, already clear that IgT chains do exist, drawing from the same V_H-gene pool as their corresponding B cell Ig partners. Whether there exist specific IgT molecules for T cells with varying functions is entirely possible but no size differences in chains have been noted in biochemical studies of T cell chains from mixtures of MLC reactive and killer T cells[17,18].

Of practical importance in regulatory reasonings are the findings that it is possible to selectively kill idiotype-positive T cells with anti-idiotypic antibodies and complement in vitro [8]. Likewise, anti-idiotype reactive T cells with lytic ability can be shown to occur demonstrating the ability of both humoral and cellular anti-idiotypic immunity to be able to function in an eliminatory manner towards idiotypic lymphocytes.

Immune regulation via controlled auto-anti-idiotypic reactions

Several systems exist where s.c. dominating clones of antibodies constitute a major part of the antibody response against a particular antigenic determinant. In these situations it has also been possible to achieve a significant depletion of immune responsiveness using anti-idiotypic antibodies[5,23,24,25] sometimes i combination with antigen resulting in long-lived immune unresponsiveness caused

mainly by suppressor T cells. It is thus possible to induce auto-anti-idiotypic suppressor cells in adult individuals via the administration of anti-idiotypic antibodies where such suppressor T cells may then function for prolonged periods of times in vivo. In most of these systems there will, however, normally with time be a development of clones of B cells lacking the relevant idiotype but with antigen-binding specificity. This would then at a later stage allow an immune response of normal vigour towards the same antigenic determinant(s) but now using antibodies with different idiotypic determinants. It is clear that such sneaking through with time of at least B cells with "new" idiotypes may constitute a major problem when attempting auto-immune regulation using anti-idiotypic immune reactions. Likewise, highly heterogenous immune responses, where many diverse idiotypes are present on the respective responding B and T cells would also be correspondingly more difficult to regulate using anti-idiotypic measures.

We will here mostly deal with studies on immune reactions involving T cells with specificity for allo-MHC antigens. It is possible that such antigens constitute unique target structures for T lymphocytes in the sense that normal helper and killer T cells seem to function in vivo with specific reactivity for self-MHC structures being seen in conjunction with foreign material[26,27]. Our data would, however, indicate that allo-MHC reactive T cells contain self-MHC reactive T cells[22], a finding which has also been suggested by earlier workers in this field[28,29,30]. Thus, it is likely that besides providing information of potential relevance for transplantation immunologists studies on the regulation of such allo-MHC reactive T cells should also tell about the basic functions of normal T cells against "conventional" antigens.

In the systems involving anti-allo-MHC antigens one typical feature is the very high frequency of specific, participating normal responder T cells[31,32,33], amounting to several percent of the total population. When attempting to cause auto-anti-idiotypic immunity against such allo-MHC reactive T cells we were thus initially concerned about the possibility that possible auto-anti-idiotypic T cells may have been eliminated in vivo because of the high concentration of these idiotypes in the normal animals. However, using either idiotype-positive T cell receptor molecules or IgG allo-MHC antibodies in either intact form or as isolated heavy chains as auto-immunogen it was found possible both in rat and mice to induce detectable auto-anti-idiotypic immunity[34,35]. The success in these experiments is, however, irregular and can not be produced in a highly predictable manner indicating our ignorance as to several of the parameters involved in the induction of such auto-anti-idiotypic responses. Still, the