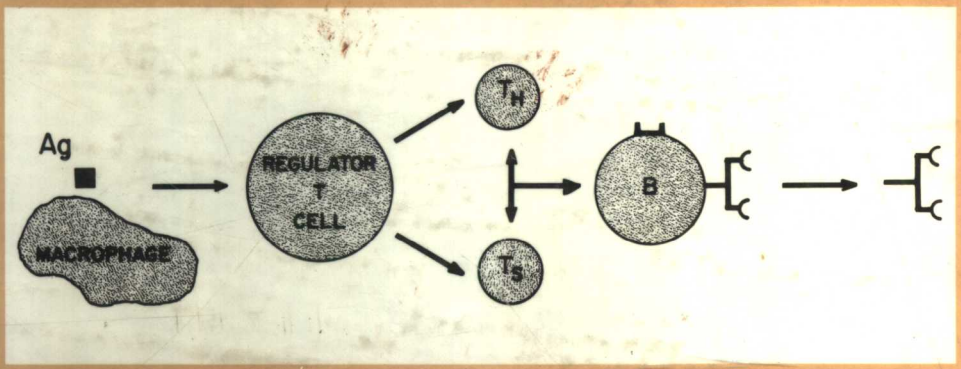
suppressor cells in human disease

immunology series volume 14



edited by

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SUPPRESSOR CELLS IN HUMAN DISEASE

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MARCEL DEKKER, INC. New York and Basel

Library of Congress Cataloging in Publication Data

Main entry under title:

Suppressor cells in human disease.

(Immunology series ; v. 14)
Includes index.
1. Suppressor cells. 2. Immune response--Regulation.
3. Immunologic diseases. I. Goodwin, James S., [date].
II. Series. [DNLM: 1. Suppressor cells--Immunology.
2. Suppressor cells--Physiology. W1 IM53K v.14 / QW 568
S9594]
QR185.8.S96S963 616.07'9 81-5565
ISBN 0-8247-1290-0 AACR2

MARCEL DEKKER, INC.

270 Madison Avenue, New York, New York 10016

Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

PREFACE

The purpose of this volume is to bring together information on the role of suppressor cells in human disease states. To this end I have invited several investigators who are actively working in this field to review the state of current knowledge in specific areas regarding suppressor cells. While the major interest of this book is in immunoregulation in humans, I have included some chapters dealing almost entirely with work in experimental animals. This was necessary because, as will quickly become apparent to the reader, understanding of immunoregulation in animals has almost always preceded similar understanding in humans. To put it another way, today's experimental findings in mice point to many of tomorrow's experiments in humans.

The first chapter of the volume is a general introduction to the concept of suppressor cells, written by the editor. In this chapter I briefly trace the history of the development of the concept of suppressor cells in immunoregulation. In addition I summarize experimental evidence implicating suppressor cells in normal immunoregulation. This chapter was written with the goal of providing an introduction to those who have had minimal exposure to the literature on suppressor cells.

The next several chapters review some of the basic mechanisms of suppressor cell generation and action in experimental animals and man. Dr. Burchiel and Dr. Melmon review the literature on the role of cyclic AMP in immunoregulation and present some recent data from their laboratories on this subject. Dr. Raff and Dr.

Stobo discuss the evidence showing both a positive and negative immunoregulatory role for macrophages. Dr. Webb and I then review the evidence implicating prostaglandin as an immunoregulatory agent and present recent findings on the prostaglandin-producing suppressor cell.

The remaining chapters of the book deal with the role of suppressor cells in the altered immunity associated with specific diseases. Dr. Engleman summarizes the evidence from his laboratory on genetically-restricted suppressor cells in man and then presents new data on the altered activity of such suppressor cells in Hodgkin's disease. Dr. Talal introduces the concept of disordered suppression in the pathogenesis of autoimmune disease. He also summarizes his recent exciting findings on the potential for sex hormone therapy in these conditions. Dr. Zoschke and Dr. Messner then consider the role of suppressor cells in the "autoimmune" rheumatologic diseases in humans: systemic lupus erythematosus, juvenile and adult rheumatoid arthritis, and Felty's syndrome.

The first evidence implicating abnormal suppressor cell function in a human disease was presented by Waldmann and his associates at the National Institutes of Health, who found increased suppressor T cell function in the peripheral blood of some subjects with adult combined immunodeficiency. Dr. Froelich discusses this work and comprehensively reviews more recent work on suppressor cells in this condition. Dr. Rocklin then presents recent evidence from his laboratory on the generation of antigen specific suppressor cells in two human conditions: patients with schistosomiasis and subjects undergoing allergy desensitization.

One of the fascinating unresolved problems for immunology has been the question of how the fetus, with a full complement of paternal antigens, escapes immunologic rejection by the mother. Dr. Goldberg and Dr. Frikke review the myriad explanations advanced to account for that phenomenon, including the findings of increased suppressor activity by fetal lymphocytes.

The final chapters deal with immunoregulation in tumor bearing hosts. Dr. Giorgi and Dr. Warner comprehensively review the data showing that experimental tumors are directly immunosuppressive. Dr. Bankhurst then discusses the evidence showing that tumors can induce increased suppressor cell activity in the host.

It is perhaps evident from the above descriptions that there might exist some duplication of material among the various chapters, particularly among the introductory material to the chapters. The editor has tried to avoid this whenever possible and still ensure that each chapter can be read independently from the others.

James S. Goodwin

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SUPPRESSOR CELLS: AN INTRODUCTION

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I. CONCEPT OF SUPPRESSOR CELLS

The concept of suppressor cells is simple but relatively recent. A suppressor cell is a leukocyte that functions to inhibit or turn off an immune response. The suppressor cell is still a concept and not a reality. Gershon wrote in 1975 that "the term [suppressor cell] still remains operational in that we do not know whether there is a T cell which is programmed during differentiation to act as an obligatory suppressor cell after triggering with antigen" [1]. Despite the plethora of recent work in the area, the statement is still valid today.

The concept of suppressor cells allows a fuller understanding of immunologic regulation. A lack of a humoral or cellular immune

response (e.g., tolerance or anergy) can now be seen as the result of an active process. In this chapter I will briefly review the various mechanisms that are thought to contribute to immunologic unresponsiveness. I will then describe some of the classic experiments in experimental animals performed in the early 1970's that demonstrated the existence of active suppression of the immune response. This will be followed by a summary of the current concepts of the role of suppressor cells in normal and ab normal immunologic regulation.

II. MECHANISMS OF IMMUNOLOGIC UNRESPONSIVENESS

The original concept of the immune system was that it evolved to protect the host from invasion by foreign organisms. Inherent to this conception was the idea that the immune system could distinguish self from non-self. This was thought to be genetically determined; that is, the immune system is genetically programmed to be tolerant to self antigens. These early concepts were challenged by work starting in the 1940s which demonstrated that tolerance could be acquired. First, it was shown that dizygotic cattle twins that share the same placenta accept skin grafts from one another after birth. Similarly, mice that had been inoculated in utero with cells from an unrelated donor are able to accept skin grafts from that donor. Further experiments in several species showed that it was relatively easy to cause tolerance to a whole variety of antigens by exposing animals to the antigens during their fetal or neonatal development [2]. Thus the concept of acquired immunologic tolerance arrived. It has been shown that tolerance is specific. For example, rabbits made tolerant to bovine serum albumin during fetal life still react to albumin from other species. Tolerance to specific antigens can also be induced in adults, though the antigenic dose required is generally much higher than is needed for fetal or neonatal animals.

No one mechanism yet proposed can explain all the experimental findings of immunologic tolerance. Two general classes of

tolerance can be distinguished. Transplantation tolerance involves the tolerance to or lack of rejection of a graft of foreign allogeneic or xenogeneic tissue. Tolerance in humoral immunity involves a lack of an antibody response after exposure to an antigen. Hasket et al. divided possible mechanisms of transplantation tolerance into active and passive, positive and negative processes [3]. The earliest explanations for acquired tolerance were passive, such as clonal deletion, which proposed that lymphocyte clones with specificity for the tolerized antigen are deleted; that is, the host no longer has cells capable of responding to the antigen. Another passive mechanism involves the reversible inactivation of immunocompetent lymphocytes by antigen, antibody, or antigen-antibody complexes. There is experimental evidence for both clonal deletion and the reversible "flooding" of the immune response with excess antigen or antibody. For example, immunologic responsiveness can be sometimes restored in tolerant animals by the transfer of lymphocytes from an immunocompetent animal, suggesting that the tolerance was "passive," due to a lack of immunocompetent cells in the tolerant animal.

Active mechanisms of tolerance include immunologic enhancement, whereby antibodies directed against antigenic determinants on a foreign graft delay rejection of the graft [4]. So called "blocking factors" in the serum of tolerant animals have also been described [5]. These factors can inhibit host lymphocyte cytotoxicity against the graft and may be important in prevention of tumor rejection. A third active mechanism of tolerance is the subject of this book, namely suppressor cells.

III. EVIDENCE FOR SUPPRESSOR CELLS IN EXPERIMENTAL ANIMALS

While there were several experiments performed in the 1960s that in retrospect can be viewed as providing evidence for suppressor cells, it was not until the work of Gershon and Kondo in the early 1970s that the concept of a suppressor cell began to evolve. These investigators were studying the induction of immu-

nological tolerance to sheep red blood cells (sRBC) in mice. Mice given very large amounts of sRBC (> 10^{10} cells) will not demonstrate an antibody response when rechallenged with doses of sRBC that are immunogenic in untreated mice. Gershon and Kondo studied lethally irradiated mice that were reconstituted with bone marrow cells with or without thymus cells. They found that the presence of thymus cells was necessary for the induction of tolerance [6]. They also found that the adoptive transfer of spleen cells from a mouse tolerant to sRBC specifically suppressed the antibody response to sRBC, but not to other antigens, in the recipient mouse [7]. They termed this phenomenon "infectious immunological tolerance" because they were able to transfer the tolerant state by transferring lymphocytes. It soon became clear that in this model of adoptive transfer of tolerance, the T cell was the lymphocyte responsible for suppression (Refs. 8,9, and see below).

IV. ROLE OF SUPPRESSOR CELLS IN NORMAL IMMUNOLOGIC REGULATION

A. Tolerance

Subsequent to the original experiments of Gershon, suppressor T cells have been implicated in many different models of tolerance of both the humoral and cellular immune response (reviewed in Refs. 10,11). An example of suppressor cell function in cellular immune reactions is as follows. Specific tolerance in mice to 1-fluoro-2,4-dinitrobenzene (DNFB) can be induced by intravenous injection of DNB-SO_3Na. Claman and his coworkers showed that this tolerance could be transferred to unsensitized, syngeneic recipients by the intravenous injection of 10^8 lymph node or spleen cells from tolerant mice [12]. This transfer of tolerance was enhanced when T cells were enriched from the lymph node or spleen cell preparations prior to transfer, and tolerance was abolished if the cell preparations were treated with antitheta antisera plus complement prior to transfer.

Tolerance of the humoral immune system to some antigens can be induced by the administration of either suboptimal or supra-

optimal amounts of antigen, termed low zone and high zone tolerance, respectively. Baker et al. showed that antigen-specific low zone tolerance to type III pneumococcal polysaccharide could not be induced in nude mice, and could be abrogated in normal mice by treatment with antithymocyte serum, suggesting that T cells are required for the induction and maintenance of the tolerant state [13]. Perhaps more definite evidence for a role for suppressor T cells in low zone tolerance was provided by Weber and Kolsch who showed that antigen specific low zone tolerance could be transferred into normal syngeneic mice by theta positive cells [14]. Other workers have implicated suppressor T cells in the induction of high zone tolerance [15,16].

Tolerance to a wide variety of T cell dependent [7] and T cell independent [17] antigens involves suppressor cells. While the studies cited above, as well as many others referenced in more detailed reviews [3,9-11], make it clear that suppressor T cells are important in the induction and maintenance of many types of immunologic tolerance, it is also clear that suppressor T cells are not the only mechanism whereby tolerance can be produced. In some experimental models it is possible to produce specific unresponsiveness of B cells without the presence of T cells [1,18]. The other "active" and "passive" mechanisms of tolerance mentioned earlier are probably important in some systems.

B. Suppressor Cells in the Normal Regulation of the Humoral Immune Response

Antigens can be classified as T cell dependent and T cell independent depending on their requirement for helper T cells to produce an antibody response. T independent antigens such as Type III pneumococcal polysaccharide and polyvinylpyrrolodone are not actually independent of the influence of T cells. Elimination of T cells by thymectomy or administration of antithymocyte sera prior to immunization with these antigens results in an enhanced antibody response [13,17,19-21]. It is now clear that suppressor T cells express a tonic modulation of the B cell response to these

T-independent antigens. This also might be the case for the B cell response to T dependent antigens, but methodologic problems have made the demonstration of suppressor cells in this system more difficult. Clearly the manipulations such as thymectomy or administration of antithymocyte serum, which enhance the antibody response to T independent antigens, would eliminate the responses to T dependent antigens. However recent work using antisera raised against determinants expressed on suppressor T cells has shown that the in vivo response to sRBC, a T dependent antigen, can be enhanced by administration of the "antisuppressor cell" antibody [22]. In summary, suppressor T cells modulate the normal humoral immune response to T independent antigens. Much additional work is needed to delineate the role of suppressor T cells in the normal response to T dependent antigens.

The IgE or reaginic antibody response to antigen is also controlled by suppressor T cells (reviewed in Ref. 23). Adult thymectomy or splenectomy results in an enhanced reaginic antibody response in the rat [24]. Similar results are found after sublethal irradiation [25] and after administration of cytotoxic agents [23] or antithymocyte serum [26]. This enhancement can be eliminated by the passive transfer of thymocytes or splenic T cells from previously immunized donors [27]. Thus, suppressor T cells sensitive to radiation, cytotoxic agents and antithymocyte serum cause a tonic suppression of the normal reaginic antibody response.

It has been recognized for many years that the antibody response to certain simple synthetic antigens is under genetic control. In the mouse these immune response genes are linked to genes controlling histocompatibility on chromosome number 17 (reviewed in Ref. 28). More recently it has been shown that suppressor T cells play an active and important part in the lack of antibody response to a specific antigen in strains of mice that are genetically nonresponsive to that antigen. Most of the work in this area has utilized the synthetic polypeptide made of L-glutamine, L-alanine and L-tyrosine (GAT). Kapp et al. immunized nonresponder mice with GAT and then added their T cells to GAT

stimulated cultures of splenocytes from a responder strain. The T cells from the immunized nonresponder animal suppressed the plaque forming response of the splenocytes from the responder animals [29]. This suppression could be eliminated by prior x-irradiation of the nonresponder T cells or by treatment with antithymocyte serum plus complement. The suppression was specific for the stimulating antigen, GAT; the response to other antigens was not affected. This work, as well as additional data using other synthetic antigens (reviewed in Ref. 30), would suggest that the genetic control of the immune response is mediated via suppressor cells. Nonresponder mice are nonresponder because of excess suppression after antigen stimulation, not because of an intrinsic lack of B cells capable of responding to the antigen.

C. Chronic Idiotypic Suppression

Another experimental model of specific immunosuppression that involves suppressor cells is chronic allotype or idiotype suppression. In this model treatment of mice with antisera directed against specific allotypic or idiotypic determinants on antibodies will suppress the synthesis of antibodies bearing those determinants. This was originally thought to be a good example of passive tolerance, whereby the antiallotypic or anti-idiotypic antibodies inactivated or eliminated the clone of B cells carrying these determinants. It has now been clearly shown that this suppression is active and is mediated via T cells. Chronic allotypically suppressed mice have clones of B cells in their spleens capable of producing antibody bearing the suppressed allotype when transferred to a nonsuppressed host [31]. Theta-bearing splenocytes from suppressed animals can suppress the production by normal splenocytes of antibodies bearing the target allotype [31]. Eichmann showed that chronic administration of low levels of an anti-idiotypic antibody resulted in suppression of production of antibody bearing that idiotype [32]. This suppression could be adoptively transferred with spleen cells to irradiated mice [33]. The suppression could be removed either by treatment with anti-