Advances in Immunopathology

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Preface

During the past decade considerable, important information has accrued for all facets of the immune response. During this period, research has generated enormous insight into interactions between T and B lymphocytes and macrophages, identification of cell surface antigens involved in triggering these cells, molecular and biochemical consequences of triggering events, genetic restrictions governing the activation and interaction of lymphocytes, and mechanisms responsible for the regulation of cellular and subcellular events of immune responses, once initiated. Most significantly, these recent advances are now being used by experimentalists to further understand cellular and biochemical activities leading to the initiation and regulation of autoimmunity and other in vivo consequences of antibody-antigen interactions. Thus, we are now beginning to understand the initiating factors responsible for immunologically associated diseases, the accompanying tissue damage and the regulating mechanisms leading to their exacerbation and remission. Similarly, this vast amount of information delineating the basis of immunity has improved our understanding of the cellular, molecular and genetic rationale for the containment of tumor progression as well as viral and parasitic infections.

The first half of this book is concerned with cellular events responsible for the interaction and triggering of cells involved in various aspects of the immune response. This portion also deals with the nature of cell surface receptors for both antigen and antibody and the role of their modulation in lymphocyte inactivation. The manner in which these events are regulated is considered on both cellular and biochemical bases. The first paper by David Katz gives a basic overview encompassing the collaboratory activities of T and B lymphocyte activation, their genetic restrictions and the role of major histocompatibility complex products in lymphocyte triggering. He also discusses both the genetic and regulatory events responsible for controlling the immune response. Howard Grey and co-workers present

enlightening data on the structure and function of membrane immunoglobulins of the B lymphocyte and compare their structure with those secreted into the body fluids. Norman Klinman's contribution deals with the activation of B cells through these immunoglobulin receptors. He describes the B cell repertoire, diversification, selection and generation followed by control of B cell expression. This theme is extended by William Weigle and co-workers, who treat the subject of specific cellular events in the activation of B lymphocytes through Fc receptors. These authors also cover cellular requirements in the induction, maintenance and termination of immunological tolerance in both T and B lymphocytes. The activation of specific helper T cells is addressed by DeFreitas and co-workers in terms of lymphocyte interactions. They take advantage of the T cell growth-enhancing factors to propagate clones of antigen-specific helper T cells. Such clones are used to define further the mechanisms of helper T cell activation and function. Characterization and development of specific cytotoxic lymphocyte clones are the subjects Jean-Charles Cerottini and co-workers explore. They define methods used in the generation and propagation of such clones and discuss T cell factors (lymphokines) as influences in the cloning of cytotoxic T lymphocytes. They have determined the frequency of such clones specific for antigens of the H-2 complex. Rolf Zinkernagel is working with immunoregulatory genes in respect to these cytotoxic T cells, and his paper is devoted to the major histocompatibility gene complex's part in T cell restriction during cytotoxic attact on viral-infected cells. Data on the participation of Fc receptors in modulation of lymphocytes and their activation constitute Hans Spiegelberg's presentation. He reports on the expression of Fc receptors specific for particular immunoglobulin classes and subclasses on lymphocytes and monocytes and the possible consequences of receptor/immunoglobulin interaction. Special emphasis is placed on the interaction between IgE and its Fc_ϵ receptor in the context of such receptors' function in allergic disorders.

The activation of the complement pathways by the immune system is one of the main events leading to both inflammatory responses and host defense mechanisms. Hans Müller-Eberhard addresses this point in his discussion of the function and structure of the C3 component of complement. The structure

of the active site of C3 is treated in relation to its activation and subsequent formation of biologically active factors.

The second portion of this book contains research results on the cellular, molecular and genetic events involved in autoimmunity and tissue injury resulting from in vivo interactions between antibody and either endogenous or exogenous antigens. In many instances, biochemical mediators resulting from interactions between antibody and antigen in vivo subsequently provoke tissue damage. Several of the contributions in this section concern the pathogenesis of inflammatory lesions. Charles Cochrane discusses a mechanism of inflammatory injury in which lipopolysaccharide of gram-negative bacteria is the activator of biochemical events that generate a sequence of injurious mediators. Thomas Edgington describes the triggering of T cells that results in induction of a cell membrane-associated procoagulant monokine. After defining the pathway of this reaction, he suggests its role in the pathogenesis of inflammatory lesions.

These two papers set the stage for discussion of specific disease models that are, in part, manifested by immunologic tissue damage and inflammatory lesions. One model is murine systemic lupus erythematosus, which Frank Dixon explains in terms of several murine strains that are genetically prone to this antoimmune disease. He theorizes that the hyperreactivity of their B lymphocytes is a major component of their autoimmune syndrome. After indicating the roles of intrinsic and extrinsic accelerating factors, he considers the pathogenic consequences of circulating immune complexes and their deposition in the tissues of these mice. Along similar lines, Curtis Wilson describes various mechanisms involved in renal injury. In addition to immune complex-induced glomerulonephritis, nephritogenic reactions resulting from direct binding of antibodies to glomerular capillary wall antigens are the focus of his attention. Peter Ward and Kent Johnson also report on mechanisms of inflammatory lesions, but in another target organ, the lung. In an experimental model of interstitial inflammatory disease of the lung, they have quantitated immune complexes, defined their nature and specified their sites of deposition.

Two papers are devoted to the subject of immunopathology associated with microbial infection; lymphocytic choriomeningitis and measles viruses and protozoa are the experi-

mental models. In Michael Oldstone's presentation of the immunopathology of tissue injury resulting from viral infections, he emphasizes the mechanisms of viral persistence, the manner in which viruses can elude an immune attack, the structural organization of viral polypeptides on the surfaces of infected cells and these molecules' relationship to the major histocompatibility complex. Paul Lambert and L. M. Rose then offer additional insight into the immunopathology of protozoan infections. They discuss the role of host responses in the pathological expression of these infections and give particular attention to tissue damage resulting from immune complexes formed between the parasite and specific antibody. That is, after parasitic infection effects an immune response, the parasite, in turn, determines the outcome of the immune response on infection. Their insight into the polyclonal activation of B cells and subsequent perturbation of the idiotypic network is particularly interesting.

The basic elements of immune responses to both artificial antigens and infectious agents are also applicable to tumor antigens. The biological significance of human myeloma-associated antigens is the topic contributed by A. C. Morgan and Ralph Reisfeld, who used specific antisera for the immunologic definition and characterization of these tumor-associated antigens. These investigators suggest that changes in the expression of these antigens or their glycosylation may be associated with transformational events. Joseph Feldman and Eduardo Fernandez-Cruz then present data on immunotherapy for virally and chemically induced transplantable syngeneic carcinomas. Their area of interest is the role of T cells generated in vitro by such tumors and the ability of rats transplanted with these sensitized T cells to reject established syngeneic carcinomas.

William O. Weigle, Ph.D.

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APPLICATION OF BASIC IMMUNOBIOLOGY TO IMMUNOPATHOLOGY

Immunobiology: Basic Cellular and Biological Problems

Cellular and Molecular Interactions Regulating Immune Responses

David H. Katz, M.D.

The immune system is one of the most intricate of all the bodily systems, paralleling in many respects the endocrine system, in terms of the multiplicity of functions required of it for maintaining both homeostasis and the integrity of each individual's health. Both systems exert control over discrete functions at great distances within the body by virtue of circulating components capable of performing their roles at sites quite remote from their point of origin. In that sense, they display a level of versatility not found in most other multicellular organ systems. Accordingly, the complexity of the immune system has evolved from an intriguing communications network established between the components of the system, designed in such a manner as to permit a multiplicity of effects to arise from relatively few distinct cell types. This has been accomplished by the development of sophisticated regulatory mechanisms allowing either enormous amplification or contraction of a given response, depending upon the individual's needs. Under normal circumstances, the system functions remarkably well to maintain effective defenses against foreign agents or abnormal native cells which may have undergone neoplastic transformation. These events, of course, occur either as a

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consequence of normal random mutational events or secondary to outside oncogenic influences.

Many other circumstances exist, however, in which abnormalities in one or more components of the immune system result in some form of breakdown in the network. This is manifested clinically in various ways and levels of severity. In this presentation I shall give an overview of the immune system, with particular emphasis upon the regulatory mechanisms involved in the responses developed by the system and the genetic control of such regulatory mechanisms. One of the remarkable features of the immune system is that its cellular and molecular components are so enormously complex that evolution has built into the system an incredible degree of flexibility. Rarely has the system created a single pathway to an end with no alternative avenue to take when a biological detour becomes advantageous.

The intricacies of the immune system stem from the remarkable communications network established between the main components of the system. These components are essentially the genes, molecules and cells that make it up. The interplay between them is reciprocal and circumscribed, thus laying the foundations of the regulatory mechanism controlling the system. A similar reciprocal and circumscribed relationship exists between the major cellular components of the system.

The major cellular components of the immune system are the macrophages and the lymphocytes. These cells also interact in a reciprocal and circumscribed manner. Macrophages are themselves extremely versatile in the functions they perform in a variety of immune responses, and although they themselves are not specific for any given antigen, they perform a very crucial role in concentrating and presenting antigens to lymphocytes. In particular, they appear to determine whether and which T lymphocytes will be induced to stimulation and function by various antigens. Moreover, macrophages secrete several very important, biologically active mediators capable of regulating the type and magnitude of lymphocyte responses by either enhancing or suppressing cell division or differentiation. All of this, of course, is in addition to their functional capabilities as the major phagocytic cells of the reticular endothelial system, clearing the system of debris, including molecular aggregates, foreign bacteria and dead cells.

The lymphocytes represent, of course, the specific cellular components of the system, specificity being conferred upon such cells by virtue of the existence on their surface of antigen-specific receptors. The nature of the receptor specificity is highly specialized in that each different clone of lymphocytes expresses its own unique specificity. The origin of such specialization has been very actively investigated for many years, and recent advances in molecular biology point to very interesting and sophisticated genetic mechanisms that lead to antigenic diversity.

The nature of the antigen receptors on the two major classes appears to differ in that the B cell clearly has surface immunoglobulin as its major receptor, whereas the nature of the receptor on the T cell is not yet totally defined, although there is reasonable evidence in recent years that they may use the same variable region genes for encoding the antigen-combining site. There are obviously a large number of genes and molecules that are important in the immune system. Here, I shall only highlight selected ones of major significance.

Immunoglobulin Genes and Molecules

The immunoglobulin gene system is genetically unique in that it is the only one known to involve participation of at least two discrete structural genes in the production of a single polypeptide chain. Thus, there is a structural gene for the variable, or V, region, which is that region containing the specific antigen-combining site; and this gene integrates with another structural gene for the constant, or C, region of the molecule, which is that region that determines the biological function of the molecule, such as the capacity of IgE to bind to mast cells. This results in a single polypeptide chain comprised of V and C regions — each intact immunoglobulin molecule consisting of four chains, two identical light, or L, chains and two identical heavy, or H, chains. Thus, there are VL and VH as well as CL and CH genes. Putting these together in proper fashion to make a functional immunoglobulin molecule in itself is a very complex affair.

Each immunoglobulin molecule has a unique antigen-combining site determined by the primary structure of the VL and VH genes comprising the molecule. The combining site