Mechanisms of IMMUNO-PATHOLOGY

STANLEY COHEN
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Mechanisms of Immunopathology

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A WILEY MEDICAL PUBLICATION

JOHN WILEY & SONS New York • Chichester • Brisbane • Toronto

Library of Congress Cataloging in Publication Data:

Main entry under title:

(Basic and clinical immunology) (A Wiley medical publication)

Includes index.

1. Immunopathology. I. Cohen, Stanley, 1937– II. Ward, Peter A. III. McCluskey, Robert T. [DNLM: 1. Immunologic diseases. 2. Immunity. 3. Antigen-antibody reactions. WD300 M486]

RC582.2.M37 616.07'9 78-18290

ISBN 0-471-16429-1

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Mechanisms of Immunopathology

BASIC AND CLINICAL IMMUNOLOGY

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Preface

The field of immunopathology encompasses a variety of phenomena. Perhaps most obviously, it deals with the various derangements of biologic processes that arise as a consequence of immunologic reactions. Aberrant, excessive, or inappropriate immunologic responses can lead to pathologic changes. Some examples are allergies, autoimmunity, and various kinds of immune complex-induced damage. Even when the immunologic response is initiated as a part of a normal defense reaction, pathologic alterations can result. In analogy, one can think of the reaction between the immune system and pathogen as a battle, and note that in a war, even if the right side wins, the battlefield can remain scarred.

Another aspect of immunopathology involves intrinsic defects in the immune system, and the consequence to the host of such defects. Finally, immunopathology includes a number of fields that are different from the categories mentioned above, but that involve similar kinds of mechanisms. Two examples are transplantation and the role of the immune system in aging.

From the above, it is obvious that aside from intrinsic defects of immunologic function, immunopathology involves the activation of various effector mechanisms that result in pathologic consequences. These mechanisms, for the most part, represent an interface between the immune system and the inflammatory system. To a very large extent, immunopathology depends upon immunologically induced inflammation.

Rather than attempt the usual encyclopedic cataloging of every disease entity thought to involve immunopathologic mechanisms, this book focuses on the themes outlined above. It begins with an overview of the major inflammatory mediators that can be generated via the workings of the immune system. Following are chapters that deal with our current understanding of the mechanisms of anaphylactic reactions, immune complex-induced reactions, and cell-mediated immunity. In the latter, special attention is given to the lymphocyte-derived mediators, their in vivo significance, and basic principles involving desensitization and regulation that may relate to defects of cellular immunity in disease. In these chapters, an attempt is made to explore interrelationships of the various systems, since the immune system has a great deal of built-in, fail-safe redundancy. One chapter is devoted to the role of granulocytes in cell-mediated immunity, since it is still widely and erroneously held that the unique effector cell in this class of reaction is the macrophage.

These topics plus a discussion of the relation between aging and immunity,

followed by an extensive review of tolerance, provide the introduction for the subsequent chapters dealing with various aspects of autoimmune and immune-complex disease. The chapters on tolerance and autoimmunity deal with similar topics and concepts, but examine them from different perspectives in order to provide a well-balanced view. From there we turn to defects of the immune system, not only with respect to classic immunologic deficiency states but with respect to certain kinds of mediator dysfunction and effector cell dysfunction. The book concludes with an account of some of the mechanisms involved in transplantation immunity.

Although methodology is not stressed, considerable information regarding clinically useful assay procedures is provided throughout the book. Examples include discussions on ways of detecting circulating complexes and descriptions of various in vitro and in vivo manifestations of lymphokine activity.

With this mechanism-oriented approach, we hope that the book will prove useful not only to clinicians and investigators in various fields involving immunopathologic processes but to students who wish a more in-depth exposure to these concepts than is generally available in introductory texts.

October 1978

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Chapter One

Mediators of Inflammatory Responses

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Except for those few immunopathologic reactions in which the inflammatory response and the tissue injury are attributable to direct cell-cell contact between sensitized lymphocytes and target cells, most reactions that result in tissue damage do so secondary to the induction of an inflammatory reaction. In essence, the immune response triggers a highly focused elaboration of phlogistic mediators, the outcome of which is a localized accumulation of inflammatory cells and plasma constituents. It is the presence of these blood-derived elements that is most directly associated with the tissue damage. This is true not only for antibody-mediated reactions but also for various manifestations of cell-mediated immunity, as will be discussed in subsequent chapters.

Inflammatory reactions can be looked upon in terms of the two key elements that characterize an inflammatory reaction: vasopermeability changes and the arrival of leukocytes from the circulation (1). Secondary changes include the activation of fibroblasts leading to production of collagen, and the proliferation of endothelial cells resulting in formation of new capillaries. Mediators have been described that can account for each of these changes. The increased vasopermeability is due to the transient opening of endothelial junctions, permitting egress of soluble substances such as plasma proteins, electrolytes, and water. It is of interest that virtually all the vasopermeability mediators were originally found to be capable of causing smooth muscle contraction. The mechanism by which these mediators are currently presumed to work is through their ability to induce contraction of the actin-myosin elements in endothelial cells. This causes them to become "wrinkled" and shrunken, leaving gaps in the junctional zones between endothelial cells (2). This hypothesis, which explains the mechanism of

Table 1. Some Effects of Chemotactic Factors on Leukocytes

Transmembrane fluxes of Na^+, K^+, Ca^{++}
Membrane depolarization
Cell swelling
Cell aggregation
Proesterase activation
Activation of hexose monophosphatase shunt activity
Increased glycolysis and superoxide anion production
Enhanced random migration ("chemokinesis")
Directed (unidirectional) migration
Secretion of lysosomal enzymes

vasopermeability, accounts also for the muscle-contracting activities of vasopermeability mediators, as well as their ephemeral and reversible nature.

The leukotactic mediators appear to be, in general, separate and distinct factors from the vasopermeability mediators. As a general rule, the leukotactic mediators do not contract smooth muscle, and injection of vasopermeability mediators does not result in accumulation of inflammatory cells.

Leukotactic factors have a variety of effects on leukocytes, as described in Table 1. The changes described in the table occur after contact of neutrophils with any of many chemotactic factors (C3 and C5 factors, bacterial factors, and synthetic peptides). Although studies have not been done in as great detail, it seems likely that monocytes and macrophages behave similarly after contact with these chemotactic mediators. The changes listed in the table may not all be directly related to the chemotactic movement of the leukocyte, but they cannot be dissociated; the loss of one implies the loss of all others (3). Some of the cell responses, such as cell aggregation, may relate to what has been seen in vivo (4). For instance, after infusion of chemotactic factor into a peripheral ear vein of rabbits, leukocytes accumulate along endothelial surfaces (perhaps by adherence), and they sequester as intravascular aggregates in the first capillary bed contacted, which in this example would be the pulmonary capillary network (5). These phenomena suggest that increased adherence or "stickiness" of white cells may be part of the outcome of contact of leukocytes with chemotactic factors.

In the following paragraphs I will try to highlight the current knowledge about important inflammatory mediators and will point out instances in which some of the mediators have been demonstrated in ongoing inflammatory reactions.

THE MEDIATORS

The Prostaglandin (PG) System

Details of the chemistry and function of the prostaglandin (PG) system are still emerging (6). PGs presumably arise from arachidonic acid, which is derived by the action of membrane-associated phospholipase A2 of cells. Several years ago aspirin and indomethacin, which are well known to have anti-inflammatory effects, were demonstrated to block cyclo-oxygenase, which converts archidonic

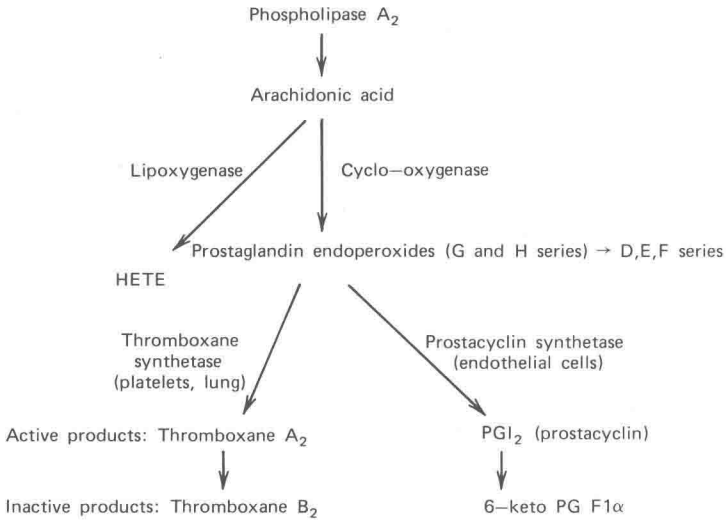

Figure 1. The prostaglandin system.

acid into the PG G and H series (Fig. 1). It was widely assumed that the blocking of PG synthesis by these drugs was proof that PGs are direct mediators of the inflammatory response (7). Since that time, as the relatively stable PGE and PGF series have been studied, it has become apparent that other PGs are probably endowed with much more biologic activity, that many highly active PGs are exceedingly unstable, and that PGs have a wide spectrum of activities that may be proinflammatory or anti-inflammatory, depending on the PG in question and the organ or tissue bed under study. This is well demonstrated by the finding that platelets and lung tissue, through their thromboxane synthetase, produce thromboxanes A_2 and B_2, the former being highly active in causing platelet clumping and arterial constriction. In contrast, endothelial cells contain a prostacyclin synthetase that leads to formation of PGI_2, an antagonist of the actions of PGA_2. Thus, the PG system is highly complex and far from being completely understood.

As is described in Chapter 2, PGs have the ability to modify profoundly the functional responses of leukocytes. The release of vasoactive amines from mast cells and/or basophils can be modulated by PGs as well as other drugs. The ultimate effect of these manipulations is, presumably, a change in intracellular levels of cyclic AMP or cyclic GMP, which subsequently depresses or enhances cell responsiveness.

The Kinin-Forming System

Generation of kinins (bradykinin, lysyl-bradykinin, and methionyl-lysyl-bradykinin) from plasma substrates occurs by an indirect activation step that involves activation of factor XII (Hageman factor) of the intrinsic clotting system (Fig. 2). These events are described in greater detail in Chapter 3. This activation, which can be initiated by bacterial lipopolysaccharide, plasmin,

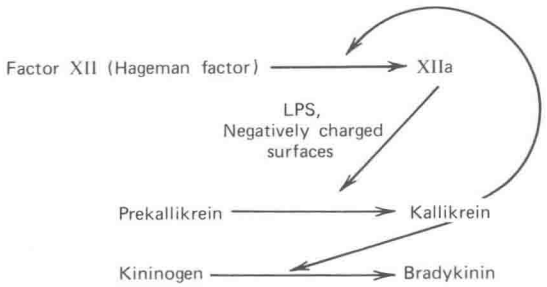

Figure 2. The kinin-forming system.

by contact of plasma with negatively changed surfaces, or by kallikrein itself, involves either a conformational change in factor XII or its fragmentation, or both. The active form of Hageman factor, or XIIa, is now known to be identical with the "permeability factor of dilution" (PF/dil.) first described by Miles and Wilhelm (8). It was noted that this permeability factor was acting as if a latent period was required for expression of activity. This can now be explained by the fact that it is an enzyme and that its effects are ultimately mediated through its role in the generation of bradykinin. The result is conversion of factor XII to its active form (XIIa), which, in turn, leads to conversion of plasma prekallikrein into the active form, kallikrein. By cleavage of an arginyl bond in a plasma substrate, kallikrein causes production of bradykinin, or the two other derivatives of bradykinin, which are listed above.

Bradykinin has long been thought to play an important biologic role, although there is no direct evidence for this contention. The biologic effects of the nonapeptide include bradycardia, hypotension, contraction of isolated strips of smooth muscle, and increased vasopermeability. Part of the difficulty in delineating a role for this peptide is the fact that it is rapidly inactivated by a plasma kininase (described in a later section). Thus, it is virtually impossible to find bradykinin in active form in biologic fluids, and this has complicated the search for its biologic significance.

The Leukokinin-Forming System

In contrast to bradykinin and its derivatives, which are very cationic peptides with molecular weights of approximately 1,000, the leukokinins represent a chemically different class of active peptides with vasopermeability effects (9). The leukokinins are acidic peptides with molecular weights of approximately 3,500. They were originally described in experiments employing extracts of lysosomal granules. These extracts, when incubated with plasma, produced a smooth-muscle-contracting and vasopermeability factor that was recognized to differ from bradykinin. It was later found that the term "leukokinin" was a misnomer, since the leukokinin-generating enzyme could be extracted not only from leukocytic lysosomal granules but also from a variety of other cell types, including tumor cells. The latter observation has led to the interesting finding that in mice with malignant tumors, which produce abundant ascitic fluid, the tumor cells release a leukokinin-generating enzyme that acts on a substrate (pres-

ent in plasma) in the peritoneal cavity (9). The generation of leukokinins appears to lead to the production of ascites, a manifestation of the increased vasopermeability. The leukokinin-generating enzyme can be blocked with pepstatin, which interferes with the formation of ascites. There is no information available on the role of the leukokinin-forming system in non-neoplastic diseases.

The Basophil (and Mast Cell) Factors

Increasingly, as emphasized in Chapter 5, basophils are known to have a prominent role in both cell-mediated immune reactions and humoral immune reactions. To date, there appears to be little difference in the release mechanisms and the products released from basophils and from mast cells. Although the mediator substances relevant to the participation of basophils in cellular immune reactions have not been identified, the mechanisms of the participation of basophils in humorally mediated reactions are reasonably clear. These can be attributed to the active secretory release of vasoactive amines (histamine and/or serotonin), the release of other anaphylactic mediators (see below), and the release of platelet activating factor (PAF), which, in turn, can lead to aggregation of platelets, inducing the release of serotonin from platelet granules (10).

The role of vasoactive amines, especially histamine, is strongly incriminated in the deposition of circulating immune complexes in renal glomerular basement membrane (see Chapter 3). The anaphylactic mediators of the basophil, described in Chapter 2, include the slow-reacting substance of anaphylaxis (SRS-A), the eosinophil chemotactic factor of anaphylaxis, and histamine. The platelet activating factor (PAF) is also released under conditions in which other "anaphylactic mediators" are also released. PAF is not yet structurally defined. It seems to be some type of acidic lipid, perhaps a prostaglandin. Its action ties together the functional responses of both basophils and platelets. It should also be emphasized that many of the products of basophil secretion, in addition to being released under anaphylactic conditions (as described above), can be released by contact of basophils with the complement-derived anaphylotoxins (C3a and C5a). (See the section on complement, below.) Thus, there are at least two separate and distinct biologic reactions that can lead to basophil secretion. It should be stressed that virtually all these products will cause smooth muscle contraction and increased vasopermeability.

Another secretory product of the basophil, the plasminogen activator, has been very recently described. This substance may, through its purported leukotactic activity and its ability to activate plasmin, have secondary effects on other mediator systems.

Factors Affecting Vascular and Stromal Elements

Two different factors affecting stromal elements have been described. These include the tumor angiogenesis factor (TAF) and the fibroblast activating factor (11,12). Since these involve soluble factors and since they affect vascular and fibrous connective tissue elements, their effects on the outcome of an inflamma-

tory response may be exceedingly important. TAF is a protein-like, diffusible substance with an estimated molecular weight of 10^5 daltons. This factor causes neovascular growth at the rate of 0.2 to 0.8 mm/day. The factor was originally found in extracts of malignant tumors and in culture filtrates of tumor cells maintained in vitro. A major problem in the demonstration of TAF has been the requirement for an in vivo assay, using either the chorioallantoic membrane of hen eggs or the cornea of a variety of animals. In the latter model, limbal vessels can be seen growing toward the corneal implant. Unless there is a continuing presence of TAF for at least the first 16 hours, rapid regression of the newly formed vessels occurs. Very recently, a nontumor cell source of angiogenesis factor has been found in cultures of macrophages activated by phagocytosis (11). These latter observations are of particular interest because of the profusion of newly formed vessels in reactions that are rich in mononuclear cells, such as the chronic inflammatory reactions of viral hepatitis, tuberculosis, chronic viral infections, etc.

Fibroblast activating factors, which lead either to proliferation of fibroblasts or to increased secretion of collagen, or both, have been described in fractions of serum, in platelets, and in culture supernatant fluids of antigen- or mitogen-stimulated lymphoid cells. These latter represent, by definition, lymphokines. None of these factors has yet been characterized in physical-chemical terms, but their recognition implies discrete control of collagen production by nonfibroblast factors.

The Complement Mediators

With few exceptions, the complement-derived phlogistic mediators are derived from the middle portion of the complement system (Fig. 3). An exception to this is the putative "C142 kinin," which was first described in association with permeability change induced in the skin of persons injected with C1 esterase (C1s) (13). This vasopermeability reaction occurred in C3-deficient but not in C2-deficient individuals. It was later demonstrated that in vitro mixtures of C1, C4, and C2 resulted in the formation of a kinin-like activity that would cause contraction of smooth muscle. This activity has not been chemically characterized, and it is not seen predictably in incubation mixtures of purified complement compo-

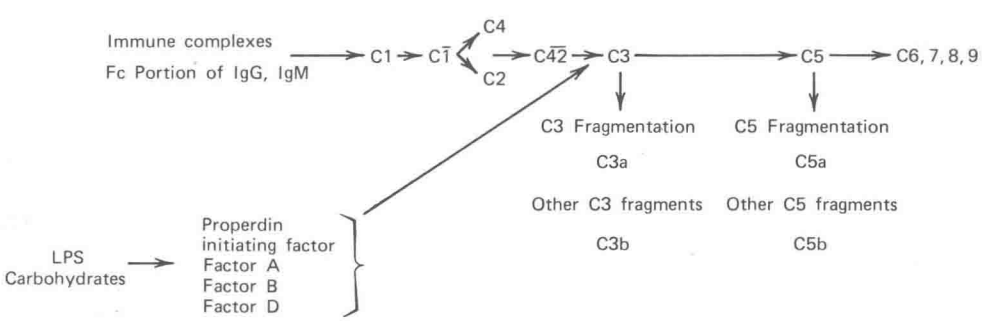

Figure 3. The complement system.