Key Facts in Immunology

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KEY FACTS in IMMUNOLOGY

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PREFACE

Key Facts in Immunology reviews the essentials of modern immunology. We recognize that opinions differ concerning what constitutes the "essentials." We feel, however, that this book, which is based on our years of teaching medical and graduate students, covers the major concepts and facts necessary for an understanding of the principles of the discipline. We do not intend *Key Facts in Immunology* to replace any of the major comprehensive texts on the subject.

The outline format of this book enhances its usefulness, providing the reader with quick means to find specific information, indicating clearly the importance of facts and concepts and their interrelationships, making the subject more "digestible," and presenting a great amount of essential information in the least amount of space. Since this book functions as a review, references for additional readings from the major texts and other books are given at the end of each chapter.

This book could not have been written without the help of many of our colleagues and the support of our families. We are especially grateful to Doctors Ron Corley and Ralph Snyderman for critiquing chapters and suggesting changes. We also appreciate the suggestions made by the following colleagues at Duke (in alphabetical order): Drs. Rebecca Buckley, Peter Cresswell, Roger Kurlander, Juliet Melzer, David Pisetsky, and Fran Ward. Many chapters were written while one of us (J.R.D.) was supported by an Eleanor Roosevelt, International Union Against Cancer, Fellowship for a sabbatical with Dr. Robert Baldwin at the University of Nottingham. We want to thank Dr. Baldwin for providing an atmosphere conducive to completing this task. We also thank Joshua Scott, who provided the artistic input for some of the figures in Chapter 3. Last, but not least, we are very grateful to the microcomputer

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CONTENTS

Section 1. Basic Elements of the Immune System

Section 2. Nature of the Immune Response

Section 3. Clinical Aspects of Immunology

Section I
BASIC ELEMENTS OF THE IMMUNE SYSTEM

1

Overview of the Immune Response and the Nature of Antigens

DEFENSE OF SELF AGAINST NONSELF

As animal species evolved, many specialized organ systems developed to help protect individuals in their environment. Several of these systems are nonspecific, but very effective. In addition to these, there is another system that specifically recognizes and responds to foreign substances, or antigens. This system—the immune system—elaborates specific products and triggers inflammatory processes to eliminate the antigen.

I. Physical barriers

Physical barriers protect the individual against exposure to antigen.

A. External surfaces
   1. Epithelium: cornified and stratified skin
   2. Secretions
      a) Sweat
      b) Tears
      c) Oils

B. Internal surfaces
   1. A single cell epithelial layer and a basement membrane (mucous membranes)
   2. Mucinous and albuminous secretions; ciliary movement; and rapid replacement of damaged epithelial cells

II. Nonspecific clearance of antigen

Internal elimination of antigens by nonspecific mechanisms

A. Reticuloendothelial system (RES)

This system of mobile and sessile (or tissue-fixed) phagocytic cells acts as a biologic filter for large particulate antigens such as bacteria, but can also distinguish effete self.

1. Kupffer's cells of the liver
2. Alveolar cells of the lung
3. Sinusoidal macrophages of the lymph nodes and spleen
4. Glial cells in the central nervous system
5. Peritoneal macrophages
6. Osteoclasts in the bone
7. Blood monocytes

B. Bloodborne phagocytic granulocytes

Predominantly polymorphonuclear leukocytes

III. Antigen-specific system (immune elimination)

Elimination of antigen by nonspecific cells is more efficient and rapid following recognition by the antigen-specific system.

A. Elaboration of products that affect the number and activity of phagocytic cells (Chapters 4 and 7)

B. Phagocytosis of particulate antigens enhanced by specific antibodies (opsonization)

C. Interaction of antigen, antibody, and complement

Elaboration of molecules which increase phagocytic cell migration and activity (Chapter 4)

IV. General characteristics of the immune system

A. Natural specific immunity

Naturally occurring cells and cell products recognize foreign bodies without prior exposure and eliminate them.

1. Natural antibodies against infectious agents may provide protection in the early stages of infection.
2. Natural cytotoxic cells (or natural killer cells) active in immune surveillance against cancer (Chapter 14) and in the early stages of viral infection

B. Acquired specific immunity

This involves specific and efficient elimination of an-

tigen as a consequence of prior recognition of and subsequent response to antigen.

1. Amplification of the initial specific response and activation of nonspecific mechanisms to eliminate antigen
2. Heterogeneity of specific response(s) to a given antigen
   a) Humoral (antibody) and cellular responses
   b) Possibly, a composite of antigen-specific responses by distinct lymphocytes
3. Memory (anamnestic responses or specific recall)
   As a consequence of first exposure, the responses to subsequent exposures to the same antigen are quantitatively and qualitatively different (Chapter 5).
4. Regulation
   The specific responses to antigen are regulated by other elements of the immune system (Chapter 9).

OVERVIEW OF THE IMMUNE SYSTEM

The antigen-specific cells of the immune system—B lymphocytes and T lymphocytes—interact with antigen presented on the surfaces of macrophages to initiate the response (Chapter 6). One of the results of recognition is proliferation of the antigen-specific lymphocyte subpopulations and acquisition of special functions (differentiation). The products of the immune response—antibody (a B-lymphocyte product) and specific T lymphocytes—react to the antigen in a variety of ways.

I. Effector functions of antibody
   A. Activation of complement components (Chapter 4) by antigen–antibody complexes results in
      1. enhancement of the inflammatory response by production of biologically active molecules.
      2. complement-induced opsonization.

3. complement-mediated neutralization of certain viruses.
4. lysis of cellular antigens.

B. Direct neutralization of certain bacteria and viruses
C. Antibody-induced opsonization
D. Triggering of mast cell histamine release (Chapter 10)
E. Feedback regulation of antibody synthesis (Chapter 9)

II. Functions of antigen-stimulated T lymphocytes
A. Secretion of lymphokines which affects delayed hypersensitivity reactions (Chapter 7)
B. Secretion of antigen-specific helper factors which influence B-lymphocyte differentiation, for example (Chapter 6)
C. Secretion of antigen-specific suppressor factors which influence both B- and T-lymphocyte function (Chapter 9)
D. Secretion of nonspecific helper and suppressor factors (Chapter 9)
E. Secretion of important growth factors, e.g., T-cell growth factor or IL-2 (Chapter 6)
F. Antigen-specific cytotoxicity (Chapter 7)

III. Elimination of antigen

This depends upon the activation and amplification of nonspecific effector cells or substances (e.g., complement activation or macrophage phagocytosis) following the interaction of specific products of the immune response with antigen.

ANTIGEN

I. Definitions

An antigen may be anything from a relatively simple macromolecule (e.g., serum albumin) to a complex infectious organism.

A. Immunogen: An antigen capable of inducing an immune response
B. Tolerogen: A molecule that induces a specific state of unresponsiveness, or tolerance

C. Epitopes (or antigenic determinants): Specific sites, expressed by the antigen and recognized by the immune system, which elicit a specific response

D. Immunodominant determinant: An epitope that dominates in the induction of an immune response

II. Types of antigens

A. Proteins and glycoproteins

1. Usually very good antigens
2. Usually express two or more different epitopes by virtue of their amino acid composition and overall conformation

B. Carbohydrates (polysaccharides)

1. May be immunogenic in certain species (e.g., in humans and mice, but not in rabbits and guinea pigs)
2. Express different epitopes by virtue of their monosaccharide composition and glycosyl linkage

C. Nucleic acids

1. Very poor immunogens, despite size and complexity
2. An immune response may be induced if the individual is immunized with nucleic acids complexed to a proteinaceous carrier.
3. Antibodies to nucleic acids can be demonstrated in many patients with autoimmune diseases.

D. Lipids

1. Not generally immunogenic
2. Example

Antibodies to cardiolipin in syphilitic patients are probably induced by complex immunogenic cell walls and membranes containing cardiolipin

III. Experimental immunogens

Chemically defined antigenic determinants or (haptens) can be used to induce a response of known specificity.

A. Hapten

A simple organic molecule (e.g., dinitrophenol) that normally expresses a single epitope or determinant and that binds to the specific lymphocyte receptor or free antibody

1. No induction of immune response in the cell that binds it

2. Induction of a hapten-specific response when physically linked (see below) to an immunogenic carrier

B. The carrier molecule
   1. Usually immunogenic alone
   2. Most foreign proteins (good immunogens) may be used for hapten conjugation and immunization.
   3. T-lymphocytes binding carrier epitopes may regulate the hapten-specific response by B-lymphocytes.

C. Nucleic acids and cardiolipin (see above)
   1. "Incomplete" immunogens or haptens in isolated form

      When a suitable immunogenic carrier is complexed with or conjugated to these molecules, immune responses to the carrier *and* the complexed lipid or nucleic acid can be demonstrated.

IV. Factors contributing to the immunogenicity of an antigen

A. Chemical nature of the antigen (see above)

B. Foreignness—antigen sensed as nonself *vs* self; correlation between phylogenetic distance of responder species and source of antigen

C. Molecular size
   1. Generally, the larger the molecule, the greater the immunogenicity
      a) Macromolecules present multiple epitopes to the immune system.
      b) Nucleic acids are a major exception.
      c) Polypeptide hormones are among the smallest natural immunogens.

D. Chemical complexity

   Composition by number and type of amino acids or monosaccharides
   1. Example—the nature of glycosidic linkages and monosaccharide composition directly influences the immunogenicity of a polysaccharide.
   2. Each of these aspects contributes to the variety and number of epitopes expressed by the antigen (e.g., by contributing to the rigidity of the molecule).

E. Accessibility of antigenic determinants
   1. Areas most easily recognized by lymphocyte cell-surface receptors and by antibodies on the hydrophilic surface of an antigen in natural (or native) conformation
   2. Expression of additional "internal" epitopes by denatured antigen

F. Host-related factors influencing the immune response
   1. Dependent on species (see above)
   2. Genetic background of the host
      Inbred strains vary considerably in their responsiveness (Chapter 8).
   3. Health and nutritional status of the host
   4. Factors controlled by the experimenter
      a) Dose of antigen administered. Antigens are immunogenic within a given optimal range of concentrations.
      b) Timing of booster inoculations for recall is important.
      c) Adjuvants augment the immunogenicity of protein antigens and the nature of the response (Chapter 6). They are thought to release complexed or captured antigen slowly and thus to maximize the local inflammatory response (granuloma).

V. Epitopes
   1. General
      Expression of two or more epitopes by most antigens
      a) These epitopes may or may not be chemically identical.
      b) Any given epitope may be considered analogous to a hapten; the remaining epitopes function as carrier determinants.
      c) An epitope may be defined by the linear sequence of five or six amino acids or a three-dimensional conformation of five or six amino acids.

d) Epitopes occur at the hydrophilic surface of antigens in native conformation.

2. Example

If a molecule, such as sperm whale myoglobin, expresses a maximum of five epitopes (linear and three dimensional):

a) In one individual, a particular subset of these determinants may be immunodominant.
b) In another individual, a different, perhaps overlapping, subset may dominate.
c) These different responses may be under genetic control.

VI. Complex antigens

An infectious agent (e.g., bacterium) expresses a variety of distinct, complex antigens, each of which may display several nonidentical epitopes. The immune response to such a complex composite immunogen is necessarily heterogeneous and complex antigens.

SUGGESTED ADDITIONAL READINGS

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2

Structure and Function of Antibodies

GENERAL CONCEPTS

I. Antigens

Antigen may induce immune system production of antigen-specific protein products, which are collectively called antibody.

II. Antibodies

A. Produced by B lymphocytes (and their fully differentiated cell form, plasma cells), having the same specificity for antigen in their cell surface receptors, i.e., binding the same antigen epitope

B. Types

1. Gamma (γ)-globulins, having the same electrophoretic mobility as serum γ-globulins
2. Beta (β)-globulins, having the same electrophoretic mobility as serum β-globulins
3. Immunoglobulin (Ig) preferred terminology

C. Major functions

1. Recognition and binding of a specific antigen epitope
2. Enhancement of antigen elimination following antibody–antigen binding

BASIC STRUCTURE OF IMMUNOGLOBULINS

I. Four-polypeptide chain structure (Fig. 2-1), composed of two light chains and two heavy chains

A. Light chains (~220 amino acids, MW, 23,000 daltons, each chain)