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(英文原版)

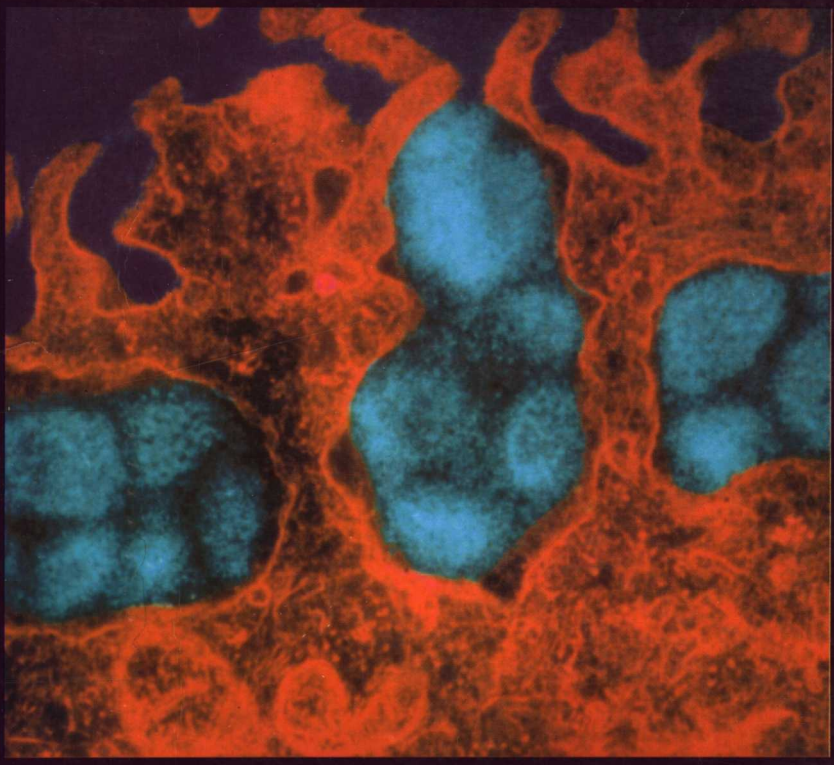
Manual of Allergy and Immunology

Fourth Edition

配英汉索引

变态反应和免疫学手册

Edited by
Daniel C. Adelman
Thomas B. Casale
Jonathan Corren



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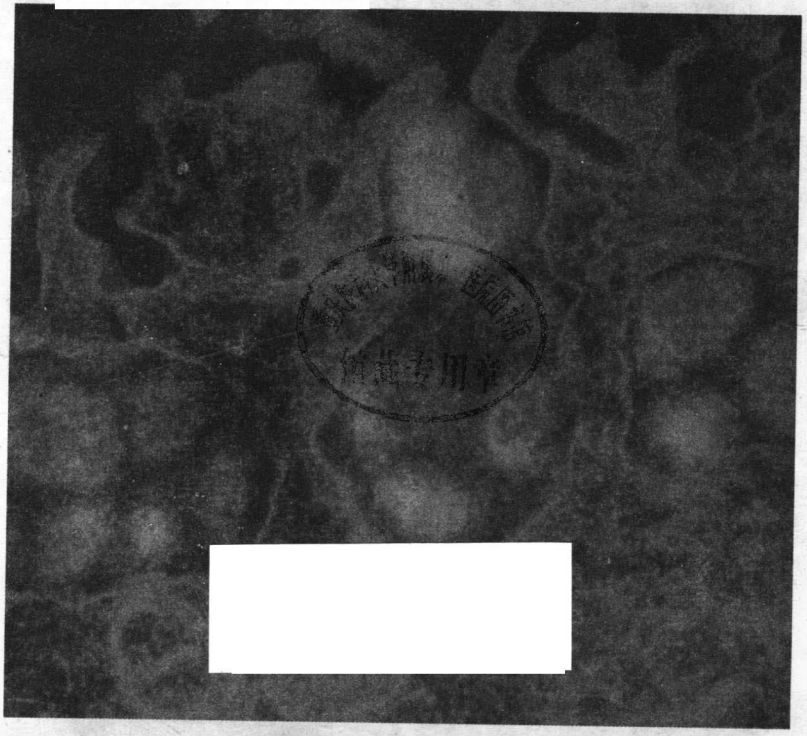

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PREFACE

The fourth edition of the *Manual of Allergy and Immunology* is designed to serve health care professionals in the diagnosis and management of allergic and other immunological disorders. Our goals have been to present the basic and essential material clearly and to provide specific information to assist in clinical decision-making and treatment planning.

We selected contributors to this edition for their specific expertise. Only currently accepted therapeutic regimens and dosages are recommended; all material that is considered investigative is so identified. We have attempted to minimize didactic material; what is included has been carefully edited to allow a basic understanding of each subject. More extensive discussions of each subject are referenced in each chapter under Selected Readings. In addition, useful addresses on the World Wide Web have been referenced when such sites are available.

Our overall goal is to have the *Manual* contain the basic information, collected in a single source, that is required for the practice of allergy and clinical immunology. The specialist will find this manual a convenient reference handbook, while the generalist will be able to use the *Manual* as a helpful guide in formulating a diagnostic and therapeutic approach to patients suspected of having an allergic or immunologic disorder, or in choosing immunologic diagnostic studies generally available for the evaluation of patients with such conditions as infectious diseases, hematologic disorders, or rheumatic disease. We hope that students, house officers, and other health care professionals will find the *Manual* a useful guide to the clinical practice of allergy and immunology.

Our heartfelt thanks to all of our contributors, for unselfishly giving their time and considerable effort preparing their respective chapters. We also thank Lippincott Williams & Wilkins for giving us the opportunity to publish the *Manual*; and our editors, Jonathan Pine and Selina Bush, for patiently giving encouragement and editorial assistance throughout the preparation of this edition.

Daniel C. Adelman
Thomas B. Casale
Jonathan Corren

CONTENTS 目 录

1. INTRODUCTION TO THE IMMUNE SYSTEM

Susann Kircher and Diana Marquardt

The function of the immune system is to distinguish self from nonself and to protect the organism from the latter. Such a system is necessary for survival in all animals. In humans, a functioning immune system is required to prevent attack by endogenous factors, such as tumors or autoimmune phenomena, as well as external factors, such as microorganisms or toxins. Dysfunction or deficiency of the immune system leads to clinical diseases of varying expression and severity, ranging from mild atopic disease to severe rheumatoid arthritis, combined immunodeficiency, or cancer. This chapter serves as a brief introduction to the complexities of the immune system. In the subsequent chapters and the suggested reading lists are additional explanations.

I. Cells of the immune system

A. Lymphocytes are responsible for the initial specific recognition of an antigen. Lymphocytes comprise approximately 40% of the total number of white blood cells. They are principally divided into **B lymphocytes** and **T lymphocytes** on the basis of their phenotypic expression of cell surface molecules (see Chapter 19) as well as their functional differences. Structurally, B and T cells cannot be distinguished from each other under the microscope, although about 10% to 15% are B cells, and 70% to 80% of circulating blood lymphocytes are T cells; the remainder of lymphocytes are neither B nor T cells, and are often referred to as **null cells**.

1. **Phenotypic identification** of B and T lymphocytes is accomplished by immunofluorescence staining using monoclonal antibodies reactive with individual cell surface molecules or antigens. **Monoclonal antibodies** are produced by antibody-producing hybridoma cell lines, which are capable of forming an antibody that is highly specific and always identical. Fusing a nonsecreting myeloma cell and the antibody-forming cell creates this hybrid cell, which results in an immortalized cell line that produces antibody recognizing a specific antigen. The hybridoma cells can be stored and retrieved to obtain the same antibody whenever needed. The display of many cell surface antigens not only differs by cell type, but also by the particular stage of differentiation and maturation of the cell; thus, the phenotypic expression of these developmentally regulated cell-surface molecules enables distinction between resting and activated cells. Dozens of monoclonal antibodies have been produced that react with cell surface antigens, enabling identification of B- and T-cell subsets and even distinction of cells by their stages of differentiation. Cell surface molecules identified by monoclonal antibodies and subsequently cloned are known as **clusters of differentiation (CD)** and are numbered sequentially. For example, CD19 is associated with mature B cells, whereas CD3 signifies activated T cells. These molecules are discussed more extensively in Chapter 19.
2. **Lymphocyte subtypes and function.** Collectively, the functions of the T and B cells encompass an entity termed the **adaptive immune system**. B lymphocytes are coated with surface membrane-bound immunoglobulin and a wide variety of other molecules; functionally, B lymphocytes produce antibody. Minor populations of B cells develop in the bone marrow, are polyreactive, and express the CD5 marker, an adhesion and cell surface molecule. These are referred to as **B1 cells**. The B1 cells express immunoglobulin M (IgM), are polyreactive, and often have a relatively low receptor binding affinity. Other B cells develop lacking the CD5 molecule and are known as B2 cells. Prior to encountering antigen, mature B2 cells coexpress IgM and IgD antibodies on their surface. However,

once B2 cells encounter antigen, they usually switch their antigen receptors to IgG, IgA, or IgE. Within secondary lymphoid tissues, complexes of antigen, antibody, and complement are localized in follicular dendritic cells. When these complexes encounter one another, **germinal centers** are formed, which can be seen on histologic examination as discrete areas in the spleen and lymph nodes. It is within these germinal centers that B2 cells encounter antigen and undergo immunoglobulin class switching via the interaction of CD40 and its ligand, CD40L (also known as CD154). CD40 is a surface marker constitutively expressed on B cells, and CD40L is expressed on an appropriately activated subset of CD4 T cells, known as T helper 2 (Th2) cells. It is the interaction of these two molecules that allows immunoglobulin class switching. It is during immunoglobulin class switching that somatic hypermutation of the antigen receptor genes occurs and high-affinity, antigen-specific IgG, IgA, or IgE are produced. The final stages of B-cell differentiation into antibody-secreting plasma cells continues to occur in secondary lymphoid tissues, but outside the germinal centers. Memory cells and plasma cell precursors are also formed in the germinal centers.

3. **T lymphocytes** mediate a number of functions, notably the **cell-mediated immune responses**, such as delayed hypersensitivity, graft rejection, and immune surveillance of neoplastic cells. Quantitative and functional differences distinguish the principal T-cell subsets. CD4 cells predominate over CD8 cells in blood by a ratio of 2:1. CD4 cells provide helper and "inducer" signals for B and T lymphocytes (through various cytokines). CD4 cells also help to mediate CD8 cell cytotoxic actions. In addition, CD4 cells provide inducer signals for macrophages that help to augment the cytotoxic capabilities of macrophages. The CD4 cells are made up of two predominant cell types: **Th1 and Th2 cells**. These T-cell subsets differentiate from the Th0 cell following antigenic stimulation. A Th1 cell is a helper cell that produces a specific phenotypic profile of cytokines such as interleukin-2 (IL-2) and interferon-γ (IFN-γ). These cytokines generally inhibit the growth and growth and differentiation of Th2 cells. Th1 cells are primarily involved in cell-mediated immunity, in that they activate macrophages and cytotoxic T cells. A Th2 cell is a helper cell that produces such cytokines as IL-4, 5, 6, 10, and 13. These cells likewise inhibit Th1 responses and are involved primarily in humoral immunity and allergic inflammation. The paradigm of the Th1/Th2 subsets will be discussed in further detail in **section III, Immune system functional components**. CD8 cells, when influenced by CD4 cells, suppress B lymphocyte immunoglobulin production and T lymphocyte responses to major histocompatibility antigens, and enhance cytotoxicity and natural killing. The **$CD8^+$ cells** are known as cytotoxic T cells and can function as both suppressor cells and mediate delayed-type hypersensitivity (DTH) reactions. CD8 molecules interact with major histocompatibility complex (MHC) class I molecules. The peptides presented by CD8 cells are derived from endogenous proteins, tumor cells, and viruses found within the antigen presenting cell (APC). Cytotoxic T cells and their relation to the Th1/Th2 paradigm will be discussed in section III.B.
4. **Null cells**, a part of the innate immune system, include a number of different cell types, including **natural killer (NK) cells**, which express the markers CD16 and CD56. These cells do not possess the typical appearance of a lymphocyte; they are slightly larger with a kidney-shaped nucleolus and have a granular appearance (**large granular lymphocytes [LGL]**). NK cells are capable of binding IgG because they have a membrane receptor for the IgG molecule. When a cell is coated with an antibody and destroyed by an NK cell, this phenomenon is called **antibody-dependent cell-mediated cytotoxicity (ADCC)**. Alternatively, NK cells can destroy cells without involvement of antibody (e.g., virally infected cells or tumor cells). Other characteristics of NK cells include recognition of antigens without major histocompatibility restric-

tions, lack of immunologic memory, and regulation of activity by cytokines and arachidonic acid metabolites.

B. Phagocytic cells are a part of the innate immune system, and consist of **monocyte–macrophages**, **polymorphonuclear leukocytes**, and **eosinophils**. These cells mature in the bone marrow, circulate in the blood for a short time as mature cells, and enter the tissue spaces by diapedesis through capillary walls, in response to cytokines and chemotactic factors.

1. **Macrophages** play a central role in the innate immune response. Derived from the blood monocytes, they circulate for a few days in the blood and then leave the vascular compartment to become active tissue macrophages. Macrophages possess receptors for carbohydrates, such as mannose, that are not normally found on the cells of vertebrates. This allows the macrophages to discriminate self from nonself. Receptors for antibodies and complement are found on both neutrophils and macrophages. This adaptation allows for enhanced phagocytosis of foreign organisms coated with antibody or complement. Macrophages have the following important functions: chemotaxis (cell movement), phagocytosis (antigen engulfment), and most important of all, processing and presentation of antigen in an immunogenic form recognizable to T lymphocytes. Microorganisms engulfed by macrophages can be destroyed when they encounter a wide range of toxic intracellular molecules produced by macrophages. Some of these molecules include superoxide anion, hydroxyl radicals, hypochlorous acid, nitric oxide, plasma proteins and peptides, lysozyme, arachidonic acid metabolites, nucleotide metabolites (cyclic adenosine monophosphate), and cytokines (IL-1, IL-6, and tumor necrosis factor [TNF]). Many tissue-specific cells are of macrophage lineage and function to process and present antigen (e.g., Langerhan cells and oligodendrocytes).
2. **Polymorphonuclear leukocytes** originate from pluripotent bone marrow stem cells. These cells circulate in the blood and tissue, and their primary function is phagocytosis and destruction of foreign antigens. These cells function in an antigen-nonspecific fashion, and have receptors for antibodies as well as for complement, so that if microorganisms are coated with either of these components, phagocytosis will be enhanced.
3. **Eosinophils**, often found in inflammatory sites or at sites of immune reactivity, play a role in host defense against parasites and other large metazoan pathogens. Although eosinophils show certain functional characteristics similar to those of neutrophils, they are only weakly phagocytic. One proposed mechanism for their ability to kill parasites is via the release of cationic proteins and reactive oxygen metabolites into extracellular fluid. In addition to releasing mediators, eosinophils also possess the ability to synthesize and secrete prostaglandins, leukotrienes, and various cytokines. Eosinophils appear to have a modulatory or regulatory function in various types of inflammation. However, in the airway inflammatory response in asthma, eosinophil-derived mediators of inflammation—including major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), and lysophospholipase (LPL)—are toxic to respiratory epithelium. Therefore, in certain instances, eosinophils promote tissue injury, and in this particular example, contribute to the pathogenesis of allergen-triggered inflammation in diseases such as asthma. The exact mechanism by which eosinophils cause oxidative damage is not known. Bromide ion is thought to be a substrate for eosinophil peroxidase, and eosinophil oxidative damage may occur via bromination of tyrosine residues.

C. Basophils and mast cells release the mediators of immediate hypersensitivity (e.g., histamine, leukotrienes, prostaglandins, and platelet-activating factor [PAF]) (see Chapter 2), which have significant effects on the vasculature and on smooth muscle. Basophils circulate, whereas mast cells are present only in tissue, and in much larger numbers. These cells have high-affinity receptors for IgE ($Fc\varepsilon RI$) and are involved in immediate and late-phase allergic reactions.

II. Development of the immune system

A. Phylogenetic development. Evolutionarily, the innate immune system evolved or developed before the adaptive immune response and appears to be inherent in all multicellular organisms. One feature that differentiates the innate and adaptive immune systems is the possession of germ-line-encoded receptors found within the innate immune system. These germ-line-encoded receptors mediate innate immune recognition. These receptors are predetermined genetically and thus have evolved through natural selection to possess specificity against infectious microorganisms. The immune system in higher animals and humans evolved with increasing complexity in terms of its specific antibody and cell-mediated immune response capacity, i.e., the adaptive immune response. Despite the complexity of the human immune system, host defense is still highly dependent on surface barriers and phagocytic mechanisms. The absence of phagocytic functions (as in severe neutropenia or in neutrophil function disorders, such as chronic granulomatous disease) or the loss of physical barriers (as with extensive cutaneous burns) can present a risk of fulminant, life-threatening invasion by microorganisms that normally are not pathogenic.

B. Ontogenetic development

1. In mature mammals, the primary lymphoid organs are the thymus and bone marrow. During fetal development the liver is one of the primary organs of lymphoid development. In early fetal development, lymphocyte precursors are derived from the fetal yolk sac. By the fourth or fifth week of gestation, lymphocytes originate from the liver and thereafter from the bone marrow. In the bone marrow, pluripotent stem cells differentiate into lymphocytes, granulocytes, monocytes, erythrocytes, and megakaryocytes. B cells undergo early growth in the bone marrow and finally emerge with membrane-bound surface IgM or both IgM and IgD, although they have not yet encountered antigen. This growth that takes place in the bone marrow is antigen-independent B-lymphocyte maturation. B cells also proliferate in response to antigen-dependent signals and eventually differentiate into antibody-secreting cells or plasma cells. This proliferation is dependent on antigen binding to the B-cell receptor. This receptor comprises membrane-bound immunoglobulin and two additional chains required for its stable expression, Ig-α and Ig-β. There are two such heterodimers that flank the membrane-bound immunoglobulin and help to mediate signal transduction. B-cell activation also requires costimulation in the form of T cell help in two ways. The first is stimulation with IL-4, produced by the $CD4^+$ T cell, which is an important B-cell growth factor. The second is T- and B-cell interaction via the molecules CD40 and CD40L (CD154); CD40 is expressed on the B cell, and CD40L is found on CD4 T cells. The interaction of these molecules facilitates class switching to IgA, IgG, and IgE. In a rare clinical immunodeficiency state, patients with X-linked hyper-IgM syndrome lack CD40L and are unable to produce antibodies of the IgA, IgG, and IgE classes. B cells also possess a cell surface molecule, B7 (CD80), which is up-regulated after ligation of CD40. B7 is a counterreceptor for CD28, a costimulatory molecule expressed on T cells. This costimulatory molecular interaction optimizes cytokine secretion and the T–B cell interaction.

A human fetus is capable of synthesizing IgM antibody by 10.5 weeks of gestation, IgG by 12 weeks, and IgA antibody by 30 weeks. The immunocompetent human infant, typically born without antigen stimulation (unless infected in utero), has little circulating IgA and IgM. IgG antibody in the newborn is almost completely derived from the mother by active and selective transport across the placenta. Adult serum levels of IgG, IgM, and IgA are attained at different developmental stages (Fig. 1.1). See Appendix V for serum immunoglobulin levels by age.

From 6 to 8 weeks of gestation, T-lymphocyte precursors migrate through the thymus, which is derived from the third and fourth embryonic pharyngeal pouches and is located in the mediastinum. The thymus func-

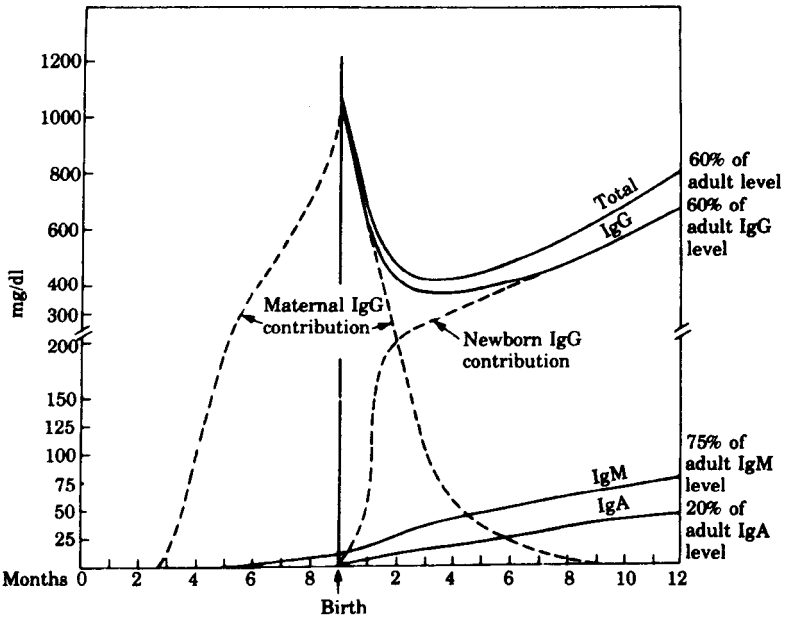

FIG. 1.1. Immunoglobulin (IgG, IgM, IgA) serum levels in the fetus and infant in the first year of life. IgG in the fetus and newborn infant is solely of maternal origin. The maternal IgG disappears by the age of 9 months, at which time endogenous synthesis of IgG by the infant is well established. The IgM and IgG at birth are entirely neonatal in origin (no placental transfer). (From Stiehm ER. Immunoglobulins and antibodies. In: Stiehm ER, Fulginiti VA, eds. *Immunologic disorders in infants and children.* Philadelphia: Saunders, 1973, with permission.)

tions to produce T lymphocytes and is the site of initiation of T-lymphocyte differentiation. A large number of T cells migrate to the thymus and become fully immunocompetent T cells. In addition, a number of T cells that are autoreactive die in the thymus. Under the influence of various cytokines (such as thymosin), T cells in the thymus undergo growth and differentiation and deletion of autoreactive clones. Functional development of cellular responses progressively matures as the fetus develops through parturition and infancy into adulthood.

2. **Phagocytic cells** are seen in the human fetus at 2 months of gestation as a few myelocytes and histiocytes present in the early yolk sac stage of hematopoiesis. Monocytes first appear in the spleen and lymph nodes at 4 to 5 months of gestation, with gradual maturation of macrophage function with advanced fetal age. The spleen, lymph nodes, and gut-associated lymphoid tissue are considered secondary lymphoid organs. Lymph nodes are peripherally dispersed throughout the body and function to localize the spread of infection. Lymph nodes are arranged in a reticular pattern with a cortex and medulla. B-lymphocytes are found in the cortex (follicles and germinal centers) as well as in the medulla, whereas T lymphocytes are primarily found in the medullary and cortical areas of the lymph nodes (see Fig. 1.2). The spleen is also divided into T- and B-cell areas similar to that of the lymph node. The spleen functions primarily to filter and process antigens from the blood.

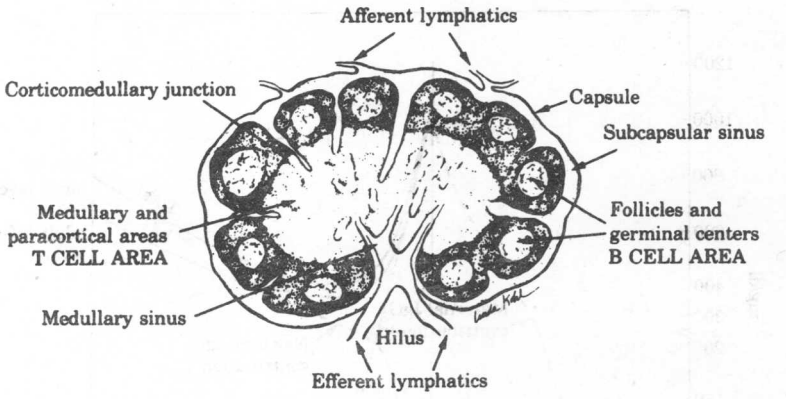

FIG. 1.2. Lymph node structure indicating primary T-cell and B-cell areas. (From Thaler MS, Klausner RD, Cohen HJ. Foundations of the immune response. In: *Medical immunology*. Philadelphia: Lippincott, 1977, with permission.)

3. **Complement components** are synthesized by the fetus early in gestation, either at the same time as or just before the beginning of immunoglobulin synthesis. There is almost no placental transfer of complement components C1q, C2, C4, C3, and C5, and the total hemolytic complement in the newborn is low. Such deficiency and dysfunction may be responsible for the relative opsonic deficiency in newborns. Complement plays a very important role in both innate and adaptive immunity. In the humoral immune response, complement opsonizes antigen as well as immune complexes for uptake by the complement receptor type 2 (CR2, CD21), is a coreceptor for B-cell activation, and is expressed primarily on B cells, follicular dendritic cells (FDC), and some T cells. Many different mechanisms are responsible for the complement-mediated promotion of the humoral immune response. These include:
   a. Enhancing antigen uptake and processing by both antigen-specific and nonspecific B cells for presentation to specific T cells.
   b. Activating a CD21/CD19 complex-mediated signaling pathway in B cells (this stimulus is synergistic to that induced by antigen interaction with the B-cell receptor).
   c. Promoting the interaction between B cells and follicular dendritic cells, in which C3d-bearing immune complexes participate in intracellular bridging. C3d is the ligand for CR2 on B cells, and is instrumental in B cell activation.

      CR2 can play a role in the development of autoimmune disease by determining B cell tolerance toward self-antigens. CR2 may be a key factor in the observed correlation between autoimmune disease and deficiency of the early complement components.

III. Immune system functional components

The immune system consists of specific and nonspecific components that have distinct, yet overlapping functions. These two entities are known as the adaptive and the innate immune systems. The antibody-mediated and cell-mediated immune systems (parts of the adaptive immune system) provide specificity and a memory of previously encountered antigens. Phagocytic cells and complement proteins (parts of the innate immune system) are nonspecific cellular mechanisms and nonspecific plasma factors, respectively. Despite their lack of specificity, these components are essential because they are responsible for the natural immunity to a vast array of environmental microorganisms.