1. Overview of the human immune response

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The human immune system mobilizes a broad repertoire of innate and adaptive responses to protect against the universe of pathogens it encounters. Central to these protective responses are its mechanisms to distinguish self from nonself. This overview describes the major mechanisms used by the immune system to respond to invading microbes and identifies settings in which disturbed immune function exacerbates tissue injury. (J Allergy Clin Immunol 2006;117:S430-5.)

Abbreviations used

APC: Antigen-presenting cell
ITAM: Immunoreceptor tyrosine-based activation motif
NF-κB: Nuclear factor κB
NK: Natural killer
TCR: T-cell receptor
TLR: Toll-like receptor

Key words: Adaptive immunity, atopy, dendritic cell, inflammation, innate immunity, Toll-like receptors

The primary function of the immune system is to protect the host from infectious microbes in its environment. Environmental pathogens threaten the host with a large spectrum of pathologic mechanisms. The immune response therefore uses a complex array of protective mechanisms to control and usually eliminate these organisms. All of these mechanisms rely on detecting structural features of the pathogens that mark them as distinct from host cells. Such host-pathogen discrimination is essential to permit the host to eliminate the pathogen without excessive damage to its own tissues.

Host mechanisms for recognition of microbial structures are of 2 general classes: (1) hard-wired responses that are encoded by genes in the host’s germline and that recognize molecular patterns that are shared by many microbes but are not present in the mammalian host (constituting innate immune responses) and (2) responses that are encoded by gene elements that somatically rearrange to assemble antigen-binding molecules with exquisite specificity for individual unique microbial and environmental structures (constituting the adaptive immune response). Because the recognition molecules used by the innate system are expressed broadly on a large number of cells, this system is poised to act rapidly after an invading pathogen is encountered. Thus it provides the initial host response. Because the adaptive immune system initially produces only small numbers of cells with specificity for any individual pathogen, cells that encounter and recognize a pathogen must proliferate to attain sufficient numbers to mount an effective response. Thus the adaptive response generally expresses itself temporally after the innate response in host defense. A key feature of the adaptive response is that it produces long-lived cells that persist in an apparently dormant state but that can re-express effector functions rapidly when they encounter their cognate antigen for a second time. This allows the adaptive response to express immune memory, resulting in a more effective host response against specific pathogens when they are encountered a second time, even decades after the initial sensitizing encounter.

DISCRIMINATION OF SELF FROM NONSELF

Because the immune system uses many different effector mechanisms to destroy the broad range of microbial cells and particles that it encounters, it is critical for the immune response to avoid unleashing these destructive mechanisms against its own tissues. This avoidance of destruction of self-tissues is referred to as self-tolerance. Mechanisms to avoid reaction against self-antigens are expressed in many parts of both the innate and the adaptive immune response. Failure of self-tolerance underlies the broad class of autoimmune diseases.

GENERAL FEATURES OF INNATE AND ADAPTIVE IMMUNITY

The innate immune system includes all defense mechanisms that are encoded in the germline genes of the host. These include the epithelial barriers and the mucociliary blanket that sweeps away ingested or inhaled particles. They also include soluble proteins and bioactive small molecules that are either constitutively present in biologic fluids (eg, the complement proteins and defensins) or that are released from cells as they are activated (including cytokines that regulate the function of other cells, chemokines that attract inflammatory leukocytes, lipid mediators of inflammation, and bioactive amines and enzymes). Lastly, the innate immune system includes cell-surface receptors that bind molecular patterns expressed on the surfaces of invading microbes.

Unlike the innate immune system, the adaptive immune system manifests exquisite specificity for its target...
antigens by virtue of the antigen-specific receptors expressed on the surfaces of T and B lymphocytes. The antigen-specific receptors of the adaptive response are assembled by means of somatic rearrangement of germline gene elements to form intact T-cell receptor (TCR) and immunoglobulin genes. The assembly of antigen receptors from a collection of a few hundred germline-encoded gene elements permits the formation of millions of different antigen receptors, each with potentially unique specificity for a different antigen.

The innate and adaptive immune systems are often described as contrasting separate arms of the host response; however, they usually act together, with the innate response representing the first line of host defense and the adaptive response becoming prominent after several days as antigen-specific T and B cells have undergone clonal expansion. Furthermore, the antigen-specific cells amplify their responses by recruiting innate effector mechanisms to bring about the complete control of invading microbes. Thus although the innate and adaptive immune responses are fundamentally different in their mechanisms of action, synergy between them is essential for an intact and fully effective immune response.

**ANTIGEN RECOGNITION BY T LYMPHOCYTES**

**MHC molecule-antigen complexes**

A major function of T lymphocytes is to identify and destroy cells that have been infected by pathogens that multiply intracellularly. For intracellular pathogens, the host cell provides a favorable microenvironment for the organism to replicate protected from many of the host defense mechanisms that target extracellular microbes. In fact, if the immune system had only one recognition system that was equally able to recognize extracellular microbes and infected cells, a microbe that generated large numbers of extracellular organisms might overwhelm the recognition capacity of the immune system, allowing the infected cells to avoid immune recognition. The very mechanism by which the T cell recognizes its target antigen focuses the T-cell response on infected cells or on cells that have taken up microbial antigens by means of phagocytosis or pinocytosis and not on the free antigen in solution. T cells recognize a molecular complex of a microbial antigen plus a self-structure. The self-structures are the antigenic peptide-binding MHC molecules (also designated HLA antigens), 2 classes of cell-surface glycoproteins that bind fragments of proteins that either have been synthesized within the cell (class I MHC molecules) or that have been ingested by the cell and proteolytically processed (class II MHC molecules).

**Class I MHC molecules**

There are 3 major HLA class I molecules designated HLA-A, HLA-B, and HLA-C. The class I molecules are cell-surface heterodimers consisting of a polymorphic transmembrane 44-kd α-chain associated noncovalently with the 12-kd nonpolymorphic β2-microglobulin protein. The α-chains, encoded by genes located within the MHC on chromosome 6, determine whether the class I protein is an HLA-A, HLA-B, or HLA-C molecule. The β2-microglobulin gene is encoded on chromosome 15.

The structures of the class I molecules and their mechanisms of acquiring, binding, and presenting endogenously synthesized peptide antigens to T cells have been recently reviewed in detail. Briefly, the membrane distal portions of the α-chain fold into 2 α-helices that are supported over a β-sheet structure, forming a peptide-binding groove for presentation of fragments of protein antigens as a complex with the HLA protein. Unlike peptides presented by class I molecules, the peptides that are presented by class II HLA molecules are generally derived from exogenous proteins that were taken up by the antigen-presenting cell (APC) by means of phagocytosis and degraded into peptides within a lysosomal or endosomal compartment before transport to the specialized class II loading compartment. Thus although class I proteins present peptide fragments of proteins that are synthesized within the APC (primarily components of intracellular pathogens), class II proteins present fragments of proteins taken up by means of phagocytosis or endocytosis from the extracellular compartment.
Like the class I proteins, structural polymorphism of the class II proteins is central to their function. Altogether, there are almost 500 alleles of the HLA-DR molecules. The HLA-DQ subregion encodes 1 polymorphic α chain (28 alleles) and 1 polymorphic β chain (66 alleles). The HLA-DP subregion encodes 1 polymorphic α chain (23 alleles) and 1 polymorphic β chain (119 alleles). As for the class I molecules, the total repertoire of peptide-binding class II HLA molecules is huge.

## T LYMPHOCYTES

The major class of T cells is defined by its surface expression of the αβ TCR. This receptor recognizes peptide antigens presented in a complex with class I or class II MHC proteins. αβ T cells differentiate into several different subsets, including CD8⁺ T cells, which act to kill cells infected with intracellular microbes, and CD4⁺ T cells, which regulate the cellular and humoral immune responses.

### T-cell development

Individual T cells bear TCRs with a single specificity. A repertoire of T cells that can protect against the vast universe of microbial pathogens must therefore include a very large number of cells encoding a huge array of discrete TCRs. The mechanisms leading to the somatic rearrangement of TCR gene elements to form functional αβ TCRs and the mechanisms governing selection in the thymus of MHC-restricted but not autoreactive T cells have been recently described.

### T-cell activation through the TCR

Interaction between the TCR and peptide-MHC provides only a partial signal for cell activation and can, under some conditions, lead to T-cell anergy. Full activation requires the additional interaction between the costimulatory molecule CD28 on the T cell and CD80 or CD86 (also designated B7.1 and B7.2, respectively) on the APC.

The cytoplasmic portions of each of the CD3 chains contain sequences designated immunoreceptor tyrosine-based activation motifs (ITAMs). When tyrosines in these ITAMs are phosphorylated by the receptor-associated kinases Lck and Fyn, the ITAMs interact with the linker proteins ZAP-70 (ζ-chain–associated phosphoprotein of 70 kd), LAT (linker for activation of T cells), and SLP-76 (SH2 domain-containing leukocyte protein of 76 kd), leading to activation of phospholipase C, the G proteins Ras and Rac, protein kinase C, and the mitogen-activated protein kinases. Activation of these pathways leads to expression of genes that induce cell proliferation and differentiation. The pathways that downregulate the activation pathways are less well understood but include the protein phosphatase CD45.

### T-cell activation by superantigens

Conventional antigenic peptides bind to a subset of MHC molecules and to a very small fraction of the huge array of TCRs, activating only a very small fraction of the total pool of T cells. Superantigens, in contrast, are microbial products that bind to large subsets of TCR proteins and MHC molecules, so that a single superantigen can activate up to 20% or more of the total T cells in the body. Superantigens do this by binding without proteolytic processing to the MHC molecule outside of the antigen-binding groove and to TCR proteins outside of their antigen-MHC binding site. For example, the toxic shock syndrome toxin 1 produced by Staphylococcus aureus can bind to and activate all T cells with TCRs using the Vβ2 and Vβ5.1 chains. The activation of large numbers of T cells induced by superantigens results in the massive release of cytokines, producing clinical conditions such as toxic shock syndrome.
of p35 and p40 subunits. A close IL-12 homolog designated IL-23 consists of a p40/p19 heterodimer. IL-23 appears to play an important or even dominant role in several models of autoimmune disease, perhaps because it drives the development of a unique subset of CD4 T cells that produce IL-17, a cytokine known to elicit destructive inflammation in several experimental arthritis models. Another member of the IL-12 family, IL-27, is a heterodimer of one p28 subunit (a structural homolog of IL-12 p35) and of one EBI3 subunit (a structural homolog of IL-12 p40 first identified as a molecule induced by EBV). IL-27 can have both proinflammatory (exacerbating tissue specific autoimmune phenomena) and anti-inflammatory (enhancing Th2-type responses) effects.

Understanding the factors that govern whether a Th1 response adopts a predominantly Th1-type or Th2-type response is crucial to the allergist–clinical immunologist. Recent progress using immunization with different types of adjuvants (eg, CpG DNA) demonstrates the feasibility of reprogramming allergic Th2-type responses in atopic patients to nonallergic Th1-type responses. Additional insights based on an understanding of the roles of the IL-17, IL-23, and IL-27 cytokines might uncover additional therapeutic opportunities to interrupt atopic responses.

B LYMPHOCYTES

B cells, representing approximately 15% of peripheral blood leukocytes, are defined by their production of the immunoglobulin antigen-binding proteins. A fundamental difference between antigen recognition by immunoglobulin and by the TCRs is that immunoglobulin can recognize complex 3-dimensional structures (described as conformational determinants), whereas the TCR recognizes only short linear peptide epitopes when bound in the groove of class I or class II MHC molecules.

Although the dominant function of B cells is to produce antigen-specific Ig, they can also present antigen through their class II proteins to T cells. This latter process is critical for the cellular interactions underlying T-cell help for immunoglobulin production. The molecular mechanisms for assembly of immunoglobulin heavy and light chains share many features with those supporting the formation of TCR chains, and these, as well as mechanisms underlying isotype switching, somatic mutation, signaling through the B-cell antigen receptor, and T cell–dependent and independent activation, have been recently reviewed.

LYMPHOID TISSUES

Protective immunity, particularly helper T cell–dependent production of high-affinity antibody and immune memory, requires cell–cell interactions. The naive subject must bring rare antigen-specific B cells together with rare antigen-specific T cells and with APCs presenting the specific antigen. This occurs in the secondary lymphoid tissues, organs with separate B-cell zones (follicles), and zones enriched for T cells. The follicles also contain clusters of follicular dendritic cells that bind antigen–antibody complexes and provide sites for B-cell matura-
tion, somatic mutation, and selection of high-affinity B cells. The T-cell zones contain dendritic cells that are potent APCs for T-cell activation. Specialized high endothelial venules express adhesion molecules that facilitate egress of naive T and B cells from the circulation into the lymphoid organ. Dendritic cells that have taken up antigen in peripheral tissues enter into lymph nodes through afferent lymphatics, and efferent lymphatics export effector and memory cells back into the circulation.

EFFECTORS OF INNATE IMMUNITY

Initially, the innate and adaptive immune responses were thought to act independently, with innate immunity providing the first line of defense against invading microbes and adaptive immunity acting later to sterilize the infection. It is now apparent that the adaptive response has co-opted many of the innate effector mechanisms to enhance its effectiveness. Thus these 2 arms of the immune response should be viewed as complementary and cooperating.

Toll-like receptors

Toll was first identified in Drosophila species, where Toll controlled polarity of the developing embryo and later was recognized to participate in antifungal immunity in flies. The human Toll-like receptors (TLRs) are transmembrane receptors with extracellular domains that contain leucine-rich repeating units and cytoplasmic domains with homology to the cytoplasmic domain of the IL-1 receptor (designated the Toll/IL-1 receptor [TIR] domain, Fig 1). Ten human TLRs have now been defined. The primary function of the TLR is to signal that microbes have breached the body’s barrier defenses. They appear to do this largely by recognizing common structural features of microbes known as pathogen-associated molecular patterns. These molecular patterns include LPS from gram-negative bacteria, peptidoglycan, lipoteichoic acid, lipooligosaccharides, and unmethylated DNA with a CpG motif characteristic of microbial DNA. TLRs are particularly found on macrophages and dendritic cells but also are expressed on neutrophils, eosinophils, epithelial cells, and keratinocytes. Most TLRs are cell-surface transmembrane proteins, but TLR9 and TLR3 are expressed intracellularly. Activation of most Toll receptors induces cellular responses associated with acute and chronic inflammation.

When TLR ligands interact with their specific TLRs, intracellular adaptor proteins transduce signals that lead to enhanced expression of genes encoding cytokines and other inflammatory mediators (Fig 1). For example, binding of bacterial flagellin to TLR5 or bacterial unmethylated DNA containing CpG sequences to TLR9 induces recruitment of the intracellular protein MYD88 to the Toll/IL-1 receptor domain of the TLR. This then signals to the
Complement

Complement is a critical effector pathway in both adaptive and innate immunity, particularly in association with Ig. The complement system is composed of more than 25 plasma and cell-surface proteins in 3 activation pathways and in downmodulating regulatory pathways. The features of the downmodulating regulatory pathways, the 3 activation pathways, and the acquired and inherited complement deficiency states have been recently reviewed.1,4

Phagocytic and natural killer cells

The major phagocytic cells are neutrophils, macrophages, and monocytes. These cells engulf pathogenic microbes and use intracellular vacuoles to focus toxic molecules, such as nitric oxide, superoxide, and degradative enzymes, on their destruction. Phagocytic cells use a variety of Fc receptors and complement receptors to enhance uptake of particles that have been marked by the adaptive and innate immune systems for destruction.

Natural killer (NK) cells represent a distinct lineage of lymphoid cells that develops in the bone marrow under the influence of IL-2 and IL-15. When activated, they adopt the morphology of large granular lymphocytes. NK cells have no antigen-specific receptors. Rather, they have both inhibitory and activating receptors that recognize self-MHC molecules and other cell-surface ligands.14 They have prominent antitumor effects and are potent killers of virally infected cells.

NK T cells are a distinct lineage of CD3+ T cells that display NK surface antigens.15 They are listed among innate effector cells because they express a limited repertoire of TCR chains (mostly Vα24 and Vβ11) and respond quickly to glycolipid antigens presented by the HLA class I homolog CD1. They have potent cytotoxic activities but can also produce IL-4 and IL-13, suggesting that they might play important roles in the pathogenesis of asthma and allergic disease.16

IMMUNOPATHOLOGY AND ATOPY

Properly regulated immune responses protect the host from pathogens and other environmental challenges. Often it is impossible to eradicate an invading pathogen without destroying infected cells. By using cellular apoptosis to remove infected cells, damage to nearby normal cells is minimized. Local inflammation, however, is often an important part of an effective response. With inflammation comes the danger of significant tissue damage and fibrosis during the resolution of the inflammatory state. Usually this damage is physiologic and tolerated; however, if inflammation is intense or chronic, it can lead to severe organ dysfunction and scarring.

All too commonly, patients present with conditions of tissue damage that appear to occur without an underlying stimulus. When this occurs in the form of autoimmune or atopic diseases, there appears to be a fundamental misdirection of the immune response, with tissue damage when no real danger was present. The cellular and humoral immune responses against components of self-tissues that occur in most autoimmune disorders generally manifest features of a T_{H1}-type response. Atopic diseases, in contrast, appear to represent an overly aggressive T_{H2}-type response, leading to hypersensitivity to a broad spectrum of normally encountered environmental antigens. At least superficially, autoimmune and atopic diseases appear to
represent opposite ends of a spectrum of a diathesis in the regulation of helper T-cell phenotype differentiation. Such a simple interpretation, however, is not supported by epidemiologic studies showing that the presence of atopy provides little protection against development of the Th1-dominated illness rheumatoid arthritis. In fact, some studies have suggested that patients with a Th1 illness are more likely to have a Th2 illness, suggesting that they have a common underlying cause. The identification of novel cytokines and regulatory cell subsets, including those producing IL-23 and IL-17, offers hope for deeper understanding of the mechanisms underlying autoimmune and atopic diseases and the development of new and effective therapies.

REFERENCES

2. Update on primary immunodeficiency diseases

The pace of discovery in primary immunodeficiency continues to accelerate. In particular, lymphocyte defects have been the source of the most impressive expansion in recent years. Novel forms of agammaglobulinemia, class-switch defects, and T-B severe combined immunodeficiency have been described. Little by little, the genetic heterogeneity of the common variable immunodeficiency and IgA deficiency phenotypes continues to be unraveled as new molecular defects have been reported in these patients as well. The phenotypic spectrum of DiGeorge syndrome has been further developed, along with promising advances in therapy. Defects of nuclear factor κB regulation and Toll-like receptor signaling have been described, along with defects of chemokine receptors and cytoplasmic proteases. Clinically defined immunodeficiencies, such as hyper-IgE syndrome and idiopathic CD4 lymphocytopenia, are also discussed. Finally, significant adverse effects in some patients have tempered initial enthusiasm for gene therapy. (J Allergy Clin Immunol 2006;117:S435-41.)

Key words: Genetic diseases, human, immunodeficiency, immunology, infection

This updated chapter on primary immunodeficiency serves as a companion to the chapter published in the most recent edition of the full Primer on Allergic and Immunologic Diseases. This update contains important new material, as well as useful information that was not included in the original chapter because of space constraints. Potential new literature sources for this update were collected through a PubMed search using the MeSH major topic “immunologic deficiency syndromes” with the Boolean operator “NOT” linked to HIV and AIDS. Changes have been made to all of the tables, and they are included here in their entirety. Table I describes the major classes of infectious susceptibilities associated with each of the principal categories of immunodeficiency (lymphocyte defects resulting in antibody deficiencies, cellular immune deficiencies, and combined deficiencies, as well as phagocyte and complement defects). Table II contains a listing and classification of selected molecular defects associated with primary immunodeficiency. Table III indicates the alterations in the major subpopulations of peripheral blood lymphocytes in several forms of severe combined immunodeficiency (SCID). A more