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.)

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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

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 inhaled or ingested particles. They also include soluble proteins and bioactive small molecules that are either constitutively present in biologic fluids (eg, the complement proteins[1] and defensins[2]) 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.[3]

Unlike the innate immune system, the adaptive immune system manifests exquisite specificity for its target

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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.[4] 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.[5]

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 β_2-microglobulin protein.[4] 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 β_2-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.[4] Briefly, the membrane distal portions of the α-chain fold into 2 α-helices that are supported on a sheet of β-strands. This forms a physical groove that binds 9- to 11-amino-acid-long peptides derived from protein antigens by means of proteolytic degradation. The display of antigenic peptides on the surface of cells bound within the groove of the HLA molecules is described as *antigen presentation*. Generally, the peptides bound in the grooves of the HLA class I molecules are derived from proteins synthesized within the cell that bears the class I molecules. They are, consequently, described as *endogenous* antigens.

Critical for their biologic function, HLA molecules manifest high structural polymorphism. As of July 2005, the World Health Organization Nomenclature Committee recognized 396 alleles at the HLA-A locus, 699 alleles at the HLA-B locus, and 198 alleles at the HLA-C locus, with the main structural variability in amino acids located in the floor and sides of the peptide-binding groove. Given that most individuals in the human population are heterozygous for HLA and that each class I protein can bind many different antigenic peptides, each individual can bind a very diverse collection of peptides. On a population level, the diversity of peptide-binding motifs is huge. Mutations in microbial antigens might permit the microbe to avoid binding (and, consequently, recognition) by a few HLA class I alleles, but no mutations will permit the microbe to avoid recognition broadly throughout the population.

Class II MHC molecules

The class II HLA molecules, like the class I molecules, consist of 2 polypeptide chains, but both are MHC-encoded transmembrane proteins, designated α and β. There are 3 major class II proteins designated HLA-DR, HLA-DQ, and HLA-DP. Like the class I HLA proteins, the membrane distal portions of the class II dimers fold together to form 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.