General Considerations and Terminology

At the most basic level, rejection involves recognition of a tissue that is foreign in a context that is perceived to be appropriate for a defensive response. Put another way, all rejection responses involve something on the graft that is recognized as foreign, some component of the immune system which recognizes it, and something that defines the context of the foreign object as worthy of the immune system’s attention. To begin to describe these fundamental aspects of rejection, a rudimentary vocabulary is required.

The word *antigen* is used to describe a molecule or tissue that can be recognized by the immune system. An *epitope* is the portion of the antigen, generally a carbohydrate or peptide moiety, that actually serves as the binding site for a receptor of the immune system. Thus, antigens contain one or many epitopes. Each is bound by one of two types of lymphocyte receptors: the *T-cell receptor* (TCR) of T cells, or the *antibody* (or *immunoglobulin*) of B cells. In general, a TCR or antibody binds to only one epitope and each cell expresses a single type of antigen receptor. These receptors allow a given lymphocyte to “see” and respond to only one epitope, and thus establish the *specificity* of an immune response. The signal from these receptors to the lymphocyte on which they reside defines immune recognition.

The context or appropriateness of an immune response is governed by another set of receptors on lymphocytes called *costimulation* receptors. These receptors bind irrespective of the epitope and allow the lymphocyte to determine whether the specific signal generated by the antigen receptor should evoke a response. By having separate signals for specificity and appropriateness, the immune system can carefully regulate its response to be active when a pathogenic threat is present and inactive as the threat subsides.

Given the myriad of surface receptors involved in lymphocyte function, the descriptive names that are frequently given to a newly discovered molecule are unwieldy. Thus, as new molecules are characterized, they are assigned a “cluster of differentiation” (CD) number. This nomenclature is vital to any discussion of complex cellular interactions.

Organs transplanted between genetically nonidentical individuals of the same species are termed *allografts*. Antigens from these grafts are thus *alloantigens*, and immunity toward these antigens is known as *alloreactivity*. The word *homograft* was used in earlier literature to describe allografts. The degree to which an allograft shares antigens with the recipient is referred to as the *histocompatibility* of the graft. This term generally refers to the similarity of a cluster of genes on chromosome 6 known as the *major histocompatibility complex* (MHC, also known as HLA in humans). Thus, transplant antigens are unique, genetically encoded characteristics of an individual. Basically, two different classes of MHC gene products are produced, termed *class I* and *class II*. The importance of MHC gene products stems from their *polymorphism*. Unlike most genes, which are identical within a given species, polymorphic gene products differ in detail while still conforming to the same basic structure. Thus, polymorphic MHC proteins from one individual are foreign alloantigens to another individual. Allografts that are matched to their recipient at HLA are referred to as *HLA-identical* allografts, and those matched at half of the HLA loci are termed *haplo-identical*. Note that HLA-identical allografts still differ genetically and are to be distinguished from *isografts*. Isografts are organs transplanted between identical twins, are immunologically inconsequential, and thus do not reject. *Xenografts* are organs transplanted from one species to another and were formerly described as *heterografts*.

Physiological Immunity

Two distinct but complementary arms of the immune system have evolved in vertebrates to combat disease: the *innate* and *acquired* immune systems. They differ in their fundamental responsibilities.

The innate immune system recognizes *general* motifs that
Physiological Innate Immunity

The innate immune system uses protein receptors encoded in the germ line (passed from one individual to its offspring) to identify foreign or aberrant tissues. These receptors can exist on cells, such as macrophages, neutrophils, and natural killer cells, or free in the circulation, as is the case for complement. They are limited in specificity but are broadly reactive against common components of pathogenic organisms, for example, lipopolysaccharides on gram-negative organisms or other glycoconjugates. Thus, the receptors of innate immunity are the same from one individual to another within a species and, in general, do not play a role in the recognition of a foreign graft. They may, however, come into play when an injured tissue (e.g., one that has been made ischemic and moved from one individual to another) is present.

Once activated, the innate system performs two vital functions. It initiates cytolysis for the destruction of the offending organism, primarily through the complement cascade. It also communicates the encounter to the acquired immune system for a more specific response through byproducts of complement activation and through the function of phagocytic cells.

Complement plays a central role in many innate responses. In a process known as alternative pathway complement activation, C3, the central activating enzyme of the complement cascade, can be activated when carbohydrates lacking sialic acid (a sugar moiety that is not found in most bacteria but is common on human cells) are encountered. One of the cleaved fragments of C3, C3b, is released and binds to the invader, flagging it as foreign, a process known as opsonization. C3a, another product of C3 activation, acts to recruit neutrophils to the site, while C3d enhances the immunogenicity of the organism, making it more likely to stimulate a dendritic cell to present the antigen to T cells. C3 activation also leads to formation of the membrane attack complex (MAC). This product is the result of activated C3 catalyzing the activation of C5, which in turn catalyzes the polymerization of C6, C7, C8, and C9, forming the MAC, a pore embedded in the foreign cell that results in disruption of the membrane and lysis.

Macrophages and dendritic cells not only engulf foreign cells that have been bound by complement, but also those identified through receptors for foreign carbohydrates (e.g., mannose receptors). This tissue is broken down and presented to the acquired immune system using molecules of the MHC so that specific T cells can be activated and aid in the attack. Acquired immunity can also reciprocally activate the innate system. In a pathway known as the classical complement activation cascade, antigen-bound antibody can bind to the complement molecule C1q, which in turn becomes activated and attracts C3. C3 activation products then proceed toward the MAC and serve chemoattractant functions, as described for the alternative pathway.

Physiological Acquired Immunity

The hallmark of acquired immunity is specific recognition and elimination of cells. Highly specialized receptors for distinguishing infected and transformed cells from normal tissues have evolved to facilitate this goal. The altered cell is recognized as a specific entity, not just as nonself, and a record of that encounter is retained for more rapid response to future encounters, a phenomenon known as immunological memory.

The Genetics and Structural Characteristics of Antigen Receptors

Two cell types have evolved with the ability to specifically bind to antigen: T cells and B cells (Fig. 46.1). Their receptors...