KEY CONCEPTS

Recognition and Rejection of Transplants (Allografts)

- The rejection response against solid organ transplants is initiated mainly by host T cells that recognize the foreign HLA antigens of the graft, either directly (on APCs in the graft) or indirectly (after uptake and presentation by host APCs).
- Types and mechanisms of rejection of solid organ grafts:
  - Hyperacute rejection. Preformed antidonor antibodies bind to graft endothelium immediately after transplantation, leading to thrombosis, ischemic damage, and rapid graft failure.
  - Acute cellular rejection. T cells destroy graft parenchyma (and vessels) by cytotoxicity and inflammatory reactions.
  - Acute humoral rejection. Antibodies damage graft vasculature.
  - Chronic rejection. Dominated by arteriosclerosis, this type is caused by T-cell activation and antibodies. The T-cells may secrete cytokines that induce proliferation of vascular smooth muscle cells, and the antibodies cause endothelial injury. The vascular lesions and T-cell reactions cause parenchymal fibrosis.
- Treatment of graft rejection relies on immunosuppressive drugs, which inhibit immune responses against the graft.
- Transplantation of hematopoietic stem cells (HSCs) requires careful matching of donor and recipient and is often complicated by graft-vs-host diseases (GVHD) and immune deficiency.

Immunodeficiency Syndromes

Immunodeficiencies can be divided into **primary** (or **congenital**) immunodeficiency disorders, which are genetically determined, and **secondary** (or **acquired**) immunodeficiencies, which may arise as complications of cancers, infections, malnutrition, or side effects of immunosuppression, irradiation, or chemotherapy for cancer and other diseases. Immunodeficiencies are manifested clinically by increased infections, which may be newly acquired or reactivation of latent infections. The primary immunodeficiency syndromes are accidents of nature that provide valuable insights into some of the critical molecules of the human immune system. Here we briefly discuss the more important and best-defined primary immunodeficiencies, to be followed by a more detailed description of acquired immunodeficiency syndrome (AIDS), the most devastating example of secondary immunodeficiency.

Primary Immunodeficiencies

Most primary immunodeficiency diseases are genetically determined and affect the defense mechanisms of innate immunity (phagocytes, NK cells, or complement) or the humoral and/or cellular arms of adaptive immunity (mediated by B and T lymphocytes, respectively). Although these disorders were once thought to be quite rare, some form of mild genetic immune deficiency is, in fact, present in many individuals. Most primary immunodeficiencies are detected in infancy, between 6 months and 2 years of life, the telltale signs being susceptibility to recurrent infections. Here we present selected examples of immunodeficiencies, beginning with defects in innate immunity and then defects in the maturation and activation of B and T lymphocytes. We conclude with immune defects associated with some systemic diseases.

Defects in Innate Immunity

Inherited defects in the early innate immune response typically affect leukocyte functions or the complement system, and all lead to increased vulnerability to infections (Table 6-12). Some of the defects whose molecular basis is defined are summarized next.

Defects in Leukocyte Function

- **Inherited defects in leukocyte adhesion**. Individuals with *leukocyte adhesion deficiency type 1* have a defect in the biosynthesis of the β_2 chain shared by the LFA-1 and Mac-1 integrins. *Leukocyte adhesion deficiency type 2* is caused by the absence of sialyl-Lewis X, the fucose-containing ligand for E- and P-selectins, as a result of a defect in a fucosyl transferase, the enzyme that attaches fucose moieties to protein backbones. The major clinical problem in both conditions is recurrent bacterial infections due to inadequate granulocyte function.

Table 6-12 Defects in Innate Immunity

Disease	Defect
Defects in Leukocyte Function	
Leukocyte adhesion deficiency 1	Defective leukocyte adhesion because of mutations in β chain of CD11/CD18 integrins
Leukocyte adhesion deficiency 2	Defective leukocyte adhesion because of mutations in fucosyl transferase required for synthesis of sialylated oligosaccharide (receptor for selectins)
Chédiak-Higashi syndrome	Decreased leukocyte functions because of mutations affecting protein involved in lysosomal membrane traffic
Chronic granulomatous disease	Decreased oxidative burst
X-linked	Phagocyte oxidase (membrane component)
Autosomal recessive	Phagocyte oxidase (cytoplasmic components)
Myeloperoxidase deficiency	Decreased microbial killing because of defective MPO-H_2O_2 system
Defects in the Complement System	
C2, C4 deficiency	Defective classical pathway activation, results in reduced resistance to infection and reduced clearance of immune complexes
C3 deficiency	Defects in all complement functions
Deficiency of complement regulatory proteins	Excessive complement activation; clinical syndromes include angioedema, paroxysmal hemoglobinuria, others

The table lists some of the more common inherited immune deficiencies affecting phagocytic leukocytes and the complement system.
Modified in part from Gallin JI: Disorders of phagocytic cells. In Gallin JI, et al (eds): Inflammation: Basic Principles and Clinical Correlates, 2nd ed. New York, Raven Press, 1992, pp 860, 861.

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