
CHAPTER 20

IMMUNODEFICIENCY

CONGENITAL immunodeficiencies, while generally uncommon, serve to illustrate many of the key features of the development and function of the immune system, particularly those involving the CENTRAL LIMB. The ACQUIRED immunodeficiencies, particularly those of IATROGENIC origin, are much more common and are of broad clinical importance, fueling continuing searches for more effective and selective immunosuppressive drugs.

The critical importance of the immune system to our everyday health and well-being becomes especially obvious when one observes the results of deficiencies in immune function. These immunodeficiencies can be classified into two major categories:

CONGENITAL ("PRIMARY") IMMUNODEFICIENCIES - Victims are born with these diseases, which are the result either of *inherited* or *developmental* defects.

ACQUIRED ("SECONDARY") IMMUNODEFICIENCIES - These are *acquired* as secondary results of various disease states, due either to the disease processes themselves or the therapy used to treat them.

We can also classify immunodeficiency states with respect to which of the three "limbs" of the immune response is affected, that is whether they represent defects in the AFFERENT, CENTRAL or EFFERENT limb. Remember that the Afferent limb represents *antigen processing* carried out by macrophages and related cells, the Central limb involves the *triggering and proliferation* of clonally precommitted T-cells and B-cells, and the Efferent limb is the *effector* limb, involving the various effector T-cells (T_C T_{reg} T_{DTH} ...) and the biological consequences of antibody binding (which may include complement fixation, phagocytosis and allergic responses).

We will briefly go over a few examples of immunodeficiencies, keeping in mind that these are intended only as illustrations of the importance of various elements of the immune system. This list is far from complete, and the discussion of each example will cover only a few of its most striking features.

CONGENITAL DEFICIENCIES OF THE EFFERENT LIMB

CHRONIC GRANULOMATOUS DISEASE

Syndrome: Granulocytes and monocytes carry out their normal functions of phagocytosis, but are incapable of killing the organisms they phagocytose due to a deficiency of the enzyme NADPH oxidase, required to produce the "oxidative burst". Patients are susceptible to various microorganisms which are normally of low virulence, particularly with *Staphylococcus aureus* and gram-negative bacteria.

Inheritance: This disorder can be caused by several different genetic defects, one of which is controlled by an X-linked gene; symptoms appear at about two years of age.

Treatment: antibiotic therapy for infections.

COMPLEMENT DEFICIENCIES

A variety of genetic deficiencies of complement components are known, which we will not review here. Some may have only very mild consequences, but they are often associated with differing degrees of increased susceptibility to *bacterial infections*. Interestingly, deficiencies of some of the early complement components also appear to be associated with increased susceptibility to development of *lupus* and other *autoimmune states*, underlining the importance of the early components of complement in the normal process of *clearance of immune complexes* (discussed in Chapter 5).

CONGENITAL DEFICIENCIES OF THE CENTRAL LIMB

The congenital defects of T-cell and B-cell lineages are the most biologically interesting and informative of the immunodeficiencies, although the clinically significant ones are extremely rare. As we review four examples of such conditions, it will be useful to refer to Figure 21-1, which briefly outlines some key features of the process of differentiation of hemopoietic cells, focusing on the lymphocytic lineage.

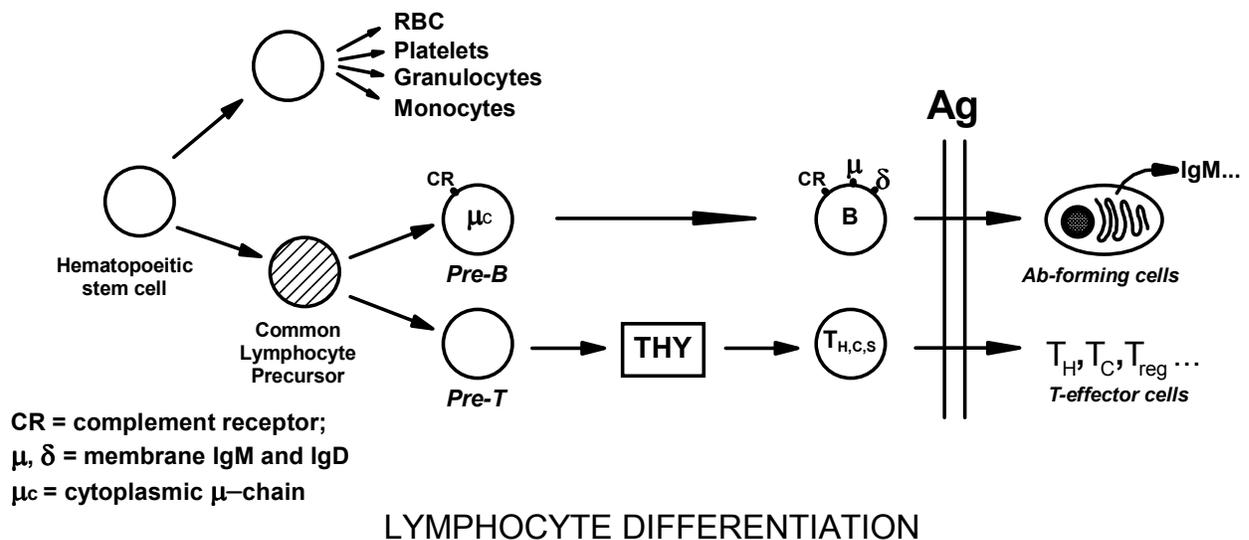


Figure 20-1

X-LINKED INFANTILE HYPOGAMMAGLOBULINEMIA (BRUTON'S SYNDROME)

Syndrome:

Extreme susceptibility to **bacterial infections** (more so than to viruses or fungi) starting at ~4-6 months of age.

Serum IgG is extremely low, other Ig isotypes absent.

B-cells (membrane Ig-bearing) are absent, but CR-bearing pre-B-cells may be present.
Faulty Ig heavy chain gene rearrangements; D/J rearrangement may occur, but no V/D/J.

T-cell numbers and function are normal.

No follicles or germinal centers, or plasma cells.

Inheritance: X-linked recessive gene, frequency ~ 1 in 10^5 . This gene has been identified as encoding a tyrosine kinase ("Bruton's Tyrosine Kinase", or BTK) which is expressed selectively in developing B-cells.

Treatment: Includes chronic treatment with gamma-globulin (*intravenous* IgG for passive immunization) and antibiotics.

This genetic defect prevents B-cell precursors from developing into functional B-cells; replacement therapy with human IgG is very effective. Since the development of IV-Ig, these patients have been surviving well past their fourth decade. Nevertheless, live vaccines are dangerous for these patients and should be avoided.

CONGENITAL THYMIC APLASIA (DiGEORGE SYNDROME)

Syndrome:

Hypocalcemic tetany is evident within 24 hrs. of birth (due to a deficiency of PTH, or parathormone, which is normally produced by the parathyroid and regulates potassium and calcium metabolism).

Repeated infections with **viruses and fungi**, (also bacteria); *Candida* and *Pneumocystis carinii* are characteristic.

No functional thymus (hypoplasia or aplasia).

Few or no T-cells.

B-cells present, but with variable function (serum Ig levels are also variable).

Primary follicles present in lymphoid tissues but without germinal centers, and empty thymus-dependent areas.

Inheritance: This disease is most commonly sporadic (not inherited) due to *de novo* deletion of a region of chromosome 22q11 (remember the distinction between "congenital" and "inherited"). This deletion results in a *developmental defect* of the 3rd and 4th pharyngeal pouches which give rise to both the thymus and parathyroid. Often associated with malformations of the heart and face, DiGeorge is considered as one manifestation of the larger complex of diseases collectively known as *cardiovelofacial syndrome*. The frequency of the deletion is ~ 1 in 10^4 , the appearance of severe immunodeficiency is less common.

Treatment: Successful treatment may be carried out with **fetal thymus transplant**; the transplant need not contain lymphocytes, only a small amount of thymic epithelium. Any therapy must consider the danger of GvH reaction; for this reason one must not use adult thymus tissue, and any transfused blood must be first X-irradiated. No *live* vaccines should be given.

This disease is the result of the absence of T-cell development through failure to provide an appropriate environment for differentiation. The patient's lymphocytes themselves (pre-T cells) are perfectly capable of developing into mature cells, and if the appropriate environment is provided (by a thymic transplant) they will colonize it and develop normally.

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

Syndrome:

Overwhelming infections in first year of life.

No functional T- or B-cells (abnormal B-cells may be present).

Thymus and peripheral lymphoid tissues empty or severely depleted of lymphocytes.

Inheritance: *Several different known genetic defects* can cause this disease, including both X-linked and autosomal recessive forms, with an overall frequency around 1 in 10^6

Treatment: The only successful treatment is replacement of the hemopoietic stem cells by bone marrow transplant. Prevention of GvH is a key to success (by removing cells of the T-cell lineage).

This genetic defect is expressed in the *common lymphocyte precursor* of T and B-cells indicated in the diagram above, and prevents their further development. If a source of competent stem cells is provided (*e.g.* by bone marrow transplantation), they will colonize the thymus and peripheral lymphoid tissues in a normal fashion.

SELECTIVE IgA DEFICIENCY

Syndrome:

Very low serum levels of IgA (<0.05 mg/ml), normal levels of other isotypes.

Normal cell-mediated immunity.

Increased susceptibility to viral and bacterial sinopulmonary infections, although it may often be asymptomatic. Can also be associated with autoimmune or allergic states.

Inheritance: Genetic basis variable and poorly understood; frequency up to 1 in 300.

Treatment: No specific treatment other than antibiotic therapy. IgA should not be administered, as it can trigger an anti-IgA autoimmune or allergic responses (see Chapter 21).

This is the most common of several isotype-specific Ig deficiencies; it is not known whether it is a defect in the precursors of IgA-producing cells, or in the (unknown) mechanism by which their differentiation is regulated.

ACQUIRED IMMUNODEFICIENCIES

A. SECONDARY TO DISEASE

- 1) Many **infectious diseases** result in more or less general immunosuppression. In the case of Human Immunodeficiency Virus (HIV), the agent which causes Acquired Immunodeficiency Disease (AIDS), its pathogenicity is a direct consequence of its severe depression of immune responsiveness.
- 2) **Malignancies** can often result in immunosuppression, either by generally interfering with normal physiological functions, or through the production of factors which specifically suppress immune functions (this may be a significant aspect of the natural biology of malignancy).
- 3) **Renal failure** can cause the loss of large amounts of serum immunoglobulins into the urine, resulting in humoral immunodeficiency.
- 4) **Enteropathies** can lead to loss of immunoglobulin through the gut, with similar results.

B. IATROGENIC. (*"Caused by the healer"*; referring to a condition which is the result of therapeutic treatment.)

This category includes *the most common immunodeficiency conditions* which most physicians will encounter. They are the result of various forms of therapy which have either as their goal or as a major side effect the suppression of immune responsiveness. Increased susceptibility to infections is an important consequence of immunosuppression which must always be considered, and balanced against the therapeutic benefits of a particular treatment. Some therapeutic treatments which can have this result are:

- 1) **Corticosteroids.** Prednisone is widely used for both its anti-inflammatory effect and immunosuppressive capability; lymphocytes in general are very sensitive to steroids.
- 2) **Cytotoxic drugs.** Many anti-tumor drugs (such as azathioprine and cyclophosphamide) are strongly immunosuppressive as well, and may also be used intentionally for this purpose. Susceptibility to infections may therefore be a major side effect of anti-tumor therapy, in a patient who may already be immunosuppressed by the presence of the tumor itself.
- 3) **Anti-Lymphocyte Antibodies.** Sera from horses immunized with human thymocytes contain effective anti-T-cell antibodies, and have been used extensively since the 1950's to inhibit rejection of transplanted organs; such preparations are known as Antilymphocyte Serum (ALS) or Anti-Lymphocyte Globulin (ALG). Their use is much more limited now than in the past, as a result of the increasing availability of more selective monoclonal antibodies (see Chapter 14 and APPENDIX 13) and the development of new classes of immunosuppressive drugs (such as cyclosporin and FK-506, mentioned below).

- 4) **Ionizing Radiation.** X-rays or gamma-rays, often used in tumor therapy, also destroy whatever lymphoid tissue happens to be in their path. While ionizing radiation generally kills proliferating cells in a highly selective manner (which is the basis for its anti-tumor effectiveness), *resting lymphocytes are unusually sensitive to such radiation.*

CYCLOSPORIN A AND FK506 (*Tacrolimus*)

Since the early 1980's Cyclosporin A, a fungal peptide, and FK506, a bacterial macrolide, have served as remarkably effective immunosuppressive agents in human transplantation. They inhibit T-cell function to a greater extent than B-cells or phagocytic cells, selectively blocking T_H cell function by interfering with the production of and response to IL-2, but without killing the cells. While they are less effective in inhibiting *established* immune responses, they have nevertheless been tremendously useful in prolonging kidney, liver and heart transplants. Their molecular target, however, is not restricted to cells of the immune system, and they exhibit a variety of often serious side effects, including nephrotoxicity. Although they have not completely replaced steroids and cytotoxic drugs in clinical immunosuppressive therapy, cyclosporin and FK506 have allowed the use of lower doses of these drugs, resulting in far less severe generalized immunosuppression and other side effects in the management of transplant recipients.

CHAPTER 20, STUDY QUESTIONS:

1. For each of the congenital immunodeficiency diseases discussed, identify the relevant biological defect and describe how it leads to the symptoms of the disease.
2. What situations may result in iatrogenic immunodeficiency states?