Immunodeficiency Disease

Immunodeficiency diseases are caused by defects in various components of the immune system and result in increased susceptibility to infections and some cancer. There are two types of Immunodeficiency diseases; Congenital (Primary) immunodeficiency diseases are caused by genetic abnormalities, and Acquired (secondary) immunodeficiencies are result of infections, malnutrition, or treatments for other conditions that adversely affect the cells of the immune system.

I. **Congenital immunodeficiencies:** are caused by genetic defects that lead to blocks in the maturation or functions of different components of the immune system.

a. Congenital immunodeficiencies caused by defects in Lymphocyte Maturation.

1. Disorders in both T and B cells (e.g Sever combined Immunodeficiency SCID):

- X-linked SCID are caused by mutations in the signaling subunit (called common γ chain) of a receptor for cytokines. When the gamma chain is not functioning, immature lymphocyte at the pro-T and pro-B cells stages cannot proliferate in response to the major growth factor for these cells. The consequence is decrease in the numbers of mature T cells, deficient cell mediated immunity, and defective humoral immunity because of absent T cell help.
- autosomal SCID (Half of the cases) are caused by mutations in: A. enzyme called adenosine deaminase (ADA) which is involved in the breakdown of purines. Deficiency of ADA leads to the accumulation of toxic purine metabolites in proliferating cells. B. common gamma chain subunit of cytokine receptor. **C.** RAG1 and RAG2(VDJ recombinase) that are required for IG and T cell receptor.

2. Syndrome caused by block in B cell maturation (e.g X-linked agammaglobulinemia): In this syndrome**,** B cell in the B.M. fail to mature beyond the pre-B cell stage result in sever decrease or absence of mature B cells and serum Ig. This disease is caused by mutation in the gene encoding kinase called B cell tyrosine kinase (Btk) resulting in defective production or function of the enzyme. The exact role of Btk is not known, but it is believed to participate in delivering biochemical signals that promote maturation of these cells.

3. Defect in T cell maturation (e.g DiGeorge syndrome) result from incomplete development of the thymus (and the parathyroid glands) and failure of the T cell maturation.

b. Congenital immunodeficiences associated with defect in lymphocyte activation and effector function.

1. The X-linked hyper-IgM syndrome is characterized by defective B cell heavy chain class switching, resulting in IgM being the major serum antibody, and sever deficiency of cell-mediated immunity against intracellular microbes. The disease is caused by mutations in CD40 ligand that bind to CD40 on B cells and macrophages and thus mediates T cell-dependent activation of B cells and macrophages. This leads to defective T cell dependent B cell response, such as

class switching in humoral immunity, and defective T cell dependent macrophage activation in cell mediated immunity.

2. The bare lymphocyte syndrome is disease caused by a failure to express calss II MHC molecules as a result of mutations in the transcription factors that normally induce class II expression. This lead to defect in the maturation and activation of the T cell in thymus and peripheral lymph nodes, respectively.

C. Congenital immunodeficiencies caused by defect in innate immunity.

1. Chronic graulomatous disease is caused by mutations in the enzyme phagocyte oxidase, which catalyzes the production of microbicidal reactive oxygen intermediates in lysosomes. As a result, neutrophils and macrophages are unable to kill microbes. The immune system tries to compensate for this defective microbial killing by calling in more and more macrophages, and by activating T cell, which stimulate recruitment and activation of more phagocytes, this leads to granuloma formation.

2. Deficiencies of C2 and C4 result not in immunodeficiency but in immune complex mediated diseases like lupus.

II. Acquired Immunodeficiency: Abnormalities aquired during life. The most important of these abnormalities is:

1. HIV infection.
2. Malnutrition
3. Cancer treatment with chemotherapeutic drugs and irradiation.

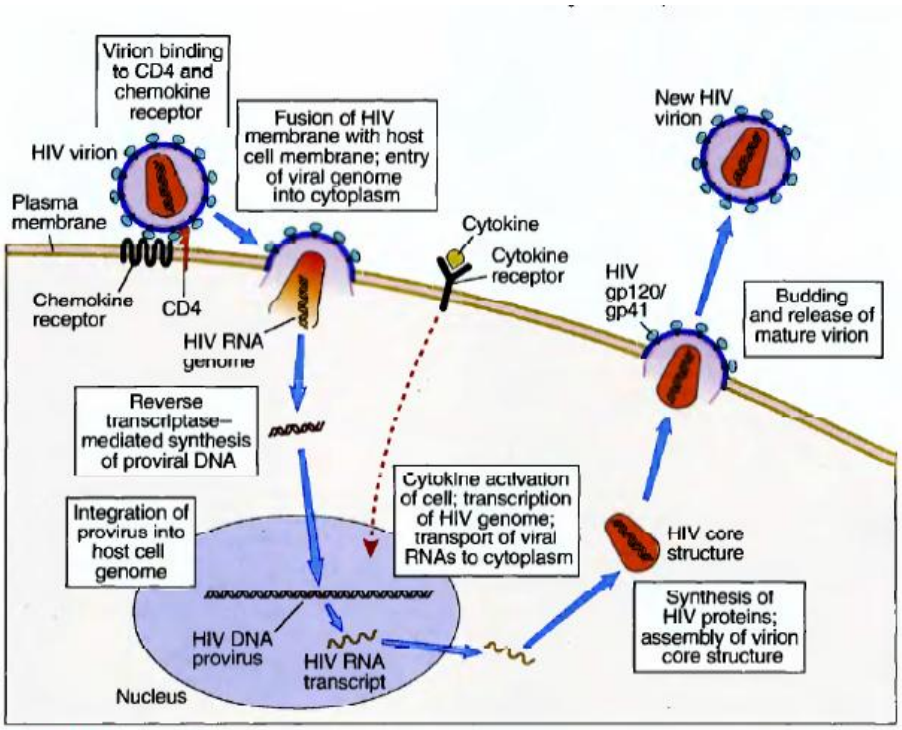

Figure 12–8 The life cycle of HIV-1. The sequential steps in HIV reproduction are shown, from initial infection of a host cell to release of a new virus particle (virion). For the sake of clarity, the production and release of only one new virion is shown. An infected cell actually produces many virions, each capable of infecting nearby cells, leading to spread of the infection.

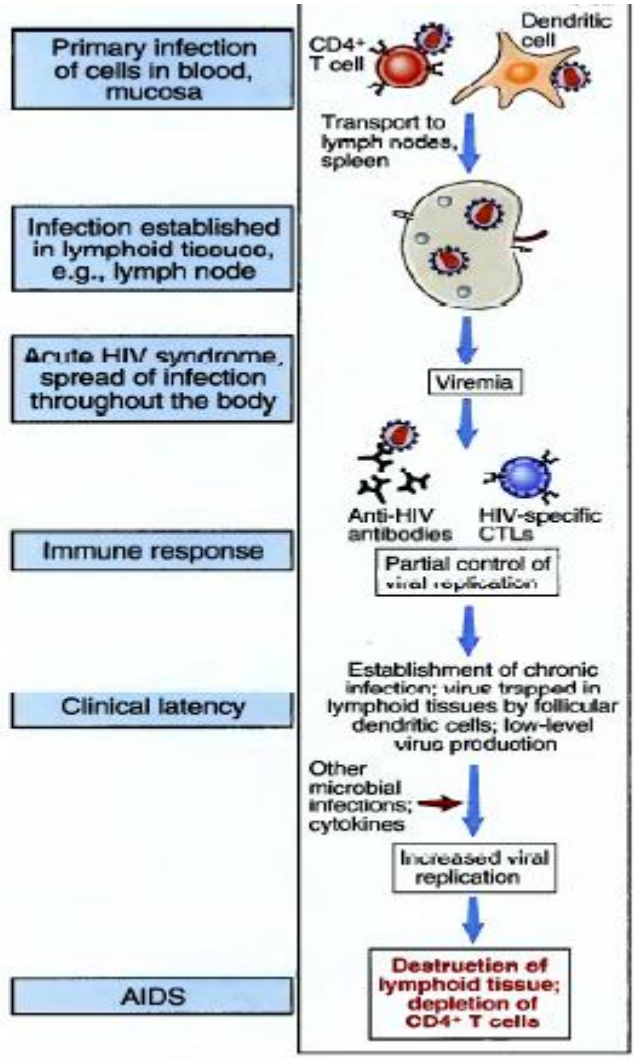

Figure 12–9 The pathogenesis of disease caused by HIV. The stages of HIV disease correlate with a progressive spread of HIV from the initial site of infection to lymphoid tissues throughout the body. The immune response of the host temporarily controls acute infection but does not prevent establishment of chronic infection of cells in lymphoid tissues. Cytokines produced in response to HIV and other microbes serve to enhance HIV production and progression to AIDS.