

Immunodeficiency
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Objectives

1. Understand Primary and Secondary immunodeficiencies
2. Characterization, diagnosis and treatment of various immunodeficiencies
3. Studies on HIV and Development of AIDS
4. Analysis of Strategies for Prevention and Treatment of AIDS

Immunodeficiency is the failure of the immune system to protect against disease or malignancy.

Primary Immunodeficiency is caused by genetic or developmental defect in the immune system. These defects are present at birth but may show up later on in life.

Secondary or Acquired Immunodeficiency is the loss of immune function as a result of exposure to disease agents, environmental factors, immunosuppression, or aging.

Types of Primary Immunodeficiency Disorders

Defect in the **hematopoietic stem cells** results in **reticular dysgenesis** that leads to generalized immune defects and subsequent susceptibility to infections. This condition is fatal if left untreated, but can be successfully treated with bone marrow transplantation.

Myeloid Lineage deficiency: This deficiency involves myeloid progenitor cells and affects innate immunity. Inasmuch as, phagocytosis is affected, the patients are susceptible to bacterial infections.

Congenital Agranulomatosis:

Patients have a decrease in the neutrophil count. It is due to a defect in the myeloid progenitor cell differentiation into neutrophils. These patients are treated with granulocyte-macrophage colony stimulating factor (GM-CSF) or G-CSF.

Chronic Granulomatous Disease (CGD):

This is characterized by defective reactive oxygen species (ROS) production which normally kills phagocytosed bacteria. However, they exhibit inflammatory reaction with neutrophils, macrophages and T cells resulting in the formation of granulomas. The disease is detected by a negative reaction in the nitroblue tetrazolium test which in normal individual turns blue due to reduction by superoxide anions. This is an autosomal recessive or X-linked trait. Treatment is with interferon- γ (IFN- γ).

Leukocyte adhesion Deficiency (LAD):

Lack of CD18 (β chain) on T cells and macrophages impairs adhesion of these cells to endothelium thereby preventing inflammation. Treatment is with bone marrow (devoid of T cells and MHC-matched) transplantation or gene therapy.

Lymphoid lineage immunodeficiency:

If the lymphoid progenitor cells are defective, then both the T and B cell lineages are affected and result in the **severe combined immunodeficiency (SCID)**. They are less common but are very severe. Such infants suffer from recurrent infections especially by opportunistic microorganisms. These include the following disorders.

Patients having both T and B cell deficiency lack **recombinase activating genes** (RAG1 and 2) that are responsible for the T cell receptor and Ig gene rearrangements. These patients are athymic and are diagnosed by examining the T cell receptor (TCR) gene rearrangement. They also lack B cells although they do have Abs in

early infant life because of passive transfer from mother. NK cells are normal in these patients. This is an autosomal recessive trait.

Interleukin-2 Receptor (IL-2R) may be lacking in patients thereby preventing signaling by IL-2 and other cytokines which act as growth factors. This would lead to defect in the proliferation of T cells, B cells and NK cells. This is an autosomal recessive trait.

Adenosine deaminase (ADA) is an enzyme responsible for converting adenosine to inosine. ADA deficiency leads to accumulation of adenosine which results in production of toxic metabolites that interfere with DNA synthesis. The patients have defects in T, B and NK cells.

These SCID are autosomal recessive traits. Treatment is by gene therapy or stem cell transplantation.

T cell deficiency affects both cell-mediated and humoral immunity. The patients are susceptible to viral, protozoal and fungal infections. Infection with viruses such as cytomegalovirus or attenuated measles vaccine can be life-threatening in these patients.

DiGeorge Syndrome or congenital thymic aplasia patients lack a thymus. This deficiency results from deletion of a region on chromosome 22 during development of 3rd and 4th pharyngeal pouch. Because of this, this deficiency is also responsible for facial and heart defects. This is an autosomal dominant trait. Treatment is with a thymic graft.

B cell deficiency may result from the absence of B cells, plasma cells, total Igs or selective Igs. These patients have recurring infection with extracellular bacteria, but are capable of eliciting an immune response against intracellular bacteria as well as viruses and fungi.

X-linked Agammaglobulinemia (X-LA): In such patients, mature B cells are absent as they exist in the pre B cell stage with H chains rearranged but not L chains. They also have no Igs and suffer from recurrent bacterial infections.

X-linked hyper-IgM Syndrome: Such patients exhibit deficiency in IgG, IgA and IgE but elevated IgM levels. This is due to a defect in the differentiation of IgM producing cells to cells producing other Igs.

Selective Deficiency of Ig classes: IgA deficiency results from a defect in the class switching. Such patients suffer from respiratory and genitourinary tract infections.

Common Variable Immunodeficiency: Also known as Late Onset hypogammaglobulinemia. B cells fail to differentiate into plasma cells. Treatment is with Igs.

Complement defects:

Defects in C components results in immunodeficiency. The patients are susceptible to bacterial infections.

Acquired or Secondary Immunodeficiencies:

All acquired immunodeficiencies have been outdone by the AIDS that is caused by **Human Immunodeficiency Virus (HIV)-1**. It was first discovered in 1981 and the patients exhibited fungal infections with opportunistic organisms such as *Pneumocystis carinii* and in other cases, with a skin tumor known as Kaposi sarcoma. HIV-1 and 2 have been discovered with the strain frequently found in N. America being HIV-1. HIV is spread through homosexual and promiscuous heterosexual intercourse, infected blood and body fluids as well as during delivery from mother to offspring. HIV was discovered by Luc Montagnier in Paris and Robert Gallo in Bethesda in 1983. It is a retrovirus with RNA that is reverse transcribed to DNA by reverse transcriptase (RT) following entry into the cell. The DNA is integrated into the cell genome as a provirus that is replicated along with the cell. HIV-1

does not replicate in most other animals but infects chimpanzees although it does not induce AIDS in them. Severe combined immunodeficient mice (SCID) reconstituted with human lymphocytes can be infected with HIV-1.

HIV-1 virion has an envelope made up of the outer lipid bilayer of the host cell in which are embedded glycoproteins composed of the transmembrane gp41 along with the associated gp120. The gp120 binds the CD4 expressed on host cells. Within the viral envelope is the viral core or nucleocapsid consisting of a layer of matrix protein composed of p17 and an inner capsid made up of p24. The viral genome consists of 2 ssRNA associated with 2 reverse transcriptase (RT) molecules as well as other enzymes including a protease and an integrase.

Replication cycle and targets of therapy:

The virus attaches to the CD4 molecule on Th cells, monocytes and dendritic cells through the gp120 of HIV. For HIV infection, a coreceptor is required. The coreceptor is a chemokine receptor such as CXCR4 or CCR5. CCR5 expressed predominantly on macrophages and CXCR4 on CD4+ T cells serve as coreceptors for HIV infection. After the fusion of HIV envelope and the host membrane, the nucleocapsid enters the cell. The RT synthesizes viral DNA which is transported to the nucleus where it integrates with the cell DNA in the form of a provirus. The provirus can remain latent till the cell is activated when the provirus also undergoes transcription. The virions consisting of the transcribed viral RNA and proteins are produced. These are budded out of the host cell membrane from where they acquire the envelope. Thus, therapeutic agents have been developed that target viral entry and fusion, as well as serve as RT, protease and integrase inhibitors. Highly active anti-retroviral therapy is a cocktail of 3 or more such agents.

Immunological Changes:

The virus replicates rapidly and within ~2 weeks the patient develops fever. The viral load in the blood increases significantly and peaks in 2 months after which there is a sudden decline because of the latent virus found in germinal centers of the lymph nodes. CTL develop very early whereas antibodies can be detected between 3-8 weeks. The CTL killing of Th cells around 4-8 weeks leads to decrease in CD4+ T cells. When the CD4+ T cell count decreases below 200/mm³, full blown AIDS develops.

Immunotherapy:

There are several barriers to development of an effective HIV vaccine.

- 1) Attenuated vaccine itself may induce the disease
- 2) Heat-killed virus is not antigenic
- 3) CD4+ T cells may be destroyed by the vaccine
- 4) Antigenic variation of HIV due to induction of mutations results in escape from CTL.
- 5) Low immunogenicity of the virus by downregulation of MHC molecules
- 6) Lack of animal models in which HIV grows
- 7) Lack of in vitro tests to study HIV infection and growth.

The following immunological agents have been considered in developing vaccines

- 1) The use of soluble CD4 which could compete for binding with gp120.
- 2) Anti-gp120 Abs may bind to CD4 and block entry of the HIV
- 3) Chemokines that compete for the co-receptors may inhibit binding and entry of HIV.
- 4) Immunization with deletion mutants to reduce pathogenicity.
- 5) Vaccination with some recombinant proteins
- 6) Gene encoding proteins introduced into virus vectors may be used for vaccination
- 7) IL-2 to boost the Th cells.

Reading: Immunology By Male, Brostoff, Roth and Roitt, 7th Edition, Pages299-324