15.2: Secondary Immunodeficiency

Learning Objectives

1. State what is meant by secondary immunodeficiency and list four possible contributing factors.
2. Briefly give at least four mechanisms of HIV-induced immunodeficiency.

In the case of secondary immunodeficiency, one is born with normal immune responses but some secondary factor or occurrence causes a decrease in immune responses. Secondary immunodeficiency is induced by factors such as:

- Malnutrition. Inhibits lymphocyte maturation and function.
- Some viruses, e.g., HIV. Depletes T4-lymphocytes.
- Irradiation - exposure to X-rays and gamma rays. Causes a decreased production of lymphocyte precursors in the bone marrow.
- Cytotoxic drugs such as many used in cancer chemotherapy. Causes a decreased production of lymphocyte precursors in the bone marrow.
- Corticosteroids – anti-inflammatory steroids. Damages lymphocytes.
- Leukemias, cancers of the lymphoid system, metastases. Reduces areas for lymphocyte development.
- Aging. Adaptive immunity, especially cell-mediated immunity, tends to diminish with aging.
- Removal of the spleen. Decreased ability to remove microbes that enter the blood.

A secondary immunodeficiency of current notoriety is of course Acquired Immunodeficiency Syndrome or AIDS, a secondary immunodeficiency caused by Human Immunodeficiency Virus (HIV). As we saw in Unit 4, HIV, via its gp120, primarily infects cells with CD4 molecules and chemokine receptors on their surface, namely, T4-lymphocytes, macrophages, and dendritic cells. The median incubation period for AIDS is around 10 years.

During early or acute HIV infection the virus primarily infects and destroys memory T4-lymphocytes which express the
chemokine receptor CCR5 and are very abundant in mucosal lymphoid tissues. Here HIV also encounters the dendritic cells located throughout the epithelium of the skin and the mucous membranes where in their immature form called Langerhans cells they are attached by long cytoplasmic processes. The envelope glycoproteins gp41 and gp120 of HIV contain mannose-rich glycans that bind to mannan-binding proteins (pattern recognition receptors; also called lectin receptors) on the dendritic cells.

Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by pro-inflammatory cytokines, the dendritic cells detach from the epithelium, enter lymph vessels, and are carried to regional lymph nodes. By the time they enter the lymph nodes, the dendritic cells have matured and are now able to present antigens of HIV to naive T-lymphocytes located in the lymph nodes in order to induce adaptive immune responses.

At this point the infection has transitioned from the acute phase to the chronic phase. The chronic phase of HIV infection is characterized by viral dissemination, viremia, and induction of adaptive immune responses. The viremia allows the viruses to spread and infect T4-helper lymphocytes, macrophages, and dendritic cells found in peripheral lymphoid tissues.

During the chronic phase of HIV infection, the lymph nodes and the spleen become sites for continuous viral replication and host cell destruction. During most of this phase, the immune system remains active and competent and there are few clinical symptoms. A steady state-infection generally persists where T4-lymphocyte death and T4-lymphocyte replacement by the body are in equilibrium. In a person infected with HIV, somewhere between one and two billion of these T4-cells die each day as a result of HIV infection and must be replaced by the body's lymphopoietic system in the bone marrow. It is estimated that 10 billion virions are produced and cleared in an infected individual each day. However, the enormous turnover of T4-lymphocytes eventually exhausts the lymphopoietic system and it becomes unable to replace the T4-cells being destroyed. A variety of mechanisms then eventually lead to immunodeficiency.

Mechanisms of HIV-induced immunodeficiency include:

- Direct HIV-induced cytopathic effect on infected T4-lymphocytes. This can occur through:
  - Increased cell permeability as a result of gp41 expression in the host cell membrane and viral release by budding;
  - Inhibition of host cell protein synthesis as a result of viral replication within the infected cell; and
  - Fusion of infected T4-cells with numerous uninfected T4-cells resulting in syncytia formation.
- Killing of HIV-infected T4-cells by cytotoxic T-lymphocytes or CTLs.
- Killing of HIV-infected T4-cells by antibody-dependent cytotoxicity or ADCC.
- Apoptosis of T4-cells as a result of chronic activation by HIV and by cytokines.
- Shedding of gp120 molecules by HIV. This subsequently triggers a series of events that cause the adaptive immune system to become less and less effective, primarily by altering the normal balance of immunoregulatory Th1 and Th2 cells in the body.
- Impaired function of HIV infected macrophages and dendritic cells.

To further complicate problems, during the replication of HIV the reverse transcriptase of HIV exhibits a high error rate as it transcribes the RNA genome into DNA. As a result, HIV readily mutates to become more immunoresistant, more drug resistant, and able to change the preferred cell type it is able to infect, e.g., M-tropic to T-tropic as shown in Figure [PagelIndex(2)].
Progression to AIDS is marked by a viral load that progressively increases in number while the immune system weakens as a result of the destruction of increasing numbers of T4-lymphocytes and the inability of the body to continually replace these destroyed cells. The loss of T4-helper lymphocytes leads to a marked decline in cells called cytotoxic T-lymphocytes (CTLs), the primary cells the body's immune responses use to destroy virus-infected cells. Once a person progresses to full-blown AIDS he or she becomes susceptible to a variety of opportunistic infections by:

- bacteria such as *Mycobacterium avium* complex (MAC), *Salmonella*, and *Nocardia*;
- protozoa such as *Cryptosporidium* and *Toxoplasma*;
- viruses such as cytomegalovirus (CMV), herpes simplex viruses types 1 and 2 (HSV-1, HSV-2), and varicella zoster virus (VZV);
- *Candida, Cryptococcus, Coccidioides, Histoplasma*, and *Pneumocystis*.

There is also an increased incidence of tumors, such Epstein-Barr virus-associated B-cell lymphomas, other lymphomas, cervical cancer, and Kaposi’s sarcoma. Wasting syndrome and encephalopathy are also common.

Summary

A secondary immunodeficiency is one in which a person is born with normal immune responses but some secondary factor or occurrence causes a decrease in immune responses. Causes of secondary immunodeficiencies include malnutrition, some viruses such as HIV, irradiation, cytotoxic drugs used in cancer chemotherapy, anti-inflammatory steroids, leukemias, aging, and removal of the spleen. HIV infects and destroys T4-lymphocytes and when the body becomes unable to replace the T4-lymphocytes as fast as they are being destroyed, secondary immunodeficiency results.

Contributors and Attributions

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