15.1: Primary Immunodeficiency

Skills to Develop

1. Define primary immunodeficiency.
2. Compare and contrast conventional and novel primary immunodeficiencies.
3. Name four categories of conventional immunodeficiencies and give an example of each.

A primary immunodeficiency is usually an immunodeficiency that one is born with. Until recently, primary immunodeficiencies were defined as a rare recessive genetic defect in the immune responses that involved the development of B-lymphocytes, T-lymphocytes, or both and resulted in multiple, recurrent infections during infancy. Depending on the disorder, the lymphocytes in question were either completely absent, present in very low levels, or present but not functioning normally. These disorders represent the conventional immunodeficiencies.

However, based on our increased understanding of the human genome and immune responses it now appears that there are a multitude of common, less severe primary immunodeficiencies involving just one or more of the huge number of genes involved in the immune responses. These so called novel primary immunodeficiencies involve the decreased ability to combat just a single type of infection or a narrow range of infections. The conventional primary immunodeficiencies were grouped as follows:

Conventional: B-lymphocyte Disorders

In the case of B-lymphocyte disorders, there may be may be greatly decreased humoral immunity but cell-mediated immunity, mediated by T-lymphocytes, remains normal.

1. Agammaglobulinemias: Few if any antibodies are produced and there are reduced B-lymphocyte numbers. The person is very susceptible to recurrent infections by common pyogenic bacteria such as *Staphylococcus aureus*,
Streptococcus pyogenes, Streptococcus pneumoniae, Neisseria meningitidis, and Hemophilus influenzae. These bacteria have antiphagocytic capsules that are normally eliminated by antibodies through opsonization. Examples include X-linked agammaglobulinemia and Autosomal recessive agammaglobulinemia.

2. Hypogammaglobulinemias /Isotype Defects: Decreased general antibody production or decrease production of a single isotype of antibody. Examples include:

- **IgG2 subclass deficiency**: A person is unable to produce the subclass of IgG called IgG2 but can produce other classes of antibodies. There is increased susceptibility to bacterial infections.
- **Selective IgA deficiency**: A person is unable to make IgA but can produce other classes of antibodies. There is increased susceptibility to bacterial infections and certain protozoan infections.
- **Combined Variable Immunodeficiency (CVID)**: Hypogammaglobulinemia with normal or decreased numbers of B-lymphocytes.

More severe forms such as agammaglobulinemia are treated with artificially-acquired passive immunization - periodic injections of large amounts of immune globulin (IG or IVIG).

**Conventional: T-lymphocyte Disorders**

In the case of T-lymphocyte disorders, there is little or no cell-mediated immunity if the disorder involves T8-lymphocytes and/or T4-lymphocytes. There may also be decreased humoral immunity if there is a disorder involves T4-lymphocytes.

1. **MHC Expression Defects**

- MHC-I deficiency. Decreased levels of MHC-I production and reduced T8-lymphocyte numbers.
- Bare lymphocyte syndrome. Decreased levels of MHC-II, decreased numbers of T4-lymphocytes, and decreased T4-dependent antibody production by B-lymphocytes.

2. **T-Lymphocyte Signaling Defects**

- Wiskott-Aldrich syndrome. Defective T-lymphocyte activation and defective leukocyte mobility.
- Proximal TCR signaling defects. Defective cell-mediated immunity and defective T4-dependent antibody production by B-lymphocytes.

3. **Familial Hemophagocytic Lymphohistiocytosis**

- Perforin deficiencies. Defective CTL and NK cell function; uncontrolled activation of macrophages and CTLs.
- Granule fusion defects. Defective CTL and NK cell function; uncontrolled activation of macrophages and CTLs.
- X-linked lymphoproliferative syndrome. Defective CTL and NK cell function; uncontrolled activation of macrophages and CTLs. Uncontrolled Epstein-Barr virus - induced B-lymphocyte proliferation.

**Conventional: Combined B- and T-lymphocyte Disorders (Severe Combined Immunodeficiency Disease or SCID)**

Severe combined immunodeficiency disease or SCID affects both humoral immunity and cell-mediated immunity. There is a defect in both B-lymphocytes and T-lymphocytes, or just T-lymphocytes in which case the humoral deficiency is due to the lack of T4-helper lymphocytes.
1. Cytokine-Signaling Defects

- **Autosomal recessive SCID.** Shows a marked decrease in T-lymphocytes but normal to increased levels of B-lymphocytes. There is reduced antibody levels due to the lack of T4-helper lymphocytes.
- **X-linked recessive SCID.** Shows a marked decrease in T-lymphocytes but normal to increased levels of B-lymphocytes. There is reduced antibody levels due to the lack of T4-helper lymphocytes.

2. Defects in Nucleotide Salvage Pathways

- **PNP deficiency.** Shows a progressive decrease in both T-lymphocytes, B-lymphocytes, and NK cells, as well as reduced antibody levels.
- **ADA deficiency.** Shows a progressive decrease in both T-lymphocytes, B-lymphocytes, and NK cells, as well as reduced antibody levels.

3. Defects in V(D)J Recombination (Combinatorial Diversity)

- **RAG1 or RAG2 deficiency.** Shows an absence or deficiency of both T-lymphocytes and B-lymphocytes, as well as reduced antibody levels.
- **ARTEMIS defects.** Shows an absence or deficiency of both T-lymphocytes and B-lymphocytes, as well as reduced antibody levels.

4. Defective Thymus Development

The thymus is needed for the development of T-lymphocytes from stem cells.

- **DiGeorge syndrome.** Shows decreased levels of T-lymphocytes, normal levels of B-lymphocytes, and reduced antibody levels.
- **Defective pre-TCR checkpoint.** Shows decreased levels of T-lymphocytes, normal or reduced levels of B-lymphocytes, and reduced antibody levels.

**Conventional: Innate Immunity Disorders**

- **Chronic granulomatous disease.** No oxygen-dependant killing pathway in phagocytes. Recurrent intracellular bacterial and fungal infections.
- **Leukocyte adhesion deficiencies.** Defective leukocyte adhesion, diapedesis, and migration. Recurrent bacterial and fungal infections.
- **Chediak-Higashi syndrome.** Defective vesicle fusion and lysosomal function in neutrophils, dendritic cells, macrophages and other cells. Recurrent infections by pyogenic bacteria.

**Novel Immunodeficiencies**

While the rare conventional primary immunodeficiencies mentioned above are still very important, based on our increased understanding of the human genome and immune responses it now appears that there are a multitude of common, less severe primary immunodeficiencies. These so called novel *primary immunodeficiencies* relate to an individual's own unique genetics and can involve one or more of many immunity genes, ranging from any of the huge number of genes conferring protective immunity in general, to individual genes conferring specific immunity to a single pathogen.

It is now thought that almost every person suffers from one form of primary immunodeficiency or another. Unlike the classical primary immunodeficiencies, however, these primary Examples include:
• Disorders of the interleukin-12/interferon-gamma pathway appear to make individuals more susceptible to *Mycobacterium* and *Salmonella* infections.

• Disorders of the TLR-3 pathway makes individuals more susceptible to herpes simplex virus encephalitis.

• Disorders of the toll-interleukin 1 receptor/nuclear factor kappa B pathway makes individuals more susceptible to staphylococcal and pneumococcal infections.

• Disorders of properdin and terminal components of the complement pathways make individuals more susceptible to *Neisseria* infections.

• People with chronic sinusitis that does not respond well to treatment have decreased activity of TLR-9 and produce reduced levels of human beta-defensin 2, as well as mannan-binding lectin needed to initiate the lectin complement pathway.

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**Summary**

1. Immunodeficiency results in an inability to combat certain diseases.

2. A primary immunodeficiency is usually an immunodeficiency that one is born with.

3. Conventional primary immunodeficiencies are rare recessive genetic defect in the immune responses that involved the development of B-lymphocytes, T-lymphocytes, or both and resulted in multiple, recurrent infections during infancy. Depending on the disorder, the lymphocytes in question were either completely absent, present in very low levels, or present but not functioning normally.

4. Conventional primary immunodeficiencies include B-lymphocyte disorders, T-lymphocyte disorders, Severe combined immunodeficiency disease or SCID, and innate immunity disorders.

5. B-lymphocyte disorders may result in greatly decreased humoral immunity but cell-mediated immunity, mediated by T-lymphocytes, remains normal.

6. T-lymphocyte disorders may result in little or no cell-mediated immunity if the disorder involves T8-lymphocytes and/or T4-helper lymphocytes. There may also be decreased humoral immunity if there is a disorder involves T4-helper lymphocytes.

7. Severe combined immunodeficiency disease deficiencies affect both humoral immunity and cell-mediated immunity may result in a defect in both B-lymphocytes and T-lymphocytes, or just T-lymphocytes in which case the humoral deficiency is due to the lack of T4-helper lymphocytes.

8. Innate immunity disorders are due to defects in genes that play a role in innate immune responses.

9. Novel primary immunodeficiencies include a multitude of common, less severe primary immunodeficiencies involving just one or more of the huge number of genes involved in the immune responses resulting in the decreased ability to combat just a single type of infection or a narrow range of infections.

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**Contributors**

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