Immunodeficiency

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Origins of Immunodeficiency

- Primary or Congenital
  - Inherited genetic defects in immune cell development or function, or inherited deficiency in a particular immune molecule

- Secondary or acquired
  - A loss of previously functional immunity due to infection, toxicity, radiation, splenectomy, aging, malnutrition, etc.
Infectious Consequences of Immunodeficiency

- **Antibody deficiency**, **Phagocyte deficiencies**, or **Complement protein deficiencies** are associated with recurrent infections with extracellular pyogenic bacteria (pneumonia, otitis media, skin infections).

- **Deficiency in Cell-mediated immunity** is associated with recurrent or chronic viral, fungal, or protozoal diseases.

<table>
<thead>
<tr>
<th>Name of deficiency syndrome</th>
<th>Specific abnormality</th>
<th>Immune defect</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe combined immune deficiency</td>
<td>ADA deficiency</td>
<td>No T or B cells</td>
<td>General</td>
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<tr>
<td></td>
<td>FNP deficiency</td>
<td>No T or B cells</td>
<td>General</td>
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<tr>
<td></td>
<td>X-linked acid, thymidine chain deficiency</td>
<td>No T cells</td>
<td>General</td>
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<tr>
<td></td>
<td>Autsosomal acid DNA repair defect</td>
<td>No T or B cells</td>
<td>General</td>
</tr>
<tr>
<td>DiGeorge's syndrome</td>
<td>Thymic aplasia</td>
<td>Variable numbers of T and B cells</td>
<td>General</td>
</tr>
<tr>
<td>MHC class I deficiency</td>
<td>TAP mutations</td>
<td>No CD8 T cells</td>
<td>Chronic lung and skin inflammation</td>
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<tr>
<td>MHC class II deficiency</td>
<td>Lack of expression of MHC class II</td>
<td>No CD4 T cells</td>
<td>General</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>X-linked; defective WASP gene</td>
<td>Detective anti-polyaccharide antibody and impaired T cell activation responses</td>
<td>Encapsulated extracellular bacteria</td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>Loss of Btk tyrosine kinase</td>
<td>No B cells</td>
<td>Extracellular bacteria, viruses</td>
</tr>
</tbody>
</table>

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### B cell Deficiencies

- **Congenital hypogammaglobulinemia**
  - Symptoms at 9 mo. to 2 yr of age
  - Treat with intravenous immunoglobulin (IVIG)
- **Hyper IgM**: defective CD-40L expression
- **Selective IgA deficiency**
  - Occurs in 1:600-1:800 people
  - Possible connection with increased sinopulmonary infections and allergies

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<th>Susceptibility</th>
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<tbody>
<tr>
<td>X-linked hyper-IgM syndrome</td>
<td>Defective CD40 ligand</td>
<td>No isotype switching</td>
<td>Extracellular bacteria, Pneumocystis carinii, Cryptosporidium parvum</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>Unknown; MHC-linked</td>
<td>Defective IgA and IgG production</td>
<td>Extracellular bacteria</td>
</tr>
<tr>
<td>Selective IgA</td>
<td>Unknown; MHC-linked</td>
<td>No IgA synthesis</td>
<td>Respiratory infections</td>
</tr>
<tr>
<td>Phagocyte deficiencies</td>
<td>Many different</td>
<td>Loss of phagocyte function</td>
<td>Extracellular bacteria and fungi</td>
</tr>
<tr>
<td>Complement deficiencies</td>
<td>Many different</td>
<td>Loss of specific complement components</td>
<td>Extracellular bacteria especially Neisseria spp.</td>
</tr>
<tr>
<td>Natural killer (NK) cell defect</td>
<td>Unknown</td>
<td>Loss of NK function</td>
<td>Herpes viruses</td>
</tr>
<tr>
<td>X-linked lymphoproliferative syndrome</td>
<td>SH2D1A mutant</td>
<td>Inability to control B cell growth</td>
<td>EBV-driven B cell tumors</td>
</tr>
<tr>
<td>Aloiia telangiectasia</td>
<td>Gene with PI-3-kinase homology</td>
<td>T cells reduced</td>
<td>Respiratory infections</td>
</tr>
<tr>
<td>Bloom's syndrome</td>
<td>Defective DNA helicase</td>
<td>T cells reduced Reduced antibody levels</td>
<td>Respiratory infections</td>
</tr>
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</table>

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T Cell Deficiencies

- Congenital Thymic aplasia
- Chronic Mucocutaneous Candidiasis
### Severe Combined Immunodeficiency

- **X-linked SCID**:  
  - Defect in IL-2 receptor
- **Swiss-Type SCID**  
  - Adenosine deaminase deficiency
- **Bare Lymphocyte syndrome**  
  - Absence of MHC Class II gene products

### Phagocyte Deficiencies

- **Chronic Granulomatous Disease**  
  - NADPH oxidase defect
- **Chediak -Higashi Syndrome**  
  - Abnormal lysosome formation
- **Leukocyte Adhesion Deficiency**  
  - Absence of leukocyte adhesion molecules
### Complement Deficiencies

- **Single component deficiencies**
  - Example: C3 deficiency
- **Hereditary Angioedema**
  - C1 Inhibitor deficiency
- **C5,C6,C7,C8, or C9 deficiency**
  - Recurrent bacterial meningitis due defective membrane attack complex

### Causes of Acquired Immunodeficiency

- Cancer (immunoproliferative diseases)
- Cytotoxic drugs or radiation
- Malnutrition
- Splenectomy
- Immunosuppressive therapies
- Stress/emotions
- Aging (thymic atrophy)
- Infection
**Immunopathogenesis of HIV-Infection**

- HIV infects and ultimately destroys CD4+, CCR5+ or CXCR4+ T cells, monocytes, & dendritic cells.

- **Primary HIV Infection**: A vigorous immune response to HIV controls the primary infection. (clonal Cytotoxic T cells, suppressive chemokines, poorly neutralizing antibody)

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**Immunopathogenesis of HIV-Infection. (continued)**

- **Chronic Asymptomatic Phase**: Viral trapping & replication in lymphoid tissues, high rate turnover of virus and CD4 T cells, loss of CD4 functional help to CTL and antibody responses, destruction of lymph tissue, viral mutation and escape from recognition, exhaustion or viral inhibition of CD4 T cell renewal.
Immunopathogenesis of HIV-Infection. (continued)

- Overt AIDS: CD4 count declines, viral load increases, opportunistic infections.
Imune response to HIV

- Antibodies against HIV Env
- HIV-specific CTL
- Antibodies against HIV p24
- Infectious virus in plasma

4–8 weeks | 2–12 years | 2–3 years | 0–1 years

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Progression of HIV disease

- Primary infection of cells in blood, mucosa
- CD4+ T cell
- Drainage to lymph nodes, spleen
- Dendritic cell

Infection established in lymphoid tissues, e.g., lymph node

Acute HIV syndrome, spread of infection throughout the body

Immune response

Partial control of viral replication

Anti-HIV antibodies

HIV-specific CTLs

Increased viral replication

AIDS

Other microbial infections; cytokines

Clinical latency

Establishment of chronic infection; virus trapped in lymphoid tissues by follicular dendritic cells; low-level viral production

Destruction of lymphoid tissue; depletion of CD4+ T cells

From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 20-7
<table>
<thead>
<tr>
<th>Mechanisms of CD4+ T cell depletion- Dysfunction</th>
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<tbody>
<tr>
<td>• Accumulation of unintegrated viral DNA</td>
</tr>
<tr>
<td>• Loss of plasma membrane integrity due to viral budding</td>
</tr>
<tr>
<td>• Elimination of infected cells by HIV-specific immune effectors</td>
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<tr>
<td>• Syncytium formation</td>
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<tr>
<td>• Autoimmunity</td>
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<tr>
<th>Mechanisms of CD4+ T cell depletion- Dysfunction (continued)</th>
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<tr>
<td>• Superantigenic stimulation</td>
</tr>
<tr>
<td>• Apoptosis</td>
</tr>
<tr>
<td>• Infection of stem cells and interference with lymphopoiesis</td>
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