Types of Primary Immunodeficiency (PI) Disorders — Definition and Pathogenesis

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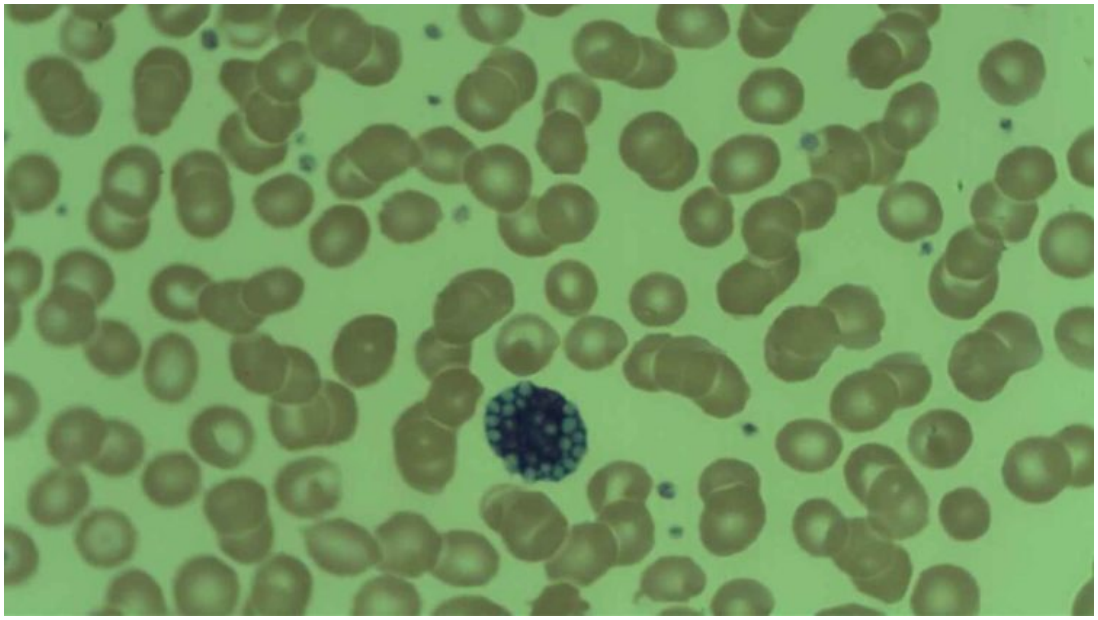
Primary immunodeficiencies differ from secondary immunodeficiencies (acquired immunodeficiencies) in that they arise from birth as a result of genetic defects. However, not all primary immunodeficiencies are present at birth and many present in adolescence or adulthood. In contrast, secondary immunodeficiencies are typically secondary to infection (e.g., HIV) or therapies (e.g., corticosteroids). The following article covers the most important primary immunodeficiencies and their underlying pathophysiology.



Definition

Primary immunodeficiency is a group of disorders that occurs due to defects in the development and function of immune system.

Complement Deficiencies

Under normal human physiological conditions, complement proteins circulate in the blood in an inactive form. When activated by a foreign body, they become enzymatically active and trigger several molecules in a series of reactions. They perform a number of functions, including:

- Promoting inflammation
- Recruiting immune cells
- Killing foreign bodies.

- Increasing immune response
- Acts as mediator in pathogenesis and prevention of immune complex diseases like SLE

Defective gene	Disorder	Typical infections
C1q, C1r, C1s, C2, C3, C4, Factor I	Impaired clearance of immune complexes, systemic lupus erythematosus	Pyogenic bacteria
C5, C6, C7, C8, C9, Factor D, Properdin	Deficiencies of these components	Disseminated Neisseria gonorrhoeae and N. meningitidis
MASP-2	MASP-2 deficiency	Streptoccocus pneumoniae
MBL	MBL deficiency (prevalence ~5 %)	Usually none

Complement reactions occur in two distinct pathways: the classical and the alternative pathway.

Classical pathway: an immune complex binds to C1, which then cleaves proteins C2 and C4. This causes cleavage of C3 and then of C5,6,8,9. A membrane attack complex forms, and cell lysis occurs.

Alternative pathway: Bacterial cell wall activates C3, causing its cleavage and then cleavage of C5,6,8,9. A membrane attack complex forms, and cell lysis occurs.

Epidemiology

Complement deficiencies comprise 1-10% of the total immunodeficiencies.

Type	Primary immunodeficiency cases
B-cell/antibody	50 %
Combined T-cell and B-cell	20 %
Phagocytes	20 %
T-cell	10 %

Pathogenesis

During a disease, complement systems can either be **overactive** or **underactive**. Complement deficiencies of the molecules that inhibit the system will cause an overactive response. Deficiencies in proteins that activate the system (like C3) lead to underactive responses. This means that patients are more susceptible to bacterial and viral infections.

Deficiencies in decay-accelerating factor (DAF)

In normal human physiology, this protein will inhibit C3 and C5 convertase, **stopping membrane attack complex formation** and the attack on human cells.

Clinical features

Due to deficiency of factor,red blood cells, in particular, are much more susceptible to lysis, leading to destruction of cells and patients present with **paroxysmal nocturnal haemoglobinuria**.

Deficiencies in C1 esterase inhibitor (hereditary angioedema)

Definition

Deficiency in C1 esterase inhibitor will result in an overactivity of C1. This causes **excess production of anaphylatoxins**, which leads to swelling of the dermis, subcutaneous tissue, mucosa and submucosal tissues, i.e., **angioedema**. C1 esterase inhibitor deficiency is known as hereditary angioedema.

Epidemiology

It is an autosomal dominant hereditary condition that occurs in 1 in 10,000 individuals. Individuals with **C2 deficiency** have an increased risk of infection.

Clinical Features

Symptoms are the result of swelling triggered by stress or trauma. Sometimes occur without any trigger. Feature of angioedema are:

- Swelling of parts, most commonly affected parts are face, limbs, gastrointestinal tract, and respiratory tract.
- Abdominal pain
- Nausea and vomiting
- Respiratory distress may result from morbid airway obstruction.

Deficiencies in C2 and C4

Loss of the complement system by deficiencies in C2 and C4 results in **underactivity** and **lack of immune activity**. These conditions can present similarly to autoimmune disorders like **systemic Lupus erythematosus**. Some C2 deficiencies have been associated with autoimmune diseases like Lupus.

C3 deficiencies

C3 deficiencies are associated with a number of conditions. Reduced levels of C3b increase the probability of developing **infections** with severe pyogenesis. This is caused by **reduced opsonization**. Individuals with C3 deficiencies are also more susceptible to **type III hypersensitivity reactions** (reduced clearance of antigen-antibody-C3b complexes from the circulation causes increased risk of hypersensitivity reactions).

C5-8 deficiencies

As noted above, C5-9 form the membrane attack complex that causes cell lysis. Without this, **gram negative bacteria** are far more likely to cause a serious infection. Of note, patients with C5-8 deficiencies are particularly susceptible to *Neisseria* infections.

Phagocytic Cell Disorders

Phagocytic cell disorders interrupt the development or functioning of phagocytes, which under normal physiological conditions ingest and digest pathogens as part of a **humoral immune response**.

Chronic granulomatous disease

In normal human physiology, phagocytes (such as neutrophils) phagocytose (or ingest) bacteria before breaking them down via reactive oxygen species. To form these reactive oxygen species, an “oxidative” burst is precipitated by enzymes such as NAPDH oxidase.

Polymorphisms in the gene that codes for NADPH oxidase can result in chronic granulomatous disease. In CGD, the oxidative burst does not occur, and phagocytes are unable to break down invading pathogens. There are several types of CGD, and around 1 in 200,000 individuals are diagnosed with the disease.

An inability to break down pathogens causes an increased susceptibility to a number of bacterial and fungal infections.

Chediak-Higashi syndrome

This is a rare autosomal recessive disorder caused by **defective neutrophil lysosome function**. It is characterized by recurrent streptococcal and staphylococcal infections.

Job’s syndrome

T-helper cells are unable to produce IFN-ɣ. This reduces macrophage activation. TH2 pathway is increased and histamine is released. Increased histamine causes **neutrophil chemotaxis,** and the patient may suffer from **recurrent “cold.”** The syndrome can also result in **atopic dermatitis** and **staphylococcal abscesses**.

Cyclic neutropenia

This autosomal dominant condition causes **irregular production of G-CSF** (which stimulates the production of granulocytes). Usually, patients will have a **neutropenia** for 3 days every 21 day cycle. During this period, they are susceptible to **bacterial infections**.

Leukocyte adhesion deficiencies

Polymorphisms in integrins on leukocytes cause improper neutrophil migration and **recurrent infections**. It is also important to note that this syndrome can cause **delayed umbilical cord separation**.

Receptor deficiencies

Both IL-12 and IFN-ɣ receptor can be defective. In **IL-2 receptor deficiency**, TH1 responses are suppressed. In **IFN-ɣ receptor deficiencies**, macrophage activation is inhibited. Both lead to **mycobacterial infections**.

Shwachman’s syndrome

This syndrome can clinically resemble cystic fibrosis. It is often characterised by **pyogenic infections** and **exocrine pancreatic insufficiency**. **Neutropenia** is caused by a defect in neutrophil migration.

Autoinflammatory Disorders

Autoinflammatory disorders are not to be confused with autoimmune disorders. In autoinflammatory disorders, the innate immune system causes inflammation without a known input. Autoinflammatory disorders will typically present with **fever**, **rash** etc. (signs of inflammation).

Familial Mediterranean fever

This disease typically results in **1-3 day episodes of fever**. Mutations on the gene encoding IL-1β cause the disease.

Epidemiology

It presents in childhood in patients of Jewish, Arab or Turkish descent (among others).

Behcet's disease

This typically presents in adults with **oral and genital ulcers**. It is common in the Middle East and Asia. The disease causes **inflammation of blood vessels**. However, the genetic underpinnings of the disease are currently unknown.

Neonatal onset multisystem inflammatory disease

This disorder often develops in the first few weeks of life and causes **inflammation in multiple organ systems,** including the nervous system, skin, etc. Newborns can develop fever and meningitis. Mutations in NLRP3 account for around 60% of patients with the disease. However, the underlying mechanism that causes the inflammation is currently unknown.

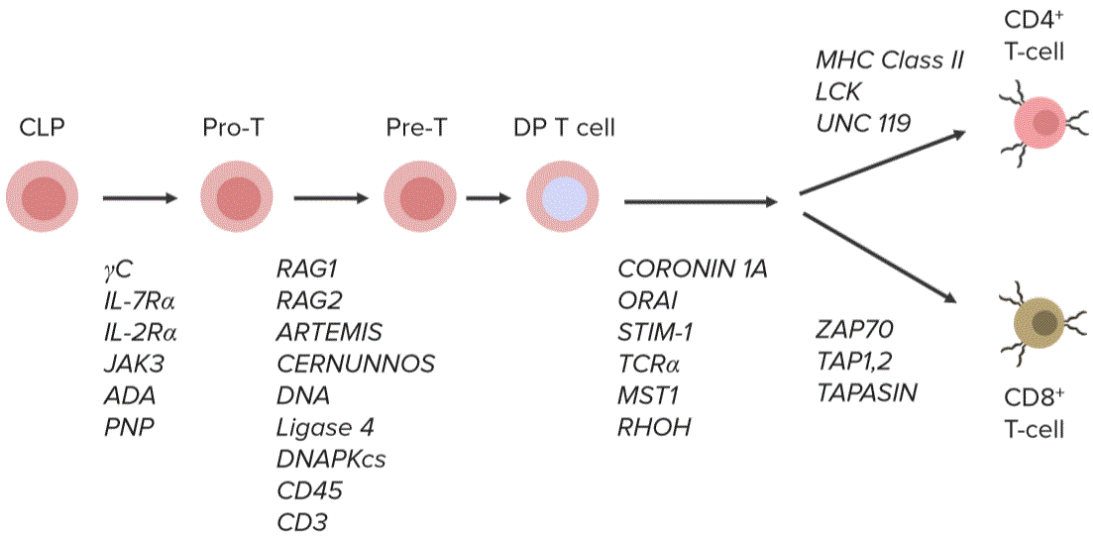
Mutations Affecting T-Cell Maturation

Mutations affecting T-cell maturation can often lead to **autoimmune conditions** whereby the immune system attacks self-antigens. **Mutations** can occur in a number of different areas including the **thymus** during T-cell selection and in **regulatory T-lymphocytes**.

Typically, during T-cell maturation, TCR's (T-cell receptors) with high affinity for self-antibodies are deleted in the thymus. The thymus expresses self-antigens in order to select TCRs with high affinity. Therefore, mutations in genes causing expression of self-antigens in the thymus can lead to autoimmune conditions.

Mutations in the AIRE gene (this gene is involved in the expression of thymic self-antigens) can lead to **autoimmune polyglandular syndrome** – whereby patients develop a number of autoimmune diseases.

In some patients, mutations can occur in regulatory T-lymphocytes. For instance, mutations in the Foxp3 gene (a transcription factor for T-regulatory lymphocytes) can cause **IPEX** (Immune dysregulation, Polyendocrinopathy, Enteropathy, X linked syndrome). Patients develop a number of autoimmune conditions after birth, including type 1 diabetes.



"Mutations affecting t-cell maturation" Image created by Lecturio

B-Cell Immunodeficiencies

Common variable immunodeficiency

This type of immunodeficiency characteristically presents in **early adulthood** with **recurrent upper and lower respiratory tract infections**. IgG levels are typically below 0.5 g/L. The disease is caused by a myriad of genetic mutations and typically affects 1 in 50,000.

X-linked agammaglobulinemia

Definition

This heritable disease is caused by a **lack of B cells**. B-cell development falters at the pre-B stage. An **X-chromosome gene polymorphism for tyrosine kinase** causes a loss of function mutation that inhibits B-cell maturation.

Clinical Features

The disorder will present shortly after birth, when maternal immune (IgG) protection falls. Presentations with recurrent respiratory tract infections are characteristic.

Treatment

Treatment is usually given as **IV immunoglobulins**.

Prognosis

Prognosis was historically poor, but recently, patients have survived into adulthood.

Complications

Chronic lung disease and **lymphomas** are complications that can cause mortality.

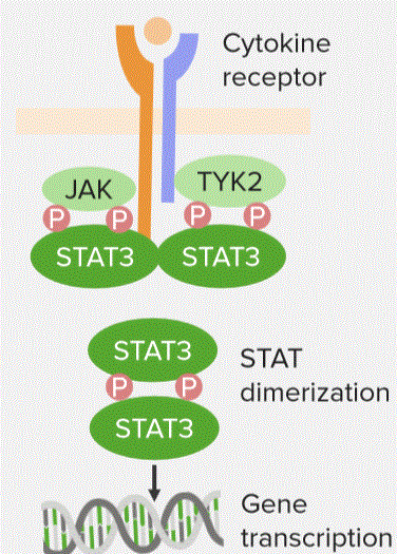
Selective IgA deficiency

This is a relatively common primary immunodeficiency, occurring in 1 in 600 people in

some parts of Europe. Recurrent infections typically cause presentation. There is no known pathogenesis.

T-Cell Immunodeficiencies

Hyper IgM syndrome



"Hyper-IgE Syndrome" Image created by Lecturio

X-linked mutation in the CD40 ligand gene causes abnormal signaling between B- and T-lymphocytes. Typically, CD40 is involved in the generation of B-lymphocytes with high affinity immunoglobulin. It is also involved in the maturation of T-cells. The disease is mild and often only presents in later life. Opportunistic infections will occur.

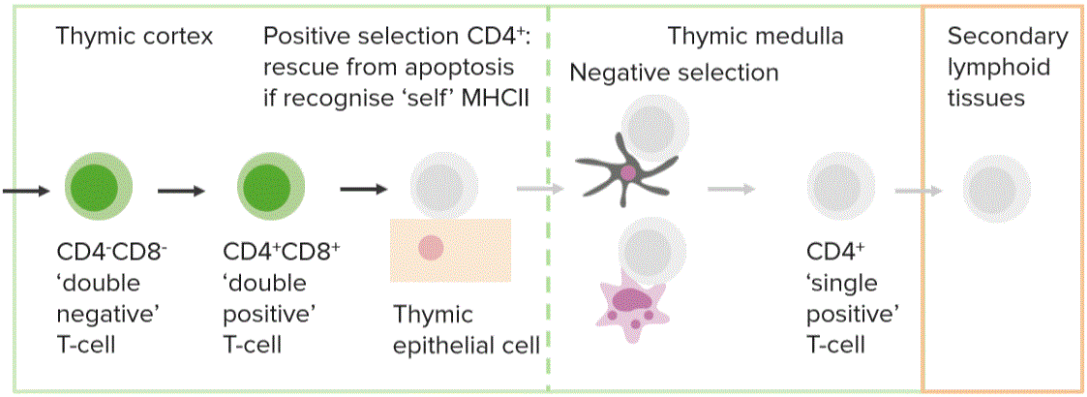
Immune dysregulation IgE eosinophils, B-cells, NK-cells, CD8+ T-cell proliferation and activation. Autosomal dominant mutation is in STAT 3 or autosomal recessive mutations in TYK2 or DOCK 8. STAT3 and TYK2 signaling through several cytokine receptors.

Wiskott-Aldrich syndrome

This is an **X-linked condition** causing **cytoskeletal functional deficits**. **Eczema** and **thrombocytopenia** are observed.

MHC class II deficiency

This deficiency is often referred to as **bare lymphocyte syndrome**. It is a rare immunodeficiency; it accounts for a small (5%) portion of severe combined immunodeficiency. The syndrome causes **lack of HLA class II expression**. This results in a **lack of T-cell immune response**. Patients are highly susceptible to **infection**.



"MHC class II deficiency" Image created by Lecturio

Examples of Immunodeficiencies affecting T-Cells

Defective gene	Disorder	Typical infections
CD40L, CD40, AID, NEMO or UNG	Hyper-IgM syndrome	Pneumocystis jirovecii, Toxoplasma, Cryptosporidium parvum
STAT3, TYK2, DOCK8	Hyper-IgM syndrome	Extracellular bacteria, staphylococci, Aspergillus spp., Candida albicans
TBX1	DiGeorge syndrome	Multiple
WASP	Wiskott-Aldrich syndrome	Encapsulated extracellular bacteria
TAP1, TAP2 or tapasin	MHC class I deficiency	Bronchopulmonary
CIITA	MHC class II deficiency	Bronchopulmonary

Severe Combined Immunodeficiency (SCID)

Definition

SCID is an umbrella term to describe a number of disorders resulting in **impaired B- and T-cell activity**.This leads to recurrent infections.

Epidemiology

It affects just 1 in 100,000 individuals.

Pathophysiology

The most common mutation is found on the **IL-2 receptor gene**.

Typically, **newborns** will suffer **intracellular pathogenic infections**, as humoral immunity is received by IgG and IgA in breast milk. Newborns suffer from **opportunistic infections,** and without treatment the disease is fatal**.**

Clinical Features

SCID is a life threatening syndrome.Patients present before three months of age with recurrent infections. Common features are:

- Diarrhea
- Dermatitis
- Failure to thrive due to repeated infections and malnutrition.

Treatment is typically one of the following:

- Stem cell transplantation
- Gene therapy
- Enzyme replacement therapy.

Prognosis

SCID is highly fatal disease. Death results from repeated infections before the age of 2years.

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