Complement System

Learning Outcomes

1. List the stages of complement activation
2. Describe the various steps and three pathways involved in activation of complement
3. Describe and compare the formation of the C3 convertase and C5 convertase complexes in the three pathways of complement activation
4. Illustrate the role of antibodies (IgM, IgG) in activation of C1 complex
5. Apply knowledge of the role of complement proteins in complement action to explain how a deficiency in complement protein(s) may lead to increased susceptibility to infection

Overview of Innate Immunity

Innate immunity is an ancient defense mechanism present in higher order animals and plants for over 400 million years. It is the first line of defense against infectious microorganisms and diseases, functioning from birth. Unlike adaptive immunity, which is acquired and developed over time, innate immunity is always available to protect against pathogens.

Components of Innate Immunity

The first encounter of pathogens is with barrier tissues, which include:

- Skin
- Mucosa
- Respiratory epithelia
- Intestinal lining

These barriers serve as physical or anatomical defenses. If these barriers fail, the body employs pre-formed chemical mediators, including:

- Antimicrobial peptides
- Enzymes that break down bacterial cell walls
- Complement proteins: soluble factors that become activated upon encountering foreign substances, initiating a cascade of immune responses.

Role of Cytokines and Effector Cells

If initial defenses fail, cytokines are produced to recruit effector cells, which include various immune cells that can engulf pathogens, kill infected cells, or activate further protective responses. If these mechanisms are insufficient, the adaptive immune response is activated.

Introduction to the Complement System

The complement system was discovered in the early 1900s by Jules Border, who identified heat-labile factors in serum that enhanced the antimicrobial function of antibodies. The complement system consists of approximately 30 proteins, primarily produced by the liver (+macrophages and monocytes), that exist as inactive pro-enzymes or zymogens until activated in a cascade. They are widely distributed in tissues and bodily fluids.

Functions of Complement Proteins

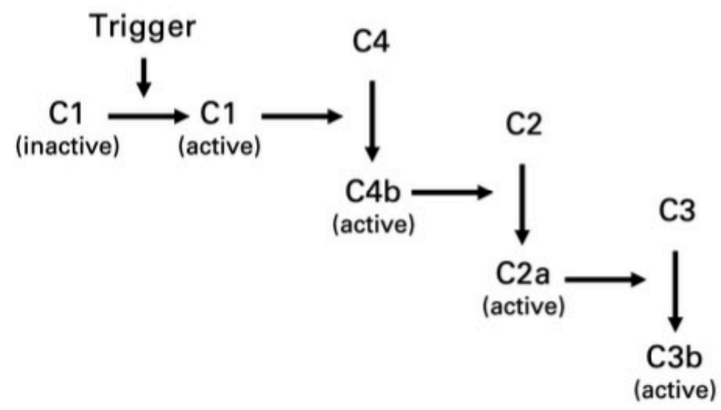
Activation of the complement system leads to several outcomes:

- Lysis of bacteria and infected cells
- Facilitation of phagocytosis through opsonization
- Promotion of inflammation and recruitment of immune cells

Complement proteins make up about 10% of the globulin fraction in plasma and are crucial for both innate and adaptive immune responses.

Activation of the Complement Cascade

The complement cascade is activated in a sequential manner, starting with an initial trigger that activates the first protein, leading to a series of amplifications. The proteins are cleaved into smaller (a) and larger fragments (b),, respectively, with the exception of C2, where the larger fragment is called C2a.



Activation and Cell Attachment

Complement activation typically occurs on the surface of pathogens or other cells. Some products of complement activation can bind to the surfaces of:

- Bacteria
- Parasites
- Infected cells
- Foreign (transplant) cells

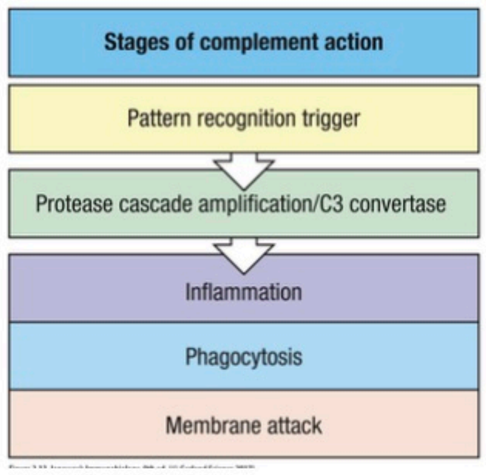
Either alone, or bound to antibody

Regulation of Complement Activation

Complement activation is tightly regulated to prevent damage to host cells. Host cells express regulatory proteins that inhibit complement binding, ensuring that complement proteins primarily target microbial surfaces. Any activated complement components that do not bind to microbial surfaces are quickly deactivated.

Stages of Complement Action

1. Pattern recognition trigger
2. Protease cascade amplification/C3 convertase
3. Inflammation + Phagocytosis + Membrane attack complex

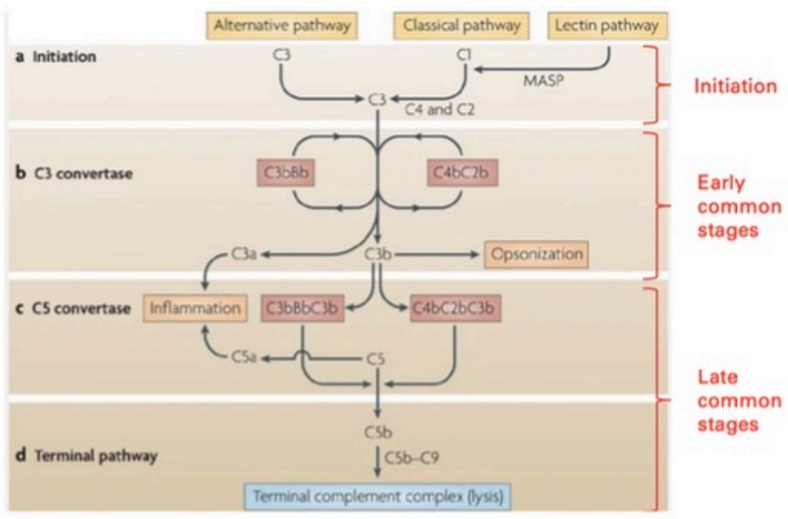


Complement Activation Pathways

There are three main pathways for complement activation:

- **Classical Pathway:** Involves antigen-antibody complexes (IgM and IgG) and is an effector mechanism of humoral immunity.
- **Alternative Pathway:** Involves direct binding of spontaneously activated complement proteins to microbial surfaces, independent of antibodies.
- **Lectin Pathway:** Initiated by the binding of lectins to sugar residues on microbial surfaces.

All pathways converge to generate a complex known as C3 convertase, which cleaves C3 and initiates further complement activation. C3b is critical for opsonization.



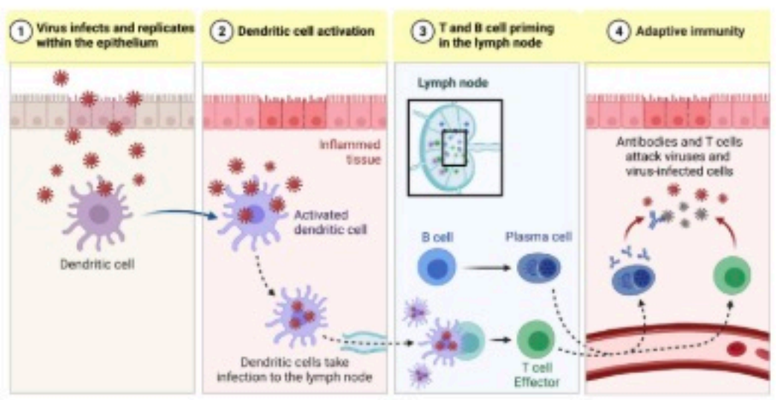
Effector Mechanisms in Cell-Mediated Responses

Learning Outcomes

- Describe the signals involved in T cell priming by dendritic cells
- Understand the regulation of CD8+ T cell homing to skin and intestine
- Explain the mechanism of CD8+ T cell mediated target cell killing
- Outline the major subsets of effector T cells, including the cytokines involved in their differentiation and function

Overview of Infection Process

When an infection occurs, such as in the skin, the virus replicates within the skin cells, particularly keratinocytes. This leads to the release of foreign antigens, which are then processed into peptides. These peptides are loaded onto Major Histocompatibility Complex (MHC) class I and II molecules.



Dendritic Cell Activation

Dendritic cells (DCs) play a crucial role in the immune response. Upon encountering antigens, they become activated and change shape, developing long protrusions that enhance their ability to capture and process antigens. Activated dendritic cells then migrate to the draining lymph node, where they facilitate the activation of T cells.

Lymph Node Functionality

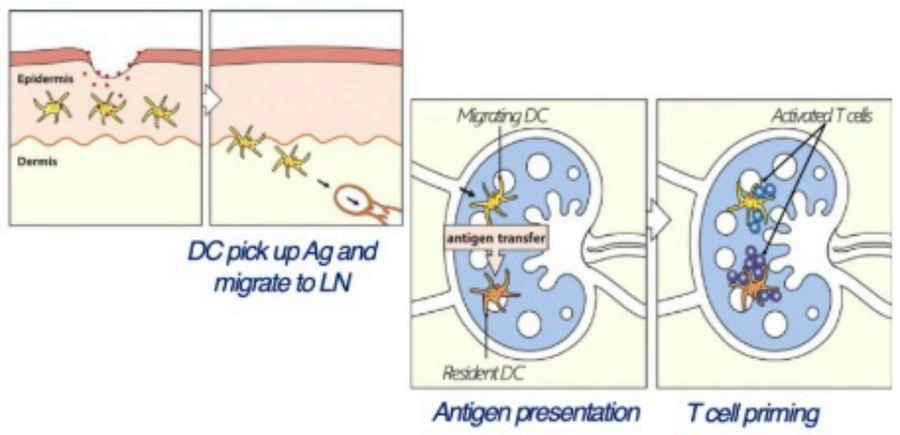
The lymph node is highly compartmentalized, allowing for efficient T cell activation. Dendritic cells utilize chemokine gradients to locate T cells in the T cell zone, where they present antigens and provide necessary signals for T cell activation. This process is essential for initiating the adaptive immune response.

Adaptive Immune Response

Once activated, T cells exit the lymph node and travel to the site of infection, guided by chemokine gradients. Some T cells differentiate into long-lived memory cells, which enhance the immune response upon re-exposure to the same pathogen.

Dendritic Cell Subsets

Dendritic cells can be categorized into two main subsets: resident DCs, which remain in the tissue, and migratory DCs, which transport antigens to lymph nodes. This antigen handover is critical for T cell priming and activation.

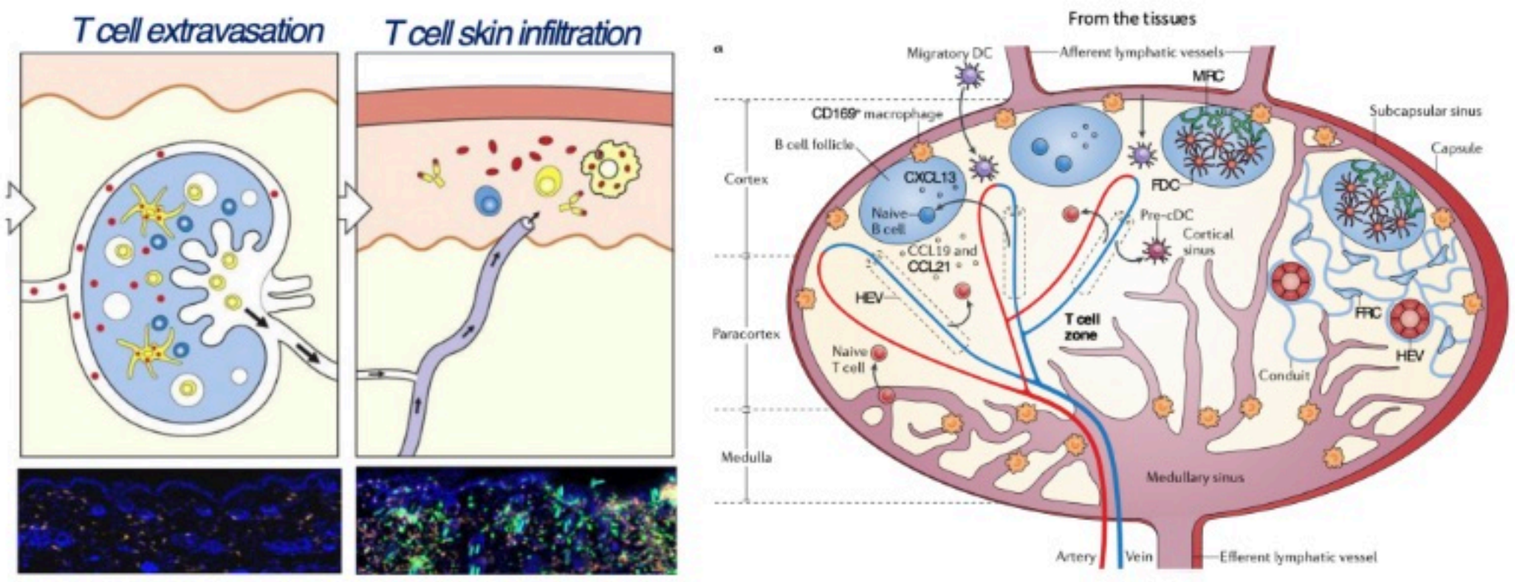


T Cell Nomenclature

In immunology, terminology can vary. Activated T cells are often referred to as effector T cells. The terms naive, activated, and memory T cells are commonly used, with some variations in terminology across different texts. For example, CD8 T cells may be referred to as cytotoxic T lymphocytes (CTLs).

Real-Life Observations

In experimental models, such as mice, the dynamics of T cell infiltration can be observed. Initially, the skin may show few T cells, but by five days post-infection, activated T cells flood the area, demonstrating the effectiveness of the immune response.

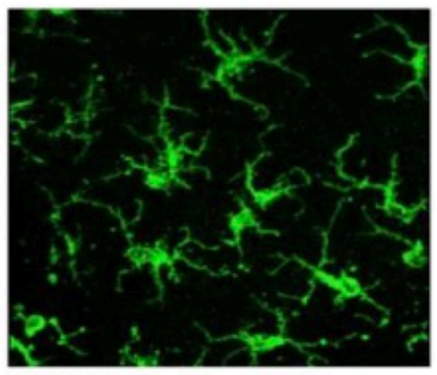


Homing Mechanisms

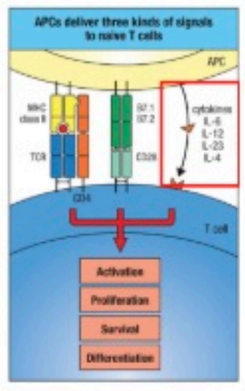
T cells utilize specific molecules for homing to lymph nodes, primarily chemokine receptors like CCR7. This receptor is essential for T cell priming and response efficacy. Other markers, such as L-selectin, also play a role in T cell trafficking.

Dendritic Cell Network in the Skin

Dendritic cells in the skin are strategically positioned to capture antigens. Upon activation, they migrate to lymph nodes, where they interact with T cells, providing co-stimulatory signals and cytokines that dictate T cell differentiation.



DC (GFP⁺) network in murine skin



Cytokine Signaling and T Cell Differentiation

Dendritic cells not only present antigens but also secrete cytokines that influence the type of immune response. For instance, during a viral infection, cytokines like IL-12 promote the differentiation of CD8 T cells, leading to a type 1 immune response characterized by interferon-gamma production.

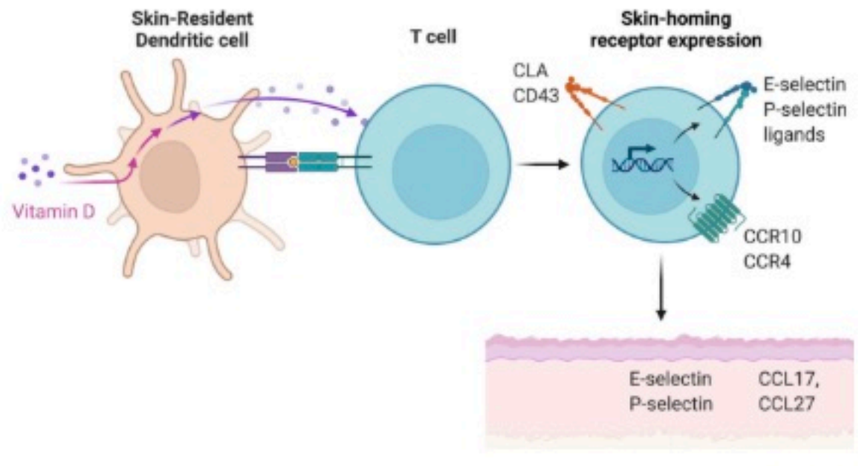
Types of Immune Responses

Immune responses can be categorized based on the cytokines produced:

- **Type 1 Response:** Characterized by interferon-gamma, typically associated with viral infections.
- **Type 2 Response:** Involves IL-4 production, often related to allergic reactions.
- **Type 17 Response:** Associated with IL-17 production, relevant in conditions like psoriasis.

Role of Dendritic Cells in T Cell Guidance

Dendritic cells (DCs) play a crucial role in directing T cells to specific tissues. In the epidermis, DCs are exposed to high levels of vitamin D, which they process and use to signal T cells. This interaction leads to the upregulation of skin-homing molecules on T cells.



Vitamin D and T Cell Homing

When T cells are exposed to vitamin D, they increase the expression of various skin-homing markers, including:

- CCR10
- CCR4
- E-selectin
- P-selectin
- CLA

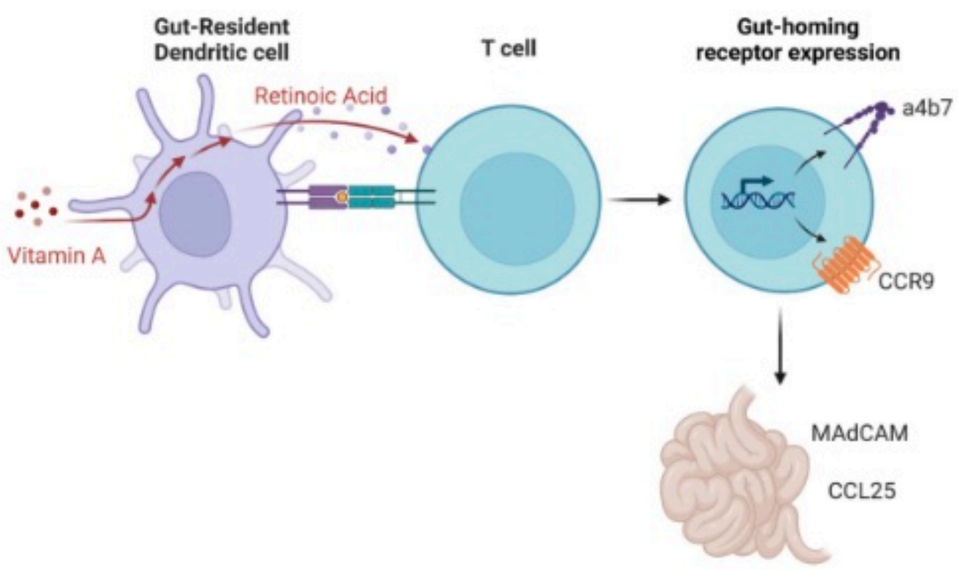
These markers facilitate the migration of T cells back to the skin, where their corresponding ligands are present, effectively providing a "postcode" for the T cells.

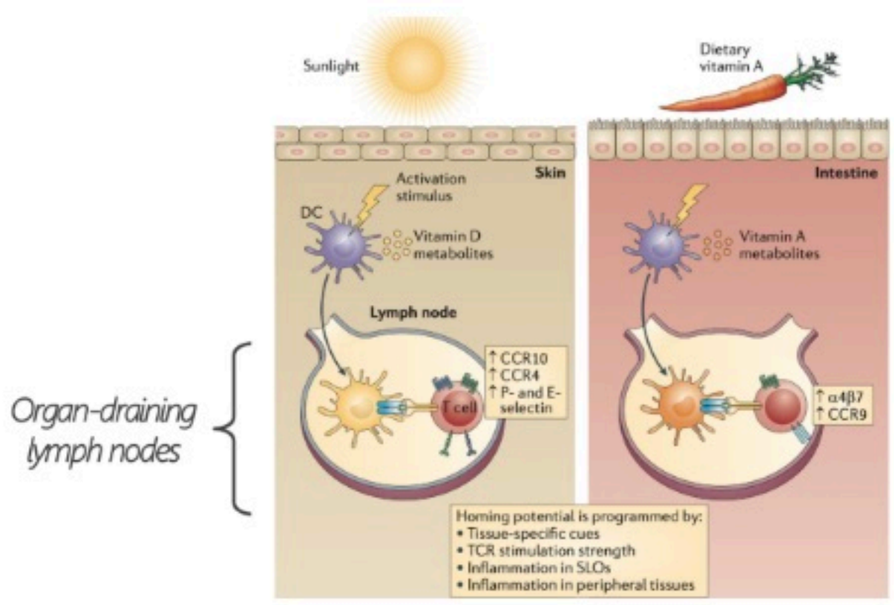
Similar Mechanism in the Gut

In the gut, a similar process occurs with vitamin A. Dendritic cells in the gut convert vitamin A into retinoic acid, which induces the expression of specific markers on T cells, such as:

- CCR9
- Alpha 4 Beta 7 integrin

These markers guide T cells to the gut, ensuring they reach the appropriate location for immune response.





Experimental Evidence

Recent studies, such as those conducted by Brian Sheridan, demonstrate the importance of the route of infection in T cell priming. For example, when mice are infected with Listeria through food, the gut-resident dendritic cells become activated and promote the expression of gut-specific markers on T cells. In contrast, if Listeria is introduced via the bloodstream, T cells are primed in the spleen and do not express the necessary markers to migrate to the gut.

Immunodeficiencies

Definition and Complexity of the Immune System

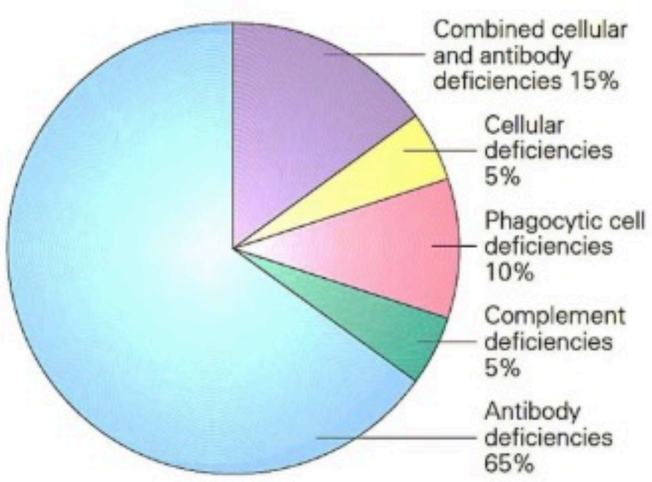
Immunodeficiencies occur when a component of the immune system is defective, which can involve a multitude of components due to the immune system's complexity. Mutations or genetic defects can lead to various immune deficiencies, affecting different parts of the immune response.

Immunocompromised States

Individuals with weakened immune systems are termed immunocompromised. This condition can be genetic or acquired, such as through immunosuppressive drugs.

Types and Prevalence of Immunodeficiency Diseases

There are over 100 immunodeficiency diseases, broadly categorized into combined cellular and antibody deficiencies, with SID being a severe form affecting both B and T cells. The majority of these deficiencies are antibody-related, with symptoms varying based on the specific defect in immune pathways.



Impact of Defects in Immune Pathways

Defects can occur at different points in immune pathways, such as thymic maturation affecting T cells or isotype switching affecting antibody production. The severity of immunodeficiency depends on the defect's location and nature within these pathways.

Role of Immunodeficiencies in Immunology Research

Studying immunodeficiencies has significantly advanced immunology by helping to understand gene functions and immune mechanisms. Modern techniques like CRISPR allow for creating genetic defects in animal models to study immune responses, which can then be correlated with human conditions.

Categories of Immunodeficiencies

Immunodeficiencies are mainly divided into primary and acquired types:

1. **Primary Immunodeficiency Disorders (PID):** Inherited genetic mutations causing immune failure, often X-linked or autosomal recessive. More than 60% affect males due to X-linkage.
2. **Secondary (Acquired) Immunodeficiencies:** Develop due to external factors like infections (e.g., HIV), cancer, autoimmune diseases, or immunosuppressive treatments.

Examples of Acquired Immunodeficiencies

- **HIV/AIDS:** Depletes CD4 T cells, impairing immune response and increasing susceptibility to infections and cancers like EBV-related B cell lymphoma.
- **Cancer and Viral Infections:** Certain viruses infect immune cells, leading to immune suppression and malignancies.
- **Immunosuppressive Drugs:** Used in autoimmune diseases or post-transplant, these drugs reduce immune function, increasing vulnerability.

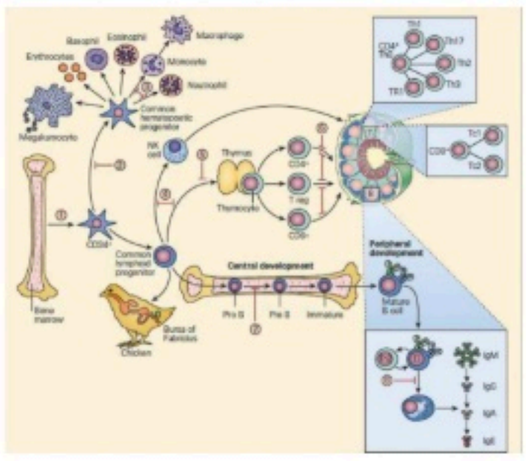
Diagnosis of Immunodeficiencies

Most primary immunodeficiencies manifest early in life with recurrent infections, including opportunistic pathogens, as well as allergy, autoimmunity, cancer. Diagnostic tests include measuring serum antibody levels and lymphocyte counts, which help identify immune deficiencies.

Treatment Strategies

Treatment varies depending on the defect:

- **Immunoglobulin Replacement:** Regular infusions of IgG or IgA are common, especially for antibody deficiencies, and are lifelong.
- **Enzyme Replacement Therapy:** For example, ADA deficiency was the first condition treated with genetically engineered enzyme replacement.
- **Bone Marrow Transplant:** The definitive treatment for severe combined immunodeficiency (SID), aiming to restore immune function entirely.



- Phagocytic cell deficiencies
- Complement deficiencies
- B cell deficiencies
- T cell-mediated deficiencies
- Combined cellular and antibody deficiencies (severe combined immunodeficiencies [SCID])