University of Basrah
Medical College, Microbiology Dep.

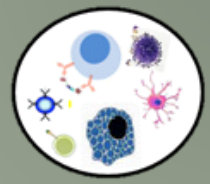
Ministry of Higher Education
& Scientific Researches

Microbiology/ 3rd Year M.B.CH.B. Students
Part V: Basic & Clinical Immunology (17 hours)
Lecture 15
Duration: 1 hour

Immunodeficiency Diseases

Assist. Prof. Dr. Nibras S. Al-Ammar

Reference: Roitt's Essential Immunology 13th Edition



For more detailed instruction, any question, cases need help please post to the group of session.

Key definitions

Pathogen-associated molecular patterns (PAMPs): particular molecular patterns that are typically associated with infectious agents. PAMPs after being recognized, trigger activation of the innate immune system.

Pattern recognition molecules: present either as cell-associated receptors (PRR) on the surface of the immune cells [Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-1-like receptors (RIRs)] or soluble molecules [complement, mannose binding lectin, C-reactive protein, and lysozyme]. Pattern recognition molecules can recognize the PAMPs.

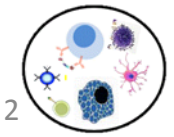
(NADPH): nicotinamide adenine dinucleotide phosphate

NK cells: natural killer cells play important roles in surveillance & subsequent destruction of infected cells & production of cytokines such as IFN-γ.

Factor I: a protein regulates the complement system activation by cleaving cell-bound or fluid phase C3b & C4b

MyD88: adaptor protein is required for signaling through a number of Tool-like receptors (TLRs).

IL1R-associated kinase-4 (IRAK4): involved in signaling through IL-1 & IL-18 receptors, also through a number of Tool-like receptors (TLRs).



Key definitions

cold urticaria: is a skin reaction to cold that appears within minutes after cold exposure. Affected skin becomes reddish & itchy. Some people have minor reactions to the cold, while others have severe reactions.

Hereditary angioedema: **a disorder characterized by recurrent episodes of severe swelling (angioedema). The most common areas of the body develop swelling are the limbs, face, intestinal tract, and airway.**

Mannose-associated serine proteases (MASPs): enzymes (proteases) that found in circulation bounded to MBL & Ficolin, involved in lectin pathway of complement system and responsible for cleaving C4 & C2 into fragments to form C3- convertase (activated when MBL bound to PAMPs).

Key definitions

Mannan Binding Lectin (MBL) & Ficolin: proteins found in circulation bounded with proteases, known as the (MASPs). MBL & Ficolin can bind with PAMPs leading to activation of MASPs.

Myeloid cells: **nucleated hematopoietic cells in the body consisting of a range of cell types with diverse functions. They have a critical role in immune system. (monocytes, macrophages, DCs & granulocytes)**

Key definitions

Infantile agammaglobulinaemia (Bruton's syndrome): is a disorder at birth (congenital) characterized by low or completely absent levels of Igs in bloodstream.

X- linked: is a trait where a gene is located on X chromosome (human have two sex chromosomes, X & Y. In X-linked disease, usually males are affected because they have a single copy of the X chromosome that carries the mutation.

Thymic Aplasia (DiGeorge Syndrome): T-cell deficiency, characteristic face, congenital heart disease & hypocalcemia. It is caused by abnormal formation of certain tissues during fetal development.

Key definitions

Hyper IgM syndrome: rare disorder in which immune system does not function properly (irregularities in cell development and/or cell maturation process of the immune system.

Severe combined immunodeficiency disease (SCID): typically presents in infancy results in a weak immune system that is unable to fight even mild infections.

Learning Objectives:

Definition of immunodeficiency	LO.1
Deficiencies of pattern recognition receptor (PRRs) signaling	LO.2
Phagocytic cell defects	LO.3
Primary immunodeficiency affecting other cells of innate response	LO.4
Complement system deficiencies	LO. 5
Cytokines & cytokine receptor deficiencies	LO.6
Examples of congenital immunodeficiency	LO.7
Secondary (Acquired immunodeficiency)	LO.8
Laboratory investigation of immunodeficiency	LO.9

What is immunodeficiency?

“State in which the immune system is unable to respond appropriately and effectively to infectious microorganisms”

Infections suggesting underlying immune deficiency defined as:

SPUR

S: Severe

P: Persistent

U: Unusual

R: Recurrent

What makes an individual “immunocompromised”?

Factors that cause defective Immunity:

1. **Congenital** (Intrinsic defect)----- **Primary immunodeficiency**
   - Single-gene disorder
   - Polygenic (??)
   - HLA Polymorphisms

2. **Acquired**------- **Secondary immunodeficiency**

(Diseases or conditions affecting immune components)

Deficiencies of pattern recognition receptors (PRRs) signaling:

Examples:

1. MyD88 deficiency:

- **Patients with MyD88 deficiency suffer from severe life-threatening infections with pyogenic bacteria (pneumococci & *Salmonella*).**

2. IL1R-associated kinase-4 (IRAK4)

-IRAK4 deficient individuals, Gram +ve pyogenic bacteria (*Streptococcus pneumonia & Staphylococcus aureus*) are most commonly seen.

Phagocytic cell defects

LO.3

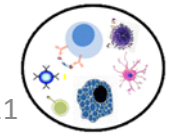
Chronic Granulomatous Disease:

Patient suffers from relatively restricted range of infectious pathogens.

Monocytes & neutrophils fail to produce reactive oxygen intermediates; defect in (NADPH) oxidase system.

The most common are:

- *Staphylococcus aureus*
- *Candida albicanus*
- *Aspergillus fumigatus*



Primary immunodeficiency affecting other cells of innate response

- **NK cells** (susceptible to viral and mycobacterial infections)
- **Dendritic cells**
- **Monocytes**
- **Mast cells** (defect in certain gene causes cold urticaria in which patient's mast cells spontaneously degranulate in cold temperatures.

Complement system deficiencies

LO. 5

1. Lacking Factor I ------- inability to destroy C3b lead to continual activation of the alternative pathway

- **very low C3 & Factor B levels**
- **Normal C1, C4 & C2 levels**

Repeated life-threatening infection with pyogenic bacteria.

2. Defect in C1 inhibitor ------- hereditary angioedema

3. **Deficiencies in C1q, C1r, C1s, C2, C3, & Factor I** --------

------ can all predispose to development of immune-complex mediated autoimmune diseases (SLE).

4. **Patients deficient in components of MAC** exhibit increased susceptibility to disseminated *Neisseria gonorrhae.*

5. **Patients with MASP-2 deficiency** have increased pyogenic infections (such as *Streptococcus pneumonia).*

Q: Reduced levels of MBL are fairly common but does not result in a detectable increase in infections in most cases.

Explain Why ???

Cytokines & cytokine receptor deficiencies

Examples:

Mutations in the genes encoding:

1. **IL-10, IL-10 R1 & IL-10 R2 lead to defective regulation of myeloid cells & development of inflammatory bowel disease.**
2. **IL-17 ------ increased susceptibility bacterial infections & candidiasis.**

Examples of congenital immunodeficiency

(LO.7)

B- cell deficiencies:

Infantile agammaglobulinemia (Bruton's syndrome)

- pure B cell deficiency syndrome.
- X- linked due to lack of tyrosine kinase which results in failure of B cell development and few or absent B cell count with low immunoglobulin levels .
- patient presented with repeated **pyogenic** infection .

(LO.7)

Clinical case example of Bruton's disease:

- **12-month-old boy with 4 episodes of severe gram-positive bacterial pneumonia in the last 6 months.**

Age | Frequency | Severity | Microbes | When?

- **Had recurrent diarrhea (Giardia lamblia) & his tonsils are barely detectable.**

Microbes

- **Below the norm for height and weight.**

Failure to grow

- **Recommended pediatric immunizations (low IgG & low B cells).**

Lab.

- **Has 3 healthy sisters aged 3, 5, & 7 years. The family lost a boy at 10 months of age due to bacterial pneumonia 8 years ago.**

Family history

IgA deficiency

(LO.7)

- The **most common** immunodeficiency.
- Very low IgA level with normal B cell count.
- Some have recurrent infections, especially of the **sinuses** and **lung**, caused by pyogenic bacteria.
- Anti-IgA antibodies can be detected in about one-third of the patients.

Hyper IgM syndrome

- This syndrome is characterized by low levels of IgG, IgA, and IgD in association to a marked elevation of IgM.
- The helper T cells have a defect in the surface protein CD40L that interact with CD40 on the B cell surface.
- This results from inability of B-cell to switch from the production of IgM to other classes.

Combined immunodeficiency

(LO.7)

Severe combined immunodeficiency disease (SCID)

- Recurrent infections caused by bacteria, viruses, fungi and protozoa occur in early infancy (3 months).
- Deficiency of both B-cell and T-cell function.
- It is inherited disease due to defect in differentiation of an early stem cell.

Secondary (Acquired immunodeficiency)

(LO.8)

1. Immunodeficiency caused by drugs

Drugs causing neutropenia, when neutrophil count <500ul , it predispose to severe infections caused by pyogenic bacteria and enteric gram negative rods.

- Cytotoxic drugs in cancer chemotherapy;
- Immunosuppressive drugs in autoimmune disease;
- Corticosteroids

2. Immunodeficiency caused by infection

- In patients with AIDS, human immunodeficiency virus (HIV) alters T cell immunity and allows further infection with opportunistic pathogens.
- Certain bacteria release toxins that function as super antigens

3. Other causes of Immunodeficiency

- Renal failure
- Diabetes
- Malnutrition
- Liver Failure

Laboratory investigation of immunodeficiency (1)

(Look for secondary immunodeficiency General):

(LO.9)

- **Full blood count and differential**

Tests of humoral (antibody) immunity

Tests for Cell mediated immunity

Tests for phagocytic cells

Tests for Complement

Definitive tests:

Molecular testing and Gene mutations

Thank You