University of Sulaimani
Faculty of Medical Sciences
School of Medicine
Department of Microbiology
Third Year
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IMMUNOLGY COUSE BOOK

Contents

Course coordinator and list of teachers on this course

1- Name of the Course: **Immunology**

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Course Overview

Immunology is one of the basic medical sciences; it discusses the immune phenomena against microorganisms, tumours and foreign cells entering the human body. The course is arranged for third year medical students as part of the basic medical science subjects to serve their understanding of diseases and also as a window to know about immune mediated diseases.

Immunology is an essential part to understand the pathogenesis of many of human diseases especially infectious diseases, tumour pathogenesis and also as a major player behind several disorders such as autoimmune disorders, allergic disorders and transplantation medicine. The medical side of immunology will reflect on all these problems but to understand the processes basic immune reaction will be illustrated.

The knowledge of immunology will be needed in treatment of several diseases, prevention of diseases and vaccination. The integration of immunology with medicine is important to understand the disease process in human.

Course objectives

The objectives of the immunology course are to:

- ✓ Identify the elements of the human immune system, this include the cells, molecules and tissues responsible for immune reaction.
- ✓ Understand the function of the cells, tissues and molecules that play role in immune reaction.
- ✓ Understand the interaction network between immune cells, immune molecules and other human cells.
- ✓ Identify the role of immune system in human protection against infectious agents and to the effect of immune deficiency on human.
- ✓ Understand the role of immune reaction in several diseases including allergic and autoimmune disorders.
- ✓ Understanding the effect of immune system on tissue and organ transplantation.
- ✓ Using immune modulators in treatment of many disorders.

Course Reading list

Text books

1. Kuby Immunology, 6th Edition.

2. Rich Clinical Immunology: Principles and Practice, 3rd Edition.

Periodicals for further readings

1. The Journal of Allergy and Clinical Immunology (JACI), the official scientific journal of the American Academy of Allergy, Asthma and Immunology (AAAAI).

2. Annals of Allergy, Asthma and Immunology, the official publication of the American College of Allergy, Asthma, & Immunology (ACAAI).

3. Immunology and Allergy Clinics of North America.

Syllabus

No.	Subjects	Hours	Lecturer's Name
1	Introduction to immunology	1	Dr. Sherko A. Omer
2	Cells of the adaptive immune system	3	Dr. Sherko A. Omer
3	The lymphoid organs and tissues	1	Dr. Sherko A. Omer
4	Major histocompatibility complex (HLA)	1	Dr. Sherko A. Omer
5	Antigens	1	Dr. Sherko A. Omer
6	Molecules that recognize antigen (Immunoglobulin, TCR)	2	Dr. Sherko A. Omer
7	Cytokines	1	Dr. Sherko A. Omer
8	The complement system	1	Dr. Sherko A. Omer
9	Antigen-antibody interaction	1	Dr. Sherko A. Omer
10	Adaptive immune response	1	Dr. Sherko A. Omer
11	Regulation of immune response	1	Dr. Sherko A. Omer
12	Mucosal immune system	1	Dr. Sherko A. Omer
13	Immunodeficiency Disorders	3	Dr. Dana M. Tofiq
14	Hypersensitivities & Allergic Diseases	4	Dr. Dana M. Tofiq
15	Transplantation	2	Dr. Dana M. Tofiq
16	Tumor Immunology	2	Dr. Dana M. Tofiq
17	Autoimmune Diseases	2	Dr. Dana M. Tofiq
18	Immune Manipulation	2	Dr. Dana M. Tofiq

Subject: **Introduction to immunology**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The meanings of immunology, immunity and immunization
- ✓ The concept of specificity and memory in immune response.
- ✓ The benefit if immunity on human protection against infection.
- ✓ To identify the differences between Innate and adaptive immune system.
- ✓ The natural and artificial induction of immune system.

In this session the basic terms that describe immunology, immunity, immunization will be defined, the rise of immunology as a science will be illustrated A detailed outline is presented on the main difference between **innate** (**non specific)** and **adaptive (acquired)** immune responses with examples for each mechanism and those mechanism that may work on both arm.
Memory is the ability of immune system to remember those materials it has been **exposed** to previously. **Specificity** means the ability to react specifically to that antigen. Memory, specificity and ability to discriminate **self from non self** are the characteristics if adaptive immune system

Subject: **Cells of the adaptive immune system**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The principle playing- role cells of the immune system.
- ✓ The use of cluster of designation (CD) to identify different cells
- ✓ The morphology, distribution function and interaction of adaptive immune response cell.

In this session the cells that play role in immune response will be classified according to their importance and role. The importance of cluster of designation (**CD**) as a method to name surface molecules will be outline and the importance of CD will be illustrated regarding the cell type, developmental stags and in malignancies where condition.
The student should understand the importance of **lymphocytes (T, B and natural killers cells NK)** as the main cells of immune response, classification, identification and functional role of these cells will be essential to understand the immune response.
Different subgroups of T lymphocytes such as **T helper (CD4$^+$)**, **cytotoxic** (**CD8$^+$**) have different surface molecules and function as their name may indicate. On other hand B cells is responsible for antibody formation as they mature to antibody secreting **plasma cells** while **NK** cells as their name indicate they are non antigen specific killer cell again virally infected, **allograft** and tumor cells.
The second important functional group of cells i.e. **antigen presenting cells**, the cells which server antigen presentation will be discussed. Different cell may server this function such as **monocyte macrophage linage** and **B cells.**
Cells that play a role in inflammatory response will be identified and their relation to immune response will be discussed. These include **neutrophils**, **basophils**, **eosinophils**, **mast cells** and **endothelial cells.** A part from their detailed functions each cell is recognized through specific surface markers

Subject: **The lymphoid organs and tissues**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The principle differences between primary and secondary lymphoid organs.
- ✓ Functional and structural characteristic of each organ.
- ✓ The mechanisms behind lymphocyte circulation and homing.

The cells that play role in immune response aggregate mainly in tissues and organs, these are called lymphoid tissue and organs. Organs and tissues that serve maturation of immune cells , T or B lymphocytes such as **thymus** or **bone marrow** respectively are called **primary lymphoid organs** while the exposure of these cells to immune system to antigens take place in **secondary lymphoid organ**.
The **mucosa associate lymphoid tissues (MALT)** are tissues that play role in immune response and positioned on different mucosal surfaces, mainly in gastrointestinal, respiratory and genitourinary tract, immune cell circulate between these tissues and other organs through **lymphatics** and can enter lymphoid organs as they migrate to these tissues in regions called **high endothelial venules.**
The circulation and homing of the immune cells between lymphoid organs is based on **ligand–receptor** pattern and this will make cells circulation selective.

Subject: **Major histocompatibility complex (HLA)**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The immune function of human leukocyte antigen HLA
- ✓ The inheritance of *HLA* gene
- ✓ The surface expression of HLA molecules on different cells
- ✓ The importance of HLA molecules in antigen presentation.
- ✓ The importance of HLA molecular in relation to transplant rejection.
- ✓ The role of HLA in some diseases.

The **major histocompatibility complex (MHC)** is a group of genes that are complexed in a specific region on chromosomes. In human it is situated on short arm of chromosome and when expressed the are called human leukocyte antigen **HLA.** Although called leukocyte antigen but they are also expressed on the surface of other cells. The main molecules are classified in to Class I and Class II molecules, the Class I is expressed on all nucleated cells while Class II is expressed on antigen presenting cell and B lymphocytes.
Many gene are responsible for HLA molecules and each cell will expresses at least 12 molecules (6 for each Class) but the inheritance of the gene is **codominant.**
These molecules are play an important role in antigen presentation, certain cell can recognize antigen only when the antigen in presented in a association with HLA molecules (MHC restriction) so that **$CD4^+$** cell only recognize antigen in association with **Class II** molecules and that **$CD8^+$** cell only recognize antigen in association with **Class I** molecules.
The HLA play a role as **transplantation antigen** and their compatibility is importance in the acceptance of **different graft.**

Subject: **Antigen**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The difference between antigen and immunogen.
- ✓ The factors that make a material an immunogen
- ✓ The difference between thymus dependent and independent antigens
- ✓ How antigen presenting cell process and present antigens.

A substance that induce an immune response is called **immunogen** while the term **antigen** is restricted to those substance that react with TCR or Immunoglobulin, although antigen is used in many occasion instead of antigen. Certain chemical and physical properties must be available in a material so that it induce the immune system but addition of materials (**adjuvant**) can increase this response. Although an immunogen make an immune response but the responses—recognition— is directed against fewer areas on the immunogen, these areas —**epitope**—is in the form of few amino acid usually forming a **domain.**
The recognition and response to an immunogen can be **thymus dependent** i.e. it need help from $CD4^+$ cells or **thymus independent** and the result of the former immunogen will be a better response with a good memory.

Subject: **Molecules that recognize antigen (Immunoglobulin, TCR)**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The relation of the immunoglobulins structure to their function
- ✓ Biological and functional differences of immunoglobulins.
- ✓ The genetics of immunoglobulin and TCR
- ✓ The structure and distribution of TCR

The molecules that can recognize antigens are either **immunoglobulin**s or **T cell** receptors. Immunoglobulin are bi-functional molecules that can recognize antigens specifically and at the same time perform defined biological function such as complement activation. **Five classes** of human immunoglobulin exist, each with a different structural, biological and functional properties.
Immunoglobulin for the **humoral** arm of immune response, they are synthesized by activated **B lymphocytes** called **plasma cells**.
TCR are antigen recognizing molecules on the surface of **T cells**, two structurally different types of TCR are observed. Unlike immunoglobulin, TCR recognize antigens presented with appropriate HLA molecules.
Although human posses fixed number of genes to produces Immunoglobulins and TCR but million of different above molecules can be produce due to the somatic recombination of the responsible gene segments.

Subject: **Cytokines**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The structure of cytokines
- ✓ The role of cytokines in immune, inflammatory and hematopoietic systems.

Cytokines are low-molecular-weight proteins that are produced and secreted by a variety of cell types. They play major roles in the induction and regulation of the cellular interactions involving cells of the **immune**, **inflammatory** and **hematopoietic** systems. Cytokines function as a chemical messenger between cells via **specific receptors** on the membrane of target cells, triggering signal-transduction pathways that ultimately alter gene expression in the target cells. Different cytokines are produces in minute amounts but they have many effects, these effect were utilised in treatment of some diseases.

Subject: **The complement system**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The different components of complement system.
- ✓ The pathways of complement activation.
- ✓ The biological consequences of complement activation.
- ✓ The regulation of complement system.

Complement system include a set of proteins that are produced by liver and play role both in **innate** and **adaptive** immune response. Activation of the proteins follow a cascade manner and in several regulatory points are seen to prevent their over activation. Activation is achieved by three mechanism; the classical pathway, the alternative pathway and the lectin pathway but these pathways will meet at certain points. Activation of complement proteins lead to biological consequences namely releases of **chemotactic** and **inflammatory mediators**, formation of opsonins and formation of membrane attach complex **MAC**

Subject: **Antigen-antibody interaction**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The concept of epitope and paratope interaction
- ✓ The intermolecular forces of antigen-antibody interaction.
- ✓ The concept of specific, cross and none reaction

The association between an antibody and an antigen involves various noncovalent interactions (intermolecular forces) between the **epitope** of the antigen and the **paratope** region of the antibody or TCR These forces include hydrogen bonds, ionic bonds , hydrophobic interaction and Vander Waals force.

Although antigen-antibody reactions are highly specific, in some cases antibody elicited by one antigen can **cross-react** with an unrelated antigen.
Cross-reactivity usually characterised by less avidity than specific reaction which occur between antibody and the original antigen. This cross reaction my be behind the pathogenesis of some diseases

Subject: **Adaptive immune response**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ How the body deals with immunogen to form an immune response.
- ✓ The steps of immunogen process and presentation.
- ✓ B lymphocyte activation and proliferation
- ✓ The phases of humoral immune response.
- ✓ T lymphocyte activation and proliferation.
- ✓ Mechanisms of antigen elimination.

When an immunogen enter human body, elements of immune system will try to process and present it to specific cell to produce an immune response. Immunogen enters via several route and in each route a different response may be produced. Depending on the nature of the immunogen either B or T or both with respond as **humoral** (antibody) or **cell mediated response**. Both these responses may lead to either elimination or control of the offending antigens and my render the host protective against the antigens. The immune response can be staged into several time dependent events starting after exposure to the antigen until an immune response become evident, these stages can be utilized in process of vaccination.
If an immune response was formed against an immunogen, several element will come in action to eliminate the antigens and this may depend on the natures of the antigens and the immune response elements against it

Subject: **Regulation of immune response**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The regulatory elements in immune response.
- ✓ How immune regulation will affect the host?
- ✓ The role of immune regulation in some diseases.
- ✓ The immune tolerance.

The immune response is not a one way response, like most of body activities there are elements in the immune system which **regulate** or **suppresses** the function of immune system. This regulation is achieved either cells or cytokines and they works at several stages. The immunity systems can get tolerance against some, **tolerance** can developed by different mechanisms, when lost, and this may affect the development of some auto immune diseases.

Subject: **Mucosal immune system**
Lecturer name: Dr Sherko A Omer

Objective:

The student should learn:

- ✓ The components of mucosal immune system
- ✓ Function of mucosal immune system
- ✓ Role of secretory immunoglobulin.
- ✓ Immune benefits of breast feeding.

The mucosal immune system can be separated from the general immune system in some aspect, their distraction in mucosal surfaces (**MALT**), some specific **regulatory elements** and related secretory **IgA** all make it a complete system that combats pathogens and offending antigens entering body. The system also have a system (hepatic clearance) that can filter antigens in blood and eliminate them through bile into elementary tract
Breast feeding offer immune protection infants, as it contain IgA and some cells so they give a natural passive immunity. For this there are a system of cells circulating mucosal surfaces and breast tissue to produce such effect in the mother

Subject: Immunodeficiency Disorders
Lecturer: Dr. Dana M. Tofiq

Learning Objectives:
Students should be able to:
1. Classify the immunodeficiency disorders.
2. Characterize the genetic basis of the primary disorders.
3. Recognize the diseases and syndromes associated with the primary disorders.
4. Know the available therapies for the primary disorders.
5. Know the impacts that HIV infection has on the immune system, mode of transmission, treatment and prevention plans.

The immunodeficiency disorders can be broadly categorized into primary and secondary disorders. The primary immunodeficiency disorders occur as a result of defects in almost any stage of differentiation in the whole immune system due to genetic defects, while secondary disorders may arise as a secondary consequence to environmental factors of malnutrition, lymphoproliferative disorders, agents such as X-rays and cytotoxic drugs, and viral infections.
The primary disorders are further categorized into four categories:

1. Defects in the innate immune responses, which include both phagoctic cell defects and complement system deficiencies.
2. Immunoglobin deficiencies.
3. Primay T-cell deficiency.
4. Combined immunodeficiency disorders (which include defects in more than one of the above three defects).

Acquired immunodeficiency syndrome (AIDS) which is caused by human immunodeficiency virus (HIV) infection is the most important cause of secondary immunodeficiency disorders, due to its global economic burden and disease associated mortality and morbidity.
Subject: Hypersensitivity and Allergic Diseases
Lecturer: Dr. Dana M. Tofiq

Learning Objectives:
The students should be able to:
1. Classify different types of hypersensitivity reactions.

2. Know the exact mechanisms that mediate different hypersensitivities.
3. Know the different types of allergic diseases with their underlying type of hypersensitivity reactions.

Coombs and Gell defined four types of hypersensitivity. Types I, II and III depend on the interaction of antigen with humoral antibody, whereas type IV involves T-cell recognition.
Type 1 allergic disease, often referred to as atopic disease, is a group of conditions occurring in people with a hereditary predisposition to produce immunoglobulin E (IgE) antibodies against common environmental antigens (allergens). These conditions include some of the commonest causes of ill health including allergic rhinitis, asthma and atopic eczema.
Type II is called antibody-dependent cytotoxic hypersensitivity which is due to an abnormal antibody directed against a cell or a tissue.
Type III is called immune complex-mediated hypersensitivity in which under a number of circumstances the body may be exposed to an excess of antigen over a protracted period. The union of such antigens with the subsequently formed antibodies forms insoluble complexes at fixed sites within the body where they may well give rise to acute inflammatory reactions.
Type IV is called cell-mediated (delayed-type) hypersensitivity results from an exaggerated interaction between antigen and the normal cell-mediated immune mechanisms.

Subject: Transplantation
Lecturer: Dr. Dana M. Tofiq

Learning Objectives:
The students should be able to:
1. Know the consequences of major histocompatibility complex (MHC) incompatibility.
2. Explain the mechanisms of graft rejection.
3. Classify different forms of graft rejection.
4. Know the different strategies used in prevention of graft rejection.
5. Know the clinical examples of organ transplantation.
6. Know the association of HLA type with disease.
7. Explain why the fetus which is an allograft is not rejected by the mother.

The replacement of diseased organs by a transplant of healthy tissue has long been an objective in medicine but has been frustrated to no mean degree by the uncooperative attempts by the body to reject grafts from other individuals.
There are four types of grafts:
1. Autograft, the tissue is grafted back onto the original donor.
2. Isograft, graft between syngeneic individuals (i.e. of identical genetic constitution) such as identical twins.
3. Allograft, graft between allogeneic individuals (i.e. members of the same species but different genetic constitution), e.g. human to human.
4. Xenograft, graft between xenogeneic individuals (i.e. of different species), e.g. pig to human.
It is with the allograft reaction that we are most concerned. The most common allografting procedure is blood transfusion where the unfortunate consequences of mismatching are well known. Considerable attention has been paid to the rejection of solid grafts such as skin, and the sequence of events is worth describing.

Subject: Tumor Immunology
Lecturer: Dr. Dana M. Tofiq

Learning Objectives:
1. Know the changes on the surface of tumor cells.
2. Understand the immune response to tumors.
3. Know the mechanisms used by tumor cells to evade the immune response.
4. Know different approaches to cancer immunotherapy.
5. Characterize different lymphoid malignancies.

It has long been suggested that the allograft rejection mechanism represented a means by which the body's cells could be kept under immunologic surveillance so that altered cells with a neoplastic potential could be identified and summarily eliminated. For this to operate, cancer cells must display some new discriminating surface structure which can be recognized by the immune system. Indeed tumor antigens can be recognized by raising monoclonal antibodies against them or by specific cytotoxic T-cells (Tc). Identification of tumor

antigens recognized by T-cells is crucial for the future production of vaccines which target solid tumors.

Subject: Autoimmune Diseases
Lecturer: Dr. Dana M. Tofiq

Learning Objectives:
1. Classify different types of autoimmune diseases.
2. Understand the factors that contribute to autoimmune diseases.
3. Characterize different autoimmune diseases according to the underlying pathogenic factors.
4. Know diagnostic value of autoantibody tests.
5. Know different strategies for treatment of autoimmune disorders.

The immune system balances precariously between effective responses to environmental antigens and regulatory control of potentially suicidal attack against self molecules.
The monumental repertoire of the adaptive immune system has evolved to allow it to recognize and ensnare microbial molecules of virtually any shape. In so doing it has been unable to avoid the generation of lymphocytes which react with the body's own constituents. The term (autoimmune disease) applies to conditions where the autoimmune process contributes to the pathogenesis of the disease. This is different to situations where apparently harmless autoantibodies are formed following tissue damage, for example heart antibodies appearing after a myocardial infarction. Autoimmune diseases count amongst the major medical problems of today's societies.
There are, for example, over 6.5 million cases of rheumatoid arthritis (RA) in the USA, and type 1 diabetes is the leading cause of end-stage renal disease.

Subject: Immune Manipulation
Lecturer: Dr. Dana M. Tofiq

Learning Objectives:
1. Know the concept of immune manipulation
2. Explain different methods used for immunosuppression
3. Explain different methods used for immune potentiation
4. Know the other ways used for immunomodulation

Although the immune system usually responds appropriately to foreign antigens, there are patients whose disease is caused by immune responses which are excessive or defective. The aim of clinical immunology is to correct these abnormalities. Two major approaches are possible: **immunosuppression** or **immunopotentiation**.
An overactive, self-damaging immune system requires some degree of immunosuppression; this is the mainstay of the management of organ transplantation and certain life-threatening autoimmune diseases.
Improving a naïve or defective immune system requires immunopotentiation like immunization, bone marrow transplantation and gene therapy.

Exams
The immunology exam is carried out with parasitology, there are two major exams during the study year, mid year and final exams, time allocated for each is 3 hours. Student failed achieving the success score (50 out of 100) will have another chance to fulfill the success score. The score in each exam is equally shared between immunology and parasitology.
The student is advised how to answer each questions.

Samples of question and their answers

Question

Explain the following:

a. The secondary immune response has a short lag period and results in production of high quality of IgG.
b. In haemolytic disease of the newborn (Rh isoimmunisation), the first baby may escape the disease.

Answers

These question are answered with short essay, the student should answer only points wanted to be cleared as following;

a. The secondary immune response has a short lag period because with the introduction of the antigen, memory cells will come to action and produce their efferent rather that virgin cells in primary immune response. IgG is formed because of class switching from IgM
b. In this condition the first baby usually escape because he become Rh +ve and some of its RBC enter maternal circulation, the mother need time to be sensitized to produce antibodies against the Rh antigens. So usually the first baby escape the maternal effect but the next baby may not.

Question and answers

Fill in the blanks, answer in the provided spaces, only in these spaces the answers will be marked

1. Two types of TCRs are exist, one is composed from .. αβ chains and is present in the majority of T lymphocytes and the other is composed from…γδ…chains.

2. B lymphocytes arise from stem cells that migrate to .. **fetal liver** and latter to **Bone marrow** , they are called B lymphocytes after the **Bursa of Fabricious** ..which is a lymphoepithelial organ near the **cloca** … of birds.

3. NK cells lack …**antigen receptor** , they are different from both T and B cells and mostly appears as **large granular lymphocytes** ., NK cells can kill through…**ADCC**.. when they carry cytotoxicity on antibody coated cells.

Mach the items of group A to those of group B, any item must have only one match. Arrange your answer in a table

Group A

T regulatory cell C3b C1 inhibitor deficiency IgE Secretory IgA mIgD Properdin C5b678(9)n T helper Immunoglobulin M

Group B

$CD4^+$ $CD25^+$ $FoxP3^+$ CD4 +ve Primary humoral immune response

Mast cells Opsonin Hereditary angiodema B lymphocytes

Polymeric immunoglobulin Membrane attach complex (MAC) Complement activation

Answer

Group A	Group B
T regulatory cells	$CD4^+$ $CD25^+$ FoxP3
C3b	Opsonin
C1 inhibitor deficiency	Hereditary angiodema
IgE	Mast cells
Secretory IgA	Polymeric immunoglobulin
mIgD	B lymphocytes
C5b678(9)n	Membrane attach complex (MAC)
T helper	CD4 +ve
Properdin	Complement activation
Immunoglobulin M	Primary humoral immune response