HUMANITAS MEDICAL SCHOOL

Course: Mechanisms of diseases II

Year: 2nd

Period: 2nd semester

Credits: 10 CFU

Teachers: Valeria Cento, Maria Rescigno, Marinos Kallikourdis, Sebastien Jaillon, Alberto Mantovani, Raffaella Bonecchi, Cecilia Garlanda, Mauro Teixeira, Seppo Meri

Objectives

The course will offer an integrated introduction to the major microbial agents that cause human diseases (microbiology II), the principal mechanisms of defense to injury (adaptive and mucosal immunity), and the general processes of the most relevant causes of human diseases (immunopathology).

Application of knowledge and understanding:

At the end of the course students will gain an understanding of:

- generalities and special characteristics of the most clinically relevant viral, fungal and parasitic pathogens;
- the pathogenesis of infectious diseases by different types of microorganisms;
- normal and abnormal functions of the innate and adaptive immune system;
- general pathological mechanisms leading to cell injury and death.

Making judgements; Communication skills; Learning skills

By the end of the course students will have developed abilities to communicate and work in team, and acquired learning skills such as study in a group, organize knowledge, revise and retain information, select information.

Prerequisites

To take the exam students must have passed the exams of Principles of the living matter, The Cell: Molecules and Processes, Building bodies: from gametes to organs, and Body architecture.

Contents

The course can be divided into 4 modules: Clinical Microbiology II (clinical virology, mycology and parassitology), Adaptive Immunity, Mucosal Immune System and Microbiota, Immunopathology. The syllabus is organized by learning outcomes specific for each lecture or for a group of lectures.

CLINICAL MICROBIOLOGY II (Prof. Valeria CENTO, Prof. Seppo MERI, Prof. Mauro TEIXEIRA; 3 CFU)

Learning objectives

At the end of these lectures and activities, students should be able to

- Describe fungi and associated diseases; describe pathogenic mechanisms and the resulting pathology at the cellular, tissue, and organism levels; and the clinical manifestations.
- Describe RNA and DNA viruses and associated diseases; describe pathogenic mechanisms and the resulting pathology at the cellular, tissue, and organism levels; and the clinical manifestations.
- Describe parasites (protozoan, helminths, arthropod vectors) and associated diseases; describe pathogenic mechanisms and the resulting pathology at the cellular, tissue, and organism levels; and the clinical manifestations.
- Compare mechanisms characteristic of infection with particular categories of pathogens.

Lectures

1. **Viral pathogenesis and evolution**
2. **Pathogenic DNA viruses**
    a. Poxviridae (Smallpox, Molluscum contagiosum)
    b. Polyomaviridae (Polyomavirus)
    c. Adenoviridae
    d. Parvoviridae
3. **Herpesviridae**
    a. Herpes simplex
    b. Varicella-Zoster
    c. Epstein-Barr
    d. Cytomegalovirus
4. **Pathogenic RNA viruses (I)**
    a. Picornaviridae (Enteroviruses, Rhinoviruses)
    b. Caliciviridae (Noroviruses)
    c. Reoviridae (Rotavirus)
    d. Togaviridae: Rubella virus
5. **Pathogenic RNA viruses (II)**
    a. Paramixoviridae (Measles, Mumps, Respiratory syncytial virus)
    b. Orthomyxoviridae (Influenza)
6. **Pathogenic RNA viruses (III) (**Prof Teixeira**)**
    a. Arboviruses: Togaviridae, Flaviviridae
    b. Bunyaviridae, Arenaviridae
    c. Rhabdoviridae
7. **Hepatitis viruses**
8. **Retroviridae and Coronaviridae**
9. **General mycology**
10. **Mycology (I)**
    a. Classification of mycoses
    b. Dermatophytes
    c. Endemic mycoses
    d. *Pneumocystis jirovecii*
11. **Mycology (II)**

a. Fungal agents of opportunistic invasive infections (*Candida* spp; *Aspergillus* spp.; *Cryptococcus* spp.)

12. **Pathogenic parasites**
    a. To describe the epidemiology of the more important protozoan and helminthic parasites, life cycles, mechanisms of disease.
13. **Parasites protozoa** (Prof Meri)
    a. Apicomplexans: malaria
14. **Parasites protozoa** (Prof Meri)
    a. Ciliates
    b. Amoebae
    c. Flagellates
15. **Parasites** (Prof Meri)
    a. Helminths
    b. Arthropod vectors

ADAPTIVE IMMUNITY (Prof. Marinos KALLIKOURDIS, prof. Raffaella Bonecchi; 3 CFU)

Learning Objectives

At the end of the lecture course, students should be able to:

- Understand and explain to others the function of adaptive immunity, *with all its associated features and physiopathological facets* (see below).
- Understand the key biological problems that drove the evolutionary selection of adaptive immunity as an answer to these problems.
- Be able to identify mechanisms driven by adaptive immunity when faced with a complex clinical problem.

Lectures

1. Introduction to adaptive immunity:

- key concepts

2. MHC, antigen processing and presentation:

- Intro and link to other lectures
- Initiation of adaptive responses
- Antigen presentation; lymph nodes
- Nomenclature and historic overview of MHC studies
- Haplotypes
- Dominant epitopes; superantigens
- Topology issues
- MHC processing for Class I and Class II
- Cross-presentation.

3. Dendritic cells/antigen presenting cells (delivered by Prof Bonecchi)

- Origin and heterogeneity of dendritic cells
- Maturation and function
- Clinical use.

4. T cell development and functions - Lecture 1

- T cell development
- Generation of T cell receptor diversity
- Assembly of the mature TCR
- Thymic selection (an introduction)
- T cell signalling (T cell activation).

5. T cell development and functions - Lecture 2

- T cell functions
- Immune synapses
- Costimulation - checkpoint blockade
- Cytotoxic function.

6. B cell development and functions - Lecture 1

- BCR diversification
- B cell development

7. B cell development and functions - Lecture 2

- Th-B cell interactions; germinal centers
- affinity maturation/somatic hypermutation, class-switch recombination, AID and Neuberger.
- class switching and polarization of responses
- Memory B cells
- Antibody structure and function; integration with innate immunity
- Monoclonal antibodies and Cesar Milstein; uses in diagnostics and therapy; patent of the technology
- Humanized monoclonal antibodies; Neuberger and Winter
- Future directions of monoclonal antibody technologies, bispecific antibodies, fully humanized antibodies.

8. Polarization and memory:

- Th1 Th2 Th17, innate/adaptive immunity coordination
- Nomenclature issues on M2-like vs Th2 and Treg
- Development and function of polarized responses
- Clinical examples
- Autoimmunity
- Allergy (Atopy)
- Memory responses
- Vaccines

PPP portfolio: obesity, rash, shock

9. Tolerance and negative regulation of immune responses:

- Central tolerance; Peripheral tolerance
- Intracellular mechanisms of immunoregulation: via signaling; via degradation; via inhibition of costimulation
- Mechanisms of peripheral tolerance at the level of cell-cell interactions
- Treg cells
- Other suppressive populations

PPP portfolio: Rash, Chest Pain, Shock, Cough, Shortness of Breath or Dyspnea, Sore Throat

10A. Small Team Work – Flipped Classroom: Immunological issues in reproduction

10B. Immunology of pregnancy:

- Immune evasion mechanisms

- Medawar
- Treg
- Consequences of maternal-fetal tolerance for the evolution of immune system control

MUCOSAL IMMUNE SYSTEM AND MICROBIOTA (Prof. Maria RESCIGNO, 2 CFU)

Learning Objectives

At the end of the lecture course, students should be able to:

- Understand the structure of the mucosal immune system (the sites where the response is initiated)
- Understand how immune responses are initiated or repressed at mucosal sites
- Understand how immune homeostasis is carried out at mucosal sites.
- Understand the bases of several disorders initiated at mucosal surfaces (allergies, asthma, metabolic disorder, etc.)
- Understand what is the microbiota, its activities on our well-being and how we tolerate

Lectures

1. Development and structure of Mucosal tissue

- Description of the mucosal associated lymphoid tissues
- Nasal associated lymphoid tissue (NALT), Waldeyer's ring
- Broncho-alveolar associated lymphoid tissue (BALT),
- Gut associated lymphoid tissue (GALT), Peyer's Patches, Isolated lymphoid follicles

2. Cellular constituents of the mucosal immune system I: Epithelial cells and antigen uptake

- Epithelial cells,
- Bile acids and enterohepatic circulation,
- Antigen uptake
- Initiation of oral tolerance to food

3. Cellular constituents of the mucosal immune system II

- Intraepithelial lymphocytes, dendritic cells, macrophages, Mast cells and neutrophils
- Atypical CD8 T cells
- gd T cells
- iNK T cells
- Innate lymphoid cells
- ILC and chronic disorders

4. Lymphocyte trafficking and oral tolerance

- Lamina propria lymphocytes
- T regulatory cells (thymus derived and peripherally derived)
- T regulatory cells and IBD

5. ASTHMA

- Pathogenesis
- Allergic and non-allergic airway inflammation
- Atopic dermatitis and atopic rash

6. The Microbiota and its impact on immune responses

- What it is
- How to analyse the microbiota
- Microbiota and Th17 and Tregs
- Th17 and brain disorders

7. The Microbiota and cancer

- How the microbiota impact on cancer
- Protumorigenic and anti-tumorigenic bacteria
- Microbiota and cancer treatment

PPP portfolio: food intolerance, celiac disease, inflammatory bowel disease, NAFLD/NASH, colorectal cancer, hepatocellular carcinoma, neurodegenerative disorders

MODULE OF IMMUNOPATHOLOGY (prof. Sebastien JAILLON, prof Alberto MANTOVANI; 2 CFU)

Learning Objectives

At the end of the lecture course, students should:

- be able to understand and explain the general mechanisms and effector functions of the immune system.
- be able to understand and explain the causes and the pathogenesis of the main alterations of the immune response.
- be able to understand and explain the mechanisms involved in the rejection of tissue transplants.
- be able to understand and explain the mechanisms involved in the alterations of the immune system in tumors and the principles of immunotherapy.
- be able to understand and explain the importance of biomedical research in immunopathology and cancer.

Lectures

1. Hypersensitivity reactions (1) (Prof Jaillon)

- Overview of the normal immune response
- Classification of hypersensitivity diseases
- Immediate (type I) hypersensitivity

*PPP portfolio: Rash, Chest Pain, Shock, Cough, Shortness of Breath or Dyspnea, Sore Throa*t

2. Hypersensitivity reactions (2) and autoimmune diseases (Prof Jaillon)

- Antibody-mediated (type II) hypersensitivity
- Immune complex-mediated (type III) hypersensitivity

- T cell-mediated (type IV) hypersensitivity
- Autoimmune diseases: The central and peripheral tolerance
- Mechanisms of autoimmunity
- General features of the most common autoimmune diseases (Systemic Lupus Erythematosus)

PPP portfolio: Rash, Jaundice, Chest Pain, Fever, Shortness of Breath or Dyspnea

3. Rejection of tissue transplants and immunodeficiency syndromes (Prof Jaillon)

- Rejection of tissue transplants: Generalities and definition, Type of rejection reactions
- Graft-versus-host disease
- Immunodeficiency syndromes: Primary immunodeficiencies
- Primary immunodeficiencies: Defect in innate immunity
- Primary immunodeficiencies: Defect in adaptive immunity
- Secondary immunodeficencies: Acquired immune deficiency syndrome (AIDS)

PPP portfolio: Rash, Chest Pain, Fever, Cough

4. Vaccines (Prof Alberto Mantovani)

5-6. Immune responses to tumors and principles of cancer immunotherapy (Prof Jaillon)

- Introduction
- The immunosurveillance hypothesis
- Defensive mechanisms against tumors
- Mechanisms of cancer immune evasion
- Cancer immunoediting
- Principles of cancer immunotherapy (antibodies, inhibitors of immune checkpoints, CAR-T cells)

7.Inflammation and cancer (Prof Alberto Mantovani)

- Epidemiologic evidence
- Myeloid-derived suppressor cells
- Tumor-associated macrophages: origin and function
- Tumor-associated neutrophils

8. Innate immunity in translational medicine (Prof Jaillon)

- Recognition and elimination of pathogens
- Role of neutrophils in tumors and response to therapy

Collaborative lectures

1. **Small group - Sepsis** (Bonecchi, Jaillon, Kallikourdis, Cento, Garlanda)
2. **Small group - HIV** (Bonecchi, Jaillon, Kallikourdis, Cento, Garlanda)
3. **Small group - Infections and cancer** (Bonecchi, Jaillon, Kallikourdis, Cento, Garlanda)

Teaching Methods

Lectures: the main purpose of lectures is to transfer knowledge to students by guiding them through the most relevant subjects of the disciplines. Collaborative lessons with teachers of the

course and recap lessons will be done in order to increase the integration of the different modules. All lectures will be held synchronously, either in presence or using Teams.

Group work activities/activation of knowledge: the purpose of these activities is to activate and solidify knowledge acquired during lectures and independent study, in a collaborative learning setting. For these activities, students will be divided in groups that will remain the same through the semester. Participation is mandatory. Student that cannot be on Campus for reasons related to the pandemics will participate in teams.

Problem based learning (PBL) during each semester a PBL will be presented and discussed with students. Students are encouraged to actively participate to the lectures with questions and comments.

Attendance is mandatory, an absence rate of 25% will be tolerated. For higher absence rates university rules will be followed.

Assessment

Students' evaluations will be assessed through one multiple choice exam at the end of the course and by evaluation of the PBL activity.
The faculty reserves the possibility to have an oral exam.

Content of the Exam (40 questions): 14q on Microbiology, 10q on Adaptive Immunity, 8q Mucosal Immune System and Microbiota, 8q on Immunopathology.

Exam evaluation: 40 questions, each question 0.75 points.
To pass the test you need to answer at least 24 questions correctly.
A minimum of 60% correct answers must be reached.

PBL evaluation: students will be evaluated by tutors and experts following the table below.
For every column of the table, the scale will be: 4= Excellent; 3=Good; 2=Satisfactory; 1= Poor.
Extra points will be added to the exam evaluation following these ranges
Evaluation range 10-13: 1 point; 14-17: 2 points; 18-20: 3 points.
Each point is a 0.75 to add to final grade.

Level of participation (Contributes to group process; encourages others)	**Level of professional behavior in group** (Demonstrates respect; shows punctuality; well-prepared)	**Level of small group leadership and initiative qualities** (Takes initiative; provides leadership; thinks and works independently)	**Student's level of desire of feedback and response to criticism** (Asks classmates or tutor for feedback; puts suggestions to good use)	**Ability to deal with the process** (Identifies problems; suggests hypothesis; provides interpretations of data)

Texts

- Robbins and Cotran, Pathologic Basis of Diseases, 10th edition, 2020; Elsevier

- Cellular and molecular immunology 10th edition, 2021; Elsevier
- Bauman RW, Microbiology with Diseases by Taxonomy, 6th edition, Pearson
- Updated scientific literature and clinical guideline (EBM, Evidence Based Medicine)