# Basic Immunology (Dentistry)

#### Lecture 1.

Introduction, phylogenesis of the immune system (innate-, adaptive- and natural immunity).

#### University of Pécs, Medical School, Department of Immunology and Biotechnology



Director: Prof. Dr. Timea <u>Berki</u>

Address: 7624, Pécs, Szigeti út 12.; Tel.: 06-72-536-288; Fax.:06-72-536-289 www.immbio.hu



#### Introduction 1.

- Please follow our website <u>www.immbio.hu</u> through the whole semester for up-to-date informations about our education. Please pay attention that the published lecture slides alone are not suitable for learning the subject Basic Immunology because they are incomplete without the live explanations and additions given on the lectures by our teachers. For the complete understanding of our topics we expect that students take part on the lectures and <u>make their own notes</u> as well as the use of the Textbook: Abul K. Abbas et al.: Molecular and Cellular Immunology 10th Edition 2021.
- Student preparation and learning will be controlled with the help of the "moodle.pte.hu" website. At the beginning of the semester all students will be registered automatically with their specific neptun codes. After activation you will use this platform for completing the semester tests as well as the exam test.

#### Introduction 2.

- 2 lectures / week (preparation of own lecture notes!) Name list will be led every week. <u>Maximum 3 absences allowed!</u>
- Semester tests: We will check the progress of learning during the semester on 2 occasions (7. and 13. weeks). These tests (30 questions, 45min) will be written using "moodle.pte.hu" in the Computer Rooms of the University. For the acknowledgement of the semester 50% is required on both tests. When a student gets more than 25 points in both tests, we will offer a 5 (excellent) for the exam. There will be make up tests on the 8. and 14. weeks for those who miss one test or do not reach the 50% in one of the tests.
- Exam: online test exam in "moodle.pte.hu" from the lectures. Evaluation: minimum level: 60%; satisfactory 60-71%, average 72-77%, good 78-83%, excellent 84%
- Website: www.immbio.hu

## Introducing the subject 3.

• Our official books you can learn from:



Abul K. Abbas, Andrew H.H. Lichtman, Shiv Pillai: **Cellular and Molecular Immunology**, 8th edition, 2015.



Abul K. Abbas, Andrew H.H. Lichtman, Shiv Pillai: **Basic Immunology**, 4th edition, 2012.

• Attention! Our department has never published or lectored any notes for students, therefore we recommend you to be cautious in case you decide to study from them.

# Introducing the subject 3.

- What makes immunology worth studying?
  - The immune system is involved one way or another in almost all human pathological conditions.
  - Many of the laboratory diagnostics are based on immunological methods. (see later)
  - More and more diseases get treatable by manipulating the immune system. (see later)
  - Autoimmune diseases affect 7-8% of the population, they are chronic and generally incurable, yet many can be treated effectively. (see later)
  - The number of immunocompromised patients increased recently. (Due to therapeutic immunosuppression and HIV, see later)
  - Laypeople also seem to have strong opinions regarding immunology. →
     Media tends to mix medical facts with quackery and pseudoscience.

First Case of Diphtheria in Spain Since 1986 After Parents Shun Vaccination



A news report from June of

### **Our approach**

#### Molecules

Cells

• Organs

Functions

# Special emphasis on topics related to dentistry.

#### **Basic terms**

- Immunis,- e (Julius Caesar) = exempt, free of burden (E.g. tax, law, or diseases)
- **IMMUNE:** individuals who do not capitulate to a disease when infected;
- IMMUNITY: status of specific resistance to a disease;
- IMMUNOLOGY: branch of theoretical biology focuses on mechanisms responsible for both self and non-self recognition, elimination of the invaders and protection of the basic structural elements.

Definition of the antigen Detre (Deutsch) László (1874-1939): ANTIBODY GENERATOR: foreign substance induces antibody production (1899)

Modern definition: substance, which is recognized by T cell and/or B cell receptors, and it is able to induce active immune response or tolerance according to the host immunogenetic background (MHC haplotype).

#### Main tasks of the immune system

 The immune system is a structural and functional network.

 Preserving the integrity of an organism

 Vector

 Vector

 Defense against external

 Elimination of one's pathologically

altered cells (e.g. virally infected

cells, cancer cells)

pathogens (e.g. viruses,

bacteria, parasites)

Altered self- and foreign structures must be **recognized** and **distinguished** from the organism's own healthy cells.

IMMUNE RESPONSE (either an aggressive response or immunological tolerance)



#### **Composition of the immune system**

#### **Innate**

- None antigen specific
  No immunological memory
  Rapid reactivity
- •Linear amplification of the reaction

#### Adaptive



Antigen specific
Immunological memory
Activated after a latency
Exponential amplification of the reaction

#### Natural

Innate-like immunity with adaptive features



#### Innate immune system

- Pattern recognition receptors (PRR)
- Pathogen associated molecular patterns (PAMP)
- First line defence
- Low number of molecularly distinct receptors and high number of recognized patterns
- Main molecular components: Antibacterial peptides, Complement factors and their receptors, Heat shock proteins, Fc receptors, Inflammatory cytokines, Growth factors, Histamine

 Main cellular components: Macrophages, Monocytes, NK cells, Granulocytes, Mast cells



## Adaptive immune system

- Antigen receptor (BCR,TCR)
- Epitope specific in a given antigen
- Adaptive immune response



- High number of distinct antigen receptors and high number of recognized antigens
- Main molcelar components: Antibodies, MHC, T and B cell receptors, Lymphatic citokines
- Main cellular components: T cells (both αβ and γδ), B cells, Antigen presenting cells



#### Natural immune system

 Antigen recognition receptors (BCR,TCR) with limited specificity

- Patern recognition profile
- Innate-like immune response

 Limited number of distinct antigen receptors and high number of recognized antigens

Main cellular components: iNKT cells, iγδT cells,
 MAIT cells, IEL cells, CD5+ B1 cells

Main molcelar components: natural (auto)antibodies



#### Theoretical scheme of the adaptive immunity



# Organs of the immune system

- The immune system is organized into a **network** of cells and organs. (the entire body must be protected from pathogens)
- Lymphoid organs:
  - **<u>Primary</u>** (production of immune cells)
    - Bone marrow, thymus, embryonic liver (+bursa of Fabricius in birds [nomenclature: "B" lymphocytes originating from the bursa and "T" cells from the thymus<sup>[1.]</sup>])
  - **Secondary** (site of antigen recognition, immune response)
    - Lymph nodes, spleen, MALT (mucosa-associated lymphatic tissue), SALT (skin-associated lymphatic tissue)
  - **<u>Tertiary</u>** (pathological, usually due to chronic inflammation)
    - E.g. ectopic (=at an abnormal site) lymphoid follicles



## Bone marrow (medulla ossium)

- Spongiform tissue found within bones which constitutes 4-5% of the total body weight in adults. (≈2,6 kg)<sup>[2.]</sup>
- Red bone marrow (medulla ossium rubra):
  - Found in short and flat bones (sternum, ribs, clavicle, scapula, pelvis, vertebrae, skull) and the epiphysis of long bones (e.g. femur)
  - Role: Producing blood cells (hematopoiesis) → 10<sup>11</sup> new cells daily of neutrophils alone<sup>[3.]</sup> (the human body is made of approx. 3,7x10<sup>13</sup> cells)<sup>[4.]</sup>
- Yellow bone marrow (medulla ossium flava):
  - Found in the diaphysis of long bones
  - Mainly composed of adipocytes, can turn into red bone marrow when needed (e.g. after blood loss)

#### Structure of the red bone marrow





- Spongy bone tissue with sinusoids, spaces are filled with cells of various lineages undergoing hematopoiesis (see later), stromal cells and adipocytes.<sup>[2.]</sup>
- Mature and naive B cells leave the bone marrow, whereas T cells produced by the bone marrow are still immature and must undergo further maturation in the thymus.
- Mature: capable of recognizing an antigen
- Naive: haven't yet encountered an antigen

# Clinical significance of the bone marrow

- Bone marrow biopsy or aspiration for histological or cytological assessment in case of hematological diseases (e.g. leukemias, aplastic anemia, etc.)
  - Performed from: iliac crest or sternum<sup>[5.]</sup>
- Collecting hematopoietic stem cells (HSC) to perform bone marrow transplantation
  - Usually gathered from the peripheral blood after cell mobilization<sup>[6.]</sup>





## Thymus

- A lobulated organ located in the superior mediastinum, it is the primary site of T cell maturation.
- Consists of 2 lobes further divided into lobules separated by connective tissue septa. The inner layer of the lobules is called medulla, the





Thymus (H&E staining): the peripheral, basophilic layer is the cortex. The inner medulla seems more eosinophilic because it contains less cell nuclei.

## Histology of the thymus



- T cell precursors (=immature cells) produced by the bone marrow enter the thymus through blood vessels → MATURATION (see later) → Mature and naive T cells leave the thymus and enter circulation
- Main cellular components of the thymus: T cells (thymocytes), thymus epithelial cells, dendritic cells, macrophages, epithelioreticular cells<sup>[7.]</sup>

### Involution of the thymus



# Clinical significance of the thymus

- Congenital abnormalities (e.g. ectopic thymus or thymic aplasia [=absence of thymus] for instance in DiGeorge syndrome → immunodeficiency)
- Tumors (thymoma, thymus carcinoma)<sup>[8.]</sup>
  - May be associated with autoimmune disorders such as myasthenia gravis (see later)
  - Might compress nearby structures (e.g. superior vena cava syndrome, dysphagia, see later in the clinical phase of your studies)



Thoracic CT angiography (dye seen in blood vessels): The red line marks a thoracic mass later confirmed to be a thymoma by histological evaluation.

#### Lymph node (nodus lymphaticus)

- They act as **filters of the lymph**: lymph reaching the node through the afferent lymphatic vessels is filtered for **pathogens** and **cancer cells**. (one of the organs where the adaptive immune cells can meet with antigens the first time)
- This is the place where the antigens that entered the lymphatic system will be **recognized** by the adaptive immune cells followed by cell **proliferation** and **differentiation**.
- Tremendous clinical significance: Infectious agents and cancer cells may



Retroperitoneal lymphadenomegaly (=enlarged lymph nodes) seen on a CT scan image. Arrows mark enlarged lymph nodes.

#### Structure of lymph nodes



## Structure of lymph nodes

- Have outer fibrous capsule from which trabeculae radiate towards the inner part of the organ.
- Layers from outermost to innermost: **cortex**, **paracortex** and the **medulla**.
- Afferent lymphatic vessels enter through the convex surface; the efferent lymphatic vessels and blood vessels (artery and venule) are located at the hilum.
- Reticular connective tissue forms the frameworks of the lymph nodes.
- Sites where immune cells enter:
  - From the bloodstream: high endothelial venules (HEV)
  - From the lymphatic system: afferent lymphatic vessels
- Cellular zones:<sup>[9.]</sup>
  - Cortex: B cells organized into follicles, cells that recognized an antigen proliferate and form germinal centers
  - Paracortex: T cells and dendritic cells diffusely
  - Medulla: mainly antibody-producing plasma cells

### Structure of lymph nodes 3.



The cellular organization is controlled by **chemokines**. (see later in lectures)



# High endothelial venules (HEV)

HEVs in a lymph node HEVs



L-selectin ligand on T cells binding to HEV Bendothelial cells (IHC) (frozen section assay)





T cells HEV

D HEV (electron microscopy image)



- Lymphocytes use HEVs to enter lymphoid organs. (through L-selectin, see later)
- Found in all secondary lymphoid organs (e.g. lymph nodes, tonsils, Peyer's patches), **EXCEPT THE SPLEEN**<sup>[10.]</sup>

## Filtration of lymph by nodes



- 1. Infection on the periphery
- 2. The same antigen may enter the **lymphatic vessels** in different forms:
  - Native bound antigen (e.g. living bacteria)
  - Native soluble form (e.g. proteins derived from dead bacteria)
  - Processed form: dendritic cells phagocytose the antigen and present it as a peptide to helper T cells (see later)
- Lymphocytes enter lymph nodes either through afferent lymph vessels or HEVs and meet with the antigens.



# Spleen (lien or splen)

- Located in the left hypochondriac region of the abdomen, weighs approx. 150-200 grams.
- Functions:
  - Immunological: filtering the blood for pathogens
  - Hemoglobin metabolism: elimination of aged red blood cells by the reticuloendothelial cells→ formation of bilirubin
  - Site of hematopoiesis in the embryo as in the liver (can produce red blood cells in pathological conditions even in adults)
  - Acts as a storage of red blood cells and platelets (less significant in humans)



## Structure of the spleen 1.

- Has a fibrous capsule and trabeculae.
- THERE ARE NO afferent lymphatic vessels and HEVs.
- Tissue architecture:<sup>[11.]</sup>
  - Red pulp: sinusoids with an open circulation filled with blood: has a reticular framework populated mainly by red blood cells, macrophages, plasma cells and reticular fibrocytes.
  - White pulp: lymphoid tissue
    - PALS (periarteriolar lymphatic sheath): T cells, dendritic cells
    - Follicles (Malpighian follicles): B cells and follicular dendritic cells (FDC)
    - Marginal zone: special, marginal zone B cells (MZB, see later) and MZ macrophages



#### Structure of the spleen 2.



# Clinical significance of the spleen

• Splenomegaly (=enlarged spleen):

Can have several causes such as hematological malignancies, hypersplenism (e.g. hemolytic anemia), increased pressure in the portal veins (cirrhosis), infections (mononucleosis, malaria), storage diseases<sup>[12.]</sup>

• Splenic rupture (ruptura lienis):

Caused by trauma or an underlying pathological condition, high risk of intra-abdominal hemorrhage

 Splenectomy (=surgical removal of the spleen): Leads to increased vulnerability to polysaccharide encapsulated bacteria (see later)<sup>[13.]</sup>



CT scan of a patient with chronic lymphocytic leukemia (CLL) showing massive splenomegaly.

#### MALT (mucosa-associated lymphoid tissue)

- Mucosa = **enormous surface** for the pathogens to enter the body!
- MALT = The **biggest lymphoid tissue**.
- MALT: can be further classified based on location:[14.]
  - GALT (gut-associated lymphoid tissue)
  - BALT (bronchus-associated lymphoid tissue)
  - NALT (nasopharynx-associated lymphoid tissue)
- Organized MALT (site of antigen recognition):
  - Lymphoid cells form organized structures such as follicles (e.g. tonsils of the Waldeyer-ring, Peyer's patches, cryptopatches, isolated follicles, see in the lectures)
- Diffuse MALT (has effector functions):
  - Lymphocytes diffusely scattered in the epithelial layer and lamina propria of mucosal surfaces (IEL=intraepithelial lymphocyte)

## Organized MALT

Peyer's patches in the ileum (H&E, Waldeyer-ring (tonsils): cross-section): **Tubal tonsil** Pharyngeal tonsil **Palatine tonsil** Lingual tonsil

Peyer's patch Intestinal villi Lumen

Both tonsils and Peyer's patches have tissue architecture similar to that of lymph nodes (follicles with B cells, separated T cell zones, HEVs), but unlike lymph nodes **they do not have fibrous capsules**.

# SALT (skin-associated lymphoid tissue)

Langerhans cells capture the antigen in the epidermis, then process it and move to draining lymph node the through lymphatic vessels. In the lymph node they the present processed antigen to helper T cells.[15.] Several cell types participate in the immunological defense skin. of the (e.g. keratinocytes, macrophages, γδ T cells, see later)



Interdigitating dendritic cell

# Example for tertiary lymphatic tissue

#### **IT IS PATHOLOGICAL!**





Healthy thyroid tissue (medium magnification)

Ectopic lymphoid follicles in the thyroid gland in Hashimoto's thyroiditis (small magnification)

#### Thank you for your attention!

