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Chapter 1
MAIN CONCEPTS

Immunology is a science about immunity. In the Russian Federation "Allergology and Immunology" is an official medical specialty that teaches structure and functions of the human immune system in normal and pathological states, including immune system disorders. In the wide sense of the word, immunology studies an organism's defense against genetically foreign factors by means of the immune system.

Organism protective systems

A multicellular organism needs to defend its internal medium against penetration and destructive action of various external substances and objects (Fig. 1-1). This task is performed by two components: nonspecific (**innate** protective mechanisms) and specific (**adaptive** immunity). The following biological mechanisms are involved:

- **Integumentary tissues** (skin, mucous membranes).
- **Microbicidal secretions** (hydrochloric acid of stomach, bactericidal compounds of saliva, digestive enzymes in the gastrointestinal tract, etc.).
- **Vascular reactions** prevent external factors from penetrating inside the body (quick swelling at the site of injury).
- **Acute-phase proteins** — C-reactive protein (CRP) and mannose-binding lectin (MBL). They are synthesized by liver cells (hepatocytes). These proteins are able to bind the blood-infecting bacteria, viruses and unicellular fungi. Phagocytes express specific receptors (Rc) that bind complexes of acute-phase proteins and microorganisms. Therefore, acute-phase proteins may function as opsonins.
- **Phagocytosis** of microbes by neutrophils and macrophages. This evolutionary conserved innate cellular defense mechanism originates from the alimentary function of unicellular organisms. *The same cell* — phagocyte — will attempt to take up *various* objects in order to digest.
- **Adaptive immunity (lymphocyte immunity)** — specific protection mediated by T- and B-lymphocytes and characterized by immunological memory.

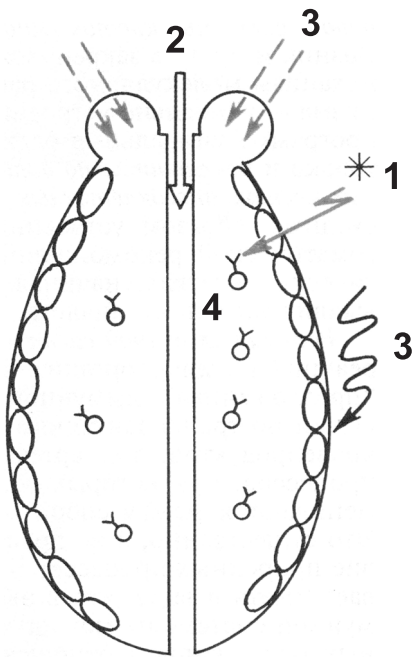

Fig. 1-1. Protection of multicellular organism's internal medium against damaging factors. 1 — infections; 2 — indigested food substances; 3 — inhaled and applied substances; 4 — lymphocytes — specialized immune cells.

- **Common sense prevention** (avoid contact with infected persons, wash hands, properly sterilize medical instruments, be properly dressed for weather, etc.).

The complex of organs, tissues, cellular and molecular components that protect organism's integrity on multiple levels constitutes the immune system. Immunology as a separate scientific discipline studies structure and functions of the immune system under normal and pathological conditions, including defects in the immune system itself (immunopathology). Mechanisms of organism's protection are also studied by other disciplines (therapy, surgery, infectious diseases, oncology, cardiology, gastroenterology, pulmonology, dermatology, etc.). Therefore, dealing with a certain patient, a physician should remember that an organism is an integral whole, hence in some cases a systemic analysis is useful, necessary and perhaps solely possible.

Immunity constitutes the cornerstone of host defense.

The concept of immunity

The Latin word *immunis* has some ten meanings. As a medical term this word was first used B.C. with the following meanings: inviolable, clean, untouched by disease, safe, under good protection, resistant to infectious disease. The meaning of the verb *immunio* is to strengthen, to protect, to defend. Protection against infections is the main natural function of immunity as we understand it. Among protective reactions of multicellulars, adaptive immunity is evolutionarily the most recently acquired and is capable of fine-tuning. Immunocompetent cells that include different subsets of lymphocytes

possess this ability. As the most recent in evolution, adaptive immunity is supported and embedded with other protective systems of multicellulars. Adaptive immunity never acts independently but always together with the other systems.

The key idea of immunity is the immune system's capability to identify *non-self (foreign)* and to direct specific immune reactions towards its neutralization and elimination. Identification of "foreign" is determined by a huge variety of T- and B-lymphocyte clones and by means of the major histocompatibility complex (MHC class I and MHC class II). Neutralization of "foreign" is performed by antibodies (AB) **(humoral immunity)** circulating in the organism fluids and by cytotoxic lymphocytes **(cellular immunity)**. Immunity can be innate or acquired.

- **Innate immunity** is a genetically determined resistance to infections, typical for each species.
- **Acquired immunity** (active and passive) is formed during a life-time.
  - **Active acquired immunity** — a resistance to infections formed after the infectious disease course or after vaccination (the organism itself generates appropriate antibodies).
  - **Passive acquired immunity** — a resistance to infections due to antibodies administration to the organism (in this case organism itself does not generate antibodies).

Features of specific immune response: ability to discriminate "self" and "non-self", specificity and immunological memory.

- **To discriminate "self" and "non-self"** is to distinguish components of an organism's self tissues from foreign invaders. Specific resistance to self tissues means *immunological tolerance.* If an organism mistakenly recognizes self components as foreign an *autoimmune response* develops.
- **Specificity** is defined by the fact that infection caused by a pathogen generates protection *against the very same* or a closely related pathogen.
- **Memory** occurs after the development of an immune response to a specific pathogen and, as a rule, is preserved for life as a defense mechanism against re-infection by the same pathogen. This mechanism is provided by the immune system's capacity to remember antigenic determinants of the pathogen. The mechanism of immunological memory mediates a fast and powerful immune response (secondary immune response) to re-infecting. It is the basis for immunization. In other words, it is a natural or artificially induced immune defense against the infection.

Hence the word "immunity" means:

- An organism's resistance to the invasion of substances genetically and antigenically foreign to the host (bacteria, viruses, rickettsia, parasites, fungi, allotransplant cells, tumor cells, etc.).
- An organism's reactions providing an immunobiologic defense against foreign antigens (Ag).
- The physiological form of an organism's reactivity to an immunogen that is observed when immune system cells contact foreign genetic or antigenic structures. Such structures are being blocked and destroyed.

Definition of "adaptive immunity"

Adaptive immunity is a specific biological property of multicellular organisms. At normal state its natural function is to protect the organism against genetically foreign factors, such as infectious agents and other external pathogens capable of entering the internal medium and making strong bonds with cells and/or intercellular substance. Specialized cells (lymphocytes) provide this protection. The unique and distinctive capacity of lymphocytes as a cell type is to recognize a multitude ($\sim 10^{18}$) of molecular objects — antigens. After recognition, the lymphocyte initiates and mobilizes both its own and general inflammatory mechanisms in order to destroy a pathogen and pathogen-damaged tissues, resulting in their elimination. Briefly:

Immunity = recognition + destruction of both pathogen and tissues damaged by pathogen.

The combination of these processes is known as the immune response.

Immune response

An immune response can be defined by the following scheme (Fig. 1-2). All stages of immune response are drafted below.

Immune response = contact with antigen/pathogen
+ induction of inflammation
+ antigen processing by antigen-presenting cells
+ antigen recognition by lymphocytes
+ activation of effector mechanisms — destruction of antigens
+ excretion of products of destruction

Fig. 1-2. Scheme of major stages of immune response.

- **Recognition of antigen by innate immune cells and induction of inflammation**: secreted cytokines and chemokines activate cells that uptake antigen, in particular, dendritic cells (DC, pl. DCs) and endothelial cells.
- **Antigen recognition** by lymphocytes occurs in peripheral lymphoid organs (immune response begins with proliferation and differentiation of effector and regulatory lymphocytes).
- **Specific destruction of antigen and tissues** damaged by pathogen (this process starts when the regulatory lymphocytes "recruit" the effector lymphocytes and/or inflammatory leukocytes such as neutrophils, monocytes, basophils, mast cells, eosinophils, and humoral lytic systems such as complement).
- **Removal of destruction products** by the organism's excretory system.

Immunocompetent cells

Concepts of what mediates protective immune reactions (they can be called "classical concepts") were defined by the last quarter of the 20th Century and formulated as follows:

Immunocompetent cells. Immunocompetent cells immediately involved in the immune system's functions are comprised of Antigen-Presenting Cells (APCs), T- and B-lymphocytes, and NK-cells.

Cytokines. Many immunocompetent cells as well as cell types beyond the immune system carry out synthesis and secretion of multiple biological active substances (called cytokines) into the organism's internal medium. Cytokines control various aspects of interactions between subsets of immunocompetent cells and other cells, directly or indirectly involved in the organism's defense.

Today these classical concepts are not revised *in toto*, but are significantly extended due to an avalanche-like increase of data characterizing the molecular mechanisms of functioning and identification of different types and subtypes, populations and subpopulations of immunocompetent cells. *Classical concepts* on immunocompetent cells are summarized below and would help the readers to master the submitted material.

- **Antigen-presenting cells.** APCs comprise macrophages, dendritic cells (DCs) of lymph nodes, spleen and other tissues, including epidermal Langerhans cells, M-cells of gastric lymphatic follicles and other mucous membranes, B-lymphocytes, and interdigitating DCs of thymic medulla. These cells capture, process, and present antigen on their surfaces to T-lymphocytes (Fig. 1-3).

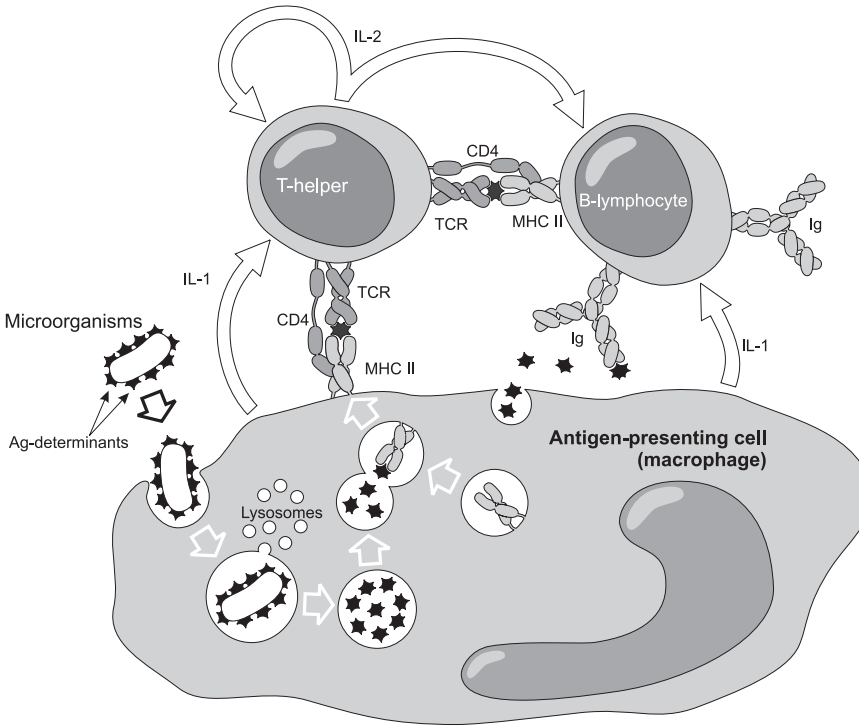

Fig. 1-3. Cellular interactions during humoral immune response. The T-helper receptor (TCR) recognizes the antigenic determinant (epitope) expressed by the APC together with MHC class II molecule. The T-helper surface marker — CD4 — is involved in the interaction. As a result, the APC secretes interleukin-1 (IL-1), which stimulates synthesis and secretion of IL-2 by the T-helper as well as recruitment of IL-2 receptors to the plasma membrane of the same T-helper (IL-2 also stimulates T-helper proliferation). B-lymphocytes are selected during antigen interaction with BCR expressed on their cell surface (right part of the figure). The antigenic determinant in the complex with MHC class II molecule is recognized by the TCR, then the T-lymphocyte secretes cytokines, which stimulate B-lymphocyte proliferation and differentiation into plasma cells producing antibodies specific to the antigen.

- **T-lymphocytes** are responsible for so-called cellular immunity and assist B-cells to react to an antigen during humoral immune response. Each T-lymphocyte contains Ig-like integral membrane glycoprotein (see Fig. 5-1, B and Fig. 6) — T Cell Receptor (TCR) of a unique specificity i.e. interacting with a single antigen. By expression of CD (Cluster of Differentiation) surface markers T-cells are divided into two major groups: $CD4^+$ and $CD8^+$.

- **CD4$^+$-lymphocytes:** T-cells positive for CD4 marker are subdivided into effector (Th1-, Th2- or Th17-helper) and regulatory (Treg) subsets.
  - **T-helpers** specifically recognize antigens when interacting with APC; Th2 induce humoral immune response when interacting with B-cells (see Fig. 1-3), and Th1 induce cellular immune response to extracellular pathogens when interacting with macrophages and cytotoxic T-lymphocytes (CTL). Th17 promote inflammation and induce response to intracellular pathogens.
  - **Treg** control scale and intensity of immune response.
- **CD8$^+$-lymphocytes**: T-cell subpopulation that express CD8 membrane molecules. **Cytotoxic T-lymphocytes (CTL)** or **T-killers** perform lysis of target cells carrying foreign antigens or modified self-antigens — autoantigens (for example, tumor cells, transplant cells, virus-infected cells carrying surface viral antigens). Cytotoxic effect of T-killers is mediated by pore formation in target-cells (created by specific proteins — perforins) and further secretion of specific serine proteases — granzymes — into the pores. Disturbed osmotic balance with extracellular medium results in cell death (Fig. 1-4). Granzymes induce a programmed cell death called apoptosis.
- **Memory T-cells** — long-lived recirculating small lymphocytes are formed during initial immune response, and "remember" specificities of antigenic determinants. When the same antigen repeatedly stimulates lymphocytes, they develop a fast and elevated response against the antigen which induced their formation. Memory T-cells differ from naïve T-lymphocytes by their higher frequency, expression of high levels of membrane molecules, and by a lesser requirement in pro-inflammatory mediators and coreceptor signaling for the development of the effector stage of immune response.

- **B-lymphocytes** are responsible for so-called humoral immune response. B-cell antigen receptor (BCR), Ig monomer, is present on every B-lymphocyte membrane. The life-time of most B-lymphocytes (if they are not antigen-activated!) does not exceed 10 days. The B-cell subsets are: effector, memory and regulatory (secrete IL-10).
  - **Effector B-lymphocytes**. Activated B-lymphocytes proliferate and terminally differentiate into antibody-secreting plasma cells (see Fig. 5-9) — generating immunoglobulins (Igs) of all known classes.
  - **Immunological memory B-lymphocytes** — long-lived recirculating small lymphocytes. They do not differentiate into plasma cells, but maintain immunological "memory" about the antigen. Memory cells are acti-

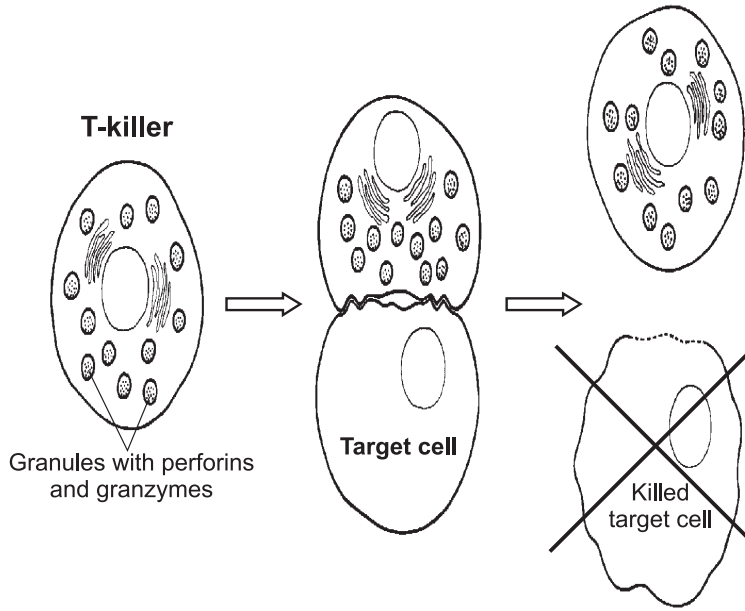

Fig. 1-4. Target cell destruction by cytotoxic T-lymphocyte (CTL). The T-lymphocyte approaches the target cell, and after specific interaction with its membrane molecules, the T-lymphocyte kills the target cell

vated by their repeated stimulation with the same antigen. In this case memory B-lymphocytes (T-cells and some other factors must be involved) provide both fast secretion of large amounts of specific antibodies reacting to foreign antigens, and initiation of efficacious immune response.

- **NK-cells** (Natural Killers) — these lymphocytes do not express either CD markers characteristic of T- and B-cells, or antigen-recognizing receptors — TCR or BCR. These cells play an important role in innate resistance of organisms (see Chapter 3) destroying transformed, virus-infected and foreign cells.

Objectives of immunology

Immunology is now increasingly important for the reasons listed below:

- **Appearance and epidemic rise of new infectious diseases.** Viral infections, including HIV, avian flu and Ebola, prion infections (for instance, spongy

encephalopathy) exemplify such diseases. These diseases are referred to as "beyond medical control" (or incurable), debilitating (gradual impairing of vital capacity), and mortal. Elucidation of pathogenetic mechanisms of these diseases and their possible diagnostics are the objectives of immunology.

- **Noticeable increase of infectious disease morbidity,** including industrialized countries. By the 21st Century, infectious diseases were ranked by mortality rates as follows: first place — pulmonary infections, second — diarrhea, third — tuberculosis, fourth — HIV, malaria, etc. Why? Perhaps widespread use of antibacterial and other anti-infective agents during the last decades helped the organisms with a weakened immune system escape from the pressure of natural selection. As a result, a significant proportion of immunodeficient genotypes have accumulated within populations. Further, microorganisms evolve much faster as compared to development of novel anti-infectives: that's why microbes win the competition.
- **Significant increase of allergic disease morbidity**. In industrialized countries, as well as in Russian cities, up to 20% of the population (or more) suffer from allergies. Allergology, though not a synonym for immunology, is a related discipline. Moreover, comprehension of allergology is always based on the knowledge obtained from fundamental immunology.
- **The increasing importance of vaccinations**, caused by the alarming rise of antibiotic resistance of microorganisms and the emergence of new infections. The introduction of antigenic material into the body of humans and animals in order to induce immunity to infectious diseases has been successfully used since the 18th century, when small-pox vaccination began to spread throughout Europe, including Russia.
- **Unreasonable manipulation with immune stimulators and modulators**. Modern immunology leaves no ground to think that "the more immunity the better".
- **Practically all medical specialties are using ideas provided by immunology** in comprehension of pathogenesis of specific nosologies and/or apply immunological methods for diagnosis. This is due to the nature of immunity as well as to basic functions of the immune system in organism: the immune system is among integrating systems of organism (similar to nervous, circulatory and endocrine systems) with its specific physiological aims and ways to fulfill them.