Contradictions of clinical immunology: Nonspecific and specific mechanisms in immunogenesis

Abstract

The interrelations between nonspecific and specific mechanisms for maintaining immune homeostasis, the mechanisms for induction, regulation, and possibilities for targeted immune correction are discussed. Immunity is the capability of multicellular organisms to resist harmful microorganisms from entering it. Immunity involves both specific and nonspecific components. The nonspecific components act as barriers or eliminators of a wide range of pathogens irrespective of their antigenic make-up. Other components of the immune system adapt themselves to each new disease encountered and can generate pathogen-specific immunity.

An immune system may contain innate and adaptive components. The innate system in mammalians, for example, is composed of primitive bone marrow cells that are programmed to recognize foreign substances and react. The adaptive system is composed of more advanced lymphatic cells that are programmed to recognize self-substances and don't react. The reaction to foreign substances is etymologically described as inflammation, meaning to set on fire. The non-reaction to self-substances is described as immunity, meaning to exempt or as immunotolerance. These two components of the immune system create a dynamic biological environment where "health" can be seen as a physical state where the self is immunologically spared, and what is foreign is inflammatorily and immunologically eliminated. "Disease" can arise when what is foreign cannot be eliminated or what is self is not spared.

Keywords: Nonspecific resistance, immunity, regulation

Introduction

Immunity is the ability of an organism to protect living bodies and substances bearing at their own different genetic information, characterized by the change in the functional activity of immunocytes, by a marked regulatory effect and by its response predominantly at inflammation site [1].

The immune system is composed of many phenomena/mechanisms employed in the event of emergencies, such as ancient self-defense mechanisms (innate), nonspecific defense mechanisms (general) and adaptive defense mechanisms (specific, target).

Nonspecific, Natural Resistance

It is not an immune response. However, nonspecific resistance is linked to specific immune mechanisms, when protecting the body against chemical, physical, biological (infectious and non-infectious) agents. It includes the following components: (1) Surface barriers (the skin, mucous membranes), including low pH due to oils and lactic acid, mucus (mucin protein), ciliary activity, activity in lymph nodes, inflammation; (2) local vascular defense response (microcirculatory vasospasm and/or vasodilatation , serous exudate, blood components); (3) temperature rise, excretory processes (cough, rhinitis, sneezing, sweat secretion, diarrhoea), antagonistic activities of resident (normal) flora, intestinal motility; (4) microbicidal exo secretion (gastric acid, antimicrobial function of saliva, digestive enzymes in the intestine etc.); (5) humoral, antibacterial and lytic products of blood serum and interstitial fluids (serum proteases, complement system, properdin system, acute-phase proteins, lysozyme, β-lysine, cationic serum proteins, fibronectin (cold-insoluble globulin), collectins, interferons, normal antibodies); (6) intracellular mechanism of resistance against pathogens (viruses), including

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genes/products of protein kinase R (PKR) and 2'-5'-oligoadenylate synthase (OAS); (7) cell constituents (basophils, neutrophils, eosinophiles, natural killers, mast cells, dendritic cells, monocytes/macrophages, pre-immune, primary phagocytosis by neutrophils and macrophages to activate digestion. These mechanisms response immediately or in a few hours.

■ Tachyphylaxis

There is a second mechanism of non-specific defense resistance (tachyphylaxis), induced after parenteral or oral administration of foreign serum, saline solutions, low-molecular-weight nucleic acids, endotoxins, etc. Macrophages are vital components of tachyphylaxis.

■ Nonspecific innate immunity

It is a collective term that includes species immunity as well as nonspecific species resistance to anti-infective drugs that is connected with temperature conditions, lack of adhesion receptors, food substrates for microorganisms, etc.; naturally acquired passive immunity from the mother to the foetus, mainly due to IgG antibodies transfer; individual fetal immunity in response to intrauterine infection, and innate immunity itself (II).

■ Characteristic features of innate immunity

They are inheritance at birth, non-specificity, stability, rapid response. Innate immunity also termed as essential, or paleo immunity is found in all multicellular organisms both in animal and plant kingdoms. It dates back 1.5 billion years. Humoral and cell-mediated types of innate immunity (II) response occur within seconds, minutes, hours. They lack immunological memory. Innate immunity (II) does not recognize any specific pathogens, and it is based on the recognition of their images (molecular patterns) or common structures of pathogenic microorganisms or molecules released from its damaged cells. The first subgroup of molecules is associated with viruses, gram-positive and gram-negative bacteria, fungi, protozoa, parasites and is marked as "non-self." The second one is marked as "missing self" for stress factors etc. Either group is eliminated through the set of reactions, the most important of which is phagocytosis.

The mentioned processes occur at the site of inflammation. Inflammation is a universal, typical, genetically programmed response to an injury and is initiated to accumulate protective factors at the site of infection and to eliminate aggressive substances. 70%-80% of human diseases are directly associated with an inflammatory process.

The innate system's line of defense comes into action if a pathogen succeeds in entering the inside of the body. The critical event is the contact of a pathogen with the innate immunity system's cells that are present in all tissues and surface barriers first. They are mainly macrophages. As these cells contain pattern recognition receptors, their activation is triggered and manifested by synthesis of proinflammatory cytokines (IL-6, -8, -1β, -1α, tumor necrosis factor alpha-α). Cytokines involve other cells-epithelial and endothelial cells, and dendritic cells-into the line of defense and induce white blood cells to migrate to the site of infection from the blood circulation.

Full local defense at the site of inflammation is firstly ensured by a move of mobile macrophages (neutrophils) with 70% of phagocytic activity, and thus, the polynuclear stage of inflammation begins. Subsequently, in 24-48 hours the monocytes migrate to the site where they can differentiate into various tissue macrophages (into osteoclasts in bone tissue, into alveolar macrophages in the lungs, into peritoneal macrophages in the abdomen, into neuroglia in the nerve tissues, into Kupffer cells in the liver, etc.).

It is essential that all these mechanisms form the mononuclear stage of inflammation when not only pathogens and destroyed cell debris are eliminated, but also neutrophils containing it are removed.

Natural killers (NK-cells) are an essential component of innate immunity (II). At their level recognition of "self" is implemented, i.e., normal body cells are not attacked by NK cells. All other cells, including malignant cells, are destroyed.

There is a real possibility to induce natural resistance and innate immune response through nonspecific stimulants, which include nucleic acids preparations, polysaccharides, synthetic analogs of bacterial structures, interferons and interferon inducing agents, drug-free modalities, such as autohemotherapy, UV-irradiated autologous blood, etc.

Vaccines and serums are also capable of activating antigenically non-specific anti-infectious immunity and others.

In the period from 4 to 96 hours the second, more powerful line of defense develops, called inducible response that is caused by those mentioned above nonspecific cell-mediated and humoral mechanisms, as well as cytokines [2].

Specific Mechanisms

They include recognition, presentation, activation, differentiation, proliferation, and others, that begin to develop in 3-7 days to 2-4 weeks from the point of pathogen's penetration into the organism, and implement various immune phenomena: immediate-type hypersensitivity, delayed type hypersensitivity, memory, antibody formation (primary and secondary immune responses), immune deficiency, tolerance, paralysis, deviation, strengthening, formation of sensitized lymphocytes, lymphokines, transplantation barrier, GVHD graft-versus-host disease, immune surveillance, etc. [3,4].

■ Specific, adaptive, acquired, neo immunity (AI)

This type of immunity arose not more than 500 million years ago in the period of Cambrian explosion during the massive attack of pathogenic microorganisms on vertebrates. It is identified in 1.5% of animal species only, that is in cartilaginous fishes, bony fishes, amphibians, reptiles, birds and mammals respectively. Adaptive immunity (AI) was first found in jawled fish in the form of lymphocytes. It is commonly believed that T-cells and B-cells have emerged from the transfer of RAG-1/RAG-2 genes that encode enzymes, responsible for recombination of immunoglobulin genes and T-cell receptors, into gametes of ancient fishes as a result of retroviral infection. The formation of lymphoid tissues led to the formation of the basic features of Adaptive Immunity (AI) such as specific antigen-independent and antigen-dependent differentiation of T-cells and B-cells that determined the survival of vertebrate animals.

Adaptive immunity is not hereditary but acquired by an individual in the course of life. It is characterized by specificity, and in some cases low tension and relatively short duration, it has exact inertia for formation, comprising few days-weeks and is governed by humoral and cellular mechanisms, specific antibodies and sensitized lymphocytes. It has free memory that is kept for subsequent contact with a pathogen.

Classification of Adaptive Immunity

■ By origin

Naturally acquired

It is considered as naturally acquired passive immunity since it is acquired passively when antibodies are naturally transferred during intrauterine growth from the mother to the fetus across the placenta. Antibodies transferred are directed against pathogens of those diseases, which the mother suffered through or against which she was immunized. If a child is breastfed, it gets even and secretory immunoglobulins A. However, active acquired immunity also exists, which is acquired through suffering the disease. Moreover, it is individually acquired, and its duration varies. It can arise in a 1-2 week after the onset of the disease and can remain for months, years or even for life.

Artificially acquired

Artificially acquired passive immunity is that which develops as a result of the introduction of "ready-made" antibodies." It occurs immediately, lasts for 2-3 weeks with heterologous antibodies (e.g., derived from a horse) and for 3-4 weeks with human antibodies. Artificially acquired passive immunity develops after the introduction of vaccines, toxoids, Transfer Factor.

■ By pathogen contact

Sterile (postinfection)

It persists after the elimination of a pathogen from the body (measles, diphtheria). Non-sterile (infection) is that which exists until there is a pathogen in the body (tuberculosis, syphilis).

■ By coverage in the body

Systemic

Systemic immunity covers the whole body whereas local immunity is limited to a particular organ or tissue. The central role belongs to subclass IgA2. These immunoglobulins bind antigens, impede the microbial adsorption by blocking their receptors.

■ By the mechanism

It is divided into humoral, cell-mediated and combined (primary).

■ By action

It refers to antitoxic immunity realized against exotoxins and enzymes (toxins and endotoxins). Naturally, it is based on the humoral immune response.

Antitoxic Immunity (Elimination of Toxins)

It develops through the interaction of antibodies with a toxic group of toxin and through its neutralization, modification of toxin receptors (as toxin cannot attach to the target cell) and precipitation. There is also antibacterial immunity where antibodies are generated against any bacterial antigens, but antibodies synthesized against protective antigens exercise protection.

Antibacterial Immunity (Elimination of Bacteria)

It depends on bacterial localization. If bacteria are extracellular, their elimination takes the following way:- bacteria+antibodies+complement →immune damage. Antibodies induce opsonization of bacteria, and this contributes to phagocytosis. If bacteria are present intracellularly, elimination involves the formation of infectious granuloma (by T-cell effector pathway). If the body is not weakened, the microorganism either dies in the granuloma or stays viable for a long time. Otherwise, a disseminated infection can "seed" other areas of the body after granuloma is destroyed.

Antiviral Immunity (Elimination of Viruses)

It depends on viral localization. Typically, the virus stays inside cells, where it lives and proliferates. After penetration into the cell and resting inside the cell, the virus changes the antigenic structure of cell membranes, and Killer T-cells are produced by the organism to kill such infected cells. Also, granuloma can be formed (T-cell effector pathway). In response to extracellular virus-specific antibodies are produced, that come in contact with such virus, forming "virus-antibody" involved to be captured by the macrophage.

In some cases, the antibody-dependent cell-mediated cytotoxicity occurs when antibody bounds to the surface of a cell infected with a virus, and natural killer cells excrete same perforin substances, cause the death of cells by destroying its membrane. Influenza viruses, parainfluenza, adenovirus, coronavirus are highly changeable, so the concentration of specific antibodies in the mucus against them is always insufficient. Damage of epithelial layer by agents raises the penetration of viruses into the inside and triggers the antiviral immune response. Damaged epithelium surface can be colonized by bacteria which easily penetrate the inside of the body, which in turn induces a humoral immune response. Both defense responses needed simultaneously such as cell-mediated (against viruses) and humoral (against bacteria) one provoke competition for cytokines, and it weakens both mechanisms. Therefore, it is necessary to use immunotropic therapy in such patients.

Humoral mechanisms can eliminate viral infections that spread hematogenous (poliomyelitis, measles, epidemic parotitis, chicken pox), and this condition is usually characterized by a prolonged incubation period. At the same time, pathogens that proliferate directly at the site of infection (influenza) have a short incubation period, which can be dangerous due to certain inertia for the development of the immune response and severe course of a disease. Because viruses are intracellular parasites, cellular response provides the primary line of defense against them. The frequent occurrence of delayed-type hypersensitivity in patients proves this point.

Antifungal Immunity (Fungal Elimination)

This type of immunity is similar to antibacterial immunity but still has its characteristic features. Since fungus contains many polysaccharides, they can exist in the form of spores and vegetative forms. Nonspecific factors contribute to the alternative pathway of the complement system activation. In addition to the fungal cell death proteins of the complement system attract inflammatory cells to fungus, and the development of inflammatory response accompanies it. Cells of the fungus may also become targets for normal killer cells. Humoral pathway of

pathogen elimination is possible, and it is when complex "fungus+antibodies+complement" is accompanied by lysis. In fungal diseases immunoglobulins, E is produced which are involved in the development of allergic reactions with immediate-type hypersensitivity, and this contributes to the development of inflammation. The cell-mediated immune response takes place (when T-helper cells synthesize interferon, which activates phagocytosis, and T- effector cells produce infectious granuloma). Energy can arise as a result of the repeated stimulation of regulatory T-cells. It represents the absence of an immune response or the formation of a very "weak" immune response.

Antiparasitic Immunity (Elimination of Parasites)

It should be considered that many parasites have several stages of development, the different antigenic composition according to which specific antibodies are formed. When changing the stage, a parasite can for some time "escape" from antibody exposure, and it hinders the formation of the immune response.

Anthelmintic Immunity (Elimination of Helminths)

On the one hand, helminths render immunosuppressive effect, and, on the other hand, they have a complex life cycle. They often contribute to the stimulation of the synthesis of IgE with induction of atopic, immune complex reactions, cellular allergic reactions, and under certain circumstances can produce infiltrate at the site of infection, consisting of eosinophils, basophils and mast cells. However, sometimes the parasitic worms can avoid detection by the immune system due to the layer of various antigens on the surface of the parasite, which hinders its elimination by the host.

General Characteristic Features of Adaptive Immunity

They are non-inheritance at birth, individual (personal) contacts of the subject with pathogenic agents, high specificity, and in some cases insufficient tension and short-term duration.

Adaptive immune system "is triggered after innate immunity is activated and in response to at least partial elimination of pathogens. Also, it develops after a few days, starting with 3-4 days and more, as it is associated with proliferation and differentiation of cells. There is some intermediate specific phase for innate and adaptive immunity in connection with "professional" phagocytic cells using opsonic antibodies, as well as antibody-dependent killing and effect of specific γ-interferon.

According to the "danger" concept, the induction of Adaptive Immunity (AI) is based on the activation of dendritic cells with the production of cytokines and antigen recognition. As such, a dendritic cell captures an antigen, process it as a complex with MHC and delivers to the corresponding specific clone of T-lymphocytes. "Naive" T-helper cells begin to differentiate into Th1, Th2, Th 9 and Th17 subpopulations, rendering corresponding responses. Thus, Th1 is responsible for delayed-type hypersensitivity and defense against viruses. Th9 is responsible for antiparasitic immunity, and Th17 deals with autoimmune processes.

T-helper cells and corresponding cytokines interact with B-cells, inducing antibody formation (humoral immunity response) in three options: (1) thymus-dependent immune response with sequential switching using all types of Th from IgM to IgG and IgA; (2) thymus dependent Th2 immune response with switching of secreted antibodies to IgE, IgG4 and (3) thymus independent immune response with the production IgM only.

A wide range of activating effects on adaptive immunity has been worked out. Firstly, these include (1) the specific vaccines/toxoids, (2) serums/immunoglobulins, actively and passively potentiating specific defense response. Secondly, it is (3) immunomodulators, capable non-specifically stimulate different components of the immune system, (4) antivirals, interferons, interferon inducing agents (5) adjuvants, intensifying induced immune responses, (6) adsorbents to bind suppressor factors (7) metabolic, normalizing oxidation and antioxidant mechanisms, etc.

Indirect evidence of the unity of nonspecific and specific mechanisms in immunogenesis are the paradoxes of clinical immunology. They ensure the successful diagnosis of the immune disease using nonspecific immune methods for identifying populations, subpopulations of lymphocytes, immunoglobulins, phagocytosis, etc. and its successful removal by nonspecific immune correctors [5].

Antigenic Mimicry of Normal Microflora

It is known that the presence of cross-reacting antigens in microorganisms of various genera and species is a nonspecific mechanism of induction of specific immune response in the body. Thus, Afanasiev S.S [6] showed that the saprophytes, extracted from the intestine, mouth, conjunctiva of rabbit (6 *E. coli* strains, 2 *Enterococci* strains, para-intestinal bacteria, *Proteus*, *Staphylococcus aureus* and *Albus*, Micrococcaceae and yeast) detected antigens related to typhoid, paratyphoid fever A and B , and Flexner dysentery, *E. coli* enteritidis 0111 and 037. These antigens are introduced to determine the formation of specific complete and incomplete antibodies against pathogens. Also, common antigens were identified in *Escherichia*, *Salmonella*, and *Shigella*, *Brucella, Proteus* and in *Provacheks rickettsia.*

Antibody Spectrum in Normal and Specific γ-globulins in Humans and Animals

VA Romanov [7] discovered antibodies in normal human γ-globulin against *S. typhi*, *S. typhimurium*, *S. cholerae* suis, *S. enteritidis*, *E. coli*, whooping cough-altogether against 31 archival and freshly isolated microorganisms.

AN Sekunova [8] revealed in ox anti-Leptospira γ-globulins, the complete and incomplete antibodies against 33 diagnostic antigens and *Salmonella* cultures, against 34 dysentery agents, some other pathogenic, potentially pathogenic, saprophytic *Escherichia*, *Staphylococci*, *Diplococci*, and *Enterococci*).

BD Trutnev [9-11] found in equine specific antirabic γ-globulin antibodies against tick-borne encephalitis, 34 *Salmonella* species, pathogenic *E. Coli*, 15 *Staphylococci aureus* strains, *Streptococci*, *Diplococci*, brucellosis, *Klebsiella pneumonia*, whooping cough, listeriosis, ozaena agents, rhinoscleroma. Altogether 172 intact antibodies and 59 incomplete antibodies were identified.

Thus, the presence of 180-200 complete and incomplete antibodies against a wide range of pathogenic, potentially pathogenic, saprophytic microorganisms in the normal and specific immunoglobulins of animals and humans were documented, extending the applicability of serum products for prevention and treatment of infectious diseases and others.

Nonspecific Effects of Immunoglobulins

The accumulation of immunoglobulins A and M in the body and simultaneous antigen arrival nonspecifically stimulates an immune response to it. However, IgG has, in contrast, the ability to suppress the formation of specific antibodies under such conditions. It should be noted that products of catabolic processes in these proteins also have high biological activity. Thus, $F(ab)_2$ fragments of homologous IgG can nonspecifically enhance immunogenesis. Degraded Fc fragment of the immunoglobulin of various classes increase migration and viability of polymorphonuclear leukocytes, stimulate antigen presentation with accessory cells, contribute to T-helper cell activation, and enhance the immune response to thymic-dependent antigen. Nonspecific immune effect of the official human IgG preparation (e.g., gabriglobin), identified by us in the prevention and treatment of burn sepsis, postoperative purulent-septic complications and multiple organ failure etc. has an extremely broad range of activity and therefore can be used in various immune disorders beyond burns only because the preparation is useful in the following situations: (1) It addresses the shortage of B-cells (2) Activates and normalizes the activity of phagocytes, (3) Eliminates the deficiency of T-lymphocytes, t-helper cells, natural killer cells, t-cytotoxic lymphocytes (4) Restores the imbalance of proinflammatory\ anti-inflammatory cytokines (5) Suppresses the formation of pro-inflammatory cytokines and activates the formation of anti-inflammatory cytokines, (6) Neutralizes the function of C3b-subcomponent of the complement which activates phagocytes, (7) Suppresses pro-inflammatory activity of the compliment.

In model experiments on animals after induction of specific antibodies formed at the peak of their concentration temporary decline in activity in immunoglobulin Class M of heavy chain were documented with no reduction in blood serum concentrations at the expense of formation of the albumin factor in the liver. Non-specific surveillance of antigen-binding capacity of antibodies was found. It ensured humoral immune response against infectious

agents, mechanisms of self-purification of the body as well as the risk of induction of autoaggressive reactions [12].

Other Factors of Non-Specific Regulation of Specific Immune Responses [2,13,14]

When various microbial and somatic cells are destroyed during the process of infection, endogenous stimulants are released such as acute phase proteins, low molecular weight nucleic acids, etc., which activate the body's natural and specific resistance.

Interleukins (IL)

These include factors of a polypeptide nature that are not immunoglobulins, synthesized by lymphoid and non-lymphoid cells, and cause a direct effect on the functional activity of immunocompetent cells without induction of a specific immune response. For example, IL-1 activates the proliferation of antigen-sensitized T-and B-lymphocytes, IL-2 enhances the functional activity of T-and B-lymphocytes, their subpopulations, NK cells, macrophages. IL-3 is a growth factor for stem and early hematopoietic cell precursors, etc.

Myelopeptides

In the process of a healthy metabolism, they are synthesized by the bone marrow cells of animals and humans; they do not have allogeneic and xenogenic restrictions; they are a complex of peptides that are unable to induce an immune response, but have immunoregulatory immunostimulating properties.

Thymic Peptides

They are synthesized by the thymus gland constantly, and not in response to an antigenic stimulus. With reduced levels of immune status, they increase the functional activity and the transformation of immature T-lymphocytes into mature ones and activate helper and killer activity.

■ The endocrine system

Endogenous hormones have been found to be regulators of immune homeostasis. The spectrum of action of these compounds includes non-specific stimulation and suppression of specific immune responses triggered by specific antigens. For example, cortisol suppresses cellular and humoral immune responses, and mineralocorticoids enhance the inflammatory response and the synthesis of immune globulins. ACTH suppresses immune reactions, and STH stimulates inflammation and proliferation of plasma cells.

■ Cyclic nucleotide system (cAMP-cGMP)

3'5'-AMP inhibits the reaction of phagocytosis in neutrophils, the proliferation and differentiation of lymphocytes, cellular and humoral reactions to antigens, and cGMP stimulates these processes.

■ Revaccinating effect of low molecular weight nucleic acids

In model animal experiments and clinical observations on volunteers, the ability of low molecular weight ribonucleotides due to the re-deponing of antigens of a previously vaccinated organism to induce the production of specific antibodies against typhoid fever and paratyphoid fevers, the activation of specific anti-infective immunity against intestinal infections was shown [5].

Adjuvants

The adjuvants include drugs that are unable to independently induce a specific immune response, but implement its non-specific stimulation. These drugs are divided into depositors that delay the removal of antigen from the body (Freund's adjuvant, liposomes) and factors that nonspecifically activate the immune system through the migration and cooperation of immune cells, the formation of complexes with antigens, the formation of immunoglobulins, etc. [2].

Immunomodulators

These compounds include a wide range of immunoreactive substances-derivatives of the thymus, bone marrow, spleen, lymph nodes, erythro-, leukopoetins, lymphocytes, synthetic preparations of microbial cell structure analogues, lipo-and polysaccharides, interferons, interferon inducing agents, etc., which can regulate nonspecific\inhibit excessively stimulated or activated suppressed specific immune responses.

Vaccination Effect

The ability of some vaccines to determine

not only specific immune responses but also nonspecifically contribute to the formation of "anamnestic" antibodies against anamnestic antigenic contacts of the body has been established.

■ The ratio of nonspecific and specific mechanisms of anti-infective resistance

Under natural conditions, 3 levels of anti-infective resistance formation are postulated, which are digitally displayed as 2:1-two non-specific and one specific. The first is due to pre-immunological mechanisms, which is complemented by an antigen-oriented specific immune response, representing the second specific level of response, subject to non-specific regulation, which is the third non-specific level of correction.

When immunomodulators are administered to a patient, 3 levels of sequential response are also implemented: (1) operational non-specific mobilization of natural resistance, (2) non-specific stimulation of a specific immune response, (3) its subsequent inhibition due to specific suppressor mechanisms.

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