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Research Article

Subsystems of the immunity

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ABSTRACT: This article describes subsystems of the immunity – skin, mucous membranes, ear, throat and nose organs, the respiratory, digestive and urinary tracts. It covers opportunities of the targeted correction of their functional violations that can influence targeted immunotherapy options.

Key words: subsystems of the immunity, mechanisms of immunity, lymphoid tissue, immunotherapy.

INTRODUCTION

At the start the paper reports that systemic and local immune disorders have been specificated, and new methods to manage and deliver corrective drugs in case of particular organ systems disorders have been developed recently. Apparently, classical concepts of local and general immunity and their treatment options are in need of certain development. Taking this into account it seems appropriate to highlight subsystems of the immunity, such as skin, mucous membranes, ear, throat and nose organs, the respiratory, digestive and urinary tracts, and identify options of the targeted correction of these immune subsystems [1, 2, 3].

The point to be emphasized is that protective reactions of the abovementioned organs and systems include certain general mechanisms – mechanical barriers (skin, mucosa), encapsulated and non-encapsulated lymphoid tissue associated with them, and serous and extracorporal antibacterial factors. Besides, there is normal microflora, systemic and regional highly specific immune mechanisms conditioned by immune globulins, lymphoid cells, granulocytes, phagocytes, cytokines, interferons and interferon inducers etc. [4 – 7].

Discussion

A) Subsystem of the skin immunity

Skin amounts to approximately 20% of the human body mass with the total area of about $2m^2$, and has the following functions: respiration (oxygen absorption), thermoregulation, synthesis of enzymes and mediators, detoxication, water excretion, blood storage, reception, immunity. It has functional linkage with hypophysis, adrenal glands, connective tissue and others; what is more, there is an opinion that with aging skin starts replenishing fading function of the thymus gland.

Laminated epithelium of healthy skin is usually impenetrable for microbes and macromolecules. However, in case of microdamages, inflammation, insect bites, burns and injuries intradermal transmission of infectious and antigenic factors is possible. Viruses and certain bacteria at that can penetrate into macroorganism intercellularly and intracellularly with the help of phagocytes and other ways.

Skin successfully provides the function of bactericidal, bacteriostatic and mechanic barrier, develops protective local vascular reactions (spasm or/and vasorelaxation of microcirculation, exudation of a serous blood component). Sebaceous and sweat glands exude lactic, fatty, acetic, formylic acids decreasing hydrogen pH value to 5.5 and resulting in the acidic media. Representatives of the normal microflora of the skin are included into the exo-polysaccharidic-mucin matrix as biological film resistant to various impacts. Normal microflora of the skin is considered to be a natural "counter-agent" of the pathogenic and opportunistic pathogenic flora. There are from 25 million to 1 billion microorganisms per 1 cm^2 vegetating on the surface of the skin and in its deeper layers. This amount is normally stable and does not increase as a result of the bactericidal sterilizing factors effect. For example, α-globulins, IgA and IgG immunoglobulins, transferring, lysozyme, other anti-microbial factors have been found in the sweat. Self-cleaning processes are enhanced on the clearly washed skin surface. Non-pathogenic staphylococci and diphtheroids at that reveal maximal antagonistic activity towards accidental opportunistic microorganisms. *Candida* yeast-like fungi, enteric bacteria and bacteroids should not appear on the skin of healthy adults. Presence of colibacilli on the skin is reported to be an unfavourable sanitary-hygienic finding.

Limphoid subsystem of the skin includes disseminated intraepithelial lymphocytes and regional lymphatic nodes, as well as vessels of lymphatic drainage. Since skin is constantly in contact with aggressive factors of the environment, it is considered to be the first target of immune and allergic reactions, and is provided with a certain specific immune function. Generally, skin is regarded as an organ, where local immune reactions are developed, and signals aimed at the involving the whole body system into response are generated. Nonetheless, skin does not contain large structural accumulation of lymphocytes but is able to induce systemic reactions to antigens, isolate, and display foreign objects with

the help of indigenous histiocytes, mast cells, Langerhans' cells, Greenstein reticular cells, epidermis and dermis, lymphocytes and granulocytes [4].

Subsystem of the mucous immunity

Mucous membrane of the gastro-intestinal tract, airways and the urinary tract contains a significant amount of reticular fibers, which appears to be one of the elements supporting the frame of the blood-forming organs. As a rule, lymphocytes forming lymphatic follicles are accumulated there. Lymphoid tissue may be of several types: MALT – mucosal-associated lymphoid tissue; GALT - gut-associated lymphoid tissue – tonsils, appendix, Peyer's glands; BALT – bronchus-associated lymphoid tissue; VALT – vulvovaginal-associated lymphoid tissue; NALT – nose-associated lymphoid tissue. In fact, all the above-mentioned structures contain subpopulations of intraepithelial lymphocytes. Liver is also related to the specified organs, because it "provides" a lymphoid barrier to blood of the portal vein carrying all substances absorbed in the intestine and other organs.

Mucosal-associated lymphoid tissue

Lymphocytes are located separately in mucous membranes, where there is no persistent and long-lasting effect of antigens, and form diffuse lymphoid tissue. In the regions, where frequent contacts with antigens and allergens are observed, lymphocytes are accumulated into small and big dense formations, which are called lymphoid nodes. Lymphoid nodes with germinal centres are located in the regions of persistent and strong impact of antigens. Lymphocytes of the intestinal Peyer' glands, lymphoid follicles of appendix, tonsils of the throat, lymphoid follicles of the sub-mucosal layer of the upper respiratory ways and bronchi and the urinary tract are located directly under mucous epithelium closely associating with epithelial cells. All stages of the specific immune response occur in lymphoid tissues associated with mucous membranes: activated B-lymphocytes are differentiated into plasma cells producing specific antibodies related to immunoglobulins IgA. The latter having passed through epithelial cells adjoin the secretory piece and pass out on the mucosal surface as secretory immunoglobulin SIgA, which provides local antibacterial and antiviral defense. There are immunocompetent T-lymphocytes, dendritic and epithelial cells able to display antigens, in the epithelial layer and proper mucous plate. Besides organized lymphoid tissue there are single plasma cells, activated T- and B-lymphocytes, natural killers, cells of the immune memory, quiescent lymphocytes, monocytes, granulocytes, eosinophils in mucous membranes.

Immunotherapy of disorders of the skin and mucous membranes

Local (intradermal and intramucosal) introduction of immunotropic medications is recommended as additional therapeutical methods in case of disorders of the skin and mucous membrane.. In this context supracutaneous, intracutaneous, subcutaneous – with the help of applications, needless injection device, electrophoresis and so on – introduction of vaccines and modulators (Sodium Nucleinate, Derinat, polysaccharidic and thymic derivates, complex immunoglobulin preparation, Polyoxidonium, Dapsonum) is considered to be very effective; introduction of allergens, Heparin, histamine, antihistamine preparations appears to be the most effective in case of specific and non-specific hyposensibilisation; intramucosal introduction (intranasal, aerosol, peroral, under bronco-alveolar lavage, when using pulmonary microcatheters) of nucleonic modulators – Derinat, Ridostin, Sodium Nucleinate, their synthetic variants (poly A:U, I:C, Poludanum, Isoprinosine, Encadum), polyelectrolytes and thymomimetic drugs, mielopeptides, Complex immunoglobulin preparations, Licopid, activated lymphocytes, circulating leucocytes, interferonogens - is of great significance. Common and low-immunogenic vaccines, serous preparations, allergens for therapy and provocative allergic tests, ozonized physiological solution NaCl, corticosteroids – in suppositories, drops, when doing lavage – all these are also included there [8. 9].

B) Subsystem of the immunity of ear, throat and nose organs

Oral cavity is a structural beginning of both digestive and respiratory tracts; it performs functions of reception, neutralization, analysis and "memorizing" a wide range of air, food, water and other objects antigens. Oral mucosa in contrast to other mucous membranes of the human body is resistant to the influence of physical, thermal and chemical stimuli and to infection transmission, and its regenerative capacity is increased. Superoxide anion radical, lysozyme lactoferrin, enzymes of cell lysis and defense – amylase, acid phosphatase, esterase, aldolase, complement, SigA, IgM and G - are reported to be antibacterial factors of the saliva. Polymorphonuclear neutrophils, macrophages act as cellular elements of non-specific defence of the oral cavity. There are large amounts of lymphoid tissue – a lymphoepithelial tonsillar ring, – palatal, pharyngeal, lingular, tubal, laryngeal tonsils and gingival lymphoid accumulations in the mucous membrane on the boundary between the oral cavity and throat; they perform protective function of microbial decontamination and formation of lymphocytes participating in reactions of the humoral and cellular immunity. T-, B-lymphocytes, plasmacytes and mastocytes ensure specific immunity. Microflora of the oral cavity has great influence on anti-infectious resistance amounting to more than 700 of bacterial species. It stimulates development of lymphoid tissue, antagonism of generation of pathogenic bacteria; supports physiological inflammation in the mucous membrane; provides self-cleaning of the oral cavity; supplies a body with aminoacids and vitamins and promotes secretion of salivary glands.

In mucous membrane of a nose and its paranasal sinuses, as well as connective tissue, there are cells of the lymphoid range and their small accumulations – lymphoid follicles consisting of B-cells, perifollicular T-cellular zones, suprafollicular epithelium with M-cells, specific endothelium in blood vessels. Penetration of nasal mucosa is significantly increased in case of acute inflammation; this results in "passing out" of IgG, which are not usually transported in healthy state or under chronic inflammation on its surface.

The middle ear is considered to be a potentially immune organ and becomes immune-active after the impact of pathogens with the development of local and general protective reactions. Local immunity includes both – proper immune mechanisms conditioned by specific antibodies, sensibilized lymphocytes, and non-specific reactions conditioned by mucociliary clearance of mucous membranes and skin - lysozyme, interferons, a complement complex, properdin, various inhibitors and others. The auditory tube is lined with mucous membrane with ciliated cells having lymphoid nodes that form the tubal tonsil and parotid lymph nodes. Cellular structure of

the immune system of the middle ear is represented by macrophages, populations of T- and B-lymphocytes, monocytes.

Immunotherapy of ear, throat and nose disorders

Local application of non-resistant specific stimulators – such as Sodium Nucleinate, Superlymph, polysaccharides, Diucifonum, interferons, interferonogenes - directly into the cavum conchae is recommended as the additional immunotherapy, since violations of anti-infectious resistance of ear, throat and nose organs are mainly caused at first by the damage of the phagocytic component of innate immunity, then – by T-dependant and next – B-dependant protective reactions. Vilosen, Thymogen, mielopeptides, Derinat, ozonized NaCl are introduced into the nasal cavity in addition to the above-mentioned preparations. Sodium Nucleinate, thymomimetic drugs, Licopid, some low immuno-genic vaccines, complex immunoglobuline preparation are administered in the oral cavity and sublingually. In severe cases of immuno-pathology in patients with ENT disorders all the indicated immuno-tropic medications should be combined with the additional metabolic therapy (CigaPan, Hypoxenum, Limontar, Apilac, Tykveol, vitamins, Pentoxylum, Methyluracil and others), as well as the systemic immune-correction.

C) Subsystem of the immunity of the respiratory tract

Walls of the respiratory organs that breathe in foreign bodies together with air have an apparent instrument of immune defense – lymphoid tissue accumulations in the mucous membrane of a throat, trachea and bronchus and cells of the lymphoid range disseminated in the mucous membrane. They act as a barrier to defense the internal environment against aggressive action of infectious, allergically dangerous antigens and others. Accumulations of the lymphoid tissue (lymphoid nodes) are located in the mucous membrane of the respiratory tract under the surface epithelium. They contain committed T- and B-lymphocytes that are mainly concentrated in the area of connection of bronchioles with alveoli and are separated from the lumen of bronchus by specialized lympho-epithelium, which is frequently interrupted at these sites providing cells' ability to catch a corpuscular antigen, and clean airways from dust and other foreign bodies.

Bronchus-associated lymphoid tissue is regarded as a reservoir of immuno-competent cells, which contain lymphocytes migrating to various regions of airway walls being a component of the whole lymphoid body system. A lymphoid follicle formed mostly by B-lymphocytes with insignificant T-cells amount is considered to be the important structure of this tissue. Epithelial cells are an important component of the broncho-pulmonary segment. They function as barrier secretory cells in the presence of undamaged mucous lining; however, they acquire properties of immunocytes under disturbing actions (damage, infections, impact of bacterial products, cytokines). Furthermore, in the broncho-pulmonary tissue there exist specialized M-cells able to bind and display antigens, secrete cytokines, and involve lymphocytes in the inflammatory process. Antigens representing **dendrite cells** of marrowy origin that are responsible for initiation of the mucosal immune response, macrophages – mostly tissue-fixed, neutrophils emigrating from the blood flow and mast cells and eosinophils are reported to be an important part of the respiratory mucosa.

Humoral factors of the respiratory anti-infectious defense include the whole range of relations with specific and non-specific functions. Immune A-globulins – secretins – perform major defense function in the broncho-pulmonary system. They are either synthesized directly by plasma cells disseminated in the mucous membrane, or carried into by the blood flow. Commonly believed, the upper part of the respiratory tract is screened by IgA, lower – by IgG. In addition to immune globulins there are non-specific humoral factors – lysozyme, acute-phase protein, natural peptide antibiotics, various proteases, inhibitors of viral expansion, α- and γ-interferons, β-lysines, X-lysines, the properdin system, a complement, pro- and anti-inflammatory cytokines, corticosteroids and others in the respiratory tract.

Immunotherapy of the respiratory tract disorders

Immunotherapy of the respiratory tract disorders, except systemic correction, includes local application (intranasal, aerogenic, endoscopic, broncho-alveolar lavage, intradermal – with the help of needless injector device, electrophoresis etc.) of immunotropic preparations: low-immunogenic vaccines, derivatives of nucleic acids, polysaccharides, thymus, interferons, interferon inducers, as well as peripheral lymphocytes, drug-free factors – laser radiation of low intensity, physiotherapeutic impact, acupuncture and others.

D) Subsystem of the immunity of the digestive tract

Intestinal mucous membranes are constantly under antigenic influence of food products, microorganisms, which amount to $> 10^{14}$ bacteria of 400 species. This number is obviously increased in case of intestinal infections. The digestive tract develops certain protective non-specific mechanisms against pathogenic antigenic factors: antibacterial factors of the saliva, microbicidal exo-secretes (gastric hydrochloric acid, pancreatin, bile, secretion of proteolytic activity, digestive enzymes of the intestine). Intestinal motility, specific ultra-structure of the mucosal surface and its anti-microbial factors (protease, peptide-antibiotics, microbe-binding proteins) may be also included there. Local vascular reactions of defense (spasm and vasodilation of microcirculation, exudation of the blood serous component), normal microflora etc. are of great significance. The specific immune system of defense localized in the digestive tract and composing an important part of the whole multi-component immune system of a human should be also mentioned as a non-specific barrier mechanism.

Lymphoid tissue of the gastro-intestinal (GI) mucosa is reported to be powerful barrier formation separating the internal environment of a body from antigenic material, including infectious and allergenic, coming from the lumen of the intestine. This tissue is represented by formations of several kinds. One of them is diffuse-located separate cells infiltrating layers of epithelial cells (T-lymphocytes) and a proper plate (Lamina propria), as well as sub-mucous layer (B-lymphocytes). Another type of lymphoid tissue is small accumulations located near small blood vessels; this includes pleura, abdomen and other tissues. More organized lymphoid tissue of the mucosa is represented by follicles – dense accumulations of cells of round or oval forms (primary follicles) forming germinal centres under the influence of antigenic stimulation (secondary follicles). Bursa of fabricius in birds and appendix are related to structural lymphoid organs associated with the intestine. The appendix performs functions of "an abdominal tonsil" responsible for colony-resistance of the normal microflora on the mucosa of the entodermal canal and non-specific anti-infectious resistance in the intestine

being an organ of immunogenesis and formation of immune globulins, major populations and subpopulations of lymphocytes. This organ histomorphologically consists of a dome with a crown, follicles located under the dome, the thymus-dependant zone and the mucous membrane in the shape of fungi-form ridges related to it. Dome epithelium is specified by the presence of M-cells. Cellular composition of the lymphoid tissue of the appendix is represented by lymphoid cells of various maturity degree and macrophages [10, 11].

Cells composing the lymphoid tissue of the GI tract absorb and fragment antigens, form AG-specific and T- and B-lymphocyte pool, synthesize and secrete cytokines, develop immune response in the form of production of specialized immunoglobulins – anti-bodies (B-lymphocytes) – or determine cells-mediated defense of the mucous surface (T-lymphocytes). Plasma cells synthesize and secrete immunoglobulins (G, M, A, D, E class). Protective function in the external secrets is mainly performed by secretory IgA (SIgA); being associated with bacteria and viruses SIgA prevents their adhesion to the epithelial surface and provides "the first line of defense" of mucous membranes from the impact of antigens. Dendrite cells ensuring absorption, fragmentation and transportation of antigens to regional lymphatic nodes are reported to be an important component of the lymphoid tissue of mucous membranes.

Normal microflora of a human is considered to be an "extracorporal" organ performing the following functions: 1) providing mucosal colony-resistance; 2) stimulation of the process of developing the immune system in the newborns and supporting regular immunity in adults; 3) participation in the regulation of motor-evacuative function of the intestine; 4) inactivation of toxic products of endogenic and exogenic origin; 5) maintaining blood carcinolytic properties and realization of the anti-mutagenic action; 6) facilitating the digestive processes; 7) synthesis of aminoacids, proteins, vitamins; 8) participation in the water-salt metabolism, regulation of the intestinal gas composition, metabolism of proteins, carbohydrates, fatty and nucleic acids, cholesterol and others; 9) realization of genetic function by the passage of genetic information from one microorganism to another through the process of phagocytosis; 10) the morphokinetic role in the development of organs and tissues, inflammation, change of epithelium etc.

E) Subsystem of the immunity of the urinary tract

Lymphoid formations of the urinary tract perform functions of "a guard" in relation to those foreign substances that get into them from the outside by ascending way or are formed in their upper segments. In spite of the fact that urine is considered to be the natural product of the life-sustaining activity, it includes foreign substances – proteins, dead epithelial cells, which entered the urinary bladder and ureters by the ascending way of microorganisms. In the walls of **the urinary bladder** there are considerably more lymphoid nodes than in **ureters**, because the latter function only to pass urine from kidneys to the urine bladder, where urine is stored and retained for a long period of time. Prevailing majority of the lymphoid nodes of the human urinary tract does not have germinal centres; this probably explains short duration of contact of the mucous membrane with urine in dieresis. Lymphoid nodes of the urinary tract (ureters, the urinary bladder, urethra etc.) have linear longitudinal arrangement between folds or in the thick plate of the mucous membrane to provide defense on the passing way of urine containing aggressive antigens [12].

Protective factors of genitals are determined by biological protective barriers as well: "mechanical", which is considered to be (1) closed position of the interlabial space, which is obtained by normo-tonus of muscles of the perineum and the vulvar ring; (2) vaginal, which is determined by physiological desquamation and cytolysis of the superficial epithelial cells regulated by cyclic steroidogenesis; (3) acidic pH of the vaginal medium and colony-resistance of Doderlein bacillus and others; (4) narrowness of the outer and inner mouth, isthmus of the uterus and functional load of endocervical cylindrical epithelium and cervical mucus.

The important components of the vaginal barrier are factors of the immune defense at the level of the mucous immune system (lymphoid tissue associated with mucous membranes) that provide rapid localization of the infectious process under the development of minor inflammatory reactions without tissue damage. This is achieved under complex interaction of both - non-specific effector mechanisms (the opsonocytophagic system) and specific immune response, primarily –formations of antibodies; they include neutrophils and the macrophagal phagocytic system, the system of interferons, immunoglobulin profile (SIgA, IgG).

Limphoid formations of uterus. T-lymphocytes compose 50% of lymphocytes of the functional layer. They are mainly T-cytotoxic suppressors. In females macrophages and plasma cells appear in endometrium very rarely. Diffuse lymphoid tissue achieves maximal development at 10-20 years of age, and this condition persists during the whole fertile period. Involution of this tissue is observed during menopause especially in the elderly women.

Lymphoid nodes of gastrocolic omentum. Gastrocolic omentum being a derivative of mesogastrium contains a large amount of lymphoid nodes and is reported to be an organ of the immune system providing the body immune defense in the abdominal cavity. Antibodies forming function of milk spots of this organ, presence of phagocytic, lymphoid, plasmatic, mast cells, granulocytes and others have been established in this organ.

Microflora of infectious-inflammatory diseases. Vaginal infections and dysbiosis of **the lower part of the female genital sphere** result from opportunistic microflora with 30 to 80% frequency [10]. The most commonly widespread diseases are considered to be bacterial vaginosis, Candida and non-specific bacterial vaginitis; the last-mentioned condition is characterized by the replacement of anaerobic lactobacilli into aerobic, Escherichiacoli, Staphylococcusaureus, S. epidermidis, Klebsiella,Proteus, nonsporeforming anaerobes Prevotellabivia, Peptostreptococcus, specific causative agents - Chlamydiatrachomatis, Trichomonasvaginalis u Neisseriagonorrhoeae, viruses of herpes simplex, human papillomas.

Inflammatory diseases of **the upper part of the female genital sphere** result from opportunistic, aerobic-anaerobic associations: Escherichiacoli, Staphylococcusaureus, S. epidermidis, S. saprophyticus, Bacteroides, Prevotellabivia, Clostridium, Pepto-streptococcus, and also - Chlamydiatrachomatis, Neisseriagonorrhoeae,Ureaplasmaurealyticum, Mycoplasmahominis, Mycoplasmagenitalium. Therefore, resistance of the internal genitals to the impact of pathogenic

microorganisms is determined to a large extent by combination of the following factors: (1) cyclic processes occurring in the functional layer of endometrium (cyclic desquamation during menstrual periods); (2) redox-oxidative and antibiotic potential of the epithelial covering of uterine walls; (3) peristaltic contractions of uterine tubes with the ciliary type of movement of superficial ciliated tubular epithelial cells towards the lumen of the uterus; (4) presence of germ epithelium covering the surface of ovaries; (5) immune defense mechanisms of peritoneal fluid (lysozymes, immunoglobuline profile).

Principles of immunotherapy of the urogenital disorders

In addition to preparations that activate the systemic immunity, it is recommended to apply stimulators of local anti-infectious resistance vaginally and rectally – Kipferon, Viferon, Superlymph, eubiotics in suppositories, liquid dosage forms, enemas, irrigation of genitals with ozonized NaCl and so on.

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