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FEATURES OF LOCAL MUCOSAL IMMUNITY OF THE UPPER RESPIRATORY BODIES

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SUMMARY

Today, the issues of studying the local immunity of the mucous membranes are insufficiently studied. In this regard, this direction is promising and relevant, therefore, research in this area is important in order to study the local immunity of the mucous membranes of the respiratory tract and the features of their functioning.

The immune system of the mucous membranes of the respiratory tract is the first barrier to the entry of pathogenic microbes into the lungs. Among the most important nonspecific factors of local protection are the phagocytic function of granulocytes and alveolar macrophages, mucociliary clearance of the mucous membrane of the respiratory tract, as well as a number of antibacterial and antiviral components that make up the secretion of the respiratory tract, these are lysozyme, lactoferrin, complement, interferon, surfactant. To prevent the penetration of pathogenic microorganisms, the mucous membrane has an autonomous immune system, the components of which are local B- and T-lymphocytes, macrophages, and their secretion products.

KEYWORDS: local mucosal immunity, nasal cavity, upper respiratory tract, innate immunity, acute respiratory viral infections.

Currently, the issues of studying the local immunity of the mucous membranes are insufficiently studied. A promising direction in the field of applied immunology is the study of the state of the immune system of the mucous membranes of the respiratory tract and the peculiarities of their functioning.[1,5]

The immune system of the mucous membranes of the respiratory tract is the first barrier to the entry of pathogenic microbes into the lungs. Among the most important nonspecific factors of local protection are the phagocytic function of granulocytes and alveolar macrophages, mucociliary clearance of the mucous membrane of the respiratory tract, as well as a number of antibacterial and antiviral components that make up the secretion of the respiratory tract: lysozyme, lactoferrin, complement, interferon.[1, surfactant 4,8,10] To prevent the penetration of pathogenic microorganisms, the mucous membrane has an autonomous immune system, the components of which are local B- and T-lymphocytes, macrophages, as well as products of their secretion.[2,3,5,9] The course of a nonspecific inflammatory process is characterized by structural and functional rearrangement of cellular elements at three levels: systemic, organ and cellular. Of considerable scientific and practical interest is the study of local immunity in health and disease, in particular, in acute infectious diseases.[4,9]

The immune system is a collection of organs, tissues, cells and proteins that protect the host from pathogens at any point of their penetration and limit their spread throughout the body. In the course of evolution, a specific lymphoid tissue (Mucosa associated lymphoid tissue (MALT)) was organized in the mucous membranes, where the protective reactions of the innate and adaptive response to pathogens are formed. The lymphoid tissues of the mucous membranes of different departments have their own characteristics that meet the needs of their anatomical location. Thus, the mucous membrane of the oropharynx provides for the simultaneous processing of both food and respiratory antigens, while maintaining the main immune homeostasis. This review examines the structure and features of the organization of the immune response of the oropharyngeal mucosa.

Within the immune system, a number of anatomically different regions can be distinguished, each of which is specially adapted to generate a response to pathogens present in it. The cascade of immune responses induced in one area is largely limited by it. Thus, in the human body, 4 conditional zones of immunity can be distinguished:

1) systemic immunity - the immune response to antigens that have penetrated into tissues or entered the blood;
2) local immunity of the mucous membranes - the area of the formation of the immune response in the zone where the majority of pathogenic microorganisms penetrate;
3) immunity of body cavities (peritoneum and pleura);
4) skin immunity.[2,7]

The mucous membranes are a thin and permeable barrier that lines the internal parts of the body and has a pronounced physiological activity: participation in gas exchange (bronchopulmonary system), digestion (gastrointestinal tract), sensory activity (eyes, nasopharynx and oropharynx), excretion and reproduction (urogenital tract). It is the mucous membranes that are the first barrier to the overwhelming majority of infectious agents, therefore, in the course of evolution, they have formed an immunobiological complex of effective defense mechanisms aimed at ensuring the integrity of the macroorganism.[5,12,15,19] Here, protective reactions of the innate and adaptive response to pathogens, tolerance to non-pathogenic organisms (commensals) and food antigens are formed, various pathological (allergic, autoimmune, infectious-dependent) reactions develop. All these functions are provided by the organized lymphoid tissue associated with the mucous membranes, known under the abbreviation MALT (from English: Mucosa associated lymphoid tissue). Depending on the anatomical location of the mucosal lymphoid tissue, NALT (nasopharynx-associated lymphoid tissue), BALT (bronchus-associated tissue), GALT (gut-associated lymphoid tissue) and SALT (skin-associated lymphoid tissue) are distinguished. The lymphoid tissues of the mucous membranes of different departments are interconnected due to the recirculation of lymphocytes between them. At the same time, the lymphoid tissue of the mucous membranes is to a certain extent isolated from other (peripheral) secondary lymphoid organs due to the autonomy of the lymphocyte recirculation pathways.[6,9,11,14]

Unlike systemic immunity, which functions in a sterile environment and reacts vigorously to pathogens, MALT protects structures that are colonized by foreign bodies and therefore must economically select appropriate effector mechanisms and regulate their intensity to avoid tissue damage.[7,13]

The oropharynx is the NALT area of activity. The oropharyngeal mucosa provides the simultaneous treatment of both food and respiratory antigens, therefore it has the general characteristics of the gastrointestinal and respiratory tract, and also has its own distinctive features. Oropharyngeal mucosa forms a mechanical barrier that is thicker and denser than the mucous membrane of the gastrointestinal tract. Morphologically, it consists of stratified squamous epithelium, lamina propria (loose connective tissue underlying the epithelium, which contains blood and lymph vessels), and a submucosal layer.[5,12,16,19] The immunological apparatus of the mucous membranes of the oropharynx is represented by organized tissue structures - unencapsulated clusters of follicles surrounded by lymphoid tissue (Pirogov-Waldeyer ring: lingual, palatine, tubal and pharyngeal tonsils), and diffuse lymphoid tissue.[7] Functionally distinguish between afferent (inductive) and efferent (effector) zones of the lymphoid tissues of the mucous membranes.[3,8,14,16] The afferent (inductive) zone of the oropharyngeal mucosa is anatomically represented by the palatine tonsils, salivary glands, lymphoid follicles and regional lymph nodes. Here, antigen recognition, perception of a foreign signal, and further processing of immunological information take place. These functions are provided mainly by dendritic cells. Dendritic cells, "imprinted" during the capture of antigen in different parts of the lymphoid tissues of the mucous membranes, migrate to the regional lymph nodes. Here they present the antigen to T-lymphocytes, inducing expression on the forming effector T-lymphocytes and memory T-cells, adhesion molecules and chemokine receptors. Thanks to these structures, effector T-lymphocytes and T-cells of memory "find" the section of the mucous membranes, in which the capture of antigen by certain dendritic cells took place. The ability of cells to find "their place" in the body is called homing. This process involves 2 mechanisms - contact, provided by adhesion molecules that are on the surface of lymphocytes, and chemotaxis, which determines the direction of cell movement and depends on the presence on their surface.[7,14,18,20] In a similar way, the "targeting" of migration into the mucous membranes of effector B-lymphocytes - the precursors of antibody-producers and memory B-cells - is provided. The effector (executive) department of the immune system of the mucous membranes is anatomically located in the epithelium, lamina propria and submucous layer. Activated lymphocytes, functional representatives of the effector zone, migrate here. All types of effector T-cells, formed in the regional lymph node, leave it with efferent lymph and enter the general bloodstream as part of the lymph of the thoracic duct. As already mentioned, the further distribution of effector T cells is determined by their expression of adhesion molecules and chemokine receptors. These cells migrate mainly to the regions from which the induced dendritic cells originate. Activated T cells enter the epithelial layer and the lamina propria through the squamous epithelium of the vessels. The migration of lymphocytes into the mucous membranes is enhanced by an inflammatory reaction, when the vascular endothelium of the mucosal lymphoid tissue is activated.[2,7,8,12] Toll-like receptors (TLR) are an evolutionarily ancient system that includes 10 types of receptors in humans, located both extracellularly (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10) and intracellularly (TLR3, TLR7, TLR8, and TLR9). They recognize microbial products with specific structural features, classified as pathogen-associated molecular

patterns (PAMP). Expression of TLRs is almost ubiquitous on immune cells, where they control the mechanisms of innate and adaptive immunity, and less abundant in cells of non-hematopoietic origin, such as epithelial cells. Recognition of PAMP prepares the cells of innate immunity to perform the main function - the removal of foreign agents from the internal environment of the body.[8,13,15,17] Since TLR specializes in recognizing microbial products, it is reasonable to assume their high concentration in the places of greatest contact of the surfaces of the macroorganism with pathogens, namely, on the mucous membranes. The expression of TLR proteins is highly variable and depends on the area of the mucous membrane and its state (normal or inflamed). In addition to contact with pathogens (PAMPs), the mucosal immune system actively interacts with the commensal microbiota (microorganisms that inhabit humans, but do not cause diseases), therefore the term CAMPs was introduced for commensal-associated molecular patterns (or the more general term MAMPs - for microorganisms associated with molecular patterns), which are also recognized by the TLR system. In addition, endogenous ligands that induce inflammation in the absence of infection can also activate a TLR-dependent signal and are defined as danger-associated molecular patterns (molecular patterns associated with danger - danger-associated molecular patterns, DAMPs).[10,11,13,19]

The composition of the population of cells of the immune system in the submucous layer is more diverse and is similar in spectrum to the secondary lymphoid organs and blood. The submucosal layer contains typical T and B lymphocytes, NK cells, macrophages, dendritic cells, neutrophils, eosinophils and mast cells. The ratio of subpopulations of T-lymphocytes in the submucous layer is close to that in the blood and lymph nodes. Although the cells that previously contacted the antigen (memory cells) predominate here, naive lymphocytes migrating into these tissues from the bloodstream are also detected.[7,15,16,20] The most important role in triggering immune processes is played by macrophages - tissue variants of monocytes. The transformation of a monocyte into a macrophage occurs under the influence of the tissue microenvironment and is accompanied by the expression of new genes, that is, it can be considered as cell differentiation. This differentiation is regulated by the macrophage colony-stimulating factor (M-CSF).[2,8,18,20] Resident tissue macrophages are long-lived cells: their lifespan is calculated in months and years. If they are not mobilized to the site of infection or inflammation, they can die, migrating to the spleen or lymph nodes. A large number of resident macrophages are found in connective tissue, lymph nodes and lymphoid tissue associated with mucous membranes, including the mucous membranes of the airways. The second population is represented by relatively short-lived macrophages of monocytic (bone marrow) origin. The relative content of such cells in a tissue depends on its type and the age of the organism. The number of macrophages of monocytic origin increases sharply during inflammation and normalizes after its end. Inflammatory tissue macrophages are formed from CD14 ++ CD16 monocytes, which contain on their surface many receptors for inflammatory chemokines, primarily CCR2, which is a marker of CD14 ++ CD16 monocytes and is absent in resident macrophages, due to which CCR2-expressing monocytes migrate in the foci of inflammation.[7,18] Inflammatory macrophages are one of the main effector cells of innate immunity, as they carry out phagocytosis and intracellular killing of most pathogens. By producing a large number of pro-inflammatory cytokines, these cells stimulate the development of a protective inflammatory response and involve other cells of the innate and adaptive immune system in it. Thus, the main functions of monocytes / macrophages are phagocytosis, antigen presentation and secretory activity.

Another group of membrane molecules are receptors for cytokines. Macrophage receptors are especially important for interferon-gamma (IFN-gamma), for proinflammatory cytokines, which they themselves secrete (interleukin-1, tumor necrosis factor-IL-1, TNF), as well as receptors for interleukins 6, 8, 12 (IL-6, IL-8, IL-12), granulocyte-macrophage colony-stimulating factor (GM-CSF). In addition, macrophages express receptors for chemokines, especially proinflammatory.[4,14] Among the secretory products of macrophages, cytokines play the most important role in the development of inflammation and innate immune responses. Their secretion occurs, as a rule, after cell activation. The spectrum of cytokines secreted by macrophages is very wide: cytokines of the IL-1 family, TNF-a, IL-6, IL-12, IL-23, IL-27, GM-CSF, G-CSF, M-CSF, IFN-a, IFN-r, IFN-y, IL-15 (homeostatic), suppressor cytokines (IL-10, TGF-R), growth / angiogenic factors, pro-inflammatory chemokines, macrophage inflammatory and chemotactic proteins.

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