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The role of innate immunity receptors in infectious diseases and maintenance of organism homeostasis

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The systematic review provides a justification for the value of innate immunity as an initial, necessary and determinant stage in the development of adaptive immunity. The participation of TLRs as a leading component of PRRs-system in maintaining natural congenital anti-infection resistance and homeostasis of the organism, in launching and dynamics of development of adaptive immunity to pathogens of infectious and non-infectious genesis was studied in detail. The importance of the influence of these pathogens on the homeostasis of the organism, on the formation of disturbances in anti-infective resistance at the organism and local levels, revealing new pathophysiological and immunological pathogenetic mechanisms of the development of these pathological processes is established. The colossal gap between fundamental studies of the biology and morphology of microorganisms and clinical studies of the diseases they cause is shortening. In an accessible form, explanations are provided for the absence of symptoms, the possibility of atypical manifestations, and the asymptomatic course of infection. There are new wide opportunities to improve and enhance the information content and personalization methods of diagnosis, treatment and prevention, as well as the creation of pharmaceuticals that act detrimental to all forms of cycle of development of pathogens, and new immunomodulatory drugs for the most effective treatment and prevention of diseases.
Key word: innate immunity, adaptive immunity, TLRs as a leading component of PRRs-system, anti-infection resistance, homeostasis of the organism, pathogenetic mechanism

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Роль рецепторов врожденного иммунитета в инфекционной патологии и поддержании гомеостаза организма

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В представленном систематическом обзоре обосновывается значимость врожденного иммунитета как начального, необходимого и определяющего этапа в развитии адаптивного иммунитета. Детально изучено участие TLRs как ведущего компонента PRRs-системы в поддержании естественной врождённой антиинфекционной резистентности и гомеостаза организма, в запуске и динамике развития адаптивного иммунитета на патогены инфекционного и неинфекционного генеза. Установлена значимость влияния этих патогенов на гомеостаз организма, на формирование нарушений в антиинфекционной резистентности на организменном и местном уровнях с выявлением новых патофизиологических и иммунологических патогенетических механизмов развития этих патологических процессов. Сокращается колоссальный разрыв между фундаментальными исследованиями биологии и морфологии микроорганизмов и клиническими исследова-

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ниями заболеваний, которые они вызывают. Объективизируются объяснения отсутствия симптоматики, возможность атипичных проявлений, бессимптомного течения инфекции. Открываются новые возможности совершенствования и повышения информативности и персонализации методов диагностики, лечения и профилактики, а также создания фармпрепаратов, воздействующих губительно на все формы цикла развития возбудителей, и новых иммуномодулирующих препаратов с целью наиболее эффективного лечения и профилактики заболеваний.
Ключевые слова: врожденный иммунитет, адаптивный иммунитет, TLRs как ведущий компонент PRRs-системы, антиинфекционная резистентность, гомеостаз организма, патогенетический механизм

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The human body is in permanent contact with different microorganisms and other endogenous or exogenous foreign substances and pathogenic agents. It has powerful innate (natural) and acquired (adaptive) systems of immune protection. Their coordinated functioning may prevent the development of infectious and non-infectious processes at any stage of development, regardless of the way the pathogen is received. They also can destruct or eliminate foreign substances and agents, which contributes to the maintenance of homeostasis.

Adaptive (synonyms: acquired, lymphocytic) immunity is present in only 1.5% of all species of organisms that exist on the earth. The ability of T-lymphocytes to respond to a wide range of potential antigens through the expression of specialized surface receptors to antigens and production of their antigen-specific antibodies in the phylogeny appeared only in vertebrates [1, 2]. This mechanism is a powerful targeted protection that provides the pathogen specific immune response with the formation of immunological memory [3].

Innate immunity is considered as a hereditarily fixed protection system of a multicellular organism from any pathogenic, opportunistic microorganisms (OM), endogenous factors and products of tissue destruction. Almost all multicellular organisms, animals, plants, invertebrates and unicellular eukaryotes have Innate immune recognition, which is based on non-clonal receptors [4–7]. The systems of innate immunity are extremely important in the initial stages of adaptive immunity reactions [1, 5, 8]. The adaptive immune response is only the effector part of the innate immune system. Non-specific protection systems play an exclusive protective and adaptive role in the early stages of infectious and non-infectious pathological processes. Non-specific mechanisms of innate immunity represent a phylogenetically more ancient system of defence against the aggressive impact of microorganisms compared to the adaptive immune system that is unique to vertebrates [1, 2, 9].

The system of innate immunity is comprised of four components:

• anatomic barriers (skin and mucous membranes);

• cells of mucous membranes (including epithelial) – innate immunity factor;

• physiological barriers (temperature, low pH in the stomach, anti-infective soluble proteins or humoral factors such as lysozyme, interferons (IFNs), natural IgM antibodies, components of the complement system, induced by foreign substances endogenous antimicrobial peptides – defensins, etc.;

• phagocytic barrier (neutrophils, basophils, eosinophils and monocytes, tissue macrophages, mast cells);

• cellular elements of innate immunity intraepithelial lymphocyte subpopulations – Tγδ-cells, natural killer cells (NK cells), killer and lymphokine-activated killer cells (LAK-cells) and so-called Pit cells, subpopulation of NK-cells with phenotype $CD56^+/CD16^-$;

• inflammatory barrier (chemokines, eicosanoids, limitation of inflammatory reactions in the lesion) [1, 2]. The main function of innate immunity is the detection of pathogens and their destruction using phagocytosis or endogenous synthesized antibacterial peptides. If these mechanisms do not result in the loss of the pathogen properties and do not provide its elimination, the innate protection mechanisms prepare the pathogen to interaction with T-lymphocytes for the subsequent development of adaptive immune response. Unlike adaptive immunity, which is operated by T-and B-lymphocytes, the innate protection mechanisms do not have any differentiated cell system but represent a variety of receptors, molecules and their complexes, which are constitutionally present in different cells and have the same functional purpose [1].

During the life of the human innate immunity factors, which are controlled by genes of the germinal centre, remain unchanged and are subsequently passed on to offspring [10]. Unlike the specific response of the immune system, which takes some time to develop, the response of unspecific protection mechanisms is almost instantaneous. Innate immunity provides recognition and elimination of pathogens in the first minutes and hours after their invasion. The key effectors of congenital immunity are dendritic cells and natural killer cells (NK). The operation of innate immunity cells manifests itself in the reactions of phagocytosis, cytolysis, including bacteriolysis and many others. Macrophages together with neutrophils perform a phagocytic function, and plasma proteins (complement proteins, C-reactive protein and others) react to bacteria carbohydrates. The factors of innate immunity, which are predominantly recognizing foreign proteins and carbohydrates of infectious and non-infectious nature, are activated immediately after the agent's impact. The distinguishing feature of the innate immune system cells is that they do not form clones and do not undergo positive and negative selection unlike adaptive immunity cells. Dendritic cells are considered as a link between innate and adaptive immunity [11–13].

The innate immune system of higher vertebrates has two ways of recognition of foreign conservative molecular structures of infectious origin – (during the life or death of an infectious agent; peculiar "molecular identification pattern" for a particular class of micro-organisms, pointing to their species) – pathogen-associated molecular patterns – PAMPs, are components of bacterial and fungal cell wall (LPS-lipopolysaccharide, lipopeptides, lipoproteins, peptidoglycan, β-glucagon), or microbial nucleic acids or proteins (flagellin, profilin); the second is the recognition of endogenous factors, damage-associated molecular patterns (DAMPs) – endogenous molecules that are released in case of infection or other cellular distress (for example the violation of cell ion balance, cells necrosis) or synthesized de novo, or appear in unusual forms [1, 14].

PAMPs and DAMPs are recognised by the special PRRs receptor group (pattern-recognition receptor), which are integral to innate anti-infectious immunity. Membrane PRRs include macrophage scavenger receptor (class A, SR-A), macrophage mannose receptor, β2-integrins, participating in the PAMPs recognition process and initiating phagocytosis [15]. Known PRRs include: – *TLR family* (Toll-like receptors), consists of 23 subtypes which are localized either on the cell surface or on the endosomes; – The family of RIG-I-like receptors (RLRs); It is localized in cytoplasm and consists of RIG-I (retinoic acid-inducible gene-I), MDA-5 (melanoma differentiation-associated gene 5) and LGP-2 (Laboratory of Genetics and Physiology 2) cells sensors that recognize intracellular dsRNA; RLRs bind to RNA-ligands and recognize different classes of viruses; – *The family of NOD* (nucleotide-binding oligomerization domain)-like receptors (NLRs); *The family of intracellular DNA receptors*, which consists of DAI receptor (DNA-dependent activator of IFN-regulatory factors) and other unidentified members. PRRs include some other membrane receptors (CD14, CD18, CD11/ CD18, MD2, selectins) for conducting an activation signal, induced by TLRs as well as soluble molecules that can recognize PAMPs – glycosylphosphatidylinositol (sCD14), mannose binding lectin (MBL), LBP – LPS binding protein, and complement system components; LBP binds soluble LPS, and complement components trigger the alternative or lectin pathway of the complement system activation. At the same time, one white cell can express PRRs of different specificity, which allows one cell to respond to different types of pathogens. TLRs are considered as carriers of the evolutionary memory of multicellular organisms about what is "ours" and how it differs from "alien". They play a crucial role in protection against infections, maintaining homeostasis and ensuring the normal flora of the intestine [1, 16–19].

In humans, there are about 23 members of TLR family. TLR are single-chain transmembrane polypeptides with similar structure: the extracellular N-terminal region responsible for binding pathogen → transmembrane area → intracellular part is the TIR-domain, which represents the C-terminal conservative region of TLR, responsible for the transmission of the activation signal of the mediated signalling pathway. Provide a link between the recognition of a pathogen/antigen and the development of inflammation, and between congenital and acquired immunity. Each TLR is encoded by its own genes [5, 7, 16]. Both exogenous and endogenous substances can act as TLR ligands. A particular feature of congenital immunity is the direct binding of the pathogen to the membrane receptor complex (without antigen-antibody intermediaries) for the direct destruction of the pathogen and its elimination from the body [20]. Exogenous TLR ligands are PAMPs of infectious agents, and endogenous are native molecular structures of the organism, resulting from cell damage (damage associated molecular patterns-DAMPs) – described more than 50 of such endogenous ligands [21, 22] (protein S100 family, amphoterin, heat shock proteins, purine metabolites, adenosine phosphate, uric acid, inert matrix proteins – hyaluronic acid and oligosaccharides, fibronectin, fibrinogen, oxidized low density lipoproteins (LDL), B2-glycoprotein-I and related phospholipids, nonhistone nuclear protein HMGB1) and alarmins. DAMPs also appear as a result of cell damage during the brain death of the organ and tissue donor during the transplantation, cold conservation and subsequent graft reperfusion (ischemia-reperfusion injury) [23–25]. Therefore, brain death and cerebral damage resulted in deterioration in the vitality of the organs, reduced function after transplantation and a poor prognosis for preservation and survival of the graft [26, 27]. Alarmins are cytokines which include thymic stromal lymphopoietin (TSLP), IL-25 and IL-33. TSLP refers to IL-7 like growth factors, which stimulate lymphocyte proliferation [28].

Different pathogens after the interaction of PAMPs and DAMPs to their specific TLRs can trigger the development of a common activation pathway of the inflammatory response. This is a unspecific defensive reaction of the organism to the impact of any exogenous or endogenous damaging factor in order to eliminate the pathogenic agent, to localize its operation and to repair the damaged organs and tissues [29]. Two fundamentally different signal paths are described: – activation of the early proinflammatory response involving TLR-2, 4, 5, 7, 9 and intracellular molecules MyD88 and kinases; – MyD88-independent signaling pathway activation of antiviral response and late proinflammatory response involving TLR-3 and TLR-4 and molecules of intracellular signaling cascade. In the first stage proinflammatory cytokines are synthesized with the stimulation of inflammatory reaction and activation of leukocytes, dendritic cells (DC), T- and B-lymphocytes, NK-cells, leading to the destruction and elimination of the pathogen; at the second stage production of anti-inflammatory cytokines is activated to complete inflammation, normalize homeostatic balance and develop reparative processes and prevent hyperreactivity and damage of its own tissues (if inflammatory cytokines are induced too early, it may cause a state of immunosuppression). Cytokines determine all the steps and the result of the local inflammatory process (edema, cellular infiltration, thrombosis of capillaries, etc.), for protection of the body. They operate through receptors on the surface of target cells, perform pro- and anti-inflammatory, immunostimulating, Immunosuppressive, and hematopoietic influence. Activation signal from different TLRs may lead to the development of different protective reactions [18, 30, 31]. After binding appropriate ligands all TLRs undergo dimerization and conformational changes required to release the sites of interaction with cellular adaptor molecules in the TIR-domain and start the signal transduction cascade. TIR-domain directly interacts with adaptor molecule MyD88, which is necessary for attracting kinases, releasing the dimer NFκB and its translocation to the nucleus. There are three more described types of adaptor molecules – MAL/TIRAP-1, TICAM-1 (TRIF) and TICAM (TRAM). NFkB directly binds the promoter sites of a number of genes of molecules, activating and regulating the development of inflammatory reaction, including cytokines genes (control the synthesis of proinflammatory cytokines IL-1, IL-6, IL-12, TNFα, activates IRF-factor – regulates members of the interferons (IFN) family. The IRF family consists of three functional subgroups:

1) transcription activators – IRF-1, IRF-3, IRF-9 (p48, interferon-stimulated gene factor 3γ – ISGF3γ);

2) transcription repressors, IRF-8 (interferon consensus sequence binding protein ICSBP);

3) proteins, which have properties of both activators and repressors of transcription – IRF-2, IRF-4/Pip/ISCAT, IRF-5, IRF-6, IRF-7, IRF-10. The transcription factors IRF are the regulators of the production of interferons type I (IFN-α, IFN-β, IFN-ω, IFN-τ, IFN-δ, IFN-κ, IFN-ε, IFN-ζ/limitin). IRF induce more than 650 genes and lead to maturation of antigen-presenting cells, mobilize macrophages and NK, stimulate the synthesis of antiviral substances and production of cytokines that activate T- and B-lymphocytes, induce apoptosis of infected cells, predetermining the process of sanogenesis of infec-

tious diseases caused by viral intracellular bacterial agents [32]. There is a relationship between TLRs and interferon system. Five types of TLR: 1, 5, 6, 9, and 16 participate in the biosynthesis of three main interferon classes. I type interferons (IFNα and IFNβ), which are produced by many cells types, primarily by plasmacytoid DC, are used for protection against viral infections. Effector mechanisms of antiviral action of these interferons consist, first, in blocking the translation, which prevents the expression of viral proteins, and, second, in the degradation of viral RNA by activating RNase L. Translation block realizes by phosphorylation of initiation factors of the special protein-kinase R. Antiviral action of type I interferons can also lead to the programmed death of the infected cells [33].

TLR hyperactivation with the action of endogenous and heterogeneous ligands can lead to the development of excessive inflammatory response with tissue injury. This is considered as one of the main mechanisms of the immunopathogenesis of various diseases [5, 34, 35]. Infection is one of the main factors influencing the change of TLRs expression. TLR expression level directly correlates with the severity of the process, which in some cases allows considering these receptors as early markers of infection [36, 37]. TLRs are expressed in immune competent tissues (tonsils, lymph nodes, spleen, thymus), in the integumentary tissues (skin, respiratory, gastrointestinal, urogenital, corneal, and conjunctival epithelium), in the internal organs cells (liver, spleen), placenta, adipose tissue, and nervous system. At the cellular level, TLRs are widely expressed on structural cells (epithelial, fibroblasts, endothelial) and immune cells (monocytes, macrophages, neutrophils, antigenpresenting DC, natural killer cells (NK granular lymphocytes in the peripheral blood and lymphoid organs) and to a lesser extent on eosinophils, lymphocytes [38–40]. Congenital immunity cells – macrophages – express all TLRs classes except TLR8, neutrophils – TLR2, TLR3, TLR4, TLR6, TLR7, TLR9, dendritic cells – all TLRs, natural killer cells – TLR2, TLR4, basophils – TLR1, TLR2, TLR4, TLR6, TLR9; mast cells – TLR1, TLR2, TLR3, TLR4, TLR6, TLR9, monocytes are deprived of TLR3, TLR6, TLR7 and TLR10 expression. Inactive TLRs are located in the membrane in the monomer state and during activation, they dimerize [5, 41, 42]. Receptors are not constantly expressed on the surface, but appear after the interaction with antigens or other cytokines. Some receptors or their subunits can be secreted by the cell and dissolved circulate in the blood [1, 5, 41]. The distinctive features of innate immunity are: direct pathogens recognition using a limited number of genetically programmed TLRs, interacting with the molecular structures of the pathogen; the simultaneous expression of several TLRs of different specificity; innate immunity may increase the expression level of TLRs in the same cell in the absence of immunological memory [1, 16, 41]. The family of TLRs consists of five subfamilies (TLR2, TLR3, TLR4, TLR5, TLR9). The division is based on similarity of amino acid composition and also on genetic homology. Certain types of TLR work in pairs: TLR-1 with TLR-2, TLR-2 with TLR-6. The combination of TLR1/2 recognizes a special lipopeptide type, which is synthesized only in bacteria, and the combination of TLR2/6 recognizes lipoteichoic acid (another common component of the walls of gram-positive bacteria). Thus, TLR2/6 recognizes gram-positive bacteria, mycobacteria, and fungi, TLR1/2 – all of the bacteria [7, 43]. There are receptors located on the cytoplasmic membrane (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10), their ligands are microorganisms surface structures (lipoprotein, lipopolysaccharides, flagellin, zymosan), and in intracellular membrane compartments (endoplasmic reticulum, endosome, lysosomes, endolysosomes, Golgi apparatus), thus preventing the contact of TLR3, TLR7, TLR8 and TLR9 (which recognize microorganisms nuclear structures molecules, but also can be activated by damaged molecular structures of its own organism) and endogenous nucleic acids of the cells of innate immunity in eosinophils, macrophages, neutrophils [5, 11, 43, 44]. Binding of intracellular receptors with ligands occurs only after they enter the cell [45]. If the nucleic acids released from the damaged tissues as a result of any infectious or non-infectious processes and thus are outside the cell, they are absorbed by endocytosis and are presented to intracellular PRRs. The nucleic acids of bacteria and viruses, that reproduce inside the cell, are captured by membrane vesicles and delivered to TLRs located in endosomes. The intracellular TLR location restricts contact of the ligand and receptor, resulting in preventing excessive inflammatory response in the host organism [46]. TLR3, TLR7, TLR8, and TLR9 recognize viral nucleic acids. The specificity of the nucleic acid to a potential pathogen is achieved, first, by the specific ligand localization in special cellular organelles (endosomes or phagosomes) and, secondly, by some differences in the structure of the nucleic acids of the virus and the host. TLR3 dimer recognizes double-stranded RNA that is formed during the replication cycle of most viruses, while TLR7 and TLR8 recognize a single-stranded RNA, so they are involved in the recognition of only those viruses whose genome presents single-stranded RNA, such as influenza virus. TLR7 and TLR8 can recognize single-strained RNA viruses and bacteria [5, 11, 41, 43].

The main function of the TLRs system is to activate the immune system cells after a contact with a pathogenic biological agent. Great attention is paid to the study of the natural protective reactions of the organism in the pathogenesis of various diseases. The first line of protection from pathogens is the innate immunity, the components of which do not change during life [4, 5, 18, 19, 47, 48]. Depending on the nature of the pathogen, there is a growing expression of TLR. Stimulation of TLRs, with the exposure of infectious and non-infectious pathogens, initiates a synthesis of non-specific protection factors in the first phase. A family of antimicrobial peptides (AMP) acts as endogenous natural antibiotics, performs the function of killing microbes and as signal molecules, causes the activation of immune cells; acts as mediators involved in inflammation and antigens, inducing the activation of T cells. Endogenous AMP are small molecules, composed of amino acids. They are an important component of the innate immune system of eukaryotes, which provides protection against pathogens. AMP are effective against a broad spectrum of bacteria, fungi, protozoa and enveloped viruses. The action of small AMP mainly leads to disruption of the structure and function of the cytoplasmic membrane of microorganisms, which leads to their death. AMP act not only as endogenous antibiotics, they also play an important role in the development of inflammation, the maintenance and regulation of the adaptive immune system. There are three families of peptides-antibiotics discovered in human: defensins, cathelicidins, and histatins. Proteins with homologous molecular structure (BPI) are divided in a separate molecular family. They are involved in the protection of the respiratory tract in acute respiratory infections and bacterial infections, chronic pulmonary diseases, cystic fibrosis. BPI molecular family includes BPI protein, proteins of the subfamily of products of palate-lung-nasal epithelium clone (PLUNC), PLTP, and CETP. The balance of proinflammatory and anti-inflammatory BPI family proteins determines the nature of the immune response in the infectious process. Disruption of this

balance can lead to hypo- or hyper reactions, causing an uncontrolled course of the infectious process [11, 49]. AMP are able to modulate the innate immune response and protect against infection, not only causing, but also suppressing the inflammatory response [50]. These conservative molecules are secreted by phagocytes and epithelial cells. These peptides are key components of innate immunity, especially on epithelial surfaces, at the primary contact with the pathogen. AMP are contained in mucus and other fluids located on the border between the cells of the host and environment, they are the first line of defense of the organism [51]. In high concentrations, these peptides are able to destroy the microbial cytoplasmic membrane and shells, and in lower concentrations act as modulators of innate immunity. Cathelicidins (CC) is a family of antimicrobial proteins which are mainly found in the peroxidase-negative granules of neutrophils. These compounds are synthesized in the form of preproproteins. The human cationic antimicrobial protein (hCAP18, 18 кDa M. M.) is the only identified by human CC. In addition to neutrophils, hCAP18 is identified in lymphocytes and monocytes, in the squamous epithelium (mouth, tongue, esophagus, cervix, and vagina), pulmonary epithelium tissue, keratinocytes in inflammatory diseases and epididymitis. Antibacterial C-terminal fragment of hCAP18 – LL37 (37 amino acids), exhibits antimicrobial activity against gram (–) and gram (+) bacteria, fungi, some viruses, and protozoa. LL37 can bind LPS and neutralize its ability to induce endotoxic shock. LL37 acts as a chemotactic agent for neutrophils, monocytes, and T-cells. Ll37 prevents the sperm from being defeated by micro-organisms on the way to the egg and during fertilization [52]. Thymic stromal lymphopoietin (TSLP) is produced by cells of barrier organs: in the skin – by keratinocytes, in the lung – by epithelial cells; in gastrointestinal tract – by enterocytes; discovered in culture of thymic cells; smooth muscle cells, pulmonary fibroblasts, activated by IgE binding mast cells, and activated dendritic cells express and produce it in large quantities [53–57].

Specific components of adaptive immunity. Cytokines produced by cells of the innate and adaptive immunity have the interrelated effect on the system of innate and adaptive immunity [58, 59]. The relationship of innate and adaptive immunity is carried out by DC, specialized phagocytes concentrated in the spleen, lymph nodes, and skin. Being antigen-presenting cells, DCs are responsible for the stimulation of immune competent cells. They express the high level of stimulant molecules needed to activate T-lymphocytes, which is the beginning of specific immunity. DC activation and differentiation program is started only after a meeting with a pathogen and stimulation through TLRs. In humans, different types of DC (myeloid and plasmacytoid) differ in their ability to respond to different pathogens due to the different expression of TLRs. Plasmacytoid DC are the major producers of type 1 interferons that activate NK and NKT lymphocytes. The local inflammatory response is initially developing. Myeloid DC, which came to the focus of infection, phagocytose destroyed infected cells [1, 2, 5]. In the initial stages of development of acquired immunity TLRs are involved in DC activation and differentiation: – activation of phagocytosis, processing, and presentation of antigens; induction of expression of co-stimulatory molecules CD40, CD80, and CD86; secretion of cytokines that stimulate differentiation of T-helper cells, cytotoxic lymphocytes, and NK cells. TLRs activation increases the expression level of co-stimulatory molecules CD80/CD86 on antigen-presenting cells (APC) that interact with the co-stimulatory molecule CD28 of T lymphocytes and lead to a decrease in the activation threshold of T cells, increase in the IL-2 expression, increase in T-lymphocytes proliferation and increase in their resistance to apoptosis. T cells, without co-stimulation, on the contrary, pass into a state of anergy to the antigen. Interaction of the patterns of pathogens with different TLRs leads to the refocusing of the immune response, either by cellular or humoral path. This is due to the fact that the activation of APC through different TLRs leads to the production of cytokines complex, having the opposite effect. Depending on I or II antigens class of the major histocompatibility complex (MHC) are expressed on APC, the antigen will be presented to T helper cells ($CD4^+$) or T killer cells ($CD8^+$), and then the response of the acquired immune system will be formed. Regulation of the selection of different populations of the regulating cells-helpers is done at the level of certain cytokines production. The key cytokines regulating Th1 selection are IFNγ, interleukin IL-2, 4, 6, 5, 8, 10 and 13. Production of IFN-γ Th1 inhibits the production of IL-4, and production of IL-10 Th2 inhibits production of Th1 IFN-γ. Different cytokine profile stimulates conversion of Th0 to either Th1 or Th2. Activation of Th1 leads to the development of cellular inflammation, Th2 direct immune response by the humoral way, providing the synthesis of antibodies. TLR4 causes differentiation of Th1 and activation of the TLR2 – Th2, that is, specific TLRs depending on the type of the pathogen can guide the way certain choices in the development of acquired immunity [1, 2, 18, 60]. Among Th-helper cells in addition to Th1 and Th2 populations, there are cells, the main role of which consists in the regulation of the immune response – $CD4^+CD25$. They constitute 5–10% of the T-helper population and appear after the stimulation of CD4 cells. This is the third population of Th1, Th2, Th3 (per). These cells activate the immune response to self-antigens, as well as some alien – infectious. They maintain tolerance to self-antigens [61]. γ/δ T lymphocytes are found mainly in the tissues, mucous membranes, epithelial layer. γ/δ T-lymphocytes phenotype and functionally different from α/β T lymphocytes of peripheral blood by the structure of their receptors. In the peripheral blood, their level is not very high. They have on their surface HML-1-antigen (human mucosal lymphocyte antigen-1), which does not exist in the T-lymphocytes of peripheral blood. In a state of rest, γ/δ T lymphocytes do not have subpopulations of $CD4^+$ and $CD8^+$, but after antigen stimulation are differentiated: most of them (60%) have $CD8^+$ markers and only about 6% – $CD4^+$. A feature of γ/δ T cells is that they recognize an antigen that is not associated with the major histocompatibility complex, and only with heat shock proteins (HSP). These cells participate in resistance to infections [61].

From the 14^{th}–15^{th} day of the embryonic period until birth, TLRs are widely represented in the lung tissue on the surface of the alveolar epithelial type 2 and alveolar macrophages. Changes in the expression of TLRs may be associated with lung pathology in the early postnatal period [62]. TLR2 and TLR4 are normally identified on the basolateral surface of intestinal epithelial microvilli in human fetuses from 18 to 21-week-old, and changes in their expression may be associated with the pathogenesis of ulcerative colitis [63]. The expression of TLR4 is found on the apical surface of amniotic epithelium from the 9th week of fetal development. TLR4 on the basal surface of amniotic epithelium correlates with development of chorioamnionitis [64]. The importance of TLRs in protecting the newborns from infections is indirectly confirmed by the presence in breast milk of a large number of soluble TLR2, which is likely to complement the protective role of SIgA and IFNα [65–67]. Gestational age affects the level of expression of TLRs: in prema-

ture newborns expression level of TLRs is minimal compared to full-term and older. Therefore, LPS-stimulated via this receptor, the secretion of IL-6, IL-8, IL-1β and TNFα in children born prematurely reduced, which results in high susceptibility to gram-negative infections [68, 69]. Analysis of the system of TLRs in healthy people of different age groups revealed increased values of the effector functional activity and surface expression of TLR2 in healthy children aged 0.5 to 3 years compared to children of 10-15 years, and adult donors 20-40 years [5, 70]. With age, the level of expression of TLR decreases, which explains the reduced immune reactivity in the elderly [41].

The innate immune system responds to various changes in the environment (both external and internal, regarding both the body and individual cells) and is also responsible for changes in metabolism, structural or energy, and for the maintenance of homeostasis of the organism as a whole. Diseases with a metabolic disorder such as type 2 diabetes, obesity, hyperglycemia, cause disruption of the inflammatory response [71, 72]. Plasma TLRs bind to various endogenous ligands, many of which are lipid in nature, including various fatty acids and their derivatives. This indicates the close relationship between lipid metabolism and the innate immune system [43, 73]. Activation of the innate immune system entails the launch of the antioxidant system [74]. The antioxidant system provides protection against oxidative stress, provides protection from free radicals, thereby affecting the severity of the inflammatory process and the degree of destruction of tissue. Obesity has the infectious origin. IAT (inflammatory reaction of adipose tissue) has no clinical manifestations. The launch component of IAT is LPS. The source of LPS is the flora of the intestine: with the death of gram-negative bacteria component of their membrane translocates in the capillaries of the intestine and then into the circulating blood. The binding of LPS with TLR4 in adipocytes leads to the activation of various intracellular kinases, which results in the nuclear translocation of factor NF-kB in the cell nucleus [75, 76], where it stimulates the transcription of genes encoding inflammatory synthesis of regulatory substances, including cytokines, chemokines. Developing in response to activation of TLRs intracellular reactions, changes in the secretion of numerous regulatory substances lead to paracrine and endocrine ways to change metabolism and inflammation in adipose and other tissues and organs. Activation of TLR4 in adipocytes stimulates them to release saturated fatty acids, which in their turn bind to TLR4 and trigger in adipocytes the same as LPS processes. This reaction, causing the activation of TLR4 after elimination of the causative agent, increases glucose and lipids in the blood and, thereby, the processes of recovery in the post-infectious period. But lack of physical activity and excess food especially in modern man there is the unintended evolution of the state, when received dietary glucose and lipids join these substances from the liver and adipocytes through the activation of TLRs in saturated fatty acids and the development of insulin resistance (IR) in fat, liver and muscle cells. A result of these reactions is an increase in the blood glucose level and lipids, as energy and plastic substrates essential for the functional activity of immune system cells. Glucose is the primary energy provider for the immune system [77, 78]. Lipids are the large and functionally most important part of cellular membranes, defining the characteristics of cell receptors and cells structures. Activated immune cells have mechanisms to facilitate their increased absorption of glucose and lipids. The physiological significance of activation of TLRs in cells of the adipose tissue, liver and muscle cells, with the subsequently increased allocation of glucose and lipid, is in the adequate immune responses with energy and plastic material [41, 79, 80]. As a result, increases the level of glucose, accumulated fat and increases the level of saturated fatty acids and triglycerides in the blood. In terms of demand for energy substrates the level of glycemia rises, accumulated fat and increases the level of saturated fatty acids and triglycerides in the blood, stimulation of TLRs is growing, developing immune system dysfunction, local and systemic inflammation. The fact of increasing the level of LPS during Chlamydia pneumoniae infection [81] indicates a possible activation of these receptors. There is no doubt that the ways and mechanisms of the effects of viruses, microbes, and parasites on metabolism and the morphological state of the fatty tissue are very different.

Thus, the systematic review provides a justification for the value of congenital immunity as an initial, necessary and determinant stage in the development of adaptive immunity. The participation of TLRs as a leading component of PRRs-system in maintaining natural congenital anti-infection resistance and homeostasis of the organism, in launching and dynamics of development of adaptive immunity to pathogens of infectious and non-infectious genesis was studied in detail. The importance of the influence of these pathogens on the homeostasis of the organism, on the formation of disturbances in anti-infective resistance at the organism and local levels, revealing new pathophysiological and immunological pathogenetic mechanisms of the development of these pathological processes is established. The colossal gap between fundamental studies of the biology and morphology of microorganisms and clinical studies of the diseases they cause is shortening. In an accessible form, explanations are provided for the absence of symptoms, the possibility of atypical manifestations, and the asymptomatic course of infection. There are new wide opportunities to improve and enhance the information content and personalization methods of diagnosis, treatment and prevention, as well as the creation of pharmaceuticals that act detrimental to all forms of cycle of development of pathogens, and new immunomodulatory drugs for the most effective treatment and prevention of diseases.

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